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CASE REPORT

AGGRESSIVE CENTRAL GIANT CELL GRANULOMA- CASE REPORT AND REVIEW

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ABSTRACT

Central giant cell granuloma (CGCG) is a benign intraosseous lesion predominantly involving the mandible in young females. Exact etiology of this lesion is controversial and remains unknown. However, three competing theories are prevailing which states that it could be a reactive lesion, a developmental anomaly or a benign neoplasm. CGCG has been grouped into non-aggressive and aggressive variants on the basis of clinical, radiographic and histopathologic features. This paper reported a case of 29 year old female patient, presented with complain of pain and swelling in right vestibule region for one and half month. Based on clinicoradiologic findings, provisional diagnosis of aggressive CGCG was given and the lesion was surgically intervened. Histopathological report revealed central giant cell granuloma. The healing was uneventful and no complication noted till date. The purpose of this article is to review the clinical, radiological, histopathological features and management of aggressive CGCG and highlight the importance of early diagnosis in management of aggressive CGCG.

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INTRODUCTION

The World Health Organization (2005) has defined central giant cell granuloma as a localised benign but sometimes aggressive osteolytic proliferation consisting of fibrous tissue with haemorrhage and hemosidrin deposits, presence of osteoclast- like giant cells and reactive bone formation (Barnes et al., 2005). It accounts for approximately 7% of all benign tumors of the jaws (Daryani, 2011). It was first described as giant cell reparative granuloma (GCRG) by Jaffe in 1953, to distinguish it from the histologically and clinically differing giant cell tumor of long bones (Baskaran et al., 2015). Currently the term 'reparative' is not used for description because of the destructive nature of the giant cell granuloma.[4] CGCG has been grouped into non-aggressive and aggressive variants on the basis of clinical, radiographic and histopathologic features following reliable clinicopathologic studies carried out by Choung et al in 1986[5] and Ficara et al in 1987. Here an aggressive variant of CGCG is reported with emphasis on its unique clinical and radiologic manifestations.

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CASE REPORT

A 29 year old female reported with a complaint of a swelling associated with dull continuous pain in the right lower back teeth region for the past one and half months with no history of trauma. Approximately 15 days back the patient had consulted a dentist regarding above complaint following which an endodontic treatment was initiated for right lower premolars, but pain and swelling had persisted afterwards. The patient's medical, family and personal history were non-contributory. Extraorally, no gross facial asymmetry of face was noted on inspection. However, a swelling of approximately 3x2 cm in size was palpable in right mandibular body region with no increase in local temperature and no changes in the overlying skin. The swelling was hard in consistency and tender. No evidence of paraesthesia in the overlying soft tissue region was noted. Intraorally, a well-circumscribed dome shaped smooth swelling of approximately 3x2 cm in its maximum dimension was noted in right vestibular region extending from mid-surface of 43 to distal surface of 45 obliterating the vestibule (Figure-1) The overlying mucosa appeared normal in colour and texture. On palpation, swelling was bony hard, tender with buccal cortical plate expansion.

The involved teeth in the region were not displaced and were non-mobile. However canine in that region was tender on vertical percussion. Tooth colored restoration was noted in relation to 43 and 44 which were non vital on Pulp vitality. On radiographic investigation, IOPAR wrt 43, 44, 45 and 46 region revealed a well defined radiolucency in the middle one-third of the coronal portion of the 44 and 45, extending from occlusal aspect to the cervical aspect and involving enamel, dentine and pulp. Periodontal ligament (PDL) space widening was noted in relation to 43. A solitary ill-defined radiolucency with indistinct borders, extending from the distal aspect of 43 to the mesial surface of 46. The radiolucency occupies the inter-radicular portion of 44 and 45, superio-inferiorly extending from the alveolar crest, whereas inferior extent cannot be appreciated on this radiograph. The internal aspect of the lesion is completely radiolucent with indistinct borders of roots of apical one third of root of 44, 45 suggestive of multiplanar root resorption with displacement of roots. (Figure-1) Mandibular cross-sectional occlusal radiograph demonstrated expansion of buccal cortical plate in relation to 44-46 region (Figure-2).

