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Review Article

Journey of Dentigerous Cyst to Neoplasms: A Narrative Review

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ABSTRACT:
Dentigerous cysts are one of the complex heterogenous lesions reported in the literature. They diverse from self-limiting to most aggressive ones and with neoplastic transformation showing different behavior and histology. Various theories are proposed to support its histopathogenesis. Pathologists and surgeons often face challenges in its diagnosis, treatment, and prognosisowing to its tendency of malignant transformation.This review gives an insight of various biological behaviors of the dentigerous cyst besides its origin. Thorough understanding of biological behaviors and their mechanism of transformation may prompt innovative ideas for their detection and administrating different approaches in treatment for optimizing its prognosis.

Key words: dentigerous cyst, neoplastic transformation, inflammation, oxidative stress, biological behavior, odontogenic cysts, malignant transformation

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OBJECTIVE

Dentigerous cysts are known to exhibit various potential complications apart from their recurrence. Rare incidences ofdevelopment of secondary neoplastic lesions are documented. Thus, we would review the characteristics of dentigerous cyst that transformed into malignant lesions and to look for potential causes of this phenomena.

PATHOPHYSIOLOGY OF DENTIGEROUS CYST

Dentigerous cysts are the most commonly reported cysts. It is considered developmental in origin. Various researchers have proposed intrafollicular and extrafollicular theories to explain its histopathogenesis. As the rise of the cyst appears to be envelopmental, the extrafollicular theory for the origin of dental cystis questionable.[1]However, the accumulation of fluid between the inner and outer enamel epithelium during tooth development makes the intrafollicular theory more plausible. The enamel hypoplasia theory proposed by Al-Taban and Smith in 1980 indicated the degeneration of the stellate membrane during early tooth development leading to cyst formation.[2] On the other hand, Main's theory in 1970 proposed that a tooth embedded in follicles blocks venous outflow, leading to rapid transudation of serum through capillary walls. The resulting hydrostatic pressure causes fluid accumulation, leading to separation of the crown from the surrounding follicle with or without reduced enamel epithelium.[3]Another concept proposed by Browne and Smith et al., in 1988 suggested that a change in cyst fluid osmolality causes rapid cyst growth. This is due to the increased permeability of glycosaminoglycans such as hyaluronic acid, heparin and chondroitin sulfate.[4] However, in 2005, Edamatsu M et al., elucidated its molecular basis by comparing the immunoexpression of Fas, Bcl-2, and single-stranded DNA (ssDNA) and Ki-67 in dental vesicles and dental cysts to explain their possible role as apoptotic factors and proliferative markers. Expression of Fas and ssDNA in epithelial cells on the surface of both follicles and cysts indicates areas of apoptotic cell death, while Ki-67 expression in the suprabasal layer with a higher number of positive cells is observed in dental cysts, suggesting cellular sites to spread. A significantly higher positive ratio of the apoptosis-

inhibiting agent Bcl-2 in dental cysts indicates that it is a pathogenic factor. All these features indicate an effect of Bcl-2 expression on apoptotic responses and proliferation of epithelial component cells in dental vesicles and dental cysts. Thus, apoptosis and cell proliferation play a role in the pathogenesis of dental cysts.[5]

ROLE OF INFLAMMATION IN MALIGNANT CHANGES

Dental cysts can be inflammatory or non-inflammatory. A non-essential deciduous tooth can lead to an inflamed tooth cyst, while the non-inflammatory type occurs due to the pressure exerted by the erupting tooth on the damaged follicle. However, long-term chronic inflammation is thought to lead to malignant transformation of the dental cyst. Although the frequency of such neoplastic transformations is exceptionally low, transformation of odontogenic cystic epithelium into benign odontogenic tumors and non-odontogenic malignancies have been documented.[6] The exact mechanism is not yet known. Jain M et al., found long-term chronic inflammation to be the most likely etiopathological factor in the neoplastic transformation of a benign odontogenic cyst. Therefore, features of chronic inflammation must be taken into consideration to predict the malignant transformation.[7]

