Central Giant Cell Granuloma: Uncommon Yet Important

Dr. Mohammad Ehtisham1, Dr. Prabhjot Kaur2, Dr. Sheeba Nissar3, Dr. Firdous Wani4, Dr. Iram Jan5

1P.G Student, Department of Oral Pathology and Microbiology, Institute of Dental Studies and Technologies, Kadrabad, Modinagar, India.
2P.G Student, Department of Oral Pathology and Microbiology, Swami Devi Dayal Dental College & hospital, Barwala (Haryana) India
3P.G Student, Department of Periodontics & Oral Implantology, Shree Bankey Bihari Dental College&ResearchCentre, Ghaziabad, (U.P.), India.
4P.G Student, Department of Oral Pathology and Microbiology, Shree Bankey Bihari Dental College & ResearchCentre, Ghaziabad, (U.P.), India.
5P.G Student, Department of Oral Medicine & Radiology, Shree Bankey Bihari Dental College & ResearchCentre, Ghaziabad, (U.P.), India.

Abstract: The central giant cell granuloma is an uncommon, benign and proliferative pathological condition accounting for less than 7% of all benign lesions of the jaws whose etiology is not clearly explained. 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 an increased predilection for mandible and females, in younger age groups. Some of the lesions are thought to display a markedly 'aggressive' behavior and a clinically 'aggressive' model of CGCG has been proposed. Smaller, 'nonaggressive' tumors generally respond very well to conservative enucleation or curettage but recurrence is seen to be common with 'aggressive' lesions. The clinical differential diagnosis for a solitary or multilocular CGCG includes ameloblastoma, GCT, granuloma, odontogenic myxoma, and odontogenic keratocyst. Various medical therapies including injections of intralesional steroids, subcutaneous calcitonin and interferon have been proposed for the treatment of 'aggressive' lesions. This article will review current concepts in relation to etiology, histopathology, diagnosis, and management of giant cell lesions of the jaws.

Keywords: Central Giant Cell Granuloma, Giant-cell reparative granuloma, Granuloma

I. Introduction

Central Giant Cell Granuloma (CGCG) is rare benign pathology seen in the jaws. CGCG of the jaws reflects a non-neoplastic and localized benign proliferation, which may sometime, shows aggressive osteolytic behavior. It is typically characterized by destruction of the bone, facial asymmetry and displacement of tooth and tooth germs, especially in younger patients5. Neville et al classified this lesion to be a non-neoplastic lesion and the World Health Organization (WHO) considered it as a lesion related to bony structures, not a tumor, even though its clinical behavior and radiographic features are often related to a benign tumor2. There are two lesions which are closely related to CGCG are Giant cell of tumor (GCT) of long bones and Giant cell reparative granuloma(GCRG) of small bones. Various studies concludes that these lesions are histologically and phylogenetically similar5.

II. Definition

The World Health Organization has defined it as “an intraosseous lesion consisting of cellular fibrous tissue that contains multiple foci of haemorrhage, aggregations of multinucleated giant cells and occasionally trabeculae of woven bone”2.

Chuong et al stated that aggressive giant cell lesions were defined as lesion exhibiting size greater than 5 cm as and show rapid growth, tooth displacement, root resorption, perforation or thinning of cortical bone, recurrence after curettage, equal to or greater than 5 cm and/or that recurred after curettage5.

What’s in the Name?

Jaffe in 1953, described CGCG as a “Giant-cell reparative granuloma”. The designation “reparative” has been deserted since due to the differentiation of central giant cell lesions between aggressive and non-aggressive lesions. Still, the literature does not reach on an agreement that most correct term used for these lesions5. There are various terms for this lesion like central giant cell granuloma, central giant cell reparative granuloma, giant cell lesion, and benign giant cell tumors by various authors, in the subsequent discussion.
about this lesion, we will use the CGCG as it is the most frequently used term; readers can also use the more equivocal term 'giant cell lesion'. The term CGCG has been preferred to be used to explain both for a reactive response to hemorrhage or trauma, and a neoplasm. These days it is designated as 'central giant cell granuloma' or 'central giant cell lesion'.

III. Clinical Features

CGCG is intrabony non-odontogenic pathology and its occurrence is less common than its counterpart peripheral giant cell granuloma (PGCG). Lesions are chiefly reported in children and young adults, with mostly lesions (as high as 75%) representing before 30 years of age. Often females are more affected in comparison to males, in a ratio of 2-11. High estrogen conditions, such as pregnancy, have been connected in CGCL proliferation, lesions, however, rarely express estrogen receptors. CGCG occurs predominantly in the mandible followed by anterior maxilla, although isolated cases in facial bones also have been reported. It tend to involve the jaws anterior to the permanent molar teeth and sometimes extended across the midline. In a very few incidences, the lesions involve the posterior jaws, including the ramus and condyle.

