

# Aggressive central giant cell granuloma mimicking giant cell tumor

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## ABSTRACT

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**Introduction:** Giant cell granulomas (GCGs) of the jaws are lesions that arise either peripherally in periodontal ligament, mucoperiosteum, or centrally in the bone. Histologically, both peripheral and central giant cell granuloma (CGCG) are characterized by the presence of numerous multinucleated giant cells (MGCs) in a prominent fibrous stroma. CGCG are further categorized into aggressive and non aggressive variant. **Case Report:** The present case highlights the difficulty in diagnosing aggressive CGCGs from Giant cell tumors (GCT), with which they share similar histopathology, behaviour and prognosis. **Discussion:** The recurrent nature of the present case and the extensive destruction caused in the hard and soft tissues suggests the possibility of true ‘tumors’ (Giant cell tumors) existing in the jaw.

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## INTRODUCTION

Giant cell granulomas (GCGs) of the jaws are lesions that arise either peripherally in periodontal ligament, mucoperiosteum, or centrally in the bone. Histologically, both peripheral and central variants of giant cell granuloma are characterized by the presence of numerous MGCs in a prominent fibrous stroma. Foci of hemorrhage with liberation of hemosiderin pigment and newly formed osteoid or bone are often seen. The MGCs are concentrated in the areas of hemorrhage and present adjacent to blood vessels. Jaffe (1953) distinguishes CGCG from GCT of the bone on clinical and histologic grounds and suggested that MGCs in CGCG represent a phagocytic response to hemorrhage [1]. CGCG affects females more often than males, in a 2:1 ratio and is seen most frequently under the age of 30 years. One study of 38 patients shows 74% to be less than 30 years of age and 61% to be less than 20 years of age. The lesion commonly presents as a solitary radiolucency with a multilocular appearance or less commonly, a unilocular appearance. It is more prevalent in the anterior than the posterior jaws, often crossing the midline, and the mandible is more commonly affected than the maxilla. This lesion has also been reported in the small bones of the hands and feet. The behavior of CGCG is variable, most commonly producing an asymptomatic expansion of

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the jaws. However, it can be clinically aggressive, associated with pain, osseous destruction, cortical perforation, root resorption, and recurrence. Cases of CGCG occurring with neurofibromatosis (type1), Noonan-like syndrome, or both have been reported. The treatment of CGCG includes simple curettage or curettage with peripheral ostectomy; resection for lesions of the maxilla or paranasal sinuses has been advocated as the thin bony cortices and sinuses do not provide a good anatomic barrier. Corticosteroids and calcitonin are used for non-surgical management [2]. The current report highlights a case of recurrent and aggressive form of CGCG in the mandible.

### CASE REPORT

A 22-year-old man presented with a swelling in the left ramus of the jaw two years ago. Examination revealed a unilocular radiolucent lesion, with a scalloped inferior border. (Figure 1) A CT scan revealed a well defined hyperdense expansion of the soft tissue seen in the region of and below the left coronoid process of mandible, with suspicion of sclerosis. A partial mandibulectomy was performed and a reconstruction plate with a mini plate at the anterior region along with a fibular graft in the jaw was inserted to repair the defect. (Figure 2) Light microscopy of the biopsy specimen showed changes consistent with a central giant cell granuloma.

After one year, the patient, now 23 years old, complained of a recurrent swelling in the same region. An intraoral growth in the left buccal mucosa was identified at the level of the occlusal plane. (Figure 3A) The resection specimen upon histopathological examination was diagnosed as a recurrent central giant cell granuloma. The first molar along with the premolars were removed, the region was curetted and a new reconstruction plate was inserted.

A year later, the patient now 24 years old, was referred to the Department of Oral Surgery with the complaint of pain and recurrent swelling of the left jaw. The patient had difficulty in opening his mouth. There was no paraesthesia and both medical and familial histories were non contributory. We observed a lesion extending from the corner of the mouth to the anterior aspect of the left tragus, which measures 4 x 4 cm, was irregular in shape with a rough texture. The swelling was hard in consistency, showed no secondary changes and was non tender on palpation. Intraoral examination revealed an exophytic growth present posteriorly near the junction of the buccal mucosa and pterygomandibular fossa region, at the level of the occlusal plane, sized 1 x 1.5 cm and soft in consistency. It had a smooth surface with no fluctuation on palpation. (Figure 3B)

In a CT scan an expansile destructive mass (4.3 x 3.8 x 4.3 cm) was observed in the left coronoid process,



Figure 1: Orthopantomograph showing a unilocular radiolucent lesion in the ramus of left jaw. The inferior border of the lesion is scalloped.



