

Orthokeratinized odontogenic cyst – critical appraisal of a distinct entity

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Abstract

The orthokeratinized odontogenic cyst (OOC) is a rare developmental jaw cyst. Recognition of OOC as a unique entity has long been due, yet its inexplicable radiographic presentation resembling dentigerous cyst, histological likeness to odontogenic keratocyst (OKC) and inconsistent cytokeratin expression profiles overlapping with both as well as with the epidermis, makes it rather confounding. Diagnosis of OOC is important as the pathologic behavior, clinical outcome and the surgical management of OOC is disparate. This is the report of a case of OOC in relation to an impacted mandibular third molar and critical review of this entity with an emphasis on its biologic characteristics is highlighted.

Keywords: orthokeratinized odontogenic cyst, odontogenic keratocyst, keratocystic odontogenic tumor, intraosseous epidermoid cyst.

Introduction

It has long been documented and established that in addition to odontogenic keratocyst (OKC), the majority of odontogenic cysts produce orthokeratin. Although orthokeratinized odontogenic cyst (OOC) was first described as early as in 1927 by Schultz¹, it was first considered to be a variant of OKC. However, with the World Health Organization (WHO) redefining OKC as a neoplasm and redesignating it as keratocystic odontogenic tumor (KCOT) in 2005, it became imperative that OOC had to be separated out from KCOT as a distinct entity. This distinction was germane as the pathogenesis and the progression and prognosis of these two seemingly similar odontogenic cysts is diverse. Equally bewildering of OOC is its resemblance to a dentigerous cyst when it occurs around the crown of an impacted tooth. This report presents a case of OOC in relation to an impacted mandibular third molar and discusses its possible pathogenesis.

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Case Report

A 36-year-old male patient presented with a swelling in the right posterior region of the lower jaw of 6 months duration. History revealed that the swelling grew progressively in size with no significant aggravating or relieving factors. Past dental history and medical history was non-contributory. On clinical examination, an intraoral swelling measuring about 2x3 cm in size was observed

in the right posterior region of mandible. The swelling was diffuse, asymptomatic, and bony hard on palpation with the overlying mucosa intact.

Orthopantomographic examination showed a well-defined radiolucency approximately 2x4 cm in size, in relation to the right ramus of the mandible associated with a distally impacted mandibular right third molar (Figure 1).

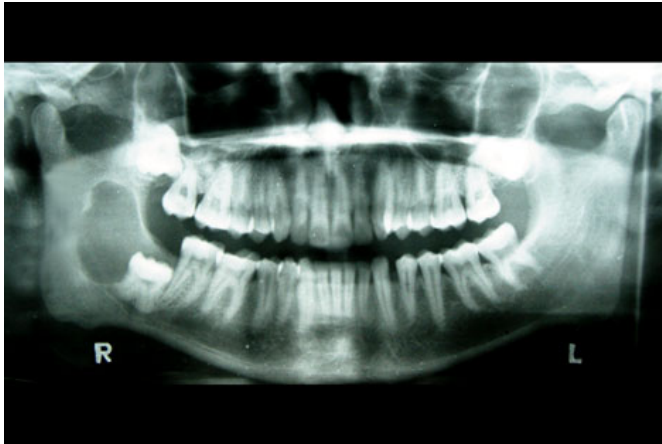


Fig. 1: Orthopantomogram showing a well-defined radiolucency, 2x4 cm in size, in relation to right ramus of mandible associated with impacted mandibular right third molar

Based on the clinical and radiographic evaluation, a preliminary diagnosis of dentigerous cyst was made. Odontogenic keratocyst and a benign odontogenic tumor were considered in the differential diagnosis. The lesion was surgically enucleated along with the extraction of affected third molar, under local anesthesia and submitted for histopathological examination. Gross examination of the specimen revealed a thin cystic sac attached at the neck of the associated tooth, measuring about 2x4 cm in size. The surface of the cystic lumen appeared smooth and contained white cheesy material (Figure 2).



