J. Oral Diagn 2025;10:e281

ORIGINAL ARTICLE

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Histomorphologic study of giant cell lesions of the jaws and giant cell tumour of bone

Abstract:

Objective: This study aimed to determine the cytometric differences in giant cell lesions of jaws (GCLs) and giant cell tumour of bones (GCTB). **Methods:** This was a retrospective study where histology of GCLs and GCTB were reviewed to determine number of giant cells per 5 high power field (5HPF) and nuclei number per giant cell by manual counting. Data were analyzed using SPSS version 23. Chi-square test was used to determine association between variables. The level of significance was set at $p<0.05$. **Results:** Forty-five cases were analysed, 17 males (37.8%) and 28 females (62.2%) with a M: F of 1.0:1.7. The mean age was 27.1±11.8 years while peak age of occurrence was the third decade of life. The mandible and associated gingivae (20/44.4%) were the most affected sites, followed by long bones with 14 (31.2%) cases. Mean number of giant cells per 5 HPF in central giant cell granuloma (CGCG) and GCTB was 10.0±3.5 and 10.5±4.19 respectively (p=0.67). Mean number of nuclei per giant cell was 12.8±3.8 in CGCG and 14.6±3.2 in GCTB (p=0.51). **Conclusion:** GCTB and CGCG cannot be differentiated by cytometric parameters alone. Standardized methods for assessing cytometric differences are advocated, to allow for better comparison.

Keywords: Giant Cell Lesions Jaws; Giant Cell Tumour Long Bones; Cytometric.

INTRODUCTION

Giant cell granulomas (GCGs) and giant cell tumour of bone (GCTB) are uncommon lesions of bone[1-3], and can be quite similar to other giant cell lesions (GCLs) in the orofacial region[1,2]. They may display high recurrence rates as well as rapid expansive progression[3].

Central giant cell granuloma (CGCG) is a rare benign lesion and is commonly seen in the third decade of life[4]. It primarily affects the jaw bones and has a female preponderance[5]. CGCG can present with variable radiographic features ranging from small unilocular lesions to large multilocular lesions with displacement of teeth, tooth germs, root resorption and cortical perforation[4].

Statement of clinical significance

Giant cell lesions of the jaws and giant cell tumour of bone have similarities and can be mis-diagnosed for each other particularly when they occur in same sites. Both are rare and require near accurate diagnosis because the clinical course, treatment and outcomes quite differ. In this study, the cytomorphological parameters of these lesions are been examined to ascertain the differences that may exists between these lesions. This would help in differentiating the types of giant cell lesions and enhance the diagnosis in order to achieve an appropriate treatment plan. However, the findings in this study revealed no statistically significant differences exists in the cytometric parameters of these lesions. Thus, a standardized way of determining cytometric features of giant cell tumours is being advocated.

Histologically, CGCG consists of cellular fibrous tissue that contains multiple foci of hemorrhage, aggregations of multinucleated giant cells (MGCs) and occasional trabeculae of woven bone[6].

Both peripheral giant cell granuloma (PGCG), and CGCG have giant cells concentrated in areas of hemorrhage adjacent to blood vessels[6]. The giant cells can have up to 30 nuclei each. The mean number of giant cells can be as low as 3.43, and the mean number of nuclei per giant cell can be up to 23.8[6].

Conversely, GCTB is a benign but locally aggressive bone neoplasm of young adults 20-40 years of age[7,8]. It constitutes about 4-5% of all bone tumours and about 18% of all benign bone neoplasms[9,10]. It is slightly more common in females.

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Received on November 21, 2024. Accepted on February 3, 2025.
https://doi.org/10.5327/2525-5711.281

[9, 10] Radiographically, GCTB presents as a large lytic mass of the epiphysis of long bones, often having a narrow zone of transition and expansion without prominent peripheral sclerosis and periosteal reaction[10]. In the head and neck region, GCTB is rare and the mandible is the more commonly affected jaw bone[11]. It has a different prognosis when compared to other GCLs and it should be distinguished from others[9,10].

