REVIEW ARTICLE

Osteosarcoma of jaws

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ABSTRACT

Tumors of jaw bones are among the most uncommon of all types of neoplasms. Osteosarcoma of jaw bones represents a distinct group of lesions from the conventional type commonly occurring in long bones. Nonetheless, our present knowledge of the tumor allows us to affirm that its clinical behavior and pathologic features differ markedly from those of its homolog in the long bones. The maxillary tumors show predilection for posterior portion of the alveolar process and the antrum, whereas the body is most commonly involved in the mandible followed, by angle, symphysis, and ascending ramus. We have reviewed around 300 cases of osteosarcoma of varied racial origin from PubMed indexed journals spanning from 1967 to 2010 and present their etiology, pathogenesis, features and treatment modalities.

Key words: Chondroblastic osteosarcoma, fibroblastic osteosarcoma, osteoblastic osteosarcoma, osteosarcoma of jaws

INTRODUCTION

Osteosarcoma referred to as osteogenic sarcoma is the most common primary malignant bone tumor excluding plasma cell tumors. It commonly involves the appendicular skeleton. It accounts for approximately 15% of all primary bone tumors confirmed at biopsy.[1]

ETIOPATHOGENESIS

There are numerous variants of osteosarcoma of jaw bones [Table 1], but these are generally classified into two types primary and secondary.[2] The etiology of primary type is unknown; may be due to genetic influence or other environmental factors. Secondary craniofacial osteogenic sarcomas occur in older patients of skeletal Paget's disease,[3] fibrous dysplasia of bone and as a late sequela to craniofacial irradiation.[4] A number of risk factors had been attributed for the cause of osteosarcoma which includes rapid bone growth[5] as the incidence increases during adolescent growth spurt and because of the typical location of tumor near the metaphyseal growth plate of the long bones. However, osteosarcoma of jaws peaks one or two decades after adolescence which excludes rapid bone growth as the major etiologic factor. Environmental factors such as ionizing radiation and chromic oxide, a radioactive scanning agent have been incriminated.

Genetic mutations in tumor suppressor gene P_{53} and mutated retinoblastoma gene have been claimed to be amongst other etiologic factors. In older patients, this lesion has been found secondary to benign bone lesions such as Paget's disease and fibrous dysplasia.

CLINICAL FEATURES

They affect the most rapidly growing parts of the skeleton; metaphyseal growth plates in femur, tibia and humerus being the commonest sites. Patients of primary craniofacial osteosarcomas are younger (mean age 48 years). Majority of craniofacial osteosarcomas occur in skeletally mature patients in contrast to those that affect the appendicular skeleton. Osteosarcoma of jaw bones have some distinct features such as older age at presentation, longer median survival, rare metastases and local recurrences difficult to control, typically leading to death of the patients.[1] They comprise only 6.5% of all osteosarcomas.[5] In maxilla and mandible, the presentation of the tumor at later age (around fourth decade) and its higher survival rate helps to differentiate it from osteogenic sarcomas in other locations. Mean age according to Garrington *et al*[5] ranges from 34 to 36 years. Distant metastases are less frequent according to some but Garrington and his colleagues reported distant metastases in approximately 50% of the cases. Men seem to be more commonly affected. August *et al*[6] reported gender predilection for males and found male:female ratio to

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be 1.1:1. In another study by Mardinger *et al*[7] the male:female ratio was found to be 1.2:1. This has been attributed to longer period of skeletal growth and additional volume of bone in men, though neither has been confirmed.

In a study by Forteza *et al*[1] on 81 cases of osteosarcoma, maxillary osteosarcomas occurred in females with the ratio of 4:1 whereas mandibular lesions occurred only in males. Few reports state even distribution of the lesion between

Table 1: Variants of osteosarcoma[2]

