Central Giant Cell Granuloma of the Jaw Bones: A Review

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Abstract

Central giant cell granuloma (CGCG) is an uncommon, benign, proliferative, and non-odontogenic lesion whose etiology is not defined. Thought to represent a reparative response to intrabony haemorrhage and inflammation, CGCG was once regarded as a reactive lesion. Central giant cell granuloma usually is an asymptomatic lesion, which may become evident during routine radiographic examination or as a result of painless but visible expansion of the affected jaw. The clinical differential diagnosis for a solitary or multilocular CGCG includes ameloblastoma, odontogenic myxoma, and odontogenic keratocyst. Here, we present a review on the clinical, radiological, histological features of central giant cell granuloma along with discussion on treatment modalities.

Key words: Giant cell, granuloma, multilocular.

Introduction

Central giant cell granuloma (CGCG) is an uncommon, benign, proliferative, and non-odontogenic lesion whose etiology is not defined. It was Jaffe who first introduced the term central giant cell reparative granuloma to distinguish this lesion from the giant cell tumor of long bones. However, since a reparative response was quite rare and most of these lesions were found out to be destructive rather than reparative, the word ‘reparative’ was omitted from that term.\(^1\)

The World Health Organization has defined it 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”.\(^2\)

Pathogenesis

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 occasionally aggressive behaviour, and because of its possible relationship to the giant cell tumor of long bones, CGCG is best classified as a benign neoplasm.\(^3\)

The histogenesis of CGCG of the jawbones remains controversial, as speculations are still debated regarding the possibility that it represents
a reactive, an inflammatory, an infective, or a neoplastic process. Another theory is the vascular hypothesis that suggests that CGCG belongs to the spectrum of mesenchymal proliferative vascular primary jaw lesions. Angiogenesis is a phenomenon modulated by several cytokines and growth factors. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are the most potent inducers of angiogenesis and have a synergistic effect. It is produced and released from activated monocytes and macrophages.4

Perhaps the most widely held view is that the initial CGCG is an endosteal hemorrhage. In 1962, Kramer stated that if the process is concerned with the repair following hemorrhage, then the repair follows a peculiar pattern complicated by repeated new haemorrhages.5 El-Labban (1997) studied CGCG and confirmed Kramer’s statement. She observed that majority of vessels showed intravascular fibrin thrombi and endothelial cell damage with gaps in the cell walls. Plasma, erythrocytes and fibrin were seen subendothelially. She also noted that one of the gaps in a vessel had been sealed by a giant cell. The author suggested that the presence of the giant cell closed the gap and stopped hemorrage and the main purpose for the presence of the stromal cells is the repair not only of the hematoma but also of its contributing vessels.6

The primary tumor cells of CGCGs are fibroblasts. Secondary cells, which are microscopically the most prominent, are multinucleated giant cells. Accessory cells, seen in considerably smaller numbers, include macrophages, factor XIIIa+ dendrocytes, and endothelial cells. The fibroblasts make up the proliferative component of CGCGs, since they express proteins that are indicative of cells in the cell cycle. Tumor fibroblasts are also believed to be responsible for recruitment and retention of monocytes and subsequently for transformation into multinucleated giant cells.3

Clinical features

The lesion is found predominantly in children and young adults, with more than 60 percent of all cases occurring before the age of 30 years. There is a distinct sex predilection, with a female-to-male ratio of 2:1,2 which may be explained by recent suggestions of the association between hormonal secretion and the appearance of CGCG in females.7

Central giant cell granuloma primarily occurs in the jaws and facial bones, though it also appears in other areas of the body.1 Lesions occur more frequently in the mandible than in the maxilla. Lesions are more common in the anterior region of the jaws, and mandibular lesions frequently extend across the midline.5

In the studies conducted by Stavropoulos F, Katz J (2002) no correlation was found between the size of the lesions, their location and the appearance in different age groups, although the size of the lesion was largest in the younger age group (<30 years). This may be explained by the increased metabolic rate and associated hormonal effects in adolescents; however, scientific evidence to support this hypothesis is not currently available.3

