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ORIGINAL ARTICLE

A systematic review of the clinical and radiographic features of hybrid central giant cell granuloma lesions of the jaws

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ABSTRACT

Objective: Central giant cell granuloma (CGCG) can coexist with other benign lesions of the jaw. These hybrid lesions are diagnostically challenging to both oral pathologists and radiologists. This work systematically reviews the clinical and radiographic features of hybrid-CGCG lesions in the jaws.

Materials and methods: Three reviewers conducted an electronic search of five databases for histologically diagnosed hybrid-CGCG lesions in human jaws.

Results: Thirty-four of 1224 articles met the inclusion criteria. Of 39 hybrid-CGCG lesions, 14 (35.9%) were central odontogenic fibroma, 11 (28.2%) were central ossifying fibroma, seven (17.9%) were fibrous dysplasia, and seven (17.9%) were other bone conditions. There were 22 females and 17 males with a mean age of 30.5 ± 19.9 years. 89.5% of hybrid-CGCG lesions were well defined, 57.9% were non-corticated, 60.5% were radiolucent, and 66.7% were in the posterior mandible. Most hybrid lesions affected the cortical plates by thinning, expansion, or perforation (93.1%), displaced, or resorbed teeth (60%).

Conclusion: The radiographic features of hybrid-CGCG lesions vary according to the concurrent bony lesion. Hybrid-CGCG lesions altered the radiographic appearance with the following entities: fibrous dysplasia, melorheostosis, and Paget's disease. Optimal imaging modalities are crucial to detail radiographic features and direct representative biopsy of suspicious sites that may host a CGCG hybridisation.

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Introduction

Central giant cell granuloma (CGCG) is a benign osseous lesion of the jaws. The exact aetiology of this lesion is still controversial, but the literature suggests three theories [1,2]. The first proposes a reactive origin to a local irritant; the second suggests that it is a developmental anomaly, and the third implicates a neoplastic aetiology [2]. CGCG accounts for 7% of all benign jaw tumours [3]. Histopathological examination reveals giant cell proliferation, numerous spindle-shaped mesenchymal cells, and erythrocyte extravasation in a fibrous stroma [4,5]. It is normally a slowly growing lesion, although an aggressive behaviour is not uncommon [3].

Radiologically, CGCG can be unilocular or multilocular with wispy-septation, undulating borders, cortical expansion, and perforation. The degree of cortical expansion and perforation varies depending on its clinical aggressiveness (large size, high rate of growth, or recurrence) [1,2]. CGCG commonly presents in the anterior region of the mandible with a notable predilection in young females [1,2]. Recurrence has been noted more in aggressive lesions [1,2].

In several case reports, CGCG presented with other benign lesions of the jaws such as central odontogenic fibroma and ossifying fibroma, hence named "hybrid lesion" [4,6,7]. The combined radiographic and histologic features of both lesions forms the "hybrid" presentation. The diagnosis of these lesions remains challenging to both oral pathologists and radiologists [7].

The purpose of this paper was to systematically review the clinical presentation and radiographic features of hybrid-CGCG lesions, that is, associating with any other bone lesions of the jaws. This review focuses on hybrid-CGCG lesions, meaning they coexist in the same location with other lesions in the jaws. Enhancing the knowledge of the clinical and radiographic interrelations between the individual associated lesions may improve clinician's understanding and, eventually, the diagnosis of these rare hybrid lesions.

Methods

Following the PRISMA guidelines [8], the three phases of search are as follows:

Phase I: Identification and screening

The following databases were searched during May 2019 and concluded in the third week of September 2019: PubMed, Scopus, Web of Science, Ovid, and Google Scholar.

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Inclusion criteria: CGCG coexisting with another bone lesion, present in the jaws, in humans only, histopathologically confirmed lesions, and use of radiography. Editorials/letters to the editor were excluded.

Keyword search for each database: [central giant cell granuloma, central giant cell lesion, CGCG, brown tumour, multinucleated giant cell, hybrid lesion], AND [mandible, mandibular, maxilla, maxillary, jaw, jaws, alveolar bone], AND [radiograph, radiography, diagnostic imaging, three-dimensional imaging, x-ray]. Keyword search for Google scholar: central giant cell hybrid lesion/lesions/granuloma (all in title). The titles and abstracts of the articles were reviewed for inclusion in the next phase. All electronic databases search keywords, and hits are provided in Appendix A.

