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History and Histopathology of Odontogenic Keratocyst,Cyst or A Tumor: A Literature Review

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ABSTRACT: Odontogenic keratocyst, a common but histologically important odontogenic lesion which have a varying behaviour in literature. The nomenclature of this lesion in literature has various contributions varying from cholesteatoma to keratocystic odontogenic tumour and to the present odontogenic keratocyst. Theentity is hence consideredas cystand as a tumour by various authors considering the behaviour of odontogenic keratocyst as a tumour while the histological appearance favour the definition of a cyst. The OKC was considered to be a cyst by WHO in the classification of odontogenic lesions in 1992 which was later classified as a tumor in WHO 2005 and back as a cyst in 2017 classification of WHO. In this review we aim to discuss the histology of odontogenic keratocyst and to correlate the histology and pathophysiology in considering the lesion to be a cyst or tumour.

KEYWORDS: Odontogenic Keratocyst; Cyst; Tumour

I. INTRODUCTION

In the earlier literature, Hauer, 1926 &Kostecka, 1929 first used the terminology of cholesteatoma to denote the odontogenic lesion occurring in the jaw with features of present odontogenic keratocyst (OKC).[1] Later Shear and Altini in 1976 and Pindborg in 1971 called similar lesions to be a primordial cyst.[2] Browne in 1969 argued that they could not be primordial cysts because he defined a primordial cyst, according to the original description of Robinson (1945), as one which arose by breakdown of the stellate reticulum of the enamel organ before any mineralised tissue was formed.[3] Hence it developed in place of a tooth which might have been one of the normal series or a supernumerary. Forssell and Sainio (1979), preference for the term 'primordial cyst', showed that in these lesions ('genuine keratocysts') the epithelium was distinctly parakeratotic with cuboidal or columnar palisaded basal cells, and occasionally orthokeratotic.[4]The term 'odontogenic keratocyst' was introduced by Philipsen in 1956. In a subsequent paper published in 1962 byPindborget al, and in a paper by Pindborg and Hansen in 1963, the term'keratocyst' wasused to describe any jaw cyst in which keratin was formedto a large extent.[5]

II. DISCUSSION

OKC presents usually as a swelling most commonly in the mandibular angle region than in maxilla.[5,6] The case frequency is more in males than females showing bimodal age distribution with peak frequency in the second and third decades and a second peak in the fifth decade. The racial distribution in the world literature shows lower prevalence among black population.[4,5,7]A clinician encounters an OKC as a painless swelling in the jaw which seldom produce pain and discharge.[8] Occasionally the patient complains of paraesthesia of lower lip regions as larger lesions tend to impinge the inferior alveolar nerve.[9] The radiologist encounters the OKC as a radiolucent cystic cavity which show a tendency of medullary spread with mild displacement of the teeth.[5,9,10] One-third of maxillary cysts caused buccal expansion, but palatal expansion was very rarely seen. About half of the mandibular lesions produced buccal expansion and one-third produced lingual expansion. It was Dayan et al. in 1988 who have described the occurrence of alesion entirely within the gingiva, which had the clinicalfeatures of a gingival cyst of adults but the histologicalcharacteristics of a typical OKC and hence termed it as peripheral odontogenic keratocyst.[11]

Pathogenesis of Okc

The origin of OKC in the jaw is proven to be from the dental lamina remnants. The peripheral variant on the other hand is thought to arise from extensions of basal cells from the overlying oral

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epithelium. Case reports in literature shows that OKCs are located even in the ascending ramus and have no relationship to a tooth follicle or dental lamina. Such cysts, may have arisen from basal cell offshoots or basal cell hamartias which originated from the overlying oral mucosa. Induced by residual ectomesenchymal influence in the tooth-bearing areas of the jaws[5,12]

Histopathology of Okc]

