



Aggressive Central Giant Cell Granuloma of Mandible: A Case Report & Review of Literature

Saurabh L Sabnis¹, Pravin P Walunjkar², Sanjay G Thete³, Deepak M Vikhe⁴

¹Associate Professor, Department of Oral Pathology & Microbiology, Rural Dental College, Pravara Institute of Medical Sciences, Loni, Maharashtra, India.

²Assistant Professor, Department of Oral & Maxillofacial Surgery, C.S.M.S.S Dental College & Hospital, Aurangabad, Maharashtra, India.

³Associate Professor, Department of Oral Pathology & Microbiology, Rural Dental College, Pravara Institute of Medical Sciences, Loni, Maharashtra, India.

⁴Associate Professor, Department of Prosthodontics, Rural Dental College, Pravara Institute of Medical Sciences, Loni, Maharashtra, India.

Case Report

Address for Correspondence Author

Dr. Saurabh L Sabnis; Department of Oral Pathology & Microbiology, Rural Dental College, Pravara Institute of Medical Sciences, Loni, Maharashtra, India.

E-mail: drabhisabnis@gmail.com

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ABSTRACT

Central giant cell granuloma [CGCG] is a relatively uncommon pathological condition accounting for less than 7% of all benign lesions of the jaws. CGCG is a locally aggressive reactive bone lesion with variable clinical behaviour that manifests with pain, cortical perforation, and root resorption. A Case of a 32-year-old male is reported occurring in mandible. The present case is discussed as a diagnostic challenge to distinguish Central giant cell granuloma [CGCG] from Giant cell tumour [GCT], as they show similar biologic behaviour, histopathologic features & prognosis.

Keywords: Aggressive, Central Giant cell Granuloma [CGCG], Benign Tumour.

Introduction

Giant cell granuloma [GCGs] was first described by Jaffe in 1953¹ as “giant cell reparative granuloma”, but currently does not refer to as reparative, because of its locally destructive nature. It is classified as peripheral if it affects the extremities and central if it develops in the midline [being the least common type]. Giant cell granulomas [GCGs] of the jaws are lesions that arise either peripherally in the 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 multinucleated giant cells [MGCs] in a prominent fibrous stroma. Foci of hemorrhage with the liberation of hemosiderin pigment along with newly formed osteoid or bone are often noticed. The MGCs are concentrated mostly in the areas of hemorrhage and present adjacent to blood vessels. Jaffe [1953] has distinguished Central giant cell granuloma from Giant cell tumor [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 spotted most frequently with peak incidence under the 30 years of age. However, it is widely accepted, that this benign tumour exhibits a variable clinical behavior and histopathological features.² Furthermore, the radiographic appearance of CGCG is not pathognomonic and may be confused with several other lesions of the gnathic area, such as brown tumour of hyperparathyroidism, fibrous dysplasia, aneurysmal bone cyst, and fibro-osseous lesions.³

The behavior of CGCG is variable, most commonly produces an asymptomatic, painless expansion of the jaws. However, it can present as clinically aggressive lesion, 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 in the literature. 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.⁴ The literature review suggests very few cases reported of an aggressive variant of CGCG. We report an uncommon case in the mandible of a 32-year-old person highlighting the aggressive form of CGCG.

Case Report

A 32-year-old male patient reported with a chief complaint of swelling in the lower right back region of the jaw for the past 6-7 months. Upon intraoral examination, diffuse, expansive irregular swelling was noticed in the mandibular right posterior region & obliteration of the buccal vestibule in the region of 45, 46, 47 was present. The swelling was firm, tender, non-fluctuant, and non-pulsatile on palpation. Submandibular lymph nodes were palpable and tender. The patient had undergone extraction of the mandibular right first premolar & second molar 4 months back. Unilocular radiolucency was noticed in the 45, 46 regions. Differential diagnosis of giant-cell tumor [GCT] of bone, Cherubism, Fibrous dysplasia, ameloblastoma was made. Incisional biopsy was done & reported as aggressive central giant cell granuloma. Surgery was performed and thorough curettage was done and the excisional specimen was sent for confirmation and histopathological diagnosis.

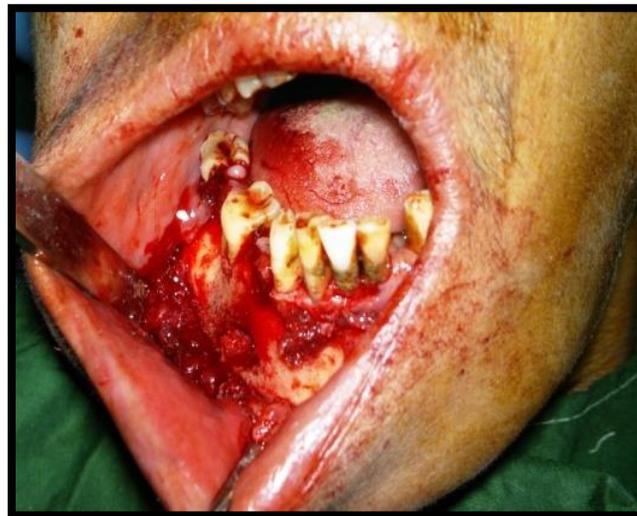


Figure 1: Intraoperative Photograph Showing Perforation of Buccal Cortical Plate and Local Destruction



