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REVIEW

Keratocystic odontogenic tumor: a review

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Abstract The odontogenic keratocyst is a very well known odontogenic cyst. There are many types of cysts of the jaws, but what makes the odontogenic keratocyst unusual are its characteristic histopathological and clinical features, including potentially aggressive behaviour, high recurrence rate, and an association with the nevoid basal cell carcinoma syndrome. The characteristic histologic feature i.e. the presence of parakeratin, is unique amongst all the different inflammatory and developmental cysts that occur in the jaws. Many treatment modalities have been advocated for its treatment, but none in particular has been regarded as the best treatment option. The 2005 WHO classification now uses the term 'keratocystic odontogenic tumor'. We present a review of treatment modalities of the KCOT.

Keywords Odontogenic tumor · Cyst

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Introduction

Ever since Philipsen in 1956 first described a cyst of the jaws lined by keratinizing epithelium which was known as odontogenic keratocyst, surgeons have been toiling to find an ideal treatment for it. The knowledge regarding the treatment of the odontogenic keratocyst, now renamed as the Keratocystic Odontogenic Tumor (KCOT) [51], has been ever increasing over the past few decades, and yet, the issue is still a debate in oral and maxillofacial surgery. Various treatment modalities have been tried for the successful treatment of the KCOT, ranging from simple enucleation to resection, but none has been regarded as the ideal treatment. The KCOT behaves like a tumor in many ways, for e.g. involvement of large areas of the bone, high recurrence rate, distinctive histopathological features of the lesion, disregulation of the PTCH (patched) gene in both Nevoid basal cell carcinoma syndrome associated and sporadic odontogenic keratocysts, etc. On the other hand, successful treatment by marsupialization denies its tumor characteristics. Truly, cases of carcinoma arising in KCOT have been reported [1,2]. In fact, recurrence of the lesion has been reported in a bone graft [3]. In this article, we present a review of treatment modalities of the KCOT.

Discussion

Mikulicz in 1876 first described the KCOT as a part of a familial condition affecting the jaws, but the term odontogenic keratocyst was first introduced by Philipsen in 1956. In 1960, Shear [4] stated that, 'in most respects, the diagnosis of primordial cysts is of academic importance only. They are entirely simple in nature and will not recur if enucleated. Since then, a wide range of treatment modalities have been put forward for its treatment.

Eyre and Zakrzewska [5] in 1985, have stated the following treatment options for the KCOT -

1. Enucleation:
   - with primary closure
   - with packing
   - with chemical fixation
   - with cryosurgery
2. Marsupialization:
   - only
   - followed by enucleation
3. Resection:

Bramley [6], in 1971, proposed a treatment plan for the keratinising cystic odontogenic tumor due to its tendency to recur. He suggested:

1. Unilocular cysts to be treated by intra-oral resection.
2. In areas of difficult access, decompression and secondary enucleation is advocated.
3. Large multilocular cysts should be treated by resection and primary bone graft.

In a systematic review of the treatment and prognosis, Blanas et al. [7] in 2000, have concluded that a simple enucleation results in an unnecessarily high recurrence rate when treating the KCOT. For a routine KCOT in a person who is likely to return for a follow-up treatment, Carnoy's solution appears to be the least invasive procedure with a lowest recurrence rate. If the lesion is very large, decompression of the cyst followed by enucleation will also have a low recurrence rate. Use of Carnoy's solution should also be considered at the enucleation stage. If the patient is unlikely to return for follow-up, the lesion should be resected.

Bradley and Fischer [8], in 1975, have described the combined enucleation and cryosurgical treatment of the KCOT. Webb and Brockbank [9] in 1984, have presented the treatment of the KCOT of the mandible using a combination of enucleation and

cryosurgery. They have followed up the case for 5 years and have found no recurrence. They suggest that cryosurgery, as an adjunct to enucleation, may prove to be a conservative and reliable method of treatment with a low recurrence rate.

Recurrence of the KCOT ranges from 2.5% [11,12] to 62% [10,12]. Different studies show different recurrence rates (Table 1). The possible mechanisms of recurrence have been described by Voorsmit et al. [11] in 1981. These state that any lining epithelium left behind in the oral cavity may give rise to a new lesion formation. Daughter cysts, microcysts or epithelial islands can be found in the walls of the original cysts. New KCOTs may develop from epithelial offshoots of the basal layer of oral epithelium [12].

Both conservative approach as well as aggressive approach has been advocated for the treatment of the KCOT. Conservative approach, however, has not gained much popularity, because complete removal of the KCOT can be difficult because of the thin friable lining, limited surgical access, skill and experience of the surgeon, and desire to preserve adjacent vital structures. The goals of treatment should involve eliminating the potential for recurrence while also minimizing the surgical morbidity [13,14,15].

