REVIEW ARTICLE

Odontogenic Keratocyst: An enigma in maxillofacial surgery

Ashish Sharma[1], Pranshu Chauhan[2], Sourav Kumar[2], Musaab Khan[2]Tushar Dubey[2],Shyamalendu Laskar[2]

Abstract

The classification of odontogenic cysts is complicated and can create confusion for both clinicians and pathologists. The odontogenic keratocyst (OKC) is an enigmatic developmental cyst that deserves special attention. It has characteristic histopathological and clinical features; but, what makes this cyst special is its aggressive behavior and high recurrence rate. Despite of many classifications and nomenclature, unfortunately the clinicians still have to face difficulties in the management of this commonly found jaw lesion. This article is an effort to provide an overview of various aspects of OKC with emphasis on nomenclature, recurrence, molecular aspects, and management of OKC.

Keywords: Classification, keratocystic odontogenic tumor, nomenclature, odontogenic keratocyst, odontogenic cyst, odontogenic tumors.

INTRODUCTION

In 2005, the World Health Organization renamed the lesion previously known as an odontogenic keratocyst as the keratocystic odontogenic tumor (KOT or KCOT).[1,2] The term odontogenic keratocyst was first used by Philipson in 1956, [3] and its clinical and histologic features were confirmed by Browne in1970 and 1971.[4,5] At that time, it was believed to be a benign, but potentially aggressive and recurrent, odontogenic cyst, and probably represented the lesion previously termed a primordial cyst.[6] Although most of these cysts were lined by parakeratinized epithelium, a few were orthokeratinized.

1. *Professor*
2. Postgraduate student
Department of Oral and Maxillofacial surgery
Corresponding author
Dr. Pranshu Chauhan
Postgraduate student
Department of Oral and Maxillofacial surgery
Kothiwal dental college and Research Centre
Moradabad
Chauhanpranshu1@outlook.com

Over the years, it has generally been agreed that the orthokeratinized versions have a lower incidence of recurrence than the para-keratinized version. As initially described, it was believed that the primitive nature of the epithelium may have a premalignant potential,[7]but this is now believed not to be true, and the incidence of malignant transformation is probably extremely low.[8]However, since its designation, some have believed that although it was designated as an Odontogenic cyst, the lesion behaved more like a tumor.[9–11] The reasons for this belief include its clinical behavior, with a high recurrence rate after simple enucleation, the histologic appearance, and more recently, the presence of tumor markers within the cyst.

These markers consist of specifically proliferating cell nuclear antigen(PCNA), Ki67, BCE 2 sequence of the enzyme dihydro-lipoyl acetyl transferase, matrix metalloproteinase(MMP) 2 and 9, and p53.[12–14] This combination of features led to the 2005 re-classification of this lesion.

In the recent World Health Organization classification of tumours of the head and neck, the name keratocystic odontogenic tumour (KCOT) has been changed again to odontogenic keratocyst (OKC). This decision has caused some confusion and has

regarding this potentially very aggressive lesion. Apart from the known tendency of OKCs to recur, their potential aggressiveness has been well documented by Emerson et al., who described the extension of two recurrent OKCs in the mediastinum, extended via the neck. Worral and Abe´ et al. reported OKCs penetrating into the temporalis muscle, while Makaria et al. and Yamamoto et al found the same in the masseter muscle. Liu et al. described a recurring OKC in an autogenous lyophilized bone graft, with extension into the masseter muscle. It is clear that extension into the soft tissues makes it very hard to remove this lesion in one piece. There will be a considerable risk of leaving some cells behind; thus, recur- rences are almost unavoidable. Jackson etal.[15,] Franc et al., and Soost et al. have described the extension of an OKC into the base of the skull. The potential danger of this phenomenon does not require further elaboration.

CAUSE

It is generally believed that these lesions originate from remnants of the dental lamina in the same way as the primordial cyst.[16] However, a tooth is generally not missing and, therefore, they are believed to originate from additional remnants of the lamina not involved in tooth formation. Alternatively, in some cases they may arise from the oral mucosa, particularly in the retromolar region, because daughter cysts are found between the oral mucosa and the cyst in the retromolar area.[17] Therefore, there may be 2 possible sites of origin of this lesion.

The presence of clusters of epithelial cell nests, also called basal cell hamartias[11], in a high percentage of OKCs, often accompanied by micro-cysts in the mucosa overlying the OKC, has been un-equivocally proven by Stoelinga et al. Over the last 50 years, numerous studies have been reported that show the high tendency for OKCs to recur after surgical treatment, be it marsupialization with or without secondary enucleation, with or without additional treatment, or even segmental resections. Five case reports have been published showing recurrent OKCs in a bone graft. The latter phenomenon almost proves that the source of some of these newly developing cysts is located in the mucosa covering the area where the OKC has been removed.

