ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 12, Issue 2, 2019

Online - 2455-3891
Print - 0974-2441

Review Article

A RECENT UPDATE ON HISTOGENESIS OF ADENOMATOID ODONTOGENIC TUMOR: A REVIEW

SAHANAZ P AHMED*, NANDAKUMAR ARULMOZHI, RAMADAS RAMYA, KRISHNAKUMAR KARUNYA

Department of Oral and Maxillofacial Pathology, SRM Dental College, Chennai, Tamil Nadu, India. Email: sahanaz.praveen87@gmail.com

Received: 13 July 2018, Revised and Accepted: 22 October 2018

ABSTRACT

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.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i2.28452

INTRODUCTION

Odontogenic tumors are defined as a spectrum of lesions ranging from benign and malignant neoplasms to dental hamartomas; formed generally in the same sequence as in normal tooth development and all arising from dental remnants, that is, derived either from epithelial, ectomesenchymal and/or mesenchymal elements of the tooth-forming apparatus [1]. Knowledge of the basic elementary characters of different odontogenic tumors such as site of occurrence, age distribution and radiographic appearance is important in arriving at a clinical differential diagnosis [2,3]. Odontogenic tumors like any other neoplasm can mimic its cell of origin histologically [2,4]. The epithelium contributing to odontogenic tumor may be derived from the pre/post functional dental lamina, basal cell layer of the gingival epithelium, dental papilla/follicle, and remnants in the periodontal ligaments [5,6].

Adenomatoid odontogenic tumor (AOT) is a relatively rare, deviant, hamartomatous, benign, epithelial lesion of odontogenic origin [7], and constitutes about 2–7% of odontogenic cysts and tumors combined [5]. The WHO classification of odontogenic tumors has defined AOT as being comprised of odontogenic epithelium in an array of histoarchitectural patterns, embedded in mature connective tissue stroma, and characterized by gradual but progressive growth [8] with generally no tendency of recurrence. AOT is generally intraosseous, primarily in the anterior maxilla; the lower and upper canine area has more affinity to this lesion; however, it can also be seen in peripheral locations. More commonly seen in young patients, females are affected twice as commonly as males with a ratio of 1:1.9 [9]. AOT is a non-invasive tumor and recurrence rate is very low [10]. Different types or variants of AOT are central (or intraosseous) variants which are further divided into follicular (or pericoronal) type and extrafollicular (or extracoronal) type and the peripheral (or gingival) variant (PAOT) [11]. AOT could remain intraosseous or peripheral in the jaw bones, depending on the spatial position of the tumor and associated tooth. In deeper impacted teeth, there would be more possibility of AOT to be intraosseous follicular or extrafollicular (in the case of tooth eruption) lesion. In tooth impactions next to the alveolar ridge, the tumor could occasionally involve the gingiva during or after the eruption process, which would justify the peripheral variant [12,13].

The review of AOT was carried out using PubMed and Google Scholar databases. The keywords used were (AOT, histogenesis, odontogenic tumors, and histology) and all articles were taken for initial evaluation. Review articles on AOT and case reports on other odontogenic tumors other than AOT were excluded from the search. We also excluded clinical trials and animal research. In the present review, we studied the following 39 articles from the year 2001 to 2016 which contributed to the histogenesis of AOT were included for review (Table 1) [8,12,14-19,25-32,35-51]. The earlier articles were excluded since no significant research on histogenesis was available before this year, and earlier concepts were already addressed in articles included for this study. The purpose of this review was to delineate the clinical, histopathological, and immunohistochemical (IHC) profile of AOT to aid its diagnosis and alleviate confusion between other tumors in this category.

There are legitimate reasons for characterizing and renaming an entity, and foremost among these is when it can be established that it behaves and can be managed differently from other members of its original group. In most cases, it will be recognized as having distinguishable histopathological features also [33]. Thus, it becomes a new clinicopathological entity. The extensive review of literature of AOT has been enlisted in Table 1. This was how the AOT emerged from the then variants of ameloblastomas [34].

WHY AOT WAS CLASSIFIED AS EPITHELIAL TUMOR?

Based on the classification of odontogenic tumors that are based on the inductive influences between epithelial and mesenchymal tissues during odontogenesis, AOT has been included in the epithelial category rather than the mixed group, despite the presence of abnormal hard tissue elements within the tumor [52,53]. This was supported in a recent IHC study that used bone morphogenetic protein (BMP) to divide odontogenic tumors into those that were purely epithelial (i.e., negative for BMP) and those that formed hard tissue (i.e., positive for BMP) [54]. The epithelial component of this tumor is cellular where the pre-ameloblast like cells are arranged radially with interspersing spindle-shaped cells in some areas, whereas the other areas show epithelial cells which are arranged in interlacing strands resembling that of plexiform ameloblastomas [55,56].

