IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

ODONTOGENIC KERATOCYS, CLINICAL PRESENTATION & TREATMENT MODALITY: A REVIEW OF LITERATURE

Anurag Singh, Prasanna Kumar P., Ankita Raj, Ankur Rathaur,
Rama Dental College, Hospital and Research Center,
Kanpur, Uttar Pradesh, India.
taransh1441099@gmail.com

ABSTRACT

Odontogenic keratocysts are jaw developing cysts that need to be properly diagnosed because they can grow aggressively locally, recur, and have a genetic relationship. One of the most contentious changes in the terminology of odontogenic lesions in recent years has been the renaming of odontogenic keratocysts as keratocystic odontogenic tumors in 2005, followed by the WHO's designation of an odontogenic cystic lesion in 2017 after a 12-year period. Odontogenic keratocysts are jaw developing cysts that need to be properly diagnosed because they can grow aggressively locally, recur, and have a genetic relationship. In 2005, odontogenic keratocysts were renamed as keratocystic odontogenic tumors. Twelve years later, the World Health Organization classified these lesions as odontogenic cystic lesions in 2017, has been one of the more contentious alterations to the nomenclature of odontogenic lesions in the last few years. In order to explain the significance of this lesion, this article examines the etiopathogenesis, clinical, radiographic, histological, immunohistochemical, and therapeutic aspects.

INTRODUCTION

Odontogenic cysts are a really prevalent ailment that comprise a significant portion of all biopsies that are obtained by a pathology agency. This heterogeneous collection of lesions presents in a variety of ways, starting from a tiny benign lesion that could be unintentionally discovered to a very aggressive, destructive lesion that could potentially develop into a cancer. The most well-known of the latter kind are odontogenic keratocysts (OKC). One of the uncommon odontogenic cysts, OKC draws a lot of attention from researchers because of its distinct features. Before odontogenesis is finished, OKC arises from the dental lamina remains in the mandible and maxilla. It could also come from the basal cells of the epithelium that covers it.

In 1876, OKC was first recognized and documented. In 1956, Phillipsen classified it further. Pindborg and Hansen proposed the histological criteria in 1962 that are required for the diagnosis of OKC. The World Health Organization (WHO) has recommended the term "keratocystic odontogenic tumor" (KCOT) in place of "cystic neoplasm" for this lesion in recent years because it more accurately describes the lesion's aggressive clinical behavior, high mitotic rate observed histologically, and correlation with chromosomal and genetic abnormalities. The OKC is a mysterious developmental cyst that requires particular consideration. Since OKC forms internal compartments, it appears to have a high recurrence rate and probable great growth potential.

ISSN PRINT 2319 1775 Online 2320 7876

Research Paper , UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

The pathologists and surgeons have encountered significant challenges due to these lesions. Since the beginning, the surgeons have experimented with several treatment approaches for OKC in an attempt to find a way to treat it without any recurrences. However, distinguished pathologists have been unable to ascertain the actual cause of OKC in order to formulate a clear course of treatment.

Oral pathologists have been working to comprehend the causes, symptoms, and treatments of diseases that impact the oral and maxillofacial areas over the years. Only the classification, reclassification, and classification of these illnesses have been accomplished in this process.

Many prior attempts have been made to classify these cysts in a logical manner. It all started as early as 1887, when Bland–Sutton subdivided odontomes into cysts.

Later Gabell, James, and Payne in 1914; Thoma and Goldman in 1946; Pindborg and Clausen 1958; World Health Organization (WHO) in 1971; and finally WHO in 1992 followed this ritual of classifying and reclassifying
odontogenic cysts.[1]

Despite of many classifications and nomenclature, unfortunately the clinicians still have to face difficulties in the management of this commonly found jaw lesion. This article is an effort to provide an overview of various aspects of OKC with emphasis on nomenclature, recurrence, molecular aspects, and management of OKC.

