A Comparative Study of Sporadic and Multiple Keratocystic Odontogenic Tumor: a Review of 196 Tumors

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Abstract: From the files of the Division of Pathology, Department of Diagnosis & Therapeutic Sciences, Meikai University School of Dentistry, 196 tumors diagnosed as keratocystic odontogenic tumor (KCOT) based on the guidelines of the 2005 classification of the World Health Organization (WHO) were studied. The features of 152 sporadic KCOTs were compared with those of 44 multiple KCOTs. The age and sex of the patients, the site of occurrence, and the association with nevoid basal cell carcinoma syndrome were taken in consideration. The mean age of patients with multiple KCOTs was lower (22.9 years) than that of patients with sporadic KCOTs (35.6 years). The peak incidence of the tumors was in the third and second decades of life for single and multiple KCOTs respectively. There were no significant histological differences between the two groups except for a greater amount of daughter cysts and a tendency for multiple recurrence in the multiple KCOT group. The term multiple KCOT refers to the lifetime history of the patient and does not necessarily imply that more than one tumor is present at a given time.

Key words: keratocystic odontogenic tumor (KCOT), odontogenic tumor

単発性および多発性角化囊胞性歯原性腫瘍の比較研究：
196 例の検討

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要旨: 明海大学歯学部病態診断治療学講座病理学分野で、2005 年 WHO 分類の基準にもとづいて角化囊胞性歯原性腫瘍（KCOT）と診断した 196 例について検討した。単発性 KCOT 152 例と多発性 KCOT 44 例の特徴を比較するとともに、年齢、性別、発生部位および基底細胞腫症候群との関連について検討した。平均年齢では、多発性 KCOT（22.9 歳）は単発性 KCOT（35.6 歳）よりも低かった。好発年齢は、単発性 KCOT が 20 歳代。多発性 KCOT が 10 歳代であった。組織学的所見では、多発性 KCOT 群で囊胞がよくみられること以外に大きな違いはなかった。多発性再発は多発性 KCOT 群で認められ、多発性 KCOT は単に複数の KCOT が同時に生じたということに限定されず、その患者の生涯において診ていくべき意味合いを含んでいる。

索引用語: 角化囊胞性歯原性腫瘍、多発性角化囊胞性歯原性腫瘍、歯原性腫瘍
Introduction

Keratocystic odontogenic tumor (KCOT) is an aggressive intraosseous lesion with a recurrence rate of approximately 25–60%\(^1\). The age when KCOT appears varies to a great extent from the first to the ninth decades, with a peak in the second and third decades\(^2\). It has been suggested that there may be histological differences between tumors that occur as multiple lesions and those that occur singly\(^3\). KCOTs, particularly the multiple form, are one of the most frequent and well-recognized features of nevoid basal cell carcinoma syndrome (NBCCS), a rare autosomal-dominant condition with high penetrance and variable expression\(^4−7\). However, not all multiple KCOTs have been confirmed to be associated with the syndrome; for example Branon\(^8\) reported that only half of examined cases of multiple KCOTs of the jaws occurred in patients affected by the syndrome. In any event, the mean age of patients with multiple KCOTs, with or without NBCCS, is lower than that of patients with single, non-recurrent KCOTs\(^5\). The term “multiple KCOT” does not necessarily mean that the patient has more than one tumor at a given time, i.e. multifocal tumor growth; rather it refers to the occurrence of KCOT over the lifetime of the patient\(^5, 9\).

People who do not have any known family members with NBCCS and are affected by the syndrome may comprise 60% of all patients with NBCCS, 35–50% of these cases representing new mutations\(^4\). Because of the variation in expression, the criteria for diagnosis is difficult, and the syndrome may occur in a minor form without either basal cell carcinoma or KCOT\(^9\). However, any patient with multiple KCOTs (excluding recurrence) may show some other features of the syndrome, and thus the possibility of NBCCS must be considered\(^5, 9\).

We conducted a study of a total of 196 KCOTs, single and multiple, focusing on the age and gender of the patients to determine any differences between the two forms.