The histological features of OKC are so characteristic and unique aiding an easy identification for histopathologist. The cyst wall is usually thin, collapsed and folded. The lining of the cyst is by a regular, narrow, keratinised, stratified, squamous epithelium which is usually about 5–8 cell layers thick and without rete ridges. The form of keratinisation is exclusively parakeratotic in about 80–90% of cases, but is sometimes orthokeratotic both forms may be found in different parts of some cysts.[5,12,13]Presently the Ortho keratinised variant is classified as a different entity by the WHO in its 2017 classification of odontogenic lesions as Ortho keratinised odontogenic cyst. [14] The major histologic feature differentiating both are the presence of a stratum granulosum associated with the orthokeratin layer in somebut not all casesparakeratoticlesions. There is a well-defined, often palisaded, basal layer consisting of columnar or cuboidal cells or a mixture of both. The cuboidal basal cells occur relatively more frequently in relation to the orthokeratinised linings than par keratinised while the flattened basal cells may also be found in some orthokeratinised linings. The nuclei of the columnar basal cells in the parakeratotic linings tend to be orientated away from the basement membrane and in the majority of cases are intensely basophilicdesquamated keratin is present in many of the cyst cavities.[5,15,16] The cells superficial to the basal layer are polyhedral and often exhibit intracellular oedema.Mitotic figures are found in the basal layer but more frequently in the suprabasal layers .Occasional linings show features of epithelial dysplasia.Van der Waal et al. in 1985 reported a well-documented case of an OKC that underwent change to a squamous cell carcinoma.[17]MacLeod and Soamesin 1988 reported a case of an OKC that showed areas of epithelial dysplasia and transformation to an infiltrating welldifferentiated squamous carcinoma.In their study they found that OKC with epithelial dysplasia had a large additional peak to the right of the diploid G0/G1 peak and represented a DNA aneuploid G0/G1 component which has a DNA index of 2.0.[18]

Radiological Features of Okc

The radiology of a cyst is evident radiolucency within the jaw. A small, round or ovoid, radiolucent area with a distinct sclerotic margin is the usual radiological presentation. The adjacent tooth root resorption is rare. Most unilocular lesions have scalloped /smooth margins. The scalloped margins suggest that unequal growth activity may be taking place in different parts of the cyst lining. The unequal growth potential of the cyst lining is also a point of discussion by many authors.[19] Larger lesions show displacement of the inferior alveolar canal and resorption of the lower cortical plate of the mandible. OKCs may occur in the periapical region of vital standing teeth, giving the appearance of a radicular cyst and may impede the eruption of related teeth, resulting in a ‘dentigerous’ appearance.[5,10]Browne in 1969 advocated that this occurred when an enlarging OKC involved the follicle of an unerupted tooth and fused with the reduced enamel epithelium. Such cysts the epithelium immediatelyaround the neck of the tooth was notkeratinised and showed inflammatory changes in the underlying capsule.[20]Later it was Main in 1970 who gave the radiographic variants of OKC and has referred this variety of OKC to be Envelopmental which means that the lesion embraces an adjacent unerupted tooth. The other variants are the replacement which forms in the place of a normal tooth, the extraneous variant which forms in the ascending ramus away from the tooth germ.[5,9,21] The collateral variant forms adjacent to the roots of teeth, usually in the mandibular premolar region. This variant forms major differential diagnosis of the lateral periodontal cyst regarding the radiological appearance. The Computerised tomography and magnetic resonance imaging show presence of areas of increased attenuation in CT scans, and that these areas resulted from the presence of keratin in their cavities.[22]

Factors Influencing Growth and Behaviour Of Okc

The Cyst like Feature

The principle behind initiation proliferation and growth of cyst is well explained by Toller et al in literature. OKC also follow the basic principles of cyst enlargement and growth but there are many features which make OKC different from other cyst and even for considering it a tumour. The rate of growth of OKC is studied by many authors in which Forssell in 1980 estimated the rate of growth of OKCs varied from 2 to 14mm a year, with an average of about 7mm and that the

rate was slow in patients over 50years of age. They inferred that rate of enlargement of OKCs may not be greater than that of other jaw cysts, its growth was more unremitting.[5]

Role of osmolality in growth of the cysts

Toller et al considered the part played by the osmolality of the cyst fluid in enlargement of OKCs. They found that the mean osmolality of the OKCs is 296± 15.6mOsm when compared to the mean osmolality of serum which is 282±14.75mOsm. [5, 23] Osmotic differences between sera and cyst fluids were not directly related to proteins in cyst fluids and may be the result of the liberation of the products of cell lysis which may not be proteins. They inferred that the raised osmolality have an important, even if not the sole, role in the expansive growth in the size of the OKC as well as other jaw cysts. The theory advocated the unilocular and equally expansile lesion but the drawbacks were explained by Main, Browne and Kramer as occurrence of multilocular and loculated outlines exhibited by some OKCs. Such growth pattern were difficult to interpret on the basis of unicentric hydrostatic expansion alone.[5]

