

An Insight into the Pathogenesis of Odontogenic Hamartomas Involving Oral Cavity

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ABSTRACT

Introduction: Hamartomas are non-neoplastic lesions and they can be noted in any part of the body. Hamartomas involving head-neck region are relatively rare. They usually depict the overgrowth of tissue indigenous to the native area. There are also several molecular expressions regulating the pathogenesis of odontogenic hamartomas and often these findings are suggestive of the hamartomatous nature of these lesions. They should be properly differentiated from choristoma, teratoma, benign and malignant lesion.

Objective: To discuss the pathogenesis of different odontogenic hamartomas to delineate their true biological behavior.

Materials and methods: Data were obtained and analyzed from previously published literature and electronic database searches from PubMed and Google Scholar.

Conclusion: Proper diagnosis of hamartomas involving the oral cavity is of utmost importance for definitive treatment modalities. Hamartomas can produce a diagnostic dilemma and overtreatment or under treatment can be a result of improper diagnosis of hamartoma. Here, in this brief review the pathogenesis of odontogenic hamartomatous lesions involving the oral cavity are discussed.

Keywords: Hamartoma, odontogenic, pathogenesis.

Oral and Maxillofacial Pathology Journal (2020): <http://www.ompj.org/archives>.

INTRODUCTION

The terminology "hamartoma" emanates from greek 'hamartia' (defect, error) and 'oma' (tumor-like growth)^{1,2}. The term was first used by Albrecht in 1904³. According to the NCI (National Cancer Institute) dictionary of cancer term, hamartoma is "A benign (not cancer) growth made up of an abnormal mixture of cells and tissues normally found in the area of the body where the growth occurs". They usually imitate a dysmorphic proliferation of tissue which is native to the field. They have limited growth capacity and do not penetrate neighboring tissue⁴. Although hamartomas infrequently affect the head-neck region, liver, kidney, lung, pancreas, spleen are common sites of occurrence⁵. Hamartomas of odontogenic origin include adenomatoid odontogenic tumor, squamous odontogenic tumor, ameloblastic fibro odontoma, cementoblastoma, periapical cemental dysplasia, dens invaginatus, dens evaginatus, odontoma, talon's cusp, enameloma⁶. Herein the pathogenesis-related to odontogenic hamartomas are discussed briefly.

Adenomatoid Odontogenic Tumor

Philipsen and Birn coined the term adenomatoid odontogenic tumor (AOT) which is an intraosseous or peripheral hamartomatous lesion with a slow, progressive growth pattern⁷. Probably AOT derives from the enamel organ, remnants of the dental lamina, epithelial rests of Malassez of the deciduous or permanent tooth,

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How to cite this article: Mukherjee D. An insight into the pathogenesis of odontogenic hamartomas involving oral cavity. Oral Maxillofac Pathol J 2020;11(2): 64-66

Source of Support: Nil

Conflict of Interest: None

the epithelial lining of the dentigerous cyst but in most of the cases, there is a close organization between the successional tooth development and pathogenesis of AOT⁸. It was noted that more than 96% of AOT arise from the dental lamina in the gubernacular cord of a developing permanent incisor, canine, or premolar⁸.

The findings which were corroborative to the fact that AOT is a hamartomatous growth rather than neoplastic are: a) mean values of the labeling index for Ki-67 is lower in AOTs (1%) than solid ameloblastomas (4%), an odontogenic benign tumor b) values for B-cell lymphoma 2 (BCL-2) is also lower in AOTs (26%) than solid ameloblastomas (63%)⁹. Weaker p53 and MDM2 expression along with intense expression of enamel proteins (amelogenin,

amelotin, and ameloblastin) and TGF- β /SMADs in AOT are also suggestive of less aggressive biological behavior⁹.

Squamous Odontogenic Tumor

Squamous odontogenic tumor (SOT) was firstly defined by Pullon et al in 1975⁷. Some authors designated SOT as a hamartomatous lesion⁷. SOT usually located in the periodontium as an infiltrative, slow-growing benign odontogenic lesion⁷. SOT may develop from epithelial rests of Malassez or remnants of the dental lamina (rests of Serres)¹⁰. Peripheral SOT can emerge as a “dropping off” from the gingival surface epithelium⁷.

