

Pharmacological Management of Central Giant Cell Granuloma of Jaws - A Narrative Review

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Abstract

Central giant cell granuloma (CGCG) of the jaws is a benign but potentially aggressive osteolytic lesion characterized by multinucleated giant cells and a proliferative stromal component. Conventional management has largely relied on surgical approaches; however, these may be associated with recurrence and significant functional and aesthetic morbidity, particularly in extensive lesions. In recent years, pharmacological therapies have gained attention as alternative or adjunctive treatment modalities. This narrative review aims to summarize the current evidence on the pharmacological management of CGCG, focusing on agents such as intralesional corticosteroids, calcitonin, interferon- α , and denosumab. These therapies target key pathogenic mechanisms, including osteoclastogenesis and angiogenesis, thereby promoting lesion stabilization or regression. Intralesional corticosteroids and calcitonin are commonly used for non-aggressive lesions, whereas interferon- α and denosumab are considered in aggressive or refractory cases. Although promising outcomes have been reported, the response to these treatments is variable, and long-term therapy is often required. Additionally, concerns regarding cost, adverse effects, and the limited availability of high-quality evidence persist. A multidisciplinary and individualized approach remains essential in selecting appropriate therapy. Further well-designed clinical studies are needed to establish standardized treatment protocols and optimize outcomes in the management of CGCG.

Keywords: Central Giant Cell Granuloma (CGCG), Calcitonin, Denosumab, Interferon & Intralesional steroids.

INTRODUCTION

Central giant cell granuloma (CGCG) is a benign intraosseous lesion originally described by Jaffe. It represents a localized reparative process rather than a true neoplasm.^[1] The World Health Organization characterizes CGCG as an intraosseous entity composed of a cellular fibrous stroma containing multiple haemorrhagic areas, aggregates of multinucleated giant cells, and variable amounts of woven bone.^[2] The lesion may demonstrate an aggressive clinical course, manifesting as progressive swelling, pain, rapid expansion, cortical bone perforation, displacement of adjacent teeth, and associated root resorption.^[3] Central giant cell granuloma occurs predominantly in children and young adults under 30 years of age. It shows a higher predilection for the mandible, where it is observed approximately twice as often as in the maxilla.^[4,5,7] In the maxilla, the lesion most commonly arises in the anterior region rather than the posterior region. It occurs more commonly in females, with a reported female-to-male ratio of approximately 1.5:1. The etiology of this lesion remains uncertain; proposed theories include a reactive process, a developmental anomaly, or a benign neoplastic proliferation.^[6] Despite its benign nature, several clinical series have documented relatively high recurrence rates, and a subset of lesions demonstrates distinctly aggressive behaviour. Chuong *et al.* was the first to distinguish aggressive from non-aggressive lesions based on clinical signs, symptoms, and histopathological characteristics (Fig 1). Aggressive lesions are defined by the presence of one or more characteristics, including pain, paraesthesia, root resorption, rapid expansion, cortical bone perforation, and an increased likelihood of recurrence following surgical curettage.^[8] Non-aggressive lesions generally grow slowly with little to no symptoms, do not breach the cortical bone, and are associated with a low recurrence rate. Radiographically, CGCGs present as uni or multilocular radiolucent lesions with well-defined margins. In some instances, however, they may show cortical perforation and associated root resorption.^[9]

Classification of CCGG: Aggressive vs Non-Aggressive		
	Aggressive	Non-Aggressive
1. Major Criteria	• Size $\geq$ 5 cm • Recurrence	• Slow growth • Less recurrence • Size < 5 cm
2. Minor Criteria (Aggressive features):	2. Minor Criteria (Aggressive features): • Root resorption • Recurrence • Tooth displacement • Cortical bone thinning • Cortical bone perforation • Rapid growth • Pain / paresthesia	

Fig 1. Chung *et al* criteria of CGCG

Several treatment modalities have been proposed for central giant cell granuloma, with simple curettage, curettage combined with peripheral ostectomy, and marginal bone resection being the most frequently employed.^[5] The choice of treatment depends on biological behaviour and the extent of the lesion. Non-aggressive lesions are usually treated with conservative surgical approaches such as simple curettage or curettage with peripheral ostectomy, although recurrence remains possible. Aggressive CGCGs characterized by rapid growth, cortical perforation, or root resorption may require more extensive procedures, including marginal or en bloc resection. When surgery carries significant morbidity, medical therapies such as intralesional corticosteroids, calcitonin, interferon- α , bisphosphonates, and denosumab serve as effective alternatives or adjuncts, particularly for large or recurrent lesions.^[3,5,7]