Materials and Methods

Of the 196 tumors in the files of the Division of Pathology, Department of Diagnosis and Therapeutic Sciences, Meikai University School of Dentistry, collected between 1978 and 2007 that fulfilled the diagnostic criteria of the World Health Organization (WHO) for KCOT\(^2\), 152 were sporadic single tumors and 44 were multiple in nature.

For recurrent tumors, each file was entered as a separate record. For the patients whose tumors were associated with NBCCS, the age at the time of initial diagnosis was considered as a reference.

A KCOT was considered to be recurrent if it was located in exactly the same area of a previously removed tumor, or if there was a reliable history of cyst removal at the same location.

The data were analyzed in two groups: Group 1, 152 sporadic KCOT; Group 2, 44 tumors that exhibited multiple growth confirmed by histopathology at a given time, or that developed within the lifetime of a patient, excluding recurrence.

The significance of the following features was considered:
1. Sex of the patient
2. Age at presentation of primary KCOT
3. Site of occurrence
4. Presence or absence of recurrence
5. Interval between the primary tumor and recurrence
6. Lifetime history of patients with more than one KCOT occurring at different times and different sites
7. Histopathologic appearance
8. Association with NBCCS

Results

Group 1 included 152 tumors, 86 (56.6%) occurring in males and 66 (43.4%) in females (male to female ratio 1.3 : 1); the sex of 3 patients was unknown. Group 2 included 44 tumors, 16 (36.3%) in males and 28 (63.7%) in females (male to female ratio 1 : 1.7).

In Group 1, the mean patient age at KCOT removal was 35.6 years, with a range of 10 to 78 years. There

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was a peak incidence in the third decade of life, followed by another peak in the second decade (Fig 1). The mean age at KCOT removal in males and females was 36.1 and 35.0 years, respectively. The age distribution was similar in both genders, with no remarkable difference between them.

In Group 2, the mean patient age was 22.9 years, with a range of 6 to 68 years. The peak incidence was in the second decade of life, followed by another peak in the third decade, and a considerable decrease in the incidence of tumors in subsequent decades. The mean age at KCOT removal was lower for males (20.2 years) than for females (24.5 years) (Fig 2).

The distribution of all KCOT sites is shown in Table 1. Eighty-nine (58.5%) tumors in Group 1 occurred in the mandibular posterior region: the mandibular molar area was involved in 72 cases and the mandibular molar to ramus area in 17. The corresponding figure in Group 2 was 52.3% (23 tumors); multiple tumor growth, at any given time, in the mandibular posterior region occurred in 15 cases, the mandibular molar area being involved in 7 cases and the maxillary molar area in one. In both groups, the mandibular bone was affected considerably more often than the maxillary bone.

Among the 152 sporadic KCOTs in Group 1, 11 (7.2%) were recurrences, the time of presentation of the recurrence ranging from 1 to 10 years. Five males and 6 females were affected. At the time of tumor recurrence, the patients ranged in age from 19 to 69 years (mean 34.3 years). Nine tumors (81.8%) occurred in the posterior region of the mandibular bone, and 2 (18.2%) in the maxillary posterior region.

Among the 44 multiple KCOTs, 15 were recurrences, the period after initial presentation ranging from 2 to 23 years. Five cases were in males and 10 in females. The patients ranged in age from 11 to 62 years (mean 24.0 years). Nine tumors (60%) recurred in the mandibular bone, 4 (26.7%) in the maxillary bone, and two of the tumors occurred and then recurred in both bones.

In both groups, recurrent KCOTs of the maxillary bone alone were more frequent (7 out of 36; 19.44%) than in the mandibular bone alone (18 out of 153; 11.8%).

The KCOTs in Group 2 were tumors with multiple growth at a given time, or had a history of multiple growth at a given time.
maxillary or mandibular surgery. On all of these occasions except for two, the tumors were diagnosed as either OK or KCOT; in two cases the primary diagnosis was dentigerous cyst, and after their recurrence, both of them were confirmed to be KCOT associated with NBCCS. All 44 tumors were re-evaluated according to the 2005 WHO classification for KCOT.