Panoramic radiograph showed a well defined solitary pear shaped radiolucency with non-corticated borders approximately 3.5 x 2.5 cm in its greatest dimension, occupying the interradicular bone between 44 and 45with diverging roots. The internal structure showed few coarse faint wispy septa with root resorption in multiplanar pattern in relation to 44 45.

A well defined radiopacity with distinct periphery, smooth borders and with no trace of radiolucent capsule at the periphery, irregular in shape and of approximately 3mm in its maximum dimension is noted in relation to the mesial root of 46 suggestive of dense bony island.(Figure-2) CBCT imaging of mandible was performed with 4x5 cm FOV and isotropic resolution which revealed a well- defined expansile lytic lesion, with thinning and expansion of overlying buccal cortex. The lesion measures approximately19.7x17x18.5mm (APxCCxML) in its maximal dimensions (Figure-3).

Based on the clinico-radiological findings a working diagnosis of aggressive central giant cell granuloma was arrived. CGCG secondary to hyperparathyroidism, Ameloblastoma, odontogenic myxoma and Aneurysmal bone cyst were considered as differential diagnosis. Serum calcium (9.2mg/dl), serum phosphorus (3.7mg/dl), parathormone levels (41.50 pg/ml) and routine blood investigations were found within normal limits. Under local anaesthesia, the lesion was approached by deep vestibular incision intraorally.

Enucleation with curettage was done with the removal of a small amount of marginal bone followed with primary closure of the surgical site with 3-0 silk suture. Histopathological examination of enucleated specimen showed hypercellular connective tissue stroma consisting of multinucleated giant cells.(Figure-4) Based on the histopathological findings, a final diagnosis of central giant cell granuloma was given. Healing was uneventful and endodontic treatment was completed for 44 and 45. Post-operative OPG taken after an interval of 5 months showed a decrease in the size of the lesion and increase in the opacity of the lesion (Figure-5). In view of the increased propensity of recurrence of aggressive CGCG, long-term follow-up of the patient has been maintained.

DISCUSSION

The incidence of CGCG in the general population is estimated to be 0.0001% with 60% of cases occurring before the age of 30 years.[7] Interestingly, the exact prevalence of aggressive CGCG has not been studied extensively. Variation has been reported in the prevalence of aggressive CGCG ranging from 57(40%) of the lesions out of 142 cases.[8] to 10 out of 30 cases of CGCG with retrieved data of corresponding clinical and radiographic findings.[9] Such variations could be due to the limited studies and lack of standardisation in retrospective analysis of aggressive CGCG. A definite female predilection (2:1) exists.(7) The present case is also reported in a female patient less than 30 years of age. Although the nature of this lesion is not well understood till date, Jaffe considered it as a locally reparative reaction of bone, possibly due to either an inflammatory response, hemorrhage or local trauma.[10] However, subsequently three competing theories (Kamble, 2016) have prevailed regarding the etiopathogenesis wherein CGCG is considered as:–-Reactive lesion; due to an exacerbated reparative process related to previous trauma and resultant intraosseous haemorrhage resulting in accumulation of tissue consequent to multicentric haemorrhages and hemodynamic disturbance (Kurra, 2013).

