Giant Cell Granulomas of Jaws: a Clinicopathologic Study

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ABSTRACT

Objectives: The purpose of present study was to investigate and correlate the histological findings in central giant cell granuloma and peripheral giant cell granuloma of jaws with clinical and radiographic interpretations of the lesion.
Material and Methods: In present study, data from 14 cases of central giant cell granuloma (CGCG) and 9 cases of peripheral giant cell granuloma (PGCG) were analysed, focusing on demographic, clinical and radiographic features. For each patient, microscopic slides were assessed in terms of histologic features of giant cells i.e. number of giant cells, mean number of nuclei/giant cell, pattern of distribution, size and relative size index of giant cells, percentage fractional surface area (FSA) occupied by giant cells and stromal characteristics. Data collected was subjected to statistical analysis. Fisher-exact test, Pearson's correlation coefficient, one-way ANOVA test and Student's t-test were used for analysis.
Results: No significant difference was found between PGCG and CGCG in relation to all the traits that were evaluated. It was observed that mean number of giant cells and mean FSA was more in aggressive CGCG as compared to non-aggressive CGCG.
Conclusions: Further studies on large sample size are required to confirm the relationship between histomorphometric features of giant cells and behaviour of giant cell granulomas of jaws.

Keywords: behavior; granuloma; giant cells; jaw; jaw diseases.

INTRODUCTION

Giant cell lesions in the maxillofacial region vary from asymptomatic radiolucencies discovered on routine radiograph to rapidly expanding aggressive lesions [1]. Giant cell granulomas of jaws are recognized clinico-radiologically in two forms i.e. central giant cell granuloma (CGCG) occurring within the bone or peripheral giant cell granuloma (PGCG) involving the gingiva or edentulous alveolar process [2]. Histologically, both CGCG and PGCG of jaws present with abundant multinucleated giant cells within the background of mononuclear stromal cells in fibrous connective tissue stroma. CGCG and PGCG of the jaws are benign reactive lesions with unknown aetiology and pathogenesis [3]. Initially, researchers used the term giant cell reparative granuloma for CGCG of jaws, but nowadays term reparative is no more accepted for this lesion because of its destructive and aggressive potential [4]. Giant cell granulomas of jaws present with distinct biological behaviour and thus, an ambiguity persists regarding their true nature and for their clinical and biological behaviour. This difference in their behaviour raises the question regarding any relationship between their behaviour and morphological features of giant cells. Until date, few studies have been found in literature that has studied the relationship between morphological features of giant cells and clinical and biological behaviour of the giant cell granuloma of jaws. However, there is scarcity of studies, which compared the morphological features of giant cells in CGCG and PGCG of jaws [2-3,5-6].

The aim of present study was to investigate and correlate the histological findings in CGCG and PGCG of the jaws with clinical and radiographic interpretations. The objectives of study were: to the correlate the demographic, clinical and radiographic findings with the morphometric findings of giant cells in giant cell granulomas of jaws; to compare the morphometric histological findings between CGCG and PGCG of jaws; to compare the histomorphometric findings between aggressive and non-aggressive CGCG of jaws; and to record and relate the stromal features in CGCG and PGCG of jaws.

MATERIAL AND METHODS

The present retrospective study included histologically confirmed 14 cases of CGCG and 9 PGCG cases retrieved from the archival records of Department of Oral Pathology, Post Graduate Institute of Dental Sciences, Rohtak, from September 1, 2012 to September 14, 2018. Records of each included case were analysed for the demographic, clinical and radiological findings. Evaluation of radiological features of giant cell granulomas was performed using radiological records obtained from orthopantomogram assessment. None of the affected patients showed abnormal serum calcium, phosphorus and alkaline phosphatase levels. Clinico-radiological evaluation along with biochemical analysis ruled out cherubism, hyperparathyroidism, fibrous dysplasia and aneurysmal bone cysts, which histologically resembles giant cell granulomas of jaws. According to the criteria adapted from Choung et al. [1], CGCG was categorized into aggressive and non-aggressive lesions. Three histopathologists, who were unaware of the histological diagnosis examined the hematoxylin and eosin stained histological slide of each case for stromal features like: prominent areas of hemorrhage and/or hemosiderin deposits within the lesion; pattern of distribution of giant cells; foci of acute or chronic inflammatory cells; prominent osteoid or bone formation within the lesion; prominent fibrosis and cellularity in the lesion; prominent type of mononuclear stromal cells (spindle or ovoid) [4]; type of nuclei in giant cells (vesicular or solid); and separation of giant cells from the stroma. A feature was considered to be present, when two histopathologists confirmed it in the lesion.

