Case I – Conventional osteosarcoma

Introduction and definition:
Definition by WHO – primary intramedullary high grade malignant tumor in which neoplastic cell produce osteoid, even in only small amount.

Osteosarcoma can be defined as a malignant tumor of bone in which malignant mesenchymal tumor cells have the ability to produce osteoid or immature bone. There may be profuse osteoid matrix production and extensive mineralization throughout the tumor, or both may be minimal in extent and very focally distributed. The osteoblastic nature of the tumor can be easy to identify both radiographically and microscopically, or extensive sampling and a great deal of expertise may be required for its recognition.

One of the better characterized genetic alterations associated with osteosarcoma is loss of heterozygosity of the retinoblastoma (RB) gene. Presence of this mutation has been associated with decreased survival rates in patients with osteosarcoma. TGF-β is a growth factor found in higher levels in high-grade osteosarcoma than in low grade lesions and is a known inhibitor of the RB gene product, perhaps contributing to the aggressive behavior of these tumors. Mutations of the p53 gene, another tumor suppressor, are also associated with osteosarcoma, and some combined inactivation of Rb and p53 is found in most osteosarcomas. Human epidermal growth factor receptor (HER-2 or ERB-2) is another molecular alteration associated with osteosarcoma. Its over expression is associated with a more clinically aggressive tumor, increased metastatic potential, shorter recurrence-free intervals and worse overall survival rates. Similar associations have been reported for P-glycoprotein, an important mediator of multi-drug resistance in tumor cells and VEGF, a growth factor responsible for tumor angioneogenesis.

Incidence and demographics:

Osteosarcoma is the most common primary malignant tumor of bone. When all aspects of its presentation taken into consideration, it is evident that this term is used to describe a heterogeneous group of lesions with diverse morphology and clinical behavior. Osteosarcoma accounts for approximately 20% of all primary sarcomas of bone.

The age distribution is bimodal, with the first major peak occurring during the second decade of life, and the second, much smaller peak being observed in patients older than 50 years. Most patients (-60%) are between 10 and 20 years old. The sex ratio varies among the series but clearly indicates a male predominance (1.3:1 to 1.6:1). The peak incidence of osteosarcoma in adolescents corresponds to the peak period of skeletal growth. The frequency of tumor occurrence within a specific bone corresponds to the site of greatest growth rate. Accordingly, the distal femoral and proximal tibial metaphyses, where most growth occurs during adolescence, are the most common sites for osteosarcoma.
Less than 10% of osteosarcomas occur in the mandible and other craniofacial bones.

**Symptoms and presentation:**

The most common symptom is pain that has usually continued for several weeks to months. The pain gradually becomes more severe and eventually is accompanied by swelling. The overlying skin feels warm and has prominent superficial vasculature. Swelling is often accompanied by some limitation of motion. The level of serum alkaline phosphatase is frequently elevated in patients with osteosarcoma. Elevation of the alkaline phosphatase level after surgery indicates persistent, recurrent, or metastatic disease.

**X-Ray appearance and imaging findings:**

In most variants of osteosarcoma, the plain radiographs may be virtually diagnostic. Classically, these lesions are located in the metaphyses (the ends) of long bones, most commonly about the knee. Lesions are poorly marginated, associated with destruction of the cancellous and cortical elements of the bone, and show ossification within the soft tissue component. Lesions may appear radiolucent, radiodense or mixed lucent and dense, depending on the degree of osteoid mineralization (Kesselring 1982). Surface variants are different in that they appear to rest atop the bone. Destructive involvement of the medullary canal in surface lesions is typically absent, though may be evident in advanced disease.

Telangiectatic osteosarcomas often are completely radiolucent. These may be confused with benign lytic tumors such as aneurysmal bone cysts. If any question exists, a biopsy should be performed.

Other imaging modalities have a role in the initial evaluation of suspected osteosarcoma, particularly magnetic resonance imaging (MRI). MRI has replaced computed tomography (CT) as the test of choice for elucidating the extent of local disease. While CT better details the extent of bony destruction, MRI has the advantage of providing multi-axial images, more detail regarding the soft tissue component and its relationship to nearby neurovascular structures, and is more sensitive in quantifying the extent of intramedullary involvement.

