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Ossifying Fibromas of the Craniofacial Skeleton

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1. Introduction

Ossifying fibromas (OF) of the craniofacial skeleton, as described in WHO classification of odontogenic tumors (2005)(Barnes L 2005), are benign fibro-osseous neoplasms characterized by the replacement of normal bone by a fibrous cellular stroma containing foci of mineralized bone trabeculae and cementum-like material that vary in amount and appearance.(Brannon and Fowler 2001; El-Mofty 2002; Cruz, Alencar et al. 2008) The accurate nature and classification of OF has undergone considerable debate among pathologists, resulting in a confusing evolution of competing nomenclatures.(Brannon and Fowler 2001; Sarode, Sarode et al. 2011) Contemporary reviews have classified benign fibro-osseous lesions of the craniofacial complex into neoplasms, developmental dysplastic lesions and inflammatory/reactive processes. [Table 1](Eversole, Su et al. 2008) In this reviews, subtypes vary with regard to behavior and propensity for recurrence after surgical excision. The definitive diagnosis can rarely be rendered on the basis of histopathological features alone and is usually dependent upon assessment of microscopic, clinical and imaging features together. This review will discuss the clinical, microscopic, radiological and therapeutic aspects of ossifying fibromas in this localization.

2. Definition and histological subtypes

Neoplasms with a fibro-osseous histology are represented by the ossifying fibroma group of lesions. These are neoplasms in the true sense, exhibiting progressive proliferative capabilities with boney expansion and, importantly, well defined margins radiologically. According to their pattern of mineralization, four overlapping clinicopathological entities have been historically identified: juvenile psammomatous ossifying fibroma (JPOF), juvenile trabecular ossifying fibroma (JTOF), gigantiform cementoma (GC) and cemento-ossifying fibroma (COF) not otherwise specified (NOS), implying that the clinicopathologic features

do not conform to the other types of ossifying fibromas. GC may show an autosomal dominant genetic or "familial" underpinning. Most ossifying fibromas are single focal lesions; however gigantiform cementoma is typically multifocal and may occur in all four jaw quadrants in a single patient. There are also reports of lesion multiplicity in the other forms of ossifying fibroma yet such occurrences are quite rare. Notwithstanding these entities, it must be emphasized the contrast of OF with the much more common fibrous dysplasia (FD), a developmental hamartomatous fibro-osseous lesion, from which the differential is difficult based solely on clinical or radiographic criteria (Brannon and Fowler 2001; El-Mofty 2002; Noudel, Chauvet et al. 2009).

I. Bone dysplasias
    a. Fibrous dysplasia
        i. Monostotic
        ii. Polyostotic
        iii. Polyostotic with endocrinopathy (McCune-Albright)
        iv Osteofibrous dysplasia[a]
    b. Osteitis deformans
    c. Pagetoid heritable bone dysplasias of childhood
    d. Segmental odontomaxillary dysplasia
II. Cemento-osseous dysplasias
    a. Focal cemento-osseous dysplasia
    b. Florid cemento-osseous dysplasia
III. Inflammatory/reactive processes
    a. Focal sclerosing osteomyelitis
    b. Diffuse sclerosing osteomyelitis
    c. Proliferative periostitis
IV. Metabolic Disease: hyperparathyroidism
V. Neoplastic lesions (Ossifying fibromas)
    a. Ossifying fibroma NOS
    b. Hyperparathyroidism jaw lesion syndrome
    c. Juvenile ossifying fibroma
        i. Trabecular type
        ii. Psammomatoid type
    d. Gigantiform cementomas

[a]Osteofibrous dysplasia is found in the fibula and tibia only

Table 1. Classification of fibro-benign lesions of the cranio-facial complex

3. Epidemiology

According to WHO classification (2005) OF most commonly occurs in the 2nd to 4th decades and shows a predilection for females. The mean age of the histological subtypes varies. In patients with JPOF it is about 20 years compared to 35 years in cases of conventional ossifying fibroma. JTOF has a still lower mean age range (8.5-12 years).

4. Clinical and imagiological features

The commonest fibrous-osseous lesions of the orbit and sinonasal tract are OF and FD. The diagnosis between these two entities may be challenging, because they share similar features. There are four main clinical subtypes of FD: monostotic (affects one bone, and accounts for 85% cases of FD), polyostotic (affects multiple bones), McCune–Albright syndrome in which multiple disseminated lesions of bone are accompanied by skin hyperpigmentation and endocrine disturbances; and osteofibrous dysplasia (Brannon and Fowler 2001; Smith, Newman et al. 2009).

