

## Fibrous dysplasia- A review

Omar. A. Rageh

B.D.S, Dept. of Oral and Maxillofacial Pathology, Faculty of Oral & Dental Medicine - Cairo University

**\*Corresponding Author:**

Email: omar.ra015@gmail.com

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### Abstract

**Objective:** To collect and conclude a literature review on the diagnosis and management of facial fibrous dysplasia in head and neck region.

**Materials and Methods:** The review was searched and collected from many sources about fibrous dysplasia, to discuss all revealing to diseases as clinical features, radiographic image, cytogenetic, histopathology, and immunohistochemistry as master keys and parameters for perfect diagnosis of diseases. The database of literature was collected through the search of PubMed, Cochrane Library, and scholar Google databases. The keywords used for the search were fibrous dysplasia, physiopathology, radiography, histopathology, cytogenetic, and immunohistochemistry. A manual search to many of the reference lists of the identified articles and the authors' article files and recent reviews was made to find additional publications. Those studies that showed new features about fibrous dysplasia were included in this review.

**Results:** In total 20 literature sources were searched and reviewed. Studies that described new features about fibrous dysplasia and illustrated new or advanced modules can conduct to state the diagnosis.

**Conclusion:** We summarized in this study the keys of diagnosis from clinical criteria to cytogenetic in one paper to make fully covered idea about diseases to facilitate the therapy targeting to diseases.

**Keywords:** Fibrous Dysplasia, Physiopathology, Radiography, Histopathology, Cytogenetics, and Immunohistochemistry.

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### Introduction

Fibrous dysplasia is a formative tumor-like condition that is portrayed by substitution of ordinary bone by an excessive expansion of fibrous connective tissue intermixed with sporadic hard trabeculae.<sup>(2)</sup>

It is a hereditary, non-acquired infection that occurs due to transformation of the Gs alpha subunit of protein coupled receptor leading to up-direction of cAMP that prompts to abandon activation of osteoblasts with stimulating creation of irregular bone in a prominent connective tissue stroma.<sup>(3)</sup>

Fibrous dysplasia is a benign intramedullary fibro-bony lesion initially depicted by Lichtenstein in 1938 and by Lichtenstein and Jaffe in 1942.<sup>(4)</sup>

The genuine frequency and commonness of fibrous dysplasia are hard to evaluate; however, the lesions are not uncommon; they are accounted for to speak to roughly 5% to 7% of benign bone tumors.<sup>(5)</sup>

Fibrous dysplasia can display in one bone (monostotic) or numerous bones (polyostotic) and can be connected with other conditions, for example, café-au-lait skin spots, as well as endocrine disorders (precocious puberty, renal phosphate wasting, hyperthyroidism, and additionally development hormone abundance).<sup>(4)</sup>

The lesions of fibrous dysplasia occur during bone growth and development and have a variable normal advancement. Clinical presentation may happen at any age, with the larger part of lesions being recognized by the age of thirty years. The lesions have no gender orientation preference. Most frequency sites are long bones, ribs, craniofacial bones, and the pelvis.<sup>(6)</sup>

### Etiology, genetics, and molecular Biology

The basic reason for FD is not completely caught on. Scientists trust that the lesions are created by a mutation in a gene called GNAS1 (guanine nucleotide-binding protein, a stimulating activity polypeptide I). This quality change happens after preparation of the developing life (somatic mutation) along these lines not acquired nor will influence people to pass the transformation on to their kids.<sup>(6)</sup>

Affected people have a few cells with normal gene copy and a few cells with mutant gene copy. The difference in FD manifestation is occurring due to the ratio of healthy cells to abnormal cells. The GNAS1 gene is situated on the long arm (q) of chromosome 20 (20q13.2) Chromosome 6.<sup>(7)</sup>

The normal function of the GNAS gene is given guidelines to making one part, the stimulatory alpha subunit, of a protein complex called a guanine nucleotide-restricting protein (G protein). Every G protein is made out of three proteins called the alpha, beta, and gamma subunits.<sup>(8)</sup>

The G protein made with the subunit created from the GNAS gene induces the activity of a chemical enzyme called adenylate cyclase. This protein is included in controlling the generation of a few hormones that manage the activity of endocrine glands, for example, the thyroid, pituitary organ, ovaries and testicles (gonads), and adrenal glands.<sup>(9)</sup>

Adenylate cyclase is additionally accepted to assume a key part in signaling pathways that control the development of bone (osteogenesis). Along these lines,

the enzyme keeps the body from creating bone tissue in the wrong place (ectopic bone).<sup>(10)</sup>

