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CASE REPORT

So-called Hybrid Central Odontogenic Fibroma/Central Giant Cell Lesion of the Jaws. A Report on Seven Additional Cases, Including an Example in a Patient with Cherubism, and Hypotheses on the Pathogenesis

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Abstract *Background* Central odontogenic fibroma (COF) is characterized by poor to cellular fibroblastic proliferation and a variable odontogenic epithelial (OE) component. Central giant cell lesions (CGCL) are osteolytic fibroblastic proliferations characterized by osteoclast-like multinucleated giant cells (MGC). Rare examples of hybrid COF/CGCL have been described. Two pathogenetic theories prevail based on clinicopathologic characteristics. One regards the CGCL component as reactive to the COF, while the other regards the CGCL as inductive of a COF-like proliferation. The possibility of colliding tumors seems unlikely. *Methods and materials* Seven patients with hCOF/CGCL, among them one with cherubism, were studied. Immunohistochemisty for cytokeratin 19 was applied to better appreciate the epithelial component. *Results* Six patients were males and one female and their age ranged from 15 to 73 years old. All lesions occurred in the premolars and molars of the mandible and presented as radiolucencies with primarily well-delineated borders. All patients underwent surgical excision and recurrences have not been reported to this date in 6 out of 7 patients (mean follow-up 60.6 ± 36.25 months). The COF component predominated in 3 cases and the CGCL component in 3. Zones of collagen fibers featuring a whorling pattern and containing multiple nests of OE were present. In four cases there were hyalinized deposits in OE, while some foci of MGC contained few OE. *Conclusions* Gender predilection in our series is in contrast with previously published reports. However, when all previously reported cases are reviewed there is still female predilection. The predominant site, as previously reported, is the tooth-bearing areas of the posterior mandible. This is the first report of hCOF/CGCL in cherubism. The pathogenesis of hCOF/CGCG remains obscure and molecular interactions would be of interest to be investigated.

Keywords Central odontogenic fibroma · Central giant cell lesion · Hybrid · Cherubism

Introduction

Central odontogenic fibroma (COF) is a benign neoplasm of the jaws that represents less than 5% of all odontogenic tumors [1–4]. It is characterized by fibroblastic proliferation that ranges from poorly cellular and myxoid without significant odontogenic epithelial component, to cellular, featuring interlacing collagen fascicles with abundant odontogenic epithelium and occasional foci of calcifications resembling dysplastic dentin or cementum [1–4]. The terms simple type or epithelium-poor type and WHO type or complex or epithelium-rich type, have been, respectively, designated to those lesions. Small hyaline globules resembling basement membrane material, as well as hyalinization around the epithelium may be found in the cellular type. The epithelial component has been described as inactive-looking and, therefore, COF is regarded of mesenchymal origin. Both jaws are equally involved, with maxillary lesions being more common and occurring anterior to the first molar while mandibular lesions predominate in the

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molar region [2]. COF is usually slow-growing and may progressively cause painless bone expansion and displacement or root resorption of adjacent teeth [1–4]. From the approximately 70 cases of central odontogenic fibroma reported in the English-language literature up to 2004, a predilection for young females is evident [1–3].

Central giant cell lesions (CGCL) are uncommon, localized benign but occasionally aggressive osteolytic, vascularized mesenchymal spindle cell proliferations with presence of osteoclast-like multinucleated giant cells [5]. The giant cells are usually clustered in areas of hemorrhage and hemosiderin deposition, while trabeculae of woven bone are seen in the periphery or in fibrous septae traversing the stroma. Central giant cell lesions can be seen in hyperparathyroidism ("brown tumors"), cherubism, Noonan syndrome and neurofibromatosis type 1 [6]. In the last two, this association may be coincidental.

In 1992 Allen et al. [7] reported three cases of epithelium-rich COF, with "unusual associated giant cell reaction". "Giant cell reaction" was found by Fowler et al. [8] in 3 of 24 central odontogenic fibromas, while Odell et al. [9] gave detailed microscopic description of 8 patients with "hybrid central giant cell granuloma and central odontogenic fibroma-like" (hCOF/CGCL). A patient with "combined central odontogenic fibroma and giant cell granuloma-like lesion" was described by Mosqueda-Taylor et al. [10]. Finally, Kessler presented a case diagnosed as central odontogenic fibroma with central giant cell granuloma in the 2006 Meeting of the Western Society of Teachers of Oral Pathology bringing the total number of reported patients, known to the authors, to 16. Also there are reports associating CGCL with ameloblastoma, and non-odontogenic fibro-osseous lesions [11–13].