All quantitative measurements for giant cells were done by one investigator, who was unaware of the diagnosis and site of origin of the lesion. Each slide was scanned under x10 magnification and the measurements for giant cells in each histological case were performed in 25 random high-power magnification fields (HPF, magnification x400) by capturing the image using a conventional light microscope (Nikon Eclipse Ni-U) and an image-analysing program (NIS Elements from Nikon). In order to avoid duplication, each slide was systematically examined, left to right in clockwise direction. No cell with three or more nuclei was ignored, unless the cell border was not well defined. The characteristics of giant cells evaluated were:

- Number of giant cells in 25 HPF.
- Size of giant cells (each giant cell was classified into large, intermediate and small on the basis of their area). The investigator manually traced the boundary of giant cells and the software automatically calculated the area in μm^2. Giant cells with area ≤ 500 μm^2 were labelled as small, 501 - 1000 μm^2 as intermediate and ≥ 1001 μm^2 as large giant cells.
- Total number of nuclei in giant cells seen in 25 HPF and mean number of nuclei/giant cell.

- Percentage fractional surface area (FSA) occupied by giant cell in 25 HPF.
- Relative size index (RSI) of giant cell (RSI = fractional surface area x 100/number of giant cells in 25 HPF [7]).
- Arrangement of nuclei in giant cell (calculated by dividing mean area of giant cell by mean number of nuclei in giant cell). The lower value represents that nuclei were closely packed in giant cells and vice-versa [4].

Statistical analysis

The collected data was subjected to statistical analysis. Parametric data expressed as mean and standard deviation (M [SD]). Fisher-exact test, Pearson's correlation coefficient, one-way ANOVA test and Student's t-test were used for analysis. The criterion for significance was $P < 0.05$.

RESULTS

The present study included 14 cases of CGCG and 9 cases of PGCG. Mean age (range) for CGCG and PGCG was 26.28 (11.99) years (range 8 to 52 years) and 33.77 (13.7) years (range 9 to 50 years) respectively. All the subjects in PGCG group were females whereas in CGCG group nine were females and five males. Maxilla and mandible was equally (7 cases each) involved in CGCG whereas mandible (5 cases) was predominantly involved in PGCG. Left side was predominantly involved in PGCG (6 cases) whereas CGCG showed slight predilection for right side (8 cases) followed by left side (4 cases) while in two cases, lesion crossed the midline. In CGCG, posterior region was predominantly involved (8 cases) followed by both anterior and posterior (4 cases) and anterior (2 cases). In PGCG, four cases each were found in posterior as well as both posterior and anterior region while only one case was found in anterior region of the jaw. A significant relation was observed between side of lesion and mean number of giant cells in CGCG ($P = 0.017$). Five cases of CGCG were associated with pain. Since pain was found to be associated with aggressive lesions [8], an attempt was also made to find any association of pain with histological features of giant cells and it was found to be non-significant.

On evaluation of radiological records of 14 cases of CGCG, 11 cases showed unilocular radiolucency whereas three cases presented with multilocular radiolucency. There was no perforation found in any of the cases, whereas eight cases showed bony expansion. One and five cases exhibited trabeculation and opacification respectively. Two cases showed root resorption, whereas six cases revealed tooth displacement (Figure 1).
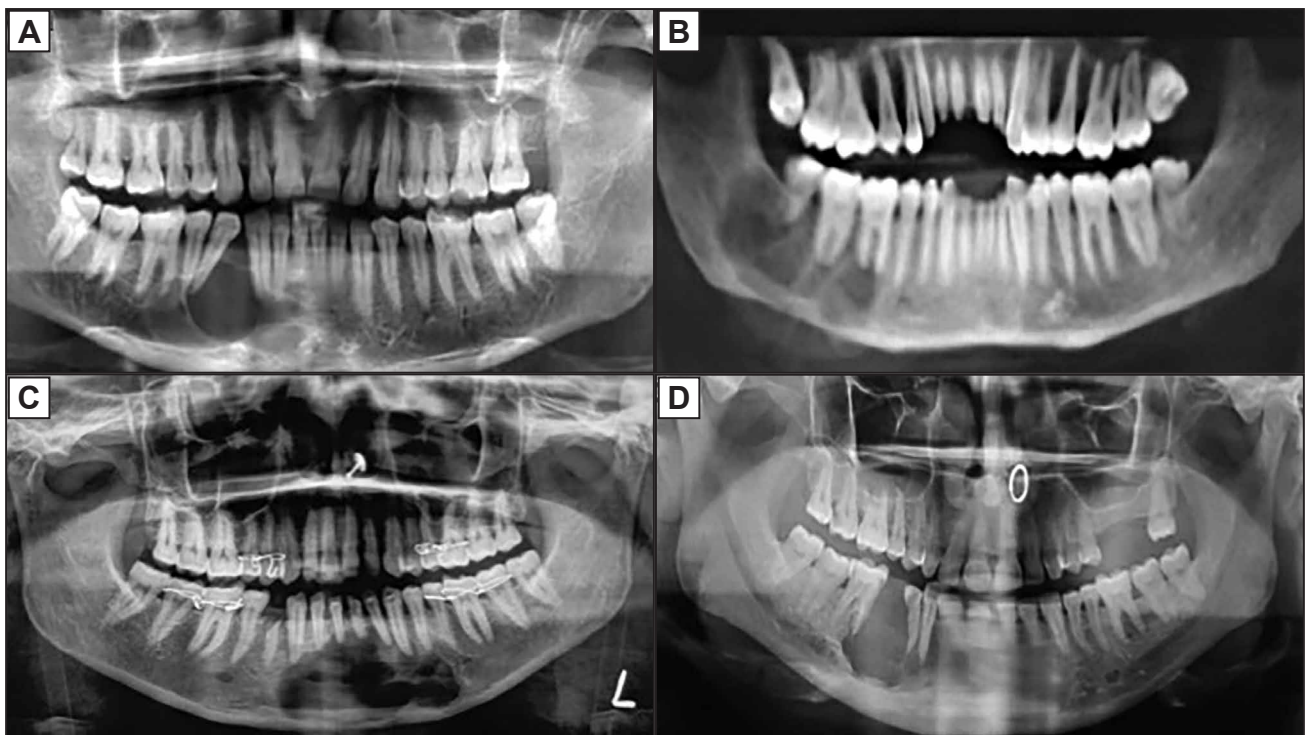
Figure 1. Orthopantographs depicting: A = unilocular radiolucency with well defined margins and displacement of tooth; B = multilocular radiolucency; C = mixed radiopaque and radiolucent lesion crossing the midline with root resorption and displacement of tooth; D = radiolucency with displacement of tooth.

