J Bras Patol Med Lab. 2018 Jun; 54(3): 183-188.

10.5935/1676-2444.20180032

Quantification of bone gain in central giant cell granuloma of the jaws submitted to intralesional corticotherapy

Quantificação de ganho ósseo em lesões centrais de células gigantes dos maxilares submetidas à corticoterapia intralesional

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ABSTRACT

Introduction: The central giant cell granuloma (CGCG) is a bone alteration of unknown etiology that can affect the jaws and presents varied clinical behavior. **Objective:** To analyze radiographs from patients with CGCG submitted to intralesional corticosteroids, in order to quantify bone gain after treatment. **Methods:** Sixteen patients with the microscopic diagnosis of CGCG were selected from the Batista Memorial Hospital, in Fortaleza, Ceará, Brazil. Thirty-two radiographs (16 initial and 16 final) were evaluated by the mean pixel values of the affected region before and after the complete corticosteroid intralesional application protocol (six applications in biweekly intervals of triamcinolone hexacetonide). **Results:** Of the patients submitted to the study, 14 (87.5%) presented a mean increase in the values of pixels, understood as bone gain, in the radiographs after treatment with intralesional injections, and two (12.5%) did not present it. The comparison of the mean pixel values between the initial and final test sides showed $p = 0.0027$, which was statistically significant, confirming the increase in density in the studied regions. **Conclusion:** The tools for analysis of pixel values were useful in the quantification of bone gain in patients submitted to intralesional corticosteroid therapy, and these tools should be further explored and used during treatment as auxiliary methods in the evaluation of its efficacy.

Key words: therapeutics; radiography panoramic; diagnosis.

INTRODUCTION

The central giant cell granuloma (CGCG) is a non-odontogenic condition that represents around 10% of all benign jaw lesions. It has an incidence of 0.0001% in the general population, and was first described by Jaffe in 1953[1]. CGCGs tend to occur in young patients, under the age of 30, having been reported in children up to 2 years, with a slight predilection for females[2-6].

Clinical and radiographic findings show a wide spectrum of behavior, ranging from aggressive to non-aggressive[2]. Non-aggressive lesions are characterized by no symptoms, slow growth, absence of cortical perforation, and low recurrence rate. Aggressive lesions, less common, are associated with pain, rapid growth, cortical perforation, root resorption and high recurrence rates[7]. CGCGs can appear as unilocular or multilocular radiolucencies, of well-defined or ill-defined margins and varied degrees of cortical expansion. They can be confused with other jaw lesions, such as brown tumor of hyperparathyroidism, fibrous dysplasia, aneurysmal bone cyst, and other fibro-osseous lesions[3, 8].

The most common treatment for CGCGs is still curettage[9-13], which can be used along with cryosurgery, in some cases[14], and with peripheral ostectomy, in others[2]. Although the surgical treatment is still widely recommended, daily systemic doses of calcitonin[10, 11] and intralesional injections of corticosteroids[15] have been increasingly investigated. The corticosteroid intralesional injection causes the decrease of the lesion and even the resolution of the case, being a conservative, simple and low-cost treatment.

First submission on 03/07/18; last submission on 05/02/18; accepted for publication on 05/20/18; published on 06/20/18

While conservative treatment shows favorable results, bone gain is assessed just visually by means of radiographic images, and no form of quantification of such a gain is established[15-20]. Therefore, the objective of this study was to analyze radiographs from patients with CGCG who underwent intralesional corticotherapy, aiming at quantifying post-treatment bone gain.

METHODS

This study was conducted with prior approval by the Ethics Research Committee (protocol no.79/08). The studied population was composed of patients with histopathological diagnosis of CGCG registered in the files of Hospital Batista Memorial de Fortaleza, Ceará, Brazil. Patients included in the sample were those with: complete identification, clinical information on the existence or not of symptoms, description of clinical signs, and imaging tests with initial and follow-up panoramic radiographs. Patients were excluded when diagnosed with brown tumor of hyperparathyroidism or cherubism, as well as when errors in radiographic technique, patient positioning or radiograph processing occurred.

