ODONTOGENIC KERATOCYST REVISITED: A COMPREHENSIVE REVIEW

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Abstract

OKC or odontogenic keratocyst is a common entity comprising the majority of cysts being reported. These lesions constitute a large group showing varying presentations from small lesions identified accidentally to highly destructive and aggressive lesions transforming into malignancy. It is a rare odontogenic cyst being an area of interest owing to its unique nature. OKC on radiograph can also resemble lateral periodontal cyst. As OKC resembles many other cysts, it is vital to do a histologic examination of all the cysts removed surgically. The majority of the OKCs are seen as a single lesion, however, in a few cases, 2 OKCs are seen, and in others, it can resemble BCNS.

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INTRODUCTION

OKC arises from the remnants of the dental lamina in the maxilla and mandible before the completion of odontogenesis.[1] OKC can also arise from basal cells of the epithelium overlying and be first reported in 1876 and was first classified in 1956 by Phillipsen. It was Hansen and Pindborg in 1962 that suggested the vital role of histology in the identification of OKC.[2] Recently, WHO released the term cystic neoplasm/ keratocystic odontogenic tumor (KCOT) for OKC as it presents chromosomal and genetic abnormalities, high mitosis histologically, and aggressive clinical behavior. It is a developmental and enigmatic cyst requiring attention with a high potential for growth and recurrence rates by forming compartments.[3]

It poses a high challenge to pathologists and surgeons leading to changes in the nomenclature and classification many times. In 1877, odontomas were subdivided into cysts by Bland-Sutton whereas odontogenic cysts were reclassified by Gabell, James, Payne, Thoma and Goldman, Pindborg and Clausen, WHO, and WHO in 1914, 1946, 1958, 1971, and 1992 respectively.[4]

With various nomenclatures, OKC is still a challenge to clinicians. Hence, the present article is aimed to review OKC from various aspects focusing on classification, etiopathogenesis, incidence, prevalence, recurrence, and management of OKC.

Cholesteatoma

In 1976, Mikulicz described OKC as a familial condition affecting the jaw and was named cholesteatoma in 1926 for the first time meaning an open or cystic mass of keratin squames having a living matrix. Cystic jaw swellings were first described by Scultetus in 1654 and later Fauchard in 1728 suggested their connection with the teeth. These cysts were identified before X-ray discovery in 1774 by John Hunter. The term dentigerous cyst was coined by Paget in 1953.[5]

Primordial cyst

The term was coined in 1945 by Robinson as the cyst was thought to have a more primordial origin as it arises from the dental lamina remnants or enamel organs before the formation of the enamel. The term primordial cyst was also preferred by Forssell and Sainio and depicted that in OKC, a distinct parakeratotic epithelium is seen having columnar or cuboidal palisaded basal cells with occasional orthokeratosis.[6]

Odontogenic keratocyst

In 1956, Phillipsen along with Pindborg named the cyst an odontogenic keratocyst. Keratocyst describes any cyst in the jaw that produces a large extent of keratin. OKC showed a show a typical histopathologic appearance and is characterized well. OKC shows a uniform and thin stratified squamous epithelium lining showing the tendency to detach from the capsule of underlying connective tissue, thin fibrous capsule lacking inflammatory cell infiltrate, flat junction of epithelial-fibrous tissue with no rete ridges, 4 to 8 cells thick spinous cell layer having intracellular edema, thin corrugated parakeratin surface layer.[7]

Rechristened

In 2002, Reichart and Philipsen revised the classification of odontogenic tumors and renamed OKC as KCOT (keratinizing cystic odontogenic tumor) where it was placed under the category of benign neoplasm of odontogenic epithelium with mature, fibrous stroma; odontogenic ectomesenchyme not present. The classification was approved by WHO/IARC at the Editorial and Consensus Conference in 2003. The renamed KOT is defined as a benign uni-or multicystic, intraosseous tumor of odontogenic origin, with a characteristic lining of para keratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior. The term KOT is recommended by WHO as it suggests the neoplastic nature. Recent data suggest heterozygosity loss of certain tumor suppressor genes in many KOTs.[6]

Benign or malignant nature of OKC

Hansen and Pindborg were the first ones to report the OKC as having an aggressive nature. However, in 1967, Toller suggested that OKC is a benign neoplasm compared to a conventional cyst based on its clinical nature. In 1984, Ahlfors et al reported that OKC should be classified as true benign epithelial neoplasm and treatment should be modified accordingly.[5]

Shear pointed to the aggressive nature of OKC and named it a benign cystic neoplasm with the term keratocystoma. Ragezi et al explained the pathogenesis of OKC and reported that mechanisms favor the expansion and growth of OKC including expression of matrix metalloproteinase 2 and 9, overexpression of antiapoptotic proteins (bcl-2), and high proliferation rate. Mutation of the patched gene (PTCH1) is considered a pathogenic factor for the cyst.

