

The central giant cells granuloma of the mandible: a report of two cases and a review of the literature

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Abstract

The central giant cells granuloma (CGCG) is a benign intraosseous lesion of the jaws. CGCG is found predominantly in children and young adults, most commonly in the anterior portion of the mandible. Although many theories have been proposed to explain the aetiology and pathogenesis of CGCG, its true nature is still unknown. In this study, two cases of CGCG are presented. The first case is about a 7-year-old patient with a lesion of the mandible and the ectopic displacement of teeth n° 3.2 and n° 7.4. The second case is about a 68-year-old man with a recidivant lesion of the mandible, that produced an external root resorption of 3.3, in the same site of a previously excised CGCG. In both cases a surgical excision of the lesion was performed and a histological diagnosis of CGCG was made. The clinical and radiographic 4-years follow-up in the first case and a 2-years follow-up in the second case did not reveal any recurrence of the lesion. So we may conclude that early and precise diagnosis of CGCG allows conservative management without risks for the adjacent teeth or bone.

Keywords: central giant cells granuloma, mandible, surgical excision

1.Introduction

The central giant cells reparative granuloma (CGCRG) has been first described by Jaffe in 1953; the same Author used this term to describe a reactive lesion to an intra-osseous haemorrhage. However, many patients with CGCRG have no history of trauma [1]. The term “reparative” has been out of use since the differentiation of central giant cell lesions between aggressive and nonaggressive lesions [2]. The central giant cells granuloma (CGCG) is a benign intraosseous lesion of the jaws, which is found predominantly in children and young adults (most frequently in young women). It may occur at any age, but it is most commonly seen (between 42% and 72%) before the age of 30 and initial presentation beyond age 50 was unusual [3 - 7]. Many theories have been proposed to explain the

aetiology and pathogenesis of CGCG, but its true nature still remains unknown. Females are commonly affected twice more than males [8, 9]. Whitaker and Bouquont investigated the correlation between hormonal influence and female predominance and their findings suggested that factors other than ovarian hormones, estrogen and progesterone are involved in the development of CGCG [9]. Lesions are more common in the anterior portion of the jaws, and the mandible has been identified as a more common location for CGCG development (it occurs at least twice as often in the mandible than in the maxilla) [7, 11, 12]. CGCG is often an asymptomatic lesion, which may become evident during routine radiographic examination or as a result of painless but visible expansion of the affected jaw [3, 13]. CGCG is a vascularized lesion and it macroscopically appears like a dark brown mass of non-calcified soft tissue with a

The central giant cells granuloma of the mandible

tendency to bleed. The radiographic appearance of the CGCG ranges from unilocular to multilocular radiolucent defects with well-defined or ill-defined borders. Small, unilocular radiolucent lesions often are seen at or near the apices of vital mandibular anterior teeth. The multilocular radiolucent lesion typically occurs in tooth-bearing areas of the jaws that have held primary teeth [3, 7, 14, 52]. Surgery is the traditional and most accepted form of treatment for CGCG; an aggressive curettage is recommended as the treatment of choice and this has been associated with a high success rate (80%) [15, 16]. In the literature some non-surgical therapies for CGCG are reported; these include intralesional corticosteroid injections [17, 18, 19], calcitonin injections [19], and subcutaneous alpha-interferon injections [19]. However, before administering the intralesional injections, the clinician must confirm the nature of the lesion performing a biopsy.

2. Case Report #1

A 7-year-old boy came to our attention, in the Department of Odontostomatologic Science of “Sapienza” University of Rome (Italy), for the evaluation of an expansile lesion of the mandible (Fig. 1).



Figure 1. Case Report #1: Intraoral view of the lesion; the picture highlights the dimensions and the clinical aspect of the CGCG.

Intraoral examination revealed a painless swelling extending from the distal surface of tooth n° 3.2 to the mesial surface of tooth n° 7.3.

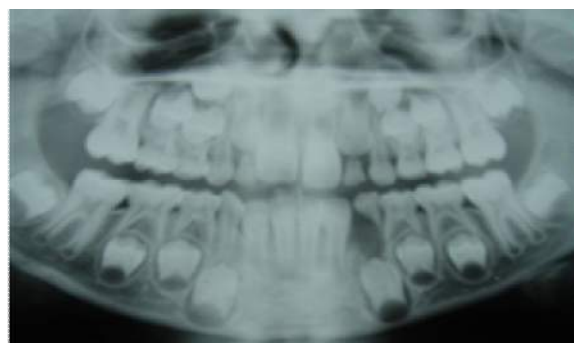


Figure 2. Case Report #1: Ortopantomography showing a diffuse radiolucent area in the left mandible.