SOTs express a strong positivity to involucrin in the ‘centers of the epithelial islands of the squamous differentiating cells’⁷. Strong positivity for keratin 13 and 16 are corroborative to the proliferative activity of the odontogenic epithelium of SOT⁷.

Ameloblastic Fibroma

A group of cystic tumors of the mandible was depicted by Kruse in 1891 which are now familiar as ameloblastic fibromas (AFs)⁷. There are several schools of thought regarding the pathogenesis of AF. One group AFs are neoplastic type which has no induction phenomena of epithelial and mesenchymal component and the other group is the hamartomatous type showing inductive effects⁷. Both the neoplastic and hamartomatous type cannot be differentiated histopathologically because they both have proliferating odontogenic epithelium embedded in a cellular, odontogenic ectomesenchymal tissue resembling the dental papilla⁷.

Ameloblastic Fibrodentinoma

The ameloblastic fibrodentinoma (AFD) was first characterized by Straith in 1936⁷. Philipsen et al. have proposed that AFD has two variants (neoplastic and hamartomatous) without any differentiating histopathology¹¹. The hamartomatous variant can progress into an ameloblastic fibro odontoma or complex odontoma¹¹. Histologically AFD showed dentinoid as a result of inductive changes⁷.

AFD revealed strong expression of CK19, E-cadherin, syndecan-1 in the island, and strands of odontogenic epithelium¹². It revealed weak expression of Ki-67 which is corroborative to its less aggressive biological behavior¹².

Ameloblastic Fibro-odontoma

Ameloblastic fibro odontoma (AFO) is a hamartoma with a more inductive effect to form enamel matrix and dentinoid⁷. AFO was first depicted by Hooker in 1967¹³. One theory suggests that non-neoplastic hamartomatous lesions of ameloblastic fibroma (AF) may undergo inductive changes to produce AFO^{7,13}. The presence of dentin in conjunction with enamel suggests more progressing inductive changes in AFO than AF and AFD⁷.

Loss of heterozygosity (LOH) at tumor suppressor gene loci on 3p,9p,11p,11q and 17p of AF, AFO demonstrate a higher mean fraction of allelic loss (FAL) in AFO than AF¹⁴. 62% of p53 and 55% of CHRN1 showed mainly LOH of 17p13.1 loci¹⁴. In a few reported cases of AF and AFO demonstrate BRAF V600E mutation¹⁴.

Odontoma

The term odontoma was first used by Paul Broca in 1867¹⁵. According “continuum concept” of Cahn and Blum AF can undergo matu-

ration to form an odontoma⁷. It is a self-limiting hamartomatous lesion consisting of ‘nondescript masses of dental tissues’⁷. Local trauma, infection, odontoblastic hyperactivity, genetic mutation of postnatal tooth development, hereditary anomalies (Gardner’s syndrome, Hermanns syndrome) may play an important role in the formation of odontoma^{7,15}. Complex odontoma is basically a hamartomatous lesion with all the well developed dental hard tissue in a more or less disorderly pattern. On the other hand dental tissues are more orderly arranged in compound odontoma (‘tooth-like structure’). In compound odontoma enamel, dentin, cementum, pulp are organized similarly to normal tooth but it is different morphologically⁷.

Few cytokeratins expression is common for both normal developing/developed dental tissue and odontoma¹⁶. Odontomas reveal the expression of following cytokeratin: a) cytokeratin 14 (absent in advanced amelogenesis) b) cytokeratin 7 (present in Hertwig root sheath and stellate reticulum)¹⁶. On the other hand, odontomas does not reveal the expression of cytokeratin 19 (strongly expressed in preameloblasts and secretory ameloblasts)¹⁶. These findings are corroborative to the fact that odontomas are compeer of developing tooth germ but they do not have the capacity for complete differentiation of preameloblasts and ameloblasts for which abnormal enamel organ mineralization occurs¹⁶.

