Adenomatoid odontogenic tumor (AOT) is a relatively rare benign epithelial tumor of odontogenic origin. There is varying class of thoughts contemplating this lesion to be a hamartoma or neoplastic growth of odontogenic epithelium. Controversy regarding the histogenesis of the lesion is plentiful in earlier literature. The recent advent of immunohistochemical and ultrastructural studies has aided in throwing light on the tissue of origin of this tumor. This review aims at understanding the evolving concepts of histogenesis of AOT to better understand the biological behavior of the lesion. The review of AOT was carried out using PubMed and Google Scholar databases and 39 articles from the year 2001 to 2016 which contributed to the histogenesis of AOT were included for review. Since the origin of the cystic lining is similar to a reduced enamel epithelium and not the dental lamina, we propose the former to be the progenitor of AOT. Furthermore, we consider extra-follicular, as well as peripheral AOTs, originate from the remnants of Hertwig's epithelial root sheath (epithelial rests of Malassez), which complies with the common histology for all these variants.

KEYWORDS: Adenomatoid odontogenic tumor, Odontogenic tumor, Histogenesis.
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Author/year</th>
<th>Age Gender</th>
<th>Site</th>
<th>Clinical features</th>
<th>Histopathological features</th>
<th>Special investigations</th>
<th>Concept proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Takahashi et al. 2001 [14]</td>
<td>22 years old male</td>
<td>Maxilla</td>
<td>Lesion expanding to sinus</td>
<td>-</td>
<td>Positive staining for iron-binding proteins (transferring, ferritin) and proteinase inhibitor (alpha-one-antitrypsin) in various cells of AOT indicating their role to the pathogenesis of AOT.</td>
<td>Detected the neoplastic nature of AOT by immunohistochemistry.</td>
</tr>
<tr>
<td>2.</td>
<td>Crivelini et al. [15]</td>
<td>Archival blocks used</td>
<td>Lesion expanding to sinus</td>
<td>Positive staining for iron-binding proteins (transferring, ferritin) and proteinase inhibitor (alpha-one-antitrypsin) in various cells of AOT indicating their role to the pathogenesis of AOT.</td>
<td>-</td>
<td>Detected the neoplastic nature of AOT by immunohistochemistry.</td>
<td>Adopted the hypothesis of AOT being a simple hamartoma, whose histogenesis would be related to the reduced enamel epithelium.</td>
</tr>
<tr>
<td>4.</td>
<td>Handschel et al. 2005 [36]</td>
<td>23 years old male</td>
<td>Right mandibular canine region</td>
<td>Associated with an impacted canine</td>
<td>Well defined radiolucency, root resorption</td>
<td></td>
<td>Rare case with respect to the age of the patient and the localization of the AOT in the lower jaw.</td>
</tr>
<tr>
<td>5.</td>
<td>Motamedi et al. 2005 [37]</td>
<td>13 years old female</td>
<td>Left mandibular canine region</td>
<td>Associated with an impacted canine</td>
<td>Well defined radiolucency</td>
<td></td>
<td>Describes the treatment of an impacted mandibular canine associated with an AOT.</td>
</tr>
<tr>
<td>6.</td>
<td>Nigam et al. 2005 [38]</td>
<td>15 years old female</td>
<td>Left maxillary incisor to pre-molar region</td>
<td>Associated with an impacted canine</td>
<td>Well defined radiolucency</td>
<td></td>
<td>Suggested that AOT should be considered in the differential diagnosis of radiolucent jaw swellings.</td>
</tr>
<tr>
<td>8.</td>
<td>Vera Sempere et al. 2006 [40]</td>
<td>9 years old female</td>
<td>Left mandibular canine region</td>
<td>Associated with an impacted canine</td>
<td>Well defined radiolucency</td>
<td></td>
<td>Excluded a possible hormone dependence in AOT that could explain the observed female predominance.</td>
</tr>
<tr>
<td>9.</td>
<td>Nonaka et al. 2007 [41]</td>
<td>13 years old female</td>
<td>Left maxillary canine to pre-molar region</td>
<td>Associated with an impacted canine</td>
<td>Well defined radiolucency with radiopaque areas</td>
<td></td>
<td>AOT associated with dentigerous cyst.</td>
</tr>
<tr>
<td>11.</td>
<td>Jiran et al. 2007 [42]</td>
<td>40 years old male</td>
<td>Right mandibular premolar to molar region</td>
<td>No associated impacted teeth</td>
<td>Well defined radiolucency with root resorption</td>
<td></td>
<td>They suggested (AOT) to originate from the reduced enamel epithelium of the dental follicle.</td>
</tr>
</tbody>
</table>

