Keratocystic Odontogenic Tumour: Reclassification of the Odontogenic Keratocyst from Cyst to Tumour

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ABSTRACT

The purpose of this paper is to review the features and behaviour of the odontogenic keratocyst (OKC), now officially known as the keratocystic odontogenic tumour (KCOT); to analyze a series of histologically confirmed KCOT cases; and to review and discuss the redesignation of KCOT and the implications for treatment. Based on a literature review, more aggressive treatment — either resection or enucleation supplemented with Carnoy's solution with or without peripheral ostectomy — results in a lower recurrence rate than enucleation alone or marsupialization. However, the recurrence rate after marsupialization followed by enucleation is not significantly higher than that after aggressive modalities. In a case series of 21 patients (27 KCOTs), recurrence rate was 29%, consistent with published data; all recurrences occurred within 2 years after intervention. The size of most lesions was 0–15 cm^2 (average 14 cm^2) measured radiographically. WHO's reclassification of this lesion from cyst to tumour underscores its aggressive nature and should motivate clinicians to manage the disease in a correspondingly aggressive manner. The most effective treatments are enucleation supplemented with Carnoy's solution, or marsupialization with later cystectomy. Future treatment may involve molecular-based modalities, which may reduce or eliminate the need for aggressive surgical management.

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First described by Philipsen in 1956,[1] the odontogenic keratocyst (OKC) is now designated by the World Health Organization (WHO) as a keratocystic odontogenic tumour (KCOT) and is defined as "a benign uni- or multicystic, intraosseous tumour of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behaviour."[2] WHO "recommends the term keratocystic odontogenic tumour as it better reflects its neoplastic nature."[2] In light of the reclassification, it is appropriate to review the salient features of this well-known lesion and to consider the implications for treatment.

Case Series

To assess the impact of treatment modality and lesion size on KCOT recurrence, 21 patient files on 27 histologically confirmed KCOTs were reviewed (**Table 1**). The 27 KCOTs included 5 recurrences of a lesion treated elsewhere, 16 de novo lesions and 6 recurrences

Table 1 Description of keratocystic odontogenic tumours and treatment in a series of 21 patients

Patient's date of birth	Tumour			Treatment	Follow-up period
	Location	Size; cm	Surface area; cm^2		
1912-08-18	Anterior mandible	8 × 3	24	Curettage	1 year
1918-01-13	Left mandibular body and ramus[a]	6.5 × 3	19.5	Marsupialization	1 year
1921-11-16	Right posterior maxilla	3 × 1.5	4.5	Curettage	Recurrence at 1.5 years
	Right posterior maxilla	1 × 1	1	Curettage	5.5 years
1922-07-17	Right mandibular body	4.5 × 1.5	6.75	Curettage	5 years
1925-07-22	Left mandibular ramus[a]	5.5 × 3.5	19.25	Marsupialization	3.5 years
1925-11-27	Right mandibular body and ramus	6.5 × 2.5	16.25	Curettage	2.5 years
1927-07-07	At teeth 44 and 45	1 × 1	1	Curettage	Recurrence at 1 year
	At teeth 44 and 45	1 × 1	1	Curettage	Recurrence at 2 years
	At teeth 44 and 45	1 × 1	1	Curettage	6 years
1929-01-19	Left mandibular coronoid process[a]	4.5 × 1.5	6.75	Resection	5 years
1959-09-07	Right mandibular ramus	4 × 3	12	Curettage	2 months
1933-05-15	Right mandibular body and ramus	2.5 × 1.5	3.75	Curettage	5.5 years
1936-06-08	Right mandibular body, at teeth 41–47	6.5 × 3	19.5	Curettage	Recurrence at 8 months
	At teeth 44–46	2.5 × 2	5	Curettage	5 years
1946-03-03	Right mandibular body and ramus	9 × 2.5	22.5	Curettage	1 year
1949-01-13	Right mandibular body and ramus[a]	10 × 4.5	45	Resection	6 years
1949-03-22	Anterior mandible	6 × 3	18	Curettage	Recurrence at 9 months
	Anterior mandible	4 × 2	8	Curettage	7 years
1957-08-28	Left mandibular body and ramus[a]	7 × 3	21	Marsupialization	1.5 years
1957-12-01	Left mandibular angle and ramus	2.5 × 3.5	8.75	Curettage	16 months
1960-07-18	At tooth 23, left maxilla and sinus	4.5 × 4.5	20.25	Curettage	18 months
1961-04-04	Right mandibular body and ramus	8 × 4.5	36	Curettage	1 year
1966-09-23	Left posterior maxilla	4 × 3	12	Curettage	Recurrence at 1.5 years
	Left posterior maxilla	3.5 × 1.5	5.25	Curettage	2 years
1975-12-26	Left mandibular body and ramus	6 × 4	24	Curettage	2.5 years
1986-05-06	Right maxilla	5 × 2	10	Curettage	2 years