Border of lesion showed a significant relation with total number of nuclei in giant cells (P = 0.007) and mean number of nuclei/giant cell (P = 0.023). Thirteen out of 14 cases showed well-defined margins.

Table 1 depicts the comparison of quantitative data between PGCG and CGCG. In the present study, none of the factors studied for giant cell showed any significant difference between PGCG and CGCG (Figure 2).

Table 2 depicts the comparison between PGCG and CGCG according to the size of giant cells.

Table 1. Comparison of quantitative giant cell data between CGCG and PGCG

Factors	PGCG	CGCG	P-value[a]
	Mean (SD)	Mean (SD)	
Giant cells in 25 HPF	71.22 (26.56)	69.57 (26.43)	0.885
Nuclei in giant cells in 25 HPF	468.55 (229.29)	509.78 (273.25)	0.711
Nuclei/giant cell	6.34 (0.9)	7.08 (1.68)	0.244
Area of giant cell	988.51 (122.51)	977.68 (213.22)	0.892
Percentage FSA occupied by giant cells	3.4 (1.46)	3.18 (1.06)	0.675
Relative size index	4.72 (0.6)	4.78 (1.3)	0.9
Arrangement of nuclei in giant cells	157.18 (20.68)	144.88 (43.7)	0.441

[a]Statistically significant at the level P < 0.05 (Student's t-test).
CGCG = central giant cell granuloma; PGCG = peripheral giant cell granuloma; SD = standard deviation; FSA = fractional surface area; HPF = high power field.
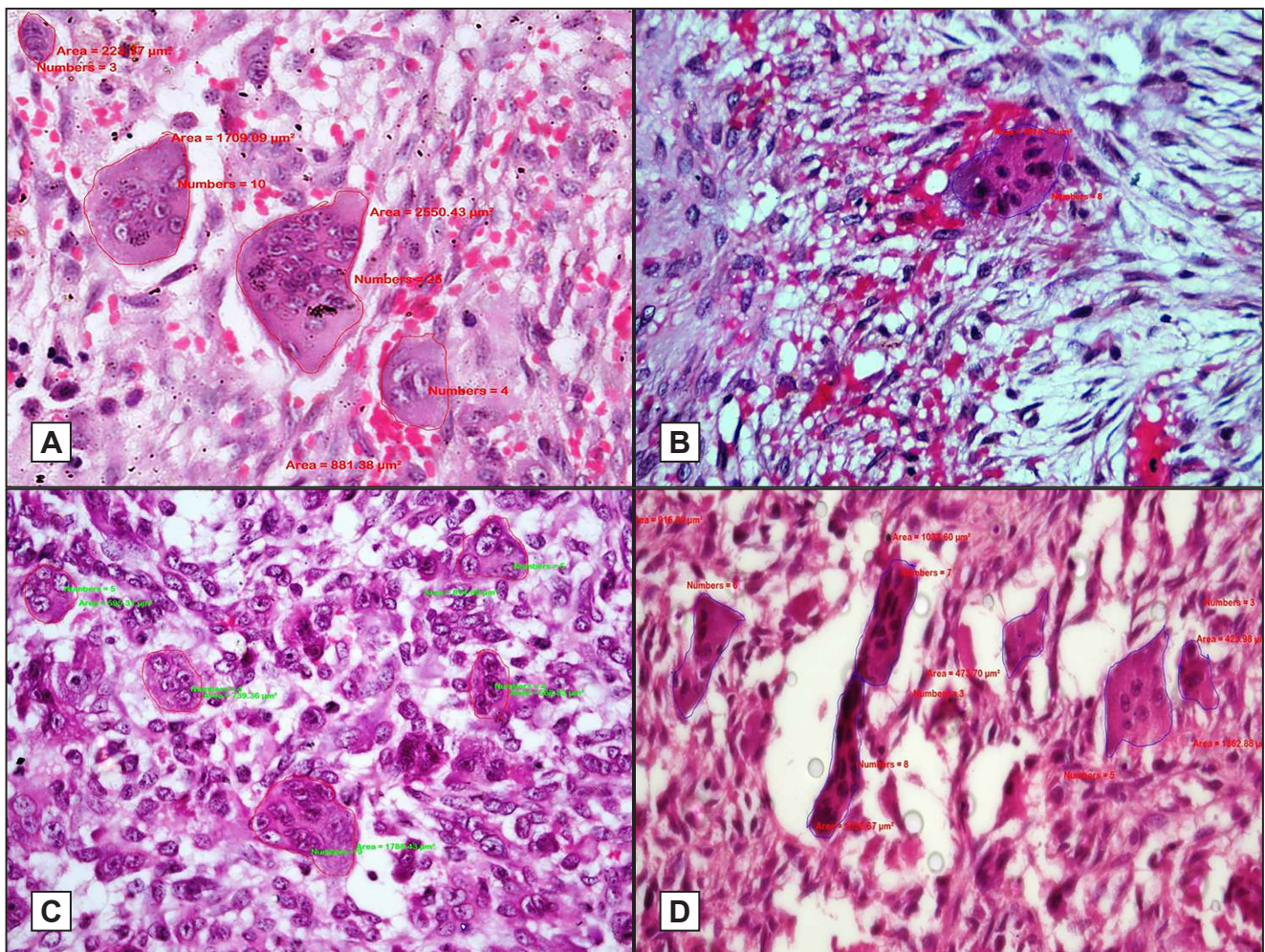
Figure 2. A and B = depicts measurements of giant cells in CGCG. C and D = depicts measurements of giant cells in PGCG. B and D = shows solid nuclei in CGCG and PGCG respectively. A and C = shows vesicular nuclei in CGCG and PGCG respectively. Hematoxylin and eosin stain, original magnification x40.

Table 2. Giant cell data in PGCG and CGCG according to their size

Giant cell		PGCG	CGCG	P-value[a]
		Mean (SD)	Mean (SD)	