Types	Clinical features	Histopathology
Multifocal	Divided into synchronous and asynchronous	
a. Synchronous	Pulmonary metastasis absent	Osteoblastic with high grade histology
	Childhood form most common confined to medullary cavity	Adult form usually better differentiated
	Adult form less common with mean 37 years	Lesions discovered within 6 months of each other
		Often symmetric appearance with similar size. Osseous metastases rare
b. Asynchronous	Develop less than 24 months after the initial lesion	
Telangiectatic	0.4-12 per cent of all osteosarcomas, is seen commonly in adolescence and early adulthood	Contains large blood filled spaces
	Pathologic fractures seen in 25 per cent of cases	
	May be confused radiographically with an aneurysmal bone cyst or giant cell tumor	
	Hemorrhagic and necrotic areas seen in tumor	
Small cell	1-4 per cent of all osteosarcomas	Small round cells with at least focal osteoid
	Presentation similar to conventional osteosarcomas	Focal hemangiopericytoma like pattern may be common
	70 per cent in first or second decades of life	May have Ewing's sarcoma like pattern in 2/3 of cases and lymphoma like pattern in 1/3 of cases
	90 per cent have at least focal osteoblastic features	
Intraosseous well-differentiated	1-2 per cent of osteosarcomas	Well-differentiated mature appearing bone with small central osteocytes within fibroblastic stroma with mild atypia
	Peak incidence third decade	Mitotic figures 1-2/10 high power field
	Metaphyseal regions of long bones are commonly affected site	
	In radiographs, 85 percent cases appear as central medullary lesions	
Intracortical	Very rare	Osteoblastic sclerotic tumors
	Diaphyses of lower extremity long bone	
	Radiographically presents as intracortical radiolucency surrounded by sclerosis	
Periosteal	< 2 per cent of osteosarcomas	Chondromatous foci predominate with focal malignant osteoid
	Subtype of surface osteosarcomas	
	Occurs in older patients	
	Predilection for diaphyseal region of long bones	
	Arises from cortex but usually encircles the bone	
	Located on the external surface of the cortex and extends into the surrounding soft tissue	
	May not invade the medullary cavity	
Paraosteal	5 per cent of all osteosarcomas	Long narrow trabeculae or ill-defined islands of osteoid and woven bone separated by fibrous stroma
	Can be seen in childhood or adulthood	Trabeculae may undergo maturation resulting in the formation of lamellar bone
	Arises from juxtacortical region of the long bones	Spaces between bony trabeculae filled with spindle cells with minimal cytologic atypia
	Striking predilection for distal femur, especially the posterior aspect	May contain foci of dedifferentiation and these tumors have very poor prognosis.
	Dense mushroom shaped mass attached to the outer metaphyseal cortex by broad base	

Table 1Contd...

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Types	Clinical features	Histopathology
High-grade surface	Arises from outer cortex of the bone with minimal intramedullary expansion Involves diaphyseal, diaphyseal-metaphyseal regions, distal femur most common site of occurrence Very rare Median 20 years Partially mineralized mass attached to outer cortical surface with some cortical erosion High grade neoplasms with microscopic foci of intramedullary extension in 60 per cent of cases	

maxilla and mandible. Clinically, osteosarcoma of long bones presents as pain during activity compared to osteosarcoma of jaw bones where swelling rather than pain is the commonest finding.[5,8] In a study by Nissanka *et al*[9] most patients related the occurrence of tumor to previous dental treatment, most commonly, dental extractions. The reason for this is most likely to be rapid growth of tumor immediately after tooth extraction, a phenomenon often shown by bone tumors.[10]

RADIOGRAPHIC FEATURES

Osteosarcoma shows varied radiographic appearance ranging from osteolytic to mixed to osteogenic pattern of bone. If the tumor invades the periosteum, many thin irregular spicules of new bone may develop outward and perpendicular to the surface of the lesion producing the so-called 'sun ray appearance.' Lindquist *et al*[11] reported that the widening of periodontal ligament space and inferior dental canal, together with sunburst effect are almost pathognomonic of osteosarcoma of jaw bone. Not all the lesions show such peculiar characteristics. Forteza *et al*[1] reported that the presence of destructive unicentric lesion with poorly defined margins and a predominantly sclerotic, lytic or mixed radiographic pattern should lead one to suspect an osteogenic sarcoma.

The preoperative diagnosis of these neoplasms is often difficult because of its nonspecific nature. The importance of special investigations such as computerized tomography (CT) and magnetic resonance imaging (MRI) lies in assessing the size of the lesion for staging, intramedullary and extramedullary involvement, tumor calcification and invasion into adjacent tissues.

HISTOPATHOLOGIC FEATURES

The varied radiographic appearance of this lesion highlights the importance of histopathologic analysis in the diagnosis of osteosarcomas. The diagnosis of osteosarcoma is based on recognition of osteoid production by tumor cells.[12] Depending upon the predominant type of extracellular matrix present, osteosarcomas are categorized histopathologically into osteoblastic, chondroblastic, fibroblastic subtypes.[13] The osteoblastic variety consists of tumor osteoid surrounded by bizarrely arranged fibroblast--like cells.

