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Glandular Odontogenic Cyst or Mucoepidermoid Odontogenic Cyst- A Pathogenetic Dilemma

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Running title: Glandular odontogenic cyst and its pathogenesis

Clinical relevance: Glandular odontogenic cyst, and its origin, to be determined from the odontogenic apparatus, or the salivary gland.

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ABSTRACT

Glandular Odontogenic Cyst (GOC) is a rare odontogenic cyst that is unique, with respect to its histopathologic features and its abstract histogenesis. Due to the morphological similarity with other lesions, diagnosis of this lesion is a challenging task for the pathologists.

Aims and Objectives: There has been a lot of speculation regarding the exact etiopathogenesis of the glandular odontogenic cyst. It was initially presumed to arise from the salivary glands although recent theories, states its origin from the rests of dental lamina. This lesion has an aggressive course, and there is a high recurrence rate. This review aims to understand the etiopathogenesis of the glandular odontogenic cyst.

Materials and Methods: Articles published in English literature, spanning through years 2004- 2016, available on online databases such as Scopus, Medline, and Google, using the key words; cyst, glandular odontogenic cyst, dental lamina rests, rests of Serre and rests of Malassez were chosen. For inclusion, the articles had to meet pre-determined criteria. The authors selected 12 articles from journals, clinical reports, and web links.

Results: Origin from the rests of the dental lamina is the most plausible theory of origin of the glandular odontogenic cyst.

Conclusion: The exact tissue of origin of the glandular odontogenic cyst is not confirmatory. The most likely theory of origin is from the rests of dental lamina, for which confirmation is done by using immunohistochemical markers.

Keywords: odontogenic cyst, glandular odontogenic cyst, rests of dental lamina, rests of Serre.

INTRODUCTION

It was in 1987 that Padayechee and Van Wyk first described an unusual cyst of the jaws, which did not find mention in the standard classification of odontogenic cysts and tumors. Due to its unusual histopathologic features, they recommended a term "sialo-odontogenic cyst," to symbolize a possible origin or association with salivary gland tissue.

DISCUSSION

History

In 1988, Gardner, et al. reported the first case of this cyst and used the term: glandular odontogenic cyst. He stated that the presence of mucous cells in the cyst lining did not presume an origin from salivary glands. Glandular odontogenic cyst (GOC) was found to be the most apt name to date and is the name recognized by the WHO in 1992, to describe this new cystic lesion. It is also known as the Polymorphous Odontogenic Cyst. It is introduced under the heading of developmental odontogenic cysts, although terminology and origin, until date, remains controversial.

Clinical presentation:

Age, sex, site and race: The lesion occurs at no specific age, and there is no specific gender, race or ethnic predilection. It occurs mostly in middle-aged men, especially in the anterior mandible.

Presentation

The Glandular odontogenic cyst presents as an asymptomatic, slow- growing swelling. It can be asymptomatic or may cause pain, slow-growing swelling, and tooth displacement.

Radiology

These cysts may be unilocular or multilocular with a well-defined border.

Description of the histopathologic features of this cyst is an amalgamation of findings from a botryoid odontogenic cyst and a mucoepidermoid carcinoma, often causing a diagnostic predicament for pathologists.

Pathology

Histopathologic findings such as:

(1) A cystic cavity lined by a varied thickness of epithelium with the absence of rete pegs between the epithelium and underlying connective tissue,

(2) Variable numbers of mucous and clear cells in the epithelium,

(3) Eosinophilic cuboidal cells in the superficial layer,

(4) Localized plaque-like thickenings of the epithelium,

(5) Little inflammation,

(6) Occasional findings of hyperchromatic basal cells within the cyst lining. [1]

The histological features of GOC strongly suggest an origin from the remains of dental lamina; the microscopic features being a cystic cavity lined by nonkeratinized, stratified squamous epithelium, localized plaque-like thickenings of the epithelium, variable numbers of mucous secreting cells in the surface layer of the epithelium, tendency to subepithelial fibrous tissue formation, multiple cysts and absence of inflammation. The superficial layer of the epithelium consists of eosinophilic cuboidal cells in the cyst wall lining of non-keratinized epithelium, with papillary projections, nodular thickenings, mucous filled clefts and ‘mucous lakes' which makes the surface, irregular. It also includes cuboidal basal cells, which are sometimes vacuolated.

