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RESEARCH

Central giant cell granuloma of the jaws—long-term clinical and radiological outcomes of surgical and pharmacological management

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Abstract

Objectives To compare long-term results of different treatment modalities in central giant cell granuloma of the maxillofacial-skeleton. Primary resection may result in major defects. Alternative treatments include pharmacological agents. As yet there has been no consensus on the use of the variety of treatment options, and few studies have reported clarifying long-term results.

Materials and methods This retrospective study on 22 patients with 25 lesions evaluated clinical, radiological and histological features, treatment preformed and lesion recurrence. Success was defined as regression/calcification and failure as recurrence, progression or un-responsiveness.

Results Of the presenting patients, 77% were under age 40. Lesion prevalence was higher in the anterior mandible and left posterior maxilla. Most cases exhibited pain, tooth-mobility or mucosal-expansion. The appearance was predominantly unilocular in the maxilla and multilocular in the mandible, which also exhibited higher prevalence of cortical perforation. Up to 80% of lesions were classified as aggressive.

Intralesional steroids/calcitonin were used in 7 cases. Mean follow-up was 39.8 months. Two cases showed recurrence. In 71% of the cases treated pharmacologically, calcification/regression were observed.

Conclusions Our analysis indicates better outcomes using a combined approach, including both pharmacological and surgical treatments in large aggressive lesions. Pharmacological treatment resulted in decreased size or well-defined lesions, thus reducing the need for extensive bone resection. Dual treatment with corticosteroids and calcitonin showed no superior outcomes, but a larger cohort should be assessed.

Clinical Relevance There are several protocols for treatment of central-giant-cell-granuloma lesions, but most are not fully established. It is important to report results that contribute to the establishment of proven protocols. This report attempts to establish the relevance of the combined approach: pharmacological treatment followed by surgical resection.

Keywords CGCG · Surgery · Steroids · Calcitonin · Jaws · Lesion · Aggressive

Introduction

Central giant cell granuloma (CGCG) is a benign, aggressive, destructive, osteolytic lesion of osteoclastic origin [1]. It is an intraosseous non-neoplastic lesion, consisting of cellular fibrous tissue containing multiple foci of haemorrhage, aggregations of multinucleated giant cells and trabeculae of woven bone [2]. CGCG most commonly occurs in patients under the age of 30, predominantly in females, and it accounts for 7% of all benign tumors of the jaws [1, 2]. The etiology of CGCG is controversial. Jaffe, who first identified the entity, related it to reparative mechanisms

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following trauma (Jaffe). Another theory associated it with inflammatory responses [3]. Clinically, the lesion is often a painless, slow growing lesion causing expansion of the cortical bone [4]. The lesions are most commonly identified during routine radiologic imaging. Size is highly variable, and resorption or displacement of tooth roots is a common finding. Radiologic appearance may exhibit a unilocular or a multilocular radiolucency [4, 5].

The accepted classification of CGCG is of debate. It consists of an aggressive form and non-aggressive form. Diagnosis is mostly based on clinical and radiological findings. Non-aggressive lesions are painless and slow-growing, whereas aggressive lesions are larger than 5cm, rapid-growing, cause bone expansion, tooth displacement/root resorption, and higher recurrence rates [1, 4, 6, 7]. Aggressive lesions are mostly treated using wider resections whereas more conservative surgical approaches can be used in non-aggressive forms [7–9]. Reconstruction options for the aggressive type may include free bone grafts or vascularized flaps in major resections [8, 9].

Alternative, non-surgical or pre-surgical treatments are becoming more popular in the past two decades. These included calcitonin [7, 10–14], corticosteroids [7, 15, 16], interferon α-2a [7, 17, 18] and, most recently, denosumab [19]. Intralesional corticosteroids were introduced in 1988 and were thought to reduce bone resorption by effecting lysosomal proteases [20]. Later, the use of calcitonin was described [21] and thought to influence lesion progression by inhibiting osteoclast activity. Interferon α-2a was used initially by Kaban et al., in 1999 [18]. The mechanism of action proposed to effect CGCG progression was based on anti-angiogenic properties [22].

These treatments are used to reduce the size of the lesions and in some cases may eradicate them, thus avoiding large resections that result in major functional and aesthetic deformities.

Although various treatment options have been available for some time now, there is no consensus regarding the management of CGCG, and only a few studies have reported consistent long-term results.

The aim of this study was to review and compare long-term results from a cohort of patients with CGCG treated in our institute, surgically and/or pharmacologically.

