

ORIGINAL RESEARCH**Histopathological Study of Tumour and Tumour Like Lesions of Bone****¹Dr. Anvita Nilekani, ²Dr. Thippeswamy M.T.R., ³Dr. Indumathi S.**

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Abstract

Background: In this study, we wanted to evaluate the bone tumours and tumour-like lesions as they have a very diverse morphology and overlapping patterns. Also, bone microenvironment is an ideal site for metastasis.

Materials and methods: This was a hospital based retrospective and prospective study, conducted among 65 patients who presented with bone tumour and tumour-like lesions to the Department of Pathology, JJM Medical College, Davangere, over a period of 5 years with 3 years of retrospective from June 2014 to May 2017 and 2 years of prospective from June 2017 to May 2019 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Results: Bone tumours and tumour-like lesions comprised of 0.7% of all the neoplasms diagnosed during the study period. Of which, benign bone tumours formed the majority (70.8%). Most of the cases were seen in 2nd decade, femur (43.1%) being the most common site. Osteochondroma was the most common tumour overall with 25 cases (38.6%) followed by giant cell tumour with 10 cases (15.4%). Osteosarcoma was the most common malignant tumour (6.2%). The histopathological and clinic-radiological correlation showed perfect agreement.

Conclusion: Bone tumours and tumour-like lesions are mostly diagnosed on histopathology. Correlating with clinical and radiological data is of utmost importance. Benign bone tumours are most commonly encountered with propensity for long bones, especially femur. Immunohistochemistry is of limited value and no set makers are easily available for diagnosing and differentiating bone tumours.

Keywords: Bone Tumours, Benign, Malignant, Osteochondroma, Osteosarcoma

Introduction

The skeletal system of the body provides mechanical and structural support. The bone is a connective tissue which is composite in nature due to presence of various components such as minerals, water, collagen, non-collagenous proteins, lipids etc., which helps in its continuous process of growth and remodelling; thus providing the tensile strength to the body.^[1] The complex pathology of the skeletal system leads to broad spectrum of diseases, including those caused by genetic (sporadic and inherited), malformative, inflammatory, metabolic, circulatory, traumatic, iatrogenic, and neoplastic disorders; and thereon having various morphological expression. Bone tumours, including both neoplasms and various conditions

that may simulate them, is one of the most challenging areas in surgical pathology for several reasons. First and the foremost being that bone tumours are uncommon, making it difficult to acquire the necessary skill to diagnose their histological variants and mimics. The pathology training programs have unsatisfactory expertise to provide medical students and young pathologists with the knowledge needed to diagnose these lesions accurately and precisely.^[2] The correct diagnosis requires careful incorporation of radiological imaging studies and clinical findings. Bearing in mind that the implications of a single diagnosis on a patient can be profound, the study of these lesions becomes of paramount importance. Skeletal cancers may arise in a bone as primary tumours, or as a consequence of the metastatic dissemination of tumour cells from distant sites and thereby giving rise to secondary or tertiary tumours. Progression of malignant tumour in bone is nurtured by the multipotent bone marrow stromal cells and the complex cellular environment that they give rise to, including hematopoietic stem cells, bone marrow endothelial cells, osteoblasts, osteoclasts and their precursors. They adapt and remodel the bone marrow microenvironment. This leads to enhancement of tumorigenicity by changing the genotype and phenotype of cancer cells in bone. This is demonstrated by the cultured bone cells that have been in contact with cancer cells for extended time periods which have the ability to transform non-tumorigenic cells to tumorigenic cells, thus making it apparent that bone cells undergo phenotypic and genotypic modifications during skeletal cancer progression.^[2] Constituents of the complex bone milieu contribute significantly to the growth and proliferation of primary cancers, such as osteosarcoma or myeloma and also aid in the process of metastasis of epithelial-derived cancers such as prostate or breast cancer.^[2] Bone tumours and tumour-like lesions are rare among all the tumours of human body. Bone tumours are known for their diversities. And this diverse nature of it makes it crucial to diagnose them correctly and treat them adequately.^[3]

Aims and Objectives

1. To study the distribution of bone tumours and tumour-like lesions.
2. To elaborate the spectrum of bone tumour and tumour-like lesions by histopathological examination and to correlate with the clinico-radiological data.
3. To classify these lesions by WHO classification 2013.

