Review Article

KCOT /OKC clinical-molecular pathogenesis, surgical treatment & prognosis: A review

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ABSTRACT

Odontogenic keratocysts (OKCs) are epithelial developmental cysts. It occurs mainly in the second and third decades, with a slight predilection for males. Usually, OKCs are solitary lesions. They may occur mostly in the mandible; most commonly in the posterior body and ascending ramus. Radiographically, OKCs present as a well-defined radiolucent lesion with smooth and corticated margins. They may present as a multilocular or unilocular radiolucent lesion. In most of the cases, there is an unerupted tooth involved with the lesion. OKC’s is one of the most aggressive odontogenic Cysts due to its high recurrence rate and its tendency to invade adjacent tissue. Treatment Approaches vary in different studies from marsupialization and enucleation, which may be combined with Adjuvant therapy such as cryotherapy or Carnoy’s solution, BIPP to marginal or radical resection.

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1. Introduction

Keratoctytic odontogenic tumor (KOT), previously known as odontogenic keratocyst, is a cystic benign neoplasm that originates from the odontogenic epithelial remnant first described by Philipsen (1956). It is mostly seen in the second, third and fourth decades of life with male predilection. Its local invasive behavior, high recurrence rate, and association with a genetic mutation that may or may not be associated with the nevoid basal cell carcinoma syndrome (NBCCS) have attracted the attention of researchers worldwide. World Health Organization described OKC as a locally aggressive, cystic jaw lesion with a putative high growth potential and a propensity for recurrence. Odontogenic keratocyst is a developmental odontogenic cyst typically occurring in the mandible and maxilla, with a predilection for angle and ascending ramus of the mandible. The OKC involves approximately 11% of all cysts in the jaws and can be associated, although not in all cases, with an impacted third molar. Radiographically, OKCs present as a well-defined radiolucent lesion with smooth and usually corticated margins. They may present as either a multilocular or unilocular radiolucent lesion. In 25% to 40% of cases, there is an unerupted tooth involved in the lesion. It may give the appearance of a periapical cyst, dentigerous cyst, lateral periodontal cyst, nasopalatine duct cyst, traumatic duct cyst and even tumors such as ameloblastoma. KCOT arises from cell rests of the dental lamina, typically showing 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. It tends to grow in the anteroposterior direction within the medullary cavity of the bone without causing obvious bone expansion thus causing its delayed observation by the patients. Most of the researchers have found increased immunohistochemical expression of the proliferation markers Ki67 and PCNA in the OKC.
compared to other odontogenic lesions. Non-neoplastic proliferative lesions may also demonstrate high expression of some proliferative markers. The Ki-67 expression is also seen in low grade mucoepidermoid carcinoma, a malignant neoplasm, which is significantly lower than that in glandular odontogenic cysts, an odontogenic cyst. Recent advances in genetic and molecular research, i.e., PTCH1 mutations and involvement of the Hedgehog signaling pathway, have led to increased knowledge of OKC pathogenesis which hints at potential new treatment options. Treatment of KCOT are generally classified as conservative or aggressive. Conservative treatment usually 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.

1.1. Clinical-molecular pathogenesis

The OKC grows primarily in the marrow spaces and in an antero-posterior direction. Only when they reach a considerable size they expand bucco-lingually and become evident clinically when seen by the clinician most of them are large and may have perforated the bone especially lingually where the capsule is in close contact with the periosteum. A considerable number of OKCs are asymptomatic and hence are detected only by incidental radiographic findings. When they are symptomatic, swelling and intra-oral drainage appear to be most common. Lesions found in children are often indicative of multiple cysts as a component of NBCCS. Approximately 5% of patients with OKCs/KCOTs have multiple cysts and another 5% have NBCCS.

OKCs /KCOTs are found in the mandible in approximately a 2:1 ratio. In the mandible, the posterior portion of the body and the ramus region are most commonly affected, and in the maxilla, the third molar area is mostly affected.

Radiographically, an OKC/KCOT characteristically presents as a well-circumscribed radiolucency with smooth radiopaque margins. Multilocularity is often present and tends to be seen mostly in larger lesions. Most lesions, however, are unilocular, with as many as 40% noted adjacent to the crown of an unerupted tooth (dentigerous cyst presentation). Approximately 30% of maxillary and 50% of mandibular lesions produce buccal expansion. Mandibular lingual enlargement is occasionally seen.

The World Health Organization (WHO) has recommended the use of the term keratocystic odontogenic tumor (KCOT), rather than odontogenic keratocyst (OKC), because the former name better reflects the neoplastic behavior of the lesion. Genetically, the lesion shows a repeatable chromosomal abnormality (PTCH gene on chromosome 9q22.3-q31). Neviod basal cell carcinoma syndrome is a rare inherited multisystem disorder that is a result of mutations in the PTCH gene. Classical triad composed of the syndrome is multiple basal cell carcinoma, OKC, Bifid ribs. Other variety of possible abnormalities are, cutaneous anomalies, dental and osseous anomalies, ophthalmologic abnormalities, neurologic anomalies sexual abnormalities etc.

The epithelial lining of OKC expresses higher levels of p53 than any other cyst types. This overexpression is not only due to mutation of p53 gene, rather reflects overproduction or stabilization of normal p53 protein. Other genes that can be correlated to OKC/KOT are PTCH2 and SUFU. Few authors also have demonstrated loss of heterozygosity in p16, MCC, TSLC1, LTAS2, and FHIT genes. These findings thus explain the aggressive behaviour of OKC. The defining histologic feature—the presence of parakeratin—is unique among the myriad inflammatory and developmental cysts that occur in the jaws. Typically corrugated, rippled or wrinkled epithelium. Uniform thickness of epithelium, usually ranging from 6 to 10 cells layer Prominent, polarized basal layer of cells give picket fence or tombstone appearance. Lumen of the cyst may be filled with a thin straw coloured fluid or might be thicker creamy material. In presence of inflammation epithelium loses keratinized surface and may thicken, may develop rete process or ulceration may occur. The major histopathological 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, parakeratization of the surface layer, suprapapillar split of the epithelial lining, subepithelial split of the epithelial lining, presence of remnants/cell rests as well as daughter cysts.

