Case I – Fibrous dysplasia (FD)

Introduction and definition:

Definition by WHO – Benign medullary fibro-osseous lesion which may involve one or more bones.

Fibrous dysplasia is an uncommon, benign disorder characterized by a tumor-like proliferation of fibro-osseous tissue. The cause of fibrous dysplasia is unknown. Most cases of fibrous dysplasia display no particular pattern of inheritance. Fibrous dysplasia can present as an autosomal dominant disorder affecting the mandible and maxilla bones in children in their teenage years.

FD is a genetic non-inherited condition caused by missense mutation in the gene GNAS1 on chromosome 20, that encodes the alpha subunit of the stimulatory G protein-coupled receptor, Gsα. The activating mutations occur post-zygotically, replacing the arginine residue amino acid with either a cystein or a histidine amino acid. The mutation selectively inhibits GTPase activity, resulting in constitutive stimulation of AMP-protein kinase A intracellular signal transduction pathways. The systemic manifestations of the mutated Gsα protein-coupled receptor complex include autonomous function in bone through parathyroid hormone receptor; in skin through melanocyte-stimulating hormone receptor; in ovaries through the follicle-stimulating hormone receptor; and in the thyroid and the pituitary gland, through the thyroid and growth hormone receptors respectively. FD is a somatic mosaic disorder with a broad spectrum of phenotypic heterogeneity. The extent of the disease is related to the stage at which the post-zygotic mutation in Gsα had occurred, whether during embryonic development or postnatally.

Polyostotic FD can affect bones derived from mesoderm or neural crest, and is associated with pregastrulation mutation. The same process associated with multiple-organ manifestations of Gsα mutation is referred to as McCune-Albright syndrome. The mutated pluripotential cell develops into a mutated clone of cells affecting bones in the case of FD, and affecting multiple organs together with bones in the case of McCune-Albright syndrome.

Monostotic FD and polyostotic FD without either craniofacial skeletal or extraskeletal organ involvement can develop from a post-gastrulation mutation; but since polyostotic FD nearly always involves craniofacial bones, it is reasonable to assume that the monostotic FD is the only form of FD that can develop post-gastrulation.

Severity and extent of Gsα mutation-associated diseases are not related to the stage of embryogenesis when the mutation occurred, but rather are functions of survival of mutated cells within the clone during migration, growth and differentiation, and of the ratio of mutated to normal cells at the affected anatomical site.
The cells have an increased number of hormone receptors, which may explain why these lesions become more active during pregnancy.

Also, polyostotic fibrous dysplasia is known to have multiple associations with other disorders. The combination of polyostotic fibrous dysplasia, precocious puberty, and “cafe au lait” spots is called Albright's syndrome. The association of fibrous dysplasia and soft tissue tumors has been given the name Mazabraud's syndrome. Other endocrine abnormalities including hyperthyroidism, Cushing's disease, goiter, hypophosphatemia, and hyperprolactinemia have been associated with fibrous dysplasia.

**Incidence and demographics:**

This tumor is normally a monostotic (solitary) tumor that arises during periods of bone growth in older children and adolescents and slowly enlarges. Monostotic fibrous dysplasia accounts for 75 to 80% of cases. Polyostotic fibrous dysplasia may occur as multiple lesions in adjacent bones. It accounts for 7% of benign bone tumors. Most patients are diagnosed with fibrous dysplasia in the first three decades of life. Cases of polyostotic fibrous dysplasia are typically diagnosed in the first decade of life. Females and males are equally affected.

FD can occur anywhere but is usually found in the proximal femur, tibia, humerus, ribs, and craniofacial bones in decreasing order of incidence. Skeletal deformities can occur as a result of repeated pathological fractures through affected bone. Polyostotic cases can affect multiple adjacent bones or multiple extremities.

**Symptoms and presentation:**

Monostotic fibrous dysplasia may be completely asymptomatic and is often an incidental finding on x-ray. Pain and swelling at the site of the lesion can also be present. Female patients may have increased symptoms during pregnancy. This tumor can also present as a pathological fracture.