Two pathogenetic theories prevail based on clinicopathologic characteristics. One regards the CGCL component as reactive to the COF while the other regards the CGCL as inductive of a COF-like proliferation. The possibility of colliding tumors has been discussed but regarded unlikely [9].

The purpose of this paper is to report on the clinicopathologic characteristics of seven additional examples including one occurring in a patient with cherubism. Such association has not been previously recorded in the literature. In addition, we discuss two possible pathogenetic mechanisms for such lesions.

Methods and Materials

Seven cases with hCOF/CGCL were retrieved from the files of the Division of Oral and Maxillofacial Pathology, University of Minnesota, School of Dentistry from 1991 to 2005. In cases 1 to 6 the completely resected tumor was available, while case 7 was an incisional biopsy. Multiple 5 μm-thick, formalin fixed and paraffin embedded (FFPE) sections were stained with hematoxylin and eosin in order to better verify, first which one of the two histologic components, COF or CGCL, was predominant, and second the arrangement of the two components. Furthermore, immunohistochemical stain for cytokeratin 19 (CK19, Dako, Carpinteria, CA), was utilized to better visualize the epithelial component.

Results

The clinicopathologic characteristics of our series are summarized in Table 1. Six patients were males and one female and their age ranged from 15 to 73 years old (mean: 37.14 ± 23.2 years). All lesions occurred in the mandible and presented as radiolucencies with primarily well-delineated borders (Fig. 1). They occurred in the area of the premolars and molars.

Case 7 was a 25 year old male with diagnosed cherubism. According to his medical history, his mother had more pronounced cherubism, while the radiographic presentation was highly suggestive of the disease (Fig. 2). During a

Table 1 Clinicopathologic characteristics of 7 hCOF/CGCL

Case #	Age/gender	CGCL	COF	Odontogenic epithelium hyaline deposits	Follow-up
1	18 M		Predominant	Y	Lost to follow-up
2	20 F	Predominant		Y	No recurrence/117 months
3	50 M		Predominant	N	No recurrence/28 months
4	73 M	Predominant		Y	No recurrence/43 months
5	15 M	Predominant		N	No recurrence/76 months
6	59 M		Predominant	N	No recurrence/39 months
7[a]	25 M			Y	Lost to follow-up

[a] Patient with cherubism

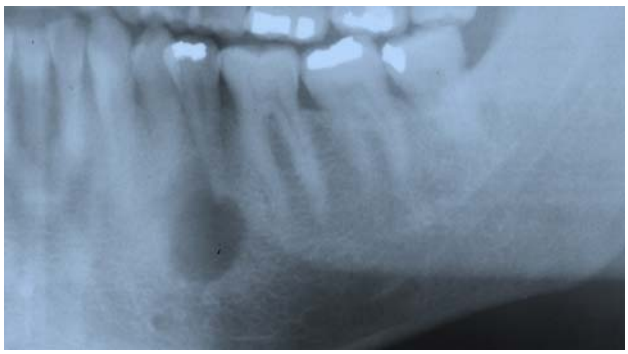

Fig. 1 Case 3. 50-year-old male with radiolucent lesion at the apice of to the second premolar

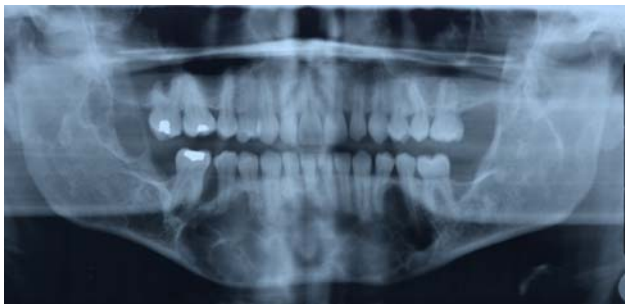

Fig. 2 Case 7. Patient with cherubism. The lesion was present between the right mandibular second premolar and molar

routine clinical and radiographic examination a perforation was found on the attached gingiva between the right second premolar and first molar, and an incisional biopsy was performed.

