

## Controversial Odontogenic Hamartomas- Review on Their Pathogenesis and Histopathology

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### ABSTRACT

Odontogenic tumour represents as growth and swellings of varied origin. The histopathological features of hamartomatous odontogenic entities are not very distinct from neoplasms, but they exhibit different biological behavior. The pathobiology of these lesions is so-

metimes understated. There always lays a big controversy depicting an entity as hamartoma. Hamartomas are frequently encountered in major organs like liver, lung, pancreas etc. but the occurrence in oral cavity is rare. The lesions enlisted in this review may not be true hamartomas but depicts strong correlation to neoplasms. Understanding the hamartomatous nature of an odontogenic entity will help us understanding the outcome of the treatment and chances of fatality

**Key words:** Hamartoma; Odontogenic

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### HAMARTOMAS

Hamartomas, which are dysmorphic or morphologically altered proliferation of cells native to the organ in which they arise, gain a certain size before ceasing their proliferation. This type of biologic behavior may be expansile and is locally resorptive of bone but does not invade adjacent tissue.

### ODONTOGENIC GINGIVAL EPITHELIAL HAMARTOMA (OGEH)

There are two important sources that are responsible for the development of the odontogenic group of lesions; cell rests of Serres (remnants of dental lamina) and cell rests of Malassez (remnants of Hertwig epithelial root sheath). These cell rests are found as clusters which upon getting stimulus give rise to pathological entities. The terminology OGEH was initially suggested by Baden *et al*<sup>[1,2]</sup>. This lesion has a rare occurrence, prevalent mostly in the middle age group (3<sup>rd</sup> to 5<sup>th</sup> decade) and most commonly seen in females (M: F- 1: 7)<sup>[1,2,3]</sup>. The lesion present as a slowly growing, recurrent in occurrence in the soft tissues like gingiva and vestibule.

Histopathologically it shows clusters of odontogenic epithelial which are bordered by a fibrous pseudocapsule. Each nodule is separated from each other by loose fibrous stroma containing thin lined blood vessels. The entire nodules are composed of numerous round nests of epithelial cells of odontogenic origin. The cells are usually polyhedral in shape with a basophilic rounded nucleus. Focal areas show clear cell changes without any involvement of inflammatory cells, which suggest an absence of inducing stimuli; hence they are derived from the dental lamina<sup>[4,5]</sup>. These lesions are essentially non neoplastic as they lack uncoordinated and abnormal growth features. The abnormal mixtures of cells are native to their part of origin. In rare cases, the odontogenic epithelial cells were found to be in direct continuity with the basal layer of the overlying stratified squamous epithelium. The unique presentation and the lack of invasiveness separate OGEH from peripheral ameloblastoma and WHO-type peripheral odontogenic fibroma<sup>[3]</sup>.