Analysis of clinical data

For analysis of clinical data, information were gathered about type of adopted treatment, lesion site, microscopic characteristics obtained from incisional biopsy (**Figure 1**) and data relative to patient follow-up. The overall analysis of available data in each case was intended for a better evaluation of response to treatment, besides correlation with radiographic data.

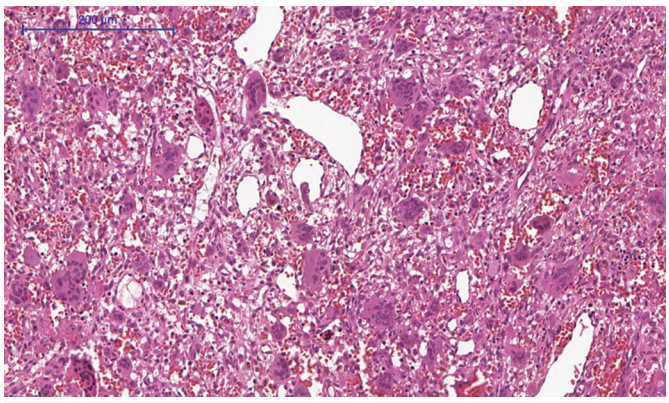

FIGURE 1 – *Microscopic aspects of CGCG: proliferation of mononuclear mesenchymal cells associated with a population of multinucleated giant cells in a matrix of dense fibrous conjunctive tissue, presenting extravasated red blood cells (HE, 200 µm)*

CGCG: central giant cell granuloma; HE: hematoxylin and eosin.

Radiographic assessment

Radiographs were scanned at an optical scanner PowerLook II (Techville - Dallas-USA) with spatial resolution of 600 dpi, and analyzed with the program ImageJ® [1.29× (NIH-USA)] at a flat-screen computer (Sony LED screen 15.5"- Intel Core i3-2350M).

Images were opened at a computer that runs on Windows® platform, and the room was darkened during radiograph analysis, for better visualization. Similarly to what was performed by Teixeira *et al.* (2011)[21], in each of the images, an area corresponding to the region of interest (ROI) was opened in the oval format and saved so that its size and format could be maintained in all measurements for each of the studied patients.

Two distinct regions of the same image were selected. One presented healthy bone, being considered bone image of initial control; the other, containing affected bone, was designated initial test area. Later, both regions were compared to the same areas evaluated after the complete protocol of intralesional corticoid (six biweekly applications of triamcinolone hexacetonide) application, aiming at assessing bone gain after the employed treatment (**Figures 2** and **3**). Using the resources of ImageJ® program, the mean pixel values of the evaluated area and its standard deviation (SD) were recorded, according to data provided by the histogram. Such a measure was taken both in the test area (undergoing corticotherapy) and in the control area, in the 32 images (16 initial and 16 final). The examiner was allowed to adjust brightness and contrast of the visualized image. The histogram of ImageJ® software provided data on the mean pixel values at a scale of 8 bits, attributing the zero value to the darkest grey (black) and 255 to the lightest (white). The ROI measures were obtained by two examiners separately, obeying the same technique.

A second analysis was conducted, 30 days later, for the evaluation of intraexaminer and interexaminer agreement, and the obtainment of reproducibility of pixel value measurements by means of the histogram. In case of different values, an average of the procedure was taken. After obtainment of a mean pixel value of the test and control areas, subtraction between the value on the control side and the test side was conducted (ROI test - ROI control), aiming at the control area to have a value always equivalent to zero, to minimize variations inherent in radiographic exposure and processing, both in initial and final images. Next, a comparison of the initial result was done with the final result (ROI final test - ROI initial test) aiming at quantifying bone gain in that region. The mean pixel values of initial and final test sides were submitted to the Friedman test in Bioestatic 5.0 program, in which a significance level of 5% ($\alpha = 0.05$) was adopted.