Bone scans (nuclear scintigraphy) and FDG-PET are useful adjuncts, but are more pertinent to staging than for evaluation of the primary lesion. The most valuable use of bone scan for evaluation of osteosarcoma is the detection of metastatic deposits within the skeleton.

The radiographic appearance of craniofacial osteosarcomas does not differ significantly from that of tumors located in the long tubular bones. However, the complex anatomic structure of craniofacial bones requires special expertise in evaluating lesions involving this site. The
constellation of bone destruction, mineralized matrix production, and periosteal new bone formation is typical for the radiographic presentation of osteosarcoma.

Pathology findings:

Osteosarcoma represents one of the most heterogeneous tumors known in human pathology. The two basic microscopic components of osteosarcoma are the sarcomatous tumor cells and the extracellular matrix. The relationship between the tumor cells and the matrix is very important for diagnosis. Evidence of direct production of osteoid matrix by sarcomatous tumor cells is required to classify the lesion as an osteosarcoma. The histologic hallmark of osteosarcoma is the presence of frankly malignant mesenchymal spindle cells producing osteoid. Variations are common. Currently, the World Health Organization (WHO) recognizes three distinct subtypes of conventional osteosarcoma: osteoblastic, chondroblastic and fibroblastic. The presence of woven bone with malignant appearing stromal cells, regardless of associated chondroid or fibrous matrix, makes the diagnosis of osteosarcoma.

Osteoblastic osteosarcoma is microscopically composed of malignant appearing osteoblasts with woven bone as the predominant matrix. Chondroblastic osteosarcoma is composed of matrix that looks like cartilage with the malignant spindle cells found in the lacunae. The fibroblastic variant looks like a malignant spindle cell tumor, with scant osteoid being the only indicator of the presence of osteosarcoma. In reality, mixed appearances are common. While knowledge of these subtypes may aid the pathologist in considering the diagnosis when the histology is unclear, there is no data to support a difference in clinical behavior or prognosis based on these microscopic criteria.

Osteosarcomas of craniofacial bones do not differ microscopically from those located in the long bones. The only significant difference is the preponderance of the chondroblastic type, which in the mandible and the maxilla accounts for approximately 30% of the cases. These lesions produce tumor osteoid, but this can be very focal and minimal in extent.

In some cases, the cartilaginous differentiation of the tumor is so dominant that some observers postulate that these tumors should probably be classified as chondrosarcomas. This disagreement may be academic but highlights the less aggressive biologic behavior of these tumors compared with that of conventional high-grade osteosarcomas.

Nearly half of the cases involving the jaw bone are histologic grades 1 and 2. Whether the less aggressive behavior of osteosarcoma of the jaws is related to their chondroblastic features or to their better differentiation is still unclear. Regardless of minimal atypia, chondroid differentiation in craniofacial bone tumors, especially in the mandible and maxilla, should be considered a warning signal of malignancy. Exclusive of callus, cartilaginous differentiation is almost never seen in benign conditions of these bones.

*Immunohistochemistry* is not helpful.
Differential diagnosis include: conventional chondrosarcoma, malignant fibrous histiocytoma of bone, fibrous dysplasia, fibro-osseal lesion of cranial bones.

**Treatment options and prognosis:**

**Treatment options:** The past thirty years have seen great progress in the treatment of osteosarcoma. Recognition of the importance of multimodal therapy in addition to advances in imaging is largely responsible. Not only have dramatic improvements in survival been achieved, but so has the ability to safely perform limb-sparing procedures in the majority of patients with osteosarcoma.

The standard treatment of patients with conventional osteosarcoma consists of combination chemotherapy and surgery.