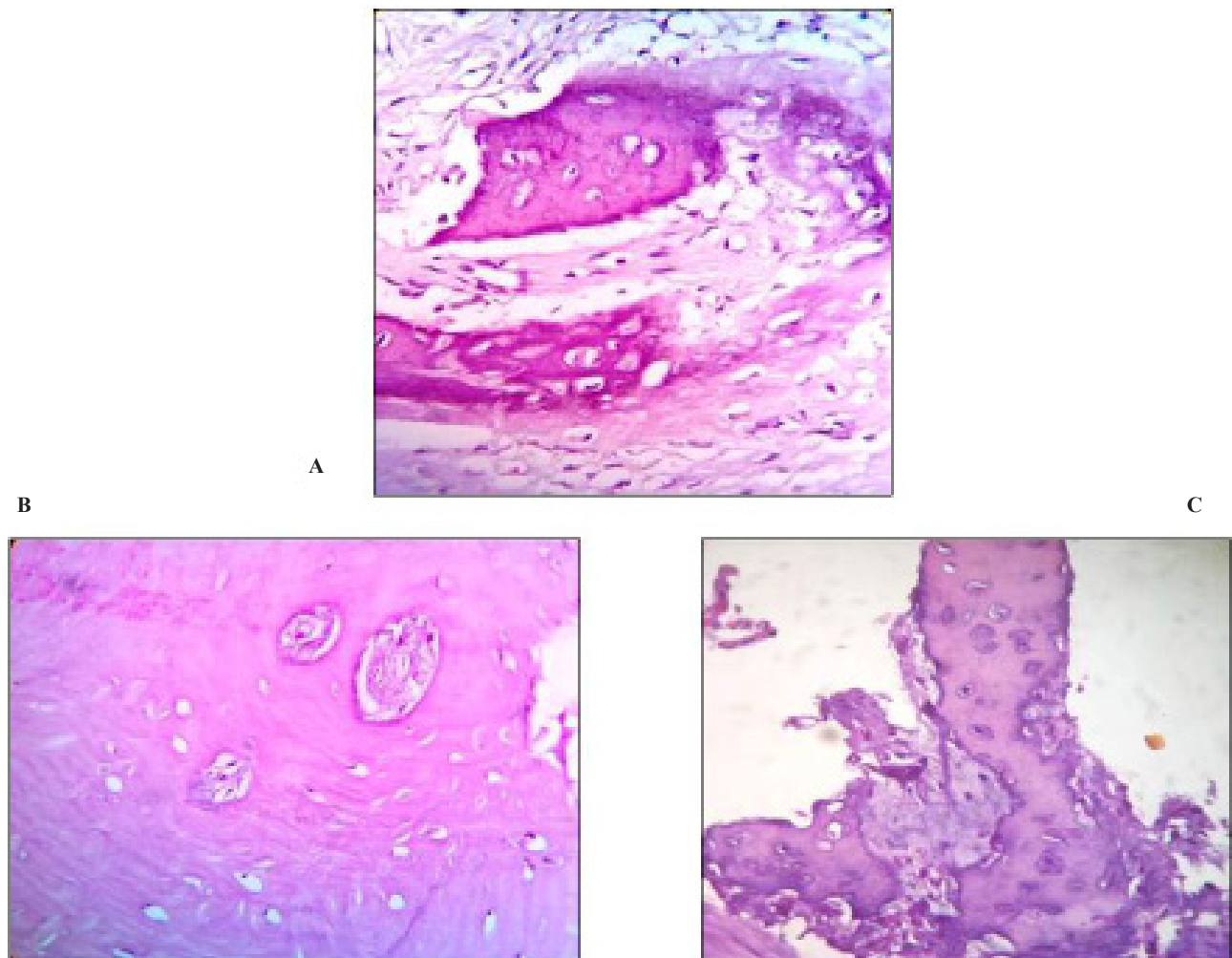
### PERICORONAL HAMARTOMATOUS LESIONS (PHLs)

This group of lesion is frequently associated with the dental follicle and hence has a close link to the dental follicle hamartomas. The association is seen with the opercula of the unerupted or delayed erupted second and third molars<sup>[6,7]</sup>. Previous literature has reported lesions like odontogenic giant cell fibromatosis (OGCF) and

peripheral myxofibrous hyperplasia (PMH)<sup>[8]</sup>. OGCF was described by Philipsen *et al*<sup>[8]</sup>, the histopathology of the tissue shows no encapsulation with dense fibrous connective tissue containing large multinucleated giant cells, proliferating odontogenic islands with occasional squamous metaplasia. PMH shows hyperplasia of the myxomatous connective tissue (resembles odontogenic ectomesenchyme), giant cells and flecks of calcifications<sup>[9,10]</sup>. PHLs have strong histopathological similarities to peripheral odontogenic fibromas. The etiology of the peripheral odontogenic fibroma whether reactive or hamartomatous is always debatable. The significant recurrence of the lesion suggests its neoplastic character and the lack of giant cells in the histopathology suggest that PHLs are unique as an entity<sup>[7]</sup>.