Materials and methods

This retrospective study of patients diagnosed with CGCG and treated in our institute between 2000 and 2018 examined demographic details, clinical and radiological features of the lesion and treatment preformed. We documented age, gender, location of the lesion, treatment preformed, clinical and radiological features prior to and following the treatment, and postoperative follow-up including associated morbidity and recurrences. Radiologic features were obtained using computed tomography or panoramic imaging performed prior to and following treatment. These included size, locularity, borders of the lesion, cortical changes/perforation and root displacement/resorption prior to treatment. Clinical signs such as mucosal expansion and pain/paresthesia were also noted. Signs of recurrence as a negative response or bone healing as a positive response were noted. Classification of the lesions as well as the treatment performed, reconstruction, response, morbidity and follow-up duration were recorded. Lesions were classified as aggressive, minor aggressive or non-aggressive according to Chuong et al. and Kaban et al. [6, 23]. Major criteria were size (more than 5 cm) and recurrence. Minor criteria included root resorption, tooth displacement, cortical bone thinning, cortical bone perforation, rapid growth and pain/paraesthesia.

Patients diagnosed with CGCG who were admitted to our hospital and treated in our institute between 2000 and 2018 were evaluated for inclusion in the study. Patients lacking proper documentation, radiographic images or adequate follow-ups were excluded.

Treatment success was defined as bone healing, lesion regression or calcification as response to pharmacological/surgical treatment. Treatment failure was defined as recurrence, no response or progression of the lesion following pharmacological/surgical treatment.

Results

Twenty-two patients met the inclusion criteria. Eleven females and eleven males. The mean age was 30-years old, ranging from 4 to 77. Eleven lesions were located in the mandible and fourteen in the maxilla, these included recurrences or a second primary. Details of all the maxillary and mandibular lesions can be observed in Figs. 1 and 2 accordingly and include; age, gender, location, follow-up duration and recurrences. Mean follow-up of the maxillary cases was 46 months. Mean follow-up of the mandibular cases was 31 months. Two recurrences were observed in the maxilla, both in patients aged less than 18, and one second primary was found in the mandible five years following treatment of the maxillary lesion. One recurrence was observed in the mandible in a patient treated at a different hospital by enucleation two years post treatment. He was 6-years old when he presented with the recurrence and is currently being treated pharmacologically with denosumab. Mean age of the maxillary cases was 26. Mean age of the mandibular cases was 39.

Distribution of the lesions in the jaws can be observed in Fig. 3. In the mandible most were observed in the anterior and left body of the mandible. In the maxilla most were located on the anterior and left part of the maxilla.

Fig. 1 Details of maxillary CGCG lesions. Details include age, location, gender, follow-up and recurrence

Patient Number	Age (years)	Side	gender	Region	Follow up (months)	Recurrence
1	32	L	F	Premolar-molar	7	No
2	12	R	F	Canine-premolar	12	No
3	18	L	F	Premolar-molar	8	On same site
3*	19	L	F	Premolar-molar	42	No
4	34	L	F	Incisor-canine	10	No
5	66	R	M	Premolar-molar	21	No
6	17	R/L	M	Incisor-canine	87	No
7	28	R	F	Incisor-canine	188	No
8	8	L	M	Premolar-molar	49	No
9	72	L	M	Premolar-molar	60	On mandible
10	9	L	F	Incisor-canine	63	On same site
10*	15	L	F	Incisor-canine	14	No
11	4	R	M	Incisor-canine	14	No
12	11	R	M	Premolar-molar	Ongoing treatment	

*Recurrence of CGCG in the same site

Patient Number	Age (years)	Side	Region	gender	Follow up (months)	Recurrence
9$	77	Symphysis		M	3	No
13	13	L, R	Ramus	M	63	No
14	32	Symphysis		M	21	No
15	60	L	Body	F	24	No
16**	22	Symphysis + L body		F	54	No
17	74	L	Body	F	34	No
18	27	Symphysis		F	44	No
19	12	L	Body	M	78	No
20*	6	Symphysis		M	Ongoing treatment	
21	67	R	Angle	M	6	No
22	36	R	Ramus	F	12	No

*Recurrence of CGCG in the same site
**Diagnosis of CGCL and FD
$Recurrence of CGCG in another site

Fig. 2 Details of mandibular CGCG lesions. Details include age, location, gender, follow-up and recurrence

Gender distribution was equal between all cases. Age distribution showed the highest number of cases between 11–20 years old, followed by 0–10 and 31–40 years old (Fig. 4).

Figures 5 and 6 detail the clinical and radiological findings of the lesions in the maxilla and mandible respectively. Figure 7 summarizes these findings. In the mandible most lesions were multilocular, whereas those in the maxilla were mostly unilocular. It is evident that almost all lesions affected the cortex, and perforation occurred at higher rates in the mandible. In both jaws, lesions were more likely to be well-defined.

