CASE REPORT

BIOLOGICAL BEHAVIOR OF CENTRAL GIANT CELL GRANULOMA: A CASE WITH REVIEW

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Abstract

Central Giant Cell Granuloma (CGCG) is a relatively common, localized, osteolytic lesion that almost exclusively occurs in the jaw bones. Females are more frequently affected while the average age of involvement is below 30 years. The lesion predominantly occurs in the mandible, occasionally extending across the midline, whereas involvement of the posterior jaw is decidedly uncommon. Having an uncertain origin, CGCG have been the center of active debate and research regarding its nature and behavior for the last few years.

Here in a case of CGCG affecting an 18 years old female involving the posterior mandible is presented. Through this article an attempt will be made to collect and collate the current information pertaining to the nature and biological behavior of CGCG by critically reviewing the available literatures.

Key Words Central giant cell granuloma, giant cell tumor of long bone, reparative, reactive, neoplastic, giant cells

INTRODUCTION

Central Giant Cell Granuloma (CGCG) is a relatively common, localized, osteolytic lesion that almost exclusively occurs in the jaw bones. Although traditionally described as 'non-neoplastic', some CGCGs display an aggressive clinical course. Other than maxilla and mandible, as a few isolated cases have been reported to occur in the small bones of the hands and feet, they are supposed to be 'non-odontogenic'.[1] Jaffe (1953) first introduced the term 'central giant cell reparative granuloma' to distinguish the lesion from 'Giant Cell Tumor of long Bones'(GCTB).[2] However, since most of the lesions exhibit a destructive rather than a reparative biologic behavior, the word 'reparative' was abandoned. Still, the literature does not reach a consensus on the designation of the most correct term for these lesions and a number of confusing terminologies such as 'Central Giant Cell Granuloma'[3], 'Benign Giant Cell Granuloma'[4], or a noncommittal term 'Central Giant Cell Lesion'[5] has been advocated. The World Health Organization (WHO) in 2005 has been defined this lesion as a 'proliferation' "consisting of fibrous tissue with hemorrhage and hemosiderin deposits, presence of osteoclast- like giant cells, and reactive bone formation".[5] Clinically, CGCGs are reported to occur predominantly in children and young adults, with most cases (75%) presenting before 30 years of age and a 2:1 predilection ratio towards females.[6] The lesion predominantly occurs in the anterior mandible, occasionally extending across the midline, whereas involvement of the posterior jaw is decidedly uncommon. Rarely, lesions involve the posterior jaws, including the mandibular ramus and condyle. Radiographically, CGCG may occur initially as a unilocular, cyst like radiolucency, but as it grows larger, it frequently develops an architecture that causes a soap-bubble type of multilocular radiolucency.[7] The borders of the lesion, in 56% of cases, have been reported as well defined, whereas the margins are generally noncorticated.[8] It is

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also known to scallop the inferior border, displace teeth, resorb interradicular bone and tooth roots to some degree.[9] Microscopically, CGCG is characterized by patchy or evenly distributed numerous multi nucleated giant cells embedded in a highly cellular stroma composed of spindle-shaped stromal cells and round monocytes-macrophages. Extravasated erythrocytes and hemosiderin-laden macrophages are usually evident.[1,8] Foci of osteoid may be present, particularly around the peripheral margins of the lesion.[1] Depending on their aggressiveness, a number of surgical and non-surgical treatment modalities have been implicated in recent years with variable therapeutic outcomes.