[a] *Initial presentation due to recurrence of previous tumour.*

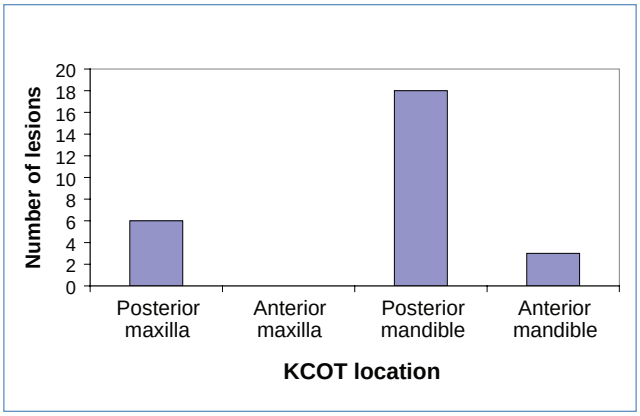

Figure 1: Keratocystic odontogenic tumour (KCOT) location among patients in our study group.

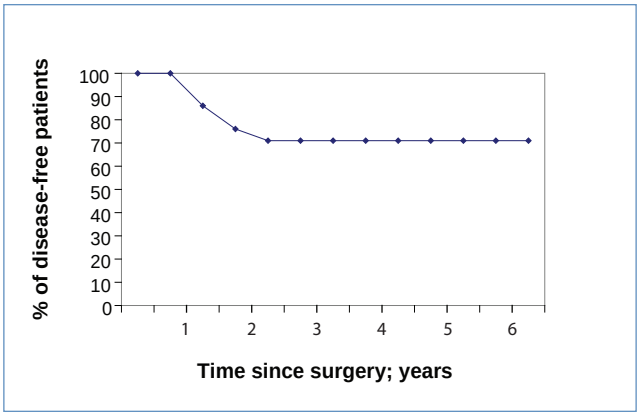

Figure 2: Percentage of disease-free patients over time.

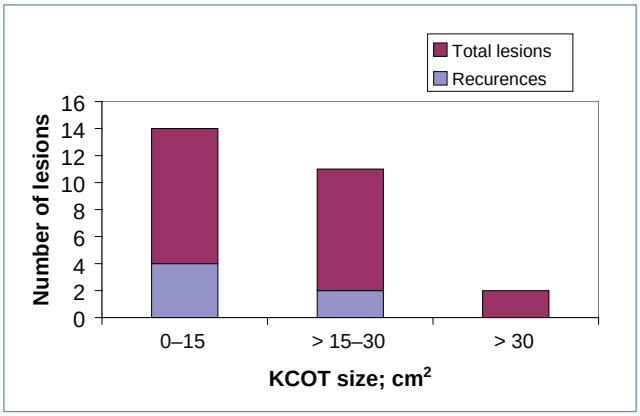

Figure 3: Relation between KCOT size and recurrence.

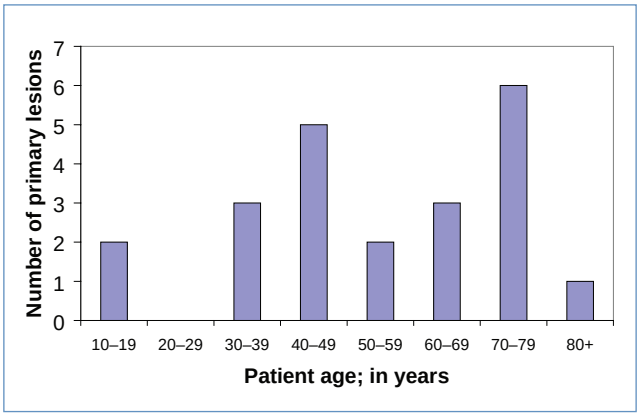

Figure 4: KCOT distribution by age.

of lesions treated in our clinic. There were 18 lesions in the posterior mandible, 3 in the anterior mandible and 6 in the posterior maxilla (**Fig. 1**). Treatment consisted of enucleation and curettage for 22 of the lesions, resection for 2 and marsupialization for 3. Follow-up periods varied from 2 months to 7 years. Overall, the recurrence rate was approximately 29%.