Tooth n° 7.3 presented high mobility and teeth n° 3.2 and 7.4 were displaced. The ortopantomography (Fig. 2) showed root resorption and the presence of a unilocular radiolucency, measuring approximately 15 mm at the largest diameter. The radiographic views revealed an irregular shape of the lesion with well-defined limits; however the bone sclerotic borders of the lesion were evident.

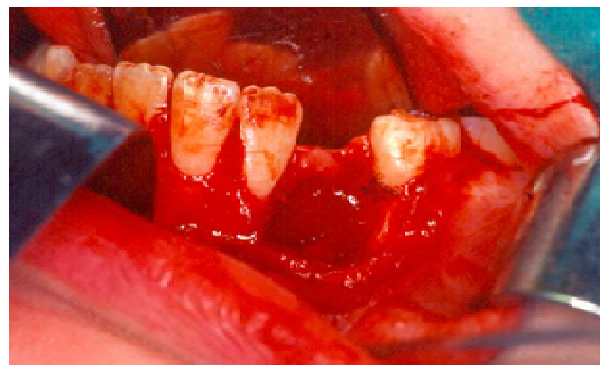


Figure 3. Case Report #1: The remaining bone cavity after surgery.

Tooth n° 7.3 was preliminary extracted and the excision of the lesion was subsequently planned in general anesthesia since the patient's compliance and age. The surgical site was infiltrated with 3% mepivacaine added of epinephrine. An incision with a Bard-Parker n°15 scalpel was performed and a trapezoidal flap was designed to allow the complete excision of the lesion, that was completely isolated via subperiosteal dissection and totally removed. The remaining bony cavity (Fig. 3) was thoroughly curetted, the bone margins regularized and the surgical area irrigated with buffered saline solution. The flap was reapproximated and closed with 3-0 silk line sutures.

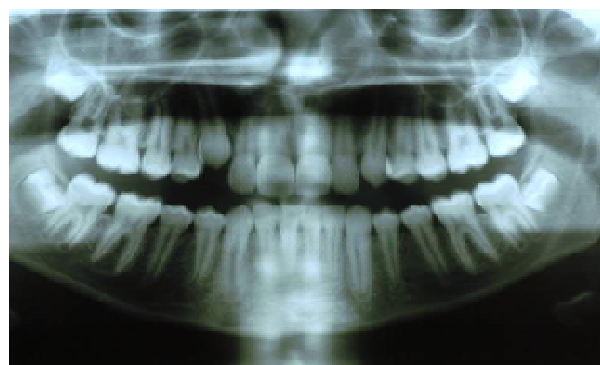


Figure 4. Case Report #1: Radiographic control 4 years after surgery.

The lesion was submitted to histopathological examination. The sutures were removed after 7 days and a new orthopantomography was performed. Post-surgical instructions and antibiotic therapy (amoxicilline +

clavulanate 1g/12 hours for 6 days) were given to the patient. Antinflammatory treatment with FANS and an antiedemigenous therapy with cortisone were administrated. The patient performed oral rinses with clorexidine 0,2% and he well tolerated the surgical procedure and there were no postoperative complications. The histopathological response of the lesion referred that histological characteristics of central giant cell granuloma are present. Once the diagnosis was certain, the patient was submitted to a clinical and radiological follow-up (Fig. 4). The lesion was an obstacle for the eruption of tooth n° 3.3. Right after the excision of the mechanical obstacle the tooth was able to continue its eruptive course. Even if we approached this aggressive lesion with a conservative surgery treatment, the follow-up showed full recovery.



Figure 5. Case Report #2: A clinical intraoral view of the lesion; the picture highlights the dimensions and the clinical aspect of the CGCG.

3. Case Report #2

A 68-years-old man referred to the Department of Odontostomatologic Sciences ("Sapienza" University of Rome), for the evaluation and treatment of a recidivant expansile on the adherent gingiva mesial to 3.3. The mass was noticed four months before, after a tooth extraction, and had progressed slowly. The patient reported, in his medical history, 15 years before, a surgical intervention for the removal of a lesion in the same site.



Figure 6. Case Report #2: The pre-operative orthopantomography.

