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Original Research Article

Prognostic marker in giant cell granulomas

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ABSTRACT

Introduction: Giant cell granulomas intraosseous or extraosseous are a group of pathological entities with similar histopathological features characterized by MGCs in fibroblastic vascularized connective tissue background with a varying clinical behavior. Peripheral giant cell granuloma (PGCG) is a reactive lesion. Central giant cell granuloma (CGCG) exhibits a non-neoplastic proliferative behavior and can be aggressive and nonaggressive based upon clinical and radiographic features and has a high rate of recurrence. A marker to predict its behavior may be helpful in assessing the clinical outcome. The aim of this study was to compare and determine the biologic nature and clinical behavior of these lesions by immunohistochemical expression of Factor VIII-RA in CGCG and PGCG.

Materials and Methods: Immunohistochemical expression of Factor VIII-RA was assessed in formalin fixed paraffin embbeded tissue block of 12 cases of PGCG and CGCG (aggressive and non- aggressive) each.

Results: In total, 12 cases of PGCG and 12 cases of CGCG were studied. The average age of CGCG, and PGCG was 21.2 ± 10.43 and 38.17 ± 21.58 respectively. Both occurred more often in the mandible than the maxilla (Table I). CGCG presented as painless swelling in 66.6% (8case) and 33.4% (4case) different cases were symptomatic. Immunohistochemical evaluation of the two groups examined showed a positive reaction for factor VIII-RA. Number of stained cells and intensity of staining decreased from PGCG, non-aggressive CGCG to aggressive CGCG.

Conclusion: Higher factor VIII RA in endothelial cells of central giant cell lesions indicates a less aggressive form, suggesting its potential use in clinical assessment and treatment planning.

1. Introduction

Giant cell granulomas intraosseous or extraosseous are group of objects with similar histopathological features characterized by multinucleated giant cells (MGCs) in fibrocellular vascularized stroma with varying biologic behavior. It comprises 9.29% of all oral giant cell lesions.

Jaffe (1953) introduced the term central giant cell reparative granuloma. He introduced these lesion from the giant cell tumor of long bones. Based on locally invasive and destructive in nature, the term reparative has been discontinued. On the basis of clinical and radiographic features CGCG can be aggressive and non-aggressive. Aggressive type grows rapidly, shows pain, tooth displacement, cortical perforation, root resorption and tend to recur after treatment. Non-aggressive types are slow growing and do not show root resorption or cortical perforation and often show new bone formation peripherally. Histological features of CGCG are defined by WHO as an intraosseous lesions consisting of fibrous tissue containing multiple foci of hemorrhage, aggregation

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of multinucleated giant cells and occasionally trabecular of bone.

Peripheral giant cell granuloma (PGCG) is relatively common extraosseous reactive lesion of the oral cavity. It originates from the periosteum of the tooth. Exact etiology is not known, local irritation, periodontal diseases, poor dental restorations, ill-fitting dental appliances, dental extractions and chronic infection has been suggested as contributing factors. PGCG bears microscopic resemblance to CGCG despite different clinical features.

A marker to predict the behavior of these lesions may be helpful in assessing the clinical outcome. According to available literature FactorVIII-RA complex has a direct effect on osteoclastogenesis and has a role in bone remodeling. Therefore the aim of this study was to compare the factor VIII-RA immunoreactivity in aggressive, nonaggressive CGCG and PGCG of the jaws which may be useful to determine the biologic nature and clinical outcome of these lesions and may lead to a new treatment modality.

2. Materials and Methods

In this retrospective study, 12 formalin fixed paraffin embedded tissue block of CGCG (04 aggressive and 08 non-aggressive) and 12 blocks of PGCG were collected from the archives of the department.

