10.5005/jp-journals-10015-1137
CASE REPORT

Keratocystic Odontogenic Tumor of the Maxilla: Report of a Rare Case and Review of Literature

A Nagraja, Praveen S Anigol, Venkatesh Vishwanath Kamath, Krishnanand P Setlur

ABSTRACT

The odontogenic keratocyst (OKC) has recently been reclassified by the WHO (2005), as keratocystic odontogenic tumor (KCOT) based on clinical, histological and immunohistochemical parameters. KCOT more commonly occurs in the mandible and cases involving the maxilla are infrequent. We report an unusual and rare case of a KCOT of the maxilla in a middle-aged individual with extensive involvement and displacement of the maxillary third molar to the zygomatic region. A discussion of the parameters involved in the reclassification of the lesion as a tumor is presented alongwith a review of literature.

Keywords: Odontogenic keratocyst, Keratocystic odontogenic tumor, KCOT, OKC.

How to cite this article: Nagraja A, Anigol PS, Kamath VV, Setlur KP. Keratocystic Odontogenic Tumor of the Maxilla: Report of a Rare Case and Review of Literature. World J Dent 2012;3(1):100-108.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

The proliferation of odontogenic epithelial remnants within the jaws to form cysts and tumors is a relatively common event. These jaw cysts and tumors arise from odontogenic remnants most commonly present in the gingivae (cell rests of Serres), periodontal ligament (cell rests of Malassez) and in the third molar region (rests of dental lamina). Yet another source is the basal cells of the overlying oral epithelium in the jaw. The odontogenic keratocyst (OKC) first described, as such by Philipsen in 1956[1] is a distinctive entity characterized by a keratinized lining, presence of satellite cysts and association with the nevoid basal cell syndrome. The propensity for recurrence and the aggressive behavior clinically and histologically has necessitated the reclassification of the lesion by the World Health Organization (WHO, 2005) as a 'keratocystic odontogenic tumor' (KCOT). The KCOT is defined as 'a benign uni- or multicystic, intraosseous tumor of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior'.[2]

Odontogenic keratocysts (KCOT) differ from other odontogenic cysts in that they have a biologically-aggressive behavior because of a high proliferative activity of the lining epithelium, a tendency to extend along bony cancellous spaces, and a considerable high rate of recurrence. Despite the voluminous reports, OKC (KCOT) has generated considerable controversy with regard to its true nature. It exhibits paradoxical behavior and may have clinicopathologic features of both simple cysts and benign neoplasms. KCOT may arise sporadically or may be associated with nevoid basal cell carcinoma (Gorlin's syndrome).

Here, we present a rather unusual case of an aggressive KCOT in the upper right third molar region in a middle aged individual treated with conservative surgical curettage. A review of literature and the controversies involved in reclassification of the lesion are also discussed.

CASE REPORT

A 43-year-old male patient came to the outpatient department of Dr Syamala Reddy Dental College, Hospital and Research Centre, Bengaluru complaining of pain and discharge in the right upper molar region of jaw. Pain was localized, dull in nature which was aggravated on having hard food and relived on medication. There was no facial asymmetry or evidence of swelling over the cheek extraorally (Fig. 1). Patient was a long standing hypertensive on medication for the past 2 years. He had a dental history of extraction of 18 (upper right third molar) 8 years back.

On intraoral examination, there was a diffuse solitary swelling in the right posterior palatal region extending from gingival margin to midpalatine raphae beyond the maxillary

Fig. 1: Lateral view of face showing no swelling in the zygomaticomaxillary region

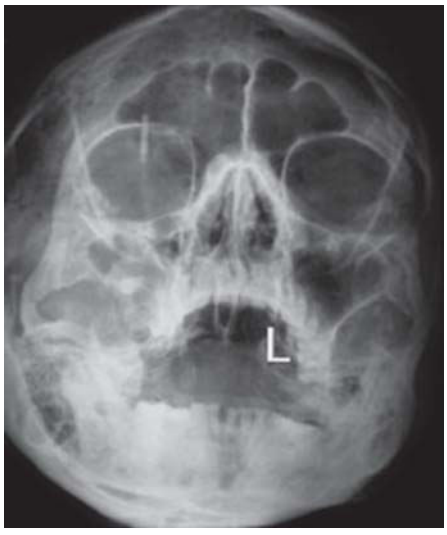

Fig. 2: Water's view showing radiolucency extending to base of zygoma

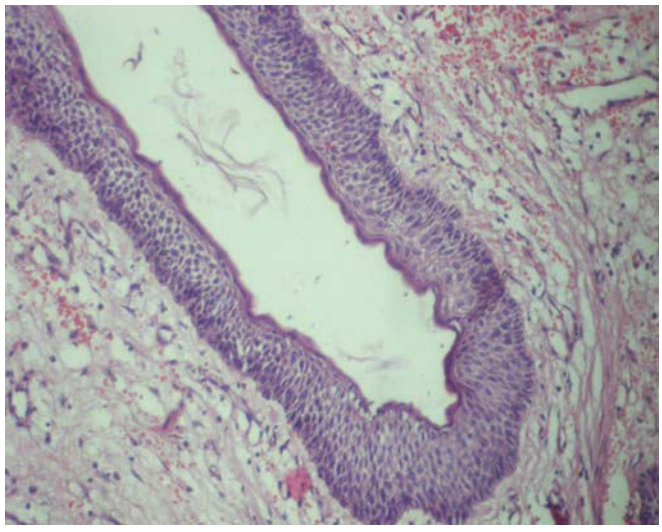

Fig. 4: Microscopy (×10) showing typical epithelial features of OKC (KCOT)