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

*Radiographically*, fibrous dysplasia appears as a well circumscribed lesion in a long bone with a ground glass or hazy appearance of the matrix. There is a narrow zone of transition and no periosteal reaction or soft tissue mass. The lesions are normally located in the metaphysis or diaphysis. There is sometimes focal thinning of the overlying cortex, called "scallopings from within". The radiological appearance can also be cystic, pagetoid, or dense and sclerotic. T-99 bone scan uptake may be normal or increased. Bone scans are not helpful in diagnosing these lesions but can be useful in identifying asymptomatic lesions. MRI scans or CT scans can be helpful in delineating the extent of the lesion and identifying possible pathological fractures. Sarcomatous change within the lesion can be identified by MRI or CT scans.
Pathology findings:

On gross appearance, the tumor is a solid white or tan mass. The cut surface is gritty or sandy because of the fine bone spicules it contains.

Microscopically, fibrous dysplasia appears as irregular foci of woven bone arising from a cellular fibrous stroma. The stroma has a whorled appearance and is highly vascular. The short, irregular bone segments or trabeculae are not rimmed by osteoblasts. These irregular trabeculae have been described as "Chinese letters" or "alphabet soup". No lamellar bone is found within a fibrous dysplasia lesion. FD comprises irregular trabeculae of woven bone, blending into the surrounding normal bone and lying within a cellular fibrous stroma with osteoblast progenitor cells resembling fibroblasts. These trabeculae of woven bone have been fancifully said to resemble Chinese script writing. Early craniofacial FD is characterized by minimally mineralized deposits of woven bone with a continuum progressive lamellation of the woven bone trabeculae as FD becomes more mature. This is in contrast to FD lesions in long bones where mature lamellar bone is not found. Differential diagnosis include: fibroosseous dysplasia, ossifying fibroma, osteosarcoma, intraosseal desmoids, MPNST of bone, meningioma.

Treatment options:
A biopsy may be needed to confirm the diagnosis, but surgery is not necessary for an asymptomatic lesion unless there is a risk for pathological fracture. Lesions whose behavior is latent (see more about that here) do not need any evaluation or treatment unless there is a risk of pathologic fracture (more about that here). Surgery with curettage of the lesion can be associated with high rates of local recurrence.

Case II – Cemento-ossifying fibroma (COF)

Introduction and definition:

Definition by WHO

Cemento-ossifying fibroma is benign fibro-osseal lesion of cranial bones.

Cemento-ossifying fibroma (COF) is a well-demarcated lesion composed of fibrocellular tissue and mineralized material of varying appearances. It is benign odontogenic tumor that belongs to a group of bone-related lesions. In addition to COF, this group of bone-related lesions comprises of fibrous dysplasia, osseous dysplasias, and central giant cell lesion (granuloma), cherubism, aneurismatic bone cyst, simple bone cyst. Cemento-ossifying fibroma was formerly classified as the one of the fibro-osseous lesions that contains cementum. Numerous synonyms that were equally used (cementifying fibroma, ossifying fibroma, and cemento-ossifying fibroma) are used in the literature.
Incidence and demographics:
Cemento-ossifying fibroma can occur in both jaws, but more frequent occurrence of COF is in the mandible, in females. Most patients are diagnosed with COF in the third decades of life, between the age of 20 and 30.

Symptoms and presentation:
Typical symptoms are: pain, swelling, teeth displacement. Paresthesia are rare symptom, and could be early sign of disease. Small lesions seldom cause any symptoms and are detected only on radiographic examination. Clinical symptoms in maxilla are more prominent and besides the pain and swelling were manifested by teeth displacement. COF in maxilla often expand into the maxillary antrum and may cause eye protrusion. Displacement of maxillary teeth is typically inferiorly.

X-Ray appearance and imaging findings:
Radiologically, a well-defined radiolucency with or without sclerotic border is typically seen in COF. However, radiographic findings of COF depend on its maturity, i.e., the duration of the lesion. The early tumor often manifests as well-circumscribed radiolucent lesion, resembling ground glass, and it is almost impossible to be distinguished from fibrous dysplasia. On panoramic radiographs, computed tomography (CT) and magnetic resonance, COF is usually presented as lytic lesion of the bone with well-defined sclerotic edge. With the maturing of the tumor, the more intensive forming of spherules resembling cementum in it is present, and radiological image shows calcification within the osteolytic lesion. Old lesions can be purely radiopaque.

Histopathology findings:
Histological features of COF are typical and they are different from other benign fibro-osseous lesions. The tumor consists of multiplied fibroblasts in storiform arrangement that produce collagen fibers. The presence of mitoses without signs of atypia and pleomorphism is also possible. The stroma of the tumor typically contains bone spherules-cementum granules that vary in number and size. However, it does not contain signs of haemorrhage, inflammatory cells, and signs of hyaline cartilage.

