Review Article

Osteosarcoma of Jaws: An Insight into Literature

Fatema Saify, Shilpa Jain

Department of Oral Pathology, Government Dental College, Raipur, Chhattisgarh, India

ABSTRACT

Osteosarcoma (OS), referred to as osteogenic sarcoma, is the most common primary malignant bone tumor excluding plasma cell tumors. It accounts for approximately 15% of all primary bone tumors confirmed at biopsy. It commonly involves the appendicular skeleton. Like, its counterpart in the long bones, OS affecting the head-and-neck region shows the distinct yet diverse clinical, histologic, and prognostic characteristics. Its diagnosis is a challenge to oral pathologists and is especially important in early stages to improve its prognosis. The data have been taken from the published articles and standard books and are summarized. In this review, in addition to summarizing the current understanding of OS etiology and diagnostic methods, various experimental therapeutics have been described that provides evidence to encourage a potential paradigm shift toward the introduction of immunomodulation, which may offer a more comprehensive approach to battling cancer.

KEYWORDS: *Bone, chondroblastic, fibroblastic, mandible, osteoblastic, osteosarcoma*

Received: September, 2018.
Accepted: September, 2018.

INTRODUCTION

Osteosarcoma (OS) arising from the jaw comprises 2.1% of all malignant oral and maxillofacial tumors. OS of jaw differs from the OS of the long bones in its biological behavior, presenting a lower incidence of metastasis and a better prognosis with approximately 40% 5-year survival rate as compared to 20% for nonjaw lesions.[1] It arises in bone during periods of rapid growth and primarily affects the adolescents and young. OS of jaw is classified into two types such as primary and secondary. 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, fibrous dysplasia of bone, and as a late sequel to craniofacial irradiation.[2]

ETIOPATHOGENESIS

Conventionally, our understanding of OS has been largely anatomical. However, the recent developments in molecular biology have provided insight into the molecular pathogenesis of OS. Although the identification of tumor pathways and specific mediators of OS progression, novel approaches for targeting OS are being developed. It can be explained as follows.[3]

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Quick Response Code:

Website: www.ijofb.org

DOI: 10.4103/ijofb.ijofb_9_18

Related to bone growth

OS has a predilection for developing in rapidly growing bone.[3] A number of studies have established a correlation between the rapid bone growth experienced during puberty and OS development. The patients affected by Paget's disease, a disorder characterized by both excessive bone formation and breakdown, also have a higher incidence of OS.[4] However, the OS of jaws peaks one or two decades after adolescence which excludes rapid bone growth as the major etiologic factor.[2]

Environmental factors

Physical, chemical, and biological agents have been suggested as carcinogens for OS. Among these, the role of ultraviolet and ionizing radiation is the best established. The chemical agents linked to OS formation include methylcholanthrene and chromium salts, beryllium oxide, zinc beryllium silicate, asbestos, and aniline dyes.[3] Previously, a viral origin had been suggested for OS. This stemmed from the detection of simian virus 40 (SV40) in OS cells. However, the

Address for correspondence:
Dr. Fatema Saify, E-mail: saify5152@rediffmail.com

How to cite this article: Saify F, Jain S. Osteosarcoma of jaws: An insight into literature. Int J Orofac Biol 2018;2:41-6.

presence of SV40 in these cells was later concluded to be the result of laboratory contamination by plasmids containing SV40 sequences.[5]

Genetic correlation

A number of chromosomal and genetic syndromes have been linked to OS. OS has been reported in the patients with Bloom syndrome, Rothmund–Thomson syndrome, Werner syndrome, Li–Fraumeni syndrome, and hereditary retinoblastoma (Rb).[6] Numerical chromosomal abnormalities associated with OS include loss of chromosomes 9, 10, 13, and 17 as well as gain of chromosome.[7]

Dysfunction of tumor-suppressor gene

When human cells are exposed to environmental insults, DNA may be damaged. Such DNA damage may not necessarily give rise to a malignant cell as there are a number of tumor-suppressor mechanisms. These mechanisms may either repair the DNA damage or induce apoptosis of these cells. The p53 and Rb genes are well-known tumor-suppressor genes. However, these genes may themselves become mutated, resulting in the loss of their protective function.[7] The p53 gene is mutated in 50% of all cancers and 22% of OSs. The Rb tumor suppressor has also been implicated in the tumorigenesis of OS. Both germ-line and somatic mutations of Rb confer an increased risk of OS. Loss of the Rb gene may even explain the familial risk of OS.[8]

