Hybrid Central Odontogenic Fibroma with Giant Cell Granuloma like Lesion: A Report of Three Additional Cases and Review of the Literature

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Abstract Central odontogenic fibroma (COF) is an uncommon intraosseous neoplasm of the gnathic bones which is composed of fibrous connective tissue, with or without calcifications, and variable amounts of inactive odontogenic epithelium. It makes up less than 5% of odontogenic tumors and is more commonly seen in females. Central giant cell granuloma (CGCG) is a locally destructive but benign lesion of the jaws containing osteoclast-like multinucleated giant cells in a fibrovascular stroma. CGCG makes up approximately 10% of all benign jaw tumors and typically occurs in females younger than 30 years of age. A hybrid lesion with histologic features of both COF and CGCG is very rare and was first described in 1992. To date, fewer than 50 cases of this lesion have been reported. In this study, we present three additional cases of COF developing in conjunction with giant cell granuloma-like lesion, as well as provide a comprehensive literature review. Two of the lesions presented in our study were located in the posterior mandible and one occurred in the anterior mandible. Buccal and/or lingual expansion was noted in two patients and no recurrence was reported. Histologically, all three lesions demonstrated a blend of odontogenic epithelial islands with numerous multinucleated giant cells in a highly cellular connective tissue stroma. Immunohistochemical staining with CK19 and CD68 highlighted the odontogenic epithelium and multinucleated giant cells respectively. The precise nature of these hybrid lesions

remains obscure and additional molecular studies may be of help in understanding their pathogenesis.

Keywords Central odontogenic fibroma · Central giant cell granuloma · Hybrid central odontogenic fibroma with giant cell granuloma-like lesion · World Health Organization

Introduction

Central odontogenic fibroma (COF) is a rare odontogenic tumor known to occur in patients in the age range of 4–80 years (mean age, 40 years). Over the years, several attempts have been made to clarify the diagnostic criteria of COF [1–3]. COF makes up approximately 4–5% of all odontogenic tumors [4, 5]. The maxilla and mandible are equally affected, and most maxillary lesions occur anterior to the first molar. In the mandible, these tumors are mostly located posterior to the first molar [6]. Approximately one-third of COFs may be associated with an unerupted third molar [7]. Studies suggest that COFs associated with unerupted teeth arise from the dental follicle, and those not associated with unerupted teeth arise from periodontal ligament [2, 8]. Radiographically, they present as well-defined unilocular or multilocular radiolucent lesions that may result in cortical expansion [6]. In the maxilla, lesions anterior to the first molar may present as a palatal cleft or depression [8]. In 2005, the World Health Organization (WHO) classified COF into two histologic variants: the simple or epithelium-poor type and the WHO type [9]. The connective tissue in simple odontogenic fibroma is relatively acellular with delicate collagen fibers interspersed with variable amount of ground substance. Rests of odontogenic epithelium may be seen but are seldom numerous [3].

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In contrast, the stroma of WHO type odontogenic fibroma is more cellular and the fibroblastic strands are often interwoven. Odontogenic epithelium is an integral part and foci of calcified material resembling cementum, dentin or osteoid may be seen [3]. In the 2017 WHO classification, the consensus group dropped the sub-classification of “epithelium-poor or simple type” of odontogenic fibroma as they decided it was poorly defined [10]. Other histologic variants of COF are granular cell odontogenic fibroma [11], odontogenic fibroma composed of pleomorphic fibroblasts [12] and odontogenic fibroma exhibiting a giant cell reaction [13, 14]. Due to their low recurrence rates and indolent biologic behavior [8], COFs are usually treated by enucleation and curettage.

Central giant cell granulomas (CGCG) are more commonly seen in the anterior mandible and they frequently cross the midline. These may be non-aggressive, slow growing tumors that may present with few or no symptoms. Cortical perforation usually is not present. Aggressive CGCGs are rapidly growing and characterized by pain, cortical perforation, and root resorption. They tend to be larger, develop in somewhat younger individuals and have high recurrence rates [6]. Histologically, CGCGs consist of fibrous connective tissue stroma containing aggregates of multinucleated giant cells, multiple foci of hemorrhage, and sometimes trabeculae of woven bone. These histologic features are not specific for CGCGs because presence of multinucleated giant cells may be seen in several other lesions like aneurysmal bone cysts, brown tumors of hyperparathyroidism, and in multifocal giant cell lesions of cherubism, Noonan-like/multiple giant cell lesion syndrome, Ramon syndrome, Jaffe-Campanacci syndrome, and neurofibromatosis type 1 [6, 15]. CGCGs are usually treated by thorough curettage or en bloc resection, and have recurrence rates of 10–20% [9, 16].