Figures 8 and 9 detail the classification of the lesions, treatment performed, reconstruction performed, response to the treatment, morbidity and follow-up duration in cases treated by surgical means alone or pharmacologically prior to surgery.

Most lesions were of the aggressive type, both in the mandible and the maxilla (Fig. 10).

For cases treated initially by pharmacological means, 71% exhibited calcification or regression of the lesion, one case did not respond, and one showed progression. Intralesional steroid treatment with or without nasal calcitonin showed good results in shrinking the lesions prior to the surgical treatment.

Figures 11, 12 and 13 document the treatment of patient number 19. The pre-operative radiographs show severe progression of the lesion. Calcification of the lesion is observed following pharmacological treatment. The borders of the lesion can be seen in the CT imaging. This enabled a more conservative surgical approach. Finally, a three-year follow-up indicated no sign of recurrence.

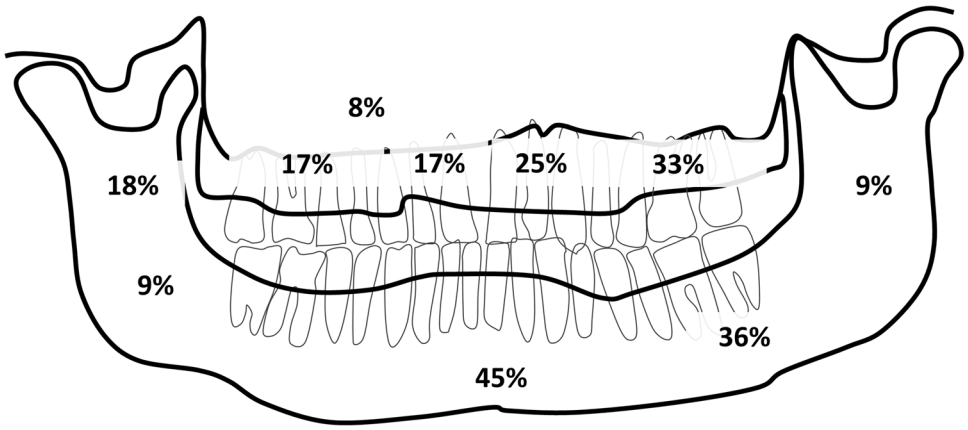

Fig. 3 Distribution of Central giant cell lesions in the maxillomandibular complex

Age	No. Males	No. Females	Total, n (%)
0-10	3	1	4 (18%)
11-20	4	2	6 (27%)
21-30	0	3	3 (14%)
31-40	1	3	4 (18%)
41-50	0	0	0 (0%)
51-60	0	1	1 (5%)
61-70	2	0	2 (9%)
> 71	1	1	2 (9%)
Total	11	11	22 (100%)

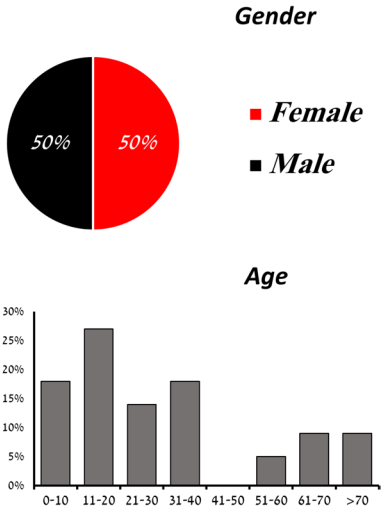

Fig. 4 Distribution of Central giant cell lesions according to age and gender

Patient Number	Recurrence	Size (cm)	Locularity	Border definition	Cortical thinning	Cortical perforation	Root displacement	Root resorption	Mucosal expansion	Pain/ Paresthesia
1	No	6.5X4.5X3	Multilocular	Well-defined	Yes	Yes	Yes	Yes	Yes	No
2	No	3X3.5X2	Unilocular	Well-defined	Yes	No	Yes	No	Yes	No
3	Yes	3.5X3.5X2.5	Multilocular	Well-defined	Yes	Yes	Yes	Yes	Yes	Yes
3*	No	3.5X2X1	Unilocular	Ill-defined	Yes	Yes	No	No	Yes	No
4	No	4X2X2	Unilocular	Ill-defined	Yes	Yes	Yes	Yes	Yes	Yes
5	No	3X5X1.5	Unilocular	Ill-defined	Yes	Yes	Edentulous	Edentulous	Yes	No
6	No	10X5X4	Unilocular	Ill-defined	Yes	No	Yes	Yes	Yes	Yes
7	No	3X2X0.5	Unilocular	Well-defined	Yes	No	Yes	Yes	Yes	No
8	No	1X1X0.5	Unilocular	Well-defined	No	No	No	No	Yes	Yes
9	Yes	7X2.5X2	ND	ND	ND	ND	Edentulous	Edentulous	Yes	No
10	No	3X2.5X3	Unilocular	Well-defined	Yes	No	Yes	No	Yes	Yes
10*	Yes	2X2X2	Unilocular	Ill-defined	No	No	No	No	Yes	Yes
11	No	0.6X1.4X1	Unilocular	Well-defined	No	No	No	No	Yes	No
12^	No	4X3.5X3	Unilocular	Well-defined	Yes	Yes	Yes	Yes	Yes	Yes

