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Epithelial Modulation of a Calcifying Odontogenic Cyst after Active Decompression

Pedro Moreno-Rodríguez[1], Jairo Bustillo-Rojas[2], Lidia M. Guerrero[3], Jaime Castro-Núñez[4,5*]

[1]Oral and Maxillofacial Surgery Care Center, Quibdó, Chocó, Colombia

[2]Oral and Maxillofacial Pathology Department, School of Dentistry, Pontificia Universidad Javeriana, Bogotá, Colombia

[3]Professor and Program Director, Oral and Maxillofacial Surgery Department, School of Dental Medicine, University of Puerto Rico-Medical Sciences Campus, San Juan, PR, USA

[4]Oral and Maxillofacial Surgery Department, School of Dental Medicine, University of Puerto Rico-Medical Sciences Campus, San Juan, PR, USA

[5]Research Department, School of Dentistry, Institución Universitaria Colegios de Colombia, Bogotá, Colombia

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***Corresponding Author:** Jaime Castro-Núñez, Oral and Maxillofacial Surgery Department, School of Dental Medicine, University of Puerto Rico-Medical Sciences Campus, San Juan, PR, USA Research Department, School of Dentistry, Institución Universitaria Colegios de Colombia, Bogotá, Colombia, Tel. No: +939400-9772; Email: jacastron@hotmail.com

Abstract

The association between the presence of inflammatory cells in the connective tissue of odontogenic cystic conditions and changes in the nature of their lining epithelium has been recognized by oral pathologists since the late 1960's, mainly in the context of the more common Odontogenic Keratocyst (OKC). This relationship, however, is less documented in other odontogenic cystic entities, such as the Calcifying Odontogenic Cyst (COC). The objective of the present article is to report the epithelial modulation and related subepithelial histologic changes that took place in a calcifying odontogenic cyst treated by means of Active Decompression and Distraction Sugosteogenesis (ADDS). The histopathologic study of the enucleated sample after ADDS demonstrated chronic inflammatory cells with subsequent epithelial dedifferentiation, which was followed by a realignment in the biologic behavior of the pre-treatment lesion.

Keywords: Odontogenic cystic conditions, Odontogenic keratocyst and Cyst.

Introduction

The relationship between inflammation and changes in the character of the lining epithelium of odontogenic cystic pathologies was noted during the late 1960s and 1970s [1-5]. Such observations, somewhat tangential, led Rodu et al., [6] to further investigate the histologic changes that take place in the epithelium of Odontogenic Keratocyst (OKC) when inflammation is present. They found that inflammation has a high positive predictive value for epithelial transformation. Since then, other groups have studied said association, especially in the context of the OKC when treated by means of

marsupialization or decompression [7-11]. This histologic finding, nevertheless, is less reported in other odontogenic entities, such as the Calcifying Odontogenic Cyst (COC). COC, also known as Gorlin cyst, was described by Gorlin et al., [12] in 1962 and although it was renamed "Calcifying Cystic Odontogenic Tumor" (CCOT) by the World Health Organization (WHO) in 2005 to denote its neoplastic behaviour [13] it was reclassified as a developmental odontogenic cyst. The COC has an epithelial lining composed of a well-defined basal layer of columnar cells with an overlying layer that is typically many cells thick, which may resemble the stellate reticulum, and masses of ghost epithelial cells that may be present in either the capsule or the lining [13,14].

Various treatment modalities have been proposed for this entity, with enucleation/curettage and decompression being the most common [15-19]. Recently, Active Decompression and Distraction Sugosteogenesis (ADDS) has been introduced and employed for the treatment of various odontogenic cystic conditions. [20]. The purpose of this article is to describe the epithelial modulation and related histologic changes that took place in a COC treated by means of ADDS.