Figure 2: Orthopantomograph showing the reconstruction plate repairing the defect in the left jaw.



Figure 3: A) Intraoral photograph showing growth in the left buccal mucosa; B) Intra oral photograph depicting exophytic growth in the junction of the left pterygomandibular fossa region and buccal mucosa.

with thin residual septae of osseous density observed in the soft tissue. This soft tissue mass showed near isodensity compared to the adjacent muscles of the left masseteric space. The lesion expanded the insertion of the left temporalis muscle and bulged anteriorly into the left buccal space and posteriorly into the left condylar head and neck and left parotid gland. Medially, the lesion led to mild pressure erosion with thinning of the buccal cortex of the left maxillary tuberosity and bulged against the left medial pterygoid muscle. (Figure 4) Routine haemogram and urine examination were normal. On the basis of clinical and radiological examination a provisional diagnosis of CGCG was made. The serum chemistry of calcium, phosphorous, parathyroid hormone was normal, there by excluding the possibility of hyperparathyroidism.

Surgery was performed by a submandibular incision at the site of the previous scar, with the removal of the reconstruction plate, mini plate and graft, along with the condyloid process. The tumor mass and surrounding normal tissue was removed to obtain a clear margin. A careful and thorough curettage of the residual bone cavity was also performed. The defect was repaired by a reconstruction plate attached to a condylar graft.

Histopathological examination of excised specimen revealed evenly dispersed (2 - 3 / HPF) giant cells each having 2-8 nuclei in them, in close approximation with proliferating blood vessels admixed with areas of haemorrhage. (Figure 5) The tumor mass had infiltrating margins and residual bony spicules were present at the periphery. Even the bone graft attached to the condyle contained presence of tumor giant cells (Figure 5, Inset).

The patient is being followed for any further changes.

## DISCUSSION

CGCG is a nonneoplastic proliferative lesion of unknown etiology. The etiology and pathogenesis of CGCG of jawbones has not been clearly established. However, it has been suggested that the lesion results from an exacerbated reparative process to previous trauma and intraosseous haemorrhage which triggers the reactive granulomatous process [3]. Donoff and Rosenberg discussed a case of an uncomplicated extraction for pericoronitis and suggest that the local changes in the blood flow to the bone and bone dysplasia are possible etiologic factors [4]. Unal et. al. [5] presented a 12 year-old girl with CGCG in the mandible occurring after a molar tooth extraction and suggested that trauma as an etiology. Association of t(X;4)(q22;q31.3) with GCG has been reported.

Although CGCGs are benign osseous lesions, some authors separate CGCG into two types, referring to its clinical and radiographic features: (a) Nonaggressive lesion which are slow growing and asymptomatic,



Figure 4: CT scan showing the extent of the lesion during the second recurrence.

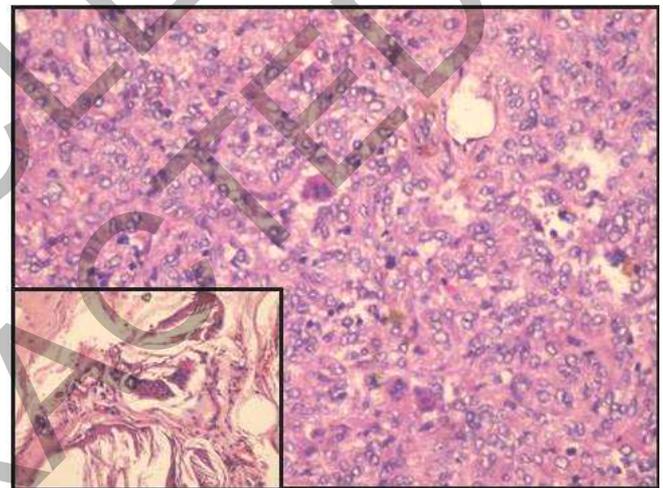


Figure 5: Photomicrograph showing giant cells in a vesiculated fibroblast connective tissue stroma (H & E, X40). (Inset) Photomicrograph showing presence of giant cells near the condylar region (H & E, X40).

