Hybrid Central Odontogenic Fibroma with Giant Cell Granuloma-like Component: Case Report and Review of Literature

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Abstract Central odontogenic fibroma (COF) is a rare benign ectomesenchymal tumor of the jaws. Only 12 cases of COF with giant cell granuloma (GCG)-like lesion have been reported in the English literature. Here, we present a new case of COF epithelium rich type with a GCG-like component. Radiographically, this lesion presented as a well defined unilocular radiolucency in the body of the mandible. Histologically, the lesion showed a unique confluence of odontogenic epithelial rests with multinucleated giant cells (MNGCs) in a highly cellular fibrous connective tissue stroma, with osteoid and cementoid deposits. A distinct area showed the typical histological picture of each component separately. Immunohistochemical staining with pancytokeratin (CK) highlighted the odontogenic epithelial component merging with the GCG component throughout most of the lesion. The significance of GCG-like areas within COF is the reported increased risk of recurrence following curettage, possibly necessitating more aggressive therapy.

Keywords Central odontogenic fibroma · Giant cell granuloma · Multinucleated giant cells · Odontogenic epithelial rests

Abbreviations

COF Central odontogenic fibroma
GCG Giant cell granuloma
MNGCs Multinucleated giant cells
CGCG Central giant cell granuloma

Introduction

Central odontogenic fibroma (COF) is a rare benign tumor of odontogenic ectomesenchymal origin, characterized histologically by the presence of variable amounts of inactive looking odontogenic epithelium scattered within a mature fibrous connective tissue stroma [1]. COF is an uncommon and somewhat controversial lesion with regards to its inception and definition [2–4]. In 1975, Wesley et al. was the first to clarify the diagnostic criteria of COF [5]. Clinically, as a central slowly growing lesion that causes painless cortical expansion, radiographically as a unilocular or multilocular radiolucency, and histologically as mature collagen fibers with numerous interspersed fibroblasts where the presence of small nests and/or strands of inactive odontogenic epithelium is a variable feature [5]. The tumor is benign and responds well to surgical curettage with no malignant transformation potential [5]. Thereafter, further attempts to simplify, classify and clarify the clinical and histological picture of COF were contemplated [6–11].

To date, there are an estimated 93 reported cases of COF in the English literature including our case [12–24]. Clinically, COF is reported to occur from 4 to 80 years of age (mean 40 years) with 2.2:1 female predilection. It accounts for 0.1–1.5% of all odontogenic tumors and 6.1% of tumors if odontoma is excluded [2, 19]. Approximately 45% of the cases occur in the maxilla with most anterior to the first molar and often presenting with a palatal cortical depression rather than expansion [4, 12, 17, 19]. When present in the mandible,
the opposite is true, where half of the cases present posterior to the first molar and up to one-third accompany an unerupted third molar [14]. Smaller COFs are typically asymptomatic while larger lesions are often associated with pain, localized bony expansion or loosening of teeth [2].

Histologically, COF shows two main subtypes. The simple COF (epithelium-poor) type and the complex (epithelium-rich) type [1, 2, 11]. Histological variants of COF include: granular cell, pleomorphic fibroblast and GCG-like variants [22–27]. To our knowledge 12 cases of COF with GCG-like lesion have been reported in the English literature (Tables 1 and 2) [22–24]. The COF with GCG-like lesion accounts for approximately (13.98%) of all COFs [12–24]. This tumor was first reported by Allen et al. in 1992 who reported three cases [22], followed by Odell et al. in 1997 who reported eight cases [23], and finally by Mosqueda et al. in 1999 who described one case [24]. These three authors described the same combined histological picture of a densely collagenous to delicate fibromyxoid stroma containing apparently inactive odontogenic epithelial strands and nests, with some showing duct like spaces or hyaline basement membrane globules. These areas merged with a variably collagenous stroma of plump and narrow spindle-shaped mononuclear cells that contained MNGCs. Some lesions showed osteoid deposits. The merge between the two components was reported to occur sparsely in some areas, especially at the interface [22–24].

