INTRODUCTION

Giant cell lesions of the maxillofacial skeleton and other bones are a controversial matter and uncertainty still exists regarding their basic pathology and biologic behavior. Varying clinical and histological parameters have attracted the interest of many researchers towards understanding this diverse group of lesions which sometimes behave neoplastically.1-3 Before 1953, workers generally did not distinguish between giant cell lesions of the jaws and giant cell tumors of the jaws. Jaffe4 introduced the term giant cell reparative granuloma of the jaws and was the first to distinguish this lesion from giant cell tumors that usually involve the epiphyseal regions of long bones.5-9

Giant cell granulomas may occur within the bone (central giant cell granuloma, CGCG) or on the gingival or edentulous alveolar process (peripheral giant cell granuloma, PGCG). CGCG is an intrabony, non-neoplastic, slow-growing lesion affecting women more often than men. CGCG is a relatively...

ABSTRACT

Objective: Computer-assisted image analysis was attempted to ascertain, if any of the previously described histologic features along with argyrophilic nucleolar organizer regions (AgNORs) could be used to determine the aggressiveness of the central giant cell granuloma of the jaws (CGCG), peripheral giant cell granuloma of the oral cavity (PGCG) and giant cell tumor of the long bones (GCT).

Study Design: The study consisted of 20 cases of CGCG, 20 cases of PGCG and 5 cases of GCT. The histological features included were number of giant cells, number of nuclei in each giant cell, number of blood vessels, fractional surface area (FSA) and relative size index (RSI) of giant cells. The histologic parameters were measured using Motic image plus analyzer and AgNORs were evaluated using silver stain.

Results: The statistical analysis showed significant differences among various histological parameters between CGCG, PGCG and GCT. A statistically significant difference was noted for the mean number of nuclei, FSA and RSI when GCT was compared with CGCG and PGCG. FSA of histologically aggressive central giant cell granuloma (HA-CGCG) was more compared to histologically non-aggressive central giant cell granuloma (HNA-CGCG). No statistical correlation was observed for AgNORs of multinucleated giant cells and mononuclear cells among CGCG, PGCG and GCT.

Conclusion: Based on the present study findings, CGCG and GCT are distinct and separate entities and not a continuum of a single disease process. Histological parameters alone have a little implication on predicting clinical behavior of CGCG. AgNORs alone as a proliferative marker has a limited value in assessing the proliferation potential of giant cell lesions.

Key words: Argyrophilic nucleolar organizer regions, central giant cell granuloma, giant cell tumor, peripheral giant cell granuloma
uncommon, locally aggressive bone lesion, with variable clinical behavior. It accounts for less than 7% of all benign jaw lesions, with more than 60% of all cases occurring before the age of 30 years.[7] The radiographic appearance of CGCG is not pathognomonic and may be confused with other lesions, such as ameloblastoma, odontogenic keratocyst, aneurysmal bone cyst and hyperparathyroidism. Histologically, it is characterized by the presence of few to many multinucleated giant cells and mononuclear cells within a fibrous stroma. In contrast, PGCG is a relatively common lesion thought to arise in reaction to local stimulatory factors and runs an indolent course.[8,9]

Giant cell tumor of long bones (GCT) is a locally aggressive, neoplastic lesion with a high recurrence rate. Malignant transformation occurs in 15-30% of the cases. Histologically, GCT consists of evenly distributed numerous giant cells lying in a cellular matrix composed of spindle-shaped cells and scanty collagen. The giant cells measure about 100 microns in diameter and contain numerous vesicular nuclei up to 50 or more, which are situated towards the center of the cell, leaving a clear area of cytoplasm around the periphery.[4]

The literature of the last few years contains several references to so-called giant cell lesions of jaws and pathologists have attempted to identify histopathologic parameters in order to predict clinical behavior and prognosis of giant cell lesions.[1-5]

Nucleolar organizer regions (NOR) represent the loops of DNA actively transcribing to ribosomal RNA and thus to ribosome and ultimately to protein. NORs are associated with acidic argyrophilic non-histone proteins, which are visualized with the use of silver staining technique, the argyrophilic region (AgNOR). Some authors have applied AgNOR technology and found a positive correlation between AgNOR and recurrences and/or aggressiveness of the giant cell lesions, whereas others have found no correlation between PGCG and CGCG.[10,11] So far, not a single study has been performed to compare AgNOR count between CGCG, PGCG and GCT. Therefore, the visualization of NOR distribution appears to be a promising method to diagnose and assess the prognosis of giant cell lesions. As giant cells are an interesting and promising area of research, the present study used image cytometry to examine various histologic parameters along with AgNOR count to assess the aggressiveness of the giant cell lesions of the jaws.

