

# Management of central giant cell granuloma of the jaws with intralesional steroid injection and review of the literature

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## Abstract

**Purpose** We report the results of the intralesional steroid injections for the management of central giant cell granuloma (CGCG) of the jaws.

**Methods** Seven CGCGs were treated with intralesional injection of corticosteroids. To accomplish this, 3.5 mL of triamcinolone and 3.5 mL of 0.5 % marcaïne with 1/200,000 epinephrine (total 7 mL) were mixed. An adequate amount of steroid was injected into different areas of the lesion. This procedure was repeated on a weekly basis for 6 weeks.

**Results** Clinical and radiological examination showed complete resolution and ossification of the lesions in four patients. Partial recovery was achieved in two patients. One patient did not respond to the treatment and underwent surgical curettage.

**Conclusions** We suggest that intralesional steroid injection is safe and effective for the treatment of CGCG, especially in non-aggressive lesions.

**Keywords** Giant cell granuloma · Intralesional injections · Corticosteroid · Triamcinolone acetonide

## Introduction

The central giant cell granuloma (CGCG) is a benign lesion of the maxillofacial area. It was first described in 1953 by Jaffe [1], and it is defined by the World Health Organization as an intraosseous lesion consisting of cellular fibrous tissue. It contains multiple foci of hemorrhage, aggregations of multinucleated giant cells, and occasionally, trabeculae of woven bone [2]. Although the terminology of “giant cell reparative granuloma” has also been used, the word “reparative” has not been preferred by most pathologists because the lesion is typically destructive and sometimes aggressive [2]. CGCG exclusively occurs in the maxilla or in the mandible [3]. The disease mainly affects children and young adults between 2 and 25 years old, and the occurrence is estimated to be 1.1 in 1 million [4]. Clinically, these lesions are characterized by a painless and slow-growing mass. Pain and numbness are rare.

Intraorally, a swelling in the affected area and malocclusion arising from displacement of teeth can be observed. Radiographically, CGCGs appear as unilocular or multilocular radiolucent areas with relatively well demarcated borders. However, in some cases, the overlying cortical bone is perforated and root resorption can be seen [5]. Choung et al. [6] divided the disease in two different groups named non-aggressive and aggressive lesions on the basis of clinical symptoms and radiographic features. Non-aggressive lesions exhibit a slow, almost asymptomatic growth that does not perforate the cortical bone and have a low tendency to recur. Aggressive lesions are characterized by pain, rapid growth, root resorption, cortical perforation and have a high recurrence rate after surgical curettage. These lesions are also larger in size and histologically demonstrated a larger fractional surface area occupied by giant cells [4].

The differential diagnosis for CGCG includes ameloblastoma, fibrous dysplasia, primer or seconder hyperparathyroidism, cherubism, and aneurysmal bone cyst. The

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microscopic appearance of the lesions is indistinguishable from the brown tumor of hyperparathyroidism. High serum level of parathyroid hormone and alkaline phosphatase indicates hyperparathyroidism [5]. Differential diagnosis of aneurysmal bone cyst is made by determining sinusoidal blood spaces within the tumor mass. Cherubism can be diagnosed by the presence of characteristic facial abnormalities or synchronous symmetric lesions. Furthermore, the cherubism gene (SH3BP2) is not mutated in CGCG. The other rare syndromes with multiple giant cell lesions known as Noonan syndrome (PTPN11 gene) and neurofibromatosis type 1 are diagnosed with DNA analyses [4].

Treatment methods of CGCG include en bloc resection, curettage, radiotherapy, systemic calcitonin, interferon (IFN), osteoprotegerin, AMG 62, imatinib, bisphosphonate, denosumab, and intralesional steroid injections. En bloc resection is recommended for aggressive or recurrent lesions. But it results in large surgical defects in the jaws that can alter the facial contours, which are undesirable in children or young adults [7]. The literature has reported a high recurrence rate of curettage for the treatment of CGCG especially in aggressive lesions [4, 8].

The calcitonin therapy, initially reported by Harris [9], has been used subcutaneously or as nasal spray for the treatment of giant cell lesions. In an immunohistochemical study using osteoclast-specific monoclonal antibodies, it has been demonstrated that the giant cells in CGCGs are osteoclasts. Therefore, it is considered that calcitonin directly inhibits the function of giant cells [10].

