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Case Report Article

Central giant cell granuloma (CGCG) in childhood: surgical treatment by maintaining the tooth germs

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giant cell granuloma; mixed dentition; oral pathology.

Abstract

Introduction: Central Giant Cell Granuloma (CGCG) is a non-neoplastic benign process, of unknown etiology, more common in children and young adults. When aggressive, the lesion may result in considerable bone destruction and deformation. Oral and Maxillofacial surgery strongly depends on the nature of injury and it may vary from more conservative to more aggressive approach. **Case report:** The aim of the present study is to report and analyze, a giant cell central lesion in a 7-year-old patient on the right side of mandible body treated by surgical enucleation, curettage, and maintenance of the tooth germs. **Discussion:** In less aggressive lesions, curettage followed by radiographic monitoring is the most widely suggested treatment choice. However, the "gold standard" for aggressive and deforming lesions would be en-bloc resection with a safety margin. Most revisions show recurrence rates of 15 to 20%, thus clinical monitoring is necessary at least one year after the intervention. **Conclusion:** After 12 months, panoramic radiograph and computed tomography indicated new bone formation and no recurrence. In addition, good healing of soft tissues and correct eruption of the teeth #42, #43 and #44 were observed.

Introduction

Central giant cell granuloma (CGCG) is considered a benign proliferative non-neoplastic process, of unknown etiology, more common in children and young adults aged less than 30 years (60% of cases) [2]. Jaffe first described CGCG in 1953, as a "reparative fibrous dysplasia" of jaw bones. Studies suggest greater female involvement when compared to men (72.7% of cases in women) [7]. CGCG is typically reported as a slow-growing, painless lesion of the jaw that may cause a mass effect on surrounding tissues [2, 7].

Radiographically, CGCG has unilocular or multilocular radiolucent areas with irregular or relatively regular edges, having a predominance of small cases where the lesion is present in multiple loci in both the mandible and maxilla, and shows cortical bone expansion [21]. Considering the location, the highest number of recorded injuries reports the lower jaw as preferred site (twice frequently in mandible when compared to maxilla) [20]. Upon variation in biological behavior, CGCG is classified between aggressive and non-aggressive, according to the presence of symptoms, duration, root resorption and recurrence rate. Both radiologic and histologic characteristics are critical to determinate response to therapy and clinical behavior. Radiographic features of aggressive lesions include rapid growth, cortical thinning or perforation, size greater than 5 cm, recurrence after surgery, tooth displacement or resorption. In addition, histologically, aggressive lesions show a large area occupied by giant cells, great size, greater nucleolar organization and high expression of CD34 adhesion factors [9, 27].

Martin *et al*. suggested that this lesion should be differentiated from brown tumor in association with hyperthyroidism. Because both diseases have identical clinical and histopathological features, PTH levels should be examined. No PTH deviation encourages us to determine CGCG diagnosis [24].

Treatment should be planned according to clinical signs and symptoms and can vary from simple curettage associated with conservative therapies to en-bloc resection [25]. However, recurrences rates after surgical intervention are reported to be higher than 70%. To minimize surgical morbidity, especially in children, medical treatments acting on tumor proliferation have been proposed [12]. However, there is no evidence suggesting any superiority for medical over surgical treatment [29].

Alternative and adjunctive CGCG treatments, such as intralesional steroid injections, are reported to be an effective alternative to surgery. Other studies, however, suggested a paradoxical effect, promoting growth of lesion in some patients. Calcitonin therapy, via intranasal sprays as well as subcutaneous injections, also has been used successfully in CGCG treatment. Calcitonin is a hormone produced by thyroid gland that inhibits bone resorption of multinucleated giant cells while lowering serum calcium levels and stimulating osteoblasts [26, 29].