*Recurrence of CGCG in the same site
^Patient is currently on pharmacological treatment

Fig. 5 Radiological and clinical characterization of CGCG in the maxilla. Parameters documented included recurrence, size, locularity, border definition, cortical thinning, cortical perforation, root displacement, root resorption, mucosal expansion and pain/paresthesia

Patient Number	Recurrence	Size (cm)	Locularity	Border definition	Cortical thinning	Cortical perforation	Root displacement	Root resorption	Mucosal expansion	Pain/ Paresthesia
9$	No	3.3*2.5X2	Multilocular	Well-defined	Yes	Yes	Edentulous	Edentulous	Yes	No
13	No	3.2X2.5X3 2.8X1.5.X2	Multifocal & Multilocular	Well-defined	Yes	No	No	No	No	No
14	No	2.3X6X2.5	Multilocular	Ill-defined	Yes	Yes	Yes	Yes	Yes	Yes
15	No	6X1.5X6	Multilocular	Well-defined	Yes	Yes	Edentulous	Edentulous	Yes	No
16**	No	8X4X2.5	Multilocular	Ill-defined	Yes	Yes	Yes	Yes	Yes	Yes
17	No	5X2X2	Multilocular	Ill-defined	Yes	Yes	Yes	Yes	Yes	Yes
18	No	8X3.5X3	Multilocular	Well-defined	Yes	Yes	No	No	Yes	Yes
19	No	5x4x1.5	Unilocular	Well-defined	Yes	Yes	No	No	Yes	No
20*,^	0	2X3X3	Unilocular	Well-defined	Yes	Yes	Yes	Yes	Yes	Yes
21	No	2X2.5X3	Unilocular	Well-defined	Yes	No	No	No	Yes	No
22	No	1X1X0.3	Unilocular	Well-defined	No	No	No	No	No	Yes

*Recurrence of CGCG in the same site
**Diagnosis of CGCL and FD
$Recurrence of CGCG in another site
^Patient is currently on pharmacological treatment

Fig. 6 Radiological and clinical characterization of CGCG in the mandible. Parameters documented included recurrence, size, locularity, border definition, cortical thinning, cortical perforation, root displacement, root resorption, mucosal expansion and pain/paresthesia