Transcription factors

Transcription is the process of forming single-stranded messenger RNA sequences from double-stranded DNA. Myc is a transcription factor that acts in the nucleus to stimulate cell growth and division.[3] Myc amplification has been implicated in OS pathogenesis and resistance to chemotherapeutics. Overexpression of Myc in bone marrow stromal cells leads to OS development and loss of adipogenesis.[9]

Growth factors by tumor cells

OS cells produce a range of growth factors that exert autocrine and paracrine effects. Dysregulated expression of growth factors such as transforming growth factor, insulin-like growth factor, and connective tissue growth factor leads to the accelerated proliferation of cells. Growth factor receptors may be overexpressed and constitutively activated. Signal transduction associated with these receptors may also be overactivated.[3]

Anoikis and anchorage-independent growth

Anoikis is a form of apoptosis that is induced when cells are no longer attached to a basement membrane or matrix. This is of particular interest in OS given the propensity of OS cells to detach from the matrix components and to metastasize. OS cells are resistant to anoikis and proliferate despite deranged the cell-cell and cell-matrix attachments. This resistance to anoikis is termed anchorage-independent growth.[3]

Role of angiogenesis

Tumor angiogenesis is essential for sustained OS growth and metastasis. A balance between the proangiogenic and antiangiogenic factors regulates the angiogenesis. Vascular endothelial growth factor (VEGF) is the best-characterized proangiogenic factor, and it stimulates the processes of endothelial cell proliferation and migration.[10] In addition to VEGF, the proliferating tumor cells releases a fibroblast growth factor, platelet-derived growth factor, angiopoietin 1, and ephrin-B2.[3] Antiangiogenic proteins such as thrombospondin1,[11] troponin I, pigment epithelial-derived factor,[12] and reversion-inducing cysteine-rich protein with Kazal motifs[13] are downregulated in OS.

Role of proteases

Invasion of the surrounding tissues by OS also involves degradation of the extracellular matrix. Matrix metalloproteinases (MMPs) are principally involved in the breakdown of the extracellular matrix.[3] The urokinase plasminogen activator (uPA) system is the other key regulator of OS invasion, which interacts with MMPs. uPA cleaves the plasminogen to plasmin which breaks down the extracellular matrix.[14]

Role of osteoclast

OS invasion of bone relies on interactions between the bone matrix, OS cells, osteoblasts, and osteoclast. Osteoclasts are the principle bone-resorbing cells, and the substantial osteolysis exhibited by some OSs is the direct result of increased osteoclastic activity.[3] Increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL) is a key mediator of osteoclast differentiation and activity, and OS cells have been noted to produce RANKL independently.[15]

Clinical Features

OS can originate along the cortex or periosteum as well. The most common of these juxtacortical lesions is parosteal sarcoma, which constitutes about 1%–6% of all OS cases. These lesions are found on the metaphyseal regions of the long bones, typically the distal femur and have a "stuck-on" appearance.[16] Majority of craniofacial OSs occur in skeletally mature patients in contrast to those that affect the appendicular skeleton. OS 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.[2] They comprise only 6.5% of all OSs. Men seem to be more commonly affected. Maxillary OSs occurred in females with the ratio of 4:1, whereas mandibular lesions occurred only in males. Few studies state even distribution of the lesion between the maxilla and mandible.[17] The patients with OS often present with nonspecific complaints, including pain in the affected area. Pain during sleep, enlarging mass, and worsening pain without clear signs of infection or injury are particularly worrisome signs. Physical examination findings may reveal a palpable mass, restricted joint motion, pain with weight bearing, or localized warmth and erythema.[18] In OS of jaw bones where swelling rather than pain is the most common finding.[2] Loosening of teeth, paresthesia, and nasal obstruction may also be present.[17] Most patients relate the occurrence of tumor to previous dental treatment, most commonly, dental extraction[19] and a rapid growth of tumor immediately after the tooth extraction, a phenomenon often shown by bone tumors.[20]