Typically CGCG represented as an asymptomatic pain-less swelling of the affected jaw. Thinning or perforation of cortical plates but rarely involves gross soft tissue as often remains limited to its effects on periosteum. Despite the lesion have expansive and invasive nature; it does not usually involve perineural sheets so paresthesia is usually not observed in these patients. Even though the nature of this lesion is considered benign, there are still some studies in literature reported metastasis. Osteosarcoma or fibrosarcoma have been reported as malignant transformations in some lesions.

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

<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE: &lt; 30 Years, Children &amp; Young adults</td>
</tr>
<tr>
<td>Gender: Female &gt; Male</td>
</tr>
<tr>
<td>Site &amp; Location: Mandible&gt; Maxilla, Anterior to Molars</td>
</tr>
<tr>
<td>Incidence: Rare benign tumour, 7% of tumors of jaws</td>
</tr>
<tr>
<td>Less common than its peripheral counterpart.</td>
</tr>
<tr>
<td>Associated Condition: Brown Tumour of Hyperparathyroidism, Cherubism, Jaffe-Campanacci Syndrome, Neurofibromatosis-Type I</td>
</tr>
</tbody>
</table>

IV. Etiopathogenesis

(Origin cell induces; giant cell causes CGCG)

Origins: Unknown, but genetic abnormalities may be implicated. The exact reason behind the pathogenesis of CGCG remains unknown. It was thought that there is a reparative response to intrabony haemorrhage and inflammation, CGCG was once considered as a reactive lesion. CGCG is best classified as a benign neoplasm because of its unpredictable nature, occasionally showing aggressive behavior and its possible relationship to the giant cell tumor of long bones. The histogenesis of CGCG of the jawbones remains controversial, as speculations are still debated regarding the possibility that it represents a reactive, an inflammatory, an infective, or a neoplastic process.

Vascular hypothesis suggests that CGCG belongs to the spectrum of mesenchymal proliferative vascular primary jaw lesions. Angiogenesis is a phenomenon modulated by several cytokines and growth factors. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are the most potent inducers of angiogenesis and have a synergistic effect. It is produced and released from activated monocytes and macrophages.

Perhaps the most widely held view is that the initial CGCG is an endosteal hemorrhage. In 1962, Kramer stated that if the process is concerned with the repair following hemorrhage, then the repair follows a peculiar pattern complicated by repeated new haemorrhages. El-Labban (1997) studied CGCG and confirmed Kramer’s statement. She observed that majority of vessels showed intravascular fibrin thrombi and endothelial cell damage with gaps in the cell walls. Plasma, erythrocytes and fibrin were seen subendothelialy. She also noted that a giant cell had sealed one of the gaps in a vessel. The author suggested that the presence of
the giant cell closed the gap and stopped haemorrhage and the main purpose for the presence of the stromal cells is the repair not only of the hematomas but also of its contributing vessels.

The primary tumor cells of CGCGs are fibroblasts. Secondary cells, which are microscopically the most prominent, are multinucleated giant cells. Accessory cells, seen in considerably smaller numbers, include macrophages, factor XIIIa+ dendrocytes, and endothelial cells. The fibroblasts make up the proliferative component of CGCGs, since they express proteins that are indicative of cells in the cell cycle. Tumor fibroblasts are also believed to be responsible for recruitment and retention of monocytes and subsequently for transformation into multinucleated giant cells 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 some 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 proposed 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 favors this hypothesis.

V. Radiological Features

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

VI. Histopathology

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.

VII. Aggressive’ Vs. Nonaggressive’ Lesions

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. However, there are no histological differences between the aggressive and non-aggressive varieties what is agreed upon is that their clinical behavior, which marks them as progressive lesions that can be aggressive. Chuong et al suggested that the term ‘nonaggressive’ and ‘aggressive’ should be used with CGCG based on clinical behavior. When CGCG is a slow-growing lesion, it can be asymptomatic and discovered on a routine radiographs, while pain and facial swelling characterize the rapidly expanding aggressive variety.
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 aggressive giant cell lesions on the presence of pain, paresthesia, 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' types 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 behavior 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.

VIII. Differential Diagnosis

There are various conditions, which 'mimic' the histological presentation of CGCG. The histopathological differential diagnosis includes PGCG, GCT, Brown Tumour of hyperparathyroidism, Cherubism, Aneurysmal bone cyst 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 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 that 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 per-formed 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.

