INTRODUCTION
Odontogenic keratocysts (OKCs) are developmental odontogenic cysts of epithelial origin, first identified and described in 1876 and further characterized by Phillipsen in 1956 as "a benign unilocular or multicystic, intraosseous tumor of odontogenic origin, with a characteristic cementing layer of lamellar bone and a lining of parakeratinized stratified squamous epithelium with potential for aggressive, infiltrative behavior". Pindborg and Hansen suggested the histological criteria necessary to diagnose OKC in 1962. The initial terminology for an odontogenic keratocyst (OKC) was "primordial cyst". And renamed as "odontogenic keratocyst " by World Health Organization (WHO) in 1992 based on histologic typing. Recently the cyst has been reclassified into benign neoplasm (KCOT). Histopathologically OKC/KCOT typically shows a thin, friable wall, which is often difficult to enucleate from the bone in one piece, and have small satellite cysts within the fibrous wall. Therefore odontogenic keratocysts often tend to recur after treatment.

The treatment of the OKC/KCOT remains controversial. Treatments are generally classified as conservative or aggressive. Conservative treatment generally includes simple enucleation, with or without curettage or marsupialization. Aggressive treatment generally includes peripheral ostectomy, chemical curettage with Carnoy’s solution, cryotherapy, or electrocautery and resection. The choice of treatment should be based on multiple factors; patient age, size and location of the cyst, soft tissue involvement, history of previous treatment and a histological variant of the lesion. The goal is to choose the treatment modality that carries the lowest risk of recurrence and the least morbidity.

Epidemiology
Odontogenic keratocysts (OKCs) account for approximately 3-11% of all cysts in the jaws. They occur in all ages, with a peak incidence in the second and fourth decades of life, with the youngest patient reported at age 5 years.

Etiology
Odontogenic keratocysts (OKCs) are generally thought to be derived from remnants of the dental lamina (rests of Serè), traumatic implantation or down growth of the basal cell layer of the surface epithelium, or reduced enamel epithelium of the dental follicle. Studies have suggested a genetic cause, specifically a PTCH gene aberration, in the etiology of these cysts.

Location
Odontogenic keratocysts (OKCs) can be found in the mandible and the maxilla but are twice as common in the mandible, with a predilection for the angle and ascending ramus. Rare examples of these cysts arising from the temporomandibular joint(TMJ) have been reported. Mandibular cysts can cross the midline, and maxillary cysts may involve the sinus and floor of the nose. Although most odontogenic keratocysts (OKCs) are encountered as intra-osseous lesions, peripheral manifestations have been reported, primarily involving the buccal gingival soft tissue in the canine area of the mandible.
Clinical and Radiological Features

Clinically, odontogenic keratoctysts (OKCs) generally present as a swelling, with or without pain. The cyst classically grows within the medullary spaces of the bone in an anteroposterior direction, causing expansion that is at first minimal. Buccal expansion is noted in approximately 30% of maxillary and 50% of mandibular lesions. It has been demonstrated that the collagenase activity in the cysts' epithelium with its resorbative properties appears to regulate the ability of the lesion to grow expansively in bone.

Radiographically, odontogenic keratoctysts (OKCs) present as a well-defined radiolucent lesion that is either unilocular or multilocular, with smooth and usually corticated margins, unless they have been secondarily infected. In 25-40% of cases, there is an unerupted tooth involved with the lesion, adjacent teeth may be displaced, but root resorption is rarely seen. Maxillary lesions tend to be smaller than mandibular lesions; however, more extensive involvement can be appreciated in the maxilla because of the cancellous nature of the bone. Larger lesions can cause bony expansion with or without perforation of the cortical plates.

Gross Findings

The epithelial lining and connective tissue wall of the odontogenic keratocyst (OKC) is characteristically thin and friable, thus causing the specimen to fragment when treated. Grossly, the lesion often has a bosselated, gray, cystic appearance mimicking the appearance of a glove.

