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Vagaries of osteosarcoma at a tertiary care center in Southern India

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ABSTRACT

Background: Osteosarcoma (Os) is the greatest histologic mimicker of all bone tumors. We conducted a retrospective study on its various histopathological patterns, vis-à-vis, clinical and diagnostic features, highlighting its variations. **Aims and Objectives:** The objective of this study was to study the demographic distribution of Os presenting to our centers and appreciate the histological variations of the disease prevalent in this part of the world as such a study had not been done before. **Materials and Methods:** Over a period of 25 years, we encountered 100 cases of Os at our institution. The clinical details, investigative findings, gross appearance of tumor tissue obtained, and their hematoxylin and eosin-stained microscopic appearance were studied. **Results:** The majority were in the 2nd and 3rd decades with a male-to-female ratio of 1.8:1. Long bones were most commonly involved. Microscopically, apart from the conventional type, the histological variants encountered were small cell, soft tissue, malignant fibrous histiocytoma-like, telangiectatic, and juxtacortical including parosteal, periosteal, and dedifferentiated parosteal. Patients were treated with radical amputations, chemo-radiotherapy, and limb salvage surgeries. **Conclusion:** Being obvious that Os presents with a variety of presentations eluding any prediction regards its biologic behavior, the pathologist should be keen on thorough sampling of tumor tissue and correlate the histologic type with the radiological appearance and clinical presentation.

Key words: Osteosarcoma; Variations; Histopathology; Lymph node metastasis; Metachronous multicentric

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INTRODUCTION

Osteosarcoma (Os) is the most common malignant primary tumor of the bone after multiple myeloma. Clearly, the diagnosis of Os is a great deal more complicated than it is considered. For those not used to the vagaries of tumor mimicry by Os, it could be misdiagnosed for another bone tumor or tumor-like lesion. The present study was undertaken to elucidate the incidence of histological variants of Os and highlight any unusual findings.

Aims and objectives

The objective of this study was to study the demographic distribution of Os presenting to our centers and appreciate the histological variations of the disease prevalent in this part of the world as such a study had not been done before.

MATERIALS AND METHODS

This is a retrospective study over the past 25 years at a tertiary care center in Southern India. After obtaining the Ethics Committee clearance of the Institution, the data were collected from the Departmental Registry Database. A total of 100 cases of Os were reported to the Department of Pathology. Clinical details including age, gender, symptoms, and radiological findings were retrieved. The radiological data were available in 54 cases. The histological reports and the hematoxylin and eosin (H&E) stained sections were available for all patients. The histology

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was recorded in terms of growth pattern, cell morphology, stromal features, inflammatory cell infiltration, extent of tumor invasion of surrounding tissue, and mitotic rate.

Compilation and analysis of data using appropriate statistical methods were done. The Statistical Package for the Social Sciences 16.00 was used for the analysis while assessment of other categorical variables was done using the Chi-square tests. Statistical significance was taken for $P<0.05$. All such data were entered into a database, critically scrutinized, and statistically analyzed for the proposed implications of the study.

RESULTS

Os was encountered in all age groups till the 6th decade in males and the 5th decade in females. However, the age group of 10–29 years old was most common, forming 82% of the total studied cases (Table 1). The youngest patient was a 5-year-old male and the oldest was a 57-year-old male. The male-to-female ratio was 1.8:1.

The sites of occurrence were varied, though the most common sites were the long tubular bones (94%) (Figure 1), of which the femur constituted (36/94 of cases) 38.29%. The most common site of occurrence was the proximal tibia (27%) followed by the distal femur (25%) around the knee joint. Seventy-seven out of 94 (81.91%) cases were in the metaphysis; extending into the diaphysis in (9/94 of cases) 9.57% of cases and into the epiphysis in (13/94 of cases) 13.82%; there were (11/94 of cases) 11.70%, exclusively occurring in the diaphysis. There was cortical erosion in 16% of cases and a breach in the marrow in 5%.

