ORIGINAL ARTICLE

ADENOMATOID ODONTOGENIC TUMOUR: DILEMMA IN CONSENSUS OF IT'S CLASSIFICATION – A CASE STUDY

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ABSTRACT:
Odontogenic tumors (OTs), neoplasms, and other lesions related to the jawbones have for years been recognized as presenting clinical, radiologic, and histopathologic challenges. Benign OTs have been subclassified into three groups in which a universal consensus in categorization of various tumors has been arguable. One such debatable OT is AOT. Adenomatoid odontogenic tumor is a clinically benign lesion with a relative frequency of 2.2 - 7.1% of all OTs. It is predominantly found in young age group, female patients, located more often in the maxilla and in most cases associated with an unerupted permanent tooth. As the histogenesis of AOT is still uncertain, there is considerable confusion regarding the origin and classification of AOT with the most recent WHO classification including AOT as a hamartoma showing metaplastic mineralization. We report a case of an eighteen year old male patient with swelling in the upper left front region of jaw. This case report is aimed to study and discuss the nature of AOT as being an inductive tumor or a hamartoma with metaplastic mineralisation by histochemical and immunohistochemical staining. An attempt has been made to conceptualize the nature and classification of AOT.
Key words: Adenomatoid odontogenic tumor, Hamartoma, Neoplasm

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INTRODUCTION

Adenomatoid odontogenic tumor (AOT) has long been the subject of debate with regards to its origin and nature. It is considered as benign, non neoplastic lesion with slow but progressive growth.[1] In 1969, term AOT was introduced by Philipsen and Birn.[2] This was later adopted by WHO in 1971[3] in its first edition of classification of odontogenic tumors ('Histological Typing of Odontogenic Tumours, Jaw Cysts and Allied Lesions'). It was listed under the category of tumors arising from Odontogenic epithelium with odontogenic ectomesenchyme, with or without hard tissue formation) in the 1992 version of WHO's classification[4] of odontogenic tumors. With the continued research on AOT, certain doubts have been expressed regarding its inductive capability. It is now considered to be a hamartoma rather than a true neoplasm and the hard tissue presence in it isn't inductive but metaplastically produced mineralization.[5,6] Thus now the classification has been revised and the tumor is listed under the category of tumors containing odontogenic epithelium with mature, fibrous stroma; odontogenic ectomesenchyme not present. This change was based on the facts that AOT is composed of mature fibrous connective tissue stroma, without the evidence of odontogenic ectomesenchyme, thus lacking its inductive effect.

AOT can occur at any age (range: 3yrs to 82yrs) but commonly occurs in the second decade. It shows slight female predilection (F: M = 1.9 : 1). AOT has central/intraosseous and peripheral/extraosseous types.[1,7] Central type of AOT shows two variants namely, follicular/tooth associated and extrafollicular. It has site favorability for maxilla than mandible (especially anterior maxilla). Frequently it is associated with unerupted permanent

canine[8] (other teeth associated with it can be permanent molars, deciduous teeth, supernumerary teeth, etc).[1] Regardless of the true nature of AOT, it is believed to have derived from odontogenic epithelium[1](evident from the fact that it usually occurs in the tooth bearing areas of the jaw, is associated with unerupted tooth, shows histologic resemblance to parts of enamel organ).[5,9] Different odontogenic epithelium suggested as the sources are, dental lamina, reduced enamel epithelium, stratum intermedium, enamel organ.[10,11] Philipsen et al[12] argued in favour of the origin being from dental lamina and its remnants.

Radiographically, central variety of AOT appears as a well defined unilocular radiolucency with corticated/sclerotic borders.[1,7] Although multilocular cases have been reported by Tsaknis et al.[13] and Giansanti et al.[14] Follicular variant is associated with an unerupted tooth resembling a dentigerous cyst. Radio-opaque foci are seen present in the lesion which are usually small and are described as flocculent. AOT exhibits diverse histopathologic features. It is made up of multinodular proliferation of spinous, cuboidal and columnar cells in a variety of patterns comprising of scattered duct like structures, eosinophilic material and calcifications in several forms; delimited by a fibrous capsule of variable thickness. Distinctive feature of AOT is varying number of duct or pseudo ductular like structures with lumen of varying size, lined by a single layer cuboidal to columnar epithelial cells that have nuclei polarized away from the lumen. The lumen of these duct like structures is lined by eosinophilic rim of varying thickness (hyaline ring). Stellate reticulum like cells and polygonal cells dominate the tissue between the nodules. Small amounts of eosinophillic material or calcification may also be present between these cells.[7] Here we describe a case of AOT of follicular variety, affecting the left maxillary anterior region in a boy of 18 years of age. During this case study histochemical and immunohistochemical staining was done to visualize the nature of AOT as being hamartoma or a tumor with inductive capacity.