Histologically, GCTB consists of cellular fibrous tissue, made up of young fibroblasts, along with multiple foci of hemorrhage, aggregations of MGCs and occasional trabeculae of woven bone[10,11]. The MGCs in GCTB are usually larger with a higher number of nuclei per giant cell than in CGCG[12]. However, a study reported no difference between the sizes of MGCs and the number of nuclei per giant cell between GCTB and CGCG[6].

Therefore, the cytomorphological differences that may exist between GCLs of the jaws and GCTB are not completely defined and there is a paucity of studies reporting such indices for GCLs in Africa. Hence, the hypothesis for this study is that: there is a difference in the number of multinucleated giant cells and the number of nuclei per giant cell in GCLs of the jaws and GCTB.

Thus, this study aimed to determine the cytometric variations in the number of giant cells and number of nuclei per giant cell in CGCG, PGCG and GCTB, as well as to evaluate the cases seen at our institution. The knowledge of these differences would further assist in distinguishing GCLs of the jaws from GCTB.

MATERIALS AND METHODS

Ethical approval for this study was obtained from the University of Ibadan/University College Hospital Ethics Review Committee (UI/EC/18/0363). This was a retrospective study conducted at the Department of Oral Pathology and Department of Pathology, University College Hospital, Ibadan. Reports of all biopsies submitted for the period 1998 to 2019 and histologically diagnosed as CGCG, PGCG and GCTB were obtained from the archival records of both departments and reviewed. Subsequently, identified cases that fulfilled the inclusion criteria, were recruited into the study and divided into three equal groups according to their diagnosis. The inclusion criteria for this study were cases whose formalin-fixed paraffin-embedded (FFPE) tissue blocks were available and had adequate tissue. Exclusion criteria were cases with missing and inadequate FFPE tissue blocks as well as cases with non-specific diagnoses. Subsequently, the FFPE tissue blocks, and the hematoxylin and eosin (H&E) stained slides were retrieved, and the diagnoses were verified. Furthermore, Cohen's kappa statistics were done to ascertain interobserver reliability and the interobserver agreement was k=0.820, ($p<0.001$). The slides were then viewed under the microscope (Olympus CX23) by two of the authors (ROO and AOA) independently to determine the number of giant cells per 5 high-power field (5HPF) and the number of nuclei per giant cell by manual counting at magnification x400. In cases where the opinions of the two authors differed, a third reviewer (AOL) was involved in a joint session and a consensus was reached. Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 23 (IBM Corp., Armonk, N.Y., USA). The results were subject to descriptive analysis and data were presented in the form of tables. Categorical (non-continuous) data like gender and site of lesion were presented in frequencies and percentages. Quantitative (continuous) data like number of giant cells, number of nuclei per giant cell and age were expressed as mean±standard deviation, using one-way ANOVA for the statistical analysis of the first two parameters. Chi-square statistical test was employed to determine the association between variables. Where the expected cell frequency was less than five in up to 20% of the cells, Fisher's exact test was employed. The level of significance was set at 5% ($p<0.05$).

RESULTS

A total of 45 cases were included in this study, consisting of 17 males (37.8%) and 28 females (62.2%) with a M: F of 1:1.7. The age range of GCLs of the jaws and GCTB was six to 75 years and the mean age of cases was 27.1±11.8 years. Also, the peak age of occurrence of these lesions was in the third decade of life consisting of 18 cases (40%) (Table 1).

The mandible and associated gingiva were the most affected sites, recording 20 cases (44.4%), followed by the long bones with 14 cases (31.2%), then, the maxilla and associated gingiva with 10 cases (22.2%) as well as the frontal bone with one case (2.2%). Further distribution of the cases according to the specific sites showed CGCG was diagnosed more commonly in the mandible, recording 11 (24.4%) cases while the maxilla recorded four cases (9 %) (Figure 1). In addition, 3 (20%) cases of CGCG were diagnosed as aggressive variants of CGCG, while 12 (80%) cases were non-aggressive CGCG

