CASE REPORT

Treatment of mandibular central giant cell granuloma with administration of systemic calcitonin: A case report*

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ABSTRACT

Treatment of mandibular central giant cell granuloma with administration of systemic calcitonin: A case report

Cenrtal giant cell granuloma (CGCG) is a benign aggressive, destructive, intraosseous lesion of jaw that occurs before the age of 30 years and predominantly in females. Curettage is the most preferred therapy but in recent years also conservative therapy is commonly used. This report presents the treatment modality of 11 years old boy that had CGCG on mandibular molar area. The patient was examined clinically and radiologically and incisional biopsy was performed. CGCG was the definitive diagnosis and systemic calcitonin therapy was begun intranasally once a day and stretched 6 months. After 6 months and regression of the lesion size and callus formation was determined. For six years follow- up there wasn't any findings of recurrence, abnormal dental eruption or functional disturbance. SDHG therapy with systemic calcitonin to avoid functional and aesthetic deformities in young patients is a non-surgical, minimally invasive and preferred method of treatment.

KEYWORDS

Calcitonin, central giant cell granuloma, mandible

ÖZ

Mandibulada görülen santral dev hücreli granülomun sistemik kalsitonin uygulamasi ile tedavisi: Bir olgu sunumu

Çene kemiklerinde görülen santral dev hücreli granulom (SDHG) çoğunlukla kadınlarda ve 30 yaş öncesinde görülen, iyi huylu, agresif, intraosseöz bir lezyondur. Tedavisinde sıklıkla küretaj tercih edilmesinin yanında, son yıllarda konservatif yöntemlerden de faydalanılmaktadır. Bu olgu raporunda 11 yaşında erkek hastanın, mandibular molar bölgesinde teşhis edilen SDHG' ye tedavi yaklaşımından bahsedilecektir. Hastanın klinik ve radyolojik muayenesinin ardından, insizyonel biyopsi yapılmış ve SDHG tanısı konulmuştur. Hastanın tedavisi haftada 1 kez intralezyonel steroid uygulaması şeklinde başlamış ve beş hafta süreyle devam etmiştir. Ancak kontrol radyograflarında lezyonda herhangi bir rezolusyona veya yeni kalsifiye alana rastlanmamıştır. Sonrasında hastaya 6 ay boyunca günde bir kez olacak şekilde intranasal kalsitonin kullanmaya başlanmıştır. 6 ayın sonunda alınan kontrol radyografında lezyonda belirgin küçülme olduğu ve kemikte kallus formasyonunun başladığı gözlenmiştir. 6 yıllık takipte herhangi bir rekürrense rastlanmamıştır. Genç hastalarda fonksiyonel ve estetik deformitelerden kaçınmak için sistemik kalsitonin ile SDHG tedavisi, cerrahi olmayan, minimal girişimsel ve tercih edilebilir bir tedavi yöntemidir.

ANAHTAR KELİMELER

Kalsitonin, santral dev hücreli granulom, mandibula

Central giant cell granuloma (CGCG) is a benign aggressive, destructive osteolytic lesion of osteoclastic origin[1] that occurs in the mandible and maxilla and accounts for approximately 7% of all benign tumors of jaws.[2] CGCG is an uncommon lesion that occurs in young adults before the age of 30 years with a female preponderance.[3] There was a peak incidence for males between the age of 10-14 years and for females between 15-19 years of age. It is more frequent in the anterior mandible than in the maxilla.[4]

The World Health Organization (WHO) defined CGCG as an intra-osseous non-neoplastic lesion, consisting of cellular fibrous tissues that contain multiple hemorrhage multinucleated giant cells, and, occasionally trabeculae of woven bone.[5] The nature of CGCG is still controversial. Jaffe was hypothesized that this was a reactive and self-curing lesion and included the terminology of "giant cell reparative granuloma".[5,6] Later, the neoplastic hypothesis was raised to explain the aggressive subtype. Recently, it is accepted that both reparative and neoplastic assumptions are true so that CGCG lesions are partially reactive and partially neoplastic.[7] Histological characteristics are highly cellular, fibroblastic stroma with plump, spindle- shaped cells with a high mitotic rate and; the vascular density is high. The multinucleated giant cells are prominent throughout the fibroblastic stroma but are not necessarily abundant. They