Enucleation followed by chemical cauterization using Carnoy's solution along with excision of overlying attached mucosa has been used for the treatment of KCOT. Stoelinga [16] in 2001 has concluded in a long term follow up study that this method gave rise to a fairly low number of recurrences. Peripheral ostectomy combined with carnoy's solution may give nil recurrence rate [15]. In our experience, we have treated a series of five patients by enucleation followed by chemical cauterization. All the cases radiographically show a complete resolution of the lesion (Figs. 1, 2, 3 and 4). The patients are still under periodic observation in our institute, and show no signs of recurrence at present. A strict follow up protocol, which allows for early surgical intervention in case of recurrence, limits the extent of second surgery and thus, gives rise to less morbidity. It seems likely that offshoots of the basal layer of the epithelium of the oral mucosa are a major cause for the development of some KCOT and some recurrences.

Resection of the lesion supposedly gives the least recurrence rate out of all treatment modalities. Bataineh and Al Qudah [17] in 1998 have advocated resection without continuity defects as a radical treatment, in which removal of the cyst, teeth and the overlying soft tissue is followed by packing of the resulting cavity to minimize the risk of recurrence.

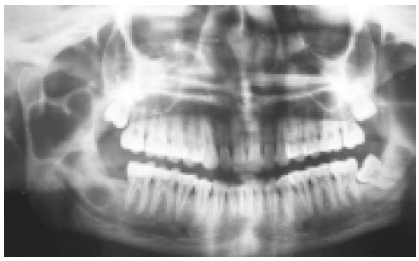

Fig. 1 Preoperative radiograph

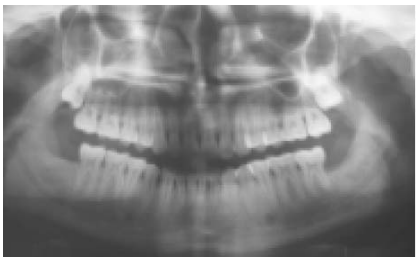

Fig. 2 Postoperative radiograph (6 months)

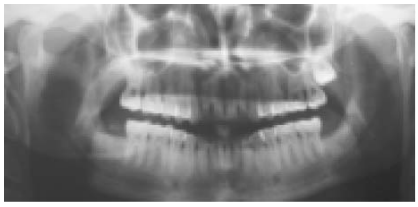

Fig. 3 Postoperative radiograph (12 months)

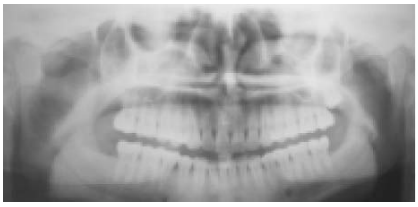

Fig. 4 Postoperative radiograph (17 months)

Nakamura et al. [18] in 2002 have stated that Marsupialization, as well as decompression, has the purpose of relieving the pressure within the cystic cavity and allowing the new bone to fill the defect. It, consequently, saves the contiguous structures such tooth roots, the maxillary sinus or the inferior alveolar canal can be saved from surgical damage. They have concluded in their study that marsupialization was highly successful in reducing the size of the KCOT before surgery. It was more effective in the mandibular body than the ramus region. It did not adversely affect the recurrence tendency. The characteristics of the KCOT may become less aggressive during the course of marsupialization.

Some authors have advocated marsupialization as a viable treatment for the KCOT [19,20]. Pogrel and Jordan [20,21] in 2004, have treated 10 KCOTs by marsupialization, and they found out that all the 10 KCOTs resolved completely with this form of treatment alone. Their study also suggested that the cyst lining may get replaced by normal epithelium during this treatment.

According to Stoelinga [16,22], complete elimination of recurrences is probably not possible for two reasons. First, some cysts are still treated like ordinary odontogenic cysts because a preoperative diagnosis was not made and the cysts were not treated according to the suggested protocol. Second, despite excision of the overlying mucosa there may still be epithelial islands or even microcysts left behind in the mucosa, which develop into a new KCOT.

Sometimes the KCOT may mimic the appearance of an endodontic lesion. In a case reported by Pace R et al. [23] such a lesion was successfully treated by complete enucleation and application of Carnoy's solution. At 2-year follow-up, no clinical signs or symptoms were found and the lesion had disappeared radiographically. Rai S and Gauba K [24] have successfully treated a case of jaw cyst bifid rib basal cell nevus syndrome. Cystic changes can arise in relation with unerupted lower third molars. Chye CH and Singh B [25] have described a case of a large KCOT which developed rapidly and aggressively over a short period of 2 years and presented with acute symptoms. The KCOT was enucleated and the residual cavity was treated with Carnoy's solution. Kumar M, Bandtopadhyay and Thapliyal GK [26] have reported a case of a KCOT occurring in the anterior mandible, an uncommon site, with the lesion crossing the midline being a unique occurrence.

In a retrospective study of 255 chinese patients, Zhao YF et al. [27] have concluded that KCOT treated with enucleation alone have a higher recurrence rate. Enucleation with adjunctive treatment can decrease recurrence rate. Radical excision has no recurrence but does have the highest morbidity rate and should be reserved for multiple recurrent cysts after conservative means.

