Fibrous Dysplasia and Ossifying Fibroma - Solving the Diagnostic Dilemma

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Abstract

Fibrous dysplasia (FD) and Ossifying fibroma (OF) of the jaws belong to a group of lesions called benign fibro-osseous lesions of the craniofacial skeleton (BFOL). This group of intraosseous disease processes which are comparable in their microscopic features are characterized by hypercellular fibroblastic stroma containing various combinations of bone or cementum-like tissue and other calcified structures. Of these lesions, FD and OF are the most closely related, and although FD is recognized as a harmatomatous lesion and OF a tumour, these lesions are difficult to distinguish both clinically and histologically from each other. This review of current literature aims to highlight emerging features clinically, genetically and histologically that can help in distinguishing these two lesions.

Keywords: Fibrous dysplasia, Ossifying Fibroma, Diagnostic Dilemma.

Introduction

Benign fibro-osseous lesions (BFOLs) are characterized by the replacement of normal bone with a benign connective tissue matrix with varying degrees of mineralization in the form of woven/lamellar bone or cementum-like round acellular intensely basophilic structures[1,2]. Generally, they often exhibit resemblance in clinical presentation, radiographic appearance and histologic criteria, and therefore present difficulties in diagnosis and management[3,4]. It is generally acceptable that oral and maxillofacial BFOLs can be divided into three main categories namely; osseous dysplasia (OD), fibrous dysplasia (FD) and ossifying fibroma (OF)[5,6]. FDs and OFs are the important and challenging types to differentiate due to the overwhelming inter-relationship that exists between these two lesions, which results in difficulties in specific identification[1,4,7].

FD is defined as a benign lesion, presumably developmental in nature, characterized by the presence of nonspecific fibrous connective tissue with a characteristic whorled pattern and containing trabeculae of immature non-lamellar bone[8]. It is widely considered by authors to be a hamartomatous or developmental malformation[6,8,9]. OF is a benign osteogenic neoplasm which is rarely encapsulated but well demarcated from its surrounding normal tissue. It consists of fibrous tissue containing varying amounts of mineralised material that resembles bone and/or cementum[10].

This review discusses the epidemiology, aetiology, clinical, radiologic, histologic features and prognostic aspects of FDs and OFs with updated information on underlying genetic and molecular pathogenic mechanisms of these diseases.

Epidemiology

BFOLs are said to constitute an overall incidence of 2.0% - 5.0% of all head and neck tumours and between 10.0% - 15.0% of jaw bone tumours[1,11]. Globally, studies have unequivocally confirmed FD and OF as the most important, most frequent and most difficult types of BFOLs of the jaws to differentiate, even though the clinicopathological and radiological presentations of both lesions have been extensively documented in the scientific literature[2,12,13]. The craniofacial skeleton may be

involved in either of the two types of FD; monostotic and polyostotic. Polyostotic FD is less common and a few may also be associated with skin pigmentation and endocrine abnormalities, a condition known as the McCune Albright's syndrome which is more common in female patients. Monostotic FD occurs in the craniofacial skeleton, particularly the maxilla and mandible in 25.0% of the cases[14].

OF of the craniofacial skeleton is separated into two main clinicopathologic entities: Ossifying fibroma of odontogenic origin referred to as Cemento ossifying fibroma/ossifying fibroma (OF), and Juvenile ossifying fibroma (JOF), which is further divided into two distinct types: the trabecular juvenile ossifying fibroma (TrJOF) and Psammomatoid juvenile ossifying fibroma (PsJOF)[15]. Cemento-ossifying fibroma/ossifying fibroma (OF) is the more common type and more likely to imitate FD as a clinical entity. 80.0% of craniofacial FD cases are diagnosed within the first two decades of life, while the peak age incidence of OF is the third and fourth decades[2].

