

# A COMPARATIVE HISTOPATHOLOGICAL STUDY OF EPITHELIAL LININGS OF ODONTOGENIC CYSTS AND UNICYSTIC AMELOBLASTOMAS

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## ABSTRACT

The epithelial cystic linings and adjacent connective tissues of 61 cases of odontogenic cysts (radicular cysts[RC], dentigerous cysts[DC] and odontogenic keratocysts[OKC]) and unicystic ameloblastomas(UA) were described and compared histopathologically. The type of epithelium in relation to the presence of rete processes and the distribution of chronic inflammatory cells were analyzed statistically. Significant associations between the presence of rete processes in the non-keratinized epithelial linings and inflammation in the subjacent connective tissues of RC and DC were found in this study. There was also a statistically significant association between the presence of rete Processes and non-keratinized epithelial linings in OKC. The results also showed that in inflamed OKC, the cystic lining epithelium exhibited hyperplasia indistinguishable from lining epithelium of RC and DC. This study further showed that ameloblastomatous-like epithelial cystic linings were present in inflamed odontogenic cysts. All except for one case of unicystic ameloblastomas in this study showed ameloblastomatous epithelial cystic linings. It is recommended that the lining epithelium of RC and DC be examined carefully in order to rule out OKC. Similarly, ameloblastomatous-like lining epithelium arising from chronic inflammation in RC and DC should be differentiated from true ameloblastomatous cystic lining. Such careful examinations are diagnostically important in view of the similarities of epithelial cystic linings of inflamed OKC with DC and RC aggressive behavior of OKC and UA.

**Keywords:** odontogenic cyst, unicystic ameloblastoma, histopathological features

## INTRODUCTION

The epithelial linings of radicular cysts (RC), dentigerous cysts (DC) and odontogenic keratocysts(OKC) histologically may appear similar in areas of inflammation(1). Some of these cysts such as the dentigerous cysts may have hyperplastic epithelium, which may appear as ameloblastomatous-like proliferations. Rests of odontogenic epithelium may also be present in odontogenic cysts which could be mistaken for ameloblastoma and salivary gland tumours(2). Since 1925, many had reported the development of ameloblastoma within the walls of odontogenic cysts and the most commonly cited was the dentigerous cyst (3-7). In 1977, Robinson and Martinez used the term 'unicystic ameloblastoma'(UA) for such lesions(3). The term unicystic ameloblastoma was later used in many reports and is now a generally accepted termi-

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nology. Unicystic ameloblastoma describes a unilocular ameloblastoma that has a single cystic space in which there is intraluminal or mural growth. This terminology may also represent an odontogenic cyst in which there has been ameloblastic transformation of the epithelial lining (8)

The odontogenic keratocyst linings in inflamed areas may present as a non-keratinized stratified squamous epithelium, which may appear similar to RC and DC. Such similarities in the appearance of odontogenic cyst linings (RC, DC and OKC) associated with inflamed areas would pose a diagnostic problem for odontogenic keratocyst as it maybe mistaken for dentigerous cysts. Such misdiagnoses should be avoided since the biologic activities of OKC differed from those of radicular or dentigerous cysts. Most radicular and dentigerous cysts grow slowly and do not attain a large size. However, the OKC shows a more aggressive biologic behaviour where a high recurrence rate was observed in OKC as compared to radicular and dentigerous cysts (9,10). Similarly, the appearance of ameloblastomatous-like epithelial linings in inflamed radicular or dentigerous cysts may lead to overdiagnosis of unicystic ameloblastomas. Unicystic ameloblastoma has a better prognosis; conventional ameloblastoma. However, the mural type of UA where ameloblastomatous islands of epithelium have perforated the cyst wall, may behave aggressively similar to a conventional ameloblastoma(15). Thus, it is very important to distinguish UA from RC and DC as UA requires a close follow-up.

In view of the similar histopathological features and the presence of ameloblastomatous-like epithelial linings observed in different types of odontogenic cysts in areas of inflammation, it is the purpose of this paper to describe and compare the histopathological features of cyst linings of odontogenic cysts (RC, DC and OKC) and unicystic ameloblastomas.

