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# Stromal myofibroblasts in central giant cell granuloma of the jaws cannot distinguish between non-aggressive and aggressive lesions

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**OBJECTIVE: To investigate correlations between myofibroblast density (MFD) and biological behavior of a large series of non-aggressive and aggressive central giant cell granuloma lesions (CGCGs).**

**METHODS: Twenty-four non-aggressive and 17 aggressive lesions were immunohistochemically stained with alpha smooth muscle actin. MFD was assessed using the point counting method in the lesions' core tissue and in control areas that consisted of non-involved, connective tissue surrounding the lesion.**

**RESULTS: All CGCGs contained myofibroblasts among the stromal cells. No significant differences were found in the mean percentage of MFD (%MFD) of non-aggressive (20.8 ± 15.7%) and aggressive (23.7 ± 22.9%) lesions ($P > 0.05$) or in the mean %MFD of the respective control areas (1.4 ± 2.2% and 1.7 ± 4.1%; $P > 0.05$). The mean core tissue %MFD of both lesion types was significantly higher than that of the control areas ($P < 0.001$).**

**CONCLUSION: Myofibroblasts were an integral component of CGCG stromal cells, but their density could not distinguish between non-aggressive and aggressive lesions.**

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**Keywords:** central giant cell granuloma; myofibroblasts

## Introduction

Myofibroblasts are mesenchymal spindle cells that share features of both fibroblasts and smooth muscle cells (1). Since they were first identified about four decades ago in contractile granulation tissues and wounds (2), efforts to characterize them have been ongoing. In physiologic conditions, such as wound healing, myofibroblasts appear to represent a temporary functional stage of fibroblasts and disappear, by means of apoptosis, after the wound has healed (1). With the advent of diagnostic electron microscopy and immunohistochemical markers, it became evident that myofibroblasts are a major component in reactive conditions as well as a stromal response in various neoplasms (3), in addition to their being part of a recognized group of true myofibroblastic tumors (4).

A central giant cell granuloma (CGCG) is a localized osteolytic lesion of variably aggressive nature that affects the jawbones (5). It encompasses both non-aggressive, asymptomatic, incidentally discovered lesions cured by simple curettage as well as aggressive, symptomatic, large, destructive lesions that frequently recur and require extensive surgical treatment. In spite of many attempts to identify morphological, morphometric and histochemical parameters for distinguishing between the non-aggressive and aggressive variants of CGCG, the issue still remains controversial (6).

Histologically, CGCGs are composed of a large number of multinucleated giant cells in a mononuclear stroma of spindle- and round-shaped cells (7). The origin and nature of the multinucleated giant cells that are the hallmark of these lesions has been the subject of much debate. Although there is evidence showing that the giant cells are either osteoclasts or macrophages (8), their formation is accredited to the stromal mononuclear cell compartment of CGCGs (9).

Cells with a myofibroblastic phenotype have been identified among the stromal mononuclear cell population of CGCG lesions based on electron microscopic studies (10, 11) and immunohistochemistry (12). Their abundance in one study led the authors to suggest that CGCGs are primarily fibroblastic and myofibroblastic lesions (12).

Presence of stromal myofibroblasts has been linked to the biological behavior of both benign and malignant tumors (13–15). Therefore, the present study was

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designed to identify stromal cells with a myofibroblastic phenotype in CGCG by means of immunohistochemistry and to investigate whether there is a correlation between the density of these cells and the biological behavior of the aggressive compared with the non-aggressive types of lesions in a large series of CGCGs.

## Materials and methods

*Samples*

From the files of the Department of Oral Pathology and Oral Medicine, School of Dental Medicine, Tel Aviv University (Israel), cases of CGCG received between the years 1995 and 2003 were reviewed. Forty-one cases with adequate clinical and radiographic documentation were selected. These cases derived from 23 females and 18 males (mean age 38.6 years, median age 37 years, range 2–86 years). Nineteen lesions were located in the maxilla and 22 in the mandible. According to the clinical records, patients had normal blood levels of Ca, P and PTH. None of the patients received any pharmacological treatment (e.g. calcitonin or corticosteroids) prior to the time of the biopsy procedure.

*Criteria for assessing the biological behavior of CGCG*

The lesions were classified as non-aggressive or aggressive based on the criteria established by Chuong *et al.* (10) and validated by several other studies on the biological behavior of CGCG (12, 16, 17). Consequently, in the present study 24 cases were clinically classified as non-aggressive lesions characterized by minimal or no symptoms, slow growth, absence of root resorption or cortical perforation and a low tendency to recur. The remaining 17 cases were classified as aggressive lesions since they met the criteria of pain, rapid growth, root resorption, cortical perforation and had a tendency to recur.