Table 1: Histogenesis of AOT

(Contd...)

<table>
<thead>
<tr>
<th>S. No.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>12.</td>
<td>Santos et al. 2008 [43]</td>
<td>22 years old male</td>
<td>Left anterior maxilla</td>
<td>No associated impacted tooth. No associated impacted teeth</td>
<td>Odontogenic epithelium with oval, angular, elongated cells forming a cribriform pattern</td>
<td>Unilocular radiolucency</td>
<td>Unusual presentation was a cribriform pattern in AOT. Described it as Adenomatoid dentinoma.</td>
</tr>
<tr>
<td>13.</td>
<td>Kemp et al. 2008 [44]</td>
<td>15 years old male</td>
<td>Left mandibular molar region</td>
<td>Associated with impacted canine. Unusual rapid growth</td>
<td>Sheets of the spindle and epithelial cells, duct-like spaces, areas of amorphous calcification</td>
<td>Unilocular radiolucency with radiopaque foci</td>
<td>Supported its aggressive and neoplastic nature.</td>
</tr>
<tr>
<td>15.</td>
<td>Fredrich et al. 2009 [18]</td>
<td>16 years old male</td>
<td>Left maxillary alveolar region</td>
<td>Peripheral strand of smaller cells which form net-like proliferations</td>
<td>Immunoreactivity for cytokeratins, vimentin, and p63, and was focally immunoreactive for alpha-smooth muscle actin and epithelial membrane antigen</td>
<td>Adenomatoid odontogenic tumor of maxillary sinus, and pointed its neoplastic and aggressive nature.</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Carlos-Bregni 2009 [45]</td>
<td>19 years old female</td>
<td>Left mandibular molar region</td>
<td>No associated impacted teeth</td>
<td>Cuboidal cells resembling ameloblasts and stellate reticulum, the presence of enamel matrix overlying dentin</td>
<td>Unilocular radiolucency</td>
<td>Suggested (AOT) to originate from the reduced enamel epithelium of the dental follicle.</td>
</tr>
<tr>
<td>17.</td>
<td>Carlos-Bregni 2009 [45]</td>
<td>13 years old female</td>
<td>Left mandibular molar region</td>
<td>No associated impacted teeth</td>
<td>Globular dentin, enamel matrix, stellate reticulum, odontogenic epithelium</td>
<td>Unilocular radiolucency</td>
<td>Supported the benign behavior of this hamartomatous tumor AOT developing together with a cystic complex odontoma.</td>
</tr>
<tr>
<td>20.</td>
<td>Yilmaz et al. 2009 [19]</td>
<td>15 years old female</td>
<td>Mandibular anterior region</td>
<td>No associated impacted teeth</td>
<td>Ameoblast-like cells forming duct-like structures, eosinophilic droplets, and odontogenic calcifications</td>
<td>Periapical radiolucency with fine calcifications</td>
<td>Extrafollicular variant, with slow-growing and symptomless pattern</td>
</tr>
<tr>
<td>22.</td>
<td>Phillips et al. 2010 [17]</td>
<td>16 years old male</td>
<td>maxilla</td>
<td>Swelling with the associated impacted tooth.</td>
<td>Odontogenic epithelium in duct-like pattern, eosinophilic coagulum</td>
<td>Well defined unilocular radiolucency</td>
<td>Rare subvariant of the extrafollicular type of AOT mimicking periapical disease radiographically.</td>
</tr>
<tr>
<td>23.</td>
<td>Tejasvi et al. 2010 [18]</td>
<td>15 years old male</td>
<td>Left maxillary incisor region</td>
<td>No associated impacted teeth</td>
<td>Whorls, rosettes, and duct-like pattern of epithelial cells with calcification</td>
<td>Well defined unilocular corticated radiolucency</td>
<td>AOT associated with a dentigerous cyst in the posterior maxilla.</td>
</tr>
<tr>
<td>S. No.</td>
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<tr>
<td>25.</td>
<td>Soares et al. 2011 [19]</td>
<td>2 years old female</td>
<td>Maxilla</td>
<td>slow-growing swelling in the maxillary region</td>
<td>Solid nodules, whorls, and rosettes pattern with eosinophilic material and areas of abortive enamel. Nests of ghost epithelial cells found in the lining of an ameloblastomatous epithelium.</td>
<td>Large unilocular radiolucency with multiple radiopaque clusters and a well-demarcated radiopaque border immunohistochemically positive for Bcl-2 and estrogen receptor.</td>
