Odontogenic Keratocyst : A Review of Histogenesis, Classification, Clinical Presentation, Genetic Aspect, Radiographic Picture, Histopathology and Treatment

Review Article

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ABSTRACT

The odontogenic keratocyst (OKC), which makes up approximately 10% of odontogenic cysts, is a locally-aggressive cystic lesion that affects the maxilla or the mandible and is capable of causing major destruction. OKCs have been a topic of debate ever since they were discovered and named. The origin of OKC is still debatable, the OKC mostly occur intraosseusly and is thought to be derived from odontogenic epithelium as the dental lamina and its remnants after the organ has served its purpose. The WHO had classified OKC under 'developmental odontogenic cysts of jaw' in the 1971 and 1992 classifications . Nevertheless, the 2005 WHO classification controversially considered OKC an odontogenic neoplasm and gave it the name 'keratocystic odontogenic tumor' (KCOT) . The reasons for this change were the lesion's high recurrence rate, aggressive clinical behavior, association with nevoid basal cell carcinoma syndrome and mutations in the PTCH tumor suppressor gene. The designation of OKC changed once again in the 2017 WHO classification, reverting back to the more accepted term 'odontogenic keratocyst'. OKCs grow in an antero-posterior direction, infiltrating the cancellous bone of the jaws, often without obvious bone expansion, so it is commonly asymptomatic despite its aggressive nature. The presence of multiple OKCs is especially correlated to nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome , the radiographic appearance of OKC ranges from well-defined unilocular lesions to extensive multilocular lesions with ill-defined borders. This review will cover the history of this lesion's classification , nomenclature, as well as its histogenesis, clinical presentation, histopathology, radiography, genetics, treatment, prognosis and complications.

Received: 16 January 2021, **Accepted:** 14 April 2021

Key Words: Inflammed okc, OKC, parakeratin.

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ISSN: 1110-0559, Vol. 45, No.2

INTRODUCTION

Cysts are considered a common pathosis that affect people of all ages and occur anywhere on the body. Odontogenic cysts are those formed from tissues that are involved in odontogenesis[1]. The odontogenic keratocyst (OKC), which makes up approximately 10% of odontogenic cysts, is a locally-aggressive cystic lesion that affects the maxilla or the mandible and is capable of causing major destruction[2]. OKCs have been a topic of debate ever since they were discovered and named. This review will cover the history of this lesion's classification, nomenclature, as well as its histogenesis, clinical presentation, histopathology, radiography, genetics, treatment, prognosis and complications.

HISTOGENESIS

The origin of OKC is still debatable, the OKC mostly occur intraosseusly and is thought to be derived from odontogenic epithelium as the dental lamina and its remnants after the enamel organ has served its purpose. OKCs arising in dentate areas of both maxilla and mandible are thought to have origin from these remnants. However, there is no remnants or offshoots of dental lamina present in the mucosal area of the third molar, so the presence of epithelial islands in the mucosa overlying the OKC and attached to it reveals that the extensions of the basal cell layer of epithelium of oral mucosa may play a role in the etiology of the cyst[3-6].

The peripheral OKC rarely occurs, mainly present in gingiva and buccal mucosa. Peripheral keratocyst located in the gingiva supports the concept of its origin from remnants of dental lamina found in gingiva or from basal cells of oral epithelium[7].

 DOI: 10.21608/ejh.2021.58363.1419

Peripheral keratocyst that occur in the buccal mucosa has a debatable origin. As its epithelium resembles the sebaceous gland duct epithelium and given the name "cutaneous keratocyst" or "steatocystoma" as a result of presence of sebaceous gland found in the buccal mucosa which is called the Fordyce spots and it is considered from the skin adnexa[6,8].

Moreover, peripheral keratocyst can occur around the parotid papilla but the Fordyce spots are not centered around the parotid papilla which makes the sebaceous gland origin doubtable[8]. Some findings stated that migration of dental lamina remnants to the buccal tissues during embryogenesis might trigger the occurrence of the peripheral keratocyst[6]. Thus, there is still a debate on the origin of peripheral keratocyst occurring in the buccal mucosa whether it has odontogenic origin or not.

CLASSIFICATION

In 1876, the OKC was first described by Mikulicz as a dermoid cyst. However, later in 1926, it became known as cholesteatoma, meaning a cystic mass with keratin in a living matrix[9]. The name 'primordial cyst' was first suggested by Robinson in 1945 since it was believed to have a primordial origin as it arose from the dental lamina or enamel organ before the initiation of enamel formation[10]. In 1956, Philipsen was the first to use the term 'odontogenic keratocyst' to describe a cyst with keratinization of its epithelial lining[11]. From as early as 1967, however, there was debate on its designation when Toller suggested that OKC is a benign neoplasm due to its clinical behavior[3].

The WHO had classified OKC under 'developmental odontogenic cysts of jaw' in the 1971 and 1992 classifications[12]. Nevertheless, the 2005 WHO classification controversially considered OKC an odontogenic neoplasm and gave it the name 'keratocystic odontogenic tumor' (KCOT)[13]. The reasons for this change were the lesion's high recurrence rate, aggressive clinical behavior, association with nevoid basal cell carcinoma syndrome and mutations in the PTCH (Protein patched homolog 1) tumor suppressor gene[14].