## MATERIALS AND METHODS

### Materials

A total of 61 cases of odontogenic cysts and unicystic ameloblastomas (RC=18; DC=16; OKC=15; UA=12) was

studied. These specimens had been fixed in 10% buffered formalin and had been embedded in paraffin wax. Four micrometer (µm) paraffin sections of selected specimens were stained with haematoxylin and eosin. The specimens used were biopsy materials from the Department of Oral Pathology, Oral Medicine and Periodontology, Faculty of Dentistry, University of Malaya.

### Criteria

The criteria used for odontogenic cysts were according to the WHO classifications in 1992(1) where a radicular cyst is defined as a cyst arising from the epithelial residues (rests of Malassez) in the periodontal ligament as a consequence of inflammation, usually following the death of the dental pulp. The dentigerous cyst is defined as a cyst, which encloses the crown and is attached to the neck of an unerupted tooth and develops by accumulation of fluid between the reduced enamel epithelium and the crown, or between the layers of the reduced enamel epithelium. The odontogenic keratocyst is defined as a cyst arising in the tooth bearing areas of the jaws, or posterior to the mandibular third molar, and characterised by a thin fibrous capsule and a lining of keratinized stratified squamous epithelium usually about five to eight cells in thickness and generally without rete ridges.

The criteria for unicystic ameloblastoma is an ameloblastoma which radiographically presents as a unilocular radioluscent lesion mimicking odontogenic cyst and had developed in the wall of an odontogenic cyst or had extended into the lumen of the cyst or involve only the cystic lining (1,3,8).

### Methodology

Clinical characteristics of the patients were obtained from the information written by clinicians in the biopsy forms. The age of the patients, ethnicity and gender distribution according to the type of lesions were recorded.

The histopathological features of odontogenic cysts and unicystic ameloblastomas were noted. Evaluation for the type of epithelium in relation to the presence of rete processes and the distribution of chronic inflammatory cells within the subjacent connective tissue wall was carried out for odontogenic cysts. The correlation between the types of epithelium, presence of rete processes and distribution of inflammation in the subjacent connective tissue of these lesions were analyzed statistically using Kolmogorov

Table 1 :The distribution of lesions according to the type of cyst lining epithelium.

Type of lesions	Keratinized stratified squamous	Non-keratinized stratified	Cuboidal-columnar	Ciliated-pseudo stratified	Total
Radicular cyst	0	16*	0	2###	18
Dentigerous cyst	1	11 **	3	1	16
Odontogenic keratocysts	10	5#	0	0	15
Unicystic ameloblastoma	0	12	0	0	12
Total	11	44	3	3	61

\* 9 cases of non-keratinized epithelium in radicular cysts consist of the mixtures of:  
non-keratinized + ameloblastomatous-like (6)  
non-keratinized + ameloblastomatous-like + cuboidal (2)  
non-keratinized + ameloblastomatous-like + parakeratinized (1)

\*\* 11 cases of non-keratinized epithelium in dentigerous cysts consist of:  
non-keratinized + ameloblastomatous-like epithelium (1)  
non-keratinized + ameloblastomatous-like + parakeratinized epithelium (1)

# 5 cases of predominantly non-keratinized epithelial lining in OKC. However, typical features of OKC in other areas were evident.

### 2 cases showing predominant areas of ciliated pseudo-stratified lining. However, there are areas showing a non-keratinized epithelial lining.

Smirnov test. The significant association was decided if the value of D maximum was higher than the critical value at 0.05 level.

## RESULTS

### Clinical characteristics

The mean age of all the 61 patients with lesions in this study was 32.75±15.34 years. For patients with RC, DC, OKC, and UA, the mean ages were 33±14.54, 35.5±17.97, 31.6±16.75, and 30.17±11.79 years respectively. Their range of ages were 14 to 68 years for RC, 8 to 74 years for DC, 12 to 67 years for OKC, and 16 to 47 years for UA.

For all lesions, there was almost an equal distribution in men and women with men to women ratio of 1:1.03. There was a higher predilection for women for RC, OKC, and UA while there was a higher predilection for men for DC (Figure 1).