Role of inflammatory exudate in growth of the cysts

Inflammatory exudate has a negligible role in OKC enlargementfluid contains low quantities of soluble protein, composed predominantly of albumin and only relatively small quantities of immunoglobulins. This can be explained by the permeability of lining epithelium of OKC whichis not a barrier readily penetrable by proteins thus OKCs are usually free of inflammatory cell infiltrate.[5,24]

The fibrous capsule of OKC

The fibrous capsule of a cyst is a usual finding but the capsule of OKC is how distinctive features than other cyst of jaws. The OKC is usually thin with relatively few cells widely separated by a stroma which is often rich in mucopolysaccharide and resembles mesenchymal connective tissue .Inflammatory cells are very infrequent but there may be a mild infiltration of lymphocytes and monocytes. In the presence of an intense inflammatory process, the adjacent epithelium loses its keratinised surface, may thicken and develop rete processes, or may ulcerate.Hyalinisation is sometimes seen in the capsules of cysts removed fromolder patients.The attachment between epithelium and the connective tissue capsule tends to be weak and in many areas separation occurs. The collapsed and folded thin-walled cysts may give an erroneous impression of multilocularity in histological sections. infoldings' of the epithelial lining into the fibrous cyst wall with resultant inlets of the lumen or cryptsSatellite cysts, epithelial rests and proliferating dental lamina are sometimes seen in the cyst capsules, particularly in patients with multiple cysts and with the Nevoid Basal cell Carcinoma syndrome (NBCCS).Melanin pigmentation has occasionally been observed in the epithelial linings of OKCs.[25]Mucous metaplasia, hyaline bodies and cholesterol clefts are sometimes present in the walls of OKCs.[5,26,27,28]]

The Tumor like Features

The Proliferative Potential Of Okc

Many features of OKC are of cystic while some are of a tumour. Main et al showed that the mitotic value of OKC linings ranged from 0 to 19 with a mean of 8.0. This value was similar to that in the ameloblastoma and in dental lamina, and higher than that found in non-odontogenic cysts which had a mean mitotic value of 2.3, and in radicular cysts with a mean mitotic value of 4.5.[5,29]Toller et alestimated mitotic activity in an autoradiographic study following the in vitro incubation of cyst linings with tritiated thymidine in tissue culture medium. His results showed mean labelling indices of 13.0% for a series of six OKCs compared with 1.7% for five non-OKC cysts and 7.0% for human buccal mucous membrane. [5,30,31] Nuclear morphometric variables of the epithelium of OKCs, compared with those of dentigerous and radicular cysts in a study by Gunhan et al in 2003the number of cells in the basal layer was higher in the OKCs than in the others. The mean nuclear area of the basal cells of the OKCs was smaller than that of the intermediate cells of all three cyst types and the basal cells of the OKC nuclei were more ovoid than those of the other cysts. The H3-thymidine study in literature shows that proliferation patterns of the epithelium and connective tissue of an OKC and a radicular cyst found that the epithelium of the OKC, mainly in the basal and suprabasal cells as marked with, showed a higher rate of proliferation than the radicular cyst with a mean value of 4.5 proliferating cells per mm2 compared with a mean value of 0.51 proliferating cells per mm2 in the radicular cyst.[5,32]Microscopically, the auto radiographic sections showed that proliferation of the epithelium and the connective tissue of the OKC was irregular and in clusters, not homogeneous, but some areas shows simultaneous proliferation. Exclusively passive expansion of the

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cyst connective tissue as a reaction to the growth of the OKC was unlikely and that active growth of the connective tissue wall contributed to the invasive growth of this cyst.

Role Of Glycosaminoglycans In Growth Of Okc

The extracellular matrix is usually seen in relation to the pathogenicity of a tumor than a cyst. In OKC the matrix associated hyaluronic acid showed the highest frequency and abundance. The heparin sulphate showed a higher frequency and abundance in the OKC than the other cysts. The origin of these protiens was uncertain but probably derived from both the connective tissue and the epithelium of the cyst wall. The connective tissue wall of OKC demonstrated appreciable amounts of extracellularglycosaminoglycansand proteoglycans, predominantly hyaluronic acid. The inference of its presence comparing to that of a tumour is that the major source of the glycosaminoglycans and proteoglycans in cyst fluids is from the ground substance of the connective tissue capsule, released as a result of normal metabolic turnover and inflammatory degradation. Degranulating mast cells released heparin and hydrolytic enzymes and the latter facilitated the breakdown of the glycosaminoglycans and proteoglycans.[5,33]

