Diagnosis and Management of Benign Fibro-Osseous Lesions of the Jaws -

A Current Review for the Dental Clinician

Gisele N. Mainville, DMD, MSc, FRCD(C), Dipl. ABOMP[1]

Daniel P. Turgeon, DMD, MSc, FRCD(C), Dipl. ABOMR[1]

Adel Kauzman, DMD, MSc, FRCD(C)[1]

[1]Department of Stomatology, Faculty of Dentistry, Université de Montréal, Montreal, QC, Canada

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Corresponding author

Gisele Mainville, DMD, MSc, FRCD(C), Dipl. ABOMP

Assistant Professor of Oral and Maxillofacial Pathology
Department of Stomatology
Faculty of Dentistry
Université de Montréal
Montreal, QC, Canada
Tel : 514-343-6111 x37381
Fax : 514-343-2233
gisele.mainville.1@umontreal.ca

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Abstract

Benign fibro-osseous lesions of the maxillofacial skeleton constitute a heterogeneous group of disorders that includes developmental, reactive (dysplastic) and neoplastic lesions. Although their classification has been reviewed multiple times in the past, the most common benign fibro-osseous lesions are fibrous dysplasia, osseous dysplasia, and ossifying fibroma. For the dental clinician, the challenges involve diagnosis and treatment (or lack thereof). A careful correlation of all clinical, radiologic and microscopic features is essential to establish a proper diagnosis and a clear treatment plan. This article aims to review the clinical, radiological and histopathological characteristics of benign fibro-osseous lesions of the jaws, with emphasis on their differential diagnoses. With a deeper understanding of benign fibro-osseous lesions, clinicians will be better prepared to manage these lesions in their practice.

Introduction

Benign fibro-osseous lesions (BFOLs) of the jaws represent a group of disorders in which normal bone is replaced by fibrous connective tissue forming variable quantities of osteoid, bone or cementum-like calcifications. A mixture of these three tissues is often present within an individual lesion (Waldron, 1985). BFOLs include many conditions that, in spite of their microscopic and radiologic similarities, differ in aetiology and clinical behaviour. The classification of BFOLs has remained a challenging and controversial topic throughout the years, giving rise to many classification systems (Waldron, 1985, Waldron, 1993, Yoon et al., 1989, Slootweg, 1996, Slootweg and Muller, 1990, Eversole et al., 2008, Noffke et al., 2012, Eversole, 1997). Among them, Waldron's classification (Waldron, 1993) became the most acknowledged and applied in practice (Brannon and Fowler, 2001). Of all revisions made to Waldron's classification, Brannon and Fowler's 2001 classification remains the best adapted for clinical use. BFOLs are separated into three disease categories: neoplastic (ossifying fibromas), dysplastic lesions presumably of periodontal ligament origin (osseous dysplasia), and developmental (fibrous dysplasia) (**Table 1**). With the systematic application of this classification system in practice, our understanding of the radiological presentation and clinical behaviour of these lesions, as well as the applied therapeutic approaches evolved. For instance, while radiotherapy was an accepted treatment for certain BFOLs in the 1940s, it is now a known cause of sarcomatous transformation and is contra-indicated (Neville et al., 2016).

The final diagnosis of BFOLs of the jaws relies on careful correlation between the clinical history and presentation, radiographic appearance, intraoperative findings and histopathological features (Waldron, 1993, Summerlin and Tomich, 1994, Brannon and Fowler, 2001). Patient age, gender, ethnic group, and the lesional site(s) and distribution are also important elements to consider when making the diagnosis (MacDonald-Jankowski, 2004, MacDonald, 2015).

Diagnostic errors can arise when these data are not carefully considered, and can have therapeutic and prognostic repercussions. Some authors consider that a histopathologic diagnosis without clinical and radiographic correlation only becomes possible if the biopsy specimen includes the interface between lesional and normal adjacent tissue (Slootweg and Muller, 1990). Nevertheless, they acknowledge that in practice, such is a rare occurrence. Most frequently, in the absence of adequate clinical and radiologic information, the pathologist will decline to render a definitive diagnosis, preferring to designate a given biopsy as a *benign fibro-osseous lesion* (MacDonald-Jankowski, 2009b, Waldron, 1993, Abramovitch and Rice, 2016). Unfortunately for the clinician, this non-specific diagnosis does not provide much guidance towards the proper treatment course.

This article presents a review of the most common BFOLs of the jaws, with the aim of familiarizing the general practitioner with their clinical, radiologic and histopathologic characteristics. Differential diagnosis and clinical management will also be discussed.

Ossifying Fibroma

Ossifying fibroma (OF) is a fibro-osseous neoplasm that primarily arises during the 3rd to 4th decade of life (Su et al., 1997a, Summerlin and Tomich, 1994, Eversole et al., 1985a, MacDonald-Jankowski, 2009b). Women are affected 2.5 times more frequently than men (MacDonald-Jankowski, 2009b). OF primarily affects white people, followed by patients of African descent (Mintz and Velez, 2007, Su et al., 1997a, Eversole et al., 1985b). The molar and premolar regions of the mandible are the sites of predilection. When presenting in the maxilla, the canine fossa and zygomatic arch are most frequently affected (White and Pharoah, 2014). Although currently considered to be an osseous neoplasm by the World Health Organization (WHO), some authors have argued OF likely represents a primary odontogenic tumor (Slootweg and El-Mofty, 2005, Woo, 2015).