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are often located most numerously around of hemorrhage.[4] Clinically; CGCG shows a wide variety behavior that is ranging from a non-aggressive, asymptomatic (indolent) and slow growing lesions to an aggressive, large, expansive lesion with rapid growth and aggressive sign and symptoms.[4] The differences between aggressive and non-aggressive types of CGCG were first described by Choung *et al*[8] Signs, symptoms and histological features of lesions were the parameters for determined the type of lesion. If the lesion gives rise to pain, paresthesia, root resorption, cortical perforation, this mean the lesion has the aggressive character and maybe shows a high recurrence rate after surgical curettage. In addition, histologically, giant cells with larger surface area are detected in these type lesions.[4,8]

Radiologically, the lesion appears as a radiolucent area, and it can be unilocular or multilocular with either well-defined or ill-defined margins.[9] Multiple lesions are rare and are often associated with a syndrome (i.e. Noonan syndrome, neurofibromatosis type I) or cherubism.[4] The radiological and histological appearances of CGCG are not pathognomonic. Therefore, further examination such as blood tests, including calcitonin, phosphate, parathyroid hormone and alkaline phosphate levels should be performed to confirm the diagnosis and to exclude hyperparathyroidism.[9]

One option to treat CGCG is curettage with or without adjuvant therapy, (i.e. liquid nitrogen, cryosurgery, peripheral ostectomy and Carnoy's solution). Another treatment modality is aggressive en- bloc resection, resulting in varying degrees of deformity.[1] It results in severe disablement of the jaw and face. Loss of teeth and dental germs in young patients is also often unavoidable. In growing patients, to preserve both esthetic and functional integrity, non-surgical methods such as intralesional injections with corticosteroids, denosumab, IFN-α 2a and systemic doses of calcitonin are increasingly used by clinicians. These alternative therapeutic strategies are useful for large aggressive lesions to cure or reduce the size and thus decrease the need for extensive surgical resection that can result in functional and esthetic deficits in young patients.[10,11,12]

Harris[13] first announced calcitonin therapy for CGCG in 1993 and since then several case reports have been published on successful treatment of this lesion using different types of calcitonin and various strategies of administration.[3] Calcitonin has been administered as a nasal spray or as subcutaneous daily injections. This hormone increases the influx of calcium into the bones, functions as an antagonist to parathyroid hormone, and inhibits osteoclastic bone resorption. Calcitonin has also been hypothesized to inhibit giant cells directly.[14]

In this report, a patient with a massive, aggressive CGCG is presented. He was treated with salmon calcitonin as a single treatment modality, after initial treatment with intralesional steroid had failed.

CASE REPORT

An 8-year old male patient was referred to us, in 2010, complaining of a non-tender swelling that arose in 2 weeks, on the left mandibular molar area. The patient had no bleeding, paresthesia or limitation of mouth opening, and there was not a history of trauma. Intraoral examination revealed a 2 cm swelling with normal mucosal color and expansion of buccal cortex on deciduous molar area. Radiographically, a multilocular radiolucent area extending from left deciduous canine to left first permanent molar was identified (Figure 1). Permanent first and second premolars, which were below the lesion, were displaced inferiorly. Radiological appearance was similar to multilocular odontogenic keratocytes, CGCG, brown tumor, central hemangioma, aneurysmal bone cyst and ameloblastoma. Laboratory investigations were required to eliminate hyperparathyroidism (brown tumor) before treatment. Parathyroid hormone, alkaline phosphatase (ALP) and serum calcium and phosphorus levels were found in normal reference ranges, and hyperparathyroidism was eliminated. Then, an incisional biopsy was performed. Histopathologic evaluation was showed several hemorrhagic areas and multi-nucleated giant cells with fibroblastic stroma, which indicated CGCG (Figure 2).