Molecular mechanism involved in fibrous dysplasia. The transformations in GNAS result in progressive intracellular cAMP levels that induce the activation to many genes whose promoter contains a cAMP-responsive component (CRE). This pathway prompts to generation abnormal bone matrix proteins and to progressive c-fos expression, leading to abnormal recruitment and function of osteoblastic cells, and to abnormal bone matrix production.<sup>(11)</sup>

The cAMP overproduction prompted by the transformation lead to prompts to expanded the creation of interleukin-6 which thusly stimulate osteoclastic bone resorption. These molecular systems prompted by the Gsa transformations result in the development of dysplastic bone lesions.<sup>(1)</sup>

### Clinical and radiographic features

The common history of fibrous dysplasia is exceedingly factor and is dictated by the type of fibrous dysplasia with which the lesions exhibit. The monostotic presentation is more incessant, and lesions develop in the extent to skeletal development. The polyostotic form is less frequent.<sup>(5)</sup>

### Monostotic fibrous dysplasia of the jaws

At the point when the restricted to a solitary bone, it is named monostotic fibrous dysplasia. This lesion represents around 80% to 85% of all cases, with the jaws being among the most usually influenced location. Despite the fact that the postnatal mutation of GNAS1 may happen during infancy, adolescence, or adulthood, most cases of monostotic fibrous dysplasia are analyzed detected the second decade of life. Male and females are influenced with about equivalent recurrence. painless swelling of the influenced zone is the most widely recognized criteria (Fig. 1).<sup>(12)</sup>

Despite mandibular lesions are absolute monostotic, maxillary lesions frequently include nearby bones (e.g., zygoma, sphenoid, occipital) and are not entirely monostotic. The assignment of craniofacial fibrous dysplasia is suitable for these lesions. Teeth required in the lesions more often than not remain firm yet might be dislocated by the hard mass.<sup>(13)</sup>

The typical radiographic element is a fine "ground glass" opacification that outcomes from the superimposition of a myriad of inadequately calcified bone trabeculae arranged in a scattered pattern. Radiographically, the lesions of fibrous dysplasia are not all around delineated. The edges of lesions mix vaguely into the neighboring typical bone so that the margin points of the lesions might be hard to characterize (Fig. 2&3). In the prior stages, the lesions might be to a great extent radiolucent or mottled.<sup>(14)</sup>

Involvement of the mandible is occurring due to the expansion of lower border of the mandible in addition to ulging of buccal and lingual plates. Displacement of the

inferior alveolar canal is rare. Periapical radiographs of the included dentition regularly exhibit narrowing of the periodontal ligament space with characterizing defined lamina dura that mixes with the abnormal bone pattern.<sup>(15)</sup>

At the point when the maxilla is included, the lesional tissue dislocated the sinus floor superiorly and generally obliterates the maxillary sinus. Imaging concentrates on in cases with maxillary inclusion may indicate expanded thickness of the base of the skull including the occiput, sphenoid, roof of the orbit and frontal bones (Fig. 4). This is said to be the most hallmark radiographic element of fibrous dysplasia of the skull.<sup>(16)</sup>



**Fig. 1: Fibrous dysplasia. Expansile mass of the left maxilla in a 45-year-old woman**

This lesion was known to have been present for at least 20 years.



**Fig. 2: Fibrous dysplasia. Panoramic radiograph of the patient shown in Fig. 14-32**

A diffuse "ground-glass" radiopacity is evident. (Courtesy of Dr. Richard Brock.)



**Fig. 3: Fibrous dysplasia. Occlusal radiograph showing localized expansion of the mandible and the “ground-glass” radiographic appearance. The margins of the lesion are not well-defined and blend into the adjacent bone. (From Waldron CA, Giansanti JS: Benign fibro-osseous lesions of the jaws: a clinical radiologic- histologic review of 65 cases. I. Fibrous dysplasia of the jaws, Oral Surg Oral Med Oral Pathol 35:190-201, 1973)**