IFN is an antiangiogenic and antiviral agent that is mainly used as a therapy for tumors and viral infections. The effects of IFN on the angiogenesis have been mainly attributed to the inhibition of basic fibroblast growth factor production by tumor cells. Because the aggressive CGCGs are considered proliferative vascular lesions, it would possibly respond to antiangiogenic therapy with IFN [11].

Both osteoprotegerin and AMG 62 inhibit the action of receptor activator for nuclear factor  $\kappa$ B ligand (RANKL). RANKL affects the differentiation of mononuclear precursor cells into mature giant cells, and it also stimulates osteoclast bone resorbing activity. Because the giant cells in CGCG are osteoclasts, the progression of lesion can be obstructed by inhibition of RANKL [4, 12].

Imatinib is a protein tyrosine-kinase inhibitor used in the treatment of multiple cancers such as chronic myelogenous leukemia and gastrointestinal stromal tumors [13, 14]. In an experimental study, it was shown that imatinib inhibits the differentiation and function of osteoclasts at concentrations within the therapeutic dose range. These results suggest that imatinib may be useful in the treatment of skeletal diseases involving excessive osteoclast activity [15].

Intralesional steroid injection (ISI) was first reported in CGCG lesions by Jacoway et al in 1988 [16]. In 1994, Terry

and Jacoway [17] introduced the treatment protocol using a weekly intralesional injection of a mixture of equal parts of triamcinolone acetonide (TA) (10 mg/mL) and a local anesthetic (bupivacaine 0.5 % with epinephrine 1:200,000). The recommended dose is 2 mL/2 cm of radiolucency, and the injection should be given in different locations throughout the lesion for at least 6 weeks. It is hypothesized related with the mechanism of corticosteroids in the treatment of these lesions that the extracellular production of bone resorption through lysosomal proteases by the giant cells is inhibited and steroids induce apoptotic action of osteoclast-like cells. These two mechanisms could cause cessation of bone resorption [18].

In this paper, we present seven cases of CGCG of the jaws treated with ISI. Four of them healed completely, two responded partially, and one case did not respond to treatment.

## Patients and methods

Seven patients (four males and three females; aged between 11 and 48 years) with CGCG were treated. In four cases, the lesions were located in the mandible while the other three were found in the maxilla. All patients had vestibular expansion. Patients had single lesions and one patient (case 6) had facial asymmetry. Incisional biopsy was performed and all lesions were identified as CGCGs. Laboratory analysis of parathyroid hormone, calcium, and phosphorus values were within normal limits in all patients, ruling out hyperparathyroidism. The patients were managed by using the protocol defined by Terry and Jacoway [17]. For this purpose, 3.5 mL of TA (Kenacort-A) and 3.5 mL of 0.5 % marcaine with 1/200,000 epinephrine (total 7 mL) were mixed. This mixture was injected into the lesion, distributing as equally as possible. This procedure was repeated on a weekly basis for 6 weeks. First injections were performed by using a 10-mL syringe with dental needle because the lesions were mostly fragile. However, the lesions became firmer in the later phases of treatment and injection procedure became more difficult. Therefore, a 21-gauge needle was used with a 10-mL syringe in subsequent injections. The course of treatment was followed by the radiographs taken every 3 months. Mean follow-up of patients was 39 months.

## Results

Table 1 provides a summary of the results of treatment with ISIs for the cases. During and after treatment, the side effects were not observed due to the steroid therapy in any patient. However, menstrual irregularities occurred in one patient after six injections (case 6). Radiographic appearance showed complete resolution and ossification of the lesions for four patients

**Table 1** Data for the 7 patients with CGCG treated with intralesional injections of triamcinolone acetonide and period of follow-up

Case no.	Gender	Age	Site	Initial size of lesion (cm)	Treatment	Follow-up
1	M	12	Anterior mandible	4	Steroid injection only	59 months, no recurrence
2	M	12	Right maxilla	3.5	Steroid injection + curettage	54 months, no recurrence
3	F	17	Right maxilla	2	Steroid injection only	42 months, no recurrence
4	M	15	Left maxilla	5	Steroid injection, followed by resection in another center	Connection lost after resection
5	M	11	Right mandible	4	Steroid injection only	34 months, no recurrence
6	F	13	Left mandible	4	Steroid injection + curettage + graft	38 months, no recurrence
7	F	48	Right mandible	4.5	Steroid injection only	35 months, no recurrence