<td>Areas of CCOT with abortive enamel formation. AOT associated with CCOT termed as hybrid tumor.</td>
</tr>
<tr>
<td>29.</td>
<td>Li et al. 2013 [50]</td>
<td>22 years old female</td>
<td>Swelling of the right maxilla</td>
<td>Associated with missing tooth</td>
<td>Cystic lesion surrounded by prominent fibro-osseous reaction corresponding to ossicles and cementicles.</td>
<td>Large unilocular radiolucency</td>
<td>AOT with solid portion showing calcified spherules characteristic of ossifying fibroma AOT associated with odontoma.</td>
</tr>
<tr>
<td>30.</td>
<td>Gomez et al. 2013 [51]</td>
<td>32 years old male</td>
<td>Left posterior mandible</td>
<td>Expansion of the retromolar trigone</td>
<td>Solid areas formed by dentin with lacunar borders lined by ameloblast-like cells with areas showing enamel matrix-like appearance odontogenic islands in the form of rosette-like structures.</td>
<td>Unilocularity of dense tumor</td>
<td>Extracapsular central variant of AOT</td>
</tr>
<tr>
<td>31.</td>
<td>Prakasam et al. 2013 [25]</td>
<td>19 years old female</td>
<td>Maxilla</td>
<td>Swelling and displacement of teeth</td>
<td>Columnar cells in the form of nests and rosette-like structures, with eosinophilic amorphous material “tumor droplets.” Connective tissue showed clear cell changes.</td>
<td>Well-defined intrabony radiolucency with sclerotic margins. diastase digestion PAS positive. Glycogen content done for clear cell change.</td>
<td>Clear cell change can be an indication of the process of cellular degeneration or its odontogenic epithelial origin concomitant occurrence of AOT, dentigerous cyst and CEOT.</td>
</tr>
<tr>
<td>32.</td>
<td>Mohanty et al. 2014 [17]</td>
<td>20 years old male</td>
<td>Left maxilla</td>
<td>Buccal and palatal cortical plate expansion.</td>
<td>Cystic epithelium resembling reduced enamel epithelium, rosette-like structures about a central space containing eosinophilia material</td>
<td>Well-demarcated, unilocular radiolucencies corresponding to that of a follicular (pericoronal) type of AOT. Unilocular, well-delimited radiolucency with a suggestive image of peripheral opaque bone condensation</td>
<td>Suggested that all AOTs begin as a cyst derived from either REE or HERS.</td>
</tr>
<tr>
<td>33.</td>
<td>Rathod et al. 2014 [26]</td>
<td>13 years old male</td>
<td>Mandible</td>
<td>Associated with an impacted tooth</td>
<td>Intranulomonal proliferation of the epithelium, with polarized nuclei with rosette and spiral pattern and structures resembling ducts</td>
<td>Well-defined radiolucency with sclerotic rim</td>
<td>Adenomatoid odontogenic tumor in a pediatric patient.</td>
</tr>
<tr>
<td>34.</td>
<td>Bonardi et al. 2015 [27]</td>
<td>7 years old female</td>
<td>Mandible</td>
<td>Associated with an impacted tooth</td>
<td>Cystic epithelium resembling reduced enamel epithelium, rosette-like structures about a central space containing eosinophilia material</td>
<td>Large unilocular radiolucency with multiple radiopaque clusters and a well-demarcated radiopaque border immunohistochemically positive reaction for Bcl-2 and estrogen receptor.</td>
<td>AOT enlargement during pregnancy.</td>
</tr>
<tr>
<td>35.</td>
<td>Grover et al. 2015 [28]</td>
<td>14 years old male</td>
<td>Left maxillary region</td>
<td>Firm, non-tender swelling, associated with impacted maxillary canine</td>
<td>Large unilocular radiolucency with multiple radiopaque clusters and a well-demarcated radiopaque border immunohistochemically positive reaction for Bcl-2 and estrogen receptor.</td>
<td>Unilocular radiolucency, root resorption</td>
<td>Tumor-associated with a dentigerous cyst in a pediatric patient.</td>
</tr>
</tbody>
</table>
found that AOTs are monoclonal and, therefore, neoplastic [59]. Certain characters or features of AOT which suggest it to be true neoplasm or hamartoma as stated by various authors