Pathogenesis of Glandular odontogenic cyst:

Disintegration of the Dental Lamina:

Shortly after the laying down of the hard tissues of the teeth, such as enamel and dentin, the complex pattern of dental laminae begins to break up or disintegrate due to ectomesenchymal invasion and

programmed cell death. From the zone where the dental lamina joins with the oral epithelium, disorganization or fragmentation of the dental lamina progresses towards the developing enamel organ. Some cells of the laminae persist and tend to aggregate through proliferation into nests, known traditionally as epithelial pearls (Serres pearls or glands of Serres). The successional laminae (for formation of permanent teeth enamel organ) as well as the accessional laminae (for formation of supernumerary teeth or salivary gland) also disintegrate and give rise to epithelial cell remnants. [2] Cells deactivate epithelial markers (E-cadherin, cytokeratin), up-regulate Slug and MMP2 (matrix metalloproteinase-2), and activate mesenchymal markers (vimentin), while residual lamina cells are removed by apoptosis. [3] Sometimes the dental lamina cells persist as rests (rests of Serre) that may later become active to form odontogenic cysts and tumors. [2]

The histological features of GOC strongly suggest an origin from the remnants of dental lamina because of the below mentioned features.[4]

A. Rests of dental lamina:

1. Because of its histological features comprising of

    a. Nonkeratinized epithelial lining

    b. Mucus Metaplasia of rest cells

    c. Aggressive nature of the cyst may indicate that it arises from the dental lamina rests. [5]

2. High, recurrence rate. [6]

3. Cytokeratin (CK), 7,13,14,19 is positive on immunological testing and negative for CK 8 and 18 indicating an origin from odontogenic epithelium, rather than the salivary gland.[7]

4. Wysocki et al. (1980) have pointed out that the characteristic glycogen-rich clear cells so commonly seen in dental lamina-derived cysts and remnants are never found in cysts derived from reduced enamel epithelium or rests of Malassez. Similarly, the epithelial linings of radicular and dentigerous cysts, which are derived from the latter, do not contain such clear cells.[2]

B. **Salivary gland origin:** The earlier authors assumed the GOC to be derived from salivary gland tissue because of the following factors**.**

a. Histological features are similar to low-grade central mucoepidermoid carcinoma (LGMEC).

b. First named as a sialo-odontogenic cyst.

c. Contains mucus cells.

d. Is aggressive in nature, like a malignant neoplastic salivary gland lesion.

e. The distinguishing feature in GOC is found to be the typical thin epithelial lining without any solid epithelial proliferation as normally seen in MEC.

f. Swirling spherical/ epithelial plaque that is often seen in GOC is not observed in MEC.

g. In cases where a diagnosis of GOC or LGMEC cannot be made based on the morphological features alone, especially in small incisional biopsy samples, mammary serine protease inhibitor (maspin) immunolocalization can be used to distinguish these two lesions. The high levels of maspin in the epithelial-mucous cells (in both cytoplasm and nuclei) in LGMEC may serve as a tool to differentiate it from GOC**.** It has been suggested that many cases formerly diagnosed as central MEC can be the examples of GOC, and some LGMECs would have originated from GOCs**.**

h. CK expression has been demonstrated in GOC and central MEC. They found differences in CK18 and 19. CK18 is expressed by all MECs (mucoepidermoid carcinoma), but it is only expressed by 30% of the GOCs, whereas CK19 is expressed by all GOCs and only 50% of the central MECs. They suggested that GOC and central MEC are distinct entities that and expression of CKs 18 and 19 can be useful adjunctive tools in differentiating these two lesions. Immunohistochemical studies using cytokeratin 7, 13, 14, and 19 and their positivity strongly support the odontogenic nature.[8]

i. The detection of osteodentin and negative reaction for EMA (epithelial membrane antigen) in the glandular structure show that these features are not of glandular origin and support the concept of odontogenic differentiation in GOC.[7]

j. Platelet Derived Growth Factor (PDGF) signaling is a possible mechanism involved in the interaction between epithelial and neural crest-derived mesenchyme in the development of salivary glands. These results suggest that the FGF/FGFR, ShhPtc, and Eda/Edar signaling cascades are critical for salivary gland organogenesis namely the submandibular gland.[9] Similarly multiple signaling molecules, including BMPs, FGFs, Shh, and Wnt proteins, have been implicated in tooth development.

