# World Cancer Research Journal wcrj 2021; 8: e2045

# FIBROUS DYSPLASIA **OF THE MANDIBLE: DIFFERENTIAL DIAGNOSIS**



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**Abstract** – Fibrous dysplasia is one of the benign fibro-osseous lesions. It may have more common monostotic form (a single bone lesion) or polyostotic form (multiple bone lesions) which is less common and may be associated with McCune-Albright Syndrome (that is hyperfunctioning endocrinopathies and hyperpigmented skin lesions). Fibrous dysplasia is common in its monostotic form in the maxillofacial skeleton. What is essential in a dental practice of each clinicist is not only knowledge of classification of diseases of the jaws but also being able to differentiate them, make a proper diagnosis beforehand for a subsequent suitable treatment. The aim of this article is to outline the differences between FD, the most common lesions such as ossifying fibroma, but also other nosologic entities of this heterogeneous group of diseases.

KEYWORDS: Fibrous dysplasia, Benign fibro-osseous lesions, Emento-ossifying fibroma, Florid cemento-osseous dysplasia, Osteosarcoma.

#### INTRODUCTION

Fibrous dysplasia (FD) is a benign developmental disorder characterized by a dysplastic process of altered osteogenesis with subsequent substitution of normal bone by fibrous tissue that undergoes abnormal mineralization. Its pathogenesis is associated with a mutation in the alpha-subunit (Gs-alpha) of the G signaling coupling protein encoded by gene GNAS (Guanine Nucleotide binding protein Alpha Stimulating)<sup>1-4</sup>. Mutations occur in the form of replacement of the Cysteine or Histidine amino acids by Arginine in position 201 (>95% of cases) or Glutamine in position 227 (<5%), disturbing the guanosine triphosphatase function and increasing levels of cyclic adenosine mono-phosphate (cAMP), which stimulates endocrine receptors<sup>1,2,4</sup>. It is responsible for the increased cellular activity, bony metaplasia

and increased and disorganized fibrotic content<sup>4</sup>. This article is focused mainly on the monostotic form present in the mandible and differential diagnosis from other lesions which are affecting this site. Under consideration are taken radiological examination, age of onset, gender predilections (if present), etiology, clinical and histopathological characteristics. Proper distinction is of high importance due to the differences in the management of cases. The correct diagnosis is important because it will help dictate treatment, and the current treatment paradigms vary depending on the diagnosis: for instance, most texts state that ossifying fibromas require complete excision and curettage, but FD may be observed and monitored in certain cases<sup>2</sup>. Lesions to be considered in the differential diagnosis include inflammatory lesions, fibro-osseous lesions, and benign and malignant neoplasms<sup>5</sup>.



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# **MATERIALS AND METHODS**

In this study, search was conducted via PubMed online database and Google Scholar, including articles published in English, in order to find already existing studies, report cases and reviews on lesions that can be differentiated from FD of the mandible. The research was focused on clinical, radiological and histological aspects.

# **RESULTS**

FD is a rare, benign disease of bone, where fibrous tissue replaces the normal bone<sup>6</sup>. Monostotic FD is highly prevalent (80-85%) cases. There is no gender predilection. The lesion is most frequent in the maxillofacial region, unilateral, with higher prevalence in posterior maxilla than in mandible. In 90% of cases is present unilateral tumefaction and in much lower percentage pain – 18%. It rarely happens to be diagnosed incidentally while conducting a radiological examination for other reason (2%). A reason may be that these lesions on conventional radiographs have poorly defined margins; therefore, are often missed by the dentist if of small size. Almost all cases present to a clinician with symptoms, because in majority of cases FD of the jaws does not become "quiescent during puberty" as it is typical of extragnathic cases where complete arrest of growth of the lesion is noted when osseous maturity is reached <sup>7,8</sup>. Appears from the first to the third decade of life<sup>1,9</sup>, although most monostotic cases are detected for the first time later in life due to absence of earlier symptoms. Cases of reactivation later in life are reported<sup>7</sup>. The earlier the mutation, the more widespread and the more severe will be the manifestations<sup>8</sup>. In the craniofacial region, 90% of all the lesions were detectable by bone scan by age 3.4, and no new lesions in the craniofacial region are very reported beyond the age of 10<sup>3</sup>. Most cases of FD develop slowly, the early oral and maxillofacial symptoms are not obvious, and they can easily be ignored by patients. As the disease progresses slowly, the symptoms such as occlusion disorder and loosening of teeth can develop<sup>6,7</sup>. FD displays an overwhelming predilection for the posterior sextants of both jaws8. It also happens to be noticed by a family member as a facial asymmetry. More than half of jaw tumors in pediatric cases with swelling and asymmetry are of mesenchymal cell lineage, of which almost half are fibro-osseous lesions with high prevalence of FD. That is the reason why the FD should be highly considered in differential diagnosis of children with asymmetries and swelling<sup>3</sup>. Level of Alkaline Phosphatase may be elevated, it is not a specific marker though. Sudden rise of this marker may indicate malignant transformation, especially if associated with bone pain and other specific symptoms<sup>4</sup>.

