J. Oral Diag. 2017; 02:e20170023.

ORIGINAL ARTICLE

Histological analysis of a clinical case of central giant cell lesion treated with triamcinolone

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Abstract:

Introduction: Central giant cell lesion (CGCL) is an osteolytic lesion mainly found in gnathic bones of children and young adults. It is a benign lesion with variable clinical and radiographic behavior but it may be aggressive. Intralesional corticoid application has been proposed as an alternative and complementary procedure to radical surgical treatment, to minimize functional and aesthetic damage. **Objectives:** This paper aims to report a case of a pediatric patient with CGCL of the jaw, which was treated withconservative treatment of two intralesional applications of triamcinolone and discuss if there is an ideal waiting period between nonoperative treatment and the need for surgical intervention. **Methods:** This report shows a quantitative analysis of histological alterations induced by intralesional infiltrations of triamcinolone into a clinical resistant CGCL. A 7-year-old patient was submitted to a conservative treatment of two intralesional applications of triamcinolone into a mandible CGCL. **Results and Conclusion:** Histological evaluation showed reduction in the number of blood vessels and of giant multinucleated cells, beside an increased collagen production. The triamcinolone induced histological alterations seem to interfere in the clinical behavior of the lesion thus, recommending a less radical surgical treatment.

Keywords: Giant Cells; Triamcinolone; Histology

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Article received on April 6, 2017.
Article accepted on June 7, 2017.

DOI: 10.5935/2525-5711.20170023

INTRODUCTION

The central giant cell lesion (CGCL) is defined by the World Health Organization as a benign intrabone lesion, constituted by fibrous tissue containing multiple hemorrhagic spots, multinucleated giant cell aggregates and occasionally bone tissue trabeculae[1]. It is not a very common osteolytic lesion, representing less than 7% of all benign maxillomandibular lesions and of unknown etiology[2]. Some authors consider that it originates from proliferative inflammatory, reactional, infective or neoplastic processes[3], while others credit the condition to a genetic nature[4]. It occurs preferentially in children or young adults, 75% of cases being diagnosed before 30 years of age. Females have the disease in a proportion of 2:1 in relation to males.

Some systemic conditions may be associated to CGCL, like the brown tumor of hyperparathyroidism and Paget disease. Type I neurofibromatosis, cherubism and Noonan syndrome[5] should not be considered.

CGCL is frequently found in gnathic bones, more common in the mandible than the maxilla but it may be diagnosed in other regions of the human body. The lesion is generally localized in the anteroinferior region tending to cross the median line[6]. Its clinical behavior is variable and it was classified by Chuong and Kaban as a lesion both aggressive and non-aggressive. The aggressive one evolves rapidly, attains large extensions, may induce cortical expansion and or perforation, radicular reabsorption, dislodged teeth and pain, besides having high recorrence. Although rare, paresthesia may be observed. The nonaggressive lesion is generally asymptomatic, of slow growth, does not induce cortical perforation and radicular absorption and shows less recurrent episodes[7].

Histologic analysis reveals numerous multinucleated giant cells, irregular distribution of fibroblasts in fibrous stroma and vascular channels. Giant cells may be of different sizes, forms and number of nuclei. Microscopically, CGCL is not distinguishable from the brown tumor of hyperparathyroidism, differences being established by laboratory tests like high levels of PTH, serum calcium and alkaline phosphatase, besides reduction of serum phosphorus[8].

CGCL has been treated by classical surgical procedures, which vary from simple curettage for non- aggressive lesions to large block resections when aggressive characteristics are detected[9]. Calcitonin, alpha-interferon and intralesional corticoids have been proposed as alternative isolated treatments or associated to surgery. These therapies reduce lesion size and the extension of surgical resection in aggressive conditions[3].

The mutilating nature of surgical procedures may lead to permanent teeth losses and interfere in mandible growth centers, thus compromising facial and dental development. Considering that CGCL is more common in young patients, the study of alternative less mutilating therapies is of utmost importance.

This report shows a quantitative analysis of histological alterations promoted by triamcinolone in a CGCL clinical and radiographically non-responsive to corticoid intralesional therapy.

CASE REPORT

Dark skinned 7-year-old boy, showing a painless volume increase in the left anterior region of the mandible that extends to the ipsilateral parassymphysis with an evolution of about seven months. On examination was detected a discrete facial asymmetry, disappearance of the vestibular bottom and displacement of dental units 31 and 32. Panoramic radiography showed a well defined radiolucent image, with irregular contours extending from the left first molar to the right canine and dental displacement of elements 31, 32 and 41, besides the included 33, 34 and 35 units (Figure 1).