Incidence and prevalence

Among all the jawbone cysts, OKC constitutes nearly 8% with a reported incidence between 4% to 16%. OKC affects subjects from all age ranges with the majority of subjects from 2nd and 4th decade of

life. In children, OKC presents as multiple cysts affecting whites. Males are commonly affected with a male: female ratio of 1.6:1. Nearly double prevalence is seen in the mandible compared to the maxilla. The most commonly affected site is the ascending ramus area of the mandible with nearly 70-83% incidence crossing the midline. In the maxilla, it can reach 3rd molar, pre-maxilla, nasal floor, and maxillary sinus area with common origination from TMJ. It is an intra-bony disease. However, the extra-bony cyst is seen in the buccal area of canines having male: female ratio of 2.2:1.[8]

ETIOPATHOGENESIS

OKC arises from dental lamina that rests in the jaw or from the basilar cell layer of oral epithelium. Its etiopathogenesis is attributed to high proliferation showing high expression of antiapoptotic proteins (MMPs 2 and 9 and Bcl-2) and PCNA (proliferating cell nuclear antigen).

Literature work on sporadic OKC and BCNS (basal cell nevus syndrome) depicted a proofed two-hit genetic structure at two or more chromosome loci, 9q22.3 causing overexpression of various proteins namely p 53 and cyclin D1. Mutations in a tumor suppressor gene, PCTH at chromosome 9p22.3-q31 associated with etiopathogenesis of OKC. The protein from PTCH is a constituent of the Hh (hedgehog) signaling pathway which is vital for cell signaling in adulthood and life growth in the embryo. Various signaling proteins and Sonic Hh protein is suppressed by PTCH gene proteins.

In cases with a nonfunctional PTCH gene, smoothened proteins and sonic Hh are over expressed causing increased cell proliferation. PTCH suppresses the Hh-signaling pathway and binds to Hh ligands. In case of receptor absence, smoothened receptors are inhibited by PTCH that downstream glioma-associated oncogene (Gli) transcription factors (Gli1 and 2) and activates the Hh pathway.

Apart from its association with OKC and BCNS, activation of Hh by PTCH mutations is seen in pancreatic, ovarian, and colon cancer. Hence, it was considered to change OKC to KCOT. Genetic assessment showed LH for various tumor suppressor genes namely FHIT, LATS2, TSLC1, MCC, p53, and p16 in various OKCs.[9]

The etiopatho genesis of OKC can be summarized as follows:

- Mutations are seen in medulloblastomas of BCNS and basal cell carcinomas
- PTCH mutation in syndromic and non-syndromic OKCs
- Overexpressing Intrleukin-6 Interleukin-1a, TGF, and MMPs-2 and -9
- Overexpression of Bcl-2
- High proliferation rate—PCNA and Ki-67

Odontogenic keratocyst growth

The growth pattern of OKC is destructive seen via trabeculae of the bone in anteroposterior orientation which separate it from other cysts of the jaw that shows a unicentric ballooning pattern expansion. Previous literature data depicts various mechanisms for the enlargement of OKC. However, the main patterns are:

Cellular activity in the connective tissue capsule: An active growth for the capsule is seen along with various areas of proliferation in the epithelium. The osteoclasts are seen present in the lining projection tips that grow into the cancellous spaces.[4,5]

Active epithelial growth: It shows a region of high mitotic activity. The proliferation of epithelial lining is not uniformly distributed, rather it is seen in clusters that lead to foldings in the lining and projections of the cyst into the cancellous spaces.[10]

Sign and symptoms

In the majority of cases with OKC, there have no symptoms present unless these cysts are secondarily infected. This can be the reason for the non-presentation of the cyst until the 5th decade of life. OKCs are usually identified during routine radiographic assessment, mainly on OPGs (Orthopantomograms). The growth of OKCs is usually slow in the anteroposterior fashion showing large size with no swelling in the bone.