Hamartoma or neoplasm

There is two class of thought, while some contemplate this lesion as a developmental outgrowth or hamartoma, other groups account them

Table 1: Histogenesis of AOT

S. No.	Author/year	Age Gender	Site	Clinical features	Histopathological features	Special investigations	Concept proposed
1.	Takahashi *et al* 2001 [14]	22 years old male	Maxilla	Lesion expanding to sinus	-	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.	Detected the neoplastic nature of AOT by immunohistochemistry.
2.	Crivelini *et al*. [15]	Archival blocks used	Paraffin sections of formalin-fixed tissue were used for both histological and immunohistochemical evaluation.	-	-	CK7 CK13 CK14 CK18 CK19 vimentin laminin collagen IV PCNA p53	Adopted the hypothesis of AOT being a simple hamartoma, whose histogenesis would be related to the reduced enamel epithelium
3.	Batra [16,35]	17 years old female	Right mandibular canine region	Associated with an impacted canine	Ductal lamina surrounded by epithelial cells filled with eosinophilic material	Well circumscribed radiolucency	A rare case of AOT in the lower jaw
4.	Handschel *et al*. 2005 [36]	23 years old male	Right mandibular canine region	Associated with an impacted canine	Whorles, sheets and plexiform arrangement of cells, duct-like structures with calcifications.	Unilocular radiolucency	Rare case with respect to the age of the patient and the localization of the AOT in the lower jaw.
5.	Motamedi *et al*. 2005 [37]	13 years old female	Left mandibular canine region	Associated with an impacted canine	Rosettes of spindle-shaped epithelial cells with duct-like structures	Well-defined radiolucency	Describes the treatment of an impacted mandibular canine associated with an AOT.
6.	Nigam *et al*. 2005 [38]	15 years old female	Left maxillary incisor to pre-molar region	Associated with an impacted canine	Nests, cords, and ducts of epithelial cells with eosinophilic amyloid-like material	Well defined radiolucency, root resorption	Suggested that AOT should be considered in the differential diagnosis of radiolucent jaw swellings.
7.	Vargas *et al*. (2006) [39]	16 years old male	Left mandibular region	Associated with an impacted canine	Odontogenic hard and soft tissues, similar to a dental germ was seen. Dental papilla and dentin were seen.	Well defined unilocular radiolucency with discrete areas of radiopacities	Proposed the term adenomatoid odontogenic hamartoma.
8.	Vera Sempere *et al*. 2006 [40]	9 years old female	Left mandibular canine region	Associated with an impacted canine	Whorled nests of odontogenic epithelium with calcified basophilic spherules, irregular hyaline, and amorphous deposits	nuclear positivity for p63, limited Ki-67 positivity, Absence of reactivity for hormonal receptors (RE and RPg)	AOT revealed a scant proliferative activity. Excluded a possible hormone dependence in AOT that could explain the observed female predominance.
9.	Nonaka *et al*. 2007 [41]	13 years old female	Left maxillary canine to pre-molar region	Associated with an impacted canine	Islands and sheets of globular cells with duct-like structures, amorphous eosinophilic material, and calcified areas	Well defined radiolucency with radiopaque areas	AOT associated with dentigerous cyst.
10.	Cawson *et al*. 2007 [12]	16 years old female	Left mandible	Associated with an impacted tooth	Rosettes of spindle-shaped epithelial cells with duct-like structures	Well defined radiolucency	Adenomatoid odontogenic tumor in the third molar region of the mandible.
11.	Jivan *et al*. 2007 [42]	40 years old male	Right mandibular premolar to molar region	No associated impacted teeth	Clusters and strands of cuboidal cells arranged in a lace-like pattern with hyaline material	Well defined radiolucency with root resorption	They suggested (AOT) to originate from the reduced enamel epithelium of the dental follicle

(*Contd...*)

Table 1: (*Continued*)