### CEMENTOBLASTOMA

It accounts for less than 1% of the entire odontogenic tumour. The initial case was reported by Norberg in 1930. It is considered as a hamartomatous proliferation of cementoblasts forming dysmorphic and disorganized cementum around the apical half of the root. It usually present as a hard expansion in the jaw mostly reported in the mandibular molars and in the young adults<sup>[11]</sup>. Histopathologically it shows hypocellular masses of cementum embedded in fibrovascular connective tissue surrounded by a thin fibrous capsule continuous with the periodontal ligament. The cemental mass is in association



**Figure 1 Cementoblastoma.** A: Areas of cementum like masses formation with active cells entrapped, these cemental masses are surrounded by loose stroma X40. B: Dilated blood vessels with thick cemental mass containing cementocytes. C: Irregularly formed cemental matrix with entrapped cells.

with the root of the tooth. The proliferating cemental mass is lined by numerous plump cementoblasts. Prominent basophilic reversal lines can also be appreciated in the cemental mass which gives a pagetoid appearance. The fibrous connective tissue stroma is loose, may contain multinucleated giant cells (cementoclasts) and numerous dilated small blood vessels which is the hallmark of the lesion<sup>[11,12]</sup> (Figure 1).

## AMELOBLASTIC FIBROMA-

A debatable entity till date even after WHO has enlisted ameloblastic fibroma in the neoplastic group of lesions. It is rare odontogenic tumour exhibiting the proliferation of both the odontogenic epithelial component and the Mesenchymal component. The tumour mostly occurs in the children and young adults, though seen in other age groups too. The tumour is mostly seen in posterior mandible than in maxilla. This lesion is usually associated to impacted or unerupted teeth in majority of the cases, sometimes it is also seen associated to missing teeth<sup>[13,14]</sup>. The histopathology of the mixed odontogenic group of lesions resembles the stages of odontogenesis<sup>[15]</sup>. Ameloblastic fibroma also included in the category of mixed odontogenic lesions. The identity of the ameloblastic fibroma has always been a source of debate where one school of oral pathologists considers it to be a hamartoma; as if the ameloblastic fibroma is allowed to progress or left undisturbed it may progress further to ameloblastic fibro-odontoma and then to odontoma while the other group of oral pathologist considers it as neoplastic because of its recurrence of the tumour (16.3%), occurrence even after 22 years when there should be no odontogenesis and the malignant transformation of ameloblastic fibroma to ameloblastic fibrosarcoma (6.4%)<sup>[13,14]</sup>. As per Trodahl *et al.*, ameloblastic fibroma histopathologically resembles two entities; early odontome and the other is true neoplasm lacking inductive potential<sup>[16]</sup>.

Histopathologically, the proliferating odontogenic epithelium is arranged in form of strands, cords and islands. The strand often exhibits double or triple layer of cuboidal cells which has a close resemblance to dental lamina. The odontogenic islands resemble ameloblastic islands which show peripheral arrangement of columnar to tall cuboidal cells. Stellate reticulum like cells are also displayed in the centre of those islands. The ectomesenchymal cells resembling primitive dental papilla are seen surrounding the islands and strands (Figure 2). There is usually a juxta epithelial hyalinization around those islands signifying the process of epithelial mesenchymal interaction<sup>[17]</sup>. Immunohistochemical markers like proliferating cell nuclear antigen (PCNA) and MIB-1 has been studied where it was found that MIB-1 has been expressed in the mesenchymal component suggesting the higher labeling indices in the Mesenchymal component rather than the epithelial component<sup>[18,19]</sup>. The role of these markers helped in understanding the growth and aggressive potential of the tumours.