Out of 61 cases of odontogenic cysts and UA, 41 cases (67%) occurred in Chinese. The prevalence in Chinese was 61%(11/18) for RA, 63%(10/16) for DC, 67%(10/15) for OKC and 83%(10/12) for UA. There was no OKC in Malays and no UA in Indians in this sample.

### Histopathological features

Table 1 shows the distribution of lesions according to the types of epithelial cystic linings. Out of a total of 18 cases of RC, 16 cases (89%) were lined by a non-keratinized stratified squamous epithelium while 2 cases were predominantly lined by a ciliated pseudostratified squamous epithelium with small foci of non-keratinized stratified squamous epithelium.

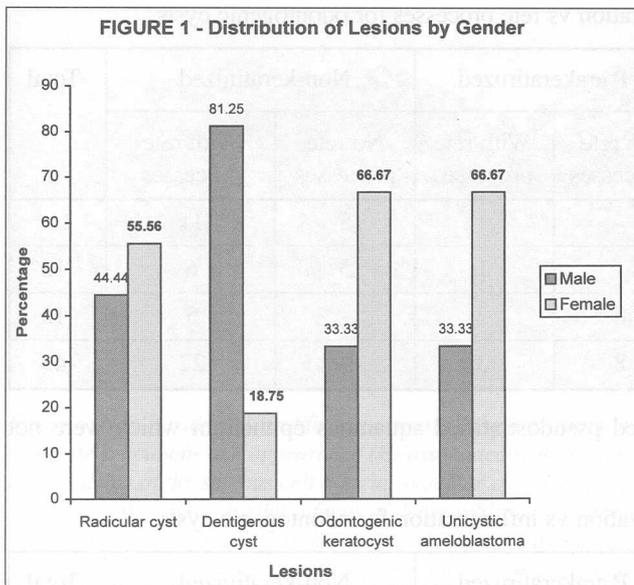


Figure 1: The distribution of odontogenic cysts and unicystic ameloblastoma according to gender

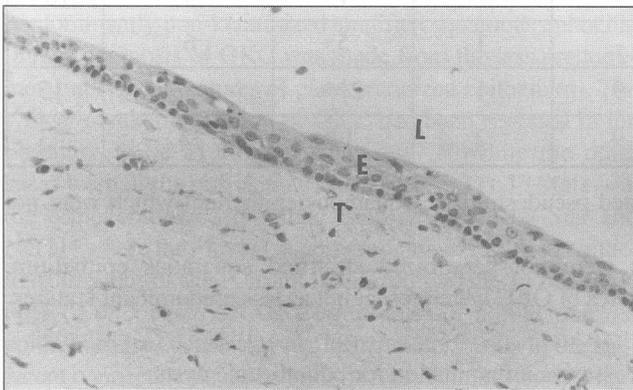


Figure 2: Thin non-keratinized stratified squamous epithelium with no rete processes in dentigerous cyst. (Haematoxylin and Eosin stain; Original magnification - 50X). L = lumen; E = cyst lining epithelium; T = connective tissue in cyst wall.

lial linings. For DC, 11 out of 16 cases (68.8%) were lined by a non-keratinized stratified squamous epithelium (Figure 2) while 5 cases showed other varieties of epithelium. All cases of OKC in this study had parakeratinized epithelium (Figure 3). Approximately 33.3% (5 of 15 cases) of these parakeratinized epithelium showed the mixtures of pare and non-keratinized stratified squamous epithelium with a predominance of non-keratinized stratified squamous epithelium. All cases of UA showed a non-keratinized stratified squamous epithelium linings.