Materials and methods

This was a hospital-based retrospective and a prospective study, conducted among 65 patients who presented with bone tumour and tumour-like lesions to the Department of Pathology, JJM Medical College, Davangere, over a period of 5 years with 3 years of retrospective from June 2014 to May 2017 and 2 years of prospective from June 2017 to May 2019 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Inclusion Criteria

All the histologically diagnosed tumours and tumour-like lesions of bone in patients irrespective of their age and sex.

Exclusion Criteria

1. Infectious and inflammatory lesions of bone
2. Metabolic lesions of bone
3. Haematological malignancies with bone marrow involvement

Study Procedure

The excision biopsy samples were collected and fixed in 10% formalin and were grossly examined. The bony bits and soft tissue were segregated. The soft tissue was sent for processing. The hard bony bits were subjected to decalcification with formic acid and concentrated formalin in 3:1 ratio. The large bone specimens were sawed into smaller bits and then subjected for decalcification. After adequate decalcification, the tissue was processed under Leica tissue processor and embedded in paraffin blocks. Sections of 3 μ to 5 μ thick were cut using Leica rotator microtome, and haematoxylin and eosin stained slides were obtained. Immunohistochemistry was done as and when required. The slides were observed under light microscope; histopathological diagnosis was made and classified accordingly. The radiological and clinical details given were analysed and correlated with that of histopathological diagnosis.

Statistical Methods

Statistical analysis was done in the form of frequency tables, ratios and percentages. Cohen's kappa value was derived to know the clinic-radiological and histopathological correlation. The formula and the criteria used were:

$$\kappa = \frac{p_o - p_e}{1 - p_e} = 1 - \frac{1 - p_o}{1 - p_e},$$

p_o = the relative observed agreement p_e = the hypothetical probability of chance agreement

- 0 = agreement equivalent to chance.
- 0.1-0.20 = slight agreement.
- 0.21 – 0.40 = fair agreement.
- 0.41 – 0.60 = moderate agreement.
- 0.61 – 0.80 = substantial agreement.
- 0.81 – 0.99 = near perfect agreement
- 1 = perfect agreement

Sample Size Estimation

Prior to beginning of the study, according to the pilot study done for two years (2015 and 2016), a total of 20 cases of bone tumours and tumour-like lesions were reported in our institution, with an average of 10 cases per year.

For the study to be statistically significant, according to the previous studies; a minimum of 50 cases should be included. Hence, the duration of the present study was taken as four years (including three years retrospective and two years prospective) Sample size estimation formula:

$$n = Z^2 PQ / e^2$$

n: sample size

Z: z score for 95% confidence interval= 1.96

P: Estimated proportion of bone tumour and tumour like lesions in population = 0.007 Q: 1-

P= 0.994 e: margin of error= 5%= 0.05 After calculation n= 10

For five-year study: 10x5= 50

Estimated sample size- 50 cases (minimum)

Results

Total histopathology biopsies	63597					100%
Bone biopsies	300					0.5%
Bone tumours	65					0.1%
Incidence of bone tumours						
Category	Frequency					Percentage (%)
Benign	46					70.8
Malignant	07					10.7
Tumour-like lesions	12					18.5
Total	65					100
Distribution of bone tumours						
Age		Gender				Total
		Male	Female			
≤10	03	08.8%	00	00%	03	04.7
11-20	12	35.3%	16	51.6%	28	43.0
21-30	12	35.3%	08	25.8%	20	30.8
31-40	04	11.8%	03	09.7%	07	10.8
41-50	02	05.8%	03	09.7%	05	07.7
51-60	00	00%	01	03.2%	01	01.5
≥60	01	03.0%	00	00%	01	01.5
Total	34	100%	31	100%	65	100%
Combined Age and Gender Distribution of Cases						
<i>Table 1</i>						

Bone biopsies were 300 in number (0.5%). Of which, 65 cases of bone tumours were seen. Thus, bone tumours made up to 0.1% of the total biopsies, 0.7% of all the tumours and 21.7% of the total bone biopsies.

The benign tumours were in predominance with 46 cases out of the total 65 cases (70.8%). Followed by tumour-like lesions with 12 cases (18.5%) and 07 cases of malignant tumours (10.7%).