Developmental; the association of t(X; 4) (q22; q31.3), was also suggested as an aetiology of CGCG (Kurra et al., 2013). Also, SH3BP2 gene mutation has some influence on the Msx-1 regulation of tooth development and that the development of Giant Cell Granuloma could be linked to dysregulation of the Msx-1 gene (O'Connell, 2013). Benign neoplasm-Thought to represent a reparative response to intrabony haemorrhage and inflammation, CGCG was once regarded as a reactive lesion. However, because of its unpredictable and occasional aggressive clinical behaviour, histological features, dynamic biological character, and because of its possible relationship to the giant cell tumor of long bones, CGCG is best classified as a benign neoplasm (Shrivastava, 2012). In the present case, patient presented with aggressive behaviour with no reported history of trauma thus accomplishing the benign nature of the central giant cell granuloma. In the jaws CGCG arise either peripherally in the periodontal ligament, in the mucoperiosteum of the alveolar ridge, or centrally within the bone. Although it may begin centrally, it can perforate the cortical plate to present as mucosal lesions (Reddy et al., 2012). CGCG mainly confines to the tooth bearing areas of anterior jaws, with a tendency to cross midline (50%). It occurs at least twice as often in the mandible (Baskaran et al., 2013; Kruse-Lösler et al., 2006) with an epicentre anterior to the first molar in young patients. The site of lesion observed in the present case is the right mandibular body region. There is tendency for the epicentre to occur in the posterior aspect of the jaws after the first two decades of life. In the maxilla, the epicentre is more commonly anterior to the canine (Jadu, 2011). Radiographically, CGCG commonly presents as a lytic expansile solitary lesion with a multilocular appearance[16] or, less commonly, a unilocular appearance (Indra, 2014) with displacement and resorption of roots. The borders may be well-defined or ill-defined and show variable expansion and destruction of the cortical plates.[7] This case presents as unilocular radiolucency with resorption of roots. The internal structure may show granular pattern of calcification which is organized into ill-defined, wispy septa which emanate at right angles to the periphery of the lesion (Kamble et al., 2016), simulating as soap bubble appearance (Baskaran, 2015).

Table 1-Differentiating features between Non-aggressive and aggressive CGCG

Features	Non-aggressive	Aggressive
SIZE	Usually <2 cm	Usually >2 cm
GROWTH RATE	Slow	Rapid
PAIN	Pain may or may not be present	Usually associated with pain
PARAESTHESIA	Absent	Present
RADIOGRAPHIC FEATURES	Minimal cortical expansion	Multiplanar root resorption, cortical expansion perforation
HISTOLOGICAL FEATURES	Smaller fractional surface area occupied by smaller giant cells	Larger fractional surface area occupied by larger giant cells
RATE OF RECURRENCE	No recurrence	High rate of recurrence

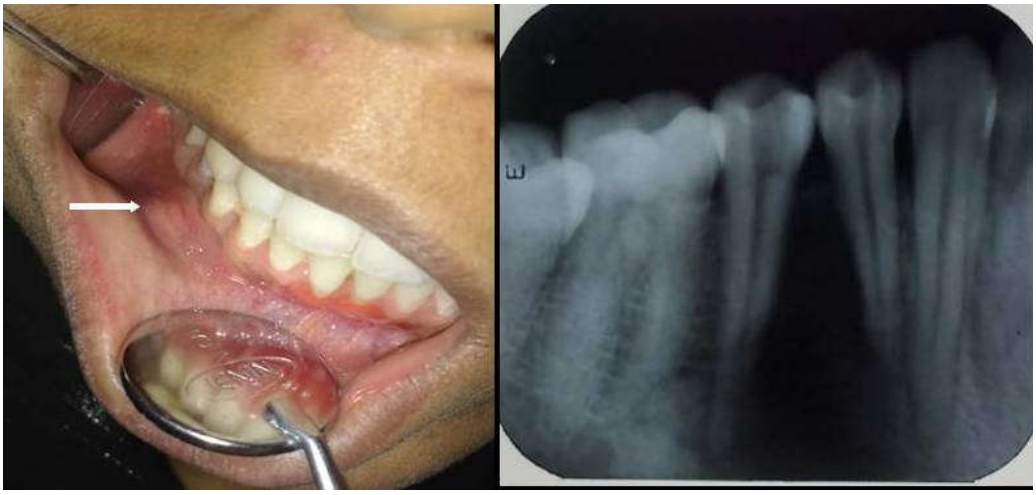

Figure 1- Vestibular obliteration in right mandibular premolar region and IOPAR of the region revealed an ill-defined radiolucency with indistinct borders and multiplanar root resorption.