The designation of OKC changed once again in the 2017 WHO classification, reverting back to the more accepted term 'odontogenic keratocyst'[15].

This reversal was due to insufficient evidence to support the theory of neoplastic origin as several papers showed that the PTCH gene mutation was found in other non-neoplastic lesions such as the dentigerous cyst and that the resolution of many cases following marsupialization was not concurrent with tumor characteristics[16,17].

CLINICAL PRESENTATION

OKC is a locally aggressive cyst which makes up approximately 10% of odontogenic cysts[18].

It affects males twice as much as females and has a wide age distribution, occurring anywhere from the first decade to the eighth decade with two main peaks: the first peak is at 25-34 years and the second is at 55-64 years[19]. OKCs are typically intraosseous, affecting the mandible more frequently than the maxilla with only a few peripheral cases recorded[20]. They are commonly associated with impacted teeth (24 to 40%) with a strong predilection for the posterior body of the mandible and the ascending ramus[21]. When affecting the maxilla, OKCs are mainly found between the canine and lateral incisor or in the third molar area[18].

OKCs grow in an antero-posterior direction, infiltrating the cancellous bone of the jaws, often without obvious bone expansion, so it is commonly asymptomatic despite its aggressive nature. In fact, 5.2 to 42.5% of cases are accidentally diagnosed during routine dental examination[19,22]. However, large lesions in the mandible may cause trismus and those in the maxilla may expand into the maxillary sinus and cause ipsilateral nasal obstruction. In addition, slowly growing lesions stimulate bone apposition, causing bone expansion without cortical perforation (Figure 1)[23]. Spontaneous drainage of cyst fluids, paresthesia and pain are other rare manifestations that can occur[11].

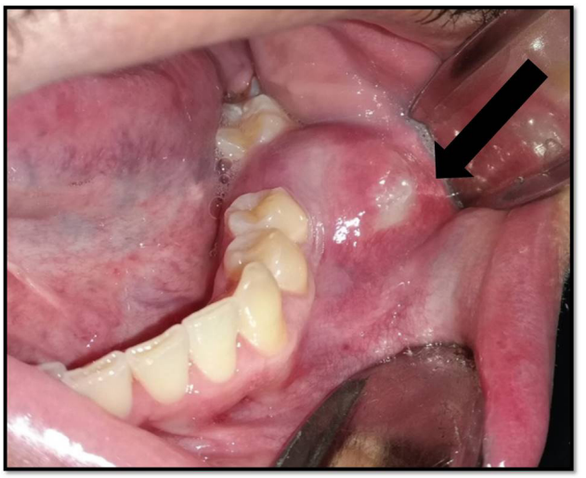

Fig. 1 : Infected OKC (black arrow) causing swelling in the region of missing molar[23]

Clinically, lesions are far more aggressive and recur more often when associated with syndromes such as Gorlin-Goltz syndrome, Marfan syndrome, Noonan syndrome, Ehlers danlos syndrome, Orofacial Digital syndrome and Simpson- Golabi-behmel syndrome[24]. The presence of multiple OKCs is especially correlated to nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome, which is a hereditary autosomal dominant multi-systemic disease characterized by multiple neoplasms and other developmental abnormalities. Multiple keratocysts and a decreased age of incidence are major indicators that alert physicians of the likelihood of diagnosing this syndrome[18]. Nevertheless, in his analysis of 312 OKC cases, Brahnon found that 5.8% of patients

with multiple cysts were nonsyndromic[25]. Therefore, the examination of skin lesions and other associated defects such as bifid ribs is vital (Figure 2)[26].

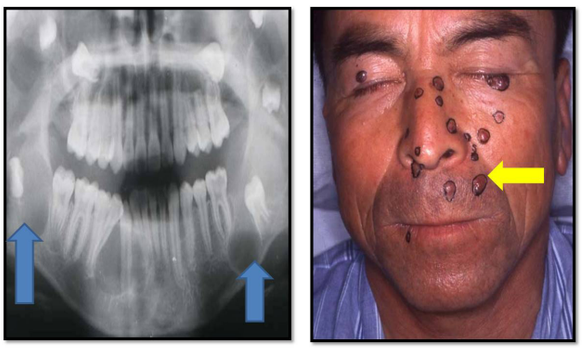

Fig. 2: NBCCS Patient showing multiple BCCs(yellow arrow) along with multiple OKCs (blue arrows)[26]

GENETIC ASPECT OF OKC

Hedgehog Signaling Pathway (Hh Signaling Pathway):

This signaling pathway is responsible for the embryonic development, proliferation control and fate of cells[27]. This pathway is composed of two receptors playing a principle role forming what is called transmembrane receptor complex present on the cell membrane acting in cooperation with each other named PTCH1 and smoothened receptor (SMO)[27].

The ligand, which activates the receptor PTCH1 is called Sonic Hedgehog Signaling Molecule (SHh). In the absence of this ligand the PTCH1 inhibits the signaling action of SMO preventing the unneeded cell proliferation but during the presence of the SHh ligand[28] or mutational inactivation of the PTCH[29] this results in failure of PTCH1 to inhibit the action of SMO.