Radiographically FD presents itself as a diffuse opacity with a ground glass (granular pattern resembling small fragments of shattered windshield), peau d'orange, stippling or thumb print (swirling bony trabeculae) or salt and pepper which describes the abnormal and unorganized arrangement of the trabeculae<sup>4,7,9</sup>. The lesion is poorly defined with a 1 mm zone of transition8. The buccal and lingual cortices become expanded and thinned but are rarely interrupted<sup>7,8</sup>. Based on the distribution of the osseous and fibrous component three radiographic patterns are described such as pagetoid, sclerotic and radiolucent (lytic). Pagetoid appearance is more common followed by sclerotic type. Radiolucent variant is least common among all radiographic appearances<sup>4,9</sup>. This can be attributed to the fact that most of the times the patient never report during the initial stages of the disease9. The lesions may be more radiolucent at initial stages which may present as a lytic pattern of trabeculae, with one or several, usually well-defined, polycyclic rarefactions in an otherwise normal bone. At later stages it becomes radiopaque, as the lesion matures, which may present as an osteosclerotic form, with uniform sclerosis, often passing over smoothly into a normal bone structure. Between these two basic forms, transitional ones are seen, the most common being a combination of irregularly outlined, often confluent sclerotic areas of varying size, and osteolytic areas in the bone, usually sharply delimited and with irregular outlines<sup>7,9,10</sup>. Although Petrikowski suggested that the upward displacement of inferior alveolar nerve is pathognomonic to FD, further studies demonstrated that the nerve can be displaced in each direction: superiorly, inferiorly, buccally, lingually<sup>2,5,9</sup>. FD can also affect the dentition and proper occlusion as it may cause displacement of teeth and roots and root resorption, resulting in malocclusion, spacing or dental crowding<sup>1,2</sup>. This is caused by rapid alveolar bone expansion, which may affect positions of teeth in an improper way. In the microscopic picture are visible irregularly shaped trabeculae similar to Chinese characters or alphabet soup<sup>1,7</sup>. Size and degree of calcification is variable and typically is not rimmed by osteoblast, although there may be presence of rimming<sup>7</sup>. In 18% of the cases has been reported recurrence or reactivation, lesions that can develop in vicinity of the affected site are simple bone cyst, central giant cell granuloma (CGCG) or aneurysmal bone cyst (ABC)11.

CT is recommended as a part of radiographic examination as it may be helpful in evaluation of hard and soft tissues. Although, MRI is considered more sensitive to pathological changes than CT, in case of FD MRI produces low signal intensity which leads to difficult interpretation. Nevertheless, use of CBCT as an alternative for CT is indicated by some scientists due to the fact that it affects prevalently

younger patients, and a reduced dose of radiation is recommended8. Periapical radiographs may as well prove helpful in imaging of internal structure of FD due to closer placement to the jaw9. Any widening of periodontal gap has to be taken under further examination as in FD lamina dura is replaced by dysplastic bone and the space appears to be narrower than normal8. Although histopathologic examination is often important part of diagnosis, caution is needed as biopsy can cause bleeding (FD lesions may be very well vascularized)3. Risk of a fracture triggered by a biopsy is significantly smaller than in case of extragnathic FD8. GNAS mutational analysis has an important role in diagnosis, in fact is considered as a "gold standard", due to similarity of FD both clinical and histological to some other benign fibro-osseous lesions<sup>1,2</sup>. However, sensitivity of used technique and the level of mosaicism in the affected tissue may alter the results of GNAS mutation tests<sup>2</sup>.

