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Research Article

Odontogenic Keratocyst- Identity Unearthed: A Systematic Review

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Abstract

Background: The odontogenic keratocyst (OKC) is a conundrumatic odontogenic cyst which is developmental in origin, commonly seen in the oral and maxillofacial region has gained traction since last two decades. This cyst is very distinctive because of its high recurrence rates and its aggressive behaviour; it also has characteristic clinical and histopathological features. The venture of classification of this cyst began in 1887, finally to WHO 2017. This cyst was formerly classified under the developmental odontogenic cyst of jaw in 1971 and 1992 by WHO. In the WHO classifications of head and neck tumors in 2005, OKC was renamed and reclassified as Keratocystic Odontogenic Tumor (KCOT), due to its aggressive nature and behaviour, specific histopathological characteristics and high recurrence rates. In the recent 2017 classification of HEAD AND NECK PATHOLOGY, KCOT was reclassified back into the category of CYSTS. Regardless of copious nomenclature and classifications of OKC, it is still challenging for the clinicians for identification, know the true nature, and its management.

Aim of the Study: To detect the significance and also describe and analyse the nomenclature of Odontogenic Keratocyst.

Materials and Methods: 30 articles were selected from the MEDLINE DATABASE having gone through the randomized control trial. 25 articles (studies) out of these were selected, which were best suitable for systematic review.

Result and Conclusion: We can say that the concepts of molecular pathophysiology of the OKC became clearer with advancements in scientific knowledge, various nomenclatures came forth and finally it has been accepted as a cyst today.

Keywords: Classification; Keratocyst; Odontogenic; Neoplasm; Mutation

Introduction

A cyst is a pathological cavity which may or may not be lined by epithelium consisting of fluid, semi fluid or gaseous contents but not by pus and surrounded by connective tissue capsule.

Odontogenic keratocyst

First report of jaw cyst was dated back in 1774 by John hunter. Then it was named as cholesteatoma- cystic or open mass of squamous of keratin with a living matrix. Later was named as primor-

dial cyst- It arouse before the enamel formation from remnants of dental lamina. Then term odontogenic keratocyst was coined [1,2]. OKC was first described by Philipsen in the year 1956.

Definition: "A benign uni or multicystic, intraosseous tumor of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior".

OKC is an ambiguous cyst of developmental origin. The odontogenic keratocyst (OKC) is a controversial odontogenic developmental cyst that has undergone conceptual and terminological changes in recent decades. There were variations in clinical behavior of OKC and also, there emerged controversies in the nomenclature of OKC. Classification of OKC was complicated and created confusion for both clinician and pathologists.

This cyst is exceptional due to high recurrence rate and destructive behaviour. The aggressive behaviour of the odontogenic keratocyst was first revealed by Pindborg and Hansen. Later in 1967, TOLLER proposed Odontogenic keratocyst to be classified under benign neoplasm. The discoveries of chromosomal abnormalities and genetic alteration such as mutation of PTCH gene, appeared to confirm this concept. In 2005 WHO named OKC as keratocyctic odontogenic tumor.

"A tumor is an abnormal mass of tissue, the growth of which exceeds and is coordinated with that of normal tissue and persists in the same excessive manner even after the cessation of stimuli which evoked this change".

Finally in the year 2017 keratocystic odontogenic tumor was renamed back to odontogenic keratocyst [3-6].

Aim of the Study

The aim of this study is to detect the significance and also describe and analyse the nomenclature of Odontogenic Keratocyst.

Objective of the Study

To authenticate the significance by a decade study of articles of journey of nomenclature of Odontogenic Keratocyst.

Materials and Methods

With Medline, Medknow and Cochrane were taken as sources for legitimate scientific research data, 30 articles were selected having gone through the randomized control trial. 25 articles (studies) out of these were selected, which were best suitable for systematic review the selection criteria have been described below.