Large	Giant cell	28.55 (13.087)	25.5 (10.044)	0.534
	Nuclei	244.44 (150.45)	246.21 (117.276)	0.975
	Nuclei/giant cell	8.08 (1.632)	9.66 (3.172)	0.183
Intermediate	Giant cell	32.22 (11.454)	31.35 (16.556)	0.893
	Nuclei	180.44 (72.889)	202.21 (146.099)	0.684
	Nuclei/giant cell	5.52 (0.392)	5.93 (1.636)	0.467
Small	Giant cell	10.44 (7.568)	14.28 (7.457)	0.244
	Nuclei	42.77 (31.208)	61.5 (38.262)	0.234
	Nuclei/giant cell	4.07 (0.52)	4.23 (1.042)	0.682

[a]Statistically significant at the level P < 0.05 (one-way ANOVA).
CGCG = central giant cell granuloma; PGCG = peripheral giant cell granuloma; SD = standard deviation; HPF = high power field.

Maximum giant cells in both PGCG and CGCG were intermediate in size followed by large and small giant cells. Maximum mean number of nuclei/giant cell in both PGCG and CGCG was observed in large (8.08 and 9.66 respectively) followed by intermediate and small giant cells. In both aggressive and non-aggressive CGCG, intermediate giant cells were observed predominantly followed by large and small giant cells. In aggressive and non-aggressive CGCG, total number of nuclei in giant cells in 25 HPF in large giant cells were 264 (131.521) and 243.25 (120.89), in intermediate were 159 (93.338) and 209.41 (155.04) and in small were 59 (26.87) and 61.91 (40.782) respectively. Mean number of nuclei/giant cell found in aggressive and non-aggressive CGCG were 8.42 (0.175) vs 9.87 (3.4) in large, 4.92 (0.339) vs 6.10 (1.713) in intermediate and 3.67 (0.055) vs 4.32 (1.103) in small giant cells.

The comparison of quantitative data of giant cells between aggressive and non-aggressive CGCG presented in Table 3. There was no significant difference between aggressive and non-aggressive CGCG with respect to all the traits measured for giant cells.