CASE REPORT

An 18 year old male patient reported with the chief complaint of swelling in the upper left front region of jaw since two months. The swelling was slowly progressive and gradually increased in size to the present size of 3cm x 2cm, that resulted in facial asymmetry and obliteration of nasolabial fold. On palpation the swelling was bony hard in consistency and non tender in nature. There was no history of associated pain, discharge or neurological deficit. Intraorally, on examination, a well circumscribed swelling was seen involving buccal aspect of left upper maxillary region resulting in obliteration of muccobuccal fold and the buccal vestibule. Oral mucosa over the affected area was smooth. Hard tissue examination revealed missing left maxillary canine.

Radiographic examination showed a well defined unilocular radiolucent lesion with an impacted maxillary canine, causing root divergence of the adjacent lateral incisor. Within the radiolucency were seen some radio-opaque foci. Thinning and expansion of the cortical bone was also seen. A provisional diagnosis of an odontogenic tumor was made.

Enucleation of the lesion under local anesthesia was done. Grossly it was a globular mass which was brownish in color measuring approximately 2.5 cm x 2cm and having a smooth and uniform outer surface. It was associated with a well developed impacted canine (Figure 1)

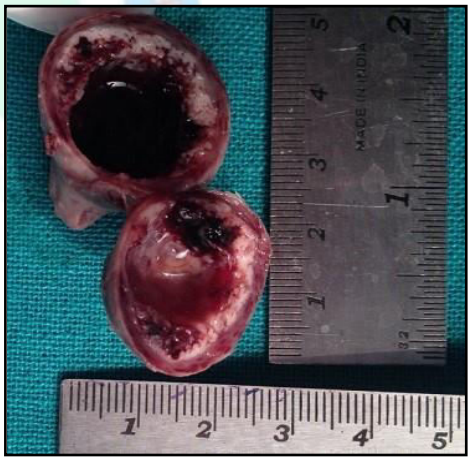

Figure 1: Gross specimen cut into two longitudinally, showing intramural nodules with chocolate colored fluid, along with an impacted canine.

Microscopic examination showed multisized solid nodules of cuboidal or columnar epithelial cells forming ducts, nests or rosette like structures with minimal stromal connective tissue (Figure 2 inset). Spindle-shaped and polygonal epithelial cells with dark eosinophilic cytoplasm and round hyperchromatic nuclei were seen in the spaces between the epithelial nodules. At places, the

central space of rosette like structures contained small amount of eosinophilic material (Figure 2). Scattered throughout the lesion were duct like structures, the lumen of which was lined by a single row of columnar to cuboidal cells with nucleus polarized away from the lumen (Figure 3). Uncalcified eosinophilic amorphous masses were present extracellulary in the form of tumor droplets. One end of section shows fibrous capsule around the tumor. A final diagnosis of Adenomatoid odontogenic tumor was reached at.

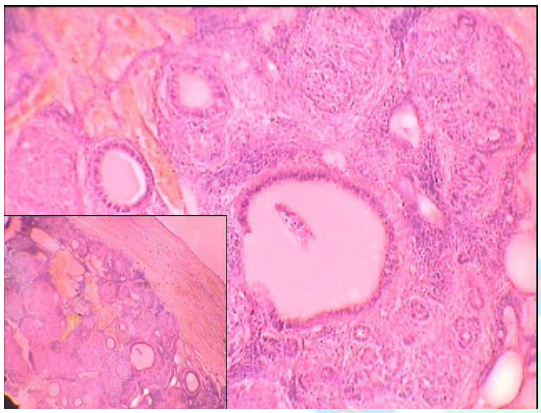

Figure 2: Multisized solid nodules of cuboidal or columnar epithelial cells forming rosette and duct like structures containing eosinophilic material. Spindle-shaped and polygonal cells are seen in spaces between the nodules. (H & E, X10 with inset of X4)