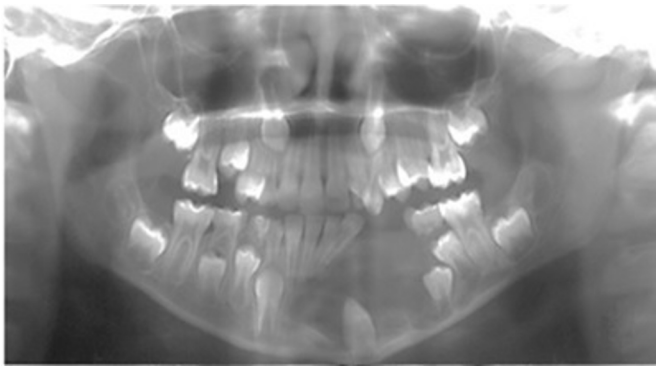


Figure 1. Panoramic radiograph that was taken after intralesional triamcinolone.

The condition was diagnosed as CGCL by histological analysis. Hyperparathyroidism was discarded by the normal levels of serum calcium and phosphorus, PTH and alkaline phosphatase found in laboratory analysis. Triamcinolone hexacetonide (20mg/mL) was applied in 10 sessions according to the following protocol: Weekly injections of sterile suspension (0.5mL) into different lesion sites. Control radiographs did not show regression after one year following.

A new incisional biopsy confirmed the diagnose of CGCL. A conservative treatment was repeated by the application of corticoid during 6 weeks. After 4 months,

the absence of a clinical or radiographical response indicated the use of a surgical procedure, a curettage associated to peripheral ostectomy and removal of associated dental units (75, 32, 33 and 35). Postsurgical follow up showed new bone in the curettage area and absence of recidivating signs (Figure 2).

Currently, the patient has a follow up and a temporary prosthesis maintains the prosthetic space, as a warranty for the rehabilitating treatment with implant supported prosthesis.

The legal guardian of the patient has given full authorization by signing the Informed Consent Form, allowing photographic records and subsequent publication of the case in the scientific literature, according to regulations already approved by Ethics Committee of the Bahia School of Medicine and Public Health.

The quantitative histological study of biopsy material was conducted on slides stained with hematoxylin and eosin, PAS and Sirius Red. The staining protocol allowed the determination of the number and size of multinucleated giant cells, the number and size of blood vessels and the collagen amount, respectively. A microscope fitted with a 400X objective was used for the histomorphometric analysis of the structures, randomly capturing 10 fields through the Motic Images Advanced 3.0 program.

The biopsy samples were collected in three specific occasions: M1 at the start of the study; M2, obtained one year after the first ten applications of triamcinolone and M3, was the enucleated surgical piece collected four months after the six additional applications of triamcinolone. The MS Excel created data bank was analyzed with the R software (version 2.15.2). The descriptive analysis identified the general and specific characteristics of the samples, the averages and medians, the dispersions,

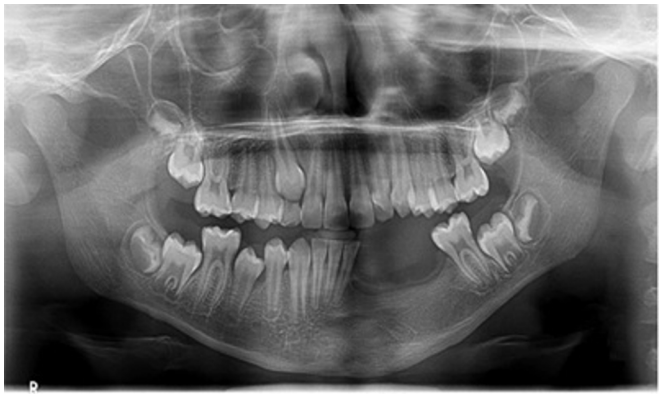
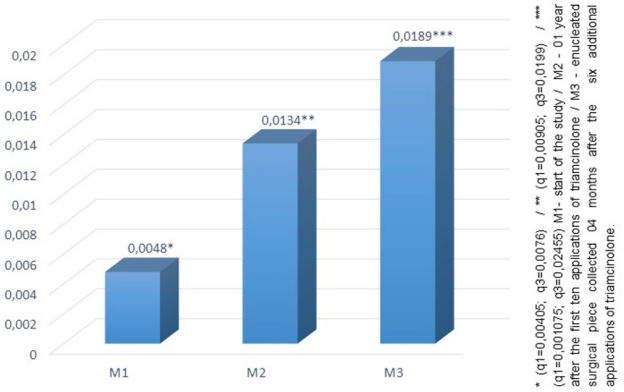


Figure 2. Panoramic radiograph, 19 months after curettage and peripheral ostectomy.

standard deviations and 1º and 3º quartis, respectively. Significant differences between the three samples were evaluated through ANOVA followed by the Bonferroni test for parametric measurements, and by the exact Friedman test followed by the Dunn test for nonparametric evaluation.

