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OKC or KCOT – From Diagnosis to Treatment

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ABSTRACT

Odontogenic Keratocyst (OKC) has been center of interest for the pathologist and surgeons alike. It is a dilemmatic cyst of oral and maxillofacial region which has gained attention in past years. It has characteristic clinical and histopathological features due to its aggressive behaviour which may lead to high recurrence rate. Earlier it was classified under developmental odontogenic cyst of jaw by WHO in 1971 & 1992, OKC has been reclassified and renamed in 2005 as keratocystic odontogenic tumor (KCOT) in the WHO classification of head and neck tumors. However in Classification of Head and Neck pathology, 2017, WHO reclassified KCOT back in the category of cyst. An attempt is hereby made to review various aspects of OKC.

Keywords: Keratocystic odontogenic tumor, Odontogenic cyst, Odontogenic Keratocyst, Odontogenic tumors.

INTRODUCTION

The lesion was first described by Mikulicz in 1876 as dermoid cyst. Hauer in 1926 and Kostecka in 1929 described it as cholestoma and Robinson described it as primordial cyst. The term Odontogenic keratocyst was coined by Philipsen in 1956. Further, In 1963 Pindborg and Hansen used the term "keratocyst". Shear In 2003 used the term "keratocystoma" to describe this lesion.[1] In 2005, WHO proposed the terminology as keratocystic odontogenic tumor (KCOT) as it shows neoplastic behaviour.[2] In 2017, the new WHO classification of Head and Neck pathology re-classified it into the cystic category. However, the orthokeratinised OKC was classified distinctly as orthokeratinised odontogenic cyst as they are not aggressive biologically, no significatnt recurrence seen, and are not associated with nevoid basal cell carcinoma syndrome.[3]

It is believed to arise from the remnants of dental lamina or epithelial cell rests, the odontogenic keratocyst (OKC), is considered to be of developmental origin. It is a benign unicystic or multicystic intraosseous tumor of odontogenic origin with characteristic lining of parakeratinised stratified squamous epithelium which shows potential for aggressive and infiltrative behaviour. The recent immunohistochemical studies have indicated its nature to be that of a benign cystic neoplasm rather than a true cystic lesion.[4]

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Clinical Features

The OKC is a predominantly mandibular lesion with predisposition for the molar ramus region. A peak frequency is seen in the 2nd and 3rd decade. Bimodal age distribution with a second peak in the 5th decade or later is seen. It occurs in males with a greater frequency than females (1.5:1).[5] The lesion has been associated with pain, swelling or discharge. Enlarging cyst displaces the teeth and affects anatomical structures causing pathological fractures extending in medullary cavity & expansion occurs in later stage due to multicentric and infiltrative growth pattern. In maxilla, due to infection it is diagnosed at an earlier stage.[6]

Pathogenesis

It is a developmental abnormality which arises from odontogenic epithelium having two main sources dental lamina or its remnants & extensions of basal cells from the overlying oral epithelium. The influence of inductive residual Ectomesenchyme along with role of basal cell offshoots originating from overlying oral mucosa and dental lamina was also noted.[7] Keratocysts tend to extend along the cancellous component of the bone reaching huge size before being diagnosed clinically. Growth rate is similar to other epithelial cysts of the jaw which averages 7mm / yr. Keratocysts show higher rate of proliferation with a mean value of 4.5 proliferating cells /mm2 (R.C-0.51 proliferating cells/ mm2).[8]

The role of osmolality in growth of the cysts is eminent as increase in osmolality leads to expansion of the cyst (Mean osmolality of OKC 296±15.6 mOsm and Mean serum osmolality 282±14.75 mOsm). Osmotic differences may be the result of the liberation of the products of cell lysis which may not be proteins. Epithelium proliferates in the form of mural growth during enlargement of

OKCs. Epithelial barrier of OKC is relatively less permeable than other cysts which may be the reason for the low quantities of soluble proteins (albumin & immunoglobulins) in the cystic fluid.[2,9] The role of glycosaminoglycans like Hyaluronic acid, Chondroitin -4- sulphate & Heparin sulphate were also seen in growth of the cyst.[10]

Collagenase degrades types I & II collagens at equal rates with no significant degradation of type III collagen. Polymorphonuclear collagenase type is associated with the growth of OKCs as it is related to connective tissue destruction. PMN collagenase (in absence of inflammatory cells in the OKC) stimulates specific OKC antigen-induced immunocomplexes by direct contact with connective tissue being destroyed resulting in degranulation of subcellular compartments.[11] Ahlfors in 1984 mentioned that active epithelial proliferation along with collagenolytic activity within the fibrous capsule leads to resorption of bone causing infolding of epithelial lining within the capsule.[12]

