Central giant cell granulomas of the jaws: A review of the literature with its emphasis on differential diagnosis on related lesions

Bhagyalaxmi Praveen Hongal1, Priya Joshi1, Venkatesh Kulkarni2, Prachi Baldawa3

1Department of Oral & Maxillofacial Pathology & Microbiology, Vasantdada Patil Dental College & Hospital, Sangli, Maharashtra, India, 2Department of Oral & Maxillofacial Pathology & Microbiology, Bharati Vidyapeeth Deemed University, Dental College & Hospital, Pune, Maharashtra, India, 3Department of Oral & Maxillofacial Pathology & Microbiology, M.A Rangunwala College of Dental Science Research Centre, Pune, Maharashtra, India

Abstract

Central giant cell granuloma (CGCG) is an uncommon benign intraosseous lesion that occurs almost exclusively in the jaws that has variable clinical behavior and is difficult to predict. The CGCG of the jaws is usually a non-neoplastic bone lesion accounting for fewer than 7% of all benign tumors of the jaws. Before the early 1950s, central giant cell lesions (GCLs) of the jaws were generally diagnosed as giant cell tumor (GCT) usually found in epiphyseal regions of long bones. Giant cell lesions (GCLs) are mandatorily diagnosed in consideration with clinical and radiological features which predicts its aggressive and non-aggressive behavior. The incidence in the general population is very low and patients are generally younger than 30 years. CGCG belongs together with GCT, brown tumor of hyperparathyroidism and cherubism to the so-called GCLs, which can be difficult to distinguish solely by microscopic examination. GCT of the long bones is practically identical with CGCG of the jaws on histopathologic examination and is considered by some authors as a manifestation of the same disease, where age and local factors are responsible for different clinical characteristics. The aim of this review is to focus on general considerations of CGCG along with its management and to differentiate between various centrally placed GCLs which mimic each other histologically and sometimes clinically.

Keywords: Aggressive granuloma, calcitonin, central giant cell granuloma, giant cell tumor, non-aggressive granuloma, reparative

Introduction

Central giant cell granuloma (CGCG) is an uncommon locally destructive, but benign lesion that occurs in the craniofacial region especially in jaw bones.[1,2] There are only sporadic case reports with extragnathic skeleton involvement.[3] The incidence of CGCG is very low and is commonly seen in patients younger than 30 years. Before the early 1950s, central giant cell lesions (GCL) of the jaws were generally diagnosed as giant cell tumor (GCT) which was usually found in epiphyseal regions of long bones. Although its etiology and pathogenesis are unknown, its histology and clinical behavior has been studied in detail and are now well established thus differentiating CGCG from other GCLs.[4] Recently, WHO has defined it as a localized benign but sometimes aggressive, osteolytic proliferation consisting of fibrous tissue with hemorrhage and hemosiderin deposits and presence of osteoclast-like giant cells with reactive bone formation.[5] Although originally termed as giant cell reparative granuloma, the clinical behavior of many of these lesions has been inconsistent with a reparative process, so the term "reparative" has been omitted today.[6] Clinically CGCG may behave variably ranging from asymptomatic slow growth to aggressive growth with pain, cortical perforation or root resorption. The treatment of choice for CGCG is local curettage. However, aggressive CGCG may recur which may necessitate extensive bone surgery resulting in defects in jaws.[7]
multinucleated giant cells and occasionally trabeculae of woven bone.\(^{[6]}\) This condition was considered to be malignant, when first described 140 years back. Jaffe et al. in 1940, considered it to be a true neoplastic GCT of the bone and in 1952 suggested the term giant cell reparative granuloma; however, at present it is considered as a GCL.\(^{[9]}\)