Microscopic Findings

In 1962, Pindborg and Phillipson and Henriksen established strict histologic criteria for the diagnosis of an odontogenic keratocyst (OKC). These criteria include an epithelial lining that is usually thin and uniform in thickness, with little or no evidence of rete ridges; a well-defined basal cell layer, the component cells of which are cuboidal or columnar in shape and often fashioned in a palisaded arrangement; a thin, spinous cell layer which often shows a direct transition from the basal cell layer; spinous-cell layer intracellular edema; surface keratinization that is corrugated and predominantly parakeratotic; and a fibrous connective tissue cyst wall that is thin and usually uninflamed.

Additionally, satellite cysts, solid epithelial proliferations, odontogenic rests (see the image below), and basal layer budding have been described in association with the odontogenic keratocyst (OKC). The incidence of daughter cysts in the cyst wall is reported to range from 7% to 30.1%. Mineralization in the fibrous connective tissue wall may occur, along with inclusion of cholesterol crystals and Rushton bodies.

A number of studies have discussed the histologic variants of the odontogenic keratocyst (OKC): (1) Parakeratinized (2) Orthokeratinized (see the second image below) and (3) combined. There appear to be no statistical differences between orthokeratinized and parakeratinized odontogenic expansion. The scalloped margin of a simple bone cyst and its tendency for minimal expansion can be similar to that of an odontogenic keratoctyst (OKC); however, the margins of a simple bone cyst are more delicate and difficult to detect.

Keratoameloblastoma, a rare histologic variant of the ameloblastoma, can resemble an odontogenic keratocyst (OKC). The epithelium lining of keratoameloblastoma differs from the OKC in that it is not always of uniform thickness, and there is typically separation and edema between the basal cell layer and the rest of epithelium in the keratoameloblastoma.

Radiographically, differentiation between an odontogenic keratocyst (OKC) and other odontogenic cysts and tumors can be challenging. The radiographic features of odontogenic keratoctysts (OKCs) are not pathognomonic, and the presentation can be similar to that of other odontogenic cysts and tumors. Odontogenic keratoctysts (OKCs) can present as dentigerous cysts, primordial cysts, residual cysts, lateral periodontal cysts, or cysts in a nasopalatine location. Misinterpretation of an odontogenic keratocyst (OKC) as a lesion of endodontic or periodontal origin can confuse treatment planning.to diagnosis (see).

Figure 1: Computed tomography scan a multilocular odontogenic keratocyst. demonstrating extensive compartmentalization of mandibular odontogenic keratocyst.

Figure 2: Typical odontogenic keratocyst lining.
keratocysts (OKCs) when age, race, sex, symptomatology, and the clinical impression are compared. The recurrence rate, however, is much higher in the parakeratinized variant, thus, some investigators have suggested that the orthokeratinized variant be classified as a separate entity.

**Immunohistochemistry**

Strong p63 staining has been demonstrated in the epithelium of odontogenic keratocysts (OKCs), especially in the suprabasal layer of the epithelium. It has been postulated that p63 plays a role in blocking apoptosis-inducing and growth inhibitory actions, which may facilitate the proliferative potential of epithelial cells due to its capability of blocking wild type p53, thus enhancing the biologic aggressiveness of these cysts.

Matrix metalloproteinases (MMPs) are enzymes thought to play an important role in regulating the integrity and composition of the extracellular matrix (ECM) and consequently degradation, proliferation, differentiation, and cell death. MMP-1's expression is thought to be associated with odontogenic keratocyst (OKC) degradation of the organic bone matrix, favoring dissemination of these cysts through the trabecular spaces. With immunohistochemistry, MMP-2s have also been observed to reside in the basement membrane of odontogenic keratocysts (OKCs), and they have been implicated in the degradation of the extracellular matrix surrounding the cysts.

Vascular endothelial growth factors (VEGFs) comprise a family of multifunctional proteins and act as a sensitive measure of the angiogenic potential of a lesion. VEGFs have been implicated in the pathogenesis of cystic tumors and radicular cysts and they have been documented to be intensely expressed in odontogenic keratocysts (OKCs).

**Contents of Cyst**

Heparin sulphate, chondroitin 4 sulphate, Hyaluronic acid, GAG. On aspiration there it is whitish, cheesy material with keratin flecks. There is low protein content (< 4mg/dl) with specific gravity 1.018.