A relatively new CGCG treatment modality is the use of systemic interferon alfa. Interferon mechanism of action remains unclear; however, its effect might be related to its antiangiogenic effect on aggressive vascular components of the lesion [16]. It was previously reported that interferon therapy alone has shown mixed results, since complete resolution to failure. However, the use of daily dose of interferon for an extended period together with conservative treatment has shown positive results and enabled preservation of teeth and other vital structures, which might have been sacrificed in traditional resections [16, 19]. This new therapy modality has different side effects and potentially serious toxicity, so its use has been restricted to patients whom conservative approaches have failed.

Treatment with denosumab has also been described in literature. Denosumab is a IgG2 human monoclonal antibody type which targets the RANK/RANKL system. RANKL is an essential mediator to function, formation, and osteoclast survival [30]. RANKL inhibition leads to activity reduction of CGCG aggressive osteoclast function. Some previous studies reported denosumab utilization to treat CGCG in children, showing a volume reduction as well as an ossification of the lesion. Side effects, on the other hand, were reported to be headaches, dorsal and extremities pain [30, 31].

Bisphosphonates had also been described to treat CGCG in childhood. Bisphosphonates are drugs used to treat osteoporosis due to inhibition of osteoclast activity. In 2009, Landesberg *et al*. and Chien *et al*. reported CGCG cases in children treated with Alendronate. It was observed in both cases a secondary reossification of the lesion and conservation of tooth germs, avoiding

surgery and large debridement. Nevertheless, oral bisphosphonates have been reported to increase osteonecrosis risk mainly when associated with tooth extractions [8, 18].

The most common surgical procedure to treat CGCG is the curettage or surgical en-bloc resection, also removing approximately 5 mm of adjacent healthy tissue [1, 13, 22, 34]. Due to high relapse rates, CGCG treatment is reported to be aggressive even in children, although an intermediate technique consisting in en-bloc resection with conservation of basilar board and/or posterior board have also been suggested [5]. The present study treatment choice was enucleation and curettage of lesion with conservation of tooth germs.

Case report

Male patient, leukoderma, 7 years old, was referred to the Oral and Maxillofacial department of the Federal University of Parana (UFPR) with an important and visible facial asymmetry on the right side of the body region of mandible, with 8 months of evolution. Patient reported moderate pain in the region. Significant occlusal changes and swelling were observed. Permanent teeth were not erupted due to lesion interposition, blocking physiological eruption of affected teeth.

Cone beam tomography showed bone fenestrations as well as cortical expansion and perforation. Panoramic radiograph showed a well-described, unilocular lesion in intimate relationship with posterior tooth germ.

Surgical treatment was chosen, consisting of removing the lesion through enucleation. To try to prevent recurrences, the team decided to conduct this removal with safety margin through osteotomy and removal of healthy tissue adjacent to lesion. Since the patient was young, we opted for a more conservative approach, so there would be no loss of the teeth involved. The tooth germs (#43, #44 and #45) were maintained. Only the teeth #74 and #75 were extracted. Suture of the region was conducted using vicryl.

At 12-month follow-up appointment, new complementary exams, such as panoramic radiograph and cone beam computed tomography of head were taken. No relapses of the lesion were observed. Results of laboratory tests indicated bone formation on the site previously occupied by injury, and suggested an absence of recurrence. Good soft tissue healing and correct eruption of teeth #42, #43 and #44 was also observed.