Clinical information of the cases including age, gender and location was retrieived. The CGCG were grouped into aggressive and non-aggressive based on Choung and Kanban's classification system. Paraffin-embedded tissue sections of the lesions were immunohistochemically stained for Factor VIII- RA. (External control – colon, Internal control –squamous epithelial cells)

IHC Scoring (Factor VIII-RA) method

Immunohistochemical expression of Factor VIII-RA was assessed in endothelial cells in eight high power fields (40X). Each field was evaluated for the number of stained cells & staining intensity. Staining intensity was graded as 0 – negative; 1- light staining; 2 – moderate staining; 3 intense staining .The proportion score of stained cells for factor VIII –RA was assessed as 0 - no stained cells; 1 - <25% stained cells; 2 - 25 to 50% stained cells; 3 - > 50% stained cells. Integrated score= Score for % of stained cell × Intensity score. The data was analysed with SPSS software Package. Data analysis was performed using One way ANOVA with post hoc tukey HSD test .Significance was established at P value <0.01.

3. Results

In total, 12 cases of each CGCG and PGCG were studied. The average age of CGCG, and PGCG patients was 21.2 ± 10.43 and 38.17 ± 21.58 respectively. Both lesions occurred more often in the mandible rather than the maxilla (Table 1). CGCG were more common in the anterior mandible, often crossing the midline. PGCG common in molar and premolar area of mandible. 66.6 % (8) cases of CGCG presented as painless swelling and 33.4 % (4) cases were associated with pain and displacement of teeth.

Immunohistochemical evaluation of the two groups examined showed a positive reaction for factor VIII-RA except one case of CGCG. Immunoreactivity score of factor VIII-RA was observed in endothelial cells of all the groups. The most of CGCG (41.67%) showed proportion score of 2 where as in PGCG (75%) cases it was 3. The 0 score was obtained in 8% cases of CGCG. The overall mean of proportion score of CGCG and PGCG was as 2.1 and 2.75 respectively.

The analysis of intensity score of factor VIII-RA in endothelial cells presented a discrete predominance of score 0 and score 2 in CGCG and PGCG respectively. (Figures 1 and 2). Intensity was more remarkable at the periphery of the lesions especially in PGCG. Data analysis demonstrated statistically significant difference among groups regarding factor VIII-RA expression (p>0.05). The overall mean of intensity score of CGCG and PGCG was as 1.5 and 2.67 respectively.Table 2

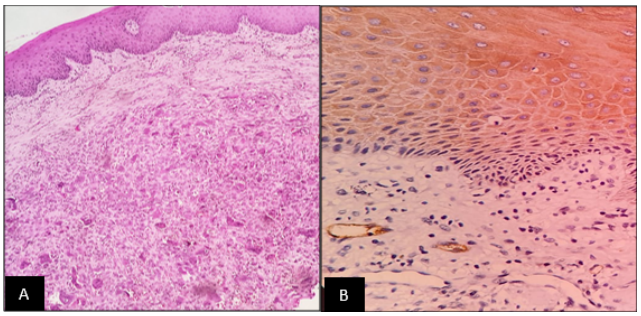


Figure 1: Photo micrograph; **A:** Showing H & E stained and Photo micrograph; **B:** Showing IHC Factor VIII-RA stained sections of PGCG

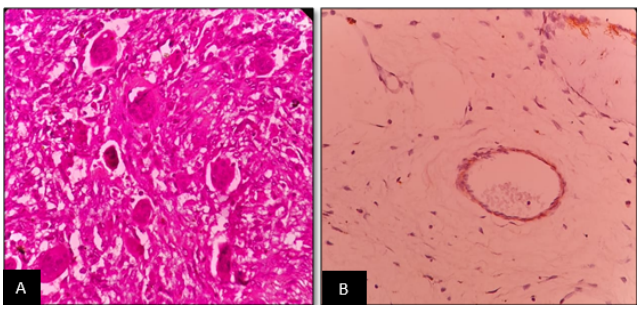
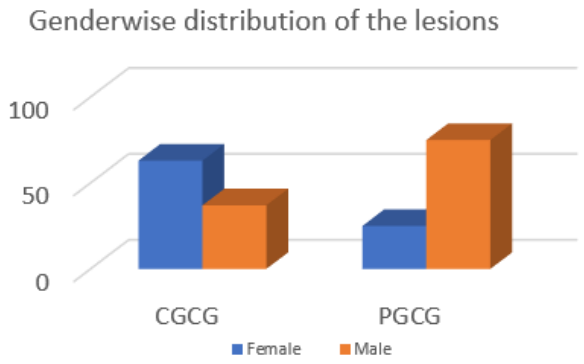
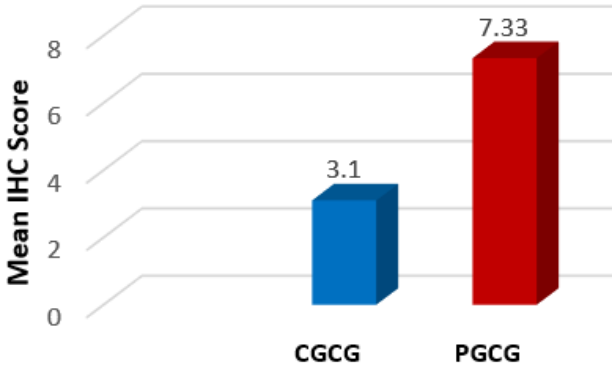


