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Odontogenic Keratocystic Tumor: A Clinical and Histopathologic Retrospective Study Based on the New WHO Classification

Tumor Odontogénico Queratoquístico: Estudio Clínico e Histopatológico Retrospectivo Basado en la Nueva Clasificación de la OMS

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ABSTRACT: The aim was to review previous cases of Odontogenic Keratocyst or Keratocystic Odontogenic Tumor according to the new WHO classification. We used all cases diagnosed as Odontogenic Keratocyst or Keratocystic Odontogenic Tumor registered in the archives of the Pathologic Anatomy Laboratory of the Department of Pathology and Oral Diagnosis of the School of Dentistry of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, which were collected from September, 1983 until September, 2008. The terms "Keratocyst" or "Keratocystic Odontogenic Tumor" were searched for and the following data were collected from the case files: age, sex, location of the lesion(s), and patients' chief complaints. Hematoxilin and Eosin slides were reviewed according to the 2005 WHO criteria. The results found are in accordance with the literature. Due to its benign features, the Orthokeratinized Odontogenic Keratocyst found in our sample had its diagnosis changed to Orthokeratinized Odontogenic Cyst, as recommended by the WHO. Histopathologic exams are required for every bone lesion, in order to establish correct diagnosis. Because of its features, the Keratocystic Odontogenic Tumor must have more aggressive treatment, compared with odontogenic cysts, and long-term follow-up is mandatory.

KEY WORDS: odontogenic keratocyst, keratocystic odontogenic tumor, orthokeratinized odontogenic keratocyst, orthokeratinized odontogenic cyst.

INTRODUCTION

In 2005, the WHO established a new classification to the former known Odontogenic Keratocyst, which is now known as Keratocystic Odontogenic Tumor (KCOT) (Philipsen, 2005). Among the main reasons for this change are its potentially aggressive biological behavior, high recurrence rates, association with the Nevoid Basal Cell Carcinoma Syndrome (NBCCS), the presence of daughter cysts in the capsule, budding of the epithelium basal layer, increase of the mitotic activity, and the influence of genetic alterations, such as mutations of the PTCH gene and loss of heterozygosis of the 9q22 chromosome (Agaram *et al.*, 2004; Madras & Lapointe, 2008; Vered *et al.*, 2009).

The KCOT is slightly more frequent among men, and may occur at any age range, with peaks between the second and third decades of life. It can be located anywhere in the jaws, most frequently in the mandible posterior region (Ali & Baughman, 1984; González-Alva *et al.*, 2008; Habibi *et al.*, 2007; Hodgkinson *et al.*, 1978; Chow, 1998; Morgan *et al.*, 2005; Myoung *et al.,* 2001). It may be asymptomatic, or present symptoms, such as expansion of the bones, pain, paresthesia, and purulent discharge (Habibi *et al.*; Hodgkinson *et al.*; Chow).

The radiographic presentation varies widely, which makes the diagnosis based exclusively on clinical and radiographic features difficult to determine. KCOTs may present as unilocular images, occasionally in association with roots, simulating other lesions (Ali & Baughman; Nohl & Gulabivala, 1996), or as multilocular images, often imitating ameloblastomas, with "soap

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bubble" or "honeycombed" appearance (Omura *et al.,* 1997). These images frequently demonstrate a thin sclerotic border of bone, either well or ill-defined (Brannon, 1976).

KCOTs are histologically composed of a thin squamous epithelium of approximately 5 to 8 cells thick, covered by a thin parakeratinized layer. The basal layer is classically well-defined, with columnar or cuboidal cells in palisade. There may be daughter cysts and epithelial islands in the capsule, and budding of the basal layer (Philipsen; Slootweg, 2006).