Phase II: Eligibility

The reviewers independently reviewed the full article and applied the inclusion criteria. Using the references of the included articles, the reviewers completed a manual search for relevant articles possibly missed from the electronic search.

Phase III: Included studies

Murad et al. [9] tool for methodological quality and risk of bias assessment was customised and used in this review. The main domains of assessment before and after customisation are provided in Appendix B.

The reviewers collected demographic data, clinical presentation and radiographic features, type of associated lesion, and recurrence for each study.

Three reviewers (RM, RS, RF) individually conducted the review. Disagreement about an article was resolved by consensus among the three reviewers and the supervisor (NAA).

Results

Database search

The PRISMA flowchart, Figure 1, shows the total number of articles that resulted from the systematic search. A total of 1216 articles resulted from the database search, with 452

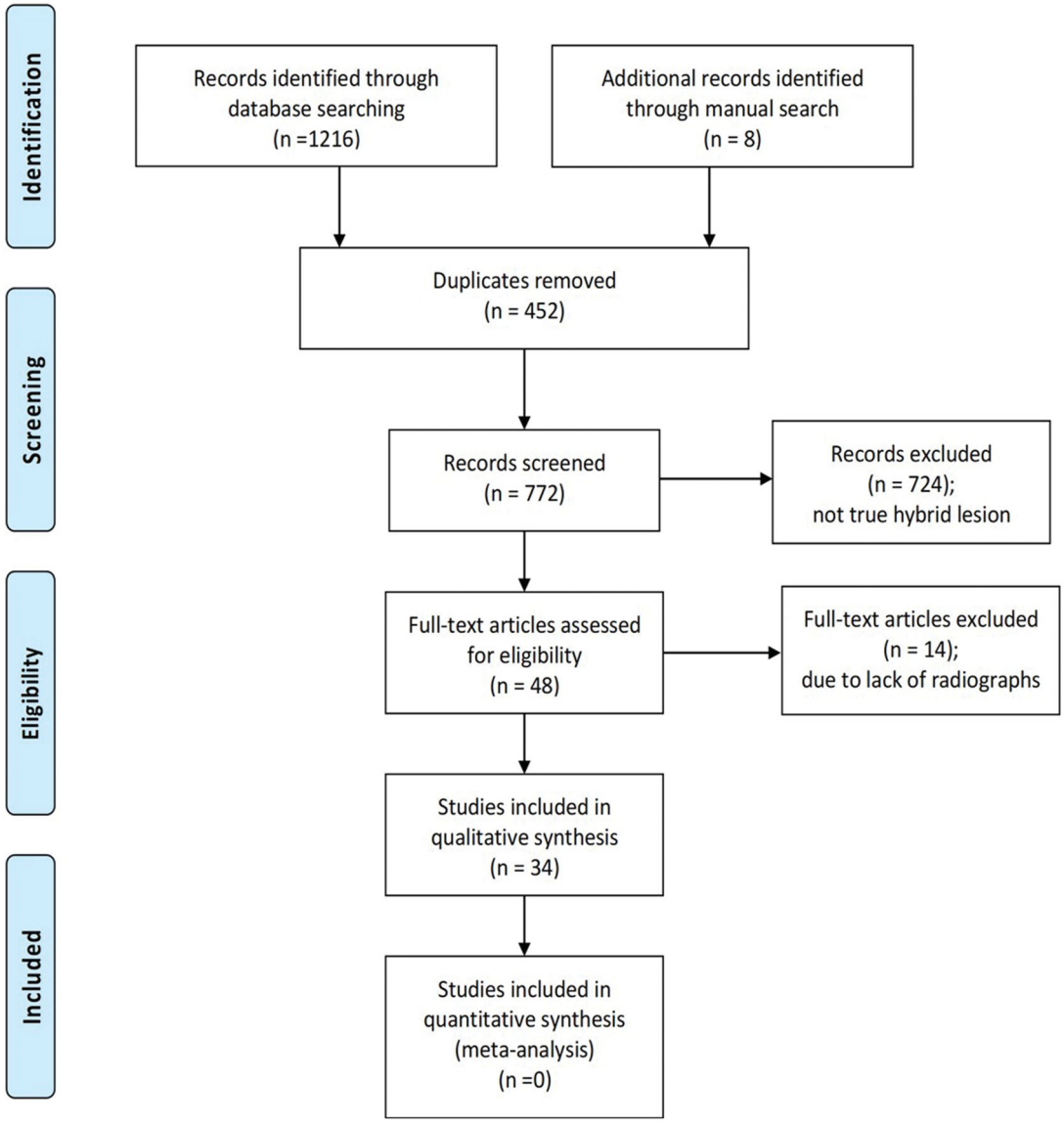

Figure 1. PRISMA flowchart of article inclusion.

duplicates, eight articles resulted from manual search, and 738 were excluded per criteria (14 excluded due to lack of radiographs, 724 excluded for not being a hybrid lesion). Final studies included were 34 articles published from 1978 to 2019.