Figure 2 depicts the percentage of patients who remained free of recurrent KCOTs after the initial intervention at our clinic. Included are the 5 patients who presented with recurrence of a lesion treated elsewhere, as well as patients whose lesion recurred after initial treatment at our clinic. All recurrences of lesions (previously recurrent or new lesions) treated at our clinic were within 2 years.

The average surface area of the lesions measured radiographically was 14 cm^2. Most lesions were within the 0–15 cm^2 range and lesions in this range resulted in the greatest number and proportion of recurrences (**Fig 3**).

No relation was found between age and number of primary lesions among our patient group (**Fig. 4**).

Sample Cases

Patient 1 (born 1949, date of surgery: Dec. 16, 1999)

This patient presented initially with recurrence of a KCOT (treated elsewhere 10 years earlier) of the right mandible. The tumour measured 45 cm^2 radiographically (**Fig. 5**). Because of the size, multilocularity and extent of soft tissue involvement in the lesion, resection was determined to be the most appropriate treatment method. This included complete removal of the right mandible from the condyle to the bone distal to tooth 44. The tumour did not recur during the 6-year follow-up period.

Patient 2 (born 1925, date of surgery: Nov. 22, 2001)

This patient presented with a primary KCOT measuring 19 cm^2 radiographically and involving the left mandibular ramus (**Fig. 6**). The cyst was marsupialized and followed up for 3.5 years. Bone fill proceeded normally and there were no recurrences during that period.

Patient 3 (born 1949, date of surgery: Sept. 17, 1993)

This patient presented with a de novo KCOT of the anterior mandible, measuring 18 cm^2 radiographically (**Fig. 7**). It was treated by curettage. Nine months later,

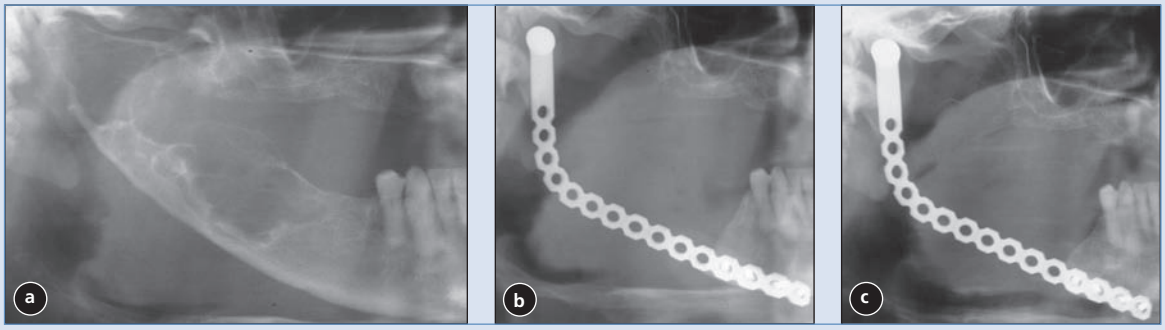

Figure 5: Partial panoramic radiograph taken **(a)** pre-operatively and **(b)** 6 days and **(c)** 6 years after resection.