The juvenile variants of ossifying fibromas share many similarities, but they have been distinguished on the basis of their histopathological features, site, and age of recurrence (Shields, Peyster et al. 1985; Noudel, Chauvet et al. 2009; Smith, Newman et al. 2009). Their location is also different: JPOF arises mainly around paranasal sinuses and orbits, whereas JTOF usually affects the maxilla. The last entity, COF, is an odontogenic neoplasm arising from the periodontal ligament and affects the tooth-bearing areas of the jaws, mandible, and the maxilla; the cementicles are the characteristic feature instead of the bone elements. JTOF also known as trabecular desmo-osteoblastoma affects mainly the jaws of children and adolescents. Only 20% of the patients are over 15 years of age. In a review of a number of case series the mean age range was found to be 8.5–12 years (Slootweg and Muller 1990; Slootweg, Panders et al. 1994; El-Mofty 2002). Origin in extragnathic locations is extremely rare. Clinically, it is often characterized by a progressive and sometimes rapid expansion of the affected area; pain is a rare symptom. Cystic degeneration and aneurysmal bone cyst formation has been reported in a few cases. Radiographically, JTOF is an expansive lesion and may be fairly well demarcated, with cortical thinning and perforation. Depending on the amount of calcified tissue produced, the lesion will show varying degrees of radiolucency or radiodensity. Ground-glass as well as a multilocular honeycomb appearance has been described.

