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HISTOLOGICAL REVIEW AND MANAGEMENT OF KERATOCYSTIC ODONTOGENIC TUMOR BY ITS UNIQUE CHARACTERIZATIONS

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ABSTRACT

First mentioned as 'primordial cyst;' in 1945 by Robinson, and currently as Keratocystic odontogenic tumour(KCOT); KCOT is known for its aggressive behavior and recurrence. With a peak frequency between 2nd and 3rd decade and higher incidence in mandible in angle ramus region. Recurrence rate with enucleation alone without curettage range from 9% to 62.5% so the minimal treatment modality would be at least curettage after enucleation. Thus knowing the treatment options and histological features will help in the treatment planning of KCOT.

INTRODUCTION

Keratocystic odontogenic tumor is a cystic lesion of odontogenic origin which was first mentioned as 'primordial cyst;' by Robinson in 1945 because it developed from enamel organ before enamel formation took place[1]. The term odontogenic keratocyst [OKC] was first coined by Philipsen in 1956 for all cysts that showed keratinization histologically. He believed that keratinization in a cyst took place as a further stage of development of a non-keratinized cyst[2,3].

In 1971 WHO stated that primordial cyst and OKC were synonymous and emphasis was placed on histologic features[1]. Later for cysts with keratinized lining the term odontogenic keratocyst was preferred in the histological typing of cysts and tumours by WHO in 1992[4]. Because of its aggressive and neoplastic nature WHO in 2005 has reclassified OKC as Keratocystic odontogenic tumour (KCOT) and has defined it as "a benign uni- or multicystic, intraosseous tumour of odontogenic origin, with a characteristic lining of Para keratinized stratified squamous epithelium and potential for aggressive, infiltrative behaviour[5].

Madras *et al*. Mentions local destruction, budding of the basal layer into the connective tissue, presence of mitotic figures in the suprabasal layer, a high recurrence rate and mutation of tumour suppressor PTCH gene on chromosome 9q22.3–q31 as factors responsible for reclassification of OKC to KCOT[6].

Classification

KCOT can be classified based on the number of lesion as solitary or multiple. The multiple variety is commonly seen to be a part of inherited naevoid basal cell carcinoma syndrome (NBCCS)[5]. Based on its association with other systemic manifestations— {as mentioned in the morphology code of the international classification for diseases for oncology (ICD-O) is 9270/0} two variants of this cyst are: -the sporadic cyst and cyst associated with the Naevoid basal cell carcinoma syndrome[7]. Based on radiological appearance KCOT can be unilocular or multilocular. Normally they are seen as solitary, radiolucent, unilocular lesion with smooth, corticated borders[8].

Based on histology three types of odontogenic keratocyst (OKC) are mentioned parakeratinised, orthokeratinised and a combination of both. But the recent classification of WHO (2005), recognizes only the parakeratinised variant as a neoplasm of cystic variety –KCOT[9].

Etiology

The origins of KCOT have been suggested as either primordial, including dental lamina rests or the basal cells of the oral epithelium, or dentigerous-like reduced enamel epithelium of the dental follicle[10]. The lesions are said to be originating from the oral mucosa and burrow into the bone according to some authors. Ostrowsky suggested epithelial residues or the possibility of epithelial offshoots of lamina posterior to third

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molar crypts and their association with development of KCOT[11].

The *PTCH* (patched) gene, a tumor suppressor gene, known to be involved in NBCCS, KCOT, basal and squamous cell carcinoma and other epithelial tumors[6,12]. The hedgehog signaling pathway and PTCH mutations explain the pathogenesis of KCOTs[6] Barreto *et al*. in their study on gene mutations summarized that the PTCH gene encodes for a trans-membrane protein that functions in opposition to the hedgehog signaling protein which controls cell fate and growth in various tissues including teeth[11]. PTCH binds to and inhibits the oncogene SMO (smoothened) which has a suppressor effect on growth-signal transduction. When PTCH is mutated this inhibitory effect is lost and triggers proliferating and stimulating effect[6,13].

Incidence

Age :Occurrence of keratocyst has been noted over a wide range of age, the earliest being 1st decade and as late as the 9th decade, with a peak frequency between 2nd and 3rd decade .40% – 60% of patients come under this age group[14].

Gender: Higher male predilection of KCOT is noted. Male-to-female ratio is 1.6:1. Predilection[15].

Site: Both the maxilla and the mandible are affected, but in mandible (molar –ramus region) it occurs more frequently with a ratio of 2:1[16].

Histological Features

WHO (2005) gave a series of features to differentiate KCOT from other keratinizing tumors, which include

1. Well defined, often pallisaded, basal layer of columnar or cuboidal cells
2. Intense basophilic nuclei of the columnar basal cells oriented away from the basement membrane.
3. Mitotic figures frequently present in the suprabasal layers
4. Parakeratotic layers with an often corrugated surface and may show presence of keratin in the lumen[5].