The more mature the lesion, the more emphasized is the described bone formation of psammoma-like bodies, thus becoming a predominant histomorphologic criterion in pathohistological diagnostication. The bone in COF is the newly formed, the so-called “woven bone” with peripheral lamellar maturing. On the surface of the bone spiculae, there are inactive osteoblasts focally. The number and mineralisation of bone spherules varied during tumor maturation. The number and appearance of psammoma-like bodies depended on the disease duration, i.e., on “maturity” of the tumor. The number of the so-called psammoma-like bodies is smaller in cases with short evolution of the disease, but the greater aggression of the lesion. Fast clinical course and short duration of the disease is present in the patients whose histological findings, together with typical COF manifestation, also showed the symptoms of atypical reactive
inflammation in the stroma of the tumor (emphasized lymphoplasmacytic infiltrates) or in the area of intralesional hemorrhage.

Histologically could be recognized two types of COF: juvenile trabecular ossifying fibroma (JTOF) and juvenile psammomatoid ossifying fibroma (JPOF). They have different clinical course.

JTOF is lesion in younger patients, mean age range 8.5-12 years. Contrary, JPOF occur in patients about 20 years. It is well known that JTOF has trabecular and anastomosing lattice, while JPOF is characterized by a small ossicles resembling psammoma body.

Differential diagnosis include: fibrous dysplasia, fibrooseous dysplasia, ossifying fibroma, osteosarcoma, intraosseal desmoids, MPNST of bone, meningioma.

**Treatment options:**

Having established the diagnosis based on the pathohistological finding, the treatment method is defined which is solely surgical. With regard to the absolutely benign nature of the lesion, simple curettage, enucleation, or excision are sufficient for a cure, and the recurrence of the disease are rare.

**Case III – Epithelial Odontogenic Ghost Cell Tumor (EOGCT)**

**Introduction and definition:**

**Definition by WHO**

The epithelial odontogenic ghost cell tumor is odontogenic tumor closely linked histologically to the calcifying odontogenic cyst.

The epithelial odontogenic ghost cell tumor (EOGCT) is an uncommon odontogenic lesion that is closely linked histologically to the calcifying odontogenic cyst (COC). Most investigators today accept that EOGCT is a neoplastic, solid tumor counterpart of COC. The true nature of COCs has been the subject of much controversy. The fact that not all COCs are cystic and that their biological behavior is often not compatible with a cyst has raised the question of whether COC is a cyst or a tumor. Two organizing principles of classification of COCs have been put forward: monistic and dualistic. The monistic concept, best exemplified by the World Health Organization (WHO) classification, postulates that all COCs are neoplastic in nature, even though the majority are cystic in architecture and appear to be nonneoplastic. In contrast, the dualistic concept, favored by most researchers, proposes that COCs contain two different entities, a cyst and a neoplasm.

Numerous names have been used to describe EOGCT, reflecting diverse histopathologic characteristics and confusion about the origin and nature of the tumor. Occasionally, EOGCT can be locally aggressive, and histologic evidence of malignant transformation has been reported.
Incidence and demographics:

Demographic study confirmed that EOGCC is more prevalent in Asians than in other racial groups. More frequent occurrence of EOGCT is in the maxilla, mandible is affected in 20% of all described cases.

Symptoms and presentation:

The main symptoms are pain and swelling. Tooth root resorption was reported, as well as tooth displacements.

X-Ray appearance and imaging findings:

X – Ray examination showes mixed radiolucent and radiopaque lesions pattern. Mix litic and sclerotic lesion is the most frequent radiologic presentation. Often tumor showes poorly defined borders, but well defined borders between tumor and host bone is also described. Root resorption and tooth displacements are also radiologic characteristic of EOGCT.

CT studies of the jaw shows a large, poorly defined, lobulated, heterogeneous mass. The mass caused irregular destruction of the body of the jaw. Scattered foci of presumed calcification could be discovered within the mass. After administration of contrast material cystic areas become visible.