Figure 2: Photo micrograph; **A:** showing H & E and Photo micrograph; **B:** IHC Factor VIII-RA (endothelial cell) stained sections of CGCG

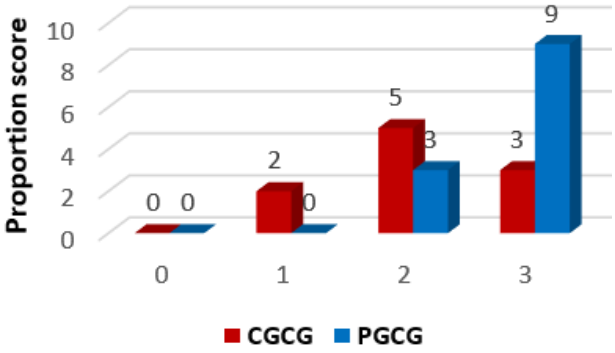
The Kruskaal-Wallis analysis showed a significant difference in factor VIII-RA intensity score in endothelial



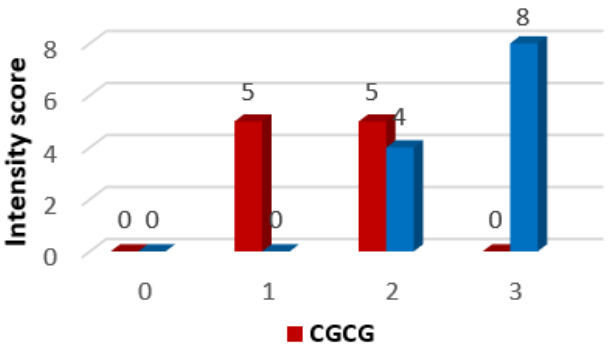
Graph 1: Gender wise distribution of Giant cell lesions



Graph 4: Comparison of mean integrated score among groups



Graph 2: Comparison of proportion score of endothelial cells factor VIII-RA among groups



Graph 3: Comparison of intensity score of endothelial cells factor VIII-RA among groups

Table 1: Results of PGCG & CGCG

S.No.	Age/Sex	Proportion score	Staining Intensity	Integrated Score
PGCG				
1.	10/F	3	3	9
2.	65/M	3	2	6
3.	25/M	2	2	4
4.	50/M	3	3	9
5.	30/F	3	3	9
6.	42/M	3	3	9
7.	19/M	2	3	6
8.	45/M	3	2	6
9.	47/M	3	2	6
10	7/M	3	3	9
11.	80/F	3	3	9
12.	38/M	2	3	6
		CGCG		
1.	14/M	2	1	2
2.	5/M	3	1	3
3.	35/F	2	2	4
4.	32/F	1	1	1
5.	19/F	3	2	6
6.	18/F	2	1	2
7.	35/F	2	2	4
8.	14/F	3	1	3
9.	27/F	2	2	4
10	13/M	1	1	1
11.	17/M	1	1	1
12.	53/F	0	1	0

Table 2: Demographic details of patients with CGCG and PGCG

Parameter	CGCG	PGCG
Age (Mean ± SD)	21.2 ± 10.43	38.17 ± 21.58
Gender		
Female (%)	66.67%	25%
Male (%)	33.33%	75%

Table 3: Comparison of proportion score of endothelial cells factor VIII-RA among groups