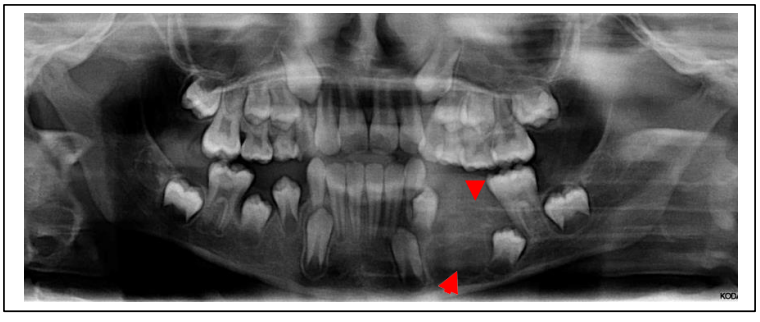

Figure 1.

Initial radiograph of the patient. High radioopasity and abnormal trabeculae can be seen at left mandibular molar area

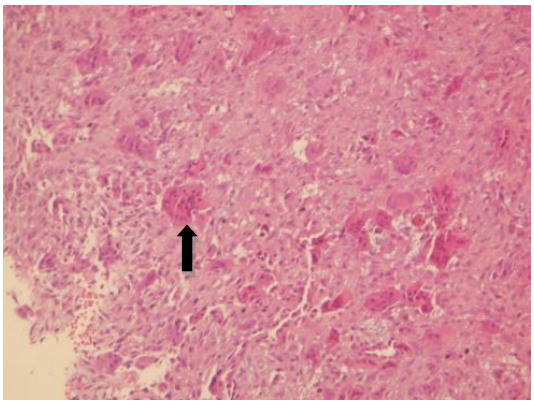

Figure 2.

Multinucleated giant cells and spindle shaped fibroblasts in a high vascularized fibrous stroma (H and E stain, magnification 40x)

After final diagnosis of the lesion, because of the patient's age and dental development status, a more conservative therapy was preferred and making intralesional steroid injections was planned. The patient had no any medical contraindications (e.g. Cushing syndrome, peptic ulcer, renal failure). Intralesional steroid injections of 5 mL per injection of 10 mg/mL triamcinolone (Kenacort-A, Bristol-Myers Squibb S.p.A, Loc.ta Fontana del Ceraso, Angani, Italy) with equal amount of Lidocaine 2% was administered with a 27G disposable syringe. Injections were made once a week for five weeks with a solution of Kenacort-A. During the treatment, any complications or side effects were not seen. The lesion was evaluated with a panoramic radiograph after five weeks and resolution or calcification of the lesion could not be detected, which indicates an unsuccessful treatment. After the steroid treatment was failed, the patient started to use intranasal salmon calcitonin (Miacalcic® 200 IU/day nasal spray. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA) once a day and it was continued for 6 months. The nostrils were used alternately to prevent an epistaxis. No side effects were seen, and the patient was showed exceptionally good cooperation with the treatment.

Four months later, a panoramic radiograph was showed opacification and regression of the lesion. Six months later, callus formation was determined on the radiograph (Figure 3), and the lesion had no any intra-oral signs. Therefore, calcitonin therapy was stopped, and the patient was invited for examination in every three months in the first year and a panoramic radiograph was taken after the end of calcitonin treatment, at 4th month (Figure 4). Compared to preoperative x-ray it was noted that the reduction in lesion radiolucency. Next year, the patient was invited for examination in every six months. Panoramic radiographs were obtained each year, and it was determined that the radiolucent area of the lesion was decreasing.

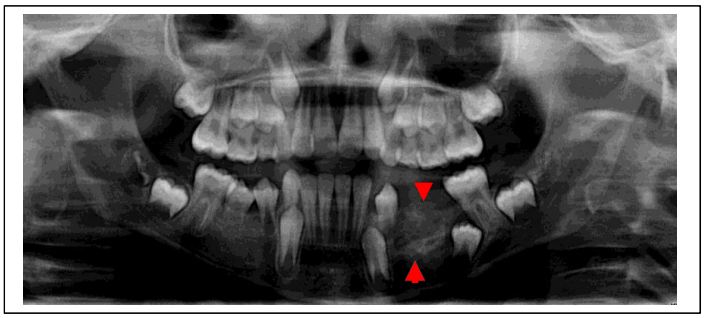

Figure 3.