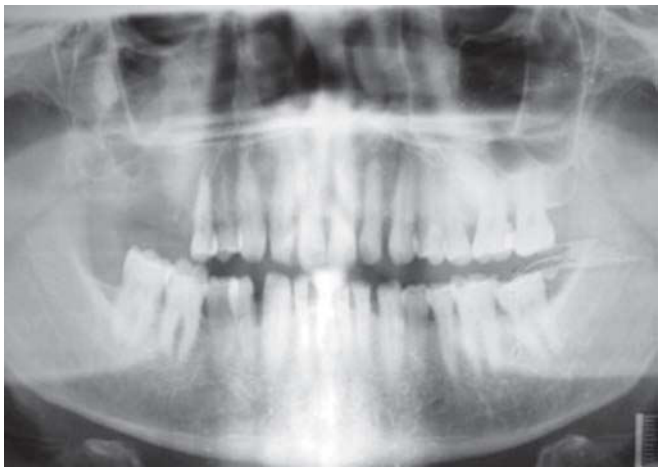

Fig. 3: Orthopantomograph showing apparent relationship to sinus

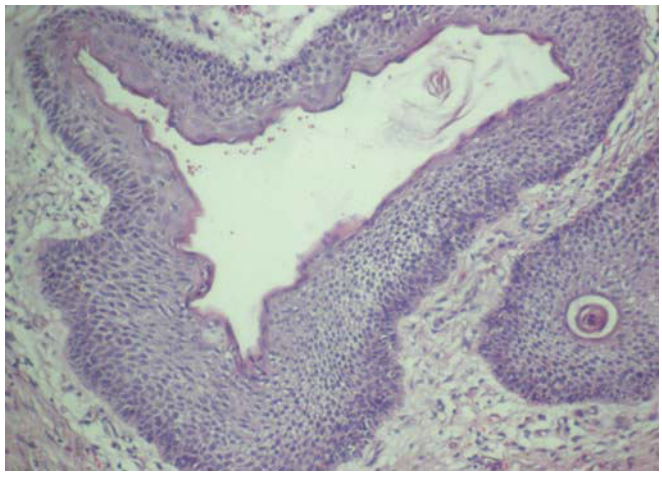

Fig. 5: Microscopy (×10) showing islands of OKC (KCOT) in the connective tissue

canine, measuring 2 × 3 cm. The lesion was smooth and edematous on the alveolar ridge.

A purulent discharge through a sinus opening was noted on the crest of alveolar ridge.

Water's and Panoramic projections showed unilocular radiolucency in the molar area with tooth embedded near the tuberosity area (Figs 2 and 3). Border of the lesion was sclerotic and irregular in shape.

Under local anesthesia, an incisional biopsy of the lesion was carried out. A histopathological diagnosis of KCOT was returned. The patient was informed about the diagnosis and treatment modalities. In view of the known aggressive biological behavior and the extent of the lesion, a partial maxillectomy was advocated but the patient was quite insistent on a conservative approach not compromising maxillary function and esthetics. Having willingly accepted the possibility of a recurrence and signing consent he was posted for a surgical enucleation of the lesion under general anesthesia. The lesion was approached intraorally via a vestibular incision in the maxilla. Intraoperatively the tooth was found to have been embedded posterior to the root of the zygomatic arch and was removed with great care. The lining was found to be friable in most places and a thorough curettage was carried out. Postcurettage the ends of bony margins were trimmed with a large bud-shaped bur initiating bone bleeds. Areas of copius bleeding were controlled with bone wax. Surprisingly no involvement of the maxillary sinus was noted. The operative site was closed primarily with a small opening for insertion of a drain. Adequate postoperative care facilitated the removal of the drain on the 5th postoperative day. The patient is under review and no signs of recurrence have been detected 1 year later.

Microscopic features of excised cyst tissue showed hyperplastic keratinized cystic lining with prominent palisading basal cell layer and nuclear hyperchromasia (Fig. 4). Islands of epithelium in the connective cyst wall

also showed keratinization (Fig. 5). Immunohistochemical staining with cytokeratins 8 and 19 (CK 8 and 19) and with amelogenin antibodies were done. There was mild expression in the epithelial islands with CK 8 while CK 19 showed more intense expression. Amelogenin was negative in the epithelium. There was no evidence of sinus epithelium or sinus tissue in the given sections indicating the cavity to be separate from the sinus.

DISCUSSION

The odontogenic keratocyst was first described as a cholesteatoma.[3,4] The term 'odontogenic keratocyst' was introduced by Philipsen (1956).[1] Recently, the WHO[2] has redesignated this lesion as 'keratocystic odontogenic tumor' based on histological and behavioral characteristics.