Meghji et al in 1992, explained the role of Interleukins & TNF in bone resorption, as Keratinocytes synthesize IL-1 & IL-6, IL-1 & IL-6 + TNF which possess bone resorbing properties leading to expansion of cyst. The developed positive pressure increases the secretion of MMP-1, MMP-2, MMP-3 and MMP-9 in a co-culture of OKC fibroblasts & the epithelial cells leading to proteolytic activity of cyst.[13]

Genetic mechanisms

It has been discussed that the OKC may be a benign cystic neoplasm because few cases of OKC and those associated with nevoid basal cell carcinoma syndrome (NBCCS) have been demonstrated to have mutation in patched gene (PTCH1), a gene located at 9q22.3 for tumor suppression.[14] Point mutations or loss of heterozygosity in the region of the PTCH1 gene may lead to dysregulation of oncoproteins resulting in proliferation- stimulating effects. The odontogenic keratocysts tend to grow in an antero-posterior direction along the cancellous component of the bone without producing much expansion of the cortical plates.[14] The OKC was labeled as a benign cystic neoplasm, renaming the cyst as a keratocystic odontogenic tumour to reflect its aggressive, often infiltrative behavior and potential for recurrence. The most significant evidence that OKC is a neoplasm comes from genetic studies demonstrating loss of heterozygosity of the tumour suppressor genes e.g. p53 and p16.[1,15]

Radiographic Features

On the radiograph OKCs appear as well-demarcated, small, round radiolucencies, which can be either unilocular (73.7%) or multilocular (26.6%) having sclerotic or diffuse margins. Large unilocular OKCs might resemble cystic ameloblastoma. The lesion's proximity to the tooth may cause displacement (28.3%) and/or root resorption (5%).[1]

The OKC which are increasing in size involve the follicle of an unerupted tooth & fuse with reduced enamel epithelium. Epithelium immediately around neck of tooth is not keratinized & show inflammatory changes in the underlying capsule. Main in 1970 categorized OKC on the basis of radiographic features as:[2]

- Replacement type – cyst which forms in the place of the normal teeth
- Envelopmental type – cyst which embraces an adjacent unerupted tooth
- Extraneous type – cyst which occur in ascending ramus away from the teeth
- Collateral type – cyst which occurs adjacent to the root of teeth which are indistinguishable radiologically from lateral periodontal cyst.

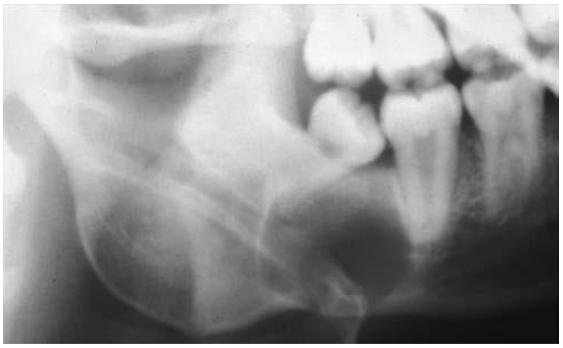

Figure 1A: Radiograph of a small OKC

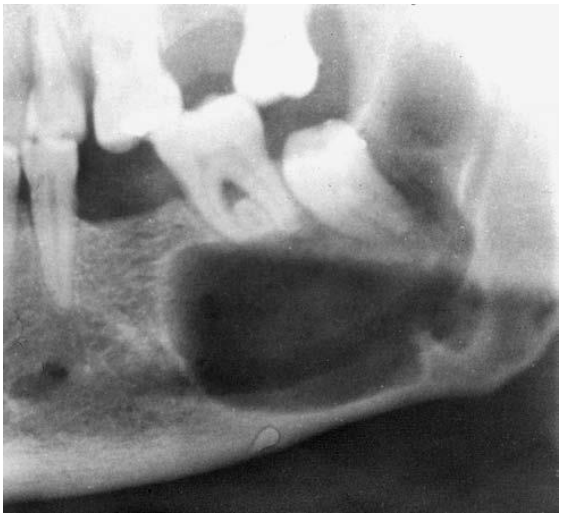

Figure 1B: Radiograph of an OKC with scalloped margins

Histopathological Features

Keratocysts are rarely received intact, unless small due to unequal growth, which is responsible for scalloped margins. The cystic lining of OKC is histologically composed of a regular, narrow, keratinized stratified squamous epithelium of uniform thickness of 5 to 8 cells. The basal layer is classically well-defined, hyperchromatic, columnar

or cuboidal cells showing reversal of polarity. The epithelial layer lacks rete ridges thus appears uniform.[1,4] The capsule of OKC is thin and loosely arranged which show mild chronic inflammatory cell infiltration. If the inflammation is intense then epithelium loses its keratinized surface and thickens, developing rete ridges and may ulcerate. The walls of the OKC show hyaline bodies, cholesterol clefts, mast cells or mucous metaplasia. There may be daughter cysts and epithelial islands in the capsule, and budding in the basal layer can be seen.[1,4] Satellite cysts or the daughter cysts are the islands of proliferating epithelial cells derived from small epithelial rests which reach a large size leading to cystic breakdown followed by formation of cyst.[16] Roger M Browne classified satellite cyst into three types:[17]