**Prognosis:** The most important reason for therapeutic failure in craniofacial osteosarcoma is local recurrence. Nearly 50% of mandibular osteosarcomas recur locally after resection. The recurrence rate is even higher with maxillary-and skull lesions (80% and 75%, respectively). Metastases are less frequent than local recurrence and occur in about one third of patients with craniofacial osteosarcomas. They typically occur within 2 years after initial treatment, predominantly in the lungs. Occasionally cervical lymph nodes can be involved, necessitating a radical neck dissection. Once metastases are identified, the average survival rate is less than 1 year. The overall 5-year survival rate for mandibular tumors after combined modality treatment is approximately 75%. The survival rates for maxillary and skull de novo lesions are similar.
Case II – Ewing sarcoma/ PNET (ES/PNET)

Introduction and definition:

**Definition by WHO** – round cell sarcomas that show varying degrees of neuroectodermal differentiation.

Ewing’s sarcoma (ES) was first described by James Ewing in 1921 as a "diffuse endothelioma of bone" (Ewing 1921). He observed that this highly aggressive bone “cancer” was remarkably sensitive to radiation therapy.

Since the time of his description, many theories have evolved regarding how Ewing sarcomas arise. While the origin of these tumors is still not definitively known, the two theories with the most support suggest that these tumors arise from a primitive cell derived either from an embryologic tissue called the neural crest, or from resident cells in the body (called mesenchymal stem cells) that have a capability to become one of a variety of tissue types. Pathologists have long known that Ewing sarcoma looks very similar to an even rarer soft tissue tumor called primitive neuroectodermal tumor (PNET). By the early 1980’s, ES and PNET were found to not only have similar features when examined under a microscope, but in greater than 95% of cases they also had an identical genetic abnormality called Ewing’s translocation - **Translocation (11;22)(q24;q12)**. Subsequently, these two tumors have been grouped into a class of cancers entitled Ewing’s Sarcoma Family of Tumor (ESFT), all of which demonstrate this translocation.

Tumors in the Ewing’s family of sarcomas are made of primitive cells, which are cells that haven't yet decided what type of cell they are. They look blue to a pathologist because of the staining that is used when identifying the tumor, so the cells are referred to as "small round blue cells." The Ewing's family of sarcomas includes:

* Ewing's sarcoma of the bone
* Extrasosseous Ewing's sarcoma, also referred to as extraskeletal Ewing's sarcoma (tumor growing outside of the bone)
* Primitive neuroectodermal tumor (PNET)
* Peripheral neuroepithelioma
* Askin's tumor (Ewing’s sarcoma of the chest wall)
* Atypical Ewing’s sarcoma

**Translocation (11;22)(q24;q12)** is seen in approximately 90% of Ewing's sarcomas /PNET.

**Alternative translocations in Ewing's sarcoma and PNET** - It has been shown that EWS may be translated to other locations and form alternative chimeric genes. The second alternative cytogenetic abnormality, t(21;22)(q22;q12), is present in approximately 10% of Ewing's sarcomas and PNETs. This translocation fuses the 5’ portion of the EWS gene from 22q12 to the ERG gene located on 21q22. This translocation is associated with no visible alteration on chromosome 21.
The third cytogenetically identifiable translocation present in Ewing's sarcomas and PNETs is t(7;22)(p22;q12), which again fuses the EWS gene, this time with ETV-located on chromosome 7p22.

**Incidence and demographics:**

ESFT is not so rare (16% from all primary bone and soft tissue sarcomas). In 90% of the cases, ESFT is found in patients between 5 and 25 years of age. About 25% of cases occur before age 10, while 65% arise between ages 10 and 20 years old. Approximately 10% of patients are older than 20 years when they are diagnosed. Boys and young men are affected more frequently than girls and young women. Males also do less well than females in terms of survival.

The pelvis is the most common location, followed in order by the femur, tibia, humerus, and scapula. Cranial bones are very rare affected.

**Symptoms and presentation:**

People with ESFT initially complain of pain and sometimes notice a mass. Generally, the mass will continue to grow over the course of a few weeks to months. Sometimes the tumor eats away the bone and causes a fracture. Approximately a quarter of patients will complain of a fever and/or weight loss.

**X-Ray appearance and imaging findings:**

Radiographically ESFT presents as a central lytic tumor of the diaphyseal-metaphyseal bone. It creates extensive permeative destruction of cortical bone, and as it breaks through under the periosteum, it takes on a typical "onion skin," multilaminated appearance. Another radiographic feature is the reactive "hair-on-end" appearance created by bone forming along the periosteal vessels that run perpendicularly between the cortex and the elevated periosteum.