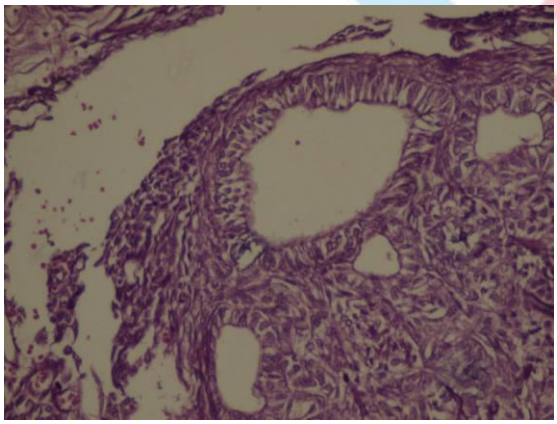

Figure 3: Odontogenic epithelial cells showing ductular pattern along with adjacent cells arranged in sheets (H& E, X 40)

Histochemical staining with Periodic Acid Schiff reagent(PAS) (Figure 4) and Masson's trichrome (Figure 5) and immunohistochemical staining with laminin (Figure 6) was done to know the nature of AOT, of being a hamartoma showing metaplastic properties or tumor with inductive ability. The luminal rim in the ducts and rosettes and eosinophilic tumor droplets present within the epithelial cells showed positivity for PAS, Masson trichrome and laminin.

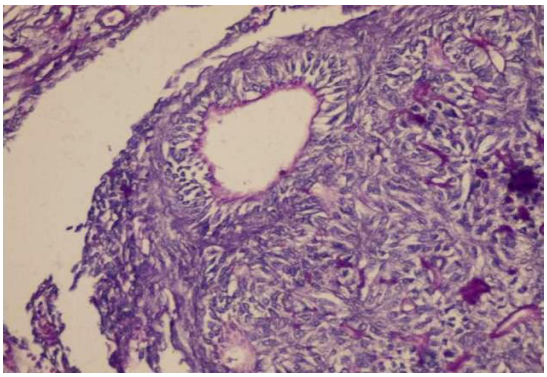

Figure 4: Pseudo-ductular structures lined on the luminal aspect by eosinophilic material and tumour droplets amongst sheets of spindled epithelial cells showing positivity (PAS, X40).

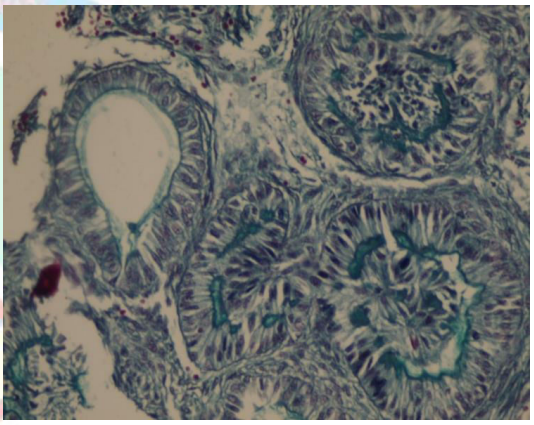

Figure 5: Luminal rims of AOT ductular pattern showing a bright green colour. The basement membrane material in the rosettes stained a similar colour (Masson's trichrome, X40).

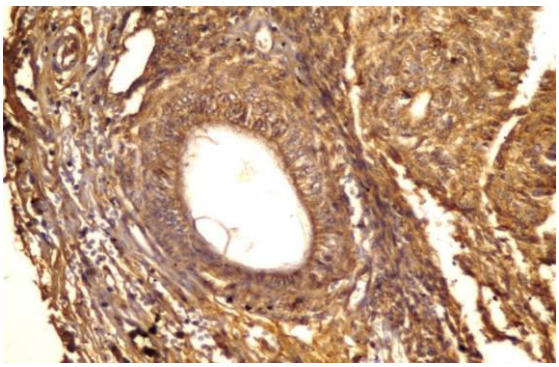

Figure 6: Pseudo-ductular structure showing positivity for laminin stain forming a luminal rim.(IHC, Laminin, X40)

