Odontogenic Keratocyst- The Controversies in Nomenclature and Treatment Modalities

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Abstract: Summary: Odontogenic keratocysts (OKC) now officially known as Keratocystic odontogenic tumor (KCOT) is a benign odontogenic intraosseous tumor which is potentially agrressive having distinguished clinical and histopathological features. 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. 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 purpose of this paper is to review and discuss the redesignation of KCOT and the implications for treatment. [Maheta D NJIRM 2014; 5(5):70-76]

Key Words: Odontogenic Kerotocyst, Keratocystic Odontogenic Tumor, jaw cysts, marsupialization, nucleation

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Introduction: Cysts of the jaw are a common clinicopathological finding. Cysts can be divided into odontogenic (lining of the cystic sac arising from epithelial remnants of embryonic tooth base) and non-odontogenic (the cyst lining is of another origin).[1] In 1956, Phillipsen published an article in Danish and first suggested the term "odontogenic keratocyst."[2] As compared with other types of odontogenic cysts, OKCs appear to have an intrinsically higher growth potential and a propensity to recur following surgical treatment and the potential risk of neoplastic change.[3]

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." WHO recommends the term keratocystic odontogenic tumour as it better reflects its neoplastic nature.[4]

Etiology, Prevalence and Distribution: In the past, odontogenic keratocysts (OKCs) were considered to originate from the primordium of a tooth before mineralization had taken place. Recently it is believed that remnants of the dental lamina played a role, particularly because many OKCs seemed to have an atypical relation to teeth when presenting in the dentate area.[6]

The frequency of OKC has been reported to vary from 2-4% to 11-14% of all the odontogenic cysts.[5,7,8,9,10,11] OKC occur as early as the first decade and as late as the ninth. There has been a pronounced peak frequency in the second and third decades (about 40%- 60%).[12] OKC affect the mandible more frequently than the maxilla, with the mandibular posterior region being the most commonly affected site. OKC are commonly associated with impacted teeth (mandibular third molar most commonly). Swelling was found to be the most common presenting complaint in more than half of all patients. OKC sometimes tend to enlarge silently without any swelling or pain to alert the patient or physician. The overall radiographic appearance of OKC can range from well-defined unilocular lesions to extensive multilocular lesions with ill-defined borders. Root resorption was not found to be a significant feature of OKC.[13] Panoramic radiographs depicted the location and expansile nature of most lesions. CT images revealed position and morphologic features of OKCs, such as areas of thinning, perforation, and cortical loculation of the cortex.[14] Cone beam computed tomography (CBCT) and magnetic resonance imaging (MRI) may be useful as supplemental assessment of some cases with cortical perforation and soft tissue involvement. The risk of injuries involving adjacent anatomic structures (e.g. the inferior dental and lingual nerves), as well as the risk of mandibular fracture, became obvious through the images.[15] The recurrence rate has ranged from as low as 3% to as high as approximately 62%. [3,4,7,8,9,10,16,17,18]

The Controversies in Nomenclature: Mikulicz in 1876 first described OKC as a part of a familial condition affecting the jaws. However in 1926 it was first known as a "cholesteatoma" - simply means a cystic or "open" mass of keratin squames with a living "matrix". The concept of "Primordial cyst" was first mentioned by Robinson in 1945 because the cysts were believed to arise from remnants of the dental lamina or the enamel organs before enamel formation has taken place.[18]

Philipsen in 1956 named and described the "odontogenic keratocyst." The designation "keratocyst" was used to describe any jaw cyst in which keratin was formed to a large extent. The typical histologic features of the OKC include an epithelial lining of regular parakeratinized stratified squamous epithelium. The epithelium is thin, ranging from six to ten cells thick, and lacks rete pegs, which produce the characteristic flat interface between the epithelium and connective tissue. Separation of the epithelium from the supporting connective tissue of the cyst is common. Small ''daughter'' or ''satellite'' cysts may be present in the connective tissue wall of the cyst, although this finding is more common when the OKC occurs as a component of the nevoid basal cell carcinoma syndrome.[19]

Pindborg and Hansen in 1963 who suggested the histologic criteria for describing the essential features of the OKC.

The 7 histologic criteria described were as follows:

1. The lining epithelium is usually very thin and uniform in thickness, with little or no evidence of rete ridges.
2. There is a well-defined basal cell layer, the component cells of which are cuboidal or columnar in shape and often seen in a palisaded arrangement.
3. There is a thin spinous cell layer that often shows a direct transition from the basal cell layer.
4. The cells of the spinous cell layer frequently exhibit intracellular edema.
5. Keratinization is predominantly parakeratotic, but it may be orthokeratotic.
6. The keratin layer is often corrugated.
7. The fibrous cyst wall is generally thin and usually uninflamed.

