REVIEW

Pathogenesis of Odontogenic Cysts

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Abstract

Context: Although, there is abundance of literature available on their nature, character and treatment modalities, the exact pathogenesis still remains under continual scrutiny.

Objective: Cysts of oral cavity are a subject of importance to pathologists and practising dental surgeons hence needs to be reviewed.

Materials and Methods: Two reviewers independently collected data from books, case reports and review articles published in electronic databases including Google search, Research gate, Pub Med and Science Direct.

Result and Conclusion: This article summarizes the concepts put forth by a number of investigators to explain the pathogenesis of Odontogenic Cysts and their causation mechanisms, thus enhancing our understanding.

Keywords: Cavity; Egg-shell; Globulin; Osmosis.

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Introduction

Cysts occur in the jawbones and soft tissues, categorized as those arising from tooth forming tissues and non-tooth forming tissues, namely Odontogenic and Non-Odontogenic cysts with the Odontogenic being most common.[1] Most of the Odontogenic cysts are lined by epithelium derived from Odontogenic epithelium. These cysts are again categorized as Developmental and Inflammatory Cysts. Modifications in their classifications and terminologies were made over the years since 1868 with the addition of newer concepts and deletion of old ideas. In 2017 the 4th edition of the World Health Organization's Classification of Head and Neck Tumours was given to enable the diagnosis of Odontogenic cysts, tumours and other allied bone tumours.[1,2] The changes in the classifications aid in better understanding of the pathogenesis of the cysts.

The Inflammatory Odontogenic cysts are: Radicular Cyst and Inflammatory Collateral Cyst. The Developmental Odontogenic cysts are: Dentigerous Cyst, Odontogenic Keratocyst, Lateral Periodontal Cyst And Botryoid Odontogenic Cyst, Gingival Cyst, Glandular Odontogenic Cyst, Calcifying Odontogenic Cyst and Orthokeratinized Odontogenic Cyst. These cysts are usually asymptomatic, with the potential to become extremely large causing cortical expansion and erosion, while some can be aggressive, with jaw destruction or can be frequently recurrent.[3] Both developmental and inflammatory types, share a nearly identical cytomorphology. Therefore, unravelling mechanisms of tooth development provides insights into the pathogenesis of these Odontogenic cysts.

Inciting Factors

Tooth development is an event filled process marked by interactions between the ectomesenchymal cells originating from cephalic neural crest and, the first pharyngeal arch ectoderm, leading to the dental mesenchyme formation, the dental pulp, odontoblasts, dentine matrix, cementum and periodontium.[4] The whole event is a nexus involving induction, proliferation, differentiation, morphogenesis, and maturation regulated by signalling molecule families leading to the formation of a primary dental lamina as a thickening of oral epithelium.[5,6] The mesenchymal tissue surrounding this developing enamel organ responds by proliferation to form a dense mass of cellular tissue, the dental papilla and the follicular sac for each tooth bud.[7] Conserved signalling molecules regulate the differentiation process of the ameloblasts from the epithelium, odontoblasts and cementoblasts from mesenchyme which later deposit the matrices of enamel, dentin and cementum respectively. A large portion of this epithelial tissue is lost during the tooth eruption process.[4,6] The remnants of dental lamina may persist as Epithelial pearls or islands within the jaw &/or gingiva. Odontogenic cysts arise from these cellular remnants

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of post-functional state of dental lamina entrapped within the epithelial remains of the Malassez or the gingiva named epithelial rests of Serres or either arises from the accumulation of fluid between the reduced enamel epithelium of the dental follicle and the crown of the unerupted tooth.8 The presence of abundant epithelial remnants in the jaws makes the prevalence of cysts higher in the jaws than any other human body part.[9,10,11]

Pathogenesis

Shear (1960) documented that, cysts arising from cell rests gave rise to simple epithelial linings which increase in size gradually due to degenerative characteristics of their linings, with rise in osmolality of the cyst contents. The absence of lymphatic access is thought to be fundamental to sustained cyst growth. In contrast, cysts derived from epithelial residues of the dental lamina which is non-contributory to a stable tooth structure are most likely to be lined by a keratinizing membrane, showing the characteristics of cell maturation rather than degeneration. They may increase in size predominantly by process of epithelial cell multiplication. These two types of cysts exhibit different clinical behaviour, as well as fundamental differences in the activity of their epithelial linings at the cellular level.[12] Harris, mentions the odontogenic cyst growth occurs with resorption of the surrounding bone and with accumulation of intracystic contents which may be: (1) cyst epithelium and its products of autolysis; (2) plasma proteins derived from transudation, exudation, and intracystic haemorrhage; (3) tissue fluid is drawn into the cyst owing to the high osmolality created by (1) and (2); and (4) mucus secreted by the goblet cells which are found in some follicular and nasopalatine cyst walls, either of these create expansile force.[13,14,15,16] The capsule, an essential supporting connective tissue matrix, is probably induced by the proliferating epithelium similarly to that described in tumours by Folkman. An equally important consideration is the resorption of the surrounding bone.[17,18,19,20] Humoral agents like parathyroid hormone, vitamin D (I,25-dihydroxycholecalciferol), prostaglandins, and a lymphokine produced by stimulated B lymphocytes, the osteoclast-activating factor activate the bone-resorbing cells.[21,22,26] As the cyst grows in size, the periosteum is stimulated to form a layer of new bone, and this deposition later involves the outline of the affected portion of the jaw producing enlargement. Initially, the lateral expansion causes smooth, hard, painless prominence. Bone covering the centre of the convexity is thinned with the cyst growth which can be indented with pressure. In some cases, an area with no bone results in a window as the periosteum is unable to maintain the new bone formation. This fragile outer shell of bone becomes fragmented and the sensation imparted on palpation. Further distension of cyst wall can lead to a discharge of fluid into the mouth.[23]

