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REVIEW ARTICLE

KERATOCYSTIC ODONTOGENIC TUMOR (PARAKERATINISED OODONTOGENIC KERATOCYST) - A REVIEW

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ABSTRACT:
Cysts constitute about 17 percent of the tissue specimens submitted to oral pathology biopsy services. Odontogenic keratocyst (OKC) is quite unique among odontogenic cysts in its specific clinical characteristics, histological features and aggressive biological behavior. Despite the voluminous reports, OKC has generated considerable controversy with regard to its true nature. Therefore the Working Group of WHO in 2005, reclassified parakeratinised OKC as a Keratocystic Odontogenic Tumor, (KCOT) suggesting this lesion to be a benign cystic neoplasm. Therefore this article aims at reviewing the etiology, clinical, histological, radiographic features as well as the advances made in understanding the aggressive biological behavior and the high recurrence rate of KCOT in detail.
Keywords: Keratocystic Odontogenic Tumor, Odontogenic Keratocyst.

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INTRODUCTION:

Odontogenic Keratocyst (OKC) is the third most common cyst occurring in the oral cavity. (5.4- 17.4 percent of all odontogenic cysts)[(1)] It exhibits paradoxical behavior and may have clinicopathological features of both simple cysts and benign neoplasms. [(2)] Its origin, development and propensity to recurrence have been the subject of much research over the last 40 years. [(3)]

Keratocystic Odontogenic Tumor, formerly known as parakeratinised odontogenic keratocyst is a benign unicystic or muticystic intraosseous neoplasm of odontogenic origin which arises from remnants of dental lamina. It has long been of particular interest because of its potential for local destructive behavior, its recurrence rate and its tendency for multiplicity particularly when associated with nevoid basal cell carcinoma syndrome.[(4)] Philipsen first used the term "odontogenic keratocyst" in 1956 to designate an odontogenic cyst with keratinization of its epithelial lining. [(5)] In 2005, the Working Group of WHO considered OKC to be a tumor and recommended the term, "Keratocystic Odontogenic Tumor" separating the lesion from the orthokeratinised variant which is now considered an odontogenic cyst. As most of the studies carried out on the OKC previous to 2005 were generalized; where both parakeratinised and orthokeratinised OKCs were considered as a single category of OKC, the words KCOT and parakeratinised OKC are used synonymously in this article.

PARAKERATINISED OKC AS KERATOCYSTIC ODONTOGENIC TUMOR (KCOT): A BENIGN CYSTIC NEOPLASM

It was Toller who initiated the idea that OKC might be a benign cystic neoplasm. The diagnostic

metamorphosis of OKC into a recognized cystic neoplasm, keratocystic odontogenic tumor occurred after observation of its biological behavior and modern investigations revealed chromosomal and genetic abnormalities consistent with neoplastic progression.[6] The reasons for calling parakeratinised OKC as KCOT are manifold,

- Clinically the parakeratinised odontogenic keratocyst (KCOT) show aggressive growth.
- A tendency to recur after surgery.
- Increased mitotic activity in cystic epithelium.
- Potential for budding of the basal layer.
- Presence of daughter cysts in the cystic wall. (7%-30.1%)
- There is an association with nevoid basal cell carcinoma syndrome.
- The discovery of chromosomal abnormalities and genetic alterations such as mutation of PTCH gene.
- Recurrence within 5-7years.[6]

SYNDROMES ASSOCIATED WITH KCOT:

The keratocystic odontogenic tumor is a solitary lesion; however in 5%-10% of lesions where KCOT appears as a manifestation of naveoid basal cell carcinoma syndrome (NBCCS), it appears in multiple forms. The mean age of patients with multiple KCOTs, with or without the NBCCS, is lower than those with single non-recurrent KCOTs. [6]

The Naveoid Basal Cell Carcinoma Syndrome (NBCCS)

This syndrome was first described by Gorlin and Goltz in 1960. Multiple KCOTs occur in high proportion of patients with NBCCS and are the most consistent and common manifestation of the syndrome occurring in 65%-100% of NBCCS patients. [6] It is an autosomal dominant disorder with complete penetrance but variable expressivity. The gene locus has recently been elucidated on chromosome 9q 22.3 to q31. [7]

