ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Keratocystic Odontogenic Tumour : A Review of Literature

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ABSTRACT

Keratocystic odontogenic tumors (KCOTs) comprise a unique pathological entity characterized by aggressive/destructive behavior and propensity to recurrence. There are many types of tumours of the jaws, but what makes the kcot unusual are its characteristic histopathological and clinical features, including potentially aggressive behaviour, high recurrence rate, and an association with the nevoid basal cell carcinoma syndrome. Keratocystic odontogenic tumour is a locally aggressive tumour affecting the maxilla and mandible. The purpose of this paper is to review the features and behaviour of the odontogenic keratocyst, now officially known as the keratocystic odontogenic tumour (KCOT).

Keywords: Keratocystic odontogenic tumour, odontogenic keratocyst, NBCC syndrome, Ki-67

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ISSN: 0975-8585

INTRODUCTION

Odontogenic keratocysts, recently reclassified as keratocystic odontogenic tumors (KCOTs) [1], are among the most controversial and frequent pathological entities affecting the maxillofacial region [2-4]. Their aggressive/destructive behaviour and proneness to recurrence have led the condition to be classified as a benign neoplasm, in spite of actually being a simple cystic lesion [5]. It is so named keratocyst, because the cyst epithelium produces excessive keratin which fills the lumen.

Keratocystic odontogenic tumours (KCOTs) account for approximately 3-11% of all tumours in the jaws.[7,10] They occur in all ages, with a peak incidence in the second and fourth decades of life,[12,10] with the youngest patient reported at age 5 years.[7] The mean age of patients with multiple keratocystic odontogenic tumours (KCOTs) , with or without NBCCS, is younger than those with single nonrecurrent KCOTs. KCOT is predominantly a disease of white individuals, primarily Northern Europeans, and there is a reported male-to-female ratio of 1.6:1 [7,10] although Chirapathomsakul et al reported that KCOTs are slightly more common in women than men.[10] Peripheral keratocystic odontogenic tumours (KCOTs) have a female predominance with a female-to-male ratio of 2.2:1.[9]

In 1967, Toller suggested that the OKC may be regarded as a benign neoplasm rather than a conventional cyst based on its clinical behavior [32]. In the years since, WHO reclassified the lesion as a tumour. Several factors form the basis of this decision.

- Behaviour: KCOT is locally destructive and highly recurrent.
- Histopathology: According to Ahlfors et al there is budding of the basal layer into the connective tissue.[23] According to WHO, there are mitotic bodies frequently present in the suprabasal layer.[1]

Definition

Keratocystic odontogenic tumour (KCOT) 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.”[1], these lesion were in the earlier days considered as an odontogenic keratocyst [6]. Several investigators suggested that odontogenic keratocysts be regarded as benign cystic neoplasms rather than cysts, and in the latest WHO classification of odontogenic tumours(2005), these lesions have been given the name " keratocystic odontogenic tumor.

Etiology

Keratocystic odontogenic tumours (KCOTs) are generally thought to be derived from remnants of the dental lamina (rests of Seres), traumatic implantation or down growth of the basal cell layer of the surface epithelium,[1] or reduced enamel epithelium of the dental follicle.[11]

Location

Keratocystic odontogenic tumours (KCOTs) can be found in the mandible and the maxilla but are twice as common in the mandible, with a predilection for the angle, ascending ramus, and following the anterior ramus. In the maxilla, the most common site is the 3rd molar area followed by the cuspid region. According to Brannon et al the mandible is involved 65% of the cases, whereas in the maxilla it is about 35% only. Rare examples of these tumours arising from the temporomandibular joint (TMJ) have been reported. Mandibular tumours can cross the midline, and maxillary tumours may involve the sinus and floor of the nose. Although most KCOTs are encountered as intraosseous lesions, peripheral manifestations have been reported, primarily involving the buccal gingival soft tissue in the canine area of the mandible.[12]

Clinical Features

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, therefore if there is multiple keratocysts present, it is indicated to check for other manifestations of the syndrome.[12]

Clinically, keratocystic odontogenic tumours (KCOTs) generally present as a swelling, with or without pain.[11,13] The tumour classically grows within the medullary spaces of the bone in an anteroposterior direction, causing expansion that is at first minimal.[14] Buccal expansion is noted in approximately 30% of maxillary and 50% of mandibular lesions.[11] It has been demonstrated that the collagenase activity in the epithelium with its resorbative properties appears to regulate the ability of the lesion to grow expansively in bone. [15]

According to Brannon et al 50% of the patients, were symptomatic before seeking treatment and the most common features were pain, soft tissue swelling and expansion of bone. Also associated with drainage and neural manifestations such as paresthesia of lip.[12] KCOT in maxilla has a high tendency of being secondarily infected as it may be in close proximity to the maxillary sinus.[12]

Radiographic Features

Radiographically, keratocystic odontogenic tumours (KCOTs) 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[10]. In 25-40% of cases, there is an unerupted tooth involved with the lesion[10] ; 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.[13] Larger lesions can cause bony expansion with or without perforation of the cortical plates.[16]

When keratocystic odontogenic tumours (KCOTs) are seen in a pericoronal location, differentiation from a dentigerous cyst may be difficult. Radiographic connection of a cyst to a tooth at a point apical to the cementoenamel junction, with no expansion, favors a KCOT.

The typical multilocular appearance of an KCOT can be mistaken for that of ameloblastoma or odontogenic myxoma, although ameloblastomas typically present with significant clinical expansion. The scalloped margin of a simple bone cyst and its tendency for minimal expansion can be similar to that of a KCOT; however, the margins of a simple bone cyst are more delicate and difficult to detect.[17]

Misinterpretation of a KCOT as a lesion of endodontic or periodontal origin can confuse treatment planning ; thus microscopic assessment is the key to diagnosis.