CASE REPORT

An 18 years old female reported to the Dept. of Oral and Maxillofacial Pathology, GNIDSR, Panihati, Kolkata with a complaint of pain and swelling in relation to lower left side of the face since one and a half years. Extraoral examination revealed a relatively large, rapidly growing, fairly localized, firm to hard, slightly tender swelling, covered by normal appearing skin without any cutaneous or deeper structure fixity (Figure-1). No paresthesia or regional lymphadenopathy was elicited. Intraorally, there was a large (2.5cm.x1.5cm.), well circumscribed, exophytic, firm, moderately tender growth with regionally ulcerated, non-pigmented surface involving the buccal gingival aspect of #36 and #37, obliterating the vestibulae. Lingually, there was no appreciable swelling and the cortical plate seemed to maintain its normal contour and consistency. Regional teeth were non-carious, immobile, slightly linguoverted, and mildly tender on percussion (Figure-2). OPG revealed a well circumscribed, unilocular radiolucency with well demarcated border and noncorticated margin involving the left body of the mandible extending from the mesial aspect of the roots of # 37 to the distal aspect of # 38 (Figure-3). The first molar exhibited slight widening of the periodontal ligament spaces with no apparent root resorption. Serum calcium and alkaline phosphatase assays were performed and the values were within normal limits. Radiologically, the lesion was differentially diagnosed as ameloblastoma, odontogenic keratocyst, aneurysmal bone cyst, odontogenic myxoma and central hemangioma of bone. As the patient belongs to the younger age group, ameloblastic fibroma, cemento ossifying fibroma (early stages), and adenomatoid odontogenic tumor were also added to this list. Negative results in aspiration, however, ruled out the possibility of vascular jaw lesions. Incisional biopsy was performed under local anesthesia and the formalin-fixed, paraffin-embedded, hematoxylin and eosin stained sections revealed hyperplastic stratified squamous surface epithelium being backed by connective tissue characterized by the presence of numerous multinucleated giant cells dispersedly embedded in a highly cellular, fibrovascular stroma (Figure-4a). Most of the stromal cells were plump,

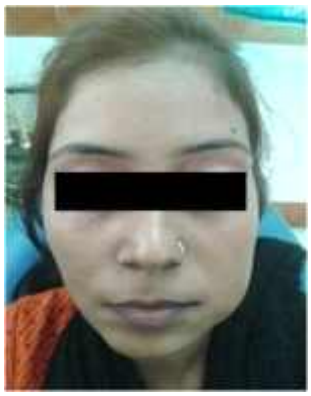


Figure-1: Relatively large, diffuse swelling on the lower left posterior third of face.

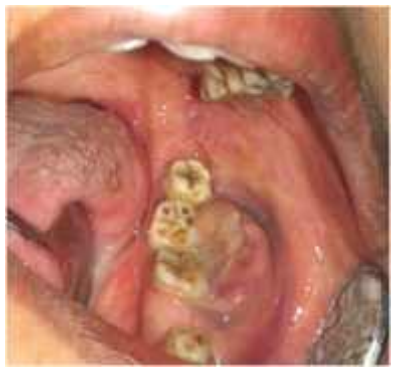


Figure-2: A well circumscribed, exophytic growth associated with slightly linguoverted lower left molar teeth.

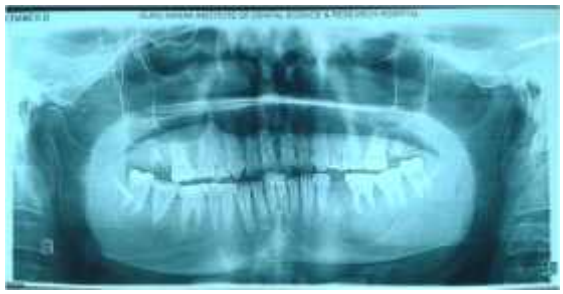


Figure-3: OPG reveals a well circumscribed, unilocular radiolucency with intervening faint wispy trabeculations and well demarcated, regular, non-sclerotic margin.

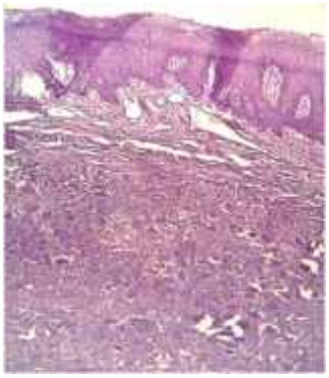


Figure-4a : Hyperplastic stratified squamous surface epithelium (arrow) backed by connective tissue showing numerous multinucleated giant cells (arrow-heads) (H&E 4X).