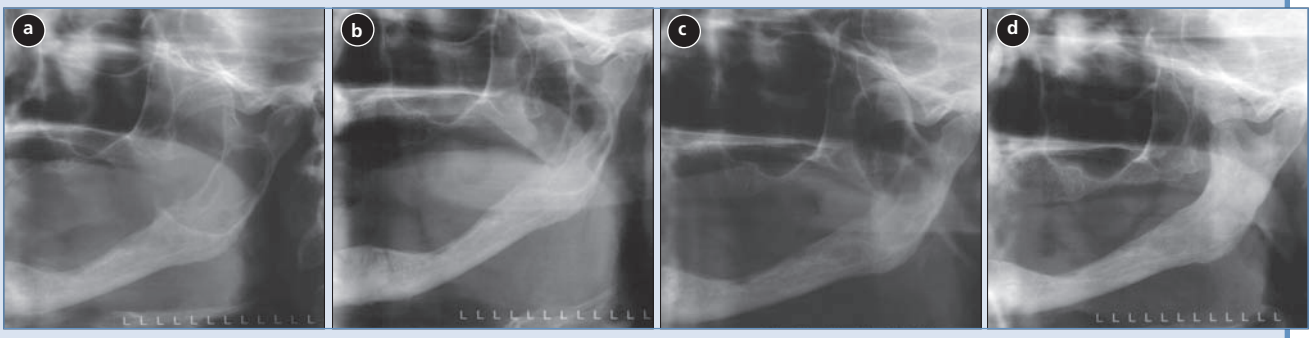

Figure 6: Partial panoramic radiograph taken **(a)** pre-operatively, **(b)** 9 days, **(c)** 3 months and **(d)** 3.5 years after marsupialization.

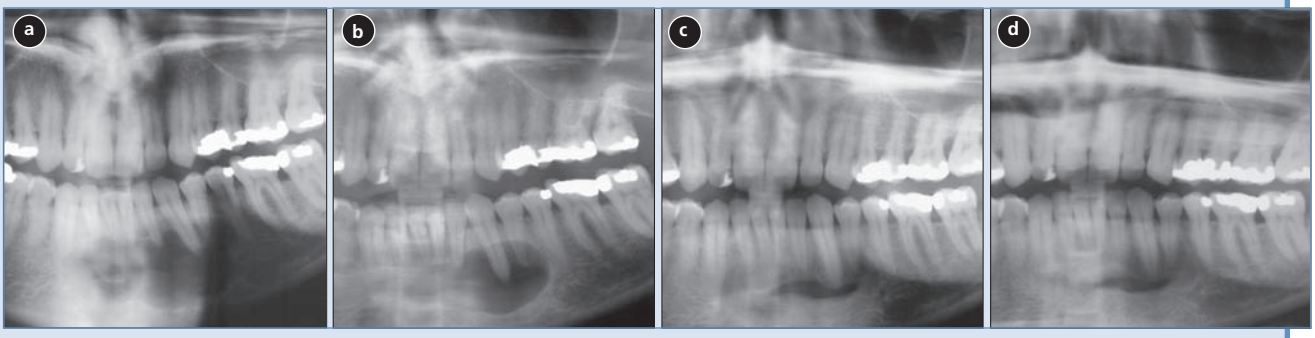

Figure 7: (a) Pre-operative radiographic appearance of the lesion. **(b)** Recurrence at 9 months after curettage; and **(c)** 16 months and **(d)** 7 years after curettage of the recurring tumour.

recurrence was observed. This was curetted and followed up for 7 years.

Clinical Features

KCOTs comprise approximately 11% of all cysts of the jaws.[3] They occur most commonly in the mandible, especially in the posterior body and ramus regions.[2,4,5] They almost always occur within bone, although a small number of cases of peripheral KCOT have been reported.[6–11] 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 nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin-Goltz syndrome. KCOTs have a high recurrence rate, reportedly between 25% and 60%[12] (when associated with NBCCS, the recurrence rate is about 82%[13]). In addition to multiple KCOTs, NBCCS is also characterized by nevoid basal cell carcinomas, bifid ribs, calcification of the falx cerebri, frontal bossing, multiple epidermoid cysts and medulloblastoma.[14]

In 1976, Brannon[5] proposed 3 mechanisms for KCOT recurrence: incomplete removal of the cyst lining, growth of a new KCOT from satellite cysts (or odontogenic rests left behind after surgery) and development of a new KCOT in an adjacent area that is interpreted as a recurrence.[15] The wide range in reported recurrence rates has been attributed to the variation in follow-up times used by examiners, the surgical technique used and the number of cases incorporated into the studies.[16] Most