A hybrid lesion comprising of COF with an associated giant cell granuloma-like lesion (GCGL) component is very rare and was first reported in 1992 [13]. Allen et al. presented three cases of this rare variant and considered them to be a unique presentation of COF which induced a giant cell reaction [13]. They also considered the possibility of this neoplasm being a “collision tumor”, although the probability that both COF and CGCG would arise synchronously was extremely small. Shortly after, eight cases were reported by Odell et al. [14] and one case by Mosqueda et al. [15]. Over the years, more reports of this lesion have been documented [17–23]. In addition to these published cases, several cases have been presented at professional meetings. In 1993, Fowler et al. reported an associated giant cell reaction in three of the 24 cases of COF [24]. Kessler presented a case diagnosed as COF with CGCG in the 2006 Meeting of the Western Society of Teachers of Oral Pathology [25]. In 2008, Hassan et al.

presented seven additional cases of the hybrid lesion at the 62nd Annual Meeting of American Academy of Oral and Maxillofacial Pathology (AAOMP) [26]. Two cases were presented at the 71st Annual Meeting of AAOMP in 2017 [27, 28]. This brings the total number of reported cases of COF with GCGL lesion to 40, and the number of published cases to 27. In this study, we report three additional cases and perform a literature review of the previously reported cases of COF with GCGL component. Table 1 summarizes all the reported cases of this hybrid lesion, including the cases described in this study.

Materials and Methods

Three cases of hybrid COF and GCGL lesion were identified from the University of Florida Oral Pathology Biopsy archives. Multiple 4 µm-thick formalin-fixed paraffin-embedded sections were stained with hematoxylin and eosin (H & E). Biopsy of the completely resected tumor was available in case 1, whereas lesions in cases 2 and 3 were representative of incisional biopsies. Immunohistochemical stains for cytokeratin 19 (CK19, Dako, Carpinteria, CA) and CD68 (Dako, Carpinteria, CA) were used to better visualize the odontogenic epithelium and multinucleated giant cells respectively.

Case Reports

Case 1

A 10-year old male presented to the oral surgeon with a well-defined radiolucency of the anterior mandible, in the area of impacted left mandibular canine (tooth # 22). The tooth was displaced horizontally to the inferior border of mandible (Fig. 1). There was expansion of both labial and lingual cortical bones, but no perforation was noted. Some resorption of the root of tooth # 21 was seen. The lesion extended from left mandibular first premolar to right lateral incisor (i.e., teeth # 21–25). The contiguous teeth (# 23–25) were displaced laterally and some shifting was present (Fig. 1). The lesion measured 1.9 × 1.8 cm in its greatest dimension and no history of trauma to the area was reported. The lesion was treated by curettage and there was no evidence of recurrence at 6 year follow-up.

Case 2

A 63-year old female was referred to the oral surgeon for evaluation of a painless left mandibular swelling. An expansile lesion, which had been present for a few years, was noted in the left posterior mandible (Fig. 2). It was located in the molar area and presented as a well-circumscribed

Table 1 Clinicopathologic characteristics of reported cases of hybrid COF and GCGL lesions^a