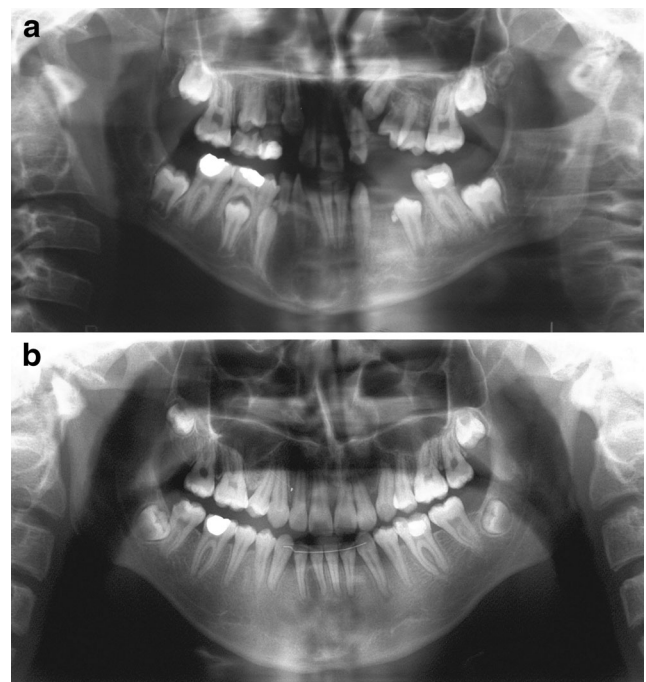
(Figs. 1a, b; 2a, b; 3a, b; and 4a, b). In one patient (case 2), the lesion was not totally resolved but it became much smaller. A surgical procedure similar to periodontal flap operation was carried out to remove the residual lesion. The patient healed uneventfully. In case 6, the healing was not achieved at the end of the six injections in the lesion. After that, we performed nasal calcitonin spray. But the patient did not want to maintain calcitonin therapy due to the bleeding of the nose, whereupon curettage was performed on the lesion. Premolars were extracted and the region was grafted simultaneously. No recurrence was seen after 38 months (Fig. 5a–c). Another patient (case 4) had a mass that was in relation to maxillary teeth. Eight months after steroid injections, the lesion became smaller, but it was not completely healed. A new steroid injection therapy was planned, but we lost contact with the patient. Two years later, we reached him. It was seen that the patient was operated in another center. We obtained the histopathological sections of this resection, which had been performed without our knowledge, and re-examined them. Histopathologic examination revealed lobules of giant cell granuloma separated with broad interstitial fibrous connective tissue bands. Lobules of giant cell granuloma were composed from stromal fibrohistiocytic cells and osteoclast-type giant cells. Comparing with the previous histopathologic appearance of the lesion, this new view may suggest maturation of the original background granulation tissue (Fig. 6a–b).

## Discussion

Conventional treatment modalities of CGCG involve surgical interventions such as curettage or bloc resection. Although vigorous surgical curettage is known to yield partially successful outcomes, recurrence rates of up to 70 % have been reported with this technique [6]. Damage to the teeth and their tooth follicle and alveolar bone loss are other possible complications. Resections reduce the recurrence risk, but it requires demanding reconstructive procedures along with possible