Case Presentation

The patient, a 14y old black female, presented to the clinic complaining about a swelling in the symphysis. The condition had started 10 months earlier and had been increasing in size. During clinical examination, a painful, localized tumefaction was documented. Intraorally, there was a prominent swelling with fullness in the lower vestibule. Her medical history was unremarkable. Panoramic radiography and computed tomography showed a 10 × 4.5 cm radiolucent, well-defined lesion extending from the lower left second premolar to the lower right second premolar associated to an impacted lower right canine (Figure 1). Differential diagnosis included dentigerous cyst and unicystic ameloblastoma. After informed consent and under general anesthesia, an incisional biopsy was taken and ADDS therapy initiated by using a custom-made Evocyst, as described by one of us [20-22]. The histopathologic diagnosis was consistent with COC (Figures 2 and 3). After 5 w of ADDS, when the Evocyst was removed, there was a remarkable reduction of the clinical and radiographic presentation of the cyst with increased radiopacity consistent with adequate bone repair (Figure 4). The patient left town and did not return for follow-up until 8 months later, when cystic enucleation and extraction of the involved tooth were performed. Contrary to the first surgical procedure when obtaining a sample was challenging due to friable cystic capsule and thin cortical bone, the material obtained during the enucleation stage was thick and easily detachable from the bone (Figure 5). Histopathologic analysis demonstrated that the appearance of the wall had completely changed character, with a prominent chronic subepithelial inflammation. Of note, a small fragment of nonkeratinized stratified squamous epithelium was seen, which was consistent with epithelial modulation (Figures 6-8).

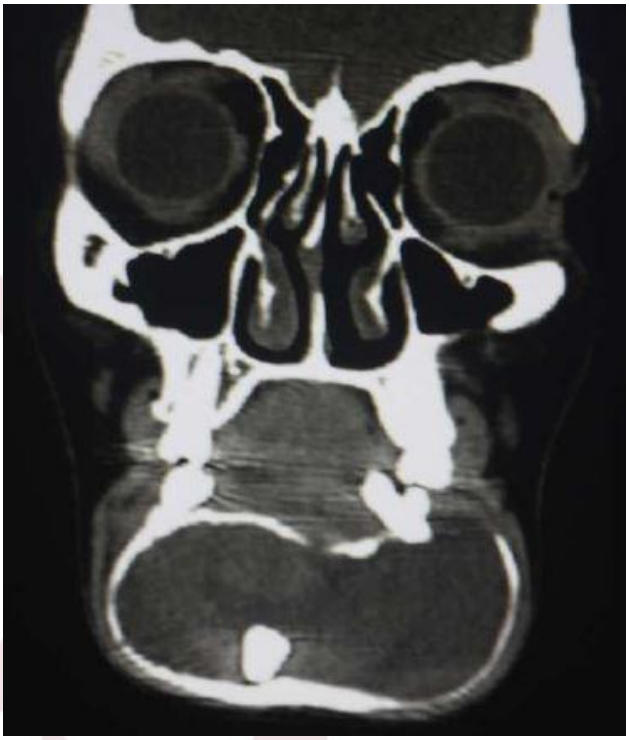

Figure 1. Computed tomography showing an extensive cystic lesion associated to an impacted lower right canine.

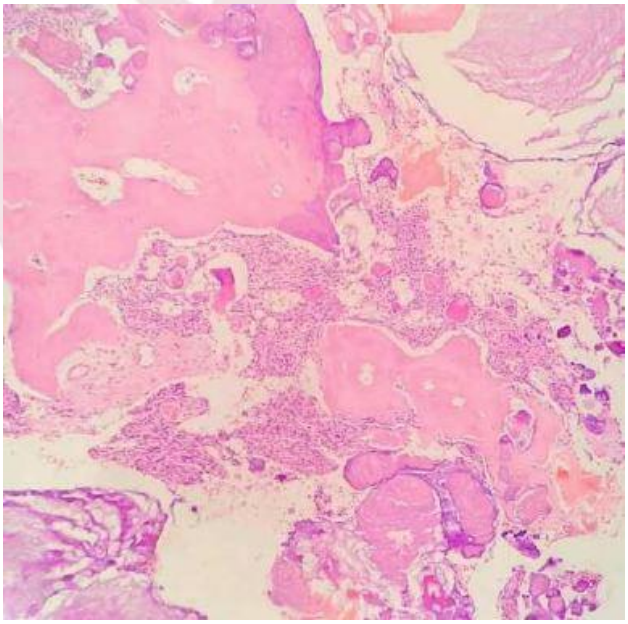

Figure 2. Photomicrograph showing cyst lining composed of an outer layer of odontogenic epithelium four to six cells in thickness. Numerous ghost cells and calcifications are identified within the epithelial lining. Diagnose: calcifying odontogenic cyst. H&E x 10X.

