CURRENT CONCEPTS IN CENTRAL GIANT CELL GRANULOMA

*MUHAMMAD RAFIQUE CHATTHA, BDS, MDS (Hons), FCPS
**KAMRAN ALI, BDS, FDSRCS (Eng), FCPS
***ADNAN ASLAM, BDS
****BILAL AFZAL, BDS
****MUHAMMAD ASIF SHAHZAD, BDS

ABSTRACT

Central Giant Cell Granuloma is a nonneoplastic intraosseous lesion, and constitutes a common nonodontogenic pathology to occur in the jaws. It is characterized histologically by cellular fibrous tissue containing multiple foci of haemorrhage, aggregations of multinucleated giant cells, and occasionally, trabeculae of woven bone. Various theories brand it from being a 'reactive' to hamartomatous to a neoplastic lesion. It has now been hypothesized that it is the mononuclear spindle shaped cell which controls the proliferative activity of this lesion, as opposed to the more frequently seen giant cell. It has an increased predilection for mandible and females, in younger age groups. Various radiological and histopathological differential diagnoses should be considered in case of giant cell lesions. Some of the lesions are thought to display a markedly 'aggressive' behaviour and a clinically 'aggressive' model of CGCG has been proposed. Smaller, 'nonaggressive' tumours generally respond very well to conservative enucleation or curettage but recurrence is seen to be common with 'aggressive' lesions. Various medical therapies including injections of intralesional steroids, subcutaneous calcitonin and interferon have been proposed for the treatment of 'aggressive' lesions.

ABBREVIATIONS

CGCG- Central Giant Cell Granuloma  
GCT- Giant Cell Tumour
GCRG- Giant Cell Reparative Granuloma  
PGCG- Peripheral Giant Cell Granuloma
ABC- Aneurysmal Bone Cyst  
TGF- Transforming Growth Factor CT-  
IFN- Interferon  
Computer Tomography
IU- International Units

Key words: Giant cell lesion, nonodontogenic tumours of jaws, central giant cell granuloma, giant cell tumour, calcitonin, triamcinolone, interferon-alpha

Publication Type: Literature review

Dean & Project Director, de, Montmorency Institute of Dental Sciences, Lahore, Pakistan
Assistant Professor, Department of Oral & Maxillofacial Surgery, de, Montmorency College of Dentistry/ Punjab Dental Hospital, Lahore, Pakistan
Resident, Oral & Maxillofacial Surgery, de, Montmorency College of Dentistry / Punjab Dental Hospital, Lahore, Pakistan
Senior House Officer, Oral & Maxillofacial Surgery, Charing Cross Hospital, London, UK
For Correspondence: Prof Rafique Chattha, Dean & Project Director, de, Montmorency Institute of Dental Sciences, Lahore, Pakistan, TeL.+(92) (42) 765 9021, Email: chatha@yahoo.com
INTRODUCTION

Central Giant Cell Granuloma is a commonly seen pathology in the jaws. During the last few years, they have been the centre of an active debate and research among the clinical scientists in the field of Oral & Maxillofacial Surgery and Pathology. Still, the literature does not reach a consensus on the designation of the most correct term for these lesions. They have been labeled as central giant cell granuloma,1 central giant cell 'reparative' granuloma,2 giant cell lesion,’ and 'benign' giant cell tumours4 by various researchers, in the succeeding discussion on these lesions, we have stuck to using CGCG as it is the most frequently used term; readers can also use the more noncommittal term 'giant cell lesion'). This stems from an etiopathogenesis that is not still properly understood.