Present study revealed that a statistically significant difference existed between PGCG and CGCG in relation to bone or osteoid formation. However, for all other stromal characteristics difference between the two lesions was statistically non-significant (Table 4).

DISCUSSION

Data regarding site, clinical and radiological features of jaw lesions is essential for correct diagnosis and treatment planning [9]. CGCG of jaws is a benign osteolytic lesion, which accounts for nearly 7% of all benign tumours of jaws [7-8]. It shows predilection for young females below 30 years of age [8], as observed in our study also. In present study, 11 out of 14 subjects were below 30 years of age. CGCG is more commonly located in mandible and frequently crosses the midline but no site predilection within

Table 3. Comparison of quantitative giant cell data between aggressive and non-aggressive CGCG

Factors	CGCG		P-value[a]
	Non-aggressive	Aggressive	
	Mean (SD)	Mean (SD)	
Giant cells in 25 HPF	67.75 (26.76)	80.5 (30.4)	0.549
Nuclei in giant cells in 25 HPF	514.41 (290.71)	482 (197.98)	0.884
Nuclei/giant cell	7.27 (1.75)	5.94 (0.21)	0.322
Area of giant cell	985.49 (228.6)	930.81 (105.14)	0.751
Percentage FSA occupied by giant cells	3.1 (1.01)	3.63 (1.74)	0.543
Relative size index	4.85 (1.4)	4.41 (0.49)	0.68
Arrangement of nuclei in giant cells	142.98 (47.07)	156.29 (12.07)	0.707

[a]Statistically significant at the level P < 0.05 (Student's t-test).
CGCG = central giant cell granuloma; SD = standard deviation; FSA = fractional surface area; HPF = high power field.

Table 4. Stromal characteristics in PGCG and CGCG

Stromal characteristics		PGCG	CGCG	P-value[a]
Prominent hemorrhage or hemosiderin		55.55%	85.72%	0.162
Prominent bone or osteoid formation		11.11%	85.72%	0.001
Prominent fibrosis		44.44%	64.29%	0.417
Prominent cellularity		77.78%	92.85%	0.538
Foci of acute or chronic inflammatory cells		33.33%	14.28%	0.343
Type of stromal cells	Spindle	55.55%	78.57%	0.363
	Ovoid	45.45%	21.43%	
Type of nuclei in giant cells	Vesicular	44.41%	35.71%	1
	Solid	55.59%	64.29%	
Pattern of distribution of giant cells	Diffuse	100%	71.42%	0.127
	Focal	0%	28.58%	
Separation of giant cells from stroma		66.67%	64.29%	1

[a]Statistically significant at the level P < 0.05 (Fisher-exact test).
CGCG = central giant cell granuloma; PGCG = peripheral giant cell granuloma.

jaws has been reported [9-10]. However, in present study, both maxilla and mandible were equally involved and only two out of 14 lesions crossed the midline.

PGCG of jaws can occur at any age with predominance in 5th - 6th decade of life [3]. In our study, mean age of occurrence was 33.77 years, which was in accordance with findings of other studies [2-3]. All subjects in present study were females, which was in accordance with other studies in literature revealing female predilection [3,11]. Mandible showed slight predilection over maxilla in our study, which was also in accordance with published literature [3,11].

The association of demographic data with quantitative traits of giant cells could help in determining the behaviour of these lesions. Previously published literature stated that young patients should be considered as distinct group because craniofacial skeleton is growing and primary dentition is in the process of replacement by permanent dentition [12]. The role of hormonal changes in pathogenesis of these lesions should not be neglected, as they may be the possible cause of higher incidence in female patients [7]. In our study, CGCG showed a significant relation between side of lesion and mean number of giant cells only. However, no significant relation existed between demographic findings and quantitative data for giant cells both in CGCG and PGCG. Other researchers observed a significant relationship between mean number of nuclei in giant cells and age but they did not find any significant relation between number or size of nuclei in giant cells and gender in both CGCG and PGCG [3].

In radiological analysis of CGCG, 78.57% lesions revealed unilocular radiolucency which was in accordance with other researchers (85% of cases) [13]. However, many other studies reported unilocular radiolucency in 39 - 55% of cases [10]. The literature suggests that CGCG causes tooth displacement more frequently than root resorption as longer duration is required for root resorption and in younger patients lesion is diagnosed before root resorption occurs [9,12]. Similar findings were observed in our study as 14.28% and 42.85% cases showed root resorption and tooth displacement respectively. These findings were in agreement with some studies [9,13] but in disagreement with other studies which reported root resorption and displacement of structures in 37% and 50% cases respectively [10]. Our findings with respect to border of lesion were in association with findings reported in literature, which suggests that CGCG is a slow-growing lesion, thus, radiologically it mostly produces well-defined borders [9]. Bony expansion was found in 57.14% of cases, which was in accordance with other studies [10]. Perforation was not found in any of the cases whereas one (7.14%) case showed trabeculation, however, other studies reported perforation and trabeculation in 50% of cases [10]. This disagreement between radiological findings of our study and other studies could be explained on the fact that CT scan has been more useful in detecting trabeculation, amount of bone destruction, extension into adjacent structures and lesion boundaries [8,12], whereas in our study we had orthopantomograph (OPG) as record in all cases. Radiological features except the border of lesion did not show significant relation with giant cells, which was in agreement with the findings of other studies [3]. Mean number of giant cells, nuclei in giant cells in 25 HPF and mean number of nuclei/giant cell in CGCG