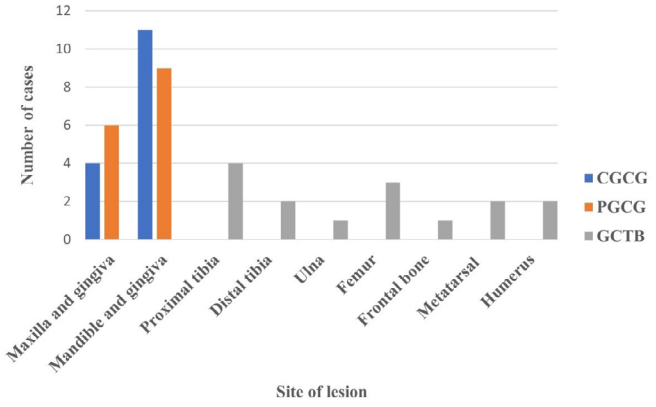
(Figure 2). Also, GCTB was seen in the long bones, with the proximal tibia being the most common site, with four cases (9%) (Figure 1). Other sites of occurrence for GCTB were the femur 3 (6.7%) cases; distal tibia, humerus and metatarsal bone, recording 2 (4.4%) cases each while the frontal bone, as well as the ulna, recorded one case (2.2%) each (Figure 1). PGCG (Figure 2), was more commonly diagnosed in the mandibular gingivae, with nine cases (20%) while the maxillary gingivae recorded six cases (13.3%) (Figure 1).

The mean number of giant cells in CGCG cases per 5HPF was 10.0±3.5, and the mean number of giant cells in PGCG per 5HPF was 12.2±9.9 (Figure 3). Also, the mean number of giant cells in GCTB cases per 5HPF was 10.5±4.2. There was no statistically significant

Table 1. Frequency distribution of the prevalence of central giant cell granuloma, peripheral giant cell granuloma and giant cell tumour of bones by age and gender.

	Histologic diagnosis			
	CGCG n=15	**PGCG n=15**	**GCTB n=15**	**Total n=45**
Age group (years)				
0–9	3 (6.7)	-	-	3 (6.7)
10–19	4 (8.9)	5 (11.1)	1 (2.2)	10 (22.2)
20–29	5 (11.1)	6 (13.3)	7 (15.6)	18 (40.0)
30–39	1 (2.2)	3 (6.7)	5 (11.1)	9 (20.0)
≥40	2 (4.4)	1 (2.2)	2 (4.4)	5 (11.1)
Mean age	25.8±14.3	25.6±10.4	29.8±10.2	27.1±11.8
Gender				
Male	6 (13.3)	5 (11.1)	6 (13.3)	17 (37.8)
Female	9 (20.0)	10 (22.2)	9 (20.0)	28 (62.2)
Male: Female	1: 1.5	1: 2	1: 1.5	1:1.7

CGCG: central giant cell granuloma; PGCG: peripheral giant cell granuloma; GCTB: giant cell tumour of bones.



CGCG: central giant cell granuloma; PGCG: peripheral giant cell granuloma; GCTB: giant cell tumour of bones.

Figure 1. Case distribution of central giant cell granuloma, peripheral giant cell granuloma and giant cell tumour of bones according to site of occurrence.