Role of Inflammation

Carcinogenesis is a multistep process and oxidative stress acts in all three steps (Figure 1): initiation, promotion and progression.[8,9,10] The initiation process of carcinogenesis is thought to be due to continuous chronic inflammation, followed by the introduction of gene mutations and structural changes in DNA as a result of ROS production. It is a reactive oxygen species (ROS)-mediated reaction that can be direct (oxidation, nitration, halogenation of nuclear DNA, RNA, and lipids) or mediated by signaling pathways activated by ROS released by macrophages, neutrophils, and dendritic cells. The high reactivity of ROS is due to the presence of unpaired valence electrons or non-static bonds. However, at higher concentrations, lipids, proteins, carbohydrates and nucleic acids easily react with ROS, which causes serious damage to cellular structures and accumulates oxidative stress.[11]During inflammation, mast cells and leukocytes accumulate at the site of injury, resulting in a "respiratory burst". This is due to increased oxygen consumption, which increases the release and accumulation of ROS at the site of injury.[12,13]Additional contributions of ROS to abnormal gene expression, suppression of cell-to-cell communication and alteration of secondary communication systems during the promotion phase result in reduced cell proliferation or apoptosis of the initiated cell population. Finally, during the progression of the cancer process, oxidative stress can also play an important role by increasing DNA changes in the initiated cell population.[14] Thus, the development and progression of cancer can be associated with oxidative stress, which leads to increased DNA mutations or induced DNA damage, genome instability and cells.[15]On the other hand, inflammatory cells produce soluble mediators such as arachidonic acid metabolites, cytokines and chemokines.These metabolites contribute to the further accumulation of inflammatory cells at the site of injury and produce more reactive species(Figure2).This prolonged inflammatory/oxidative environment results in a vicious cycle that damages healthy adjacent epithelial and stromal cells and leads to carcinogenesis in the long term.[16]Indeed, the ability to recruit inflammatory cells and stimulate them to produce ROS is an important property of tumor promoters[17,18] and considerable evidence has implicated ROS as a link between chronic inflammation and cancer in recent years.[19,20,21] In fact, recent studies have shown that ROS are responsible for inducing genomic instability, activating specific signaling pathways and thus promoting tumor development by regulating cell proliferation, angiogenesis and metastasis.[22]On the contrary, Borrás-Ferreres J etal., reported neoplastic transformation of a follicular cyst in the absence of chronic inflammation, suggesting other oncogene-related physiopathological mechanisms.[23]