were 69.57, 509.78 and 7.08 respectively, which was in accordance with other researchers [4]. However, in study by Al Sheddi et al. [14] mean number of giant cell/4HPF and mean number of nuclei/ giant cell was 9.8 and 11 respectively. Kashyap et al. [2] reported mean number of giant cell per 25 HPF and mean number of nuclei/ giant cell to be 3.43 and 23.853 respectively. Mean area of giant cell in our study was closely associated with findings reported by other studies [4-5]. Our findings related to arrangement of nuclei in giant cell (mean area/mean number of nuclei in giant cells) were in accordance with other studies [4]. Findings related to percentage FSA occupied by giant cells and RSI in present study were in disagreement with other studies, which reported mean FSA of giant cells and RSI to be 7.12 and 1.11 [14]. This difference could be explained by the fact that they have studied giant cells in 4 HPF only in comparison to 25 HPF in our study.

In PGCG, mean number of giant cells, nuclei in giant cells in 25HPF and mean number of nuclei/giant cell were 71.22, 468.55 and 6.34 respectively. Percentage FSA occupied by giant cells and RSI was 3.4 and 4.72. Kashyap et al. [2] found mean number of giant cells per 25 HPF, mean number of nuclei/giant cell, FSA and RSI to be 3.19, 26.97, 0.0031 and 0.091 respectively. Flórez-Moreno et al. [5] found mean number of giant cells, mean number of nuclei to be 53.95 and 10.25 respectively. Mean giant cell area in present study was closely associated with findings of other studies [5].

Previous studies compared histomorphometric data of PGCG and CGCG and found a variation in giant cell number, size and shape [2,5-6], but there is no agreement amongst the researchers. Hence, we compared a morphometric data for giant cells between two lesions and found that no statistically significant difference existed between them. This was in accordance with previously published literature where researchers did not find any significant difference between two lesions with respect to giant cell number and area of giant cell [5]. However, other researchers observed a significantly higher FSA and RSI in PGCG as compared to CGCG [2]. CGCG is known to have higher recurrence rate and aggressive behaviour than PGCG [2,5]. But our findings were not consistent with the clinical behaviour of these lesions as we found slightly higher number of giant cells in 25 HPF, mean area of the giant cells and percentage FSA occupied by giant cells in PGCG as compared to CGCG. The various studies in literature [7,15,16] reported significantly higher number of giant cells, FSA and non-significant but higher RSI in aggressive CGCG when compared with non-aggressive CGCG. Thus, our observations point towards the importance of clinico-radiological evaluation of every PGCG case to rule out central origin of these lesions. Further, more studies are required to clarify all these aspects while considering the role of inflammation in PGCG [2]. We found that nuclei were more closely packed in CGCG as compared to PGCG.

In aggressive CGCG, number of giant cells in 25 HPF and percentage FSA was higher as compared to non-aggressive CGCG. However, in comparison to non-aggressive, aggressive CGCG presented with less number of nuclei/giant cell, lower mean area and RSI of giant cell. This could be explained by the fact that in our study only two cases of CGCG fulfilled the criteria to be labelled as aggressive. Comparison of these morphometric parameters amongst aggressive and non-aggressive CGCG with other studies has been discussed in Table 5 [1,7,15-16].

In both aggressive and non-aggressive CGCG, intermediate giant cells (33 [21.213] vs 31.08 [16.806]) were predominantly seen followed by large (31.5 [16.263] vs 24.5 [9.357]) and small giant cells (16 [7.071] vs 14 [7.781]) but literature suggests predominance of small giant cells in non-aggressive lesions as compared to aggressive which indicates true functional nature of small giant cells as in reactive process whereas true neoplasms have few or no functional cells [17].