Differing from JTOF, JPOF is a lesion that affects predominantly the extragnathic craniofacial bones, particularly centered on the periorbital, frontal, and ethmoid bones (El-Mofty 2002). First described by Gogl in 1949 and Margo in 1985, JPOF seems to stand out as a separate clinicopathologic entity different from the gnathic cemento-ossifying fibroma.(Gogl 1949; Margo, Ragsdale et al. 1985) Patients are young, although the average age of incidence has varied in different studies from 16 to 33 years with an age range of 3 months to 72 years (in general a few years older than those with JTOF). The greatest majority of the reported cases of JPOF originated in the paranasal sinuses, particularly frontal and ethmoid. About 10% have been reported in the calvarium. Around 7% may occur in the mandible. Orbital extension of sinonasal tumors may result in proptosis, and visual complaints including blindness, nasal obstruction, ptosis, papilledema, and disturbances in ocular mobility. Radiographic examination of JPOF shows a round, well-defined, sometimes corticated osteolytic lesion with a cystic appearance. Sclerotic changes are evident in the lesion which may show a ground-glass appearance (Su, Weathers et al. 1997). The lesions appear less dense than normal bone. **Figure 1** and **figure 2** show an example of a JPOF invading the left periorbit and ethmoid sinus.
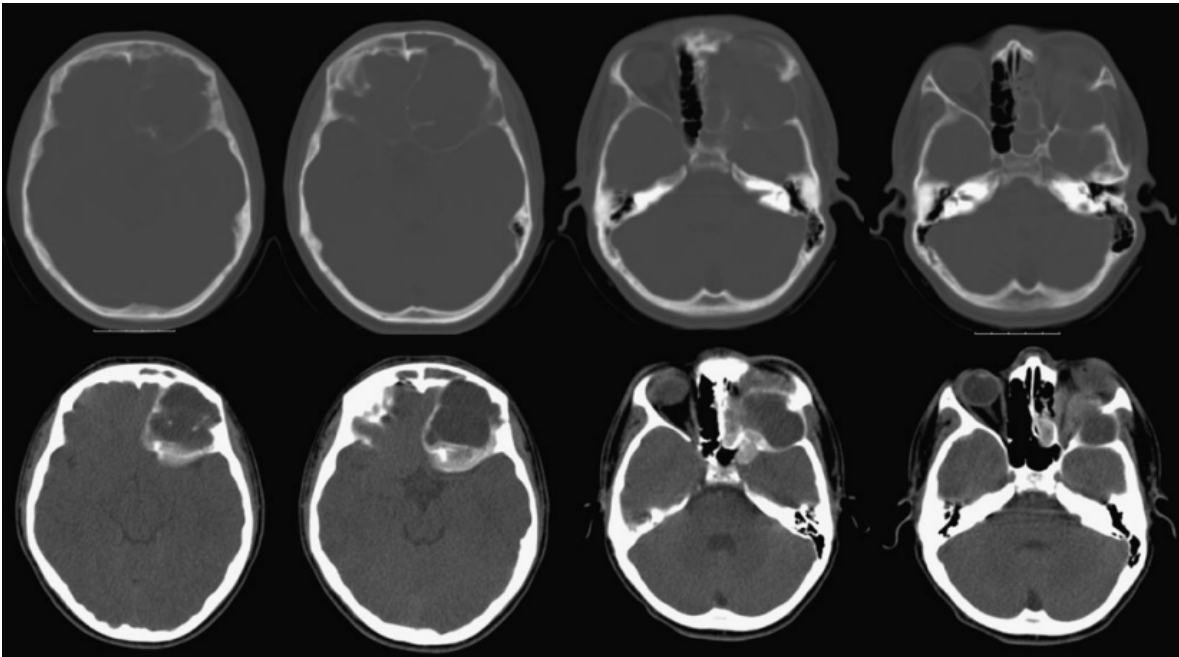
Figure 1. Axial CT scan showing a fibrous-osseous lesion (JPOF) of the left orbit and ethmoid sinus.
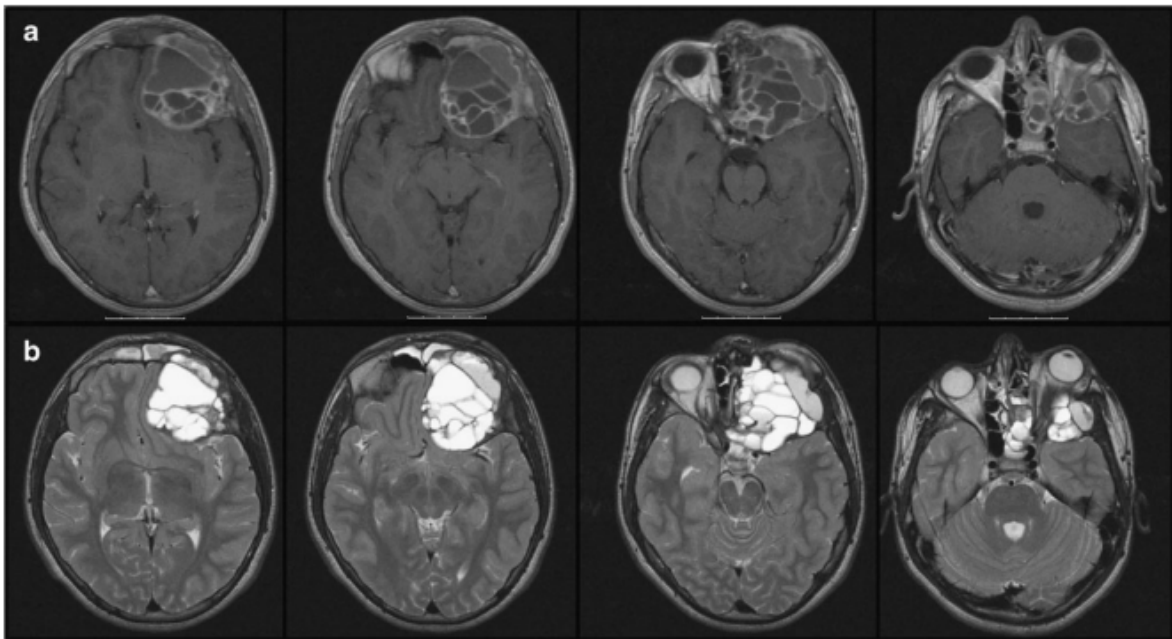

Figure 2. Gadolinium-enhanced axial T1-weighted (a) and T2-weighted (b) magnetic resonance imaging (MRI) showing an expansive cystic lesion (JPOF) invading the left periorbit and ethmoid sinus.

Gigantiform cementoma is an extremely rare form of ossifying fibroma, usually multifocal with tumors that are often massive. Lesions arise during childhood and progressively expand to cause facial deformity during early adult years (Young, Markowitz et al. 1989; Rossbach, Letson et al. 2005).