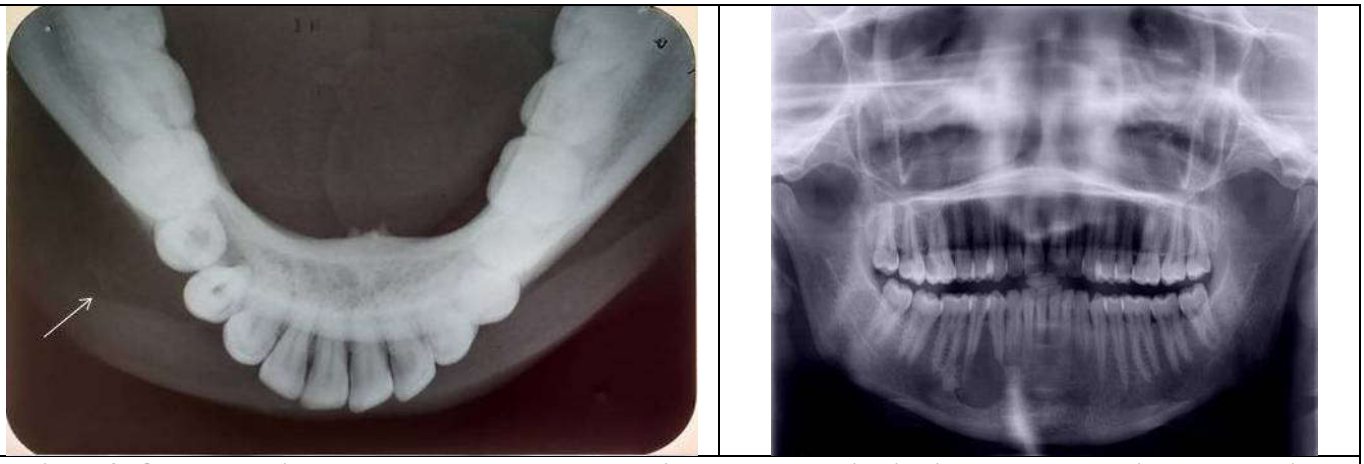

Figure 2- Occlusal radiograph demonstrates buccal cortical plate expansion in right premolar region. Panoramic radiograph revealed a single well defined, unilocular radiolucency in relation to 43-46 with presence of dense bony island in its posterior relation

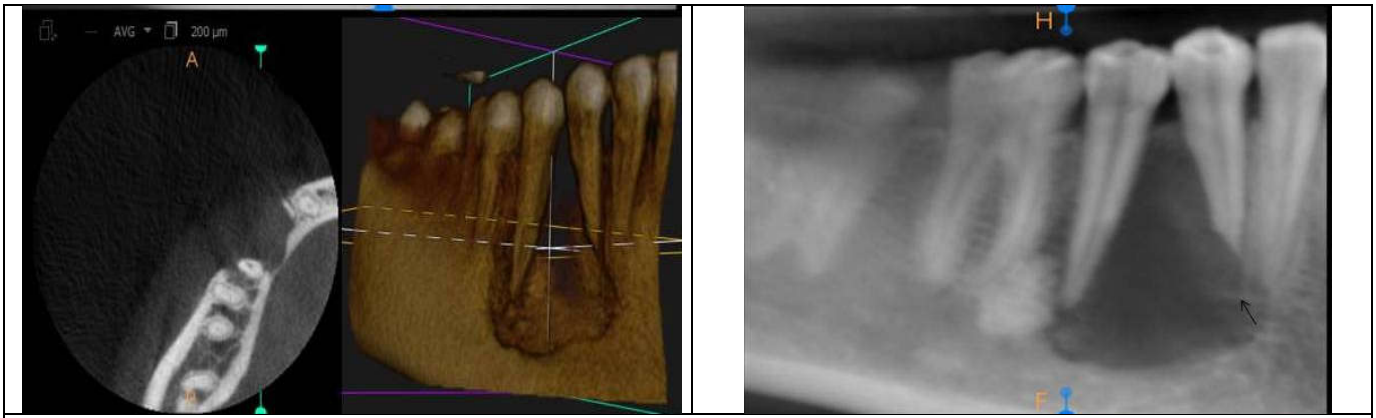

Figure 3- CBCT revealed distinct radiolucency with thin wispy septa in the 43 to 46 region with dense bony island. Axial section revealed breach of buccal cortex and thinning of lingual cortex. 3D reconstruction revealed destruction of the buccal cortical plate.