Our findings with respect to hemorrhage or hemosiderin deposit and prominent type of stromal

Table 5. Comparison of findings of various studies with respect to morphometric data of giant cells in aggressive and non-aggressive CGCG

Studies	HPF	Giant cells		Nuclei/giant cell		Fractional surface area		Relative size index	
		Aggressive	Non-aggressive	Aggressive	Non-aggressive	Aggressive	Non-aggressive	Aggressive	Non-aggressive
Choung et al. [1]	20	134	233	-	-	4.6%	7.8%	4.1	3.4
Reddy et al. [7]	25	164.6	121.3	9.8	8.1	8.5	4.9	5.1	3.8
Kruse-Losler et al. [15]	25	160.6	115.3	9.5	7.8	8.2%	4.4%	5.3	3.9
Ficarra et al. [16]	25	42.7	23.31	6.89	6.4	0.087	0.041	0.198	0.163

CGCG = central giant cell granuloma; HPF = high power field.

cell (spindle) in CGCG was in association with other studies [4]. However, our findings with respect to prominent osteoid formation, fibrosis and foci of inflammatory cells in CGCG were in disagreement with other studies [4]. It has been reported in literature that presence of osteoid at the periphery of the lesions was more in non-recurrent lesions as compared to recurrent ones [17], but main limitation of our study was that record on recurrence was not available. In PGCG, 55.55% and 11.11% of cases showed prominent hemorrhage and bone or osteoid formation respectively, which was not in accordance with findings of other studies who observed interstitial hemorrhage and bone or osteoid formation in 83.9% and 44.6% cases respectively [11]. This difference could be attributed to the small number of PGCG in the present study. A significant difference existed between CGCG and PGCG with respect to prominent osteoid or bone formation only. To confirm the association of stromal features with biological behaviour of lesions, further studies on larger sample size are required considering the role of inflammation in PGCG.

Two types of giant cells were reported in literature, type I metabolically active giant cells with lightly basophilic cytoplasm and many large or ovoid vesicular nuclei and prominent nucleoli and type II dying giant cells with eosinophilic cytoplasm and small pyknotic nuclei [11]. In present study, type II giant cells were predominantly observed in both lesions (Figure 2).

This study sought to assess the biological behaviour of giant cell granulomas of jaw through histomorphometric analysis. On the other hand, there are various studies in literature that have used various histochemical markers like AgNOR, CD68, vascular endothelial growth factor (VEGF), Ki-67, p53, osteopontin, integrin α_v, Src protein, TRAP (tartrate-resistant acid phosphatase), Mouse Double Minute 2 homolog (MDM2), Proliferating Cell Nuclear Antigen (PCNA), factor XIII, MMP-2, MMP-9, CD105, CD34, CD31, Cathepsin D [2,5,15,18-21]. However, there is no consensus amongst the authors regarding the role of these histochemical markers in determining the behaviour of giant cell granulomas of jaw; hence, we are planning to conduct a study in future using some of these markers to clarify their role in assessing the behaviour of these two lesions.

CONCLUSIONS

Currently, no consistent histologic criterion is available to determine the behaviour of the two lesions. The results of this study suggest that there is no significant difference between the two lesions with respect to giant cell component. Thus, a histomorphometric study on larger sample size is required to determine behaviour more accurately, which could be used as a basis in formulating treatment of giant cell granulomas of jaws. This study emphasizes on the radiological evaluation of every peripheral lesion to rule out any bony involvement. As very, less is known about the histomorphometric differences between central giant cell granuloma and peripheral giant cell granuloma of jaws and the relation of histomorphometry with their behaviour, hence, this study provides a data for these two lesions, which could act as compliment data for establishing a baseline.

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REFERENCES

1. Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A. Central giant cell lesions of the jaws: a clinicopathologic study. J Oral Maxillofac Surg. 1986 Sep;44(9):708-13. [Medline: 3462363]. [doi: 10.1016/0278-2391(86)90040-6]
2. Kashyap B, Reddy SP, Desai R, Puranik RS, Vanaki SS. Computer assisted histomorphologic comparision and the expression of AgNORs in the central and peripheral giant cell lesions of the oral cavity and giant cell tumor of the long bone. J Oral Maxillofac Pathol. 2014 Sep;18(Suppl 1):S54-9. [Medline: 25364180] [PMC free article: 4211239] [doi: 10.4103/0973-029X.141350]
3. Aghbali A, Sina M, Vahid Pakdel SM, Emamverdizadeh P, Kouhsoltani M, Mahmoudi SM, Janani M. Correlation of histopathologic features with demographic, gross and radiographic findings in giant cell granulomas of the jaws. J Dent Res Dent Clin Dent Prospects. 2013 Fall;7(4):225-9. [Medline: 24578821] [doi: 10.5681/joddd.2013.036]
4. Auclair PL, Cuenin P, Kratochvil FJ, Slater LJ, Ellis GL. A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. Oral Surg Oral Med Oral Pathol. 1988 Aug;66(2):197-208. [Medline: 3174054] [doi: 10.1016/0030-4220(88)90094-1]

5. Flórez-Moreno GA, Henao-Ruiz M, Santa-Sáenz DM, Castañeda-Peláez DA, Tobón-Arroyave SI. Cytomorphometric and immunohistochemical comparison between central and peripheral giant cell lesions of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 May;105(5):625-32. [Medline: 18299236] [doi: 10.1016/j.tripleo.2007.08.032]