Table 2 summarizes some of the clinical, radiographic and microscopic characteristics of these entities.

Disease	Clinical features	Radiologic findings	Histopathology
Fibrous dysplasia	Expansion of bone Unilateral, painless Alk phosphatase Mono/Polyostotic	Diffuse radiolucent/ ground glass	Trabecular ''Chinese/Hebrew''
Ossifying fibroma Not otherwise specified	Expansile, painless Rarely multifocal Jaws	Circumscribed lucent or target lesion Root divergence	Trabecular Cementifying
Ossifying fibroma Trabecular variant	Expansile, painles Root divergence Aggressive	Circumscribed lucent Floccular opacities	Trabecular Giant cell foci Fibroplasia
Ossifying fibroma Psammomatoid	Expansile Facial bone Aggressive	Circumscribed Dense floccular opacities	Psammoma
Gigantiform cementoma	Massive, expansile Multiquadrant Often familial	Well delineated lucent with floccular opacities	Trabecular Cementifying

Table 2. Clinical, radiographic and microscopic parameters that distinguish among Ossifying Fibromas and Fibrous Dysplasia.

5. Etiopathogeny

The etiology of OF is unknown but odontogenic, developmental and traumatic origins have been suggested, (Caylakli, Buyuklu et al. 2004; Noudel, Chauvet et al. 2009; Mohsenifar, Nouhi et al. 2011) and thought to be of periodontal ligament origin because of their capacity to produce cementum and osteoid material (Slootweg and Muller 1990).

It has been hypothesized that JPOF originates from overproduction of the myxofibrous cellular stroma normally involved in the growth of the septa in the paranasal sinuses as they enlarge and pneumatize. These stromal cells secrete hyaline material that ossifies and connective tissue mucin that initiates the cystic areas (Sarode, Sarode et al. 2011).

6. Macroscopical and microscopical analysis

6.1. Ossifying fibromas

Ossifying fibroma NOS shows three histologic patterns or a mixture of these patterns:

(1) Ossifying form: common, similar to fibrous dysplasia, shows a pattern with small irregular osteoid trabeculae that are typically rimmed by osteoblasts (**figure 3a**). The stromal element is

hypercellular and the fibroblastic cells are devoid of atypical cytologic features. Early formative tumors show woven bone patterns when assessed under polarized light, and in mature lesions osteoblastic rimming is minimal and the irregular trabeculae are often lamellar.

(2) Cementifying form: is similar to the psammomatoid variant. Most also contain more typical osseous trabeculae in addition to the cemental structures which are ovoid or droplet in shape. These ovoid calcifications resemble normal cementicles that are present in the periodontal ligament. In previous publications the ovoid lesions have been referred to as cementifying fibromas while those with both osseous and cementoid calcifications are labeled as cemento-ossifying fibromas.

(3) Storiform form: typified by streaming of the fibroblastic stromal elements in a pinwheel configuration similar to benign fibrous histiocytoma (**figure 4**). Dispersed throughout are wispy calcifications that appear like dystrophic bone and many also show an ovoid configuration (Eversole, Su et al. 2008).
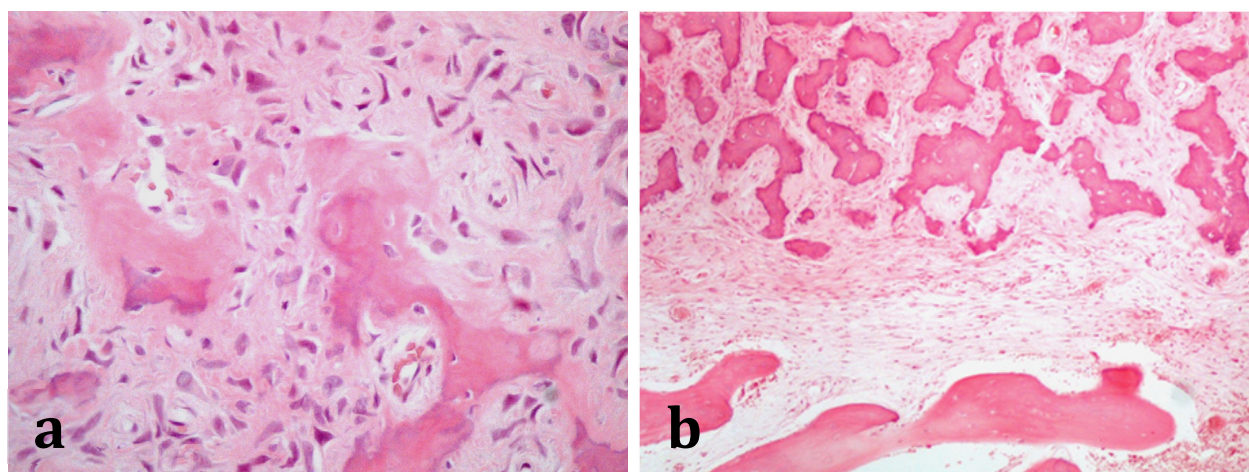