S. No.	Author/year	Age Gender	Site	Clinical features	Histopathological features	Special investigations	Concept proposed
12.	Santos *et al*. 2008 [43]	22 years old male	Left anterior maxilla	No associated impacted tooth.	Odontogenic epithelium with oval, angular, elongated cells forming a cribriform pattern	Unilocular radiolucency	Unusual presentation was a cribriform pattern in AOT.
13.	Kemp *et al*. 2008 [44]	15 years old male	Left mandibular molar region	No associated impacted teeth	Sheets of the spindle and epithelial cells, duct-like spaces, areas of amorphous calcification	Unilocular radiolucency with radiopaque foci	Described it as Adenomatoid dentinoma
14.	Garg *et al*. 2009 [8]	20 years old female	Right maxillary incisor premolar region	Associated with an impacted canine. unusual rapid growth	Cells arranged in whorl-like, ductular, ring-like, and ribbon-like patterns with bands of eosinophilic material	Ill-defined radiolucency with radiopaque foci.	Supported its aggressive and neoplastic nature.
15.	Fredrich *et al*. 2009 [18]	16 years old male	left maxillary alveolar region	Swelling associated with impacted canine	Peripheral strand of smaller cells which form net-like proliferations	immunoreactivity for cytokeratins, vimentin, and p63, and was focally immunoreactive for alpha-smooth muscle actin and epithelial membrane antigen	Adenomatoid odontogenic tumor of maxillary sinus, and pointed its neoplastic and aggressive nature.
16.	Carlos-Bregni 2009 [45]	19 years old female	Left mandibular molar region	No associated impacted teeth	Cuboidal cells resembling ameloblasts and stellate reticulum, the presence of enamel matrix overlying dentin	Unilocular radiolucency	Suggested (AOT) to originate from the reduced enamel epithelium of the dental follicle.
17.	Carlos-Bregni 2009 [45]	13 years old female	Left mandibular molar region	No associated impacted teeth	Globular dentin, enamel matrix, stellate reticulum, odontogenic epithelium	Unilocular radiolucency	
18.	Ide 2009 [46]	22 years old female	Right mandibular pre-molar region	No associated impacted teeth	Tubular and duct-like structures, globular calcifications	Unilocular radiolucency with snow-flake-like radiopacities	supported the benign behavior of this hamartomatous tumor
19.	Martínez *et al*. 2009 [47]	10 years old female	Left mandibular molar region	No associated impacted teeth	Rosette and duct-like structures with intercellular eosinophilic material, calcified masses of tubular dentin and dentinoid material with enamel matrix foci	Unilocular radiolucency with radiopaque mass	AOT developing together with a cystic complex odontoma
20.	Yilmas *et al*. 2009 [19]	15 years old female	Mandibular anterior region	No associated impacted teeth	Ameloblast like cells forming duct-like structures, eosinophilic droplets, and odontogenic calcifications	Periapical radiolucency with fine calcifications	Extrafollicular variant, with slow-growing and symptomless pattern
21.	Kothari *et al*. 2010 [16]	25 years old female (second trimester of pregnancy)	Maxilla	Firm swelling	Cystic lining component of reduced enamel epithelium continuous with a more basaloid appearing lining epithelium, with microcyst	well-defined oval radiolucency, loss of lamina dura	Adenomatoid odontogenic tumor mimicking a periapical cyst in pregnant woman
22.	Phillips *et al*. 2010 [17]	16 years old male	maxilla	Swelling with the associated impacted tooth.		well-defined oval radiolucency	Features of ameloblastic fibro-odontoma, calcifying odontogenic cyst seen with AOT.
23.	Tejasvi *et al*. 2010 [18]	15 years old male	Left maxillary incisor region	No associated impacted teeth	Odontogenic epithelium in duct-like pattern, eosinophilic coagulum	Well defined unilocular radiolucency	Rare subvariant of the extrafollicular type of AOT mimicking periapical disease radiographically.
24.	John *et al*. 2010 [12]	39 years old female	Left maxillary pre-molar to molar region	Associated with impacted molar tooth	Whorls, rosettes, and duct-like pattern of epithelial cells with calcification	Well defined unilocular corticated radiolucency	AOT associated with a dentigerous cyst in the posterior maxilla.

(*Contd*...)