## AMELOBLASTIC FIBRO-ODONTOMA

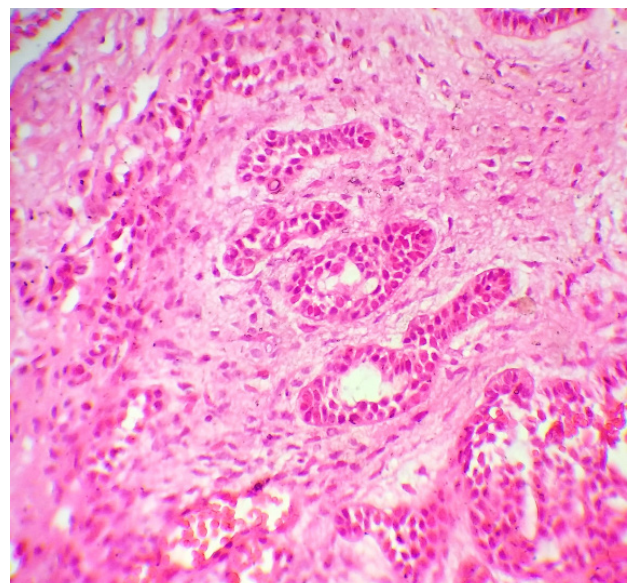
Ameloblastic fibro-odontoma (ABFO) is considered to be a hamartomatous tumour which holds similarity to ameloblastic fibroma but show inductive changes (formation of hard structures of tooth)<sup>[13,20]</sup>. It represents 1-3 % of the occurrence of the total odontogenic tumours<sup>[21,22]</sup>. Chau *et al* suggested ameloblastic fibroma as a distinct entity from ameloblastic fibroodontome with neoplastic potential<sup>[23]</sup>. It was suggested by Buchner and Vered that ameloblastic fibro odontoma can occur as a recurrent lesion of previously occurred ameloblastic fibroma (age before 22 years)<sup>[14]</sup>. Philipsen

and Slootweg have suggested ABFO as a hamartomatous lesion, though histologically indistinguishable from complex odontoma<sup>[24,25]</sup>. ABFO is more prevalent in the young age group, Philipsen reported the mean age of occurrence to be 9 years<sup>[24]</sup>. The posterior mandible is most common site of occurrence followed by the posterior maxilla. This tumour is usually associated to the unerupted tooth and radiographically present as a well circumscribed radiolucent lesion which may or may not contain radio-opaque foci.

Histopathologically the tumour presents in forms of odontogenic epithelial strands, cords and islands distributed in the ectomesenchymal stroma. There is a formation of the dentinoid or osteodentin material with an occasional presence of enamel (fibrillar and key hole patterns). Ameloblastic layer can be seen attached to the formed enamel like matrix. All of these features resemble an early tooth or a combination of the tooth structures (Figure 3). Few studies have even reported that ABFO represents histological combination of ameloblastic fibroma and complex odontoma<sup>[13,26]</sup>. ABFO can be also distinguished from ameloblastic fibro-dentinoma by the additional presence of disorganized enamel like material which the later does not exhibit. The definite arrangement of the soft tissues and the overall presentation of tooth structures development can give a clue to reach diagnosis. ABFO is not an aggressive tumour hence treated with extensive curettage or by block resection to prevent recurrence of the lesion.

**Adenomatoid Odontogenic Tumour (AOT):** - It is a relatively rare neoplasm constituting about 2-7% of odontogenic cysts and tumours combined. The current terminology used for AOT has had a history of frequent changes with *adenoameloblastoma ameloblastic adenomatoid tumour*, *epithelioma adamantinum*, *pseudoadenoma adamantinum* by Dreyblatt, and *glandular adamantinoma* to name a few<sup>[27]</sup>.

AOT is traditionally being believed to be derived from the odontogenic apparatus due to its close association with impacted tooth as well as tooth bearing areas of the jaw and its cytological resemblance to the remnants of enamel organ epithelium, reduced enamel epithelium and rests of Malassez have been postulated as possible sources<sup>[28,29]</sup>.



**Figure 2 Ameloblastic fibroma**, Cords of odontogenic epithelium scattered throughout the immature connective tissue stroma x40.



