The Enigmatic Giant: Histopathological Study of Giant Cell Tumour of the Long Bones and Central Giant Cell Granuloma of the Jaws
Anita Dhupar, Anita Spadigam, Shaheen Syed, Shruti Nagvekar

Abstract

Background: Giant Cell Tumour of the long bones is a benign but locally aggressive bone tumour occurring in the young. Jaffé in 1953 distinguished ‘Central Giant cell granuloma of the jaw bones’ from the Giant Cell Tumour on the grounds that the jawbone lesions were relatively less aggressive than those occurring elsewhere. Some investigators believe that the two lesions represent two distinct entities, whereas others consider them to be different expressions of the same disease process. The aim of the current study was to determine whether the histopathological features could be used to differentiate between the two lesions. Materials and Method: Four cases of each were retrieved from the archives of the Departments of Oral and Maxillofacial Pathology and General Pathology. The data was analyzed for the following parameters namely: age, gender, histopathological and morphological features. Results: Both groups showed a definite male predilection. The mean age at presentation of Central Giant cell granuloma of the jawbones was 22.25 years. Three cases showed a homogenous distribution of giant cells and two cases showed osteoid formation. Giant Cell Tumour of the long bones presented at a mean age of 35 years. None of the cases of the latter presented with a homogenous distribution of giant cells, whereas osteoid formation was seen in three cases. Plump stromal cells were seen in three of the four cases in both groups. Mean surface area, perimeter and the nuclear count within each giant cell were also comparable in both the groups. Conclusion: The study concludes that the lesions are histopathologically similar and supports the hypothesis that the two could be different expressions of the same entity.

Keywords: Bone Tumour; Central; Giant cell; Giant cell tumour; Granuloma;

Introduction

Central giant cell granuloma of the jawbones (CGCG) and Giant cell tumour of the long bones (GCTB) are well-recognized essentially benign entities. Although the behavior, prognostic factors and histogenesis have been widely investigated, these still need further clarification.\(^1\)\(^,\)\(^6\) The biologic behavior of CGCG ranges from a quiescent lesion to a lesion showing an aggressive phenotype.\(^1\) Factors determining the aggressiveness largely remain unknown. Although several cytogenetic abnormalities have been detected in CGCG, the exact pathogenesis is unclear; and the uncertainty whether CGCG should be considered as a granuloma or a benign neoplasm continues.\(^7\)\(^,\)\(^8\)

Jaffé (1953) coined the term “Central giant cell reparative granuloma” to distinguish it from other giant cell rich lesions. It was then thought to represent a reactive-reparative process that might heal spontaneously.\(^9\) Since then a number of aggressive variants of CGCG have been studied. The aggressive biological behavior of a few cases is reminiscent of that of GCTB, and it was proposed by some (Whitaker and Waldron, 1993) that CGCG and GCTB belong to the same spectrum of lesions.\(^1\)\(^,\)\(^10\) CGCG occurs most commonly in the anterior part of the mandible of young patients and has a predilection for females.\(^10\) It can present in non-aggressive and aggressive forms. Non-aggressive lesions are characterized as asymptomatic, slow-growing, non-perforating (cortex) and non-recurring; and aggressive lesions are described as painful, rapidly growing, cortex perforating and recurring.\(^11\) Histologically CGCG shows the presence of multinucleated giant cells and mononuclear cells within a fibrous stroma.\(^12\) GCTB accounts for 21% of all benign tumours of bone, presenting as a lytic lesion at the articular ends of tubular bones.\(^13\) Histologically it shows almost an identical picture to CGCG of the jaw bones, however a few authors mention histological criteria to differentiate the two.\(^2\) The following histopathological parameters namely: stromal characteristics; distribution, area, perimeter and the nuclear count within each giant cell; and osteoid formation were
considered to be important diagnostic clues in categorizing the lesions. The objective of the present study was to evaluate the aforementioned parameters in distinguishing the studied lesions.

Materials and Method
Four cases of CGCG from the Department of Oral and Maxillofacial Pathology, Goa Dental College and Hospital and four cases of GCTB from the Department of General Pathology, Goa Medical College and Hospital, were evaluated in the study. Clinical data was obtained from the archival files and analyzed, focusing on age and gender of the patients. Serum calcium, phosphorous, alkaline phosphatase and parathormone levels were within normal limits.

Histological evaluation of the specimens
Formalin fixed paraffin embedded tissue sections of 4μm thick were stained with hematoxylin and eosin stain. The microscopic slides were assessed in terms of the histologic features of the stroma; distribution, area, perimeter and the nuclear count within each giant cell; and osteoid formation by using the OLYMPUS® BX53 System Pentahed Research Fluorescence Microscope (Model No: 3A40538). Although histologic features sometimes varied from field to field, the overall and predominant histologic appearance was the focus of histologic profiling.

Image analysis of giant cells
For each case; the surface area, the perimeter of the giant cells and the nuclear count were analyzed under high power magnification (400×) with the help of the ProgRes® Capture Pro 2.8.8 software. Giant cells having well delineated cell borders with a minimum of two or more than two nuclei were considered.

Results
A definite male predilection was seen in both the groups (three of the four cases of GCTB & CGCG). The mean age at presentation of GCTB was 35 years whereas of CGCG was 22.25 years (Graph 1). Homogenous distribution of giant cells was seen in three of the four cases of CGCG (75%) (Figure 1) but was not evident in the GCTB cases (0%) (Figure 2). Plump stromal cells were seen in three of the four cases (75%) in both groups (Figure 3). Three cases of GCTB (75%) and two cases of CGCG (50%) showed osteoid formation (Figure 4). No statistically significant difference was observed in the nuclear count, area and perimeter of the giant cells in the two groups (Table 1).