The true nature of CGCG is unknown, and they have not been able to be ascertained as either a reactive, hamartomatous or neoplastic process. It can be that there is a reactive form (nonaggressive CGCG) and a neoplastic form (aggressive CGCG) and scientists have not been able to devise tools to scientifically separate the two. What is agreed upon at is their clinical behaviour which marks them as progressive lesions that can be aggressive. The origin is unknown, but there are indications that genetic abnormalities may be implicated.6,7

Nevertheless, they are defined by the World Health Organization as an intraosseous lesion consisting of cellular fibrous tissue containing multiple foci of haemorrhage, aggregations of multinucleated giant cells, and occasionally, trabeculae of woven bone.8

Two lesions closely related to CGCG are GCT of long bones and GCRG of small bones and comparative literature review indicates that these lesions are histologically and phylogenetically similar:9-11

ETIOPATHOGENESIS

(Spindle cell induces; giant cell causes CGCG)

The exact process behind pathogenesis of CGCG remains unknown. While the giant cell remains to be the most prominent feature of these lesions, it is actually the mononuclear spindle cell which is the proliferating cell (in cell cycle). This is indicated by the expression of the cell cycle protein Ki-67 in CGCGs. It is believed by some9,12 that this spindle cell (fibroblast or fibroblast-like) recruits monocytes from the vascular system and induces them to differentiate into osteoclastic giant cells through release of cytokines. It has been proposed9 that this spindle cell takes its origin from the mesenchyme of marrow and an epigenetic event (poorly understood) signals them to release cytokines and finally the osteoclastic giant cell causes bone resorption making the hallmark feature of CGCG.

Another hypothesis is that CGCG is a vascular proliferative lesion, which means that angiogenesis under the influence of the tumour cells is required for tumour growth, invasion, and destruction of local tissue. The possible spontaneous involution theory favours this hypothesis.

Are They Really 'Reparative'?

The original description of CGCG branded it 'reparative' in nature and self healing2, and it was supported by Worth13 who reported a series of CGCG that were not surgically treated but followed radiographically and appeared to resolve spontaneously. A biopsy several years later yielded only a fibrous scar. It was further lent support by the data that these lesions are generally found in young people 7 to 25 years old and are rarely found in older people, which further supports a spontaneous healing theory.

However, some authors opine that as the clinical behaviour of many of these lesions is inconsistent with a reparative reaction, the designation central giant cell granuloma or the more noncommittal term, giant cell lesion, is more widely used today.'

CLINICAL FEATURES

Though CGCG is one of the commonest intrabony nondentogenic pathology seen at our centre, it occurs less commonly than its peripheral counterpart (PGCG). Lesions are found predominantly in children and young adults, with most cases (as high as 75%) presenting before 30 years of age. Females are affected more often than males, in a ratio of 2 to 11

CGCG occurs almost exclusively in the mandible followed by anterior maxilla, although isolated cases in facial bones have been reported. They tend to involve
the jaws anterior to the permanent molar teeth, with occasional extension across the midline. Rarely, the lesions involve the posterior jaws, including the ramus and condyle.

CGCG typically produces an asymptomatic painless expansion or swelling of the affected jaw. Cortical plates are thinned, with sometimes perforation but gross soft tissue involvement is rare as often remains limited to its effects on periosteum.

Besides the similar features with the Brown Tumour of Hyperparathyroidism and Cherubism, it has also been associated with Neurofibromatosis-Type I or Neurofibromatosis-Type I with a Noonan-like phenotype.

**Radiological features and related differential diagnoses**

The CGCG may occur initially as a unilocular, cystlike radiolucency, but as it grows larger, it frequently develops an architecture that causes a soap-bubble type of multilocular radioluency. This multilocular soap-bubble appearance is associated with a later presentation, and is one of the commoner radiographic patterns seen in patients with CGCG at our centre. Different researchers have reported the unilocular lesions to comprise 39 to 84% of the total number of CGCGs.

Generally, if the lesion is located anterior to the permanent molars and possibly crossing midline, with a multilocular radiographic pattern with the patient under 30 years of age, a provisional diagnosis of CGCG can be considered. However, if the biopsy proves it to be a case of CGCG, serum chemistry for hyperparathyroidism has to be done to exclude Brown Tumour. Furthermore, in multiple lesions of CGCG, possibilities of cherubism and Noonan syndrome also have to be considered.