CLINICAL FEATURES

The clinical features associated with the KCOT show it to be a unilocular or multilocular radiolucency, occurring most frequently in the posterior mandible (the same site as the primordial cyst). It may or may not be associated with a missing tooth (usually not) (Fig. 2&3). Expansion of the buccal and lingual plates occurs late with this lesion (Fig. 4) (in contrast to the ameloblastoma), because it primarily tends to invade the marrow. However, it does cause some expansion of the lingual plate and can cause lingual plate perforation (Fig. 5).Inferior alveolar nerve involvement occurs late. Clinically, the lesion has a high recurrence potential if purely enucleated. Reports in the literature vary, but can show a recurrence rate of from 25% to 60% after local enucleation.[17–21] The reasons for this recurrence rate are believed to be 3-fold:

- They have a thin lining, which is friable, and portions are easily left behind.
- Daughter cysts occur beyond the visible margin of the lesion.

Some of these lesions may originate from the oral mucosa and daughter cysts are seen between the oral mucosa and the cyst itself. Unless these lesions are removed, recurrence is likely (Fig. 6).

The basal cell nevus syndrome (also called Gorlin syndrome or Gorlin-Goltz syndrome) is a genetic condition with an autosomal- dominant inheritance pattern that includes a triad of KCOTs of the jaws, other skeletal abnormalities (often including bifid ribs, abnormalities in the length of the fingers and toes, frontal bossing, and calcification of the falxcerebri), as well as cutaneous manifestations such as basal cell carcinomas, palmar pitting of the hands, and other skinabnormalities.[18,19]

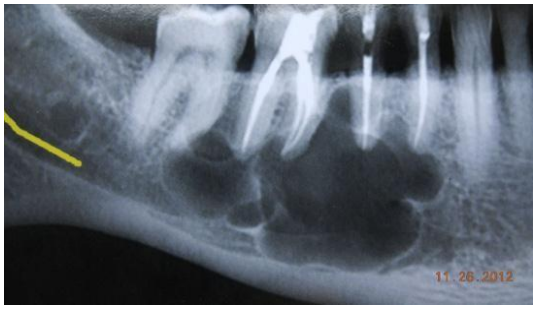

Fig. 2. A multilocular, multicystic KCOT of the right mandible not associated with a missing tooth. The complexity of the lesion contributes to difficulty intotal removal.

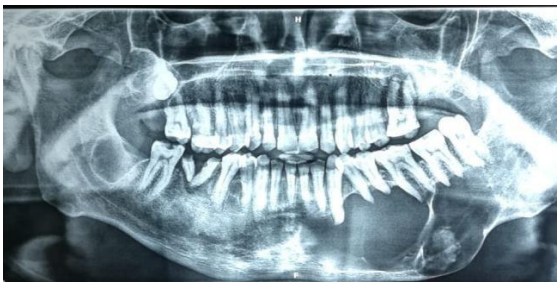

Fig.3Multilocular odontogenic keratocyst

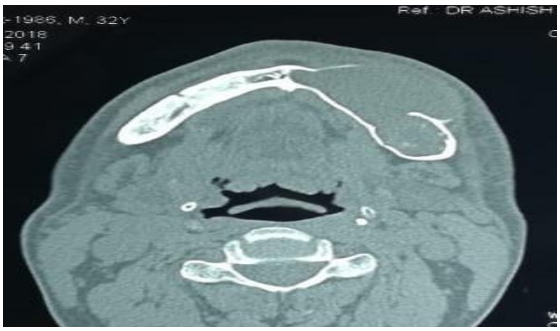

Fig.4 Axial view showing buccal and lingual expansion.

Renal abnormalities and medullo-blastomas in the newborn may also be manifestations of this condition. Whether sporadic or hereditary, most cases are related genetically and show aberrations in the hedgehog signaling pathway. The hedge hog signaling pathway involves a dynamic relationship between a series of tumor suppressor genes andoncogenes.

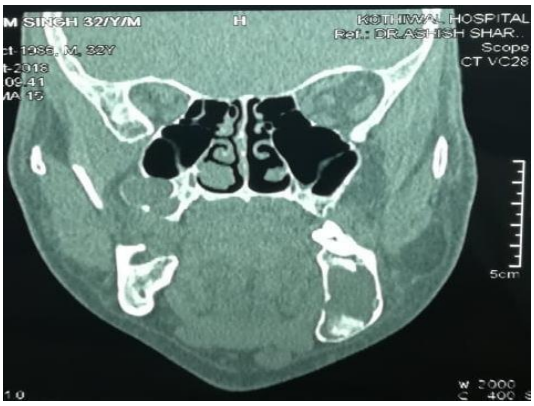

Fig. 5. A coronal cone-beam computed tomographyscan showing a multilocular, multicystic KCOT, withlingual perforation.