There are varying opinions in the literature about the degree of frequency of FD and OF amongst the BFOLs. In some European studies, in which FD and OF were documented as percentages of FOLs, FD and OF were reported as 36.0% and 40.0%[16], and 63.6% and 36.4%[17] respectively. Other studies that reported FD and OF as percentages of FOL include 42.6% and 50.8% in Thailand[2], 43.1% and 22.3% in South Korea[12], 48.9% and 31.3% in Jamaica[18], 30.8% and 69.2% in Ghana[19] and 25.3% and 74.4%[20] and 42.86% and 57.14% in Nigeria[21].

Aetiology

The precise aetiology for the development of FD is currently unknown, although several factors have been suggested. These include a complex endocrine defect causing disturbance of metabolism of calcium and phosphorus, lipid granulomatosis of bone, increased secretion of oestrogen and a congenital anomaly with an incidental localizing mechanism[22] and chronic glandular dysfunction of the parathyroid gland caused by hyperphosphatemia[23]. Others are congenital lesion with an autosomal recessive trait[24], arrest of bone at an immature woven stage secondary to trauma, and disturbance of post-natal cancellous bone maintenance[25]. The precise aetiology from studies has been elucidated to be due to somatic mutations in the guanine nucleotide-binding protein, α-stimulating activity polypeptide 1, GNAS 1 gene[26,27], that encodes alpha subunit of stimulatory G protein (Gsα) occurring post-zygotically, leading to up-regulation of the cAMP. This event has been implicated as the molecular mechanism underlying the pathogenesis of FD[26,27]. A recent study[28] found GNAS mutations in 90.0% of fibrous dysplasia in their series. It has however been documented in literature that diagnosis of fibrous dysplasia could not be ruled out when no mutation is detected due to the technical concerns regarding regular Polymerase Chain Reaction (PCR) and direct sequencing, which require high quality and quantity of DNA. Also because of a mutant threshold of about 20.0% in the total population; the somatic nature of the mutations in fibrous dysplasia may not meet this level of sensitivity. In some cases, especially the older ones, as reported by Kuznestov et al[29], the percentage of mutated cells within a given lesion may decrease with age.

Although the cell of origin remains unknown, OF is widely thought to be derived from elements within the periodontal ligament space due to its close proximity to the periodontal ligament which has the inherent potential to differentiate into osteoblasts or cementoblasts, thereby producing cementum and osteoid, both of which are characteristically found in OF[30]. The presence of lesions microscopically identical to these but located in areas remote from maxillofacial region such as the ethmoid, orbit, frontal, sphenoid, temporal bone and long bones, has caused persistent controversy over the exact origin of OF[31]. The notion that the tumour arises from ectopic periodontal tissue in locations distant from oral region by Hammer et al[32,33] was however discredited by Kausen et al[34] who were unable to find any proof to support this theory. The occurrence of OF in areas distant from periodontal ligament however remains unexplained, although Eversole et al[4] and Quan et al[33] postulated that primitive mesenchymal cells in areas such as the ethmoid bone and long bones may produce a calcific like material resembling cementum at sites distant from the odontogenic tissue. Recently, alterations in the tumour suppressor gene CDC73 (formerly known as HRPT2), with chromosome location in 1q24-q32, that encodes for a protein named parafibromin, have been linked to OF[7,35]. This gene is inherited in an autosomal dominant manner and spans 1.3 Mb of genomic DNA[36].

Clinical features

Both OF and FD are slow growing lesions that result in facial asymmetry with estimated median time of awareness ranging from between 3-4 years[37,38]. FD has been described to rarely cross the midline with maxilla and mandible being the common sites of occurrence in the oral and maxillofacial region, extragnathic locations such as the sinonasal and ethmoidal regions have occasionally been reported[36,37] (Fig. 1).