Bone Resorption and Okc Growth

Studies showed that OKC with presence of collagenase degraded types I and II collagens at almost equal rates as that of collagenase produced by human polymorphonuclear (PMN) type. Studies on Interleukins, tumour necrosis factor, matrix metalloproteins, tenascin, fibronectin and collagen IV, myofibroblasts, parathyroid hormone related proteins shows that these factors favouring extensive bone resorption are present surprisingly high amount in OKC similar to a tumor when compared to other cyst of jaw. [5,34,35,36, 37,38,39,40] IL-1α was the principal osteolytic cytokine produced by OKCs leading to boneresorption but that the role of IL-6 was less clear. Theexpression of IL-1α mRNA and the epithelial cell-proliferating activities were reduced proportionally by marsupialisation, strongly suggesting a close association between positive intracystic pressure, IL- 1α expression and epithelial cell proliferation in OKCs. Positive pressure enhanced the expression of IL-1α mRNA and protein in the epithelial cells of the OKC, and increased the secretion of MMP-1, MMP-2, MMP-3 and PGE2 in a co-culture of OKC fibroblasts and the epithelial cells.[41,42] The pressure-induced secretions were inhibited by an IL-1 receptor antagonist. GelatinasesMMP-1 and MMP-9 were present in jaw cyst tissueextracts in both latent and activated formsMMP-2 and MMP-8 were also present.Mast cell tryptase (MCT) was also detected in few cases of OKC.[43]MMP-1 and MMP-8 in cyst extracts showed asignificant mediator of tissue destruction. Expression of tenascin,fibronectin , collagen IV and Tenascin was present in a continuouspattern at the epithelial–connective tissue and this expression is believed tocorrelate with cell proliferation and migration, such as inwound epithelialisation and connective tissue invasion similar to that of a tumour. The higher tenascin and fibronectin expression in the capsules of the OKCs suggested instability in the structure of the cysts and speculated that this might contribute to its aggressive behaviour.

Role of Myofibroblast In Okc

Myofibroblast is common finding in the margins of a locally invasive tumour front while not in a cyst. The presence of myofibroblasts at the invasion front of a neoplasm is not part of the host defence mechanism against its capacity to infiltrate, but actually promotes the lesion. Studies on OKC show that the mean number of αSMA-positive cells denoting myofibroblast per field was 25.7± 11.4 when compared to other lesions like that of solid ameloblastomas(29±7) ,ameloblasticfibroma/ameloblastic fibro-odontoma(5.6±7.5), dentigerous cysts (8.7±11.6) and even squamous cell carcinomas (21.3±5.3) [5,38,39,44]

Parathyroid Hormone-Related Protein (Pthrp) In Okc

PTHRP is known to be associated with many bone tumours and even associated with invasion of the mandible by oral squamous cell carcinoma. Studies in OKC showed reactivity for PTHrP localised mainly to the basal and suprabasal cells of OKC linings when compared with those of the dentigerous and the radicular cysts.The studies infer that PTHrP might modulate growth and bone resorption in odontogenic cysts and might act synergistically with IL-1 to increase bone resorption or stimulate osteoblasts and inhibit osteoclasts, resulting in reduced resorption, through its TGFβ-like activity.[5,40]

Immunohistochemistry of Okc

Various markers are being studied on OKC to explain the behaviour of this lesion. Cytokeratinsmaily the 13, 14 and 19 and other epithelial cell markers proves the orgin to be from reduced enamel epithelium and the cell rests of Serres and Malassez. [45] Epidermal growth factor

and transforming growth factor expression through the full thickness of lining epithelium in OKC including the basal cell layer in some cases indicate that these cysts have an intrinsic growth potential similar to that of a tumour and is not present in any other odontogenic cyst.[46] Other rare marker like Elafin which is a skin-derived antil eucoprotein a seinhibit or (SKALP), an epithelial-specific, cationic elastaseinhibitor that has been identified in cultured keratinocytesand its expression has been studied in OKCepithelium. OKC epithelia showed strong, uniform cytoplasmic staining in all layersthere was increased elafin expression in neoplastic epithelium compared with normal oral epithelium. OKCs showed dense staining of bone morphogenic protein-4 indicative of abnormal epidermal differentiation.[47]

