CASE REPORT

CENTRAL GIANT CELL GRANULOMA: A DIAGNOSTIC PREDICAMENT

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ABSTRACT:
Central giant cell granuloma (CGCG) was first described by Jaffe in 1953, as an idiopathic non-neoplastic proliferative lesion. It accounts for about 10% of all benign lesions of the jawbones. Much controversy surrounds the nature of CGCG. Initially, it was not distinguished from giant cell tumor of the extragnathic skeleton, but later it was described by Jaffe as giant cell reparative granuloma. The clinical behavior of the lesion varies from an asymptomatic osteolytic lesion that grows slowly without expansion, to an aggressive, painful process accompanied by root resorption, cortical bone destruction, and extension into the soft tissues. Histologically and radiographically CGCG resembles giant cell tumor, giant cell lesion of hyperparathyroidism, cherubism, and aneurysmal bone cyst. Here we present a case report highlighting the clinical, radiological and histological features of central giant cell granuloma, laying emphasis on differentiating it from other similar multilocular radiolucencies.
Key words: Central giant cell granuloma, aggressive, non-aggressive.

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INTRODUCTION

Giant cell lesions in the oral tissues occur as intraosseous growths within the jaws and as extrabony lesions in the soft tissues. The intrabony lesions comprise the giant cell tumor of bone, the central giant cell granuloma (CGCG) and the focal giant cell lesion or "BrownTumor" of hyperparathyroidism. The one that occurs in the jaws has been characterized by 'Jaffe' as giant cell granuloma since it seems unlikely that the lesion is reparative.[1]

Much controversy surrounds the nature of CGCG. Initially, it was not distinguished from giant cell tumor (GCT) of the extragnathic skeleton, but later it was described by Jaffe as giant cell reparative granuloma. In recent years the word 'reparative' has been deleted from the term, since it was realized that many of these lesions are more 'destructive' than 'reparative'.[2]

The clinical behaviour of CGCG of the jaws is variable and difficult to predict. It occurs mainly in adolescents and young adults.[1] It affects females more often than males in a 2:1 ratio and is seen most frequently under the age of 30 years.[1] One study of 38 patients shows 74% to be less than 34 years of age and 61% to be less than 20 years of age.[1] It occurs more often in mandible than in the maxilla. The vast majority of the lesions appear anterior to the first permanent molar region, often crossing the midline and practically all occur in the tooth bearing area.[1]

CGCG typically produces a painless expansion or swelling of the affected jaw.[3] The teeth may become loose and exfoliate.[1] Cortical plates are thinned; however, perforation with extension into soft tissue is uncommon.[3] Multiple central giant cell lesions have been reported in association with Noonan-like/multiple giant cell lesion syndrome, and other features of the disease include a short stature, webbed neck, cubitus valgus, pulmonic stenosis, and multiple lentigenes.[4]

The radiographic features of CGCG consist of a multilocular or, less commonly, unilocular radiolucency of bone. The margins of the lesion are

relatively well demarcated, often presenting scalloped borders.[3] Histologically, CGCG is composed of two distinct populations of cells viz. multinucleated giant cells and spindle shaped stromal cells. CGCG has a haemorrhagic background with presence of fewer giant cells with smaller number of nuclei, which are uniformly distributed.[5] The treatment of CGCG includes simple curettage or curettage with peripheral ostectomy.[1]

Hereby we present case of central giant cell granuloma, laying emphasis on distinguishing it from other multilocular radiolucencies.

CASE REPORT

A 26 year old female presented with a swelling on the right side of the mandible since 6 months. The swelling was slow growing, expansile, firm in consistency and slightly tender on palpation. There was facial asymmetry with respect to the right side of the face involving the body of the mandible. Swelling extended 1 cm posteriorly from the midline of jaw; to 3 cm anteriorly from angle of mandible across the body of mandible.