Histologically, the COF component predominated in 3 cases, the CGCL component in 3 while in the patient with cherubism we did not feel that seeking a predominant component was appropriate. Zones of mesenchymal cell proliferation featuring a whorling pattern and focal myxoid areas, and containing multiple cords and small nests of odontogenic epithelium (OE) were present (Figs. 3 and 4). Occasionally, the OE exhibited cytoplasmic clearing. In four cases hyaline globules (Fig. 5) were observed. CGCL areas were alternating with COF areas in all cases. The CGCL component featured spindle cell proliferation, mononuclear cells and multiple multinucleated giant cells (MGC). Areas of hemorrhage, especially where MGC were present and dystrophic calcifications were observed. Some foci with MGC contained few OE that were more distinctly revealed by CK19 (Fig. 6).

All patients underwent surgical excision and recurrences have not been reported to this date in 5 out of 6 patients (mean follow-up 60.6 ± 36.25 months). The patient with cherubism has been lost to follow-up.

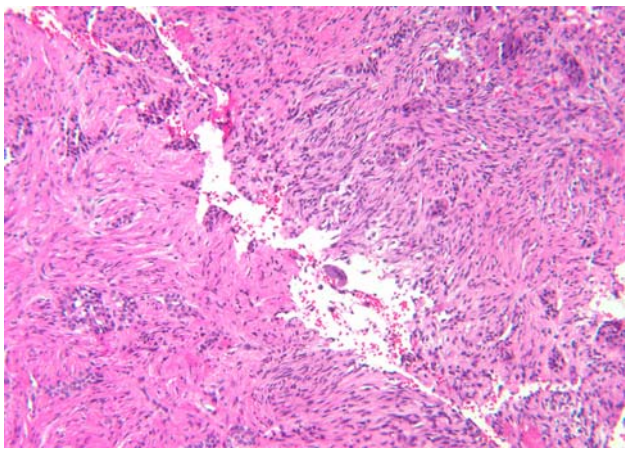

Fig. 3 Areas of COF and CGCL. These are alternated in all examples. Note the close proximity of COF and CGCL in the middle upper part (H&E, original magnification 10×)

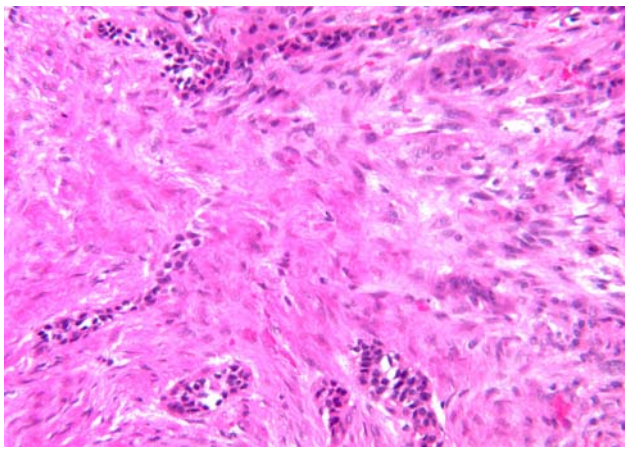

Fig. 4 Odontogenic epithelial cords featuring cytoplasmic clearing and in close apposition to giant cells (H&E, original magnification 20×)

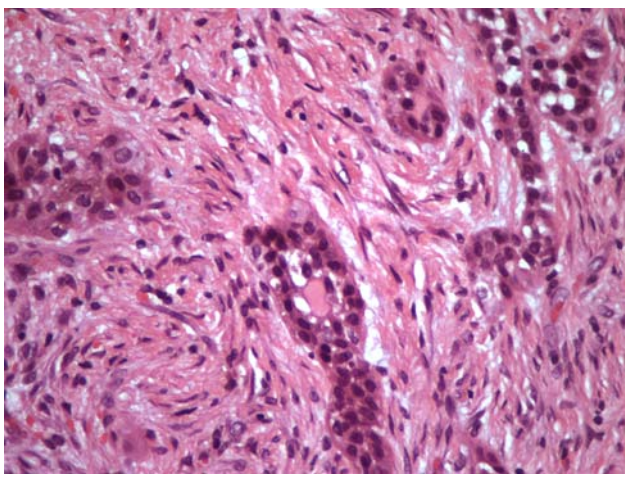

Fig. 5 Hyaline globule in an odontogenic islands. This material has, reportedly, properties of basement membrane (H&E, original magnification 40×)