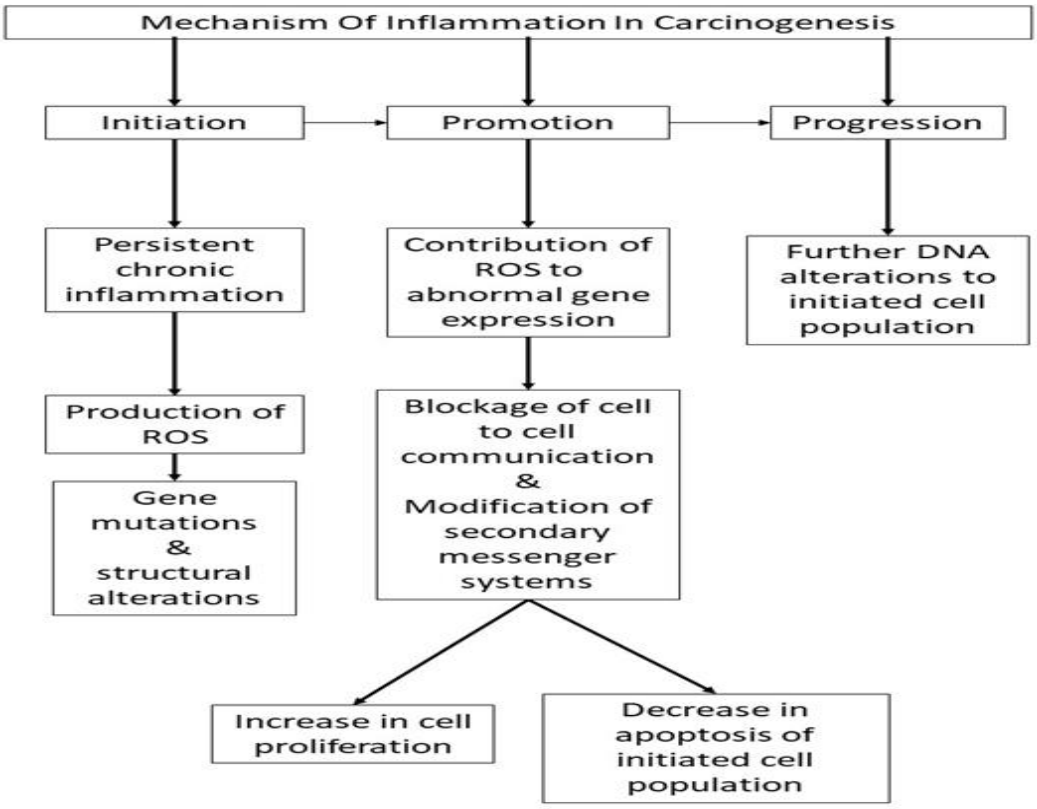

Figure 1:- Mechanism Of Inflammation In Carcinogenesis

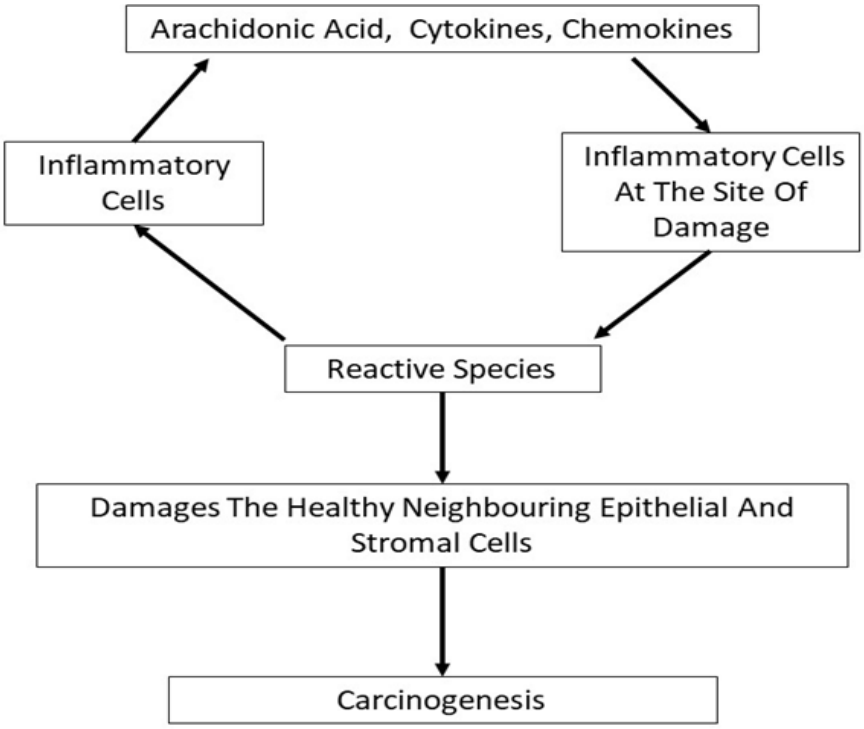

Figure 2:- Role Of Inflammatory Cells In Carcinogenesis

MECHANISM OF DENTIGEROUS CYST TRANSFORMING TO VARIOUS NEOPLASMS:-

In literature, although rare, benign and malignant transformation of dentigerous cyst have been reported, frequently noted for its inflammatory type (Table 1).

