FIBROUS DYSPLASIA: A REVIEW

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Abstract

Fibrous dysplasia has been regarded as a developmental skeletal disorder characterized by replacement of normal bone with benign cellular fibrous connective tissue. It has now become evident that fibrous dysplasia is a genetic disease caused by somatic activating mutation of the Gsα subunit of G protein coupled receptor resulting in up-regulation of cAMP. This article reviews on fibrous dysplasia emphasizing on its etiology, pathophysiology, radiographic features, histopathology along with the malignant transformation and its differential diagnosis.

Key Words: - Fibrous dysplasia, genetic, somatic, Gsα subunit, cAMP.

Introduction

Fibrous dysplasia (FD) is a benign intramedullary fibro-osseous lesion originally described by Lichtenstein in 1938 and by Lichtenstein and Jaffe in 1942.[1] This is a benign dysplastic process of altered osteogenesis that may occur within a single bone (monostotic) or multiple bones (polyostotic),[2] and is best understood as a dysplastic anomaly of bone forming mesenchymal tissue.[3] It is a sporadic benign skeletal disorder that can affect one bone (monostotic form), or multiple bones (polyostotic form) which forms a part of the McCune Albright syndrome (MAS) or of the Jaffe Lichtenstein syndrome.[4] The hallmark of the disease is a solitary focal, or generalized multifocal inability of bone forming tissue to produce mature lamellar bone, and an arrest at the level of woven bone.[3]

History

Fibrous dysplasia of bone (FD) is a sporadic, uncommon, fibro-osseous skeletal disorder with a broad severity spectrum. Initially, it was identified as a distinct entity in association with skin spots and hyperfunctioning endocrinopathies by Donovan McCune and Fuller Albright. Albright described it as Osteitis fibrosa disseminata as it reflects the similarity to the skeletal disease of hyperparathyroidism, Osteitis fibrosa cystica.[5]

Fibrous dysplasia was reliably reported one century ago by Von Recklinghausen when he described the patients with a pathologic condition of the bone characterized by deformity and fibrotic changes that he termed as Osteitis fibrosa generalisata.[6] The disease was labeled polyostotic fibrous dysplasia (PFD) by Lichtenstein in 1938, and it was Lichtenstein and Jaffe who initially described the spectrum of the clinical, radiological and histological features. Additionally, they introduced the idea that FD results from the ‘‘perverted activity of the specific bone-forming mesenchyme.’’[5]

Etiology and Pathophysiology

The exact cause of fibrous dysplasia is not known. It is classified by W.H.O. as developmental in origin. The condition is not thought to be hereditary.[7]The etiology has been linked with a mutation in the Gsα gene, located at chromosome 20q13.2-13.3. The specific location of the mutation is at position 201, which is usually occupied by arginine (R201) and is replaced by either a cysteine (R201C) or a histidine (R201H).[1]

1. The GNAS1 (guanine nucleotide binding protein, α-stimulating activity polypeptide) gene encodes a G-protein that stimulates the production of cAMP. The mutation results in the continuous activation of the G-protein leading to overproduction of cAMP in affected tissues.[7]Hyperfunction of affected endocrine organs, frequently giving rise to precocious puberty, hyperthyroidism, growth hormone and overproduction of cortisol.
2. There is increased proliferation of melanocytes resulting in large cafè-au-lait spots.
3. cAMP is thought to have effect on the differentiation of osteoblasts leading to fibrous dysplasia.[7]

In 2012, Koutlas et al limited the evaluation to the expression of TWSG1 (Twisted Gastrulation) as an example of a BMP-binding protein because of its known role in regulating BMP activity during mandibular morphogenesis and post natal bone remodeling.[8]

Classification[9]

1. Monostotic Fibrous Dysplasia
2. Polyostotic Fibrous Dysplasia
    a. Jaffe's type.
    b. Albright syndrome.
3. Craniofacial form
4. Cherubism

Monostotic Fibrous Dysplasia

This term is applied to those forms of the disease in which only one bone is affected. It occurs in about 70 - 80 % of the cases of FD. The clinical term "*leontiasis ossea*" has been applied to cases of Monostotic FD which affects maxilla or facial bones and give the patient a leonine appearance.[7]

Etiology: The etiology is unknown. Earlier, it was suggested that it is due to aberrant activity in the bone forming mesenchymal tissue. There is also clinical evidence which indicates that local infections or trauma to the bone results in this peculiar reparative reaction by bone. However, some cases have been reported to be congenital that represent an autosomal recessive disorder.[10]

Clinical features: Monostotic fibrous dysplasia occurs with equal predilection for males and females, with a mild predominance for females. It is more common in children and young adults than in older persons.[7] It occurs at the age of 20-30 years,[11] with the mean age of occurrence is 27-34 years.[7]

Ribs and craniofacial bones are most commonly affected. Other bones affected include clavicle, tibia, femur etc.[11] Maxillary involvement is more common than mandibular. Both maxillary and mandibular lesions occur as bony hard swellings that expand the jaws and are not tender on palpation.[12] The overlying mucosa is almost invariably intact over the lesion. There may be some mal-alignment, tipping or displacement of the teeth due to the progressive expansile nature of the lesion.[7]

Radiographic features: The radiographic appearance of FD varies with the stage of development and amount of bony matrix within the lesion.[13]There are 3 basic patterns which may be seen:

- In one type, the lesion is generally a rather small unilocular radiolucency.
- In second type, the pattern is similar except that increased trabeculation renders the lesion more opaque and typically mottled in appearance.[7]
- Third type is a quite opaque type with many delicate trabeculae giving a ground glass or peau d' orange appearance to the lesion. It is not well circumscribed and blends into the adjacent normal bone.[10]

In all the three types, cortical bone becomes thinned because of the expansile nature of the growth but this bony plate is seldom perforated.[14] Waters sinus views of maxillary lesions will frequently show a radiodense area that largely obliterates the maxillary sinus and involves the zygoma and lower rin of orbit.[13,15]

Treatment: Active treatment is not necessary but some trimming of the bone may be required for cosmetics.[16]Radiation therapy is contraindicated, as it carries the risk of post irradiation bone sarcoma. Some examples of spontaneous sarcomatous changes have also been reported.[14]

Polyostotic Fibrous Dysplasia

Weil in 1922 recognized the case of polyostotic FD associated with skin lesions and endocrine disturbance. The condition has been specifically described by Albright, from where the apparent syndrome derives its eponym. 'Polyostotic' have been applied to those lesions in which more than one bone is affected. There are two apparently separate types of Polyostotic FD (PFD) which include Jaffe's type and Albright's syndrome.[4] In addition to these, the occasional occurrence of multiple intramuscular soft tissue myxomas as extra-skeletal manifestations of PFD has also been noted.[17]

Etiology: A sporadic mutation occurs in a single cell (bright spot) at some point early in the development. If this occurs at the inner cell mass stage (embryonic stem cell stage), tissue from all the three germ layers will be affected. As the cells derived from this mutated clone are dispersed throughout the organism, the final phenophyte emerges i.e. McCune Albright Syndrome.[9]

Clinical features: PFD occurs in about 20-30 % cases of FD. It most commonly occurs in childhood. Median age of onset of symptoms is 8-10 years, with the most cases occurring before the age of ten. The disease has occurred in women with a male: female ratio of 1:3.[11] Because of the severe bone changes, spontaneous fractures are a common complication of the disease. The curvature of the femoral neck and proximal shaft of the femur markedly increase causing a *'shepherd crook deformity'*, which is a characteristic sign of the disease.

Two apparently separate types of Polyostotic FD are described as -

1. Jaffe's type - FD involving a variable number of bones, accompanied by pigmented lesions of the skin or "*cafe-au-lait*" spots of thin light brown color. It is mild and non- progressive form. This type occurs in about 50% of the cases.
2. Albright's syndrome – Fuller Albright first described this syndrome in 1937. McCune Albright syndrome is defined as the association of polyostotic fibrous dysplasia, precocious puberty, cafè-au-lait spots, and other endocrinopathies due to hyperactivity of various endocrine glands.

Cutaneous pigmentation in PFD is ipsilateral to the side of bony lesions, a feature that differentiates pigmentation of this disease from that in neurofibromatosis.[7]The location and shape of the spots usually can help to distinguish between them. The spots in McCune Albright Syndrome have jagged borders (coast of Maine), whereas those in neurofibromatosis are smooth (coast of Calfornia).[9]

Mazabraud's syndrome is a rare disease caused due to association of FD and intramuscular myxoma that occur in the same anatomical region. Patients with soft tissue myxomas should be thoroughly examined for FD as greater risk of sarcomatous transformation in FD with Mazabraud's syndrome has been reported. Malignant transformation of fibrous dysplasia may include:

- OsteosarcoMcCune Albright Syndrome (most common),
- ChondrosarcoMcCune Albright Syndrome,
- FibrosarcoMcCune Albright Syndrome
- LiposarcoMcCune Albright Syndrome.

These malignancies occur most commonly in the setting of therapeutic irradiation exposure. Females may have a greater risk for breast cancer, probably due to their prolonged exposure to elevated estrogen levels. The underlying GS alpha gene mutation may also play a role in this.[7]

Oral manifestations: The oral manifestations of PFD are related to severe disturbance of bony tissue. One third of

the polyostotic patients have lesions in the mandible. There may be expansion and deformity of the jaws with the disturbed eruption pattern of the teeth because of loss of support of the developing teeth. The endocrine disturbance also, may alter the time of eruption of the teeth.[7]

Radiographic features: A radiological regime for polyostotic FD is scintigrahy complimented by computed tomography (CT), which is useful in confirming the diagnosis and assessing the extent of FD in the craniofacial skeleton.[18]The lesions include a radiolucent lesion in the diaphysis or metaphysis with endosteal scalloping. It may be present with or without cortical expansion. The radiolucent lesion has a thick sclerotic border and is called '*rind sign*'.[7] The clinical basic behind the roentgenographic changes are due to rarefaction of the medullary portion of the bone. Irregular bony trabeculature along with variations in cortical thickness.[19]

1. **Psuedo type**: Orange or Ground Glass appearance: alternating areas of granular density and lucency, giving a radiographic appearance resembling the rind of an orange, most common type – 40% of cases.
2. **Whorled plaque like**: The matrix of the well circumscribed expansive lesion was composed of plaques of amorphous material of radio density intermediate between bone and soft tissue which, on close examination, are seen to be arranged in a whorled, onion peel, or whirl pool pattern and is seen in 20% of cases
3. **Diffuse sclerotic type**: This type presented as a homogeneously dense area of involvement, with no clear of lesion and normal bone. These lesions have varied shapes and sizes and are usually extensively seen in 16% of cases.
4. **Cyst like**: on close examination faint ground glass matrix due to mineralization in fibrous dysplasia.
5. **Pagetoid type**: In this radiologic type of lesion the affected area of bone was markedly expanded and showed alternating areas of radiopacity and radiolucency, such as seen in Paget's disease of bone.
6. **Chalky type**: The matrix consisted of amorphous radiodense material with sharply, marginated lesions containing whorled plaque like densities – rare type.

Craniofacial Fibrous Dysplasia

The craniofacial region may be affected by a form of fibrous dysplasia that is not restricted to a single bone, but may be confined to a single anatomical site. This type of fibrous dysplasia does not meet the precise criteria for the monostotic and polyostotic forms and has been termed as craniofacial fibrous dysplasia.[20]

Clinical features: This pattern of the disease occurs in 10-25% of patients with monostotic form and in 50% with the polyostotic form. It also occurs in an isolated craniofacial form. In the isolated variety, no extracranial lesions are present.[7]It typically presents at around 10 years of age and then progress throughout adolescence.[21]
Site of involvement most commonly include the frontal, sphenoid, maxillary and ethmoidal bones. The occipital and temporal bones are less commonly affected.[7]The clinical presentation depends on the site, duration, extent and nature of the lesion. It ranges from a mild local swelling with little or no pain to a gross deformity.[21]Hypertelorism, cranial asymmetry, facial deformity, visual impairment, exopthalmos, and blindness may occur because of the involvement of orbital and periorbital bones.[7]

Radiographic features: Craniofacial sites of involvement are often more radiodense, owing to the higher proportions of bone, which is frequently slightly more mature than in appendicular lesions.[3]The margins of extra-gnathic FD appear well defined whereas they are poorly-defined in the jaws. An objective definition of marginal definition has been described by Slootweg and Muller. A lesion with a zone of transition less than 1 mm can be considered to be well-defined. This can be quickly and cheaply appreciated on plain film radiographs.[18]

Treatment: Mere presence of fibrous dysplasia of craniofacial region is not in itself an indication for treatment. Many small solitary lesions will remain static and asymptomatic for long periods. In 1990, Chen and Noordhoff developed a treatment protocol based on the location of the lesions in a series of 28 patients with craniofacial fibrous dysplasia.[20]

Laboratory Findings of Fibrous Dysplasia

Serum alkaline phosphatase (ALP) is occasionally elevated, but calcium, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels in most cases of FD are normal. Persons with extensive polyostotic FD may have hypophosphatemia, hyperphosphaturia and osteomalacia.[17] Premature secretion of pituitary follicle stimulating hormone is found. There may be an elevated basal metabolic rate.[7]

Macroscopic Features of Fibrous Dysplasia

Surgical exposure of fibrous dysplasia reveals a yellowish white tissue with a distinctive gritty feel, imparted by the small trabeculae of bone scattered throughout the lesion. The lesion can be easily peeled away from the encircling shell of reactive bone by blunt dissection, and lesions rarely, if ever, penetrate the reactive shell and extend into soft tissue.[1]

Histological Features of Fibrous Dysplasia

The microscopic appearances are those of a hypercellular and cytologically uniform fibrous stroma within which delicate and irregularly shaped trabeculae of woven bone are deposited. The configuration of these bony trabeculae are often referred to as resembling Chinese characters (Figure 1).[6]

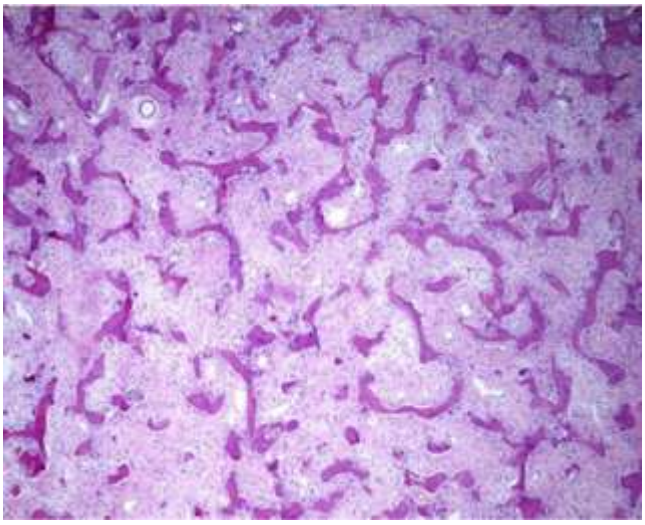

Figure 1: - Cellular stroma with "Chinese character" delicate bony trabeculae of fibrous dysplasia. (H&E, ×40).

It is composed of spindle cells with a whorled or storiform arrangement with interspersed trabeculae of immature woven bone, devoid of rimming osteoblasts or osteoclasts.[3] The trabeculae consist of immature, nonlamellar (woven) bone without osteoid rims or osteoblasts (Figure 2).[17]

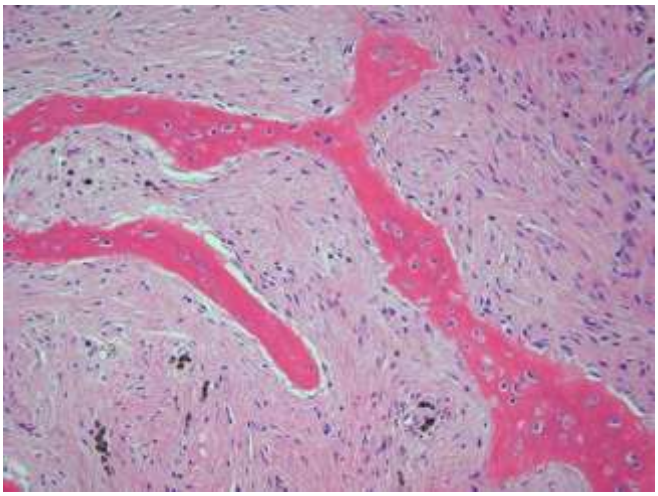

Figure 2: - The mesenchymal stroma surrounding the dysplastic trabeculae is relatively hypocellular. There is a lack of osteoblastic rimming surrounding the dysplastic trabeculae. Both features are characteristic of fibrous dysplasia (H&E, ×200).

Areas of moth eaten spicules devoid of osteoblastic activity can also be seen in some lesions which represent a *burned out phase*. The presence of lamellar bone does not confirm a diagnosis of FD. Other morphological forms of calcification, including small rounded bodies (cementum bodies or globular calcifications) and minute basophilic and laminated calcification may be seen in FD. Giant cells may also be seen in some cases.[7]

The most helpful clues for diagnosis of FD are the radiological appearances and the ill-defined nature. A biopsy that includes the interface between the abnormal and normal bone is therefore helpful as merger of the lesional and non-lesional bone can be seen.[16]

Secondary changes in fibrous dysplasia may alter the typical microscopic appearance and make it difficult to diagnose. Hemorrhage and secondary fibrohistiocytic reaction may be prominent focally, and a diffuse infiltrate of foamy, lipid-filled histiocytes may obscure the characteristic microscopic features of the lesion. Such lesions may be incorrectly designated as xanthomas or fibroxanthomas of bone. Intralesional hemorrhage in fibrous dysplasia can provoke a conspicuous giant cell reaction, which may lead to confusion with giant cell tumor. Secondary aneurysmal bone cysts may arise as a later phenomenon in these areas of intralesional bleeding. Myxoid change in the stromal tissue can be focal or very extensive in some lesions.[3]

Malignant Transformation

Malignancies in fibrous dysplasia are rare. They can occur in monostotic and polyostotic fibrous dysplasia and their frequency ranges from 0.5% (in monostotic disease) to 4% in Albright's syndrome. The first documented case was reported by Coley and Stewart in 1945. The most common of the malignancies was osteosarcoma, followed by fibrosarcoma and chondrosarcoma. The possibility of sarcomatous change in fibrous dysplasia without prior irradiation seems well established.[22]

Most malignant neoplasms develop in patients who previously have undergone radiation therapy to the affected area; however, de novo sarcomatous transformation has been identified. Overall, there is a 0.4% to 0.5% incidence of secondary malignant neoplasms in FD, with males and patients with polyostotic disease experiencing a greater risk. Osteosarcoma makes up more than half of all the malignant diagnoses, followed by fibrosarcoma and chondrosarcoma. Secondary angiosarcomas and a malignant fibrous histiocytoma also have been reported.[13]

Differential Diagnosis

The primary differential consideration for FD of the jaws is Ossifying fibroma (OF). The well circumscribed OF as compared with the diffuse FD often serves as the differentiating factor. Other differentiating features are (Table 1).

McCune Albright Syndrome is most commonly confused with neurofibromatosis, usually when a child presents with a large cafè-au-lait spot. The location and shape of the spots usually can help to distinguish between them. The spots in McCune Albright Syndrome have jagged borders (coast of Maine), whereas those in neurofibromatosis are smooth (coast of Calfornia). In MAS, the skeletal disease (PFD) almost always involves one or both proximal femurs and/or the skull base, as well as other locations. Skeletal involvement in NF is uncommon and usually involves the diaphyses of the long bones, especially the tibiae, often leading to pseudoarthrosis.[9]

Fibrous Dysplasia	Ossifying Fibroma
1st and 2nd decade	3rd and 4th decade
Maxilla > Mandible	Mandible > Maxilla
Diffuse Opacity	Circumscribed
Self-Limited	Continuous Growth
One or more bones	One Bone
Vascular Matrix	Cellular Fibrous Matrix
Woven bone trabecullae	Bony islands and trabeculae
Hormone Related	Not hormone related
Recontouring for cosmetics	Excision
Osteocalcin immunohistochemistry demonstrate abundant osteocalcin.[23]	Osteocalcin immunohistochemistry demonstrate deficiency of osteocalcin.[23]
Lesional bone merges imperceptibly with the adjacent cancellous bone or with underlying cortex.[20]	The margin of the lesion shows an area of fibrous tissue separating lesional bone from the overlying cortex.[20]
Lesion has monotonous cellularity and the fine pattern of bony trabeculae is repeated throughout the lesion.[20]	Pattern of mineralized varies from place to place within the lesion.[20]

Table 1:- Differentiating features between Fibrous Dysplasia and Ossifying Fibroma

Treatment

There is no cure for FD, and the existing guidelines for treatment are not universally accepted. Spontaneous resolution of FD does not occur. Surgical intervention is required when important structures are in danger of compression.[4]

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