Clinically, 31% of OFs are asymptomatic and fortuitously discovered on routine radiographs (MacDonald-Jankowski, 2009b). Average size at diagnosis is 1cm to 5cm in greatest diameter (Eversole et al., 1985a, Su et al., 1997a). OF often behaves in a minimally aggressive fashion, slowly increasing in volume. With time, OF reaches more important dimensions (Neville et al., 2016), presenting with bucco-lingual expansion in 84% (**Figure 1**), facial swelling in 66% and pain in 16% of cases (Waldron, 1985, Mintz and Velez, 2007, MacDonald-Jankowski, 2009b). With increasing growth, OF can displace teeth, the inferior alveolar nerve, the lower border of the mandible, as well as the floor of the maxillary sinus (White and Pharoah, 2014, MacDonald-Jankowski, 2009b). External root resorption is visible in 20% of cases (MacDonald-Jankowski, 2009b). Most cases present as a unilocular, well demarcated to corticated radiolucency (Su et al., 1997a). Multilocular lesions have been reported (MacDonald-Jankowski, 2009b), however this is an exceptionally uncommon presentation mostly related to the synchronous development of an aneurysmal bone cyst. The internal appearance of the lesion depends upon its maturity and the quantity of mineralized tissue produced by the stroma (MacDonald-Jankowski, 2009b). Early lesions are entirely radiolucent, and radiopaque foci become apparent within the radiolucency at later stages (**Figure 1**). In long-standing lesions, a thin radiolucent line is often visible at the periphery, representing a fibrous interface separating the calcified mass from the adjacent normal bone.

Microscopically, OF presents as a proliferation of cellular fibrous tissue that contains a variable quantity of mineralized material (**Figure 2**). The degree of cellularity can vary considerably from one area of the lesion to another, with hypocellular, collagenized areas merging with more hypercellular areas (Slootweg, 1996). The mineralized material can have the shape of bony trabeculae or of ovoid basophilic cementum-like structures (Brannon and Fowler, 2001, Eversole et al., 1985a). Tumours generally present a combination of these calcified

structures. The bony trabeculae of OF can show a thick peripheral “brushed border” of osteoid, or can be rimmed by osteoblasts. In contrast, osteoblastic rimming is normally absent in fibrous dysplasia (FD) (Brannon and Fowler, 2001). The fibrous tissue of OF is well vascularized, but does not contain foci of haemorrhage commonly seen in focal osseous dysplasia (FocOD) (Waldron, 1993, Su et al., 1997b). Finally, this well-demarcated lesion is separated from the surrounding normal bone by a thin layer of fibrous tissue (or capsule).

OF is treated by conservative surgical resection. Larger examples may necessitate resection and reconstruction with a bone graft (Mintz and Velez, 2007). Because of the presence of a fibrous capsule, the tumour typically easily comes out in one piece from its bony crypt during removal (Slootweg, 1996, Waldron, 1993). This tendency to shell out in one or a few pieces clinically differentiates OF from FocOD, which will generally fragment into small pieces during curettage. Microscopically, the presence of a fibrous capsule separating the tumour from adjacent bone can be a useful distinguishing feature (Waldron, 1993). Recurrence rate is highly variable according to different studies. Some authors claim it is very low or inexistent (Brannon and Fowler, 2001, Waldron, 1985), while others have reported a 12-28% recurrence rate (Eversole et al., 1985a, MacDonald-Jankowski, 2009b). No microscopic feature distinguishes the tumours that have a higher risk of recurrence (Eversole et al., 1985a). Long-term radiographic follow-up is therefore recommended for patients with OF. For cases with rapid growth, a tendency to recur, especially affecting children, a diagnosis of juvenile ossifying fibroma (JOF) should be considered. Hyperparathyroidism-jaw tumour syndrome, a rare autosomal dominant syndrome caused by mutations in the tumour suppressor gene *HRPT2*, should be suspected in patients presenting OF of the jaws, familial hyperparathyroidism, renal cysts and Wilms tumours (Chen et al., 2003).