Among the males, the cases ranged from 7 to 62 years of age; majority were in second and third decade (35.3%) with the mean age of 23 years. In female, the cases ranged from 11-45 years; the majority being in 2nd decade of life (51.6%) with the mean age of 24.4 years. Among the 46 benign tumours, the age group ranged from 07 to 62 years, mean age being 23.5 years. The benign cases showed male sex preponderance with 27 cases and 19 cases were seen in females. The male to female ratio in benign lesions were 1.4: 1. The age group of males with benign lesions ranged from 07 to 62 cases, mean being 24.4 years. The age group of females with benign lesions ranged from 11 to 45 years, mean being 22.4 years. In the twelve tumour-like lesions, the age ranged from 8 to 40 years, mean age being 20.8 years. There was seen female majority with seven cases, ratio of male to female being 1: 1.4. The age group of females ranged from 15 to 40, mean age being 22.4 years. Five male cases ranged from 8 to 36 years of age with mean being 18.6 years. Of the seven malignant tumours, the age ranged from 12 to 52 years; mean age being 30.1 years. There was female sex predilection among the malignant tumours. Male to female ratio was 1:2.5 The two cases of male, ages were 22 and 33 years; mean age being 27.5 years. The five female malignant cases, age ranged from 12 to 52 years; mean age being 30.4 years. Most of the paediatric tumours (0-16 years) were benign. Tumour-like lesions peaked in second decade. Malignant lesions showed equal predominance in second to third decade.

Age (Years)	Tumour Behaviour			
	Benign	Malignant	Tumour-Like Lesions	Total
≤10	02	00	01	03
	04.3%	00.0%	08.3%	
11-20	19	02	07	28
	41.4%	28.7%	58.3%	
21-30	16	02	02	20
	34.8%	28.7%	16.7%	
31-40	05	01	02	08
	10.8%	14.2%	16.7%	
41-50	03	01	00	04
	06.5%	14.2%	00.0%	
51-60	00	01	00	01
	00.0%	14.2%	00.0%	
≥60	01	00	00	01
	02.2%	00.0%	00.0%	
Total	46	07	12	65
	100%	100%	100%	100%
Age Distribution of Cases Based on Tumour Behaviour				
Gender	Tumour Behaviour			
	Benign	Malignant	Tumour-like Lesions	Total
Male	27	02	05	34
	58.7%	28.6%	41.7%	
Female	19	05	07	31
	41.3%	71.7%	58.3%	
Total	46	07	12	65
	100%	100%	100%	
Gender Distribution of Cases Based on the Behaviour of the Tumour				

Table 2

Most of the tumours in both males and female were benign, with male sex preponderance (58.7%). Malignant lesions showed and tumour-like lesions were seen in majority in females with 71.7% and 58.3% respectively.

Bone Involved	Site	Frequency	Total	Percentage(%)
Femur	Proximal	07	28	43.1
	Shaft	01		
	Distal	20		
Tibia	Proximal	04	08	12.3
	Distal	04		
Fibula	Proximal	01	01	01.5
Humerus	Proximal	05	08	12.3
	Distal	03		
Radius	Proximal	01	03	04.6
	Distal	02		
Vertebra	Sacrum	02	02	03.1
Craniofacial	Maxilla	04	12	18.5
	Mandible	04		

	Temporal	02		
	Nasal bone	01		
	External auditory canal	01		
Metatarsal	-	03	03	04.6
Total		65	65	100
Distribution of Cases Based on the Site of Lesion				
Bone Involved	Site	Frequency	Total	Percentage (%)
Femur	Proximal	02	19	41.2
	Shaft	01		
	Distal	16		
Tibia	Proximal	03	07	15.2
	Distal	04		
Fibula	Proximal	01	01	02.2
Humerus	Proximal	03	06	13.0
	Distal	03		
Radius	Proximal	00	02	04.4
	Distal	02		
Vertebra	Sacrum	02	02	04.4
Craniofacial	Maxilla	02	07	15.2
	Mandible	01		
	Temporal	02		
	Nasal bone	01		
	External auditory canal	01		
Metatarsal	-	02	02	04.4
Total		46	46	100
Site-wise Distribution of Benign Bone Tumours				
Bone Involved	Site	Frequency	Total	Percentage (%)
Femur	Proximal	03	06	85.7
	Distal	03		
Tibia	Proximal	01	01	14.3
Total		07	07	100
Site-wise Distribution of Malignant Bone Tumours				
Bone Involved	Site	Frequency	Total	Percentage (%)
Femur	Proximal	01	02	42.3
	Distal	01		
Tibia	Proximal	01	01	13.3
Humerus	Proximal	02	02	13.3
Radius	Proximal	01	01	04.4
Craniofacial	Maxilla	02	05	15.6
	Mandible	03		
Metatarsal	-	01	01	04.4
Total		12	12	100
Site-wise Distribution of Tumour-like Lesions				