The patient was systemically healthy with no history of trauma or dental problem. On intraoral examination, the swelling extended from the right lateral incisor to the first molar region causing obliteration of the labial vestibule. The mucosa over the swelling was normal and teeth #44 and #45 were slightly mobile. No evidence of cervical lymphadenopathy was found.

CT scan revealed a hypodense, non-mineralized osteolytic lesion with some hyperdense haemorrhagic regions. The tumor showed thinning, expansion and interruption of the cortical bone involving both the buccal and lingual sides. On OPG, it presented as a multilocular radiolucent lesion with regular well defined borders involving right mandibular canal, right mental foramen and roots of # 44 and # 45 tooth leading to its periapical resorption.

Keeping in mind the clinical and radiographic appearance, a provisional diagnosis of CGCG and a differential diagnosis of brown tumor (osteitis fibrosa cystica/ hyperparathyroidism), ameloblastoma and aneurysmal bone cyst was established.

Routine haemogram and urine examinations were normal. The serum chemistry of calcium, phosphorus and parathyroid hormone was normal, excluding the possibility of hyperparathyroidism.

Pre-operative biopsy was performed which showed a highly vascular immature fibrous tissue containing a mixture of mononuclear cells and multinucleated giant cells against a background of extravasated blood cells, small capillary vessels and chronic inflammatory cells. **(Figure 1)** The mononuclear stromal cells were ovoid and spindle shaped. The multinucleated giant cells were 5-8/HPF; showed varying numbers of nuclei ranging from 2-12; which were either vesicular or pyknotic. **(Figure 2)** Few foci of bony trabaculae in the form of osteoid and woven bone were seen.

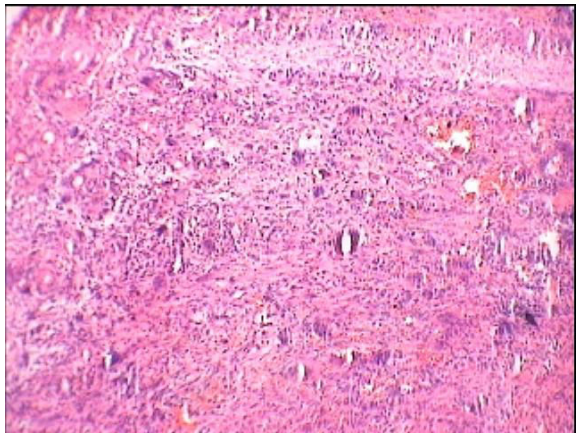

Figure 1: A fibrocellular vascular connective tissue stroma with numerous giant cell (H & E, X 10)

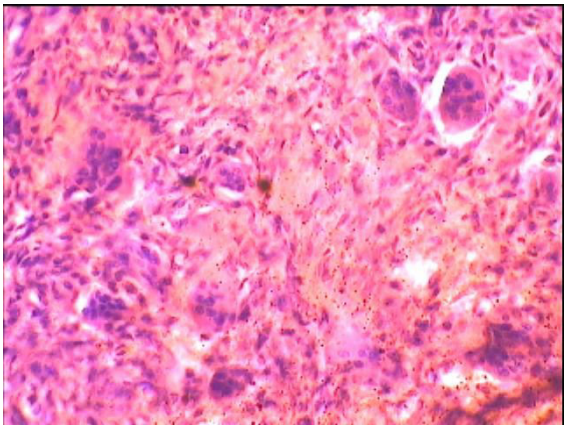

Figure 2: 5-8 multinucleated giant cells/HPF showing varying number of nuclei. (H & E, X 40)

DISCUSSION

Central giant cell granuloma was classified as a true neoplasm and a reactive proliferative process at the same time because of its histologic features, dynamic biologic characteristics, and variable clinical patterns.[6] The etiopathogenesis of CGCG of jawbones has not been clearly established but it has been suggested that it is the result of an exacerbated reparative process related to previous trauma and intraosseous haemorrhage that triggers the reactive granulomatous process.[7]