The radiological differential diagnosis can include Ameloblastoma, odontogenic keratocyst and Aneurysmal Bone Cyst, and sometimes also odontogenic myxoma and central haemangioma of bone (the latter two often exhibit more of a honey-combed appearance though). For patients in the young age range for CGCG, ameloblastic fibroma, cemento osseous fibroma (early stages), and adenomatoid odontogenic tumor might be added to this list.

The borders of the lesion have been reported as well defined in 56% of cases, poorly defined in 30% of cases, and diffuse in the remaining 14%. They are generally seen to be well delineated, but the margins are generally noncorticated. Whitaker and Waldron showed that though most of the 142 cases of CGCGs in their study were well delineated, only 19% showed well-corticated borders.

**HISTOPATHOLOGY & RELATED DIFFERENTIAL DIAGNOSES**

CGCG is composed of uniform fibroblasts in a stroma containing various amounts of collagen. Haemosiderin-laden macrophages and extravasated RBCs are usually evident, although capillaries are small and inconspicuous. Multinucleated giant cells are present throughout the connective tissue stroma, and they may be seen in patches or distributed evenly. It has been reported that the multinucleated giant cells exhibit characteristics of the osteoclasts phenotype. Others suggest these cells may be aligned more closely with macrophages. In some cases, the stroma is loosely arranged and oedematous; in others, it may be quite cellular. Foci of osteoid may be present, particularly around the peripheral margins of the lesion. Although red cell extravasation can be extensive in some CGCGs, it does not make these lesions fundamentally vascular, as the proliferating cells are not endothelial cells. The red cell extravasation can probably be explained by vascular permeability caused by cytokine release through mononuclear spindle cells.

There are various conditions which 'mimic' the histological presentation of CGCG. The histopathological differential diagnosis includes PGCG, GCT, Brown Tumour of hyperparathyroidism, Cherubism, ABC and Fibrous dysplasia.

PGCG is inseparable histologically from CGCG and it is the clinical manifestation of a peripheral, soft tissue origin in case of PGCG that distinguishes the two.

GCT of long bones can sometimes be differentiated from CGCG because of larger giant cells with more nuclei and a homogenous pattern. Malignancy in GCT of the bone was reported by Bertoni et al. in 1.8% of the cases described. These malignancies can be either...
primary or secondary, including giant cell-rich osteosarcomas, fibrosarcomas, and malignant fibrous histiocytomas. Some authors have regarded the GCT and CGCG as a continuum of the same disease process, by reporting some histopathological pictures of ‘aggressive’ CGCGs which were totally indistinguishable from GCT of long bones.’ This led these scientists to believe that CGCGs and GCTs of the extragnathic skeleton are not distinct and separate entities but rather represent a continuum of a single disease process modified by the age of the patient, location, and possibly other factors that are as yet not clearly understood. There have been a few case reports of a reported GCT occurrence in the jaws that metastasized or locally transformed into a malignancy,” which fail to clearly report a spontaneous malignant transformation of a previously benign CGCG. What is unclear in most of them whether it was a primary bone malignancy (osteosarcoma, chondrosarcoma etc.) with a large giant cell population or a radiation-induced sarcomatous change.

Brown Tumour of hyperparathyroidism is histologically indistinguishable from CGCG. Termed brown as the haemosiderin-laden tissues give it a brown-coloured appearance, it is imperative to exclude Brown Tumour after every histological diagnosis of CGCG. Serum Chemistry consisting of Calcium, Phosphorus and Parathormone profile along with the classic manifestations of stones (renal stones), bones (bone changes), moans (psychic moans) and groans (abdominal groans), are used to assess bone lesions in hyperparathyroidism.