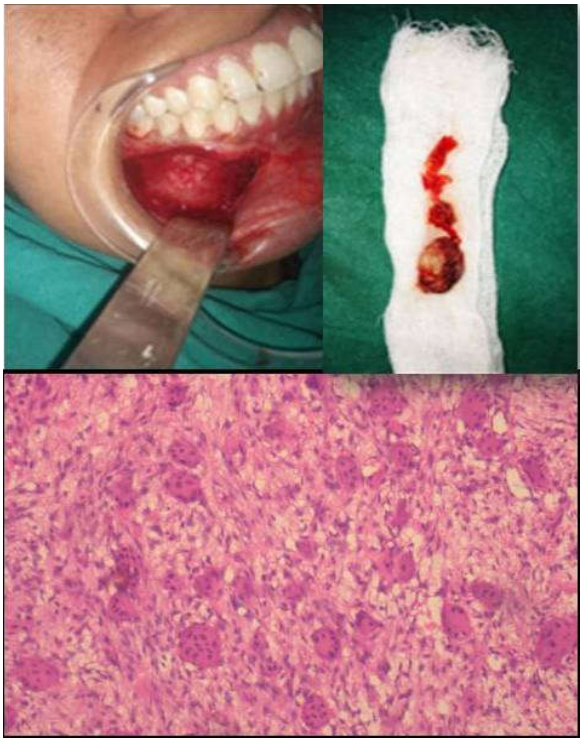

Figure 4. Intra-operative image and the excised specimen Photomicrograph showing numerous multinucleated giant cells (40X)

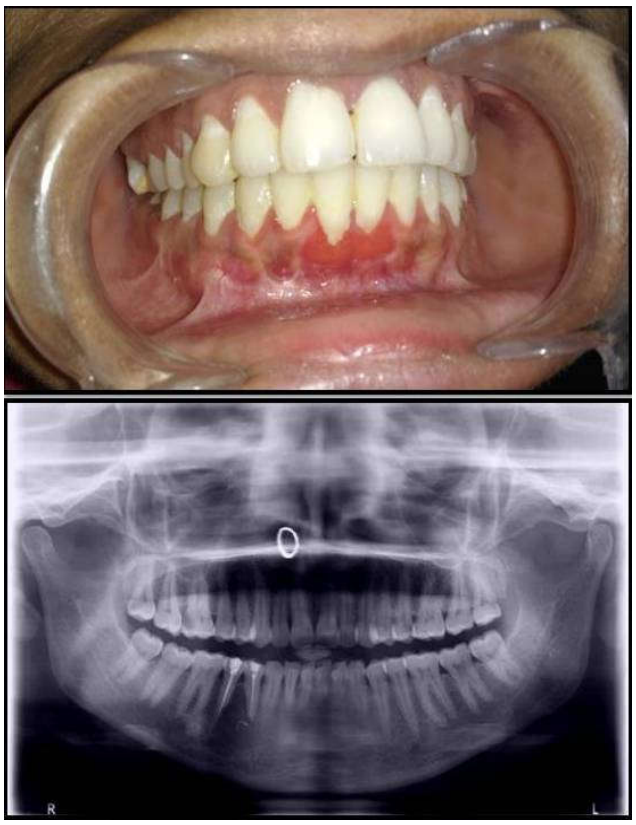

Figure 5. Post operative image and OPG after 5 months of follow up depicting uneventful healing of the lesion.

The radiographic feature in this reported case is not pathognomonic for CGCG. Histologically, CGCG is characterized by two characteristic types of cells: - (a) Multinucleated giant cells and spindle-shaped stromal cells distributed in a collagenous stoma. The multinucleated giant cells are of a foreign body type or osteoclast-like having up to 30 nuclei and fairly evenly distributed around the lesion. (b) The stromal cells are considered to be the proliferating cells, which are osteoblast like and induce osteoclast formation from mononuclear blood cells via receptor activator of nuclear factor kB ligand interaction. The stromal cells may be of two types — one type may resemble myofibroblast having oval to spindle shaped with a cigar shaped nucleus and exhibiting coarse chromatin; the other type resembles macrophages having smaller round nucleus and exhibiting dense chromatin. Areas of hemorrhage, hemosiderin pigment, thin-walled vascular spaces, and trabeculae of woven bone may be seen in the connective tissue stroma (Baskaran, 2015). Histologically, the features of CGCG are indistinguishable from Brown tumor of hyperparathyroidism and giant cell lesions, but biochemical tests such as serum calcium, phosphorus, and alkaline phosphatase can be taken into consideration to rule out these lesions. Similar histological features are also seen in, aneurysmal bone cyst, and cherubism and needs to be differentiated.