Discussion
Giant cell tumour of the long bone is a benign, locally aggressive neoplasm which is composed of sheets of neoplastic ovoid mononuclear cells interspersed with uniformly distributed large, osteoclast - like
giant cells. Jaffé in 1953 described Giant cell granuloma of the jaw bone as a distinct identity from the GCTB. Jaffé defined it as a reactive intraosseous lesion of the mandible and maxilla developing as a result of intraosseous hemorrhage induced by trauma.

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In the current study, CGCG predominated in the younger age group. Other studies have also reported a similar finding. It showed a slight male predominance, whereas other authors have found a female predilection. The morphological features of the giant cell and the stromal characteristics were thought to be useful in predicting the aggressiveness of the lesions. Our study is in accordance with several other studies which have shown that a subset of jaw lesions clearly fall within the histological profile accepted for GCTBs and conversely some long bone lesions show the histological features widely accepted for CGCGs. Thus the study demonstrated that histopathological features of the two lesions are similar.

Clinically both entities show aggressive and non-aggressive forms. The non-aggressive forms are characterized by absence of symptoms, slow growth and low recurrence rates. Pain, extensive bone destruction, rapid growth and higher recurrence rates are evident in the aggressive variants. Sheddi et al noted recurrence rates of 40% and 45.5% for CGCG and GCTB respectively. Rate of distant metastasis in GCTB is about 3%, although rare, there have been case reports of distant metastasis noted in the aggressive forms of CGCG of the jaw bones.

A number of immunohistochemical studies were undertaken to check for differences, which would allow for proper categorization of the lesions. de Souza PE, et al., found that p53 inactivation by MDM2 expression may be involved in the pathogenesis of giant cell lesions of the jaws as well as the long bones. They investigated the percentage of Ki-67 and PCNA-positive cells in both the groups, and found that CGCG had greater number of these cells compared to GCTB. Kauzman A et al, in their study showed that the two groups demonstrated similar immunohistochemical staining patterns for the cell cycle proteins - cyclin D1, cyclin B1.

In a study by AragãoMdo S, et al., the immunoexpression of CD68 in mononuclear cells and multinucleated giant cells was found to be similar in both the groups. Also, the staining patterns of fibronectin and tenasin seen in CGCG were comparable to that detected in GCTB. Wang, et al suggested that c-Src may be a common signaling cascade during osteoclastogenesis in both CGCG and GCTB. Aggressive and non-aggressive CGCGs, both showed comparable staining for antibodies against CD34, factor XIIa, smooth muscle actin, prolyl 4-hydroxylase, Ki-67, p53 protein, RANK and glucocorticoid receptor alpha.

Several genetic abnormalities have been observed in GCTB such as chromosomal gains in chromosomes 11, 16, 19, 20, 21; reduction of telomere length, marker chromosomes, double minutes, chromosome fragments, ring chromosomes, and polyploidy. The most common cytogenetic anomaly seen in GCTB is telomeric association, frequently affecting chromosomes 11p, 13p, 14p, 15p, 19q, 20q and 21p. Carcino, et al., (2005) found

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of nuclei/giant cell</th>
<th>Area of giant cells ($\mu^2$)</th>
<th>Perimeter of giant cells ($\mu$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGCG</td>
<td>28.8</td>
<td>1554.050</td>
<td>167.8550</td>
</tr>
<tr>
<td>GCTB</td>
<td>24.75</td>
<td>1194.030</td>
<td>149.0275</td>
</tr>
<tr>
<td>Mean</td>
<td>16.5</td>
<td>428.0697</td>
<td>24.63717</td>
</tr>
<tr>
<td>SD</td>
<td>15.3</td>
<td>906.9477</td>
<td>55.25947</td>
</tr>
</tbody>
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Table 1: The mean number of nuclei, area and perimeter of the giant cells.
several up and down regulated genes in CGCG of jaw bones, which were related to a broad range of functional activities: cell cycle regulation; signal transduction; and vesicular transport. Buresh, et al., (1999) have implicated the role of t (X; 4) (q22; q31.3) in the etiology of CGCG. Categorizing the lesions clinically, immunohistochemical and cytogenetically has thus been difficult, although GCTB has been shown to harbor greater number of genetic abnormalities.

Conclusion
The observations of the current study depict that the histological parameters of CGCG and GCTB correlate with each other. The two lesions show similar biological behavior, minor differences could be attributed to the variations in the anatomical sites, the presence of the teeth, histological structure of the jawbone and bone marrow activity. We suggest that the evident facial asymmetry, typical anatomical location of the maxillary and the mandibular jaw bones and frequent radiographic screening of the facial skeleton usually lead to an early detection of such lesions in the head and neck region. A longer duration of the lesion within the jawbones can lead to a more aggressive clinical outcome as a result of cumulative effects of aberrations occurring at the genetic level. Giant cell granuloma of the jawbones and giant cell tumour of the long bones can thus be considered to be a continuum of a disease process presenting in aggressive and non-aggressive forms. We recommend that further studies should be directed at investigating the predictors of aggressiveness rather than trying to classify the lesions into Tumour or Granuloma categories. Till then treatment of all such central giant cell lesions of the jawbones should be aimed at complete excision.

Acknowledgement
We would like to acknowledge the staff members of the Dept. of Oral Pathology for their support and guidance.

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Source of Support: Nil, Conflict of Interest: None Declared.