**MATERIALS AND METHODS**

The study comprised of 20 previously diagnosed cases of CGCG, 20 cases of PGCG and 5 cases of GCT retrieved from the archives of Department of Oral Pathology. Complete clinical information and follow-up data was obtained for all 45 cases. Serum calcium or phosphorous, alkaline phosphatase and parathormone levels were within normal limits. Clinical data for CGCG was reviewed for clinical presentation, radiological appearance, treatment and follow up, without knowledge of the histopathologic findings. Based on the previously established by Chuong et al.,[2] we divided the 20 cases of CGCG into two groups (a) clinically non-aggressive lesions (CNA-CGCG), characterized by pain, rapid growth, root resorption, cortical perforation and no recurrences; (b) clinically aggressive lesions (CA-CGCG) characterized by pain, rapid growth, root resorption, cortical perforation and recurrences.

**Hematoxylin and eosin staining**

Formalin-fixed, paraffin-embedded hematoxylin and eosin stained sections of 4-μm thickness were assessed under light microscope by two observers so as to divide them into (a) histologically aggressive (HA-CGCG) and (b) histologically non-aggressive (HNA-CGCG) lesions based on the established criteria by various investigators,[1-5] which included size, shape, characteristics of nuclei and mononuclear cells, presence or absence of osteoid and vascularity of the lesion.

**Image analysis of giant cells**

For each case, giant cells in 25 random high-power magnification (400×) fields were measured with a computerized Motic Plus 3.0 version (Motic India, India). No cell with two or more nuclei was ignored, unless the cell border could not be delineated. The parameters assessed were the number of giant cells, the mean number of nuclei per giant cell, number of blood vessels, the fractional surface area (FSA) occupied by the giant cells and relative size index (RSI). RSI was calculated as

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\text{FSA} \times 100
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**AgNOR staining and interpretation**

AgNOR staining and counting was performed according to Ploton et al. method.[11,12] The final working solution was freshly prepared by mixing of one volume of 2% gelatin in 1% formic acid solution and two volumes of 50% aqueous silver nitrate solution. Slides were incubated with this silver solution for 30 minutes at 45°C in the dark. The silver reaction product was observed as discrete black dots under routine light microscopy (×1000 magnification). One hundred nuclei from multinucleated giant cells and 100 nuclei from mononuclear cells were randomly selected and the AgNOR dots were counted for each case. Randomness was accomplished by moving the slides in a sequenced fashion where adjacent fields did not overlap.

**Statistical analysis**

All statistical analysis were performed by using SPSS 15.0 (SPSS, Chicago, IL). Data were expressed as mean ± SD.
ANOVA test and Student’s t-test were used for analysis. The criterion for significance was $P < 0.005$.

**RESULTS**

A total of 45 cases of giant cell lesions consisted of 20 cases of CGCG, 20 cases of PGCG and 5 GCT cases. We observed 10 CA-CGCG and 10 cases of CNA-CGCG lesions depending on their clinical behavior.

**Clinical features**

**Age and gender**

The median age at the time of initial diagnosis was 35, 25, 33 and 30 years for PGCG, CA-CGCG, CNA-CGCG and GCT, respectively. The ratio of males to females was 6:14, 4:6, 3:7 and 4:1 for PGCG, CA-CGCG, CAN-CGCG and GCT, respectively. A distinct gender predilection for females was noted as 62% of patients were females [Table 1].