Radiograph shows new callus formation at the molar area after six months calcitonin treatment

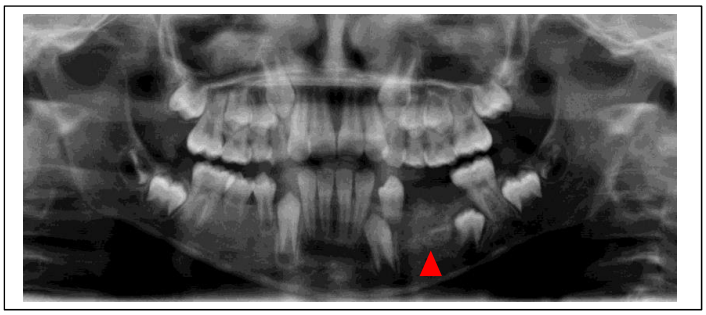

Figure 4.

This panaromic radiograph shows the reduction in lesion radiolucency after the end of calcitonin treatment, at 4th month

After three years follow-up, total remission of the lesion took place, and normal trabeculae and calcification of the bone could be seen (Figure 4). Additionally, permanent dentition continued to develop in the ordinary course (Figure 6). Based on radiological and clinical assessment, there was no need to perform a surgical intervention.

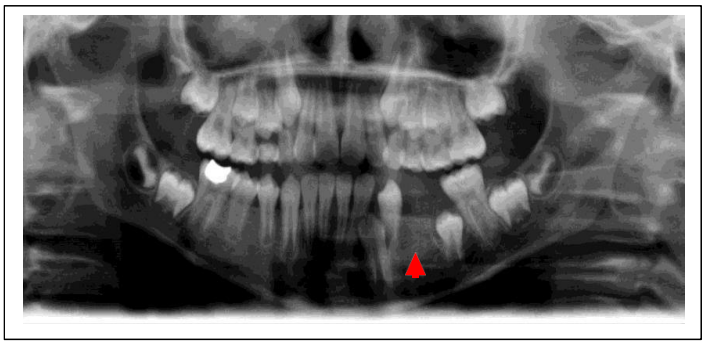

Figure 5.

Mandibular bone trabeculae are seen normally in the radiograph at the left molar area after one year calcitonin therapy

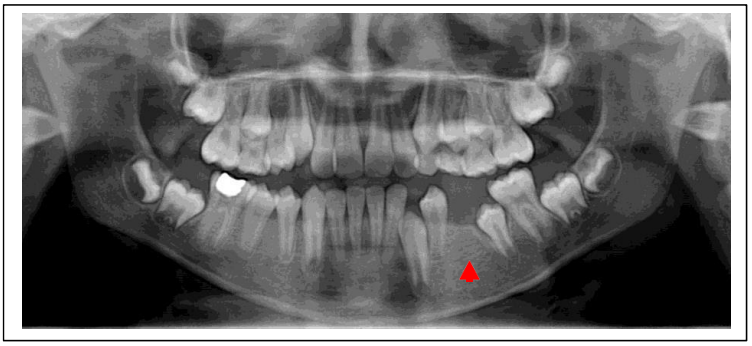

Figure 6

After third year follow-up the radiograph shows permanent dentition continued to develop in the ordinary course

DISCUSSION

CGCG is an uncommon lesion that occurs more frequently in females with a female-male ratio of approximately 2:1.[15] In most cases, it appears before the age of 30 years. Mandibular lesions are seen more often than the maxillary lesions with a ratio of 2:1.[2] In the mandible, the anterior and posterior regions are equally involved.[16] According to some authors, the anterior maxilla is usually more affected than posterior maxilla.[17] Clinically, CGCG may be a swelling that unnoticed growing or presents pain, local bone destruction, root resorption or tooth displacement. Based on clinical and radiographic features CGCG is classified into two types. Non-aggressive CGCG is characterized slow and asymptomatic growth that has a moderate tendency to recur. Aggressive CGCG is characterized by pain, rapid growth, expansion, and perforation of the cortical bone, radicular resorption and high tendency to recur. The patient described in this case report complies with the definition of non-aggressive type.[8]