The histological diagnosis of the past lesion was CGCG. The intraoral examination showed a sessile fibrous soft lesion with a rough surface of about 15 mm on the adherent gingiva, covering the alveolar ridge mesial to 3.3 (Fig. 5). The lesion was asymptomatic and vitality test revealed that mandibular left canine was necrotic. The ortopantomography (Fig. 6) showed external root resorption of 3.3 in the apical third and presence of a unilocular round-shaped radiolucency, of about 15 mm, on the mesial side of 3.3.



Figure 7. Case Report #2: An intraoperative view of the remaining bone cavity after surgery.

The lesion had well defined limits, without a perilesional bony sclerotic border. The swelling was not associated with any systemic symptoms. Due to the previous diagnosis, an incisional biopsy of the lesion was decided before the total excision of the lesion.



Figure 8. Case Report #2: Clinical view after a two-years follow up.

The histological evaluation revealed features consistent with a CGCG. Therefore, an excisional biopsy was decided at the same time with the extraction of the adjacent tooth (3.3) that was involved in the lesion. After local anesthesia with 3% mepivacaine with epinephrine the lesion was excised using a BP n° 15 scalpel, and the residual bone cavity was thoroughly curetted (Fig. 7), the bone edges were made smooth and the cavity was

irrigated with buffered saline solution. Then, 3-0 silk line suture were applied.



Figure 10. Case Report #2: Radiographic control after 2 years from the surgical excision.

The excised lesion was sent for the histopathological examination. The patient underwent a clinical and radiographical follow up at 1 week, 1, 3, 6 months, 1 and 2 years (Fig. 8.). Post-surgical instructions and antibiotic treatment were given to the patient. Antinflammatory treatment with FANS was administrated. The patient performed oral rinses with chlorhexidine 0,2% and he did not report any post-operative complications.

The definitive anatomopathological report of the excised lesion was compatible with reparative giant cell granuloma.

4. Discussion

CGCG was classified by the World Health Organization in 2005 as a “rarely aggressive idiopathic benign intraosseous lesion that occurs almost exclusively in the jaws” [20, 6]. This osteolytic lesion histologically consist of proliferation of fibrous tissue, that contains multiple foci of haemorrhage, hemosiderin deposits, aggregation of multinucleated osteoclast-like giant cells and occasionally trabeculas of woven bone and reactive bone formation [21, 6].

There is controversy in the literature about whether it is a true neoplasm or a reactive response [22]. It has been suggested that it might be an inflammatory lesion, a reactive lesion, a true tumor or an endocrine lesion; one hypothesis suggests that CGCG belongs to the spectrum of mesenchymal proliferative vascular primary jaw lesions. As Vered et al. reported, the low mean microvascular volume (MVV) of Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblast Growth Factor (bFGF) positive blood vessels implies little angiogenic activity, which contradicts the description of CGCG as true proliferative vascular lesion [23, 24]. Chuong and Ficarra suggested to separate the jaw giant cell lesions into aggressive and nonaggressive types since clinical and radiologic considerations; aggressive types

have rapid growth, root resorption, paresthesia, perforation of the cortical bone or pain and very high recurrence rates after curettage [25 - 27].

Recurrence rates vary widely, ranging from 10% to 69% [28, 29]. More recently, in the literature recurrence rates vary between 11% and 35% [7]. Whitaker reported that a mean interval between initial treatment and treatment of a recurrence was 21 months, and stated that very few recurrences were manifested after 2 years of initial treatment. These authors also have reported that lesions over 3 cm in greatest diameter are more likely to recur than smaller lesions [12]. Chuong and Ficarra reported 72% recurrence rate in the aggressive lesions, 3% recurrence rate in the nonaggressive lesions [26, 27]. According to De Lange, there is no significant difference in recurrence rates between the mandible and the maxilla [7]. CGCG is more common in the anterior portion of the jaws, and the mandible has been identified as an eligible location for CGCG development (at least twice as often in the mandible than in the maxilla) [7, 11, 12]. CGCG of the jaw is usually unifocal and the occurrence of multifocal lesions is reported to be extremely rare; most multifocal lesions are associated with some form of inherited syndrome or systemic disease such as brown tumor of hyperparathyroidism (in the majority of cases), fibrous dysplasia, ossifying fibroma, Paget disease, fibro-osseous or odontogenic fibroma. A number of syndromes were associated with multiple giant cell lesions of the jaws, including cherubism, Noonan syndrome, neurofibromatosis type-1 and Ramon syndrome [7]. CGCG is usually an asymptomatic lesion, which may become evident during routine radiographic examination or as a result of painless but visible expansion of the affected jaw. It can cause tooth mobility, tooth displacement and root resorption (it is considered to be an important indicator of aggressiveness), but it does not invade the perineural sheets, so paresthesia is not usually observed [3, 7, 13, 14].