The radiographic differential diagnosis for OF includes FD, periapical and focal osseous dysplasia, and desmoplastic ameloblastoma (White and Pharoah, 2014, Neville et al., 2016). Distinguishing amongst these diagnoses is important since treatment considerably varies between them. FD has ill-defined borders, a large transition zone between lesional and normal bone, and a more homogenous "ground-glass" internal structure. A biopsy of the lesion that includes overlying cortical bone would show merging of the lesion with the cortex in the context of FD, whereas OF would show a fibrous interface between the lesion and the cortex (Speight and Carlos, 2006). FD also has the capacity to displace adjacent structures, but not in a concentric, outwardly manner, starting from an epicentre, as is the case with OF. Periapical osseous dysplasia (POD) is characterized by multifocal, periapical involvement of the mandibular incisors. Radiologic distinction between FocOD and OF can be more difficult and will be discussed further. Desmoplastic ameloblastoma is a rare histological variant of ameloblastoma that does not present the usual clinico-pathologic characteristics of ameloblastomas. Desmoplastic ameloblastomas more commonly affect the anterior jaws. They can resemble OFs radiologically because of their well demarcated borders and mixed radiopaque and radiolucent internal structure. This mixed radiographic appearance is due to metaplastic bone formation within the desmoplastic stroma that characterizes this odontogenic tumor (Savithri et al., 2013). Calcifying odontogenic cyst (Gorlin cyst or calcifying cystic odontogenic tumour), calcifying epithelial odontogenic tumour (Pindborg tumour), and adenomatoid odontogenic tumour are other considerations within the differential diagnosis (Mintz and Velez, 2007), owing to their mixed radiologic appearance.

Juvenile Ossifying Fibroma (Juvenile Active Ossifying Fibroma)

JOF is a rare and aggressive fibro-osseous tumour that most often affects patients under the age of 30 years and shows a predilection for the craniofacial bones. From a clinical, radiological and microscopic standpoint, distinction from the conventional OF can sometimes be difficult to accomplish (Brannon and Fowler, 2001, Waldron, 1985, Waldron, 1993, Urs et al., 2013). Clinically, JOF shows active and rapid growth. It often reaches important dimensions, causing local destruction and facial asymmetry. Involvement of the orbital bone or paranasal sinuses can provoke nasal obstruction, exophthalmia, and visual changes. Some authors do not believe that JOF always behaves aggressively, and is not limited to children and adolescents (Brannon and Fowler, 2001). Radiographically, OF can be distinguished from JOF by the appearance of the lesion's periphery. Both JOF and OF have well defined margins. However, OF displays a thin capsule radiologically (appearing as a radiolucent line visible on conventional intraoral radiographs), whereas JOF does not (MacDonald, 2015, Urs et al., 2013).

In addition to clinical aggressiveness, JOF differs from OF histopathologically. The WHO recognizes two histological variants of JOF: trabecular and psammomatoid (Slootweg and El-Mofty, 2005). The trabecular variant primarily affects men aged 8 to 12 years. The maxillary bone is the site of predilection (Slootweg and El-Mofty, 2005). Radiographically, the tumour resembles conventional OF, however its clinical course is more aggressive. Microscopic examination reveals highly cellular fibrous tissue, osteoid-like deposits and bony trabeculae surrounded by plump osteoblasts (**Figure 3 A**). In addition to the immature bone formation, collections of multinucleated osteoclast-like giant cells are characteristically found in the fibrous tissue (Odin et al., 2012). Mitotic activity is present (which explains the rapid tumour growth), but cytonuclear atypia and abnormal mitoses are absent (Odin et al., 2012, Slootweg, 1996) (**Figure 3 B**). The recurrence rate following surgical ablation ranges from 30 to 58% (Neville et

al., 2016), which is much higher than for conventional OF. Radiographic follow-up is therefore necessary.

More frequent than the trabecular variant, the psammomatoid variant also affects young patients but over a wider age range (Urs et al., 2013). This tumour more often involves the orbital bones and paranasal sinuses, and less frequently the maxillary bones (Slootweg and El-Mofty, 2005, Slootweg et al., 1993). Microscopically, these lesions show a proliferation of fusiform fibroblastic cells and spherule-like acellular calcifications surrounded by an eosinophilic rim (psammomatoid calcifications). Recurrence rate following excision is nearly as high as with the trabecular form of JOF.

Osseous Dysplasia

Previously referred to as cemental dysplasia, cemento-osseous dysplasia or cementoma, osseous dysplasia (OD) is the most commonly encountered BFOL of the jaws in clinical practice. In this context, *dysplasia* signifies an abnormal and disorganized production of bone with no associated risk of malignant transformation.

The aetiology and pathogenesis of OD are not well understood (Brannon and Fowler, 2001). Since OD develops in the alveolar bone, an odontogenic origin has been proposed. Histologic similarities between osteoblastic, cementoblastic and fibroblastic cells present in the periodontal ligament as well as in OD lesions have supported the progenitor role of PDL fibroblasts (Slootweg and Muller, 1990, Waldron, 1985, Waldron, 1993, Brannon and Fowler, 2001, Summerlin and Tomich, 1994). In this article, the term *osseous dysplasia* will be preferred, as it was by Pharoah, Brannon and Fowler, and by the WHO's most recent classification (Brannon and Fowler, 2001, Slootweg and El-Mofty, 2005, White and Pharoah, 2014).

OD is classified into three clinico-radiological patterns that represent a spectrum of the disease process: periapical osseous dysplasia (POD), focal osseous dysplasia (FocOD) and florid osseous dysplasia (FOD) (Summerlin and Tomich, 1994, Waldron, 1993). Much rarer and of hereditary origin, familial gigantiform cementoma will be discussed separately.