Table 1: (*Continued*)

S. No.	Author/year	Age Gender	Site	Clinical features	Histopathological features	Special investigations	Concept proposed
25.	Soares *et al*. 2011 [19]	2 years old female.	Maxilla	slow-growing swelling in the maxillary region nontender.	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.	large unilocular radiolucency with multiple radiopaque clusters and a well-demarcated radiopaque border	Areas of CCOT with abortive enamel formation. AOT associated with CCOT termed as hybrid tumor.
26.	Sekia *et al*. 2011 [48]	21 years old female	Right maxillary incisor to molar region	Associated with an impacted canine	Pseudo-tubular structures, acidophilic hyaline-like material, dystrophic calcifications	immunohistochemically positive reaction for Bcl-2 and estrogen receptor	AOT enlargement during pregnancy.
27.	Agarwal *et al*. 2012 [49]	15 years old female	maxilla	Non-tender expansion of the left maxilla with missing canine tooth	solid nodules of columnar cells and spindle-shaped cells of odontogenic epithelium forming nests and rosette-like structures.	Unilocular radiolucency, root resorption	Tumor-associated with a dentigerous cyst in a pediatric patient.
28.	Laheji *et al*. 2012 [24]	13 years old male	Mandibular left the anterior region	Associated with missing tooth	Dentinoid-like deposits a Follicular variety of AOT, mimicking as a dentigerous cyst	Unilocular radiolucency, root resorption	Follicular variety of AOT, mimicking as a dentigerous cyst
29.	Li *et al*. 2013 [50]	22 years old female	Swelling of the right maxilla	Associated with missing tooth	Cystic lesion surrounded by prominent fibro-osseous reaction corresponding to ossicles and cementicles	large unilocular radiolucency	AOT with solid portion showing calcified spherules characteristic of ossifying fibroma
30.	Gomez *et al*. 2013 [51]	32 years old male	left posterior mandible	expansion of the retromolar trigone	solid areas formed by dentin with lacunar borders lined by ameloblast-like cells with areas showing enamel matrix-like appearance	Unilocularityofdense tumor.	AOT associated with odontoma.
31.	Prakasam *et al*. 2013 [25]	19 years old female	Maxilla	Swelling and displacement of teeth	odontogenic islands in the form of rosette-like structures.	Well-defined intrabony radiolucency with sclerotic margins.	Extrafollicular central variant of AOT
32.	Mohanty *et al*. 2014 [17]	20 years old female	left maxilla	Buccal and palatal cortical plate expansion.	Columnar cells in the form of nests and rosett-like structures, with eosinophilic amorphous material "tumor droplets." Connective tissue showed clear cell changes.	diastase digestion PAS positive. Glycogen content done for clear cell change.	Clear cell change can be an indication of the process of cellular degeneration or its odontogenic epithelial origin
33.	Rathod *et al*. 2014 [26]	13 years old male	Mandible	Associated with an impacted tooth		Well-demarcated, unilocular radiolucencies corresponding to that of a follicular (pericoronal) type of AOT.	concomitant occurrence of AOT, dentigerous cyst and CEOT.
34.	Bonardi *et al*. 2015 [27]	7 years old female	Mandible	Associated with an impacted tooth	intraluminal proliferation of the epithelium, with polarized nuclei with rosette and spiral pattern and structures resembling ducts	Unilocular, well-delimited radiolucency with a suggestive image of peripheral opaque bone condensation	adenomatoid odontogenic tumor in a pediatric patient.
35.	Grover *et al*. 2015 [28]	14 years old male	Left maxillary region	Firm, non-tender swelling, associated with impacted maxillary canine	cystic epithelium resembling reduced enamel epithelium, rosette-like structures about a central space containing eosinophilia material	Well defined radiolucency with sclerotic rim	Suggested that all AOTs begin as a cyst derived from either REE or HERS.

(*Contd*...)

Table 1: (*Continued*)

S. No.	Author/year	Age Gender	Site	Clinical features	Histopathological features	Special investigations	Concept proposed
36.	Manjunatha *et al*. 2015 [29]	20 years old female	Maxilla	Swelling on the palatal aspect, mild pain and associated with impacted tooth	Non-keratinized stratified squamous epithelial lining typical of dentigerous cyst, odontogenic epithelial cells arranged in clusters and adenoid pattern	Welldefined, unilocular radiolucent lesion	AOT associated with a dentigerous cyst, represents an odontogenic cyst with neoplastic transformation.
37.	Motamedi *et al*. 2015 [30]	15 years old female	Mandible	Associated with impacted tooth	Tumorous areas of the cavity wall showed the characteristic patterns of AOT histomorphology.	Well-demarcated, unilocular radiolucencies	Follicular (pericoronal) type of AOT believed to arise from a dentigerous cyst
38.	Hemalatha *et al* 2016 [31]	17 years old male	Maxilla	Diffuse swelling.	Tumor cells with scant cytoplasm, uniform nuclei, and bland chromatin. Intervening areas of homogenous hyaline material and calcified deposits	expansile radiolucent lesion with a well-defined radiosclerotic margin enwrapping a tooth within it.	Adenomatoid odontogenic tumor mimicking dentigerous cyst
39.	Kundoor *et al*. 2016 [32]	50 years old male	Maxilla	Swelling, not associated with any unerupted tooth.	odontogenic columnar epithelial cells arranged in the form of numerous rosettes, cords, duct-like structures and central lumen filled with Eosinophilic material.	Well-defined unilocular radiolucency with sclerotic border	Extrafollicular adenomatoid odontogenic tumor

AOT: Adenomatoid odontogenic tumor, REE: Reduced enamel epithelium, HERS: Hertwig's epithelial root sheath

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].