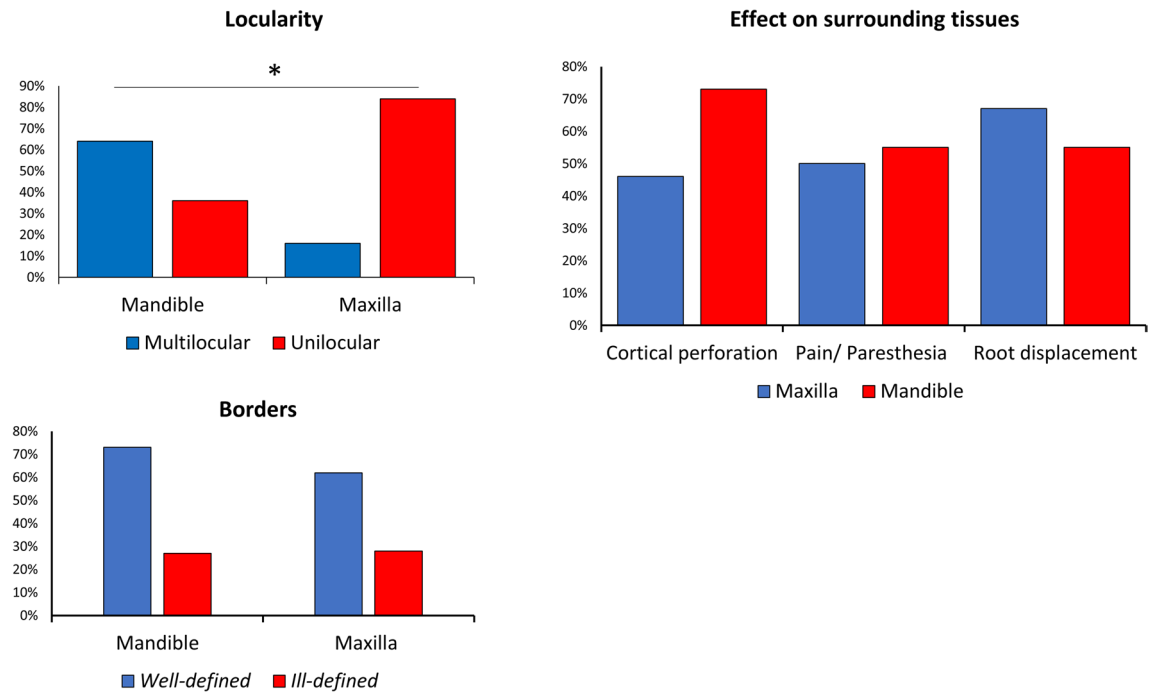

Fig. 7 Characteristics of the lesions and their effect on surrounding tissues. Locularity, borders, cortical perforation, pain/paresthesia and root displacement as distributed in the different jaws

Discussion

CGCG is a benign, often aggressive lesion. Its progression leads to destruction of the original anatomy and loss of bony tissue, as well as resorption and displacement of dental roots. These lesions are most commonly identified through routine radiographs and thus tend to be large and in need of extensive surgical treatment. Because these lesions are most common in patients under the age of 30, and many times are found in children during their growth period and prior to dento-alvelar maturation, the resulting surgical treatment is associated with high morbidity.

Patient Number	Sex	Age (years)	Site	Size	Type	Primary	Treatment and Reconstruction		Long-term response	Postoperative morbidity	Follow up (months)
1	F	32	Maxilla	6.5X4.5X3	A	Yes	Enucleation & Peripheral ostectomy	~	Complete remodeling	Teeth loss (n=1)	7
2	F	12	Maxilla	3X3.5X2	Non-A	Yes	Resection	Iliac crest	Complete remodeling	Teeth loss (n=3)	12
5	M	66	Maxilla	3X5X1.5	A	Yes	Enucleation & Peripheral ostectomy		Limited remodeling	non	21
7	F	28	Maxilla	3X2X0.5	A (mA)	Yes	Enucleation & Peripheral ostectomy	I- Iliac crest II- DO	Complete remodeling	Teeth loss (n=3)	188
8	M	8	Maxilla	1X1X0.5	Non-A	Yes	Enucleation & Peripheral ostectomy	~	Complete Remodeling	Hypoesthesia	49
9	M	72	Maxilla	7X2.5X2	A	Yes	Resection	Local flap	Limited remodeling	~	62
9$	M	77	Mandible	3.6*2.4X2	A	No	Resection	Rib	Limited remodeling	~	3
10	M	9	Maxilla	3X2.5X3	A (mA)	No	Curettage	~	Limited remodeling	~	63
10*	M	15	Maxilla	2X2X2	A	Yes	Resection	Calvaria	Complete remodeling	~	14
11	M	4	Maxilla	0.6X1.4X1	Non-A	Yes	Enucleation & Peripheral ostectomy	~	Complete remodeling	~	14
13	M	13	Mandible	3.2X2.5X3 2.8X1.5.X2	Non-A	Yes	Enucleation & Peripheral ostectomy	~	Complete remodeling	~	63
15	M	60	Mandible	6X1.5X6	A	Yes	Resection	Allograft + Recon plate	Limited remodeling	~	24
16**	F	22	Mandible	8X4X2.5	A	Yes	Curettage	Xenograft + TGF-b + Bio-guide	Complete remodeling	~	54
17	F	74	Mandible	5X2X2	A	Yes	Resection	Iliac crest + Recon plate	Limited remodeling	Osteomyelitis	34
21	M	67	Mandible	2X2.5X3	Non-A	Yes	Curettage	~	Complete remodeling	~	6
22	F	36	Mandible	1X1X0.3	Non-A	Yes	Curettage	~	Complete remodeling	~	12

*Recurrence of CGCG in the same site
**Diagnosis of CGCL and FD
$Recurrence of CGCG in another site
^Patient which is currently on pharmacological treatment
A - aggressive, A (mA) - minor aggressive, Non-A - non-aggressive

Fig. 8 Details regarding the patients treated by surgery alone: location of the lesion, treatment performed, reconstruction if performed, response of the bone to the treatment, morbidity and duration of follow-up