Based on the clinical and radiographic features CGCG is of two types, namely- aggressive lesions and non-aggressive lesions. Features of aggressive and nonaggressive types of CGCG have been tabulated in **Table 1.**

Table 1: Comparison of 2 types of central giant cell granuloma of the jaws.[7,2]

Features	Non Aggressive	Aggressive
Pain	Asymptomatic	Painful and can cause paraesthesia
Growth rate	Slow growing	Shows rapid growth
Cortical perforation	Occur without cortical perforation	Present with cortical perforation
Root resorption	Shows no root resorption	Root resorption occurs
Re-occurrence	Less	Marked

Table 2: Differential diagnosis of lesions presenting as multilocular radiolucencies.[23]

Lesion	Gender	Age (years)	Predominant region	Histologic Features	Additional features
Multilocular cysts (OKC)	M=F	>16	Posterior mandible Rare in maxilla	5-8 layered parakeratinized epithelial lining. Picket fence or tombstone appearance.	
Ameloblastoma	M=F	20-50 (av. 40)	Posterior mandible	Tall columnar cells at the periphery showing palisading pattern with reversal of polarity. Central stellate reticulum like cells	Paraesthesia in some cases
Central giant cell granuloma	F:M 2.4:1	<30 (av. 26)	Mandible (anterior to second molars)	Multinucleated giant cells; loose connective tissue stroma Small capillaries	Serum chemistry levels normal. 20% cross midline
Hyperparathyro-idism	F:M 7:1	30-60	Mandible	Endothelium lined blood spaces Multinucleated giant cells	Polydipsia, polyuria, serum Ca increased, serum phosphate decreased. and serum alkaline phosphatase increased
Cherubism	M>F	2-20	Ramus and molar region of mandible Sinus and orbital floor in maxilla	Multinucleated giant cells; Spindle shaped fibroblasts Collagenous stroma	Familial history
Aneurysmal Bone Cyst (ABC)	M~F	<20 (70%)	Ramus and molar region of mandible	Fibrous connective tissue stroma Sinusoidal blood filled spaces	Tender

The present case showed a swelling which increased rapidly in size over a period of 6 months and microscopically, 5-8 giant cells/HPF were seen in a highly cellular background showing its inclination towards an aggressive nature. However, studies have failed to identify any biochemical or histological differences between the aggressive and nonaggressive variants.

There have been studies suggesting that the greater functional surface area occupied by giant cells and large relative size of giant cells may identify tumors with aggressive behavior. Recently, Kruse-Losler[6] 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.[7] However, other studies have not been able to predict the clinical course of CGCGs from known histological and immunohistochemical features.

Concerning the mode of origin of giant cells there have been some deliberations. Wiegert, Baumgarten, Bakacs, Lubarsh and others were of the opinion that giant cells were formed by continued nuclear division. Krauss, Mallory and Wells were among those who favoured fusion of individual cells as the explanation for formation of these cells. Lewis and Webster in 1921 believed that the epithelioid cells were formed by mitosis of the nucleus, but a later paper by Lewis takes the opposite view that they are formed by the fusion of epithelioid cells.[9]

Geschickter and Copeland suggested that the giant cells might be derived from proliferating giant cells associated with resorption of deciduous teeth. There has been considerable support for another theory of origin from endothelial cells of capillaries. There is some basis in fact for such an idea, the chief being the common occurrence of the giant cells within vascular channels, suggesting that they arise here through fusion of endothelial cell. [2]

Some investigators believe that the giant cells show immunohistochemical (IHC) features of osteoclasts, while other authors suggest the cells are from the mononuclear phagocyte system. There is a debate whether the giant cells are fibroblast in origin or from monocyte/macrophages. A recent study by Itonaga et al [10] indicated that the giant cells in CGCG of the jaw are osteoclast like and formed from monocyte/macrophage precursors which differentiate into osteoclasts. Studies by Liu B et al. also supported this hypothesis.[2]