RESULTS

Collagen quantities increased progressively after triamcinolone applications, the medians determined in the first sample (M1) being 0.0048mm² and the last one (M3) 0.0189 mm² (p value=0.0239). The difference between M1 and M3 is significant while other comparisons are not (Graph 1).



Graph 1. Median variation in collagen quantities (mm²) found in biopsy samples collected after applications of triamcinolone for the treatment of CGCL.

The number of blood vessels was reduced when the first M1 sample was compared to the second (M2), with average values of 16.4 (σ=4.169) and 10.4 (σ=3.627), respectively. In the M3 sample the value was 9.4 (σ=2.459) (p value=0.0003). Significant differences were between M1 and M2 and M1 and M3.

The number of giant multinucleated cells was reduced when M1 was compared to M2, with averages of 17.8 (σ=6.161) and 5.4 (σ=2.757), respectively. However, the number increased between M2 and M3 to an average of 10.8 (σ=4.872). The differences between the three values were significant (Figure 3; Graph 2).

The sizes of giant cells showed a discreet increase in the average perimeter, when comparing M1 and M2, the average values being 0.1492mm (σ=0.02315mm) and 0.1505mm (σ=0.02323mm), respectively. The average perimeter of giant cells determined in M3 was 0.1277mm (σ=0.0198) (p value=0.0091) indicating a significant difference when compared to M2. Thus, aver-

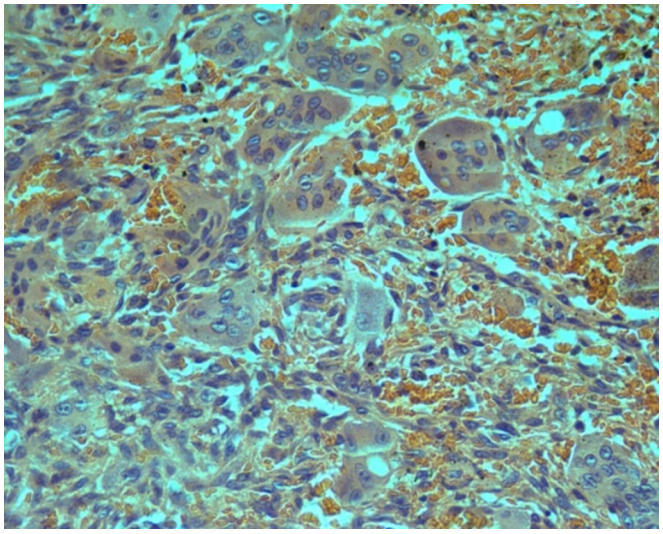
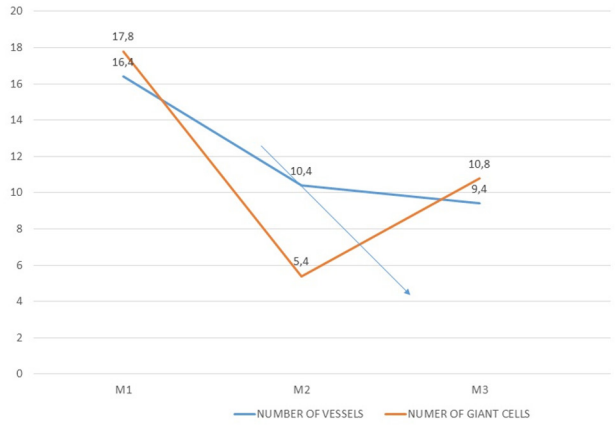


Figure 3. Numerous giant cells in biopsy sample, PAS staining, 400X.



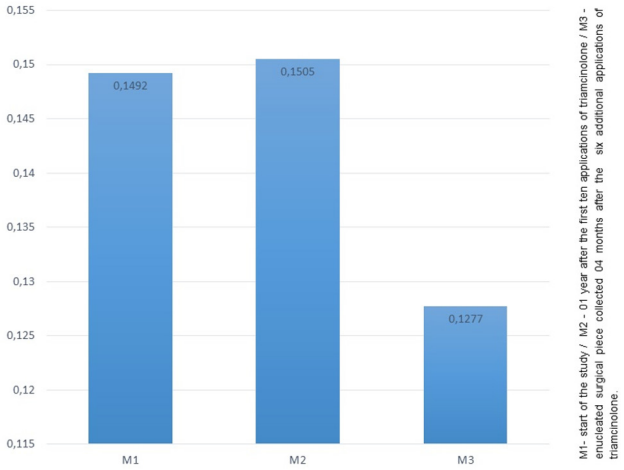
Graph 2. Variations in the average numbers of blood vessels and of multinucleated giant cells that was determined in biopsy samples after triamcinolone applications for the treatment of CGCL.

age perimeters in giant cells were significantly different between M1 and M3 and M2 and M3 (Graph 3).

