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REVIEW ARTICLE

Advantages and disadvantages of surgical and non-surgical treatment of central giant-cell granuloma: A Review of literature

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Abstract

Background: Central giant-cell granuloma (CGCG) is a non-neoplastic benign bony lesion of unknown origin. However, genetic abnormalities, trauma, inflammation, and intrabony hemorrhage are likely causative factors. It occurs most frequently in young adults under 30 years of age; females are affected more frequently than males and the anterior part of the jaw and the mandible are the sites most affected. In radiography, it appears either as a unilocular or multilocular radiolucency. According to its biological characteristics, two variants exist: The aggressive variant shows rapid growth with pain, root resorption, tooth displacement, jaw expansion, and a tendency for recurrence ; the nonaggressive variant, is usually asymptomatic and slow growing. **Aim**: This study aims to highlight the advantages and disadvantages of the primary approaches to the treatment of CGCG through review of the existing literature. **Conclusion:** The different clinical behaviour of the lesions, that are difficult to distinguish histologically, lead to different treatment modalities ranging from radical resection to non-surgical therapy in the form of steroids, calcitonin, or interferon. Non-surgical therapy outcomes fail to achieve the surgery results in monitoring the lesions with restricted long-term follow-up. Most cases require further surgical intervention. Newer combination therapy is under investigation, using both surgical and the medical treatments to control the lesions. Although this is a rare bone tumor, controlled clinical studies with standardized procedures should be implemented to increase understanding. **Clinical Significance:** There is significant lack of agreement between the different treatment options (ranging from surgical to non-surgical). This is due to the diverse clinical behaviour of the lesion. Surgical treatment is widely accepted and regarded as the common treatment choice. However, it is also variable, with *en bloc* resection giving the most desirable outcome. Non-surgical options (corticosteroids, calcitonin, and interferon) have been applied and their valuable outcomes that must be considered.

Keywords: Calcitonin, central giant-cell granuloma, corticosteroids, interferon, primary non-surgical treatment, primary surgical treatment

Introduction

Central giant-cell granuloma (CGCG) is an uncommon, benign, and aggressive intraosseous localized lesion that occurs within the jawbones. CGCG represents approximately 7% of all benign jaw tumors and was first described by Jaffe in 1953 as "an idiopathic, non-neoplastic, proliferative lesion."[1] The World Health Organization defines CGCG as "an intraosseous lesion consisting of cellular fibrous tissue that contains multiple foci of hemorrhage, aggregation of multinucleated giant cells, and occasional trabeculae of woven bone."[2-5]

The exact nature of CGCG is unknown and debatable. Suggested theories include a reactive lesion, developmental anomaly, or benign neoplasm. In addition, the etiology of the lesion is uncertain, despite the hypotheses defining it as an aggressive inflammatory process or neoplastic proliferation. Furthermore, local trauma, bleeding, and genetic abnormalities are also suggested as possible etiologies.[3,6,7]

CGCG is one of the most common lesions that cause jaw expansion; it occurs with a frequency similar to various odontogenic cysts.[8] On physical examination, the lesion appears smooth surfaced with spongy to firm consistency.[9] It predominantly occurs in children or in young adults under 30 years of age, with a clear predisposition toward females. It occurs twice as frequently in the mandible than the maxilla, with restriction to the tooth-bearing areas of the jaw. In the maxilla, it favors the anterior region, while in the mandible, it commonly occurs anterior to the first molar tooth and extends to cross the midline.[1,6,9]

CGCG usually occurs as a single lesion, although multiple lesions may arise in rare cases where they are associated with syndromes such as Noonan Syndrome, neurofibromatosis type 1, or even cherubism.[10]

Different biological characteristics may be observed clinically, classifying CGCG into non-aggressive and aggressive variants. The non-aggressive variant is a relatively symptomless, slow-growing lesion that is usually discovered on routine radiograph. Conversely, the aggressive variant is commonly expansive with rapid growth producing pain, displacement of teeth and cortical perforation, and commonly recurs after removal.[1,11,12]

CGCG radiological appearance may be different, demonstrating unilocular or a multilocular radiolucency, with varying degrees of expansion of the cortical plates being reported.[11,12] Histological examination reveals multinucleated giant cells scattered within the fibroblastic stroma, with spindle- and ovoid-shaped cells and extravasated red blood cells.[12]

Treatment options for CGCG include conservative treatment, curettage, excisional biopsy, and surgical resection. The recurrence rate of the aggressive lesions is generally high. Rare cases with spontaneous regression have also been reported.[3,5] Due to its variable clinical behaviors, choosing a treatment option is often problematic. Thus, the objective of this article is to provide thorough information through a review of treatment options, namely, surgery as primary treatment, and alternative modalities for managing CGCG.