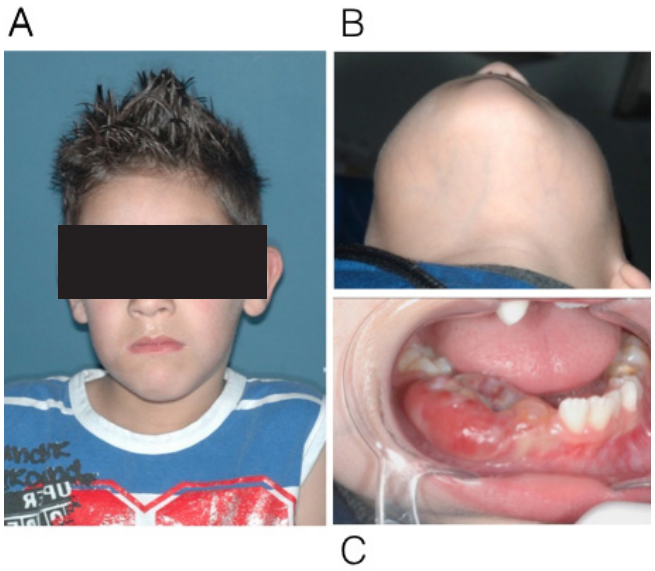

Figure 1 – Pre-operative photographs. A) Important and visible facial asymmetry on the right side of the body region of mandible, with 8 months of evolution. Patient reported no pain in the region. B) Mandible basilar region. It is possible to observe asymmetry and discrepancy between the right and left sides. C) Significant occlusal changes and swelling were observed (figure 4). Permanent teeth were not erupted due to lesion interposition, blocking physiological eruption of affected teeth

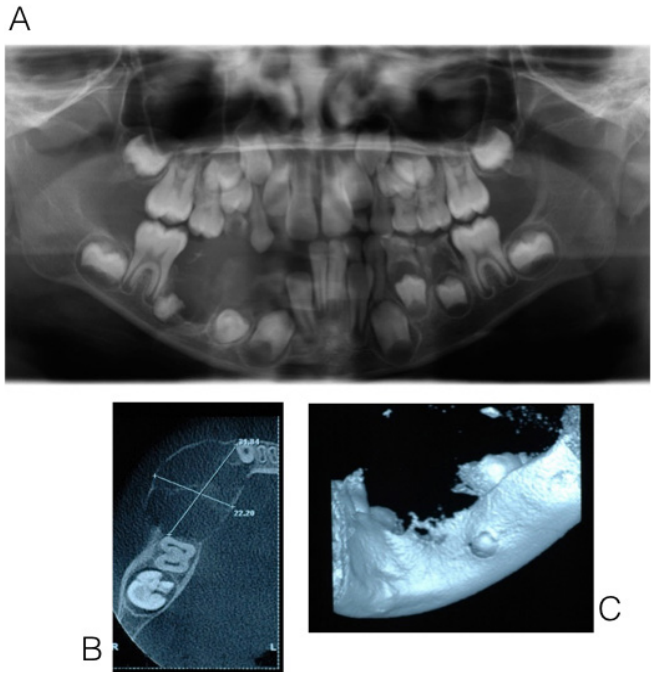

Figure 2 – Pre-Operative Imaging. A) Panoramic radiograph showing a well-described, unilocular lesion in intimate relationship with posterior dental germ. B and C) Cone beam tomography showed bone fenestrations as well as cortical expansion and perforation. Figure B also shows the intimate relationship of tooth roots with the lesion. CBCT resources were also used to measure lesion size, classified as aggressive due to its size and evolution time