Table 3

Femur was the most common site involved with 43.1%; The majority was localised to distal femur (30.7%) and among these, the knee joint per se (distal femur and proximal tibia), were involved in 15 cases. Craniofacial bones comprised of 18.5% cases, followed by tibia (12.3%) and humerus (12.3%). Radius and fibula comprised of 4.6% and 1.5% cases respectively. Among the smaller bones, only metatarsals were involved in three cases (4.6%). Vertebra was involved in two cases (3.1%) both involving the sacral part of the vertebra.

Most of the benign bone tumours were located in femur (41.2%) followed by craniofacial region (15.2%). Within the femur, the distal part of the femur was most commonly involved. Within the craniofacial bones, maxilla and temporal bone were involved in two cases each. Rest of the bones, including mandibles, nasal bones and bone of the external auditory canal were involved in single cases each. Tibia and humerus were involved in seven and six cases respectively. Within the tibia, the distal portion was mostly involved, whereas the humerus showed equal proportion of proximal and distal involvement. Two cases involved the distal radius, sacral region of vertebra and metatarsals each.

The malignant cases were localised predominantly in femur (85.7%) followed tibia (14.3%).

The tumour-like lesions are mostly located in craniofacial region predominantly, especially the mandible was involved in three case.

Location	Frequency	Percentage
Epiphysis	20	30.8%
Epi-metaphysis	08	12.3%
Metaphysis	28	43.1%
Meta-diaphysis	04	06.2%
Diaphysis	02	03.1%
Joint space	03	04.5%
Total	65	100%
Distribution of Cases Based on the Location within the Bone		
Diagnosis	Frequency	Percentage (%)
Osteochondroma	25	38.6
Synovial chondromatosis	03	04.6
Chondroblastoma	01	01.5
Chondrosarcoma	01	01.5
Osteoid osteoma	02	03.1
Osteoma	05	07.7
Osteosarcoma	04	06.2
Ewing's sarcoma	01	01.5
Giant cell tumour	10	15.4
Aneurysmal bone cyst	02	03.1
Simple bone cyst	01	01.5
Fibrous dysplasia	09	13.8
Metastasis	01	01.5
Total	65	100
Distribution of Cases Based on Histopathological Diagnosis		
<i>Table 4</i>		

Within the bone, the metaphysis was majorly involved with 28 cases (43.1%) followed by epiphysis (30.8%). The epiphyseal-metaphyseal and the metaphyseal-diaphyseal junction were involved in 12.3% and 6.2% cases respectively. Two cases (3.1%) were located in the diaphyseal region of the bone. The joint space of the knee was involved in three cases (4.5%). Based on histopathological diagnosis, majority of the cases were benign followed by tumour-like lesions and least were malignant cases. The benign cases were osteochondroma majorly,

synovial chondromatosis, giant cell tumour, osteoma and osteoid osteoma. The tumour-like lesions comprised of cystic lesions of bone like two cases of aneurysmal bone cysts and a case of simple bone cyst. Nine cases of fibrous dysplasia of bone were also seen. The malignant cases were mostly primary malignant lesions of bone, osteosarcoma being predominant followed by chondroblastoma and chondrosarcoma. There was a single case of metastatic bone deposits.

Osteochondroma was diagnosed in 25 cases (38.6%). Mostly they were solitary lesions. Two of the 25 cases showed multiple lesions, suggesting osteochondromatosis. This was followed by 10 cases of giant cell tumour (15.4%) all of which were benign in nature with no features of anaplasia. There were three cases (4.6%) of synovial chondromatosis, all of them presented in the knee joint. The osteoma (7.7%) and osteoid osteoma (3.1%) were seen in five and two cases respectively. All the osteomas were located in craniofacial region.

Among the tumour-like lesions, fibrous dysplasia (13.8 %) was seen in majority with nine cases. A single case of simple bone cyst (1.5%) and two cases (3.1%) of aneurysmal bone cysts were seen.

There were four cases (6.2%) of osteosarcoma among the malignant lesions. One case each of chondroblastoma and chondrosarcoma (1.5%). Chondrosarcoma was of lower grade. One case of Ewing's sarcoma was seen for which CD99 marker showed diffuse membranous positivity. One single case of metastasis to bone was seen.