**Fig. 4: Fibrous dysplasia. Computed tomography (CT) image showing the extensive involvement of the maxilla and skull**

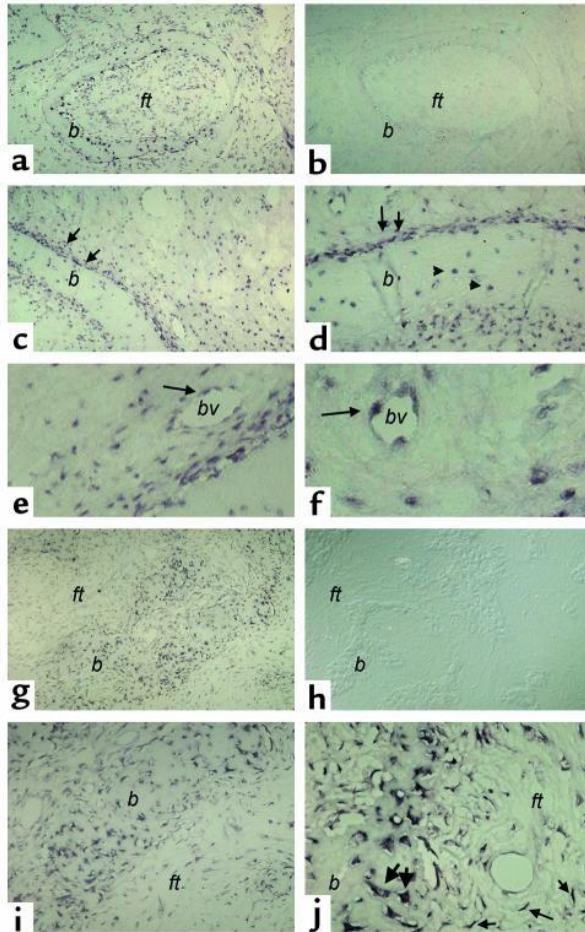
Fibrous dysplasia Inclusion of at least two bones is named polyostotic fibrous dysplasia, a generally rare condition. The account of included bones shifts from a few to 75% of the whole skeleton. At the point when seen with cafe au lait (coffee with milk) pigmentation, the condition is named Jaffe-Lichtenstein syndrome. Polyostotic Fibrous dysplasia likewise might be joined with cafe au lait pigmentation and different endocrinopathies, for example, sexual precocity, pituitary adenoma, or hyperthyroidism. This condition is known as the McCune-Albright syndrome.<sup>(15)</sup>

#### Laboratory investigation

This examination should be possible with any number of tests that measure bone metabolism and incorporate the bone development markers alkaline phosphatase, osteocalcin, bone-specific alkaline phosphatase, and etc., and serum and urine markers of bone resorption N-telopeptide of collagen, pyridinium crosslinks, and deoxypyridinoline crosslinks, and so on.<sup>(17)</sup>

#### Cytogenetic

Identified the Gs mutation in DNA by using the PCR in which the Purified gDNA (200 500 ng) was amplified.<sup>(7)</sup> In situ hybridization. In situ hybridization analysis: of FGF-23 expression in FD of bone. Biopsy specimens of the FD-involved iliac crest (Fig. 5).<sup>(18)</sup>

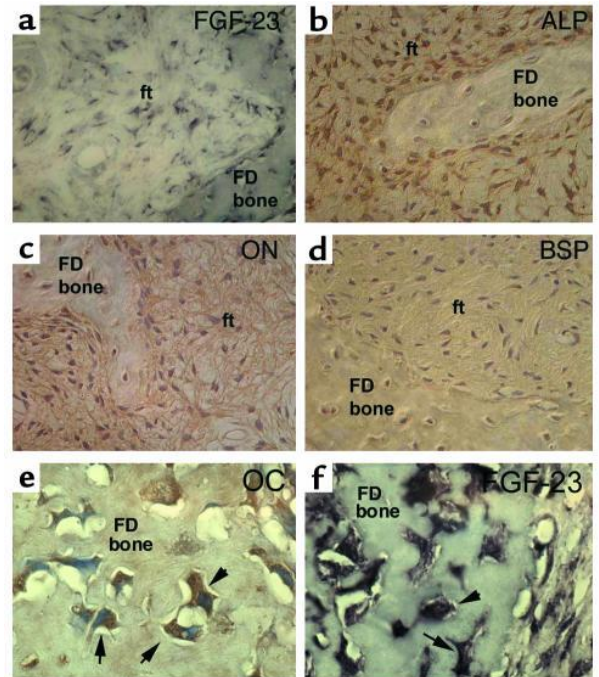


**Fig. 5:** In situ hybridization examination of FGF-23 expression in FD of bone. Biopsy examples of the FD-included iliac peak. Serial segments from two FD phosphaturia patients were hybridized with antisense and sense RNA tests for FGF-23 mRNA. (a–f) Patient 1. (a and b) Expression of FGF-23 is plainly watched both in the stringy part of the sore and in bone cells connected with anomalous bone trabeculae (a). No signals were seen in segments hybridized with the sense (control) test (b). (c and d) Strong articulation of FGF-23 mRNA is seen in the unusual bone cells connected with the surface of strange bone trabeculae (twofold bolts) and with individual osteocytes in that (sharpened stones) (d). (e and f) Expression of FGF-23 mRNA is likewise seen in cells (endothelial cells as well as pericytes) inside the dividers of microvessels in the FD tissue (single bolts). (g–i) Patient 2. Strong hybridization signal in abnormal bone cells (g, i, j; the thick arrows in j) and in fibroblastic cells in the fibrous connective tissue (thin arrows in j). No expression is showed in sections hybridized with the sense probe (h)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC182207/figure/F1/>

