REVIEW ARTICLE

Pediatric Osteosarcoma: A Review

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ABSTRACT

Osteosarcoma is the most common primary malignant tumor of bone in adolescents and young adults. It accounts for approximately 15% of all primary bone tumors confirmed at biopsy. Roughly 1,000 new cases are diagnosed each year, with 400 of these diagnosed in pediatric patients under 18 years. There are numerous types of primary osteosarcoma including intramedullary (high grade, telangiectatic, low grade, small cell, osteosarcomatosis and gnathic), surface (intracortical, parosteal, periosteal, and high-grade surface), and extraskeletal. The treatment protocol is multimodal consisting of preoperative chemotherapy followed by surgery and postoperative chemotherapy, and has a 60-70% five year survival rate.

KEYWORDS: Osteogenic Sarcoma, Osteoblastic, Chondroblastic, Tumor

INTRODUCTION

Osteosarcoma (OS) is a rare malignant tumour of osseous origin which arises from primitive bone- forming mesenchyme. OS most commonly involve the metaphyses of long bones of the extremities. Osteosarcoma shows characteristic bone or osteoid formation. While the incidence is low, adolescents and young adults are predominately affected by osteosarcoma, and if not treated it is lethal. The 5- year survival rate for patients diagnosed with osteosarcoma is confined to 60%–70% although modern treatment protocols such as combination of chemotherapy, surgery, and sometimes radiotherapy is used.[1] Osteosarcoma referred to as osteogenic sarcoma which commonly involves the appendicular skeleton.[2] Amputation was considered to be the chief therapeutic modality prior to 1970s, and was associated with a 5-year survival of less than 20%.[3] Several milestone studies established better results with 5 –year survival rate of patients approaching 70% when surgery was combined with neoadjuvant and adjuvant chemotherapy.[4]

Incidence: Among all the primary malignant bone tumor osteosarcoma is the most commonest one. The osteosarcomas accounted for 27.5% of all malignant tumors and 19.2% of all bone tumors.

Age: Although a few patients with osteosarcomas are in the first decade of life, the peak incidence is in the second decade, and there is a steady, gradual decrease thereafter. Rarely patients are older than 60 years. Of these, most of them had a preexisting condition: Paget disease, previous radiation, infarct, chronic osteomyelitis, and cyst of degenerative joint disease. The most common occurrence is during the growth phase of an individual. Rapid bone growth appears to predispose patients to osteosarcoma, as suggested by the increased incidence at the time of the adolescent growth spurt and typical location near the metaphyseal growth plate of long bones.

Sex: Osteosarcomas have a male predilection. Approximately 58% of the patients with osteosarcoma and 55% of the patients with osteosarcoma of the jaws are male.

Site: The metaphyseal part of the long bones is the site of predilection and almost one-half of the osteosarcomas are found in the knee region.

Symptoms: Intermittent Pain and swelling are the cardinal symptoms of osteosarcoma. As these symptoms are nonspecific, one should not ignore the possible seriousness of these complaints, especially when they occur in children, adolescents, or young adults. It is extremely uncommon for patients with osteosarcoma to be asymptomatic. Pathologic fracture is uncommon is cases of osteosarcoma. A painful mass in the affected region is usually apparent. Large tumor masses may be associated with overlying prominent veins and even edema distal to the lesion. Physical examination is noncontributory in some patients with tumors covered by a thick layer of tissue.

Radiographic findings: The radiographic appearance varies greatly depending on the amount of ossification and calcification in the osteosarcoma. Tumors may range from being completely lytic to predominantly sclerotic, but they usually have a combination of these features. The destructive process may be limited to the medulla, but it usually involves the cortex as well, and the cortex is nearly always perforated by the growing tumor.