Genetic Background of Okc Favouring Tumor Like Feature

The expression of protein Gp38 in OKC epithelium suggests alteration in gene expressionan epithelial-specific38kD cell surface glycoprotein. This protein has been shown to bestrongly expressed in basal cell carcinomas(BCC) but notin squamous cell carcinomas or various proliferative disordersof squamous epithelium. Studies show a consistent heavy cell surface staining of basaland suprabasal layers of OKCs including the satellite cysts. [48,49] Literature on tumour and malignancy marker proteins like p53, proliferating cell nuclear antigen, Ki-67, nucleolar organiser regions, calretinin expressions were detectable in the lining epithelium of OKC than other cysts inferring the tumor like behaviour of OKC.[49,50] The IPO-38 antigen which was first described by Thosaporn et al in 2004 whose expressionis constant through most stages of the cell cycle exceptduring mitosis where a 400-fold increase in concentration. IPO-38 antigen is expressed in a range ofmalignant tumourswith a mean labelling indices of IOP-38-positive epithelial cells, per 100 cells, were 76.1±14.6 inthe ameloblastoma ,in the OKC 75.8±18.7. his study concluded that the proliferation indiceswere useful in predicting the different biological behaviourof the odontogenic lesions, and moreover that theOKC should be regarded as a benign tumour rather thanan odontogenic cyst.[51]

Other markers of study in OKC were the apoptotic markers bcl-2 and bcl-1 (cyclin D1). The expressions of which were variable in OKC but similar to other tumors. Caspase-3, a member of the IL-1b converting enzyme(ICE) or cell death effector-3 (CDE-3) family, is involvedin the induction of apoptosis. Positive staining forcaspase-3 was detected in the cytoplasm and nuclei ofbasal to suprabasal or superficial cells, the lining epitheliumof all groups of OKCs. Positivity for p21 protein was detected in basal tosuperficial cells, whereas that for p27 protein was locatedin parabasal to superficial cells in the OKC lining epithelium. Fas ligand (FasL) is a molecule that binds to a cellsurfacereceptor named Fas (also called CD95), andsignals the cell to begin the apoptosis programme. Expression of Fas was detected in the cell membranes andcytoplasm of suprabasal to superficial cells in both controlgingival and lining epithelium of OKCs.[52]

The identification of nevoid basal cell carcinoma (NBCCS) gene mapped to chromosome9q22 and probably functioned as a tumour suppressorby deletion of this region in OKC was a strong supporting factor to be classified as a tumor by WHO in 2005.In an early progenitorcell of dental lamina, it was suggested, there could bea homozygous inactivation of the PTCH gene leading to either abnormal migration, abnormal differentiationor failure to undergo programmed cell death. Itwas postulated that the PTCH gene inactivation in syndromeOKCs and over-expression of bcl-1 were not incidental findings but causative in their pathogenesis. WithPTCH gene inactivation there was loss of control of proliferativeactivity in the lining of a sporadic OKC and thiscould act synergistically with the over-expression of cyclinD found in syndrome OKCs.Theaggressiveclinical behaviour and an over-expression of bcl-1 andp53, supported the hypothesis that the OKCs, at leastthose associated with the NBCCS, should be regarded asbenign cystic neoplasms. But on recent studies, the presence and possibility of NBCCS gene mutation in other non-invasive cysts and lesions weakened the sole reason to link this gene mutation to a tumour.[5,53]

Treatment and Recurrence Of Okc

The lesion is managed surgically managed with additional attention taken due to the higher reccurence rates. Decompression and marsupialisation as a treatment for the odontogenic keratocyst. Certain studies mention the use of liquid nitrogen cryotherapy in the management of the odontogenic keratocyst. Excision of the overlying, attached mucosa, in conjunction with cyst enucleation and treatment of the bony defect with Carnoy solution. Peripheral osteotomy is recommended by certain authors while En bloc osseous resection is considered for some cases. OKC has the highest chances of recurrence among other odontogenic cysts. The reason for this high

rate of recurrence is mainly the incomplete removal and remains of lining epithelium after surgery. Other reasons include the occurrence of satellite cysts within the cyst wall, proliferations of the basal cells of the oral mucosa or the basal cell hamartias, particularly in the third molar region and ascending ramus of the mandible.[54,55]

III. CONCLUSIONS

The nature of Odontogenic Keratocyst either cystic or tumor, has been a matter of discussion since decades and few researchers classified the OKC as a benign tumor. In last decade in 2005 the WHO has given the term "keratocystic odontogenic tumor" to r the place the term "odontogenic keratocyst" , as it closely reflects the neoplastic property of the pathology. The aggressive behavior of the cyst, high histological mitotic activity, and evidence of associated genetic and chromosomal abnormalities often seen in neoplasia are some major reasons which serve as the basis for this new classification. But again WHO has categorized OKC into Odontogenic and non-odontogenic developmental cysts (2017). This new WHO classification of Head and Neck pathology re-classified OKC back into the cystic category. It is no longer considered a neoplasm as the evidence supporting that hypothesis like clonality is considered insufficient.