Tolstunov and Treasure [28] have advocated a surgical treatment algorithm for KCOT where they have reported a combined treatment of KCOT and mandibular defect with marsupialization, enucleation, iliac crest bone graft, and dental implants. Meara et al. [29] have

Table 1 Recurrence rate related to treatment

Sl . No.	Author	Year	No. of cysts	Treatment	Recurrence
1.	Pindborg and Hansen [10]	1963	16	Enucleation and marsupilization	62.5%
2.	Voorsmit, Stoelinga and Van Haelst [11]	1981	50	Enucleation	14%
			42	Enucleation, excision of overlying mucosa and carnoy's solution	2.5%
3.	Bataineh and Al Qudah [17]	1998	31	Resection	0%
4.	Stoelinga [16]	2001	82	Enucleation, excision of overlying mucosa and carnoy's solution	11 %
5.	Browne [44]	1970	12	Marsupialization	25%
			42	Enucleation and primary closure	26.2%
			30	Enucleation and packing open	20%
6.	Brondum and Jensen [45]	1991	44	Marsupialization	18%
7.	Partridge and Towers [43]	1987	2	Marsupialization	0%
			30	Enucleation and primary closure	36.7%
			11	Radical curettage, removal of overlying mucoperiosteum and packing	9%
			2	Resection and immediate bone graft	0%
8.	Forssell, Forssell and Kahnberg [46]	1988	28	Enucleation in single piece	18%
			41	Enucleation in multiple pieces	56%
			5	Marsupialization	60%
9.	Irvine and Bowerman [47]	1985	7	Enucleation	16.7%
			6	Radical enucleation	0%
			2	Resection	0%
10.	Eyre and Zakrzewska [5]	1985	4	Marsupialization	25%
11.	Pogrel and Jordan [20]	2004	10	Marsupialization followed by cystectomy	0%
12.	Schmidt and Pogrel [48]	2001	26	enucleation and liquid nitrogen cryotherapy	11.5%
13.	Maurette, Jorge and De Moraes [49]	2006	30	Marsupialization followed by Enucleation	14%
14.	Jung, Lee and Park [19]	2005	2	Decompression	0%
15.	Morgan, Burton and Quian [15]	2005	11	Enucleation only	54.5%
			11	Peripheral ostectomy	18.2%
			13	Peripheral ostectomy with Carnoy's solution	0%
			2	Enucleation with Carnoy's solution	50%
			3	En bloc Resection	0%
16.	Meara, Shah, Li and Cunningham [29]	1998	49	Enucleation	35%
17.	Madras J and Lapointe H [50]	2008	16	Curettage	37.5%
			3	Marsupialization	0%
			2	Resection	0%

found out an overall recurrence rate of 35%, and the average time to recurrence of 4 years in their clinicopathologic review. Simple enucleation (without curettage) is no longer advocated as an appropriate method of treatment KCOT. Recurrence rates are highest with this method of treatment and range from 9% to 62.5% [30,31]. Scharfetter et al. [32] in their study on KCOT proliferation, have suggested that a minimum 5-mm bony margin is adequate to ensure satellite cyst removal.

Conclusion

Although the literature contains many reports regarding management of KCOT, debate still exists as to the most effective treatment for this lesion. According to Ghali [33], as with any odontogenic lesion, initial evaluation must include a thorough history and physical examination, radiographic studies, and the development of a probable differential diagnosis. Depending on size, location, and behavior, the clinician should decide on an incisional versus excisional

biopsy. Prior aspiration may be helpful. In patients with multiple KCOTs, evaluation for the presence of basal cell nevus syndrome should be undertaken. Larger KCOTs, with possible cortical perforation, deserve specialized radiographic assessment, such as CT in addition to plain films.

Treatment of the KCOT varies from enucleation and curettage to osseous resection. Various factors that should be considered in the selection of the appropriate treatment include size and extent, location, presence of perforation or soft tissue involvement, age of individual, and primary or recurrent nature of lesion. Long-term follow-up is suggested because KCOTs have been known to have late recurrences. Recent factors support emerging molecular evidence that the KCOT is more likely to be a benign cystic neoplasm than a simple odontogenic cyst [34–36]. Even peripheral KCOTs are known to re-occur [37–40]. Our article attempts to bring out the importance of clinical awareness of the KCOT. It also emphasizes the importance of a careful histological examination and the necessity of obtaining biopsy materials from various areas to prevent a misdiagnosis of large-sized lesions. In the light of literature, it may be concluded that an aggressive treatment modality like enucleation with application of carnoy's solution might be considered as a viable treatment modality for the KCOT.

Future trends

Genetic studies have thrown light on new modalities of treatment of the KCOT at a molecular level. According to some studies, cyclopamine, a plant-based steroidal alkaloid, inhibits the cellular response to the Sonic Hedgehog signal. It is found that cyclopamine blocks activation of the Sonic Hedgehog pathway caused by oncogenic mutation making it a potential 'mechanism-based' therapeutic agent for human tumours whose pathogenesis involves excess Sonic Hedgehog pathway activity [41], as it is seen in the KCOT. Other studies have shown that antagonists of Sonic Hedgehog signaling factors could effectively treat KCOT [42].

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