Eleven out of 16 cases of RC(69%) and 6 out of 11 cases of DC(55%) with non-keratinized epithelium lining showed irregular epithelium downgrowth where in some the rete processes formed arcades(Figure 4). For OKC, 80%(8/10) of cases with parakeratinized epithelium showed no rete processes while in all 5 cases where there are predominant areas of non-keratinized stratified squamous epithelium, there were rete processes associated with such epithelium

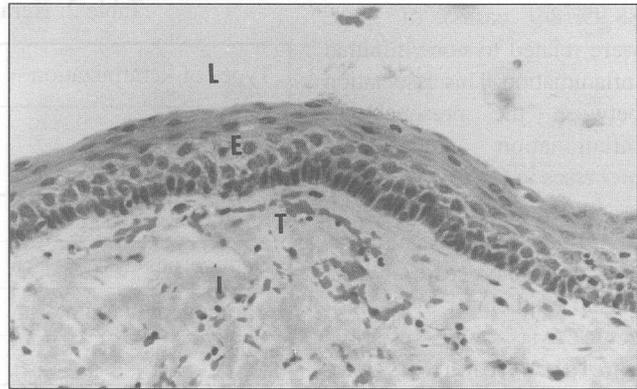


Figure 3: Thin parakeratinized stratified squamous epithelium with palisading of basal cell nuclei in odontogenic keratocyst. No or minimal inflammation in the cyst wall. (Haematoxylin and Eosin stain; Original magnification - 50X). L = lumen; E = cyst lining epithelium; T = connective tissue in cyst wall.

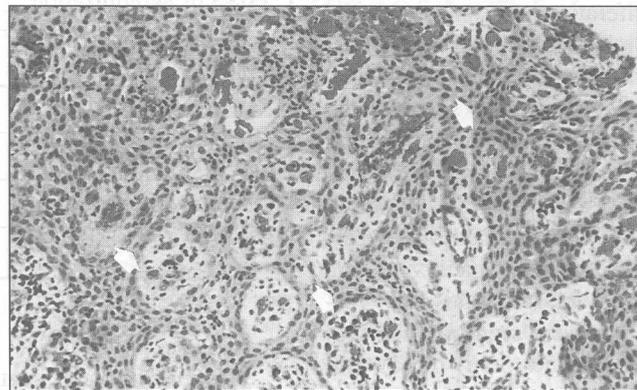


Figure 4: Radicular cyst showing epithelial proliferation into irregular rete processes forming arcades (white arrowheads). The subjacent connective tissue contains an abundance of inflammatory cells. (Haematoxylin and Eosin stain; Original magnification - 100X). L = lumen; T = connective tissue in cyst wall.

(Table 2). The association between the presence of rete processes and non-keratinized epithelium linings in OKC was found to be statistically significant ( $D = 0.71 > 0.70$ ).

Table 3 shows 56% (9/16) of RC, 53%(6/11) of DC and 60%(3/5) of OKC with predominantly non-keratinized stratified squamous epithelium cyst linings were associated with dense distribution of chronic inflammatory cells in the subjacent connective tissue. However, these associations between non-keratinized stratified squamous epithelium cyst lining and the presence of chronic inflammation were not statistically significant.

Table 4 shows that 90%(8/9) of RC and all cases of DC with the rete processes were related to areas of dense chronic inflammation in the subjacent connective tissue. The association between the presence of rete processes and dense chronic inflammation in the subjacent connective tissue was found to be statistically significant for RC ( $D = 0.78 > 0.64$ ) and DC ( $D = 1 > 0.68$ ). For OKC, 50% of cases with rete processes were related to dense chronic inflammation and the other 50% to none/minimal inflammation in the subjacent connective tissue. Among the cases with no rete processes

88.9%(8/9 cases) of OKC were related to none/minimal inflammation. This association between the presence of inflammation and rete processes in OKC was however, not significant.

Other than presenting as irregular rete processes, hyperplastic epithelium in odontogenic cysts may resemble ameloblastomatous-like epithelium when associated with heavily inflamed subjacent connective tissue(Figure 5). The latter epithelial feature in areas of inflammation seemed to arise from the proliferation of cystic epithelial lining into the underlying connective tissue with intercellular oedema in the spinous cell area of cyst epithelium leading to a stellate reticulum-like appearance while the basal layer maintained its hyperchromatic nuclei. Such ameloblastomatous-like features were seen in 50%(9/18) and 12.5%(2/16) of RC and DC respectively. True ameloblastomatous epithelial cyst linings (Figure 6) were observed in all UA except for 1 case. The diagnosis of UA was made for this single case without ameloblastomatous lining based on the presence of ameloblastomatous islands within the cyst wall.