**Location**

In the PGCG group, there were 16 cases in the mandible and 4 cases in the maxilla. In the CGCG group, there were 14 cases in the mandibular posterior region, posterior to the permanent mandibular first molar and 6 in the maxilla. There were 6 cases in the mandible and 4 in the maxilla in the CA-CGCG group, while the CNA-CGCG group comprised of 10 mandibular lesions. All 5 cases of GCT were of the long bones [Table 1].

**Histologic features**

We observed 5 HA-CGCG and 15 HNA-CGCG lesions, irrespective of their clinical features. Their cytometric parameters are summarized in Tables 2-4.

**Number of giant cells**

The mean number of giant cells per 25 HPF in PGCG, HA-CGCG, HNA-CGCG and GCT was 3.19, 4.14, 1.03 and 4.56, respectively. The difference was not statistically significant when CGCG and PGCG were compared, but when PGCG and CGCG were compared with GCT, a significant difference was observed. There was no statistically significant differences were observed between HA-CGCG and HNA-CGCG and between HA-CGCG and GCT for number of giant cells.

**Number of nuclei per giant cell**

The mean number of nuclei per giant cell in PGCG, HA-CGCG, HNA-CGCG and GCT were 26.97, 27.07, 9.85 and 150.25, respectively. No significant difference was observed between CGCG and PGCG, but a significant difference was observed when PGCG and CGCG were compared with GCT. No significant difference was noted between HA-CGCG and HNA-CGCG, but a significant difference was observed between HA-CGCG and GCT for mean number of nuclei per giant cell.

**Number of blood vessels**

The mean number of blood vessels in PGCG, HA-CGCG, HNA-CGCG and GCT was 2.19, 2.47, 0.69 and 1.10, respectively. There was no significant differences were observed between PGCG, CGCG and GCT and no difference was noted when HA-CGCG and HNA-CGCG were compared.

**Table 1: Demographics of PGCG, CGCG and GCT according to age, gender and location**

| Variables          | PGCG (n=20) | CA-CGCG (n=10) | CNA-CGCG (n=10) | GCT (n=5) |
|--------------------|-------------|----------------|-----------------|-----------|
| Median age (years) | 35 (10-60)  | 25 (6-45)      | 33 (9-60)       | 30 (25-35) |
| Gender             |             |                |                 |           |
| Female             | 6           | 4              | 3               | 4         |
| Male               | 14          | 6              | 7               | 1         |
| Location           |             |                |                 |           |
| Maxilla            | 4           | 0              | 6               | Tibia     |
| Mandible           | 16          | 10             | 4               |           |

PGCG: Peripheral giant cell granuloma, CGCG: Peripheral giant cell granuloma, CA: Clinically Aggressive, CNA: Clinically non-aggressive lesions, GCT: Giant cell tumor

**Table 2: Comparison of quantitative giant cell data between CGCG and PGCG**

| Histopathological parameter | CGCG (n=20) | PGCG (n=20) | P value |
|-----------------------------|-------------|-------------|---------|
| Mean number of giant cells  | SD=1.20     | SD=1.01     | 0.48    |
| Mean number of nuclei per giant cell | SD=10.54 | SD=8.89     | Not significant |
| Mean number of blood vessels | SD=1.08     | SD=1.04     | Not significant |
| Mean FSA                    | 0.0021      | 0.0031      | 0.022   |
| Mean RSI                    | 0.057       | 0.091       | 0.0002  |

PGCG: Peripheral giant cell granuloma, CGCG: Peripheral giant cell granuloma, SD: Standard deviation, FSA: Fractional surface area, RSI: Relative size index

**Table 3: Comparison of quantitative giant cell data between HA-CGCG and HNA-CGCG**

| Histopathological parameter | HA-CGCG (n=5) | HNA-CGCG (n=15) | P value |
|-----------------------------|---------------|-----------------|---------|
| Mean number of giant cells  | 4.14          | 1.03            | 0.13    |
| Mean number of nuclei per giant cell | 27.07     | 9.85            | 0.44    |
| Mean number of blood vessels | 2.47          | 0.69            | 0.59    |
| Mean FSA                    | 0.0033        | 0.0009          | 0.041   |
| Mean RSI                    | 0.072         | 0.020           | 0.10    |

