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Case Report

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Cd68 Expression In Central Giant Cell Granuloma - Report Of 2 Cases.

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Abstract
The central giant cell granuloma is an unusual bony, non-neoplastic, non-odontogenic lesion that comprises approximately 7% of all benign lesions of the jaws. It presents commonly in children and adults. Central giant cell granuloma affects females more than males, in 3:1 ratio and is seen mostly in first to fourth decade when hormonal changes are most pronounced. This case report presents two cases of central giant cell granuloma, occurring in two females with an age of 14 and 45 years. Each case was studied by immunohistochemical analysis to investigate the CD68 expression and the pattern of immunoreactivity in mononuclear and multinucleated giant cells. The aim of the report is to determine the probable origin of stromal mononuclear cells and multinuclear giant cells.

Key Words
Central giant cell granuloma (CGCG), immunohistochemistry, multinucleated giant cells, CD68.

Introduction

Central giant cell granuloma (CGCG) is relatively an unusual bony, non-neoplastic tumor accounting for approximately 7 % of all jaw benign lesions.[1],[2] Jaffe, first introduced a very uncommon lesion in 1953 and named it as central giant cell reparative granuloma, [1],[2] but reparative response is quite rare and the lesion was found to be more destructive. Nowadays, the word reparative has been erased from the term central giant cell reparative granuloma.[3],[4] WHO defines CGCG as an intra-osseous lesion consisting of cellular fibrous tissue that contains multiple foci of haemorrhagic aggregation of multinucleated giant cells and occasionally trabeculae of immature woven bone.[5],[6]

CGCG more frequently occurs in the patients below the age of 30 years and predominantly affects females more than the males (ratio-3:1). It is presumed that the lesional cells would exhibit receptors for estrogen and progesterone hormone.[7],[8] Anterior mandibular region is the most common site with the prevalence of 65-85%. [1],[3],[9]

Mostly CGCG occurs on the gingival or alveolar mucosa and appears as a soft red or blue, haemorrhagic, painless, nodular swelling[10] and present as an asymptomatic expansion of the jaws. It can be aggressive; and associated with pain, osseous destruction, cortical plate perforation, root resorption and recurrence.[11] This report presents two interesting cases of CGCG in a 14-year-old female and a 45-old-year female. The aim of this report is to describe the clinical presentation, investigation, diagnosis and attempt to histopathological and immunohisto chemical means.

Case Analysis

Case –I

A 14-year-old female reported to the Department of Oral Medicine with the complaint of loss of teeth on anterior region. The patient also noted a swelling, which started as a small nodule, and progressed to the present size over a period of one year.

On extra-oral examination, a diffuse swelling was seen on the right side of the face in the region of anterior maxilla. Intraorally, the swelling extended from 11 to 14 region, and also loss of 12 and 13 were noted. **(Fig-1)** The overlying mucosa was normal, and on palpation the swelling was slightly tender. The radiographic examination (PA Water's view) revealed an unilocular radiolucent lesion with poorly circumscribed margins. **(Fig-2)**

Provisional diagnosis of CGCG was made and the relevant haematological and biochemical investigation carried out were normal. Incisional biopsy was done from the intraoral site from the labial aspect, under local anaesthesia. Histopathological examination revealed moderately cellular connective tissue stroma, with numerous multinucleated giant cells in the background of ovoid to spindle shaped mesenchymal cells. The giant cells were distributed uniformly throughout the lesional tissue. Areas of extravasated RBCs were observed at certain regions. Foci of osteoid formation were also evident. **(Fig-3)**

Immunohistochemical analysis was performed by the avidin-biotin

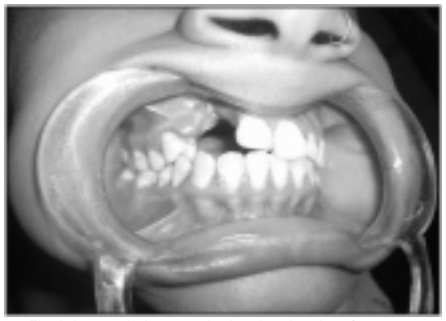

Fig. I: Intraoral photograph showing the site of surgery.