CGCG is a vascularized lesion and it macroscopically appears like a dark brown mass of non-calcified soft tissue with a tendency to bleeding. The radiographic image of the CGCG ranges from unilocular to multilocular radiolucent defects with well-defined or ill-defined borders. Small, unilocular radiolucent lesions often are seen at or near the apexes of vital mandibular anterior teeth. The multilocular radiolucent lesion typically occurs in tooth-bearing areas of the jaws that have held primary teeth [3, 7, 14].

The presence of wispy septa within the lesion is the most significant radiographic sign associated with CGCG [30]. The radiographic findings are not pathognomonic, and they change with the size of the lesions: small lesions usually appear to be unilocular

radiolucent and without bone septa; large lesions, instead, usually appear to be multilocular radiolucencies with wispy bony septa [3, 22, 31, 32]. Small unilocular lesions can be confused with periapical cysts, and multilocular giant-cell lesions cannot be radiographically distinguished from ameloblastomas or other multilocular lesions [30, 33].

A variety of histological features and patterns can be seen in a CGCG of the jaws. The histological feature is the presence of multinucleated giant cells in a background of collagenous stroma containing spindle cells [8]. Some lesions exhibit considerable fibrosis of the stroma and foci of osteoid and newly formed bone tissue [1, 34]. The multinucleated giant cells have a patchy distribution and are usually associated with haemorrhagic areas. The giant cells typically possess four to eight randomly arranged nuclei that may be hyperchromic, oval, stippled or any combination of the three, with prominent nucleoli [8]. The nature of histopathological features and origin of giant cells have been discussed by many authors. What is acknowledged is that giant cells may arise from stromal elements as a reaction to the epithelial elements which behave as a foreign body. However, the microscopical findings can be similar with those of brown tumor of hyperparathyroidism and cherubism [26].

Brown tumour of hyperparathyroidism is histologically very similar to CGCG. To make the diagnosis it is fundamental that all the patients with suspected CGCG, should have right serum levels of calcium, phosphate and alkaline phosphatase, to exclude the possibility of hyperparathyroidism [35].

Cherubism is instead characteristically a bilateral expansion of the posterior portion of the mandible. Furthermore, differential diagnosis includes other giant cell lesions, such as true giant cell tumor of bone, aneurismal bone cyst, chondroblastoma. Since their different biologic behaviours, it is important to differentiate CGCG and giant cell tumor (GCT): GCT usually occurs in the epiphyses of long bones and is rare in the skull, while CGCG usually occurs in the jaws; both appear as lytic defects on radiographic examination and must be distinguished by histological analysis. In fact, GCT has larger and more rounded giant cell with a greater number of nuclei that cells are more uniformly dispersed than in CGCG; moreover GCT has less foci of osteoid and new bone and has rare hemorrhage, hemosiderin deposits or fibrosis [7].

CGCG lesions can be divided into aggressive and non-aggressive types based on clinical, radiographic and histological considerations (Tab.1) [8, 33, 36]. Whitaker and Waldron found statistically significant histological differences in the distribution of giant cells and osteoid

between recurring and non-recurring CGCG [12]. They concluded that recurrent lesions are strongly associated with an even distribution of giant cells and lack of osteoid at their periphery.

Surgical therapy is the traditional and most accepted treatment for CGCG. Several surgical methods have been described, such as curettage associated to cryosurgery, curettage associated to peripheral osteotomy, excision followed by reconstruction by using an autologous iliac crest bone graft, osseo-integrated implants and an “overdenture” prosthesis [7, 37].

Table 1. Different treatments of central giant cell granuloma.