Simpson-Golabi Behmel Syndrome is an X –linked rare congenital disease. It is associated with prenatal and postnatal overgrowth, mental retardation, typical facial appearance and multiple KCOT. [8]

THE AGGRESSIVE BEHAVIOR OF KERATOCYSTIC ODONTOGENIC TUMOR

Some papers have reported on aggressive behaviour of some OKCs to the extent that they have penetrated cortical bone and involved surrounding soft tissues. Another reported case has extended from the mandible and eventually involved the base of skull, behaving rather like a lower-grade squamous cell carcinoma, while others have extended from the maxilla into the orbit and infratemporal fossa or mandible into the infratemporal fossa. [9]

All the cysts of odontogenic origin share the same sources of odontogenic epithelium. However they all exhibit varying degree of aggressive behavior. The KCOT epithelial lining may have some intrinsic growth potential. When compared to other types of odontogenic cysts, the epithelial lining of KCOT express a higher mitotic index and higher proliferative indices. [10] The proliferation in KCOT is irregular and in clusters, indicating that there are both slow and rapid proliferating areas in different section planes. Increased proliferative potential is reflected by various proliferative markers, e.g., Ki-67, AgNOR, IPO-38; impaired expression of tumor suppressor genes and their protein products. The increased cell activity is evident by the presence of elevated level of oxidative enzymes and acid phosphatase, which indicate high metabolic and lysosomal activities. [1]

In addition, KCOT connective tissue walls have an increased level of the collagenase enzyme, leucine aminopeptidase. Autoradiography and DNA cytophotometry techniques have demonstrated a rapid proliferation of the connective tissue wall of the OKC. [9]

ETIOPATHOGENESIS:

KCOT arises from odontogenic epithelium. The available evidence points to two main sources of epithelium, the dental lamina or the remnants and extensions of basal cells from the overlying oral epithelium. Recent studies have demonstrated the role of PTCH gene in the etiology of KCOTs. [6]

CLINICAL FEATURES:

KCOT occurs over a wide age range with a peak incidence in the second and third decade of life and a gradual decline thereafter. An approximately 2:1 predominance is seen in males over females. Whites are more commonly affected. [5]

The mandible (65%-83%) is involved more frequently than the maxilla. [1] The next common site is the maxillary canine region. [1] Involvement of an unerupted tooth has been reported in 25%

40% of cases. [12] Localized swelling is the typical presentation; spontaneous drainage of cyst fluid, parasthesias, trismus, and nasal obstruction are less frequent initial manifestations. [5] KCOT are usually intraosseous or central, however 14 cases of peripheral odontogenic keratocyst have also been reported. [14]

Brannon reported that a small percentage of keratocysts exhibit both parakeratin and orthokeratin and that these cysts should be treated as parakeratinized odontogenic keratocysts because they have a tendency for recurrence intermediate between the purely parakeratinized and orthokeratinized variants. [13]

MACROSCOPIC FEATURES:

Lining are thin and fragile and usually collapsed and folded. [1]

HISTOLOGICAL FEATURES:

In 1963 Pindborg and Hansen suggested the histological criteria for describing the essential features of OKC. These have later been modified by the Working Group of WHO 2005. The characteristic histological features of KCOT are: (Figure1 and 2).

- The lining epithelium is uniform without retepeg formation, usually about 5-8 cell layers thick.
- Well defined layer of cuboidal or columnar cells often in a palisaded arrangement is seen.
- Cells of the spinous cell layer frequently show intracellular oedema.
- Keratinisation often is of the parakeratotic type but may be orthokeratotic.
- Basal layer is most often prominent with polarized intensely staining nuclei. This is an important feature in distinguishing KCOT from jaw cysts with keratinisation
- The parakeratin layer is often corrugated.
- Desquamated keratin is present in many of the cavities.
- Mitotic figures are found frequently in the suprabasal layer.
- Cyst wall is generally thin and uninflammed.
- Satellite or daughter cysts are seen in 7%-26% of cases. [5,1]
- Other features frequently seen on histopathology are the hyaline bodies (7%-32%), dystrophic calcification (10%-21%), [6] Koilocytosis (17.1%), [6] cartilage and dentinoid formation. [14]

Primary non-recurrent OKC (primary OKC without recurrence within 5 years) shows a slightly higher prevalence for dystrophic calcifications than primary OKC's that recurred. [5] Inflammation in the connective tissue wall of OKC has been found in almost 75% of the cases reported in the literature. [11] A case of solid OKC has also been reported.[15]