Figure 2: Gross Excised Specimen after Surgery

Histopathological study showed predominantly cellular connective tissue stroma of aggressive nature with ovoid to spindle-shaped, proliferating plump fibroblasts with vesicular nuclei. Plump fibroblasts are arranged haphazardly at places in a whorled pattern and fascicles. Numerous giant cells of varying sizes randomly scattered throughout the connective tissue were noticed. Numerous Blood vessels, extravasated RBCs & chronic inflammatory cell infiltrate was seen. Areas showing osteoid tissue formation were noticed at the periphery of the section. The lesion was diagnosed as and confirmed the incisional biopsy report of, Aggressive Central Giant Cell Granuloma. The patient was under follow-up for 6 months and post-operative healing was uneventful with no signs of recurrence to date.

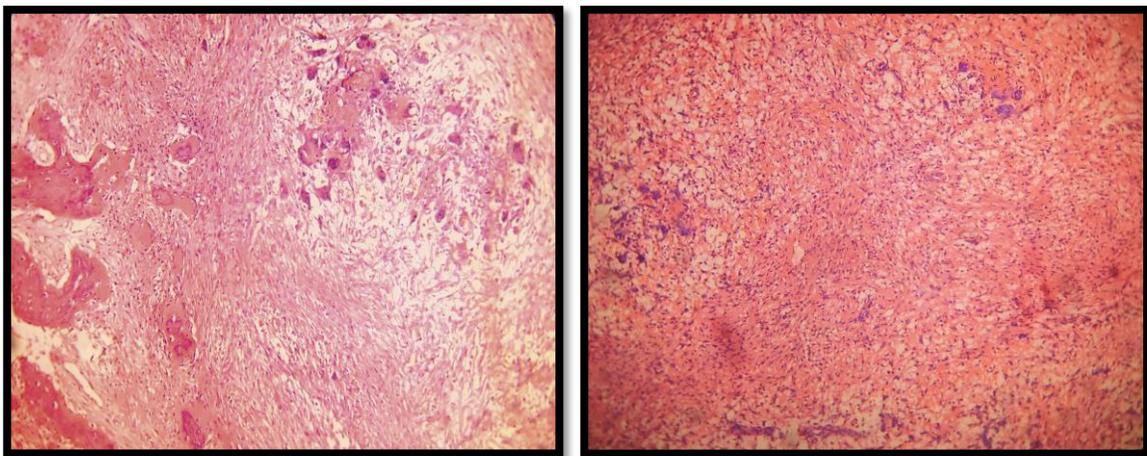


Figure 3 & 4: Numerous Multinucleated Giant Cells with Plump Proliferative Fibroblastic Stroma and Osteoid formation at Periphery.

Discussion

The WHO has defined CGCG as, an intraosseous lesion consisting of cellular fibrous tissue that contains multiple foci of hemorrhage, aggregations of multinucleated giant cells, and occasionally trabeculae of woven bone.⁵



The etiology and pathogenesis of CGCG of jawbones have not been clearly established. However, it has been suggested that the lesion may result from an exacerbated reparative process to previous trauma and intraosseous haemorrhage which triggers the reactive granulomatous process.⁶ Donoff and Rosenberg discussed a case of an uncomplicated extraction for pericoronitis and suggested that the local changes in the blood flow to the bone and bone dysplasia could be possible etiologic factors.⁷ Unal et al.⁸ presented a 12-year-old girl with CGCG in the mandible occurring after a molar tooth extraction and suggested that trauma as an etiologic factor.

Clinically, CGCG occurs most commonly in young adults with a female predilection of 2: 1. Lesions are more commonly found located in the mandible and frequently cross the midline.⁹ Wood & Goaz claim that CGCG appears as a unilocular, radiolucent cyst-like lesion, which changes to a multilocular cyst-like lesion with a bubble appearance. The variability in the description of radiographic features in the literature is consistent with the nature of CGCG. Based on the clinical and radiographic features central giant cell lesions of the jaws may be divided into two categories.¹⁰

Non-aggressive lesions- make up most cases, few or no symptoms, slow-growing, & do not show cortical perforation or root resorption of the teeth involved in the lesion.

