






Talita de Carvalho Kimura¹ 
 Renata Sari Precetti²
 Hélen Kaline Farias Bezerra¹ 
 Alan Roger dos Santos Silva¹ 
 Ana Carolina Prado-Ribeiro³ 
 Pablo Agustin Vargas^{1*} 

Central odontogenic fibroma with giant cell granuloma-like features: a case report and comprehensive literature review

Abstract:

Central odontogenic fibroma (COF) is a rare benign tumor from odontogenic mesenchyme, accounting for less than 5% of odontogenic tumors. Central giant cell granuloma (CGCG) is also benign but locally aggressive, featuring multinucleated giant cells in a fibrovascular stroma. Hybrid lesions with features of both COF and CGCG are extremely rare, with fewer than 50 cases reported. This paper presents a case of a hybrid COF-CGCG lesion in a 33-year-old female with an asymptomatic, well-defined unilocular radiolucent lesion between mandibular premolars, causing root resorption and tooth displacement. Histopathological analysis revealed a mixture of inactive odontogenic epithelium and multinucleated giant cells embedded in a dense, collagenized stroma. The patient showed no signs of recurrence after six months of follow-up. This case highlights the rarity and diagnostic challenges of COF-CGCG hybrid lesions, emphasizing the need for further research to understand its pathogenesis and guide management.

Keywords: Odontogenic tumors; Central odontogenic fibroma; Giant cell granulomas.

INTRODUCTION

Central odontogenic fibroma (COF) is a rare benign odontogenic tumor derived from mesenchymal tissue, accounting for less than 5% of all odontogenic tumors. It predominantly affects middle-aged women and is more frequently located in the anterior maxilla, though cases involving the posterior mandible have been reported^{1,2}. Histologically, COF consists of a stroma of mature collagenous connective tissue interspersed with inactive odontogenic epithelium in the form of islands or cords. Additionally, calcified materials resembling dentin or dysplastic cementum may be observed in some cases¹. These tumors generally exhibit a benign clinical course, characterized

Statement of Clinical Significance

Central odontogenic fibroma and central giant cell granuloma hybrid lesions are exceptionally rare, with fewer than 50 cases documented. This study reports a unique case in a 33-year-old female presenting with radiographic and histopathological features of both conditions. The lesion exhibited aggressive behavior, including root resorption and tooth displacement, and was successfully treated with conservative curettage.

by slow, non-aggressive growth. However, in rare instances, it may display more aggressive behavior, such as cortical bone perforation, tooth displacement, and root resorption¹. Surgical management typically involves a conservative approach, such as curettage, with low recurrence rates observed, usually related to incomplete removal³.

Several histological variants of COF have been identified, including the amyloid, granular cell, ossifying, and hybrid subtypes. The hybrid variant, characterized by the coexistence of features from COF and central giant cell granuloma (CGCG), is exceedingly rare and poses unique diagnostic challenges^{4,5}. CGCG is a benign yet locally destructive lesion, typically affecting the mandible, and is composed of multinucleated giant cells within a fibrovascular stroma.

¹Universidade Estadual de Campinas, Piracicaba Dental School, Department of Oral Diagnosis – Piracicaba (SP), Brazil.

²Universidade São Francisco – Bragança Paulista (SP), Brazil.

³Universidade de São Paulo, Faculdade de Medicina, Instituto do Câncer do Estado de São Paulo, Dental Oncology Service – São Paulo (SP), Brazil.

*Correspondence to: Email. pavargas@unicamp.br

Received on November 2, 2024. Accepted on November 28, 2024.

<https://doi.org/10.5327/2525-5711.277>



The first documented case of a COF-GCG hybrid lesion was reported by Wangerin and Harms in 1985, followed by a second report by Allen et al. in 1992^{6,7}.

Given the rarity of hybrid COF-CGCG lesions and the limited number of reported cases, this study aims to present a unique case of this hybrid entity. In addition to the case report, we conducted a comprehensive literature review to provide insights into the clinical, radiographic, and histopathological characteristics of these lesions.

CASE REPORT

This study was approved by the Research Ethics Committee of the Piracicaba School of Dentistry (FOP-UNICAMP, CAAE: 77372124.4.0000.5418). A 33-year-old Brazilian female patient was referred for evaluation of an incidental detection of a 2.0 x 2.0 cm well-defined hypodense unilocular lesion located between the mandibular premolars, identified through a tomographic examination. The lesion caused root resorption and displacement of the adjacent teeth (Figure 1). Upon clinical examination, no swelling or pain was observed, and the teeth were found to be vital and with no alterations in mobility. Considering the differential diagnosis of lateral periodontal cyst or odontogenic keratocyst, an excisional biopsy via curettage was performed.