Quality assessment

There were 27 case reports and seven case series included in this review. Seventeen articles scored 'high' with an excellent presentation of the reported cases [10–26]. Thirteen articles scored 'moderate' [4,6,7,27–36], and four articles scored 'poor' [37–40], mostly due to lack of either 3 D imaging or detailed radiographic description. Table 1 presents the results of the quality assessment.

Data analysis

The clinical and radiographic features obtained are presented in Figure 2 and Table 1, respectively. Among the 39 included hybrid-CGCG lesions; 14 (35.8%) were with central odontogenic fibroma (CODF) [7,11,16,17,23,27,29,30,32,36,37,39], 11 (28.2%) with central ossifying fibroma (COF) [6,15,18,20,25,26,31,34,38], seven (17.9%) with fibrous dysplasia (FD) [4,13,14,21,22,26,33,40], and seven (17.9%) with other bone conditions [6,10,12,19,24,28,35].

The mean age of hybrid-CGCG lesions was 30.5 ± 19.9 years (range 2–68 years). Majority of hybrid-CGCG lesions presented in females (22 of 39, 56.4%). Most cases were imaged using conventional images ($n = 31$) [4,6,7,10–18,20–23,25,27–33,35,37–40], and radiographically were well-defined (34 of 38, 89.5%), non-corticated (22 of 38, 57.9%), radiolucent (23 of 38, 60.5%), in the posterior mandible (26 of 39, 66.7%). Most hybrid-CGCG lesions affected the cortical plates by thinning, expansion, or perforation (27 of 29, 93.1%), and displaced or resorbed teeth (21 of 35, 60%).

Recurrence was documented in 31 cases. Of these, 5 (16.1%) showed recurrence and these were hybrid-CGCG lesion with CODF ($n = 2$), COF ($n = 1$), Paget's disease ($n = 1$), and ABC ($n = 1$).

Discussion

This review revealed the leading hybrid-CGCG lesions, in descending order, were with CODF, COF, and FD. Most presented as an asymptomatic mandibular swelling and radiographically were well-defined, causing cortical expansion, with minimal effect on the surrounding teeth.

Hybrid-CGCG lesions with CODF mostly depicted a cortex at the periphery (11 of 14, 78.6%) and favoured a radiolucent internal structure (11 of 14, 78.6%). Cortical expansion was described in 10 out of 14 hybrid-CGCG lesions with CODF, and all were found expansile. CODF comprises 0.1% of all odontogenic tumours. It is composed of odontogenic epithelium and fibrous stroma [41]. Radiographically presents as unilocular or multilocular radiolucency, and in rare cases, appears mixed [41]. It is radiographically indistinguishable from hybrid-CGCG lesions with CODF and mimics ameloblastoma, odontogenic keratocyst, odontogenic myxoma, and ameloblastic fibroma [41].

In contrast, most hybrid-CGCG lesions with COF and FD presented with non-corticated periphery (12 of 18, 66.7%), presence of radiopaque internal structure (11 of 18, 61.1%), displaced or resorbed surrounding teeth (10 of 15, 66.7%). Most studies reported cortical expansion in hybrid-CGCG lesions with COF and FD. COF and FD are part of the 'fibro-osseous lesions' which is an umbrella term that describes lesions where fibrous tissue and varying amounts of immature mineralised tissue replace normal bone. Although COF is a benign tumour and FD is an osseous dysplasia, they are similar histopathologically. Diagnosis in such cases is weighted heavily on their clinical behaviour and radiographic appearance.