In 54% of patients, radio-imaging data were made available. The most prominent features were the presence of osteolytic lesions in (21/54 of cases) 38.9%, osteosclerosis in (16/54 of cases) 29.6%, and periosteal reaction in (19/54 of cases) 35.2% cases. The classical Codman's triangle was visible in (6/54 of cases) 11.11% and sunburst appearance in (7/54 of cases) 12.96% of cases. The cortex was involved in (9/54 of cases) 16.67% and the medulla in (4/54 of cases) 7.4%. Pathological fracture was present in 8%. Soft-tissue involvement was detected radiologically in (10/54 of cases) 18.51% of cases.

Table 1: Age and gender distribution of osteosarcoma, as encountered in the study

Age Groups	Males		Females	
	Affected	Percentage	Affected	Percentage
0~9	3	4.68	3	8.33
10~19	26	40.63	21	58.33
20~29	26	40.63	9	25
30~39	3	4.68	2	5.56
40~49	3	4.68	1	2.78
50~59	3	4.68	0	0
	64	100	36	100

Histologically, 65% of the samples were reported to be conventional Os without the mention of any predominant matrix and 16% were reported as osteoblastic, chondroblastic, or fibroblastic. Several other histological variants of Os (19%) also were encountered (Figure 2).

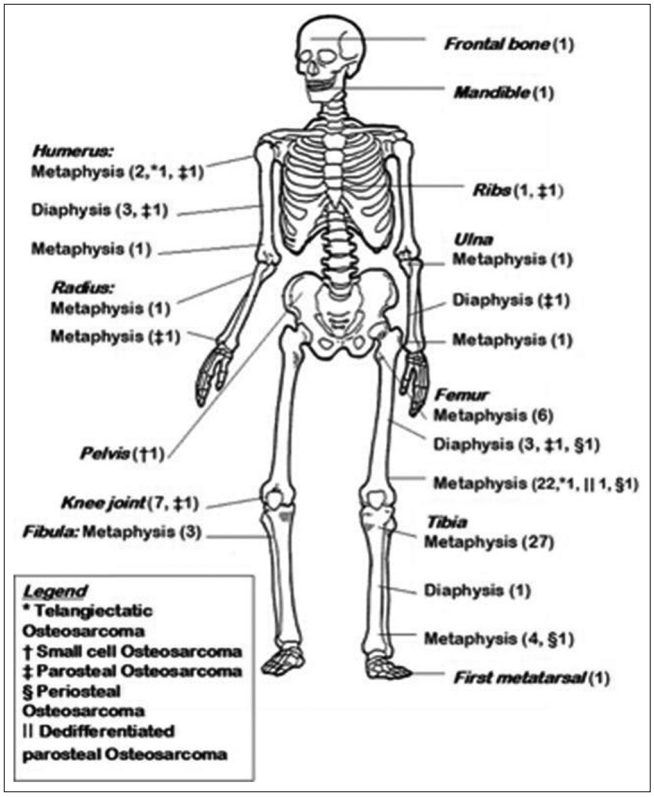

Figure 1: Osteosarcoma, occurring at different sites of the skeletal system, as observed in our study.

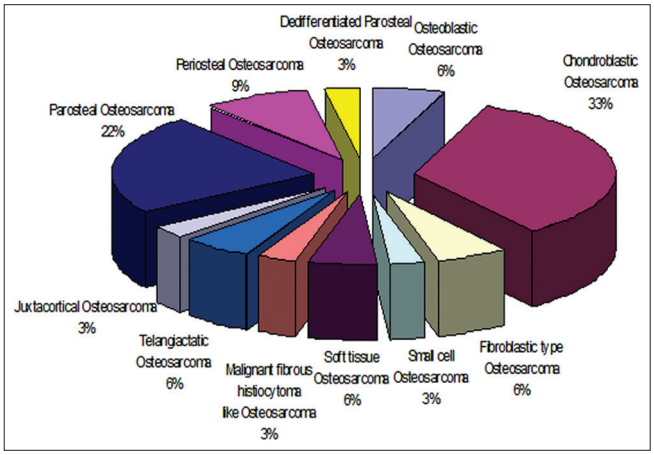

Figure 2: Vagaries of osteosarcoma, based on site of occurrence, radiological appearance, and microscopic differences, in our study.