The presence of parakeratin makes KCOT distinct from other developmental and inflammatory cysts. A Typical histologic feature of OKC is an epithelial lining consisting of stratified squamous epithelium which is parakeratinised. The epitheliumis 6-10 cells thick in which retepegs are absent thereby creating a characteristic interphase between epithelium and connective tissue. Fibrous tissue rich in mucopolysaccharides is present in non-inflamed connective tissue wall of KCOT. Degeneration of collagen in juxta epithelial region by metalloproteinases results in the separation of epithelium and connective tissue interphase[17].

Basal and para-basal epithelial regions occasionally exhibit mitosis[17]. Dysplastic features may be seen in the epithelial lining of KCOT[5], and malignant transformation into squamous cell carcinoma has been reported although rare[18,19]. In case of inflamed or infected cyst the epithelium displays high rate of proliferation as compared to non-infected cyst, but the cause of this is unknown[20]. The connective tissue wall of KCOT may present with satellite cysts (daughter cysts) which occur more commonly when it is associated with NBCCS. A protein called Tenascin which is exhibited in epithelial malignancies is also expressed in KCOT[21].

Ultra Structural Features

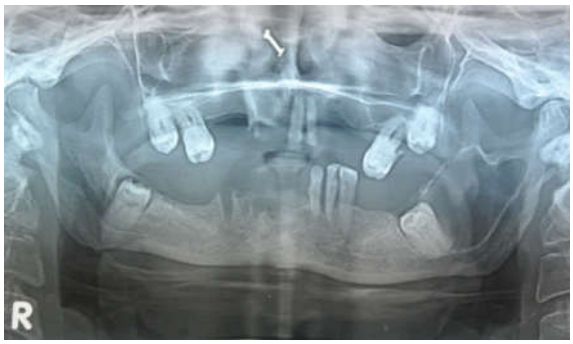
Infolds of epithelium, surface corrugations and uniform parakeratin layer, spinous cell layer being narrower compared to deeper regions, and desmosomal junctions; are visibleultra-structurally. When parakeratinised epithelium is examined under a Transmission electron microscope the interdigitations of cell cytoplasm and desmosomal junctions that lead to a better understanding of the complex nature of the cell structure of KCOT is exhibited[22]. Histological feature that differentiates KCOT from other odontogenic cysts include high mitotic count, higher turnover rate of epithelium and active collaginase[17].

In ultrastructural study; angiogenesis is exhibited as an evident feature of KCOT, which in turn is a feature of benign neoplasm thus accounting for its aggressive behavior.

In KCOT fenestrated capillaries were found, the presence of which suggests that it is related to rapid movement of the fluid in the cyst, which could be a factor associated with high proliferation of epithelium. Another marked feature degeneration of endothelial cell lining connected with thrombosis[23].

Clinical Features

Discovered under routine radiological exam, as they are symptomless in major cases, until pathologic fractures or cortical swellings occur.



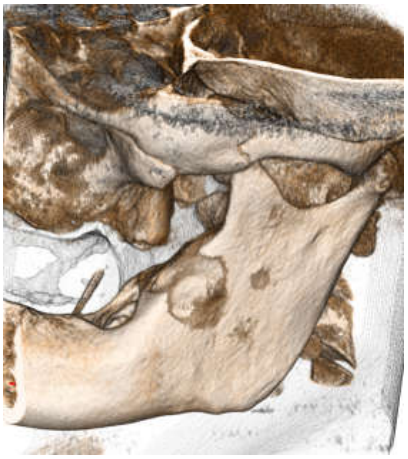


Figure 1- Radiological presentation

Swelling, associated with pain or discharge may be experienced in a slightly large cyst. KCOT tends to expand in the least resistant area; the medullary section of bone and hence the clinically appreciable swelling occurs after a significant growth of KCOT (especially in ascending ramus and angle of mandible) has already taken place[14]. It has been shown that maxillary involvement has more chances of infection and hence lead to early discovery despite of a smaller cyst compared to mandible[24].(Fig 1)

Teeth displacement due to large growth, that sometimes lead to destruction of the orbital floor leading to proptosis of the eyeball have been reported. Large aggressive lesions imitating low grade squamous cell carcinoma have been reported by some researches[18].

Recurrence

Recurrence rate for KCOT is high and variable, with values as high as 62.5% to as low as 2.5%[27]. The high rate of recurrence has been proposed as being due to, variations in treatments, age of the patient at time of diagnosis, differences in location of the lesions, presence and absence of infection, associated teeth, involvement of mucosa, histo-pathologic presence of one or more daughter cyst, size and locules of the lesion and association with nevoid basal cell carcinoma syndrome (63%) than without a syndrome (37%)[17,28].