Periapical Osseous Dysplasia

POD is most frequent in women, between 30-50 years of age, of African or south-eastern Asian descent (Slootweg, 1996, Waldron, 1985, Waldron, 1993, White and Pharoah, 2014, Zegarelli et al., 1964, Kawai et al., 1999). The reason for this racial predisposition remains unclear. The apical region of the mandibular incisors is most often affected. A multifocal distribution is typical (MacDonald, 2015). The adjacent teeth are vital, asymptomatic and the lesion is almost always discovered on routine dental radiographs (Waldron, 1985). The overlying gingiva remains unaffected by the bony changes. Despite the self-limited growth potential of POD, some cases show slight bucco-lingual cortical expansion with 3D imaging modalities (Abramovitch and Rice, 2016). Future studies using advanced radiologic imaging are needed to demonstrate if this is more common than previously reported.

POD goes through three histopathologic stages of maturation, each having a particular radiologic appearance. In the initial stage, radiolucencies are noted at the apices of the mandibular incisors (**Figure 4**). They resemble inflammatory periapical lesions, however, the teeth are vital and the periodontal ligament (PDL) space is intact. A diagnostic error at this stage can lead to useless endodontic or surgical intervention (Smith et al., 1998, Koehler, 1994, Ward, 1993). The second stage of development presents as mixed lesions. Radiopacities form at the centre of the initial radiolucencies, creating a target-like appearance. The central calcifications can be round, ovoid, or irregularly shaped. Finally, at the third stage of maturation, lesions will

appear completely radiopaque, with an irregular but well-defined border. A radiolucent rim of variable thickness, followed by a thin sclerotic band of reactive bone, surrounds the central radiopacity (MacDonald, 2015).

As mentioned above, the microscopic appearance of POD will vary depending on the stage of maturation. The histologic features of OD are identical for all three patterns (POD, FocOD and FOD). A well-vascularized, variably cellular fibrous connective tissue with scanty calcified material is seen in the early stages. Foci of haemorrhage can be seen within lesional tissue (Summerlin and Tomich, 1994, Waldron, 1993, Brannon and Fowler, 2001). Then, variable quantities of calcified material develop within the fibrous connective tissue giving rise to the mixed radiologic appearance. The calcified material can have the appearance of immature woven bony trabeculae and/or spherules of acellular calcified tissue classically described as representing cementum. The bony trabeculae can have a curvilinear shape, giving them the appearance of "ginger roots", generally lacking osteoblastic rimming (**Figure 5**). In the advanced stages, coalesced, relatively acellular and avascular sclerotic masses and sheets of lamellar bone and cementum-like tissue are seen, with little remaining fibrous stroma (Woo, 2015). Inflammation is virtually absent throughout all histopathologic stages. However, lesional contact with oral flora can lead to infection, superimposed osteomyelitis and sequestration of the sclerotic masses, which is a more common complication of FOD (Brannon and Fowler, 2001).

A biopsy is not essential for establishing the diagnosis, which can be entirely based on the clinical history and radiologic appearance. No treatment is required for POD (Slootweg, 1996). When dental implants are considered as a restorative treatment option for an edentulous ridge affected by OD, the risk of dental implant failure may be elevated. The abnormal fibro-osseous tissue can compromise the osteointegration of dental implants because of the poor vascularity of the mineralized matrix (Abramovitch and Rice, 2016). Patients should be carefully informed of

this risk before consenting to dental implant placement in an area of OD. Radiologic follow-up is recommended in order to identify a possible evolution toward FOD (Woo, 2015).

Focal Osseous Dysplasia

FocOD represents the most common BFOL of the maxillofacial region (Su et al., 1997a, Su et al., 1997b). Women of African descent are more frequently affected and the mean age at diagnosis is between 38-41 years (Brannon and Fowler, 2001, Su et al., 1997a, MacDonald, 2015). The site of predilection is the posterior region of the mandible (Brannon and Fowler, 2001, Summerlin and Tomich, 1994). The lesion is often associated with the apical region of a tooth (**Figure 6**), or located in an edentulous space (**Figure 7**). The lesional site can aid in distinguishing FocOD from OF (Su et al., 1997a). Just like POD, the radiologic appearance of FocOD varies according to the lesion's stage of maturation. It can be radiolucent with or without a sclerotic border, mixed, or entirely radiopaque. Just over half of cases (53%) have a well-defined periphery (MacDonald, 2015). FocOD is asymptomatic and usually discovered fortuitously on routine dental radiographs (Su et al., 1997a). Unless it is secondarily infected, it is rarely the source of discomfort or bony expansion (MacDonald, 2015).

Distinguishing between FocOD and OF can be a great radiological challenge, particularly when facing a small OF. For the dentist, the diagnosis will determine if the lesion is better left alone or should be removed. Two clinico-radiological criteria can aid in distinguishing both lesions. First, FocOD has a tendency to involve periapical regions or extraction sites, which are less frequent localizations of OF (Su et al., 1997a). Secondly, during surgery, FocOD will come out in multiple small curetted fragments of variable consistency, whereas OF will usually shell out as one large mass or as a few large pieces (Su et al., 1997b, Summerlin and Tomich, 1994). A biopsy may be required to confirm the diagnosis. Once diagnosed, no treatment is required for

FocOD. Periodic follow-up is recommended to identify a possible progression toward FOD (Summerlin and Tomich, 1994).