This will lead to activation of glioma-associated oncogene (GLI1) which is a transcription factor in the nucleus leading to upregulation of proliferation genes in the cell (Figure 3)[30]. Taken into consideration that PTCH1 is a tumor suppressor gene, so its mutation increases the likelihood for development of cancer[27]. In a study done by Gu, *et al*.[29] on Chinese patients, 12 samples of OKC were collected, Ten of them were non-syndromic and two were syndromic to demonstarate the PTCH mutations in both syndromic and non-syndromic cases they found 4 novel and 1 known PTCH mutations in 5 cysts, 3 of them were non-syndromic and 2 were Gorlin related keratocysts. Thus, by analysis of this study PTCH mutations occur in both non-syndromic and syndromic[29]. Another study done by Pan, *et al*.[28] to clear up the role of PTCH1 in OKC. Twelve OKC samples were taken, eight of them were non-syndromic and four associated with NBCCS, the results showed that there is PTCH1 mutations in two sporadic (non-syndromic) and three syndromic cases.

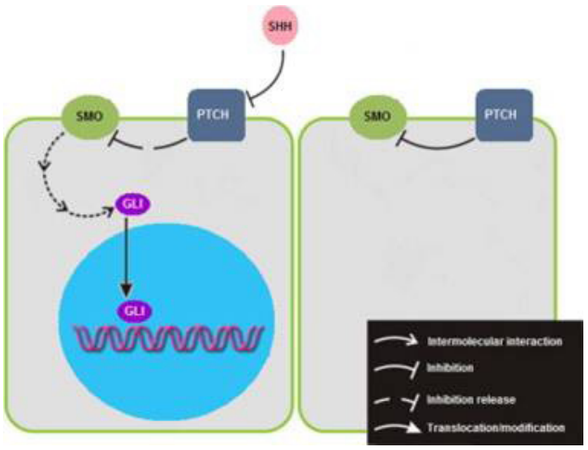

Fig. 3: Hedgehog Signaling Pathway[30]

The same study clarified the role between PTCH1 mutations and epithelial cell proliferation through determining Ki67 expression (proliferation marker present in the active phase of the cell cycle)[28,31].

In OKCs, 62 OKC samples were taken (42 of them were sporadic and 20 were syndromic) the results showed that the Ki67 labeling was higher in OKCs with PTCH1 mutation than those without PTCH1 mutation.

Also this study confirmed that the Ki67 labeling was higher in the epithelial linings of OKCs associated with NBCCS than in sporadic cases. Moreover, the Ki67 labeling in the epithelium of the lesion was higher in OKCs with truncation causing PTCH1 mutations than those without truncation causing mutations and non-mutation groups[28]. Some studies have revealed that occurrence of PTCH1 mutation in syndromic OKC (>85%) is more than that in the sporadic OKC (<30%) but a study done by Qu, et.al[32] showed that when there is epithelium separation from the stroma of these cysts, the PTCH mutation rate increases to 84% in sporadic cases to be nearly equal to that found in syndromic OKCs .

These results clarify that the lower PTCH1 rates was due to the presence of confounding fibrous tissue and that PTCH1 mutations play a principle role in the sporadic as well as syndromic OKCs[32].

P53, PCNA and Cyclin D-1

P53 is a tumor suppressor gene located on chromosome 17, which produce P53 protein, which is a nuclear protein[33]. Studies reveal that its highest expression is in the intermediate layer of the epithelium and the least expression is in the cells of the surface layer, which might reflect apoptosis in the surface layer. P53 is considered to play a role in the control of cell cycle and apoptosis as it is considered to send apoptotic signals.

It is shown to have maximum positivity in areas with high expression of PCNA and Ki67[30]. A study done by Fatemeh, *et al*.[33] to compare the P53 gene expression between OKC, dentigerous cyst, dental follicles and their

inflamed cases to assess the relationship between the expression of P53 and inflammation, showed that the mean percentage of P53 positive cells in dental follicle was 0.7%, 5.4% in the non-inflamed OKC and 17.4% for the inflamed OKC, 1.2% for the non-inflamed dentigerous cyst and 2.2% for the inflamed dentigerous cyst. P53 expression and intensity in the OKC was much more higher than its expression and intensity in dentigerous cyst and dental follicle, also as seen in the results inflammation in OKC led to higher expression of P53 than that in non-inflamed OKC. Moreover, in the same study P53 expression in the connective tissue wall was investigated to determine the role of P53 in mesenchymal cells for the growth of OKC and the result was that there was no P53 expression in the connective tissue except for the inflammatory cells that infiltrated the inflamed cysts. Thus, if it is considered in other studies that the mesenchymal cells have a role in the growth of OKC this will not be P53 mediated altered expression. Finally, significantly high expression of P53 in OKC may explain changes in cell cycle (Figure 4)[33,34]. In another study done by Malcic´, et .al[35] P53 mutation was detected in one OKC case only from 11 exmained cases this seems that P53 mutation is not a principle event in the pathogenesis of OKC . In 2018 Kaczmarzyk, *et al*.[36] revealed that there is no significant difference in the expression of P53 between the recurrent and non-recurrent OKC.