KCOTs comprise approximately 11% of all cysts of the jaws.[5] They occur most commonly in the mandible, especially in the posterior body and ramus regions.[2,6,7] KCOT has a slight predilection for men and commonly occurs in the second and third decades of life.[8] They almost always occur within bone, although a small number of cases of peripheral KCOT have been reported.[9] Patients may present with swelling, pain and discharge or may be asymptomatic. Distinctive clinical features include a potential for local destruction and a tendency for multiplicity, especially when the lesion is associated with the nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin-Goltz syndrome. KCOTs have a high recurrence rate, reportedly between 25 and 60%;[10] when associated with NBCCS, the recurrence rate is about 82%.[11] The literature suggests that less than 1% of all cases of KCOT occur in the maxilla and exhibit sinus involvement.[12] The present case is unusual and rare in this regard.

Radiographically KCOT usually presents as a unilocular or a multilocular radiolucency with scalloped and well-defined margins. When the KCOT involves the maxilla, the radiographic appearance is usually a unilocular or multilocular radiolucency which may or may not be associated with an impacted tooth. Often lateral extension into the sinus is misinterpreted as a intrasinus lesion. A rational approach is to reserve CT scanning for lesions, particularly those involving the maxilla, where extension into the nasal cavity, orbit or pterygomaxillary space may be assessed with clarity.[13]

KCOT is difficult to diagnose clinically due to a relative lack of specific clinical and radiographic characteristics. Since, KCOT can be associated with the crown of an involved tooth, the lesion must be distinguished from a dentigerous cyst radiologically. Other cystic and neoplastic diseases, such as traumatic bone cyst, lateral periodontal cyst, central giant cell granuloma, ameloblastoma, ameloblastic fibroma and plasmacytoma , can present with the same radiologic features.

Histologically, KCOT typically displays a thin and friable wall. The cystic lumen may contain a clear liquid that is similar to a transudate of serum, or it may be filled with a cheesy substance that consists of keratinaceous debris. Inflammatory infiltrate is not a common finding in this cyst. The epithelial lining consists of a uniform layer of stratified squamous epithelium, usually six to eight cells in thickness. The epithelium-connective tissue interface is often flat and rete ridge formation is inconspicuous. Detachment of portions of the cyst-lining epithelium from the fibrous wall is usually observed. The luminal surface displays flattened parakeratotic epithelial cells, which present a wavy or corrugated appearance. The basal epithelial layer consists in a palisaded layer of cuboidal or columnar epithelial cells, which are often hyperchromatic. Small satellite cysts, cords, or islands of odontogenic epithelium may be observed within the fibrous wall. In case when there is an inflammatory process, the typical features of the KCOT may be changed.[14,15]

Histologically, KCOTs have been classified by some authors into parakeratotic and orthokeratotic subtypes. These types refer to the histologic characteristics of the lining and the type of keratin produced. Some pathologists think that the orthokeratotic subtype should be classified as a separate entity and termed orthokeratotic odontogenic cyst, because of its distinct histological features and substantially less aggressive behavior.[16] There is no clinical evidence to support, such a differentiation and recent trends indicate that with the lesion being diagnosed as a tumor rather than a cyst the treatment is aggressively directed to prevent recurrences.

The present case was rather unusual in that the maxillary involvement was quite extensive and there was a hint clinically and radiologically of involvement of the maxillary sinus. This was disproved surgically and confirmed by the absence of sinus lining in the histology. In a report on a KCOT in the maxilla associated with an unerupted malformed tooth the cyst lining showed metaplastic changes to pseudostratified ciliated columnar cells and areas bordering the nasal cavity had frank respiratory lining.[17]

KCOT as Neoplasm

In 1967, Toller[18] suggested that the KCOT may best be regarded as a benign neoplasm rather than a conventional cyst based on its clinical behavior. In 1984, Ahlfors[19] suggested that:

'KCOT should be recognized as a true, benign cystic epithelial neoplasm'. Currently, the WHO[2] has reclassified

Table 1: Comparative analysis of various parameters assessed for determining neoplastic potential of KCOTs and comparison with other lesions