Aggressive Versus Non-aggressive CGCG

In 1986, Choung *et al.* classified CGCG as aggressive or non-aggressive according to six criteria: Extension of the lesion, presence of pain, rapidity of growth, root resorption of associated teeth, cortical bone perforation, and recurrence after removal. Non-aggressive lesions are relatively asymptomatic and are usually discovered on routine X-ray. They are generally slow growing, painless and are less likely to displace teeth and tooth germs. Furthermore, they display an absence of resorbed roots, perforation of cortical bone, and low tendency of recurrence after surgical removal.[2,3,11,13,14]

In contrast, aggressive lesions have a rapid rate of growth and are usually large in size: Equal to or >5 cm in diameter. In addition to causing asymmetry of the face, pain and numbness, they are further characterized by tooth displacement, root resorption, cortical bone thinning or perforation, and a high recurrence rate after conservative surgical removal. De Lange and van den Akker noted that the aggressive type most commonly arises in younger age groups.[2,3,11]

Radiographic characteristics of CGCG are not pathognomonic. Lesions may appear as an ill- or well-defined uni- or multi-locular radiolucency. Large lesions usually show internal bony septa revealing the multiloculation of the lesion. A variable degree of cortical expansion and/or perforation, root resorption of adjacent teeth, displacement of adjacent teeth, and tooth germs has been described.[11,12,15]

Histopathological examination of CGCG demonstrates multinucleated giant cells disseminated haphazardly along with mononuclear proliferating fibroblasts contained by a collagenous stroma that may contain myxoid ground substance. Multinucleated cells appear relatively variable in size, shape, and number of nuclei; they may aggregate focally or be diffusely scattered through the lesion.[16] CGCG also encloses extravasated red blood cells, hemosiderin-laden macrophages and endothelial cell-lined vascular structures accompanying proliferating fibroblasts that bear a resemblance to granulation tissue. A variable amount of osteoid and newly formed bone may be noted within CGCG lesions.[5,17,18]

The CGCG diagnosis depends on the clinical and radiological features, biological characteristics of the lesion and histopathological appearance, which are distinct and easy to recognize.[19]

Aggressive and non-aggressive lesions are histologically similar; most authors report no significant difference between the two lesions. However, some authors reported that aggressive lesions are associated with large-sized multinucleated giant cells with an increased number of nuclei and large number of cells per fraction surface occupied, compared to the non-aggressive type.[2,5]

Treatment of CGCG

CGCG is a non-reparative expansible lesion. Untreated, it results in destruction of the adjacent tissues and leads to cortical bone perforation.[2] The nature of CGCG is uncertain. Common suggestions are that it is a reactive, self-curing, spontaneously-regressing lesion, or a neoplastic aggressive type, which recurs after surgical removal. Recent studies accepted the two theories according to the different clinical behaviors and treatment response of CGCG variants.[5,19]

There is no conclusive distinction between the two variants of CGCG based on histopathological and immunohistochemical structures.[19] Consequently, responses to treatment and prognosis are difficult to predict. A recent study recommended immunohistochemical calcitonin and/or glucocorticoids (markers that stain receptors on mononuclear and multinuclear giant cells) as a relatively reliable and useful marker to be used planning treatment of CGCG lesions.[5,19] The options for treatment are surgical or non-surgical.

Surgical Treatment

Surgical treatment options for CGCG vary significantly, ranging from simple curettage and enucleation to partial or total resection of the affected bone with safety margins. CT scans assist surgical treatment planning since they determine the size of the lesion, degree of cortical bone expansion, and extent of bone destruction.[3,15] Surgical treatment is usually the treatment of choice and is the conventional cure used in most cases. Selection of the best surgical procedure depends on many factors including biological behavior (aggressive versus non-aggressive), extent of the lesion, location, and radiological appearance. Conservative treatment with or without additional medical treatment or en bloc resection for aggressive lesions is a reported treatment strategy. After surgery, antibiotics, analgesics, and steroids are required along with monitoring of clinical and radiological parameters.[2,3,5,20-22]

According to different studies, recurrence rates may vary from 10% to 50% and are commonly associated with incomplete removal of the tumor. The most common treatment of CGCG is surgical curettage, which is associated with a 16–46% recurrence rate, especially in aggressive lesions and in younger male patients.[1,3,11,23] Previous studies reported no distinction in recurrence rates between the mandible and the maxilla when using curettage as a choice of treatment. This suggests that surgical curettage is not an efficient treatment of choice for CGCG.[2,10,23]

If recurrence occurs, then curettage, peripheral osteotomy, and bone resection need to be carried out. Some authors recommend managing safe surgical margins by microdrilling using diamond bur.[2]

In aggressive CGCG, conservative surgical treatment by means of curettage enhanced by peripheral osteotomy is associated with recurrence of the lesion. Bataineh *et al.* suggested an *en bloc* resection with 5 mm healthy tissue safety margin as the treatment of choice to offer maximum confidence.[2]

Radical surgery of large lesions may results in loss of teeth in young individuals, as well as disturbances in the function of the inferior alveolar nerve. Furthermore, esthetic and functional defects may occur. Curettage in fragile bones is difficult and presents a hazard to the growth centers of facial bones. These treatments essentially require reconstruction and rehabilitation using bone grafting for functional and esthetic defects, but the consequences result in a poor outcome in most cases.[1,9,11] Therefore, the suitability of radical surgical treatment is debatable when dealing with benign lesions like CGCG.[2]