**Immunohistochemistry:**

Deparaffinized section was used for immunohistochemistry against bone metabolism markers such as FGF-23 soluble phosphatase, osteonectin, osteocalcin, and bone sialoprotein, generously gave by Larry W fig. 6.<sup>(19)</sup>



**Fig. 6:** Immunohistochemical characterization of FGF-23–producing cells in FD. Stromal cells in the fibrous tissue (ft) express FGF-23 mRNA (a), are most intensely positive for the early markers of osteogenic proliferation, ALP (b) and ON (c), but are negative for the markers of advanced osteogenic proliferation, BSP (d) and OC (not shown). Both ALP and ON immunostaining result in the decoration of a dense network of delicate cell processes of FD stromal cells. Mature osteogenic cells emerged as osteocytes in newly formed FD bone express the late marker of osteogenic differentiation, and OC (not shown) (e), and express FGF-23 mRNA (f).

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC182207/figure/F3/>

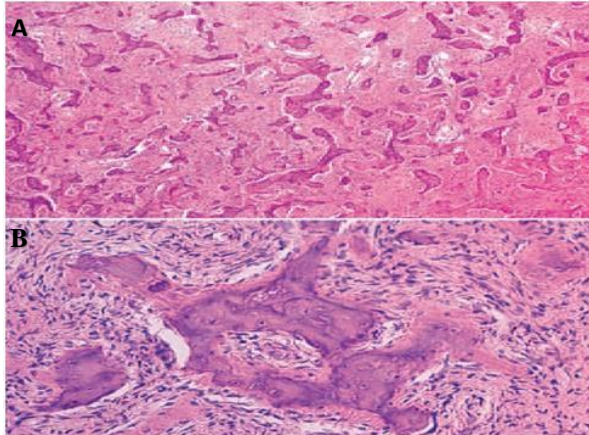
**Histopathology**

Microscopic criteria of fibrous dysplasia are different to other lesions such as ossifying fibroma and cemento-osseous dysplasia, it is typically revealed the monotonous pattern that occurring as a disorganized mixture of woven bone, lamellar bone, and spheroid particles.<sup>(20)</sup>

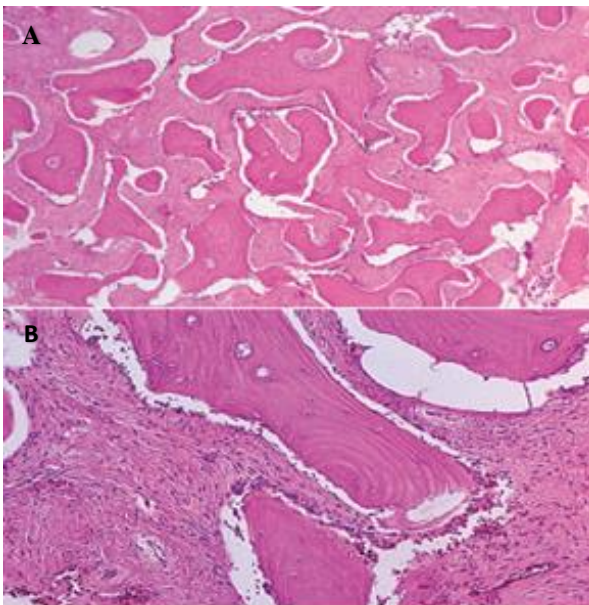
The typical microscopic findings of fibrous dysplasia revealed of abnormally shaped trabeculae of

immature (woven) bone in a cellular, loosely arranged fibrous stroma.<sup>(20)</sup>

The origin of bone trabeculae fibrous dysplasia by metaplasia in fibrous stroma, and are not surrounded by the mass of appositional so osteoblasts the rimming of osteoblast losing. Tiny calcified spherules may be seen rarely but are never numerous.<sup>(20)</sup>



**Fig. 7: Fibrous dysplasia. A, Irregularly shaped trabeculae of woven bone in a fibrous stroma. B, High magnification view showing peripheral osteoid without osteoblastic rimming**



**Fig. 8: Mature fibrous dysplasia. A., This long-standing lesion shows separate, broad trabeculae of bone within the fibrous connective tissue. B, Note the lamellar maturation of the bone**

### Conclusion

Fibrous dysplasia is a formative tumor-like condition that is portrayed by substitution of ordinary bone by an excessive expansion of fibrous connective tissue intermixed with sporadic hard trabeculae. Occurring as Monostotic Fibrous Dysplasia is limited to a single or Polyostotic Involvement of two or more bones

and associated with endocrinopathies. It is genetic lesions due to a postzygotic mutation in GNAS 1 gen. The combination of parameters and keys as biochemicals, physiopathology, radiography histopathology, cytogenetics, and immunohistochemistry utilized to perfect diagnosis of diseases.

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