The “cholesteatoma”

Mikulicz originally identified the perplexing developing cyst known as an orthodontic keratocyst (OKC) in 1876 as a component of a jaw-related familial disease. However, it was initially referred to as a "cholesteatoma" in 1926.[2] A cystic or "open" mass of keratin squames with a live "matrix" is referred to as a cholesteatoma.[3] We should review the history of jaw cysts in general to learn more about this enigmatic cyst. Scultetus appears to have first reported on cystic swellings of the jaws in 1654, and Fauchard did not propose a connection between the swellings and the teeth until 1728.[4] John Hunter's 1774 description of a tooth cyst marked the beginning of the understanding of cysts, long before x-rays were developed in 1896.[5] Fauchard continues his series of articles describing tooth cysts. In 1853, Paget's first used the word "dentigerous cyst."[6]

The “primordial cyst”

Since the cysts were thought to have a more primordial origin because they developed from remains of the dental lamina or the enamel organs before enamel development had occurred, the term "primordial cyst" was first used by Robinson[7] in 1945. Forssell and Sainio[8] preferred to refer to these lesions as "primordial cysts," and they demonstrated that the epithelium in these lesions (true keratocysts) was primarily parakeratotic, with cuboidal or columnar palisaded basal cells, and sometimes orthokeratotic.

The “odontogenic keratocyst”

In 1956, Philipsen, a senior dental student in Copenhagen working with Jens J Pindborg, gave the term and description of the "odontogenic keratocyst." Any jaw cyst in which keratin was mostly generated was referred to as a "keratocyst." The histopathology of OKC is well-characterized and usual.[9] It consists of: a flat epithelial-fibrous tissue junction, typically

ISSN PRINT 2319 1775 Online 2320 7876

Research Paper , UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

without epithelial rete ridges; a thin, uniform lining of stratified squamous epithelium with a tendency to separate from the underlying connective tissue capsule; a thin corrugated surface layer of parakeratin; a spinous cell layer, 8 to 4 cells thick, frequently exhibiting intracellular oedema; and a relatively thin fibrous capsule devoid of inflammatory cell infiltrate.

Benign neoplasm?

Pindborg and Hansen[10] were the first to draw attention to OKC's hostile actions. Toller[4] first proposed in 1967 that OKCs ought to be viewed more as benign neoplasms than like traditional cysts, primarily due to the way they behave clinically. In 1984, Ahlfors and associates[11] proposed that OKC be categorized as a genuine benign cystic epithelial neoplasm and recommended adjusted treatment plans.

After doing a thorough investigation into the aggressive characteristics of odontogenic keratocysts, Shear[12] classified them as benign cystic neoplasms. Shear named this cyst with a strong use of the term "keratocystoma."

The pathogenetic mechanisms of OKC have been sought to be explained by Regezi and others.[13] They mention the mechanisms that favor growth and expansion of OKCs are high proliferation rate, over expression of antiapoptotic proteins (bcl-2) and expression of matrix metalloproteinase (MMPs 2 and 9). Mutation in PTCH 1 (“patched”) gene has also been considered as responsible for the pathogenesis of this cyst.[12-14]

Recurrences

There has been a range in the incidence of OKC recurrence from 2.5% to 62%.[14] These studies vary greatly, primarily because some series contained cysts from patients with Nevoid Basal cell carcinoma syndrome (NBCCS). Other possible causes of this difference include the length of the follow-up period and the type of treatment that was employed.[14] Three pathways for OKC recurrence were hypothesized by Brannon[15] in 1976: incomplete removal of the cyst lining, creation of a new OKC in a nearby location, and growth of a new OKC from satellite cysts (or odontogenic remnants left behind after surgery).

The major features that can be considered to predict recurrences in OKC are

- Higher level of cell proliferative activity in the epithelium
- Budding in the basal layer of the epithelium
- . Parakeratinization of the surface layer
- Supraepithelial split of the epithelial lining
- Subepithelial split of the epithelial lining
- Presence of remnants/cell rests as well as daughter cysts.

Rechristened

Under the title "benign neoplasm of odontogenic epithelium with mature, fibrous stroma; odontogenic ectomesenchyme not present," Reichart and Philipsen[16] reclassified the odontogenic tumors in 2002, renaming OKC as keratinizing cystic odontogenic tumor (KCOT). The WHO/IARC approved this classification during the Editorial and Consensus Conference in July 2003 in Lyon, France. The OKC is now referred to as a "keratocystic odontogenic tumor" (KOT) in the current classification. KOT is currently described as an intraosseous tumor of odontogenic origin that is benign, uni-or multicystic, and has the ability to invade and cause harm. Its distinctive lining is made up of stratified squamous epithelium