Typical treatment for COF includes the complete removal of the COF by curettage as the first line of treatment. Although tumor encapsulation is absent recurrences are uncommon [28, 29]. Three out of the 12 reported cases of COF in which a GCG-like lesion was present showed recurrence and the recurrent lesion was identical histologically to the primary lesion (Table 1) [22–24]. Recurrence is common in central GCGs (CGCG) if not treated radically or with thorough curettage, although it is widely considered to be a non-neoplastic reactive lesion [30–32]. It shares a similar age range with COF with 60% of CGCG occurring before age 30 [33]. CGCG shows a variety of features, but common to all is the presence of many MNGC in a background of ovoid to spindle shaped fibroblasts in a collagenous stroma and myxoid ground substance. The MNGCs arranged focally or diffusely throughout the lesion [34].

Here we report the 13th case of COF with GCG-like lesion, containing a unique facet where both components are closely admixed together throughout most of the lesion.

### Case Report

A 57-year old caucasian female with an unremarkable medical history presented with an asymptomatic 2.0 × 2.5 cm unilocular radiolucent lesion in the body of the mandible under teeth # 29 and 30 (Fig. 1). The patient presented with bony expansion on the buccal aspect from tooth # 30 to the mental foramen. The rest of the oral and extra-oral examination was unremarkable. Upon surgical exploration, the buccal cortex was removed exposing reddish-brown friable tissue filling an osseous defect. Approximately 60% of the material was curetted and sent for pathologic examination.

Histopathologically, the incisional biopsy showed fragmented tissue filling the space and infiltrating between the

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**Table 1** Demographic data of COF with GCG-like lesion

| Demographic variables, treatment and follow up |                |
|-----------------------------------------------|----------------|
| Age: mean (range)                             | 31.35 years (5–66) |
| Sex: number (%)                               | 12/13 F (92.3%) |
|                                               | 1/13 M (7.69%) |
| Location: number (%)                          | Mandible: 11/13 (84.62%) |
|                                               | Maxilla: 2/13 (15.38%) |
| Treatment                                     | 13/13 curettage (100%) |
| Recurrence: number (%), mean                  | 3/13 (23%), 25 months |

*a* F: female, M: male

**Table 2** Clinical presentation of COF with GCG-like lesion

| Clinical presentation     | Number of cases (percentage) |
|---------------------------|------------------------------|
| Buccal expansion          | 8/13 (61.5%)                 |
| Loose tooth               | 1/13 (7.7%)                  |
| Tooth displacement        | 1/13 (7.7%)                  |
| Perforation of cortex     | 1/13 (7.7%)                  |
| Radiology                 | 4/9 MLRL* (44.4%)            |
|                           | 5/9 ULRL* (55.5%)            |
| Previous reactive stimuli at the site of the lesion | 5/13 (38.46%): two previous endodontic treatments. One active orthodontic treatment. two previous extractions. |

*ULRL: unilocular radiolucency, MLRL: multilocular radiolucency*
bony trabeculae. The lesional tissue showed a prominent blend of abundant odontogenic epithelial rests with many MNGCs, in a highly cellular connective tissue stroma, with dense collagenous fibers, showing a whorled pattern in some areas (Fig. 2a). Osteoid deposits and cementum-like spherules were also present. The periphery of the lesion showed fragments of cortical bone and large areas of hemorrhage. An initial diagnosis of COF with GCG-like lesion was made.

The area was revisited for thorough curettage, with the most extensive lesional tissue surrounding the roots of teeth #29 and #30 and extending toward the lingual area of the mandible. The excisional biopsy showed a similar unique histopathological picture with an admixture of COF and GCG-like component (Fig. 2b, c). This homogenous admixture between the two components was the predominating picture in the lesion as opposed to adjacent areas showing both components separately. A separate area showing odontogenic epithelial rests, with evidence of cellular vaculation and inductive effect, depositing eosinophilic material in the center of the epithelial nests and forming a duct-like structure, in a dense fibrous connective tissue stroma, consistent with COF (Fig. 2d). Additionally, as reported in the literature, a separate area showed many MNGCs within a highly cellular stroma formed mainly of ovoid to spindle shaped mononuclear mesenchymal cells, a pattern consistent with central giant cell granuloma (CGCG). Variable deposition of cementoid and osteoid tissue were also noted.

Immunohistochemistry for pancytokeratin (AE1/AE3/PCK26) (Ventana medical system, Tucson, AZ, USA) showed granular cytoplasmic positivity of the odontogenic epithelium (Fig. 3) and highlighted the amalgamate of COF and GCG components, as indicated by the mixture of abundant positive odontogenic epithelial rests mixed with many MNGCs in a highly cellular fibrous connective tissue stroma.