The treatment choice must take into account factors such as size and location of the tumor, as well as invasion of the surrounding tissues and previous treatments (Kolokythas *et al*., 2007). A variety of different treatment modalities have been proposed in the literature, ranging from more conservative options, for instance, marsupialization, to more aggressive ones, such as resection. However, there appears to be a consensus among most authors, according to which an association of techniques seems to be the best choice, for instance, decompression + enucleation, marsupialization + curettage, or enucleation + Carnoy's solution (Blanas *et al*., 2000; Kolokythas *et al.*; Marker *et al*., 1996; Maurette *et al*., 2006; Morgan *et al.*).

The purpose of this paper is conducting a retrospective study of past cases of KCOTs of the Department of Pathology and Oral Diagnosis of the School of Dentistry of the Federal University of Rio de Janeiro, through analysis of clinical, epidemiologic, and histopathologic data, from September, 1983, until September, 2008, based on the new WHO classification.

MATERIAL AND METHOD

All cases diagnosed as Odontogenic Keratocyst or Keratocystic Odontogenic Tumor registered in the archives of the Pathologic Anatomy Laboratory of the Department of Pathology and Oral Diagnosis of the School of Dentistry of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, were collected, from September, 1983 until September, 2008.

This information was collected through research in the register books, where the terms "Keratocyst" or "Keratocystic Odontogenic Tumor" were searched for. The following data were collected from the case files: age, gender, location of the lesion(s), and patients' chief complaints. The absence of any information was considered exclusion criteria for the epidemiologic study.

Hematoxilin and Eosin slides were re-evaluated. All cases had their histopathologic diagnosis reviewed according to the 2005 WHO criteria (Philipsen). These criteria are shown in Table I. The histopathologic evaluation was performed by an author with an Oral Pathology degree.

RESULTS

Ninety-eight cases of Keratocyst or KCOT were found, in 92 patients. These cases represent 1.3% of all samples referred for analysis in the Pathology laboratory during the studied period of time. 11 of the 98 cases were excluded from clinical and epidemiologic analysis due to absence of information.

Age and gender distribution. The ages at the moment of diagnosis were taken in consideration. They ranged from 3 to 79 years of age, with a mean of 34.7 years. The peaks were in the 2nd and the 4th decades. The decade distribution is shown in Table II. In two cases, the age was not informed. Regarding gender, there was slight male prevalence, with 48 male cases (55.2%), and 39 female cases (44.8%), with a 1.23:1 ratio.

Tumor location distribution. Among the 87 cases, the location was not informed in one case, and the side was not informed in seven. The tumor location

Table I. Histopathologic criteria for diagnosis of KCOT according to the WHO (Philipsen, 2005).

Histopatologic criteria
Regular parakeratinized stratified squamous epithelium without rete ridges
Epithelium 5-8 cell layers thick
Well-defined epithelial basal layer with columnar or cuboidal cells frequently containing basophilic nuclei
Parakeratotic layers with corrugated surface
Loss of characteristic cellular and architectural features in the presence of inflammatory infiltrates

distribution is shown in Tables III and IV. In 2 cases (2.3%), the tumor affected both maxilla and mandible simultaneously. The others affected the mandible alone most frequently, in 71 cases (81.6%). Most of these lesions occurred in the body (n=37, or 42.5% of the total). 15 tumors (17.2%) affected the maxilla, and most of these occurred in the posterior area, including bicuspids and molars (n=10, or 11.5% of the total).

NBCCS association. In this research, 4 (4.6%) patients suffered from NBCCS, with a total of 6 (6.9%) KCOTs in these individuals.

Table II. Decade distribution.

Decade	Number	Percentage
First (0-10 years)	4	4.6
Second (11-20 years)	18	20.7
Third (21-30 years)	17	19.5
Forth (31-40 years)	18	20.7
Fifth (41-50 years)	11	12.6
Sixth (52-60 years)	9	10.3
Seventh (61-70 years)	6	6.9
Eighth (71-80 years)	2	2.3

Table III. Location distribution: Mandible.