ISSN PRINT 2319 1775 Online 2320 7876

Research Paper , UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

that has been parakeratinized.[3] The term "keratocystic odontogenic tumor," which more accurately describes its neoplastic character, is recommended by the WHO.[3]

This renaming by the WHO is backed by recent molecular investigations that demonstrate loss of heterozygosity of certain tumor suppressor genes in numerous odontogenic keratocysts.[17]

Genetics

The PTCH gene is most likely a tumor suppressor; it has been localized to chromosome 9q22.3-q31.[3] A crucial component of the so-called Hedgehog (Hh) signaling system is PTCH1.[14] Normally, with the SHH ("sonic hedgehog") ligand, PTCH forms a receptor complex with the oncogene SMO ("smoothened").[18] A two-hit mechanism in the etiology of these tumors has been molecularly demonstrated by studies on NBCCS and sporadic KCOT. These studies show allelic deletion of 9q22[19,20] at two or more loci, which results in the overexpression of TP53 and bcl-1 in NBCCS. This lends credence to the theory that KCOT is a tumor.[20]

Additionally, there is mounting evidence that suggests the PTCH gene may play a major role in the development of KCOT that occurs on occasion.

Furthermore, preliminary results have shown over-expression and amplification of genes located in 12q.[21] The epithelial lining of OKC/KOT expresses higher levels of p53 than any other cyst types. This overexpression is not due to mutation of p53 gene, rather reflects overproduction and/or stabilization of normal p53 protein.[14] Other genes that can be correlated to OKC/KOT are PTCH2 and SUFU. Few authors also have demonstrated loss of heterozygosity in p16, MCC, TSLC1, LTAS2, and FHIT genes.[14] These findings are helpful to explain the aggressive behavior of OKC.

Gross appearance

The OKC typically shows "a thin, friable wall, often difficult to enucleate from the bone in one piece. The cystic lumen may contain a clear liquid that is similar to a transudate of serum, or it may contain a cheesy material that, on microscopic examination, consists of keratinaceous debris. "Unless the cyst is small, the OKCs linings are rarely received intact in the laboratory. Even if one is seen intact, the unequal growth that is responsible for the scalloped radiographic margins may be observed. The electrophoretic analysis for aspirated cystic fluids revealed that the soluble protein ratio to total protein content was lower than that in serum. The total protein content is <5 g/100 ml (Albumin; between 2 and 4 g/dl, Globulin; between 0.5 and 2.5 g/dl).

Microscopical findings

Microscopical key features can be summarized as follows:

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

ISSN PRINT 2319 1775 Online 2320 7876

Research Paper , UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

7. Particular microscopical appearance lost when infected.

Odontogenic keratocyst differential diagnosis

From a differential diagnosis standpoint, the OKC can mimic various other odontogenic cysts and tumors. 25% to 40% of cases associated with an unerupted tooth's crown, thereby resembling a dentigerous cyst. Dentigerous cysts, however, do not exhibit the regular, palisaded arrangement of cuboidal/columnar basilar cells or the corrugated surface layer of parakeratin. Orthokeratinized odontogenic cysts (OOC) also produce keratin; this keratin consists of orthokeratin associated with a subjacent granular cell layer. Besides, the basilar layer of OOCs does not exhibit nuclear palisading. Cystic ameloblastomas demonstrate a palisaded layer of columnar basal cells that could mimic an OKC. However, the ameloblastoma's basilar cells are usually more hyperchromatic and demonstrate areas with reverse polarization, in which the nuclei are pulled away from the basement membrane. What is more, the upper epithelial layers of cystic ameloblastoma are loosely arranged, reminiscent of the stellate reticulum of the enamel organ.

Few cases present in between roots of teeth can be mistaken for lateral periodontal cysts. OKC sometimes develops in the midline maxillary region in older patients, and thus these lesions can be confused with nasopalatine duct cysts. Finally, lesions located beneath tooth roots can mimic periapical cysts. It may mimic other non-odontogenic radiolucent disorders in young patients, such as traumatic bone cyst, central giant cell granuloma, or aneurysmal bone cyst.

Treatment

OKC is well known for their strong tendency to recur.[11] Much debate has been done and various studies performed, to ascertain ideal treatment modality for OKC/KOT.

Mostly these arguments revolve around whether to treat OKC as a cyst or as a benign neoplasm. Whatever modality has been implied, none of these have shown to completely prevent recurrence of the lesion, the problem is still compounded in case of NBCCS and multiple lesions.