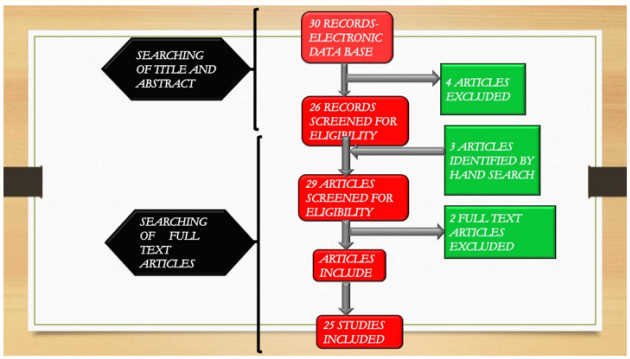


Figure 1

Result

Based on the systematic review carried out, the nomenclatures assigned to OKC over the years have been found to be very much significant taking into consideration its presentation and clinical features which make it a confusing entity. Hence as the concepts of molecular pathophysiology of the OKC became clearer with advancements in scientific knowledge, various nomenclatures came forth and finally it has been accepted as a cyst today.

Discussion

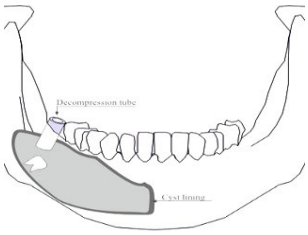
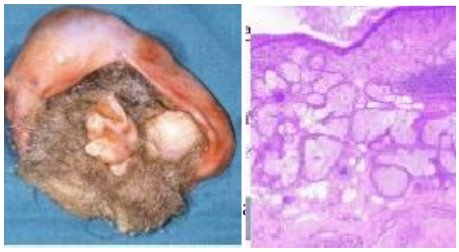
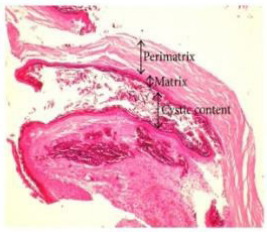
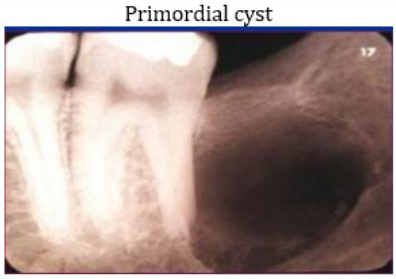
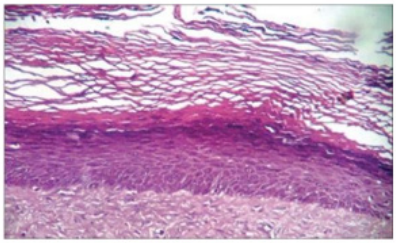
Origin and growth of cysts of jaw: Cysts were recognized long before the invention of x rays. Scultetus (1654) was the first to describe the Cystic swellings of the jaw, and Fauchard in 1728 alluded that the swellings might be associated with teeth.

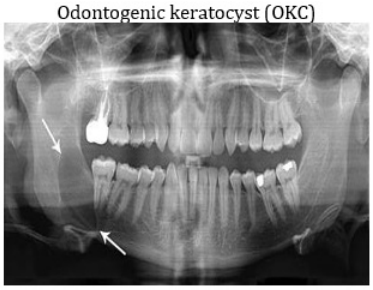
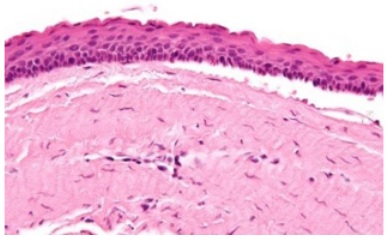
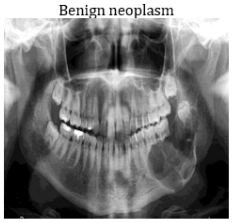
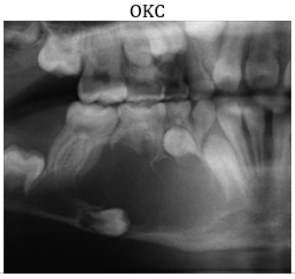
OKC: Odontogenic keratocyst is an unusual developmental cyst, but on the other hand it is locally aggressive. The cystic nature of Odontogenic keratocyst has been a subject of argument ever since decades [3,7,8].