The radiographic presentation of hybrid-CGCG lesion with COF described above is similar to the 'non-hybrid' COF. In a systematic review, COF presented with a larger radiolucent component (26% radiolucent, 58% mixed, and only 16% radiopaque) compared to fibrous dysplasia (5% radiolucent, 20% mixed, and 52% radiopaque) and is more well defined [42,43]. Because COF commonly shows radiolucent component, if CGCG coexists within COF, it does not drastically change its radiographic appearance. In contrast, hybrid-CGCG lesion with FD differs from 'non-hybrid' FD in that it presents in the posterior mandible with a multilocular radiolucent component. In a systematic review, 'non-hybrid' FD usually occurs unilaterally in the maxilla and radiographically presents as a diffuse radiopacity (52% radiopaque vs. 5% radiolucent) [43]. The radiopacity being *fine-granular or Peau d'orange* was more common (45%) than *sclerotic* (5%) [43]. We understand that the term 'sclerotic' refers to a dense radiopacity similar to that of dense bone island versus a less dense 'fine/ground-glass' radiopacity.

Melorheostosis is rare sclerosing bone dysplasia presenting as localised, diffuse thickening of the cortical bone, and rarely affecting the craniofacial complex [19,42–46]. Paget's disease is a disorder of bone remodelling with bone resorption, followed by an increase in disorganized bone formation [47]. Radiographically, Paget's disease features several stages, most of which are mixed or radiopaque [47]. Hybrid-CGCG lesion with melorheostosis or Paget's created a unique multilocular radiolucency within the thickened and sclerotic bone. It appears that CGCG cannot 'camouflage' its appearance radiographically when coexisting with a radiopaque entity such as FD, Paget's, or melorheostosis.

ABC-plus is an aneurysmal bone cyst (ABC) presented in a hybrid association with another bone pathology [10,12,48]. There are four hybrid-ABC cases in this review presented mostly as corticated, multilocular, and expansile radiolucency. ABC and CGCG are similar radiographically (on conventional or CT imaging). Histopathologically, these two are similar except for the blood collection in variably sized spaces in ABC.

Finally, a hybrid-CGCG lesion with a recurrent ameloblastoma that was marsupialized 15 years prior [28]. The radiographic features were similar to ameloblastoma, well-defined

Table 1. Demographic and radiographic data on the hybrid-CGCG lesions.

			Periphery		Internal structure			Effect on structures				
Case	Hybrid lesion Age Gender	Imaging modality	Well defined	Corticated	Unilocular RL	Multilocular RL	Mixed or RO	Teeth displacement or resorption	Cortical expansion, or perforation	Others	Recurrence	Quality score
Taylor et al. 1999 [11]	CODF 17 F	Panoramic	+	+	–	+	–	+	+		–	High
Odell et al. 1997 [37]	CODF 21 F	Panoramic	–	+	–	–	+	–	NA		NA	Poor
Younis et al. 2008 [30]	CODF 57 F	Panoramic	+	–	+	–	–	–	+		–	Moderate
Tosios et al. 2008 [39]	CODF 50 M	Panoramic	+	–	+	–	–	–	NA		–	Poor
Upadhyaya et al. 2017 [7]	CODF 10 M	Panoramic	+	+	+	–	–	+	+		–	Moderate
Upadhyaya et al. 2017 [7]	CODF 63 F	CT	+	+	+	–	–	–	+		NA	Moderate
Allen et al. 1992 [29]	CODF 66 F	Panoramic	+	–	–	+	–	–	NA		–	Moderate
Allen et al.1992[29]	CODF 30 F	Panoramic Periapical	+	–	–	+	–	–	NA		+	Moderate
Vaezi 2016 [23]	CODF 10 M	Panoramic CT	+	+	+	–	–	+	+		–	High
Eliot et al 2015 [32]	CODF 22 F	Panoramic	+	+	–	+	–	+	+		NA	Moderate
Castillo 2011 [17]	CODF 14 M	Panoramic CT	+	+	+	–	–	+	+		–	High
Molina et al. 2011 [16]	CODF 14 M	Panoramic CT	+	+	–	+	+	+	+		–	High
Vijintanawan et al. 2019 [27]	CODF 27 M	Panoramic	+	+	+	–	–	+	+		–	Moderate
Flores-Hidalgo et al. 2019 [36]	CODF 65 F	CBCT	+	–	–	+	–	–	+		+	Moderate
Asthana et al. 2014[31]	COF 56 M	Panoramic	+	+	–	–	+	–	NA		NA	Moderate
Kaplan et al. 2007 [38]	COF 5 F	Panoramic	+	–	+	–	–	+	+		+	Poor
Kaplan et al.2007 [38]	COF 13 F	Panoramic	+	–	–	–	+	+	+		–	Poor
Rebello et al. 2009 [15]	COF 38 F	Panoramic OcclusalCT	+	+	–	–	+	–	+		–	High
Arai et al. 2016 [34]	COF 44 F	CT PET-CT MRI	+	–	–	–	+	–	+	septum deviation, MS obliteration	–	Moderate
Penfold et al. 1993 [6]	COF 41 M	CT	+	–	–	–	+	NA	+	left eye elevation	–	Moderate
Fasolis et al. 2013 [20]	COF 46 M	Panoramic 3D CT	+	+	+	–	–	+	+		–	High
Geetha et al. 2011 [18]	COF 9 M	Panoramic	+	+	–	–	+	+	+		–	High
Kaplan et al. 2007 [38]	COF 68 M	NA	+	–	+	–	–	NA	+		–	Poor