Cherubism is an autosomal dominant disorder with bilateral involvement. Though it may be difficult to distinguish Cherubism from CGCG histologically, Cherubism is seen to have a distinct clinical presentation. It includes multifocal and multilocular cystic lesions of the jaws. Early stages of Cherubism may initially present with a single obvious lesion on one side of the jaw and additional lesions which are quite smaller and rather difficult to detect. Mainly in young patients with large lesions in the posterior region, very thorough radiographic examinations (intraoral occlusal radiography, CT with 3-D reconstruction) can be performed to rule out the possibility of additional lesions being part of an evolving cherubism. As a rule of thumb, cherubism is diagnosed on clinico-pathological grounds. In some lesions, however, the characteristic eosinophilic perivascular cuffing has been noted.

The diagnosis of Aneurysmal Bone cyst (ABC) is made by the identification of sinusoidal blood spaces within the tumour mass, and sometimes by aspiration of blood preoperatively.

Fibrous dysplasia shows only limited foci of giant cells. There are no defined margins radiographically, as it merges imperceptibly with the surrounding bone, at least in maxilla where it is most commonly encountered. Moreover, growth in fibrous dysplastic lesions normally ceases with maturity.

Besides the-cell cycle protein Ki-67 which is over-expressed may lead to a dysregulation of the cell cycle, CGCGs have an overexpression of the MDM2 protein/gene, and it is proposed that it might be the control protein/gene of the proliferating spindle cells. p53 (a protein with antiproliferative and apoptosis-promoting effects) is not known to have an altered expression in cases of CGCGs.

By using DNA microarrays containing 19,200 genes, Carinci et al. identified several genes who expression were significantly up- or down-regulated, and thus presented a genetic profile of CGCG. Those expressed genes cover a broad range of functional activities: cell cycle regulation, signal transduction, and vesicular transport. Those among upregulated genes include AKAP 12 (A-Kinase Anchor Protein 12), STMN1, CNTFR, ELK1 and HSPG (Heparan Sulphate Proteoglycan). Downregulated genes include TM4SF2 (Transmembrane 4 Superfamily 2), DDA3 and MPP3. It is hoped that this genetic portrait can be used to distinguish between ‘aggressive’ and ‘nonaggressive’ lesions by monitoring the relative expression in each of them.

‘Aggressive’ vs. Nonaggressive’ lesions

Some authors have suggested that a more ‘aggressive’ form of CGCG may exist, but efforts to identify such a variant histologically or by immunohistochemistry have not yielded concrete results. It has been shown that ‘aggressive giant’ cell lesions may have a higher relative size index of giant cells, with an increased rate of mitosis and less osteoid formation at the periphery, but the results have varied and have largely remained inconclusive. However, an ‘aggressive model’ of CGCG has been proposed on the basis of clinical and radiological findings which characterizes aggres-
ive giant cell lesions on the presence of pain, paraesthesia, a size of more than 5 cm, rapid growth, tooth displacement or root resorption and cortical bone thinning or perforation.

Recurrent lesions, regardless of size, would be considered 'aggressive', and may form the strongest indicator of 'aggressiveness'. These 'aggressive' type of CGCGs are seen to be commoner in younger patients with a mean age of 10.7 years compared with an average age of 22.5 years for 'nonaggressive' lesions. Kruse-Losler et al. have held tumour size to be the most reliable indicator of the 'aggressiveness' and prognosis. Such clinical features should be accounted for to improve the individual planning of the treatment and thence, follow-up. They are thought to comprise of 19.3% of all CGCGs.

So it could be that there is a neoplastic 'aggressive' variant and a reactive 'nonaggressive counterpart. However, we think that keeping the general health attitudes and other socioeconomic demographic features in mind, patients with smaller, 'nonaggressive', asymptomatic, painless lesions do not seek care early in the course of the disease. Believing the 'reparative' theory, these lesions may 'involute' with time and if some of them 'do not involute', it is often one of the symptomatic feature (such as pain or a grossly enlarged swelling) of the lesion that makes them present to the hospital. 'Aggression' in that scenario, then becomes more duration dependent than the actual clinical behaviour of the lesion. It is therefore, pertinent to mention that tooth displacement with or without root resorption is seen invariably in almost all cases seen at our setting. Incidental finding of a brewing small giant cell lesion is, if at all, a remote possibility.