**DISCUSSION**

The predominance of non-keratinized stratified squamous epithelium in RC and DC in this study was in keeping with many reports in the literature(7,10). Two cases of RC in this study had ciliated pseudostratified squamous epithelium. This type of epithelium with mucous metaplasia is usually seen as microscopic variations of the radicular cyst epithelium (8). Among these non-keratinized epithelial linings in RC, 1 case (5.5%) also showed an area of localized parakeratinization. Localized keratinization in RC was also observed by Browne (7) where he reported its presence in 2% of radicular cysts. Keratinization was seen in 1 out of 16 cases of DC(6.3%) in this study. According to Browne (7), keratin metaplasia may occur in dentigerous cyst leading to mainly

Table 2: Keratinization vs rete processes for odontogenic cysts

Types of keratinization	P arakeratiruzed		Non-keratinized		Total
	No rete processes	With rete processes	No rete processes	With rete processes	
Radicular cyst	-	-	5	11	16*
Dentigerous cyst	-	1	5	6	12
Odontogenic keratocyst	8	2	-	5	15
Total	8	3	10	22	43

\* The other 2 cases had ciliated pseudostratified squamous epithelium which were not included in this table.

Table 3: Keratinization vs inflammation for odontogenic cysts

Types of keratinization	P arakeratiruzed		Non-keratinized		Total
	Non/light	Dense	Non/light	Dense	
Radicular cyst	-	-	7	9	16*
Dentigerous cyst	-	1	5	6	12
Odontogenic keratocyst	9	1	2**	3	15
Total	9	2	14	18	43

\* The other 2 cases had ciliated pseudostratified squamous epithelium which were not included in this table.

\*\* The predominant features were non-keratinized stratified squamous epithelium. However the diagnostic features of OKC were present but as less predominant features.

Table 4: Rete processes vs inflammation for odontogenic cysts

Rete processes	No rete processes		With rete processes		Total
	Non/light	Dense	Non/light	Dense	
Radicular cyst	8	1	1	8	18
Dentigerous cyst	9	-	-	7	16
Odontogenic keratocyst	8	1	3+	3+	15
Total	25	2	4	18	49

+ These 6 cases showed predominant features of irregular rete processes. Diagnostic features of OKC exhibiting no rete processes were observed as less predominant features.

orthokeratinization of a part of the cyst lining. However, keratinizing metaplastic cases must be differentiated from an odontogenic keratocyst lining (8). This study had shown parakeratin formation instead of orthokeratin in one case of dentigerous cyst. In this case the diagnosis of odontogenic keratocyst was excluded since typical features of hyperchromatic and pallisading of basal cell nuclei were absent. Browne(7) also reported the presence of mucous metaplasia in 40% of DC. His result was higher than that found in the present study(18.8%).

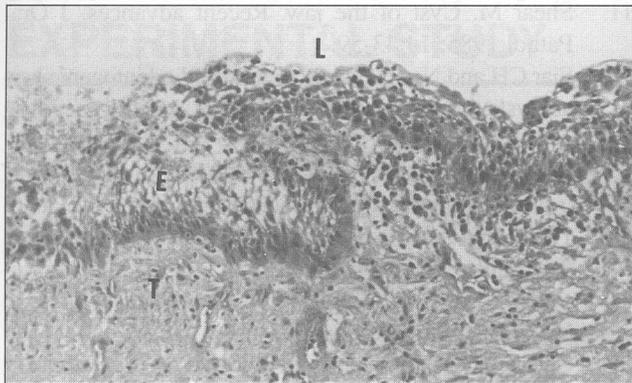


Figure 5: Non-keratinized stratified squamous epithelium exhibiting a stellate reticulum-like appearance (E) associated with intercellular oedema of the spinous cell area in radicular cyst. The subjacent connective tissue exhibit a focus of dense infiltrate of chronic inflammatory cells. (Haematoxylin and Eosin stain; Original magnification - 100X). L = lumen; E = epithelium; T = connective tissue in cyst wall.