Case	Age (years)	Gender	Location	Associated features	Radiographic findings	Treatment	Recurrence	Ref.
1	66	F	R Mandible (PM-M)	RCT tooth	MRL	Curettage	None at 6 month FU	[13]
2	14	F	L Mandible (PM-M)	Vital teeth, no expansion	URL, 3.5 cm	Curettage	None at 48 month FU	[13]
3	30	F	L Mandible (PM-M)	Orthodontic treatment, some expansion	MRL 1.5×2.0 cm	Curettage Curettage of recurrent lesion	Yes, at 14 month FU	[13]
4	5	F	Anterior maxilla	Buccal expansion	–	Curettage	None	[14]
5	11	M	Post Maxilla, extending to antrum	Buccal expansion	URL	Curettage Conservative excision of recurrent lesion	Yes after 36 months	[14]
6	20	F	Mandible (PM-M)	–	URL 1.5×1.0 cm	Curettage	None	[14]
7	21	F	Post Mandible	Buccal expansion	URL, 3×2 cm	Curettage	None	[14]
8	22	F	Mandible (PM-M)	Buccal expansion, cortical perforation	–	Curettage and extraction of involved teeth	None	[14]
9	39	F	Mandible (PM-M)	Expansion, teeth mobile	–	Curettage	None	[14]
10	43	F	Mandible	–	–	Curettage Curettage of recurrent lesion	Yes after 36 months	[14]
11	50	F	Mandible PM	–	URL	Curettage	None	[14]
12	17	F	R Mandible (C-PM)	Buccal expansion	MRL 2.5×2 cm	Curettage	None at 72 month FU	[15]
13	57	F	R Mandible (PM-M)	Buccal expansion	URL 2.0×2.5 cm	Curettage	None at 18 month FU	[17]
14	18	M	Mandible (PM-M)	–	RL	Surgical excision	Lost to FU	[18]
15	20	F	Mandible (PM-M)	–	RL	Surgical excision	None at 117 month FU	[18]
16	50	M	Mandible (PM-M)	–	RL	Surgical excision	None at 28 month FU	[18]
17	73	M	Mandible (PM-M)	–	RL	Surgical excision	None at 43 month FU	[18]
18	15	M	Mandible (PM-M)	–	RL	Surgical excision	None at 76 month FU	[18]
19	59	M	Mandible (PM-M)	–	RL	Surgical excision	None at 39 month FU	[18]
20	25	M	Mandible (PM-M)	–	RL	Surgical excision	Lost to FU	[18]
21	24	F	Mandible (R M-L M)	Cortical Expansion	–	Curettage	None at 8 month FU	[19]
22	14	M	L Mandible (M)	Buccal & lingual swelling	URL 4.0×3.2 cm	Surgical excision	None at 16 month FU	[20]
23	14	M	L Mandible (PM-M)	Buccal expansion	MRL 4.5×3.0 cm	Surgical excision	None at 24 month FU	[20]
24	42	F	Mandible, body	–	RL	Enucleation/ Curettage	None	[21]
25	27	F	Mandible, ramus	Impaction	RL	Enucleation/ Curettage	None	[21]
26	75	F	Ant Mandible	–	URL	Curettage	NA	[22]

Table 1 (continued)

Case	Age (years)	Gender	Location	Associated features	Radiographic findings	Treatment	Recurrence	Ref.
27	22	F	R Mandible (PM-M)	Expansion & swelling	MRL	Surgical excision	NA	[23]
28	22	F	R Mandible (LI-M)	Lingual & inferior expansion	Mostly URL with scalloped edge, with hint of MRL in post. area	Surgical excision	None at 24 month FU	[25]
29–35 ^b	Average 49	5 M 2 F	Mandible	–	–	NA	Yes 3 cases	[26]
36	12	F	Ant Mandible	Asymptomatic	RL	NA	–	[27]
37	42	F	L Mandible (M)	Edentulous area	–	Surgical excision	None at 12 month FU	[28]
38	10	M	Ant Mandible (C-I)	Buccal and lingual expansion, impaction	URL 1.9×1.8 cm	Curettage	None at 72 month FU	Present study
39	63	F	L Mandible (M)	Buccal expansion	URL 1.7×1.0 cm	–	Awaiting treatment	Present study
40	62	M	R Mandible (PM)	Asymptomatic	URL	Curettage	None at 12 month FU	Present study

R right, L left, Ant anterior, Post posterior, C canine, I incisor, PM premolar, M molar, RL radiolucency, URL unilocular radiolucency, MRL multilocular radiolucency, NA not available, FU follow up

^aThis table does not include the cases reported by Fowler et al

^bDemographic and clinical data of individual patients was not available for cases presented by Hassan et al

Fig. 1 Panoramic radiograph of 10-year old male (case 1) showing a 1.9×1.8 cm radiolucent lesion in the anterior mandible. The lesion involves horizontally impacted tooth # 22 (red arrow) which is displaced to the inferior border of mandible. Lateral displacement of teeth # 21 and # 23–25 was noted but there was no cortical perforation

unilocular radiolucency. The patient was partially edentulous and had posterior teeth missing on the affected side. Buccal expansion of left posterior mandible was evident but no cortical perforation was seen (Fig. 2). An incisional biopsy was performed and sent for histopathologic examination. A diagnosis of COF with GCGL areas was made. The patient is scheduled for definitive treatment and management.