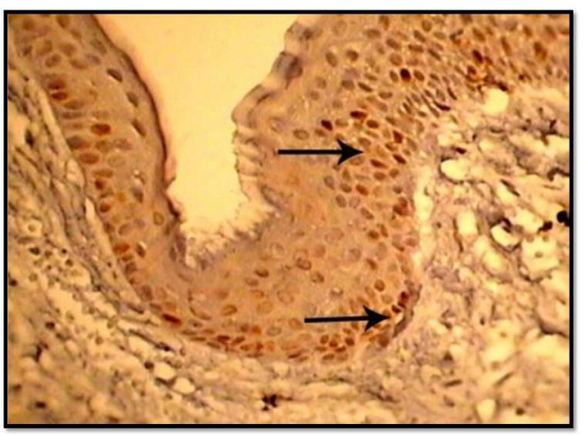

Fig. 4: Nuclear Positivity for P53 in OKC[34]

COX-2 and Bcl-2

COX-2 is an enzyme, which involved in the conversion of arachidonic acid into prostaglandins; it is thought to be playing a bilogoical role in the epithelial lining of OKC. In a study done to determine the expression of COX-2 in OKC, 20 samples were taken and studied immunohistochemically, the results revealed mild to strong expression of COX-2 in the 20 samples. This indicates that COX-2 may play a role in the biological behavior of the cyst[37]. Another study was done by Wang, *et al*.[38] on 16 OKC samples to reveal the role of decompression on decreasing the COX-2 expression, in samples analyzed before decompression there was immunopositivity of COX-2 in the whole thickness of epithelium and also the cell membrane and cytoplasm in 15 samples (93.8%) while after decompression only 3 samples (18.8%) showed immunopositivity. Bcl-2 is a protooncogene located on chromosome 18q21 its product is Bcl-2 antiapoptotic protein (G 12a) and its overexpression causes an increase in the cell growth. The study done to evaluate the expression of Bcl-2 in OKC on 16 samples by Razavi, *et al*.[39] revealed that there was high expression of Bcl-2 in the epithelial layer of OKC especially in the basal epithelial layer this was related to that apoptosis does not occur in the basal cell layer (Figure 5)[9,39]. It has been demonstrated that Bcl-2 expression is higher in syndromic OKC rather than sporadic. There is a correlation between COX-2 and Bcl-2 as COX-2 is known to increase Bcl-2 level which then will lead to apoptosis resistance and increasing the growth of the cyst[36].

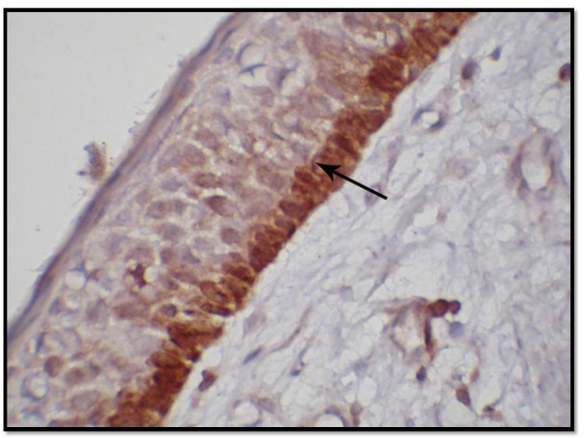

Fig. 5: Bcl-2 expression in OKC (black arrow) Presence of bcl-2 mostly in the basal cell layer[39]

TGF-alpha and EGF

TGF-alpha (Transforming Growth Factor) is an oncogene and related to the epidermal growth factor (EGF) family as it is the ligand which become attached to the EGF receptor leading to cell proliferation. The high expression of TGF-R gene in the OKC and strong binding to TGF-alpha protein with it demonstrates that TGF-alpha can act as a growth factor for this lesion. In a study done by Deyhimi, *et al*.[34] on 15 OKC samples to investigate the extent of TGF-alpha expression in OKC, the results showed that TGF-alpha is expressed in the basal and parabasal cell layers of the epithelial lining with higher expression in the basal layer (Figure 6), TGF-alpha is known to have a role in the malignant changes but this hypothesis is rare to occur according to the findings of the long term follow up of OKC[34].

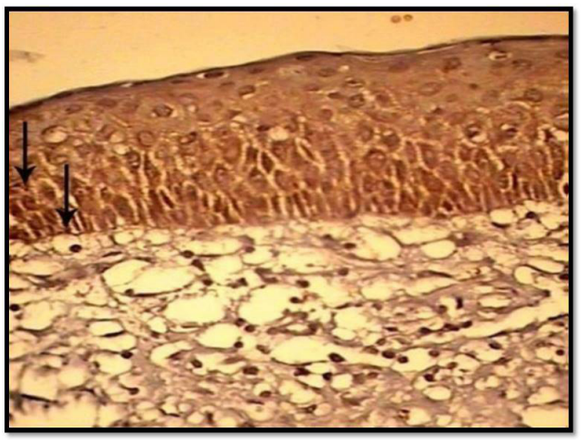

Fig. 6: TGF-alpha expression in basal and parabasal cells of OKC (black arrows)[34]

About 89% of OKCs shows higher levels of TGF-alpha compared with 50% in the dentigerous and radicular cysts[9] Previous studies showed that EGFR is expressed in high levels in OKC and this supports the intrinsic growth potential of this cyst that is not found in other odontogenic cysts[30,40]. A study done by De-Vicente, *et al*.[41] showed that EGFR was expressed in 73% of the OKC examined cases in the basal cell layer . In contrast a study was done by Razavi, et.al[39] showed that there were no expression at all for the EGFR in 16 samples of OKC thus according to this study the authors concluded that however the aggressive potential of OKC is not severe as a neoplasm like ameloblastoma which showed expression of EGFR in all of its cases in the same study .