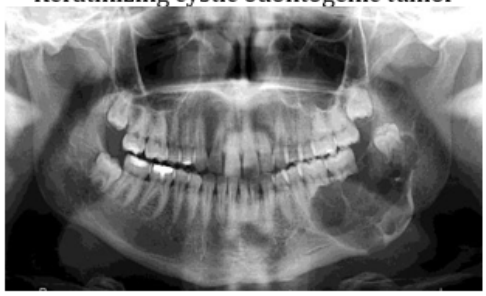
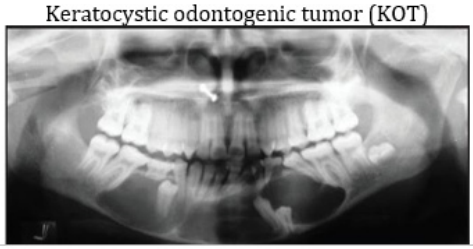
The journey of classification and nomenclature of OKC is as follows [9-13]

Histopathology of OKC [14-17]

[Pindborg, Philipsen and Henriksen in 1962, evaluated the histopathology of OKC]. They gave 7 histological criteria's. They are as follows:

Proposed by	Nomenclature	Significance/features
John Hunter (1774)		*Cysts were recogonized long before the invention of x rays. *He described that large infected maxillary cyst as a dreadful entity (a consequence of dental caries) in his classical monograph.
Mikulicz (1926)	 	*He mentioned it as a part of a familial condition affecting the jaws. * It was considered to originate from cystic degeneration of enamel organ epithelium before the development of dental hard tissue. *He described it as "cystic or open mass of keratin squames with a living matrix".
Robinson (1945)	Primordial cyst  	*The cysts were believed to have a more primordial origin as they arose from remnants of the dental lamina or the enamel organs before enamel formation has had taken place (By the degeneration of stellate reticulum). *The epithelium was distinctly parakeratotic with cuboidal or columnar palisaded basal cells, and occasionally orthokeratotic.

Philipsen (1956) Pindborg., *et al.* (1963)	Odontogenic keratocyst (OKC)  	*The designation "keratocyst" was used to describe any jaw cyst in which keratin was formed to a large extent. * The histopathology of OKC is typical and have been well characterized. *A thin, uniform lining of stratified squamous epithelium with tendency to detach from the underlying connective tissue capsule. *Thin corrugated surface layer of parakeratin; a spinous cell layer 4 to 8 cells in thickness. *Flat epithelial-fibrous tissue junction, usually devoid of epithelial rete ridges. *A relatively thin fibrous capsule that lacks inflammatory cell infiltrate. *radiographic features included- well defined radiolucency, smooth and sclerotic borders.
Toller (1967)	Benign neoplasm 	*Pindborg and Hansen were the first to point out the aggressive behavior of OKC. *Toller in 1967 suggested that OKC should be considered as a benign neoplasm rather than a conventional cyst mainly because of their clinical behavior.
WHO (1971)	OKC 	*WHO classified OKC under cyst category (namely: epithelial cysts).
Ahlfors (1984)	True benign cystic neoplasm	*Ahlfors and others suggested OKC to be classified as a true benign cystic epithelial neoplasm and suggested modified treatment schedules.
Shear	Keratocystoma	*Shear published his extensive work on the aggressive nature of the odontogenic keratocyst and finally labeled it as a benign cystic neoplasm. Shear aggressively used the term "keratocystoma" in naming this cyst. *Attempted to explain the pathogenetic mechanisms of OKC. *He also mentioned that growth and expansion of OKCs is due to high proliferation rate.