(*continued*)

Table 1. Continued

Saad et al. 2019 [26]	COF 9 F	CT	+	+	−	+	+	+	+	*	−	High
Rai et al. 2019 [25]	COF 31 F	Panoramic PA CBCT	−	−	−	−	+	+	+		−	High
Rahimov et al. 2014 [40]	FD 12 M	Panoramic	+	−	+	−	−	+	NA		−	Poor
Lustmann et al. 1978 [4]	FD 19 F	Panoramic Periapical	+	+	−	+	+	−	+	Midline shift	−	Moderate
Kurra et al. 2013 [21]	FD 18 F	3D CT Occlusal Panoramic	−	−	−	+	−	+	+		NA	High
Kuberappa et al. 2016 [22]	FD 47 F	3D CT Panoramic	+	−	−	+	−	+	+		NA	High
Jawanda et al. 2015 [33]	FD 33 M	Panoramic	−	−	−	−	+	−	NA		−	Moderate
Farzaneh et al. 2005 [14]	FD 20 F	Panoramic Occlusal	+	−	−	−	+	+	+		NA	High
Shetty et al. 2004 [13]	FD 39 F	Panoramic CT	+	+	−	−	+	−	+		−	High
Anderson et al. 2013 [19]	Melorheostosis 15 F	CT 3D CT	+	−	−	+	+	+	+		−	High
Penfold et al. 1993 [6]	Paget's disease 63 M	CT PA	NA	NA		−	+	−	NA	NA		+	Moderate
Padwa et al. 1997 [10]	ABC 5 F	CT Panoramic	+	−	+	−	−	+	+		+	High
Chandolia et al. 2018 [35]	ABC 28 M	Panoramic	+	−	−	−	+	+	NA		NA	Moderate
Pai et al. 2017 [24]	ABC 2 M	US CT	+	+	−	+	−	−	+	Displaced IANC	−	High
Yasuoka et al. 2002 [12]	ABC 16 F	Panoramic CT MRI	+	+	+	−	−	−	+		−	High
Kawakami et al. 1989 [28]	Ameloblastoma 47 M	Panoramic	+	−	−	+	−	+	NA		−	Moderate

RL: radiolucent, RO: radiopaque, CODF: central odontogenic fibroma, COD: central ossifying fibroma, FD: fibrous dysplasia, ABC: aneurysmal bone cyst, NA: not applicable, MS: maxillary sinus, IANC: inferior alveolar nerve canal. *CT 6-months after incisional biopsy.