Although, etiopathogenesis of CGCG of the jaw bones has not been clearly established; it has been suggested that it occurs as a result of an unusual exaggerated reparative process related to previous trauma and intraosseous hemorrhage which triggers the reactive granulomatous process.\(^{[5]}\) According to Geschickter and Copeland the giant cells are derived from proliferating multinucleated cells associated with the resorption of deciduous tooth roots, from fusion of endothelial cells of capillaries, fibroblasts, or monocyte/macrophage lineage.\(^{[10]}\) Although the multinucleated giant cells are prominently seen in CGCG or GCT, they are not considered as the primary proliferating tumor cells. It is hypothesized that the giant cells arise from peripheral blood mononuclear cells recruited by the spindle-shaped stromal cells, which stain positive immunohistochemically for the proliferation marker proliferative cell nuclear antigen and are considered as the proliferating tumor cells. In short, the giant-cells of CGCG are derived from a subset of mononuclear phagocytes. These mononuclear precursor cells differentiate into mature giant-cells under the influence of receptor activator of nuclear factor κB ligand (RANKL) -expressing, proliferating spindle-shaped (osteoblast-like) stromal cells. According to Sapp these cells are slightly modified osteoclasts.\(^{[11]}\)

Except for true neoplastic and dysplastically malformed giant cells, almost all other giant cells in cases of GCT, aneurysmal bone cyst and fibro-histiocytic lesion are of macrophage lineage. With repetitive nuclear divisions unaccompanied by cytoplasmic division, multinucleated giant cells are formed. This process may require heightened telomerase activity and some gene rearrangement. Exposure to certain infectious agents and endogenous or exogenous foreign substances bring about several conformational and enzymatic changes in macrophages. Exogenous foreign bodies and released endogenous unexposed substances are frequent causes of giant cell transformation of macrophages. These include haemorrhages (red cells and plasma), cholesterol, keratin, hair, milk secretion, sperms and mucin, etc. The giant cells in giant cell tumor of bone appear to be transformed circulating monocytes, many if not all of which have converted into active osteoclasts.\(^{[12]}\)

The peak incidence of CGCG is in the second decade and is more common in females.\(^{[13]}\) It is frequently reported that lesions of CGCGs are located anterior to the mandibular first molar and often cross the midline.\(^{[14]}\) A recent review of 80 cases suggested that there is an equal predilection for the posterior mandible.\(^{[15]}\) CGCGs can cause displacement of teeth and developing tooth germs, but rarely cause tooth resorption.

GCLs are usually unilocular. Multifocal lesions should alert the clinician to the possibility of hyperparathyroidism or if bilateral, cherubism or Noonan syndrome. GCLs are osteoclast-rich tumors that are histopathologically indistinguishable from those seen in cherubism and Noonan syndrome. Nevertheless, patients with isolated GCLs do not have the cherubism related germ line SH3BP2 mutation and the lesions do not contain somatic SH3BP2 mutations. This finding suggests that even though all GCLs might appear the same histologically, they are likely to have a different etiopathogenesis.\(^{[16]}\)

CGCG must be distinguished from cherubism, which is an autosomal dominant disorder with similar histologic findings but different clinical and radiologic features. Cherubism is characterized by bilateral expansion of the mandible and/or the maxilla and becomes evident within the first few years of life. It includes multifocal and multilocular cystic lesions of the jaws.\(^{[17]}\) The microscopic features of CGCG and those of cherubism also share similarities with the brown tumors of hyperparathyroidism and aneurysmal bone cysts. They reveal non-neoplastic fibrous lesions containing round and spindle-shaped, mononuclear cells and embedded scattered multinucleated giant cells. Another entity of giant cell-rich granulomatous osseous lesions is the GCT of the bone. In contrast to the CGCG, the GCT is considered truly neoplastic.\(^{[18]}\) Malignant transformation in CGCGs is a rare phenomenon. 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.\(^{[19]}\)

Multiple concurrent CGCGs are reported to be associated with some form of the inherited syndrome or systemic disease. The possibility of any associated systemic condition, such as hyperparathyroidism, should be ruled out through special investigations like endocrinology and biochemical tests, X-ray pelvis, hand wrist radiograph and chest X-ray.

Usually, CGCG presents as a well-defined unilocular or multilocular radiolucent lesion.\(^{[13]}\) Although CGCGs are considered as benign osseous lesions, some authors divides CGCG into two categories based on its clinical and radiographic features: (a) Non-aggressive lesions which are usually slow growing and asymptomatic and do not show cortical perforation or root resorption with less chances of recurrence, (b) aggressive lesions are usually seen in younger patients, are painful, grows rapidly, larger overall, often cause cortical perforation, root resorption and have a tendency to recur.\(^{[20]}\)