There appeared lesser chance of recurrence when KCOT was enucleated as a single entity than in several pieces. The presence of scalloped margins makes it difficult to enucleate in a single entity, there by increasing the chance of recurrence. The presence of an infection, perforated bony wall, presence of fistula, and multilocular radiographic feature has more incidence of recurrence than without[14,17].

The presence of daughter cysts one or more increases the chances for recurrence significantly[29]. Presence of delicate and thin lining makes it more difficult to enucleate than when cysts have thick walls. Some authors suggested a) proliferations from basal cells of oral mucosa and b) dental lamina or its remnants is the main source from which the epithelium of the KCOT develops[24,30].With regard to high rate of recurrence, it is advised to have a regular follow-up and periodic check –up annually, consistently for 5 years[31]. KCOT has 0.12% incidence for carcinoma[32]. The potential of KCOT to transform into carcinoma is essentially due to its keratinisation[33].

Treatment Options of KCOT

A thorough evaluation is required before coming to a particular treatment plan as the very nature of KCOT is high rate of recurrence. Recurrence rate with enucleation alone without curettage range from 9% to 62.5% so the minimal treatment modality would be at least curettage after enucleation[34].

Peripheral ostectomy after enucleation is another option for treatment of KCOT. It was considered as an alternative approach to enucleation when resections could be avoided. In this rotary instruments are used to remove as much bone as required to ensure the removal of all daughter cells and residual lining[27,34].

Another modality of treatment of KCOT and is called Radical enucleation in which curettage is done extensively after the entire lining has been removed; including residual lining and the overlying mucosa, followed by surrounding bone reduction to remove residual cystic epithelium.

Marsupulisation also called decompression is a surgical technique were in the pressure within the cyst, responsible for its growth is reduced. Done in large cysts or when the growth is approximating the vital structures. Later it can be followed by enucleation with minimal complication. KCOT may respond more effectively to Marsupulisation than when compared to other odontogenic cysts [35]. Resection is yet another modality for treatment of KCOT. It can be done segmentally (with continuity defect) or as marginal resection were in the continuity of the resected bone is maintained[27,] Carcinoma confirmed by biopsy is the only contra indication for this procedure[27]. It is the only procedure that gives a zero percent recurrence rate.

Voorsmit and colleagues stared and popularized the use of chemical tissue fixation using CARNOYS solution, which is a mixture of absolute alcohol, glacial acetic acid, chloroform & ferric chloride. Application of this solution for five minutes leads to bone penetration of this solution to a depth of 1.54mm, nerve penetration to 0.15mm, and mucosa to a depth of 0.51mm.Enucleation, excision of overlying mucosa, and using CARNOYS solution is an effective option for treatment of KCOT if resection cannot be considered.(Fig 2,3)

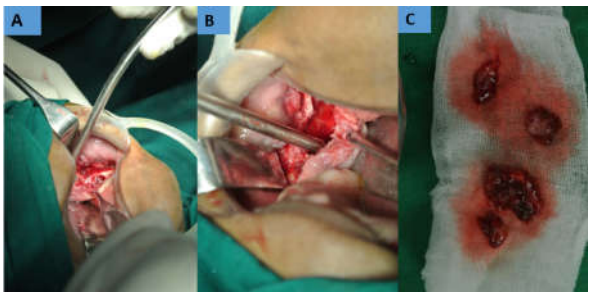


Figure 2 – Treatment procedure

A: Cystic cavity opening,
B: Cystic cavity,
C: Epithelial lining

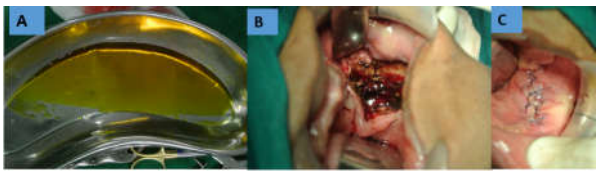


Figure 3 – Treatment procedure

A: Carnoys solution for chemical cautery,
B: Chemical Cauterization done in the cystic cavity,
C: Wound closure

Cryotherapy is another modality of approach for treatment of KCOT. It produces a cellular necrosis but yet maintains the inorganic osseous frame work A single one-minute freeze produces bone necrosis depth of 1-3mm[36].

Summary

Priorly known as Odontoatogenic Keratocyst, Keratocystic Odontogenic Tumor exhibit aggressive nature & high recurrence rate due to its infiltrative behavior. According to recent genetic and molecular study PCNA, p53, Ki-67 is some of the proliferation markers found to be certainly associated

with this tumor. Considering the high recurrence of KCOT, different treatment modalities have evolved. Adopting aggressive treatment methods like resection, which brings about least recurrence of 1.85% or enucleation supplemented with carnoys solution, seems to be a substantial approach in the treatment of KCOT.

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