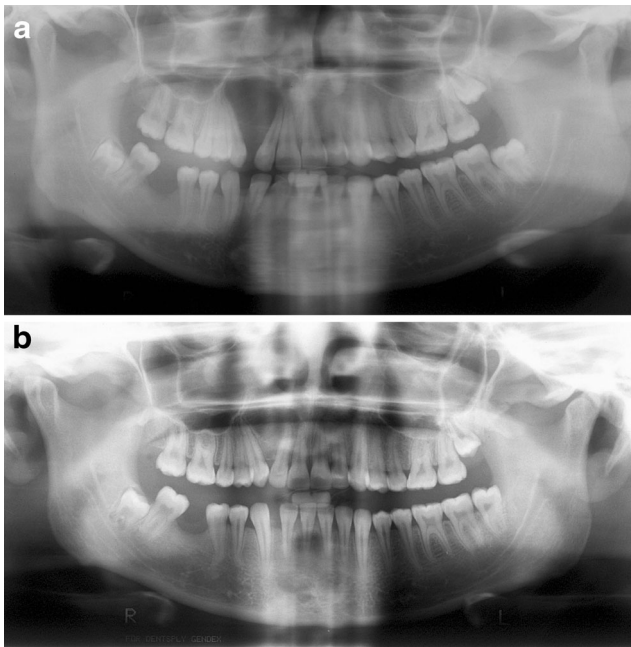
undesirable outcomes especially children and young adults, such as paresthesia, excessive bone loss, or aesthetic problems after the reconstruction [19].

These concerns motivated some researchers to find a reliable conservative technique for the management of CGCGs. Radiotherapy has been suggested as a non-surgical treatment modality, but it can lead to malignant transformations [20]. Interferon-alpha has also been used for CGCGs. Although it causes reduction of the aggressive lesions, it often requires the combined treatment such as imatinib [21]. The other non-surgical method, calcitonin therapy, has also been recommended since it was first suggested [9]. Calcitonin is given



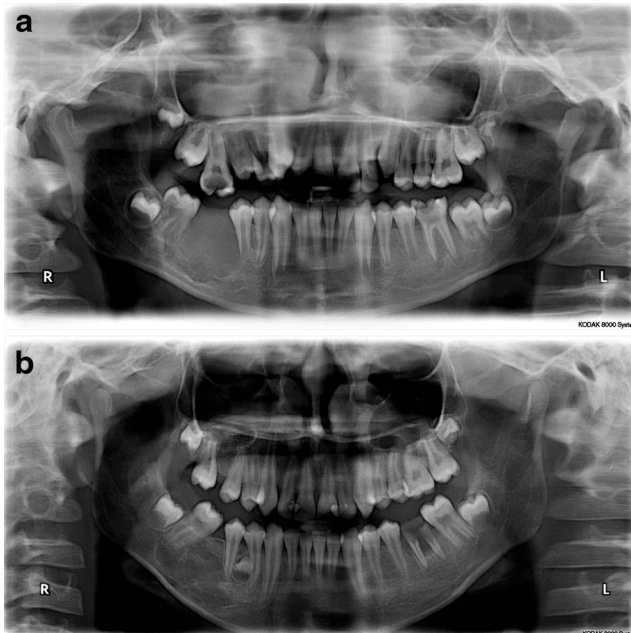
**Fig. 1** **a** Orthopantomogram (OPG) radiograph shows a well-circumscribed radiolucent lesion in right-anterior mandible. **b** After six injections, a completely healed lesion was seen at 59 months. Canine tooth was also erupted in the oral cavity



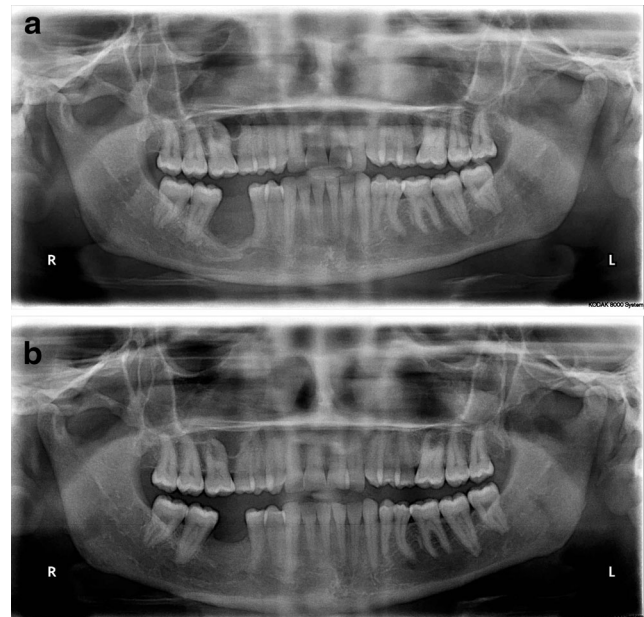


**Fig. 2** **a** OPG shows a radiolucent lesion of a 17-year-old female patient in the right maxilla. **b** At the end of the 42-month follow-up period, the lesion was completely healed

as subcutaneous injections or in a nasal spray form, and it has been found to be a viable conservative treatment modality. However, treatment period is quite long (more than 1 year), and if it is received by daily subcutaneous injections, this may be rather displeasing for patients. Furthermore, there is an assertion that the long-term use of calcitonin nasal spray might increase the risk of liver cancer [22]. Additionally, long-term



