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Original

Keratocystic odontogenic tumor: a 10-year retrospective study of 83 cases in an Iranian population

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Abstract: A retrospective analysis was conducted on patients diagnosed with and treated for keratocystic odontogenic tumor (KCOT) at Mashhad School of Dentistry between 1996 and 2006. The patients comprised 44 men and 30 women with a mean age of 27.08 years. Among the total of 83 lesions, 56 (67.5%) occurred in the mandible and 27 (32.5%) in the maxilla. Swelling tended to be the most common complaint (45.8%), while 24.1% of the lesions were diagnosed incidentally. Six patients (8.1%) with a total of 15 lesions had nevoid basal cell carcinoma syndrome; 28 lesions (33.7%) were associated with an impacted tooth, and 12 (14.5%) presented daughter cysts. Sixty-six KCOTs were treated by enucleation [5 recurrences (7.6%)], 6 by marsupialization [2 recurrences (33.3%)] and 11 by marsupialization followed by enucleation (no recurrences). KCOTs in the mandible showed a higher recurrence rate than those in the maxilla (10.7% vs 3.7%). Although the demographics of Iranian patients are closely similar to those of other nationalities, in this series KCOTs tended to develop in younger patients with a peak in teenagers. The posterior region of the mandible showed the highest likelihood of KCOT occurrence and recurrence. Marsupialization followed by enucleation resulted in the lowest recurrence rate. (J. Oral Sci. 49, 229-235, 2007)

Keywords: keratocystic odontogenic tumor; odontogenic keratocyst; nevoid basal cell carcinoma syndrome.

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Introduction

Keratocystic odontogenic tumor (KCOT), formerly known as odontogenic keratocyst (OKC), is a benign unicystic or multicystic intraosseous neoplasm of odontogenic origin (1), which arises from remnants of the dental lamina (2-6). It has long been of particular interest because of its potential for locally destructive behavior, its recurrence rate, and its tendency for multiplicity, particularly when associated with nevoid basal cell carcinoma syndrome (NBCCS) (1,7,8). The discovery of increased mitotic activity in the cyst epithelium (9), the potential for epithelial budding from the basal layer or daughter cysts in the cyst wall (10), the presence of chromosomal abnormalities (11) and the role of mutation of the PTCH gene in the etiology of KCOTs (12) resulted in reclassification of this lesion as a neoplasm in the WHO classification of head and neck tumors in 2005, and its renaming as KCOT (1).

KCOT occurs across a wide age range with a peak incidence in the second and third decades and a gradual decline thereafter (1-3). Most previous studies have noted a slight male dominance (1-3,10,13,14), although

Chirapathomsakul et al. (15) and Maurette et al. (16) reported a female to male ratio of 1.2 and 2.1 respectively. The radiographic appearance is one of a unilocular or multilocular well circumscribed radiolucent lesion with scalloped and corticated margins (3-6). Involvement of an unerupted tooth has been reported in 25% to 40% of cases (17). Radiographically, displacement of impacted or erupted teeth, root resorption, root displacement or extrusion of erupted teeth may be evident (3). Generally, KCOTs are solitary lesions; however, in 5-10% of patients, where KCOTs appear as a manifestation of NBCCS, they can be seen in multiple form (5,18,19). NBCCS is a rare entity characterized by a triad of multiple nevoid basal cell carcinomas of the skin, rib and vertebral anomalies, and multiple KCOTs (19). Thus, following positive diagnosis of multiple KCOTs, patients should be evaluated carefully to rule out the presence of NBCCS (3,19).

Keratocystic odontogenic tumor may occur in any part of the jaws with a considerable predilection for the posterior body of the mandible and ascending ramus (10,14,16,20). Signs and symptoms most frequently found include swelling (bone resorption), infection and discharge, pain, paresthesia, cellulitis, abscess and trismus (3,15). A noticeable number of cases, however, are diagnosed incidentally during routine dental examination, and the frequency of such cases has been reported to range from 5.5 to 42.5% (10,15,21). Its exceedingly high recurrence rate, which has been reported to vary from 2.5 to 62.5% (17,22), has resulted in many attempts to improve surgical techniques or develop novel treatment methods.