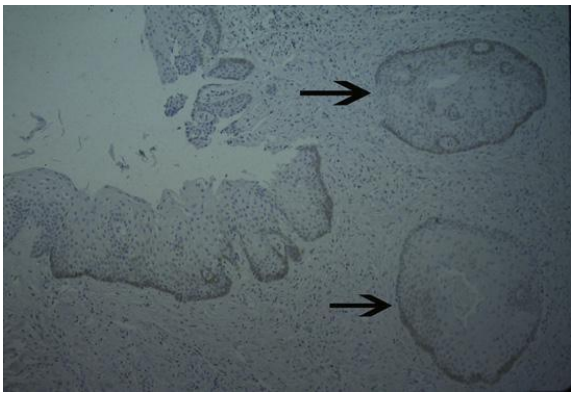

Fig. 6. Histologic specimen showing alveolar mucosa with daughter cysts (arrows) from KCOT between the alveolar mucosa and the cyst lining.

DIAGNOSIS

These tumors are normally diagnosed histologically from a sample of the lining. This diagnosis requires a surgical biopsy, and difficulties can arise when the cyst has been previously exposed or inflamed, when the lining tends to become thicker and less obviouslyparakeratinized.

Attempts have also been made to diagnose KCOTs from examination of a fluid aspirate. If subject to immediate histologic examination, keratin can often be seen under the microscope, and if the fluid is analyzed, the protein content (at <4.0 g/100 mL) is lower than that in serum (7.1 g/100 mL), which is also the protein content of a dentigerous cyst. It is also lower than that of an ameloblastoma, usually around5.5 g/100 m.[20]

TREATMENT

With simple enucleation, it seems that the recurrence rate may be from 25% to 60%. When treating the lesion as one would an ameloblastoma, including resection with 1- cm margins (this often necessitates a segmental resection), the recurrence rate can be virtually zero. However, this treatment may cause excessive morbidity. Therefore, although both of these techniques may be possible (simple enucleation in a patient with a limited life expectancy or segmental resection for a large lesion that has multiple cortical perforations),most of the search has been for an intermediate technique that gives an acceptable cure rate with an acceptable morbidity. Several of these techniques have beenproposed.

Marsupialization or Decompression

It was well known in the pre-antibiotic era that most dental cysts could be marsupialized and that this cured them. Marsupialization in its purest form consists of opening up the cyst to the oral cavity and suturing the cyst lining to the oral mucosa, creating a permanent opening into the cyst.

The cyst is, therefore, decompressed (most cysts grow by osmosis,[21] although the KCOT may also grow by bone resorption from prostaglandin production),[22] and decreases in size as new bone is laid down around it. This procedure was originally known as the Partsch I technique. With the advent of antibiotics, this technique was generally abandoned in favor of more definitive enucleation of dental cysts (the Partsch II technique).

However, the technique has been resurrected for the management of the KCOT. It is either used in its classic form of suturing the cyst lining to the oral mucosa or it is used more as a decompression technique, in which a smaller opening is made into the cyst, without suturing the liningand by useof a decompression tube of somekind.[23]

Enucleation with Peripheral Ostectomy

If one accepts that the high recurrence rate after simple enucleation is caused by the presence of retained fragments of lining plus daughter cysts that are left behind, then it may be that removal of 1 to 2 mm of bone beyond the visible margin of the lesion is of the lesion is adequate to improve the cure rate. However, it is difficult to estimate how much bone to remove with a drill. This process is made easier by the use of a vital staining technique.

Methylene blue or crystal violet (or any other vital stain) can be painted on the bony walls of the enucleated cyst and allowed to penetrate into the bone. The cavity is then washed out and any bone retaining the stain is removed with a drill . This process usually removes around 2mm of bone in the marrow and about 1 mm of corticalbone.