*Staining procedure*

The 3-μm-thick sections were mounted on positive-charged microscope slides (Optiplus$^{TM}$, Biogenex, San Ramon, CA, USA). After dewaxing in xylene, they were dehydrated in ethanol, rinsed in distilled water, placed in 3% $H_2O_2$ for 10 min and rinsed in distilled water for 15 min. For antigen retrieval, the slides were placed in citrate buffer solution, pH 6, in a microwave at 92°C for 10 min. After cooling at room temperature for 20 min, the slides were exposed to primary alpha smooth muscle actin (α-SMA) mouse anti-human antibody (Dako A/S, Glostrup, Denmark, clone 1A4), dilution 1:100, for 60 min at room temperature and then rinsed in phosphate- buffered saline (PBS) for 10 min. A universal immune peroxidase polymer anti-mouse rabbit Histofine$^{R}$ (Multi) kit (Nichirei, Tokyo, Japan) was used for antibody detection. The sections were rinsed in PBS for 10 min, reacted with an AEC substrate-chromogen kit (Zymed, San Francisco, CA, USA), rinsed in PBS for 2 min, counterstained in Mayer's hematoxylin (Pioneer Research Chemicals, Colchester, UK), and covered with GVA mounting medium (Zymed, San Francisco, CA, USA).

*Staining evaluation*

*Quantitation of myofibroblasts density within CGCGs*

Quantitation of myofibroblasts density within CGCGs was performed by a modified stereological method of measuring cell density as determined by point counting using an eyepiece graticule containing 100 squares (Olympus, Tokyo, Japan) at ×200 magnification (18, 19). Briefly, 10 fields across each section were chosen by systematic sampling. Scanning began by placing the top peripheral border of the graticule at the top left corner of the section. Whenever a graticule-square junction between a vertical and horizontal line coincided with an α-SMA positively stained stromal cell (excluding positively stained endothelial cells of blood vessel walls), it was considered as one count. After completing the cell count of one field (121 points), the grid was moved horizontally over a precise distance beyond the scanned field with reference to the peripheral borders of the grid itself and the counting process was resumed on the new field. This was repeated until the end of the first upper horizontal transverse, after which the section was moved vertically by the same distance and a second horizontal transverse cell count was carried out. As the number of fields counted on each horizontal transverse depended on the size of the section, the distance between adjacent fields was between one and four graticule widths. After all the 10 fields (i.e. a total of 1210 points) from each section were examined, the results were expressed as percentage of myofibroblast density (%MFD) per case. In addition, the mean %MFD ± standard deviation was calculated for the aggressive and non-aggressive cases.

*Quantitation of myofibroblast density in control areas*

Measurements were performed at the periphery of CGCG lesions in the surrounding areas beneath the lining oral epithelium when lesions perforated the jawbone and manifested as a gingival mass. The rationale for choosing these areas as control was based on the assumption that the cellular composition of the connective tissue of the gingiva (or the alveolar) mucosa differs from that of the lesional tissue in terms of the presence of myofibroblasts (20). Control areas in 22 cases of CGCG (14 non-aggressive and eight aggressive) that perforated the jawbone were identified and analyzed for the mean %MFD as described for CGCG core tissue.

*Statistical analysis*

The parameters of age, mean %MFD within CGCG lesions and mean %MFD in control areas were calculated for non-aggressive and aggressive CGCGs, and differences between these lesional variants were analyzed by the Mann–Whitney test. Differences in mean %MFD between the CGCG core tissue and the control areas for the aggressive and non-aggressive lesions were calculated by a one-way ANOVA with square root transformation. Statistical significance was set at $P < 0.05$. Computations were carried out using the Statistical Package for the Social Sciences (SPSS 11) software (SPSS Inc., Chicago, IL, USA).

## Results

Demographic data of the patients and the results of the mean percentage of myofibroblast density (%MFD) within CGCG core tissue and in control areas were compiled. Cases were arranged in decreasing order of mean %MFD within CGCG core tissue for both the non-aggressive and aggressive lesions (Table 1).

The two types of CGCG lesions demonstrated myofibroblasts as part of their stromal mononuclear cell component, but there was a wide range in the density of these cells in both. Figs 1 and 2 display examples of lesions classified as non-aggressive and aggressive, respectively, that demonstrate abundant myofibroblasts in the core tissue. Fig. 3 demonstrates an abundance of myofibroblasts in the core tissue and the absence of these cells in the surrounding, non-lesional connective tissue control areas (except for the vascular walls).