Imaging plays an essential role in detection, characterization, pre-surgical evaluation of focal bone lesions as well as in their postoperative follow-up.[11] Panoramic radiograph is still the imaging modality of choice, but CT with dental reformatting programme allows an optimal view of the bone and provides essential data for differentiating benign from malignant lesions and for planning correct surgical procedure.[12,13] Radiological appearance of CGCG is non-specific, and conflicting. The lesion appears with multilocular radiolucency, with well-defined margins; varying degrees of expansion and erosion of the cortical plates and occasional resorption of dental root. The radiographic appearance is indistinguishable from that of odontogenic cyst, aneurysmal bone cyst (ABC), hyperparathyroidism, ameloblastoma, odontogenic myxoma and odontogenic fibroma.[14,15] **(Table 2)**

Microscopically CGCG is composed of two distinct population of cells viz multinucleated giant cells and spindle shaped stromal cells. [7] The number of nuclei in the giant cells ranges from 3 to more than 100. No significant differences are found in the mean number of nuclei per giant cell. Spindle shaped cells 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.[16] The stromal cells and histiocytes are positive for α-1 antitrypsin.[17]

An electron microscopic examination of tissue from a giant-cell tumor of bone revealed that the fine structure of giant cells was indistinguishable from that of osteoclasts or of giant cells from other lesions.[18] The most striking feature of the cytoplasm of giant cells was the presence of large numbers of electron dense mitochondria with angulated crista.[18] Rough-surfaced endoplasmic reticulum could be seen in many giant cells usually situated toward the cell periphery. Abundant golgi bodies were uniformly distributed throughout this area. Judging from the state of development of its mitochondria and golgi apparatus, it seemed probable that the giant cell has a high degree of metabolic activity; yet from examination of many histologic sections of self- propagation, this tumor showed nothing to indicate that giant cells were capable of self propagation.[19] Other cytoplasmic features in stromal cells of this type, such as endoplasmic reticulum and lipid-containing vacuoles, varied from cell to cell.[18]

Regardless of the specific cause, CGCG seems to be a distinct entity from a true giant cell tumor of bone showing significant differences in terms of age,

distribution, and biologic behavior. **(Table 2)** IHC studies on CGCG have helped establish the lineage of 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 1 antichymotrypsin and alpha1 antitrypsin.[20] Aggressive and nonaggressive CGCGs stained for antibodies to CD34, CD68, factor Xllla, and smooth muscle actin, prolyl 4-hydroxylase, Ki-67, p53 protein, RANK, and glucocorticoid receptor alpha have revealed no phenotypic differences between the types.[21] Calcitonin receptor expression, however, has been found to exhibit a statistically significant difference with more expression in the aggressive type. IHC staining for c-Src, a protein thought to be required for osteoclast activation, has yielded no quantitative difference between CGCG, giant cell tumor, or cherubism. The mononuclear stromal cells display strong p63 immunostaining in GCTs, but this has not been detected in CGCGs. Thus, p63 is one IHC stain that may help distinguish GCT from CGCG, while also suggesting a differing pathogenesis.[22]

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. CGCG might be treated by non-surgical methods such as radiotherapy, daily systemic doses of calcitonin, and intra-lesional injections of corticosteroids. Interferon alpha therapy has also been used as a postoperative adjuvant and to prevent tumor progression. The long term prognosis of giant cell granulomas is good and metastases do not develop.

CONCLUSION

The clinical behavior of CGCG varies considerably. Asymptomatic swelling is the most common clinical presentation although it may be accompanied by pain and paraesthesia in certain cases. The biologic behavior of CGCG of the jaws ranges from a quiescent lesion with absence of symptoms, resorption or cortical perforation, slow growth, and low recurrence rate, to an aggressive pathology characterized by pain, rapid growth, root resorption, cortical perforation, and a high recurrence rate. The present article highlights the predicament in diagnosing CGCG from other lesions which masquerade with similar radiological findings and in assessing its importance in defining it from a prognostic viewpoint.

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