Case 3

A 62-year old male was referred to the oral surgeon by his general dentist for evaluation of a radiolucency in the right mandible, between teeth # 28 and # 29. He had history of a root canal treated tooth # 31 and a peripheral ossifying fibroma overlying the buccal gingiva of this tooth. The patient was asymptomatic and no expansion was noted

Fig. 2 Axial cone beam CT scan of the hybrid COF with GCGL lesion from case 2 demonstrating a well-defined unilocular radiolucency in the left posterior mandible. Considerable bone expansion is evident buccally (*red arrow*). The lesion presented in edentulous molar region

clinically. The lesion was treated by rigorous curettage with no evidence of recurrence at 1 year follow up. Microscopic examination revealed a diagnosis of COF with GCGL areas.

Histologically, the COF component predominated in cases 2 and 3 and components of both COF and CGCG were present in almost equal proportions in case 1. In this case, pockets of multinucleated giant cells were scattered in the stroma. A fibrocellular proliferation containing numerous strands, cords and islands of odontogenic epithelium were seen in all cases (Fig. 3a). Areas of mesenchymal cell proliferation, displaying a whorled and storiform pattern with strands and cords of odontogenic epithelium were seen in two cases. In case 3, multiple multinucleated giant cells were scattered towards the periphery of the lesion with the COF component located centrally. Foci of myxoid connective tissue were seen in this case. Both components abutted each other and were found to intermingle in few areas (Fig. 3b). The odontogenic epithelial cells exhibited cytoplasmic vacuolization in one case (Fig. 4a). Islands of odontogenic epithelium surrounded by a zone of hyalinization were also seen in this case. Vacuolization was noted in few multinucleated giant cells in one lesion (Fig. 4b). Osteoid or woven bone formation was also present in this case (Fig. 4b). Small duct like spaces and occasional areas of hyaline globules were present in the odontogenic epithelium in two cases (Fig. 5a, b). Multinucleated giant cells were seen in areas of hemorrhage and associated

Fig. 3 **a** Mature fibroblastic cells arranged in fascicles, exhibiting storiform pattern displaying strands and cords of odontogenic epithelium (*blue arrows*) throughout the stroma. Also seen are multinucleated giant cells (*green arrows*) in the lower part of the image (H & E, 10X), **b** Close proximity of odontogenic epithelial islands with many multinucleated giant cells in a cellular fibrous connective tissue stroma exhibiting hemorrhage. Some odontogenic rests can be seen interspersed with giant cells. Odontogenic islands are shown with *blue arrows* and multinucleated giant cells with *green arrows* (H & E, 20X)

hemosiderin deposition (Fig. 3b). Most of these giant cells contained 15–20 dispersed nuclei. Immunohistochemical staining with CK19 and CD68 highlighted the odontogenic epithelium and multinucleated giant cells respectively (Fig. 6).

Discussion

The diagnostic criteria of COF has remained somewhat controversial in view of the numerous attempts to subclassify the lesion based on its spectrum of histologic features. A few entities have been histologically confused with COF

Fig. 4 **a** Odontogenic epithelial cells arranged in islands and cords showing cytoplasmic vacuolization, shown with blue arrows (H & E, 20X), **b** Multinucleated giant cells showing vacuolization (green arrows) with osteoid or woven bone formation (blue arrow). Most of these giant cells comprised of 15–20 nuclei (H & E, 20X)

in the past. For example, several cases of hyperplastic dental follicles have been diagnosed as odontogenic fibromas [2, 3, 29]. Other neoplasms like desmoplastic fibroma, myxoma, and fibromyxoma have often been confused with COF [30, 31]. In 2005, WHO sub-classified odontogenic fibroma into two types: the simple odontogenic fibroma (epithelium-poor) and the odontogenic fibroma, WHO type (epithelium-rich) [9]. However, the “epithelium-poor or simple type” classification was dropped in the 2017 WHO classification of head and neck tumors [10].