YAP/TAZ

YAP/TAZ are known to play a role in regulation of organ size and tissue repair after injury, recently YAP and TAZ are considered oncogenes. YAP and TAZ also showed to play a role in the organ development of oral region. In oral and maxillofacial regions the dysregulated activity of YAP/TAZ is found to have a role in head and neck tumors. A study done by Man, *et al*.[42] showed upregulated expression of YAP/TAZ, higher levels of mRNA transcription factors (TEAD1, TEAD4 and RUNX2) in OKC samples. In addition, the results showed synchronous distribution and the close relation between YAP/TAZ and Ki67. These data suggested the possible role of YAP/TAZ in the proliferative activity of OKC.

RADIOGRAPHICALLY

Over all, the radiographic appearance of OKC ranges from well-defined unilocular lesions to extensive multilocular lesions with ill-defined borders[21]. The ratio of unilocular: multilocular radiolucency associated with OKC in maxilla was 6:1 while in the mandible the ratio was 1.9:1. Moreover, the perforation rate was found to be 50.8%[43]. The radiolucency is usually well demarcated and bound by a sclerotic margin; however, it may be diffuse in some areas. Displacement of adjacent teeth occurs more frequently than resorption, owing to the lesion's expansile nature[19]. The radiographic features of OKCs are not pathognomonic, especially in smaller unilocular lesions. A small unilocular OKC in the anterior sextant may simulate a radicular cyst, lateral periodontal cyst or nasopalatine cyst. It is also difficult to diagnose the multilocular variant since OKCs can appear septated, heavily mimicking ameloblastomas[22]. In order to diagnose OKCs, the most commonly used radiographic techniques are conventional radiography (mainly panoramic radiography), computed tomography (CT) and magnetic resonance imaging (MRI).

Panoramic Radiography

Panoramic radiography is useful for the preliminary assessment of OKCs (Figure 7)[44]. Even though they give an idea about the location, size, shape, margins and extensions of the cyst, the fact that it is a 2D representation of a 3D object limits this technique as it provides magnification, geometric distortion and overlapping[18].

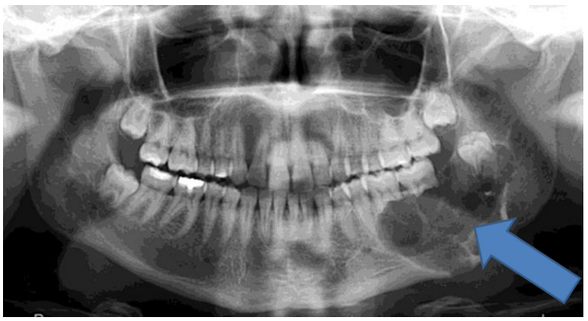

Fig. 7: Panorama showing multilocular radiolucency(blue arrow) of the left mandibular body and angle[44].

Computed Tomography

To overcome the limitations of panoramic radiography and achieve an accurate assessment of the lesion, a CT scan is required. There are two main CT techniques: cone beam CT (CBCT) and multidetector CT (MDCT). Both are used for the diagnosis and treatment planning of OKCs due to their ability to produce high quality multiplanar reconstruction images in different planes. In addition to the details shown in a panorama, a CT scan reveals other features of OKCs such as bony changes in a bucco-lingual direction, internal density and extension into soft tissue. Due to its higher spatial resolution, a CBCT scan is considered more effective in the assessment of the bony changes of the cortical plates of the jaw (Figure 8). However, CBCT offers poor contrast resolution, so a MDCT scan is favored when evaluating internal density and extension into soft tissue(Figure 9)[18].

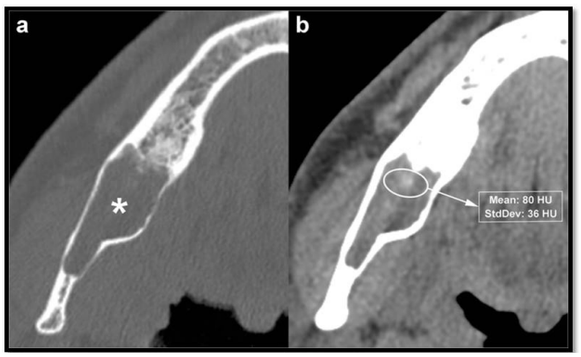

Fig. 8: Axial MDCT image with bone window (a) shows an OKC in the posterior region of the right mandible (asterisk). Axial MDCT image with soft tissue window (b) clearly demonstrates a high- density area within the mandibular lesion (ellipse ROI) with a mean attenuation value of 80 HU[18].

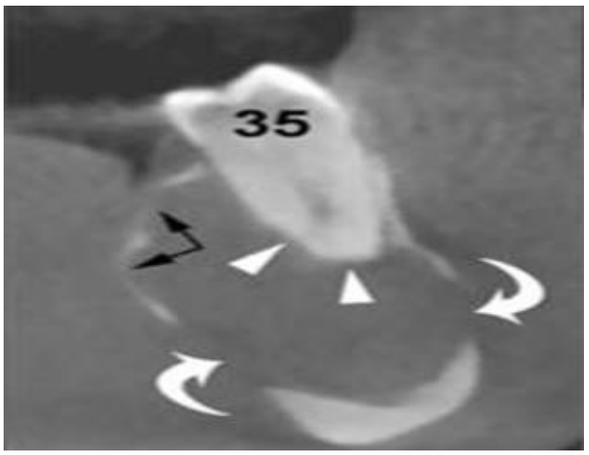

Fig. 9: Cross- sectional CBCT images show an OKC with well-defined (white arrow) and lobulated margins (black arrow) located in the interforaminal region of the mandible[18].