Proportion score	CGCG	PGCG	p-value
0	8.33%	0	
1	25%	0	
2	41.67%	25%	
3	25%	75%	0.0 270
Total	100%	100%	
Mean	2.1	2.75	
Median	2	3	
P<0.05-: Statically significant			

Table 4: Comparison of intensity score of endothelial cells factor VIII-RA among groups

Intensity score	CGCG	PGCG	p-value
0	0	0	
1	66.67%	0	
2	33.33%	33.33%	
3	0	66.67%	0.0016
Total	100%	100%	
Mean	1.5	2.67	
Median	1.5	3	
P<0.01 -: Statistically highly significant			

Table 5: Comparison of mean integrated score among groups

	CGCG	PGCG	P - value
Mean integrated score (Mean ± SD)	3.1 ± 1.449	7.33 ± 1.826	0.00001**

** p < 0.01 -: Statistically highly significant

cells among groups (P=0.016), with a higher intensity score observed in PGCG. Regarding the overall expression of factor VIII-RA, data analysis showed a significantly higher intensity score in endothelial cells of PGCG (p=0.004).Tables 3, 4 and 5

4. Discussion

Giant cells are large, multinucleated cells that are formed by the union of several distinct cells such as macrophage, epithelioid cells, monocytes, virus affected cells or anaplastic changes.[1] There are two types of giant cells such as physiological and pathological. Physiological giant cells exist in normal tissues eg. Osteoclasts in bone, Trophoblasts in placenta and Megakaryocytes in bone marrow. Pathological giant cells in inflammation are Foreign Body Giant Cells, Langhan's Giant cell and Touton Giant cells. Giant cells in tumors are Tumor giant cells, Reed Sternberg cells and Osteoclastic giant cells of bone tumors.[1,2]The malignant transformation of giant cell tumor is proliferative changes occure at the site of curettage and bone grafting or it can follow surgery.[3]

WHO classified CGCG as a non-neoplastic, benign lesion of bone. Jaffe's categorized the separate entity to distinguish it from the giant cell tumour of extra-gnathic sites.[1,4]The prevalence of CGCG reported by several authors include 0.15%, 0.17% and 0.37%.[2,4,5] Commonly seen in 2^{nd} to 3^{rd} decade of life with female predominance. In the present study CGCG was seen predominantly in 2^{nd} and 3^{rd} decade with mean age of 21.2 years and female predominance was noticed in 66.66% of cases. Chuong et al. were the first to categorize CGCG into aggressive and non-aggressive forms.[6] In the present study 33.33% cases showed aggressive behavior. Whereas, the non-aggressive type presented as a slow growing, asymptomatic swelling, occasionally revealed through radiographic examination.[1–3,7]

PGCG is postulated to arise from the periosteum of the tooth. The etiology is postulated to be local irritating factors and chronic trauma. The factors include bacterial plaque, calculus, food debris retention, traumatic extractions, defective dental restorations, ill-fitting prosthesis, dental implants, chronic infections and trauma from malocclusion.[8] PGCG has a frequency of 24.4% all the lesions of the gingiva. Commonly seen in 3^{rd} to 4^{th} decade of life with mean age 38.17 years and exhibit female predilection. They present as pink to red pedunculated or sessile growth with a smooth or ulcerated surface.[8]In children PGCG might show a rapid growth as well as aggressive and recurrent behavior.[9]The recurrence rate of PGCG varies from 5% to 70.6%.In the present study, the clinical findings were in accordance with the literature.

Radiographically CGCG is a destructive lesion with varied presentation, producing radiolucent area with relatively smooth or ragged border and may show faint trabeculae. They may present with definite loculations.[6,7] Associated findings include displacement of teeth, root resorption, loss of lamina dura, expansion and perforation of the cortical bone.[3] Although PGCG may cause superficial erosion or "cuffing" of the alveolar bone.[1,10] In the present study radiographic findings of these lesions were favorable with the previous study.