HA-CGCG: Histologically aggressive central giant cell granuloma, HNA-CGCG: Histologically non-aggressive central giant cell granuloma, SD: Standard deviation, FSA: Fractional surface area, RSI: Relative size index
**FSA**

The mean FSA for PGCG, HA-CGCG, HNA-CGCG and GCT was 0.0031, 0.0033, 0.0009 and 0.0111, respectively. The FSA occupied by the giant cells was significantly greater in PGCG than CGCG. The statistically significant difference was observed when PGCG and CGCG were compared with GCT. We observed a statistically significant difference for FSA between HA-CGCG and HNA-CGCG and also between HA-CGCG and GCT [Figures 1-3].

**RSI**

The mean RSI for PGCG, HA-CGCG, HNA-CGCG and GCT was 0.091, 0.072, 0.020 and 0.216, respectively. The RSI was significantly greater for PGCG than CGCG. A significant difference was observed for RSI when PGCG, CGCG and GCT were compared, but no significant difference was observed between HA-CGCG and HNA-CGCG.

**AgNOR staining**

No statistically significant correlation was observed for AgNOR counts of multinucleated giant cells and mononuclear cells when PGCG, HA-CGCG, HNA-CGCG and GCT were compared with each other [Figures 4 and 5] [Table 5].

**DISCUSSION**

The subject of giant cell lesions of the jaws is little understood and a matter of debate because the lesions are not pathognomonic and may be confused, both radiologically as well as histologically, with other lesions of the jaws. The question of whether or not “true” giant cell tumors exist in the jaws has been argued for many years and is still

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**Table 4: Comparison of quantitative giant cell data between HA-CGCG and GCT**

| Histopathological parameter | HA-CGCG (n=5) | GCT (n=5) | P value |
|-----------------------------|---------------|-----------|---------|
| Mean number of giant cells  | 4.14 (SD=1.52) | 4.56 (SD=0.32) | 0.56 (Not significant) |
| Mean number of nuclei per giant cells | 27.07 (SD=13.04) | 150.25 (SD=22.53) | 0.000 (Not significant) |
| Mean number of blood vessels | 2.47 (SD=1.96) | 1.10 (SD=0.82) | 0.18 (Not significant) |
| Mean FSA                    | 0.0033 (SD=0.0023) | 0.011 (SD=0.0031) | 0.002 (Significant) |
| Mean RSI                    | 0.072 (SD=0.025) | 0.216 (SD=0.061) | 0.0013 (Significant) |

HA-CGCG: Histologically aggressive central giant cell granuloma, GCT: Giant cell tumor, SD: Standard deviation, FSA: Fractional surface area, RSI: Relative size index

**Table 5: AgNOR count comparison of mononuclear cells and multinucleated giant cells among CGCG, PGCG and GCT**

|          | Mononuclear cells | Multinucleated giant cells |
|----------|------------------|----------------------------|
| CGCG     | 1.30 (SD=1.018)  | 1.131 (SD=0.12)            |
| PGCG     | 1.29 (SD=1.17)   | 1.12 (SD=0.10)             |
| GCT      | 1.36 (SD=0.22)   | 1.16 (SD=0.11)             |

PGCG: Peripheral giant cell granuloma, CGCG: Peripheral giant cell granuloma, GCT: Giant cell tumor, SD: Standard deviation
unresolved. Controversies surrounding the relationship between CGCG of the jaws and GCT of the long bones have revolved around their biological behavior, histopathologic features and clinical response to conservative therapy. In the present study, we have attempted to ascertain which, if any, previously described histologic features could be used to determine the aggressiveness of giant cell lesions of the jaws.

Age, gender and location

The mean age for PGCG, C-NA, CA and GCT appeared to be in agreement with the previous reports. Also, female predilection is observed in PGCG and CGCG, showing accordance with other studies. Although studies have shown that the mandibular anterior region is the most common location for CGCG, the present study is not in agreement with the same as the most of our case (70%) were in the mandibular posterior region, posterior to the permanent mandibular first molar.