WH0 (1992)	OKC	*WHO classified OKC under the developmental odontogenic cysts of the jaw.
Reichartand Philipsen (2002)	Keratinizing cystic odontogenic tumor 	*Renamed OKC as keratinizing cystic odontogenic tumor (KCOT) and placed it under the subheading of benign neoplasm of odontogenic epithelium. FEATURES- -Mature fibrous stroma; - odontogenic ectomesenchyme not present. *This classification got the approval by WHO/ IARC at the Editorial and Consensus Conference, held at Lyon, France in July 2003 and in the present classification, the OKC has been renamed as “keratinizing cystic odontogenic tumor”.
WHO (2005)	Keratocystic odontogenic tumor (KOT) 	*WHO “recommends the term keratocystic odontogenic tumor as it better reflects its neoplastic nature”. *KOT was classified under benign tumors in “HEAD AND NECK TUMORS”.
WHO (2017)	OKC	*OKC was classified under the “cysts of orofacial region”.

1. A thin uniform 8 to 10 cell layered stratified squamous epithelium which appears ribbon like.
2. Lack of rete ridges or rete pegs.
3. Distinctive basal cell layer (columnar or cuboidal cells) which are arranged in PALISADED pattern [Tombstone or Picket Fence pattern].
4. Thin spinous layer shows direct transition from basal cell layer. It also shows artefactual separation of epithelium near the basement membrane zone.
5. Surface keratinization is corrugated. Mostly Parakeratosis (with nuclear remnants), orthokeratosis is also seen.
6. Cystic wall- Thin, absence of inflammatory cells. Connective tissue is fibrous in nature.
7. Other findings:
   a. Solid epithelial proliferation.
   b. Satellite or daughter cysts.
   c. Mineralization of connective tissue wall.
   d. Presence of cholesterol clefts and Rushton bodies.

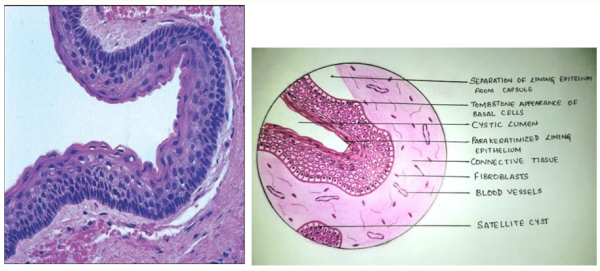


Figure 2

What made OKC a neoplasm?

EARLIER, many researchers along with REGEZI have tried to describe the pathogenesis of OKC. The growth and expansion of OKCs are by the following mechanisms [18-20]:

- High proliferation rate.
- Invasion and Infiltration- (Multicentric growth potential).
- Intrinsic growth potential (P-63, PCNA, ki-67).
- Insensitive to growth inhibitors: (Loss of heterozygosity SMO and PTCH). Tumor suppressor genes.
- Proteins which inhibit apoptosis are over expressed- (bcl-2).
- Angiogenesis and invasion into extra cellular matrix- Vascular endothelial growth factor and matrix metalloproteinase (MMP)-2 and 9.
- Epigenetic change.
- Micro mRNAs.
- Elevated recurrence rate.

To justify such reclassification, many authors have emphasized:

- The aggressive behavior, Greater growth potential than most other odontogenic cysts.
- Recurrence rate (highly recurrent).
- Histopathology.
- Possible association with the nevoid basal cell carcinoma syndrome.
- PTCH gene mutation.
- P53, P16, MCC, TSLC1, LTAS2, TP53 and FHIT mutations were also related in OKCs.

Recurrence

The recurrence rate of odontogenic keratocyst - 2.5% to 62.5%. Brannon (1976), put forward three mechanisms for recurrence of odontogenic keratocyst:

1. Incompletely removed cystic lining,
2. Development of a new odontogenic keratocyst from satellite cyst (or remnants of odontogenic rests following surgical procedure).
3. Growth of a new odontogenic keratocyst in contiguous area.

Other reasons for this variation can be due to duration of the follow-up period and method of treatment used. Histopathological features that predict recurrences are:

- Increased cell proliferation in the epithelium
- Superficial layer is parakeratinized.
- Supra and subepithelial splitting of the epithelium.
- Basal layer budding into connective tissue.
- Existence of daughter cyst, remnants or cell rests [20-22].