Diagnosis	Gender				Ratio	Frequency	Percentage
	Male		Female				
Osteochondroma	17	50.0%	08	25.8%	2.1:1	25	38.6
Synovial chondromatosis	02	05.8%	01	03.2%	2:1	03	04.6
Chondroblastoma	01	02.9%	00	00.0%	1:0	01	01.5
Chondrosarcoma	00	00.0%	01	03.2%	0:1	01	01.5
Osteoid osteoma	01	02.9%	01	03.2%	1:1	02	03.1
Osteoma	00	00.0%	05	16.1%	0:5	05	07.7
Osteosarcoma	01	02.9%	03	09.7%	1:1	04	06.2
Ewing's sarcoma	01	02.9%	0	00.0%	0:1	01	01.5
Giant cell tumour	06	17.6%	04	13.1%	1.5:1	10	15.4
Aneurysmal bone cyst	01	02.9%	01	03.2%	1:1	02	03.1
Simple bone cyst	00	00.0%	01	03.2%	0:1	01	01.5
Fibrous dysplasia	04	12.1%	05	16.1%	0.8:1	09	13.8
Metastasis	00	00.0%	01	03.2%	0:1	01	01.5
Total	34	100	31	100	1.1:1	65	100

Gender Distribution of Bone Tumour and Tumour-like Lesions

Diagnosis	Age(in years)							Mean Age	Total
	<10	10-20	20-30	30-40	40-50	50-60	>60		
Osteochondroma	02	13	07	01	01		01	20.9	25
Synovial chondromatosis				03				33.0	03
Chondroblastoma		01						42.0	01
Chondrosarcoma					01			45.0	01
Osteoid osteoma		02						13.0	02
Osteoma		02	02		01			27.4	05
Osteosarcoma		02	02					19.3	04
Ewing's sarcoma				01				37.0	01

Giant cell tumor		01	07	01	01			28.1	10
ABC				02				38.0	02
SBC		01						15.0	01
Fibrous dysplasia	01	06	02					17.0	09
Metastasis						01		52.0	01
Total	03	28	20	08	04	01	01	23.8	65
Age Distribution of Bone Tumour and Tumour-like Lesions									
<i>Table 5</i>									

Among the benign tumours, osteochondroma, synovial chondromatosis and giant cell tumours showed male preponderances with male to female ratio of 2:1 to 1.5:1. All the cases of osteoma were seen in females, whereas osteoid osteoma showed no sex predilection.

Aneurysmal bone cysts showed equal incidence in males and females whereas as single case of simple bone cyst and cases of fibrous dysplasia showed higher incidence in females.

Among the malignant cases, a single case of chondroblastoma and chondrosarcoma was seen in a male and a female respectively. Four cases of osteosarcoma were seen in which three were in females and one in male. Ewing's sarcoma was seen in a male and metastasis to bone was seen in female. The majority of osteochondroma cases were seen in second and third decade of life with 13 and seven cases respectively. Two were seen in below ten years and one in above 60 years of age. All the three cases of synovial chondromatosis were seen in fourth decade. One case each of chondroblastoma and chondrosarcoma were seen in second and fifth decade.

Two cases of osteoid osteoma were seen in second decade as well as osteomas were seen in second and third decade. Osteosarcoma cases were seen in 1227 years of age. Mean age was 19.3 years.

The giant cell tumours were seen predominantly in 3rd decade of life with mean age being 28.1 years. Both the cases of aneurysmal bone cyst were seen in 4th decade and a single case of simple bone cyst was seen in 2nd decade. The fibrous dysplasia cases presented mostly in 2nd decade, the mean age was 17 years. Ewing's sarcoma and metastatic bone tumour presented in 4th and 6th decade respectively.

Based on the World health organisation classification of bone tumours, majority of cases were chondrogenic tumours (46.1%), benign comprising the larger portion of these with 28 cases, one case of intermediate but rarely metastasizing type and one case of malignant bone tumour. Among the eleven osteogenic tumours, seven cases were benign (10.8%) and four cases (6.1%) of malignant.

The ten giant cell tumour cases (15.4%) were categorised under osteoclastic giant cell rich tumours of intermediate nature (locally aggressive, rarely metastasizing).

Tumour-like lesions were categorised under tumour of unknown neoplastic nature. Of which, ten cases (15.4%) were benign and two (3.1%) were of categorised under intermediate, locally aggressive type.