Features distinguishing GOC from **other odontogenic cysts**:

a. The immunohistochemical expression of the apoptosis- inhibiting protein bcl-2, the cell cycle-related antigen ki-67, and the P53, which is involved both in cell cycle and apoptosis regulation was lower in GOC as compared to a dentigerous cyst. They suggested that the biological behavior of GOCs might be associated with deregulation of cell death in the lining epithelium, indicated by increased expression of bcl2, while cell proliferation and P53 do not play a significant role.

b. The aggressive biologic behavior of the GOC and its propensity for recurrence might be associated with, cell kinetics in the lining epithelium as has been demonstrated in Odontogenic Keratocyst. It has also been demonstrated that the rate of recurrence increases with the radiographic complexity of the cyst. [10]

c. Botryroid odontogenic cysts, lateral periodontal cyst, are slow growing as compared to GOC though they show histological features similar to the GOC.[7]

C) Origin from epithelial **rests of malassez (ERM)**:

The formation of the ERM occurs during the development of the root, which begins before the eruption. They break up to remain lodged in the surrounding dental follicle or may disintegrate. These rests are called the rests of Malassez. Serres first identified it as 'restes de l'organe de l'email' (Rests from the enamel organ). However, Malassez, in 1885, presented the first description of the cells and their distribution. the proliferation of the ERM has been implicated in developmental cyst formation, such as the gingival or lateral periodontal cyst. Inflammatory cysts, such as the paradental and peri-apical cysts, also arise commonly from the ERM. Some of the odontogenic tumors may also arise from the ERM.[1] Growth factors are important mediators of intercellular communication between connective tissues and epithelium; several growth factors have stimulatory effects on epithelial rests of Malassez, proliferation and differentiation. The recently described keratinocyte growth factor (KGF) appears to be of particular interest. It is possible that quiescence of the rests of Malassez is normally associated with low local levels of KGF or related growth factors in the PDL but that inflammation enhances the expression of growth factors necessary for their activation. KGF production is markedly up regulated during epithelial wound healing.

The absence of inflammation and hence the reduced expression of KGF indicates that GOC does not arise from the rests of Malassez. [12]

D) Outer Enamel Epithelium:

Eriguchi (1959) has produced evidence for the existence of yet another source of odontogenic epithelial remnants not previously recognized. In embryos of 230-260 mm CRL (Crown of the fetus Rump length), the author demonstrated thin epithelial strands of polyhedric cells radiating from the outer enamel epithelium. The strands tend to proliferate and may reach 1.5-1.8 mm in length and thus, almost contacting the ridges of the overlying oral epithelium. They are often accompanied by or intermingle with minute blood vessels. The strands later show fragmentation with the formation of several spherical epithelial pearls that will blend with remnants from the dental laminae. The outer enamel epithelium-derived residues often show keratinisation similar to that found in the dental lamina-induced micro-keratocysts mentioned above. The residues are thought to act as a source for

the development of odontogenic lesions later in life, similar to those originating from dental lamina remnants. These findings have never been confirmed, and convincing evidence is thus lacking. [2]

CONCLUSION:

Due to the scantiness of case reports, questions have remained unanswered regarding the histogenesis, biologic behavior and appropriate treatment of these glandular odontogenic cysts. Dental lamina rests, salivary glands, epithelial rests of Malassez, and outer enamel epithelium have been considered in the pathogenesis. The most accepted theory of the tissue of origin is the dental lamina rests although no conclusive evidence exists regarding the same. The exclusive histopathologic features of these lesions often-present diagnostic challenges for pathologists due to the histological overlie with other established lesions. Because of the scarcity of cases with long-term follow up, the prognosis of this cyst remains unclear. The aggressive nature of the lesion was evident, especially because of the recurrence and the significant increase in size since the first diagnosis. As mentioned before, the cyst has an aggressive nature and high tendency for recurrence. Immunohistological analyses of this rare and recently described odontogenic cyst may add precision to our current understanding of the lesion.

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ABBREVIATIONS

Glandular odontogenic cyst----------GOC

Low grade central mucoepidermoid carcinoma-------LGMEC

Cytokeratin----------CK

Keratinocyte growth factor----------KGF

Epithelial rests of Malassez----------ERM

Epithelial membrane antigen----------EMA

Crown of the fetus **Rump length--------**CRL

Platelet Derived Growth Factor----------PDGF

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