**Neoplasm**

Small size and probable early detection and it’s removable before this slow-growing neoplasm reach considerable size [9]. Microscopic features show the greater difference from normal odontogenic apparatus than would have seen in a developmental anomaly [54]. It has been stated that many cases have gone undetected and untreated for many years due to their size and ultimately resulted in facial asymmetry and distortion. Using a human androgen receptor gene polymorphism assay, Gomes et al. found that AOTs are monoclonal and, therefore, neoplastic [60-63].

**Hamartoma**

In 2004, Rick stated that the limited size of AOT, its minimal growth potential, and the lack of recurrence even after incomplete removal attributed to its hamartomatous nature [6]. Low expression of BCL2 and Ki67 activity compared to ameloblastoma [58]. Medeiros et al. in 2005 conducted a study where they used proliferating cell nuclear antigen (marker for mitosis activity) and F53 (marker that indicates proliferative and anti-apoptotic activities) in AOT cases and found that IHC markers were very low thus they stated AOT as hamartoma rather than tumor [58,64].

**Histogenesis of AOT**

The origin of AOT is from the odontogenic epithelium; this fact is well established; however, the progenitor cell or tissue is not yet settled and still under discussion. The suggested cells by various authors are enamel organ [65,66], reduced enamel epithelium (REE) [67], undifferentiated odontogenic epithelium or stratum intermedium cells [68], stratum intermedium cells [69,70], and dental lamina and its remains (Philipsen and Reichart, 1999, Philipsen et al, 1992) [15].

Electron microscopic studies of duct-like structures formed within the tumor revealed the presence of hemidesmosomal junctions and evidence of basal lamina at the luminal pole of these cells. They also show secretory granules and coated vesicles near the luminal pole which are suggestive of a morphology similar to pre-ameloblasts. The eosinophilic material coexpressed basement membrane extracellular matrix proteins such as laminin, type IV collagen, heparin sulfate proteoglycan, fibronectin, and also enamel matrix proteins [71,72]. Furthermore, these cells are negative reactivity of these cells to lactoferrin and α1-antichymotrypsin anti-bodies which rule out glandular origin [14].