A molecular study by Razavi *et al*. showed that the Ki-67 labeling index was lower in AOTs as compared to SMAs, signifying a hamartomatous nature [58]. However, using a human androgen receptor gene polymorphism assay, Gomes *et al*. 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 P53 (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 a1-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 [71] 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 is supported by its positive reactivity to amelogenin, enamelin, and enamelysin although it is indistinguishable from calcified amyloid [76].

The epithelial tumor cells display features that are consistent with neoplastic (pre)ameloblasts in a state of arrested development [77]. The ameloblasts are yet metabolically active enough to produce basement membrane and enamel matrix proteins [78]. It is theorized

that the accumulation and subsequent degradation of these enamel secretory 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 (AOC)." 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 r1ot 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. Arulmozhi 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

1. Rajendran R. Shafer's Textbook of Oral Pathology. New Delhi: Elsevier India; 2009.
2. Kumamoto H. Molecular pathology of odontogenic tumors. J Oral Pathol Med 2006;35:65-74.
3. Neville BW, Damm DD, Chi AC, Allen CM. Oral and Maxillofacial Pathology. UK: Elsevier Health Sciences; 2015.
4. Garg K, Chandra S, Raj V, Fareed W, Zafar M. Molecular and genetic aspects of odontogenic tumors: A review. Iran J Basic Med Sci 2015;18:529-36.
5. Thompson L. World health organization classification of tumours: Pathology and genetics of head and neck tumours. Ear Nose Throat J 2006;85:74.
6. Philipsen HP, Reichart PA. Adenomatoid odontogenic tumour: Facts and figures. Oral Oncol 1999;35:125-31.
7. Lee SK, Kim YS. Current concepts and occurrence of epithelial odontogenic tumors: I. Ameloblastoma and adenomatoid odontogenic tumor. Korean J Pathol 2013;47:191-202.
8. Garg D, Palaskar S, Shetty VP, Bhushan A. Adenomatoid odontogenic tumor - Hamartoma or true neoplasm: A case report. J Oral Sci 2009;51:155-9.
9. Marx RE, Stern D. Oral and Maxillofacial Pathology. Chicago: Quintessence; 2003.
10. Vera Sempere FJ, Artes Martínez MJ, Vera Sirera B, Bonet Marco J. Follicular adenomatoid odontogenic tumor: Immunohistochemical study. Med Oral Patol Oral Cir Bucal 2006;11:E305-8.
11. Philipsen HP, Samman N, Ormiston IW, Wu PC, Reichart PA. Variants of the adenomatoid odontogenic tumor with a note on tumor origin. J Oral Pathol Med 1992;21:348-52.
12. Cawson RA, Binnie WH, Speight PM, Barrett AW, Wright JM. Lucas's Pathology of Tumors of the Oral Tissues. New York: Churchill Livingstone; 1998.
13. Domingues MG, Jaeger MM, Araújo VC, Araújo NS. Expression of cytokeratins in human enamel organ. Eur J Oral Sci 2000;108:43-7.
14. Takahashi H, Fujita S, Shibata Y, Yamaguchi A. Adenomatoid odontogenic tumour: Immunohistochemical demonstration of transferrin, ferritin and alpha-one-antitrypsin. J Oral Pathol Med 2001;30:237-44.
15. Crivelini MM, Soubhia AM, Felipini RC. Study on the origin and nature of the adenomatoid odontogenic tumor by immunohistochemistry. J Appl Oral Sci 2005;13:406-12.
16. Madiyal A, Ajila V, Hegde S, Babu S. Clinical and radiographic features of adenomatoid odontogenic tumour. Acta Stomatol Naissi 2016;32:1595-610.
17. Mohanty N, Routray S, Swain N, Ingale Y. Adenomatoid odontogenic tumor with clear cell changes. Indian J Pathol Microbiol 2014;57:290-3.
18. Friedrich RE, Scheuer HA, Zustin J. Adenomatoid odontogenic tumor (AOT) of maxillary sinus: Case report with respect to immunohistochemical findings. *In vivo* 2009;23:111-6.
19. Yilmaz N, Acikgoz A, Celebi N, Zengin AZ, Gunhan O. Extrafollicular adenomatoid odontogenic tumor of the mandible: Report of a case. Eur J Dent 2009;3:71-4.
20. Bhandari N, Kothari M. Adenomatoid odontogenic tumour mimicking a periapical cyst in pregnant woman. Singapore Dent J 2010;31:26-9.
21. Phillips MD, Closmann JJ, Baus MR, Torske KR, Williams SB. Hybrid odontogenic tumor with features of ameloblastic fibro-odontoma, calcifying odontogenic cyst, and adenomatoid odontogenic tumor: A case report and review of the literature. J Oral Maxillofac Surg 2010;68:470-4.
22. Avinash Tejasvi ML, Prashanth Shenai K, Chatra L. Atypical case of periapical adenomatoid odontogenic tumour. J Maxillofac Oral Surg 2010;9:99-101.
23. Soares EC, Costa FW, Neto IC, Bezerra TP, Patrocínio RM, Alves AP. Rare hybrid odontogenic tumor in a 2-year-old child. J Craniofac Surg 2011;22:554-8.
24. Laheji A, Sakharde S, Chidambaram S, Gondhalekar RR, Shankar U, Radhika A. Adenoameloblastoma: A dilemma in diagnosis. J Contemp