Central giant cell granuloma usually is an asymptomatic lesion, which may become evident during routine radiographic examination or as a result of painless but visible expansion of the affected jaw. Cortical bone plates are thinned, but perforation into surrounding soft tissue is rare.2

These lesions usually grow slowly, though they occasionally present a high rate of growth and cause some doubts about malignancy.1 The CGCG are expansive in their growth, but do not invade or grow around nerve trunks. Therefore, the lesions do not cause paresthesia.8

Central giant cell granuloma may lead to an expansion in the cortex so long as it grows up. It has been reported the enlarged size of the lesion has caused tooth mobility, tooth displacement, and root resorption. The borders of the lesions may be regular or diffuse.1

Since CGCG possesses such different features, Choung et al. (1986) and Ficarra et al. (1987) have defined the lesion into two types, referring to its clinical and radiographic features.5
1. Non aggressive lesions make up most cases, exhibit few or no symptoms, demonstrate slow growth and do not show cortical
perforation or root resorption of teeth involved in the lesion.

2. Aggressive lesions are characterized by pain, rapid growth, cortical perforation, and root resorption. They show a marked tendency to recur after treatment, compared with the nonaggressive types.

Studies have failed to identify any biochemical or histologic differences between the aggressive and nonaggressive variants. Most studies have looked for differences in giant cells to make such determinations, but no such differences have been found.²

Histological features

The surgical specimen consists of a soft, spongy, and reddish to brownish friable tissue of varying size. Since the vascular tissue bleeds easily, the specimen is often coated with fresh or coagulated blood.⁵

Histologically, these lesions are characterized by the presence of numerous multinucleated giant cells embedded in a fibrocellular stroma often found adjacent to blood vessel walls.⁴

Central giant cell granuloma is made up of a loose fibrillar connective tissue stroma with many interspersed proliferating fibroblasts and small capillaries. The collagen fibres are not usually collected into bundles; however, groups of fibres will often present a whorled appearance. Multinucleated giant cells are prominent throughout the connective tissue, but not necessarily abundant.⁹

Foci of haemorrhage with hemosiderin pigment and newly formed osteoid or bone are occasionally observed in the stroma.⁴ The stromal cells may be of at least two types: one resembles (myo) fibroblasts, oval or spindle-shaped with a cigar-shaped nucleus exhibiting sparse chromatin; the other resembles macrophages with smaller round nuclei exhibiting dense chromatin. The stromal cells project between the giant cells in swirls, with herringbone and storiform focal patterns.⁵

The aggregations of giant cells show great variation in size, morphology, and the number of the nuclei. Morphologically, the giant cells are of foreign body type or osteoclast-like. The stainability of the cytoplasm varies from light basophilia to marked eosinophilia; variations may occur within the same giant cell. Some cells may contain big, ovoid and lightly stained nucleus with prominent nucleoli and sparse chromatin. Other cells contain small, darkly stained nuclei of irregular shape. Cytoplasmic vacuoles of different sizes containing erythrocytes, iron-positive hemosiderin granules, and leukocytes are frequently found. Mitotic figures are rarely present. In many instances, the giant cells show a definite relationship to vascular channels. The function of multinucleated giant cells that typify these lesions is still controversial, although most investigators believe that the origin of these cells is related to the fusion to the fusion of stromal cells with either macrophages or (myo)fibroblast like cells.⁵

The nature of giant cell is still uncertain, but has been considered as phagocytes, foreign body cells, or osteoclasts. The relationship of giant cell with stromal mononuclear cells (MC) has not been fully elucidated. Furthermore, giant cell may simply represent a reactive component of the lesion and may be present only in response to an unknown stimulus from the stroma.⁴

Studies by Liu B et al. (2003) supported the hypothesis that the osteoclast-like multinucleate giant cells in these lesions may arise from the fusion of the mononuclear component, and that the mononuclear cells may be the osteoclast precursors. Their results suggested that the multinucleate giant cells in CGCG express the characteristic phenotypes of the osteoclasts.¹⁰

Fig.1. Photomicrographs at (a) 400X and (b) 1000X of haematoxylin- and eosin-stained slides showing sheets of (a) stromal cells and (b) multinucleated giant cells"¹¹

A patchy distribution of cellular elements is one feature that helps differentiate CGCG from true giant-cell tumors, which are more
homogenous. The histopathologic findings closely resemble, and may be identical with, those seen in cherubism, the aneurysmal bone cyst and the brown tumor of hyperparathyroidism.