Unfortunately, there is no consensus on a uniform treatment plan, and the recommended surgical managements vary from marsupialization to *en bloc* resection. The type of treatment chosen depends on several factors including patient age, lesion location and size, and whether the KCOT is primary or recurrent (4). According to the literature, the two most common reasons for recurrence are incomplete removal of the lesion and formation of new KCOTs from small daughter cysts (23). Although the majority of recurrences appear within the first 5 years after treatment (24-27), one study claimed that 25% of recurrences were found 9 or more years after the initial treatment (13). To reduce the incidence of late recurrences, complete removal with extended margins and curettage of the surrounding tissues has been recommended by some authors. Although some authors believe that KCOTs can be properly treated by enucleation and peripheral ostectomy with rotary instruments (27,28), others argue that this approach is associated with an equal or higher recurrence rate in comparison with marsupialization and resection, respectively (14,16,21,29). Some surgeons have proposed using adjuvant therapies such as cryotherapy, electrocautery and Cornoy's solution in order to decrease the recurrence rate (24-27). Blanchard (30) introduced a new method using ultrasonic debridment of the cystic cavity in an attempt to remove any possible epithelial remnants. He monitored his case for five years and reported no incidence of recurrence. Considering the complications of radical surgery, marsupialization followed by enucleation has been suggested as a conservative option by some authors (16,29,31). This procedure relieves pressure in the lumen, facilitating bone formation adjacent to the cyst walls of the tumor. In this way, the cystic covering tends to become thicker, contributing to its complete removal at the enucleation step.

The present retrospective study investigated 83 KCOTs in 74 Iranian patients who were treated at the Department of Oral and Maxillofacial Surgery of Mashhad School of Dentistry, Mashhad, Iran, between 1996 and 2006, focusing on the age and sex of the patients, lesion location, clinical features, the treatment method applied, and possible relationship to NBCCS and impacted teeth as well as the recurrence rate.

Materials and Methods

This research was approved by the ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran. In this cross-sectional retrospective study, 522 records of odontogenic cyst and odontogenic tumor biopsies performed between 1996 and 2006 in the Department of Oral and Maxillofacial Surgery, Mashhad School of Dentistry, were overviewed and 83 cases of KCOT affecting 74 patients were selected. The primary diagnosis was approved by re-evaluation of the biopsies by an experienced oral pathologist, using the diagnostic criteria outlined by the World Health Organization (1). The reason why the number of biopsies exceeded the number of patients was that 6 patients who had suffered from NBCCS had more than one KCOT lesion, leading to multiple biopsies from a single patient. Cases with inadequate demographic information, invalid or lost biopsy samples and invalid follow-up data were excluded from the study. Then, the data including patient age and gender, site of involvement, clinical manifestation, treatment modalities, recurrences, association with impacted teeth or satellite cysts and the presence of NBCCS were gathered from every biopsy record, and entered into a database. For the patients with NBCCS, each biopsy was entered into the database as a separate record and the age of the patient at the time of initial admission was considered as a reference. Statistical analysis was carried out by chi-square test and Fisher's exact probability test and the level of statistical significance

was set at 0.05.

Results

The study population comprised 44 males (59.5%) and 30 females (40.5%), with a male to female ratio of 1.47, representing an approximately 50% male preponderance. Patient age at the time of diagnosis ranged from 5 to 82 years (mean: 27.08 ± 3.68). Most of the patients were in their twenties (41.9%), followed by those in their thirties (20.3%), whereas 4 patients were less than 10 years old (5.4%) (Fig. 1). Fifty-six lesions had occurred in the mandible (67.5%), among which 8 were in the anterior region (9.6%), 8 in the premolar region (9.6%) and 40 (48.2%) in the molar and post-molar region. Twenty-seven lesions had occurred in the maxilla (32.5%), of which 11 (13.3%) were found in the anterior region, 7 (8.4%) in the premolar region and 9 (10.8%) in the molar and post-molar region (Fig.2). In two cases, the lesions had developed in the maxillary sinus, and in one case the lesion was found in the nasal cavity. In general, the most common site of involvement was the mandibular molar and post-molar region (48.2%).