## Differential diagnosis

Knowledge of similar lesions is essential for a proper diagnosis. Therefore, the differential diagnosis must include some other entities of the benign fibroosseous lesions, among which is cemento-ossifying fibroma (COF) and florid cemento-osseous dysplasia (FCOD). Moreover, it is essential to comprise in the differentiation process the following lesions such as CGCG, ABC, osteomyelitis, Paget's disease and osteosarcoma (Table 1).

**TABLE 1.** Principal radiographical aspects of FD and lesions in its differential diagnosis.

Lesion	Principal radiographical aspects
Fibrous dysplasia	Diffuse opacity with a ground glass/peau d'orange/stippling/thumb print/salt and pepper arrangement of trabeculae Appears unilaterally Poorly defined with a 1 mm zone of transition Initially radiolucent but becomes radiopaque as matures: three patterns lytic, pagetoid, and sclerotic Buccal and lingual cortices rarely interrupted More common in the posterior regions of the mandible Displacement of inferior alveolar nerve
Cemento-Ossifying Fibroma	Well-defined lesion (sclerotic border) Concentric expansion of cortical plates as of benign tumour "Shelling out" More common in the anterior regions of the mandible Small in size
Florid Cemento- Osseous Dysplasia	Widening of the periodontal ligament space with hypercementosis and loss of the normal lamina dura Appears bilaterally Initially radiolucent but becomes radiopaque as matures
Central Giant-Cell Granuloma	More common in the anterior regions of the mandible as a multilocular radiolucency Well-defined noncorticated margins
Aneurysmal bone cyst	Most common posteriorly Radiolucent Well-defined in its mature form (however larger lesions may be ill-defined) Baloonlike expansion
Paget's disease	Appears bilaterally and causes enlargement of entire jaw Cotton wool appearance Visible thickening of the cortices
Osteomyelitis	Periosteal new bone formation One or more laminations that occur parallel to the outline of the jaw
Diffuse sclerosing osteomyelitis	ill-defined radiopacity in large areas of bone (however small radiolucent zones may appear) doesn't expand unless the cortical plate is involved
Osteosarcoma	Presence of orthoradial striations Destruction of cortex with an invasion of soft-tissues Generalized widening of the periodontal ligament spaces Destruction of the lamina dura



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**COF** 

COF is a benign neoplastic lesion which is similar to FD either histologically and radiographically. In contrast to FD (which in the radiographic picture has unclear margins which merge with the normal bone), COF has well defined capsule which surrounds the lesion, which is visible in the radiographic picture as a well-defined lesion with a smooth margin and has concentric expansion of cortical plates as of benign tumour 4,5,7,11-13. While COF presents sclerotic border, in FD it is absent. Both lesions tend to expand to the bone cortex<sup>4,5,7,14</sup>. COF is more common in the anterior regions of the mandible and is smaller in size, FD presents itself more often posteriorly and lesions tend to be larger. COF is often described by surgeons that it is "shelling out"14. The age of onset of COF is the third and fourth decade of life, FD appears usually in the second decade<sup>4,5,12,14</sup>. COF has female predilection (5 to 1)14. Histologically it presents itself as spindle fibroblast-like cells with deposition of cementicles, osteoid and woven bone<sup>1</sup>. Characteristic feature which helps distinguishing both lesions is artifactual peritrabecular clefting which is present in FD7. Osteoblastic rimming is characteristic to COF, however in juvenile variants may not be present<sup>14</sup>. Differentiation of both lesions is vital to conduct a proper treatment due to the fact that the treatment procedures are diverse. In case of COF surgical excision is required: curettage and enucleation due to its tendence to recurrence. FD generally self-limits itself and the treatment is required in more severe cases to reduce pain, impaired function, and discomfort or for cosmetic reasons, resection or recontouring is usually conducted after the skeletal growth stops (it affects acceleration of growth of the lesion)<sup>1,5</sup>.