**Odontogenic Keratocysts (OKC) Reclassified as Keratocystic Odontogenic Tumor (KCOT)**

The odontogenic Keratocyst is regarded as a developmental abnormality and is generally known for its aggressive nature and high recurrence rate, especially in comparison with other developmental odontogenic cysts. In addition to a distinctive clinical aggressive biological behavior, the expression of various proliferation markers in the epithelial lining and over expression of p53 protein and mutations in p53 and PTCH genes (tumor suppressor genes) have led several investigators to consider odontogenic keratocysts as a benign cystic neoplasm.

The components of the connective tissue in KCOT revealed some resemblance with the stromal myofibroblasts, differences in the collagen fibers of the extracellular matrix, high enzymatic activity with increased matrix metalloproteinases (MMPs) and mast cell tryptase and increased expression of receptor activator of nuclear factor-kB (RANK), RANK lig-and (RANK), RANK LIG- and (RANKL), osteoprotegerin (OPG) and tumor angiogenesis. Focusing on the importance of the epithelial mesenchymal interactions in odontogenic tumors, previous studies supported that the stroma of keratocysts should not be regarded just a structural support of the cyst wall, but rather as portraying the features of a “tumoral stroma”.

However, its growing potential to a large size before manifesting clinically and the tendency to recur following surgical treatment, give rise to a discussion as to its true pathological nature and terminology. Hence in 2005 World Health organization, based on behavior, histology and genetics, reclassified the traditional designation, stressing the benign behavior of this lesion was substituted by a term that would better reflect its neoplastic nature Keratocystic odontogenic tumor (KCOT) and the lesion was thus described as benign uni or multicystic, intra-osseous tumor arising from the dental lamina or its remnants. The orthokeratinized variant of the odontogenic keratocyst is not currently included as being part of the spectrum of keratocystic odontogenic tumor. The main histopathological features defined in 2005 enable to differentiate KCOT from jaw cysts with keratinization.

- Well defined, often palisaded, basal layer of columnar cuboidal cells.
- Intense basophilic nuclei of the columnar basal cells oriented away from the basement membrane.
- Parakeratotic layers with an often corrugated surface
- Mitotic figures frequently present in the suprabasal layer

**Management**

1. **Decompression and marsupialization**

Decompression of a cyst involves any technique that relieves the pressure within the cyst as this pressure is the way by which the cyst grows by expansion. Decompression can be performed by making a small opening in the cyst and keeping it open with a drain.

Marsupialization, on the other hand, involves converting the cyst into a pouch so the cyst is decompressed, but this is a more definitive treatment than decompression as it exposes the cyst lining to the oral environment. Mandibular cysts are normally marsupialized into the oral cavity, while maxillary cysts can also be marsupialized into the maxillary sinus or nasal cavity, as well as the oral cavity.

Decompression and marsupialization of cysts is probably the earliest recommended treatment and was first suggested by Partsch in the late 19th century. In many parts of the world, marsupialization is still described as a Partsch I procedure (the Partsch II procedure is enucleation and primary closure). Although decompression or marsupialization was not recommended as treatment for the KCOT by some authors, because it was thought that the pathologic tissue would be left in situ, decompression or marsupialization has been recommended in a number of studies as a technique that allows partial decrease in size in the KCOT so that vital structures like teeth or the inferior alveolar nerve can be preserved, then the KCOT was certainly enucleated.