DISCUSSION

In order to conceptualize a unified source of origin for the diverse location of AOT, one has to look to odontogenic epithelium with a widespread occurrence in the jaws. To this requirement, only dental lamina complex and its remnants match.[12]

Disintegration of complex system of dental lamina gives rise to numerous epithelial remnants persisting in the jaw bones and in the gingiva after odontogenesis. Significantly these epithelial remnants are not haphazardly distributed, but confined to the soft tissue of gubernaculum dentis (GD). The GD is composed of fibrous connective tissue and runs in intrabony or through gubernacular canals, which connect the bony crypts of the developing permanent teeth with lamina propria of gingiva. GD is believed to guide or direct the course of erupting permanent teeth.[12]

Odontogenic tumors are said to recapitulate dental ontogeny and may show histologic evidence of reciprocal induction. It is a widely accepted fact that inductive process in odontogenic tumors follows the same principles as established in normal odontogenesis i.e. induction of ectomesenchyme should precede epithelial proliferation and dentine deposition and which in turn should precede enamel deposition. During first stage of odontogenesis, ectomesenchyme induces the overlying oral ectoderm to change and form the primary epithelial band which then forms the tooth buds. Cells of inner enamel epithelium induces cells of neighboring dental papilla to differentiate into dentine secreting odontoblasts with help of various growth factors. This results in epithelio-mesenchymal signaling leading to the terminal differentiation of odontoblasts. When dentine secretion begins, it induces inner enamel epithelium to differentiate into ameloblast to produce enamel matrix. This process shows reciprocal induction.[5,15]

It has been found that epithelial cells of inner enamel epithelium express and secrete a variety of growth factors, viz. TGF-β1, BMP-2, insulin like GF's.[15] On the other hand, the ectomesenchymal cells of the dental papilla can only become competent once a precise number of cell divisions have occurred. Thereafter they are able to express the specific cell surface receptors to enable them to respond to the growth factors.

Such complex and similar epithelio-mesenchymal interactions lead to proliferation of epithelial and ectomesenchyme in OTs such as Ameloblastic fibroma. While in some other cases the process of induction process further advances into deposition of dentinoid or even tubular dentine such as in Ameloblastic fibrodentinoma or even production of enamel or enameloid matrix as in Ameloblastic fibro-odontoma and finally resulting in formation of tooth like structures as in odontome. This newly formed dental matrix material resembles odontogenic epithelium which is characterized of tall columnar cells resembling ameloblasts/odontoblasts.

According to recent researches doubts have been cast regarding the inductive nature of AOT. Condensation or proliferation of ectomesenchyme has never been demonstrated. Infact the mesenchymal component in AOT is extremely scanty, especially where the epithelium is present in solid sheets with rosette and pseudo ductular structures. In addition Gao et al[16] have failed to demonstrate the presence of bone morphogenic proteins (BMP's) in AOT, citing this as evidence of the lack of an inductive influence. These doubts as to the existence of an inductive influence has led Philipsen and Reichart[6] to argue for a reclassification of AOT as an epithelial odontogenic tumor without induction. They have postulated that the dental matrix material is manifested not as an inductive but as a metaplastic process but have not been able to provide evidence to support this contention.[5]

AOT contains four types of cells namely polygonal, flat, star/stellate shaped and cuboidal. This arrangement of cells resemble that of enamel organ comprising of inner enamel epithelium, stratum intermedium, stellate reticulum, outer enamel epithelium. Tumor cells lining the duct like structures and small eosinophilic areas seem to be comparable to ameloblasts of differentiating stages. Recently Murata et al[19] showed evidence of synchronized biosynthesis and secretions of enamel proteins and extracellular matrix molecules by AOT cells, which also occur in normal odontogenesis. The simultaneous retention of enamel proteins and extra cellular matrix material in the duct like structures and stromal spaces of AOT suggests that they play an important role in the formation of duct like structures. Also Lee[17], El labban[18] and Murata et al[19] noted that the co-localization of basement membrane associated macromolecules as type IV collagen, laminin, fibronectin and type V collagen in the luminal space of the pseudo cystic structures is

basically similar to immunolocalisation of above molecules in lamina basalis ameloblastica. This fact suggests that AOT cells have the ability to synthesize molecules as pre-ameloblasts do.

The central focus in the present article has been on eosinophilic droplets, and eosinophilic material in the duct like structures. The focus of our attention is whether histologic evidence of induction in this so called hamartoma having occurred exists.