Because of a gradual transition from zones of pronounced lysis to zones of uninvolved bone, the borders of the lesion are indistinct. Sometimes non-neoplastic bone gets

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deposited in layers which elevate the periosteum which is called as *Codman triangle***.** With continued development of the neoplasm, a large soft-tissue mass is frequently seen adjacent to the bone(Fig.1).[5,6]

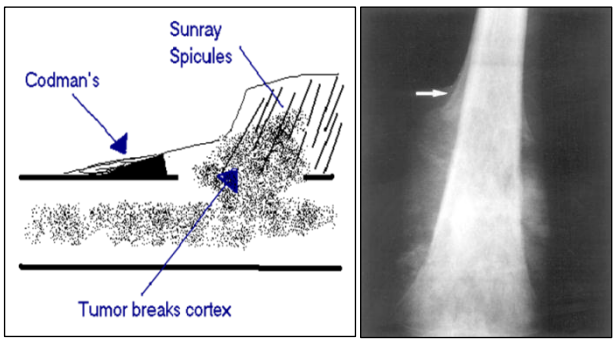

Fig. 1

Pathologic features: On gross examination, there is a good correlation with the radiological pattern with extensive bone destruction being present and in more than 90% of cases, an associated soft-tissue mass exists. The tumor's appearance and consistency vary considerably depending on the proportion of cartilage, fibrous tissue, and bone present. It may be pink to gray-white with a "fish flesh" appearance or gray to blue-gray associated with firm, white fibrous nodular masses. In tumors with abundant bone production, the tumor may be quite hard and require a saw to section. Yellow to yellow-white calcific foci is usually found throughout the lesion, as well as areas of hemorrhage, necrosis, and cystic change.

In most osteosarcomas, even those with an abundant bone formation, the peripheral soft-tissue margins usually contain highly cellular regions that are soft enough to section with a scalpel blade.[5,6]

Histopathology: Histological features of OS show a broad spectrum. Characteristics features that are constant are sarcomatous stroma having atypical neoplastic osteoblasts which produces tumor osteoid arranged in a irregular fashion along with varying degree of anaplastic fibroblast, cartilage, and myxomatous tissues. A number of divergent histopathological subtypes of OS have been described (Fig.2).

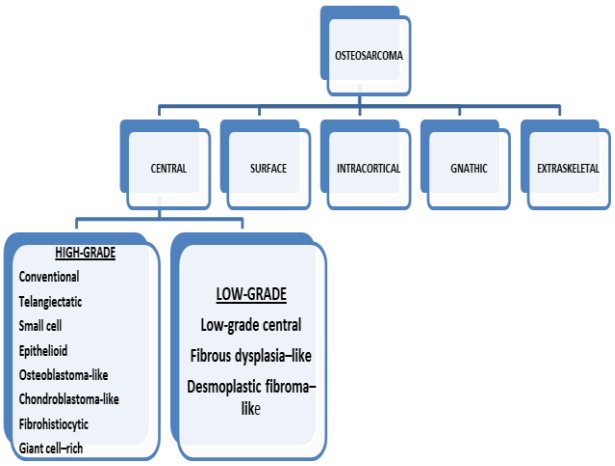

Fig: 2

Lichtenstein Tersely stated the essential criteria as *"the presence of a frankly sarcomatous stroma and the direct formation of tumor osteoid and bone by this malignant connective tissue."*

CONVENTIONAL OSTEOSARCOMA

Definition: Conventional osteosarcoma is a primary intramedullary high-grade malignant tumor in which the neoplastic cells produce osteoid, even if only in small amounts. It is important to emphasize that the finding of osteoid or tumor bone formed by malignant appearing stromal cells establishes the diagnosis of osteosarcoma regardless of the quantity of this material present. The pattern and amount of this tumor osteoid or bone vary considerably, not only from tumor to tumor but also from area to area within the tumor. Osteoid may be found *as thin, eosinophilic strands of hyaline-like material* interspersed between the malignant stromal cells, producing a *lacelike pattern* These strands may fuse to form larger, irregular seams or trabeculae. Osteoid can be found in a *filigree pattern* - thin, randomly arborizing lines of osteoid interweaving between neoplastic cells. The osteoid may also occur in broad sheet-like masses in which the malignant stromal cells become *"choked off"* and eventually disappear.