Histopathological examination revealed fibrous tissue infiltrating the bone trabeculae, with islands of inactive odontogenic epithelium. The stroma was highly cellular and collagenized, with numerous multinucleated giant cells, spindle-shaped cells, and areas of hemorrhage (Figure 2). Osteoid bone deposition

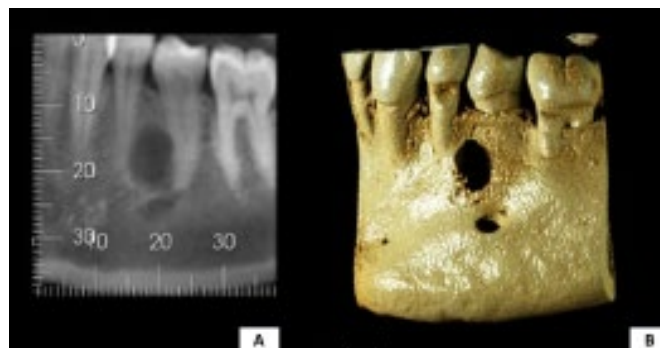


Figure 1. Tomographic aspects of the hybrid lesion of central odontogenic fibroma and central giant cell granuloma. A and B: Tomographic slices and a three-dimensional reconstruction showing a unilocular, well-defined hypodense lesion in the region between the lower left premolars, which has resulted in root resorption and tooth displacement.

was also observed in certain areas. These findings meet the essential diagnostic criteria for COF and CGCG, as established by the latest WHO classification⁸. For the COF component, essential criteria included a compatible localization with an odontogenic origin, radiological evidence of a well-defined lesion, and the presence of benign fibrous connective tissue with variable cellularity. Additionally, odontogenic epithelial nests or strands were identified as a desirable feature. Regarding the CGCG component, the essential criteria included jaw localization, the presence of clustered osteoclast-like giant cells, areas of hemorrhage, and spindle cell stroma was also identified. However, the lesion did not display the desirable characteristic of a lobular structure.

Immunohistochemical analysis demonstrated positivity for CK19 (Dako, Carpinteria, CA) and AE1/AE3 (Dako, Carpinteria, CA) in the odontogenic epithelium, and CD68 (Dako, Carpinteria, CA) positivity in the multinucleated giant cells (Figure 3). These findings were consistent with a hybrid lesion, incorporating features of FOC and CGCG. No recurrence was observed after 6 months of follow-up.

LITERATURE REVIEW

The occurrence of hybrid lesions featuring both FOC and CGCG is an exceptionally rare phenomenon. The earliest documentation of this variant dates to 1985 in Germany and was subsequently described in a 1992 study by Allen et al.^{6,7}. Allen et al. reported three cases of this uncommon variant, highlighting a distinct manifestation of FOC that induces a giant cell reaction. In 1997, Odell et al. contributed to the body of literature with eight additional cases, followed by a case reported by Mosqueda Taylor et al. in 1999^{9,10}. Since then, the number of documented cases has increased to 43^{1-7,9-19}.

A thorough review of the literature reveals that, in addition to the cases published in peer-reviewed journals, several reports have been presented at academic conferences and documented in multicenter studies²⁰⁻²⁴. However, due to the absence of detailed publications for these reports, they are not included in Table 1^{1-6,9-19}.

The hybrid FOC-CGCG lesions predominantly affect females (n=27, 62.8%), with a mean patient age of 33.3±20.4 years (5–75 years). The mandible is the most frequently involved site (39 patients, 90.7%), with a predominant localization in the posterior region (76.7%). Only four cases (9.3%) have been reported in the maxilla^{9,19}. Clinically, these lesions are characterized by bone