#### **FCOD**

It is the most common benign fibro-osseous lesion of the jaws<sup>14</sup>. It occurs more often in the mandible than the maxilla. There are three subtypes of COD: periapical, focal and florid. In differential diagnosis a florid subtype is considered mostly. COD affects only areas in proximity of teeth as it is believed to originate within the periodontal ligament<sup>15</sup>. However, the associated teeth often remain vital<sup>14</sup>. Radiographically, widening of the periodontal ligament space with hypercementosis and loss of the normal lamina dura may be observed<sup>14</sup>. COD may be diagnosed based only on the radiological examination unless the lesion is atypical, then the biopsy may be of help<sup>14,15</sup>. There is a strong gender and racial predilection – it affects mostly middle-aged women of sub-Saharan African and of East Asian origins what makes a characteristic feature in differentiation with FD<sup>8,14,15</sup>. Initially the lesion may appear radiolucent and as it matures becomes radiopaque, during this process presenting various densities and trabecular patterns same as FD. However, FCOD in contrast with FD appears bilaterally. The lesion does not present any serum biochemical disturbances, skeletal abnormalities or systemic manifestations<sup>15</sup>. While with FD arising of the tumor is usually painless, in FCOD the main complaint of the patient is pain (in other types of COD also asymptomatic)<sup>14,15</sup>. It is not uncommon for patients with Florid COD to develop osteomyelitis, that it why unlike in other types of COD where a routine follow-up is sufficient, in FCOD a treatment is required<sup>14,15</sup>.

# **CGCG**

CGCG appears as a neoplasm but there are controversies considering its etiology and three theories are suggested: first - it is a neoplastic lesion, second - it is a reactive lesion of a local irritant and third a developmental anomaly<sup>12,16</sup>. CGCG appears more common in the anterior regions of the mandible as a multilocular radiolucency, causes painless expansion of the bone, has well defined noncorticated margins, has definite female predilection<sup>4,5,12,16</sup>. In the histological picture giant cell proliferations observed, such as large amount of spindle shaped mesenchymal cells and extravasation of erythrocytes<sup>16</sup>. Age of onset is usually contained between the first and the third decade of life, but the lesion has been seen in older patients. The lesion is typically asymptomatic but may be associated with pain or paresthesia. CGCG is differentiated from early cases of FD because that is when radiographic picture of FD is still radiolucent.

#### ABC

It is a benign intraosseous lesion of the bone, a type of pseudocysts. It is a non neoplastic and unilocular lesion. ABC may occur at any age but most commonly appears in the 20s. Although there is no sexual predilection, slight female predominance is visible<sup>12,17</sup>. Higher incidence in the mandible than in maxilla (ratio 2,4:1) and occurs most common posteriorly<sup>12,17</sup>. ABC is a fibro-osseous tissue that replaces normal bone. It contains cavernous or sinusoidal spaces filled with blood<sup>17</sup>. It is not specific in its clinical picture - it may grow slowly causing modest facial asymmetry as well as enlarge rapidly with vascular swelling which in this form mimics malignant lesions<sup>17</sup>. Displacement or resorption of teeth may occur. ABC is well-defined in its mature form (however larger lesions may be ill-defined). It is in differential diagnosis with the initial stages of FD as it is radiolucent. Radiographically, baloonlike expansion helps in distinguishing this lesion. An aspirational biopsy with hemorrhagic content leads to the diagnosis. In this case as in COF a standard procedure of treatment is curettage or enucleation<sup>12,17</sup>.