In chondroblastic osteosarcoma, tumor cells lie in the lacunae and form lobules. The center of the lobule has bony trabeculae producing a feathery appearance, and towards the periphery, the tumor becomes hypercellular. Most of the times, an area of atypical chondroid tissue is also seen with large chondrocytes. Fibroblastic osteosarcoma is the least common variant where the tumor cells are spindle-shaped and characteristically arranged in herring bone pattern typically resembling fibrosarcoma. The formation of tumor osteoid differentiates this variant of osteosarcoma from fibrosarcoma [14]

Mardinger *et al*[15] reported the highest prevalence for chondroblastic osteosarcoma (42%), osteoblastic osteosarcoma being lesser (33%). Histologic diversity of osteosarcomas points to the fact that histology alone is insufficient for the diagnosis of osteosarcoma. Therefore, combined clinical, radiographic and histopathologic analysis before definitive diagnosis is prudent.

STAGING AND GRADING

Cellularity is the most important criterion used for histological grading. In general, the more cellular the tumor, the higher the grade. Irregularity of the nuclear contours, enlargement and hyperchromasia of the nuclei are correlated with grade. Mitotic figures and necrosis are additional features useful in grading.

Staging incorporates the degree of differentiation as well as local and distant spread, in order to estimate the prognosis of the patient. The universal TNM staging system is not commonly used for sarcomas because of their rarity to metastasize in lymph nodes. The system used most often to formally stage bone sarcomas is known as the Enneking system.[7,10] It is based on the grade (G) of the tumor, the local extent of the primary tumor (T), and whether or not it has metastasized to regional lymph nodes or other organs (M).

The grade is divided into low grade (G1) and high grade (G2).

The extent of the primary tumor is classified as either intracompartmental (T1), meaning it has basically remained in place, or extracompartmental (T2), meaning it has extended into other nearby structures.

Tumors that have not spread to the lymph nodes or other organs are considered M0, while those that have spread are M1.

These factors are combined to give an overall stage [Table 2].

In summary, low-grade tumors are stage I, high-grade tumors are stage II, and metastatic tumors (regardless of grade) are stage III.

There are no known specific laboratory parameters. Increase in alkaline phosphatase or lactic dehydrogenase (LDH) serum levels are observed in a considerable number of patients. Although they do not correlate reliably with disease extent, they may have negative prognostic significance.

Histopathologic grading of this neoplasm is done according to Broder's grading system developed for epitheliomas, based on degree of cellular anaplasia shown by tumor cells. Mardinger *et al*[15] stated that nearly 50% of the jaw osteosarcomas are low grade and according to Unni,[16] the most common form is grade II.

IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) plays an important role in the differentiation between chondrosarcoma and chondroblastic osteosarcoma. IHC will show chondrosarcoma to be positive for S100 and Vimentin and negative for cytokeratin and EMA (Epithelial Membrane Antigen). Chondroblastic osteosarcoma will be positive for Vimentin, EMA, S100 and rarely cytokeratin.[17]

Recently, Yoshida *et al* reported that the combination of MDM2 and CDK4 by immunohistochemical analysis shows 100% sensitivity and 97.5% specificity for the diagnosis of low-grade osteosarcoma. They concluded that MDM2 and CDK4 immunostains therefore reliably distinguish low-grade osteosarcoma from benign histological mimics, and their combination may serve as a useful adjunct in this difficult differential diagnosis.[18]

In a study by Hu *et al*, the expressions of IDH1 and p53 in formalin-fixed paraffin-embedded tissue sections from 44 osteosarcoma patients were determined by immunohistochemistry, and the correlation between them and clinicopathological features were analyzed. They concluded that osteosarcoma patients with High IDH1 expression have a very high p53 expression. Thus IDH1 may correlate with p53 and be a candidate biomarker for osteosarcoma.[19]

Table 2: Grading and staging of osteosarcomas

Stage	Grade	Tumor	Metastasis
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
IIIA	G1 or G2	T1	M1
IIIB	G1 or G2	T2	M1