The non-duct-forming columnar cells expressed amelogenin reactivity, whereas the duct-forming cells showed no reactivity to amelogenin [7] or the other enamel matrix protein (enamelin and sheathlin) antibodies [73-75]. The ultrastructural studies show that the small, irregular calcifications may be partially composed of atypical enamel matrix proteins such as laminin, type IV collagen, heparin sulfate proteoglycan, fibronectin, and also enamel matrix proteins [71,72]. The non-ameloblasts are yet metabolically active enough to produce basement membrane and enamel matrix proteins [78]. It is theorized as a neoplastic growth of odontogenic epithelium. Glickman et al. drew an inference by saying that “such a controversy is irresolvable because sound arguments can be advanced in favor of and against both hypotheses. The arguments are based on personal bias rather than on scientific evidence” [8,57].
that the accumulation and subsequent degradation of these enamel secretary products by enzymes such as enamelysin are responsible for the development of the duct-like structures [71]. These structures are in fact enclosed spherical microcysts and their nature whether completely intraepithelial or stromal is debatable [79].

The tumor may be partly cystic, and in some cases, the solid lesion may be present only as masses in the wall of a large cyst. It is generally believed that the lesion is not a neoplasm [80,81].

Although the definition states that the lesion may have a cystic nature, very few case reports have described the cystic lining. Cystic presentation of AOT has been reported way back in 1915 by Harbitz who reported the lesion as “cystic adamantoma” [82].

Philipsen et al. have strongly argued in favor of the concept of AOT being derived from the complex system of the dental lamina or its remnants [11]. Marx and Stern considered AOT as a cyst and not a tumor and further gave a new terminology for this lesion, “adenomatoid odontogenic cyst (ADC).” Marx and Stern proposed that AOTs should not be considered tumors but cysts with a hamartomatous intraluminal proliferation of epithelial cells derived from the Hertwig’s epithelial root sheath (HERS) [9]. However, Rick stated that AOTs were benign embryonal neoplasms; he disagreed with the change in terminology as the majority of lesions have a predominantly solid component instead of a fluid-filled cavity. According to Marx and Stern, the AOC does not arise from the follicle of the tooth crown but instead arises from HERS, which would explain the finding of the tooth being completely within the lumen rather than the tooth root being within a bony crypt.

Considering all the case reports of AOT associated with dentigerous cyst, it is very much evident that the tumor is originating from the cystic lining. Moreover, the WHO definition of AOT given by Philipsen et al supports this fact of cystic lining to be the progenitor for tumor in many cases. Since the origin of the cystic lining in the dentigerous cyst is REE and not the dental lamina, we propose the former to be the progenitor of AOT.

IHC, it has been shown that the immunophenotypic profile of REE and AOT epithelium is virtually identical [83]. The expression of CK14 and the ultrastructural aspects of the AOT probably indicated its origin in the reduced dental epithelium [83]. Where CK14 showed expression in the cells which were between the spindled and duct-like structures, these structures formed a cell group comparable to post-secretory ameloblasts of the REE, which was surrounded by a second group, composed of flat fusiform cells, which was similar to that of stellate reticulum. This justifies the expression in all epithelial cell elements of other AOTs and the REE, regardless of the histological characteristics [15]. Laminin was clearly present in the luminal surface of the adenomatoid structures and the lighter eosinophilic intercellular deposits, either focal or linear, which is compatible with the surface of the REE during the protective stage of amelogenesis. Nevertheless, the authors believed that some cells of AOT (cribriform areas) would resemble dental lamina (primitive cell), while others would represent histodifferentially more mature secretory phase of odontogenesis [15].

CONCLUSION

In classical AOT (solid), the proliferation of nodules originating from the cystic lining fills up the entire lumen whereas in cystic variant this process is incomplete and is thus seen only in parts of the cystic lining. Since the origin of the cystic lining is similar to a REE and not the dental lamina, we propose the former to be the progenitor of AOT. Furthermore, we consider extra-follicular, as well as peripheral AOTs, originate from the remnants of HERS (epithelial rests of Malassez), which complies with the common histology for all these variants [28].