The mean age of patients with non-aggressive CGCG lesions was 41.3 ± 17.7 years, and the mean age of patients with aggressive lesions was 34.7 ± 23.7 years ($P > 0.05$). The mean %MFD for the non-aggressive lesions was 20.8 ± 15.7% within CGCG core tissue and 23.7 ± 22.9% for the aggressive lesions ($P > 0.05$). The mean %MFD in the control areas was 1.4 ± 2.2% for the non-aggressive lesions and 1.7% ± 4.1% for the aggressive lesions ($P > 0.05$). The mean %MFD within the CGCG core tissue was significantly higher than that of the control areas in both the non-aggressive and aggressive lesions ($P < 0.001$).

## Discussion

Since the classification of CGCG lesions as aggressive and non-aggressive by Chuong *et al*. three decades ago (10), several attempts have been made to find an

**Table 1** Demographic data of the 41 patients with giant cell granuloma lesions (CGCGs: non-aggressive = cases 1–24, aggressive = cases 25–41) and the mean percentage myofibroblast density (%MFD) of the core tissue and of the control areas in each of the examined lesions

| *Type of CGCG lesion* | *Case no.* | *Age (years)/gender* | *Jaw* | *Mean %MFD of core tissue* | *Mean %MFD of control areas* |
|---|---|---|---|---|---|
| Non-aggressive | 1 | 46/F | Maxilla | 59 | 4.3 |
| | 2 | 72/F | Maxilla | 42.6 | 7.6 |
| | 3 | 53/F | Maxilla | 36.5 | 2.3 |
| | 4 | 33/F | Mandible | 33.6 | – |
| | 5 | 22/F | Mandible | 33 | 0.25 |
| | 6 | 28/M | Mandible | 31.2 | – |
| | 7 | 57/M | Mandible | 28.8 | 0.08 |
| | 8 | 45/F | Maxilla | 27.7 | 0.08 |
| | 9 | 42/F | Maxilla | 26 | 1.65 |
| | 10 | 24/F | Maxilla | 25.2 | – |
| | 11 | 29/M | Mandible | 23.4 | – |
| | 12 | 22/F | Maxilla | 21 | 0.41 |
| | 13 | 38/M | Maxilla | 19.4 | 0.83 |
| | 14 | 56/F | Mandible | 19.4 | 0 |
| | 15 | 38/M | Maxilla | 15.2 | – |
| | 16 | 66/F | Maxilla | 15.2 | – |
| | 17 | 37/M | Mandible | 14.9 | – |
| | 18 | 56/M | Maxilla | 10.6 | 0.25 |
| | 19 | 40/F | Maxilla | 4.4 | 0.5 |
| | 20 | 32/F | Mandible | 4.2 | – |
| | 21 | 14/M | Maxilla | 3.5 | 0.33 |
| | 22 | 77/M | Mandible | 1.5 | – |
| | 23 | 37/M | Mandible | 1.3 | 0.99 |
| | 24 | 28/F | Mandible | 0.7 | – |
| Mean ± SD/total | | 41.7 ± 17.7<br>10M; 14F | Mandible 11<br>Maxilla 6 | 20.8 ± 15.7 | 1.4 ± 2.2 |
| Aggressive | 25 | 2/M | Mandible | 67.4 | 0.66 |
| | 26 | 52/M | Mandible | 60 | 12.5 |
| | 27 | 70/F | Mandible | 53 | – |
| | 28 | 23/F | Maxilla | 51 | 0 |
| | 29 | 9/M | Mandible | 42.4 | – |
| | 30 | 20/M | Mandible | 36.6 | 0.08 |
| | 31 | 15/F | Mandible | 31 | – |
| | 32 | 68/M | Maxilla | 18.5 | 0 |
| | 33 | 14/F | Mandible | 16.5 | – |
| | 34 | 62/F | Mandible | 7.2 | 0 |
| | 35 | 45/M | Mandible | 6.4 | – |
| | 36 | 86/F | Mandible | 3.8 | 0 |
| | 37 | 29/F | Maxilla | 3.6 | – |
| | 38 | 25/F | Maxilla | 2.2 | – |
| | 39 | 25/F | Mandible | 1.4 | – |
| | 40 | 33/M | Maxilla | 0.7 | 0 |
| | 41 | 13/M | Maxilla | 0.3 | – |
| Mean ± SD/total | | 34.7 ± 23.7<br>8M; 9F | Mandible 11<br>Maxilla 13 | 23.7 ± 22.9 | 1.7 ± 4.1 |