Physico-chemical Treatment

Chemical treatment with Carnoy solution The only chemical agent in use to increase the cure rate of the KCOT is Carnoy solution, and this remains controversial. Originally used as a histologic fixative, it has been used clinically. Its classic ingredients are as follows:

Absolute alcohol: 6 mL
Chloroform: 3 mL Ferric chloride: 1 g
Glacial acetic acid: 1 mL

The most usual technique involves enucleation of the lesion followed by painting the sides of the cavity with Carnoysolution, leaving it in place for 5 minutes, and then washing out the cavity. After washing out, the cavity has brown, denatured bone on its wall. Some practitioners leave this bone in place, whereas others remove it with adrill to get down to normal bone. This technique generally involves a removal of 1 to 2 mm of bone. Carnoy solution is neurotoxic and chemically fixes the inferior alveolar or lingual nerves if it comes in contact with them for up to 2 minutes. The nerve should therefore be protected; bone wax can be used for protection of the inferior alveolar nerve.[34]

Physical treatment with cryotherapy

Freezing is known to cause cell death. However, to cause cell death (as in frostbite), freezing must be rapid and thawing should be slow, and temperatures less than –20_C must be achieved. The only commonly available agent that can achieve this temperature is liquid nitrogen, which boils at–196_C. Carbon dioxide and nitrous oxide both boil at temperatures high enough (–78.5_C and–89.7_C, respectively) that they cannot maintain–20_C consistently, particularly if there is any heat sink effect caused by adjacent blood vessels. The technique using liquid nitrogen involves enucleation of the lesion followed by protection of the soft tissues with a combination of wooden tongue blades and dry gauze followed by treatment of the cyst cavity with the liquid nitrogen(Fig.11)

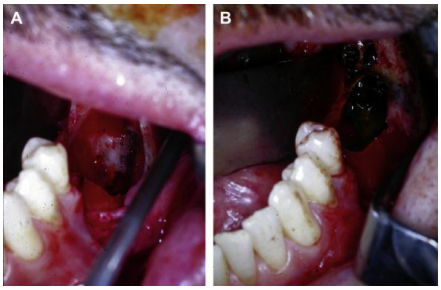

Fig. 10. (A) A KCOT of the left mandible enucleated. (B) The cavity subsequently treated with Carnoy solution.

Note the brown appearance of the treated bone, which is often removed with a pineapple bur.

Fig. 11. A typical portable liquid nitrogen cryospray.The technology can also be used with a probe.

Resection

A recurrent odonogenickeratocyst should be treated more aggressively than a primary lesion. Therefore, resection is performed, the margins should extends beyond the greatest limits of either the primary or the recurrent cyst. If cortical perforation is encountered , resection of the soft tissue to the next anatomic boundry is warranted.

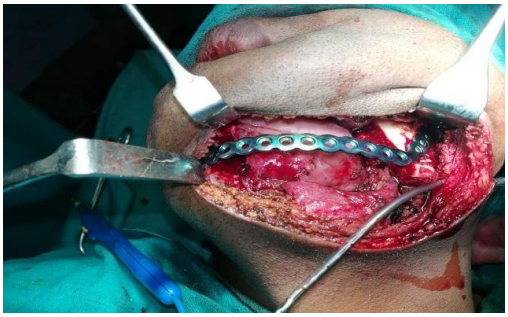

Fig .12 segmental resection of left mandible.

Future modalities

Due to the recent advances and thus determination of molecular basis of this entity, a new novel methodology concentrating on molecular aspects has been devised. The Hh pathway can be blocked at different levels, and Hh inhibitors could serve as attractive antitumor agents. According to some studies, cyclopamine, a plant-based steroidal alkaloid, blocks activation of SHh pathway caused by

oncogenic mutation. Other studies also show antagonists of SHh signaling factors could effectively treat KOT.[25-28]

CONCLUSION

So the whole process of classifying and renaming the odontogenic cysts and tumors continues as the understanding of these lesions takes a giant leap in its stride. So what is there in a name? A rose is a rose, whatever you call it. This concept is certainly not correct when it comes to OKC/KOT. There is as yet no international consensus, either on the question of the cyst's neoplastic nature, or on a name change.

A famous oral surgeon "Gordon Hardman" was quoted saying "We always knew some cysts recurred so the patient came to have them curetted out every 5-10 years. So what, we never had to give them separate names."[38]This attitude of the surgeons overlooking the multiple recurrences has always been suppressing the concept of reclassifying these lesions (favorite work of the pathologists).The controversies over the nature of OKC are in fact a reflection of our limited knowledge of this fascinating entity.[39] The term "odontogenic keratocyst" is so engraved in the literature only time can tell us whether the term "keratocystic odontogenic tumor" can substitute this term successfully or not. Recent advances in genetic and molecular understanding have led to eventually eliminate the need for aggressive treatment modalities. This article is in a hope to suggest that the naming of OKC as a benign tumor allows the surgeon to tailor their treatmentaptly.[29]

REFERENCES

1. Philipsen HP. In: Barnes L, Eveson JW, ReichartP,et al, editors.World Health Organization classification of tumours. Pathology and genetics of head and necktumours. Lyon (France): IARC; 2005. p.306–7.