DISCUSSION

Although the absolute requirement for the diagnosis of Os is direct osteoid formation by tumor cells, it can differentiate along any pathway of matrix synthesis. Hence, the histologic picture can vary widely.

Conventional Os (Figure 3) is mostly a disease of the young as (61/81 cases) 75.32% was found in the below 25 age group with the male-to-female ratio being 5:3 which correlates with the World Health Organization report that 60% of patients are under 25 years and males are more frequently affected than females, the ratio being 3:2.[1,2] The chondroblastic Os formed 12% of the study, sclerosing Os, found in 2%; one in the meta-diaphyseal region of right humerus, presenting with metastasis as multiple solitary pulmonary nodules in both the lungs and the other involving the knee; and fibroblastic Os formed 2% of the study, one at the distal end of the femur and the other at the ankle. Incidence of osteoblastic, fibroblastic, and undifferentiated pleomorphic sarcoma (UPS) of the bone, previously known as malignant fibrous histiocytoma-like Os, is reported to be 54.2%, 4.2%, and 29.2%, respectively.[3] We encountered a case of UPS-like Os with a pure lytic lesion of the distal metaphysis of the femur extending into the epiphysis in a 16-year-old female. It is more common in the <40 age group.[3]

Telangiectatic Os (Figure 4) represents 3–10% of all Os cases and is common in 2nd decade.[4] It often contains foci of osteoclast-like giant cells.[5] In the present study, 2% of cases were of telangiectatic Os with an excess of osteoclast-like giant cells in both. Telangiectatic variety of Os was strictly prevalent in the <40 age group in our study. Small cell Os which constitutes approximately 1.5% of the Os, 6 formed 1% of the total number of cases in the present study. The patient, a 26-year-old male, was affected in the pelvis with metastatic lesions in the inguinal lymph nodes. Soft-tissue Os accounts for fewer than 2% of all soft-tissue sarcomas [7] and tends to occur in the 5th and 7th decade.[8,9] We encountered two cases of soft-tissue Os one in a 28-year-old and the other in a 43-year-old male but both of high grade as against the low-grade anaplasia stated.[9]

Surface Os accounts for 4% of all Os. There is slight female predominance and most patients are young adults as about 1/3rd occurs in the third decade of life.[10] In the present study, 7% of cases were of parosteal Os (Figure 5) and one was a fibrous dysplasia-like variant of it. It is more prevalent in the less than 40 years age group (6/8 of cases=75%) than in the more than 40 years age group (2/8 of cases=25%). (4/8 of cases) 50% were male, mostly located in the long bones, the humerus being slightly more common (2/8 of cases=25%). One case of fibrous

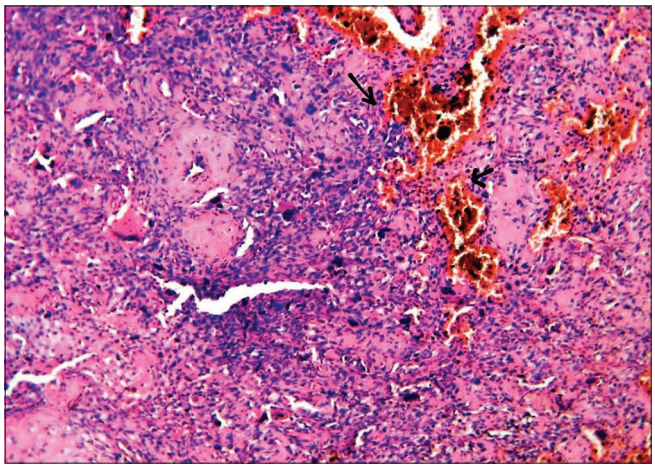

Figure 4: Telangiectatic osteosarcoma (Hematoxylin and Eosin, ×100) showing dilated blood-filled cystic spaces (black arrow) with a thick-walled lining and septa containing atypical malignant hyperchromatic spindle cells demonstrating immature osteoid production.