Histological subtypes of conventional osteosarcoma are *osteoblastic (Osteosarcomas that produce an abundance of osteoid and tumor bone), chondroblastic (osteosarcomas that produces predominance of malignant cartilage) and fibroblastic (osteosarcomas that have fibrous spindle cell areas).*

In all forms of osteosarcoma, one finds a permeative growth pattern with tumor percolating between and entrapping existing normal bone trabeculae. Mitotic activity is easily found in all forms of conventional osteosarcoma If the mitotic activity is absent osteosarcoma should be ruled out and suggests the possibility of a pseudosarcomatous tumor. Hemorrhage and necrosis are also frequent. Such spontaneous necrosis may involve 40% to 70% of the total tumor area.[5,6,7]

TELANGIECTATIC OSTEOSARCOMA

Telangiectatic OS constitutes 2.5%–12.0% of all osteosarcomas. In 1903, Gaylord used the term malignant bone aneurysm to refer to the lesion, which was described by Paget in 1854. Large hemorrhagic or necrotic cavities make up the majority of the tumor volume (90% or more) which gives a facade that may cause it to imitate an aneurysmal bone cyst. In telangiectatic osteosarcoma the walls and septa surrounding the periphery and hemorrhagic spaces are thick and nodular containing malignant cells that produce osteoid. The clinical features of telangiectatic osteosarcoma are similar to that of conventional osteosarcoma. Local tenderness or pain, a soft-tissue mass, and fracture are the presenting features of telangiectatic osteosarcoma.

Telangiectatic osteosarcomas are osseous in origin and they occur in the medullary cavity in the metaphyseal region of long bones. The classic radiographic feature of telangiectatic osteosarcoma is a lesion with multilocular bone destruction, with an extensive zone of transition, and endosteal scalloping. Expansile bone remodeling is one of the frequent features. Osteoid matrix mineralization may be seen but is indistinct on radiographs because more than 90% of the lesion is composed necrotic or hemorrhagic.[8,9]

SMALL CELL OSTEOSARCOMA

Small cell OS is an extremely rare variant of OS with histologic features combining those of OS and Ewing sarcoma It constitutes between 1% and 2% of all OS. The demographics of small cell osteosarcoma are similar to those of conventional osteosarcoma. Radiologically, majority of small cell osteosarcomas exhibit a combined lytic and blastic pattern, frequently with soft tissue extension. Cytological features of small cell OS are high nuclear/cytoplasmic ratios, small to intermediate-sized cells, round nuclei, and dark finely granular chromatin, followed by cytoplasmic vacuoles, focal and minimal anisokaryosis, nuclear molding, and scant osteoid.

EPITHELIOID OSTEOSARCOMA

Epithelioid Osteosarcoma is a variant of osteosarcoma in which the tumor cells are poorly differentiated so it is difficult to establish histologically whether the tumor is a sarcoma or a carcinoma. Some osteosarcomas have epithelioid-appearing cells. as It is well known that osteoblasts may appear epithelioid; *Kramer and coauthors and Hasegawa and coauthors* reported on epithelioid- appearing osteosarcoma in which IHC profile also showed epithelial differentiation.

Frequently, one sees only sheets of epithelioid cells with pink cytoplasm, vesicular nuclei, and prominent central nucleoli. Osteoid production may occur only in focal areas. The diagnosis of osteosarcoma should be suspected when a biopsy specimen from a bone tumor in a young person has the histologic characteristics of carcinoma. However, such epithelioid ostesarcomas may occur even in older patients, especially in association with dedifferentiated chondrosarcoma.

GIANT CELL–RICH OSTEOSARCOMA

More than one fourth of osteosarcomas contain scattered benign osteoclast-type giant cells that at times may be so numerous as to simulate a giant cell tumor (GCT). When numerous, these giant cells may obscure the malignant component. Such cells may be frequent in osteosarcomas arising in Paget's disease.[7,10,11]

SURFACE OSTEOSARCOMA

Surface OS's are subdivided into 3 subtypes low grade - parosteal, intermediate grade - periosteal and high grade - High-grade surface dedifferentiated parosteal.