Type I: Cysts lining - stratified squamous epithelium
Luminal surface – Para keratinization
Lumen - contained degenerating epithelial cells and desquamated keratin
Type II: Cystic lining- surface showing para keratinization
Lumen- filled with keratin
Type III: Cystic lining- absent
Capsule-mass of keratin layer surrounded by foreign body granulomatous infiltrate

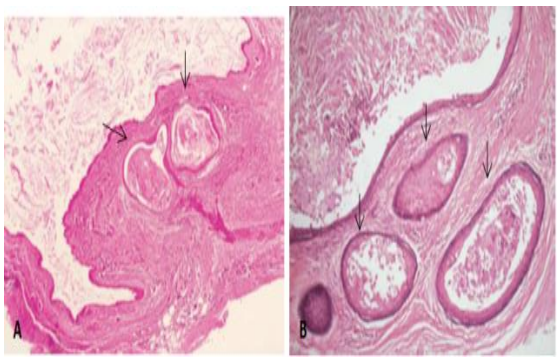

Figure 2 A & B: The arrow shows Satellite microcysts in the wall of an odontogenic keratocyst

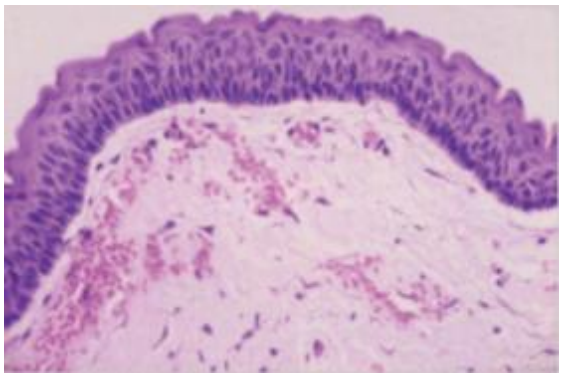

Figure 3: Histopathology of an odontogenic keratocyst.

Certain histologic findings of OKC, including the presence of one or more daughter cysts and the budding of the basal cell layer of the lining epithelium, have been reported to be related to high recurrence rates.[5] Inflammation was present in 98% of the KCOTs reviewed by A T Myoung H.[18] In the study done by Haring and Van Dis found out that the inflammation which was predominantly a chronic inflammatory cell infiltrate, was most often generalized in the pattern of distribution and not localized to a specific site. Also, the multilocular lesions showed the inflammation to be more severe than unilocular lesions.[19]

Ultrastructure

Parakeratotic variant under Scanning Electron Microscope shows complex series of elevations & depressions on the cell surfaces. Transmission Electron Microscope confirms the presence of cytoplasmic interdigitations & desmosomal junctions, giving rise to complex surface morphology. Orthokeratotic variant under SEM reveals a uniform, flat surface covered with a thick layer of leafy squames, no evidence of surface corrugations. TEM showed a loose attachment between superficial shreds of orthokeratin and a compact layer of underlying keratin.[20]

Recurrence

Recurrence rate ranges 6% to 62% due to retention of satellite/ daughter cysts following surgical treatment, thin fragile epithelial lining, especially in the large cysts, intrinsic growth potential of the epithelial lining, Any remnants of dental lamina may form target for formation of a new keratocyst, Residual basal cell proliferations of the oral mucosa due to firm adhesion of cyst to overlying mucosa, recurrences have been found to be more with cysts in patients with NBCCS.[1,16]

Laboratory Diagnosis

Kramer in an experiment demonstrated keratinised squames in stained films by aspirating cystic fluid of OKC. Cytological procedure and examination of the cystic fluid was done to estimate the soluble protein levels for the correct diagnosis. The levels of soluble protein in Keratinising cysts and Non keratinising cysts are less than 4gm/100ml and 5-11gm/ 100ml respectively. Fully keratinized linings were impervious to all the proteins.[7]