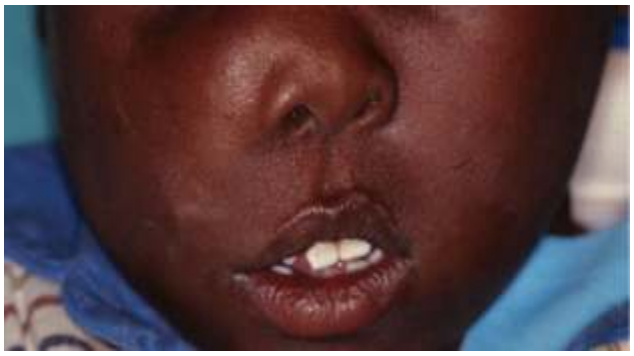

Fig 1: Fibrous dysplasia showing diffuse swelling of the Right maxilla

The monostotic FD occurs more frequently than the polyostotic type in most studies in literature[25,39] although Sazgar et al[40]. reported an equal prevalence for the two variants. OF on the other hand is a benign well-demarcated and occasionally encapsulated, slow growing, painless neoplasm primarily seen in the jaws and extragnathic locations such as the sinonasal and ethmoidal regions[36]. Monostotic FD has its peak prevalence in the 2nd and 3rd decades of life with greatest frequency seen in the second decade of life[7]. Occasional cases have been found in seventh and eight decades of life[41]. Patients with polyostotic type are often younger at the time of diagnosis when compared with monostotic FD with presentation in 1st decade of life[7]. OF occurs in patients over a wide age range, but the greatest numbers of cases are encountered during the third and fourth decades of life except in the juvenile type which often occurs in the first decade of life[36]. The global mean age range is from 19 to 35years with the lowest percentage from sub-Saharan African and highest among the Asian population[38] (Fig. 2).

Fig. 2: Ossifying Fibroma showing a well circumscribed swelling of the Left mandible

FD is not associated with any racial predilection, in contrast OF is reported to be most frequent among Caucasians (58.0%), Blacks (23.0%) and Hispanic (12.0%)[42,43]. There are contrasting reports on the sex predilection of FD with some reporting females to be more commonly affected with ratios as high as 3:1 while others report an equal sex distribution[25,37,44]. Some researchers have speculated that alteration in female sex hormones especially during pregnancy may play a major role in development of FD of the jaws[37,38] . OF is reported to occur more frequent in women with some studies reporting a female to male ratio as high as 5:1[16]. FD affects the maxilla in about 65.0% to 75.0% of cases with predilection for the molar and premolar areas[45,46], although few studies have reported anterior maxillary predilection and posterior mandibular predilection[18,38]. The posterior mandible is the most frequently reported site of occurrence of OF in most studies[47]. Findings in literature therefore suggest that FD can be distinguished from OF on the basis of site predilection[16,18,47].

Malignant transformation of FD was initially observed in 1945 by Coley and Stewart[47]. This occurred very infrequently, with reported prevalence ranging from 0.4% to 4.0%[3,9]. Signs and symptoms of malignant transformation include rapid growth of lesion, pain, invasion of cortical bone with an associated soft-tissue mass, and elevation of the alkaline phosphatase level[48]. Irradiation has been implicated as a major factor that increases the potential for malignant transformation of FD by 400 times[49]. Although multiple surgeries and spontaneous sarcomatous change[50] are reported in the development of sarcomas in FDs, Dicaprio and Enneking[51] stated that there is no conclusive evidence that FD is a premalignant disease. Malignant transformation in OF is extremely uncommon[10,52] although the potential transformation of OF exists especially in cases that have been treated with radiotherapy[7].

Radiological features

Radiographic features of FD are diverse and vary depending on the stage of development of the lesion and the proportion of mineralized bone to fibrous tissue, ranging from an early radiolucent lesion to a uniformly radiopaque mass[53-55]. Early FD of craniofacial bones is radiolucent with ill-defined or well defined borders, and this may be unilocular or occasionally multilocular. As the lesion matures, the bony defects acquire a mixed radiolucent-radiopaque appearance. Established FD exhibits

mottled radiopaque pattern, often described as "ground glass", "orange peel" or "fingerprint", with ill-defined borders that blend imperceptibly into the normal adjacent bone[53-55] (Fig. 3).