Side	Mandible: Areas						
	Body	Body+Ramus	Symphysis	Ramus	Angle	Body+Ramus+Condyle	Total
Right	17	3	0	1	1	1	23
Left	17	9	0	3	2	0	31
Right+Left	3	0	0	0	0	0	3
Middle	0	0	8	0	0	0	8
Not	0	3	0	3	0	0	6
Total	37	15	8	7	3	1	71

Table IV. Location distribution: Maxilla.

Side	Maxilla: Areas			
	Posterior (bicuspids and	Anterior (incisives and	Posterior+Anterior	Total
Right	3	2	0	5
Left	5	0	2	7
Right+Left	2	0	0	2
Middle	0	1	0	1
Total	10	3	2	15

Histopathologic features. Of the 98 cases, 29 (29.6%) slides were not available for analysis.

Keratinization: Of the 69 available cases, in 62 (89.8%), the epithelium was exclusively parakeratinized (Fig. 1). Six (8.7%) epitheliums showed mixed parakeratinization and orthokeratinization. In one (1.4%) case, the whole epithelium was orthokeratinized (Fig. 2). This case was reclassified to Orthokeratinized Odontogenic Cyst, based on the new WHO classification.

Epithelial budding of the basal layer: In 17 (24.6%) samples, there was budding of the epithelial basal layer towards the capsule (Fig. 3).

Epithelial islands and/or cords in the capsule: In 41 (59.4%) cases, there were epithelial islands and/or cords of odontogenic epithelium in the capsule (Fig. 4).

Dystrophic calcification: Dystrophic calcification was found in the capsule of 28 (40.6%) tumors.

One or more daughter cysts in the capsule: 20 (29%) samples had one or more daughter cysts in the tumor's capsule (Fig. 5).

Patient's chief complaints. The patient's chief complaints were registered in their first visit. In some cases, more than one complaint occurred simultaneously. 38 (43.7%) patients presented swelling of the face, in the area affected by the tumor, 10 (11.5%) reported purulent discharge, and one (1.2%) presented trismus. These alterations were confirmed after clinical

examination. In 8 (9.2%) cases, the patient´s complaint was pain, and in one (1.2%), there was paresthesia of the area affected by the KCOT. 41 (47.2%) cases were asymptomatic, and the lesions were incidentally discovered in radiographic exams (most of which panoramic radiographs), indicated for other reasons, such as orthodontic treatment, or extraction of third molars, and for follow-up of previously NBCCS diagnosed patients.

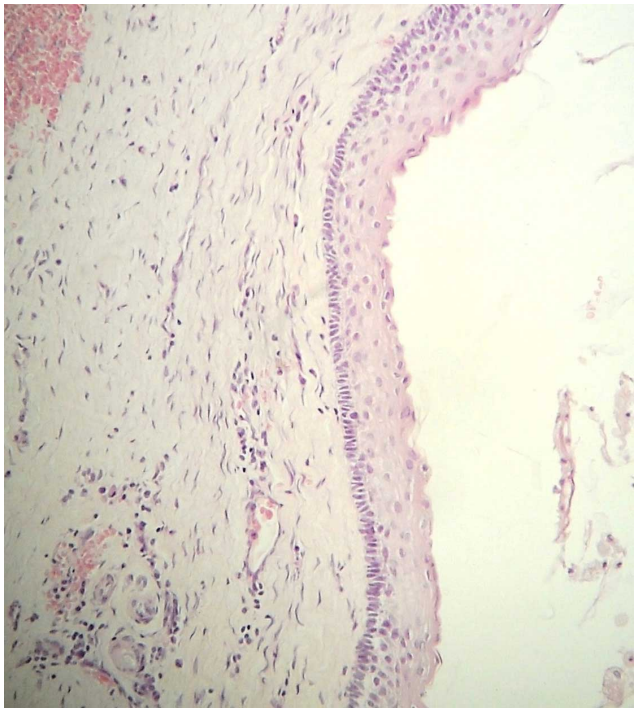

Fig. 1. Parakeratinized epithelium with prominent palisade basal cell layer and corrugated surface. (H&E staining, original magnification x 4).