The radiographic features are nonspecific, but with the clinical features, the diagnosis of Ewing's sarcomas correctly suspected in the majority of cases. The lesion involves the medullary cavity and soft tissue more extensively than is usually documented on plain radiographs.

Magnetic resonance imaging and computed tomography permit more accurate preoperative assessment of the lesion than plain films. They typically demonstrate intramedullary lesions that involve large segments of the intramedullary cavity and extend beyond the area shown to be involved on plain radiographs. Ewing's sarcoma can produce a concave defect on the bone surface that is referred to a saucerization. This type of radiographic appearance is typically seen in predominantly subperiosteal lesions. More often, saucerization is seen in intramedullary lesions in which the cortex is permeated and a secondary subperiosteal and soft tissue mass that compresses the outer surface of the cortex is formed.
**Histopathology findings:**

Ewing's sarcoma is the prototype of a nonhematologic, small round-cell tumor characterized by a proliferation of undifferentiated mesenchymal cells. The cells grow in solid, densely packed sheets and nests filling intertrabecular spaces. They have round, centrally located nuclei with indistinct cytoplasmic features. The nuclear chromatin is finely granular, and there are usually one to three clearly identifiable small- to intermediate sized nucleoli. The presence of a prominent nucleolus is generally not a feature of Ewing's sarcoma.

Often a biphasic pattern is simulated by the presence of so-called dark and light cells (i.e., cells with an open chromatin structure and cells with dark condensed nuclei). The latter represent tumor cells undergoing apoptosis. These types of cells are sometimes referred to as principal (light) and secondary (dark) cells. The ratio between these two types of cells varies from tumor to tumor and in different areas of the same lesion. In some tumors, cords or clusters of dark apoptotic cells form an interconnecting network of irregular patches that create a pseudo-organoid pattern.

Necrosis is a frequent finding in Ewing's sarcoma and varies from small patchy foci to large irregular geographic areas. Tumor cells occasionally form rosette like structures. In general, less than 20% of tumor tissue contains these structures.

These classic morphologic features are seen in a majority of Ewing's sarcomas. Microscopic cystic changes with blood-filled spaces, as well as changes resembling aneurismal bone cyst, can be superimposed on Ewing's sarcoma. In a small number of tumors, the microscopic appearance of tumor cells may deviate from the so-called classic pattern. Tumors that deviate from the usual pattern are referred to as atypical Ewing's sarcomas. According histological appearance now we can recognized 11 subtypes of ES/PNET.

**Immunohistochemistry:**

Vimentin, CD 99, NSE, PGP 9.5, neurofilament, Leu-7 and synaptophysin positive

**Differential diagnosis include:** ESFT can mimic osteomyelitis because it is a high grade lesion with resultant areas of necrosis. liquefaction of the tumor may occur and may be mistaken for pus. Furthermore, patients frequently present with systemic symptoms of low grade, intermittent fevers, elevated white blood cell count, and elevated erythrocyte sedimentation rate (ESR).

**Treatment options and prognosis:**

**Treatment options** - The management of ESFT involves physicians from multiple disciplines. It is critical that a patient diagnosed with ESFT is treated at a center very familiar with this disease and that the center has an interdisciplinary team of physicians and allied health care providers dedicated to this rare but deadly form of cancer. Medical specialties with expertise in Ewing sarcoma include orthopaedic oncology, medical oncology, pediatric oncology, radiation
oncology, musculoskeletal radiology, and musculoskeletal pathology. Spine surgeons, vascular surgeons, and plastic surgeons may also provide critical support in some cases.

Oncologic treatment include combination of chemo, radio, surgical therapy and bone marrow transplantation.

*Prognosis*- Current survival rate is estimated to be 41%. Important prognostic features include the stage, anatomic location and the size of tumor. ES/PNET of cranial bones has poor prognosis.
Case III – Mesenchymal chondrosarcoma

Introduction and definition:

Definition by WHO – rare malignant tumor characterized by a bimorphic pattern that is composed of highly undifferentiated small round cells and islands of well differentiated hyaline cartilage.