2. Discussion

Odontogenic keratocyst (OKC) is of particular interest because of its high recurrence rate and aggressive behavior. The age at diagnosis and sex distributions of patients with OKCs have been reported. As in other studies. OKC was found to occur in patients of a wide age range, with an average patient age of 30.8 years.

The ratio of men to women with OKC was believed to be 1:1 in both genders. Although several other studies have reported a male predilection for OKC. The most common clinical manifestations shown were swelling, pain, or both, which is in accordance with other studies. OKCs were sometimes symptom-free and were found incidentally during routine radiographic examination, which was consistent with the information from previous studies that the OKCs tend to enlarge in cancellous bone to a considerable size before any significant buccal or lingual expansion appears to alert the clinicians and patients of an underlying lesion. KOT is locally destructive, has a high recurrence rate, and may be associated with increased morbidity secondary to multiple surgical procedures.
Keratocysts can be located at the periapical region giving the differential diagnosis of periapical cysts; or they may envelope the crowns of unerupted teeth, mimicking dentigerous cysts. It has been postulated that several mechanisms are involved in the recurrence of OKCs, including incomplete removal of the cyst walls or the epithelial islands and/or microcysts, development of a new cyst as in BCNS, parakeratocysts, and surgical access difficulty (Stoelinga, 2005; Giuliani et al., 2006; Chiraphatomsakul et al., 2006; Tolstunov and Treasure, 2008).29,31,32

The treatment of the KCOT remains controversial. 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. 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, BIPP, cryotherapy, or electrocautery and resection.36

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).37

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.8,9 Many clinicians consider enucleation and curettage as the minimal requirement in the treatment of KCOT.38 OKCs treated with enucleation had a significantly higher recurrence rate than those treated with other methods.7,30-41

It is suggested that if enucleation is chosen as a surgical treatment, the clinician should give more attention on the dentate area and remove the teeth if there is any doubt of leaving pathologic tissue behind.42,43 Some clinical and molecular studies showed that the parakeratinized and orthokeratinized OKCs were significantly different in molecular area as well as the Recurrence rate; orthokeratinized OKCs had a lower recurrence rate than the parakeratinized OKCs, with which the relevance of the histology is not clear with respect to the behavior of both entities.36,43

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}.5 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 electrocauterization to avoid a recurrence in the soft tissues.44

The exact location of epithelial islands and microcysts remains a controversy. They may be located in the connective tissue cyst wall, in the overlying soft tissue and/or in the bony bed of the cyst. The use of liquid nitrogen, Carnoy’s solution and peripheral ostectomy is to eliminate epithelial islands and microcysts in the peripheral bone. These adjuncts, when used along with enucleation, considerably decrease the recurrence rate.1

BIPP can be used as well. BIPP is a bright yellow paste of sub nitrate 250mg/g, iodoform 500mg/g and liquid paraffin 250 mg/g. It is usually indicated to pack cavities after ear, nose and throat surgery. This paste is usually placed in cavities and left in place till the cavities heals or a graft is taken. It is not recommended to be used for open wounds.

Bismuth has topical antiseptic properties and can be used as an astringent and contributing to the antibacterial properties of BIPP by releasing dilute nitric acid on hydrolysis. Bismuth has a half-life of 5 days in the body but is known to remain in kidney for a longer duration. Bismuth has side effects like neurotoxicity because it is known to interfere with oxidative metabolism of brain. Symptoms of its toxicity include Head ache, Nausea, Stomatitis, Bismuth line in the gingiva (Bismuth line).32

Iodoform chemical name is triiodomethane. This is another component of BIPP. It has a distinctive colour as well as smell. Iodoform decomposes to release iodine which is an antiseptic. Paraffin is added into BIPP as a lubricant which aids in atraumatic placement and removal of pack.32

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 framework untouched, as a result of this, cryotherapy has been used for a number of locally aggressive jaw lesions, including KCOT, ameloblastoma and ossifying fibroma.45 Cell death with cryosurgery occurs by direct damage from intracellular
and extracellular ice crystal formation plus osmotic and electrolyte disturbances.46

Lastly leaving the option of Resection where it 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.47

3. Conclusion

Although the literature contains many reports regarding management of KCOT, debate still exists as to the most effective treatment for this lesion.

Initial evaluation must include a thorough history and physical examination of the patient along with radiographic investigations, in order to formulate a probable differential diagnosis. Depending on size, location, and behavior, the treatment can be decided, be it an incisional versus excisional biopsy. Treatment of the KCOT varies from enucleation and curettage to osseous resection. Many factors should be considered in the selection of the appropriate treatment that includes size and extent, location, presence of perforation or soft tissue involvement, age of individual, primary or recurrent nature of lesion. Long-term follow-up is suggested because KCOT's have been known to have late recurrences. Our article attempts to give a gist of the features as well as treatment modalities of the KCOT. It also emphasizes the importance of a careful histological examination and the necessity of obtaining biopsy materials from various areas to prevent a misdiagnosis of large sized lesions. In the light of literature, it may be concluded that an aggressive treatment modality like marsupialization, enucleation with or without application of camroy’s solution might be considered as a viable treatment modality for the KCOT.

4. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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None.

References

of jaw cysts: different existence of keratins in odontogenic and non-
Histopathology and immunocytochemical study of 15 cases.