Dens evaginatus

Dens evaginatus (DE) has an incidence rate of 0.5-4.3% and it has mostly occurred in Asian people⁵. DE (protuberance from the affected site of the tooth) is also known as accessory cusp, evaginatus odontomas, tuberculum dentis, crown tubercle, tuberculum coronae, leong’s premolar, occlusal pearl, and talon cusp (for anterior teeth)^{17,18}. It has an outer layer of enamel, a core of dentin, and infrequently an extension of pulp tissue¹⁸. It may be associated with supernumerary teeth, peg-shaped incisors, bifid cingulum, and dens invaginatus involving the premolars, molars, incisors, canines of both primary and permanent dentition¹⁷. Etiopathogenic factors include local hyperactivity of dental lamina, genetics, environmental factors (trauma) disturbing the tooth germ during the morpho-differentiation stage of tooth development¹⁷. Mutation of EDARADD, EDA1, EDAR gene can cause tooth loss and malformation¹⁸. DE occurs due to the evagination of internal enamel epithelium and the adjacent odontogenic mesenchyme into the stellate reticulum¹⁸. According to Thesleff and Sharpe signals from enamel knot and mesenchymal tissue regulate patterning and shaping of cusp/crown¹⁸. Thus, enamel knot has an immense importance in differentiation to morphogenesis. Fibroblast growth factors (FGF-4, FGF-9), transforming growth factor β , and bone morphogenic proteins (BMP-2, 4, and 7) are expressed by enamel knot during cusp formation¹⁸.

In 1970 Mellor & Ripa coined the term talon cusp due to its shape resemblance to an eagle’s talon¹⁹. It may be associated with Rubinstein-Taybi syndrome, Sturge-Weber syndrome (encephalotrigeminal angiomas), Mohr syndrome (oral-facial-digital syndrome type II), or incontinentia pigmenti achromians¹⁹. The most approved theory for the occurrence of talon cusp is the ‘outward folding of inner enamel epithelial cells’ along with a ‘transient focal hyperplasia of mesenchymal dental papilla’¹⁹.

Dens invaginatus

In 1856, Socrates first depicts dens invaginatus²⁰. It occurs due to invaginations of the enamel organ into the dental papilla²⁰. Causes of invaginations may be due to focal failure of growth of internal enamel epithelium, increased proliferative activity of a part of internal enamel epithelium, or distortion of the enamel organ²⁰. Genetic factors and external forces during tooth development can also be a predisposing factor for dens invaginatus²⁰.

Enameloma

In 1842 enameloma was first depicted by Linderer and Linderer²¹. It is also known as enamel pearl, enamel droplet, enamel knot, enamel nodule, enamel globule, and enamel exostoses. Differentiated ameloblasts apical to the CEJ is the main requirement for its formation. Pathogenesis includes failure of the inner cell layer of HERS to detach from the newly formed dentin matrix, proliferating buds of epithelium that have become separated at the margin of enamel structure, ameloblastic differentiation of the quiescent cells of the rests of Malassez²¹. Hereditary factors, local mechanical factors may also play a role in the pathogenesis of enameloma²¹.

Periapical cemental dysplasia

Periapical cemental dysplasia is usually noted in the anterior region of the mandible. The terminology 'cemental' is used to delineate the lesions involving the anterior mandible⁴. It is a rare lesion and it has three developmental phases: osteolytic; cementoblastic; and mature²². Periapical cemental dysplasia develops from undifferentiated cells of the periodontal ligament²². Morphologically imperfect cementum is produced in this lesion but the cells are neither neoplastic nor premalignant. Basically the structural morphology is jeopardized⁴.

Cementoblastoma

Cementoblastoma was first depicted in 1927²³. It is a hamartomatous lesion of cementoblasts and it emerges from the cellular cementum⁴. A disorganized deposition of cementum can be noted involving the apical cemental layer of the molar and premolar²³.

CONCLUSION

There are several hamartomatous lesions involving the oral cavity. They should be diagnosed properly for a definitive treatment plan which depends on the biological behavior of the lesions. Pathogenic factors for hamartoma formation are also different in a diverse group of lesions. An attempt has been made to discuss the pathogenesis of odontogenic hamartomas involving the oral cavity through this brief review.

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