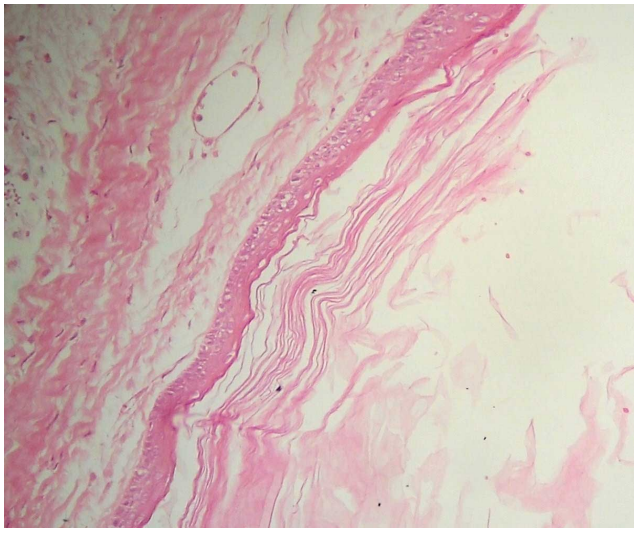

Fig. 2. Orthokeratinized epithelium. (H&E staining, original magnification x 4).

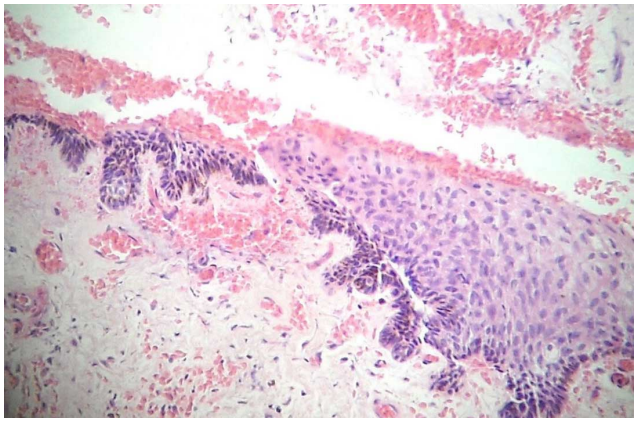

Fig. 3. Epithelial budding of the basal layer. (H&E staining, original magnification x 4).

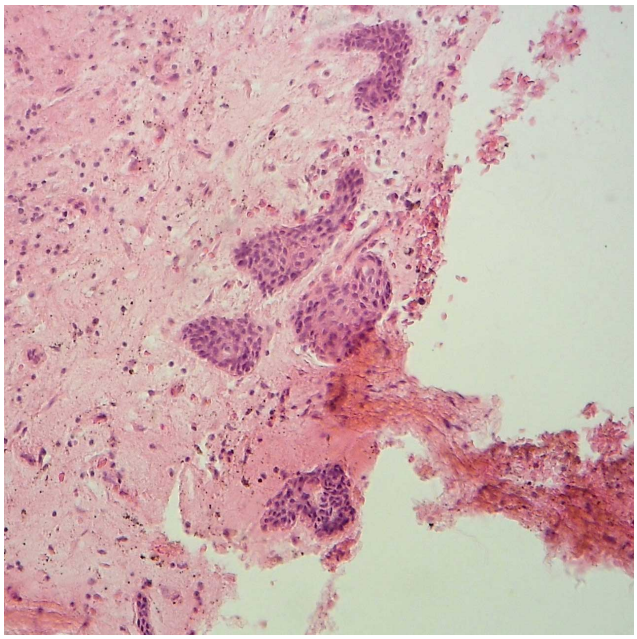

Fig. 4. Islands of odontogenic epithelium within the capsule. (H&E staining, original magnification x 4).