Surgical	Non-surgical	Combinations
Curettage+ Cryosurgery	Intralesional corticosteoid injections (6 injections)	-----
Curettage + Peripheral osteotomy	Human / salmon Calcitonin hormone By injections or by nasal spray applications	-----
Excision + Reconstruction by autologous bone graft	Radiotherapy	-----
-----	Subcutaneous alpha- interferon injections	-----

An aggressive curettage is regarded as the treatment of choice, related with a high success rate (80%) [15, 16]. Resection is performed for recurrent or more aggressive lesions, which lead to major defects and loss of teeth. However, surgical resection in the case of large lesions can be particularly mutilating in children or young adults. In the existing literature some non-surgical therapies for CGCG (to avoid the disadvantages of surgical treatment, such a severe facial mutilation and loss of teeth) are reported. These include intralesional corticosteroid injections [17, 18, 19], calcitonin injections [19], subcutaneous alpha-interferon injections [19], and radiotherapy [38]. Non-surgical treatment is probably a good treatment option for small slowly enlarging lesions; successful treatment of painful, large and rapidly growing lesions is more likely achieved by surgical removal [7]. However, before administering the intralesional injections, the clinician must confirm the nature of the lesion performing a biopsy. CGCG is composed of two distinct population of cells: multinucleated giant cells (MGC) and spindle shaped mononucleated stromal cell (MSC); the latter are thought to be proliferating tumor cells. Those cell population have further been subclassified into: 1) type I MGC, showing slightly basophilic cytoplasm and large vesicular nuclei with discrete nucleoli which correspond to metabolically active cells; 2) type II MGC, which are

smaller with eosinophilic cytoplasm and pyknotic nuclei that correspond to degenerating cells; 3) MSC with ovoid vesicular nuclei; 4) MSC with spindle-shaped pycnotic nuclei. MSC are osteoblast like cells with similar functions in fact they induce osteoclast formation from mononuclear blood cells via RANK-RANKL (*Receptor Activator of Nuclear Factor-KappaB – Receptor Activator of Nuclear Factor-KappaB Ligand*) interaction. Parathyroid hormone-related peptide (PTHrP) and parathyroid hormone/parathyroid hormone-related peptide receptor 1 (PTHrP1) are expressed in CGCG of the jaws and may be the stimulating event for the activation of the RANK-RANKL pathway. RANKL present on stromal cells influences the differentiation of giant cells from RANK expressing mononuclear cells. Both steroids as well as calcitonin affect the giant cells rather than the prime neoplastic cells i.e. the stromal cells.

Dexamethasone inhibits lacunar resorption by mature osteoclasts isolated from giant cell tumor of the bone by probably inhibiting the extracellular production of bone resorption mediating lysosomal proteases and by inducing apoptosis of osteoclastic cells. Glucocorticoid and calcitonin receptors have been identified on both the mononuclear spindle shaped cells as well as the multinucleated giant cells. Majority of authors observe a protocol of giving six injections of corticosteroid (i.e. triamcinolone acetonide as 50% mixture with local anaesthesia with adrenaline) and following up the patients with periodic radiographic examination and intervening only if symptomatic radiolucency is observed [36, 39]. Corticosteroid treatment is, however, relatively contraindicated in certain medical conditions, such as diabetes mellitus, generalized immunocompromised conditions, infections and peptic ulcer. In 1994 Terry and Jacoway presented four patients treated with steroids; a weekly injection of steroids into the lesion during a period of six weeks resulted in a complete resolution in three patients while one patient needed additional surgery [40]. Marx and Stern have reported a 65% rate of complete resolution with intralesional corticosteroid injections; in the remaining cases, the lesion either recurred in a more aggressive form or failed to respond at all [41]. After that study, a few other authors also reported favourable results from the intralesional administration of corticosteroids as a therapy for CGCG [19]. Harris was the first author to report on the use of synthetic human calcitonin as a therapy for CGCG (this therapy may be complicated by side effects, such as hypocalcemia and secondary hyperparathyroidism); in a study on 4 patients, a total remission of the lesions was obtained [42]. At present only salmon calcitonin is commercially available (theoretically its effect is stronger than human synthetic

one); however, human calcitonin could be less immunogenic. An “in vitro” study showed that there is no difference in the effect of human or salmon calcitonin on the inhibition of osteoclastic bone resorption [19]. In a report on 9 patients, treated with subcutaneous injection of salmon calcitonin, there was no tumor reduction in the first 4 to 6 months of therapy, but later, complete resolution of the lesions occurred in 8 patients during on 18 months treatment period [43].