While 20 lesions (24.1%) were diagnosed incidentally during routine dental examination with no previous symptoms, 63 (75.9%) produced symptoms including swelling, pain and discharge that prompted the patient to come to the clinic. The most common complaint of patients at the time of admission was swelling (45.8%). Discharge and pus were reported in 9 lesions (10.9%) and pain in 2 lesions (2.4%). In 16.9% of the lesions, however, patients reported two of these symptoms at the same time (Table 1). Simultaneous multiple KCOTs had developed in 6 patients (8.1%; 4 male and 2 female), all of them suffering from NBCCS. Five out of 6 patients with NBCCS were in their second decade of life at the time of initial diagnosis, and the remaining one was in his thirties. In 28 cases of KCOT (33.7%), the lesions were associated with an impacted or semi-impacted tooth. Twelve cases (14.5%) showed satellite cysts upon pathologic evaluation.

The average follow-up period was 32.5 months, with a range of 9 to 117 months. Analysis of the treatments used for the lesions showed that 66 (79.5%) were treated by enucleation, 11 (13.3%) by marsupialization and subsequent enucleation, and 6 (7.2%) by marsupialization alone. In total, 7 lesions (8.4%) had recurred in seven different individuals, 3 in female and 4 in male patients. Three of these patients were in their twenties and 3 were in their thirties. One patient was in his 6th decade of life. Patient age and gender seemed to have no significant influence on recurrence ($P > 0.05$). Regarding the location, KCOTs in the mandible had a higher recurrence rate than those in the maxilla (10.7% vs 3.7%). Moreover, lesions located in the mandibular molar and post-molar region tended to recur more frequently (5 out of 6, 83.3%). However, no marked difference was found between lesion location and recurrence ($P > 0.05$). While no recurrence was observed for cases that were treated by marsupialization followed by enucleation, 5 of the recurrences were associated with enucleation treatment alone and 2 with marsupialization alone. Statistical analysis using Fisher's exact probability

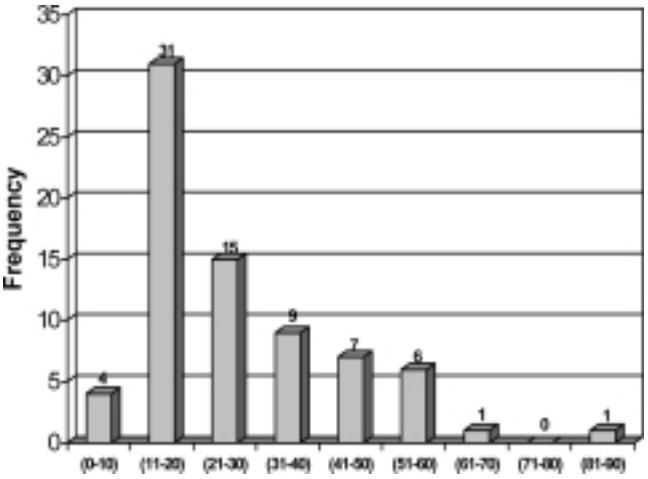

Fig. 1 Age distribution of patients with KCOTs.

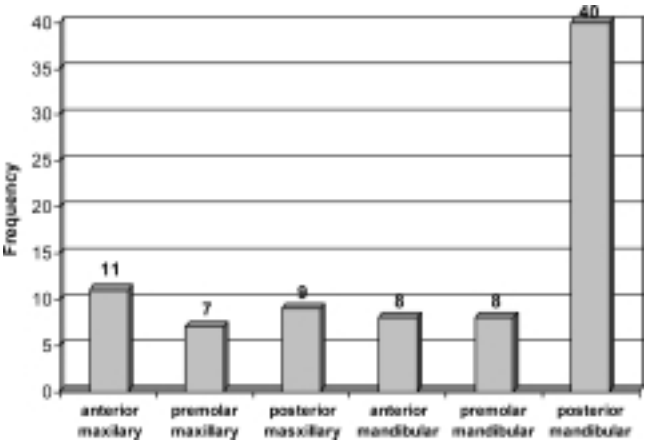

Fig. 2 Location distribution of KCOTs.