Radiological features

The radiographic appearance of CGCG is not pathognomonic and specific. It changes with the size of the lesion. Small lesions usually appear to be unilocular radiolucent and deprived of internal bone septa. However, large lesions usually appear to be multilocular radiolucent and wispy like bony septae in this area. An imaging feature that has been associated with CGCG, is the presence of a subtle granular bone pattern at the periphery of the expanded bone.

Fig. 2. Axial CT images showing an expansile, corticated lesion with an undulating border and a granular bone pattern laterally (arrow)

Kaffe et al. (1996) found in their study on 80 cases that 51% of the lesions were multilocular, 44% were unilocular, 5% were not loculated, and 68% of the multilocular lesions were in the mandible. They also determined unilocular lesions had a mean size of 4.05 cm, while multilocular lesions’ mean size was 7.38 cm. They established a statistically significant correlation between the locularity of lesions and their size. They also described a correlation between root resorption and gender. Root resorption was observed in 24% male patients and only 6% of female patients.

Differential diagnosis

The clinical differential diagnosis for a solitary or multilocular CGCG includes ameloblastoma, odontogenic myxoma, and odontogenic keratocyst. For patients in the characteristic young age range for CGCG, ameloblastic fibroma, ossifying fibroma, and adenomatoid odontogenic tumor might be added to this list.

The microscopic appearance of CGCG is virtually identical to that of the giant cell lesion associated with hyperparathyroidism. This process must be differentiated on the basis of biochemical tests. Elevated serum levels of parathyroid hormone are indicative of primary hyperparathyroidism.

The giant cell tumor of (long) bone may exhibit histologic features similar to those of CGCG. Some controversy still exists as to whether the benign giant cell tumor of bone and the giant cell granuloma of the jaws represent the same disease or two different disease processes.

The size, number of nuclei, and the distribution of the multinucleated giant cells have been compared in giant cell lesions and giant cell tumors of the jaw and lesions in other bones. Lucas stated that the giant cells in jaw lesions are often smaller than those in giant cell tumors of long bone. Cells in jaw lesions are unevenly distributed throughout, whereas numerous evenly distributed giant cells of long bones are present in practically every field of the neoplasm.

Abrams and Shear (1974) conducted a study on 10 cases of each of the two lesions and confirmed Lucas statement. They concluded that some giant cell lesions of long bones are morphologically indistinguishable from giant cell lesions of the jaws and vice versa. They also suggested that if a giant cell lesion contains giant cells in which the product of length and breadth exceeds 1500 µm², the diagnosis of giant cell tumor should be considered. Giant cell lesions are likely to have areas of less than 1500 µm².

Franklin and his associates were able to confirm only a portion of these findings but, utilizing stereological techniques, did confirm significant differences between giant cells of jaw lesions and of long bone tumors in both nuclear numerical density and mean absolute cell volume. The giant cell tumour of long bones has been recognized recently as an infrequent complication of osteitis deformans (Paget's disease of bone).

Other giant cell-containing look-alikes or entities continuing multinucleated giant cells
include aneurysmal bone cyst and cherubism. Diagnosis of aneurysmal bone cyst is made by the identification of sinusoidal blood spaces within the tumor mass. Cherubism is diagnosed on clinical pathologic grounds.\(^3\)

**Treatment & prognosis:**

Conventional management is by curettage or resection, which may be associated with loss of teeth, or in the younger patient, developing tooth germs. Non-surgical treatment includes systemic calcitonin therapy and intralesional injections with corticosteroids.\(^4\) A somewhat higher rate of recurrence has been reported in lesions arising in children and young teens. Lesions with aggressive clinical features also exhibit a tendency to recur.\(^5\)

**References**

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