**Fig. 3** **a** OPG shows a radiolucent lesion of an 11-year-old male patient in the right mandible. **b** At the end of the 34-month follow-up period, the lesion was completely healed

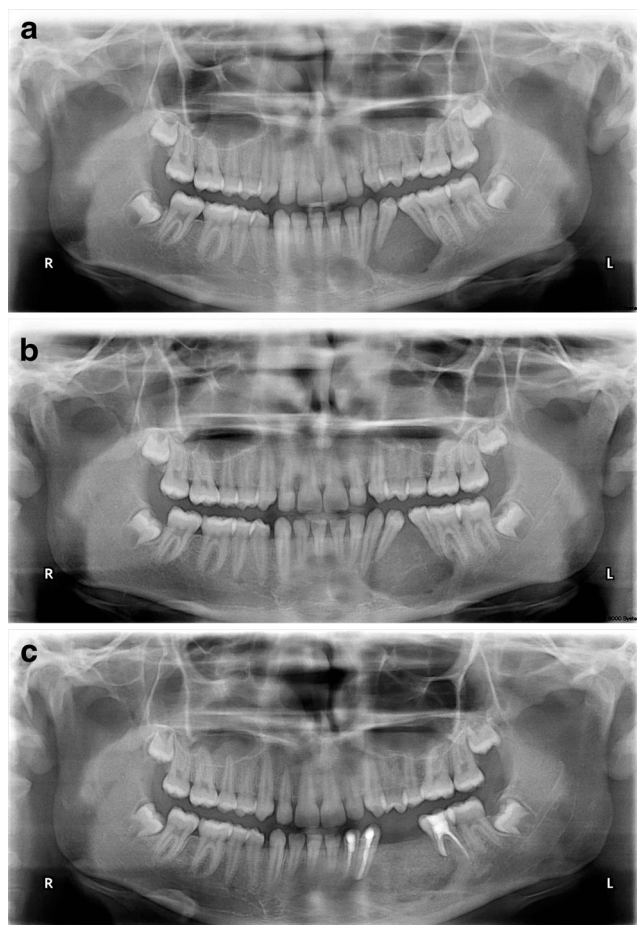


**Fig. 4** **a** OPG shows a radiolucent lesion of a 48-year-old female patient in the right mandible. **b** At the end of the 35-month follow-up period, the lesion was completely healed

use of salmon calcitonin nasal spray is not recommended by Food and Drug Administration (FDA) because of the increasing risk of cancer [23]. Other applications such as osteoprogenin, AMG 62, or imatinib are currently being investigated.

After the ISI for the treatment of CGCG was defined by Jacoway et al. [16] in 1988, many authors have reported successful results (Table 2). As we have seen, single case presentations were more common in the literature about the treatment of CGCG with ISI. When the publications of more than one case are investigated, the success rates are encountered in the following way; Terry and Jacoway [17] 75 %, Carlos and Sedano [18] 75 %, Mohanty and Jhamb [33] 50 %, and Nogueira et al. [20] 70 %. On the subject, Marx and Stern [39] also noted that in their experience, 65 % of giant cell tumors had completely resolved with corticosteroid therapy and 35 % recurred more aggressively or did not respond at all. The success rate of our results (almost 60 %) is supported by the literature.