The Ewing's sarcoma and metastatic tumour (3.1%) were under miscellaneous category of WHO bone tumours.

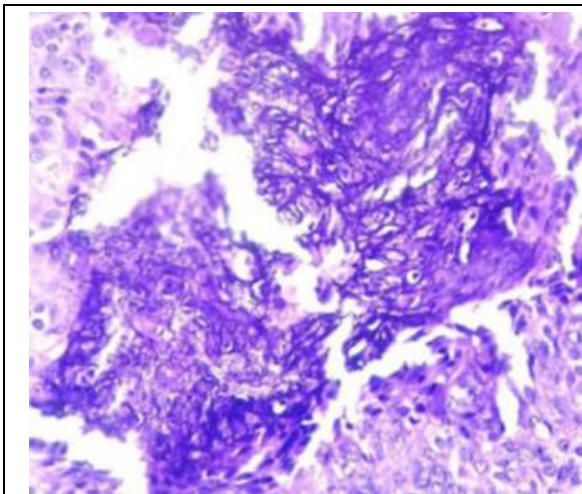


Image 1: Microscopy of chondroblastoma with pericellular chicken wire calcification, H and E, X10



Image 2: Plain radiograph image of osteosarcoma showing a radiodense lesion with soft tissue extension



Image 3: Clinical image of osteosarcoma showing an enlarging mass lesion in right knee joint.

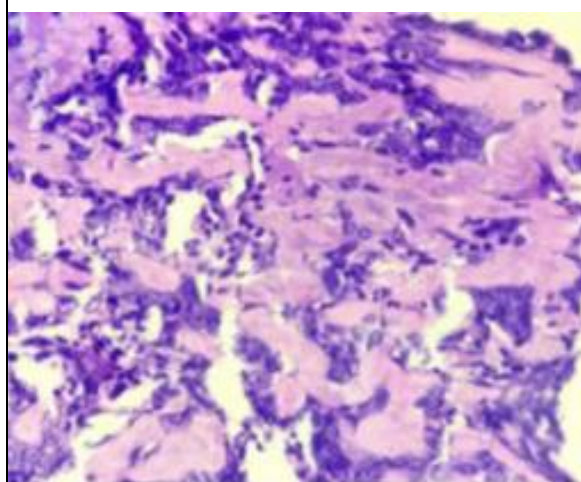


Image 4: Neoplastic osteoid as seen in Osteosarcoma, H and E, X40

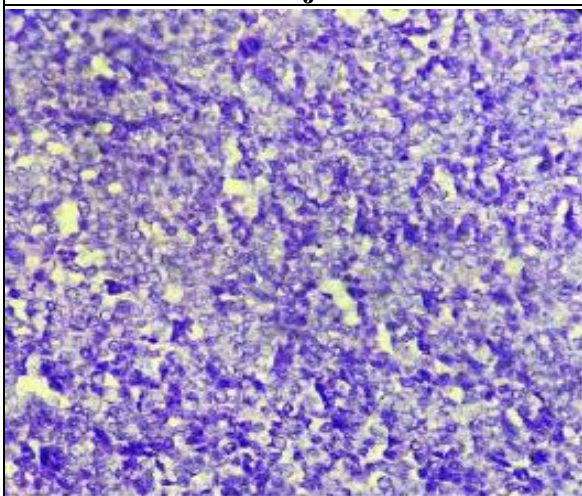
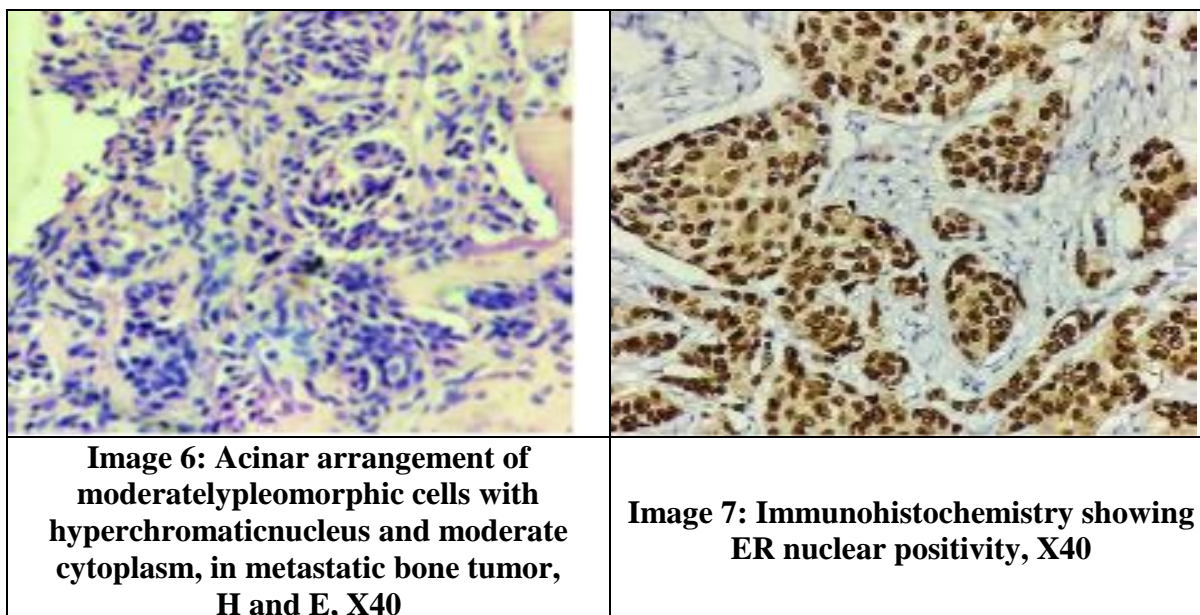