Aggressive lesions are characterized by pain, rapid growth, cortical perforation, or root resorption. They show a marked tendency to recur after treatment when compared with Non-aggressive lesions.¹⁰

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%.¹¹ 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 most reliable relatable factors to an increased risk of recurrence include a locally aggressive 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.¹²

Studies in the literature have suggested that the greater functional surface area occupied by giant cells and larger relative size of giant cells may identify tumours with aggressive behaviour. Kruse-Losler et al have demonstrated that the aggressive variant of CGCG presented a high number of giant cells, and increased mitotic activity, and a high fractional surface area.¹³ However, other studies have not been able to predict the clinical course of CGCGs from known histological or immunohistochemical features.¹⁴

A systematic review of 232 well-established cases with histopathological confirmation of CGCG published in the English literature reveals an aggressive pattern of radiographic features of the lesion. In most cases, the borders are rather ill-defined [66%], the lesions exhibit a multilocular appearance [54%], displaced teeth and anatomic structures [43%], expand cortical bone [51%], and sometimes perforate the cortices [38%]. The ominous sign of paresthesia has occurred in 6% of the cases.^{15,16}

Franklin et al has shown that in giant cell granuloma the giant cells are smaller and contain fewer nuclei than those of giant cell tumors of the skeleton.¹⁷ Itanoga et al, indicated that the giant cells in CGCG of the jaw are osteoclast-like and formed from Monocyte/ Macrophage precursors which differentiate into osteoclast.¹⁸ A variety of histologic features and patterns can be seen in a CGCG of the jaws. Common features are the presence of few to numerous multinucleated giant cells in a stroma composed of ovoid-shaped to spindle-



shaped mesenchymal cells. The giant cells typically possess four to eight randomly arranged nuclei that may be hyperchromatic, oval, stippled, or any combination of the three, with prominent nucleoli. Evidence suggests that these giant cells represent osteoclasts, although others suggest these cells may be aligned more closely with macrophages. The spindle-shaped cells appear to be of fibroblastic lineage. It has been proposed that the spindle cell component is the proliferating cell population & recruits, monocyte-macrophage precursors, inducing them to differentiate into osteoclastic giant cells by activation of the receptor activator of the nuclear factor- κ B [RANK/RANKL ligand signalling pathway. The giant cell may be focally aggregated in the tissue or diffusely spread throughout the lesion.¹⁰ The non-aggressive cases of CGCG show a minimal to moderate cellularity and a non-vesiculated fibroblastic stroma.

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, α -1antichymotrypsin, and α -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.¹⁹

Entities which are similar in appearance, Giant cell tumour [GCT] of bone is most difficult to differentiate from CGCG without clinical and histopathological information. CGCG generally occurs in the younger population than Giant cell tumour [GCT] of bone. From a histopathological perspective, CGCG has a hemorrhagic background with the presence of plump bland fibroblasts, haemosiderin pigments, and fewer giant cells with a smaller number of nuclei which are less uniformly distributed. While in the case of GCT, giant cells are uniformly scattered and have a larger number of nuclei and the absence of fibroblasts and hemorrhage. Central giant cell granuloma usually lacks diffuse sheets of large giant cells and polygonal mononuclear cells seen in GCT. Osteoid deposition is occasionally observed in CGCG which is lacking in GCT. Cystic areas like the Aneurysmal Bone Cyst component are less common as compared to GCT. Differentiation from the brown tumor is based mainly on clinical and laboratory data as well as differences in the age of onset and multiplicity of lesions.²⁰ Diagnostic tests to assess the alkaline phosphatase, serum calcium, and parathormone levels should be done, rule out Brown's tumor of hyperparathyroidism, which shows similar microscopic findings.

Surgical therapy is still considered the gold standard for the treatment of CGCG. A Conservative surgical approach was opted for treatment as opposed to resection. Central giant cell lesions of jaws are usually treated by thorough curettage. Recurrence rate ranges from 11% to 50% but, most studies indicate a recurrence rate of 15 % - 20%. Recurrent lesions often respond well to further curettage although some aggressive lesions require more radical surgery for cure.¹⁰ In patients with aggressive tumors, there are 3 alternatives to surgery.

1. Intralesional Corticosteroids
2. Calcitonin
3. Interferon alfa 2a

But the evaluation of a greater number of patients with appropriate controls is necessary to compare these therapeutic approaches to surgery adequately.¹⁰

Conclusion

We can conclude that CGCG is a relatively rare entity of benign histologic nature but can have a very aggressive local behaviour. Therefore it is essential to differentiate the non-aggressive variant of CGCG from aggressive lesion as the latter lesions are more destructive with a marked tendency to recur and thus require



more radical treatment. The final diagnosis eventually rests on histopathology since clinical and radiological features are not very specific. Central giant cell granuloma of the head & neck region remains a diagnostic challenge for pathologists and needs a multidisciplinary approach. There are multiple conditions that must be ruled out clinically and with the help of serum laboratory diagnostic tests, but the controversy surrounding the etiologic factors responsible for the pathogenesis of this aggressive variant of CGCG is yet to be definitively resolved.

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