Florid Osseous Dysplasia

This rare BFOL represents the generalized form of OD (Melrose et al., 1976). Of unknown aetiology, FOD overwhelmingly affects middle-aged women of African or Asian descent (White and Pharoah, 2014, MacDonald, 2015). The reason behind this racial prevalence remains unknown. Lesions are usually bilateral, symmetrically distributed and limited to the alveolar bone (Beylouni et al., 1998). More than one sextant needs to be involved. The mandible is always affected, whereas the maxilla is affected in two thirds of cases (MacDonald, 2015).

Radiographically, FOD classically presents as multiple, well-defined, sclerotic radiopaque masses accompanied by mixed lesions with ill-defined borders. A peripheral radiolucent rim, followed by a sclerotic border, often surrounds the radiopaque masses (**Figure 8)**. Individual lesions can coalesce to form large, irregularly shaped sclerotic masses (**Figure 9**). Extensive lesions can cause cortical expansion (**Figure 10**) and inferior displacement of the inferior alveolar nerve (**Figure 9**) (White and Pharoah, 2014). Well-defined radiolucent zones sometimes appear alongside the sclerotic masses, representing simple (traumatic) bone cyst formation (Waldron, 1993). These cysts can go through periods of growth followed by stabilization and regression. The mandibular incisors can present signs of POD (White and Pharoah, 2014, Neville et al., 2016).

FOD discovered on a routine radiographic examination is often asymptomatic. In these cases, the final diagnosis is based on the clinico-radiologic correlation and no treatment is required. A biopsy is not indicated because it may expose the poorly vascularized sclerotic masses to the oral flora, leading to osteomyelitis, pain, fistula formation and sequestration (Singer

et al., 2005). These complications may also follow a tooth extraction, advanced periodontitis or an odontogenic infection. It is therefore important for patients to maintain excellent oral hygiene to prevent odontogenic infections and dental extractions. Alveolar atrophy in edentulous patients may also lead to exposure of the sclerotic masses to the oral cavity (Neville et al., 2016). FOD is generally not considered to be a potentially precancerous condition. There exists, however, at least 3 well-documented cases of sarcomatous transformation of FOD, two of them toward osteosarcoma (Lopes et al., 2010, Schneider et al., 1999, Melrose and Handlers, 2003). Given the risk these possible long-term complications, radiologic follow-up of patients diagnosed with FOD is recommended on an annual basis, according to the authors.

Rare cases of OD with unusual progressive expansion have been reported (Nofkke and Raubenheimer, 2011, Raubenheimer et al., 2016). These cases appear to be sporadic, unlike the inherited Familial Gigantiform Cementoma (FGC, discussed below). Whether or not such reports represent new cases of FGC, or should be considered an extremely rare form of the OD spectrum, remains unclear.

Familial Gigantiform Cementoma

FGC is a rare autosomal dominant condition with variable expressivity (Young et al., 1989). This condition affects both sexes with equal frequency (Brannon and Fowler, 2001). It is more prevalent in Caucasians, but has been well documented in African and Asian patients as well. The condition first presents in childhood with bilateral lesions resembling FOD involving the maxilla and mandible. The condition rapidly progresses, causing remarkable bony expansion and facial asymmetry often requiring surgical correction (MacDonald-Jankowski, 2004, Finical et al., 1999). In late stages of the disease, the sclerotic cemento-osseous masses of FGC run a high

risk of becoming secondarily infected, which can give rise to osteomyelitis. Bony involvement by FGC is always limited to maxillofacial skeleton.

Although they differ from a clinical perspective, FGC resembles FOD both radiographically and microscopically. FGC lesions will progress through the same three radiologic stages of maturation as FOD (Finical et al., 1999). The lesions will typically be multiple and bilateral, have a mixed radiologic appearance, cause cortical expansion, and cross the midline (Abdelsayed et al., 2001). As opposed to FOD, FGC lesions involve the basal as well as the alveolar processes of the jaws (MacDonald, 2015). The histopathologic appearance of FGC resembles FOD and distinguishing between both conditions cannot be made on a microscopic basis alone (Neville et al., 2016). However, a positive family history, the initial appearance of lesions during childhood, rapid growth, bony expansion and facial deformity favour a diagnosis of FGC (Young et al., 1989).

Fibrous Dysplasia

FD represents a rare nonhereditary condition resulting from a failure in the remodelling process of immature bone to mature lamellar bone (DiCaprio and Enneking, 2005). Failure of maturation results in gradual replacement of normal bone by cellular fibrous tissue that contains variable quantities of irregular bony trabeculae and woven bone. FD lesions can be limited to one bone (monostotic), involve multiple bones (polyostotic), and be associated with cutaneous and endocrine abnormalities.