without cortical resorption or root perforation in affected teeth, which do not recur; and (b) Aggressive lesions, which are usually found in younger patients, are painful with rapid growth, often cause cortical perforation and root resorption and has a tendency to recur [6]. Predicting the behaviour of CGCGs that will exhibit a higher risk of recurrence after treatment has been problematic. The rate of recurrence varies between 13-49% [7]. Whitaker and Waldron reported a mean interval between diagnosis and initial treatment and treatment of a recurrence of 21 months, with very few recurrences two years after initial treatment. The present case recurred twice within 2 years of the initial surgery. The most reliable factors related to an increased risk of recurrence include clinical activity of lesions (72% of recurrence in the aggressive forms, 3%

of recurrence in the nonaggressive forms), younger patients, demonstrated perforation of cortical bone and tumour size [8]. There have been studies suggesting that the greater functional surface area occupied by giant cells and larger relative size of giant cells may identify tumours with aggressive behaviour. Recently, Kruse-Loser et al also demonstrated that the aggressive variant of CGCG presented a high number of giant cells, an increased mitotic activity, and a high fractional surface area [6]. However, other studies have not been able to predict the clinical course of CGCGs from known histological or immunohistochemical features [9].

We reviewed 10 archival cases of CGCGs from our department which were nonaggressive and non-

recurrent, the demographical information, location, radiographic features and histopathological features of which are summarized in Table 1.

The present case showed 2-3 giant cells per high power field, which was less compared to that seen in our archival cases. The connective tissue was minimal, but with a high cellularity and a vesiculated fibroblastic population. The nonaggressive cases of CGCG showed a minimal - moderate cellularity and a non vesiculated fibroblast population. The vascularity in the present case was minimal, which was not a differentiating factor, as cases in the archives showed a varied vascularity from minimal to marked.

The radiological appearance of CGCG is variable with either unilocular or multilocular radiolucency,

Table 1: The demographic information, location, radiographic features and histopathological features of 10 nonaggressive central giant cell granulomas are as follows

Patient No.	Age	Sex	Location	Radiographic features	Histopathological features
1	30	F	Maxilla (anterior)	Unilocular radiolucency	Number of giant cells: 7-10/ hpf Connective tissue cellularity: minimal Vascularity: moderate
2	17	M	Maxilla (posterior)	Unilocular radiolucency	Number of giant cells: 6-10/ hpf Connective tissue cellularity: minimal Vascularity: marked
3	15	F	Mandible (posterior)	Unilocular radiolucency	Number of giant cells: 4-7/ hpf Connective tissue cellularity: moderate Vascularity: minimal
4	22	F	Mandible (anterior)	Unilocular radiolucency with few trabeculations	Number of giant cells: 1-6/ hpf Connective tissue cellularity: minimal Vascularity: minimal
5	24	M	Mandible (posterior)	Multilocular radiolucency	Number of giant cells: 1-10/ hpf Connective tissue cellularity: minimal Vascularity: marked
6	30	F	Mandible (posterior)	Unilocular radiolucency with specks of radio-opacity	Number of giant cells: 2-10/ hpf Connective tissue cellularity: moderate Vascularity: minimal
7	24	M	Mandible (posterior)	Unilocular radiolucency with scalloped borders	Number of giant cells: 8-10/ hpf Connective tissue cellularity: minimal Vascularity: moderate
8	40	F	Mandible (anterior)	Unilocular radiolucency	Number of giant cells: 6-12/ hpf Connective tissue cellularity: minimal Vascularity: marked
9	34	F	Mandible (posterior)	Multilocular radiolucency	Number of giant cells: 5-12/ hpf Connective tissue cellularity: minimal Vascularity: marked
10	29	M	Mandible (anterior)	Unilocular radiolucency	Number of giant cells: 6-10/ hpf Connective tissue cellularity: minimal Vascularity: moderate

well- or ill-defined with variable expansion and destruction of the cortical plate. The final diagnosis eventually rests on histopathology since clinical and radiological features are not specific. Some lesions are more destructive with a marked tendency to recur and thus require more radical treatment [10].