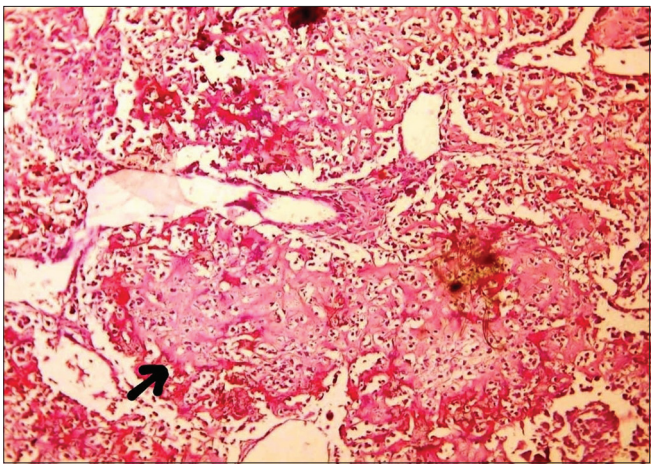

Figure 3: Conventional osteosarcoma (Hematoxylin and Eosin, ×100) showing mitosis and cellular atypia along with atypical osteoid formation as indicated by the arrowhead.

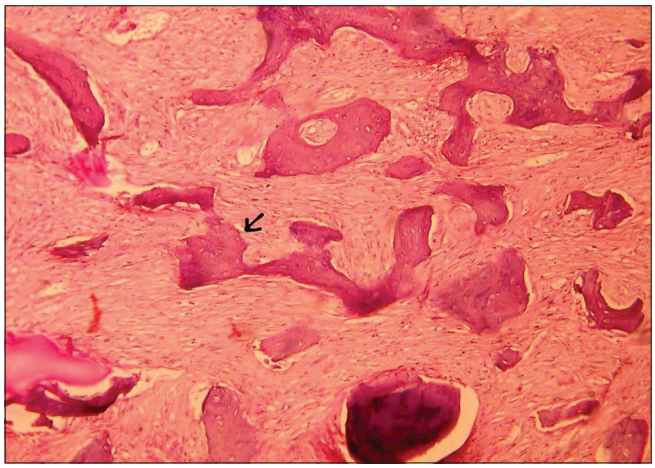

Figure 5: Parosteal osteosarcoma (Hematoxylin and Eosin, ×100) showing cartilaginous matrix, pointed by an arrow, with the area of dysplastic bone surrounded by spindle cells

dysplasia-like variant with grade II anaplasia in the rib was encountered. All parosteal Os showed a low grade of anaplasia. Periosteal Os, less common to parosteal Os, accounts for < 2% of all Os.[11] Peak incidences are in the second and third decade of life. It tends to arise between the cortex and the cambium layer of the periosteum so that there is a radiologically visible periosteal reaction.[7] It has a distinct predilection for the diaphysis or diaphyseal-metaphyseal area of the long bones, with the tibia and femur being the most involved bones followed by the humerus.[11] A case of bilateral metachronous lesion has also been reported.[12] In the present study, there were 3% cases of periosteal Os. All cases were seen in the 2nd decade of life. (2/3 of cases) 75% were found in females and diaphysis and distal metaphysis of femur and distal tibia were the sites to be affected. Radiologically, there was erosion of cortex and periosteal reaction in (2/3 of cases) 75% with soft-tissue involvement. A 17-year-old male was diagnosed to be having multicentric metachronous type of Os having grade III Os in the distal metaphysis of the femur. The other two also had grade III anaplasia. Histologically, high-grade dedifferentiation, arising in the clinical setting of recurrent parosteal Os is of the usual low-grade variety..[13] The dedifferentiation being reported as chondroblastic and telangiectatic in two series,[13,14] it might be possible that other varieties might be described as larger series were obtained. Dedifferentiation occurs in approximately one in four low-grade parosteal Os.[15] In the present study, one case of dedifferentiated parosteal Os was encountered in a 24-year-old male. Microscopically, areas with low-grade parosteal Os along with areas of chondroblastic dedifferentiation were observed. Juxtacortical Os was found to be more prevalent in the < 40 age group (11/13 cases=84.62%) than in the more than 40 years age group (2/13 cases=15.38%).