The aetiology of FD had remained obscure since its initial description in 1891 by von Recklinghausen. Since then, a link has been discovered to dominant somatic mutations of the *GNAS1* gene located on chromosome 20q13 (Weinstein et al., 1991, Weinstein, 2006). Point mutations of the *GNAS1* gene lead to the activation of the stimulatory α-subunit of a G-protein,

which results in constitutive activation of adenylyl cyclase in the affected cells (Lumbroso et al., 2002). This, in turn, increases cellular proliferation and disrupts cell differentiation (Marie et al., 1997, Marie, 2001, Chapurlat and Orcel, 2008). Clinically, these molecular changes result in overproduction of a disorganized fibrotic bone matrix, skin pigmentation and autonomous hormonal hyperproduction. They have been identified in monostotic FD, polyostotic FD as well as McCune-Albright syndrome (Lumbroso et al., 2002, Marie et al., 1997, Leitman et al., 2005). The clinical extent of disease will depend on the developmental timing of the *GNAS1* mutations and the mosaic distribution of affected cells. All daughter cells descending from the originally mutated pluripotent cell (osteoblasts, fibroblasts, melanocytes and endocrine cells) will manifest the phenotypic characteristics of the disease. The earlier the mutation, the more widespread is the disease (Cohen Jr and Howell, 1999). Other studies suggest a probable role of interleukin-6, a cytokine capable of controlling osteoclast activity (Riminucci et al., 2003). A better understanding of these molecular alterations could offer interesting tools for diagnosis and treatment of patients with FD (DiCaprio and Enneking, 2005).

Polyostotic Fibrous Dysplasia and McCune-Albright Syndrome

Polyostotic FD occurs in childhood and involves a minimum of two bones or up to over 75% of the skeleton. The clinical presentation is characterized by unilateral or bilateral bony swelling, primarily affecting the femur. The craniofacial bones, tibia, pelvis, ribs, humerus, radius, fibula and vertebrae can also be affected. Symptoms often present in the first decade of life and include bone pain, claudication, bony deformation or pathologic fractures (Waldron, 1985, Benbouazza et al., 2002). When cutaneous manifestations are present, such as *café au lait* macules, the condition is called Jaffe-Lichtenstein syndrome. McCune-Albright syndrome (MAS) is characterised by a triad of polyostotic FD, cutaneous lesions and endocrinopathies. Polyostotic

FD is also a component of a very rare condition, Mazabraud syndrome, which is also characterized by multiple intramuscular myxomas (Parekh et al., 2004, Faivre et al., 2001).

MAS affects 3% of patients affected by polyostotic FD (MacDonald-Jankowski, 2009a). Patients are primarily females and present bone lesions, *café au lait* macules of the skin and endocrine disturbances (Parekh et al., 2004). The pigmented skin macules often affect the trunk and proximal regions of the limbs. They have notably irregular borders, often described as following the topography of the coast of Maine (Neville et al., 2016, DiCaprio and Enneking, 2005). The endocrinopathies can include hyperthyroidism, hyperparathyroidism, acromegaly, and diabetes or can be due to a pituitary adenoma. However, the most frequent presentation is precocious puberty (mostly in girls), where traits of puberty can appear during the first decade of life (Hennekam et al., 2010).

Monostotic Fibrous Dysplasia

The monostotic form of FD accounts for 80 to 85% of cases (MacDonald-Jankowski, 2009a). There is no gender predilection (El-Mofty, 2014). Monostotic FD is most often diagnosed in the 2nd and 3rd decades of life, although patients may be aware of their lesion on average 5 years prior to seeking professional opinion (MacDonald-Jankowski, 2009a, MacDonald, 2015). The craniofacial bones, femur and ribs are the sites of predilection, followed by the tibia, clavicles and vertebrae. In the maxillofacial region, the monostotic form of FD is the most frequent. It primarily affects the posterior maxilla, followed by the mandible. Lesions are unilateral. Involvement of the maxilla often extends to adjacent bones such as the zygomatic, sphenoid, frontal, ethmoid and occipital bone. The name *craniofacial FD* is preferred to distinguish these FD lesions that involve more than one bone but not the rest of the skeleton (**Figure 11**) (Waldron, 1993). Almost all cases (90%) present with unilateral tumefaction, and

less frequently (18%) with pain. Only 2% of monostotic FD of the jaws are discovered incidentally during a radiologic examination prescribed for another reason (MacDonald-Jankowski, 2009a). With involvement of the skull base, signs of nerve compression, such as anosmia, visual loss or deafness, can also develop (MacDonald-Jankowski, 2009a, El-Mofty, 2014).