Dent Pr 2012;13:925-9.
25. Prakasam M, Tiwari S, Satpathy M, Banda VR. Adenomatoid odontogenic tumour. BMJ Case Rep 2013;2013:1-4.
26. Rathod V, Saluja S, Gondhalekar R, Pundir S, Dixit S, Agrawal S. Hybrid odontogenic lesion of the mandible: A rare case report with literature review. Int J Oral Med Sci 2014;12:245-50.
27. Bonardi JP, da Costa FH, Matheus RA, Ito FA, Pereira-Stabile CL. Rare presentation of adenomatoid odontogenic tumor in a pediatric patient: A case report. Oral Maxillofac Surg 2016;20:215-7.
28. Grover S, Mujib A, Rahim B, Parakkat NK, Kapoor S, Mittal K, *et al*. Case report cystic adenomatoid odontogenic tumor. Case Rep Dent 2015;2015:2-7.
29. Manjunatha BS, Harsh A, Purohit S, Naga MV. Adenomatoid odontogenic tumor associated with a dentigerous cyst. J Cancer Res Ther 2015;11:649.
30. Kumar R, Hashmi GS, Amjad SM, Ansari MK. Adenomatoid odontogenic cyst of mandible: A rare case report. Int J Heal Sci Res 2015;5:490-4.
31. Hemalatha AL, Shobha SN, Raghuveer CR, Sahni S, Kumari A. Adenomatoid odontogenic tumor : A dentigerous cyst mimic in maxilla. Int J Sci Study 2016;3:174-6.
32. Kundoor VK, Maloth KN, Guguloth NN, Kesidi S. Extrafollicular adenomatoid odontogenic tumor: An unusual case presentation. J Dent 2016;17:370-4.
33. Siwach P, Joy T, Tupkari J, Thakur A. Controversies in odontogenic tumours: Review. Sultan Qaboos Univ Med J 2017;17:e268-e276.
34. Philipsen HP, Birn H. The adenomatoid odontogenic tumour. Ameloblastic adenomatoid tumour or adeno-ameloblastoma. Acta Pathol Microbiol Scand 1969;75:375-98.
35. Batra BP. Adenomatoid odontogenic tumour: Review and case report. J Can Dent Assoc 2005;71:250-3.
36. Handschel JG, Depprich RA, Zimmermann AC, Braunstein S, Kübler NR. Adenomatoid odontogenic tumor of the mandible: Review of the literature and report of a rare case. Head Face Med 2005;1:3.
37. Motamedi MH, Shafeie HA, Azizi T. Salvage of an impacted canine associated with an adenomatoid odontogenic tumour: A case report. Br Dent J 2005;199:89-90.
38. Nigam S, Gupta SK, Chaturvedi KU. Adenomatoid odontogenic tumor – a rare cause of jaw swelling. Braz Dent J 2005;16:251-3.
39. Vargas PA, Carlos-Bregni R, Mosqueda-Taylor A, Cuairan-Ruidíaz V, Lopes MA, de Almeida OP, *et al.* Adenomatoid dentinoma or adenomatoid odontogenic hamartoma: What is the better term to denominate this uncommon odontogenic lesion? Oral Dis 2006;12:200-3.
40. Vera Sempere FJ, Artes Martínez MJ, Vera Sirera B, Bonet Marco J. Follicular adenomatoid odontogenic tumor: Immunohistochemical study. Med Oral Patol Oral Cir Bucal 2006;11:E305-8.
41. Nonaka CF, de Souza LB, Quinderé LB. Adenomatoid odontogenic tumour associated with dentigerous cyst – unusual case report. Braz J Otorhinolaryngol 2007;73:129-31.
42. Jivan V, Altini M, Meer S, Mahomed F. Adenomatoid odontogenic tumor (AOT) originating in a unicystic ameloblastoma: A case report. Head Neck Pathol 2007;1:146-9.
43. Santos JN, Lima FO, Romério P, Souza VF. Adenomatoid odontogenic tumor: An unusual case exhibiting cribriform aspect. Quintessence Int 2008;39:777-81.
44. Kemp S, Gallagher G, Kabani S, Todd R. Adenomatoid dentinoma: Case report and review of a rare odontogenic lesion. J Oral Maxillofac Surg 2008;66:1489-91.