Eyre and Zakrezewska[22] in 1985, have stated the following treatment modalities for OKC/KOT-

• Enucleation
With primary closure
With packing
With chemical fixation
With cryosurgery
• Marsupialization Only Followed by enucleation
• Resection

The choice of the treatment has always been difficult, since the patient well-being is of prime concern, although not compromising the chances of recurrences. Morgan and his colleagues[23] have categorized surgical treatment methods for KOT as conservative or aggressive. The conservative treatment is “cyst oriented” and thus includes enucleation, with or without

ISSN PRINT 2319 1775 Online 2320 7876

Research Paper , UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

curettage or marsupialization. The advantage is preservation of anatomical structures and reduced morbidity to the patient. The aggressive treatment is done considering
"neoplastic nature" of KOT and includes peripheral ostectomy, chemical curettage, or enbloc resection. It is mostly recommended for large lesions, recurrent cases and syndromic patients. Decompression has also been used to treat KOTs, which have aggressive behavior and having tendency to recur.[14]
Few authors recommend "site-and size-based" approach for the treatment of KOT. Dammer *et al*.[24] have suggested conservative approach for small KOTs (maximum 1 cm in diameter) near alveolar process, and radical excision for larger lesions near the base of the skull that has invaded soft tissue. On the contrary, Forsell and coworkers have reported that the size of the lesion does not affect the recurrence rate.[25]

Future modalities

Due to the recent advances and thus determination of molecular basis of this entity, a new novel methodology concentrating on molecular aspects has been devised. The Hh pathway can be blocked at different levels, and Hh inhibitors
could serve as attractive antitumor agents.[26] According to some studies, cyclopamine, a plant-based steroidal alkaloid, blocks activation of SHh pathway caused by oncogenic mutation.[27] Other studies also show antagonists of SHh signaling factors could effectively treat KOT.[28]

Behavior and prognosis

The recurrence rate varies from 10% to 30%, depending on how the lesion is managed, and is also related to several physical factors. In addition, the cyst epithelium's actual biological qualities, like increasing mitotic-index and producing bone-resorption agents, have an association with recurrent. Follow-up evaluation is essential. Patients should be examined for entire cystic excision, newly OKC formed, or BCNS. The majority of recurrent cases show clinical features in the five years of management. Besides cystic recurrency, ameloblastic transformation is reported in some cases. Individuals hiving multiple OKCs show an elevated recurrence-rate (30%) than patients with solitary OKC (10%). Individuals with OKC must be examined yearly by panoramic-radiography (OPG). MRI could be done two years once to monitor early recurrent lesions. Follow-up ought to be long, at least for ten years.

CONCLUSION

The biological nature of OKC has been a matter of discussion for a long time. Due to its aggressive behavior, there have always been controversies regarding the cystic or the lesion's neoplastic behavior. The use of FNA, incisional biopsy, and cell block technique may be really helpful to early diagnose OKCs, and to perform more conservative treatment for those lesions without teeth involvement and cortical bone perforation, or more aggressive surgical plan for OKCs with periosteum involvement, up to justify jaw resection for recurred lesions with high aggressiveness. Surgical removal with curettage or osteoctomy is the desired management protocol. However, it advocated that surgical decompression and marsupialization are preferred to induce cyst fading, and then OKC is enucleated. Follow-up ought to be long, at least for ten years.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

The term "odontogenic keratocyst" is so engraved in the literature only time can tell us whether the term "keratocystic odontogenic tumor" can substitute this term successfully or not. Recent advances in genetic and molecular understanding have led to eventually eliminate the need for aggressive treatment modalities. This article is in a hope to suggest that the naming of OKC as a benign tumor allows the surgeon to tailor their treatment aptly.