The radiographic appearance of FD has classically been described as a diffuse opacity with a ground glass, orange peel or finger print appearance (White and Pharoah, 2014, Akintoye et al., 2004, Petrikowski et al., 1995, MacDonald-Jankowski, 2009a). Early lesions appear radiolucent due to the abundance of fibrous tissue. FD is therefore rarely considered in the radiographic differential diagnosis at this stage. With bone deposition within the fibrous tissue, the lesion becomes mixed radiolucent-radiopaque, with ill-defined margins that transition and blend into the normal adjacent bone. Extragnathic FD lesions have better defined margins compared to gnathic lesions (MacDonald, 2015, MacDonald-Jankowski, 2009a, Speight and Carlos, 2006). The buccal and lingual cortices become expanded and thinned but are rarely interrupted (MacDonald-Jankowski, 2009a). FD can cause sclerosis of the cranial base (Brannon and Fowler, 2001, Waldron, 1993), and can displace the maxillary sinus floor superiorly, eventually causing its complete obliteration (MacDonald, 2015) (**Figure 12**). The inferior alveolar nerve canal can also be displaced superiorly, a sign which seems to be pathognomonic for FD (Petrikowski et al., 1995). Occasionally, teeth surrounded by the affected bone can become displaced and the definition of the lamina dura can be lost (Petrikowski et al., 1995). Cystic degeneration of gnathic FD has been reported (Ferretti et al., 1999).

Computerized tomography (CT scan or Cone-beam CT scan) is the technique of choice to determine the radiologic margins of FD. Magnetic resonance imagery can provide valuable information if haemorrhagic or cystic changes are suspected (DiCaprio and Enneking, 2005), or if

the lesion has undergone malignant transformation (Parekh et al., 2004). A technetium bone scan can help identify subclinical lesions, confirm multifocal involvement, determine the distribution of lesions, and provide information on whether or not lesions are still in an active growth phase (Parekh et al., 2004).

A biopsy is required only if the radiologic diagnosis is unclear (DiCaprio and Enneking, 2005). Microscopic examination of FD reveals a fibrous stroma, supporting numerous blood vessels and fusiform fibroblastic cells that show no signs of cellular atypia. Variable quantities of immature woven bone are present throughout the fibrous connective tissue (Slootweg, 1996). These trabeculae are irregularly shaped, ramified and serpentine, often having the appearance of Chinese characters (Slootweg, 1996, Waldron, 1993) or alphabet soup (DiCaprio and Enneking, 2005, Parekh et al., 2004). They vary considerably in size and in degree of calcification. Osteoblastic rimming can be noted, but is typically absent (Woo, 2015). Artifactual peritrabecular clefting is another typical finding that serves as an important diagnostic feature for distinguishing FD from OF (**Figure 13**) (Ribeiro et al., 2012). The quantitative ratio of fibrous tissue to bony trabeculae varies considerably from one lesion to another, but seems rather stable in different zones of a single lesion (Slootweg and Muller, 1990). This microscopic homogeneity is an important diagnostic element of FD (Slootweg and Muller, 1990). In craniofacial FD, particularly in later stage lesions, lamellar maturation of the bone may be seen (Speight and Carlos, 2006). Ovoid calcifications resembling cementum are rarely present, in contrast to OD and OF (Neville et al., 2016). Lesional tissue is non-encapsulated and seems to fuse with peripheral cortical bone (**Figure 14**). This histopathologic characteristic is often confirmed on radiologic examination, and is a valuable diagnostic finding in biopsies that include a margin of the lesion (Speight and Carlos, 2006). This correlation between histopathologic and radiologic findings facilitates the

distinction between craniofacial FD and OF (Brannon and Fowler, 2001, Slootweg and Muller, 1990), which, without a doubt, is harder to render based on microscopic findings only.

The growth rate of FD of long bones diminishes considerably following puberty. A complete arrest of lesional growth can even be seen following puberty, especially in the monostotic form of the disease. With polyostotic and craniofacial FD, lesions can pursue their growth even when osseous maturity is reached (DiCaprio and Enneking, 2005, MacDonald, 2015). Reports of reactivation in adult life also exist (Daly et al., 1994, MacDonald-Jankowski and Li, 2009). Therapy must be modulated in relation with the age of the patient, the degree of bone involvement and the rate of growth. Treatment must be conservative and delayed, if possible, until the lesion is quiescent (Waldron, 1993).

Aesthetics play an important role in the therapeutic management of craniofacial FD (Slootweg, 1996), with interventions varying between regular clinical and radiological follow-up to multiple surface osteotomies (Mehta et al., 2006, Waldron, 1993). Radiotherapy is contra-indicated in the treatment of all forms of FD due to the risk of sarcomatous transformation (Waldron, 1993). The use of bisphosphonates and IL-6 inhibitors in the management of FD is currently under investigation and remains off-label (Faruqi et al., 2014).

The prognosis of FD is generally good. FD of long bones can cause handicaps related to pathologic fractures and bone deformation. There exists a small risk of malignant transformation, usually to an osteosarcoma, ranging between 0.4 and 6.7% of cases. Most authors estimate the actual frequency as being inferior to 1%, although patients with McCune-Albright syndrome, Mazabraud syndrome or a history of radiotherapy are at increased risk (Qu et al., 2015). Sarcomatous change can present clinically as a pathologic fracture in long bones, swelling and pain (Qu et al., 2015). The craniofacial skeleton and proximal region of the femur are sites of

predilection for this complication of the disease (Ruggieri et al., 1994) Therefore, long-term clinical and radiographic follow-up is prudent for any patient with FD.

