Review Article

Odontogenic keratocyst: What is in the name?

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Abstract

The classification of odontogenic cysts is complicated and can create confusion for both clinicians and pathologists. The odontogenic keratocyst (OKC) is an enigmatic developmental cyst that deserves special attention. It has characteristic histopathological and clinical features; but, what makes this cyst special is its aggressive behavior and high recurrence rate. 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.

Key words: Classification, keratocystic odontogenic tumor, nomenclature, odontogenic keratocyst, odontogenic cyst, odontogenic tumors

INTRODUCTION

Odontogenic cysts are relatively common lesions and accounts to form a major part of total biopsies received by any pathology service. This diverse group of lesions exhibit varying presentations ranging from a small innocuous lesion, which may be detected accidentally or may present as a highly aggressive and destructive lesion that may even transform into a malignancy. Among the latter type most notorious are odontogenic keratocyst (OKC).

OKC is the one of the rare odontogenic cysts, which attracts many researchers due to its unique characteristics. OKC originates from the dental lamina remnants in the mandible and maxilla before odontogenesis is complete. It may also originate from the basal cells of overlying epithelium. OKC was first identified and described in 1876. Further it was classified by Phillipsen in 1956. In 1962, Pindborg and Hansen suggested the histological criteria necessary to diagnose OKC. In recent years, World health organization (WHO) recommended the term cystic neoplasm (now known as keratocystic odontogenic tumor (KCOT)) for this lesion, as it better reflects aggressive clinical behavior, histologically high mitotic rate and association with genetic and chromosomal abnormalities. The OKC is an enigmatic developmental cyst that deserves special attention. OKC exhibits putative high growth potential and high recurrence rate due to its nature of forming compartments within.

These lesions have posed a great difficulty for the surgeons and pathologists. The surgeons since the beginning have been experimenting with OKC treatment modalities to find a way of treating it without any recurrences. On the other hand, eminent pathologists have been struggling to determine the true nature of OKC so that a definite line of action can be devised.

Over the years, the oral pathologists have been trying to understand the nature, identification, and management of diseases affecting the oral and maxillofacial regions. In this process, all what has been achieved is to classify, classify, and reclassify these diseases.

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

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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"

Odontogenic keratocyst (OKC) is an enigmatic developmental cyst, which Mikulicz in 1876 first described it as a part of a familial condition affecting the jaws. However in 1926 it was first known as a "cholesteatoma."[2] Cholesteatoma simply means a cystic or "open" mass of keratin squames with a living "matrix".[3] To know the history of this mysterious cyst, we should look at the account of cysts of the jaws in general. Cystic swellings of the jaws appear first to have been described in 1654 by Scultetus, and it was not until 1728 that Fauchard suggested that they might be connected with the teeth.[4] Cysts were recognized long before the invention of x-rays in 1896, by John Hunter, who described a dental cyst in 1774.[5] Fauchard's series of articles to describe dental cysts continued. Paget's in 1853 coined the term "dentigerous cyst."[6]

The "primordial cyst"

The concept of "Primordial cyst" was first mentioned by Robinson[7] in 1945 because 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. Forssell and Sainio[8] had a preference for the term "primordial cyst," and showed that in these lesions (genuine keratocysts) the epithelium was distinctly parakeratotic with cuboidal or columnar palisaded basal cells, and occasionally orthokeratotic.

The "odontogenic keratocyst"

Philipsen in 1956,[9] while still a senior dental student working with Jens J Pindborg in Copenhagen, named and described the "odontogenic keratocyst." 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.[9] It includes: A thin, uniform lining of stratified squamous epithelium with tendency to detach from the underlying connective tissue capsule; a thin corrugated surface layer of parakeratin; a spinous cell layer 8 to 4 cells in thickness, often showing intracellular oedema; a flat epithelial-fibrous tissue junction, usually devoid of epithelial rete ridges; and a relatively thin fibrous capsule that lacks inflammatory cell infiltrate.

Benign neoplasm?

Pindborg and Hansen[10] were the first to point out the aggressive behavior of OKC. Toller[4] as early as 1967 suggested that OKC should be considered as a benign neoplasm rather than a conventional cyst mainly because of their clinical behavior. Ahlfors and others[11] in 1984 suggested OKC to be classified as a true benign cystic epithelial neoplasm and suggested modified treatment schedules.

Shear[12] 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.

Regezi and others[13] have attempted to explain the pathogenetic mechanisms of OKC. 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

The incidence of recurrence of OKC has varied from 2.5% to 62%.[14] The great degree of variation in these reports are mainly because some series included cysts from patients with Nevoid Basal cell carcinoma syndrome (NBCCS), while other reasons for this variation can be due to duration of the follow-up period and method of treatment used.[14]

In 1976, Brannon[15] proposed three mechanisms for OKC recurrence: Incomplete removal of the cyst lining, growth of a new OKC from satellite cysts (or odontogenic rests left behind after surgery), and development of a new OKC in an adjacent area.

Histopathological features that predict recurrences.

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

Meanwhile, Reichart and Philipsen[16] reclassified the odontogenic tumors in 2002 and renamed OKC as keratinizing cystic odontogenic tumor (KCOT) and placed it

under the subheading of "benign neoplasm of odontogenic epithelium with 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 "keratocystic odontogenic tumor" (KOT). KOT is now defined as "a benign uni-or multicystic, intraosseous tumor of the odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior."[3] WHO "recommends the term keratocystic odontogenic tumor as it better reflects its neoplastic nature."[3] Recent molecular studies showing loss of heterozygosity of certain tumor suppressor genes in many odontogenic keratocysts have supported this renaming by WHO.[17]

Genetics

The PTCH gene has been mapped to chromosome 9q22.3-q31 and it probably functions as a tumor suppressor.[3] The PTCH1 is an important molecule in the so-called Hedgehog (Hh) signaling pathway.[14] Normally, PTCH forms a receptor complex with the oncogene SMO ("smoothened") for the SHH ("sonic hedgehog") ligand.[18] Studies on NBCCS and sporadic KCOT have provided molecular evidence of a two-hit mechanism in the pathogenesis of these tumors demonstrating allelic loss, at two or more loci, of 9q22[19,20] leading to the overexpression of bcl-1 and TP53 in the NBCCS. This supports the concept that KCOT represents a neoplasm.[20] There is also accumulating evidence that the PTCH gene might be a significant factor in the development of sporadic KCOT. 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.

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 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]

CONCLUSION

So 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 stride. So what is there in a name? A rose is a rose, whatever you call it. This concept is certainly not correct when it comes to OKC/KOT. There is as yet no international consensus, either on the question of the cyst's neoplastic nature, or on a name change.

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."[6] This attitude of the surgeons overlooking the multiple recurrences has always been suppressing the concept of reclassifying these lesions (favorite work of the pathologists). The controversies over the nature of OKC are infact a reflection of our limited knowledge of this fascinating entity.[14] "A rose is a rose is not a rose," when it implies to OKC/KOT. 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.

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