The pathogenesis and precise nature of the hybrid COF with GCGL lesion remains elusive and different theories exist. The first theory suggests the possibility that this lesion could be a “collision tumor” which results from the synchronous occurrence of COF in the same area as a CGCG [13–15]. Given the rare nature of these neoplasms, this theory seems highly unlikely. Recurrence of

Fig. 5 **a** Odontogenic epithelial islands exhibiting duct-like spaces containing basophilic material (H & E, 20X), **b** Hyaline globules seen in some of the odontogenic islands (green arrows, H & E, 20X)

this hybrid neoplasm in six patients showed the presence of both components of the hybrid lesion in five cases [13, 14, 26]. One recurrent lesion comprised of CGCG component only [26]. The second theory postulates that growth factors, chemokines and cytokines produced by the primary CGCG lesion stimulate the proliferation of odontogenic component, and thus the formation of COF [14, 18]. The third theory proposed that COF is the primary tumor which induces a reactive GCGL reaction in response to trauma or other stimulus [13–15]. One case in our series arose in association with an impacted mandibular canine, whereas another had an endodontically treated tooth in vicinity of the lesion, with a history of a peripheral ossifying fibroma on the buccal gingiva (cases 1 and 3). Association with impacted teeth, endodontically treated teeth and teeth undergoing active orthodontic treatment has been reported in previous documented cases of COF with GCGL lesion [13, 21]. It cannot be ascertained if there is a relationship between development of this hybrid lesion and

Fig. 6 **a** Photomicrograph of odontogenic epithelium in cellular fibroblastic connective tissue showing immunoreactivity for CK19. Also seen is an osteoclast-like multinucleated giant cell (IHC, 20X), **b** Multinucleated giant cells showing immunoreactivity for CD68. Also seen in the vicinity are odontogenic epithelial strands (IHC, 20X)

endodontic treatment, impaction or a reactive lesion like a peripheral ossifying fibroma. A giant cell reaction has been reported in association with other odontogenic lesions such as ameloblastoma [32]. The authors reported that the giant cells seen adjacent to the ameloblastoma were a reactive process rather than being a separate lesion. Our cases may support this concept of a primary COF with the giant cells representing a reactive process in vicinity of the tumor.

Of the three cases reported in our study, two occurred in males and one presented in a female. The age range varied from 10–63 years. All lesions presented as unilocular radiolucencies in the mandible, two in posterior and one in the anterior region. No recurrence was noted in two patients at 6 and 1 year follow up, whereas the third patient is awaiting treatment. The clinicopathologic characteristics of this hybrid lesion are now known in 40

of the 43 cases, including three from this study (Table 1). Demographic and clinical data of the cases presented by Fowler et al. was not available. When data from all known cases was combined, females (60%) outnumbered men (40%) with a 1.5:1 female to male ratio. This is slightly different than the previously reported 2:1 female to male ratio [18]. This change in demographics may be explained by an increase in the number of documented cases of this hybrid lesion. The age range of the patients at the time of biopsy varied from 5 to 75 years, with an average age of 33.3 ± 20.4 years. Twenty patients were either 30 years of age or younger, and nine were 50 years or older. Specific demographic and clinical data for the seven cases presented by Hassan et al. was not available, but an average age of 49 years was reported in their study. The lesions occurred more often in the mandible (94.5%) and were typically located in the posterior region, especially premolar-molar area. Three cases, including one from this study, presented in the anterior mandible (Table 1). Two of these occurred in children and one in an older patient. Only two lesions were located in the maxilla, of which one was in the anterior region (case 4, Table 1). The posterior maxillary lesion extended to the maxillary antrum (case 5, Table 1). Buccal and/or lingual cortical expansion was a significant feature in majority of the cases. Associated clinical features included either swelling, displacement of teeth or mobility. Cortical perforation with recent rapid growth was noted in one patient (case 8, Table 1). These lesions may be quite extensive like in case 21 (Table 1) which extended from the left mandibular first molar to the right mandibular first molar. After curettage, a reconstruction titanium plate was used to stabilize the mandible and avoid bone fracture in this case. Mosqueda et al. reported that the mean size of the two hybrid lesions included in their study was larger than regular COFs [20]. Radiographically, the hybrid COF with GCGL lesions presented as well-defined unilocular or multilocular radiolucencies. Recurrence was noted in six patients (15%, Table 1) with a follow up period, reported for 19 cases, averaging 36.9 ± 29.2 months per patient. However, a long-term follow up may be required to determine the accurate recurrence rates of this hybrid neoplasm. Two recurrent lesions presented as markedly expansile multilocular radiolucencies. The initial lesion in case 3 was localized to the left premolar-molar region, but the recurrent lesion presented as an expansile radiolucency extending from right mandibular canine to left mandibular first molar region (Table 1) [13]. In the second patient, the hybrid lesion presented as markedly expansile multilocular radiolucency which extended to the maxillary antrum (case 5, Table 1) [14]. Nineteen lesions were treated by curettage and surgical excision was performed for 12 lesions (Table 1). Three of the six