PATHOPHYSIOLOGY

Central giant cell granuloma (CGCG) of the jaws is a benign intraosseous lesion characterised by a proliferative fibrovascular stroma containing numerous multinucleated giant cells that resemble osteoclasts. Although its exact aetiology remains uncertain, current evidence suggests that CGCG represents a reactive or neoplastic process driven by dysregulated osteoclastogenesis.^[10] The stromal mononuclear cells are considered the primary proliferative component and play a pivotal role in lesion development by expressing receptor activator of nuclear factor kappa-B ligand (RANKL), which promotes differentiation and activation of osteoclast-like multinucleated giant cells through interaction with RANK on precursor cells. This leads to increased bone resorption and expansion of the lesion. Additionally, cytokines and growth factors such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF- α) contribute to osteoclastic activity and local bone destruction. Molecular studies have also demonstrated mutations in genes such as SH3BP2, particularly in syndromic cases like cherubism, further supporting the role of abnormal signalling pathways in osteoclast activation.^[11,12]

According to Pogrel *et al*, CGCG is thought to originate from a possible epigenetic event that stimulates proliferation of spindle-shaped stromal cells. These cells secrete cytokines that recruit circulating monocytes and promote their differentiation into osteoclast-like multinucleated giant cells. The giant cells mediate bone resorption, while continued stromal cell proliferation supports lesion growth, ultimately resulting in the development of central giant cell granuloma (CGCG) (Fig 2)

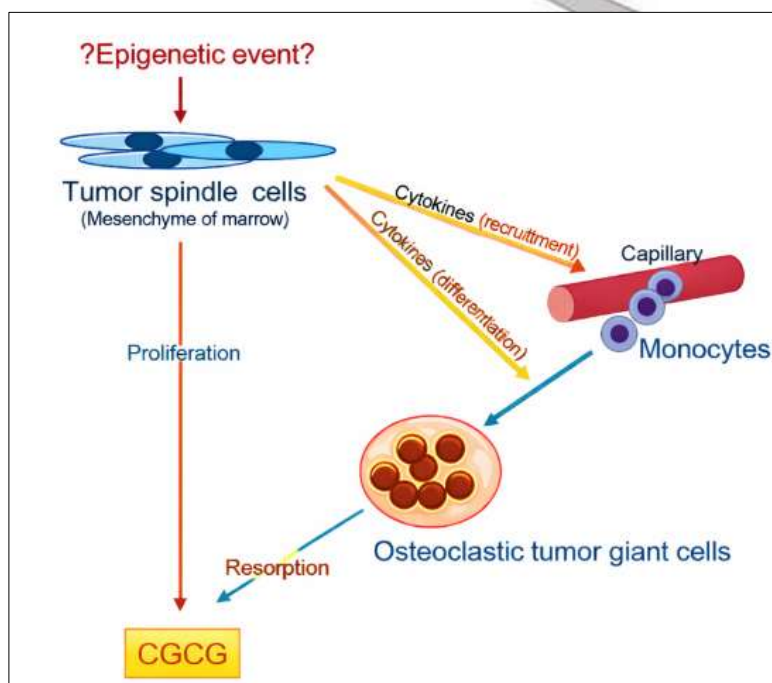


Fig 2. Hypothetical pathogenesis of CGCG by Pogrel et al ^[23] 2004

HISTOLOGICAL FEATURES

Central giant cell granuloma (CGCG) is histopathologically characterized by a highly cellular fibrovascular connective tissue stroma containing numerous multinucleated giant cells that resemble osteoclasts and are unevenly distributed throughout the lesion, often clustering around areas of haemorrhage. The stromal component consists predominantly of spindle-shaped and ovoid mesenchymal cells, which represent the proliferative element of the lesion. Frequent areas of extravasated red blood cells and hemosiderin pigment deposition are observed, indicating repeated hemorrhagic episodes. The lesion is richly vascularized, and occasional trabeculae of newly formed woven bone or reactive bone may be present at the periphery.^[10] Mitotic figures may be seen within stromal cells but are typically normal in appearance, supporting the benign nature of the lesion. In more aggressive variants, increased cellularity, higher density of multinucleated giant cells, and more prominent hemorrhagic areas may be evident, although histological features alone cannot reliably distinguish aggressive from non-aggressive forms. Immunohistochemically, multinucleated giant cells are positive for CD68, consistent with an osteoclastic phenotype, while stromal cells are implicated in osteoclastogenesis through the expression of receptor activator of nuclear factor kappa-B ligand (RANKL).