PTCH gene mutation: The patched (PTCH) gene, mapped to chromosome 9q22.3-q31 is tumor suppressor gene.

PTCH1 is a chief molecule in the Hedgehog (Hh.) signalling pathway. Generally, HH is not bound to PTCH (exerts inhibitory effect on smoothened {SMO} protein coding gene). Binding of HH to PTCH removes the inhibitory effect of SMO and it can then function as an oncogene.

'Loss of function mutations' of PTCH and 'Gain of function mutation' of SMO results in oncogenesis.

There are also evidences that the PTCH gene is a remarkable factor responsible for the development of sporadic OKC. Nevertheless, mutation is non-clonal/restricted to PTCH.

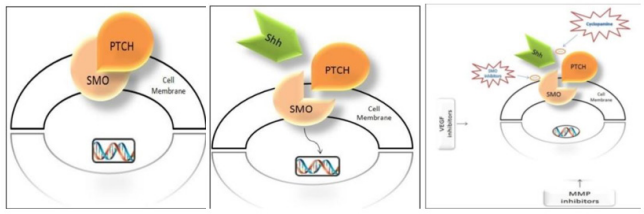


Figure 3

P53 gene expression: There is higher levels of p53 gene expressed in the epithelium of OKC when compared to any other cysts. This increased level of p53 reflects amplified production of normal p53 protein than the mutation of p53 gene. Various genes linked to odontogenic keratocyst are 'suppressor of fused homolog (SUFU) and PTCH2'. Some researchers have also found loss of heterozygosity in p16, TSLC1, MCC, FHIT, LTAS2 genes. These evidences were useful in proving the aggressive nature of odontogenic keratocyst.

Syndromic association: Various studies on nevoid basal cell carcinoma syndrome and sporadic OKC presented a molecular confir-

mation of a two-hit mechanism in the pathogenesis of OKC. This signifies loss of alleles, at 2 or more than two loci, of 9q22 which leads to the increased expression of bcl-1 and TP53 in NBCC Syndrome. This supported the neoplastic nature of keratocystic odontogenic tumor.

Even though the neoplasm is characterized by genetic abnormality, at present there is no distinctive genetic abnormality that defines this neoplasm. There are a marked genetic or molecular changes which happens to some of the odontogenic keratocysts. This has an impact on the biologic behaviour, however it, does not characterize the lesion as neoplasm, and was considered cyst.

The most dubious choice of WHO (2005) was the reclassification of odontogenic keratocyst as a neoplasm and the proposal of a new title (KOT) keratocystic odontogenic tumor, but, STERN, MARK and many others favoured to hold on to the previous terminology.

In 2017 the most debated decision of WHO reclassified KOT from tumor back to cysts and renamed this entity as odontogenic keratocyst. WHO consent does not declare that OKC is not of neoplastic origin, even though there is insufficient evidence in support to justify OKC as tumor. Odontogenic cysts that were omitted from the 2005 classification and were reincorporated in 2017 (4^{th} edition) and significantly updated after the 1992 classification. The subdivision of benign Odontogenic tumors in the 2017 classification was altered regarding its nomenclature, which was justified by the authors as a simplification [5,7,11,23-25].

Conclusion

The whole process of classifying and renaming the odontogenic cysts and tumors continues as the understanding of these lesions takes a giant leap in its tread. A famous oral surgeon "Gordon Hardman" was quoted saying "We always knew some cysts recurred so the patient came to have them curetted out every 5 - 10 years. So what, we never had to give them separate names". The Recent advancement and innovation in the molecular and the genetic level perception have led to eradicate the necessity for aggressive treatment modalities. This article look forwards to advocate that the naming of OKC as a CYST allows the surgeon to modify their treatment appropriately. "In the dearth of knowledge, we leap into worst conclusions". This is what had happened when OKC was renamed as KCOT, as "jumping to a conclusion is not an exercise".

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