CGCG is composed of two distinct populations of cells viz. multinucleated giant cells and spindle shaped stromal cells. The latter are thought to be proliferating tumour cells based on available evidence [11]. These are osteoblast like cells with similar functions. They induce osteoclast formation from mononuclear blood cells via RANK- RANKL interaction. RANKL (receptor activator of nuclear factor kb ligand) present on stromal cells influences the differentiation of giant cells from RANK expressing mononuclear cells [12].

Of the similar appearing entities GCT is most difficult to differentiate from CGCG without clinical and histological aids. CGCG generally occur in younger subjects than GCT. Histologically, CGCG have a hemorrhagic background with presence of plump bland fibroblasts, haemosiderin and fewer giant cells with smaller number of nuclei which are less uniformly distributed. While in case of GCT, giant cells are uniformly scattered and have a larger number of nuclei and absence of fibroblasts and hemorrhage. Diffuse sheets of large giant cells and polygonal mononuclear cells seen in GCT are lacking in CGCG. Deposition of osteoid is occasionally observed in CGCG which is lacking in GCT. Cystic areas (the Aneurysmal Bone Cyst component) are less common as compared to GCT. Differentiation from brown tumor is based mainly on clinical and laboratory data as well as differences in the age of onset and multiplicity of lesions [13].

Immunohistochemical studies on CGCG have helped to establish the lineage of the cells, but not to predict the aggressiveness of the lesion. Supporting the theory that the multinucleated giant cells are derived from macrophages is the immunoreactive response to muramidase,  $\alpha$ -1antichymotrypsin, and  $\alpha$ -1antitrypsin. Aggressive and nonaggressive CGCGs stained for antibodies to CD34, CD68, factor XIIIa, and smooth muscle actin, prolyl 4-hydroxylase, Ki-67, p53 protein, RANK, and glucocorticoid receptor alpha have revealed no phenotypic differences between the types. Calcitonin receptor expression, however, has been found to exhibit a statistically significant difference with more expression in the aggressive type of CGCG [14]. The management of CGCG will depend on the clinical and radiographic findings. Generally, curettage of well-defined localized lesions is associated with a low rate of recurrence. In extensive lesions with radiographic evidence of perforation of cortex, a more radical excision is mandatory. In such cases even partial maxillectomy or mandibulectomy has to be done. The medical management of CGCG as an adjunct to surgery includes treatment with steroids or calcitonin which inhibits osteoclastic activity [15].

Interferon-alpha appears useful in the management of aggressive CGCG, presumably due to its

antiangiogenic effects. Bisphosphonates have been administered intravenously in CGCG with promising results [16].

## CONCLUSION

Although extensive literature has been made available to the readers who envisage a keen interest in CGCG of the jaw, clarity to this entity with respect to terminology, behaviour and its adjunctive nature to the GCT occurring in long bones has rarely been lucid in its understanding. The concomitant presence or initiation of this entity with various other diseases like Aneurysmal bone cyst and also its histopathological similarities to diseases associated with hormonal imbalances like hyperparathyroidism/Browns tumor has compelled researchers to question its de-facto existence.

The present case highlights the difficulty in diagnosing aggressive CGCGs from Giant cell tumors (GCT) with which they share similar histopathology, behaviour and prognosis. The recurrent nature of the present case and the extensive destruction caused in the hard and soft tissues suggests the possibility of true 'tumors' (Giant cell tumors) existing in the jaw.

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## Author Contributions

Puneet Ahuja - Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

Ajit Singh Rathore - Acquisition of data, Drafting the article, Final approval of the version to be published

Shivjot Chhina - Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Adesh Manchanda - Conception and design, Drafting the article, Final approval of the version to be published

## Guarantor

The corresponding author is the guarantor of submission.

## Conflict of Interest

Authors declare no conflict of interest.

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