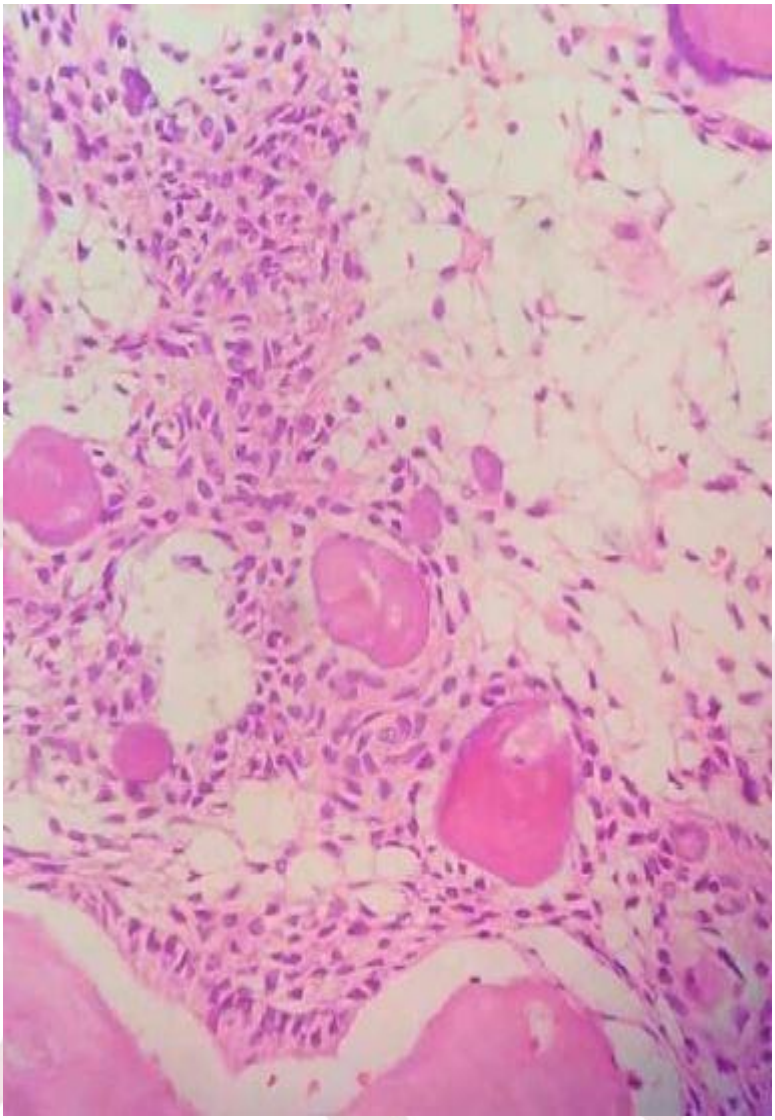

Figure 3. Photomicrograph showing the outer epithelial lining and an inner layer of cells resembling the stellate reticulum of the enamel organ. Intraepithelial calcifications are abundant. Diagnose: calcifying odontogenic cyst. H&E x 20X.

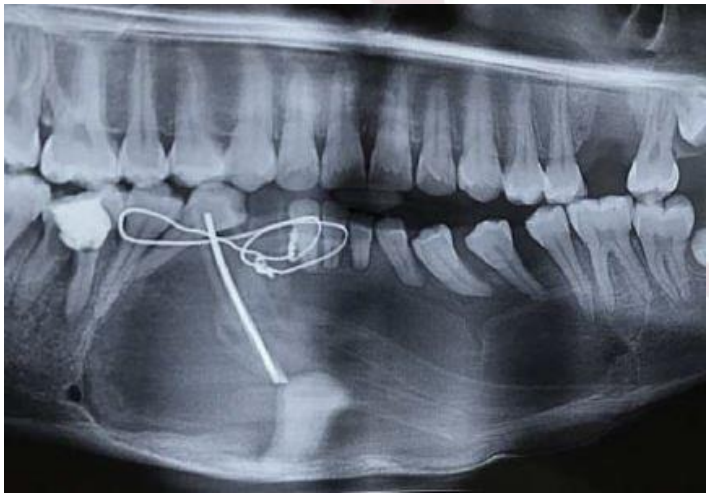

Figure 4. A remarkable reduction of the cyst with increased radiopacity consistent with adequate bone repair took place after 5 w of ADDS.