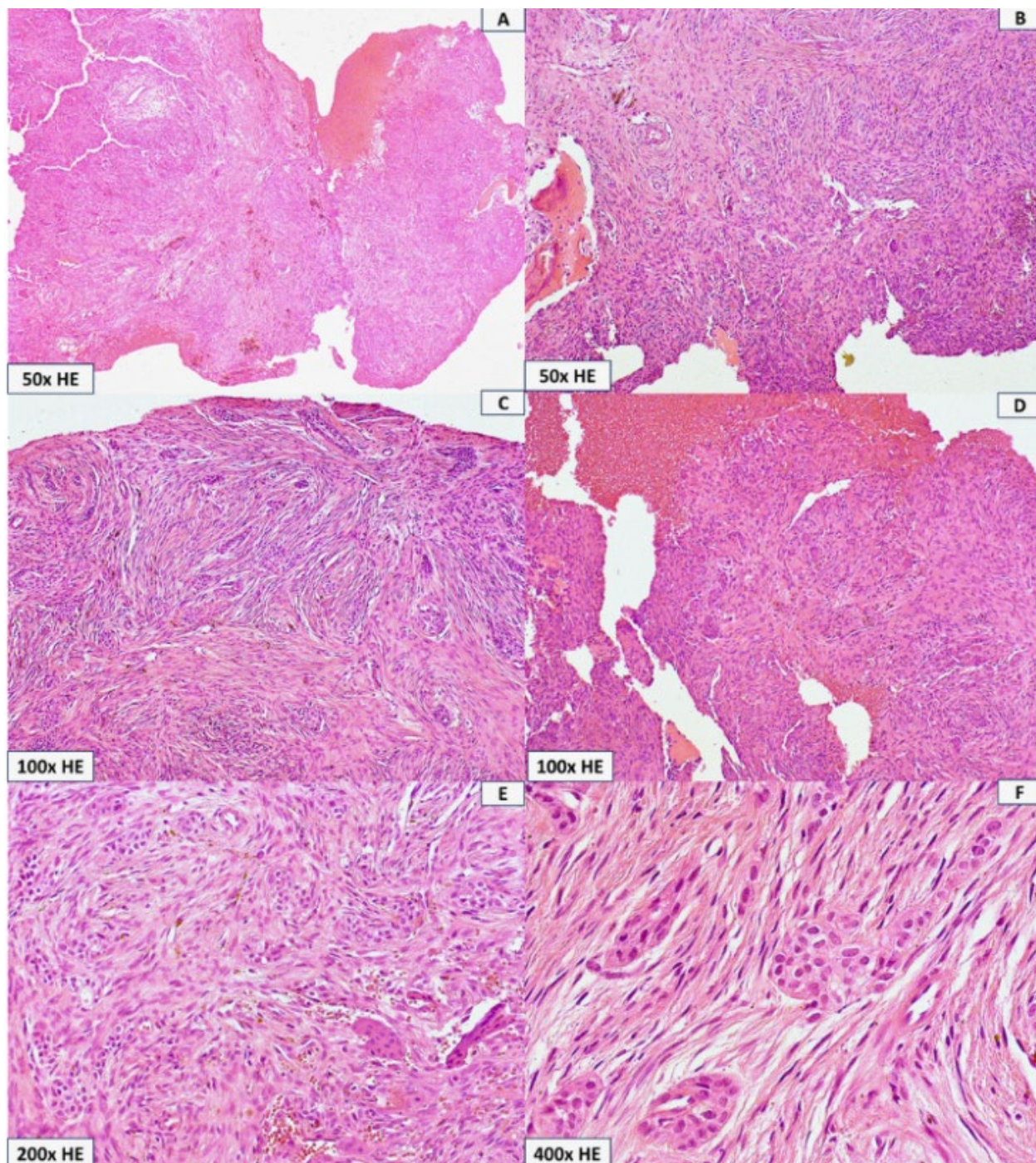


Figure 2. Microscopic aspects of the hybrid lesion of central odontogenic fibroma and central giant cell granuloma. Slides stained with hematoxylin and eosin, showing an association between the classic aspects of a central odontogenic fibroma and a central giant cell granuloma. A-D: The lesion is composed of cellularized tissue interspersed with hemorrhage, islands of odontogenic epithelium, spindle cells, and multinucleated giant cells. E: Association between islands of inactive odontogenic epithelium with multinucleated giant cells and spindle cells. F: Islands of inactive odontogenic epithelium.

expansion in 25 patients (58.6%). Radiographically, the most common finding is radiolucency, which was observed in 36 patients (83.8%). Multilocular lesions were observed in eleven cases (25.6%), while unilocular lesions were found in 16 patients (37.3%). A mixed radiographic

appearance, with radiopacities within a radiolucent defect, was observed in two cases (4.7%). The dimensions of the lesions exhibit considerable variability, with an average diameter of 3 cm and a maximum of 9 cm. Tooth displacement was observed in nine patients