45. Carlos-Bregni R, Vargas PA, Silva AR, de Miranda Chaves-Netto HD, de Moraes M, Lopes MA. Adenomatoid odontogenic hamartoma: Concerns about correct nomenclature and 2 additional case reports. J Oral Maxillofac Surg 2009;67:1779-80.
46. Ide F. Inter-radicular adenomatoid odontogenic tumor of the anterior mandible. J Oral Maxillofac Surg 2010;68:490-1.
47. Martínez A, Mosqueda-Taylor A, Marchesani FJ, Brethauer U, Spencer ML. Adenomatoid odontogenic tumor concomitant with cystic complex odontoma: Case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:e25-9.
48. Sekiya R, Yamazaki H, Izawa K, Kaneko A, Tsukinoki K. Case of adenomatid odontogenic tumor during pregnancy. Tokai J Exp Clin Med 2011;36:124-7.
49. Agarwal A, Giri KY, Alam S. The interrelationship of adenomatoid odontogenic tumour and dentigerous cyst: A report of a rare case and review of the literature. Case Rep Pathol 2012;2012:358609.
50. Li BB, Xie XY, Jia SN. Adenomatoid odontogenic tumor with fibro-osseous reaction in the surrounding tissue. J Craniofac Surg 2013;24:e100-1.
51. Gomez RS, Castro WH, Gomes CC, Loyola AM. Adenomatoid odontogenic tumor associated with odontoma: A case report and critical review of the literature. Head Face Med 2013;9:20.
52. Philipsen HP, Reichart PA. The adenomatoid odontogenic tumour: Ultrastructure of tumour cells and non-calcified amorphous masses. J Oral Pathol Med 1996;25:491-6.
53. Wright JM, Odell EW, Speight PM, Takata T. Odontogenic tumors, WHO 2005: Where do we go from here? Head Neck Pathol 2014;8:373-82.
54. Rick GM. Adenomatoid odontogenic tumor. Oral Maxillofac Surg Clin North Am 2004;16:333-54.
55. Morgan PR. Odontogenic tumors: A review. Periodontol 2000 2011;57:160-76.
56. Poulson TC, Greer RO Jr. Adenomatoid odontogenic tumor: Clinicopathologic and ultrastructural concepts. J Oral Maxillofac Surg 1983;41:818-24.
57. Philipsen HP, Reichart PA, Zhang KH, Nikai H, Yu QX. Adenomatoid odontogenic tumor: Biologic profile based on 499 cases. J Oral Pathol Med 1991;20:149-58.
58. Razavi SM, Tabatabaie SH, Hoseini AT, Hoseini ET, Khabazian A. A comparative immunohistochemical study of ki-67 and bcl-2 expression in solid ameloblastoma and adenomatoid odontogenic tumor. Dent Res J (Isfahan) 2012;9:192-7.
59. Gomes CC, da Silveira Oliveira C, Castro WH, De Lacerda JC, Gomez RS. Clonal nature of odontogenic tumours. J Oral Pathol Med 2009;38:397-400.
60. Lee JK, Lee KB, Hwang BN. Adenomatoid odontogenic tumor: A case report. J Oral Maxillofac Surg 2000;58:1161-4.
61. Raubenheimer EJ, Seeliger JE, van Heerden WF, Dreyer AF. Adenomatoid odontogenic tumour: A report of two large lesions. Dentomaxillofac Radiol 1991;20:43-5.
62. Shetty K, Vastardis S, Giannini P. Management of an unusually large adenomatoid odontogenic tumor. Oral Oncol Extra 2005;41:316-8.
63. Awange DO. Adenomatoid odontogenic tumour (adenoameloblastoma) – a review. East Afr Med J 1991;68:155-63.
64. de Medeiros AM, Nonaka CF, Galvão HC, de Souza LB, Freitas Rde A. Expression of extracellular matrix proteins in ameloblastomas and adenomatoid odontogenic tumors. Eur Arch Otorhinolaryngol 2010;267:303-10.