Patient Number	Sex	Age (years)	Site	Size	Type	Primary	Treatment	Duration	Response	Surgery and Reconstruction		Long-term response	Follow up (months)	Postoperative morbidity
3	F	18	Maxilla	3.5X3.5X2.5	A (mA)	Yes	Intralesional steroids & nasal calcitonin	11w ~3mon	Regression & Calcification	Enucleation & Peripheral ostectomy	Obturator	Limited remodeling	8	Oroantral fistula Teeth loss (n=2)
3*	F	19	Maxilla	3.5X2X1	A	No	Intralesional steroids	8w	Regression & Calcification	Resection	Obturator with implants	Limited remodeling	42	Teeth loss (n=1)
4	F	34	Maxilla	4X2X2	A (mA)	Yes	Intralesional steroids & nasal calcitonin	7w ~3mon	No response&	Resection	Obturator with implants	Limited remodeling	10	Oroantral fistula Teeth loss (n=8)
6	M	17	Maxilla	10X5X4	A	Yes	Intralesional steroids	9w	No response	Enucleation & Peripheral ostectomy	Iliac crest	Complete Remodeling	87	Teeth loss (n=3)
12^	M	11	Maxilla	4X3.5X3	A (mA)	No	Denosumab				*Ongoing*			
14	M	32	Mandible	2.3X6X2.5	A	Yes	Intralesional steroids	6w	Calcification	Resection	Iliac crest & PSI	Limited remodeling	21	Fistula
18	F	27	Mandible	8X3.5X3	A	Yes	Intralesional steroids & nasal calcitonin	6w 3mon	Regression & Calcification	Enucleation & Peripheral ostectomy	Iliac crest	Complete Remodeling	44	~
19	M	12	Mandible	5x4x1.5	A	Yes	Intralesional steroids & nasal calcitonin	11w ~3mon	Calcification	Enucleation & Peripheral ostectomy	Xenograft & Bioguide	Complete Remodeling	78	Teeth loss (n=1)
20^	M	6	Mandible	2X3X3	A	No	Denosumab				*Ongoing*			

*Recurrence of CGCG in the same site
^Patient which is currently on pharmacological treatment
A - aggressive, A (mA) - minor aggressive, Non-A - non-aggressive

Fig. 9 Details regarding the patients treated by pharmacological therapy followed by surgery: location of the lesion, treatment performed, reconstruction if performed, response of the bone to the treatment, morbidity and duration of follow-up

These features and the resulting morbidity led to a search that identified intralesional corticosteroids, calcitonin and Interferon α-2a as pharmacological treatment options for CGCG. Steroids and calcitonin showed some promise, and although not always successful, most patients benefited from the treatment [24, 25]. Interferon, on the other hand, although helpful in some cases, led to major side effects that frequently became intolerable by the patients [26].

The literature does not describe numerous cases that were treated pharmacologically: by 2018, 80 or fewer reliable cases had been treated with calcitonin and a similar number with corticosteroids [27].

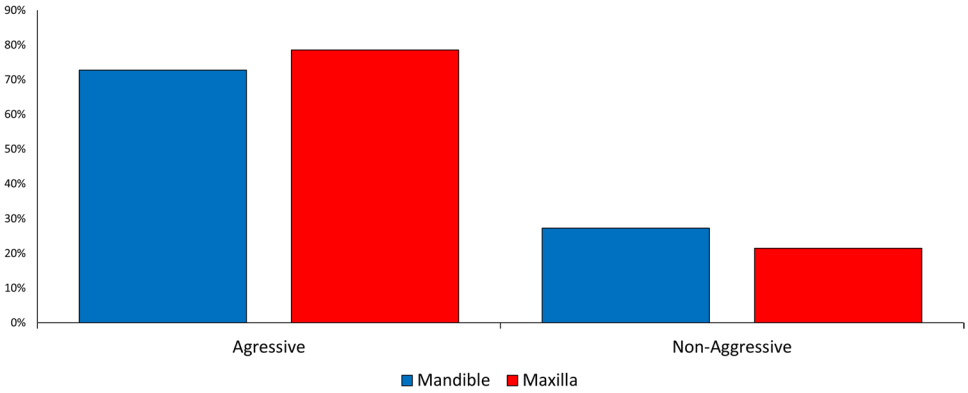

Fig. 10 Distribution of aggressive and non-aggressive lesions in the lower and upper jaws