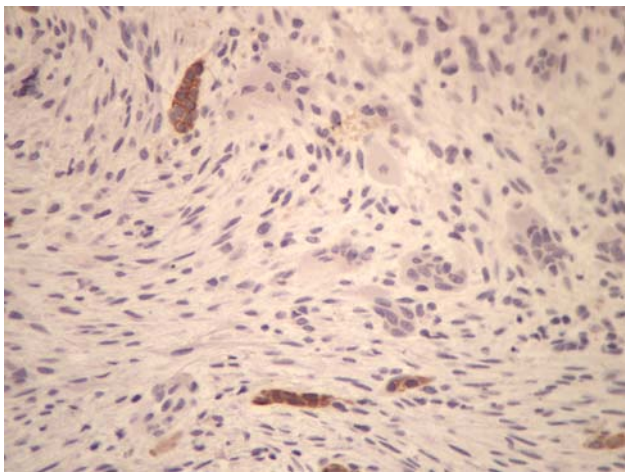

Fig. 6 CK19 discloses epithelial cords next to multinucleated giant cells (ABC-hematoxylin, original magnification 20×)

Discussion

Clinical characteristics of hCOF/CGCL have been known in 20 out of the 23 reported cases, including our seven. The data on the cases presented by Fowler et al. [8] have not been available. Up to our series, the vast majority of patients have been women. Although in our series men were far more frequently affected than females, when all reports are combined there is still a 2:1 female to male ratio. The mean age of these 20 patients at the time of biopsy was 31 ± 19.5 years with 13 patients being younger than 30 years old and five older than 50. COF and CGCL are also more frequently seen in women usually younger that 30. Also, it is worth noting that the pattern of age distribution in COF/CGCL is similar to CGCL.

Eighteen cases of hCOF/CGCL have occurred in the mandible with most cases occurring in the area of the premolars and extending from canine to molars. This location in the mandible is common for both COF and CGCL. The maxilla has been affected in 2 patients with one case occurring in the anterior aspect and the other in the posterior and extending into the antrum. All lesions have presented as well-circumscribed unilocular or multilocular radiolucencies. No recurrence has been reported in our series.

Histologically, COF and CGCL areas can be either distinct and separate, with occasional foci of CGCL surrounded by large zones or septa of COF, or traversing and intermingling [9, 10]. In all examples, the COF areas did not feature dysplastic dentin or cementum. Small clusters of epithelial cells into CGCL have been described in one case, and hyaline globules and periepithelial hyalinization in 3 and 1 case, respectively, [9]. Osteoid or woven bone are prominent features in most cases, particularly within fibrous septa running through the lesion. New bone formation is also seen in the periphery, creating the impression of infiltrative growth. However, cystic features suggestive of aneurysmal bone cyst are absent. The microscopic features of our cases are similar to those of previously reported lesions.

The pathogenesis of those unusual lesions is unknown. These tumors can represent either (a) collision tumors, (b) COF with reactive CGCL component, or (c) CGCL with an induced COF component. Odell et al. have argued against a "collision" tumor noting that incidental, synchronous occurrence of two rare lesions in the same area is very unlikely [9]. Furthermore, he considered the presence in all three of their recurrent lesions of similar proportions of COF and CGCL with the primary tumors, as an indication that both components are essential features of the lesion. Similarly, one case reported by Allen et al. recurred and featured again both components [7]. Our findings suggest that either component can be predominant and we are in agreement with the opinion of Odell et al. [9].