The results of the histological findings are presented in Table 2. The study revealed parakeratinization to be the most frequent feature in both groups of KCOTs (Fig 3a, 3b). However, the frequency of daughter cysts was higher (12 out of 44 tumors; 27.2%) for multiple, than for single KCOTs (6 out of 152 tumors; 3.9%) (Fig 4a, 4b). We found a significant proportion of tumors (26.0%) to be associated with an

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Fig 3 Typical palisade of parakeratinizing squamous stratified epithelium in an sporadic KCOT (a) (original magnification ×10); and multiple KCOT showing visible koilocytotic changes (b) (original magnification ×20).

Fig 4 Daughter cyst formation near to the main lesion in an sporadic KCOT (a) (original magnification ×2); and multiple cystic-like formations in a multiple KCOT associated with NBCCS (b) (original magnification ×20).
impacted tooth, a feature that together with inflammation can mislead the clinical diagnosis, stressing the importance of histopathologic survey (Fig 5a, 5b).

Patients whose tumors were associated with NBCCS were exclusively found in Group 2, and 5 of them had recurrence. Eleven patients with multiple KCOTs developed a total of 24 tumors; they also had additional abnormalities and were considered to be examples of NBCCS. Four (36.4%) were males and 7 (63.6%) were females (ratio 1 : 1.7); they ranged in age from 8 to 43 years at the time of initial diagnosis, with a mean age of 19.5 years (males 22.5 years, females 17 years). As a group, 20 multiple KCOTs not associated with NBCCS and 24 multiple KCOTs associated with NBCCS accounted for 22.4% of all tumors. Patients whose tumors were multiple KCOTs, with or without NBCCS, accounted for 13.1% of the total number of patients in our study (21 out of 160).

Discussion

KCOT, previously known as odontogenic keratocyst (OK) parakeratinizing variant, is a benign cystic neoplasm. Its behavior and characteristics are well documented, and it occurs most commonly as a single lesion in the jaw of an otherwise healthy person. This tumor may be associated with NBCCS, and when it does, it occurs as multiple lesions.

We found that the gender distribution of single KCOTs showed a male predilection, as reported by Branon (1.3 : 1), and similar to that reported by Jones (1.27 : 1), but different from the group of multiple KCOTs in which females are more frequently affected. Multiple KCOT is a well-recognized feature of NBCCS, and is often considered the first sign of the syndrome. Woolgar et al. found a similar distribution when comparing solitary tumors (62% males and 38% females) and tumors associated with NBCCS (45% males and 55% females). This could suggest that patients with multiple KCOT, with or without other syndrome manifestations, are probably affected by the same genetic abnormality that is involved in tumor formation. The term multiple when applied to KCOT refers to the lifetime history of the patients and does not necessarily imply that more than one tumor is present at any time. We found that the male to female ratio (1 : 1.7) of patients affected by multiple KCOTs was different from that of single KCOTs (1.3 : 1). Although single KCOT appears to be more common in males, more females seem to develop multiple tumors, as reported previously. Multiple KCOTs occurred in 13.1% of the patients, this proportion being higher than that reported by Lam and Chan (9%) or by Ahlfors et al (6%). However, as the sample sizes in all these studies, including ours, were relatively small, the significance of the re-
sults should be interpreted with caution.

The patient ages at diagnosis of KCOT vary widely, and some cases have been recorded as early as the first decade\(^{15}\). In Group 2, few of the tumors occurred in the first decade of life, and not a single such case was found in Group 1; however, there was a sharp increase of incidence in the second decade of life in both groups. Some workers have demonstrated a bimodal age distribution with a second peak in the fifth decade of life or later\(^{16,18−20}\). We were unable to confirm such a bimodal trend in either of the groups. Thus, while there was no significant difference between the genders in mean age for either single or multiple KCOTs, the mean patient age for multiple KCOT was lower than for single KCOT, as reported previously\(^{2}\).