REFERENCES

[1]. Thakur A, Tupkari JV, Joy T, Jugade SC, Chellappa N. Keratocystic Odontogenic Tumour:-An Unusual Presentation. International Editorial/Reviewer Board Prof. Raveendranath. Rajendran-Saudi Arabia.:225.

[2]. Altini M, Cohen M. The follicular primordial cyst-odontogenic keratocyst. International journal of oral surgery. 1982 Jun 1;11(3):175-82.

[3]. Browne RM. The origin of cholesterol in odontogenic cysts in man. Archives of oral biology. 1971 Jan 1;16(1):107-IN22.

[4]. Nayak MT, Singh A, Singhvi A, Sharma R. Odontogenic keratocyst: What is in the name?. Journal of natural science, biology, and medicine. 2013 Jul;4(2):282.

[5]. Shear M, Speight P. Cysts of the oral and maxillofacial regions. John Wiley & Sons; 2008 Apr 15.

[6]. Gnanaselvi UP, Kamatchi D, Sekar K, Narayanan BS. Odontogenic keratocyst in anterior Mandible: An interesting case report. J Indian Acad Dent Spec Res [Internet]. 2016 Jan 1.

[7]. Myoung H, Hong SP, Hong SD, Lee JI, Lim CY, Choung PH, Lee JH, Choi JY, Seo BM, Kim MJ. Odontogenic keratocyst: review of 256 cases for recurrence and clinicopathologic parameters. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2001 Mar 1;91(3):328-33.

[8]. Tan B, Yan TS, Shermin L, Teck KC, Yoke PC, Goh C, Balakrishnan A. Malignant transformation of keratocystic odontogenic tumor: two case reports. American Journal of Otolaryngology. 2013 Jul 1;34(4):357-61.

[9]. Ghom A, Ghom S. Odontogenic tumors. Textbook of Oral Medicine. 2014 Sep 30:235.

[10]. Verbin RS, Barnes L. Cysts and cyst-like lesions of the oral cavity, jaws and neck. Surgical pathology of the head and neck. 2001;3:1437-555.

[11]. Dayan D, Buchner A, Gorsky M, Harel-Raviv M. The peripheral odontogenic keratocyst. International journal of oral and maxillofacial surgery. 1988 Apr 1;17(2):81-3.

[12]. Bhargava D, Deshpande A, Pogrel MA. Keratocystic odontogenic tumour (KCOT)—a cyst to a tumour. Oral and maxillofacial surgery. 2012 Jun 1;16(2):163-70.

[13]. Rawal Y, Bailoor DN. Cysts of the Oral Regions. Oral Medicine and Radiology. 2005:159.

[14]. Soluk-Tekkeşin M, Wright JM. The World Health Organization classification of odontogenic lesions: a summary of the changes of the 2017 (4th) edition. Turk PatolojiDerg. 2018 Jan 1;34(1):1-8.

[15]. Wright JM. The odontogenic keratocyst: orthokeratinized variant. Oral Surgery, Oral Medicine, Oral Pathology. 1981 Jun 1;51(6):609-18.

[16]. Selvamani M, Devi AY, Basandi PS, Madhushankari GS. Prevalence and clinicopathological comparison of kerotocystic odontogenic tumor and orthokeratinized odontogenic cyst in South Indian sample population: A retrospective study over 13 years. Journal of pharmacy &bioallied sciences. 2014 Jul;6(Suppl 1):S127.

[17]. Anand VK, ArrowoodJr JP, Krolls SO. Malignant potential of the odontogenic keratocyst. Otolaryngology—Head and Neck Surgery. 1994 Jul;111(1):124-9.

[18]. MacLeod RI, Soames JV. Squamous cell carcinoma arising in an odontogenic

keratocyst. British Journal of Oral and Maxillofacial Surgery. 1988 Feb 1;26(1):52-7.

[19]. Mohanty S, Gulati U, Mediratta A, Ghosh S. Unilocular radiolucencies of anterior mandible in young patients: A 10 year retrospective study. National journal of maxillofacial surgery. 2013 Jan;4(1):66.