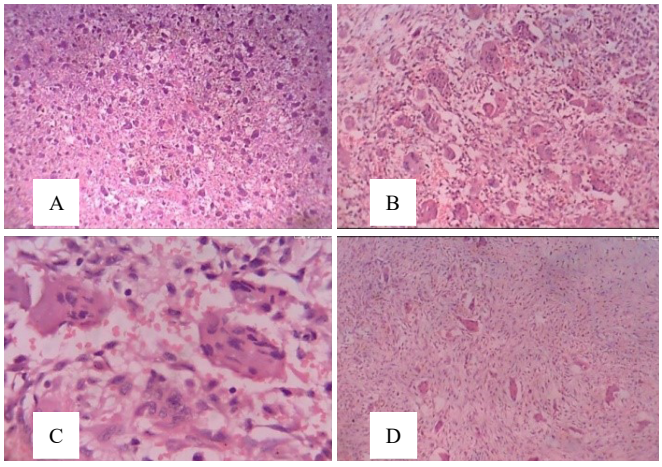
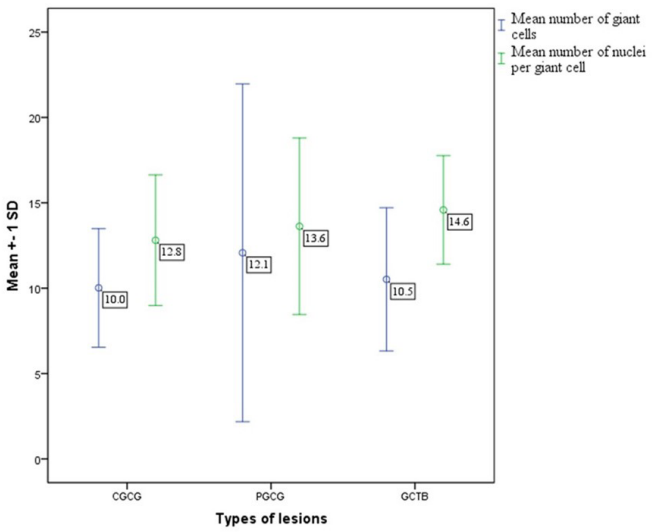


Figure 2. (A) Aggressive variant of central giant cell granuloma showing numerous, large multinucleated giant cells with a greater surface area density as well as hemosiderin deposits (magnification: x40). (B) and (C) Non-aggressive variant of central giant cell granuloma shows patchy distribution of multinucleated giant cells in a slightly vascular fibrous connective tissue stroma (magnification x100 and x400 respectively). (D) Peripheral giant cell granuloma shows the proliferation of multinucleated giant cells in a background stroma of plump, ovoid or spindle cells (magnification: x100).



CGCG: central giant cell granuloma; PGCG: peripheral giant cell granuloma; GCTB: giant cell tumour of bones.

CGCG: median number of giant cells IQR 11.0 (3.6); median number of nuclei/giant cell IQR 12.2 (3.6). PGCG: median number of giant cells IQR 7.2 (21.7); median number of nuclei/giant cell IQR 16.1 (10.8). GCTB: median number of giant cells IQR 9.0 (5.6); median number of nuclei/giant cell IQR 15.8 (4.8). p-value for mean number of giant cells and mean number of nuclei/giant cell=0.67 and 0.51 respectively.

Figure 3. Comparison of the mean values of the cytometric parameters in central giant cell granuloma, peripheral giant cell granuloma and giant cell tumour of bones in 5 high power field.

difference in the mean number of giant cells in CGCG compared to PGCG and GCTB: p=0.67. In addition, the mean number of nuclei per giant cell was higher in GCTB (14.6±3.2) per 5HPF, compared to CGCG and PGCG which had a mean number of nuclei per giant cell per 5HPF of 12.8±3.8 and 13.6±5.2 respectively. However, there was no statistically significant difference in the mean number of nuclei per giant cell in CGCG compared to PGCG and GCTB: p=0.51 (Figure 3).

DISCUSSION

Multinucleated giant cell lesions are still not well-known lesions. Nevertheless, this study observed that 80% of cases of CGCG occurred in individuals less than 30 years of age, and its peak age of occurrence was in the 3rd decade of life. This agreed with a study by Hosur et al.[4], who reported a peak age of occurrence of 2nd decade of life. Also in this study, PGCG was seen predominantly under the age of 30 years, this slightly differs from a report by Shadman et al.[13], who reported mean age of affectation was 33 years. On the other hand, GCTB was seen more frequently in individuals less than 40 years of age, and it peaked in the 3rd decade of life, like the findings by Lin et al.[7] and Sobti et al.[14]. No case of GCTB was seen in individuals less than 10 years of age and only 6.7% of cases were seen in individuals less than 20 years of age. This agreed with the study by Lin et al.[7] who reported 6.9% of GCTB cases in individuals less than 20 years of age. However, this finding was contrary to the findings by Zanati et al.[15] who reported only 4.5%, and Amelio et al.[16] who reported 12% of GCTB cases occurring in individuals less than 20 years of age. The reason(s) for the preponderance of GCLs in the 1st and 2nd decades of life is not yet clearly explained. However, we suggest it could be due to hormonal factors, following a peak of sex hormones during puberty in teenagers.