In our sample, the mandible was affected far more frequently than the maxilla, and the posterior region of both bones was most common affected. On the other hand, we also found that KCOT can occur anywhere in the jaws, including the midline of the mandible and maxilla. The high frequency of occurrence in the mandibular bone was consistent with other reports\(^{12,16−18,21}\).

It has been known for many years that KCOT has a particular tendency to recur and show aggressive clinical behavior\(^{8,22−24}\). There have been attempts to find a correlation between recurrence and age, location, method of treatment and histological features, but so far nothing conclusive has emerged. Agaram \textit{et al}\(^{14}\) have suggested that a significant loss of heterozygosity of various suppressor genes is involved in sporadic KCOT, and recommends further work to determine whether the pattern or number of tumor suppressor genes with allelic loss can predict tumor behavior\(^{14}\). Most of the KCOTs in our series recurred within 5 to 7 years, in agreement with previous reports\(^{15,24−26}\). We found that recurrent tumors occurred more in females (61.5\%) than in males (38.5\%) in both groups. Nevertheless, patients with multiple KCOTs appeared to develop more than one recurrence during life. One of our female patients in Group 2 developed tumor recurrence 23 years after the initial treatment, and both the primary and recurrent tumors exhibited multiple growth at a given time. The considerable variation in recurrence rate reported by different workers may be ascribed partly to the variation in the follow-up period and the criteria used for diagnosis\(^{20,26}\). We found that for both groups, recurrent KCOTs in the maxillary bone alone were more frequent than in the mandibular bone alone.

Histologically, epithelial changes suggestive of tumor proliferative activity were present at a higher rate in some KCOTs than in others. Considering that the number of multiple KCOTs was lower than that of single KCOTs, the presence of daughter cysts was more frequent in cases of multiple KCOT. On the other hand, there were no significant inter-group differences in histological changes, or in patient gender or age. However, KCOTs associated with NBCCS showed a higher frequency of mural proliferation and budding in the basal layer; in addition, two of these tumors showed hyaline bodies and dystrophic calcification in the epithelial islands, similar to features reported previously\(^{15,17}\). We agree with Ahlfors \textit{et al}\(^{16}\) that all the above features simply reflect morphologic variations that may be expressed by the tumor epithelium.

NBCCS probably arises in all ethnic groups, but most reports have been of caucasians\(^7\). Males and females are equally affected, and the clinical features appeared in the first three decades of life\(^4,7\). The causative gene of NBCCS is on chromosome 9 q (22.3−q 31) and has no apparent heterogeneity\(^7,27,28\). All of our patients whose tumors were associated with NBCCS were identified in the first three decades of life, with the exception of one male patient whose first known KCOT was diagnosed at the age of 43 years. Woolgar \textit{et al}\(^9,13\) found that there were significantly more syndrome than non-syndrome patients under the age of 36 years, and that in both groups females were more likely to be affected at a younger age, despite the lack of any significant difference in the mean age. In our study, out of all single and multiple KCOTs that occurred in females, 69.5\% were diagnosed within the age range of 0–39 years. We also found that 10 of the 11 NBCCS patients were diagnosed between 8 and 25 years of age. These findings suggest
that young female patients (less than 39 years of age) are more likely to have the syndrome. In addition, Brannon found that although KCOT was most common in males, more females seemed to have NBCCS. The syndrome’s inheritance is autosomal dominant; consequently there may be some differences in its penetrance and expression between sexes.

**Conclusion**

The aggressive nature of KCOT, both single and multiple, and its classification as a tumor by the WHO in 2005 emphasize the fact that it should no longer be managed as a simple cyst, and that oral health providers should be aware of this. It is possible that any patient with more than one KCOT will show some other features of NBCCS. Nonetheless, there may be minor anomalies, revealed only on full examination, including anthropometry and radiography. It is essential that a diagnosis of NBCCS be established at the earliest possible stage, to prevent patients’ possible exposure to other avoidable irradiation. As research continues, the diagnosis and treatment of KCOT may involve molecular-based modalities that may reduce or eliminate the need for aggressive surgical management.

**References**

25) Chow HT: Odontogenic keratocyst: a clinical experience in
Sporadic and multiple keratocystic odontogenic tumor


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