HISTOPATHOLOGY

History

In the first two editions of WHO classifications which were published in 1971 and 1992, OKC was described to have two histological subgroups: parakeratinized and orthokeratinized[45,46]. However, in the following years, scientists saw the need to differentiate between the two subtypes since the parakeratinized type showed more aggressive clinical behavior, higher recurrence rate and an association with NBCCS . Thus in the 2005 classification, the parakeratinized type became the KCOT under 'odontogenic epithelial tumors' while the orthokeratinized type continued under 'odontogenic developmental cysts'[47]. Even though the classification of the parakeratinized type reverted back to OKC following the 2017 classification, it still remains distinguished from the orthokeratinized cyst which is no longer considered a variant of OKC[48].

Epithelium

OKCs are lined by 5-10 layers of thin, uniform parakeratinized stratified squamous epithelium[49]. The basal cell layer is made up of palisaded and polarized columnar or cuboidal cells that are vertically oriented and often hyperchromatic giving off a 'tombstone appearance[12]. The basal cell layer usually shows some mitotic figures. This mitotic activity has been found to be significantly higher in cysts from NBCCS patients. The supra-basal cells are polyhedral and show intercellular edema and intercellular bridges. They are also far richer in mitotic figures than the basal layer[9]. These cells do not show the usual gradual flattening of cells; there is an immediate transition between them and the keratin layer. The surface keratinization shows parakeratin and is corrugated and rippled with nuclear remnants[12].

Epithelium-Connective Tissue Interface

The epithelium-connective tissue interface is flat with an absence of retepegs and a potential for budding of the basal cell layers and formation of satellite cysts[11]. Many areas of separation are seen at the interface due to the weak attachment between the epithelium and the connective tissue capsule (Figure 10)[9]. Several studies have explained that this weak attachment may be due to defective anchoring fibrils caused by the presence of active collagenolytic enzymes such as beta-naphthylamidase and leucine aminopeptidase within the OKC walls[50-52].

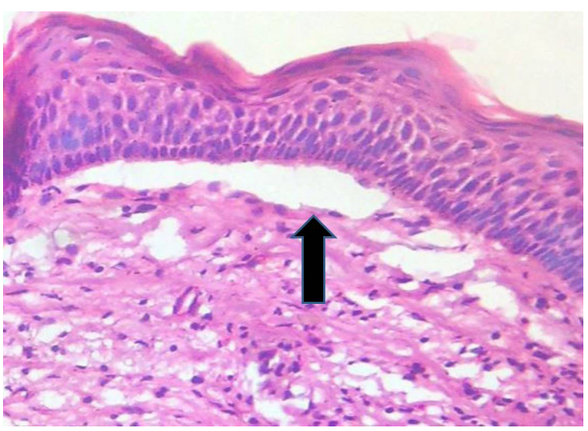

Fig. 10: Microphotograph of OKC lesion showing separation (black arrow) between epithelium and connective tissue[11]

Connective Tissue Capsule

The fibrous capsule of OKC is thin and loose with relatively few cells which are separated by stroma rich in mucopolysaccharides[9]. Daughter cysts or epithelial islands could be seen in the cyst wall in 7-21% of the cases, especially when the patient has NBCCS (Figure 11)[11].

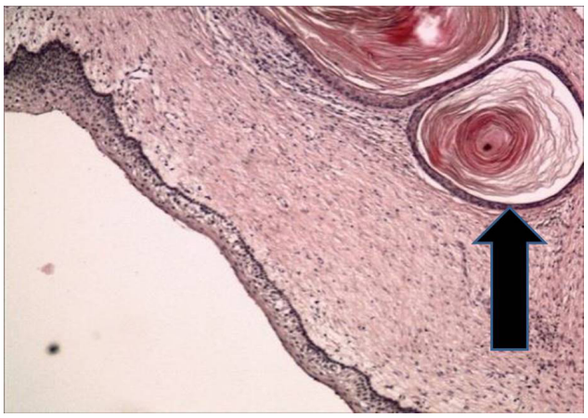

Fig. 11: Microphotograph of OKC lesion demonstrating the formation of satellite microcysts (black arrow) within the fibrous wall[44].

Cystic Space:The cystic lumen is usually filled with desquamated keratin which appears as a cheesy material. However, clear liquid may also be encountered[53].

Mucous Prosoplasia

Mucous cell prosoplasia, is the transformation of a simple squamous epithelial cell into mucous secreting cell. The origin of these mucous cells in the epithelium of odontogenic cyts has been a topic of debate till date. Different theories have been advocated concerning the occurrence of mucous cells in the cystic epithelium[54]. Among them, the theory of transdifferentiation in which Hodson, *et al*.[55] proposed that the presence of mucous secreting cells in the cystic lining epithelium might be an outcome of prosoplastic modification of normal squamous cells of the lining epithelium into mucous secreting cells in response to change in their environment. Biochemical analysis of the cystic contents of various cysts by Toller PA showed that the soluble protein contents were identical in radicular cysts (RCs) and dentigerous cysts (DCs) but different in odontogenic keratocyst[56], the keratin layer lining the cystic epithelium of odontogenic keratocyst justifies the low prevalence of mucous prosoplasia as it may guard the epithelial cells from the inductive environmental provocations that may lead to cellular transdifferentiation[57].