THE GROWTH OF KCOT:

The growth of KCOT has been attributed to increased osmolality, mural growth in the form of epithelial proliferation. The multilocular and loculated outlines exhibited by some OKCs suggested a multicentric pattern of cyst growth brought about by the proliferation of local groups of epithelial cells against the semi-solid cyst contents. The infolding of the epithelial lining into the capsule suggests that this is the result of active epithelial proliferation. The increased number of myofibroblasts in the stroma of parakeratinised OKC (KCOT) contributes to its invasiveness. [11] Donoff et al. demonstrated collagenase activity in keratocyst epithelium which appears to relate to the ability of keratocysts to grow expansively within bone.[16] Positive pressure may play a crucial role in odontogenic keratocyst growth *via* stimulating the expression of IL-1 in epithelial cells and hence the bone resorption.[17]

RADIOGRAPHIC FEATURES:

5.5% - 42.5%. of cases are diagnosed incidentally during routine dental examination. [10] Conventional panoramic radiograph and periapical radiograph are useful in diagnosis. Radiographically KCOTs may appear as small, round or ovoid unilocular radiolucencies or may be larger with scalloped margins. The radiolucency tends to be well demarcated with distinct sclerotic margins, but may be diffuse in parts. [1] There is displacement of impacted or erupted teeth, root resorption (10%-15%) [5], root displacement or extrusion of the erupted teeth. [10] The ratio of unilocular: multilocular radiolucency associated with KCOT in maxilla was 6:1 and mandible was 1.9:1.The perforation rate is noted to be 50.8%. [16] CT scanning may be helpful in detecting cortical perforation and assessment of soft tissue involvement especially in patients with NBCCS–related KCOTs. Contrast enhanced MRI may provide more detailed information. [1] (Figure 3) [18]

Table 1: Summary of recurrence rate by treatment types [20]

Treatment Type	Total Cysts Reported	Total Recurrences	Calculated Recurrence Rate (%)
Curettage	26	5	19.2
Enucleation alone	387	111	28.7
Enucleation and Carnoy's	60	1	1.6
Radical enucleation	6	1	16.7
Enucleation and cryotherapy	16	5	31.5
Marsupilization	45	11	24.4
Resection	38	0	0

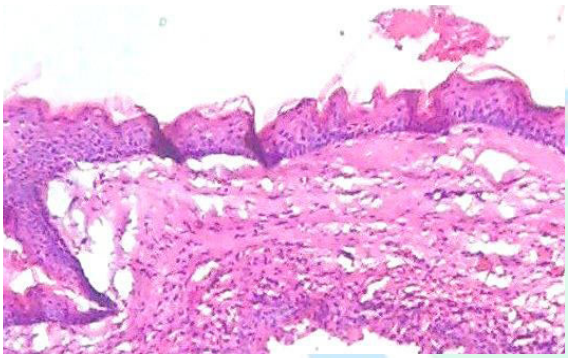


Figure 1: Microphotograph showing the histopathological features of KCOT (X10)

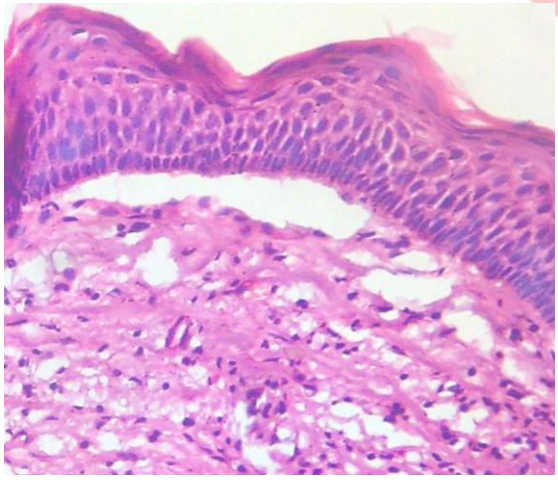
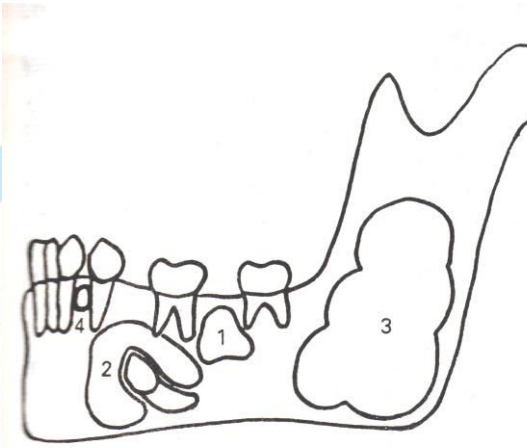