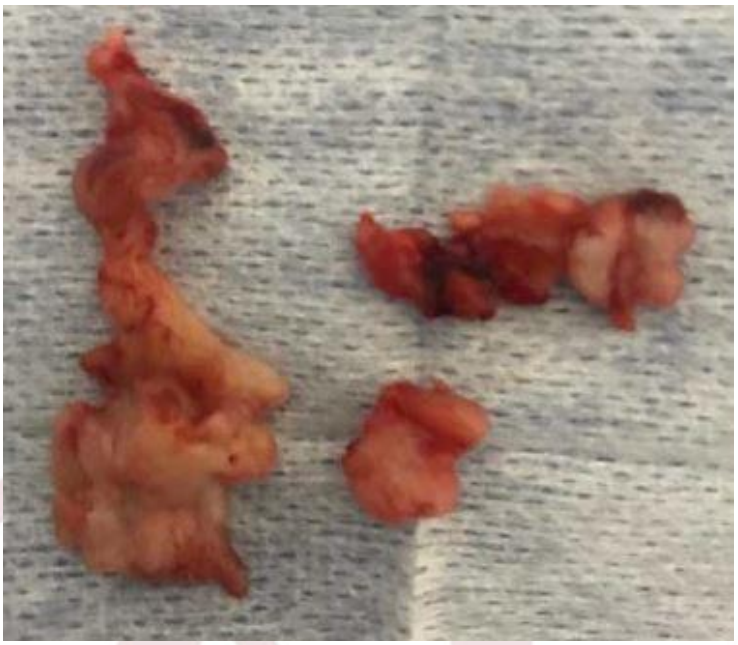

Figure 5. A thick, easily detachable sample was retrieved during the enucleation phase.

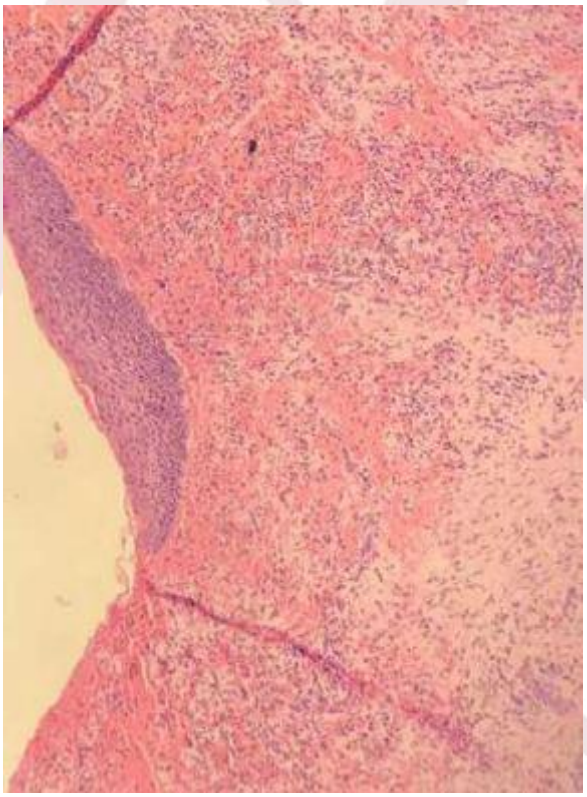

Figure 6. The histopathological analysis of the sample after DADS shows a fragment of nonkeratinized stratified squamous epithelium. The underlying connective tissue is loose with collagenous fibers and chronic lymphocytic infiltrate. Epithelial dedifferentiation is remarkable. H&E x 10X.