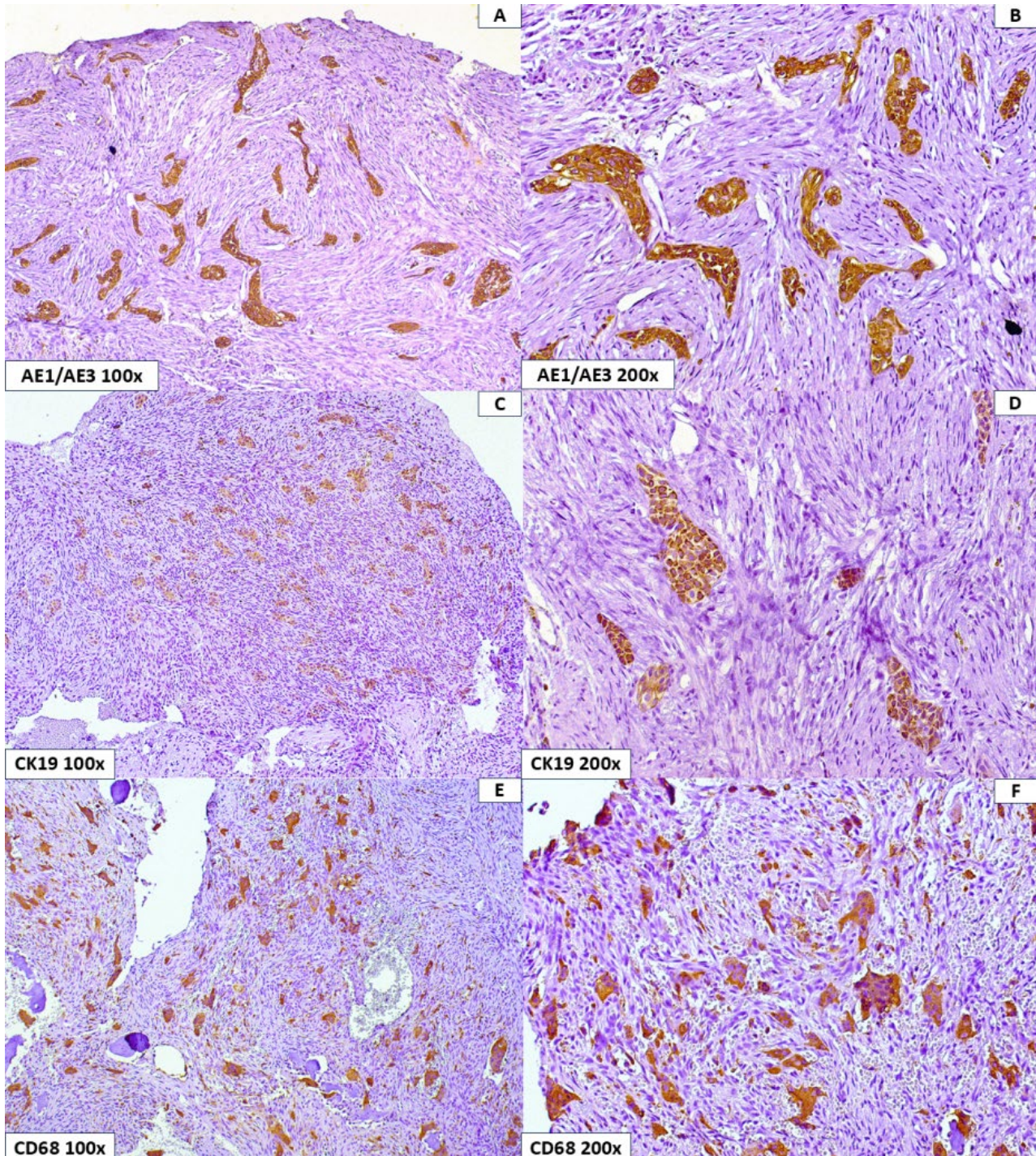


Figure 3. Immunohistochemical aspects of the hybrid lesion of central odontogenic fibroma and central giant cell granuloma. A-D: Islands of inactive odontogenic epithelium are observed in a cellularized fibrous stroma. The cytoplasm of these islands is stained positively for epithelial markers AE1/AE3 and CK19. E: Multinucleated giant cells are observed in the stroma. The cytoplasm of these cells is stained positively for the CD68 marker.