TREATMENT AND PROGNOSIS

Wide radical resection is the treatment of choice for osteosarcoma of jaws with clearance margins of 1.5–2 cm. Surgery and adjuvant chemotherapy and radiotherapy may be required sometimes. The presence of micro metastases decides the need of adjuvant therapy. In mandible, hemimandibulectomy is commonly preferred. Maxillectomy is difficult to perform due to the involvement of adjacent structures like maxillary sinus, pterygopalatine fossa and orbital fossa. A subtotal inferior maxillectomy for selected malignancies located on the alveolar ridge, palate and involving the antral floor have been described.[20] Obturators have been prescribed for the defect created. Obturators can be divided into three classes: surgical, post-surgical, and definitive. Surgical obturators are those that are placed at the time of surgery. Post-surgical obturators are those prostheses which are placed immediately after packing removal, used until tissue contracture is minimal, and prior to definitive obturator placement. They are designed with the use of a preoperative cast that is modified to account for resected areas. Time between packing, removal and obturator placement should be minimal, as tissue contraction and edema will quickly alter the shape of the defect, making it difficult to insert an obturator. The definitive obturator is designed when the surgical sight is stable, approximately 3-12 months after definitive surgery.[21]

The use of chemotherapy as an adjuvant for treatment of osteosarcomas of long bone was first reported by Jaffe[22] who used methotrexate as an anticancer drug. Since then most of the chemotherapeutic agents such as doxorubicin, cisplatin, adriamycin have been used. Rosen *et al*[23] found an increase from 15% to 60-80% in 5-year survival rate of patients suffering from osteosarcoma when chemotherapy was used as an adjuvant to surgery. According to Nissanka *et al*[9] the 5-year survival rate using adjuvant chemotherapy was 83.3%, whereas, Mardinger *et al*[15] found no significant change in prognosis. These controversial findings may be due to diversity of chemotherapeutic regimens used with different agents, dosages and intervals.

Smeele *et al*[24] investigated the value of chemotherapy in the treatment of craniofacial osteosarcoma by analyzing 201 reviewed cases. They found that the over all and disease free survival rates significantly improved with chemotherapy. Raymond *et al*[25] reported 33% 5-year survival for patients treated with adjuvant chemotherapy and surgery and 41% 5-year disease free survival for those treated with surgery alone. Radiotherapy must be confined for the treatment of residual, recurrent and unresectable tumors.

Unni KK has reported a 40% 5-year survival for jaw osteosarcomas compared to conventional osteosarcomas (20.3%).[9] Clark *et al*[26] attributed this to occurrence of predominantly chondroblastic low grade osteosarcomas in the jaws.

In one study, bone marrow and peripheral blood samples from 60 patients with suspected bone sarcoma were examined for the presence and number of micrometastatic osteosarcoma cells by a sensitive immunomagnetic detection assay, using in parallel two osteosarcoma associated antibodies. Forty-nine of the patients had osteosarcoma, and of these, as many as 31 (63%) had tumor cells in bone marrow, in many cases with a high number of cells. Only four (8%) were positive also in blood. The data showed the clinical potential of this immunomagnetic method in detection of metastasis in osteosarcoma.[27]

A number of potential prognostic factors have been identified which include the expression of HER2/CerbB2, tumor cell ploidy, and specific chromosome gains or losses, loss of heterozygosity of the RB gene, loss of heterozygosity of the p53 locus, and increased expression of p-glycoprotein. The only feature that consistently predicts outcome is the degree of histologic necrosis following induction chemotherapy. Patients with more than 95% necrosis in the primary tumor after induction chemotherapy have a better prognosis than those with smaller amounts of necrosis.[28-40]

The prognosis for patients with metastatic disease appears to be determined largely by the site(s), the number of metastases, as well as the surgical resectability of the metastatic disease. The most common site for the metastases is lung accounting for almost 20%. Prognosis appears more favorable for patients with unilateral rather than bilateral pulmonary metastases, and for patients with fewer nodules rather than many nodules. The degree of necrosis in the primary tumor after induction chemotherapy remains prognostic in metastatic osteosarcoma. Patients with skip metastases (≥2 discontinuous lesions in the same bone) have been reported to have inferior prognoses. Patients with multifocal osteosarcoma (>1 bone lesion at diagnosis) have a poor prognosis.[41-46]

CONCLUSION

Osteosarcoma is an ancient disease many aspects of which are still incompletely understood. It is a malignancy of mesenchymal cells that have the ability to produce osteoid or immature bone. Excluding hematopoeitic neoplasms, osteosarcoma is the most common type of malignancy to originate within bone. There have been a plethora of discussions and also controversies about the nature, aggressiveness, behavior, and various treatment modalities of this entity. We have reviewed more than 300 cases from PUBMED of this perilous lesion, and made a humble attempt to include cases of varied ethnic origins as well as follow the changing trends in the management of this tumor. However, for purposes of management, emphasis should be laid on the aggressiveness of this lesion which warrants an early identification and diagnosis of the lesion followed by prompt treatment.

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