MANAGEMENT OF CENTRAL GAIINT CELL GRANULOMA

Several management options have been proposed for CGCG. Conventional management of central giant cell granuloma (CGCG) primarily involves surgical intervention, ranging from simple curettage to more aggressive en bloc resection. However, these approaches are associated with variable recurrence rates, reported to be as high as 37.2%,^[13] and may result in complications such as tooth loss and facial deformity, often necessitating complex rehabilitative procedures.^[14] In recent years, there has been a growing shift toward non-surgical management strategies, which include therapies such as calcitonin, intralesional corticosteroid injections, denosumab, and surgical enucleation combined with adjunctive interferon therapy have demonstrated the potential to achieve complete lesion resolution or substantial size reduction, thereby facilitating more conservative surgical approaches when required. (Fig 3)



Fig 3. Management of CGCG

INTRALESIONAL STEROIDS

It is a widely accepted non-surgical treatment modality for central giant cell granuloma (CGCG), particularly in non-aggressive lesions and in patients where surgical morbidity is a concern. The mechanism of action involves inhibition of osteoclastic activity, suppression of lysosomal proteases, and reduction of inflammatory mediators, leading to decreased bone resorption and lesion regression. As this approach may be associated with side effects and the discomfort of a long duration of treatment, some authors have advocated their use only for aggressive lesions (Kaban and Dodson, 2006).

Intralesional corticosteroid therapy for central giant cell granuloma (CGCG) was first introduced by (Jacoway 1988, Terry and Jacoway 1994).^[13] The use of locally administered corticosteroids was originally inspired by the histopathological similarity between CGCG and sarcoidosis however, the exact mechanism underlying its effectiveness in CGCG remains unclear. The therapeutic protocol typically involves weekly intralesional injections of triamcinolone (10 mg/mL) combined in equal proportions with a local anaesthetic, such as 0.5% bupivacaine with epinephrine (1:200,000), administered for a minimum duration of six weeks.^[15]

R.L.M. Nogueira *et al* advocated the use of a biweekly injection of a 1:1 solution of triamcinolone hexacetonide 20 mg/ml & 2% lidocaine/ epinephrine 1:200,000 was adopted. The use of a higher concentration of the drug allows for greater intervals between injections, facilitating the visualisation of bone formation in imaging resources such as cone-beam CT scans and radiographs.^[16,17]

This minimally invasive approach is associated with low morbidity and can be used either as a definitive treatment or as a neoadjuvant therapy to reduce lesion size prior to surgery, thereby minimizing surgical morbidity. It is especially advantageous in children and young adults. However, administration may be challenging in extensive or multilocular lesions, and progressive cortical bone formation during treatment can hinder drug delivery, occasionally necessitating bone perforation to ensure adequate distribution within the lesion.^[17]

CALCITONIN

Immunohistochemical studies have demonstrated that the multinucleated giant cells in CGCG exhibit functional characteristics similar to osteoclasts and possess calcitonin receptors on their cell membranes. The interaction of calcitonin with these receptors induces structural alterations within the cells, ultimately resulting in suppression of cellular DNA synthesis.^[18] Harris (1993) first introduced synthetic human calcitonin as a treatment modality for maxillofacial giant cell lesions. Currently, only salmon calcitonin is widely available, which is considered to be more potent, as reported by de Lange *et al.* (2006) & Pogrel *et al.* (1999). The treatment protocols were comparable, involving either subcutaneous administration of human calcitonin at a dose of 100 IU or the use of salmon calcitonin as a nasal spray at 200 IU per day. The duration of therapy varied depending on the clinical response; however, based on our observations, treatment is generally prolonged, ranging from 6 to 34 months.^[4,10,18 &19]

Calcitonin therapy is considered a conservative and non-invasive approach with minimal side effects, such as nausea, flushing, or nasal irritation. It is particularly indicated in pediatric patients, recurrent lesions, or cases where surgery may compromise vital anatomical structures.