Salmon calcitonin, in the form of a nasal spray, has been successfully used in 4 patients. The mode of administration (subcutaneous injections or nasal spray) might also influence the therapeutic response to calcitonin; bioavailability is 70% in subcutaneous injections and 3% to 25% in a nasal spray [19]. Another possible explanation for the variety in response to calcitonin treatment is the variable number of calcitonin receptors on the giant cells and mononuclear cells [19]. In a recent report, immunohistochemistry showed a positive stain for calcitonin receptors in only 23 of 41 specimens of CGCG [44]. According to the study of Vered et al. of 2006 [24, 44], it is assumed that the appropriate therapeutic method should be based on the immunohistochemical staining scores for glucocorticoid and calcitonin receptors for each individual lesion. The principle is to initiate treatment with the therapeutic agent that targets the receptor demonstrating the most intense staining reaction.

In cases in which the therapeutic outcome is not beneficial, re-evaluation of the immunohistochemical reactivity of the glucocorticoid and calcitonin receptors should be made in additional biopsies of the lesion with subsequent adjustment of the therapeutic strategy.

In some cases, combining intralesional steroids and systemic calcitonin therapy should be considered since their action could yield a synergistically advantageous clinical outcome; this is based on the experimental findings that steroids have the ability to increase the cell-surface calcitonin receptor over several weeks. In lesions that demonstrate weak staining for both glucocorticoid and calcitonin receptors or where the clinical response is not positive to either therapeutic agent, surgery will probably remain the treatment of choice.

Table 2. Different clinical features of central giant cell granuloma.

CGCG	Clinical features				
Non aggressive	Few or no symptoms	Slow growth	No cortical perforation	No root resorption	No recurrence
Aggressive	Pain, Dimensions bigger than 5 cm	Rapid growth	Cortical perforation	Root resorption	Recurrence

An important issue in treating CGCG with steroids and calcitonin is the “escape phenomenon”; continuous

and prolonged administration of calcitonin causes a significant decrease in expression of the calcitonin receptor gene by an unknown mechanism. The ultimate result is that calcitonin no longer inhibits osteoclastic activity. By combining steroids with calcitonin, the “escape phenomenon” is usually attenuated [44]. Systemic administration of alpha-interferon (antiviral and antiangiogenic agent) is widely accepted as a treatment for highly vascularised lesions, that express high level of basic fibroblastic growth factor (FGF- β) and vascular endothelial growth factor (VEGF) [45]. Alpha-interferon seems to be able to stop rapid growth of the lesions and consolidating or even diminishing their size, but it is still necessary to use additional surgery to eliminate the lesion [23]. De Lange showed that there is only one case reported in the literature with complete remission with a combination of imatinib and α -interferon therapy [46]. The use of INF- α in combination with conservative surgery has resulted in complete remission of the tumor [47]. In another report, a patient with a rapidly expanding CGCG in the mandible was treated with INF- α without additional surgery, resulting in resolution of the lesion beginning after 3 months and complete bony regeneration after 8 months [48]. A recent report an INF- α mono-therapy in 2 patients showed a considerable regression of the lesions but a total remission could not be obtained [49].

Radiotherapy has not proven to be a satisfactory alternative, because irradiation of giant-cells lesions has been reported as a potential risk for malignant transformation of the lesion [38]. Some authors underlined the importance of a combined management of children with CGCG by the cooperation of the maxillofacial and paediatric dentistry teams, in initial diagnosis and in subsequent treatment of co-existing dental disease, in order to create a more preventive programme and provision of prosthetic replacement of teeth [50,51].

4. Conclusion

The central giant cell granuloma (CGCG) is a benign intraosseous lesion of the jaws, that is predominantly found in children and young adults with a slight predilection for females. Most authors consider the CGCG as a reactive response of the bone to a repeated unidentified trauma. CGCG is usually an asymptomatic lesion, which may become evident during routine radiographic examination or as a result of painless but visible expansion of the affected jaw. The radiographic appearance of the CGCG ranges from unilocular to multilocular radiolucent defects with well-defined or ill-defined borders. A variety of histologic

features and patterns can be seen in a CGCG of the jaws. Two case reports involving development of CGCG in the mandible of a 7 years old boy and in the mandible of a 68-years old man were presented to demonstrate the relevance of early diagnosis and treatment of this type of lesion. The reported cases have shown that only through accurate diagnosis and clinical exam, it's possible to reach a correct therapy: according to the most recent literature, the eligible therapy for CGCG is surgery. The surgical excision of the lesion, in fact, leads to a complete remission and has shown more predictable and repeatable results.

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