Fig. 2: Gross specimen showing a thin cystic sac attached to the neck of the tooth, lumen containing white cheesy material

Histopathological examination of the hematoxylin-eosin (HE)-stained sections showed a cystic cavity lined by orthokeratinized stratified squamous epithelium lining, with

surface showing sheaves of keratin arranged in many layers. The epithelial lining was about 6-8 layers with a distinct granular cell layer subjacent to cornified layer and basal layer exhibited low cuboidal morphology with absence of palisading of nuclei (Figure 3). The epithelial-connective tissue interface was rather flat and devoid of rete ridges. The capsular tissue was made up of dense fibrous connective tissue with scanty chronic inflammatory cell infiltration. Based on the clinical, radiographic and histopathological features, the cyst was diagnosed as orthokeratinized odontogenic cyst.

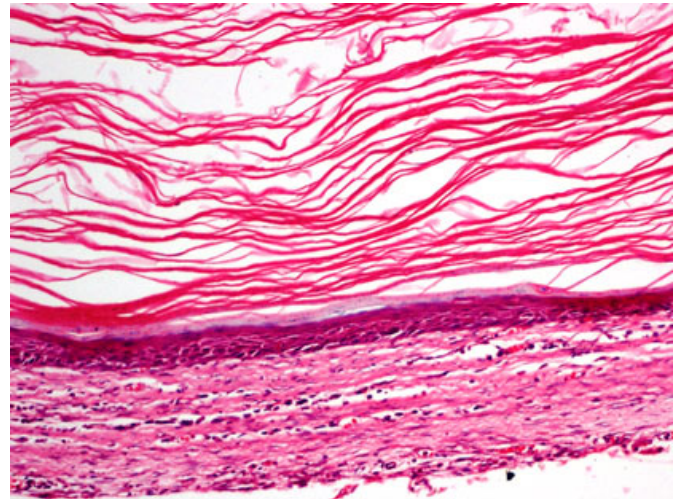


Fig. 3: Stratified squamous epithelium lining with many layers of sheaves of orthokeratin and low cuboidal morphology of basal layer cell with absence of palisading of nuclei (HE, x100)

Discussion

Jaw cysts, which exclusively result in the orthokeratinization of the lining epithelium, are rather unusual and a descriptive term “orthokeratinized odontogenic cyst (OOC)” has been used for these variants². The precise incidence of OOCs from the available literature is not consistent as there are no definitive criteria to categorize them as a separate entity. This is reflected by the conflicting documentation of its reported occurrence ranging from 3-11%². This is further complicated because the majority of them produce orthokeratin and were first considered to be a orthokeratinized variant of OKC.

OOC has been reported to occur among young adults, with a male predominance. Mandible is affected twice more commonly than maxilla, with a predilection for the most posterior region². Incidentally, about 75% of OOCs are associated with impacted teeth, clinically and radiographically mimicking a dentigerous cyst³. Clinical presentation of OOC with regard to age of occurrence, site of presentation and histochemical profile suggests that it bears a close resemblance to KCOT, yet is different from it with regard to its biologic behavior. OOC may be associated with calcifying odontogenic cyst⁴, ameloblastoma⁵, heterotopic cartilage⁶ or even squamous cell carcinoma³.

The distinction between OOC and KCOT is important as KCOTs can occur at multiple sites, be associated with

nevus basal cell carcinoma syndrome (NBCCS) and recur following surgical enucleation. More importantly, the cysts which show loss of heterozygosity in relation to PTCH gene may progress to malignancy and hence the name KCOT³. The above features such as multiplicity and association with NBCCS, which is commonly associated with KCOTs, are not observed in OOCs according to the report.

Histologically, OOC is characterized by a 4-8-cell-layer-thick orthokeratinized epithelial lining, with prominent granulosum and low cuboidal basal cells; while KCOT epithelial lining is thick, parakeratinized with the basal cells exhibiting typical palisading of the nuclei. Recent study utilizing cellblock technique confirms that the lining epithelium in KCOT shows parakeratinization⁷. Additionally, diffuse and focal epithelial hyperplasia, epithelial budding, reactive cytological alterations, dystrophic calcification, daughter cysts, odontogenic epithelial remnants and ameloblastomatous epithelium could also be noted in KCOT⁸.