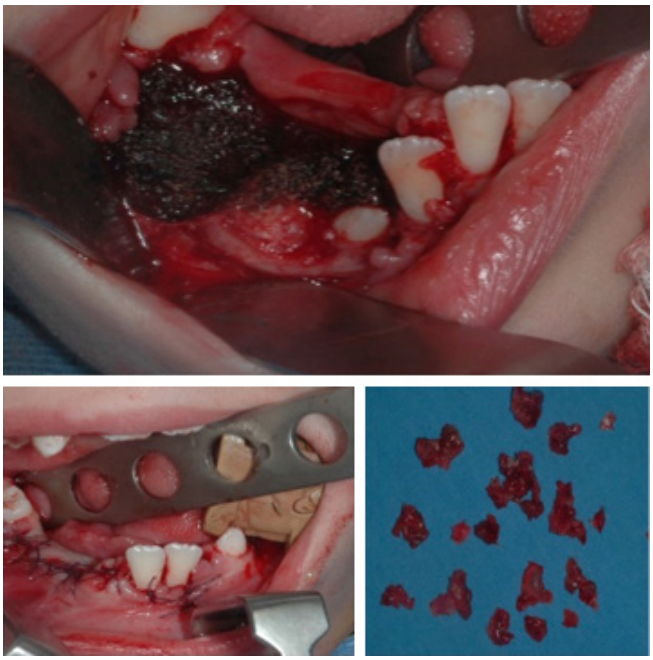

Figure 3 – Surgical procedures. Lesion was curetted and osteotomy was also conducted with TOOTH germ preservation. No teeth were extracted during surgery, even those whose root were involved in the lesion

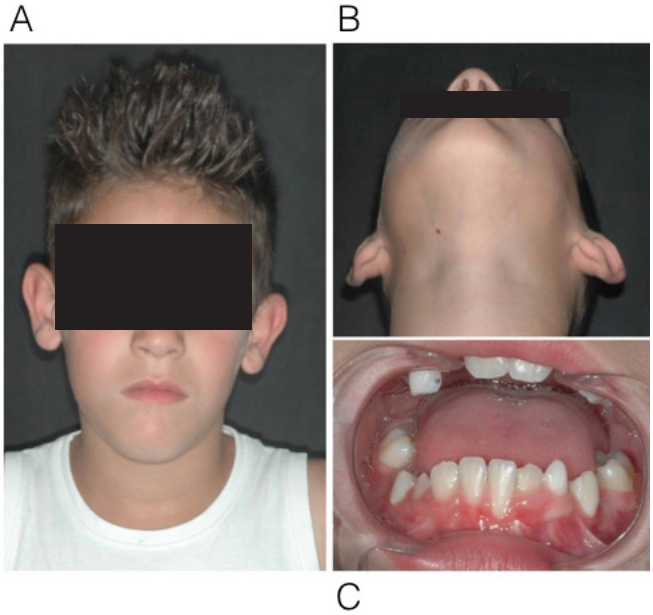

Figure 4 – One-year post-operative photograph. Patient presented no gross facial asymmetry. Basilar region of mandible with a different aspect and no clinical asymmetry sign

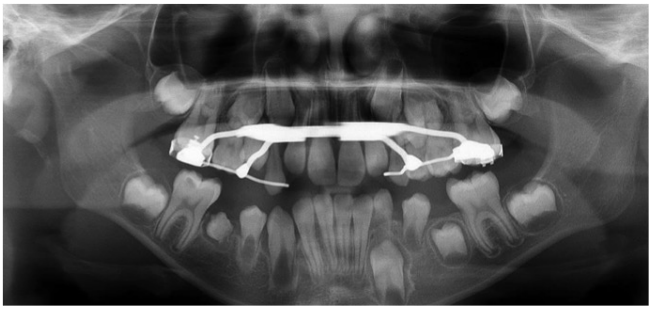

Figure 5 – One-year panoramic radiograph. No signs of relapses were observed. It is important to highlight that tooth germ preservation attempt were effective and the preserved teeth continued its physiologic eruption and are continuously being monitored until completely eruption

Discussion

Treatment modalities to central giant cell granuloma of the jaws are a dilemma, because it is hard to know which viable treatment is the best option for each patient. Although literature suggests higher CGCG prevalence in female (72.7% of cases) [33], this study reported a CGCG case in a young male patient of 7 years-old. Another decisive factor to determine the extent and predictability of treatment was the presence of tooth germs and the team's effort to not involve them in surgical treatment. The boy's legal responsible person was aware of all described methods currently used to treat the lesion.

Corticosteroid protocol to treat CGCG has shown varied results, from complete remission of lesion to tumor growth in others. No randomized controlled trials of this treatment have been conducted to determine its efficacy [6, 31].