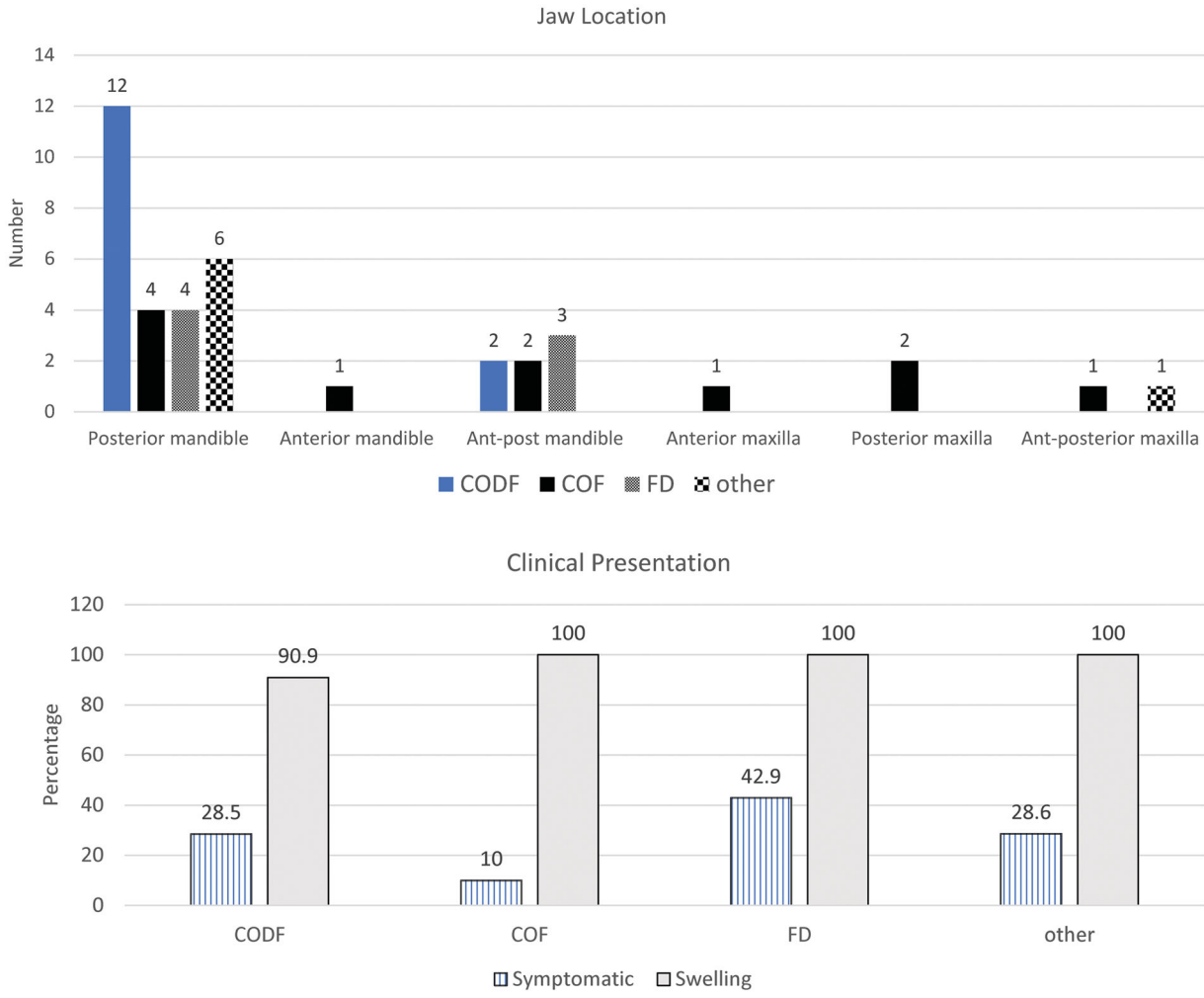

Figure 2. Clinical presentation and jaw location of hybrid-central giant cell lesions.

multilocular radiolucency associated with root resorption. Histological evidence of abundant giant cell lesions led to the diagnosis of 'hybrid'. The possibility of CGCG forming as a reactive lesion is considered in this particular case.

In conclusion, this systematic review suggests that the radiographic features of hybrid-CGCG lesions are variable according to the concurrent bony lesion. The radiographic appearance of hybrid-CGCG lesion with fibrous dysplasia, melorheostosis, and Paget's disease differed from their non-hybrid presentation. This review reveals a frustrating deficiency in utilizing optimum imaging modalities or adequate radiographic reporting in some of the included articles. Optimum imaging modalities would consist of three-dimensional imaging that allows, primarily, proper assessment of the osseous tissues such as cone beam CT or multi-detector CT. These imaging modalities will allow an adequate evaluation of location and extent, offer details about the internal structure, and depict effects on cortical plates and boundaries of maxilla, mandible, and surrounding anatomical structures. Reporting these imaging modalities by oral and maxillofacial or medical radiologists will maximise the benefits of these imaging modalities. This practice is paramount as it can reveal suspicious features or sites hosting a CGCG hybridisation, and consequently aid in selecting appropriate biopsy sites.