Furthermore, in this study, GCLs of jaws and GCTB were generally more commonly seen in females. This agreed with a study by Gupta et al.[17] who recorded a higher female preponderance for CGCG in their study. Similarly, a previous study by Mansor and Al-drobie[18] reported a female preponderance in PGCG cases. The predominance of giant cell granulomas (GCGs) in females may be due to hormonal influences, evidenced by the demonstration of estrogen and progesterone receptors in oral tissue[19]. Also, the onset of the lesions usually coincides with menarche and pregnancy. Thus, the likelihood is that the immunosuppressive action of these hormones could increase the risk of developing GCGs in females[19].

However, in contrast to findings in the present study, Lin et al.[7] and Cao et al.[8] reported a male preponderance in GCTB. This variation could be due to differences in the methodologies employed in these studies. Moreso, studies by Lin et al.[7] and Cao et al.[8] were conducted utilizing data from GCTB affecting only the radius and knee, respectively.

Regarding the site distribution of GCLs in this study, CGCG cases were diagnosed more commonly in the mandible than the maxilla which is like results obtained in studies by Hosur et al.[4] and Akinyamoju et al.[20]. This finding may be due to the susceptibility of the mandible to trauma, leading to intraosseous hemorrhage. Also, PGCG cases were seen predominantly in the mandibular gingiva in the present study. This agrees with the findings by Gupta et al.[17] as well as Martini et al.[21].

Histologically, in the present study, some GCTB cases resembled CGCG of the jaws and vice-versa which was similar to findings in a study by Abrams and Shears[12]. Previous attempts at differentiating them using cytological parameters have not been conclusive either[6,22-24]. The mean number of giant cells in 5 high power fields (HPF) and the mean number of nuclei per giant cell in CGCG recorded in this study were 10.0±3.5 and 12.8±3.8 respectively. This observation differed from the findings by Gupta et al.[17] who recorded 69.6±26.4 and 7.1±1.68 as the mean number of giant cells and the mean number of nuclei per giant cell respectively in their study. The mean number of nuclei per giant cell obtained in this study was nearly identical to 14.7±4.7 obtained in the study by Flórez-Moreno et al.[25]. However, these findings were at variance with the study by Kashyap et al.[6] that reported 3.43±1.2 and 23.9±10.5 as the mean number of giant cells and the mean number of nuclei per giant cell, respectively for CGCG. This variance could be due to the differences in methodology; while this study obtained mean numbers from 5HPF, Kashyap et al.[6] used mean numbers from 25HPF. In addition, the cytometric parameters were counted manually in this study, while Kashyap et al.[6] used computerized Motic Plus 3.0 version software to count. Also, the mean number of giant cells and the mean number of nuclei per giant cell for PGCG in this study, were 12.1±9.9 and 13.6±5.2 respectively, which differed from findings by Gupta et al.[17] (Table 2)[5,6,17,25,26]. Additionally, this was not in agreement with the study by Kashyap et al.[6] that reported 3.14±1.0 and 26.9±8.9 for the mean number of giant cells and the mean number of nuclei per giant cell, respectively. This could also be due to variation in study methods. Also, for GCTB, the mean number of giant cells in 5HPF and

Table 2. Outcomes of analysis of cytometric parameters recorded in studies on central giant cell granuloma, peripheral giant cell granuloma and giant cell tumour of bones.

Authors	Mean number of giant cells			Mean number of nuclei /giant cell			HPF
	CGCG	PGCG	GCTB	CGCG	PGCG	GCTB	
Present study	10.0±3.5	12.1±9.9	10.5±4.2	12.8±3.8	13.6±5.2	14.6±3.2	5
Gupta et al.[17]	69.6±26.4	71.2±26.6	-	7.1±1.68	6.3±0.9	-	25
Flórez-Moreno et al.[25]	54.3±10.7	53.9±14.2	-	14.7±4.7	10.3±1.2	-	12
Kashyap et al.[6]	3.43±1.2	3.19±1.0	4.56±0.3	23.9±10.5	26.9±8.9	150.2±22.5	25
Al Sheddi et al.[5]	9.8±2.4	-	11.8±2.3	11.0±4.3	-	16.3±3.9	4
Nagar et al.[26]	23.6	21.5	27.3	15.5	11.3	33.5	5