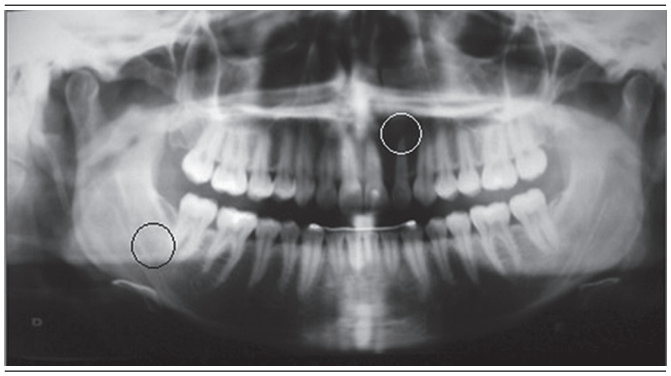

FIGURE 2 – *Panoramic radiograph prior to treatment: ROI test (white circle) and initial control (black circle) in the area before intralesional corticosteroid application*

ROI: region of interest.

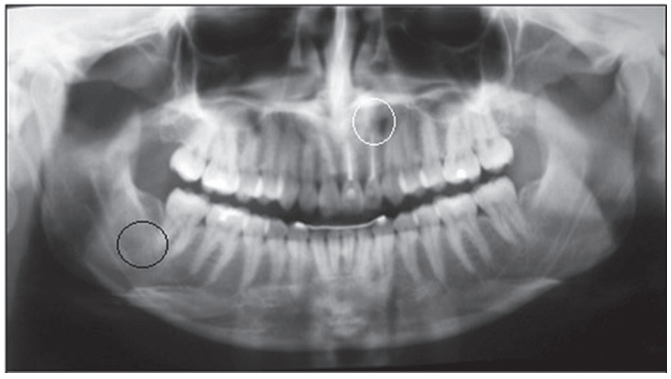

FIGURE 3 – *Post-treatment panoramic radiograph: ROI test (white circle) and final control (black circle) after the protocol of intralesional corticosteroid application*

ROI: region of interest.

RESULTS

In the present study, from a universe of 32 patients, 16 met the inclusion criteria of the study and had their panoramic radiographs undergoing analysis for bone gain quantification. Females were more affected ($n = 10$; 62.5%) than males at a F:M ratio of 1.6:1. The age of patients included in the study ranged from 7 to 25 years, with an average of 16.3 years.

Regarding complaints, all patients presented volumetric increase of the involved area, just four (25%) reported pain, and just one patient (6.25%) reported paresthesia. Ten cases involved the mandible (62.5%); and six, the maxilla (37.5%).

The radiographs revealed 12 patients (75%) presenting unilocular lesions; and the remaining (25%), multilocular lesions. Among the 16 patients, 12 (77.7%) presented tooth displacement; four (25%), tooth resorption; seven (43.75%), cortical perforation; and 14 (67.5%), cortical expansion (**Table 1**).

The defined ROI was used in the measurement of mean pixel values of test and control side images of each patient. Of the 16 cases, 14 (87.5%) presented increased mean pixel values – understood as bone gain in radiographs after treatment with intralesional injections –, and just two (12.5%) did not present this picture. Comparison of mean pixel values between initial and final test sides, described in **Table 2**, showed statistically significant difference ($p = 0.0027$).

TABLE 1 – Criteria adopted in CGCG classification, according to biological behavior

Patient	Sex	Age	Site	Pain	Cortical expansion	Tooth displacement	Tooth resorption	Cortical perforation
Patient 1	Male	10	Mandible	No	Yes	Yes	No	No
Patient 2	Female	24	Maxilla	Yes	No	Yes	No	No
Patient 3	Female	21	Mandible	Yes	Yes	Yes	Yes	Yes
Patient 4	Male	20	Maxilla	No	Yes	No	No	No
Patient 5	Female	19	Mandible	No	Yes	No	No	No
Patient 6	Male	9	Maxilla	No	Yes	Yes	No	Yes
Patient 7	Female	15	Mandible	Yes	Yes	Yes	Yes	Yes
Patient 8	Male	12	Mandible	No	Yes	Yes	No	No
Patient 9	Female	24	Mandible	No	Yes	No	No	No
Patient 10	Female	20	Maxilla	Yes	Yes	Yes	No	Yes
Patient 11	Female	9	Maxilla	No	Yes	Yes	No	No
Patient 12	Male	7	Maxilla	No	Yes	Yes	No	No
Patient 13	Male	25	Mandible	No	No	No	No	Yes
Patient 14	Female	9	Mandible	No	Yes	Yes	No	No
Patient 15	Female	18	Mandible	No	Yes	Yes	Yes	Yes
Patient 16	Female	19	Mandible	Yes	Yes	Yes	Yes	Yes

Criteria used by Chuong et al. *(1986)*[22].