AUTHOR’S CONTRIBUTION

Sahanaz P. Ahmed:Compiled full literature search and drafted the manuscript. Arulmozi Nandakumar: Developed the standards of manuscript. Ramya Ramadas: Supervised the manuscript making, and edited the manuscript. Karunya Krishnakumar: Provided guidance in the preparation of the manuscript.

CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interest.

REFERENCES

Adenomatoid dentinoma or

49. Agarwal A, Giri KY, Alam S. The interrelationship of adenomatoid

47. Martínez A, Mosqueda-Taylor A, Marchesani FJ, Brethauer U,

46. Ide F. Inter-radicular adenomatoid odontogenic tumor of the anterior

45. Carlos-Bregni R, Vargas PA, Silva AR, de Miranda Chaves-Netto HD,

43. Santos JN, Lima FO, Romério P, Souza VF. Adenomatoid odontogenic

42. Jivan V, Altini M, Meer S, Mahomed F. Adenomatoid odontogenic

39. Vargas PA, Carlos-Bregni R, Mosqueda-Taylor A, Cuairan-Ruidíaz V,

38. Nigam S, Gupta SK, Chaturvedi KU. Adenomatoid odontogenic tumor

36. Handschel JG, Depprich RA, Zimmermann AC, Braunstein S,

33. Siwach P, Joy T, Tupkari J, Thakur A. Controversies in odontogenic

31. Hemalatha AL, Shobha SN, Raghuveer CR, Sahni S, Kumari A.

29. Manjunatha BS, Harsh A, Purohit S, Naga MV. Adenomatoid

27. Bonardi JP, da Costa FH, Matheus RA, Ito FA, Pereira-Stabile CL. Rare

25. Prakasam M, Tiwari S, Satpathy M, Banda VR. Adenomatoid

20. Tatemoto Y, Tanaka T, Okada Y, Mori M. Adenomatoid odontogenic

19. Handschel JG, Depprich RA, Zimmermann AC, Braunstein S,

18. Godtcheva IC, Atanasova TM, Vrakas GI, Tanev M. Clinicopathological

17. Schlosnagle DC, Someren A. The ultrastructure of the adenomatoid

16. Hatakeyama S, Suzuki A. Ultrastructural study of adenomatoid


Index entries:


Adenomatoid odontogenic tumour with features of calcifying epithelial odontogenic tumour. (The so-called combined epithelial odontogenic tumour: clinicopathological report of 12 cases. Eur J Cancer B Oral Oncol 1993;29B:221-4.


Adenomatoid odontogenic tumour with features of calcifying epithelial odontogenic tumour. (The so-called combined epithelial odontogenic tumour: clinicopathological report of 12 cases. Eur J Cancer B Oral Oncol 1993;29B:221-4.


76. El-Labban NG. The nature of the eosinophilic and laminated masses in
the adenomatoid odontogenic tumor: A histochemical and ultrastructural
77. Yamamoto H, Kozawa Y, Hirai G, Hagiwara T, Nakamura T.
Adenomatoid odontogenic tumor: Light and electron microscopic
78. Nanci A. Ten Cate’s Oral Histology-E-Book: Development, Structure,
79. do Carmo MA, Silva EC. Argyrophilic nucleolar organizer regions
(AgNORs) in ameloblastomas and adenomatoid odontogenic tumours
80. Kramer IRH, Pindborg JJ, Shear M. Histological Typing of Odontogenic
81. Gadewar DR, Srikant N. Adenomatoid odontogenic tumour: Tumour
or a cyst, a histopathological support for the controversy. Int J Pediatr
82. Harbitz F. On cystic tumors of the maxilla, and especially on adamantine
cystadenomas (adamantomas). Dent Cosm 1915;57:1081-93.
83. Crivelini MM, de Araújo VC, de Sousa SO, de Araújo NS. Cytokeratins