SURGICAL THERAPY

The more problematic of the CGCG are the histologically similar, clinically aggressive variants and en bloc resection with negative histologic margins might be the gold standard in these lesions. However, the obviously increased morbidity with a more aggressive surgical procedure carries its own disadvantages. Traditionally, surgical curettage has been relied upon as the treatment of choice for CGCGs. Nonaggressive lesions in the jaws respond to simple curettage but aggressive lesions have reported recurrence rates from 11 to as high as 70% after enucleation or curettage. Therefore, for more aggressive lesions, surgical therapy alone may not suffice. In these cases, curettage has been combined with adjunctive therapies comprising of peripheral osteotomy, cryotherapy with liquid nitrogen, use of Carnoy's solution, radiotherapy, or postoperative use of interferon-a, all providing satisfactory to excellent results.

MEDICAL THERAPY

In patients with aggressive lesions, several alternatives to surgery are being investigated. Although a seemingly high success rate is reported with each of the following medical treatment modalities, inherent flaws mark the rationale of their use as none of these therapies targets the spindle cell hypothesized to be the main cell behind the etiopathogenesis of CGCG. Moreover, agents that have the potential to block the action of osteoclasts are currently available. It might also be that the 'reparative' theory holds true and these medical therapies only trigger the regression of these lesions. Multi-centre clinical trials making use of larger samples with similar variables and protocols comparing the different modalities would enable us to reach the most appropriate conservative non-surgical therapy.

1. Intralesional steroids

Intralesional steroids have already been used with success for treatment in unicameral (Simple, Solitary, Traumatic, Haemorrhagic) bone cysts in long bones. It has been demonstrated that there is a steroid-dose-dependent decrease in the secreted level of bone resorbing enzymes (e.g., cathepsin B, cathepsin L, beta glucoronidase, lysozyme, and tartrate-resistant acid phosphatase) secreted by osteoclasts. Moreover, steroids may have an apoptotic action on osteoclasts-like cells. It can also be that steroids may act by suppressing any angiogenic or inflammatory component in the lesion. However, it remains surprising to get good results with steroids that are otherwise known to affect bone resorption and osteoporosis.

Intralesional injections of an aqueous solution of triamcinolone with either 2% lidocaine or bupivacaine, 50% mixture by volume are used. The solution is administered with a 5-cm disposable syringe, delivering a dose of 30 mg in adults and 25 mg in children. The site of injection is gauged by clinically estimating the site where cortical bone is more expanded and thinnest.
and once inside the lesion, small amounts are injected into different areas. These injections are repeated every 3 weeks and the treatment is limited when there is a significant amount of resistance caused by the bone being formed and calcified. No side effects are reported.

ii. Calcitonin therapy

First advocated by Harris in 1993, a number of reports in literature have shown it to be a worthwhile treatment of CGCG. Based on the pretext that as CGCG appears similar albeit histologically to Brown Tumour of hyperparathyroidism, there may be a circulating Parathyroid related hormone that causes these lesions. However, this hormone, if it exists, has not been identified. Even though it may be the stromal cells, or fibroblasts that are the etiologic cells of CGCG and the giant cells themselves may be secondary or reactive, agents targeting the stromal cells are currently unavailable. On the other hand, calcitonin receptors have been identified on the giant cells of the lesion, antagonizing osteoclastic bone resorption. Calcitonin therapy takes longer to affect CGCGs. On the other hand, patients with aggressive CGCG especially with those in a younger age group with associated pain or paraesthesia require a more immediate response and a possible criticism of calcitonin therapy is its delayed effect.