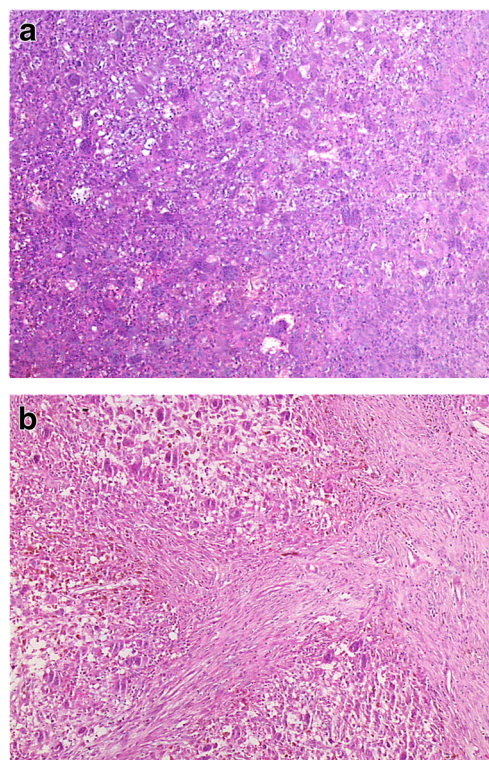
There are several hypotheses about the mechanism of action of steroids in the CGCG lesions. Osteoclasts induce bone resorption by secreting lysosomal proteases (e.g., cathepsin B, cathepsin L,  $\beta$  glucuronidase, lysozyme, and tartrate-resistant acid phosphatase). These proteases mediate osteoclastic bone resorption by creating an acidic extracellular medium. Kramer et al. [40] proved that avian osteoclasts and human osteoclast-like giant cell tumor cells respond in vitro to treatment with  $17\beta$ -estradiol ( $17\beta$ -E2) by decreased bone resorption activity. To better understand the mechanism, they investigated the effects of  $17\beta$ -E2 treatment on lysosomal enzyme production and secretion by isolated avian osteoclasts and multinucleated



**Fig. 5** **a** OPG shows a multilocular radiolucent lesion of a 13-year-old female patient in the left mandible. **b** The lesion did not respond to the injections. After 2 months, increased radiolucency was seen. **c** The curettage was performed on the lesion. Premolars were extracted and the region was grafted simultaneously. No recurrence was seen after 38 months

cells from human giant cell tumors in vitro. They concluded a dose-dependent decrease in secreted levels of these enzymes. Kameda et al. [41] also showed that  $17\beta$ -E2 was able to directly inhibit osteoclastic bone resorption. Furthermore, E2 also directly induced osteoclast apoptosis in a dose- and time-dependent manner at concentrations effective for inhibiting bone resorption. Hirayama et al. [42] reported that the dexamethasone which is a glucocorticoid has a direct effect on inhibiting the bone-resorbing activity of mature osteoclasts. On the basis of the experimental evidence, it is possible to hypothesize that the effect of intralesional corticosteroids for the treatment of CGCGs may be due to inhibition of the extracellular production of lysosomal proteases as well as steroidal apoptotic action on the osteoclast-like cells [20].

The success criteria of the treatment with intralesional steroid injections include absence of symptoms such as pain or



**Fig. 6** **a** Histological features of the central giant cell granuloma in the incisional biopsy specimen show multinucleated giant cells (HE  $\times 100$ ). **b** Histopathologic examination revealed lobules of giant cell granuloma separated with broad interstitial fibrous connective tissue bands (HE  $\times 100$ )

swelling, and increase in radiopacity can be considered. Therefore, we believe that the patients should be monitored for a long time in the postoperative period. In this case series, patients were followed for a mean of 39 months clinically and radiographically. We did not need to perform more than six injections in any patients. We planned a second protocol implementation in only one patient (case 4) because the lesion was not completely healed. But we lost contact with the patient.

The bony cortex overlying the lesion is generally quite thin, and it can be easily perforated with a needle. In these cases, first injections were applied by using a 10-mL syringe and a dental needle due to the lesions which were mostly fragile. Our aim in this procedure was to avoid damage to the soft tissues and dental follicle within the lesion and to prevent the escape of the solutions.