Histology and image analysis

The comparison of CGCG and PGCG in the present study showed no significant difference in the number of giant cells, nuclei in each giant cell and number of blood vessels present in the lesions. As per our findings, since PGCG and CGCG cannot be differentiated merely on routine histopathological examination, all PGCG cases should be subjected to through clinical and radiological examination to rule out possible central bone involvement. Surprisingly, we found a greater FSA and RSI for PGCG than CGCG, thus making PGCG more aggressive than CGCG. These findings are against the commonly observed surgical findings where CGCG is found to be more aggressive than PGCG. This needs further clarification, although possible role of inflammation cannot be ruled out.

Using histologic criteria established by various investigators, we divided 20 cases of CGCG into 5 HA-CGCG (25%) and 15 HNA-CGCG (75%) lesions. The present study observed no significant differences except a greater FSA in HA-CGCG lesions as compared to HNA-CGCG lesions, which is in agreement with other finding in the literature. However, it was noted that this histologic difference was not as readily apparent as the differences in their biological behavior. It was surprising to note that although 5 HA-CGCG lesions were clinically aggressive, the remaining 5 clinically aggressive lesions were not HA-CGCG lesions. Thus, based on the present study findings, no histologic features could be used to separate aggressive lesions from those that are clinically indolent. In other words, the lesions that show clinically aggressive course may not always exhibit concurrent histological aggressiveness. To emphasize the discrepancy between histologic appearance and biological behavior, we also prefer the non-committal term “giant cell lesion” for CGCG. Because of the variations in clinical behavior, histology and prognosis, it is better to designate CGCG as either potentially aggressive or nonaggressive collectively on the basis of their clinical, radiological and histological features, which will be of more help to the surgeon than to designate all of these lesions as giant cell granulomas.

GCT of long bone is a well-recognized neoplasm with distinctive clinical and histopathologic features. When HA-CGCG were compared with GCT, no statistically significant differences were observed in relation to number of giant cells and number of blood vessels, but we observed a striking difference in the number of nuclei per giant cells, FSA and RSI differentiating the aggressive neoplastic nature of GCT from CGCG. Thus, our findings support the viewpoint of Abrams et al. and Jaffe that CGCG and GCT are distinct lesions. Although cases of GCT were few, we do not support the previously proposed concept that CGCG and GCT represents a continuum of a single disease process.
It is well-recognized that endothelial cells represent a phenotypically diverse group of cells that vary morphologically and functionally from site to site. Various markers have been used to assess the vascularity in giant cell granuloma and suggested more number of blood vessels at the periphery of giant cell granuloma, which may be dependent on several factors.[15] Vered et al. has demonstrated low mean microvascular volume of VEGF and b-FGF positive blood vessels in CGCG implying low angiogenic activity, thus does not support the designation of CGCG as a true proliferative vascular lesion.[16] In the present study, no statistically significant difference was found in vascularity of CGCG, PGCG and GCT; thus, all the lesions were equally vascularity dependent.

The present study also examined AgNOR counts in giant cells and stromal cells of the giant cell lesions in an attempt to assess whether it could delineate the lesions of varying clinical behavior. Our results showed no statistically significant difference among the giant cell lesions of varying behavior. The differences in AgNOR counts exclusively among peripheral and central giant cell lesions of varying behavior was studied by Souza et al.,[11] who observed no difference in AgNOR counts between PGCG and CGCG in their study. On the contrary, Whitaker et al.[10] observed a significant increase in the number of AgNORs in recurrent CGCG compared to non-recurrent/nonaggressive CGCG. These differences could be attributed to the technique and sample size of various studies. Further investigations are necessary to clarify the significance of AgNOR histochemical expression in the histological behavior of giant cell lesions of the jaws.

In conclusion, based on the present study findings, we suggest that GCT and CGCG are distinct lesions and not a continuum of a single disease process. We also prefer the noncommittal designation of “giant cell lesion” for CGCG.[3] The observation of this study depicts that histological parameters of CGCG may not be correlating in all the cases of giant cell lesions in predicting their clinical behavior and prognosis. AgNORs alone as a proliferative marker has a limited value in assessing the proliferation potential of giant cell lesions of the jaws.

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