Figure 3. Ossifying fibroma NOS (**a**) irregular osteoid rimmed by osteoblasts and a fibrous stroma; (**b**) interface between an ossifying fibroma (up) and normal bone (down).
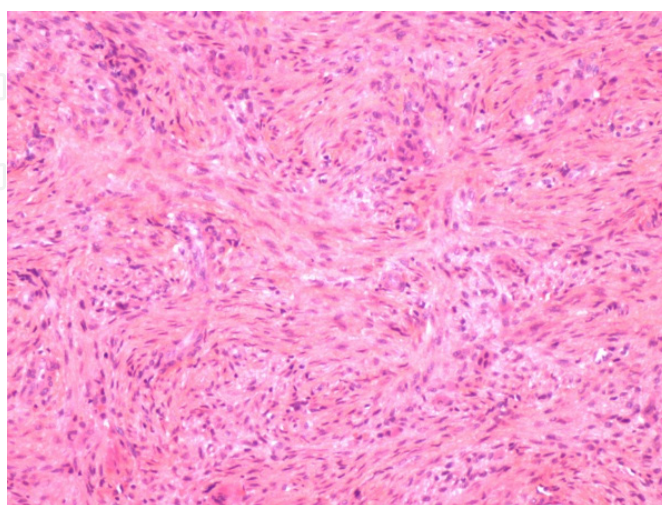

Figure 4. Ossifying fibroma NOS showing areas of fibrous stroma with a storiform pattern. Courtesy of Manuel Jácome, MD, Department of Pathology of IPOFG-Porto.

6.2. Juvenile ossifying fibromas

Two distinct clinicopathologic entities are known:

(1) Trabecular juvenile ossifying fibroma (JTOF): well-defined but unencapsulated lesion that infiltrates surrounding bone, composed of a cell-rich fibrous stroma containing bundles of cellular osteoid and bone trabeculae without osteoblastic rimming, and aggregates of giant cells (**figure 5**). Stromal cells are spindle or polyhedral and produce little collagen and the fibrillary osteoid matrix gives the tumor a characteristic loose structure. Cellular, immature osteoid, with plump eosinophilic osteoblastic cells, forms strands that may be long and slender or plump ("paint brush strokes"). The immature cellular osteoid is not always easily distinguished from the cellular stroma. Irregular mineralization takes place at the center of the osteoid strands, and progressive calcification results in anastomosing trabeculae of immature woven bone. Maturation to lamellar bone is not observed. Local aggregates of multinucleated giant cells are commonly seen in the stroma. Mitotic activity of the stromal cells may be present but is never numerous. Cystic degeneration and aneurysmal bone cystformation has been reported in a few cases.