Other Findings

Other features of the OKC that are frequently seen under the microscope are Rushton bodies (7%-32%), dystrophic calcification (10%-21%), Koilocytosis (17.1%), cartilage and dentinoid formation. Primary OKC without recurrence within 5 years shows a slightly higher prevalence for dystrophic calcifications than primary OKCs that recurred[58,59].

Inflammed OKC

A case reported by Kang, *et al*.[60] illustrated that in an inflamed OKC, the stratified squamous epithelium of OKC becomes hyperplastic at many areas showing a characteristic loss of retepegs and infiltration of acute inflammatory cells. Some areas displayed proliferation of epithelial lining with lack of surface keratin (Figure 12)[60]. The connective tissue wall showed dense infiltration of both acute and chronic inflammatory cells (Figure 13)[62]. Toller, *et al*.[61] reported that in the presence of a fairly pronounced inflammatory reaction in an OKC epithelial lining, the degree of keratinization in these areas would be altered. This change is likely to increase the permeability of the lining and result in a higher soluble protein level in the cystic fluid than that in the non-inflamed keratinizing cysts. Following inflammation, various cytokines such as IL2, IL3 will be overexpressed causing further expression of of IL2β, β convertase, prostaglandins E2 and coactivate compliment. Consequently, vascular permeability and leukotactic response will occur leading to the transformation of epithelium from keratinized to non-keratinized[60]. OKC lesions with no or mild inflammation had mostly poorly packed fibers while moderate to severely inflamed lesions had well packed and thick fibers[63].

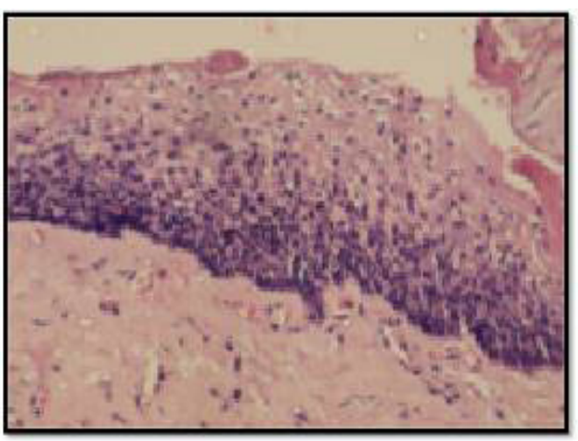

Fig. 12: Proliferation of lining with absence of surface keratinizatio[60].

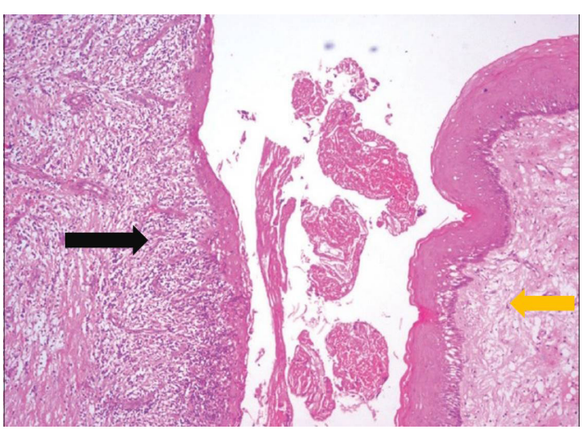

Fig. 13: Infiltration of acute and chronic inflammatory cells i (black arrow) and non inflamed OKC (yellow arrow)[62].

IMMUNOHISTOCHEMISTRY AND SPECIAL STAINS

A study conducted by de Vicente, *et al*.[41] found that immunostaining for cyclin D1, a protein required for the progression of cells through the cell cycle, was positive in 91% of OKCs and that it was expressed in a focal parabasal pattern. Basal Epidermal Growth Factor Receptor (EGFR) staining was also positive in 73% of OKCs . In addition, 19 out of 20 cases were immunoreactive for carcinoembryonic antigen (CEA) which is usually increased in certain types of malignant and benign tumors[41]. Staining for p53 was also positive in OKCs and was observed in the nuclei of cells distributed in the whole lining, but mainly concentrated basally. This protein significantly increases the proliferative potential and enhances the aggressive behavior of the lesion since it inhibits apoptosis and growth inhibitory actions[64].

Furthermore, a research was conducted by Chang, *et al*.[24] to investigate Langerhan cell (LC) count in 60 OKC cases. Anti-CD1a immunostaining of the epithelium and the sub-epithelial connective tissue showed that dendritic cells were not found in uninflamed lesions and that the number of LC increases with direct proportion to any present inflammation.

Naruse, *et al*.[65] analyzed cluster of differentiation 34 (CD34), a cell surface glycoprotein, and found that high levels of it were significantly associated with recurrence of the lesion. Likewise, Ki-67 is a proliferation marker that is usually used to demonstrate a higher proliferation rate of OKC compared to other types of cysts[66].