Histologically, CGCG is characterized by the presence of multinucleated giant cells (MGC) in a background composed of mononucleated stromal cells (MSC) with ovoid or spindle-shaped mesenchymal nuclei.[11] The giant cells are typically seen in a hemorrhagic field containing numerous poorly defined vascular channels, which may be quite prominent. Irregular distributions of cellular elements that help differentiate CGCG from true giant cell tumors.[18] In aggressive lesions, Ficarra *et al*[17] reported more numerous giant cells in CGCG and Nougeria *et al*[10] showed that in aggressive lesions MGCs are usually more numerous, larger and uniformly scattered throughout the lesion.

Flanagan *et al*[18] were the first to demonstrate that giant cells in CGCGs are osteoclasts through the osteoclast- specific monoclonal antibodies staining. This report was provided *in vitro* reaction of giant cells to calcitonin and showed the behavior of giant cells in cortical bone excavation typical of osteoclasts. It has been demonstrated that giant cells reveal calcitonin receptors.[19] It is though those giant cells are directly inhibited in their function by calcitonin.

Molecular studies examining the mechanism of CGCG formation have shown that CGCG may develop from mononuclear precursor cells which are a member of the granulocyte/macrophage family or fibrotic origin.[20] De Lange *et al*[11] also reported that mononuclear precursor cells are differentiated to mature giant cells by influence of receptor activator of nuclear factor –kB ligand (RANKL). In addition, it is known that spindle cells, which are the proliferative part of this lesion, recruit monocyte macrophage precursors, and stimulate their differentiation into osteoclastic giant cells through the RANK/RANKL signaling pathway.[4]

Recent studies have been shown not giant cells in these lesions to responsible for the cell proliferation, but mononuclear cells are proliferating compartment.[7] Nougeria *et al*[10] designed a study to determine receptors of MGCs and find out their origin. This study showed, positive immunohistochemical expression of receptor activator of nuclear factor –kB (RANK), tartrate- resistant acid phosphatase (TRAP), vitronectin receptor (VNR) and calcitonin receptor and these findings have suggested on osteoclastic phenotype for MGCs. The presence of CD68 glycoprotein and alpha-1-antichymotrypsin has suggested that MGCs have a macrophage/histiocyte origin. In the light of these findings aim of the treatment of CGCGs should include both inhibit osteoclastic activity of the lesion and inhibit the differentiation of macrophage/ histiocyte precursors into osteoblast-like cells. Traditional treatment for CGCGs is surgical curettage. Some authors proposed excision via curettage for treatment of CGCGs and the overall recurrence rate has been reported to range from 16% to 49%. A higher incidence of recurrence was found in aggressive CGCG and younger patients, especially males.[8,21,22] In growing patients, aggressive surgical approaches may result in facial deformities and patients may lose some of the tooth germs. Eisenbud *et al*[23] indicates that surgical curettage with peripheral osteotomy is still not the safest treatment for CGCGs especially in aggressive lesions. The functional and esthetic alterations, as well as the psychological consequences caused by the surgical treatment of CGCG, have encouraged researchers to look for effective alternative therapeutic strategies. Alternative therapeutic options for CGCGs are systemic calcitonin, intralesional injection of corticosteroids and IFN-α.

Calcitonin has been administered as a nasal spray or subcutaneous daily injections. Recently only nasal spray form is available. This hormone increases the influx of calcium into the bones, functions as an antagonist to parathyroid hormone, and inhibits osteoclastic

bone resorption.[11] Calcitonin has also been hypothesized to inhibit giant cells directly. Harris[13] was first reported total remission of CGCGs in 4 patients. On the contrary Kaban *et al*[24] observed a significant growth following calcitonin therapy. Response of patients to calcitonin therapy is variable. Many factors can contribute to the various responses to calcitonin which have been reported in the literature. The different types of calcitonin (human, salmon) and the various types of administration (subcutaneous injections, nasal spray) are some of these factors.