# Paget's disease

It is an autosomal-dominant condition that affects multiple bones. Although affects older population unlike FD, is in differential diagnosis especially if patient does not present any symptoms until later age. Most useful clinical feature to distinguish both lesions is that Paget's disease has bilateral tendence and causes enlargement of entire jaw, while FD unilateral<sup>4,5,11</sup>. In the radiographic picture Paget's disease has cotton wool appearance of the involved bone, thickening of the cortices is visible. Many osseous trabeculae with prominent reversal lines showing simultaneous osteoblastic and osteoclastic activity are, therefore, a histological feature<sup>5</sup>. Affected bone is surrounded by a well vascularized fibrous connective tissue stroma. Also, increased blood levels of alkaline phosphatase and male predilection are noted<sup>4,5</sup>.

# Osteomyelitis

FD is also differentiated from early stage of osteomyelitis especially if swelling is present (later demonstrates sequestra and causes jaw enlargement)5,11. However, osteomyelitis has inflammatory origin<sup>1,4,5,10</sup>. Presence of draining sinus tracts and secretion of pus are signs of osteomyelitis and do not occur in FD. Common among young patients' useful indicator of osteomyelitis is periosteal new bone formation, resulting from lifting of the periosteum, which manifests as one or more laminations that occur parallel to the outline of the jaw<sup>4,5,10</sup>. Usually it is a lesion which appears secondary to odontogenic infections of pulpal origin, but hematogenous spread from distant sites has also been reported. Usually after the successful endodontic or surgical treatment, the lesion recedes<sup>4,5</sup>.

Careful and comprehensive diagnosis is vital as co-existence of both FD and chronic osteomyelitis may mimic a malignant lesion, even though magnetic resonance imaging is being used<sup>5,11</sup>. There has been reported a case of 6-year-old girl with local pain on the right chin after severe trauma. Chronic osteomyelitis was originally diagnosed and then after the antibiotic treatment failure a malignant bone tumor was suspected based on radiological studies.

Eventually repeat biopsy one year after the onset confirmed FD of the mandible in association with chronic osteomyelitis. This delay has occurred due to initial biopsy in inappropriate site and similarities between osteomyelitis and FD both clinical and radiographic<sup>5</sup>.

# Diffuse sclerosing osteomyelitis

Radiologically appears as an ill-defined radiopacity in large areas of bone, small radiolucent zones may appear. Expansion of the lesion is absent unless involves the cortical plate what may lead to a periosteal reaction. Histologically, sclerotic bone with alternating areas of apposition and resorption is visible. Between the bone trabeculae lies fibrous connective tissue infiltrated by chronic inflammatory cells. Histopathologic examination of the bone is indicated<sup>5</sup>.

#### Osteosarcoma

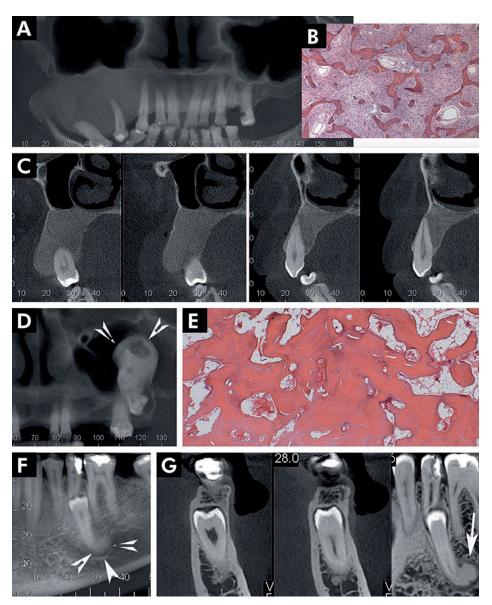
Osteosarcoma is a malignant bone tumour. Swelling, pain, loosening of teeth or paresthesia may be present. There is noticeable male predilection. As the age of onset are considered first and second decades of life1. Differential diagnosis between osteosarcoma and FD is possible in base of imaging studies. In osteosarcoma is noted a presence of orthoradial striations, destruction of cortex with an invasion of soft-tissues, generalized widening of the periodontal ligament spaces and destruction of the lamina dura<sup>5,11,14</sup>. However, histopathological examination of bone is still indicated: osteosarcoma appears as spindle-shaped tumor cells arranged in herring bone pattern and areas of osteoid formation<sup>1</sup>. Immuno-histochemical analysis with MDM2 and CDK4 may prove helpful in differentiation from FD as it does not express those markers<sup>3</sup>. Treatment of osteosarcoma requires surgical resection, radiotherapy and/or chemotherapy.