(20.7%), while tooth mobility was noted in two cases (4.7%). Six patients (13.8%) exhibited more aggressive clinical behavior with cortical perforation^{9,16}.

Histologically, the lesions exhibit features characteristic of both FOC and CGCG. The stroma is

composed of collagenized and fibromyxoid tissue, interspersed with islands of inactive odontogenic epithelium. These islands occasionally display hyaline globules suggestive of a basal membrane, vacuolized clear cells, duct-like structures, and cytoplasmic inclusions^{1,4,9-11,13,14}.

Table 1. Clinicopathological characteristics of hybrid lesions of central odontogenic fibroma and central giant cell granuloma.

Case	Author	Sex	Age (years)	Site	Evolution time (months)	Clinical appearance	Radiographic appearance	Treatment	Recurrence	Follow-up (months)
1	Allen et al. ⁶	F	66	Mandible (premolar/molar)	N.A	N.A	ML RL; N.A	Curettage	No recurrence	6
2		F	14	Mandible (premolar/molar)	N.A	No cortical bone expansion	UN RL; 3.5 cm	Curettage	No recurrence	48
3		F	30	Mandible (premolar/molar)	N.A	Cortical bone expansion	ML RL	Curettage	Recurrence	14
4		F	5	Maxilla (molar)	N.A	Cortical bone expansion	N.A	Curettage	No recurrence	N.A
5		M	11	Maxilla	N.A	N.A	RL	Curettage	No recurrence	N.A
6		N.A	14	Maxilla	N.A	Cortical bone expansion	ML RL; 3.0 cm	Conservative excision	Recurrence	36
7		F	20	Mandible (premolar/molar)	N.A	N.A	UN RL; 1.5 cm	Curettage	No recurrence	N.A
8	Odell et al. ⁹	F	21	Mandible (premolar/molar)	N.A	Cortical bone expansion and perforation	UN RL; 3.0 cm	Curettage	No recurrence	N.A
9		F	22	Mandible (premolar/molar)	N.A	Cortical bone expansion	N.A	Curettage	No recurrence	N.A
10		F	39	Mandible (premolar/molar)	N.A	Cortical bone expansion and dental mobility	N.A	Curettage	No recurrence	N.A
11		F	43	Mandible	N.A	N.A	N.A	Curettage	No recurrence	N.A
12		M	46	Mandible	N.A	N.A	N.A	Curettage	Recurrence	36
13		F	50	Mandible (premolar)	N.A	N.A	UN RL	Curettage	No recurrence	N.A
14	Taylor et al. ¹⁰	F	17	Mandible (canine/premolar)	N.A	Cortical bone expansion and dental displacement	ML RL; 2.5 cm	Curettage	No recurrence	72
15	Lima et al. ¹¹	F	24	Mandible	96	Cortical bone expansion and dental displacement	Mixed	Curettage	No recurrence	8
16		M	18	Mandible (premolar/molar)	N.A	N.A	RL	Surgical excision	Lost follow-up	-
17		F	20	Mandible (premolar/molar)	N.A	N.A	RL	Surgical excision	No recurrence	117
18	Tosios et al. ¹	M	50	Mandible (premolar/molar)	N.A	N.A	RL	Surgical excision	No recurrence	28
19		M	73	Mandible (premolar/molar)	N.A	N.A	RL	Surgical excision	No recurrence	43
20		M	15	Mandible (premolar/molar)	N.A	N.A	RL	Surgical excision	No recurrence	76
21		M	59	Mandible (premolar/molar)	N.A	N.A	RL	Surgical excision	No recurrence	39
22	Younis et al. ⁴	F	57	Mandible (premolar/molar)	N.A	Cortical bone expansion	UN RL; 2.5 cm	Curettage	No recurrence	18
23	Cortés Castillo et al. ¹²	M	14	Mandible (premolar/molar)	7	Cortical bone expansion, displacement, and dental mobility	UN RL; 3.0 cm	Curettage	No recurrence	24
24	Eversole ⁵	F	42	Mandible (premolar/molar)	N.A	N.A	RL	Curettage	No recurrence	N.A
25		F	27	Mandible (ramus)	N.A	Impaction	RL	Curettage	No recurrence	N.A

Continue...

Table 1. Continuation.