Keratinization alone is not a finding specific to the OKC because other odontogenic cysts can produce keratin.[16]

In 1967, Toller suggested that the OKC may be best regarded as a benign neoplasm rather than a conventional cyst based on its clinical behaviour. In the years since, published reports have influenced WHO to reclassify the lesion as a tumour. Several factors like Behaviour (locally destructive and highly recurrent); Histopathology (basal layer budding into connective tissue and mitotic figures frequently seen in the suprabasal layers); Genetics (PTCH ("patched"), a tumour suppressor gene) the basis of this decision.[4] Shear published his extensive work on the aggressive nature of OKC and finally labelled it as a benign cystic neoplasm. Shear aggressively used the term "keratocystoma" in naming this cyst.[20]

Meanwhile, Reichart and Philipsen reclassified the odontogenic tumors in 2002 and renamed OKC as keratinizing cystic odontogenic tumor (KCOT) and placed it under the subheading of "benign neoplasm of odontogenic epithelium with mature, fibrous stroma; odontogenic ectomesenchyme not present." This classification got the approval by WHO/IARC at the Editorial and Consensus Conference, held at Lyon, France in July 2003 and in the WHO/IARC classification, the OKC has been renamed as "keratocystic odontogenic tumor" (KOT). KOT is now defined as "a benign uni‐or multicystic, intraosseous tumor of the odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior." WHO "recommends the term keratocystic odontogenic tumor as it better reflects its neoplastic nature."[18]

Management: Treatment of OKC has been in controversy for long. There is high recurrence rate associated with this cystic lesion. Thus many treatment modalities had been advocated for the management of OKC.

The marsupialization (decompression) techniques were based on the exteriorization of the cystic cavity and result in communication with the oral

cavity. The use of marsupialization was originally described by Partsch in the late 1800s.[21] It can save the anatomic structures including the adjacent teeth, the inferior alveolar canal, and the maxillary sinus. By relieving the intracystic pressure, the size of the cyst is reduced, which can induce the eruption of impacted teeth and new bone formation.[2,21,22,23] Decompression produces pronounced changes in the cyst epithelium from genuine keratocyst to nongenuine keratocyst or nonkeratocyst.[21,24,25,26,27] On the other hand decompression or marsupialization has not been well recommended as treatment for the keratocyst, because it was thought that pathologic tissue would be left in situ.[23] The disadvantages of decompression are that 2 surgical procedures are needed and it requires a longer period of time.[24,23,28,29] Also recurrence rate is dramatically high with marsuplization alone.[30,31,32]

Enucleation is a commonly used method for surgical treatment of OKC.[33] Currently, treatment involving careful and aggressive enucleation with close follow up has been advocated for the OKC.[34] The perceived advantages of enucleation include the complete removal of the cyst and a potentially thorough histopathological examination of the lesion.[11,33] However complete removal of OKC can be difficult because of the thin, friable epithelial lining, limited surgical access, skill and experience of the surgeon, cortical perforation, and the desire to preserve the adjacent vital structure.[34,35] Thus it has been shown that enucleation alone for the management of lesions is associated with an unacceptable recurrence rate.

Enucleation with and without various adjuncts has been utilized for many years. Recurrence may result from residual epithelial islands and possibly microcysts left behind.[11] Therefore, some research recommends treatment of the cyst cavity or bone defect around the cyst with Carnoy's solution to destroy these epithelial rests in the cyst wall.[33] Also liquid nitrogen cryotherapy can be used. The aim of the use of these adjuvants is to eliminate epithelial islands and microcysts in the peripheral bone. These adjuncts, when used with enucleation, considerably decrease the recurrence rates.[36,37,38,39]

Cauterizing agent such as Carnoy's solution consists 3 ml of chloroform, 6 ml of absolute ethanol, 1 ml of glacial acetic acid and 1 g of ferric chloride.[11,30,34,40,41] The effect of Carnoy's solution on the inferior alveolar nerve was that of the alterations in neural conductivity developed after 2 min of direct application, with few signs of recovery after two weeks of follow-up.[11,41] However, it is reported that when a proper protocol is followed, the chemical treatment of the nerve can be accomplished without permanent functional damage.[30]

Using enucleation with cryotherapy, the recurrence rate is reduced considerably. The cryotherapy devitalizes an area between 1 and 2 mm beyond the visible margins of the lesion but leaves the inorganic bony framework intact. In this way, any adjacent daughter cells or cyst remnants will be destroyed. A temperature of -20°C is required to devitalize tissues, and only liquid nitrogen can deliver this on a consistent basis. A triple freeze/thaw technique is recommended with a 1-minute freeze followed by a slow thaw for each cycle.[26] despite the cellular necrosis that cryosurgery produces, advantages of the technique include a relative lack of bleeding and scarring. However, because of the difficulty in controlling the amount of liquid nitrogen applied to the cavity, the resultant necrosis and swelling can be unpredictable. The most common complication is wound dehiscence.[37] when the liquid nitrogen cryotherapy is given around the inferior alveolar nerve, the nerve is affected, and patients will have paresthesia or anesthesia.[26]