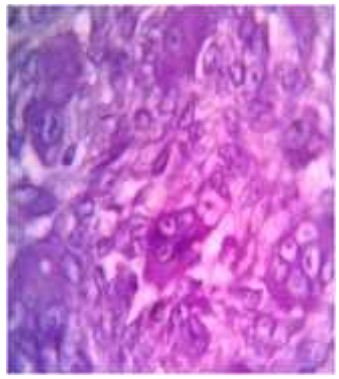
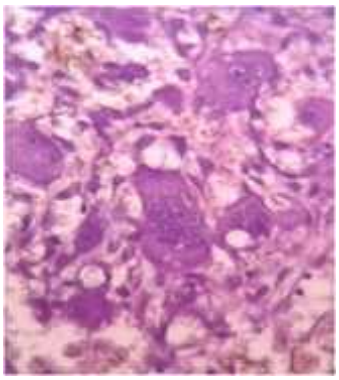


Figure-4b: Multiple giant cells (arrows) embedded in a highly cellular stroma composed primarily of round to spindle stromal cells with vesicular nuclei (arrow-heads) (H&E 40X).



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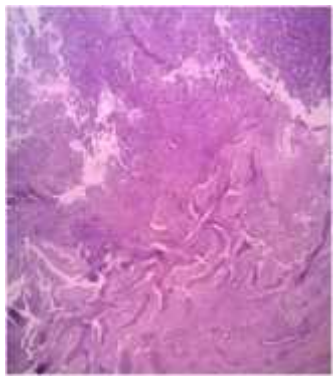

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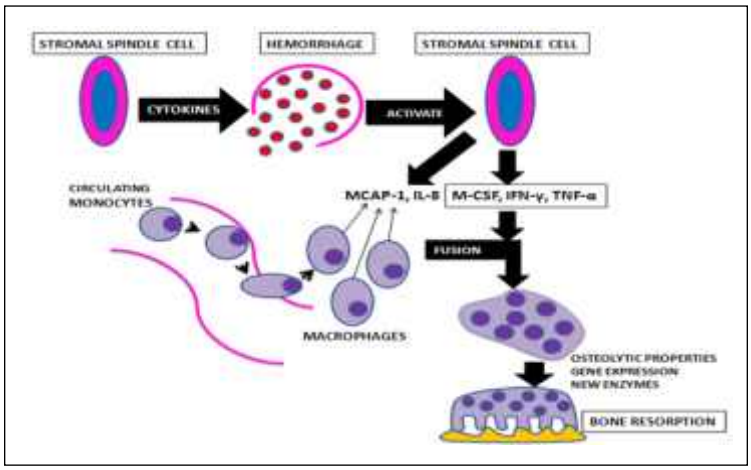

Figure-5 : Putative etiopathogenesis of CGCG: Stromal spindle cells induces hemorrhage which in turn activates the spindle cells to liberate chemokines i.e. MCAP-1 (Macrophage Chemo-attractant Protein-1), and IL-8 (Interleukin-8) to recruit circulating monocytes and subsequently facilitate their fusion by releasing M-CSF (Macrophage colony-stimulating factor), IFN-γ (Interferon-γ), and TNF-α (Tumor necrosis factor-α) to form multinucleated giant cells which acquire their osteoclastic phenotype by unknown epigenetic signaling event.

oval to spindle in shape, having enlarged vesicular nuclei, scant eosinophilic cytoplasm and indistinct cell boundaries (Figure-4b). Numerous thin walled vascular spaces, extravasated erythrocytes, and hemosiderin deposition could be appreciated throughout the lesion (Figure-4c). At the peripheral margin, foci of newly formed bones and osteoids were found to be arranged in a thin, trabecular pattern (Figure-4d). The histopathological differential diagnosis includes GCTB, brown tumor of hyperparathyroidism, cherubism, and fibrous dysplasia. GCTB was differentiated from CGCG because of larger giant cells with more nuclei and a homogenous pattern. Brown tumor of hyperparathyroidism is histologically indistinguishable from CGCG. Normal serum calcium level, however, excluded the possibility of both primary and secondary hyperparathyroidism. Early stages of cherubism may initially present with a single obvious lesion on one side of the jaw, however cherubism was excluded from the differential list by far younger age onset and the microscopic presence of characteristic eosinophilic perivascular cuffing. The possibility of fibrous dysplasia was excluded by its frequent occurrence in the maxilla, self-limiting property, elevated serum alkaline phosphatase level, and scant foci of giant cells hitopathologically. On the basis of clinico-radiographic, biochemical and light microscopic findings, the confirmatory diagnosis of CGCG had been made and the patient was referred to the Dept. of Oral and Maxillofacial Surgery, GNIDSR, for proper treatment and management.