Median values of perimeters in blood vessels did not change significantly in comparisons of M1, M2 and M3. The values determined were: M1, 0.0417mm (q1=0.03673 mm; q3=0.05325 mm); M2, 0.0426 mm (q1= 0.03418mm; q3=0.05145mm) and M3, 0.03485mm (q1=0.03078mm; q3= 0.04048mm) (*p* value=0.2223).

DISCUSSION

CGCL is a benign lesion but its varied clinical and radiographic behavior characterizes both an aggressive and non-aggressive nature[4]. Generally, non-aggressive lesions are treated by curettage associated to peripheral ostectomy, cauterized with liquid nitrogen or Carnoy



Graph 3. Variations in the average areas of multinucleated giant cells determined in biopsy samples collected after applications of triamcinolone for the treatment of CGCL.

solution while aggressive ones are removed by block resections[6]. The CGCL diagnosed in the present case justified block resection since it showed characteristics of an aggressive lesion, it was extensive, produced cortical perforation and teeth displacement.

Nonsurgical treatments have been proposed to avoid functional and aesthetic damage resulting from radical therapies. This is highly important when one considers that most patients are quite young[6]. Among the conservative measures proposed, corticoid intralesion infiltration merits prominence. It involves simple techniques and has low cost. Even with persistent or recidivistic lesions, the literature reports remission cases after intralesional corticoid applications[3]. A positive response was not observed in the clinical and radiographic results in the present case.

The corticoid mechanism of action in CGCL is not well understood, but it is suggested that osteolytic reduction is due to inhibition of the extracellular synthesis of *lysosomal* proteins as well as to an increased apoptosis activity on cells similar to osteoclasts[10]. Confirming these suggestions, Nogueira et al.[11] further postulated that the corticoid intralesional treatment may inhibit transcription factors involved in the proliferation of these cells.

The development of specific treatments is hindered by the lack of knowledge about the origin of giant cells and of the molecular mechanism involved in the pathogenesis of CGCL[12]. Some studies suggest that multinucleated cells have cytochemical and functional characteristics of osteoclasts[3]. Others demonstrate macrophage and osteoclast strain markers[13]. Recent reports

have shown that mononucleated cells are the proliferative portion responsible for the biological activity of CGCL[11].

Multinucleated giant cells, stroma mononucleated cells and CGCL endothelial cells intensely express glucocorticoid receptors[14]. However, there are indications that this is a heterogeneous lesion expressing different quantities of these receptors[11]. Some authors found an increased number of glucocorticoid receptors both in multinucleated giant cells and mononucleated cell in lesions that responded positively to intralesional triamcinolone[14]. Although corticoid receptors were not evaluated in the present study, lack of receptors may explain the absence of satisfactory clinical and radiographic results.

Selection of nonsurgical treatments for CGCL may be based on the immunochemical evaluation of glucocorticoid and calcitonin receptor quantities. It is suggested that the treatment should be conducted by the agent that induces the higher receptor expression. In nonresponsive cells therapeutic strategies may be adjusted by reevaluations of receptors since multinucleated giant cell and mononucleated ones may suffer a dynamic transdifferentiation during treatment, altering receptor expression and thus, therapy efficacy[14].

The absence of clinical and radiographical response to the corticoid intralesional treatment in the case here reported, suggested a quantitative histologic study to verify cellular and extracellular alterations, which would indicate the use of conservative surgery. The results showed that after triamcinolone applications, collagen increased significantly and the number of blood vessels and multinucleated giant cells was reduced. These findings indicated a less aggressive lesion able to respond to curettage and peripheral ostectomy instead of block resection. Other reports also showed reduction of the number of multinucleated giant cells[7] besides the intense presence of fibrocartilagenous stroma[10]. According to Vered et al.[12] a successful therapeutic strategy may be measured by reduction of lesion dimensions and the adoption of conservative surgery and not necessarily by complete resolution.

CONCLUSION

Histological modifications induced by intralesional triamcinolone applications suggested a less aggressive lesion and justified its use in pediatric patients, even in the absence of clinical and radiographical responses. Further investigations are required in order to confirm these results. These future researches should be encouraged because the development of new therapeutic approaches are relevant since they can contribute for the adoption of CGCL conservative surgical treatment, especially in cases of CGCL resistant to corticoid therapy.

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