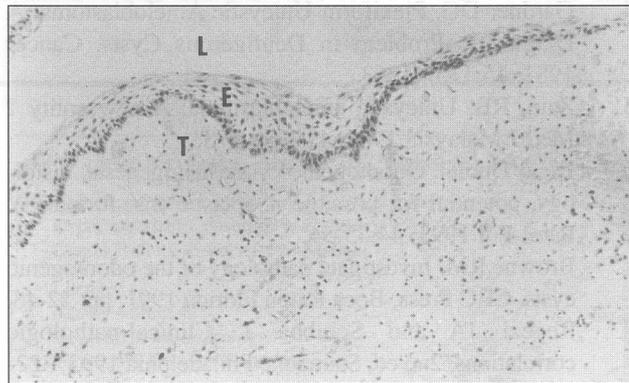


Figure 6: Unicystic ameloblastoma with ameloblastomatous epithelial lining. (Haematoxylin and Eosin stain; Original magnification - 50X). L = lumen; E = epithelium; T = connective tissue in cyst wall.

All cases of OKC in this study were of the parakeratinized type. Only 5 out of 15 cases of OKC in this study had predominantly non-keratinized stratified squamous epithelial lining (diagnosis of OKC was made from the less predominant but typical features of parakeratinized epithelium). The typical parakeratinization of OKC had been reported in the literature to be in 90-95% of cases(7,10) while the other cases were of the orthokeratinized type(7,9,11). In Malaysia, the orthokeratinized type had been described by Siar and Ng(11) where they had also observed non-keratinized epithelium in 2 out of the 9 orthokeratinized variant. In our study 60% (3 of 5 cases) of OKC with areas of non-keratinized epithelium had dense chronic inflammatory cells in the subjacent connective tissue and all the 5 predominantly non-keratinized cases of OKC were significantly related to the presence of rete processes. Such changes of epithelial lining of OKC from parakeratinized to non-keratinized type in relation to the presence of rete processes and inflammation within the OKC in this study was also described in other reports (7,9,13,14). Rodu et al (13) reported that 78% of 112 OKC exhibited marked inflammation and that this is associated to a significant degree with the transformation of the accompanying cyst lining to a non-keratinized form seen routinely in inflammatory odontogenic cysts. Similar observation was reported by Kakarantza et al (14) where 72.4% of 87 cases of OKC showed inflammation with transformation into non-keratinized epithelial lining. The transformation of epithelial lining into non-keratinized type may also influence a change in the biologic behaviour of OKC to a less aggressive lesion(14).

Hyperplastic cystic epithelial linings usually in relation to inflammation of cyst wall in many cases exhibit rete process formation. Inflamed OKC usually exhibit similar characteristics of hyperplastic cystic epithelial linings of RC and DC. This result supported previous reports that hyperplastic epithelium are often seen in areas of inflammation in RC(7,8) and such epithelial hyperplasia leading to rete process formation may also be noted in areas of inflamma-

tion or secondary infection of DC cyst linings(7). In view of the more aggressive behavior of OKC as compared to RC and DC, it is recommended that for diagnostic purposes, careful examination of most of the RC and DC cystic linings is required to rule out the possibility of an inflamed OKC which is similar to inflamed RC and DC.

Hyperplastic epithelium may also resemble ameloblastomatous lining epithelium in RC and DC as observed in this study. Such observations may raise the possibility of ameloblastoma(14). However, since this type of feature was also associated with a dense inflammatory cell infiltrate where the stellate-reticulum like epithelium was a result of intercellular oedema arising from the presence of chronic inflammation in the area, it should be considered as not diagnostic of unicystic ameloblastoma. In view of the reported ameloblastic potential of DC (15), it is thus important to be able to recognise true ameloblastomatous epithelium from ameloblastomatous-like epithelium. In most cases of odontogenic cysts, the presence of ameloblastomatous-like epithelial lining in inflamed odontogenic cysts is insufficient to diagnose unicystic ameloblastoma unless other more diagnostic features of unicystic ameloblastoma are evident. However, such features in the absence of subepithelial inflammation can be diagnostic of unicystic ameloblastoma. Otherwise, differentiation between ameloblastomatous and ameloblastomatous-like lining epithelium can be difficult and therefore additional criteria for UA as described by Robinson and Martinez(3) and Gardner(15) should be applied.

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