Allen et al. have argued that the predominance of fibroblastic and epithelial components in their examples should favor an odontogenic tumor with a reactive giant cell component [7]. They supported their position by noting the development of aneurysmal bone cysts in association with intraosseous lesions, as well as the giant cell reaction adjacent to ameloblastomas [11, 12]. Also, CGCL have been reported in association with central ossifying fibroma [13] and they can be rarely encountered with different types of benign fibro-osseous lesions [personal observation, unpublished data]. However, giant cell reaction appears to be very rare in these lesions and cystic changes suggestive of aneurysmal bone cyst have not been observed in reported hCOF/CGCL [9]. In CGCL there is evidence that receptor activator of nuclear factor-kappa b ligand (RANKL), its receptor (RANK), and osteoprotegerin (OPG),a decoy receptor for RANKL, play a crucial role in its pathogenesis [14]. Specifically, the spindle cell component recruits monocyte-macrophages precursors inducing them to differentiate towards osteoclast-type giant cells. It would be interesting to study the expression of RANKL and OPG in COF.

Odell et al. noted that certain clinical features of those lesions are "more suggestive" of CGCL than COF [9]. Wide age distribution with a slight predilection for the first three decades, predilection for females and the mandible, bone expansion, and recurrent behavior are features more frequently encountered in CGCL. However, a similar clinical presentation can be seen in patients with mandibular COF. None of the case reported so far presented calcified material resembling dysplastic dentin or cementum as seen in COF, although that is not imperative for such diagnosis. In their series, as in ours, the lesions exhibited osteoid or woven bone trabeculae which are

frequently featured in CGCL [9]. The possibility of a local irritation factor is recognized in some patients (root-canal treatment, orthodontic treatment), but such factors have not been reportedly causative for either CGCL or COF [9].

Odell et al. proposed that hCOF/CGCL are CGCG inducing proliferation of odontogenic epithelium and ectomesenchyme, normally found in the tooth bearing areas of the jaws, through the secretion of growth factors [9]. During normal tooth development in experimental models, Lim-homeobox domain (Lhx) transcription factors, sonic hedegehog (Shh) and Lef-1 are involved in the proliferation of odontogenic epithelium [15, 16]. Lhx genes expression can be induced by fibroblast growth factor 8 [17] and epithelial proliferations similar to dental lamina have been observed following placement of Shh-soaked beads to oral ectoderm [18], while Lef-1, a nuclear mediator in the Wnt pathway, is a strong inducer of odontogenic epithelium [19]. Although no evidence exist, it is possible that expression of Lhx proteins, Shh and/ or Lef-1 by mesenchymal spindle cells in some CGCL can mediate a local odontogenic epithelial proliferation leading to the development of a COL-like lesion.

Up to now there has been no reported occurrence of hCOF/CGCL with any other condition. We report here an hCOF/CGCL in a patient with cherubism that may represent an extremely rare example of COF colliding with CGCL. However, if the chance of hCOF/CGCl being a collision tumor is slim, the chance of collision tumor in our patient is even slimmer. Also, there were areas where both components were alternating and clearly indistinguishable from the other cases of COF/CGCL. Taking this into consideration it can be speculated that the CGCL of cherubism induced a COF-like proliferation. In cherubism, it has been proposed that mutation in the gene encoding the SH3-binding protein (SH3BP2) may induce delayed imbalance of factors participating in odontogenesis [20], in particular upregulation of Msx-1 that can stimulate proliferation of residual odontogenic epithelium. Increased Msx-1 expression of the same order as for tooth germs has been found in CGCL [20].

In summary, we presented seven additional examples of hCOF/CGCL. Although the vast majority of our patients were males, if our cases were added to those reported in the literature there is still a 2:1 female to male ratio. The predominant site is the tooth bearing areas of the posterior mandible. The pathogenesis of hCOF/CGCG remains obscure and molecular interactions would be of interest to be investigated.

Note Added in Proof After acceptance of our paper a series of seven patients with hCOF/CGCL was presented by Hassan, Reich and Freedman in the 2008 American Academy of Oral and Maxillofacial Pathology and International Association of Oral Pathologists joint Conference. In this series there was also strong male predilection (5M:2F) and in three patients the authors reported recurrence. More interestingly though, in one of the recurrent tumors, there was presence of only CGCL. In our opinion, this important finding further supports the theory of CGCL inducing odontogenic epithelial proliferation.

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