A suggested treatment regimen is 100 IU of calcitonin (salmon or human) per day, subcutaneously till it is ascertained radiographically that there is no further resolution of the disease. This was seen in one study to be between 19 and 21 months. Intranasal route has also been suggested, although the absorption of the nasal spray is known to be erratic and can vary between 20% to 100% absorption.

iii. Interferon-2a

In 1980, interferon alpha-2a was found to inhibit angiogenesis through a series of experiments in the laboratory. Interferon alpha has already been used to treat patients with metastatic or locally advanced, nonresectable giant cell lesions of the long bones that have recurred after previous surgery or radiation therapy. This therapy derives its rationale from the hypothesis that as CGCG is a tumour that is characterized by proliferation, marked vascularity, and bone resorption, and thus it is feasible to consider it as an angiogenic disease. Interferon also appears to encourage bone formation through stimulation of osteoblasts and preosteoblasts and inhibit bone resorption.

After necessary preoperative workup, a nerve- and teeth-preserving enucleation is carried out. Interferon alpha-2a or interferon alpha-2b is started 48 to 72 hours postoperatively at a dose of 2,000,000 - 3,000,000 units/m² administered once daily subcutaneously. During treatment, patients are evaluated for IFN side effects, including fever, flu-like symptoms, lethargy, postnasal drip, skin rash, and hair loss. Haematocrit, haemoglobin, white blood cell and platelet counts, and liver function tests are obtained every 6 weeks (sooner if indicated), and the primary tumor site is monitored by clinical examination and radiography. In cases of neutropenia or thrombocytopenia, the therapy is stopped or dose is reduced. Periodic radiographic assessment is done to monitor assessment of resolution of the lesion. When the defect appears to be filled in with bone on the panoramic radiograph, a confirmatory CT scan is done. The mean duration of treatment was seen to be 7.3 +/- 0.8 months, and no patients exhibited growth of the lesion during the treatment.

It is also suggested that Interferon-2a combined with bisphosphonates might further improve the treatment of giant cell lesions.

iv. Other emerging therapies

It has been suggested that immunohistochemical staining for glucocorticoid and calcitonin receptors on the mononuclear or multinucleated cells in giant cell lesions can help in choosing most appropriate conservative, medical therapy.

It has also been shown that osteoclastogenesis is under the influence of osteoprotegrin (inhibition of bone resorption) and its antagonist osteoprotegrin ligand (initiation of resorption) via osteoclasts receptor proteins that have been found to be present in CGCG and are known as RANK (Receptor Activator of Nuclear Factor-kB). Osteoprotegrin as a pharmacologic agent has been proposed to inhibit bone resorption which makes a similar rationale of use to calcitonin. However, the utility of osteoprotegrin is untested, and the systemic effects have not been evaluated.
Other agents such as bisphosphonates and TGF-beta, that are associated with bone metabolism deserve assessment (not yet tested in giant cell lesions).

The future holds promise for the therapy of CGCG, as with ongoing clinical and laboratory research on focus of gene and protein expression of these tumours can lead to identification of therapeutic targets.

CONCLUSION

The relatively high frequency of CGCGs in the population makes it important for clinicians to understand their clinicoradiologic presentation and clinical behaviour. Classifying these lesions as ‘aggressive’ or ‘nonaggressive’ can help in choosing the most appropriate treatment. We suggest that the ‘nonaggressive’ counterparts can be managed effectively with conservative surgical approach. However, in cases of ‘aggressive’ lesions seen more often in a younger population, instead of more morbid surgical procedures, an alternative or adjuvant therapy can be relied upon.

REFERENCES


5 Buresh CJ, Seemayer TA, Nelson M, NeJJR, Dorfman HD, Bridge J. t(X;4) (q22;q31.3) in giant cell reparative granuloma. Cancer Genet Cytogenet 1999; 115: 80-1.