Meara, *et al*.[67]. also examined the differences between the staining pattern of syndromic and non-syndromic lesions and found that cytokeratin 18 (ck-18) staining was more visible in nonsyndromic lesions while cytokeratin 17 (ck-17) stained more strongly in syndromic lesions. Further research by Ali, *et al*.[68] analyzed α-SMA positively stained myfibroblasts in OKCs , which were found in an average of 54.1 deep in the connective tissue stroma, showing an increase from the normal count which corresponds to 15.

On the other hand, a histochemical study conducted by Raj, *et al*.[69] using Picrosirius red stain found that OKC has a significantly more greenish yellow collagen fibers than the orange-red birefringence in comparison to other lesions such as dentigerous cysts indicating a more aggressive behaviour of OKC.

TREATMENT AND PROGNOSIS

Treatment of OKC is still debatable as no certain treatment that is specific for management of all cases of OKC[70,71]. Choosing the therapeutic procedure for OKC depends on minimal recurrence rate and minimal morbidity for the patient. There are many therapeutic modalities for OKC including molecular, conservative methods (enucleation, decompression and marsupialization) and aggressive methods (peripheral ostectomy using rotary instruments, Carnoy's solution, cryotherapy using liquid nitrogen and jaw resection[71]. There are factors that play a role in choosing the type of treatment for an OKC case as age of the patient, size of the lesion, recurrence status and the radiographic evidence of cortical perforation[11,72].

The molecular treatment

A case was reported by Goldberg, *et al*.[73] for a patient with NBCCS and had multiple large OKCs, the patient started a daily regimen of a drug known as GDC-0449 which is an oral drug that inhibits the Hh signaling pathway. The results of this regimen showed that there was complete resolution of 3 OKCs documented by the radiographs after 2 years of therapy[73].

In addition, treatment with SMO antagonist (cyclopamine) has resulted in Hh pathway downregulation. A clinical trial tested the usage of an oral Hh pathway inhibitor (Vismodegib) and its effect on OKC size on 6 patients associated with NBCCS, the results revealed reduction in the cyst size in 4 patients and no change in lesion size in 2 patients. Also, several epigenetic drugs are tested and have been approved to be used clinically[74].

The conservative treatment

The conservative treatment includes enucleation, marsupialization and decompression[23]. Enucleation alone is discouraged in treatment of OKC as some studies reported high recurrence rate when enucleation was done alone[71,75] but enucleation followed by open packing may be a well-chosen treatment due to its simplicity, and low recurrence rate[76].

Marsupialization is the process of conversion of a closed cavity such as a cyst or abscess into an open pouch by incision and then suturing its edges and allow it to drain freely. Marsupialization alone is associated with high recurrence rates[75]. In order to decrease this high recurrence rate, marsupialization should be followed by enucleation[70]. Decompression is opening in the cyst associated with the application of a drainage tube to allow the opening to persist and its associated with very low rates of recurrence but its disadvantages is that it requires two surgical approaches and the treatment time is long[72,77].

The aggressive treatment

The aggressive treatment includes (Carnoy's solution, peripheral ostectomy, cryotherapy and resection). Aggressive treatments are associated with lower recurrence rate but high morbidity rates to the patient. Enucleation can be applied and using adjunctive therapy as Carnoy's solution. Choosing enucleation and Carnoys' solution is one of the best treatments for OKC as it has low recurrence rate[78], after enucleating the cyst, Carnoy's solution is applied and has important role in inactivation of the epithelial remnants left behind after the enucleation, it has some disadvantages such as bone necrosis[23]. The FDA banned the use of any therapeutic agents containing

chloroform as it acts as a carcinogenic agent, Thus a Carnoy's solution without chloroform is used instead[79,80]. Due to the high recurrence rate of OKC, resection was selected as a treatment modality, although having the least recurrence rate; it has high morbidity to the patient such as loss of jaw continuity or facial disfigurement. It should be used only with the aggressive (usually large, multilocular) or recurrent (3 or more times) lesions[71,81].

Enucleation with peripheral ostectomy is removal of the cyst then reduction of the peripheral bone by a powered handpiece to ensure the removal of the epithelial residues. This method of treatment is less aggressive when compared to resection and Carnoy's solution[82].

New methods for treatment

Ultrasonic debridement of the cystic cavity is a method in order to eliminate any epithelial remnants while preservation of bone and adjacent tissues that are damaged by other methods. The case presented in the study of Blanchard[83] had no recurrence after treatment with conservative enucleation and ultrasonic debridement .

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

كيس القرنية سني المنشأ: مراجعة لتكوين الأنسجة، التصنيف، العرض السريري، الجانب الوراثي، الصوره الشعاعيه، التشريح الهستوباثولوجى والعلاج

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كيسة القرنية ذات المنشأ السني (OKC)، والتي تشكل ما يقرب من ١٠ ٪ من الأكياس ذات السنية، هي آفة كيسية عدوانية تؤثر موضعيا على الفك العلوي أو الفك السفلي وهي قادرة على التسبب في تدمير كبير. كانت موضوع خلاف منذ ان تم اكتشافها وتسميتها.

ستغطي هذه المراجعة تاريخ تصنيف هذه الآفة، والتسميات، وكذلك تكوين الأنسجة، والعرض السريري، والتشريح المرضي، والصوره الشعاعيه، والوراثة، والعلاج، والتشخيص، والمضاعفات.