Multifocal Os accounts for 1–2% of all Os,[16] affecting multiple osseous sites at varying intervals (metachronous type) in adults, without pulmonary metastasis, at initial examination.[17] In the present study, one such case in a 17-year-old male, primarily affected with periosteal Os of the femur, who underwent surgery and chemotherapy, developed lesions within 9 months on the 12th rib, C7 vertebral body, and 1st rib, and his needle biopsy showed features of chondroblastic Os of grade III anaplasia.

Metastasis of the primary lesions takes place in the lungs and rarely extrapulmonary sites probably due to prolonged longevity in Os patients given adjuvant chemotherapy.[18] In the present study, there were five cases of pulmonary metastasis and one to the bones. An 18-year-old male, having a primary lesion of Os in the thigh, had metastasis to ribs, parietal bones, distal end of the contralateral femur, spine, and scapula irrespective of hip disarticulation and chemotherapy. There were two cases of late pulmonary metastasis, one of whom had grade II chondroblastic Os in the upper metaphyseal region of the right tibia and was treated with above knee amputation and nine cycles of chemotherapy but presented with pulmonary metastasis 8 months later. The hematogenous route being the main route of spread of Os, lymph node metastasis from Os is a rare entity.[19] We encountered three cases of metastasis to the lymph nodes, two in the inguinal group, one from a small cell Os of the pelvis, and one from a low-grade Os in the proximal metaphyseal area of the fibula. Recurrence of Os was encountered in a chondroblastic Os of Grade II after 4½ years of the primary lesion in the upper third of the humerus, initially treated with curettage and chemotherapy. Adequate surgical margins if not achieved, the rate of local recurrence is very high ranging from 30% to 50%.[20]

As radical surgical treatment used alone fails in 85–90% of patients due to the high frequency of micrometastasis in high-grade Os, adjuvant chemotherapy, most commonly using combinations of high-dose methotrexate (HDMTX), doxorubicin (ADM), and cisplatin, Ifosphamide being an alternative when it is difficult to administer HDMTX, especially in adults.[21,22] We found (4/10 of cases) 40% to be treated with radical amputations followed by chemotherapy which made usage of the four drugs in varying combinations, but three of them landed up with pulmonary metastasis and one with bone metastasis. (2/10 of case) 20% were dealt with by limb salvage surgeries. One received chemotherapy of HDMTX and ADM and radiotherapy and had a disease-free period of 4 years; the other refused it and developed a solitary pulmonary nodule.

Limitations of the study

The sample size of the study could not be extended beyond 100 patients due to constraints of time and resources. Also the treatment data of many patients could not be obtained due to attrition owing to the aggressive nature of the disease, unwillingness for treatment or loss to followup.

CONCLUSION

Published data indicate that in sarcoma, a rate of diagnostic inaccuracy ranging between 20 and 30% is prevalent.[23] Being obvious that Os presents with a variety of presentations eluding any prediction regards its biologic behavior, the clinician should be keen on thorough sampling of tumor tissue and correlate the histologic type with the radiological appearance and clinical presentation.

With the introduction of neoadjuvant and adjuvant chemotherapy along with surgical clearance of the tumor since the 1970s, there had been a significant increase in the disease-free period of the patient as compared to the radical amputation alone, before that. However, there has been no significant advancement in the treatment of the disease for more than a decade now. With the slow and steady increase in our understanding of the complexities of the tumor, the cellular checkpoint inhibitors, and the development of immunotherapy and precision-based medicine, we can hope for a better disease-free survival period for our patients in the near future.

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Authors Contributions:
TD- Helped in literature search, writing the manuscript, and preparing the illustrations; **RCV-** Conceptualized the study protocol and editing the manuscript; and **AG-** Collected the data and prepared the manuscript and took responsibility for ensuring the credibility of the data. **AN-** Helped in collecting data and writing the manuscript. **RS-** Helped in evaluating the histopathology sections and editing the manuscript.

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