Examination parameter	*Comparative analysis vis-á-vis other lesions*			
	OKC/KCOT	*Other cysts*	*Odontogenic tumors*	*Other lesions (inc dental lamina)*
Growth parameters Mitotic value of epithelium[20]	0-19 (mean 8.0)	2.3 (nonodontogenic cysts) 4.5 (radicular cysts)	Similar to ameloblastoma	Similar to dental lamina
Mean labeling indices[21] (using tritiated thymidine by autoradiography on tissue culture media)	13%	1.7%	NA	7.0% (human buccal mucous membrane)
Proliferating pattern of epithelium and connective tissue (using H_3-thymidine)[22]	4.5 cells per mm^2	0.51 cells per mm^2 (radicular cyst)	NA	NA
	More irregular (in groups and clusters)	More homogeneous	NA	NA
Molecular studies enzymes				
Oxidative enzymes (NADH2- and NADPH2-diaphorase, glucose-6-phosphate, dehydrogenase, glutamate dehydrogenase)[23]	Well-defined strong cytoplasmic activity through the full thickness of epithelium, particularly strongly in the basal layer	Uneven and consistently weaker enzyme reactions	NA	NA
Acid phosphatase[23]	Strong	Weak	NA	NA
Leucine aminopeptidase[23]	Strong	Weak		
ATP-ase[23]	Strong	Weak	NA	NA
Quantitative estimation of other dehydrogenases (succinate, lactate, glutamate, glucose-6-phosphate, glycerophosphate)[24]	G6PD levels 1.49-3.49 times higher Lactate dehydrogenase levels lower Others same	1 LD levels higher Others same	NA	NA
Lactoferrin[25]	Higher (but inconsistent)	Lower	NA	NA
Keratocyst antigen[26]	Detected; related to keratin (but no follow-up papers)	Undetected	NA	NA
Blood group antigen[27]				
A	+ve	+ve	-ve	NA
B	+ve	+ve	-ve	NA
H type 2	+ve	+ve	-ve	NA
N-acetyl lactosamine	-ve	+ve	-ve	NA
Keratocyst markers Soluble protein levels[28] Smear from aspirated cyst fluid (stained by rhodamine autofluorescence)[29]	<4.0 gm/100 ml keratin squames	>5.0 gm/100 ml absent	NA	NA
Resorption parameters				
Collagenase[30]	High	Low	NA	NA
1L-1α	High	Low	NA	NA
1L-6	Inconclusive	High	NA	NA
TNF	Inconclusive	High	NA	NA
MMP-9[32]	High	Low	NA	NA

Contd...

Contd...

Width of collagen fibers in cyst wall[33] (distribution)	Same	Same	Same	
Thin (0.8 μm or less)	Higher	Lower	Higher	NA
Thick (1.6-2.4 μm)				
Parathyroid hormone related protein (PTHrP)[34]	Higher	Lower	NA	NA
Generic studies				
Gp38[35]	+ve only in parakeratinized variety	-ve	-ve	NA
p53[36,37]	+ve	-ve	NA	NA
Ki-67[38]	+ve/higher	+ve/lower	NA	NA
PCNA[39]	+ve (more in inflamed cysts)	-ve	+ve/highest	NA
AgNORs[40]	+ve (mostly in inflamed cysts)	+ve (weakly)	NA	NA
Bcl-1[41]	+ve in syndromic OKC -ve in sporadic OKC	NA	NA	NA
Bcl-2[41]	+ve	NA	NA	NA
PTCH[41]	Inactivated in syndromic cases	NA	NA	N A
Cytokeratin markers				
CK 8[42]				
CK 5/6[42]	Higher	Higher	Higher	
CK 7[42]	>RC	>RC and OKC	<DC	
CK 10[42]	Higher	<OKC	<DC	
CK 13[42]	<DC and RC	>OKC	>DC	
CK 17[42]	Higher	<RC	<OKC	
CK 19[42]	Almost absent	DC = RC +	RC = DC	Higher[1]
Podoplanin[43,44]	++ in KCOTs + in OOCs	in DCs only associated with inflammation		
Laminin-5[45]	Higher	Higher	Higher	
MMP-8[45]	Nil	Higher	Nil	
MMP-2[45]	Higher	Less, RC = DC	Less, RC = DC	
MMP-13[45]	Higher	<RC	>DC	
Perlecan[46]	Higher	Nil	NIl	
S100	Almost absent	<RC	>DC	

the lesion as an odontogenic tumor. Several factors form the basis of this decision. Table 1 presents an overview of most factors assessed in OKC (KCOT) gleaned from literature and its comparison with other odontogenic and oral tissues to support this view.

Behavior

The lesion is well established as locally destructive and highly recurrent. The statistical figures indicate that the behavior is more akin to tumors than to odontogenic cysts.[10,11]

Parameters assessed for aggressive behavior include collagenase, interleukin-6 (IL-6), interleukin-1alpha (IL-1a), tumor necrosis factor (TNF) and matrix metalloproteinase-9 (MMP-9). Both collagenase and IL-1a were found to be consistently high in KCOTs as compared with other cysts and odontogenic lesions. The results for the other factors were generally inconclusive.

Histopathology

Histological parameters which have prompted the inclusion of this lesion as a tumor include: (1) Frequent budding of basal cells into the connective tissue, (2) common presence of satellite cysts with features of independent potential for development, (3) a high mitotic index of epithelial cells in the range observed in tumors, (4) more growth potential of epithelial cells as indicated by thymidine labeling of cyst epithelial cells grown in tissue culture (indices are almost double that of normal epithelium and about 7 times more than that of odontogenic cysts).

The mitotic index of KCOT is similar to that of ameloblastoma and high compared to the other odontogenic cysts. This feature suggests the proliferative activity of epithelium of KCOT as a neoplasm similar to an ameloblastoma.[15] The proliferating pattern of KCOT was mainly in the basal and suprabasal cells of epithelium as marked with H3-thymidine, which showed a higher rate of

proliferation than the radicular cyst with a mean value of 4.5 proliferating cells per mm^2 compared with a mean value of 0.51 proliferating cells per mm^2 in the radicular cyst. It was also noted that proliferation of the epithelium and the connective tissue of the OKC was irregular and in clusters, not homogeneous. Further, it has been the type of growth mimicked by ameloblastoma corresponds to that of KCOT.[16] We suggest that the differential mode of growth of KCOT compared with other odontogenic cyst is because of high level of mitotic activity of KCOT epithelium, and non-homogeneous growth potential of KCOT epithelium can be due to the potent active cells differentiation at different site at a given time. Thus, these features drag OKC toward the odontogenic tumor category naming it as KCOT.