DENOSUMAB

Denosumab has been used in some cases of central giant cell granuloma (CGCG) based on the premise that the multinucleated giant cells resemble osteoclasts. It is a monoclonal antibody that specifically targets the receptor activator of nuclear factor kappa-B ligand (RANKL). Normally, RANKL expressed by osteoblasts binds to its receptor RANK on pre-osteoclasts, promoting their maturation into active osteoclasts responsible for bone resorption. By binding to RANKL, denosumab inhibits this interaction, thereby blocking osteoclast formation and reducing the osteolytic activity.^[18] The commonly followed dosage regimen in adults consists of 120 mg administered subcutaneously on days 1, 8, and 15 (loading phase), followed by 120 mg every 4 weeks, often with concurrent supplementation of oral 500 mg of calcium and 400 IU of vitamin D to prevent hypercalcemia. In pediatric patients, lower weight-adjusted doses (e.g., 60–70 mg) have been reported.^[20] Clinical outcomes include lesion stabilization, increased radiographic calcification, and symptomatic improvement, although recurrence may occur after discontinuation. Potential adverse effects include hypocalcemia, rebound hypercalcemia (especially in children), and a risk of medication-related osteonecrosis of the jaw, necessitating careful monitoring.^[21,22]

INTERFERON ALPHA

Interferon- α (IFN- α) is employed as an alternative or adjunctive therapy in the management of central giant cell granuloma (CGCG), particularly for aggressive, recurrent, or highly vascular lesions where surgery may result in significant morbidity. Its primary mechanism is anti-angiogenic, inhibiting endothelial cell proliferation, reducing lesion vascularity, and indirectly decreasing osteoclast-like giant cell activity through modulation of cytokines and immune responses. It is indicated in rapidly growing, recurrent lesions or those in anatomically critical areas, and may be used alongside surgical procedures.^[24] The commonly used regimen includes interferon- α -2a or α -2b at a dose of 3 million IU/m² administered subcutaneously daily or 3–5 times per week for 6–12 months, depending on response. Clinically, it can lead to reduction in lesion size, stabilization of disease, and decreased intraoperative bleeding, although results are gradual and variable.^[25] Advantages include its non-surgical nature and preservation of vital structures, while limitations involve prolonged treatment duration, high cost, and limited large-scale evidence. Adverse effects commonly include flu-like symptoms, fatigue, weight loss, mood changes, and rarely hepatotoxicity, necessitating careful monitoring.^[25,26] (Fig 4)

Therapy	Advantages	Disadvantages
Intralesional Steroids	- Minimally invasive - Easy to administer - Cost-effective - Reduces lesion size - Can avoid surgery in small/moderate lesions	- Requires multiple injections - Pain/discomfort at injection site - Variable response - Not very effective in aggressive lesions
Calcitonin	- Non-invasive (nasal spray/subcutaneous) - Inhibits osteoclast activity - Safe for long-term use - Useful in children	- Long treatment duration (months–years) - Patient compliance issues - Variable/slow response - Less effective in aggressive lesions
Denosumab	- Targeted therapy (RANKL inhibitor) - Effective in aggressive/recurrent cases - Reduces lesion size and promotes calcification - May avoid major surgery	- Expensive - Risk of osteonecrosis of jaw (MRONJ) - Hypocalcemia - Recurrence after stopping - Requires monitoring
Interferon- α	- Anti-angiogenic effect - Useful in aggressive/highlyvascular lesions - Can be adjunct to surgery	- Systemic side effects (fever, fatigue) - Costly - Requires prolonged therapy - Limited evidence compared to others

Fig 4 Comparison of Advantages & Disadvantages medical management of CGCG

CONCLUSION

Pharmacological management of central giant cell granuloma (CGCG) of the jaws has emerged as an effective alternative or adjunct to surgical intervention, particularly in aggressive, recurrent, or anatomically challenging cases. Agents such as intralesional corticosteroids, calcitonin, interferon- α , and denosumab target different

aspects of the lesion's pathophysiology, including osteoclast activity and angiogenesis, thereby contributing to lesion stabilization, size reduction, and, in some cases, complete regression. These therapies offer the advantage of preserving anatomical structures and minimizing surgical morbidity. However, their use is often limited by prolonged treatment duration, variable response rates, cost, and potential adverse effects. Despite encouraging outcomes, the lack of standardized protocols and high-quality comparative studies necessitates further research. A tailored, case-specific approach combining pharmacological and surgical modalities remains the most effective strategy for optimal management of CGCG.

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