Mesenchymal Chondrosarcoma was originally described by Lichtenstein and Bernstein in 1959 in "Unusual benign and malignant chondroid tumors of bone: a survey of some mesenchymal cartilage tumors and malignant chondroblastic tumors including a few multicentric ones and chondromyxoid fibromas", Cancer 12: 1142, 1959.

Mesenchymal chondrosarcoma is classified as malignant cartilage forming tumor (WHO). Approximately two thirds of cases of mesenchymal chondrosarcoma occur in bone while the rest occur in places outside of the bone—i.e., in extra-skeletal locations. Unlike other types of malignant chondrosarcoma, which have a tendency to grow more slowly and rarely develop metastases, mesenchymal chondrosarcoma is a fast growing tumor that spreads more often. At the same time, it can remain dormant for long periods of time.

Incidence and demographics:

It tends to affect children and young adults, but is a rare tumor, accounting for less than 1% of all sarcomas. Male and female patients are almost equally affected.

Symptoms and presentation:
Mesenchymal chondrosarcoma tends to present with some type of swelling or pain, either in a limb or another part of the body. It may be diagnosed when it causes these symptoms related to the physical location of the tumor. The symptoms may persist for more than 1 year. At times, the tumor may be detected early because it is seen on an x-ray that is done for other reasons, such as a minor, unrelated injury.

The maxilla and mandible are the most frequent sites of involvement. The other more frequent sites are the vertebrae, ribs, pelvis, and humerus. Approximately 30% of mesenchymal chondrosarcomas present as extraskeletal soft tissue lesions. The tumor can occur almost anywhere in the body, and is known to spread to the lungs, soft tissues, and other major organs. Mesenchymal chondrosarcoma may occur near the spinal cord, also known as a parameningeal presentation.

X-Ray appearance and imaging findings:

Mesenchymal chondrosarcoma appears radiographically as a radiolucent lesion with varying degrees of matrix calcification. It is often eccentrically located in bone. Stippled calcifications are frequently present and may coalesce to form large, discrete opacities. Stippled calcifications
disclosing the cartilaginous nature of the lesion also are frequently present in the soft tissue lesions. Prominent extensions into soft tissue are seen in about 50% of the cases. Surprisingly, this highly aggressive tumor may occasionally have a sharply demarcated sclerotic margin.

**Histopathology findings:**

Mesenchymal chondrosarcoma has a bimorphic histological appearance. Under the microscope, it appears to have both highly cellular areas composed mostly of only small blue round cells and other composed of well-differentiated cartilage. Islands of cartilage are present within these solid areas. Mesenchymal chondrosarcoma can have distinct areas of these two appearances or the areas can be relatively mixed up. To make the diagnosis of mesenchymal chondrosarcoma, the pathologist needs to see a combination of these two appearances on the biopsy specimen. A difficulty in making the diagnosis of mesenchymal chondrosarcoma arises when the two areas are not well mixed up and the surgeon obtaining the diagnostic biopsy samples only the "cellular" part of the tumor. Under the microscope, the cellular part of the tumor looks like a "small round blue cell tumor". Given that the tumor tends to occur in bone, a small biopsy sample showing only tumor cells can appear to be Ewing’s sarcoma. The key is to have adequate sampling showing both parts of the tumor and an experienced pathologist to review the sample.

**Immunohistochemistry:**

Immunohistochemically foci of cartilaginous differentiation are positive for S-100 protein. In contrast, primitive mesenchymal cells are negative for S-100 protein and may show focal weak positivity for neuron-specific enolase and CD 99. Rhabdomyoblastic differentiation is associated with strong focal or diffuse positivity for muscle markers (Desmin and HHF 35).

In some immunohistochemical study, nuclear positivity for the TP53 protein was observed in 22-64% of the tumour cells, with positive staining in mesenchymal as well as chondroid components. PCR analysis revealed that approximately one-fifth of the cases had significantly reduced expression of TP53. However, no mutations resulting in amino acid substitution were found within exons 5-9 of the gene. Molecular analysis of the CDKN2A tumour suppressor gene revealed low expression levels, but single strand conformation polymorphism analysis of the entire coding region did not disclose any mutations.