[20]. Shetty DC, Rathore AS, Jain A, Thokchom N, Khurana N. Orthokeratinized odontogenic cyst masquerading as dentigerous cyst. International Journal of Applied and Basic Medical Research. 2016 Oct;6(4):297.

[21]. Haring JI, Van Dis ML. Odontogenic keratocysts: a clinical, radiographic, and histopathologic study. Oral surgery, oral medicine, oral pathology. 1988 Jul 1;66(1):145-53.

[22]. Yoshiura K, Higuchi Y, Ariji Y, Shinohara M, Yuasa K, Nakayama E, Ban S, Kanda S. Increased attenuation in odontogenic keratocysts with computed tomography: a new finding. Dentomaxillofacial Radiology. 1994 Aug;23(3):138-42.

[23]. Toller P. Origin and growth of cysts of the jaws. Annals of the Royal College of Surgeons of England. 1967 May;40(5):306.

[24]. Rodu B, Tate AL, Martinez Jr MG. The implications of inflammation in odontogenic keratocysts. Journal of Oral Pathology & Medicine. 1987 Nov;16(10):518-21.

[25]. Rodrigues-Fernandes CI, Paulo-Rogério-FerretiBonan EJ, deAmorimCarvalho CS, de Almeida OP. Pigmented odontogenic keratocyst: Report of a rare case and review of the literature. Journal of clinical and experimental dentistry. 2018 Dec;10(12):e1230.

[26]. Mohtesham I, Prabhu S, Jose M, Rao BS. Odontogenic Keratocyst with Diverse Differentiation–A Case Report. Journal of Advanced Medical and Dental Sciences Research. 2014 Oct;2(4).

[27]. Cunha JF, Gomes CC, de Mesquita RA, Goulart EM, de Castro WH, Gomez RS. Clinicopathologic features associated with recurrence of the odontogenic keratocyst: a cohort retrospective analysis. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2016 Jun 1;121(6):629-35.

[28]. Song YL, Zhang WF, Peng B, Wang CN, Wang Q, Bian Z. Germline mutations of the PTCH gene in families with odontogenic keratocysts and nevoid basal cell carcinoma syndrome. Tumor Biology. 2006;27(4):175-80.

[29]. Li TJ. The odontogenic keratocyst: a cyst, or a cystic neoplasm?. Journal of dental research. 2011 Feb;90(2):133-42.

[30]. Toller PA. Newer concepts of odontogenic cysts. International journal of oral surgery. 1972 Jan 1;1(1):3-16.

[31]. Shear M. The aggressive nature of the odontogenic keratocyst: is it a benign cystic neoplasm? Part 1. Clinical and early experimental evidence of aggressive behaviour. Oral oncology. 2002 Apr 1;38(3):219-26.

[32]. Nagraja A, Anigol PS, Kamath VV, Setlur KP. Keratocystic odontogenic tumor of the maxilla: Report of a rare case and review of literature. World J Dent. 2012 Jan;3(1):100-8.

[33]. Smith G, Smith AJ, Browne RM. Quantification and analysis of the glycosaminoglycans in human odontogenic cyst linings. Archives of Oral Biology. 1988 Jan 1;33(9):623-6.

[34]. Myoung H, Hong SP, Hong SD, Lee JI, Lim CY, Choung PH, Lee JH, Choi JY, Seo BM, Kim MJ. Odontogenic keratocyst: review of 256 cases for recurrence and clinicopathologic parameters. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2001 Mar 1;91(3):328-33.

[35]. Cheng G, Gao J, Wang L, Ding Y, Wu Q, Wang Q, Xiao J, Wang S. The TGF-β1/COX-2-dependant pathway serves a key role in the generation of OKC-induced M2-polarized macrophage-like cells and angiogenesis. Oncology Letters. 2020 Oct 1;20(4):1-.

[36]. de Andrade Santos PP, de Aquino AR, Barreto AO, de Almeida Freitas R, Galvão HC, de Souza LB. Immunohistochemical expression of nuclear factor κB, matrix metalloproteinase 9, and endoglin (CD105) in odontogenic keratocysts, dentigerous cysts, and radicular cysts. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2011 Oct 1;112(4):476-83.

[37]. De Oliveira MD, De Miranda JL, De Amorim RF, De Souza LB, de Almeida Freitas R. Tenascin and fibronectin expression in odontogenic cysts. Journal of oral pathology & medicine. 2004 Jul;33(6):354-9.