CGCG presents with two major histological features firstly, a highly Cellular fibroblastic stroma with plump spindle-shaped cells with high mitotic rate and high vascular density. Second, the prominent multinucleated giant cells throughout the fibroblastic stroma, distributed irregularly often located most numerous around areas of hemorrhage. The morphology of these giant-cells varies from case to case. The cell size is variable, and the number of nuclei ranges from only a few to several dozen.\(^{[21]}\)

As the cell of origin is unknown, and both aggressive and non-aggressive CGCL appear same histologically, many authors have considered biomarkers as a means of differentiating these lesions and correlating these with the clinical behavior and treatment outcome.\(^{[22,23]}\)
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Role of Immunohistochemistry in Diagnosis
The angiogenic activity of GCLs was proposed as a determinant of the aggressive nature of GCLs. Vered et al. were unable to find elevated vascular endothelial growth factor and fibroblast growth factor in these tumors and concluded that GCLs have low angiogenic activity.[28]

Dewsnup et al. studied the expression of cluster differentiation (CD34), a cell-cell adhesion factor and cell-surface glycoprotein found in hematopoietic precursor and capillary endothelial cells. They determined that clinically aggressive GCTs have an increased vascular density compared with non-aggressive lesions based on CD34 staining. Furthermore, they suggested that CD34 evaluation can identify aggressive lesions amenable to anti-angiogenic therapy, even at the time of biopsy. These findings strongly suggest that the CD34 staining density level has a high positive predictive value for biologic behavior and might help in planning treatment and predicting the outcome.[26]

Vered et al. immunohistochemically stained mononuclear giant cells for glucocorticoid and calcitonin receptors in an attempt to provide a reliable and practical tool for selecting an appropriate therapeutic agent to treat GCLs. They found that the mononuclear giant cells of GCLs stained for both glucocorticoid and calcitonin receptors.[29]

Flanagan et al. proposed intralesional corticosteroid for GCLs. Their reasoning was that multinucleated giant cells are osteoclasts and dexamethasone has been shown to inhibit osteoclast-like cells in marrow cultures. Giant cells in GCLs have also been shown to have calcitonin receptors. Calcitonin inhibits osteoclast/giant cell function and has been suggested as a treatment modality.[30]

The expression of Ki-67, a nuclear antigen expressed in all active phases of the cell cycle was similar in both aggressive and non-aggressive CGCG and therefore is not suitable for the differentiation between aggressive and non-aggressive CGCGs. Regarding the neoplastic versus non-neoplastic nature of CGCG in the jaws, findings indicate that a factor secreted by fibroblast/osteoblast RANKL binds to stromal monocyte-derived cells to induce giant cell formation. The RANKL mechanism suggests that the giant cell component might be reactive. They also hinted at the possibility of fibroblasts/myofibroblasts in the CGCGs being lesional cells and giant cells being reactive cells.[29]

Immunohistochemistry has helped to establish the lineage of the cells in CGCG, but is of no value in assessing the aggressiveness of the lesion. However, calcitonin receptor expression is found to exhibit a statistically significant difference with more expression in the aggressive type of CGCG. Immunoreactive response to muramidase, α-1 antichymotrypsin, and α-1 antitrypsin support the theory that the multinucleated giant cells are derived from macrophages.[30]

Clinical and radiographic findings dictate the management of CGCG. Well-defined localized lesions are treated with curettage and have shown a low rate of recurrence. Whereas for extensive multiple lesions a more radical excision is necessary. Carnoy’s solution is commonly used to limit the proliferation of tumor. Additionally the treatment with steroids or calcitonin may be used as adjunct to surgery.[31]

The rate of recurrence varies between 13 and 49%. Malignant transformation in CGCGs is a rare phenomenon.[19] Therefore, in our opinion, clinical parameters, especially the tumor size, are the most reliable indicator of prognosis.

Conclusion
Based on the review of the literature and our own observations, CGCG can be classified as a reactive proliferative disease having typical histologic features, dynamic biologic characteristics and variable clinical patterns. Their site of origin, clinical, radiographic features along with routine histopathological staining are thought to indicate its diagnosis; however, the histogenesis of the tumor remains controversial. Despite the substantial progress in treatment modalities available in the present era, the wide spreading nature of this disease has a strong hold in determining the prognosis. For the improvement of diagnosis and therapy of CGCG, controlled studies based on standardized protocols on significant population may help to enhance the knowledge about this rare bone disease.

References