Disclosure statement

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Appendix A. Table detailing electronic database search

	Pubmed		Scopus		Medline		Ovid	
	Keywords	#hits	Keywords	#hits	Keywords	#hits	Keywords	#hits
1	Central giant cell granuloma	3,298	1 Central giant cell granuloma	980	*1* Central giant cell granuloma	498	*1* Central giant cell granuloma	340
2	Central giant cell lesion	487	2 Central giant cell lesion	1329	*2* Central giant cell lesion	751	*2* Central giant cell lesion	58
3	CGCG	407	3 CGCG	415	*3* CGCG	321	*3* CGCG	414
4	Brown tumour	13,695	4 Brown tumour	6331	*4* Brown tumour	3323	*4* Brown tumour	446
5	Hybrid lesion	1,653	5 Hybrid lesion	56865	*5* Hybrid lesion	4423	*5* Hybrid lesion	41
6	Multinucleated giant cell	23,805	6		Multinucleated giant cell	5493	*6* Multinucleated giant cell	3748
6	Multinucleated giant cell	335						
7	1 or 2 or 3 or 4 or 5 or 6	41,423	7 1 or 2 or 3 or 4 or 5 or 6	19080	*7* 1 or 2 or 3 or 4 or 5 or 6	12345	*7* 1 or 2 or 3 or 4 or 5 or 6	1482
8	Mandible	73,259	8 Mandible	95990	*8* Mandible	31048	*8* Mandible	65444
9	Mandibular	111,085	9 Mandibular	90215	*9* Mandibular	53197	*9* Mandibular	81178
10	Maxilla	32,826	10 Maxilla	59436	*10* Maxilla	16090	*10* Maxilla	39921
11	Maxillary	84,475	11 Maxillary	75950	*11* Maxillary	41781	*11* Maxillary	65443
12	Jaw	134,913	12 Jaw	97000	*12* Jaw	36824	*12* Jaw	54795
13	Jaws	139,306	13 Jaws	97000	*13* Jaws	36824	*13* Jaws	11773
14	Alveolar bone	33,785	14 Alveolar bone	32699	*14* Alveolar bone	16711	*14* Alveolar bone	17514
15	8 or 9 or 10 or 11 or 12 or 13 or 14	231,437	15 8 or 9 or 10 or 11 or 12 or 13 or 14	274455	*15* 8 or 9 or 10 or 11 or 12 or 13 or 14	145768	*15* 8 or 9 or 10 or 11 or 12 or 13 or 14	214867
16	Radiograph	20,177	16 Radiograph	96437	*16* Radiograph	68468	*16* Radiograph	20233
17	Radiography	1,565,366	17 Radiography	692109	*17* Radiography	53612	*17* Radiography	417931
18	Diagnostic imaging	2,597,371	18 Diagnostic imaging	530356	*18* Diagnostic imaging	125063	*18* Diagnostic imaging	1160776
19	Three-dimensional imaging	105,664	19 Three-		dimensional imaging	174937	*19* Three-dimensional imaging	90100
19	Three-dimensional imaging	2941						
20	X-ray	1,718,681	20 X-ray	2029975	*20* X-ray	1300237	*20* X-ray	755211
21	16 or 17 or 18 or 19 or 20	1,969,419	21 16 or 17 or 18 or 19 or 20	3071665	*21* 16 or 17 or 18 or 19 or 20	1584040	*21* 16 or 17 or 18 or 19 or 20	1704045
22	7 and 15 and 21	576	22 7 and 15 and 21	379	*22* 7 and 15 and 21	74	*22* 7 and 15 and 21	172

Appendix B.

Customised methodological quality and synthesis of case series and case reports evaluation tool Adopted from Murad *et al.* (9)

Domain	Marking used for this review
Selection: Q1: Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	Granted full point if demographic and selection criteria described.
Ascertainment Q2: Was the exposure adequately ascertained? Q3: Was the outcome adequately ascertained?	Question 2 granted full point if adequate histopathological confirmation was provided Question 3 granted full point if 3D imaging was provided OR at least two plain radiographs at 90 degrees to each other
Causality Q7: Was follow-up long enough for outcomes to occur?	Granted full point if period of duration and outcome were reported.
Reporting Q8. Is the case(s) described with sufficient details?	Granted full point if adequate details of histopathology or radiography are provided either in writing or figures
	High quality: score Maximum points 5 or 4 (for missing Q7)* Moderate quality: score 2 to 4 Poor quality: score 0 to1

Questions 4, 5 and 6 of the Murad et al. tool are mostly relevant to cases of adverse drug event and were not used in this review.
*Since the purpose of this study is to systematically review the clinical and radiographic presentation of hybrid-CGCG lesions at first presentation, Question 7 was recorded but not scored.