During the systemic calcitonin therapy, clinicians must be on the alert for some side effects such as bloating or swelling of the face and extremities, chills, cough, difficulty with breathing and swallowing, dizziness, fever, itching, joint pain, nausea or vomiting, nervousness, puffiness or swelling of the eyelids or around the eyes, lips, or tongue, skin rash, trouble sleeping, unusual weight gain or loss. In addition these side effects the increased risk of cancer with the use of calcitonin has been investigated in several clinical studies. Some reports showed the use of calcitonin increases the risk of basal cell carcinoma in postmenopausal women and increased prostate cancer risk (U.S. Food and Drug Administration) (FDA).[25] To ensure consensus the use of calcitonin and cancer risk the FDA convened a Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee on March 5, 2013. The meeting stated that calcitonin treatment has not direct or exact relationship with prostate cancer or another malignancy. Researchers recommended that clinicians keep in mind the balance the cancer risk and benefits in calcitonin therapy.[25]

Intralesional corticosteroids injection for CGCGs treatment was first reported in 1988 by Jacoway *et al*[26] The underlying logic of steroids injections was inhibiting the giant cells that production of bone resorption mediators and induce apoptosis of the osteoclast- like cells.[26] Although there are successful cases of the application of intralesional steroids in the literature, there are publications showing that aggressive lesions are inadequate.[27,28,29,30,31] Both the application of intralezional steroids and systemic calcitonin as a conservative option, are among the preferred treatment methods of which has a large place in the literature and has a chance of success.

Nougeria *et al*[10] indicated that multinucleated giant cells (MGCs) may be similar to osteoclasts and macrophages/histiocytes and that CGCG can be prompted to respond to calcitonin or intralesional glucocorticoid as shown in the literature. They reported the expression of glucocorticoid and calcitonin receptors in CGCG before and after treatment with intralesional injection of steroids. They concluded that glucocorticoid receptor expression in the MGCs was higher in patients with a good response. There was not statistically significance between the aggressive and non- aggressive lesions and among the patients with good or negative response in terms of calcitonin receptor expression.

Although aggressive CGCG had higher calcitonin receptor expression no significant difference in calcitonin receptor expression in different clinical forms of CGCG was found in this study.

The treatment response was determined using previously described scores. In which four criteria were considered: stabilization or regression of the lesion size evaluated clinically and in follow-up the absence of symptoms; increased radio-opacity and representing peripheral and/or central calcification of the lesion radiographs, increased difficulty in solution infiltrating the lesion during the sequence of applications. If a case provided all of these, the response was determined to be good; providing two or three criteria was committed to be moderate; and providing one criterion or no criteria implied a negative response to treatment.[32]

Another alternative therapeutic agent is IFN-α, it has angiogenic potential and it is a mediator in differentiation from mesenchymal cells to osteoblasts thus leading to an increase in bone apposition.[24,14,7] Similar to corticosteroids, IFN-α is also capable of stopping rapid growth of their lesions and reducing their size, but it still necessary to use additional surgery to eliminate the lesion. In the literature, only one case report was showed complete remission with IFN-α therapy.[33] Several reports suggest that IFN-α administered as a monotherapy for aggressive CGCGs is useful for inhibiting the rapid growth of lesions and for reducing their size. Proliferating tumor cells are not directly inhibiting by IFN-α. Therefore, there is no report that the total remission of lesion and additional surgery is probably still required to eliminate lesions.[34,4]

Denosumab is a human monoclonal antibody that inhibits RANKL, was approved by the FDA in June 2013 for the treatment of nonoperable giant cell tumors of bone in adults and skeletally mature adolescents.[35] Complications such as hypocalcemia and malign transformation due to denosumab use have been reported in the literature. Therefore potential adverse reactions must be monitored.

CGCG is found predominantly in young adults. Surgical treatment mostly causes developmental disorder of the jaws, dysfunction of mastication, tissue defects, and facial deformities. Due to this reason, minimally invasive procedures should be preferred as the first treatment option especially in young patients. However, calcitonin treatment has begun when the expected reduction in the lesion is not seen. As in this case, non-surgical treatments should be preferred to the patients who are in the developmental stage, and surgical treatment methods should be applied if treatment is not successful.

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