Image 5: Microscopy of Ewing's sarcoma showing sheets of small, round, uniform cells H and E, X40



Image 6: Diffuse membranous positivity of CD99 expression



Discussion

In a study done by Mohammed et.al, in West India, incidence of bone tumours was 1.9% over the period of nine years.^[3] In our study, we encountered 65 cases of bone tumours and tumour-like lesions which comprised of 0.7% of all the tumours which is marginally higher than the SEER statistics.

In our study, we encountered one case of pathological fracture. Katchy et al. reported 35% cases with pathological fracture.^[4] 11 of our cases were associated with limited range of motion, seven of them had visible deformity.

The benign tumours were in predominance in most of the studies. Among the benign bone tumours, osteochondroma was the most common lesion in various studies, like that of Baena-Ocampo et al., Rhusto et al., and Kumavat et al.,^[5,6,7] which corresponded with that of our study with 54.3% cases. Giant cell tumour of bone is found to have higher incidence (20% of all primary bone tumours) in south Indian population.^[8]

Excluding all the hematopoietic neoplasms involving the bone marrow, osteosarcoma (57.1%) was the most common malignant bone tumour in our study,

Among the tumour-like lesions, fibrous dysplasia (66.7%) was the most common lesion which correlated with all that of Settakorn et. al, Baena- Ocampo et. al., Rhusto et al and Kumavat et al.^[9]

The Cohen's kappa value for the given study was 0.82 which showed excellent agreement between histopathological and clinico-radiological diagnosis. Similar results were seen in a study done Negash et al. with a kappa value of 0.84.^[10]

In our study, we encountered chondrogenic tumours in majority, out of which, osteochondroma was seen in highest numbers (38.6%). Various other studies have had a similar result.

Five cases of osteoma were seen in our study, all of them were located in craniofacial region. All five were seen in females with a mean age of 27 years. Histologically, all of them had compact lamellated bone with scant intervening fibro vascular stroma, suggesting a compact type of osteoma. Boffano et al., also reported female predilection and majority of them had similar histopathological findings as our study.

Conclusion

A thorough clinico-radiological examination is must before histopathological evaluation. An excellent correlation between clinico-radiological and histopathological diagnosis is usually

seen. Therefore, histopathological diagnosis should follow after careful evaluation of clinical data and radiological findings. For this, a close coordination between the operating orthopaedician, radiologists and the pathologists is suggested. Also, it is imperative for a histopathologist to have reasonable knowledge of radiological interpretation in cases where a formal report is unavailable. Morphology of the lesions along with clinico-radiological correlation is of utmost importance for diagnosing a bone tumour. Immunohistochemistry is of limited value and is of varied help in diagnosing these lesions. However, it helps in diagnosing the small round blue cell tumours of the bone as well as an occult primary in case of metastasis to bone. In the era of chemotherapy, a cytogenetic studies and flow cytometric studies are being increasingly used in bone tumours so as to target a specific gene or molecule and thus predict response to treatment. These techniques might be useful in future for patient-centric, tailor-made targeted drug therapies.

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