65. Hatakeyama S, Suzuki A. Ultrastructural study of adenomatoid odontogenic tumor. J Oral Pathol Med 1978;7:295-310.
66. Schlosnagle DC, Someren A. The ultrastructure of the adenomatoid odontogenic tumor. Oral Surg Oral Med Oral Pathol 1981;52:154-61.
67. Courtney RM, Kerr DA. The odontogenic adenomatoid tumor. A comprehensive study of twenty new cases. Oral Surg Oral Med Oral Pathol 1975;39:424-35.
68. Tatemoto Y, Tanaka T, Okada Y, Mori M. Adenomatoid odontogenic tumour: Co-expression of keratin and vimentin. Virchows Arch A Pathol Anat Histopathol 1988;413:341-7.
69. Okada Y, Mochizuki K, Sugimura M, Noda Y, Mori M. Odontogenic tumor with combined characteristics of adenomatoid odontogenic and calcifying epithelial odontogenic tumors. Pathol Res Pract 1987;182:647-57.
70. Montes Ledesma C, Mosqueda Taylor A, Romero de León E, de la Piedra Garza M, Goldberg Jaukin P, Portilla Robertson J, *et al.* Adenomatoid odontogenic tumour with features of calcifying epithelial odontogenic tumour. (The so-called combined epithelial odontogenic tumour.) clinico-pathological report of 12 cases. Eur J Cancer B Oral Oncol 1993;29B:221-4.
71. Murata M, Cheng J, Horino K, Hara K, Shimokawa H, Saku T. Enamel proteins and extracellular matrix molecules are co-localized in the pseudocystic stromal space of adenomatoid odontogenic tumor. J oral Pathol Med 2000;29:483-90.
72. Nagatsuka H, Siar C, Nakano K, Tsujigiwa H. Differential expression of collagen IV α1 to α6 chains in basement membranes of benign and malignant odontogenic tumors. Virchows Arch 2002;441:392-9.
73. Mori M, Yamada K, Kasai T, Yamada T, Shimokawa H, Sasaki S, *et al.* Immunohistochemical expression of amelogenins in odontogenic epithelial tumours and cysts. Virchows Arch A Pathol Anat Histopathol 1991;418:319-25.
74. Mori M, Yamada T, Doi T, Ohmura H, Takai Y, Shrestha P, *et al.* Expression of tenascin in odontogenic tumours. Eur J Cancer B Oral Oncol 1995;31B:275-9.
75. Saku T, Okabe H, Shimokawa H. Immunohistochemical demonstration of enamel proteins in odontogenic tumors. J Oral Pathol Med 1992;21:113-9.

76. El-Labban NG. The nature of the eosinophilic and laminated masses in the adenomatoid odontogenic tumor: A histochemical and ultrastructural study. J Oral Pathol Med 1992;21:75-81.
77. Yamamoto H, Kozawa Y, Hirai G, Hagiwara T, Nakamura T. Adenomatoid odontogenic tumor: Light and electron microscopic study. Int J Oral Surg 1981;10:272-8.
78. Nanci A. Ten Cate's Oral Histology-E-Book: Development, Structure, and Function. UK: Elsevier Health Sciences; 2017.
79. do Carmo MA, Silva EC. Argyrophilic nucleolar organizer regions (AgNORs) in ameloblastomas and adenomatoid odontogenic tumours (AOTs). J Oral Pathol Med 1998;27:153-6.
80. Kramer IRH, Pindborg JJ, Shear M. Histological Typing of Odontogenic Tumours. New York: Springer Science and Business Media; 1992.
81. Gadewar DR, Srikant N. Adenomatoid odontogenic tumour: Tumour or a cyst, a histopathological support for the controversy. Int J Pediatr Otorhinolaryngol 2010;74:333-7.
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 in epithelia of odontogenic neoplasms. Oral Dis 2003;9:1-6.