Paraosteal Osteosarcoma: Histologically, parosteal osteosarcomas consist of streamers of bone trabeculae that often show a high degree of parallel orientation similar to what might be observed in a periosteal new bone reaction and spindle-cell fibroblast like proliferation. According to Mirra this bone formation histologically resembles "*flowing steel wool*."

When the bone spicules become thicker at the base of the lesion, there usually is a very little actual maturation of the matrix into a lamellar architecture, and the lesion does not become enveloped within the cortex. There is a cellular cartilage cap external to the osseous portion of the lesion in about 25% to 30% of cases

Periosteal Osteosarcoma: Histopathologically, the tumor demonstrates primitive sarcomatous cells within a tumor that demonstrates significant chondroblastic differentiation. Close inspection will reveal foci of tumor osteoid and immature bone formation. Periosteal osteosarcoma has more abundant and more atypical cartilage than parosteal osteosarcoma, and its spindle cell elements are larger and more atypical than the spindle cells of parosteal osteosarcoma.

High-Grade Surface Osteosarcoma: Microscopically, the tumor is entirely high grade It is possible that some high-grade surface osteosarcomas represent dedifferentiated parosteal osteosarcomas in which the high-grade component has replaced entirely the low-grade component. There usually is very little or no medullary invasion by the tumor

DEDIFFERENTIATED PAROSTEAL OSTEOSARCOMA

Wold and associates first described cases of histologically high-grade osteosarcoma arising in the clinical setting of recurrent parosteal osteosarcoma of the usual low-grade variety. This event may be indicated by changing clinical signs and symptoms, such as a difference in the quality of pain or an area of radiolucency in an otherwise radiodense lesion. It may, on the other hand, be clinically unsuspected. Grossly, the area of dedifferentiation often is apparent from the typically sclerotic areas of parosteal osteosarcoma. This may be because the higher-grade component is more cellular with respect to its matrix or because its bone matrix is less mineralized than in the lower grade areas. Less often, a higher grade area may result in cortical invasion and call attention to itself by its locally aggressive behaviorHistologically, the tissue is composed of an admixture of typical appearing low-grade parosteal osteosarcoma and high grade conventional parosteal osteosarcoma.

INTRACORTICAL OSTEOSARCOMA

Jaffe first described this very rare anatomic variant of osteosarcoma, a high-grade osteosarcoma entirely confined within the bony cortex. It usually manifests as

an area of cortical radiolucency with perilesional sclerosis.

Histologically, there usually is abundant osteoid or bone formation.Formation of cartilage is unusual but helps to distinguish the lesion from osteoblastoma and osteoid osteoma.[6,7,11]

OSTEOSARCOMA OF THE JAW BONES

Osteosarcoma of the jaws constitutes 5% to 13% of all cases of skeletal osteosarcoma. The ratio of mandibular to maxillary cases varies in the literature, with the mandible accounting for 44% to 73% of cases and the maxilla for 27% to 56%. Within the mandible, the body is the most common location, accounting for 55% to 75% of cases followed by the angle, the ramus, and the symphysis. In the maxilla, the alveolar ridge is the most common site. Most patients are in the third to fourth decades of life, generally one decade older than patients with osteosarcoma of the long bones Clinically, the majority of patients report a swelling or mass that is often, but not always, painless.

Numb chin syndrome i.e. numbness or paresthesia of the lip or chin reflects tumor involvement of the inferior alveolar nerve and is an important clue to the diagnosis of an aggressive lesion. Loosening of the teeth may be the first or even dominant manifestation of the disease. Other symptoms include nasal obstruction, epistaxis, or visual disturbances secondary to antral involvement.