REFERENCES

1. Philipsen HP, Reichart PA. Classification of odontogenic tumours. A historical review. J Oral Pathol Med 2006;35:525-9.
2. Hauer A. Ein Cholesteatom im linken Unterkiefer unter einem retinierten Weisheitszahn. Zeitsschrift fur Stomatologie 1926;24:40-59.
3. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005.
4. Toller P. Origin and growth of cysts of the jaws. Ann R Coll Surg Engl 1967;40:306-36.
5. Robinson HB. Primordial cysts versus keratocysts. Oral Surg Oral Path Oral Med 1975;40:362-4.
6. Pogrel MA, Schmidt BL. The odontogenic keratocyst. Oral Maxillofac Surg Clin North Am 2003;15:311-5.
7. Soskolne WA, Shear M. Observations on the pathogenesis of primordial cysts. Br Dent J 1967;123:321-6.
8. Forssell K, Sainio P. Clinicopathological study of keratinized cysts of
the jaws. Proc Fin Dent Soc 1979;75:36-45.
9. Philipsen HP. Om keratocyster (kolesteatom) i kaeberne. Tandlaege bladet 1956;60:963-81.
10. Pindborg JJ, Hansen J. Studies on odontogenic cyst epithelium. 2. Clinical and roentgenologic aspects of odontogenic keratocysts. Acta Pathol Microbiol Scand 1963;58:283-94.
11. Ahlfors E, Larsson A, Sjögren S. The odontogenic keratocyst: A benign cystic tumor? J Oral Maxillofac Surg 1984;42:10-9.
12. Shear M. The aggressive nature of the odontogenic keratocyst: Is it benign cystic neoplasm? Part 1 Oral Oncol 2002;38:219-26.
13. Regezi, Sciubba, Jordan. Oral Pathology Clinicopathological correlations. 4th ed. St. Louis, Missouri: Saunders Company; 2003. p. 250-2.
14. Li TJ. The odontogenic keratocyst: A cyst, or a cystic neoplasm? J Dent Res 2011;90:133-42.
15. Brannon RB. The odontogenic keratocyst. A clinicopathologic study of 312 cases. Part I. Clinical features. Oral Surg Oral Med Oral Pathol 1976;42:54-72.
16. Reichart PA, Philipsen HP. Odontogenic tumors and allied lesions. London: Quintessence Publishing: 2004.
17. Neville BW. Update on Current Trends in Oral and Maxillofacial Pathology. Head Neck Pathol 2007;1:75-80.
18. Madras J, Lapointe H. Keratocystic odontogenic tumour: Reclassification of the odontogenic keratocyst from cyst to tumour. J Can Dent Assoc 2008;74:165-65h.

ISSN PRINT 2319 1775 Online 2320 7876

Research Paper , UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, 2022

19. Levanat S, Gorlin RJ, Fallet S, Johnson DR, Fantasia JE, Bale AE. A two hit model for developmental defects in Gorlin syndrome. NatGenet 1996;12:85-7.
20. Lo Muzio L, Staibano S, Pannone G, Bucci P, Nocini PF, Bucci E, *et al*. Expression of cell cycle and apoptosis-related proteins in sporadic odontogenic keratocysts and odontogenic keratocysts associated with the nevoid basal cell carcinoma syndrome. J Dent Res 1999;78:1345-53.
21. Heikinheimo K, Jee KJ, Morgan PR, Nagy B, Happonen RP, Knuutila S, *et al*. Gene expression profiling of odontogenic keratocyst. J Oral Pathol Med 2004;33:462.
22. Eyre J, Zakrezewska JM. The conservative management of large odontogenic keratocysts. Br J Oral Maxillofac Surg 1985;23:195-203.
23. Morgan TA, Burton CC, Qian F. A retrospective review of treatment of odontogenic keratocyst. J Oral Maxillofac Surg 2005;63:635-9.
24. Dammer R, Niederdellmann H, Dammer P, Nuebler-Moritz M. Conservative or radical treatment of keratocysts: A retrospective review. Br J Oral Maxillofac Surg 1997;35:46-8.
25. Forssell K, Forssell H, Kahnberg KE. Recurrence of keratocysts. A long term follow-up study. Int J Oral Maxillofac Surg 1988;17:25-8.
26. Pasca di Magliano M, Hebrok M. Hedgehog signaling in cancer formation and maintenance. Nat Rev Cancer 2003;3:903-11.
27. Taipale J, Chen JK, Cooper MK, Wang B, Mann RK, Milenkovic L,
et al. Effects of oncogenic mutation in Smoothened and Patched can
be reversed by cyclopamine. Nature 2000;406:1005-9.
28. Zhang L, Sun ZJ, Zhao YF, Bian Z, Fan MW, Chen Z. Inhibition of SHH signaling pathway: Molecular treatment strategy of odontogenic keratocyst. Med Hypotheses 2006;67:1242-4.