Collagen is usually not observed, yet older lesions may show some collagenisation (Eversole, Leider et al. 1985; El-Mofty 2002; Eversole, Su et al. 2008).
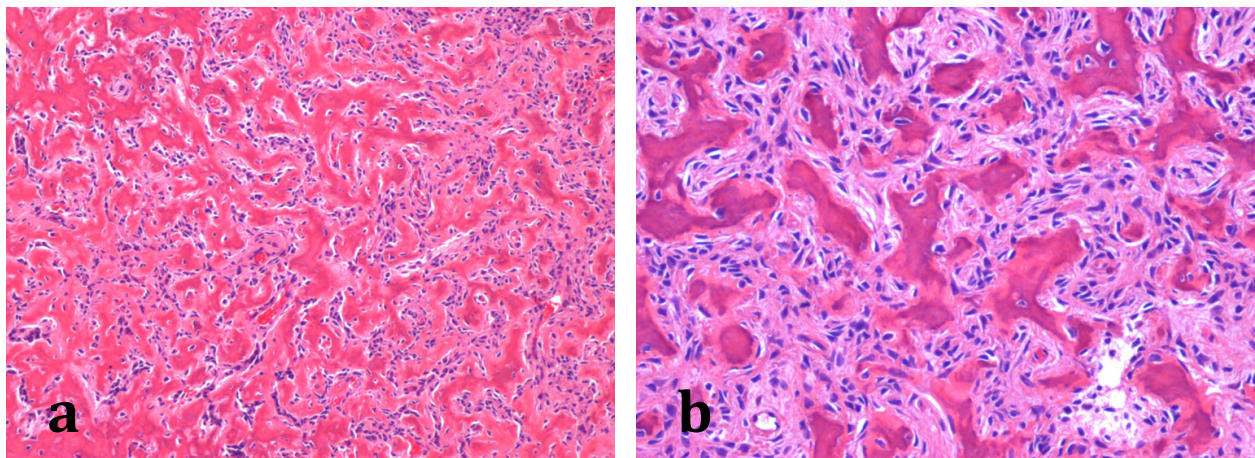

Figure 5. Juvenile trabecular ossifying fibroma (**a**) trabecular strands of immature osteoid; (**b**) immature osteoid with irregular mineralization and cellular stroma. Courtesy of Manuel Jácome, MD, Department of Pathology of IPOFG-Porto.

(2) Psammomatoid juvenile ossifying fibroma (JPOF)

On gross examination, the tumor is described as firm to hard in consistency and tan-white, grayish-white or grayish-brown in color and well demarcated from the surrounding bone, though not encapsulated. On sectioning, the cut surface is typically a tan-white, rubbery, homogeneous mass with a firm-to-gritty consistency and also displays large cystic areas (Sarode, Sarode et al. 2011).

On light microscopic examination, the tumor has multiple small acellular calcified structures, round and uniform and with concentric lamellar calcification, called ossicles/psammomatoid

bodies; they are homogenously distributed in a relatively cellular stroma that may have whorled appearance, composed of uniform, stellate, and spindle shaped cells. In some cases the stroma is myxoid and may undergo cystic change with edema, hemorrage and clusters of multinucleated giant cells, where one can also find acellular mineralized deposits with bizarre shape (Noudel, Chauvet et al. 2009; Linhares, Pires et al. 2011; Sarode, Sarode et al. 2011). Occasionally, shrunken cells become embedded in the calcified matrix of the ossicles. The psammomatoid bodies are basophilic and bear superficial resemblance to dental cementum, but may have an osteoid rim. Mitotic activity is extremely rare in the stromal cells. At the periphery of the lesion, the ossicles may be very closely packed with little intervening stroma, or coalesce and form irregular thin bony trabeculae that may become thicker, with numerous reversal lines. A shell of normal bone is usually present and may show osteoclastic resorption endosteally associated with osteoblastic activity on the periosteal surface. Cystic degeneration and aneurismal bone cyst formation is commonly reported (El-Mofty 2002; Eversole, Su et al. 2008; Linhares, Pires et al. 2011).

6.3. Gigantiform cementoma

This entity is often multifocal, with expansile masses of the maxilla and/or mandible; microscopic examination displays a benign hypercelular stroma with monomorfic appearing fibroblasts showing no mitosis, mature collagen fibers and scattered ovoid, often laminated, psammomatoid calcifications with variable size, many of them very large (Young, Markowitz et al. 1989; Abdelsayed, Eversole et al. 2001).

7. Differential diagnosis

Ossifying fibroma (OF) is often confused with focal cementoosseous dysplasia (FCOD). Importantly, the later is an endosseous nonneoplastic process that occurs around the roots of mandibular teeth and fails to expand bone. Alternatively, OF is a potentially aggressive lesion that causes cortical expansion and often causes divergence of contiguous teeth. Both lesions may show similar histological features with trabecular bone and cementifying areas. Older lesions of FCOD may show dense corticated bone islands, a finding that is not present in OF.

While fibrous dysplasia (FD) and OF may share microscopic features, the clinicoradiologic differences are now widely accepted (Linhares, Pires et al. 2011).