**Differential diagnosis include:** cartilage forming tumors, hemangiopericytoma, ES/PNET, small blue round cell tumors

**Treatment options and prognosis:**

**Treatment options** - Surgical resection is the optimal first treatment. Generally, chemotherapy is administered after surgery.

**Prognosis** - The overall prognosis for this tumor was poor. About 75% of patients with mesenchymal chondrosarcoma died of the disease between 6 months and 23 years after initial diagnosis.
Case IV – Chordoma

Introduction and definition:

Definition by WHO - low to intermediate grade malignant tumor that recapitulates notochord.

Notochordal tumours arise from remnants of the notochord and hence occur exclusively along the midline. Tumours which occur elsewhere may resemble chordomas.

The majority of the tumours occur in the sacrum or in the clivus. Involvement of the remainder of the spine is unusual. One of the characteristic histological features of chordoma is a lobulated growth pattern.

Chondroid chordomas occur exclusively in the base of the skull and show features of both low grade chondrosarcoma and chordoma. Some studies have indicated a better prognosis for this subtype.

Incidence and demographics:

It accounts for approximately 3 to 4 percent of primary bone tumors and is localized along the axial skeleton. This tumor develops predominantly in the sacroccygeal (50%), sphenoorbital (35%) and cervical (15%) region and is generally regarded as a locally aggressive tumor with slow progression growth rate and metastatic incidence ranging from 5 to 40%. Its incidence is highest in the third decade, but it can also be found in younger population, even infancy (1%). The male-female ratio among patients is 1.8-2.1.

Symptoms and presentation:

Pain is a common symptom in chordoma and can last for months to several years. Compression of the nerves in the sacroccygeal and cervical region.

X-Ray appearance and imaging findings:

On plain radiographs, chordoma typically presents as a lytic lesion. Scattered, discrete opacities representing intralosomal calcifications can be present.

Computed tomography and magnetic resonance imaging are indispensable in evaluating the extent of both the lesion and involvement of the adjacent structures. Magnetic resonance imaging, in particular, can reveal the lobulated nature of the lesion, and T2- weighted images typically show signal enhancement.
Histopathology findings:

Macroscopically, this tumor mostly presents the lobular shape with fine fibro-vascular septas between the lobes.

Microscopically, two distinct cellular patterns can be found: large, bright and vacuolated cells with excentric nucleus, called physaliphore-like cells and small, polygonal cells rich with eozinophylic cytoplasm and mild to moderate atypia of the nucleus. Both cell groups are arranged in band-like formations circumscribed by basophylic, myxoid stroma. Mitoses are rare and not necessarily pathologic.

The level of cellularity can vary considerably among cases and in different areas of the same tumor. Some tumors are highly cellular with minimal or no intercellular matrix. More often, there is a moderate amount of cellular tissue and clearly recognizable intercellular myxoid stroma. In a typical case, the tumor cells form an anastomosing pattern of cords with focal solid areas separated by a prominent intercellular matrix.

Vacuolization of the cytoplasm is almost invariably present. Frequently, it is in the form of large (single or several) vacuoles displacing the nucleus peripherally and causing the so-called signet-ring-like appearance of the tumor cells. It can also be in the form of smaller (multivesicular) structures. Occasionally, the vacuoles encircle the nucleus, which remains centered in the cytoplasm and produces the so-called physaliphorous appearance. The physaliphorous cell is a hallmark of chordoma.

Immunophenotyping of the tissue samples enables the precise differentiation of chordoma from other neoplasm. This tumor has a strong positivity to vimentin, pan CK, S-100 protein, EMA and low molecular weight CK.

Differential diagnosis include: metastatic carcinomas- RCC and signet ring carcinoma, lipomatous tumors, chondrosracmo-clear cell, clear cell sarcoma

Treatment options:

Therapeutic management, ideally, consists of complete surgical excision of the initial tumor and adjuvant chemo or radio therapy.

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