Radiographic Features

Radiographs typically demonstrate a poorly marginated or moth-eaten appearance of the bone with mixed amounts of cloudy mineralized matrix and areas of bone resorption. If the lesion has an associated soft-tissue mass, a discontinuous or broken periosteal reaction is usually seen.[16] 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 "sunray appearance." Lindquist *et al*. reported that the widening of periodontal ligament space and inferior dental canal, together with sunburst effect are almost pathognomonic of OSof jaw bone.[2] Codman's triangle may be identified, formed due to elevation of periosteum over the expanding tumor mass in a tent-like fashion.[21] Advanced imaging is best accomplished with magnetic resonance imaging (MRI) and should be performed for the entire bone. MRI will clearly demonstrate the extent of the bone marrow invasion, the presence and size of any soft-tissue mass, and the relationship to surrounding the vital structures. Tumors are hypointense on T1, hyperintense on T2, and short tau inversion recovery (STIR) imaging, usually exhibit mixed heterogeneity and surrounding the peritumoral edema and show abundant enhancement with contrast administration. Computed tomography is inferior to MRI, unless further information is needed regarding cortical integrity or the presence of fracture.[22]

Laboratory Investigations

Laboratory findings are nondiagnostic, but high levels of alkaline phosphatase and lactate dehydrogenase have been shown to predict a poorer prognosis.[2]

Staging

Staging a tumor helps estimate the prognosis of the patient, and it incorporates the degree of differentiation and distant metastasis. The universal tumor, node, metastasis staging system is not commonly used for sarcomas because of their rarity to metastasize in the lymph nodes. The system used most often to formally stage bone sarcomas is known as the Enneking system.[2] 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 the 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.[23] Tumors that have not spread to the lymph nodes or other organs are considered M_0, while those that have spread are M_1.[16] The Musculoskeletal Tumor Society Staging System [Table 1][23] and the American Joint Committee on Cancer Staging System [Table 2] have gained the acceptance for OS staging.[2,23]

Histopathologic Features

The essential microscopic criterion is the direct production of osteoid by malignant mesenchymal cells. In addition to the basic neoplastic cell, the osteoblast-like tumor cell and seven tumor cell types have been reported in OS. They are chondroblast-like, fibroblast-like, histiocyte-like, myofibroblast, osteoclast-like, and angioblast-like cells.[24] Depending on predominant type of matrix, the osteoid, cartilage, or collagen fibers produced by the tumor; the OS are subclassified into osteoblastic, chondroblastic, and fibroblastic types.[2] Osteoblastic OS is the most common subtype reported in the long bones of children. Nearly, 60% of gnathic OS are osteoblastic, 34% fibroblastic, and <10% chondroblastic.[23] In chondroblastic variant, masses of chondroid with atypical chondroblasts, the abundant pleomorphism, and hyperchromatism are found. The neoplastic osteoblasts are typically angular and hyperchromatic. Intralesional calcifications may be observed. Some areas showed bicellular strands of tissue separated by the vascular stroma suggestive

Table 1: Musculoskeletal Tumor Society Staging System

Stage 1A	Low grade	Intracompartmental	No metastasis
Stage 1B	Low grade	Extracompartmental	No metastasis
Stage 2A	High grade	Intracompartmental	No metastasis
Stage 2B	High grade	Extracompartmental	No metastasis
Stage 3	Any grade	Any site	Metastasis

Table 2: American Joint Committee on Cancer Staging System (2006)

T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_1	Tumor <8 cm in diameter
T_2	Tumor >8 cm in diameter
T_3	Discontinuous tumor in primary bone site
N_X	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
M_0	No distant metastasis
M_0	Distant metastasis evident
G_X	Grade cannot be assessed
G_1	Well differentiated - low grade
G_2	Moderately differentiated - low grade
G_3	Poorly differentiated - high grade
G_4	Undifferentiated - high grade
Stage 1A	$T_1 N_0 M_0 G_{1,2}$
Stage 1B	$T_2 N_0 M_0 G_{1,2}$
Stage 2A	$T_1 N_0 M_0 G_{3,4}$
Stage 2B	$T_2 N_0 M_0 G_{3,4}$
Stage 3	$T_3 N_0 M_0$ any G
Stage 4A	Any T N_0 M1 any G
Stage 4B	Any T N_1 any M any G or any T any N M_1 any G

Table 3: Histopathological subtypes of osteosarcomas

Central (medullary)
Conventional osteosarcoma
Chondroblastic
Fibroblastic
Osteoblastic
Telangiectatic osteosarcoma
Giant cell osteosarcoma
Small cell osteosarcoma
Large cell osteosarcoma
Low-grade osteosarcoma
High-grade osteosarcoma
Surface (peripheral)
Parosteal (juxtacortical) well-differentiated osteosarcoma
Periosteal osteosarcoma
High-grade osteosarcoma