Antigenic Expression

Keratocyst antibody (KCA) antigen was isolated by a double antibody fluorescence technique from the cystic fluid of KCOTs that was found localized to epithelial cells. This was not present in the other cysts. It was suggested that the keratin might become soluble in the cyst fluid by proteolysis and that the relationship of keratin and KCA would enable the use of commercially available antikeratin antibodies in the preoperative diagnosis of the KCOT. Surprisingly no follow-up studies were noted in the literature.[16] We strongly feel that use of antikeratin antibody could be beneficial for the diagnosis of KCOTs.

Blood group antigen A, B and H type-II were found to be expressed in sporadic KCOTs and other nonkeratinizing odontogenic cysts but negative in ameloblastomas.[16] Similar findings were observed in another study but the type of expression in follicular cyst and radicular cyst was different from that of KCOTs and none of the ameloblastomas expressed the antigens.[22] Other molecule, such as N-acetyl lactosamine was present in other odontogenic cysts but KCOTs and ameloblastomas failed to demonstrate the same.[16,22] It has suggested that these immunohistochemical findings can be used to distinguish cysts from tumors.

Toller stated that protein content of 4.0 gm/100 ml suggests OKC (KCOT) whereas above 5.0 gm/100 ml suggests radicular/dentigerous/fissural cysts.[3] Also the smears made from the cystic fluid when stained with rhodamine B fluorescence method demonstrated keratinized squames. Thus, it was suggested that both cytological assessment and protein estimation can be useful in predicting the occurrence of KCOT on aspirated samples.

Parathyroid hormone-related protein (or PTHrP) was found to be high in KCOTs compared with other odontogenic cysts.[16] This is a protein member of the parathyroid hormone family. It is occasionally secreted by cancer cells (breast cancer, squamous cell carcinoma). However, it also has normal functions. PTHrP is critical in the intraosseous phase of tooth eruption where it acts as a signaling molecule to stimulate local bone resorption.[24] Studies[25-27] have been shown that ameloblastomas express PTHrP showing the resorption property and infiltrative behavior. This concept can explain the fact that the destruction caused by the KCOTs is more leading to expansion of the lesion suggesting their aggressive behavior.

GP38, an epithelial cell surface glycoprotein was expressed strongly in parakeratinized KCOTs. The expression was negative in KCOTs that were associated with the NBCCS and orthokeratinized KCOTs. Interestingly, a strong positive expression was seen in basal cell carcinoma (BCC). Dentigerous cysts also showed negativity, however positivity was observed in reduced enamel epithelium. It was also noted that ameloblastomas were negative for the reaction. Strong reaction in parakeratinized KCOTs suggested an alteration in gene expression that is also observed in BCCs but not in normal tissues and it was felt that this might support the view that the OKC (KCOT) had neoplastic potential.[28] Another study[29] showed similar results and suggested GP38 can be used to differentiate between the two varieties (parakeratinized and orthokeratinized). It has been suggested that whenever, there is loss of classic features of KCOTs due to inflammation this molecule may play a diagnostic role and differentiate aggressive (parakeratinized) and less aggressive (orthokeratinized) KCOTs.

Molecular and Enzyme Studies

A host of enzymes have been assayed in KCOT and almost all studies show significantly higher levels as compared with other odontogenic cysts. Wherever, assessments have been done in comparison on normal oral epithelium and other odontogenic tumors most values show a range as seen in odontogenic tumors. Some of the enzymes assayed have been oxidative enzymes like NADH2- and NADPH2-diaphorase, glucose-6-phosphate dehydrogenase and glutamate dehydrogenase, acid phopshatase, leucine aminopeptidase, ATP-ase and lactoferrin.

Oxidative enzymes are the enzymes that catalyze the oxidation reaction using molecular oxygen to produce the ATPs in higher rate. Comparing the oxidative enzymes (NADH2- and NADPH2-diaphorase, glucose-6-phosphate dehydrogenase, glutamate dehydrogenase) with KCOT and other odontogenic cysts it was noted that strong reaction of these enzymes in the basal layer compared with other odontogenic cysts. The result for acid phosphatase was similar. It was suggested that incomplete removal of KCOT lining leads to high metabolic activity of the epithelium

demonstrated by high activity of oxidative enzymes representing glycolytic, citric acid and pentose-phosphate shunt mechanisms that may be likely factors for its high recurrence rate.[16] We agree and suggest that as the enzymes are biologically active substances that act substantially in well-coordinated manner catalyzing the reaction in forwarded manner provided suitable microenvironment as oxidative enzymes. A study[17] explains the high angiogenesis (mean microvascular density) in KCOT compared with dentigerous cyst. As angiogenesis is one of the crucial factor playing a dynamic role in neoplasms this might be the reason why the epithelium of KCOT grows readily with the help of these highly supportive oxidative enzymes and these two factors may be the reason for its recurrence potential.