Table 1: Neoplastic changes in dentigerous cyst

Year	Author	Type of biopsy/ Histopathological findings	Type Of Neoplastic Transformation of Dentigerous Cyst	Biological behavior	Possible Etiopathogenesis
2018	Kondamari SK et al.[24]	*Incisional*- Dentigerous cyst *Excisional*- cystic epithelial lining resembling reduced enamel epithelium along with connective tissue stroma showing focal areas of follicular ameloblastomatous islands	Ameloblastoma	No recurrence	Various proliferative & IHC studies revealed increased cell proliferation is due to disruption in cell cycle, mutations in oncogenes, or tumor suppressor genes.
2011	Moovsi Z etal.[27]	*Incisional*- Dentigerous cyst *Excisional* -gradual transformation of stratified squamous epithelial lining into elongated cuboidal, and spindle shaped epithelial cell in whorl like arrangement, with scanty fibrillar connective tissue stroma and areas of irregular basophilic calcifications towards lumen.	Adenomatoid Odontogenic Tumor	Rare recurrence	rarity of this case lies in its histogenesis
2017	Razavi SM etal.[28]	*Excisional*- 3–5 cell layersthick with non-keratinized squamous cells of odontogenic epitheliumsuggestive of dentigerous cyst with fewmucous cells in the superficial layer. The connective tissue wall was made up of loosely arranged collagen fibers and fibroblasts showing numerous cystic spaces with foci of mucous, epidermoid, and clear cells.	Low Grade Central Mucoepidermoid Carcinoma (CMEC)	No recurrence or metastasis, 1 year follow up period	50% of CMEC are associated with odontogenic cysts and impactedteeth
2015	Peng CY et al.[36]	*Excisional*-transition of odontogenic cystic epithelium to verrucous hyperplastic epithelium was observed along with moderate	Primary Intraosseous Verrucous Carcinoma	no recurrence or metastasis, 5-month follow up	long-standing chronic inflammation appears to be a predisposing factor for malignant transformation ofthe

		chronicinflammatory cell infiltrate in the fibrous cystic wall. Increased mitotic figures in the basal and parabasal epithelial cells were seen along with Mild dysplasia, focal dyskeratosis, and atypical squamous cells with prominent nuclear and cellular pleomorphism.			cyst lining epithelium.
2013	Zapała-Pośpiech Aet al.[32]	*Excisional*-non-keratinized stratified squamous epithelium focally surrounded by an extensive outgrowth of unspecific granulation tissue with purulent and chronic inflammatory infiltrate.	Primary Intraosseous Squamous Cell Carcinoma	No metastasis reported	epithelial changes within a dentigerous cyst with a strong inflammatory process.
2014	Aranjo JP et al.[33]	*Excisional*- an intraosseous squamous cell carcinoma with regional metastasis in lymph nodeswithout unruptured capsule. *IHC*- cytokeratins 5 and 14 positivity in the primary tumor and in a regional lymph node, positive in both sites	Primary Intraosseous Squamous Cell Carcinoma	No recurrence after 8 years of follow up	Strong immunopositivity of CK5 and CK14 support the hypothesis of malignant transformation of dentigerous cyst
2015	Gay- Escoda C et al.[34]	*Excisional*- a cystic cavity covered by stratified squamous epithelium with marked papillomatosis and acantholysis. Alteration on keratinocyte maturation and cytologic atypia infiltrating in stroma observed.	Primary Intraosseous Squamous Cell Carcinoma	Neither ganglionar nor metastatic affection reported post radical treatment[	Longstanding chronic inflammation might be the main predisposing factor to induce a malignant transformation in the cyst epithelium
2020	Marchal A et al.[35]	*Excisional* - infiltrated squamous cells with moderately large nucleus and abnormal mitotic activity. *IHC*- p40 and Ki67 marker rated at 20% and demonstrated intense expression of p53 marker in the infiltrating part of the tumor.	Primary Intraosseous Squamous Cell Carcinoma	No local recurrence or metastasis after 17 months follow-up.	chronic inflammation can be a predisposing factor for the malignant transformation
2020	Tahakashi etal.[31]	*Clinical diagnosis*- Pericoronitis *Excisional* - transition	Primary Intraosseous Squamous Cell	no recurrence or	Pericoronitis(chronic inflammation) may be the possible cause of

		area from the normal cyst wall epithelium to atypical epithelium with progressive areas of keratinization, condensed nuclear chromatin and occasional mitotic figures. *IHC*- CK5/6, CK14, and p40 and majorly p53 for atypical epithelium and Ki-67 positivity	Carcinoma	metastasis in 1 year follow-up period	malignant transformation

Kondamari SK et al., in 2018 reported a case confirming its final diagnosis as a Dentigerous cyst transforming into ameloblastoma.[24] The findings were supportedby the hypotheses by Robinson and Martinez on the evolution of unicystic ameloblastoma proposing 3 major causes:[25,26.]