Those authors who are against the use of marsupialization or decompression for the treatment of KCOT depend on, that this technique does not remove completely the whole cystic covering, which would lead to a continuation of epithelial proliferation and facilitate the Brondum and Jensen (1991) reported a recurrence rate of 25% in 32 (OKCT) patients...
treated with decompression of the lesion. On the other hand, other studies have shown that marsupialization of KCOT can be followed by total resolution of the lesion without any further surgery. The marsupialization technique was described by Pogrel (2005) as a window at least 1 cm in diameter is made into a cyst, and an attempt is made to suture the cyst lining to the oral mucosa. In the maxilla, the cyst is then often packed open with the packing protruding through the opening. The packing consists of iodoform gauze impregnated with bacitracin ointment. When it is removed in the maxilla, the cavity is usually self-retaining and the patient needs to irrigate twice a day to prevent food accumulation or closure of the fistula. In the mandible, there is a greater tendency for spontaneous closure of the fistula and reformation of the cyst, particularly in the posterior mandible. In these cases, we have found that the use of a nasopharyngeal anaesthesia tube suitably cut down makes an excellent stent to keep the cyst open. Again, the cavity is irrigated twice daily. Studies have shown that when the OKCT is open to the oral cavity by marsupialization, a number of changes occur in the cyst lining. Histologically, the lining of OKCT is only 5 or 6 cells thick and tears easily on attempted enucleation; which is one of the causes of the high recurrence rate. With decompression or marsupialization, the lining appears to become thicker and easier to enucleate, and histologically it does appear to change and resemble normal oral mucosa, both with routine histology and with immunohistochemistry. Pogrel (2005) concluded that, decompression and/or marsupialization has at least as high a success rate as the other more aggressive treatments with lower morbidity and preservation of important vital structures.

2. Enucleation with and without adjuncts

To enucleate is “to remove whole or clean, as a tumour from its envelope.” Curettage is defined as “the removal of growths or other material from the wall of a cavity. Enucleation with and without various adjuncts has been utilized for many years. Although enucleation/curettage has the advantage over marsupialization of providing a complete specimen for histopathologic analysis, it shows recurrence rates as high as 62.5%, which is no longer an acceptable treatment modality. This high incidence of recurrence is explained by the thin, friable wall of the OKCT, which is often difficult to enucleate from the bone in one piece, and the small satellite cysts within fibrous wall. Many clinicians consider enucleation and curettage as the minimal requirement in the treatment of KCOT. Regarding curettage, clinicians have advocated mechanical techniques (hand, rotary) alone or in combination with a chemical solution (Carnoy’s) (Stoeinga, 2003) or cryosurgical agents (liquid nitrogen).

3. Enucleation and treatment of the bony defect with Carnoy solution

As a result of the difficulty of enucleating the thin, friable wall of the KCOT as one piece, and due to the small satellite cysts, therefore, treatment should aim to eliminate the possible vital cells left behind in the defect. For this reason a mild, not deeply penetrating, cauterizing agent is used 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). This should be enough to do cauterization of the remaining cells. In case the cyst has penetrated through the lingual or buccal cortex, authors described the use electro-cauterization to avoid a recurrence in the soft tissues. Other studies showed that, although the defect was treated with Carnoy’s solution. Microcysts and epithelial islands were always seen in the overlying attached mucosa. And so recurrence took place. So, the authors of these studies recommended the complete excision of the overlying mucosa to decrease the recurrence. Also, reported in their study that the treatment with Carnoy’s solution did not show a significant association with recurrence. Yet, Voorsmit et al. (1981) reported a decreased recurrence rate following treatment with enucleation and Carnoy’s solution (2.5%) compared with enucleation alone (13.5%). According to enucleation of KCOT followed with application of Carnoy’s solution appears to be the least invasive procedure with the lowest recurrence rate. And they reported that adding Carnoy’s solution to the cyst cavity for 3 min after enucleation results in a recurrence rate comparable to that of resection without unnecessarily aggressive surgery.

The effects of Carnoy’s solution on the inferior alveolar nerve were first reported. The authors did not observe axonal damage during the first three minutes of direct application. In contrast, another important study, Wolgen et al. (1999), noted that the alterations in neural conductivity developed after 2 min of direct application, with few signs of recovery after two weeks of follow-up. However, Ju´ nior et al. (2007), reported that when a proper protocol is followed, the chemical treatment of the nerve can be accomplished without permanent functional damage.

4. Enucleation and liquid nitrogen cryotherapy

Theoretically, the ideal treatment for the KCOT would be enucleation or curettage followed by treatment of the cavity with an agent that would kill the epithelial remnants or satellite cysts. In addition, the osseous framework should be left intact to allow for osteoconduction. Liquid nitrogen has the ability to devitalize bone in situ while leaving the inorganic frame work untouched, as a result of this, cryotherapy has been used for a number of locally aggressive jaw lesions, including KCOT, ameloblastoma and ossifying fibroma. Cell death with cryosurgery occurs by direct damage from intracellular and extracellular ice crystal formation plus osmotic and electrolyte disturbances.