Based on the clinical, radiographical, and histological features, several groups of investigators have suggested that central giant cell lesions of the jaw may be divided into two categories- Aggressive and Non aggressive as described in the Table 1- Although clinical and radiological findings are pathognomonic of distinguishing between aggressive and nonaggressive types, some authors have proposed the image cytometric analysis and giant cell parameters such as presence of a high number of giant cells, an increased mitotic activity, and a high fractional surface area to be associated with aggressive CGCG (Iyengar, 2016). Chuong et al, 1986 have confirmed the importance of the clinicobiologic behavior of the giant cell lesion in determining treatment and predicting prognosis. Aggressive giant cell lesions usually occur in a younger age group, are larger at the time of diagnosis, and recur more frequently than the nonaggressive giant cell lesions. They suggested that all lesions be labelled as aggressive or nonaggressive and that treatment must be planned accordingly (Chuong, 1986).

Management: The management of CGCG will depend on the clinical and radiographic findings. Curettage is recommended for well-defined localized CGCG with low rates of recurrence. In extensive lesions with radiographic evidence of cortical perforation, a more radical excision/ aggressive curettage is mandatory. In such cases even *en bloc* resection with 0.5 cm margins of healthy tissue (Tarsitano et al., 2015), partial maxillectomy or mandibulectomy (Schütz et al., 2010) has to be done. The medical management of CGCG as an adjunct to surgery includes treatment with steroids, interferon –alpha or calcitonin which inhibits osteoclastic activity. Intralesional injection of corticosteroids (triamcinolone hexacetonide 20 mg/ml diluted in anesthetic solution of 2% of lidocaine twice weekly for 6 weeks) has been used successfully especially, in unilocular lesions which have easier accessibility whereas in multilocular lesions, some areas may be missed leading to an appreciable failure rate (Pogrel, 2012). As corticosteroids inhibit osteoclasts in marrow cultures and under conditions of bone absorption by increased apoptosis (Chawla), their use for giant cell granuloma has been advocated. Calcitonin therapy (salmon calcitonin nasal spray 200 IU/day) controls the osteoclastogenesis by inhibiting giant cells of CGCG. It can be administered in two different modes, i.e., 100 IV calcitonin subcutaneously daily or 50 IV calcitonin subcutaneously and 200 IV nasal spray daily (Chawla).

Interferon alpha INF-α injection, 3×10^6 IU/day) injection, used as adjunct to surgery, acts as antiangiogenic and inhibits bone resorption (Whitaker, 1993). Recurrence rates have been reported to range between 11% and 49% for curettage alone and can be as high as 72% for aggressie subtypes (Whitaker, 1993) and hence adjunctive treatment modalities should be given. However, Recent literature on aggressive CGCG does not report any recurrence of the lesion where the documented follow up period varies from 6 months to 12 years (Baskaran et al., 2015; Indra, 2014; Iyengar, 2016; Tarsitano et al., 2015). Although on a year's follow-up, no recurrence was identified in this reported case. Characteristics of younger age group, rapid progression, larger dimensions and resorption of roots of associated teeth enabled the grouping of the present case as aggressive CGCG.

Malignant transformation: Aggressive giant cell lesions of the jaws do not have a high rate of malignant transformation, and one case was documented by Mintz et al (1981) of metastasis to regional lymph nodes (Mintz et al., 1981). However, the incidence of malignant transformation rate in giant cell tumor of bones varies considerably among studies with an overall rate of approximately 5% was reported (Miller, 2010).

Conclusion

Giant cell granuloma of jaws is a benign tumor of unknown aetiology. When this lesion manifests with aggressive clinical behaviour, it can be locally destructive. This case report highlights the manifestations of an aggressive giant cell lesion which with prompt diagnosis and management resulted in an uneventful healing with minimal loss of bone.

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Conflict of Interest: None

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