#### **TREATMENT**

There are several factors which affect the therapy: age of the patient, size of the lesion and the rate of growth. It is important to conduct the treatment conservatively and aesthetically<sup>7</sup>. FD lesions may be divided into quiescent (however, as mentioned before in case of craniofacial FD it occurs rarely), non aggressive or aggressive. In case of aggressive lesions rapid growth is noted, there may occur pain, paresthesia, pathologic fractures, malignant transformation (<1% of cases, typically osteosarcoma, how-



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**Fig. 1.** Fibrous dysplasia: CBCT views showing a homogeneous hyperdense lesion in the right maxilla merging into the normal bone margins, and having a ground-glass appearance (*A*). Craniocaudal expansion and tooth displacement can also be observed (*A*). Histologically, FD presenting thin osteoid trabeculae with "Chinese-figure" characteristics in a hypercellular fibroblastic stroma (*B*). In cross-sectional views, it is observed as a narrowing of periodontal ligament space and ill-defined lamina dura of the affected teeth (*C*). Central osteoma: Panoramic image shows a well-defined round hyperdense mass in the maxillary sinus, associated with the apex of a maxillary tooth (*arrow head*) (*D*). Histopathological examination revealing mature, compact and trabecular bones with sparse fibrous-adipose tissue (*E*). Cementoblastoma: CBCT images showing a well-defined hyperdense round lesion attached to the root of supernumerary mandibular tooth (*arrow head*) (*F*) with a surrounding hypodense rim (*arrow*) (*G*). (Adapted from "Differential diagnosis and clinical management of periapical radiopaque/hyperdense jaw lesions" by B.S.F. Silva, M.R. Bueno, F.P. Yamamoto-Silva, R.S. Gomez, O.A. Peters and C. Estrela).

ever, chondrosarcoma, fibrosarcoma and malignant fibro-histiocytoma have been reported) and association with a secondary lesion<sup>2,3</sup>. Therefore, management varies broadly from regular, for example annual evaluations and administration of drugs, to multiple surface resections<sup>7</sup>. As radiotherapy carries risk of sarcomatous transformation, it is contraindicated<sup>7</sup>. Regular follow-up is conducted to analyze patient's symptoms, it also includes sensory nerve testing in the affected area, radiographic evaluation

– photographs and facial CT³. School of Stomatology at China Medical University conducted a study including 24 patients operated there from December 2014 to August 2016: 11 patients were treated by focal bone modification and 13 by total resection. Due to the study operation is most common as drugs are not able to eliminate the lesion entirely, so they are used as a temporary solution. Moreover, surgical operation has aesthetical effects. Focal resection does not eliminate the lesion completely, but on the

other hand complete resection may cause facial deformation and deficit of the bone which affects oral function. The conducted questionnaire proved that surgical treatment relieves pain, improves appearance and mood but there was a decrease in the quality of speech, activities and recreation (also chewing but only in the group in which was conducted total resection), however it may have been caused by the fact that the patients were still recovering. Study proved that surgical operation can improve the quality of life of patients affected by FD<sup>6</sup>.

#### **CONCLUSIONS**

As a conclusion it is important to assure that differential diagnosis of mandibular FD is essential to conduct a proper treatment of the patient affected by this lesion because the protocols to be followed are not always the same in the lesions discussed in this article. It may present itself similarly to other lesions affecting this site, that is why it is vital to consider various factors which prove helpful in distinguishing these lesions and FD among which are symptomatology, radiographic and histological features, age of onset and predominance in specific gender or ethnic group if present. However, it must be remembered that FD is not always detected at the initial stage and that is why the age of detection cannot be always considered as the age of onset.

### CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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