[38]. Vered M, Shohat I, Buchner A, Dayan D. Myofibroblasts in stroma of odontogenic cysts and tumors can contribute to variations in the biological behavior of lesions. Oral oncology. 2005 Nov 1;41(10):1028-33.
[39]. MASHHADI AF, Atarbashi MS, Moshref M, Elahi M. Immunohistochemical detection and ultrastructure of myofibroblasts in the stroma of odontogenic cysts and ameloblastoma.
[40]. Li TJ, Browne RM, Matthews JB. Immunocytochemical expression of parathyroid hormone related protein (PTHrP) in odontogenic jaw cysts. British Journal of Oral and Maxillofacial Surgery. 1997 Aug 1;35(4):275-9.
[41]. Kubota Y, Ninomiya T, Oka S, Takenoshita Y, Shirasuna K. Interleukin-1α-dependent regulation of matrix metalloproteinase-9 (MMP-9) secretion and activation in the epithelial cells of odontogenic jaw cysts. Journal of Dental Research. 2000 Jun;79(6):1423-30.
[42]. Wang J, Zhang X, Ding X, Xing S, Li H, Zhang W, Wang L, Wu H. Cyclooxygenase-2 expression in keratocystic odontogenic tumour decreased following decompression. Molecular and Clinical Oncology. 2013 Nov 1;1(6):982-6.
[43]. Teronen O, Hietanen J, Lindqvist C, Salo T, Sorsa T, Eklund KK, Sommerhoff CP, Ylipaavalniemi P, Konttinen YT. Mast cell- derived tryptase in odontogenic cysts. Journal of oral pathology & medicine. 1996 Aug;25(7):376-81.
[44]. Syamala D, Suresh R, Janardhanan M, Savithri V, Anand PP, Jose A. Immunohistochemical evaluation of myofibroblasts in odontogenic cysts and tumors: a comparative study. Journal of oral and maxillofacial pathology: JOMFP. 2016 May;20(2):208.
[45]. da Silva MJ, de Sousa SO, Corrêa L, Carvalhosa AA, de Araâaujo VC. Immunohistochemical study of the orthokeratinized odontogenic cyst: a comparison with the odontogenic keratocyst. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2002 Dec 1;94(6):732-7.
[46]. Kumamoto H, Yoshida M, Ooya K. Immunohistochemical detection of hepatocyte growth factor, transforming growth factor- β and their receptors in epithelial odontogenic tumors. Journal of oral pathology & medicine. 2002 Oct;31(9):539-48.
[47]. Shear M. The aggressive nature of the odontogenic keratocyst: is it a benign cystic neoplasm? Part 3. Immunocytochemistry of cytokeratin and other epithelial cell markers. Oral oncology. 2002 Jul 1;38(5):407-15.
[48]. Piattelli A, Fioroni M, Rubini C. Differentiation of odontogenic keratocysts from other odontogenic cysts by the expression of bcl-2 immunoreactivity. Oral oncology. 1998 Sep 1;34(5):404-7.
[49]. Smitha BR, Murthy S. Odontogenic Keratocyst–A tumor–an enigma. Journal of PEARLDENT. 2011;2(3):22-7.
[50]. Li TJ, Browne RM, Prime SS, Paterson IC, Matthews JB. p53 expression in odontogenic keratocyst epithelium. Journal of oral pathology & medicine. 1996 May;25(5):249-55.
[51]. Thosaporn W, Iamaroon A, Pongsiriwet S, Ng KH. A comparative study of epithelial cell proliferation between the odontogenic keratocyst, orthokeratinized odontogenic cyst, dentigerous cyst, and ameloblastoma. Oral Diseases. 2004 Jan;10(1):22-6.
[52]. Kimi K, Kumamoto H, Ooya K, Motegi K. Immunohistochemical analysis of cell- cycle- and apoptosis- related factors in lining epithelium of odontogenic keratocysts. Journal of oral pathology & medicine. 2001 Aug;30(7):434-42.
[53]. Barreto DC, Gomez RS, Bale AE, Boson WL, De Marco L. PTCH gene mutations in odontogenic keratocysts. Journal of dental research. 2000 Jun;79(6):1418-22.
[54]. Pogrel MA. Decompression and marsupialization as a treatment for the odontogenic keratocyst. Oral and Maxillofacial Surgery Clinics. 2003 Aug 1;15(3):415-27.
[55]. Stoelinga PJ. Excision of the overlying, attached mucosa, in conjunction with cyst enucleation and treatment of the bony defect with carnoy solution. Oral and Maxillofacial Surgery Clinics. 2003 Aug 1;15(3):407-14.