TABLE 2 – Mean initial and final pixel values, by patient

Data	Mean initial pixel values	Mean final pixel values	Result
Patient 1	-55.347	-14.278	41.069
Patient 2	- 113.976	73.408	187.384
Patient 3	- 112.468	87.596	200.064
Patient 4	-126.287	-115.515	10.772
Patient 5	-95.212	9.594	104.806
Patient 6	57.52	118.965	61.445
Patient 7	- 128.351	30.04	158.391
Patient 8	-6.209	28.188	34.397
Patient 9	-52.619	-28.417	24.202
Patient 10	-21.012	-59.995	-38.983
Patient 11	- 39.004	30.845	69.849
Patient 12	60.175	77.035	16.86
Patient 13	- 44.941	7.214	52.155
Patient 14	-78.135	33.694	44.441
Patient 15	11.659	3.096	-8.563
Patient 16	-56.089	-40.118	15.971

DISCUSSION

According to Austin *et al*. (1959)[5], CGCG represents less than 7% of all benign tumors of the jaws, but data relative to their occurrence are scarce in the literature. This low incidence hinders a better understanding of the lesion, as there are no studies with representative samples and a study with a large number of cases would be necessary for evaluation of the specific characteristics of aggressive and nonaggressive types, separately.

Nowadays, in search of more conservative treatments for several diseases, intraosseous corticotherapy has been employed successfully by some authors. However, there are no works in the literature that deal with quantification of bone gain when this treatment is employed, what would enable to prove the treatment success quantitatively. Pixel analysis by different programs has been reported in the literature, with quantification of pixel values being studied in different conditions[23].

In the current study, 62.5% of the cases were female patients, what is in agreement with some authors that state there is a discrete predilection for this sex[7, 23]. Patients' mean age was 16.3 years, what is also in agreement with the literature, which affirms that although the lesion can occur at any age, it affects mainly individuals in the first three decades of life[7, 23, 24]. The varied biological behavior of CGCG though, suggests that age group predilection is questionable, as it can be years for asymptomatic lesions to be identified, while symptomatic ones are rapidly diagnosed.

According to the literature, CGCGs affects principally the mandible, at a 2:1[7, 23, 25] proportion, similar to what was found in the present study. Some authors report that lesions affect three times more often the mandible than the maxilla[8, 17, 24]. At the current research, 62.5% of the cases occurred in the mandible, what is generally in compliance with the literature. Lesions affecting the maxilla are more common in the anterior portions, are confined to the region of the teeth and frequently cross the midline[26]. Five of our cases presented in the anterior region of maxilla, crossing the midline. The other cases that involved the maxilla were limited to the left or right side of the face. Anatomical osseous aspects of the maxilla, such as the thin cortical plates and the mouth close proximity to open spaces and orbits influence prognosis and CGCG treatment[27]. This statement allows us to understand why relapses are more frequent in the maxilla than in the mandible. In our work, one of the cases that responded negatively to treatment involved the maxilla, invading the nasal fossa, what made it difficult for the patient to breathe.

All patients underwent incisional biopsy, intralesional corticosteroid injections and final osteoplasty as treatment. Just one patient (5.55%), who presented local relapse of the lesion after corticoid treatment, underwent surgical curettage. The two patients that responded negatively to treatment were later referred to surgical treatment. In one of them the lesion was in the maxilla and invaded the nasal fossa, what made breathing difficult.