Case	Author	Sex	Age (years)	Site	Evolution time (months)	Clinical appearance	Radiographic appearance	Treatment	Recurrence	Follow-up (months)
26	Mosqueda-Taylor et al. ¹³	M	14	Mandible (premolar/molar)	6	Cortical bone expansion and dental displacement	UN RL; 4.0 cm	Curettage	No recurrence	16
27		M	14	Mandible (premolar/molar)	6	Cortical bone expansion and dental displacement	ML RL; 4.5 cm	Curettage	No recurrence	24
28	Bologna Molina et al. ²	M	14	Mandible (premolar/molar)	6	Cortical bone expansion	ML RL	Curettage	No recurrence	24
29	Damm ¹⁷	M	75	Mandible (anterior)	N.A	N.A	UN RL	N.A	N.A	N.A
30	Eliot et al. ¹⁸	F	22	Mandible (premolar/molar)	N.A	Cortical bone expansion	ML RL	Curettage	N.A	N.A
31	Upadhyaya et al. ¹⁴	M	10	Mandible (anterior)	N.A	Cortical bone expansion and dental displacement	UN RL	Curettage	No recurrence	72
32		F	63	Mandible (molar)	N.A	Cortical bone expansion	UN RL	Incisional biopsy	N.A	N.A
33		M	62	Mandible (premolar)	N.A	No cortical bone expansion	UN RL	Curettage	No recurrence	12
34	Flores-Hidalgo et al. ¹⁵	F	65	Mandible (premolar/molar)	N.A	Cortical bone expansion	ML RL; 9.0 cm	Curettage	Recurrence	9
35	Ramadan and Essawy ³	F	33	Mandible (premolar/molar)	12	Cortical bone expansion	UN RL	Curettage	No recurrence	12
36		F	42	Mandible (body)	N.A	Cortical bone expansion and perforation	ML RL; 3.0 cm	Conservative excision	No recurrence	12
37		F	22	Mandible (premolar)	N.A	N.A	Periradicular UN RL; root displacement and resorption; 2.0 cm	Conservative excision	No recurrence	144
38		F	17	Mandible (canine/premolar)	N.A	None	Periradicular UN RL; 1.0 cm	Conservative excision	N.A	N.A
39	Roza et al. ¹⁹	M	63	Mandible (premolar/molar)	3	Cortical bone expansion	Periradicular well-defined RL; cortical bone expansion and disruption	N.A	N.A	N.A
40		F	14	Maxilla (premolar)	N.A	Cortical bone expansion, perforation, tooth displacement, and palatine depression	Well-defined ML RL; 2.0 cm	Conservative excision	No recurrence	N.A
41		F	45	Mandible (incisive/canine)	N.A	Cortical bone expansion and perforation	ML, Mixed, 2.5 cm	N.A	N.A	N.A
42		F	12	Mandible (body)	48	Cortical bone expansion, perforation, tooth displacement, and alveolar ridge depression	Periradicular ML RL; 3.0 cm	N.A	N.A	N.A
43	Khiavi et al. ¹⁶	F	46	Mandible (premolar/molar)	N.A	Cortical bone expansion and perforation	UL RL	Curettage	No recurrence	24

Legend: F: Female; M: Male; ML: Multilocular; N.A: Not Available; RL: Radiolucent; Mixed: Radiolucent-radiopaque; UL: Unilocular.

Additionally, osteoclast-like giant multinucleated cells and spindle cells are dispersed throughout the tumor, often associated with areas of hemorrhage and hemosiderin deposits^{9,11,19}. In several cases, osteoid bone formation has been observed within and peripheral to the lesion^{1,3,4,9,14}.

Regarding treatment, curettage is the most frequently employed procedure (33 patients, 76.8%), with five patients (11.6%) undergoing conservative surgical excision. One case (2.3%), diagnosed via incisional biopsy, has not yet undergone treatment. Local recurrence was observed in four cases (9.3%), while 31 patients (72.1%) exhibited no signs of recurrence^{6,9}. The mean follow-up period was 38.1 months, with a range of 6 to 144 months. Recurrences were observed in patients with multinucleated radiolucent lesions, with follow-up periods of 36 months in two cases, 9 months in one case, and 14 months in one case^{6,9}.

DISCUSSION

Although COF and CGCG are well-established pathologies, the occurrence of hybrid lesions containing both components is exceedingly rare, with fewer than 50 cases documented in the literature. This rarity limits our understanding of their pathogenesis and clinical behavior. In this context, our findings add to the body of knowledge, offering further insights into these hybrid lesions.