Carnoy's solution does not maintain the osseous structure whereas cryotherapy maintains bony architecture and facilitates new bone formation.[40]

Resection refers to the surgical removal of a section of the involved jaw. Marginal resections leave behind a rim of uninvolved bone, while a segmental resection removes an entire portion of the jaw without maintaining continuity.[31] Resection should be considered for treatment of recurrent OKC and, when performed, should extend beyond the greatest extent of the lesion to ensure complete removal of remaining satellite cysts or epithelial remnants of cyst wall. Although no

recurrence was found in the patients, esthetics and oral function was usually poor after radical resection.[32,38] A rim mandibulectomy involving approximately 1 cm around the lesion was performed, leaving the lower border of the mandible and the posterior border of the ramus intact.[42] Radical excision provides efficient removal of the affected bone and soft tissue in continuity with the cyst, which minimizes the risk of recurrence. Radical resection has no recurrence rate but does have the highest morbidity rate and should be reserved for multiple recurrent cysts after conservative treatment. Radical surgery for OKCs should be, of course, reserved for those cysts that have undergone carcinomatous transformation.[32,38,42,43,44]

Table 1: Review of Literature relating treatment to Recurrent Rate

Study	Cysts	Treatment	Follow up	Rec. rate %
Al- Hajj and Anneroth (1996)[45]	63	Enucleation	4years	28.5
	16	Enucleation+cryosurgery	4years	37.5
	1	Enucleation+surgical bur	4years	0
	2	Enucleation+cryosurgery+bur	4years	50
	3	Resection	4years	0
Enislidis et al (2004)[46]	24	Decompression +resection	1-1.5 yr	0
Maurette et al (2006)[28]	30	Decompression	2years	14.3
Paul Steolinga (2001)[41]	49	Enucleation+mucosa+carnoy's solution	5years	7.3
	33	Enucleation		
Poramte et al (2010)[36]	120	Enucleation	5years	26
Schmidt and Pogrel (2001)[37]	26	Enucleation+cryosurgery	3.5years	11.5
Kolokythas et al (2005)[47]	11	Resection/enucleation+peripheral ostectomy	1.5-9years	0
	11	Decompression +enucleation	1.5-3years	18.1
Morgan et al (2005)[39]	11	Enucleation	5years	54.5
	2	Enucleation+ cornoy's solution		50
	11	Peripheral ostectomy		18.2
	13	Peripheral ostectomy+ cornoy's solution		0
	3	Resection		0
Zhao et al (2002)[38]	163	Enucleation	3-29years	17.79
	29	Enucleation+cornoy's solution		6.70
	11	Marsuplization +enucleation		0
	52	Resection		0
Titinchi et al (2012)[13]	5	Marsuplization	1-2.5years	60
	50	Enucleation		30
	9	Enucleation+cornoy's solution		11.1
	1	Resection		0
Chirapathomsakul et al (2006)[7]	13	Marsuplization	1-15 ears	16.7
	30	Enucleation		13.3
	11	Enucleation+cornoy's solution		20
	2	Enucleation+curettage		100
	1	Marginal resection		0
	6	Segmental resection		16.7
Zecha et al (2010)[48]	58	Enucleation	4-5years	20.7
	10	Marsuplization		40
Pogrel and Jordan (2004)[23]	10	Marsuplization	2-5years	0
Bataineh and Al Qudah (1998)[49]	31	Resection	2-8years	0

Thus the recurrence rate for various treatment modalities from the above chart:

Marsuplization- as low as 0% to as high as 60%

Enucleation- as low as 13.3% and as high as 54.5%

Enucleation with Cornoy's solution- as low as 6.70% and as high as 50%

Resection- 0%

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. 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 not much 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.

Future Trends: A new novel methodology concentrating on molecular aspects has been devised for management of OKC. 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.[18,50]

Conclusion: Although complete resolution of the lesion while preserving anatomy and function can be achieved with conservative treatment, the need for longterm follow-up of these patients cannot be overemphasized, because recurrence has been reported to occur up to 10 years after treatment. It appears that careful selection of treatment, taking into account the lesion's clinical behavior, radiographic and histopathologic appearance, and association with BCNS, as well as the presence of various molecular markers in the cystic epithelium, can help achieve better control of this entity.

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