Histopathological Findings

In 1962, Pindborg and Phillipsen and Henriksen established strict histologic criteria for the diagnosis of a keratocystic odontogenic tumour (KCOT).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; having a tomb-stone or picket-fence appearance, 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 wall that is thin and usually uninflamed.[18]

Additionally, satellite cysts, solid epithelial proliferations, odontogenic rests, and basal layer budding have been described in association with the KCOT.[19] The incidence of daughter cysts in the 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.[19]

These cysts are formed with a stratified squamous epithelium that produces othokeratin (10%), parakeratin (83%) or both types of keratin (7%) No rete-pegs are present, therefore the epithelium sluffs from the connective tissue, about (94%) The epithelium is thin and there is frequent mitotic activity, therefore the cyst grows in a neoplastic manner and not in response to internal pressure. [12]

Immuno Histochemistry

Matrix metalloproteinases (MMPs) MMP-1's expression is thought to be associated with KCOT 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 keratocystic odontogenic tumours (KCOTs), and they have been implicated in the degradation of the extracellular matrix surrounding the tumours.[13]

Vascular endothelial growth factors (VEGFs) comprise a family of multifunctional proteins and act as a sensitive measure of the angiogenic potential of a lesion.[22] VEGFs have been implicated in the pathogenesis of cystic tumors and radicular cysts,[22] and they have been documented to be intensely expressed in KCOTs [21,22]

Immunohistochemical studies have examined KCOTs by using various markers of proliferation and of apoptosis. The proliferative activity of the epithelial lining of KCOTs has been studied by using different markers of proliferation as Ki-67[42]. Ki-67 is the prototypic cell cycle related nuclear protein, expressed by proliferating cells in all phases of the active cell cycle[43]. The detection of Ki-67 has been used to evaluate the pro-liferative potential of healthy cells as well as of pre-neoplastic and neoplastic lesions[44].

Molecular Genetics

The epithelial lining of OKC/KCOT expresses higher levels of p53 than any other cyst types. This overexpression is not due to mutation of p53 gene, rather reflects overproduction and/or stabilization of normal p53 protein.[14] Other genes that can be correlated to OKC/KCOT are PTCH2 and SUFU. Few authors also have demonstrated loss of heterozygosity in p16, MCC, TSLC1, LTAS2, and FHIT genes.[14] These findings are helpful to explain the aggressive behaviour of KCOT.

PTCH ("patched"), a tumour suppressor gene involved in both NBCCS and sporadic KCOTs occurs on chromosome 9q22.3-q31[33-37]. Evidence has shown that the pathogenesis of NBCCS and sporadic KCOTs involves a "2-hit mechanism,"with allelic loss at 9q22[38,39]. The 2-hit mechanism refers to the process by which there is inactivation of tumour suppressor gene[40]. 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[39]. According to Lench et al[41], 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."

Treatment

KCOt is well known for their strong tendency to recur.[23] Much debate has been done and various studies performed, to ascertain ideal treatment modality for OKC/KCOT. Whatever modality has been implied, none of these have shown to completely prevent recurrence of the lesion, the problem is still compounded in case of NBCCS and multiple lesions.

Eyre and Zakrezewska [24] in 1985, have stated the following treatment modalities for OKC/KCOT

- Enucleation
  - With primary closure
  - With packing
  - With chemical fixation
  - With cryosurgery
- Marsupialization Only
  - Followed by enucleation
- Resection

The choice of the treatment has always been difficult, since the patient well-being is of primary concern, although not compromising the chances of recurrences. The recurrence rates of KCOTs ranges from 2.5% to 62%[31]. The mechanism by which recurrence occurs has been described by Voorsmit et al in 1981. It states that any lining epithelium left behind may give rise to the formation of a new lesion.[31]

Morgan and his colleagues[25] have categorized surgical treatment methods for KCOT as conservative or aggressive. The conservative treatment is "cyst oriented" and thus includes enucleation, with or without curettage or marsupialization. The advantage is preservation of anatomical structures and reduced morbidity to the patient. However it has not gained much popularity because complete removal of the lesion is difficult, therefore there are higher chances of recurrence. The aggressive treatment is done considering "neoplastic nature" of KCOT and includes peripheral ostectomy, chemical curettage, or enbloc resection. It is mostly recommended for large lesions, recurrent cases and syndromic patients. Resection of the lesion supposedly has the least recurrence rates of all the treatment modalities. Decompression has also been used to treat KCOTs, which is done by relieving the pressure within the cystic cavity and allowing new bone to the fill the space It saves structures like tooth roots, maxillary sinus and inferior alveolar canal from surgical damage.[31]. Dammer *et al*.[26] have suggested conservative approach for small KCOTs (maximum 1 cm in diameter) near alveolar process, and radical excision for larger lesions near the base of the skull that has invaded soft tissue. On the contrary, Forsell and coworkers have reported that the size of the lesion does not affect the recurrence rate.[27]

Future Modalities

Due to the recent advances and thus determination of molecular basis of this entity, a new novel methodology concentrating on molecular aspects has been devised. The Hh pathway can be blocked at different levels, and Hh inhibitors could serve as attractive antitumor agents.[28] According to some studies, cyclopamine, a plant-based steroidal alkaloid, blocks activation of SHh pathway caused by oncogenic mutation.[29] Other studies also show antagonists of SHh signaling factors could effectively treat KCOT.[30]

CONCLUSION

In conclusion,keratocystic odontogenic tumours have benign neoplastic behaviour and hence they have been reclassified as a tumour. They also show a high rate of recurrence and multiplicity. In the presence of multiple KCOTs, the patient should be evaluated for other signs suggestive of Nevoid Basal Cell Carcinoma syndrome.

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