DISCUSSION

Having an uncertain origin, CGCG have been the center of active debate and research regarding its nature and biological behavior for the last few years. Still it is not ascertained whether this intrabony, lytic lesion represent itself as either a reactive or neoplastic process. Thought to represent a reparative response to intrabony hemorrhage and inflammation, CGCG was once regarded as a reactive lesion. However, because of its unpredictable and occasionally aggressive behavior, and because of its possible relationship to the giant cell tumor of long bones (GCTB), CGCG is best classified as a benign neoplasm.[1] Although, microscopically, the multinucleated giant cells are the most prominent feature, it is actually the mononuclear spindle cells (of putative 'fibroblastic' in origin) which represents the neoplastic component of these lesion. Their proliferative property was lent support by the expression of cell-cycle marker Ki-67 in CGCG. It has been proposed that these spindle cells take its origin from the marrow-mesenchyme and being stimulated by a poorly understood epigenetic signaling event, liberate chemo-attractant cytokines that recruits circulating monocytes and induces them to differentiate into multinucleated giant cells.[10,11,12] Finally, the giant cell causes resorption of bone making the hallmark feature of CGCG. Thus, it is worthwhile to emphasize that the 'neoplastic' spindle cells induces, while the 'reactive' giant cell causes CGCG (Figure-5). However, this hypothesis cannot explain the possible reparative nature of the lesion, as originally described by Jaffe in 1953. Worth, in the last edition of his radiology textbook in 1981[13], reported a series of cases, which were treated by diagnostic biopsy only and followed radiographically, and the majority of them did appeared to resolve spontaneously in years by fibrous scarring. El-Labban in 1997 had demonstrated the presence of intravascular fibrin thrombi in majority of lesional vessels and endothelial cell damage with gaps in the cell walls, of which, one of the gaps had been sealed by a giant cell. She suggested that the presence of the giant cell closed the gap and stopped hemorrhage and the main purpose for the presence of the stromal cells is to repair not only of the hematoma but also of its contributing vessels.14 At the present time, however, most of the authors concerned about the 'reparative' nature as majority of CGCGs will continue to increase in size without definitive treatment.

In spite of Jaffe's effort to distinguish CGCG from the 'true' GCTB many years ago, the controversy still exists to opine whether they are distinct, separate entities or they represent a continuum of a single disease process.[14] Although most of the GCTBs can histopathologically be characterized by the presence of larger, homogeneously dispersed giant cells that contain more nuclei; less prominent hemorrhage and hemosiderin; and infrequent osteiod formation, a number of jaw lesions are indistinguishable microscopically from the CGCG.[1] Despite the histopathologic similarity, GCTB affecting jaw bones appear to have a biologically different behavior from the long bone lesions, which have a higher recurrence rates after curettage and show malignant change in up to 10% of cases.[8] In this issue, Philipsen HP and Reichart PA[11] did agree with Whitaker and Waldron[15] that until future research clearly delineates separation of the CGCG from the GCTB, a more noncommittal term 'Central Giant Cell Lesion (CGCL)' can be used for the giant cell lesion of the jaw bones.

The phenotype of the giant cells in CGCG had extensively been investigated as well. Based on morphologic and histochemical evidence, a number of suggestions had been proposed. Mallory[16] and others[17,18] have suggested that they develop from macrophages, and Thompson et al.[19] labeled them as foreign body giant cells. A number of workers have proposed that they arise from bone cells, or by fusion of endothelial cells and even pericytes, fibroblasts, and myofibroblasts been proposed as precursors. All these hypothetical approaches were not sufficient to conclude the clear identity and nature of the giant cells, until the elegant and conclusive work by

Flanagan A. M. et al. in 1988.[20] Based on their dynamic study on immunocyto- and immunohistochemical techniques, preparation of bone slices, cell culture, effect of calcitonin on giant cell function, and time lapse video recording systems, they concluded that "the multinucleate cells in giant cell granulomas of the jaw are osteoclasts".

The conflicting clinical behavior of CGCG is reflected to its management options as well. As a rule of thumb, clinically aggressive lesions are treated by non-surgical (intralesional injections of corticosteroids / salmon calcitonin as a subcutaneous injection or nasal spray / interferon alpha-2a alone or with bisphosphonates), whereas, non-aggressive lesions are better managed by surgical treatment modalities (simple curettage to en-block resection to segmental osteotomy).[6,9] In reports of large series of cases, recurrence rates range from 11 % to 50% or greater. Most studies indicate a recurrence rate of about 15% to 20%.[8] A somewhat higher rate of recurrence has been reported in lesions arising in children and young teens.