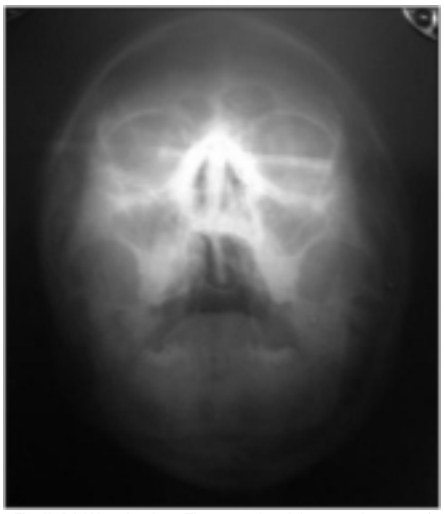

Fig. II: PA Water's view. The mass involving anterior part of maxilla.

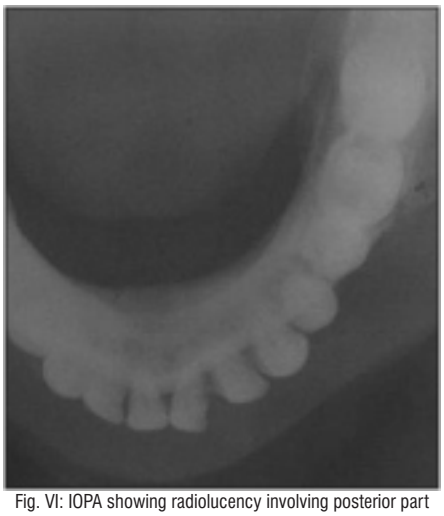

Fig. VI: IOPA showing radiolucency involving posterior part of mandible.

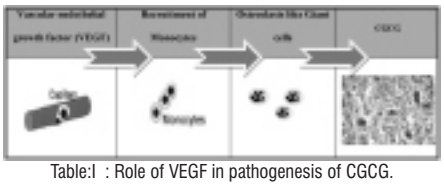

Table:I : Role of VEGF in pathogenesis of CGCG.

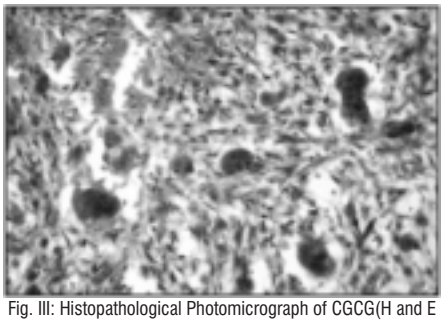

Fig. III: Histopathological Photomicrograph of CGCG(H and E stain magnification 10x)

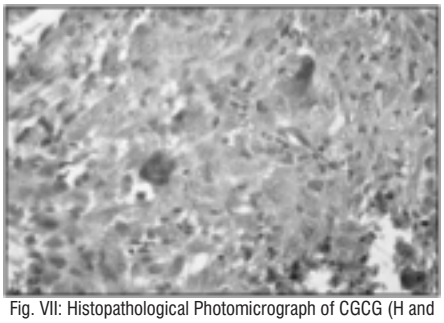

Fig. VII: Histopathological Photomicrograph of CGCG (H and E stain magnification 10x)

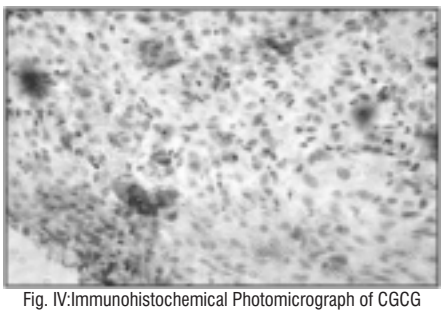

Fig. IV:Immunohistochemical Photomicrograph of CGCG (Immunohistochemical stain CD68 magnification 10x)