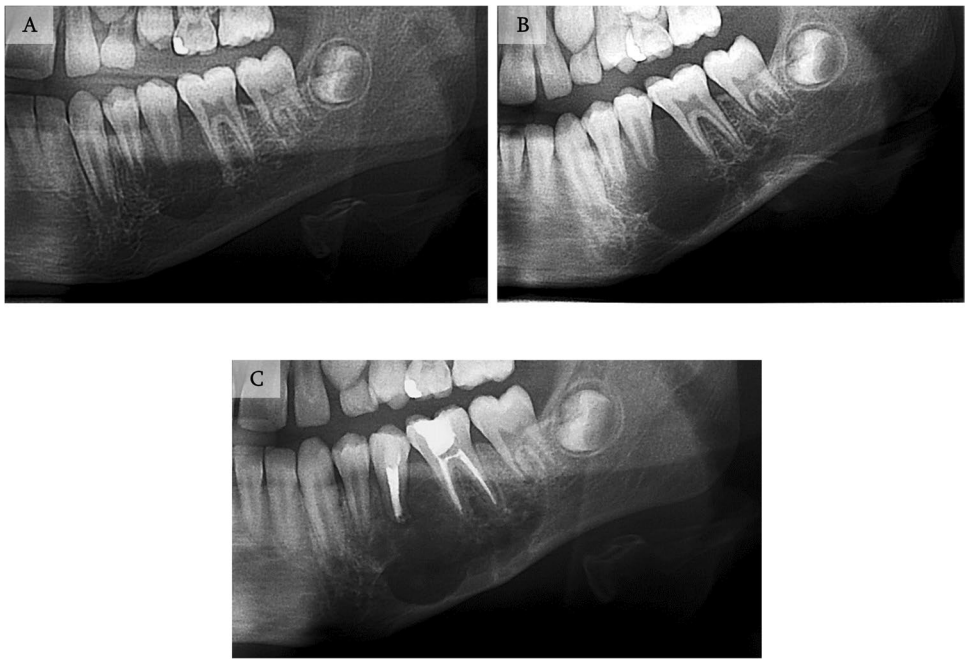

Fig. 11 Treatment and follow-up of patient 19. **A** Panoramic radiograph demonstrating a 1.3X2.4 cm lesion located in the mandible of a 12-year-old male. **B** Panoramic radiograph 3-months following diagnosis: lesion enlargement is observed due to delay in treatment. **C** Following pharmacological treatment using intralesional steroids for 11 weeks and nasal calcitonin spray daily.

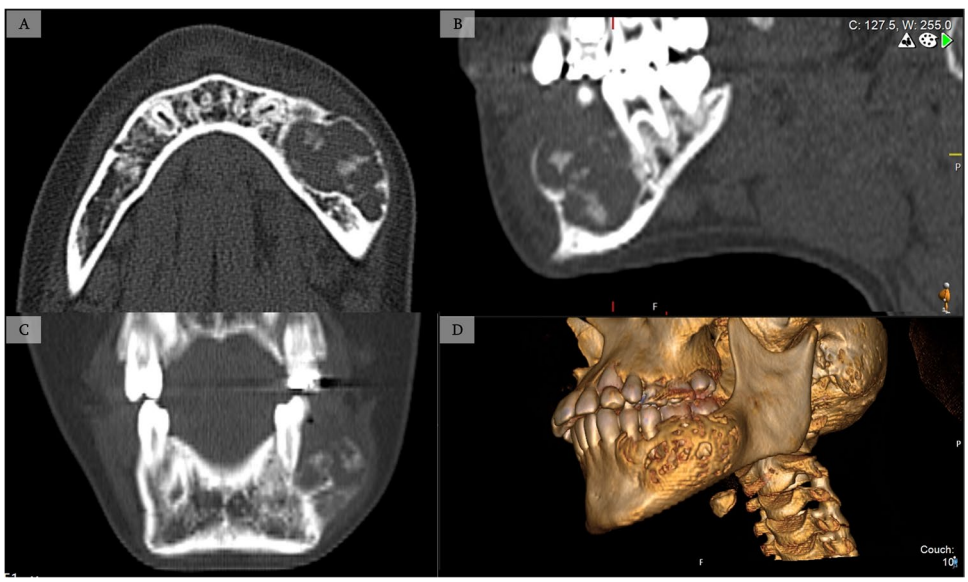

Fig. 12 CT imaging following the treatment course of the patient described in Fig. 11. (**A**) Axial (**B**) Sagittal (**C**) Coronal and (**D**) 3D reconstruction, demonstrating the aggressive lesion post pharmacological therapy with intralesional injection and nasal calcitonin as detailed previously