ROI analysis showed that mean pixel values increased in the final test side compared with the initial test side, a statistically significant result ($p = 0.0027$), demonstrating the actual bone gain in follow-up radiographs when compared with initial radiographs. Just two cases (12.5%) did not display increased mean pixel values, what is in accordance with the clinical result, as they did not present good response to treatment, and needed additional treatment.

This study was conducted *in vivo* and presents great variability of radiographs regarding exposure and processing, what interfered in the analysis and results. This happened because it is a retrospective study, and inclusion and exclusion criteria were employed to minimize those variables. The participants' initial and final radiographic images were obtained in the same extraoral radiography equipment and were submitted to automatic processing.

The digitization process also seems to be very important so as not to lose information in the highest densities, as the subtle increased radiolucencies in incipient bone gain[28]. At a scanner with specification of, for example, 1200 × 2400 dpi, the smallest number corresponds to the optical resolution, and the dpi choice is a critical factor in the use of the scanner. In order to yield resolutions greater than the optical, an interpolation is done by means of

the program, what means calculating values that occur between two known values, adding new information to the image[29]. Thus, the direct digital radiography systems are the best option for the follow-up of these patients, what was not possible to do in the present study, for two reasons. First, because it is a retrospective study. Second, because most of our participants are low-income patients, treated in the public service, where radiographs not only present poor quality but are almost always conventional, needing to go through the digitization process.

In an effort to define treatment modality, the ideal would be applying molecular, biological or genetic markers able to establish the degree of aggressiveness of the lesion for each case. However, these parameters are not well defined, being the criteria by Chuong *et al.* (1986)[22] those used up to the moment.

For Kaban *et al.* (2002)[9] and Pogrel (2003)[13], these factors must be taken into account for treatment choice: aggressive behavior versus non-aggressive behavior, site, size of the lesion, and radiographic appearance. Yet, when non-surgical treatments are chosen, the forms of evaluating treatment efficacy, as bone gain quantification, have not, so far, been suggested in the literature.

Although surgery is the treatment of choice according to the literature, this does not seem the ideal treatment option, because it can cause mutilation and high morbidity, especially in children and young patients[30].

CONCLUSION

Tools for analysis of pixel values proved useful for bone gain quantification in patients submitted to intralesional corticoid treatment. They must be properly exploited and used along with the treatment. Besides, they permit dental surgeons to follow patients with more safety, evaluating whether treatment is being effective or not in each case.

RESUMO

Introdução: *A lesão central de células gigantes (LCCG) é uma alteração óssea de etiologia desconhecida e comportamento clínico variado, que pode acometer os maxilares.* ***Objetivo:*** *Analisar radiografias provenientes de pacientes portadores de LCCG submetidos à corticoterapia intralesional, visando propor a quantificação de ganho ósseo pós-tratamento.* ***Métodos:*** *Foram selecionados 16 pacientes com diagnóstico microscópico de LCCG cadastrados nos arquivos do Hospital Batista Memorial de Fortaleza, Ceará, Brasil. Trinta e duas radiografias (16 iniciais e 16 finais) foram avaliadas por meio da média dos valores de pixels da região afetada pela afecção antes e após o protocolo completo de aplicação intralesional de corticoide (seis aplicações em intervalos quinzenais de triancinolona hexacetonida).* ***Resultados:*** *Dos pacientes submetidos à pesquisa, 14 (87,5%) apresentaram aumento da média dos valores de pixels – dado entendido como ganho ósseo – nas radiografias após tratamento com injeções intralesionais; apenas dois (12,5%) não apresentaram esse quadro. A comparação das médias dos valores de pixels entre os lados teste inicial e final mostrou* $p = 0,0027$, *o que foi estatisticamente significante, comprovando o aumento de densidade nas regiões estudadas.* ***Conclusão:*** *As ferramentas de análise de valores de pixels mostraram-se úteis na quantificação de ganho ósseo em pacientes submetidos à corticoterapia intralesional, devendo tais ferramentas ser mais exploradas e utilizadas no decorrer do tratamento como auxiliares na avaliação de sua eficácia.*

Unitermos: *terapêutica; radiografia panorâmica; diagnóstico.*

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