Table 2 Review of literature relating treatment to recurrence rate

Study	Cysts	Treatment	Follow-up period	Recurrence rate; %
Kondell and Wiberg[21]	29	Enucleation	1–8 years	24
Chow[22]	70	Enucleation + Carnoy's + peripheral ostectomy	≥ 5 years	10
Meara and others[23]	49	Enucleation	1–15 years	35
Bataineh and al Qudah[16]	31	Resection	2–8 years	0
Stoelinga[20]	82	Enucleation + Carnoy's	1–25 years	11
el-Hajj and Anneroth[24]	63	Enucleation	> 5 years	29
	16	Enucleation + cryosurgery	> 5 years	38
	1	Enucleation + surgical bur	> 5 years	0
	2	Enucleation + cryosurgery + surgical bur	> 5 years	50
	3	Resection	> 5 years	0
Marker and others[25]	23	Marsupialization + enucleation	1–19 years	9
Pogrel and Jordan[26]	10	Marsupialization + later cystectomy	1.8–4.8 years	0
Maurette and others[3]	30	Decompression then curettage	Approx. 25 months	14
Morgan and others[17]	11	Enucleation	13–288 months	55
	11	Peripheral ostectomy	13–288 months	18
	13	Peripheral ostectomy + Carnoy's	13–288 months	0
	2	Enucleation + Carnoy's	13–288 months	50
	3	Resection	13–288 months	0
Brøndum and Jensen[27]	44	Decompression + later cystectomy	7–19 years	18
Browne[4]	12	Marsupialization	> 16 months	25
	72	Enucleation	> 16 months	23
Forssell and others[28]	28	Enucleation in 1 piece	5–17 years	18
	41	Enucleation in > 1 piece	5–17 years	56
	5	Marsupialization	5–17 years	60
Jensen and others[29]	12	Enucleation	17–58 months	33
	13	Enucleation + cryotherapy	21–59 months	38
Voorsmit and others[30]	52	Enucleation	1–21 years	14
	40	Enucleation + Carnoy's	1–10 years	3
Chuong and others[31]	22	Enucleation	19 months to 10 years	18
	1	Resection	19 months to 10 years	0
Vedtofte and Praetorius[32]	57	Enucleation	≥ 5 years	51
Zachariades and others[33]	13	Enucleation	> 5 years	31
	1	Resection	> 5 years	0
	1	Marsupialization	> 5 years	0
	1	Decompression + enucleation	> 5 years	0

Table 3 Summary of treatment related to recurrence rate

Treatment	Lesions	Recurrences	Recurrence rate; %
Enucleation	465	141	30
Enucleation + Carnoy's	122	11	9
Enucleation + peripheral ostectomy	11	2	18
Enucleation + Carnoy's + peripheral ostectomy	83	7	8
Enucleation + cryotherapy	29	11	38
Marsupialization	18	6	33
Marsupialization + cystectomy	108	14	13
Resection	39	0	0

recurrences take place within 5–7 years after treatment, although some have been reported more than 10 years following initial intervention.[17] These findings emphasize the importance of long-term follow-up as an essential aspect of the KCOT treatment plan.

Common Treatment Modalities

Morgan and colleagues[17] categorize surgical treatment methods for KCOT as conservative or aggressive. Conservative treatment is "cyst-oriented" and, thus, includes enucleation, with or without curettage, or marsupialization. Its advantage is preservation of anatomical structures (including teeth), which is advocated because KCOTs commonly present in younger patients. It has been asserted that a conservative approach is applicable not only to all age groups, but also to patients with NBCCS.[18]

Aggressive treatment addresses the "neoplastic nature" of the KCOT and includes peripheral ostectomy, chemical curettage with Carnoy's solution or en bloc resection. Aggressive modalities have generally been recommended for NBCCS cases, large KCOTs and recurrent lesions.[18]

Some authors advocate a site- and size-based approach to KCOT treatment planning. For example, Dammer and others[19] suggest that "small keratocysts near the alveolar process a maximum of 1 cm in diameter should be treated by simple excision, but large keratocysts near the base of the skull which have invaded soft tissue should be treated by radical excision." This is presumably because of the potential for local invasion of the skull base, which can have catastrophic consequences.

With surgical treatment, removal of the mucosa overlying the lesion has been recommended, based on histologic evidence that clusters of epithelial islands and microcysts — presumably with the potential to cause recurrence — have been found in the area where the KCOT was connected with the mucosa.[20]

Recurrence

A review of the literature suggests that recurrence rate is relatively low with aggressive treatment, whereas more conservative methods tend to result in more recurrences (**Tables 2** and **3**). Articles reviewed were required to meet the following inclusion criteria: histologic diagnosis of OKC, a defined follow-up period and a clear description of treatment.