Neutrophils that infiltrate the cyst wall act as a source of lactoferrin in the cystic fluid which is unable to diffuse away and concentration of which may increase with time. Enzyme Histochemical studies done for G-6PD activity (basal layers), Leucine aminopeptidase, Acid phosphatase, NADH- Diaphorase showed high level of leucine aminopeptidase activity in the fibrous capsule of OKCs which implicated the invasiveness of malignant tumours. High acid phosphatase activity in the basal layers lead to increased lysosomal activity which further leads to cystic growth.[21,22]

Immunohistochemistry

The studies were done to evaluate the cytokeratin content of odontogenic cysts by using monoclonal bodies. Mainly two distinct gene families were found associated with OKC - Type I and Type II keratin. Epithelial cells undergo a gradual maturation while they migrate to upper cell layers in a keratocysts. A surprising finding was the presence of cytokeratin typical of keratinizing epithelium, cytokeratin 1, 9 and 10/11. CK 10 was seen only in OKCs, however, CK 17 was evident in the epithelial layer of all OKCs for patients with nevoid basal cell carcinoma syndrome. Expression of high levels of EGFr was seen in OKC which were indicative of intrinsic growth potential which was not present in other odontogenic cysts.[23,24]

The positive expression of p53 in basal cell layer and PCNA in all basal layers and most parabasal layers of OKC was seen in an experiment. The total PCNA count in OKC 94.4 ±22.7 cells/mm, Dentigerous Cyst 5.1±3 cells/mm, R.C 11±4.1 cells/mm, indicated greater proliferative activity in OKC linings, in accordance with their aggressive clinical behavior. The positive expression of numerous Ki-67 in supra basal layer of epithelium of OKC demonstrating greater activity of cell proliferation and higher levels of p63 in OKCs showed abnormal control of the cell cycle.[25,26]

Management

The treatment consists of both conservative and aggressive modalities and should be aimed at preventing the recurrence which is a menace with long term follow up of OKC while at the same time, minimizing morbidity. It is important to remember that Epithelial remnants or residual tissue are prime potentiators of recurrence, for this reason, the use of chemical cautery after enucleation, aggressive curettage of bony walls, cryotherapy modalities, peripheral ostectomy with a bone bur, or even radical resection of the involved jaw have been promoted as means of lowering recurrence by removing remaining epithelium. Surgical treatment requires removal of the mucosa overlying the lesion, based on histologic evidence that clusters of epithelial islands and microcysts presumably with the potential to cause recurrence have been found in the area where the lesion was connected with the mucosa.[27] Recent studies have found certain changes after conservative marsupialization with decompression, including thickening of the KCOT's wall, inhibition of IL-1a, epithelial dedifferentiation and loss of cytokeratin-10 production, may be responsible for the less aggressive behavior with decreased recurrence seen after such treatment. These findings support the view that in a selected group of patients, treatment with decompression allows for a less invasive approach with excellent results, avoiding extensive disfiguring procedures. Regardless of the fact that resection of the jaw results in the lowest recurrence rate, this procedure is extreme and non-conservative. Thus, unless resection is deemed necessary, the most appropriate action would be enucleation of the KCOT with use of Carnoy's solution or marsupialization followed by enucleation.[28] In recent years, possible new treatment methods for KCOT have been indicated. According to Taipale and colleagues, cyclopamine, a plant-based steroidal alkaloid, inhibits the cellular response to the SHH signal. It was found that cyclopamine blocks activation of the SHH pathway caused by oncogenic mutation making it a potential "mechanism-based" therapeutic agent for human tumours whose pathogenesis involves excess SHH pathway activity.[29] Zhang and others postulate that antagonists of SHH signalling factors could effectively treat KCOTs. The proposed strategies include the reintroduction of a wild-type form of PTCH, inhibiting the SMO molecule by synthetic antagonists and suppressing the downstream transcription factors of the SHH pathway. They suggest that intracystic injection of an SMO protein-antagonist has the greatest potential as a future treatment option for the management of such lesions.[30]

CONCLUSION

Odontogenic keratocyts are benign lesions of odontogenic origin characterized by an aggressive behaviour. Clinical, radiological, along with histopathological features play an important role in the diagnosis and management of OKCs and in evaluating the extent and relationship of the lesion with adjacent structures.

The aggressive nature of OKC demands an aggressive treatment strategy such as jaw resection resulting in the lowest recurrence rate. Enucleation and marsupialization may be recommended in the cases where resection of the jaw is not mandatory due to the extensive and life changing nature of the procedure. With immense research going on in the molecular field of treatment modality of OKC, the need of radical procedures may be reduced or eliminated to manage the lesions. Currently, the novel designation of the OKC as a cyst and the research that influenced this change should serve as a compass by which clinicians can navigate future treatment plans.

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