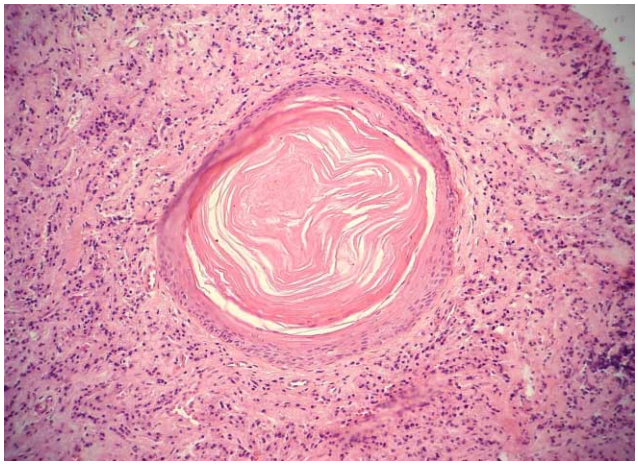

Fig. 5. Prominent daughter cyst in the capsule, containing keratin whorls. (H&E staining, original magnification x 4).

DISCUSSION

Regarding gender distribution, our findings are in accordance with those of other studies, which present male predominance (Ali & Baughman; Brannon; Habibi *et al*.). The age peaks were 2nd and 4th decades, as was registered by Oda *et al.* However, most other studies indicate peaks during 2nd and 3rd decades (Brannon; Habibi *et al*.; Chow).

Most KCOTs occurred in the mandible (81.6%), which is in agreement with other authors. However, their percentages were slightly lower, ranging from 65.4% to 76.5% (Brannon; González-Alva *et al*.; Myoung *et al*., 2001; Payne, 1972). The most common area was the body and/or ramus of the mandible, followed by the maxilla's posterior region. Similar results were found in other studies (Myoung *et al.*; Oda *et al*., 2000). It is important to note that the tumor tends to grow predominantly in the anterior-posterior direction in the mandible, which allows it to reach large sizes, without causing significant bone expansion. On the other hand, in the maxilla, due to the presence of the maxillary sinus, and to the fact that the bone is thinner, the expansion of the lesion occurs in a spherical manner, which makes it easier to be noticed in an earlier stage (Chow).

After histopathologic analysis, our results regarding epithelial keratinization were similar to those of other authors (Ahlfors *et al*.; El-Hajj & Anneroth; González-Alva *et al*.; Hodgkinson *et al.*; Myoung *et al*.). However, higher percentages related to the presence of islands of odontogenic epithelium in the capsule were found – 59.4% versus 5% and 23%. (Ahlfors *et al.*, 1984; González-Alva *et al*.) As to the presence of daughter cysts in the basal layer, our findings were similar to the ones presented by Myoung *et al.* Finally, regarding the occurrence of budding of the basal layer, our results were similar to Ahlfors *et al*. It is possible to affirm that these three alterations are significantly present, and therefore represent evidence of the neoplastic nature of the KCOTs (Ahlfors *et al*.).

In the present study, the Orthokeratinized Odontogenic Keratocyst had its diagnosis changed to Orthokeratinized Odontogenic Cyst (OOC), due to the WHO reclassification (Philipsen). This cyst has very different features compared to the KCOT, not only regarding the keratinization, considering that the OOC is composed exclusively of orthokeratinized epithelium, but particularly because of the biological behavior. Studies have been performed in order to show the differences between the two entities. An immunohistochemical study revealed a negative reaction to anti-tenascin antibody for OOC and a positive one for KCOT (da Silva *et al*., 2002). This is an important factor for the distinction between the two, because tenascin is an adhesion modulating protein, expressed in unstable environments, such as neoplasms and healing areas (da Silva *et al*.). This study also demonstrated different 10, 13, and 14 cytokeratin expressions between OOC and KCOT. Another immunohistochemical study showed that the OOC can be originated of gingival and oral mucosa cell rests, while KCOT has its origin from dental lamina cell rests (Koizumi, 2004).