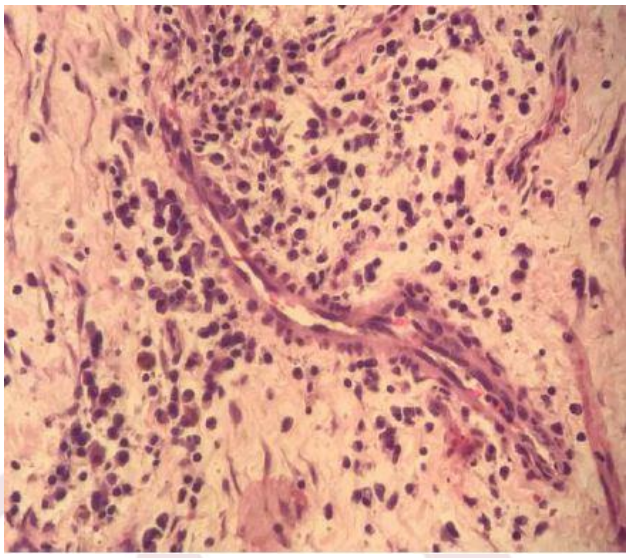

Figure 7. The subepithelial tissue contains abundant perivascular chronic inflammation: Lymphocytes, histiocytic and plasmatic cells are clearly seen. H&E x 40X.

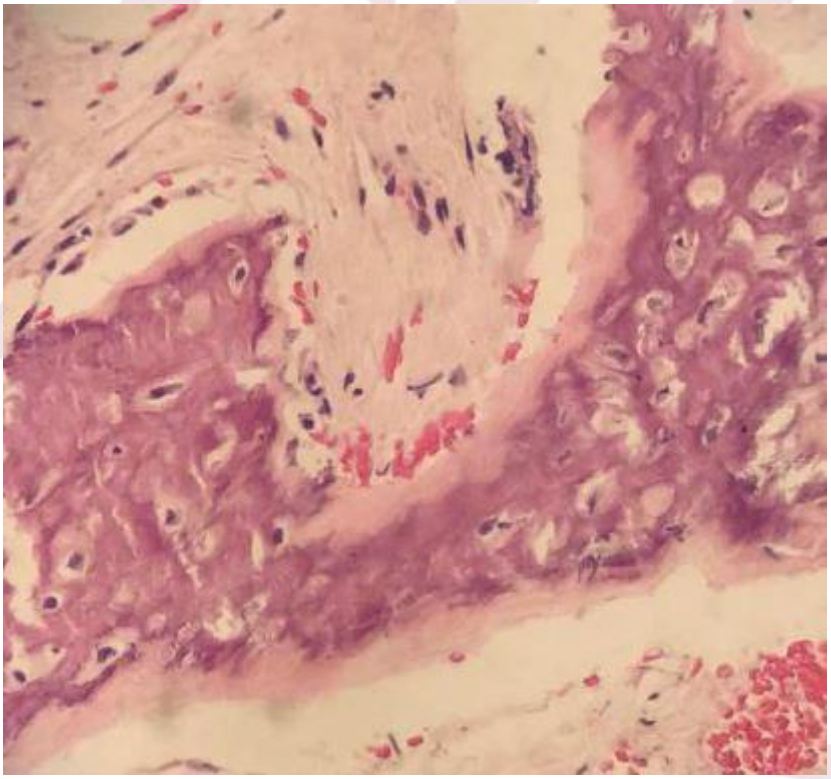

Figure 8. A fragment of mature, reactive bone surrounded by osteoid material. H&E x 40X.

Discussion

The correlation between the presence of inflammatory cells in the connective tissue of odontogenic cysts and changes in the character of their lining epithelium has been recognized by oral pathologists since the late 1960s [1-5]. However, it was Rodu et al., [6] who in 1987 conducted the first study on the subject. Analysing 112 OKC cases, they found that 85 of them (76%) presented chronic inflammation almost exclusively composed of small lymphocytes and plasma cells with occasional polymorphonuclear leukocytes. Of those, 75 (66.9%) were associated with a change in the character of the epithelial lining from a typical odontogenic keratocyst appearance to a more common nonkeratinized stratified squamous architecture. They explained that such transformation usually happened at the margin of inflamed and non-inflamed tissue. Moreover, they noted that two of their cases were treated by marsupialization and both showed marked inflammation with characteristic lining changes. They theorized that when inflammation was accompanied by a change in the appearance of the epithelial lining to that of inflammatory odontogenic cysts, it was also accompanied by a realignment in biologic behavior, which reflected such transformation. Additionally, they stated that inflammation exhibited a high positive predictive value, indicating that when it is present in the connective tissue, 88% of cases will show epithelial transformation. A negative predictive value of 100% indicated that when inflammation is not present, neither does transformation. Those findings provided additional rationale for the employment of marsupialization as a treatment option for large OKC. In the same year, Partridge et al., [23] observed that the OKC, once exteriorized, ceased to behave like a tumor, despite active growth.