Table 1 Presenting symptoms of KCOTs

Symptoms	*Frequency*	*Percentage (%)*
Swelling	38	45.8
Discharge	9	10.9
Pain	2	2.4
Pain + discharge	2	2.4
Swelling + Discharge	5	6.0
Swelling + Pain	7	8.4
Accidental Diagnosis	20	24.1
Total	83	100.0

test, however, revealed no significant association between recurrence and the type of treatment provided ($P = 0.123$). Of the total of 7 lesions that recurred, 5 had associated symptoms, while 2 of the cases were found incidentally during follow-up radiographic examinations with no other symptoms. From the total of 7 recurrences, one lesion was associated with daughter cysts (Fig. 3), one was associated with NBCCS, and 2 were associated with impacted or semi-impacted teeth. None of these three variants showed significant influence on recurrence ($P > 0.05$).

Discussion

No previous study has reported the patient demographics of KCOT for an Iranian population. The sex distribution in this study was quite similar to those of other populations, and we confirmed a male predominance of approximately 60%, as reported previously (3,10,13,14,20). Although the mean patient age of 27.08 years in this series corresponded to those in some reports (10,14,16), it was rather lower than in others (3,20,21). This may be explained by the fact that most of the studies reporting a higher mean age excluded NBCCS patients from their calculations. Since this syndrome is generally diagnosed in younger patients (17,18), therefore, the mean patient age reported by those studies is higher. Unlike other studies in this field, which mostly reported the third decade of life as the most common age of occurrence (10,15,16), most of our patients (41.9%) had been referred to the Department of Oral and Maxillofacial Surgery while they were young teenagers. The KCOTs occurred more frequently in the mandible than in the maxilla (67.5% vs 32.5%), which is comparable to the figures reported by others, ranging from 65% to 83% for the mandible (1,3,10,14,32,33). The findings of our study confirmed those of others, which reported the mandibular molar and post-molar region as the most common site of occurrence (10,14).

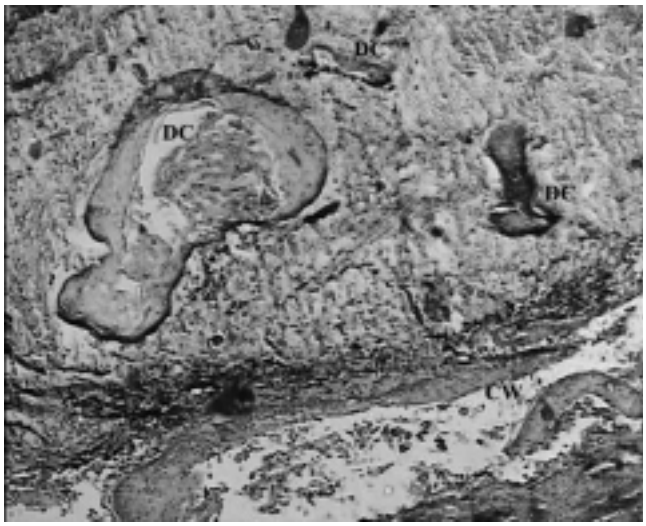

Fig. 3 Microscopic view of a KCOT, showing daughter cysts (DC) adjacent to the cyst wall (CW) of the lesion in a patient who later suffered lesion recurrence.

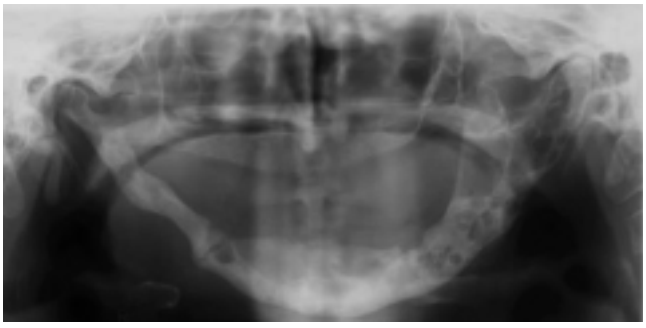

Fig. 4 Panoramic view of a NBCCS patient who had already undergone surgery by enucleation but returned after almost 10 years with new and recurrent lesions. A fracture line is also apparent in the right body of the mandible.