Many patients (47.2%) exhibited no symptoms or complaints, and had their tumors revealed by radiographic exams ordered for other reasons. This high percentage was similar only to the 49.7% found by Brannon, while other authors obtained lower, although still significant values, ranging from 5.5% to 24% (Ali & Baughman; Hodgkinson *et al*.; Chow; Myoung *et al.*). The absence of symptoms is probably related to the growth pattern of the tumor, which tends to reach a considerably large size before causing expansion of the cortical bone (Hsun-Tau). As in other studies, the most common symptom was swelling (Brannon; Habibi *et al.*; Chow; Myoung *et al*.).

The Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Gorlin-Goltz's Syndrome, is an uncommon, hereditary, autosomal dominant disorder (Fitzpatrick & Thompson, 1982). Recent genetic studies have attributed its occurrence to mutations in the PTCH gene, in the 9q21-23 chromosome (Ljubenovic´ *et al*., 2007). This syndrome is characterized by various alterations, the most significant of which are numerous basal cell carcinomas, multiple KCOTs, and muscle-skeletal malformations, such as bifid ribs and cranial calcifications (Fitzpatrick & Thompson; MacSweeney *et al.,* 1985). In the present study, 4.6% of the patients had NBCCS, which is in accordance with data obtained by other authors, whose rates ranged from 1.4% to 8.8% (el-Hajj & Anneroth, 1996; González-Alva *et al*.; Habibi *et al.*; Hodgkinson *et al*.; Chow; Oda *et al*.).

Numerous clinical, histological, molecular and genetic evidences confirm that the KCOT is indeed a tumor. One of the first studies raising the hypothesis of its neoplastic nature was performed by Ahlfors *et al*., where aggressive behavior and high recurrence rates

were mentioned as the main reasons for such classification. These authors drew attention to the invasive features of the epithelium in some of the cases in their histological analysis, and therefore recommended less conservative treatment, in order to avoid recurrence. Studies regarding KCOT demonstrate that there is loss of heterozygosity in some loci of certain chromosomes. These loci are related to DNA unbalance, revealing deletion of tumor suppressor genes (Agaram *et al*.; Henley *et al.*, 2005). In addition, cell proliferation markers, such as p53, Ki67, and PCNA, as well as certain cytokeratins and suppression of apoptosis-related markers, such as bcl-2 and Bax were also identified (Koizumi; Ogden *et al.*; Shear, 2002a; Shear, 2002b; Vered *et al*.) In order to prove the KCOT tissue invasiveness, Heikinheimo *et al*. (2007) observed reduction in the expression of genes responsible for the formation of extracellular matrix components, and Katase *et al*. (2007) noticed increase of heparanase (enzyme that is frequently increased in tumors, promoting tissue invasion, angiogenesis, and metastasis) expression in the KCOT epithelial cells.

There are reports of KCOT malignant transformation to squamous cell carcinoma, so follow-up of patients with KCOT is essential, even after the complete removal of lesion(s) (Falaki *et al.*, 2009; Keszler & Piloni, 2002; Makowski *et al.*, 2001; Yoshida *et al.,* 1996). Henley *et al*. performed a molecular study on KCOT and found loss of heterozygosity in some of the loci attributed to squamous cell carcinoma developing, which is a possible explanation for the connection between the two entities. In our sample, there were no cases of malignant transformation.