In contrast to FD, JPOF shows osteoclasts and osteoblasts typically lining the trabeculae, which are composed of entrapped lamellar bone. The entities can be distinguished from one another on the basis of molecular detection of activating missense mutations of the GNAS1 gene in fibrous dysplasia of the jaws, while ossifying fibromas are found lacking (Hasselblatt, Jundt et al. 2005; Eversole, Su et al. 2008; Nasser 2009; Noudel, Chauvet et al. 2009).

JPOF might be easily mistaken for psamomatous meningioma, and in JPOF with a neurocranial location the likelihood of a misdiagnosis is increased. Even though there is frequent immunohistochemical negativity for epithelial membrane antigen (EMA) in JPOF, there are reported cases with EMA positivity; it is also positive for vimentin, smooth muscle

actin and CD10, with lack of expression of CD34, S100 protein and cytokeratins. The diagnosis should be based on morphological, clinical and radiographic findings (Hasselblatt, Jundt et al. 2005; Noudel, Chauvet et al. 2009; Sarode, Sarode et al. 2011).

8. Genomic alterations

Cytogenetic analysis was done in only a few cases of ossifying fibroma. In one case of COF of the mandible, deletions were detected in 2q31-32 q35-36 (Dal Cin, Sciot, et al. 1993).A study of 3 cases of JPOF of the orbit demonstrated non random chromosome break points at Xq26 and 2q33 resulting in (X;2) translocations (Sawyer, Tryka,et al.1995). Regarding OF NOS there are reports that identify mutations in HRPT2 a gene that encodes parafibromin protein. Psammomatoid ossifying fibroma has been associated to chromosomal breakpoints t(X;2)(q26;q33) and interstitial insertion of bands 2q24.2q33 into Xq26.

Hyperparathyroidism associated ossifying fibroma has been associated with mutations in tumor suppressor gene HRPT2.

The rare gigantiform cementoma is related to an autosomal dominant inheritance in some cases whereas others are ''familial''. Among the few cases that have been reported, the gene appears to have a high level of penetrance with variable expressivity (Young, Markowitz et al. 1989; Finical, Kane et al. 1999; Abdelsayed, Eversole et al. 2001; Rossbach, Letson et al. 2005).

9. Treatment and prognosis

Complete excision of a OF lesion is the treatment of choice and it can be curative. Despite its benign features, they can be locally invasive, causing significant morbidity, and fatal consequences may be induced by intracranial extension (Baumann, Zimmermann et al. 2005; Cruz, Alencar et al. 2008; Bohn, Kalmar et al. 2011; Linhares, Pires et al. 2011). However, a surgical approach is dictated more by anatomic location and tumor size than by histologic subtype (Shields, Peyster et al. 1985; Hartstein, Grove et al. 1998; Smith, Newman et al. 2009).

Radiotherapy is generally contraindicated because of the risk of malignant transformation and the potentially harmful late effects in children (Nakagawa, Takasato et al. 1995; Noudel, Chauvet et al. 2009).

The clinical course of JTOF is characterized by infrequent recurrence following conservative excision. One or more recurrences were observed in 3 of 10 patients reported by Slootweg et al (Slootweg, Panders et al. 1994). Eventual complete cure could be achieved in those cases without resorting to radical surgical intervention. Malignant transformation has not been reported. Regarding JPOF, surgical excision is the treatment of choice, although recurrence even after definitive surgery is not unusual. Recurrence rates of 30% have been reported. In some cases, multiple recurrences over a long follow-up period are reported. No malignant change has been observed. Treatment for gigantiform cementoma is resection with immediate or staged reconstruction (Finical, Kane et al. 1999).

Overall recurrence rates after resection is reported to range from 30 to 56% and this is likely to be due to incomplete excision resulting from the infiltrative nature of the tumor borders more than to any intrinsic biological properties (Brannon and Fowler 2001; MacDonald-Jankowski 2004; Noudel, Chauvet et al. 2009).

10. Conclusion

Ossifying fibromas comprises entities with different morphological features that can be mistaken for other benign fibro-osseous lesions; this similarity and overlapping microscopic characteristics turns the multidisciplinary approach, comprehending clinical, radiological and pathological aspects, more reliable for a correct diagnosis.

They have locally aggressive behavior, with high recurrence rate, particularly in partial and incomplete excisions, with complete removal being the gold standard treatment. Prognosis is good, without metastases in the reported cases.

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