Histopathology findings:

Histologically, it consists of ameloblastoma-like odontogenic epithelial proliferations infiltrating the bone and connective tissue. Ghost cells are present as well as varying amounts of dentinoid, the latter being closely associated with odontogenic epithelium. EOGCTs are composed primarily of ameloblastoma-like areas and odontogenic epithelial islands with varying amounts of ghost cells showing keratinization and calcification. The most important histologic feature of EOGCT that distinguishes it from conventional ameloblastoma and other odontogenic tumors is the presence of ghost cells and dentinoid substances. Ghost cells are believed to be transformed odontogenic epithelial cells, the mechanism of which is still unclear. Although the presence of ghost cells is a defining feature for the diagnosis of EOGCT, these cells can also be observed in other tumors, such as pilomatrixcoma, craniopharyngioma, odontoma, and ameloblastic fibro-odontoma. The nature of the dentinoid substance found in EOGCT is unknown. It is amorphous eosinophilic material containing widely separated cell bodies. It lacks the tubular structure of normal dentin, and appears as an irregular mass within the connective tissue adjacent to the proliferation of odontogenic epithelium.

Differential diagnosis include: other odontogenic lesion, conventional ameloblastoma, pilomatrixcoma, craniopharyngioma, odontoma, and ameloblastic fibro-odontoma.
**Treatment options:**
The recommended treatment for EOGCT is surgical excision. For aggressive form of EOGCT surgical therapy is followed by postoperative radiation with or without adjuvant chemotherapy. However, the effectiveness of chemotherapy has not yet been determined.

**Case IV – Haemangioma of bone**

**Introduction and definition:**

**Definition by WHO**

Hemangioma of bone is a benign vasoformative neoplasm or developmental condition of endothelial origin.

**Incidence and demographics:**

Hemangiomas of bone are rare lesions, accounting for less than 1% of all primary tumors of bone. Frequent sites of skeletal involvement are vertebral bodies and cranial bones. Hemangiomas frequently occur in the craniofacial bones, predominantly in the calvarium, and in some series nearly 50% of the lesions occur at this site. Hemangiomas have a wide age distribution, ranging from the first to eighth decades of life, with nearly 70% of the cases diagnosed in patients between 30 and 60 years. Occasionally, hemangiomas become clinically evident during the first decade of life. There is no clear sex predilection, but in some series, female patients are slightly more frequently affected than male patients.

**Symptoms and presentation:**

A significant number of solitary skeletal hemangiomas are asymptomatic and are never diagnosed during life. Local swelling and pain are often presented. Pathologic fracture could be the first sign of lesion.

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

Radiographically, hemangiomas present as lucent, well-demarcated defects. The vascular nature of the lesion often is suggested by its bubbly or honeycomb trabeculated appearance. The overlying cortex is expanded and thinned, but complete cortical disruption and invasion into soft tissue are not present. The characteristic sunburst appearance of hemangioma is seen in skull lesions and is produced by fine spicules of reactive new bone in the periosteum radiating outward from the center of the lesion. The sunburst type of periosteal new bone formation should not be confused with that seen in association with osteosarcoma of long bone. Magnetic resonance imaging of hemangiomas generally reveals a low signal on T1-weighted images and a high signal on T2-weighted images.
Histopathology findings:

Hemangiomas are composed of a conglomerate of thin-walled blood vessels. The vessels can have dilated open channels (cavernous hemangioma) or less frequently may be composed of capillary-sized vessels (capillary hemangioma). A majority of bone hemangiomas are of cavernous or mixed types (cavernous and capillary). Predominantly or exclusively capillary hemangiomas are exceedingly rare in bone. The size of cavernous vessels may vary, but occasionally hemangioma can be composed of vessels that are relatively uniform in size. The vascular channels are lined by a single layer of flat endothelial cells (CD 31 positive, CD 34 positive, F VIII positive, Glut-1 positive).

Hemangiomas have a characteristic microscopic appearance and in the majority of cases are easy to recognize. However, secondary changes may alter this classic pattern and make the diagnosis difficult. Hemangiomas of any type, but especially those with large cavernous vessels, occasionally develop thromboses with calcifications. This in turn can promote the development of papillary endothelial hyperplasia. The presence of this change can alter the pattern of vascular channels and lead to the misdiagnosis of a malignant vascular tumor.

Differential diagnosis include: other vascular tumours, metastatic tumour, disappearing bone disease (Gorham’s disease), aneurismal bone cyst, solitary bone cyst

Treatment options:

Treatment is observation, and radiation therapy in cases of persistent pain. In some cases, vascular embolization is indicated, either as a definitive means of treatment or as a means of reducing blood loss during surgery.
Literature: