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FIBROUS DYSPLASIA

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Abstract: Fibrous dysplasia (FD) is a benign intramedullary fibro- osseous lesion. FD is a bone developmental anomaly characterized by replacement of normal bone and marrow bone by fibrous tissue. It involves any of the bones as single lesion (monostotic) or in multiple bone lesions (polyostotic) or all of the skeletal system (panostotic). Long bones are most involved, which mostly identified incidentally and clinically appears asymptomatic. Clinical, radiographical and histopathological findings will help in confirming the lesion. There are many treatments option available, but still management of FD remains challenging.

IndexTerms: Fibrous dysplasia

I. Introduction:

Fibro-osseous lesions are a diverse group of processes that characterized by replacement of normal bone by fibrous tissue containing a newly formed mineralized product. The commonly included fibro-osseous lesions are fibrous dysplasia (FD), cemento-osseous dysplasia and ossifying fibroma. FD is a developmental tumor like a condition characterized by replacement of normal bone by an excessive proliferation of cellular fibrous connective tissue intermixed with irregular trabeculae.[1]

II. *Etiology*

Fibrous dysplasia is not hereditary in nature and it caused by mutation in the GNAS1 (guanine nucleotide binding protein, alpha stimulating activity polypeptide) gene (20q13.2) and this gene encodes a G-protein which results in overproduction of cAMP in the affected tissues. Furthermore, there is increased the proliferation of melanocytes thus results in cafe-au-lait spots. The cAMP have effect on the differentiation of osteoblasts. [2]

III. Epidemiology

Incidence has been estimated at 1 in 5,000 to 10,000. [3] Most commonly fibrous dysplasia is first diagnosed in children or young adults. There is not a gender predilection. Overall, fibrous dysplasia constitutes 5% of all benign bone lesions. [4] The monostotic form is the most frequent, accounting for 75% to 80% of fibrous dysplasia cases. [5]

IV. Histopathology

Fibrous dysplasia has histologic elements of immature collagen and immature bone trabeculae forming a fibro cellular matrix. Trabeculae are not rimmed by osteoblasts secondary to osteoblast maturation arrest and histologic transition from normal to abnormal bone is usually abrupt. [6]

V. Clinical Features

Fibrous dysplasia has three clinical patterns namely monostotic, polyostotic, craniofacial form. About 3% of lesions associated are with skin pigmentation and hyperfunctioning endocrine disorders known as the McCune–Albright syndrome. [7] FD in infancy is rare and heralds' severe widespread disease with multiorgan involvement. Pain, fracture and deformity are common clinical features. The pain complaint is less in children and more in adults. The skull base and proximal metaphysic of femora are two sites most commonly involved. In the skull FD involves skull bases and facial bones. In childhood FD presents as facial asymmetry or a bump, but symmetric expansion of malar prominences and/or frontal bosses may be seen. Due to abnormal growth and deformity of craniofacial bones may result in encroachment on cranial nerves. [8] Female patients experience increased pain level during pregnancy and during the menstrual cycle because of estrogen receptors found in FD. [9]

VI. Pathophysiology

Bianco et al. demonstrated that FD is a disease of bone marrow stromal cells (BMSC). [10]

The BMSCs form structural framework upon which hematopoiesis occurs in the bone marrow and a subset of BMSC are multipotent stem cells capable of differentiating into multiple cells including osteoblasts, osteocytes, chondrocytes, bone marrow adipocytes and other cells. [11]

In FD BMSC differentiate along osteogenic lineage, but differentiation is arrested and instead undergo proliferation giving rise to fibro-osseous masses of tissue. [12]

Arrest in differentiation is by mutation in GNAs gene. GNAs codes alpha subunit of signaling G-protein. G-protein is central in cell originating pathway leads to the generation of intracellular second messenger, cAMP/protein kinase A signaling. All mutation in Gs alpha identified in association with FD is the 201Arg position. In > 95% cases arginine is replaced by either cysteine or histidine (R201C or R201H). This result in inhibition of intrinsic GTPase activity of Gs alpha protein and it is this aspect that leads to constitutive, ligand-independent generation of intercellular cAMP. [11,12]

Gs alpha mutation increased intracellular cAMP and interleukin-6 secretion. Interleukin-6 is responsible for increased numbers of osteoclasts and bone resorption seen in FD. Gene amplification techniques such as polymerase chain reaction is now possible to test for genetic mutation in peripheral blood samples. [13]

VII. Diagnosis

Imaging plays a chief role in the diagnosis and evaluation of the disease extent. Radiography should be utilized first in an evaluation. Advanced imaging such as computerized tomography (CT) and magnetic resonance imaging (MRI) can exclude other bone lesions; evaluate for soft tissue complications occurring from fractures, craniofacial neurovascular complications; and assess lesions for rare malignant transformation. [14]

CT and MRI also have a role in the evaluation of adrenal hyperplasia, thyroid nodules, and pituitary tumors. [15,16] Classically, bone lesions have an internal ground glass matrix on radiographs and CT, but appearance can be varied with lytic and/or sclerotic components, possible bone expansion, and cortical thinning. [17]

Bowing deformities (including the femoral shepherd's crook deformity), discrepant limb length, and short stature secondary to premature fusion of growth plates can be characterized with imaging. [18] Bone scan demonstrating increased Technetium-99m radiotracer uptake may have a role in polyostotic cases to assess disease extent. [19]

Finally, biopsy with histologic evaluation may be necessary in select cases when imaging features mimic malignant lesions. [20]

The radionuclide bone scintigraphy is useful to demonstrate the extent of disease. Actively formed lesions in adolescents have greatly increased isotope update that corresponds closely to radiographic extent of the lesion. Some characteristic feature is bar-shaped pattern, whole-bone involvement and close match between the size of the lesion on radiograph and the size of the area of uptake. The extent of the lesion is visible clearly on computed tomography, and cortical boundary is depicted more clearly than radiograph. The thickness of cortex, endosteal scalloping and periosteal new bone reaction and homogeneity of the poorly mineralized lesional tissue are well demonstrated.

Delicate trabeculae of immature bone with no osteoblastic rimming enmeshed within a bland fibrous stroma of dysplastic spindle-shaped cells without any cellular features of malignancy. Variable number of immatures, nonstress oriented, disconnected dysplastic trabeculae floating in a sea of immature mesenchymal cells that have little or no collagen about them. [21]

VIII. Complications

Usually, fibrous dysplasia is monostotic and asymptomatic. In the cases of severe bone deformity, bowing may result in musculoskeletal dysfunction or accelerate development of osteoarthritis. [22] Spine lesions may predispose to scoliosis and subsequent functional limitations. [23] Craniofacial cases may have associated cranial nerve deficits including vision and hearing loss. [24,25] Malignant transformation to sarcoma is rare but can occur with a prior history of radiation therapy. [26]

IX. Malignant Transformation: -

Malinant transformation in FD occurs very rarely, about 0.4–4%.[27] Change is noticed. The malignant transformation rate is unknown, but it is likely to be not >1%. Cancer is more likely to occur in polyostotic disease, and most common histological types were osteosarcoma, fibrosarcoma and chondrosarcoma. There are also reports suggesting that the malignant transformation may be more common in Mazabraud's syndrome (FD in association with intramuscular myxomas). [28]

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X. Consultations

- Pediatric orthopedics
- Orthopedics
- Genetics

XI. Deterrence and Patient Education

Patient education regarding the risk of fracture is important. [29] In cases of craniofacial disease, patients should be coached to monitor for evolving cranial nerve deficits including vision and hearing loss. In the setting of McCune-Albright syndrome, parents and the patient should be educated on the various manifestations of the syndrome and genetic counseling should be performed. [30]

Routine visits to an endocrinologist should be incorporated to monitor for symptoms of endocrine dysfunction. [30]

XII. Enhancing Healthcare Team Outcomes

Managing fibrous dysplasia involves an interprofessional team approach, primarily with

pediatrics/primary care, orthopedics, and radiology. Genetics and endocrinology should be added for cases of McCune-Albright syndrome. Craniofacial involvement should prompt neurology, ophthalmology, audiology, and possible neurosurgery consultation. [31]

Additional support from physical therapy and psychiatry in cases of disability or deformity may be warranted. [31]

XIII. Treatment

Bisphosphonates were postulated to inhibit osteoclastic resorption. The findings in various studies showed that high dose intravenous pamidronate decreases pain and the markers of bone metabolism. [31]

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