of filigree pattern. Fibroblastic type reveals highly cellular areas of malignant spindle-shaped cells with an enlarged nucleus. The spindle-shaped fibroblasts are densely packed and atypical with a minimal amount of tumor osteoid. The storiform arrangement of fibroblasts in few areas can be seen.[24] In general, one type of histologically predominant pattern is observed in OSs. Varied histologic pattern such as malignant fibrous histiocytoma-like osteosarcoma which shows spindle anaplastic cells, Large cell predominant osteosarcomas showing large cells with prominent nucleoli is seen. Giant cell predominant OS is characterized by anaplastic stromal cell producing streams of osteoid along with giant cells. In small cell or round cell predominant type, the osteoid-producing small malignant cells and primitive bone tissue are the characteristic. Also are hemangiopericytomatous, and osteoblastoma-like OS variant.[25] OS subtypes can be grouped into three categories: high grade, intermediate grade, and low grade. [Table 3].[23]

Immunohistochemical Analysis

Immunohistochemistry (IHC) plays an important role in the differentiation between the chondrosarcoma and chondroblastic OS. IHC will show chondrosarcoma to be positive for S100 and vimentin and negative for cytokeratin and epithelial membrane antigen (EMA). Chondroblastic OS will be positive for vimentin, EMA, S100, and rarely cytokeratin.[26] Fibroblastic OS will be positive for vimentin and S100 negative thus ruling out the neural tumors.[1] Osteonectin and osteocalcin have been widely used to study OS. Osteocalcin is specific for osteoblasts, whereas the osteonectin is not specific for osteoblasts, but consistently immunostained other cell types such as fibroblasts, pericytes, endothelial cells, chondrocytes, basal layer of the skin epithelium, nerves, and osteoclastic giant cells.[27] Focal positivity with CD68 suggests fibrohistiocytic nature of the tumors to be one of the variants of OS. The previous studies have analyzed the clinicopathological features and immunohistochemical expression of p53, MDM2, CDK4, PCNA, and Ki67 proteins in head-and-neck OS and found PCNA as one of the most favorable prognostic markers.[1]

Differential Diagnosis

Differential diagnosis for OS depends on the histologic variant. Mostly, it includes osteoblastoma, chondrosarcoma, malignant fibrous histiocytoma, and fibrosarcoma, but the presence of osteoid produced directly by the tumor cells clinched the diagnosis.

Treatment and Prognosis

Wide radical resection is the treatment of choice for OS of jaws with clearance margins of 1.5–2 cm. The surgery and adjuvant chemotherapy and radiotherapy may be required sometimes. The presence of micrometastases decides the need of adjuvant therapy. In mandible, the hemimandibulectomy is commonly preferred. Complete resection of tumors involving the maxillary bone is especially difficult and the local recurrence is more frequent than mandibular ones. Local recurrence is more common than distant metastasis in jaw bone OS and the positive margins were strongly associated with poor prognosis.[24]

Prognosis of OS is usually determined by the Enneking system, which assesses the histological grade of the tumor (G), extent of the primary tumor (T), and metastasis to nearby lymph nodes or other organs (M). Among the histological subtypes, the chondroblastic type is more resistant to treatment exhibits adverse prognosis, fibroblastic type has a better prognosis as it responds well to treatment.[28] The two main prognostic criteria of gnathic OS are the tumor size and the resectability at presentation.[24] The prognosis is more favorable for mandibular OS in comparison to those arising in the maxilla, with the maxillary antral tumors having the worst prognosis.[23]

New Therapeutic Approaches

Various biologics and small molecules have been used to target cell-surface receptors and downstream signaling pathways involved in OS pathogenesis. Tumor necrosis factor-alpha and interleukin-6 and IFN-α immunotherapy have been used in its treatment. Nonspecific immunogens, cytokines, adoptive T-cells, vaccines, oncolytic virotherapies, and checkpoint blockades have all shown the potential therapeutic promise. If deemed clinically advantageous, these new immunotherapeutics will likely be administered as adjuvants and integrated into the current standard of care.[29]

Conclusion

OS is rare in the jaws with an unusual presentation showing diversity in histopathological patterns which makes correct diagnosis difficult. Clinical appearance and radiology do not help in identification of the histopathological variant of OS. Hence, the microscopic examination of the tissue from all parts must always be done as the type of OS may affect the treatment and the prognosis. Identifying the pathogenesis responsible for the development of OS through molecular research may help in the development of newer diagnostic markers and help improve the therapeutics, leading to better prognosis and patient survival in the future. Late metastases may occur in ≥ 10 years after diagnosis, with no universally accepted stopping point for tumor surveillance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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