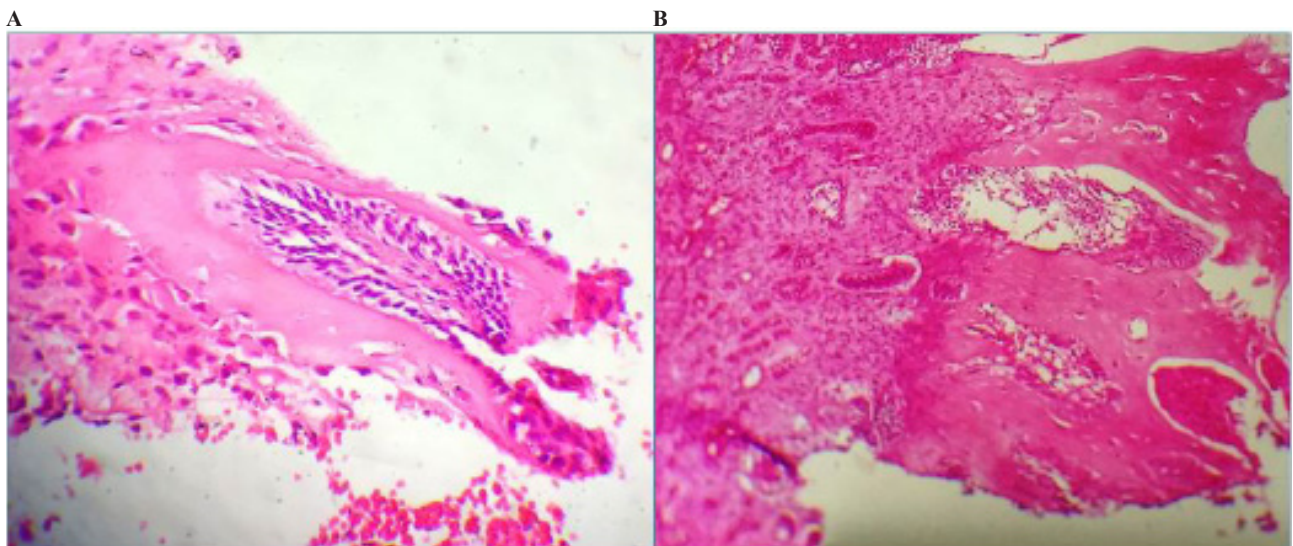
In a recent article by Ferreira *et al.*<sup>[30]</sup> described in detail both the *gubernacular cord* and the *gubernacular canal* assessed the possible contribution of these structures in the process of tooth eruption. Philpsen *et al.*<sup>[8]</sup> in their article further went ahead to state that regarding origin and pathogenesis of the AOT, it would seem that this lesion is derived from odontogenic epithelium of the dental lamina complex or its cellular remnants located in the *gubernacular cord*<sup>[30]</sup>.

AOT is also a unique lesion that presents in a fairly consistent manner, as a result of which it has come to be regarded as a “*tumor of two-thirds*,” i.e., two-thirds occur in female patients, two-thirds occur in the second decade of life, two-thirds develop in the anterior sextant of the maxilla, two-thirds are superimposed on dentigerous cysts, and two-thirds of associated unerupted teeth are permanent canines. In addition, two-thirds of cases show scattered dot-like (snowflake) opacities within the unilocular radiolucency<sup>[31]</sup>. There have been reported cases of root resorption associated with AOT<sup>[32]</sup>.

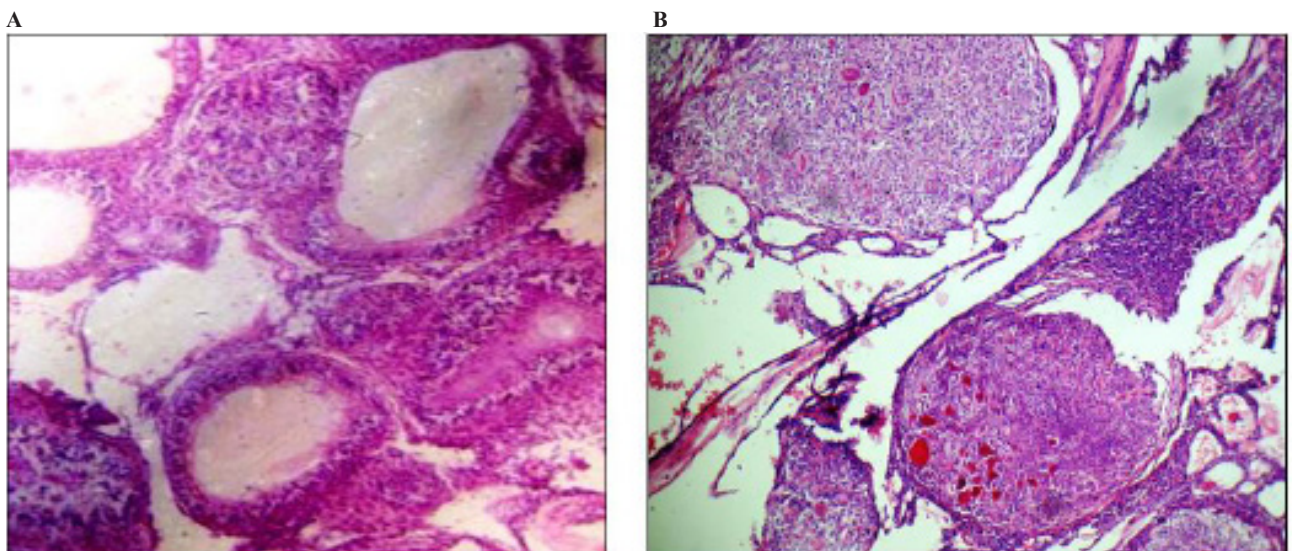
Microscopically, the histopathologic features of this lesion are very distinctive to be separated from any other odontogenic tumor. The tumor exhibits population of spindle-shaped epithelial cells that form