Figure 2: Microphotograph showing the histopathological features of KCOT(X40)



1. Replacement; 2.Envelopmental; 3. Extraneous; 4. Collateral

Figure 3: Diagram illustrating the radiographic varieties of keratocyst, drawn after main (1970) [19]

RECURRENCE RATE:

Numerous published reports have shown recurrence rates ranging from 3 to 60%. [15] The majority of the recurrence is noted in the first 5 years after treatment. [12] Higher recurrence rate is noted in the younger individuals. [6] Tumors in the maxilla have a higher recurrence rate than those that first appeared in the mandible alone. The recurrent lesions occurred more frequently in parakeratinized OKCs, symphysis-body region, and patients who had lesions associated with the remaining teeth and were treated by enucleation and enucleation with curettage. [16]

The reasons for recurrence of KCOT are removal of the cyst in piecemeal, disruption of the epithelial lining, patients with basal cell nevus syndrome, presence of satellite cyst. [5] However Ahlfor et.al

suggested that none of the histological features can be used to predict recurrence.[6]

COMPLICATIONS OF KCOT:

Some KCOTs show the characteristics of epithelial dysplasia. Tumors with such characteristics could possess the potential to evolve into ameloblastoma and squamous cell carcinoma. [6].Although rare approximately 80 such cases have been described with transformation to squamous cell carcinoma. [5]

TREATMENT AND PROGNOSIS:

There is no consensus on a uniform treatment plan and the recommended surgical treatment varies from marsupalisation to en bloc resection. The type of treatment chosen depends on various factors like age of the patient, lesion location, size and whether the lesion is primary or recurrent. [12]

Nick Blanas et.al (2008) [19] have done a systematic review of the existing literature for the treatment and follow up of OKC patients. According to them, the treatment most likely to prevent recurrence is resection with a 0% recurrence rate. (Table 1)

When the presence of an OKC (KCOT) is confirmed by examination of a biopsy specimen, 3 choices appear to have equal efficacy.

1) For a routine OKC (KCOT) in a person who is likely to return for follow-up treatment, Carnoy's solution appears to be the least invasive procedure with the lowest recurrence rate.
2) If the cyst is very large decompression of the cyst followed by enucleation will also have a reduced recurrence rate. Use of Carnoy's solution at the enucleation stage should be considered.
3) If the patient is unlikely to return for follow-up, lesion should be resected.

According to Manabu Minami et.al (1996) smaller KCOT should be treated by curettage, enucleation and peripheral osteotomy. Larger KCOT should be treated by marginal or segmental resection. [20]

Blanchard introduced a new method using ultrasonic debridement of the cystic cavity in an attempt to remove any possible epithelial remnants. He monitored his cases for 5 years and reported no incidence of recurrence. [12]

A unique surgical approach involves placing an indwelling catheter into the cyst for up to 9 months before enucleation and curettage. This method allows for decompression of the lesion with a subsequent reduction in lumen size; at enucleation the cyst wall reportedly tends to be thicker and easier to remove without tearing.The main disadvantage of this approach is that two procedures are necessary, an open biopsy for tissue diagnosis at the time of catheter placement and the later definitive resection. The most aggressive form of treatment, partial maxillectomy or mandibulectomy, is rarely necessary. [5]

CONCLUSION:

Over the time, OKC parakeratinised variant has become a recognized cystic neoplasm. It has been difficult to perform comparative analyses around the world due to the differerences in the criteria used for diagnosis. Pathological examination of the KCOT is essential in order to separate it from other odontogenic cysts. To provide appropriate treatment it is essential to avoid misdiagnosis. [7] Unfortunately, there are no morphologic or other parameters that predict which KCOT will recur or the rare KCOT that will infiltrate. The continued advances in understanding the biological behavior of this aggressive cystic neoplasm will probably simplify the nature of this tumor.

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