The complete removal of KCOT is difficult, especially due to the fact that the epithelium is thin and friable, and to the eventual presence of daughter cysts. Therefore, treatment is a challenge, for while there is concern towards avoiding the recurrence rates, there is also an effort towards reducing the surgical morbidity (Morgan *et al*.). Studies show that simple enucleation is associated with high recurrence rates (Blanas *et al*.; Morgan *et al*.), so this technique alone must be avoided. The recurrence rates are significantly reduced when other techniques, such as peripheral ostectomy, the use of Carnoy's solution, or previous decompression, are included (Blanas *et al*.; Maurette *et al*.; Morgan *et al*.). Decompression leads to alterations in the KCOT, the most important of which are thickening of the cystic wall and significant reduction of the cystic cavity, with new bone formation (Clark *et al*., 2006; Marker *et al.*). This makes it much easier to remove the whole lesion, consequently reducing the surgical morbidity. This type of strategy may even be used for large and/or multilocular KCOTs. It is effective as treatment modality when combined with enucleation or curettage afterwards, exhibiting low recurrence rates (Kolokythas *et al*.; Marker *et al*.; Maurette *et al*.). It is, however, important to point out that decompression requires patient (or his/her guardian) cooperation, for continuous irrigation of the cavity is needed, during a long period of time – which can be extended to several months. In addition, the patient must return frequently for follow-up (Kolokythas *et al*.; Maurette *et al*.). Surgical resection is very aggressive, and, therefore must only be performed in specific situations, for instance in patients who aren't likely to return for follow-up, because the recurrence rates for this type of treatment are close to zero (Blanas *et al*.). In the present study, the treatment choice for each case wasn't listed, since our institution was only responsible for the diagnosis in the vast majority of cases, and the removal of lesions was performed elsewhere. For this same reason, the recurrence rates were also not informed.

Due to high recurrence rates and aggressive behavior, as well as microscopic, molecular and genetic evidences, proving the neoplastic nature of the KCOT, now recognized by the WHO, treatment for this tumor must be more aggressive than the one performed for cysts, and patient long-term follow-up is mandatory. In addition, it is important to keep in mind that the histopathologic exam must always be performed for lesions in the jaws, in order to allow the best treatment choice.

LEITE, T. C.; MEIRELLES JR., V. & JANINI, M. E. R. Tumor odontogénico queratoquístico: estudio clínico e histopatológico retrospectivo basado en la nueva clasificación de la OMS. ***Int. J. Odontostomat., 5(3)***:227-234, 2011.

RESUMEN: El objetivo fue revisar los casos anteriores de queratoquiste odontogénico (QO) o tumor odontogénico queratoquístico (TOQ) de acuerdo con la nueva clasificación de la OMS. Fueron utilizados todos los casos diagnosticados como QO o TOQ registrados en los archivos del Laboratorio de Anatomía Patológica del Departamento de Patología y Diagnóstico Oral de la Facultad de Odontología de la Universidad Federal de Río de Janeiro, Rio de Janeiro, Brasil, registrados a partir de septiembre de 1983 hasta septiembre del 2008. Los términos "Queratoquiste" o "tumor queratoquistes odontogénicos" se buscaron y los siguientes datos se obtuvieron de los archivos del caso: edad, sexo, localización de la lesión (es), y quejas de los pacientes. Las muestras histológicas de hematoxilina y eosina fueron revisadas de acuerdo a los criterios de la OMS 2005.

Los resultados encontrados estaban de acuerdo con la literatura. Debido a sus características benignas, el queratoquiste odontogénico ortoqueratinizado encontrado en nuestra muestra había cambiado su diagnóstico de quiste odontogénico ortoqueratinizado, según lo recomendado por la OMS. Los exámenes histopatológicos son necesarios para toda lesión ósea, con el fin de establecer el diagnóstico correcto. Debido a sus características, el TOQ debe tener un tratamiento más agresivo, en comparación con los quistes odontogénicos, donde un seguimiento a mediano y largo plazo es obligatorio.

PALABRAS CLAVE: queratoquiste odontogénico, tumor odontogénico queratoquístico, queratoquiste odontogénico ortoqueratinizado, quiste odontogénico ortoqueratinizado.

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