sheets, strands, or whorled masses of cells in a scant fibrous stroma. The epithelial cells show a variety of patterns in form rosettes which appear to be formed around a central space or lumen, which may be empty or contain small amounts of eosinophilic material showing positive staining for amyloid like material<sup>[33]</sup>.

The tubular or duct-like structures may be predominant, scanty, or even absent in a given section. These tubular structures consist of a central space surrounded by a layer of columnar or cuboidal epithelial cell with their nuclei polarized away from the central lumen<sup>[6]</sup>. The lumina are frequently lined by eosinophilic rim of varying thickness popularly known as hyaline ring<sup>[3]</sup>. The mechanism of formation of these tubular structures is not entirely clear but is likely the result of the secretory activity of the tumor cells, which appear to be *preameloblasts* in nature<sup>[29]</sup>. In any event, these structures are not true ducts, and no glandular elements are present in the tumour. Small foci of calcification may also be scattered throughout the tumor<sup>[32]</sup>. These have been interpreted as abortive enamel formation (Figure 4). Some adenomatoid odontogenic tumors contain larger areas of matrix material or calcification which has been traditionally interpreted as



**Figure 3 Ameloblastic fibroodontoma.** A: Odontogenic ameloblasts like cells and adjoining matrix formation x40. B: Numerous cords of odontogenic epithelium and attempts of hard tissue formation. X10.



**Figure 4 Adenomatoid odontogenic tumour.** A: Ductal structures of varying size surrounded by columnar palisading epithelial cells, darkly stained columnar cells arranged in form of whorls and sheets of throughout the fibrous connective tissue stroma. B: Odontogenic epithelial lining arranged in a rosette and whorling pattern. Focal areas showing calcifications.

dysplastic dentin, dentinoid, osteodentin or cementum like material. Irregular to round concentric layered calcified bodies exhibiting a Leisegang ring pattern may also be evident<sup>[29]</sup>. At the periphery few of the tumors may show narrow, often anastomosing cords of epithelium in an eosinophilic, loosely arranged matrix adjacent to the capsular area. The supporting stroma is loose hypocellular and fibrovascular and may show presence of prominent vascular component<sup>[17,34]</sup>.

Recent advances in molecular mechanism have revealed that the mean values for Ki-67 when compared in solid ameloblastomas and AOTs were found to be 4% and 1%, respectively. Enamel proteins including amelogenin, ameloblastin, and amelotin, as well as TGF- $\beta$ /SMADs, are more intensely expressed in AOTs than in ameloblastomas. Thus resulting in lesser aggressive biological behavior and increased cytodifferentiation and apoptosis in AOT than ameloblastomas<sup>[35,36]</sup>. Philipsen *et al*<sup>[4]</sup> in their study have suggested to continue reporting of unusual or rare histomorphological features, immunohistochemical findings and applications of molecular biological techniques for better understanding of this unusual odontogenic tumour<sup>[27]</sup>.

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