It is generally conceived that KCOTs have their origin in the epithelial remnants of dental lamina⁹. The usual occurrence of KCOT in the posterior mandible, the increased activity of dental lamina in this region and the ability of dental lamina to keratinize support this concept. Likewise, OOC being intraosseous, having a predilection for posterior mandible where the lining epithelium keratinizes, suggests that OOC may also originate from dental lamina and its remnants. The differences in its histological presentation and contrastingly differing behavior, however, raise a few questions about its histogenesis. All the features that typify an OOC were present in the reported case. The less aggressive nature of OOC seems to correlate with its pattern of cell proliferation and differentiation in their epithelial lining, which differ greatly from KCOT.

Several studies have been carried out using specific markers to underline the differences in their origin and pathogenesis. Dong et al.¹⁰ and da Silva et al.¹¹ suggested that OOCs showed fully differentiated, mature keratinocytes, while KCOTs lacked mature keratinocytes. Also, OOCs showed a pattern of normal cellular differentiation, while KCOTs showed certain alterations in the differentiation process. With regard to the capsular tissue, OOCs seemed to be more stable than the KCOT.

A study reported by Aragaki et al.¹² on keratin (K) expression in KCOT and OOC, revealed a differential expression between the two. OOC was positive for K1, K10 and Loricrin (LOR), while KCOT was negative for all the three, thus suggesting that keratin profile in OOC was identical to that of epidermis. On the contrary, K4, K13 and K17 expression was strongly positive in KCOT, but negative in OOC, further reiterating that the keratin profile in KCOT was similar to dental lamina. This study, however, did not support the origin of OOC in dental lamina, unlike KCOT. The results of this study also indicated that KCOT and OOC expressed unique sets of keratin subtypes, suggesting that each is a distinct entity and deserve to be treated as two separate jaw cysts of odontogenic origin. Positive expression of K2 and LOR in OOC indicated that the cells were in a

completely differentiated state, and thus not aggressive in its behavior.

The most perplexing aspect of OOC is its characteristic attachment to the neck of the tooth, quite similar to a dentigerous cyst (DC), as was noted in this case. As the clinicoradiographic diagnosis of any circumscribed radiolucency around the crown of an impacted tooth is usually a dentigerous cyst, it was not different in present case as well. As the microscopic examination of the cyst fitted well in favor of orthokeratinized odontogenic cyst, the possibility of considering this as a DC with a lining epithelium with keratinization was considered. The attachment of the cystic lining to the neck of the tooth also prompted to contemplate the origin in reduced enamel epithelium. Comparison of orthokeratinized odontogenic cyst with the dentigerous cyst and KCOT was done based on the available literature, to rule out any likeliness of OOC being the orthokeratinized variant of a dentigerous cyst. A table showing the cytokeratin (CK) expression in all the three closely resembling cysts is presented (Table 1).

Table 1: Expression profile of cytokeratin and labeling index of proliferative markers in DC, OOC and KCOT

	DC	OOC	KCOT	Study
CK13	+	*	+	da Silva MJ et al. ¹¹
	*	+	+	Meara JG et al. ¹³
	*	+++	+++	Koizumi Y et al. ¹⁴
CK17	+	*	+++	Meara JG et al. ¹³
	*	+	+	Koizumi Y et al. ¹⁴
CK18	+	*	-	Meara JG et al. ¹³
	*	-	-	Koizumi Y et al. ¹⁴
CK 10	*	++	++	da Silva MJ et al. ¹¹
	*	+++	++	Koizumi Y et al. ¹⁴
	+	*	++	Stoll C et al. ¹⁶
CK 7	*	-	-	Koizumi Y et al. ¹⁴
CK 19	*	-	+ / ++	Koizumi Y et al. ¹⁴
	++	*	-	Stoll C et al. ¹⁶
Ki67 (%)	*	8.6	10.7	Koizumi Y et al. ¹⁴
	14.7	*	52.1	Stoll C et al. ¹⁶
PCNA	+	+	+++	Thosaporn W et al. ¹⁵
p63	*	+	+++	Dong Q et al. ¹⁰

CK – Cytokeratin; DC = Dentigerous cyst; OOC = Orthokeratinized odontogenic cyst; KCOT = Keratocystic odontogenic tumor
 - = Negative; + = Mild expression; ++ = Moderate expression; +++ = strong expression; * = Not performed in the study