Fig. 3: Fibrous Dysplasia- Occipitomental view of the skull showing a radiopaque mass with ill defined margins on the Right maxilla

Obisesan et al[53] in a radiographic analysis of a series of FD classified the lesion into six radiological types of which the orange-peel type accounting for 40.0% of the cases was the most common. Regardless of the radiologic type, the lesion often presents an indistinct border that blends faintly into the adjacent normal bone, although early lesion may present with a well-defined margin[56]. Tooth displacement without root resorption, narrowing of the periodontal ligament space with an ill-defined lamina dura, (best demonstrated on periapical radiograph) and superior displacement of the mandibular canal in mandibular lesions, are commonly seen[54]. Paranasal sinuses may become obliterated, and displacement of the orbit is a common feature in the maxillary lesions. CT scans may be useful in evaluating the skull base foramina[51].

The radiographic appearance of OF varies greatly depending on its stage of development. It may be lytic, sclerotic or mixed as revealed by plain radiographs and CT scans[38]. At the early stage, the lesion is totally radiolucent. The intermediate stage of the lesion exhibits mixed radiolucent and radiopaque densities (mottled) depending on the amount of the calcified material which at the late stage presents as "ground glass", "cotton wool", or "flocculent" (Fig. 4).

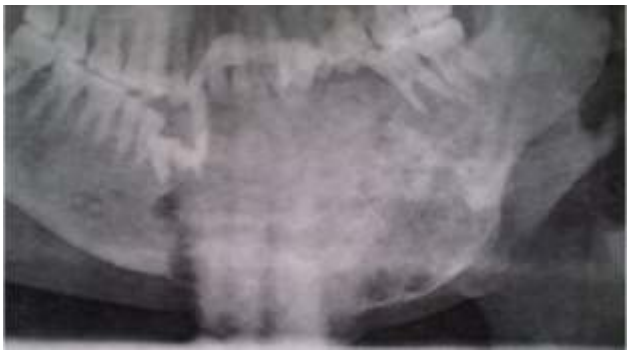

Fig. 4: Ossifying Fibroma showing a mixed radiolucent and radiopaque mass on the mandible

OF is usually seen radiographically as a well defined unilocular lesion in about 90.0% of cases with thinly corticated margin which occasionally may be sclerosed or osteolytic[2]. Less commonly, it presents as a multilocular lesion and sometimes as a mixed radiolucent/radiopaque structure that shows various degrees of opacification, depending on the relative amount of calcified material within. OF has the propensity for an outward and oval to spherical expansion in all directions, which causes expansion of cortical plates. The lesion causes buccolingual bony expansion and thinning of cortical plates in 70.0% of cases but usually there is no perforation[33,42]. Large mandibular lesions may cause a characteristic thinning and downward bowing of the inferior mandibular border. Displacement of adjacent teeth with loss of lamina dura has been reported[42]. In addition, root resorption of teeth in lesional area has been observed in 4.0%-44.0% of cases in some studies[38,42]. Expansion into the maxillary antrum with displacement of floor of maxillary sinus has been reported in approximately 80% of maxillary cases[10].

Histopathology

Both FD and OF consist of a fibroosseous connective tissue stroma histologically. A monotonous distribution of stromal content in almost equal ratio, mainly the woven bone type without prominent osteoblatic activity, is a common feature of FD (Fig. 5).