2. Reichart PA, Philipsen HP, Sciubba JJ. The new classification of head and neck tumours (WHO)–any changes? Oral Oncol2006;42:757.

3. Philipsen HP. OM Keratocyster (Kolesten-Tomer).1Kaeberne. Tandialgebladet 1956;60:963 [in Danish].

4. Browne RM. The odontogenickeratocyst. Clinical aspects. Br Dent J1970;128:225.

5. Browne RM. The odontogenic keratocyst. Histological featuresand their correlation with clinical behaviour.Br Dent J 1971;131:249.

6. Partridge M, Towers JF. The primordial cyst
7. (odontogenickeratocyst): its tumour- like characteristics and behaviour. Br J Oral MaxillofacSurg 1987;25:271.
8. Browne RM, Gough NG. Malignant change in the epithelium lining Odontogenic cysts. Cancer 1972;29:1199.

9. Anand VK, Arrowood JP Jr, Krolls SO. Malignant potential of the odontogenic keratocyst. Otolaryngol Head Neck Surg1994;111:124.

10. Shear M. The aggressive nature of the odontogenic keratocyst: is it a benign cystic neoplasm? Part 3.Immunocytochemistry of cytokeratin and otherepithelial cell markers. Oral Oncol2002;38:407.

11. Shear M. The aggressive nature of the odontogenic keratocyst: is it a benign cystic neoplasm? Part 2.Proliferation and genetic studies. Oral Oncol2002;38:323.

12. Shear M. The aggressive nature of the odontogenic keratocyst: is it a benign cystic neoplasm? Part 1.Clinical and early experimental evidence of aggressivebehaviour. Oral Oncol 2002;38:219.

13. Slootweg PJ. p53 protein and Ki-67 reactivity in epithelial odontogenic lesions. An immunohisto chemicalstudy. J

Oral Pathol Med 1995;24:393.

14. Barreto DC, Gomez RS, Bale AE, et al. PTCH gene mutations in odontogenickeratocysts. J Dent Res2000;79:1418.

15. Cohen MM Jr. Nevoid basal cell carcinomasyndrome: molecular biology and new hypotheses.Int J Oral MaxillofacSurg 1999;28:216.

16. Bhargava D, Deshpande A, Pogrel MA. Keratocysticodontogenictumour (KCOT)–a cyst to a tumour. OralMaxillofacSurg 2012;16(2):163– 70.

17. Stoelinga PJ. Long-term follow-up onkeratocysts treated according to a defined protocol. Int J OralMaxillofacSurg 2001;30:14.

18. Vedtofte P, Praetorius F. Recurrence of the odontogenickeratocyst in relation to clinical and histologicalfeatures. A 20- year follow-up study of 72patients. Int J Oral Surg1979;8:412.

19. BrannonRB.The odontogenickeratocyst. A clinicopathologicstudy of 312 cases. Part I. Clinicalfeatures. Oral Surg Oral Med Oral Pathol1976;42:54.

20. Pindborg JJ, Hansen J. Studies on odontogenic cystepithelium.2.Clinical androentgenologic aspects ofodontogenickeratocysts. ActaPatholMicrobiolScand 1963;58:283.

21. RudJ, Pindborg JJ. Odontogenic keratocysts:a follow-upstudyof21cases. JOralSurg1969;27:323.

22. Guthrie D, Peacock ZS, Sadow P, et al. Preoperative incisional and intraoperative frozen section biopsy techniques have comparable accuracy in the diagnosis of benign intraosseous jaw pathology. J OralMaxillofacSurg 2012;70(11):2566–72.

23. Scully C, Langdon J, Evans J. Marathon ofeponyms; 7 Gorlin-Goltz syndrome (naevoidbasalcell carcinoma syndrome). Oral Dis2010;16:117–8.

24. Todd R, August M. Molecular approaches to the diagnosis of sporadic and naevoid basal cell carcinomasyndrome-associated Odontogenic keratocysts.OralMaxillofacSurgClin North Am2003;15:447–61.

25. Toller PA. Protein substances in Odontogenic cyst fluids. Br Dent J 1970;128:317.

26. Toller PA. The osmolality of fluids from cysts of thejaws. Br Dent J 1970;129:275.

27. Harris M.Odontogenic cyst grow than dprostaglandin induced bone resorption. Ann R CollSurgEngl1978;60:85.