In the present case study, the pseudoductular structures stained positive for laminin which is a marker for basement membrane integrity. Laminin demonstrates large exta-cellular matrix glycoproteins present in the basement membrane of epithelia. Accordng to Crivelini et al[20] H & E staining of AOT specimens was found to contain light and dark eosinophil staining areas. The light eosinophilic areas lining the luminal aspect of adenomatoid structures and also present as small intercellular deposits was found positive for laminin in the immunohistochemical analysis therefore representing substance of the basal membrane. While the dark eosinophilic areas present as intercellular deposists were found negative for laminin and was prone to mineralization and probably corresponded to the material positive to enamel protein in the study of Takata et al.[21,22] Crevileni et al[20] in their study also showed the positivity for CK-14 (in the cords of cubic and peripheral polyhedrical cells, as well as in the fusiform and stellated cells adjacent to the solid areas of the tumor), PCNA (in solid tubules, duct like structures and adenomatoid structures), collagen IV (in the zone of the basal membrane of a few tumors).

Also certain histochemical stains like PAS and Masson trichrome were done in the present study to know whether induction exists in AOT. PAS is a stain used to demonstrate neutral polysaccharides that are present in the basement membrane and also stains mucous substances secreted from the epithelium of organs.[23]

In our case PAS positivity was found in the pseudo-ductular structure as a luminal ring and also the tumor droplets which were found scattered in the sheets of the spindled and polygonal epithelial cells. According to the study of Vibha Jivan[5] in AOT specimens, PAS positive material was extensively distributed extracellulary throughout the epithelium. PAS positive material was also present in pseudo-ductular structures as a luminal rim and as basement membrane material outlining the rosettes, which was in concordance with our study. The large eosinophilic globules of dental matrix material also stained intensely positively with the PAS stain, as did the areas showing a calcospherite-like pattern of mineralization.

Apart from this positivity for the eosinophilic material in the pseudoductular structures of AOT specimen was also seen for other histochemical stains namely, Alcian blue, Von Gieson, Congo Red, Reticulin, Mucicarmine, Masson's Trichrome. Masson's Trichrome is a connective tissue stain used for staining of collagen fibers, fibrin, muscles and RBC's.[23] In our case the inner aspect of duct like structure stained positively with this stain forming a luminal rim. The basement membrane material in the rosettes also satined positive for the same. This finding is supported by the histochemical study of Vibha Jivan.[5]

Against this hypothesis is that, many other histochemical stains such as Alcian blue, Reticulin, Mucicarmine, Von Gieson also stained the luminal aspect of the duct like structures forming a luminal rim. It is therefore possible that the deposits on the inner aspects of the pseudo-ductular structures present an 'edge' artefact.[5] It is highly unlikely that one substance regardless of what it may be will stain positively with such a diversity of histochemical stains.

According to the study conducted by Shear[24], the so called 'ducts' represented the invaginations of odontogenic epithelium that carried with them ectomesenchymal stroma and that much of stroma cut off from it's blood supply underwent atrophy or necrosis while surviving stroma, mostly at the periphery of pseudo ductular structures, retained it's inductive capacity and induced columnar cells to lay down pre-dentine matrix. To support this he demonstrated reticulin fibers as well as toulidene blue metachromasia on inner aspect of duct like structures, concluding the evidence of presence of ectomesenchyme. In contraindication to this, alcian blue stain by Vibha Jivan[5], failed to demonstrate any alcianophilic material that could have been interpreted as representing induced ectomesenchyme. This lack of mesenchymal component in between the epithelial cells was confirmed with vimentin immunohistochemistry, when no positive cells were identified.

Lack of visible ectomesenchymal component does not mean that induction has not occurred. It is

hypothesized that having completed its function the ectomesenchyme disappears. Certainly there are other examples of odontogenic tumors characterised by induction of dentinoid in which no ectomesenchymal presence can be determined. A case of ameloblastoma with dentinoid induction has been described to support this .[25]

CONCLUSION

In the present case study, an attempt has been made to conceptualize the nature and classification of AOT as an inductive tumor or a hamartoma with metaplastic mineralization. Further studies with large sample size and more histochemical and immune-histochemical stains will be necessary to arrive at a conclusion in classifying AOT.

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