If a difference in recurrence rate between 2 modalities of ≥ 15% (arbitrarily chosen) is considered the threshold for clinical significance, a few simple inferences are possible. First, enucleation plus Carnoy's solution, with or without peripheral ostectomy, results in a significantly lower rate of recurrence than enucleation alone. Second, the use of cryotherapy with enucleation appears to have no significant effect on the recurrence rate compared with enucleation alone. Third, marsupialization as a definitive treatment is associated with a significantly higher recurrence rate than when the KCOT is subsequently enucleated. Finally, resection, despite a recurrence rate of 0, is not significantly better at eliminating recurrences than enucleation plus Carnoy's solution or marsupialization plus cystectomy. Therefore, to minimize invasiveness and recurrence, the most effective treatment option appears to be enucleation of the KCOT and subsequent application of Carnoy's solution. Alternatively, marsupialization followed by cystectomy is likewise effective, as this treatment does not result in a significantly higher rate of recurrence than enucleation plus Carnoy's solution. However, as the latter option requires a protracted course of treatment, patient compliance must be considered; lesions treated in this manner require several months of at-home irrigation by the patient as well as clinical observation before enucleation.

KCOT: The Neoplasm

In 1967, Toller suggested that the OKC may best be regarded as a benign neoplasm rather than a conventional cyst based on its clinical behaviour.[34] In 1984, Ahlfors and others[35] suggested that "if the OKC were recognized as a true, benign cystic epithelial neoplasia, the question of modified treatment schedules would be raised." In the years since, published reports have influenced WHO to reclassify the lesion as a tumour. Several factors form the basis of this decision.

- Behaviour: As described earlier, the KCOT is locally destructive and highly recurrent.
- Histopathology: Studies such as that by Ahlfors and others[35] show the basal layer of the KCOT budding

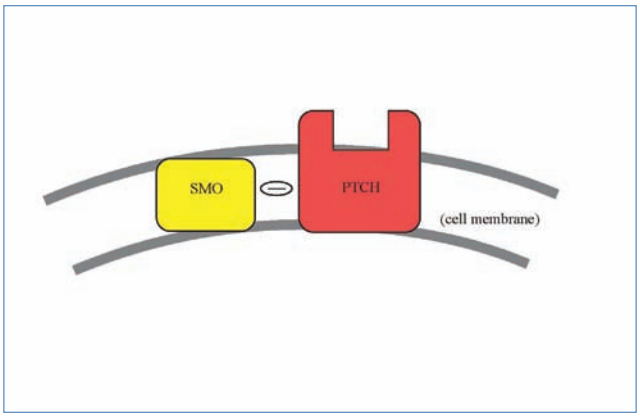

Figure 8: PTCH prevents the proliferation-inducing effect of SMO.

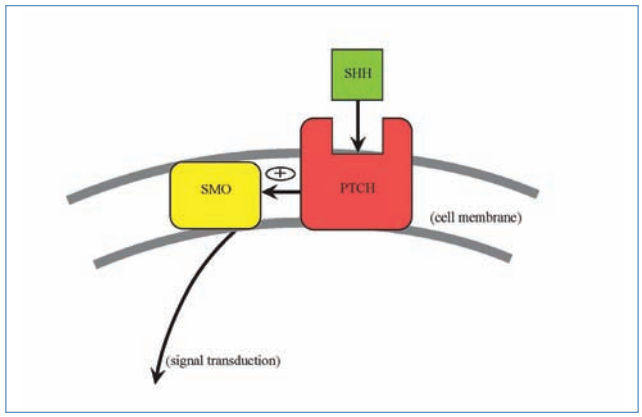

Figure 9: SHH releases PTCH from SMO, allowing signal transduction.

into connective tissue. In addition, WHO notes that mitotic figures are frequently found in the suprabasal layers.[2]

- Genetics: PTCH ("patched"), a tumour 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 inhibits growth-signal transduction (**Fig. 8**). SHH binding to PTCH releases this inhibition (**Fig. 9**).[41] If normal functioning of PTCH is lost, the proliferation-stimulating effects of SMO are permitted to predominate.

Evidence has shown that the pathogenesis of NBCCS and sporadic KCOTs involves a "2-hit mechanism," with allelic loss at 9q22.[42,43] The 2-hit mechanism refers to the process by which a tumour suppressor gene is inactivated.[44] The first hit is a mutation in one allele, which, although it can be dominantly inherited, has no phenotypic effect. The second hit refers to loss of the other allele and is known as "loss of heterozygosity" (LOH). In KCOTs, this leads to the dysregulation of the oncoproteins cyclin D1 and p53.[43] Lench and others[45] indicate that LOH in the 9q22.3-q31 region has been reported for many epithelial tumours, including basal cell carcinomas, squamous cell carcinomas and transitional cell carcinomas; they note that LOH is, "by definition a feature of tumorigenic tissue."