Osteosarcoma of the jaw bones has developed as a consequence of predisposing conditions, the most common of which is previous radiation therapy to the region; such a history is present in approximately 10% of cases.

The tumor has also developed secondary to Paget's disease, FD, and chronic osteomyelitis

RADIOGRAPHIC FEATURES OF OSTEOSARCOMA OF THE JAWS

Small streaks of bone radiate outward from the tumor giving sunburst appearance. The classic "sunburst" or "sun ray" appearance caused by osteophytic bone production on the surface of the lesion is noted in about 25% of jaw osteosarcomas. Often this is appreciated best on an occlusal projection.

Symmetric widening of the periodontal ligament space around a tooth or several teeth is an important early radiographic change in patients with osteosarcoma, occurring due to tumor infiltration.

Pathologic features of OS of jaws : Osteosarcomas of the jaw bone have ranged from 2 to 10 cm in maximum size. The histologic type has varied in different series, with some reporting a predominance of osteoblastic tumors and others reporting a chondroblastic or fibroblastic predominance. [6,7,11-14]

EXTRASKELETAL OSTEOSARCOMA

Extraskeletal OS accounts for only 2% to 5% of all osteosarcomas. Unlike its intraosseous counterpart, extraskeletal osteosarcoma occurs in older patients. The mean and median ages are in the sixth decade of life, only 5% to 10% of patients are younger than 30 years of age The majority of extraskeletal osteosarcomas occur in the lower extremity, with the head and neck region involved in less than 5% of cases. In Head and neck areas, extraskeletal osteosarcoma has occurred in the soft tissues of the face, neck, floor of the orbit, larynx, and tongue. Extraskeletal osteosarcoma has developed secondary to previous radiation therapy, including cases in the head and neck.[11,15]

STAGING AND GRADING OF OSTEOSARCOMA

Staging of a tumor is essential to assess the prognosis of the patient, and it also suggests the degree of differentiation and distant metastasis. The universally accepted TNM staging system is not used for sarcomas due to the rarity with which they metastasize to the regional lymph nodes. The Musculoskeletal Tumor Society Staging System [Table 1] and the American Joint Committee on Cancer (AJCC) Staging System [Table 2] have gained acceptance for OS staging. AJCC 2006 staging system is based on tumor size (T), regional lymph node (N), distant metastasis (M), and histopathological grade (G). The anatomic extent of the tumor is subdivided into intracompartmental (A) and extracompartmental (B), depending on whether the tumor is confined within the cortex or is invading beyond the cortex.[16,17]

Stage IA:	Low - grade	Intracompartmental	No metastasis
Stage IB:	Low - grade	Extracompartmental	No metastasis
Stage IIA:	High- grade	Intracompartmental	No metastasis
Stage IIB:	High - grade	Extracompartmental	No metastasis
Stage III:	Any grade	Any site	Metastasis

Table 1: Musculoskeletal Tumor Society staging system[16,17]

TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor
T2:	Tumor >8 cm in greatest dimension
T3:	Discontinuous tumors in the primary bone site
NX	Regional lymph nodes cannot be assessed
N0:	No regional lymph node metastasis
N1:	Regional lymph node metastasis
MX:	Distant metastasis cannot be assessed
M0:	No distant metastasis
M1a:	Distant metastasis to lung
M1b:	Distant metastasis to other distant sites
GX:	Grade cannot be assessed
G1:	Well - differentiated—low grade
G2:	Moderately differentiated—low grade
G3:	Poorly differentiated—high - grade
G4:	Undifferentiated—high - grade Stage

IA:	T1 N0 M0 G1,2 Stage
IB:	T2 N0 M0 G1,2 Stage
IIA:	T1 N0 M0 G3,4 Stage
IIB:	T2 N0 M0 G3,4 Stage
III:	T3 N0 M0 Any G Stage
IVA:	Any T N0 M1a Any G Stage
IVB:	Any T N1 Any M Any G Any T Any N M1b Any G

Table 2: American Joint Committee on Cancer Staging System (2006) [16, 17]

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