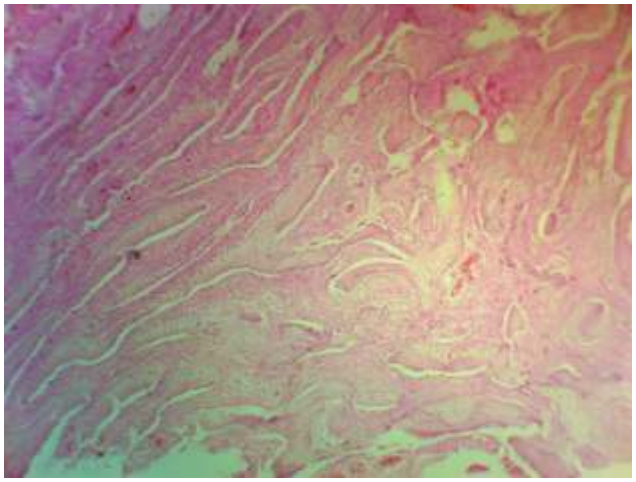

Fig. 5: Fibrous Dysplasia - Photomicrograph shows curvilinear pattern of woven trabecular bone in a moderately dense cellular connective tissue stroma and sparse presence of congested vascular channels. Also seen are artefactual retractions with absence of osteoblastic rimming (H&E x 40).

In addition, FD blends with the adjacent normal surrounding tissue and has no connective tissue capsule[44,56]. OF often presents as a partially encapsulated tissue containing variable distribution of stromal contents arranged in a storiform pattern (Fig. 6).

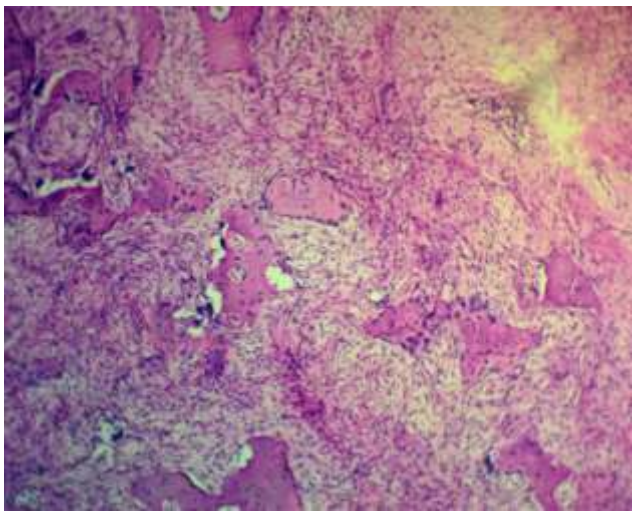

Fig. 6: Ossifying Fibroma - Photomicrograph shows a highly cellular moderately dense connective tissue stroma with fibroblastic activities within which are trabecular of woven and lamellar bone with prominent osteoblastic rimming. (H&E x 40)

Calcific-like materials in form of spherical globules and cementum are often present[16]. Many lesions lack the classic pathologic features of FD and OF and are therefore diagnosed subjectively as non-specific fibroosseous lesion, thus resulting in an enormous challenge to the histopathologists especially whose verdict determines the overall management of this patient. This diagnostic dilemma has motivated the development of new techniques to augment the routine haematoxylin and eosin histological method to improve the accuracy and reproducibility of objective diagnosis, with the aim of distinguishing between the two lesions. Among the histological studies to differentiate between these two lesions are applications of histochemical stains such as Periodic acid-Schiff stain (PAS)[12], Silver impregnated Reticulin stain[48], Von Kossa stain, Masson's trichrome stain (MT)[4] and Silver nucleolar organized regions (AgNORs) techniques[57]. Others are immuno-histochemical stain[58] and molecular and cytogenetic studies[59]. Result of an immunohistochemical study[60] in which antibodies against osteogenic protein markers such as Runx, Dentine matrix protein 1(DMP1), osteocalcin and osteopontin, were applied to FD and OF, showed that strong immunoreactivity was recorded for osteocalcin in FD as compared to weak reaction for OF. MT stain has also been found to be useful in distinguishing between FD and OF based on the proportion of woven bone to lamellar bone in the connective tissue stroma. MT stain prominently displays lamellated lines characteristic of matured bone which is mainly a feature observed in OF rather than woven bone trabeculae. It also reveals the distinct margin for lamellar bone and brush border for woven bone trabeculae[4,12]. Several diagnostic criteria have been proposed to distinguish between FOLs, but only a few of these features are truly specific and used during routine oral pathology.