6. Franklin CD, Craig GT, Smith CJ. Quantitative analysis of histological parameters in giant cell lesions of the jaws and long bones. Histopathology. 1979 Nov;3(6):511-22. [Medline: 511122] [doi: 10.1111/j.1365-2559.1979.tb03032.x]

7. Reddy V, Saxena S, Aggarwal P, Sharma P, Reddy M. Incidence of central giant cell granuloma of the jaws with clinical and histological confirmation: an archival study in Northern India. Br J Oral Maxillofac Surg. 2012 Oct;50(7):668-72. [Medline: 22196146] [doi: 10.1016/j.bjoms.2011.10.015]

8. Sun ZJ, Cai Y, Zwahlen RA, Zheng YF, Wang SP, Zhao YF. Central giant cell granuloma of the jaws: clinical and radiological evaluation of 22 cases. Skeletal Radiol. 2009 Sep;38(9):903-9. [Medline: 19582449] [doi: 10.1007/s00256-009-0740-8]

9. Kaffe I, Ardekian L, Taicher S, Littner MM, Buchner A. Radiologic features of central giant cell granuloma of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996 Jun;81(6):720-6. [Medline: 8784905] [doi: 10.1016/S1079-2104(96)80079-5]

10. Stavropoulos F, Katz J. Central giant cell granulomas: a systematic review of the radiographic characteristics with the addition of 20 new cases. Dentomaxillofac Radiol. 2002 Jul;31(4):213-7. [Medline: 12087437] [doi: 10.1038/sj.dmfr.4600700]

11. Katsikeris N, Kakarantza-Angelopoulou E, Angelopoulos AP. Peripheral giant cell granuloma. Clinicopathologic study of 224 new cases and review of 956 reported cases. Int J Oral Maxillofac Surg. 1988 Apr;17(2):94-9. [Medline: 3133432] [doi: 10.1016/S0901-5027(88)80158-9]

12. Bodner L, Bar-Ziv J. Radiographic features of central giant cell granuloma of the jaws in children. Pediatr Radiol. 1996;26(2):148-51. [Medline: 8587817] [doi: 10.1007/BF01372096] [Medline: 8587817]

13. Horner K. Central giant cell granuloma of the jaws: a clinico-radiological study. Clin Radiol. 1989 Nov;40(6):622-6. [Medline: 2598590] [doi: 10.1016/S0009-9260(89)80325-3]

14. Al Sheddi MA, Mosadomi HA, Al Dayel FH. Central giant cell granuloma of the jaws and giant cell tumor of long bones: A clinicopathological, cytometric and immunohistochemical comparative study. Saudi J Oral Sci. 2014 Jan;1(1):47-53. [doi: 10.4103/1658-6816.124190]

15. Kruse-Lösler B, Diallo R, Gaertner C, Mischke KL, Joos U, Kleinheinz J. Central giant cell granuloma of the jaws: a clinical, radiologic, and histopathologic study of 26 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Mar;101(3):346-54. [Medline: 16504869] [doi: 10.1016/j.tripleo.2005.02.060]

16. Ficarra G, Kaban LB, Hansen LS. Central giant cell lesions of the mandible and maxilla: a clinicopathologic and cytometric study. Oral Surg Oral Med Oral Pathol. 1987 Jul;64(1):44-9. [Medline: 3475657] [doi: 10.1016/0030-4220(87)90115-0]

17. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. A clinical, radiologic, and histopathologic study. Oral Surg Oral Med Oral Pathol. 1993 Feb;75(2):199-208. [Medline: 8426719] [doi: 10.1016/0030-4220(93)90094-K]

18. Aksakalli N. Evaluation of the osteopontin in oral peripheral and central giant cell granuloma. Indian J Pathol Microbiol. 2018 Jan-Mar;61(1):18-21. [Medline: 29567878] [doi: 10.4103/IJPM.IJPM_214_16]

19. Khiavi MM, Aghbali AA, Halimi M, Kouhsoltani M, Hamishehkar H. Immunohistochemical expression of Src protein in peripheral and central giant cell granulomas of the jaws. J Oral Maxillofac Pathol. 2013 Sep;17(3):358-62. [Medline: 24574652] [PMC free article: 3927335] [doi: 10.4103/0973-029X.125197]

20. Mohtasham N, Saghravanian N, Fatemi B, Vahedi M, Afzal-Aghaee M, Kadeh H. A comparative study of osteopontin and MMP-2 protein expression in peripheral and central giant cell granuloma of the jaw. Braz J Otorhinolaryngol. 2019 Mar - Apr;85(2):150-156. [Medline: 29339027] [doi: 10.1016/j.bjorl.2017.11.006]

21. Sadri D, Shahsavari F, Hezarkhani M, Shafizadeh M. Expression of CD34 and CD31 in Central and Peripheral Giant Cell Granulomas. J Dent (Shiraz). 2019 Mar;20(1):10-15. [Medline: 30937331]