According to literature, ISI is an effective method in patients with CGCG. However, it is not always possible to obtain a positive response to the treatment in the multilocular or aggressive lesions. Hence, in such cases, it is necessary to apply surgical or combined treatment methods. In addition, serum calcium, phosphorus, and parathyroid hormone levels should be examined on suspicion of hyperparathyroidism after a definitive diagnosis result of the incisional biopsy. It



**Table 2** Previous studies reporting the use of intralesional corticosteroids for the treatment of CGCG

Author	Age, gender	Location	No of injections—time	Results	Follow-up
Terry and Jacoway (1994) [17]	–	Right side mandible		Complete resolution	3 years
		Left side mandible	6 (TA)—6 weeks	Complete resolution	16 months
		Right Anterior mandible		Complete resolution	26 months
		Left posterior mandible		Incomplete resolution	–
Kermer (1994) [24]	40 years, M	Right mandible body	6 (TA)—6 weeks	Complete resolution	3 years
Rajeevan (1998) [25]	17 years, F	Right and left side mandible	6 (TA)—6 weeks	Complete resolution	10 months
Khafif (2000) [26]	36 years, F	Right side maxilla	6 (TA)—6 weeks	Complete resolution	2 years
Kurtz (2001) [27]	10 years, F	Anterior mandible	6+6 (TA) 12 weeks	Complete resolution	5 years
Adomato (2001) [28]	10 years, F	Left side mandible	6 (TA)—6 weeks	Incomplete resolution	7 months
Carlos (2002) [18]	31 years, M 34 years, M 6 years, M 2.5 years, F	Right side maxilla	20 (TA)—60 weeks	Complete resolution	7 years
		Left posterior mandible	17 (TA)—34 weeks	Complete resolution	6 years
		Left and right hard palate	4 (TA) + curettage—8 weeks	Incomplete resolution	6 years
		Left posterior mandible	4 (TA)—8 weeks	Complete resolution	2 years
Abdo (2005) [29]	14 years, F	Left side mandible	3 (not specified)—3 weeks	Complete resolution	18 months
Sezer (2005) [30]	11 years, M	Left side mandible	6 (TA)—6 weeks	Complete resolution	3 years
Comert (2006) [31]	4 years, M	Right side maxilla	8 (P) + curettage—8 weeks	Incomplete resolution	3 years
Wendt (2008) [32]	8 years, F	Anterior maxilla	11 (TA)—11 weeks	Complete resolution	6 years
Mohanty (2009) [33]	10 years, F 20 years, M	Left side mandible	5 (TA)—5 weeks	Complete resolution	18 months
		Left posterior mandible	6 + 3 (TA)—9 weeks	Incomplete resolution	13 months
Nogueira (2010) [20]	11M/10F Mean age 15.5 years	13 mandible	6 (TH) + curettage—12 weeks	Incomplete resolution (4 cases)	3 to 8 years
		8 maxilla	6(TH) + resection—12 weeks	No response (2 cases)	
			6(TH)—12 weeks	Complete resolution (15 cases)	
Shirani (2010) [7]	13 years, F	Left side mandible	6 (TA) + resection—6 weeks	No response	2 years
Ferretti (2011) [34]	16 years, F	Anterior mandible	3 (TA)—4 weeks	Complete resolution	4 years
Rachmiel (2012) [35]	24 years, F	Anterior mandible	6(TA) + calcitonin + curettage—6 weeks	Incomplete resolution	5 years
Da Silva (2012) [36]	35 years, M	Left side mandible	10(TA) + alendronate sodium—7 months	Complete resolution	4 years
Choi (2013) [37]	31 years, F	Right side mandible	6 (TA) – 6 weeks	Complete resolution	2 years
Fonseca (2013) [38]	15 years, M	Anterior mandible	6 (TA) + curettage—4 months	Incomplete resolution	30 months

M male, F female, TA triamcinolone acetonide, P prednisolone

should be noted that the images of brown tumor and CGCG cannot be distinguished histologically. And before starting the ISIs, possible diabetes mellitus and the presence of peptic ulcers or any infection should be questioned.

Apparently, the treatment with intralesional steroid injections is advantageous for large CGCG in order to reduce the size of the lesion and thus minimize the need for extensive bone resection and loss of teeth that can result in functional and aesthetic defects. The present study suggests that intralesional injection of steroids is safe and effective for the treatment of CGCG in children and young adults. The treatment method can be considered an alternative to surgical resection. More long-term controlled studies are needed to determine if intralesional injection of steroids may serve as an alternative to surgery in this setting.

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