Non-surgical Treatment

Recent studies have shifted toward non-surgical treatment of CGCG due to the high recurrence rate, tooth loss, defects, and morbidity associated with surgical treatment. In addition, results of varying success were obtained using alternative non-surgical treatments, which may decrease the need for major surgical techniques.[2,10]

Intralesional administration of corticosteroids, systemic calcitonin, and antiangiogenic drugs was targeted as pharmacological treatments of CGCG in many recent studies. The use of corticosteroids and calcitonin therapy is the result of the hypothesis that CGCG lesions are inflammatory in nature and that the giant cells possess osteoclastic characteristics. There is also an assumption that CGCG is a proliferative vascular lesion; hence, some studies reported a response to antiangiogenic therapy. Pharmacological treatments are reported to be effective in restricted clinical trials; however, the accessible long-term study data are limited. Radiotherapy has not been confirmed as a suitable alternative treatment, because irradiation may exacerbate malignancy when used to treat CGCG.[1,24]

Intralesional corticosteroid injection is one of the essential non-surgical management methods for CGCG and has been associated with successful results. The mechanism of action of corticosteroids has not been fully identified. *In vitro* studies of dexamethasone revealed that it acts on osteoclast precursors and encourages their proliferation and differentiation. Administration of intralesional corticosteroids into the bony cyst will result in fibrosis and reossification of the lesion due to inhibited secretion of lysosomal proteases, which inhibits osteoclasts and induces their apoptosis.[9,10]

Jacoway *et al.* first reported this treatment approach in 1988. An additional study conducted by Terry and Jacoway in 1994 included four patients treated with steroids. A steroid injection was administered to all patients every week for 6 weeks. Three of the four patients showed confirmed complete resolution of CGCG, while one patient required further surgical treatment.[10] Limited studies reported promising results using intralesional corticosteroids as an unconventional treatment for CGCG. Marx and Stern used intralesional injections of corticosteroids and reported a complete resolution in 65% of cases. The remaining cases either failed to respond to treatment or recurred aggressively.[10]

Encouraging results were previously achieved using intralesional triamcinolone: 71.43% showed a good response (15 of 21 patients), 19.05% a moderate response (4 out of 21 patients), and a negative response was observed in 9.52% (2 of 21 patients).[25]

The advantages of corticosteroids are their low cost, ease of administration, and conservation of adjacent tissues, especially vital structures. Conversely, they are not suitable for patients suffering from diabetes, peptic ulcers, infections, and the immunocompromised or pregnant women. Furthermore, as the lesion resolves, drug administration becomes difficult and its effectiveness decreases hence. Furthermore, there are suggestions that steroids actually stimulate the growth of some lesions.[10,13,24]

Calcitonin is a 32 amino acid polypeptide hormone composed that is secreted by parafollicular cells (C cells). This hormone stimulates osteoblastic activity and decreases osteoclastic activity, resulting in a consequent reduction of calcium levels in the serum. Recent studies reveled that multinucleated giant cells in CGCG have similar osteoclastic characteristics. Calcitonin may limit the growth of CGCG through its effects on calcitonin receptors.[9,13] The mode of action of calcitonin is not fully understood. Some authors propose that calcitonin aids

in bone deposition and directly inhibits osteoclast activity, thus decreasing bone resorption.[11]

The biological efficiency of non-mammal calcitonin, such as salmon calcitonin, is superior to human calcitonin. Calcitonin is either administered through subcutaneous injection or nasal spray. The nasal spray dose is higher than subcutaneous injection due to the reduced absorption of the drug though the nasal route. Similar results were obtained using either delivery option. Most patients favor the nasal spray treatment to avoid daily injections.[13]

The first study to propose calcitonin use was introduced by Professor Harris in 1993 used calcitonin as an alternative surgical treatment for aggressive CGCG. Patients were injected with daily subcutaneous doses of calcitonin. De Lange *et al.,* 1999, also used calcitonin effectively as a treatment of CGCG using nasal therapy and subcutaneous injections. The disadvantages reported for calcitonin include high cost, daily administration with long-term therapy, and side effects including nausea, vomiting, dizziness, and flushes.[11]

Interferon (IFN) is an antiangiogenic agent. Its use has been reported for various conditions such as hemangiomas and varying malignant tumors. IFN inhibits angiogenesis of lesions through inhibition of fibroblast growth factor. Recent studies postulate that CGCG is a proliferative vascular lesion, which may respond to antiangiogenic therapy. Furthermore, *in vitro* studies revealed that IFN aids bone deposition through stimulation of osteoblastic differentiation.[11,13,21]

Conclusion

Conservative surgical treatment is associated with a high recurrence rate, particularly in aggressive CGCG lesions. Conversely, radical surgical excision with safety margins is the best treatment for aggressive tumors but is associated with high morbidity. Non-surgical treatment demonstrates variable results, with limited cases and restricted long-term follow-up.

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