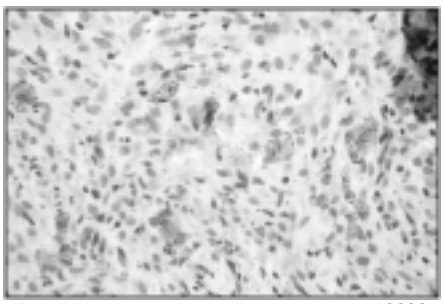

Fig. VIII: Immunohistochemical Photomicrograph of CGCG (Immunohistochemical stain CD68 magnification 10x)

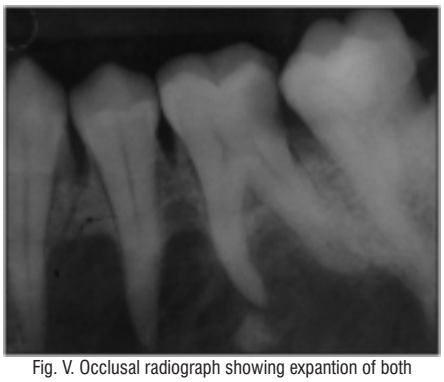

Fig. V. Occlusal radiograph showing expantion of both cortical plates.

peroxidases complex method for anti–CD68 at dilution of 1:1000. Immunohistochemically, macrophages and giant cells share similar antigenic inflammatory reaction. Immunohisto chemical analysis of CGCG under CD68 positive cells were detected in many mononuclear cells and majority of multinucleated giant cells. **(Fig-4)**

Case-2

A 45 year old female reported in the authors' institution with firm, painless swelling on the mandibular left posterior region of the jaw. Intraoral examination showed a solitary swelling measuring about 3x2 cm present in the relation to 35 to 37 and obliterating buccal vestibule. It was oval in shape with ill defined margins. The overlying mucosa appeared normal. A radiolucent lesion measuring about 3x2 cm in relation to mandibular left first molar and extending anteriorly to first premolar was noted. **(Fig-5) (Fig-6)** Routine haemogram and urine analysis were normal. Laboratory tests including calcium, alkaline phosphatase, and parathyroid hormone were normal there by excluding the possibility of hyperthyroidism (Brown's tumor).

Under general anaesthesia, the lesion was excised after extraction of involved the teeth. The lesion was grossly irregular and encapsulated. Histopathological examination of biopsy specimen showed fibrous connective tissue with evenly distributed multinucleated giant cells with varying sizes and shapes. Large blood vessels and dilated capillaries were seen with few areas of hemorrhage. In some regions bony trabeculae and calcifications were present. **(Fig-7)** Immunohistochemical analysis of CGCG under CD68 positive cells were detected in many mononuclear cells and majority of multinucleated giant cells. **(Fig-8)**

Discussion

CGCG is an asymptomatic, osteolytic lesion and usually diagnosed during routine radiological examination. It rarely occurs outside the craniofacial bones, and more frequently present in children and young adults.[6],[12] It usually occurs below the age of 30 years.[2] The case presented here is of 14 year old girl and 45 year old woman. The etiology and pathogenesis of CGCG of jawbones has not been clearly established. It appears as a mass of restricted growth which is a reaction of the organism to an irritation, most probably to bone bleeding, which may be caused by trauma.[13]

The female to male ratio is 3:1.[5],[14],[15],[16] Our report was in accordance with previous researches stating that giant cell granuloma has predilection for females (65%)[11] and occurs frequently in 10-30 years of life when hormonal changes are prominent.[2],[4],[5] Several authors have shown the relationship between sex hormones and giant cell granuloma.[6],[16],[17] According to Csilag

et.al. (1997), the occurrence of CGCG is prominent in females due to increased level of hormonal secretion.[17],[18] Several cases of CGCG occurring in pregnancy have been documented in the literature.[19],[20] McGowan was the first to suggest that the CGCG could be under the influence of the ovarian hormones.[7] Flaggert et al., reported a case of CGCG in a patient undergoing high dose estrogen therapy for Soto's syndrome.[20] These findings would suggest that both the peripheral giant cell granuloma and CGCG could be under the influence of the ovarian hormones.[21]