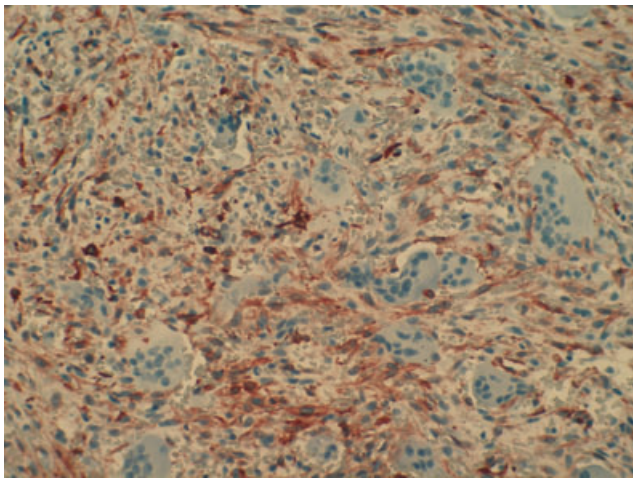

**Figure 1** Photomicrograph of a non-aggressive giant cell granuloma lesion (CGCG) in which the stroma surrounding the multinuclear giant cells consists of extravasated red blood cells and an abundant network of myofibroblasts identified by their intense alpha smooth muscle actin (α-SMA) (ABC method, original magnification ×200).

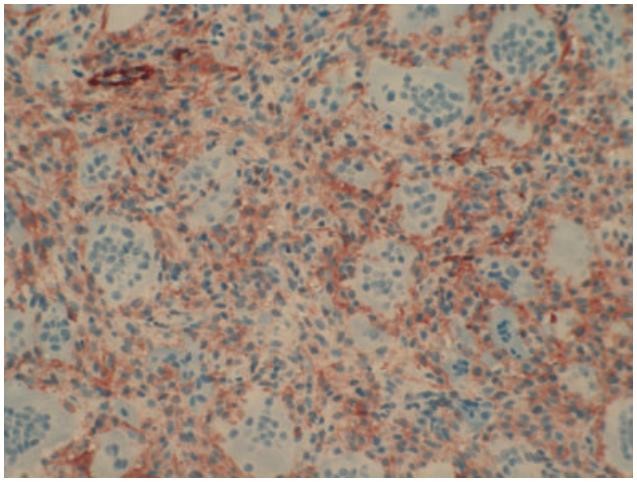

**Figure 2** Photomicrograph of an aggressive giant cell granuloma lesion (CGCG) demonstrating alpha smooth muscle actin (α-SMA)-positive myofibroblasts tightly packed on the periphery of the multinucleated giant cells (ABC method, original magnification ×200).

algorithm for predicting the biological behavior of CGCG lesions based on histopathologic features. This would have a telling impact on therapeutic management and prognosis. As giant cells are the histopathologic hallmark of CGCG, they were the obvious focus of studies that analyzed various parameters in relation to the aggressiveness of the lesions. Parameters such as the relative size index of the giant cells (10, 21), number of giant cells and fractional surface occupied by them (16, 21), mean DNA content (22) and distribution pattern of these cells (17) were studied in detail. The results of these studies were, however, controversial and no consistently significant differences were found between aggressive and non-aggressive lesions. Attention then shifted to the stromal mononuclear cells within the lesions: these cells alone, and not the giant cells, were