According to Schmidt and Pogrel (2001) the standardized technique is as follows, the initial step in management of the lesion is enucleation of the cyst. The surrounding tissues are then protected with sterile wooden tongue blades and gauze, and the cavity is sprayed with liquid nitrogen twice for 1 min, with a 5-min thaw between freezes. Bone graft can inserted in the defect simultaneously, and then mucosa is closed with watertight sutures. The advantages of liquid nitrogen over alternative methods of devitalizing the tissue beyond the visible lesion of the margin are that (1) The bone matrix is left in place to act as a clean scaffold for new bone formation,
A bone graft can be placed immediately to accelerate healing and minimize the risk of a pathologic fracture, and decrease 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 recurrence rate following enucleation and liquid nitrogen cryotherapy has been reported at 3–9%.

When the liquid nitrogen cryotherapy is given around the inferior alveolar nerve, it is affected, and patients will suffer paraesthesia or anaesthesia. However, the axon sheaths are left intact and nerve regrowth is normal such that most patients obtain partial or complete return of sensation in 3 months.

Block resection, with or without preservation of the continuity of the jaw, refers to either segmental resection (surgical removal of a segment of the mandible or maxilla without maintaining the continuity of the bone) or marginal resection (surgical removal of a lesion intact, with a rim of uninvolved bone, maintaining the continuity of the bone) which is an extreme technique that results in considerable morbidity, particularly because reconstructive measures are necessary to restore jaw function and aesthetics, wonders whether such aggressive therapy is warranted for a benign lesion that can be managed reasonably well with relatively simple means. In a systematic review done by Blanas et al. (2000), the authors reported that resection was found to have the lowest recurrence rate (0%) but the highest morbidity rate, while enucleation with application of Carnoy’s solution can result in a recurrence rate comparable to that of resection without unnecessarily aggressive surgery. Multiple studies concluded that keratocysts might be treated with a conservative approach, the only disadvantages being the extended therapeutic time. Extensive resection of the mandible with its attendant morbidity may be too radical for large KCOT and even an overtreatment.

**Decision Tree**

The decision trees on the treatment of cystic lesions of the jaws based on their location. Special consideration was given for the treatment of potentially aggressive lesions such as odontogenic keratocysts and cystic ameloblastomas.

Figure 3: Protocol for management of uni-locular cystic lesion maxilla and body of mandible.
Figure 4: Protocol for management of multi-locular cystic lesion.
Recurrences

The incidence of recurrence of OKC has varied from 2.5% to 62%. The great degree of variation in these reports are mainly because some series included cysts from patients with Nevroid Basal cell carcinoma syndrome (NBCCS), while other reasons for this variation can be due to duration of the follow-up period and method of treatment used. In 1976, Brannon—proposed three mechanisms for OKC recurrence: Incomplete removal of the cyst lining, growth of a new OKC from satellite cysts (or odontogenic rests left behind after surgery), and development of a new OKC in an adjacent area.

Histopathological features that predict recurrences.

The major features that can be considered to predict recurrences in OKC are:

- Higher level of cell proliferative activity in the epithelium
- Budding in the basal layer of the epithelium
- Parakeratinization of the surface layer

- Supraepithelial split of the epithelial lining
- Subepithelial split of the epithelial lining
- Presence of remnants/cell rests as well as daughter cysts.

Summary

OKC/KCOT is one of the most aggressive odontogenic lesion with a high recurrence rate. Multiple surgical approaches were introduced including decompression, marsupilization, enucleation with or without adjunct (Carnoy’s solution, cryotherapy) and resection. Depending on other studies KCOT can be conservatively treated with enucleation and application of Carnoy’s solution or cryotherapy. This can be used specially in the large lesions that when treated with resection, the continuity of the jaw will be interrupted. This technique shows comparable results to other more aggressive techniques.

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