Radicular Cyst arises from the proliferation of the epithelial rests of Malassez (Harris and Toller 1975) in a focus of inflammation that has led to to the formation of a periapical granuloma. Hertwig's epithelial root sheath remanants lying within this granuloma may increase due to the inflammatory stimulus and through subsequent liquefaction necrosis in the centre of these enlarged epithelial nests, a fluid-filled cyst with an epithelial lining forms.[23] It enlarges by unicentric expansion from the hydrostatic pressure of its contents. Rarely, the epithelium may be derived from the maxillary sinus in cases of maxillary teeth that have extended into the sinus wall.[24] Lin et al. explained how the epithelium-lined apical cyst is formed. As epithelial islands expand, central epithelial cells are distanced from their nutritional supply and undergo liquifactive necrosis resulting in cystic cavity (Nutritional deficiency theory). When an abscess cavity is formed in the periapical connective tissues, it becomes surrounded by epithelium because of the natural inclination of the stratified squamous epithelium to line exposed connective tissue surfaces (Abscess theory). Each epithelial cell rest proliferates due to cytokine and growth factor stimulation in the inflammatory environment to form epithelial cell strands that are polarized. Under suitable conditions and with time the strands merge, wrapping the abscess or foreign debris to become cysts. The cysts continue to expand under persisting growth stimulus, allowing the basal cell to grow and expand (Merging of epithelial strands theory).[25] The proliferative epithelial strands as a result decomposition of epithelial and granulation tissue and simultaneous convergence of multiple cavities serve as a scaffold for development of cyst wall. Some state that inflammations in the apical region of non-vital teeth or periapical granulomas are caused by bacterial endotoxins which serve as mitogens for epithelial cells and as a stimulus for cytokine production. Investigators found that the decomposition of epithelial cells, leukocytes and the accumulation of plasma exudates cause increased gamma globulin levels than the patients serum, thus internal hydrostatic pressure becomes more significant than capillary pressure leading to diffusion of tissue fluids into the cyst. Therefore, plasma protein exudate & hyaluronic acid, products of epithelial cell breakdown together contribute to the high osmotic pressure of the cystic fluid on cyst walls causing bone resorption by osteolysis, and cyst enlargement.[26]

Inflammatory Collateral Cyst possibly originates from either: crevicular epithelium, the cell rests of Malassez and the reduced enamel epithelium. Craig explained the frequent buccal location of the cyst is attributed due to the presence of an extension of reduced enamel epithelium over the enamel projections.[27] Ackermann et al. (1987) suggested that cyst formation occurs as a result of the unilateral expansion of the dental follicle secondary to inflammatory destruction of periodontium and the alveolar bone.[28] Colgan et al. believe that the food impaction in the soft tissues occludes the opening of a pericoronal pocket, and as a consequence of inflammation the fluid accumulates within this obstructed pocket by osmotic process leading to cystic expansion.[29]

Dentigerous cyst results from inflammatory exudate pooling between reduced enamel epithelium and crown of the tooth or between the layers of the enamel epithelium itself. The exudate is derived from obstructed follicular veins of an unerupted tooth.16,21 In contrast to inflammatory cysts, no epithelial proliferation is needed to form this cyst.[22] The cyst wall is derived from the dental follicle, made of scattered odontogenic epithelial rests which sometimes exhibit dystrophic calcification. Mucus-producing cells, as well as ciliated cells, may be observed in the lining, which marks the multipotentiality of the cells of the dental lamina. Cyst enlarges by unicentric expansion from the hydrostatic pressure of its contents. When secondarily inflammed this cystic epithelial lining becomes thick, forming rete ridges and densely collagenized.[17] Rarely, secondary development of neoplastic lesions like: Adenomatoid Odontogenic Tumour, Complex Odontoma, Ameloblastoma, Mucoepidermoid Carcinoma, and Squamous Cell Carcinoma have been documented. Although the precise mechanism of malignant transformation in the lining epithelium remains unknown, long-term chronic inflammation may stimulate this transformation.[18]

Odontogenic Keratocyst growth along the cancellous channels with very little cortical expansion is explained in theories including:

intraluminal hyperosmolality, active epithelial proliferation[30], the collagenolytic activity of the cyst wall[31] and synthesis of interleukin 1 and 6 by keratinocytes that tend to activate the resorption of bone around the lesions by stimulating osteoclastogenesis.[32,33] de Paula A M et al. concluded that inflammation induces increase epithelial cell proliferation which is associated with disruption of the typical structure of cyst linings. Hirshberg A et al. stated that inflammation had an impact on collagen fibre packing in connective tissue wall of cyst, as reflected by their birefringence under polarized light.[34] The expression levels of TGF-α, EGF and EGFR suggest the involvement of the growth factors in their pathogenesis.[32] The overexpression of p53 protein is related to the proliferative capacity of this entity rather than increased numbers of p53+ cells.35,36 Ki-67 expression is higher in the epithelium when compared to other developmental and inflammatory cysts, with most of the Ki-67+ cells being detected in the suprabasal layers.