A diagnosis of COF with GCG-like lesion was confirmed. The case was followed with no signs of recurrence after one and a half year, and the lesion appeared to be healing well.
Discussion

COF is defined as a rare benign tumor of odontogenic ectomesenchymal origin [1]. Yet, the concept and definition of COF remain a matter of debate. The 2005 WHO definition does not provide a specific diagnostic criteria to precisely delineate histologically COF from other similar lesions [1]. Including: enlarging dental follicle [3], myxoma [4], fibromyxoma [4], desmoplastic fibroma [16], and if the odontogenic epithelium is prominent: squamous odontogenic tumor or calcifying epithelial odontogenic tumor [33–35]. Additionally, the histologic features of the CGCG are variable and share similar histological features with a number of lesions including: cherubism, hyperparathyroidism, aneurysmal bone cyst, as well as intraosseous lesions of Noonan syndrome, and giant cell tumors of the tubular bones of the hands and feet [33, 34, 36].

Twelve cases of COF with GCG-like lesion were reported since 1992 (Table 1) [22–24]. Historically, these tumors were described as lesions containing a densely collagenous to delicate fibromyxoid stroma, containing apparently inactive odontogenic epithelial strands and nests, and showing some duct-like spaces or hyaline basement membrane globules. These areas were reported to merge independently with a variably collagenous stroma of plump and narrow spindle-shaped mononuclear cells that contained MNGCs consistent with GCG lesions, with some lesions showing osteoid deposits [22–24]. We report a case, with a distinctive feature of a homogenous mixture of the GCG component and the odontogenic epithelial rests, of the COF component (Fig. 2b, c), with only minimal areas showing each component separately.

Three hypotheses are postulated to explain the nature of this combined lesion. The first suggests the possibility that this lesion could represent a “collision” tumor [22–24]. This is unlikely as the chance of two rare lesions occurring synchronously would be extremely small, and are not typically intermixed [22–24, 38, 39]. However, some central giant cell type lesions do occur with other lesions, such as the occurrence of aneurysmal bone cyst with other bone lesions like chondroblastoma, osteoblastoma, and other fibroosseous lesions [40]. A second proposal suggests a primary COF to which a GCG reactive response is generated [22–24, 38]. This theory suggests a giant cell reparative response asserting an affinity for the inactive odontogenic epithelium of this lesion; a reaction not typically seen with the inactive odontogenic epithelium normally distributed throughout the gingiva. Additionally, the lesions reported in the literature typically present with distinct areas of COF and GCG merging only at the periphery [22–24]. A third proposal, suggests that growth factors produced by a primary CGCG lesion induce the proliferation of the odontogenic component, and consequently formation of a secondary COF, rather than the opposite. A possibility that calls for a reactive stimulus to induce the primary CGCG response [22–24, 37]. It is worth noting that four out of the 12 reported cases of COF with GCG-like lesions, had history of reactive stimuli (Table 1), suggesting a triggering event for a primary CGCG reparative response [22, 23]. Furthermore, the presence of distinctive areas with only a GCG component suggests a giant cell lesion rather than a mere reactive response [33, 37–39].

The unique histopathology of our lesion supports the second notion that COF is the primary lesion with a secondary reactive GCG; however a combined “collision” tumor with a reactive GCG reaction cannot be ruled out, since most of the present case shows a predominance of both odontogenic epithelium and MNGCs in a homogenously mixed pattern, in addition to two distinct areas of each component separately. This suggests that both components may be the primary elements of the neoplastic process, intermingled with a GCG reactive response to the COF. Importantly, this hybrid condition shares similar clinical age range, radiographic features and histology, with both COF and CGCG, making the clinical lesion difficult to determine [21, 24, 29, 30, 40, 41].

Previously, all hybrid cases of COF with a GCG-like component were treated with curettage with three (23%) showing recurrence; two after 3 years and the other after 14 months (Table 1). Therefore, careful follow-up is required. Our case was treated with thorough curettage and follow-up currently out to 1 year, with the defect showing signs of recalcification and no signs of recurrence.

In summary, the precise nature of the lesion seems to be defined by the nature of the histology, with reactive GCG-like lesions following the prognosis of a typical COF, while potential “collision” tumors follow a locally aggressive course [31, 32]. Importantly, the presence of a GCG-like component makes this lesion more likely to recur [22, 23, 31, 32].

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