lesions that showed recurrence were initially treated by curettage. The recurrent lesions in cases 3 and 10 were treated by recurettage, and a local resection was performed for case 5 (Table 1) [13, 14]. Recurrence followed within three years of curettage in these cases, and the ages at the time of recurrence were 14, 31 and 46 years. This may indicate that thorough curettage or conserved surgical excision with a long-term follow up may be the treatment of choice for these hybrid lesions. Clinical data of the three recurrent lesions reported by Hassan et al. was not available [26]. No recurrence was reported in two patients from our study at 72 and 12 month follow up. The third patient is awaiting treatment.

Histologically, the components of hybrid COF with GCGL lesion may either be sharply demarcated and distinct, or may be intermixed with each other [14, 15, 17]. Different proportions of odontogenic epithelium and giant cells have been reported in hybrid lesions. Mosqueda et al. and Allen et al. reported a predominance of odontogenic fibroma component [13, 15]. Odell et al. speculated that these lesions may arise from involvement of odontogenic epithelium by giant cell granuloma and are indicative of a primary CGCG [14]. Tosios et al. reported predominance of odontogenic fibroma component in three lesions and of giant cell component in three cases [18]. They also reported a case of hybrid lesion in a patient with cherubism. In this study, we found predominance of COF component in two cases, whereas third case presented with almost equal proportions of both components. Since two of these lesions were obtained from incisional biopsies, this histologic pattern may not be truly representative of the distribution pattern of these two components. In five recurrent lesions, the giant cell granuloma and COF components were present in proportions similar to those in the initial lesions [13, 14, 26], which suggests that the combination of the two components is an essential feature of the lesion. However one recurrent lesion comprised solely of CGCG areas [26]. Cytoplasmic vacuolization of cells, duct-like spaces and hyaline basement membrane globules in the odontogenic epithelium have been reported in previous published cases of hybrid COF with GCGL lesions. Osteoid deposits have been reported in many cases of this hybrid lesion [13–15]. In our study, in addition to these previously reported features, we also noticed vacuolization in few multinucleated giant cells as well as osteoid formation in one case (Fig. 4b). CK19 and CD68 immunohistochemical stains were used to visualize the odontogenic epithelium and multinucleated giant cells. CK19 is an intermediate filament protein which is expressed in all epithelial cells derived from the mesenchyme and has high reactivity for odontogenic epithelium [31]. CD68 glycoprotein is expressed on the cell surface

of monocyte/macrophage lineage cells and is highly positive in multinucleated giant cells [33]. The odontogenic islands and multinucleated giant cells showed immunoreactivity to CK19 and CD68 stains (Fig. 6).

Conclusion

In summary, three additional cases of hybrid COF with GCGL lesion are presented, along with a detailed review of literature of this uncommon lesion. One lesion presented in the anterior mandible and two occurred in the posterior region. When our cases were combined with those previously documented, the average age of presentation was 33.3 ± 20.4 years, with a 1.5:1 female to male ratio. Curettage and surgical excision were the treatment of choice in 19 and 12 lesions respectively. Six lesions showed recurrence (15% recurrence rate), three of these were initially treated by curettage. The higher recurrence rates of hybrid COF and CGCG lesion when compared to regular COF, support the fact that CGCG may be the driving force for the recurrence. Like CGCGs, this neoplasm has a high predilection for the mandible. Further molecular studies with a long-term follow-up information are required to understand the pathogenesis and biologic behavior of COF with GCGL lesions. Regardless of its pathogenesis, the presence of GCGL component in COF appears to produce higher recurrence. Therefore, this uncommon hybrid lesion may be treated similar to giant cell granuloma including thorough curettage or conserved excision, and a closer follow-up when compared to a regular COF.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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