Microscopically, CGCG comprises of two major cell population, i.e. the spindle to fusiform shaped cells and prominent MGCs dispersed in a fibrocellular stroma. The giant cells are irregularly distributed and often found abundantly near areas of hemorrhage. Other features include macrophages, deposition of hemosiderin, extravasated erythrocytes, osteoid material, dystrophic calcification metaplastic ossification at the periphery and predominantly mononuclear inflammatory infiltrate.[4,7,11,12] The aggressive forms show an increased mitotic activity and differences in nuclear variables in MGCs.[2] PGCG is composed of a delicate reticular and fibrillar stroma with plump ovoid and spindle-shaped mesenchymal cells, numerous MGCs, extravasated RBSs osseous metaplasia, calcifications, reactive bone and a "Grenz zone" separating the lesional tissue from the superficial epithelium.

The differential diagnosis of CGCG is a challenging task to pathologists because of their similar clinical, radiographic and histopathological behavior. GCT was ruled out, have larger giant cells, greater numbers of nuclei and generalized distribution of giant cells and absence of osteoid formation. Practically, the occurrence of giant cell tumor in the jawbones is very rare.[7] Aneurysmal bone cyst differentiated by showing blood filled cystic spaces. Clinically common in the metadiaphysis of long bones and vertebral bones and patients are already suffering from fibroosseous lesions. Cherubism was rule out from CGCG with the histological feature as Widespread and multiple osteolytic lesions of primarily the posterior mandible. Onset is in childhood, producing a classical, symmetric full cheek appearance.[13] Brown tumor of Hyperparathyroidism as histologically indistinguishable but usually present in multiple bones and with deranged bone profile results. Hyperparathyroidism can be differentiated on the basis of biochemical tests, where hypercalcemia, hypophosphatasia and increased parathyroid hormone (PTH) will point toward hyperparathyroidism.[6]

Recent studies using immunohistochemistry (IHC) and molecular methods have demonstrated overexpression of p^{63}in the stromal cells of most GCTs of bone and advocate its use as a diagnostic marker. Expression of p^{63}has been demonstrated in GCT of bone conversely, has not been detected in CGCG. factor VIII-related antigen (von Willebrand factor) is one of the immunohistochemical markers for endothelial cells. It is complex molecule physically associated with osteoprotegerin (OPG) an anti-osteoclastic protein and a soluble receptor for the proapoptotic protein which plays potential role in bone biology. Secondly synergistic effect of FactorVIII –RA complex with OPG or complex FactorVII – RA could bind to both RANKL and OPG leading to strong inhibition of RANKL activity thus inhibit osteoclastogenesis. One of the most important findings in the present study was prominent factor VIII-RA immunoexpression in capillary like blood vessels at the periphery of the lesions. Our results showed significant difference regarding mean value of factor VIII-RA positive endothelial cells amongst the group, which was least in aggressive Central giant cell granulomas followed by non-aggressive CGCG and highest in PGCG. Few studies analyzed factor VIII-RA as a vascularization marker in giant cell lesions.[10,14]

On the other hand, possible interaction of factor VIII-RA in osteoclastogenesis through regulating OPG, RANK and RANK-L may be present. They concluded that the interaction between factor VIII-RA and OPG can cause inhibition of RANK-L induced osteoclastogenesis.

Inspite of histochemistry, immunohistochemistry and ultrastructure studies focused on giant cell lesions of the jaw, the pathogenesis and nature of these lesions are still elusive. The stromal MCs are mostly spindle cells with fibroblastic/myofibroblastic and endothelial differentiation that is responsible for the proliferative activity of the lesions (20-23). Most of the researchers evaluated CD31, CD34, and VEGF expression as angiogenic markers in giant cell lesions.[10,15–17]

Interestingly, we found that endothelial cells in PGCG stained intensely with factor VIII-RA. This may represent the reactive process of PGCG, targeting higher production of pro-angiogenic factors and greater inflammatory reaction. In conclusion, the results of present study supported the histiocyte/macrophage nature of MGCs and MCs. Clinical significance of this study to rule out aggressive bhaviour and reactive nature of the lesion. Furthermore, overexpression and high intensity score of factor VIII-RA in endothelial cells represent less aggressive behavior in CGCG.

5. Conclusion

A Higher expression of factor VIII - RA in endothelial cells correlated with less aggressive behaviour of Central giant cell granuloma & thus it may be used to assess clinical behaviour and strategic of patients and strategic treatment planning of these lesions.

6. Source of Funding

None.

7. Conflict of Interest

None.

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