Several researchers have reported that 50 to 90% of KCOTs are symptomatic at the time of diagnosis (3,13,15,21,34), and the corresponding proportion of such cases in our series was 76%. The presenting symptoms were chiefly swelling combined with pain, pus discharge, or both, in line with the results of other investigators (3,10,13,33). Among the patients in our series, 8.1% had NBCCS, which is closely similar to the previously reported pattern (5,18,19). The association of the lesion with unerupted teeth in this series (33.7%) was within the average range (17) and closely similar to that reported by another author (31.3%) (15). The presence of one or more daughter cysts adjacent to the cystic wall of the tumor was demonstrated in 14.5% of lesions, which is considerably lower than the figure reported by Myoung et al. (30.1%) (10).

The overall recurrence rate was 8.4%. Six of the seven recurrent lesions were found in patients less than 30 years of age. Although patient age did not significantly affect the recurrence rate in this series ($P > 0.05$), our findings were consistent with those of Forssell (35), who reported a higher recurrence rate in younger patients. However, this may be attributable to the fact that younger patients usually receive more conservative treatment, which may lead to a higher recurrence rate. According to some authors, the site of involvement significantly affects the recurrence rate (10,31). Although we did not find any significant relationship between lesion location and recurrence, lesions in the mandibular molar and post-molar region had a higher recurrence rate. Daughter cyst formation has previously been significantly associated with higher recurrence rates (10,36); however, our results did not confirm such a relationship. In addition, contrary to some

reports indicating that KCOTs associated with NBCCS have a higher recurrence rate (22,37), the results of our series did not confirm such an association. However, since these patients have a considerable tendency to grow new lesions, a longer follow-up may be necessary (29) (Fig. 4). While it has been reported that recurrent lesions are strongly associated with remaining teeth (15), we found that impacted or semi-impacted teeth did not significantly affect the recurrence rate.

In terms of treatment modality, enucleated lesions showed a 7.6% recurrence rate, which is somewhat lower than in similar studies (10,15,21). Marsupialization resulted in a 33.3% recurrence rate, which is similar to the figures reported by Forssell et al. (8) and Ahlfors et al. (20). No recurrences were found in 11 cases treated by marsupialization in combination with secondary enucleation, which confirms the results of Zhao et al. (14). The treatment of choice for KCOT lesions is still debatable. Traditionally, enucleation followed by peripheral ostectomy is considered the best treatment for KCOTs; however, its high surgical morbidity and relatively high rate of associated recurrence mean that it cannot be considered the most ideal form of surgical management. Recent studies have revealed that marsupialization is applicable as a conservative technique for large lesions (16,38). Although it has the advantage of being less aggressive, it is not widely used by surgeons because it requires a high degree of patient cooperation, involving lesion irrigation on a regular basis and attendance for regular follow-ups (16). Since both of our patients who suffered recurrence after marsupialization of their lesions had failed to irrigate the lesion during the treatment period, our study confirmed that patient cooperation plays a major role in the success rate of this treatment plan. Since in our study the mean follow-up period was relatively short, the number of recurrent lesions was relatively small. Therefore, statistical analysis using Fisher's exact test showed that the type of treatment provided was not associated with recurrence ($P = 0.123$).

The WHO Working Group recently highlighted the neoplastic nature of this lesion and reclassified it from a cyst (OKC) to a tumor (KCOT) (1). Our recognition of OKC as a cystic neoplasm has occurred because of its observed biologic behavior, and modern investigations that have revealed chromosomal and genetic abnormalities consistent with neoplastic progression (39). Hence, there is a need to thoroughly review the treatment modality of the lesion as well. Based on the findings of this series, marsupialization with subsequent enucleation does appear to increase the success rate, although not to a significant degree.

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