Compilation of these data revealed a considerable overlap in cytokeratin expression. CK 10 and CK17 which is typically expressed in a keratinized epithelium were negative or weakly expressed in dentigerous cyst and moderately or strongly expressed in OOC and KCOT. On the other hand, CK 18 and 19, which are the markers of non-keratinized epithelium, were positive in dentigerous cyst and negative in both OOC and KCOT. With regard to the markers of the odontogenic epithelium of dental lamina and enamel organ, namely CK 7 and CK 13, dentigerous cyst expressed both weakly, OOC expressed CK 7 negatively and CK 13

strongly positive and KCOT expressed CK7 weakly and CK13 strongly positive. This implied that OOC and KCOT might have a common origin in the rests of dental lamina. Despite extensive research on CK expression in these three developmental odontogenic cysts, nothing concrete could be elucidated, as the results were often confounding. This has left the investigators clueless about the definitive cell of origin in the histogenesis of any of the developmental odontogenic cysts.

Results like these have opened the perspectives for the study of other molecular markers of proliferation and prognosis, the most commonly evaluated being p63 and Ki-67 (Table 1). Studies with these antigens suggested that KCOT is by far the most aggressive of the three and OOC, unlike KCOT, may not progress to malignancy. Amaral et al.¹⁷ compared the proliferative index (PI) and apoptotic index (AI) between KCOT and ameloblastoma. It was observed that the PI of KCOT was higher than that of ameloblastoma, though no significant difference in AI was observed among the two lesions. According to study by Nadalin et al.¹⁸, Ki-67 expression in the suprabasal layer of KCOT correlated positively with the expression and intensity of syndecan-1, supporting the previous studies proving that KCOT is highly proliferative. Another study by Goncalves et al.¹⁹ also confirmed these observations in KCOT.

It is perhaps for this reason that the surgical management of OOC is more conservative. Treatment of KCOT remains controversial, and the management modalities can be categorized as either conservative or aggressive²⁰, based on multiple factors including lesion size, anatomic relationship, recurrence pattern, and the cyst's association with NBCCS²¹. Multiple surgical protocols have been employed in the management of KCOT, which include marsupialization, enucleation, application of Carnoy's solution following enucleation, decompression, marginal or radical surgical resection, and bone implantation²². However, OOC being less aggressive than KCOT is treated conservatively by mere enucleation of the cyst². Removal of entire cystic lining along with the extraction of impacted tooth is the principal treatment modality in OOC. However, if an erupting tooth must be preserved, conservative treatment should be the treatment of choice²³.

Although these three closely related odontogenic cysts may seem to have a common odontogenic origin, the pathogenesis and progression of each one of these is distinct. Use of specific markers of odontogenic epithelium at varying stages of differentiation to rule out a possible odontogenic origin would be the first crucial step. Secondly, since OOC expresses cytokeratins, which are primarily expressed in epidermis, sequestration of the stomodial ectoderm into the developing jaw during embryogenesis is possible. Consideration of OOC as an intraosseous counterpart of epidermoid cyst within the jawbone needs to be addressed²⁴. Clinically and radiographically, both the OOC and intraosseous epidermoid cyst present as hard, progressively growing non-tender enlargement, with a well-defined radiolucency. Likewise, histopathological features of OOC overlap with epidermoid cyst, although the former is usually devoid of skin appendages²⁵. However, observations of Zhang

et al.²⁶ showed no significant histological differences between OOC and epidermoid cyst. With few reported cases of intraosseous epidermoid cysts in the maxillofacial region²⁷⁻²⁸, an intraosseous epidermoid cyst is necessarily a closely related entity, which needs to be considered as a differential diagnosis for OOC.

OOC has been considered as the developmental odontogenic cyst. The exclusivity of this case is the attachment of the cystic lining to the cemento-enamel junction, which gave an initial notion of dentigerous cyst. With the support of the literature, it was attempted to untangle the mystery of OOC with regard to its nature and origin. These studies have opened new perspectives, as understanding the pathogenesis of OOC is yet to be unraveled. Due to the overlapping disposition of the reviews and reports, the final conclusion is inscrutable. Digression of thoughts from odontogenic origin of this cyst to the inclusional origin can enlighten the source and pathogenesis of OOC and can help in accurate treatment planning.

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