CGCG: central giant cell granuloma; PGCG: peripheral giant cell granuloma; GCTB: giant cell tumour of bones; HPF: high power field.

the mean number of nuclei per giant cell in this study were 10.5±4.2 and 14.6±3.2 respectively, which were like results obtained by Al Sheddi et al.[5] who reported 11.8±2.3 and 16.3±3.9 for both cytometric parameters. Curiously, the values obtained in the present study varied largely from those of Nagar et al., who reported mean number of giant cells in GCTB, CGCG and PGCG to be 27.3, 23.6 and 21.5 as well as mean number of nuclei of giant cells to be 33.5, 15.5 and 11.3 respectively[26].

In addition, this study recorded no statistically significant difference in the mean number of giant cells and nuclei per giant cell in CGCG, PGCG and GCTB. Similarly, Gupta et al.[17], Kashyap et al.[6], and Franklin et al.[27] reported no statistically significant difference in these indices for CGCG and PGCG. However, Franklin et al.[27] found that the cytometric parameters were higher in GCTB than in CGCG and a statistically significant difference was observed.

Similarly, a study by Kashyap et al.[6] recorded no difference in the mean number of giant cells in GCTB and aggressive CGCG. However, the mean number of nuclei per giant cell in GCTB was higher than in non-aggressive CGCG and PGCG, and the differences were statistically significant. This may be so because the comparison was between aggressive CGCG and GCTB, which studies have shown to have similar histologic features[28,29]. This finding was not observed in the present study on CGCG, which included both aggressive and non-aggressive variants. However, a study by Al Sheddi et al.[5] found that the cytometric parameters were statistically significantly higher in GCTB than in CGCG, contrary to the findings in this study. This may be so because the standard Leica image analyzing and processing system was used for the counting, as opposed to the manual visual counting of the cytometric features employed in this study. In addition, Al Sheddi et al.[5] counted four fields at a magnification of x250, while this study and that of Nagar et al.[26] counted 5 fields at a magnification of x400. These differences in methodology may have influenced the number of giant cells and the number of nuclei per giant cell counted.

Limitations

The small sample size utilized in this study was due to the rarity of GCLs and the small number of cases available in our records. The scarcity of local studies on cytometric parameters made regional and global comparisons of our findings challenging. Also, paucity of funding necessitated the use of manual counting, which might have introduced the possibility of human error. However, an inter-examiner calibration was done to minimize errors. The use of a more precise assessment of the cytometric features would have been achieved with appropriate software, like the standard Leica image analyzing and processing system.

CONCLUSION

In this study, GCLs were more commonly seen in females. CGCG and GCTB had similar age group affectation, but CGCG predominantly affected the jaw while GCTB largely affected the long bones. Although the cytometric parameters recorded in both lesions were similar, the mean number of nuclei per giant cell was higher in GCTB but the difference was not statistically significant.

In general, variations exist in the methodologies employed for the assessment of cytometric parameters of GCLs in various studies. So, it is necessary that standardized advanced diagnostic techniques for determining cytometric parameters of GCLs, be determined, to allow for better identification and comparison, thereby streamlining the management of specific GCLs. Also, multicentre studies should be conducted to validate findings.

ACKNOWLEDGMENTS

The authors would like to thank the staff of the Departments of Pathology and Oral Pathology, as well as those of both laboratories, at the University College Hospital Ibadan, Nigeria, who assisted in data retrieval and collection.

AUTHORS' CONTRIBUTIONS

AOA: data curation, formal analysis, resources, writing – review & editing. ROO: conceptualization, methodology, project administration, software, writing – original draft. AOA: funding acquisition, investigation, supervision, validation, writing –review & editing. AOL: supervision, visualization, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: Ethical approval for this study was obtained from the University of Ibadan/University College Hospital Ethics Review Committee. (UI/EC/18/0363).

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