Even though different studies suggest success in isolated treatment with calcitonin therapy, there are others that indicate lack of response with intracutaneous injections and sometimes, progression of lesion after one-year treatment [25-27]. The only randomized controlled trial on CGCG calcitonin treatment also showed no complete remissions [20]. One possible reason why calcitonin therapy CGCG is effective for some lesions and not for others might rely on the fact that the expression of calcitonin receptors may vary from different populations. In one study, 41 specimens were analyzed and only 23 were reported to be positive to the receptor. A gold standard to determine whether calcitonin therapy would be effective includes immunohistochemical staining for calcitonin receptors protocols of biopsy specimens

to determine the therapy course. We did not have our specimen stained, however it is expected that more surgeons and clinicians have the staining performed [32].

Treatment with interferon has shown positive results in multiple case reports. Most part of cases combines this therapy with curettage with success and complete lesion relapse [17]. One case reported interferon therapy effective as monotherapy [10]. Other studies however, reported a decrease in the size of the lesion but not total relapse. The theory that encourages interferon protocol utilization is that it may be more effective and beneficial to aggressive types of CGGCs, as interferon is an antiangiogenic medication and more aggressive CGCGs have a stronger ratio of vascularization when compared to indolent lesions [10, 17]. Although there are promising results in the use of interferon protocol to treat aggressive CGCGs, there are harmful side effects that must be considered before applying the use of this medication, such as bone marrow suppression and hair loss. In addition, interferon therapy is not used as first linage therapy it remains as savage procedure [14].

In June 2013, FDA approved using denosumab to treat CGCG in adults and some adolescents. According to FDA the intent of this therapy for those patients is to avoid severe morbidity of surgical procedures. Denosumab mechanism of action relies on inhibiting the receptor activator of nuclear factor kappa-B (RANK) and RANK ligand\osteoprotegerin (OPG) interaction, resulting in inhibition of osteoclast activity [30]. Schreuder *et al*. reported a CGCG case of a young adult patient treated with Denosumab subcutaneous injections for 12 months after failing calcitonin and interferon therapies. They concluded that using Denosumad to treat aggressive CGCG lesions that did not respond to other therapies were effective, however, more studies are needed before it becomes a mainstay therapy. The most serious side effect of denosumab is medication-related jaw osteonecrosis and osteomyelitis [28]. This has not been seen in the treatment of CGCG to date, but a thorough dental assessment before beginning of this medication regimen is recommended.

Surgery has always been considered the traditional treatment and it is still the most accepted one. On the other hand, some authors disagree on the surgery type performed as well as its indications [9]. When teeth are associated with lesion, they are suggested to be retained if they do not compromise the removal of the lesion in question [3]. CGCGs have traditionally been treated surgically. Common therapy is curettage or resection. Eisenbud et al advocated curettage or curettage plus peripheral osteotomy with maintenance of tooth germs for treatment of CGCG in children. He also suggested recurrence to range from 16% to 49%. Lesion relapses when they are removed via curettage were suggested to be treated with peripheral osteotomy and bone resection [1].

En-bloc resection might provide the greatest certainty of cure. Bataineh *et al*. conducted a study with 18 patients with aggressive CGCG, treated with en-bloc resection with 5 mm health tissue margin. Only one patient had lesion recurrence. Most authors agree that for child and growing patients, more conservative surgery is the only applicable strategy for maintaining the tooth germs to let them erupt physiologically [4]. In general, destructive surgery (en-bloc surgical resection with 5 mm margins) seems to be the safest option for the control of recurrences but it may result in facial deformities, which are obviously of great concern. Due to aggressive characteristics observed in the patient reported in our case, we opted for conservative surgical treatment of CGCG through curettage and bone osteotomy, with success, without generate gross facial deformities and no relapse 12 months after surgery.

Conclusion

Different treatment modalities have been proposed to treat CGCG and each case must be analyzed differently regarding clinical features and lesion presentation, pathological behavior as well as patient conditions and limitations. CGCG in childhood must be looked with special attention, because invasive surgical procedures may cause facial deformities.

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