CONCLUSION

Although extensive literature has been made available to the readers who envisage a keen interest in CGCG of the jaw, clarity to this entity with respect to terminology, nature, behavior and its adjunctive relation to the GCTB has rarely been lucid in its understanding. The present case correlates with the aggressive variant of CGCG by its painful nature, rapid growth and clinico-radiographic evidence of cortical perforation and is unique in the fact that the site of occurrence (posterior mandible) which, according to some literatures is 'decidedly uncommon'.

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REFERENCES

1) Stewart JCB. Benign Nonodontogenic Tumors: Regezi JA, Sciubba JJ, Jordan RCK, eds. Oral Pathology: Clinical Pathologic Correlations. 6th ed. Philadelphia: Saunders: 303-307, 2012.

2) Jaffe HL. Giant cell reparative granuloma, traumatic bone cyst and fibrous (fibro-osseous) dysplasia of jaw bones. Oral Surg Oral Med Oral Pathol 6:159-175, 1953.

3) Gungormus M, Akgul HM. Central Giant Cell Granuloma of the Jaws: A Clinical and Radiologic Study. J Contemp Dent Pract 4: 87-97, 2003.

4) Chuong R, Kaban LB, Kozakewich H et al. Central giant cell lesions of the jaws: A clinicopathologic study. J Oral Maxillofac Surg 44:708, 1986.

5) Barnes L, Eveson JW, Reichart P et al. World Health Organization Classification of Tumors. Pathology and Genetics of Head and Neck Tumors. IARC Press. 324, 2005.

6) Chattha MR et al. Current concepts in Central Giant Cell Granuloma. Pakistan Oral & Dent. Jr. 26 (1) 71-78, June 2006.

7) Wood NK, Goaz PW, Kallal RH. Multilocular radiolucencies: Wood NK, Goaz PW eds. Differential diagnosis of oral and maxillofacial lesions. 5th ed. St. Louis: Mosby. 333- 55, 1997.

8) Neville BW, Damm DD, Alien CM, Bouquot JE, editors. Oral & Maxillofacial Pathology. 3rd ed. Philadelphia: Saunders. 626-629, 2009.

9) Robert E. Marx, Diane Stern. Oral and Maxillofacial Pathology, A Rationale for Diagnosis and Treatment. Quintessence publishing. 2nd Edition; 860-866, 2012.

10) O'Malley M, Pogrel MA, Stewart JC et al. Central giant cell granulomas of the jaws: Phenotype and proliferation-associated markers. J Oral Pathol Med 26:159, 1997.

11) Tiffee JC, Aufdemorte TB. Markers for macrophage and osteoclasts lineages in giant cell lesions of the oral cavity. J Oral Maxillofac Surg 55:1108, 1997.

12) Haque AU, Moastasim A. Giant cell Tumor of Bone: A neoplastic or a reactive condition? Int J Clin Exp Pathol 1. 489-501, 2008.

13) Worth HM, Chicago IL. Principles and practice of oral radiology interpretation. Chicago Year Book Medical Publishers. 498–505, 1963.

14) Philipsen HP, Reichart PA. Odontogenic Tumors and Allied Lesions. Quintessence Publishing Company Ltd. 319-332, 2003.

15) Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. A clinical, radiologic, and histopathologic study. Oral Surg Oral Med Oral PathoI. 75:199-208, 1993.

16) Mallory FB. Giant cell sarcoma. J M Res 24:463-467, 1911.

17) Davis JMG. The ultrastructural changes that occur during the transformation of lung macrophages to giant cells and fibroblasts in experimental asbestosis. Br J Exp Pathol 44568-575, 1963.

18) Eisenstein R. Giant cell tumor of tendon sheath. J Bone Joint Surg 50:476-486, 1969.

19) Thompson SH, Bischoff P, Bender S. Central giant cell granuloma of the mandible. J Oral Maxillofac Surg 41:743-746, 1983.

20) Adrienne M. Flanagan et al. The multinucleate cells in Giant cell Granulomas of the jaw are osteoclasts. Cancer 62:1139-1145, 1988.