Leucine aminopeptidase (LAP) is an exopeptidase that catalyzes the hydrolysis of amino acid residues, thus having a critical biological importance because of their role in protein degradation.[18] High level of this enzyme was noted in the fibrous capsule of KCOTs and may have the role of invasiveness by collagenolysis. Further the same enzyme is found expressed in other malignant tumors.[16] We suggest that LAP by their action (collagenolysis) loosen the capsule wall that help the proliferating epithelium to grow murally as there is less mechanical obstruction from the connective tissue capsule. This might be the reason why satellite cysts are formed by actively growing epithelium.

Glucose 6-P dehydrogenase (G-6-PD) is a cytosolic enzyme that helps to prevent the oxidative damage of erythrocytes through NADPH.[19] These levels were higher in KCOTs which is consistent with the clinical behavior. Also lactate dehydrogenase was found to be higher in radicular cysts than KCOTs describing the anaerobic conditions likely to be associated with the extensive inflammatory cell infiltrates and tissue necrosis.[16] Thus, it can be noted that the G-6-PD protects the erythrocytes providing more oxygen to the oxidizing enzymes helping the epithelium to proliferate. In contrast, the same enzyme is not or least expressed in other odontogenic cysts, hence there is no proliferation. The absence of lactate dehydrogenase in KCOT explains why there is no inflammation in KCOT normally except when it is secondarily infected.

Lactoferrin is a protein belonging to transferrin family and is one of the components of the immune system of the body and has antimicrobial activity.[20] KCOT cystic fluid expressed less quantity of lactoferrin compared to the dentigerous cyst and radicular cyst. It was suggested that the least or none lactoferrin in the lumen describes the impermeable nature of the KCOTs epithelium to neutrophils.[16] Another study also shows similar results.[21] It can be noted here that the resistance caused by the KCOTs is may be mainly because of its thickness and the superficial parakeratinization. This can also be due to the fact that the usual presentation of KCOTs is devoid of inflammation.

It has been shown that collagenase degraded the type-I and type-II collagen of KCOT capsule compared with the radicular cysts which showed lower rate of destruction. However, at the same time the type-III collagen was not affected significantly.[16] Collagenases are enzymes that break the peptide bonds in collagen.[23] This may be the one of the causes for the expansion of the KCOT capsule. Evaluation of the width of collagen fibers suggested that the collagen of the wall was loosely packed and might be composed of procollagens, intermediates or pathologic collagens rather than the tightly packed fibers as in the other cyst types. In contrast, this pattern had also been demonstrated in odontogenic tumors speculating that the stroma of the OKC could possibly be regarded not just as structural support, but also as playing a part in their neoplastic behavior.[16] This may be true as the collagenase degrades the collagen type-I and type-II; the wall is loosely packed with fibers. Further the collagen component in odontogenic tumors is not densely packed, thus the pattern of collagen arrangement can be used as differentiating factor between odontogenic tumors and odontogenic cysts using special stains like picrosirius red stain.

Genetics

p53 is a tumor suppressor protein that in humans is encoded by the TP53 gene. It regulates the cell cycle by functioning as tumor suppressor that is involved in preventing cancer. Thus, it has been described as 'the guardian of the genome', referring to its role in conserving stability by preventing genome mutation.[30] Normally, p53 is not detected immunohistochemically because of short life but p53 protein that is produced by mutation of p53 gene is detectable. Many of the neoplasms are positive for p53 protein. It has been shown that KCOTs express p53 suggesting their neoplastic nature.[31]

Proliferating cell nuclear antigen (PCNA) is a marker of cell replication and is also associated with DNA repair process and stimulation by growth factors. A strong positivity was observed in KCOTs compared with dentigerous cysts and radicular cysts. Interestingly ameloblastomas had stronger positivity than KCOTs.

PTCH 'patched', a tumor suppressor gene involved in both NBCCS and sporadic KCOTs, occurs on chromosome 9q22.3-q31.36-40 normally, PTCH forms a receptor complex with the oncogene SMO 'smoothened' for the SHH 'sonic hedgehog' ligand. PTCH binding to SMO inhibit

growth-signal transduction. SHH binding to PTCH releases this inhibition.[41] If normal functioning of PTCH is lost, the proliferation-stimulating effects of SMO are permitted to predominate. Interestingly inactivation of PTCH was observed in KCOTs associated with NBCC syndromic cases. No studies were found in literature related to the expression of PTCH in nonsyndromic KCOTs.

Other Markers

Perlecan, a basement-membrane type heparin sulfate proteoglycan is found as an intraepithelial deposit in the epithelium of carcinoma in situs, odontogenic tumors and salivary gland tumors. Expression of perlecan was definitively demonstrated in the epithelium of KCOTs as compared with odontogenic cysts which showed no staining; supporting the neoplastic potential of the lesion.[46]

Downregulation of S100A8 protein was found in KCOTs as compared with normal expression in radicular and other odontogenic cysts. Such lack of expression is noted in carcinomas and odontogenic tumors and the authors strongly advise usage of this marker for odontogenic tumor differentiation.[47]

CONCLUSION

The reclassification of the odontogenic keratocyst as an odontogenic tumor has finally solved the piquant controversies on its aggressive behavior and penchant for recurrence. Adequate clinical, histologically, immunohistochemical and genetic data have been previewed before the change in nomenclature. Though treatment modalities are unlikely to change drastically overnight especially in face of opposition by patients (as in our case) the potential for aggressive growth and recurrence should certainly prompt the surgeon to be more radical in his approach than in the past.