Furthermore a histomorphometric analysis was performed in an attempt to quantify whether the extent of peritrabecular clefting which was earlier considered as a retraction artifact is biologically insignificant in FD[60]. However, based on different decalcification and processing protocols performed in the centre, the presence of peritrabecular clefting in FD was significant. The authors therefore postulated that these cleftings may be associated with an abnormality in the expression of basement membrane proteins, collagenases, or other enzymes. The presence of peritrabecular clefting was a distinctive feature of FD which was not identified in OF cases and could become a distinctive feature in separating the disease entities in the future.

Treatment and prognosis

Treatment for FD generally consists of clinical observation, surgery and medical therapy[61,62]. Studies have shown that FD may burn out in early adulthood when skeletal maturity has been attained, hence the advocate for clinical observation of the patient until

adulthood[3,63]. However, other studies where patients with FDs were followed over a long period of about 10-20 years have shown that FD will continue to grow in the post pubertal period and would require surgical intervention whether conservatively or by radical excision[64,65]. The choice of surgical option depends on several factors namely; site of involvement of lesion, rate of lesional growth, patient's aesthetic disturbance, functional disruption, patient's preference, general health of the patient, surgeon's experience and the availability of a multi-disciplinary team (neurosurgeon, ophthalmologist, otolaryngologist, orthodontist)[66,67]. The standard treatment of FD among surgeons that believe FD may burn out in early adulthood when skeletal maturity is attained is surgical paring down or shaving[7]. However, other surgeons choose a more radical approach because growth sometimes continues unabated post-puberty[68]. Radical surgery may also be indicated for extragnathic lesions of the head and neck[7]. Recurrence rate of FD is reported to be generally low, although rates as high as 25.0% - 50.0% have been reported in some cases treated by surgical contouring[69]. Medical treatment using bisphosphonate therapy is reported to be effective in some patients with FD as an alternative treatment, when surgery is not indicated[7,51,70]. Relief of bone pain and reduction of osteoclastic activity with partial filling of osteolytic lesions can be achieved with intravenous bisphosphonate therapy. Bisphosphonate inhibits osteoclastic activity in bone especially in patients with polyostotic FD (pFD) or MacCunne Albright syndrome(MAS) although there is limited data on patients with craniofacial FD[70]. Also, the use of steroids as drug therapy in FD has been found to be successful, especially in the treatment of visual symptoms from optic nerve compression. Corticosteroid therapy is reported effective in reducing both the rate and number of bone forming osteoblasts[71]. Treatment with radiotherapy is contraindicated because it has been reported to cause damage of growth centres in bone and it results in malignant transformation of FD[7].

Most OF lesions grow slowly, and conservative surgical excision is the treatment of choice[1]. Untreated tumours could nevertheless attain massive sizes and may therefore require en bloc resection[42]. Also, some authors have reported recurrence rates as high as 28.0% with enucleation or curettage as the first treatment, while recurrence is less commonly observed with surgical excision which is therefore regarded as the treatment of choice[4,42]. Others conversely[16,17] reported that there was no difference in outcome between patients treated conservatively and those treated by major surgery. They therefore recommended that conservative surgery be done even with large tumours that bow and erode the inferior border of the mandible. Yet, it can be concluded that OF is a benign neoplasm that seems to have a risk for recurrence, especially if incompletely removed[1].

Conclusion

FD and OF are the most common forms of BFOL in the craniofacial region; they are both slow growing lesions that can get to very large sizes when not adequately treated. Separation of the two entities clinically, radiologically or histologically can be difficult but recent advances in immunohisto-chemistry and genetics hold some promise in distinguishing these disease entities.

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