Four years later, Brondum et al., [7] investigated and reported long-term follow-up of 44 OKCs. Although their overall recurrence rate was 18%, in a subgroup of patients (12 of 44) treated by decompression, no recurrences were reported. In agreement with Rodu et al., [6] a notorious change in the character of the residual epithelium was observed. The dedifferentiation pattern noted in the epithelial lining of decompressed OKCs prompted a subsequent investigation by the same group, who in 1996 [8] reported a long-term follow-up of 23 decompressed OKCs. In this second study, 83% of cases (19 of 23) presented histologic changes in the epithelium. In line with previous research, they confirmed that at the time of cystectomy (posterior to decompression), the appearance of the cystic wall had completely changed character. During the time elapsed from initial biopsy to cystectomy, the capsule was no longer thin and fragile, but thick and cohesive.

The histopathologic analysis of tissue removed during the initial biopsy showed that none of the cysts displayed signs of inflammation in the connective tissue, whereas signs of subepithelial inflammation were clearly seen in post decompression samples. In 19 cases, decompression resulted in the cyst epithelium changing type. They agreed with the findings of Rodu et al., [6] and went further to postulate that decompression time was essential to initiate an inflammatory response that, ultimately, would allow the cystic epithelium to undergo dedifferentiation. August et al., [9] employed cytokeratin-10 antibody staining to assess changes in OKC epithelium to determine if decompression/irrigation resulted in an epithelial modulation that may be associated with lower long-term recurrence. The average of irrigation was 8.4 months. They found that all cytological samples obtained at 3 and 6 months contained cytokeratin-10 positive epithelial cells. At the time of residual cystectomy, 9 of 14 cases were cytokeratin-10 negative and no longer showed histologic features of OKCs. The lining of these 9 cysts was hyperplastic compared with initial histology, and a mild-to-moderate inflammatory infiltrate was noted. Samples from the remaining 5 cases were histologically consistent with OKC and were cytokeratin-10 positive. They suggested that a treatment time of at least 9 months might be required for epithelial dedifferentiation to happen.

Anavi et al., [10] evaluated the effectiveness of decompression as the initial treatment for a variety of odontogenic cysts. In the process, they commented on the pre and post decompression histopathologic diagnoses, which had changed in some cases after a mean decompression time of 9 months. A paper by Schlieve et al., [11] found that 88% of odontogenic cysts and cystlike lesions treated by means of decompression were consistent with the initial histopathologic diagnosis. For the remaining 12%, a discrepancy between pre and post decompression histologic diagnose was documented. In all cases with diagnostic discrepancy (pre and post decompression), a prominent chronic inflammatory component was noted. Since pre and post decompression histologic diagnoses were concordant in the great majority of cases, they concluded that all lesions should be definitively treated after decompression based on the initial lesion diagnosis.

The epithelial modulation that takes place in odontogenic cysts when treated by means of marsupialization/decompression has been studied mostly in the context of the OKC. In this paper, we presented the epithelial dedifferentiation that took place in a COC after treated by means of ADDS, which is a variation of the conventional passive decompression method. The epithelial modulation/histological changes that took place in our patient are consistent with the findings reported by the authors cited in this discussion. In our case, we noted the inflammatory response that took place after ADDS, which probably allowed the cystic epithelium to dedifferentiate. We also agree with the other authors that when the inflammatory response is accompanied by epithelial modulation, it is followed by a realignment in its

biologic behavior. Oral pathologists have observed the relationship between inflammation and epithelial dedifferentiation since the late 1960s. Although subepithelial inflammation is known to induce metaplastic change in epithelial cells as well as loss of parakeratinzation since Rodu's-1987 paper, the implications for this finding in the context of marsupialization/decompression and ADDS are poorly understood. Authors have noted that residual cyst lining occasionally shows transformation in some regions, but not in others. Finally, epithelial dedifferentiation seems to be a gradual process and the biologic mechanism for this phenomenon remains unclear.

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