REFERENCES

1. Philipsen HP. Om keratocyster (kolesteatom) i kæberne. Tandlaegebladet 1956;60:963-81.
2. Barnes L, Eveson JW, Reichart P, Sidransky D (Eds). Pathology and genetics of head and neck tumours. Lyon: IARC Press; WHO classification of tumours series, 2005.
3. Hauer A. Ein Cholesteatom im linken Unterkiefer unter einem retinierten Weisheitszahn. Zeitschrift fur Stomatologie 1926;24:40-59.
4. Kostecvka F. Ein Cholesteatom im Unterkiefer. Zeitschrift fur Stomatologie (Wien) 1929;27:1102-08.
5. Maurette PE, Jorge J, de Moraes M. Conservative treatment protocol of odontogenic keratocyst: A preliminary study. J Oral Maxillofac Surg 2006;64(3):379-83.
6. Browne RM. The odontogenic keratocyst: Clinical aspects. Br Dent J 1970;128(5):225-31.
7. Brannon RB. The odontogenic keratocyst. A clinicopathologic study of 312 cases. Part I. Clinical features. Oral Surg Oral Med Oral Pathol 1976;42(1):54-72.
8. Blanchard SB. Odontogenic keratocysts: Review of the literature and report of a case. J Periodontol 1997;68:306-11.
9. Angela C, Chia James R, Owings Jr, Susan Muller MS, Greenville SC. Peripheral odontogenic keratocyst: Report of two cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:71-78.
10. Sapp JP, Eversole LR, Wysocki GP. Contemporary oral and maxillofacial pathology. (2nd ed). St Louis: Mosby 2004:54.
11. Dominguez FV, Keszler A. Comparative study of keratocysts, associated and non-associated with nevoid basal cell carcinoma syndrome. J Oral Pathol 1988;17(1):39-42.
12. Çakur B, Miloglu O, Yolcu U, Goregen M, Gursan N. Keratocystic odontogenic tumor invading the right maxillary sinus: A case report. Journal of Oral Science 2008;50:345-49.
13. Kerr JT, Steger J, Sorensen D. Midline maxillary odontogenic keratocyst. Ann Otol Rhinol Laryngol 2004;113:9-12.
14. Neville BW, Damm DD, Allen CM, Bouquot JE (eds). Patologia oral and maxillofacial. (2nd ed). Rio de Janeiro, Guanabara Koogan, 2004.
15. Shear M, Speight P. Cysts of the oral and maxillofacial regions (4th ed). Oxford: Blackwell Munksgaard 2007:6-58.
16. Woolgar JA, Rippin JW, Browne RM. A comparative study of the clinical and histological features of recurrent and non-recurrent odontogenic keratocysts. J Oral Pathol 1987;16(3): 124-48.
17. Yamazaki M, Cheng J, Nomura T, Saito C, Hayashi T, Saku T. Maxillary odontogenic keratocyst with respiratory epithelium: A case report. Journal of Oral Pathology and Medicine 2003;32:496-98.
18. Toller PA. Origin and growth of cysts of the jaws. Annals of the Royal College of Surgeons of England 1967;40:306-36.
19. Ahlfors E, Larsson A, Sjogren S. The odontogenic keratocyst: A benign cystic tumor? Journal of Oral and Maxillofacial Surgery 1984;42:10-19.
20. Main DMG. The enlargement of epithelial jaw cysts. Odontologisk Revy 1970;21:29-49.
21. Toller PA. Autoradiography of explants from odontogenic cysts. British Dental Journal 1971;131:57-61.
22. Scharffetter K, BaIz-Herrmann C, Lagrange W, Koberg W, Mittermayer C. Proliferation kinetics-study of the growth of keratocysts. Journal of Cranio-Maxillo-Facial Surgery 1989;17:226-33.
23. Magnusson BC. Odontogenic keratocysts: A clinical and histological study with special reference to enzyme histochemistry. Journal of Oral Pathology 1978;7:8-18.
24. Mason GI, Matthews JB. In situ determination of different dehydrogenase activity profiles in the linings of odontogenic keratocysts and radicular cysts. Histochemical Journal 1996;28:187-93.
25. Douglas CWI, Craig GT. Recognition of protein apparently specific to odontogenic keratocyst fluids. Journal of Clinical Pathology 1986;39:1108-15.
26. Kuusela P, Hormia M, Tuompo H, Ylipaavalniemi P. Demonstration and partial characterization of a novel soluble antigen present in keratocysts. Oncodevelopmental Biology and Medicine 1982;3:283-90.
27. Vedtofte P, Pindborg JJ, Hakomori SI. Relation of blood group carbohydrates to differentiation patterns of normal and pathological odontogenic epithelium. Acta Pathologica