Lateral Periodontal Cyst (LPC) origin is debatable. Various researchers provide support for the lesion developing from either dental lamina, reduced enamel epithelium or epithelial rests of Malassez.[37] Inflammation does not play a role in their development. The pathogenesis may be related to the 3 hypotheses: (1) Cyst is lined by nonkeratinized epithelium reminiscent of the reduced enamel epithelium which is supported by PCNA immunohistochemical expression. (2) related to dental lamina remnants, as it histopathologically presents glycogen-rich clear cells, which are seen in the dental lamina aswell. (3) that the epithelial remnants of malassez presented in the roots surface, the central location of the cyst, play a role.[38,39,40] The multilocular variant of Lateral Periodontal cyst is "botryoid cyst". Some consider it a result of changes in LPCs, others say it arises from fusion of multiple LPCs developing in proximity while most consider it arising from groups of converging cellular debris of serres incorporated into the periodontal tissue, or from the reduced enamel epithelium of the follicle which expands to occupy a space in the periodontal ligament during the eruptive phase, where if a portion of this remains in the gum after the eruption it forms a gingival cyst.[42] Redman et al., stated that LPCs if left untreated, may fuse to form a multicystic lesion referred as Botryoid variety.[43] Van der Waal stated that Botryoid variety could not be considered a variant of LPC as it extends well beyond the lateral area of the root.[44,45]

Gingival Cyst is thought to arise within the gingiva and, through growth and expansion, to involve the adjacent periodontal tissues. Several authors suggested its origin from: remnants of the dental lamina, enamel organ, or cell rests of malassez, from degenerative cystic changes in the rete pegs of the surface gingival epithelium or cystic degeneration of a strangulated peg from the surface epithelium, from traumatic implantation of surface epithelium in the gingival corium, from heterotopic glandular tissue resulting from developmental displacement.[46]

Glandular Odontogenic Cyst is thought to be originating: (a) from entrapped salivary gland primordia (b) from undifferentiated primitive epithelial rests that differentiate into the glandular epithelium, (b) as result of proplasia of the odontogenic epithelial lining into the glandular epithelium (c) as initial single cystic space formed in Low-grade Mucoepidermoid Carcinoma.[47] Although studies on the cytokeratin profile failed to support either an odontogenic or a sialogenic origin, and there is ample evidence to favour the former. The aggressive biologic behaviour and its propensity for recurrence might be associated with cell kinetics in the lining epithelium. Tosios et al. stated the increased expression of the anti-apoptotic Bcl-2 might be associated with deregulation of cell death in the lining epithelium, while Ki-67 and p53 role was insignificant in cell proliferation.[50, 51]

Calcifying Odontogenic Cyst is a unique lesion possessing both cystic and neoplastic potential. Praetorius argues that it is not just a developmental cyst as it often forms islands of epithelium and dentinoid in the wall; while in some an odontoma forms.[52] The cells responsible for the cyst formation are rests of serres within the soft tissue or bone. Therefore, these cysts are of primordial origin and are not associated with the crown of an impacted tooth. It most often occurs as a central lesion, with peripheral localization being a rarity.[53] McGowan and Browne, in 1982, found that the presence of mineralization was approximately twice as frequent in microscopic examination compared to radiographic analysis.[54] Several epithelial cells which are eosinophilic devoid of any nuclei, with their basic cell outline retained named as ghost cells are seen which may undergo calcification and lose their cellular outline to form a firm sheet-like area, of calcified keratin.[55,56] Ghost cells are thought to be resulting from coagulative necrosis and dystrophic calcification, or a form of normal or abnormal keratinization of the odontogenic epithelium. The ability to induce dental hard tissue formation appears to be a property of epithelial cell lining of this cyst.

Orthokeratinized odontogenic cyst (OOC) pathogenesis is yet to be unravelled. According Thosaporn et al. it should always be considered in the differential diagnosis of radiolucent lesions involving impacted teeth, in view of its origin from dental lamina.[57] CK7 and CK13, usually expressed by the dental lamina and enamel organ, are weakly positive in a dentigerous cyst, while OOC and OKC show the expression of only CK13. This supports the view that OKC and OOC may be derived from the dental lamina.[58] Also, it is shown that OOC expresses cytokeratins which are primarily expressed in epidermis, that explains the possibility of the sequestration of the stomadial ectoderm into the developing jaw during embryogenesis.[59] The expression of Ki67, p53, p63 and BCL-2 were distinctly different in OOC with reduced expression than OKC reflecting a lower cellular activity and more indolent behaviour.[60,61]

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