<table>
<thead>
<tr>
<th>DIFFERENTIAL DIAGNOSIS</th>
<th>S. NO.</th>
<th>Lesion</th>
<th>Striking Features</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGCG</td>
<td></td>
<td>Distinctive with multinucleated giant cells spread throughout the lesion but often focal in distribution around areas of possible hemorrhage.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. GCT</td>
<td></td>
<td>Larger giant cells</td>
<td>Unusual in the jaw, More aggressive nature and High degree of recurrence</td>
<td></td>
</tr>
<tr>
<td>2. Brown Tumour of hyperparathyroidism</td>
<td></td>
<td>Haemosiderin-laden tissue</td>
<td>Calcium, Phosphorus and Parathormone profile, Classic manifestations: Stones (renal stones), Bones (bone changes), Moans (psychic moans) and Groans (abdominal groans)</td>
<td></td>
</tr>
<tr>
<td>4. ABC</td>
<td></td>
<td>Sinusoidal blood spaces within the tumour mass, Sometimes by aspiration of blood preoperatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Fibrous dysplasia.</td>
<td></td>
<td>No defined margins radiographically, as it merges imperceptibly with the surrounding bone only limited foci of giant cells</td>
<td>Presence of Chinese figure like trabeculae of woven &amp; immature bone with proliferating fibroblastic stroma. Growth normally ceases with maturity</td>
<td></td>
</tr>
</tbody>
</table>

Differences Between PGCL And CGCL

<table>
<thead>
<tr>
<th>Etiology</th>
<th>PGCL</th>
<th>CGCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature</td>
<td>Non-neoplastic</td>
<td>Non-neoplastic</td>
</tr>
<tr>
<td>Site</td>
<td>Extraosseous: Gingiva and alveolar ridge</td>
<td>Intraosseous</td>
</tr>
<tr>
<td>Clinical behavior</td>
<td>Little aggressive</td>
<td>More aggressive</td>
</tr>
<tr>
<td>Recurrence potential</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Histology</td>
<td>Similar to CGCL</td>
<td>Similar to PGCL</td>
</tr>
<tr>
<td>Origin of giant cells</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Growth</td>
<td>Exophytic, slow</td>
<td>Endophytic, rapid</td>
</tr>
<tr>
<td>Bone resorption</td>
<td>Rare</td>
<td>Present</td>
</tr>
<tr>
<td>Dental root resorption</td>
<td>Rare</td>
<td>Present</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgical</td>
<td>Pharmacological and/or surgical</td>
</tr>
</tbody>
</table>

IX. Immunohistochemistry

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.

X. Genetics

In a simplified overview of osteoclastogenesis, bone marrow-derived osteoclast-precursor cells are committed to osteoclastic differentiation by intranuclear buildup of NFATc1 (nuclear factor of activated T cells). NFATc1 is amplified both by the presence of SH3BP2 protein and by stimulation of RANK (receptor activator of NF-jb), which is expressed on the osteoclast-precursor cell surface. RANK is stimulated by the RANK ligand (RANKL), which is expressed by osteoblasts. OsteoblasticRANKL expression is in turn stimulated by parathyroid hormone (PTH). Thus, the end result of PTH secretion is osteoclast proliferation, bone resorption, and calcium liberation. Pathologically sustained PTH elevation causes BTOH, which consists of mononuclear osteoclast-precursors and multinucleated differentiated osteoclasts.
Central Giant Cell Granuloma: Uncommon Yet Important

The other giant cell lesions may also represent pathologic variations of osteoclastogenesis, though their mechanisms are less well understood. CGCL and PGGC are composed of mononuclear stromal cells that mimic osteoclast-precursors and MGCs that mimic differentiated osteoclasts. NFATc1 expression is also increased in both of these lesions. They differ, however, in that CGCL arises centrally within bone, while PGGC is a gingival soft tissue lesion. The bilateral CGCLs of Cherubism are caused by an activating germline mutation of the SH3BP2 gene (chromosome 4p16.3). Sporadic SH3BP2 mutations have been identified in CGCL, but not in PGGC.

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. These expressed genes cover a broad range of functional activities: cell cycle regulation, signal transduction, and vesicular transport. Those among upregulated genes include AKAP12 (A-Kinase Anchor Protein 12), STMN1, CNTFR, ELK1 and HSPG (Heparan Sulphate Proteoglycan). Down-regulated 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.

XI. Treatment & Prognosis:
Conventional management is by curettage or resection, which may be associated with loss of teeth, or in the younger patient, developing tooth germs. Non-surgical treatment includes systemic calcitonin therapy and intralesional injections with corticosteroids.

XII. Recurrence
A somewhat higher rate of recurrence has been reported in lesions arising in children and young teens. Lesions with aggressive clinical features also exhibit a tendency to recur.

XIII. Conclusion
CGCG though a rare disease of head and neck sometimes shows an aggressive behavior and hence correct diagnosis is established by correlating clinical and histological features. Surgery is the traditional and accepted treatment but may be combined with local injection of steroids and calcitonin to avoid recurrence.

REFERENCES