Microbiologica et Immunologica Scandinavica Section A 1985;93:25-34.
28. Toller PA. Protein substances in odontogenic cyst fluids. British Dental Journal 1970a;128:317-22.
29. Clausen FP, Dabelsteen E. Increase in sensitivity of the rhodamine B method for keratinization by the use of fluorescent light. Acta Pathologica et Microbiologica Scandinavica (A) 1969;77:169-71.
30. Uitto VJ, Ylipaavalniemi P. Alterations in collagenolytic activity caused by jaw cyst fluids. Proceedings of the Finnish Dental Society 1977;73:197-202.
31. Meghji S, Henderson B, Bando Y, Harris M. Interleukin-1: The principal osteolytic cytokine produced by keratocysts. Archives of Oral Biology 1992;37:935-43.
32. Kubota Y, Ninomiya T, Oka S, Takenoshita Y, Shirasuna K. Interleukin IL-1-dependent regulation of matrix metalloproteinase-9 (MMP-9) secretion and activation in the epithelial cells of odontogenic jaw cysts. Journal of Dental Research 2000;79:1423-30.
33. Hirshberg A, Sherman S, Buchner A, Dayan D. Collagen fibres in the wall of odontogenic keratocysts: A study with picrosirius red and polarizing microscopy. Journal of Oral Pathology and Medicine 1999;28:410-12.
34. Li T, Browne RM, Matthews JB. Immunocytochemical expression of parathyroid hormone related protein (PTHrP) in odontogenic jaw cysts. British Journal of Oral and Maxillofacial Surgery 1997;35:275-79.
35. High AS, Robinson PA, Klein CE. Discrimination of parakeratinised odontogenic keratocysts from other odontogenic and non-odontogenic cyst types by expression of a 38kd cell-surface glycoprotein. Journal of Oral Pathology and Medicine 1993;22:363-67.
36. Ogden GR, Chisholm DM, Kiddie RA, Lane DP. p53 protein in odontogenic cysts: Increased expression in some odontogenic keratocysts. Journal of Clinical Pathology 1992;45:1007-10.
37. Li TJ, Browne RM, Prime SS, Paterson IC, Matthews JB. p53 expression in odontogenic keratocyst epithelium. Journal of Oral Patholgy and Medicine 1996;25:245-55.
38. Li T, Browne RM, Matthews JB. Epithelial cell proliferation in odontogenic keratocysts: Immunocytochemical study of Ki67 in simple, recurrent and basal cell naevus syndrome (BCNS)-associated lesions. Journal of Oral Pathology and Medicine 1995;24:221-26.
39. Li T, Browne RM, Matthews JB. Quantification of PCNA+ cells within odontogenic jaw cyst epithelium. Journal of Oral Pathology and Medicine 1994;23:184-89.
40. de Paula AMB, Carvalhais JN, Domingues MG, Barreto DC, Mesquita RA. Cell proliferation markers in the odontogenic keratocyst: Effect of inflammation. Journal of Oral Pathology and Medicine 2000;29:477-82.
41. Lo Muzio L, Staibano S, Pannone G, et al. Expression of cell cycle and apoptosis-related proteins in sporadic odontogenic keratocysts and odontogenic keratocysts associated with the naevoid basal cell carcinoma syndrome. Journal of Dental Research 1999;78:1345-53.
42. Stoll C, Stollenwerk C, Riediger D, Mittermayer C, Alfer J. Cytokeratin expression patterns for distinction of odontogenic keratocysts from dentigerous and radicular cysts. J Oral Pathol Med 2005;34:558-64.
43. Gonzalez-Alva P, Tanaka A, Oku Y, et al. Enhanced expression of podoplanin in ameloblastomas. J Oral Pathol Med 2010;39:103-09.
44. Okamoto E, Kikuchi K, Miyazaki Y, et al. Significance of podoplanin expression in keratocystic odontogenic tumor. J Oral Pathol Med 2010;39:110-14.
45. Wahlgren J, Vaananen A, Teronen O, et al. Laminin-5 gamma-2 chain is colocalized with gelatinase-A (MMP-2) and collagenase -3 (MMP-13) in odontogenic keratocysts. J Oral Pathol Med 2003;32:100-7.
46. Tsuneki M, Cheng J, Maruyama S, Ida-Yonemochi H, Nakajima M, Saku T. Perlecan-rich epithelial linings as a background of proliferative potentials of keratocystic odontogenic tumor. J Oral Pathol Med 2008;37:287-93.
47. Iezzi G, Piattelli A, Rubini C, et al. S100A8 calcium-binding expression in radicular and dentigerous cysts and in keratocystic odontogenic tumors. Serbian Dent J 2008;55:81-87.

ABOUT THE AUTHORS

A Nagraja (Corresponding Author)

Reader, Department of Oral Pathology and Microbiology, KLE's Institute of Dental Sciences, Yashwanthpur Suburb, Tumkur Road, Yashwanthpur-560022, Bengaluru, Karnataka, India
e-mail: nagsdoc@gmail.com

Praveen S Anigol

Senior Lecturer, Department of Oral Pathology and Microbiology PMNM Dental College and Hospital, Bagalkot, Karnataka, India

Venkatesh Vishwanath Kamath

Professor and Head, Department of Oral Pathology and Microbiology Dr Syamala Reddy Dental College, Hospital and Research Centre Bengaluru, Karnataka, India

Krishnanand P Setlur

Reader, Department of Oral Pathology and Microbiology, Dr Syamala Reddy Dental College, Hospital and Research Centre, Bengaluru Karnataka, India