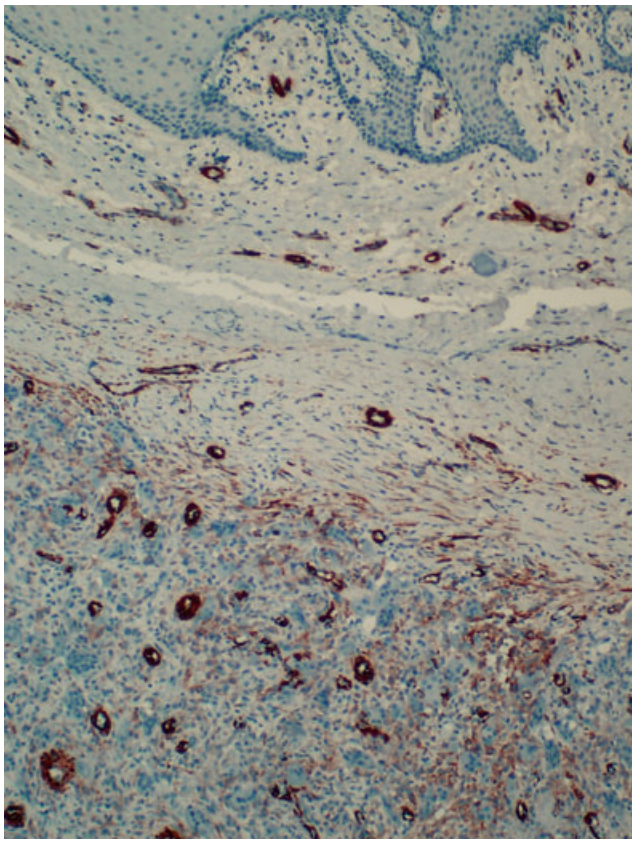

**Figure 3** Photomicrograph of the marginal region of a giant cell granuloma lesion (CGCG; lower part) that perforated the cortical bone into the gingival tissue (upper part). Alpha smooth muscle actin (α-SMA)-positive myofibroblasts are seen within the tissue core of the lesion and at the transitional area between the lesion and the adjacent, gingival connective tissue. No α-SMA-positive cells compatible with myofibroblasts can be observed in the rest of the gingival tissue, which is not involved by the CGCG and which serves as the control areas, except for the cells associated with the vascular walls (ABC method, original magnification ×100).

found to incorporate the proliferative potential of CGCG when using Ki-67 as the marker for cell proliferation (12, 23). No differences in the proliferative potential between aggressive and non-aggressive lesions were found in these studies.

Based on the fact that stromal myofibroblasts can be associated with the degree of biological aggressiveness of different conditions, both benign and malignant (13–15), we reasoned that the density of these cells could be related to the biologic behavior of CGCG. The results of the present study showed that both the non-aggressive and aggressive CGCG possess stromal myofibroblasts in a wide range of density and that there were no significant differences between the two variants. Similar results were reported in a previous study by O'Malley *et al*. (12) who quantitatively assessed the density of myofibroblasts in non-aggressive and aggressive CGCG. While we identified stromal myofibroblasts in all cases, however, they were identified in only about 50% of each variant in O'Malley *et al*.'s experiment (12).

Although we detected a considerable heterogeneity in the density of myofibroblasts in all CGCG lesions, the

mean density of these cells was significantly higher within the core of CGCG tissue than in the surrounding gingival or alveolar control tissue. Therefore, we assumed that the myofibroblasts within the CGCG core tissue constitute an integral part of the lesional cells.

One of the main components of the stromal mononuclear cell population in CGCG is the mesenchymal spindle cells of bone marrow origin (24). These cells have the ability to further differentiate into osteoblasts, fibroblasts, and histiocytes (25) as well as into myofibroblasts (26, 27). Another cellular component of CGCG stroma is the fully differentiated macrophages, which were shown to have the potential to undergo a process of transdifferentiation and acquire spindle-shaped morphology and α-SMA expression, compatible with a myofibroblast phenotype (28). Therefore, it can be assumed that myofibroblasts within CGCG lesions can be derived either from undifferentiated mesenchymal stromal cells or from differentiated mononuclear cells (i.e. macrophages). It is possible that the biological behavior of CGCG lesions could be related to the origin of the myofibroblasts (i.e. undifferentiated mesenchymal cells or fully differentiated macrophage cells) rather than their density. This issue warrants further investigation.

The diversity of the phenotypes demonstrated by the stromal mononuclear cells in CGCG lesions is not limited to macrophage and myofibroblastic lineages, but also includes features of osteoclast-like cells (8, 29). Thus, it is suggested that the mononuclear stromal cells in CGCG lesions undergo a dynamic process of transdifferentiation rather than exist in a constant state. This possibility should be taken into account when pharmacologic treatment is considered in cases of extensive lesions, with the intent of reducing lesion size, limiting surgery and avoiding functional and esthetic damage, especially in young patients. Intralesional injections with steroids target mainly macrophages as well as osteoclast-like cells, while calcitonin is directed mainly against osteoclast-like cells (29). When the relationship between the different types of cells in CGCG and the various therapeutic options will be further understood, a rational choice of the pharmacologic therapy would be feasible on the basis of the histological and immunohistochemical findings and this might also include anti-myofibroblastic agents.

In summary, the present study shows that CGCG demonstrate great variability in the density of stromal myofibroblasts; however, differences between aggressive and non-aggressive subtypes cannot be made on the histological grounds. The precise role of the stromal myofibroblasts in CGCG and their contribution to the pathogenesis of these lesions should be further investigated.

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