The data obtained from the literature review indicate that the hybrid lesions of FOC and GCCG have been more frequently observed in female patients, with a 1.5:1 female-to-male ratio, as noted in previous studies¹⁴. The age range is broad, but most cases occur in patients with an average of 33.8 years, which is consistent with the findings of previous studies and our case^{1,14}. They are predominantly located in the mandible, particularly in the posterior region, with only a few cases involving the maxilla^{9,19}. Radiographically, most cases present as unilocular or multilocular radiolucencies¹⁴. These hybrid lesions often present with asymptomatic bone expansion, although more aggressive features such as cortical perforation and tooth displacement have been documented^{9,16}. The clinical presentation of our patient aligns with aggressive presentation that is compatible with CGCG behavior, such as tooth displacement and root resorption.

Histopathologically, hybrid lesions exhibit distinct areas consistent with both COF and CGCG. The odontogenic component typically consists of islands of inactive

epithelium within a collagenous stroma, while the CGCG component contains multinucleated giant cells scattered within a fibrovascular stroma, often accompanied by areas of hemorrhage^{1,2,6,10,14}. In our case, immunohistochemical staining confirmed the presence of odontogenic epithelium with positive CK19 and AE1/AE3 staining, and CD68 highlighted the multinucleated giant cells, corroborating findings from other reports^{1-3,11,14}.

The pathogenesis and nature of these lesions remains poorly understood with three competing theories proposed. The first hypothesis suggests that the lesion may have been a collision tumor, in which the two pathologies arose synchronously^{6,9,10}. The rare occurrence of these pathologies makes such a theory highly implausible^{6,14}. Additionally, in such instances, a distinct separation of the two pathologic processes is evident, with no evidence of fusion between them³. Another hypothesis suggests that COF may induce a secondary reactive process that leads to the formation of a CGCG-like component, possibly triggered by odontogenic epithelium or external stimuli such as trauma^{6,9,14}. We consider this second theory to be more plausible. Finally, the last theory proposes that growth factors and cytokines released by the CGCG component could stimulate the development of COF^{1,9}. These mechanisms remain speculative, and further investigations into molecular and genetic factors that may drive the coexistence of these components could provide important insights.

From a clinical perspective, the management of hybrid COF-CGCG lesions requires careful histopathological evaluation to distinguish between benign and more aggressive features. Conservative surgical approaches, such as curettage, appear effective, as evidenced by the absence of recurrence in our patient and based on the literature. However, clinicians should remain vigilant for signs of recurrence, particularly in cases with prominent giant cell components, which may indicate a higher risk of aggressive behavior⁹. In these cases, a less conservative surgical approach, with broader surgical extension and longer clinical follow-up periods than nine months, is recommended, as two cases recurred after 36 months^{3,6,9,13,25}.

One of the major limitations in studying hybrid lesions such as COF-CGCG is the small number of cases available for analysis. This scarcity hinders our ability to draw definitive conclusions about their pathogenesis. Additionally, the lack of long-term follow-up in many studies, including our own case, limits the ability to assess recurrence rates and long-term outcomes. While our patient showed no signs of recurrence after six months,

longer follow-up periods are essential to better understand the biological behavior of these hybrid lesions.

CONCLUSION

In conclusion, hybrid lesions combining features of COF and CGCG are extremely rare, with fewer than 50 documented cases. This study presents a case of a 33-year-old female with a COF-CGCG hybrid lesion, characterized by radiographic and histopathological findings. The lesion exhibited aggressive features, including root resorption and tooth displacement, and was effectively managed through surgical curettage. Although the absence of recurrence at six months suggests that conservative treatment is effective, further research is required to elucidate the pathogenesis, biological behavior, and optimal management protocols for these hybrid lesions.

ACKNOWLEDGMENTS

The authors are grateful to The São Paulo State Research Foundation (FAPESP, São Paulo, Brazil, grant number 23/13091-6) for the scholarship.

AUTHORS' CONTRIBUTIONS

TCK: conceptualization, data curation, formal analysis, investigation, writing – original draft, writing – review & editing. RSP: data curation. HKFB: data curation, investigation, writing – review & editing. ARSS: data curation, formal analysis, supervision, writing – review & editing. ACPR: data curation, formal analysis, supervision, writing – review & editing. PAV: conceptualization, data curation, formal analysis, investigation, supervision, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

Funding: This study was not supported by any funding.

Competing interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval: All procedures performed in studies 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.

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