The presence of multiple OKCs is related to the BCNS (basilar cell nevus syndrome) also known as Gorlin-Goltz syndrome which is inherited as an autosomal dominant trait showing many abnormalities as multiple nevoid basal cell carcinomas and skin lesions starting from puberty. Multiple OKCs arise at different time intervals throughout the lifetime of the affected subject and occur earlier compared to sporadic cases. Skeletal anomalies seen are cleft lip/palate, polydactyly, vertebral deformities, and rib abnormalities. The effect on CNS is seen as brain tumors (medulloblastoma) and calcified falx cerebri. BCNS can arise from PTCH1 gene mutation on the 9q22 chromosome, SUFU gene on 10q24-q25, or PTCH2 gene on 1p32. All these mutations have an impact on the Hh pathway.[10]

A vital feature to consider for OKC is its recurrence following the surgical removal seen in nearly 3% to 60% of the subjects. The various reasons considered behind recurrence are

- Growth of new OKC from cell rests/ remnants/ daughter cyst/ satellite cyst.

- Remnants of dental lamina epithelium not associated with original OKC and new OKC development in the adjacent area.
- Parakeratinization of the surface layer
- Supraepithelial and Subepithelial separation of the epithelial lining
- Adherence to adjacent soft tissue
- Bony perforation
- Budding in the epithelial basal cell layer
- Increased epithelial cell proliferative activity
- Thin epithelial lining
- Incomplete removal of the cyst lining

RADIOGRAPHIC APPEARANCE

OKC usually extends into the vertical and horizontal mandibular ramus presenting a dumb-bell-shaped appearance. OKC can be unilocular, however, it is frequently multilocular radiographically. OKCs are usually reported accidentally on routine radiographic examinations. Many OKCs are misinterpreted as dentigerous cysts when found in association with the impacted teeth. However, in OKC, the cystic lumen is separated from teeth with pericoronal tissues continuous with the cyst capsule.[11]

Single OKC usually resembles a radiolucency which is well-defined having fine radiopaque borders. Multi-locular lesions are usually reported in cases with more extensive OKCs. The OKCs in the mandible usually extend and expand to other bone sides crossing the midline which is characteristic of the OKC. In OKC, tooth displacement is seen in place of root resorption. The most common presentation of OKC is unilocular. However, nearly 40% OKCs are seen associated with impacted teeth and nearly 50% of mandibular OKCs are associated with enlargement of the buccal plate with occasional lingual plate expansion. Saucerization of underlying bone is mainly seen in peripheral odontogenic keratocyst. Based on the radiographic appearance, OKC can have the following variants:[11]

a. Envelopmental variant: Cysts arise from cell rests of Serre and embrace unerupted tooth.

b. Replacement variant: Cysts forming by degeneration of stellate reticulum in enamel organ in the normal-tooth region.

c. Extraneous variant: Cysts arising from Epithelial off-shoots hamartia of the oral epithelium from the basal layer and occur in the ascending ramus of the mandible and away from the tooth.

d. Collateral variant: Cysts originating from the Epithelial rests of Malassez and occurring adjacent to the teeth' roots.[11]

MICROSCOPICAL FINDINGS

On aspiration, cytologic appearance shows mainly cellular components having keratinized cellular clusters having no nuclei. In para-keratinized cells, small pyknotic nuclei are seen as having a lesser tendency to form groups having granular debris. Few dyskeratotic parabasal cells can be seen having denser eosinophilic cytoplasm. No inflammation or dysplasia is seen on aspiration. Keratinized cell groups are easily identified in subjects with numerous inflammatory cells.

The Cyst wall is folded and thin histopathologically and is lined by the stratified squamous epithelium of a continuous layer which is 5-8 cell layers thick. A well-defined basal cell having cuboidal or columnar cells is seen.[12]

Mitotic activity is higher than in other types of odontogenic cysts, and sparse mitotic figures may be found in basal and suprabasal cells. The fibrous capsule wall of the cyst is usually thin and generally free from inflammatory cell infiltration. If the cyst becomes secondarily inflamed, the epithelial lining loses its characteristic histology, and the para-keratinized epithelial surface might be faded. Epithelial lining might be proliferated, producing rete-pegs, losing the characteristic palisading basilar cell layer. Some epithelial cell clusters resemble dental lamina rests which can be seen in cyst walls that give rise to daughter cysts/satellite cysts commonly seen associated with BCNS. Key features on microscopic examination are:

Particular microscopical appearance lost when infected, Epithelial budding at the basal cell layer and remnants of the dental lamina (odontogenic rests), microcyst formation, "daughter cysts, Keratin flakes might be present in cystic cavity, Lack of rete pegs, commonly the cyst exhibits focal separation of the epithelial lining from the adjacent connective tissue, Palisading columnar/cuboidal basilar cells, Refractile, corrugated (rippled) parakeratotic lining on its luminal surface, and Thin epithelium (6-10 cell layers).[12]

OKC represents a unique clinicopathologic condition, and not only the feature of keratin production which is also seen in dentigerous and periapical cysts secondary to metastatic epithelial changes. The lining epithelium of these cysts is usually ortho-keratinized which is not seen in OKC in histopathological assessment. Also, the recurrence rate for these cysts is relatively less common.[12]

Recurrence

The recurrence rate for OKCs ranges from nearly 2% to 63%. The huge variation in the incidence of OKC recurrence can be attributed to studies

including cysts from subjects having Nevoid Basal cell carcinoma syndrome (NBCCS), method of cyst assessment, and varying follow-up.

The three mechanisms for the recurrence of OKC as explained by Brannon et al in 1976 are the development of a new OKC in an adjacent area, growth of a new OKC from satellite cysts (or odontogenic rests left behind after surgery), and Incomplete removal of the cyst lining.[13]

Histopathological features predicting the recurrence

The features that can help to predict recurrences in OKC include: the presence of remnants/cell rests as well as daughter cysts, the subepithelial split of the epithelial lining, supra epithelial split of the epithelial lining, para keratinization of the surface layer, budding in the basal layer of the epithelium, and a higher level of cell proliferative activity in the epithelium.[14]

GENETICS

On chromosome 9q22.3-q31, the PTCH gene is mapped and works as a tumor suppressor. Hedgehog (Hh) signaling pathway is another name for a vital molecule named PTCH1. PTCH forms a receptor complex with oncogene SMO from the ligand of the sonic hedgehog (Hh). Literature data on sporadic KCOT and NDCCS reported molecular proof of a two-hot mechanism in tumor patho-genesis proving allelic loss at 2 or more loci of 9q22 causing overexpression of TP53 and bcl-1 in NBCCS. These favor the thought that KCOT is a neoplasm. Evidence also suggests the role of the PTCH gene as a vital factor in developing sporadic KCOT. Also, primary studies reported amplify-cation and over-expression of genes placed in 12q.[15]

The epithelium lining the KCOT shows a high expression of gene p53 compared to other cysts of the type. The overexpression is not secondary to p53 mutation but depicts stabilization/ over production of normal p53 protein. SUFU and PTCH2 are other genes associated with KCOT. Literature reported the heterozygosity loss in FHIT, LTAS2, TSLC1, MCC, and p16 genes. These genetic links explain the aggressive nature of OKC.

TREATMENT

One of the most peculiar features of OKC is its high recurrence rate. Controversies have been raised along with extensive research to get the ideal treatment modality for KCOT. The majority of controversies are concerned if KCOT be treated as a benign neoplasm or a cyst. Despite any management technique, the recurrence has not been prevented completely by any modality with a high probability in multiple lesions and NBCSS cases.[16]

In 1985, Zakrezewska and Eyre suggested the following treatment modality for treating KCOT including Resection, marsupialization alone or followed by enucleation, and enucleation with either cryosurgery, chemical fixation, packing, or primary closure. Selecting the treatment of choice has been challenging as the well-being of the affected subject is the main criterion with no compromise on recurrence chances.[16]

The treatment modality for KCOT has been divided as aggressive or conservative where conservative treatment is oriented to the cyst including the enucleation with/without marsupialization. The technique has the advantage of lesser morbidity and preserving the anatomical structures. The aggressive management is done for suspected lesions of neoplastic nature and includes en-bloc resection, chemical curettage, and peripheral ostectomy. It is usually done for syndromic subjects and recurrent, and large lesions. KCOT is also treated by decompression showing a high recurrence rate and aggressive behavior.

FUTURE PERSPECTIVE

Owing to recent advances and molecular determination of the cyst, a new Hh pathway modality depicting the molecular aspect has been advanced. The pathway can be blocked at various levels and the Hh inhibitors can act as attractive antitumor agents. Literature data suggests that cyclopamine, a plant-based steroidal alkaloid can block the ShH pathway activation which is caused by oncogenic mutation. Also, KOT can be treated effectively by SHh signaling factor antagonists.[17]

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