Many studies have shown that many tissues/organs and certain tumors contain receptors for the ovarian hormones, and are responsive to fluctuations in hormone levels. In 1992, Forabasco showed estrogen receptors in oral mucosa. These hormones do play a role in the biology of many types of tumor.[21] It is important to note the frequency of occurrence of these lesions on maturity, pregnancy and during menstruation. In the present case reports, both patients were female aged 14 and 45 years.

CGCG occurs most commonly in mandible (60-85%).[1] However Kaffe et al. showed in their study state that there is no site predilection.[5] The first case reported here, lesion was in maxilla while the second case was in the mandible.

CGCG is usually presents as an asymptomatic, slow growing, localized swelling with smooth surface as was seen in the present cases. In the first case the parents noted the swelling present on the face. While in second case the patient felt the painless expansion of bone with mobility of the teeth.

The biologic behaviour of CGCG of the jaws ranges from a quiescent lesion with absence of symptoms, root resorption or cortical perforation, slow growth, and low recurrence rate.[22]

Regezi AJ et al, 2004 suggested that giant cells are derived from monocytes in a mononuclear stroma of spindle mesenchymal cells and round monocyte macrophages. It is believed that this spindle cell recruits monocytes and induce them to differentiate into osteoclastic giant cells through release of cytokines. An epigenetic event occurring in the spindle mesenchymal cells of bone resulting in escape from cell cycle control and expression of proteins capable of monocyte recruitment and differentiation into osteoclasts.[23] They also suggested that VEGF (vascular endothelial growth factor) found in CGCG. **(Table-1)**

The radiographic appearance of CGCG is not pathognomic.[2],[3],[24] Multilocular lesion are common than the unilocular.[2],[4],[24] Small lesion usually appearing as unilocular radiolucent and large lesions usually appearing as multilocular.[24] Some reports have divided CGCG in two categories based on clinical, radiological and histopathologcal findings:

(1) Non-aggressive are slow growing and asymptomatic, without cortical resorption or root perforation in affected teeth, which do not recur
(2) Aggressive- are usually found in younger patients, are painful with rapid growth, often cause cortical perforation and root resorption and has a tendency to recur.[2],[25]

The present cases demonstrated as clinically and radiologically non-aggressive lesions.
Microscopically CGCG consisted of two distinct populations of cells:

1. Multinucleated giant cells
2. Spindle shape stromal cells

These multinucleated giant cells are osteoclast like cells. They induce osteoclast formation from mononuclear blood vessels. An epigenetic event occurring in the spindle mesenchymal cells.

Histopathologically, CGCG is 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.[11]

In our first case the incisional biopsy specimen revealed numerous multinucleated giant cells and plump spindle shaped fibroblast in connective tissue stoma. In our Second case numerous multinucleated giant cells and spindle cells were distributed randomly in connective tissue stoma.

The immunohistochemistry showed a strong diffuse positivity against CD68 in round mononuclear stromal cells and in multinucleated giant cells. CD68 monocyte-macrophage lineage marker has been often used in the investigation of giant cells.[22] These results suggest that multinucleated giant cell show an osteoclast phenotype and are probably derived from monocyte/macrophage lineage from the endothelial cells of the capillary. [22]

In present report CD68 positive cells were detected in many mononuclear cells and in the majority of multinucleated giant cells. [22]

Conclusion

The present report clarifies the pathogenesis and nature of the giant cell lesions. We conclude that the patients under hormone therapy with sex hormones or during pregnancy have a higher chance for giant cell granulomas.

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