1. Re-transformation of reduced enamel epithelium of the developing tooth into ameloblast like cells.
2. Appearance of neoplastic ameloblastic lining preceding the non-neoplastic stratified squamous epithelial cystic lining.
3. Multiple microcystic degeneration of ameloblastic islands in a solid tumor may subsequently fuses to form unicystic ameloblastoma.

Apart from benign transformation, few cases of dentigerous cysts demonstrateneoplastic transformation as well.Few cases reported in the literature noted the association of dentigerous cyst with adenomatoid odontogenic tumor (AOT), central mucoepidermoid carcinoma, primary intraosseous verrucous carcinoma, and primary intraosseous squamous cell carcinoma.

In 2011, Moovsi Z etal., reported a case wherein incisional biopsy gave an impression of dentigerous cyst whereas the excisional biopsy revealed the features of adenomatoid odontogenic tumor showing gradual transformation of dentigerous cyst. However, unlike dentigerous cysts, the histogenesis of AOT is proposed to originate from fully formed enamel organ, dental lamina and/or its remnants and from odontogenic cysts. Treatment of choice is enucleation with rare recurrence reported.[27]

A rare case of low grade central mucoepidermoid carcinoma arising from dentigerous cyst was reported by Razavi SM etal., in 2017. The lesion was present around the crown of maxillary impacted canine along with intact buccal and lingual cortices.[28]In explanation to this, literature suggests that central mucoepidermoid carcinoma is thought to be originating from:[29,30]

(1) neoplastic change of entrapment of salivary glands within the mandible,
(2) submandibular gland embryonic remnants enclosed in the mandible,
(3) metaplasia of the cells of epithelial lining of dentigerous cysts into mucus-secreting cells, and
(4) invasion along with the neoplastic change of the maxillary sinus epithelial lining.

Primary intraosseous verrucous carcinoma (PIOVC) and Primary intraosseous squamous cell carcinoma (PIOSCC) are the forms of malignant transformations reported by few researchers in recent years. However, long term stimulation by chronic inflammation associated with repeated infections of an odontogenic epithelial lining is thought to be its pathogenesis.[31]The diagnosis of PIOSCC is made based on following four conditions:[32]

(1) no abnormal findings observed in the oral mucosa around the tooth extraction socket.
(2) negative findings for metastatic carcinoma of primary lesion in adjoining tissue or in remote organs confirmed by PET-CT images
(3) no histopathological signs of cystic ameloblastoma in the lesion; and
(4) histopathological confirmation of normal cystic epithelium transition to squamous cell carcinoma.

Few authors like Zapała-Pośpiech Aetal.(2013)[32], Aranjo etal.(2014)[33], Gay-Escoda C et al.(2015)[34], Marchal A et al.(2020)[35], Tahakashi etal.(2020)[31], reported the cases of PIOSCC associated with history of long standing infected dentigerous cyst. A case of Primary Intraosseous Verrucous Carcinoma (PIOVC) arising from an infected dentigerous cyst was reported in a 74-year-old male patient was documented by Peng CY et al. in 2015.[36]

However, it is extremely difficult to predict the real prognosis of these malignant tumorsdue to heterogeneity of case and follow up periods.

SUMMARY

The cell origin determination has helped determination of cell of origin has helped gain deeper understanding the pathogenesis of dentigerous cystalong with their association with malignant transformation. This leads to more competent therapeutic modalities. However, under the influence of certain triggering factors, different biological behaviors of this cyst arenoted that challengethe clinicians, pathologists, and researchers. This

emphasizes the need for further in-depth clinical and molecular research with a combination of personalized, case-specific treatment options to optimize prognosis.

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