Implications and the Future of KCOT Treatment

The aggressive nature of the KCOT is universally acknowledged. WHO's formal reclassification of it as a tumour underscores the fact that this lesion should not be managed as the simple cyst it was believed to be. Although some studies advocate more conservative treatment, **Table 3** shows that an aggressive approach is more likely to reduce the risk of recurrence (and therefore the risk of trauma caused by repeated surgeries). Although one study[26] suggests treating with marsupialization alone and showed promising results (0 recurrences), the follow-up period (≤ 4.8 years) and sample size (10 patients) were inadequate to draw definitive conclusions.

Despite the fact that resection of the jaw results in the lowest recurrence rate, this procedure is extreme. Thus, unless resection is deemed necessary, the most appropriate action would be enucleation of the KCOT plus use of Carnoy's solution or marsupialization followed by enucleation.

In our case series, smaller lesions were more often associated with recurrence. This contradicts our expectations, as larger lesions should be inherently more difficult to excise in one piece and, therefore, should be more likely to recur. To date, the literature makes little mention of recurrence of large versus small lesions. The largest of our lesions was resected and, as supported by the literature, this method of treatment was associated with the lowest rate of recurrence. This could influence the results, making small lesions appear to recur more often. Thus, our results regarding lesion size and associated recurrence are inconclusive. Notably, Forssell and others[28] found that lesion size does *not* affect recurrence rate, confirming earlier observations.

Regarding a relation between treatment modality and recurrence, in the case series all recurrences followed enucleation and curettage.

In our study, the tumours presented primarily in the posterior mandible, in accordance with findings described above under "clinical features." Likewise, in agreement with earlier research, the recurrence rate we observed was 29%.[13] Our follow-up interval ranged from 2 months to 7 years, with the variability attributed to patient compliance and time since surgery. Although all recurrences took place within 2 years post-intervention, it remains prudent to suggest at least 5 years follow-up for KCOTs for reasons stated earlier.

In recent years, studies have hinted at possible new treatment methods for KCOT. According to Taipale and colleagues,[46] cyclopamine, a plant-based steroidal alka-

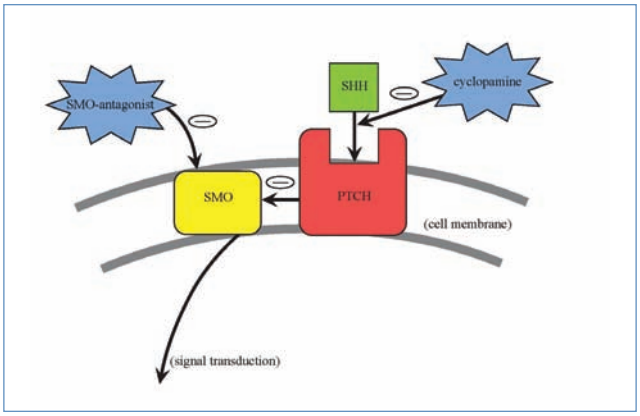

Figure 10: Cyclopamine blocks SHH signal, preventing transduction; SMO antagonist blocks SMO, preventing transduction.

loid, inhibits the cellular response to the SHH signal. They found that cyclopamine blocks activation of the SHH pathway caused by oncogenic mutation making it a potential "mechanism-based" therapeutic agent for human tumours whose pathogenesis involves excess SHH pathway activity. Zhang and others[47] postulate that antagonists of SHH signalling factors could effectively treat KCOTs. Their suggested strategies include the reintroduction of a wild-type form of PTCH, inhibiting the SMO molecule by synthetic antagonists and suppressing the downstream transcription factors of the SHH pathway. They suggest that intracystic injection of an SMO protein-antagonist has the greatest potential as a future treatment option (**Fig. 10**).

Conclusion

The aggressive nature of KCOT warrants an aggressive treatment strategy, and its recent reclassification by WHO as a neoplasm should further motivate clinicians in this direction. Resection of the jaw results in the lowest recurrence rate. However, considering the radical nature of the procedure, unless resection is necessary, it is acceptable to use enucleation in combination with Carnoy's solution or marsupialization.

As research continues, treatment may become molecular in nature. This could eventually reduce or eliminate the need for aggressive methods to manage the lesions. Currently, the novel designation of the OKC as a tumour and the research that influenced this change should serve as a compass by which clinicians can navigate future treatment plans.

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