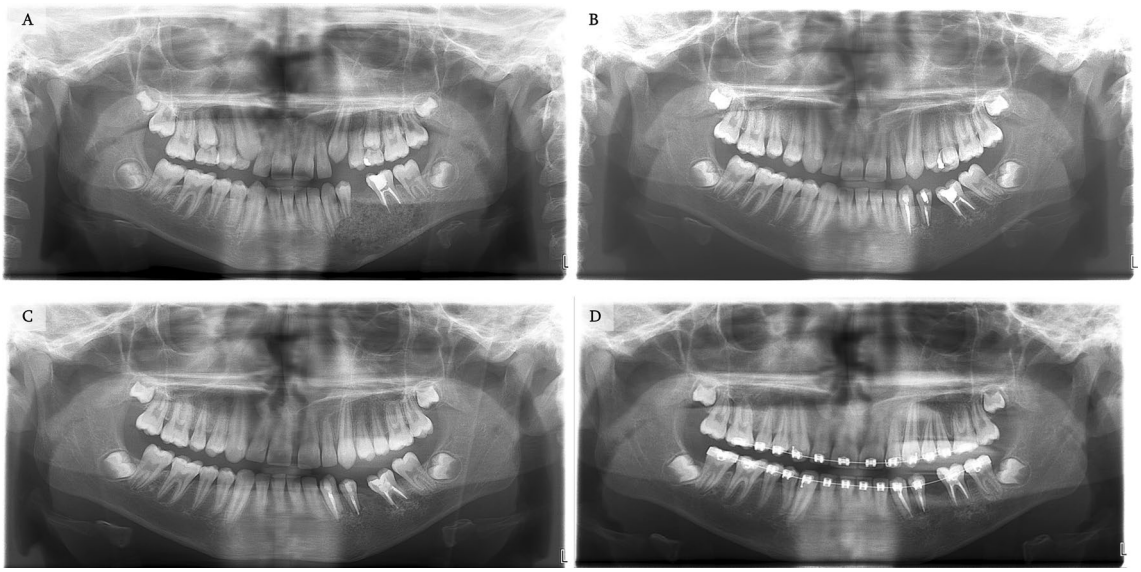

Fig. 13 Panoramic radiographs of the treatment and follow-up course of the patient described in Fig. 11. **A** Immediate post-surgical treatment comprised of a partial ostectomy and excision of the aggressive lesion, follow by augmentation with xenograft and a bio-guide membrane. **B**-**D** 1-year, 2-year, and 3-year follow-ups

The distribution of our cases was almost equal in the mandible and maxilla in contrast to the literature reporting 70% in the mandible. Our sample did not show the predominant occurrence in females observed in the literature. Consistent with the literature, the most prevalent age group in our study was 10–20. Unilocular maxillary lesions were seen more frequently in our study than the literature (84% compared to 62%), as were multilocular mandibular lesions (64% compared to 38%). All minor criteria for the aggressive type were more prevalent in our cohort than reported in the literature: cortical perforation with high incidence in the mandible (73%), pain/paresthesia and root displacement. This explains why the aggressive subtype was dominant in our sample (70–80% of the lesions), both in the mandible and the maxilla. This may be because our institute serves a large rural population in which many patients do not have routine check-ups and thus when diagnosed their lesions are larger.

Some studies in the literature reported that treatment with steroids or calcitonin resulted in complete resolution [24, 28]. Schreuder et al., used calcitonin with or without Interferon α-2a and showed ~ 50% of the lesions did not require further surgical treatment on a large cohort of 33 cases [29]. Most studies reporting the use of pharmacological treatment show improvement in up to 80% of cases, this is in accordance to our results [27]. In our cohort, all cases had to be treated surgically, but 71% responded to the pharmacological treatment, which resulted in smaller lesions that enabled a more conservative surgical approach.

The cases that did not respond to the pharmacological treatment included a patient treated with intralesional steroids and one treated with both intralesional steroids and calcitonin. Although dual therapy does not appear advantageous, the sample size is not large enough for definitive conclusions regarding the difference between treatment modalities.

It is important to mention that the use of monoclonal antibodies for the treatment of CGCG is becoming more prevalent. Following several indications for the efficiency of denosumab as a treatment modality for CGCG more centers began using it as a single [30] or combined [31] method of treatment.

This method was also tested in our institute with strong positive results. Yet they are not free of complications, and serious conditions such as hypercalcemia have been observed [32]. Recent studies suggest higher recurrence rates following cessation of treatment, possibly due to latency of neoplastic cell population or partial curettage secondary to the ossified bone [33].

We do believe these results are sufficient to recommend using pharmacological treatments prior to surgery, but it is important to monitor the response and, if progression is observed, surgical intervention should be performed without any further delay. Determining whether dual therapy is preferable to monotherapy awaits additional evidence.

Author contribution D.S.: Conceptualization, Initial draft. T.C.: Methodology and Statistics. A.K.: Data curation and Visualization. O.E. and R.A.: Writing—review and editing. D.N., J.G.: Treatment administration and Data collection. R.A.: Supervision. All authors reviewed the manuscript.

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Declarations

Competing interests The authors declare no competing interests.

Ethics approval and consent to participate This study followed the Declaration of Helsinki on medical protocol and ethics and the Institutional Ethical Review Board approved the study. Approval ref. 0322–20-RMB.

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