Conclusions

BFOLs of the jaws represent a diverse group of conditions in which the clinical, radiologic and even the histopathologic diagnosis can be difficult to establish. A consultation with an oral and maxillofacial radiologist can be very helpful. When a biopsy is indicated, it should include the interface between lesional and normal adjacent tissue, and the pertinent radiographic information should be provided to the pathologist. Achieving an accurate final diagnosis is of primordial importance since it will command appropriate therapeutic action: no intervention in the context of certain BFOLs (such as POD), or rapid and occasionally aggressive action with others (such as JOF). Correlation between the biologic behaviour of the lesion and clinical, radiologic and histopathologic data is essential in reaching an accurate diagnosis.

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Table 1. Brannon and Fowler's classification of BFOLs of the jaws (Brannon and Fowler, 2001)

Fibro-osseous neoplasms
Conventional ossifying fibroma
Juvenile (active) ossifying fibroma
Osseous dysplasia
Acquired origin (nonhereditary)
Periapical osseous dysplasia
Focal osseous dysplasia
Florid osseous dysplasia
Hereditary origin
Familial gigantiform cementoma
Fibrous dysplasia
Fibrous dysplasia and endocrinopathy (McCune-Albright syndrome)
Polyostotic fibrous dysplasia
Craniofacial fibrous dysplasia

Figure Legends

Fig. 1 Ossifying fibroma. 52 year-old female patient. An axial view of a CT scan demonstrating a well demarcated mixed lesion with central radiopacities surrounded by a radiolucent rim, causing bucco-lingual cortical expansion in the anterior left mandible and tooth displacement. (Courtesy of Dr. Michael Pharoah)

Fig. 2 Ossifying fibroma. High-magnification photomicrograph showing cellular fibrous connective tissue forming acellular calcified material of various shapes and sizes. The calcified tissue shows a peripheral « brushed border » of osteoid (arrows). H&E.

Fig. 3 Juvenile ossifying fibroma, trabecular type. Low-magnification (**A**) and high-magnification (**B**) photomicrographs showing trabeculae of bone and osteoid deposits surrounded by highly cellular stroma. Occasional mitotic activity can be observed (circle), but cytonuclear atypia and abnormal mitoses are absent. H&E.

Fig. 4 Periapical osseous dysplasia. 30 year-old female patient. Periapical radiograph showing multifocal periapical radiolucencies at the apices of the mandibular incisors. Note the intact PDL spaces on teeth #24-25, but a widening of the PDL space on tooth #23. The latter represents rarefying osteitis associated with a necrotic tooth. (Courtesy of Dr. Linda Lee)

Fig. 5 Periapical osseous dysplasia. High-magnification photomicrograph of a long-standing lesion showing curvilinear bony trabeculae with the appearance of « ginger roots », lacking osteoblastic rimming, in hypocellular fibrous connective tissue. H&E.

Fig. 6 Focal osseous dysplasia. 69-year-old female patient. Periapical radiograph showing a calcified mass surrounded by a thin radiolucent rim at the apex of the first maxillary molar. The floor of the maxillary sinus is slightly elevated. Note the intact PDL space.

Fig. 7 Focal osseous dysplasia. Panoramic radiograph showing a well-circumscribed radiopaque mass with a radiolucent rim and a sclerotic border in the right mandibular body.

Fig. 8 Florid osseous dysplasia. Panoramic radiograph showing multifocal radiopaque masses surrounded by radiolucent rims in the posterior regions of the jaws. (Courtesy of Dr. Matthieu Schmittbuhl)

Fig. 9 Florid osseous dysplasia. Panoramic radiograph showing multifocal ill-defined and coalesced sclerotic masses in the apical region of all sextants of the jaws. There is mild inferior displacement of the left inferior alveolar nerve canal.

Fig. 10 Florid osseous dysplasia. Bilateral expansion of the mandibular buccal cortex. This is the same patient as shown in figure 8. (Courtesy of Dr. Matthieu Schmittbuhl)

Fig. 11 Craniofacial fibrous dysplasia. Panoramic radiograph showing a diffuse ground-glass opacity of the left posterior maxilla, obliterating the maxillary sinus. (Courtesy of Dr. Linda Lee)

Fig. 12 Craniofacial fibrous dysplasia. A coronal view of a Cone Beam CT scan demonstrating superior and medial displacement of the floor of the maxillary sinus, reducing its aerated space. This is the same patient as shown in figure 11. (Courtesy of Dr. Linda Lee)

Fig. 13 Fibrous dysplasia. High-magnification photomicrograph showing broad trabeculae of woven bone within a cellular fibrous stroma. Peritrabecular clefting (straight arrows) and occasional osteoblastic riming (curved arrow) are present. H&E.

Fig. 14 Fibrous dysplasia. Low-magnification photomicrograph showing replacement of the cortical and medullary bone by lesional tissue. Oral mucosa is present at the top of the image. H&E.