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Case Report

A case report and short review on changing trends in the site of occurrence of adenomatoid odontogenic tumor: Unravelling the past 15 years

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ABSTRACT

Adenomatoid odontogenic tumor (AOT) is an uncommon benign odontogenic lesion, with debatable histogenesis and variable histopathology. A systematic and diverse insight into the evolution, clinical presentation, histology, and immunohistochemical findings of this lesion is reviewed and presented. We reviewed the data published from 2000 to 2014 of approximately 255 cases that revealed a significant change in the incidence of predominant site involved, in contrast to the findings published by Reichart. We have also included the chronological order of events leading to the coining of the term AOT, which shows the curiosity that has been dedicated to understanding the lesion. Immunohistochemistry is considered to be a hallmark in pathology for learning the molecular pathogenesis and giving a correct final diagnosis. Several markers have been used to investigate and understand this lesion, and a compilation of the findings has been tabulated.

Key Words: Ameloblastoma, immunohistochemistry, incidence, odontogenesis

INTRODUCTION

Adenomatoid odontogenic tumor (AOT) was first elucidated by Driebaldt in 1907 as "pseudo-adenoameloblastoma," and later as "adenomatoid odontogenic tumor."[1] The World Health Organization (WHO) in 2005 defined AOT as a tumor composed of odontogenic epithelium, presenting a variety of histo-architectural patterns, embedded in mature connective tissue stroma, and characterized by slow and progressive growth.[2]

AOT is a benign, hamartomatous, noninvasive, uncommon, epithelial lesion of the odontogenic origin. It has tendency to affect the younger age group usually during the second decade, also an apparent inclination toward female presentation, as the established male to female ratio of occurrence is 1:2. This lesion is known to be allied with unerupted canines and lateral incisors. The clinical course of the lesion is slow and remains clinically unnoticeable for a long time. The deformity produced by this lesion manifests as displacement of adjoining teeth and an obvious expansion of the surrounding bone.[1,2] Sometimes, it may be also as "two-thirds tumor" because:

- Two-third occurrence in maxilla
- Two-third female preponderance
- Two-third association with unerupted tooth
- Two-third affected teeth are canines.

The lesion when associated with an impacted (maxillary permanent canines account

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for 41.7% and all four canines for 60.1% of AOT-associated embedded teeth) and a displaced tooth is referred to as a follicular variant; the origins of this variant are considered to be the reduced enamel epithelium of the dental follicle. It contributes for 73.0–97.2% of all reported cases and is diagnosed earlier in life usually in the second decade.[3,4] When AOT mimics a radicular cyst with manifestation around the apex of a tooth, it is categorized as an extrafollicular variant; the origins of which remain unclear, but it has been suggested that odontogenic cysts or cystic tumors may undergo secondary changes to result in the formation of this benign lesion. Only 12 cases of a rare subvariant have been reported where the lesion impersonates a periapical abscess on radiographic investigation.[3,4] Sometimes, we see a peripheral manifestation which originates at a distance from the tooth germs and is rarely encountered (14 cases). They show a characteristic bone defect or ectopic growth and a significant predominance in females, the maxillary region, especially the anterior maxilla, with primary involvement seen of incisors and sometimes into the maxillary antrum. The histological features of variants of AOT are characteristic and perpetually distinguishable.[3-5]

A decade-long controversial debate on the true classification this tumor has prevailed, hamartoma or neoplasm? The followers of the hamartoma category justify their thinking by pointing to the restricted growth potential and limited sizes along with an absent inherent capacity to reoccur.[10] On the contrary, the supporters of the neoplastic theory argue to by suggesting the lesion is slow growing and early removal prevents its growth to clinically noticeable sizes and also state that many cases which have been left untreated have grown to considerable sizes causing facial asymmetry and distortion.[6] Furthermore, they point out that the spectrum of histologic patterns which are observed in AOT is inconsistent with the variation seen in a developmental anomaly.[8-10] The idea of origin of this lesion from reduced enamel epithelium is enforced by many ultrastructural and immunohistochemical studies along with the resemblance of cytological features seen in this lesion to components of derived from enamel organ; the occurrence in tooth-bearing region of jaws and its unavoidable alliance with impacted teeth has further strengthened this notion. The 1971 WHO classification stated: "It is generally believed that the lesion is not a neoplasm." However, Handschel *et al*. concluded that "such a controversy is unresolvable 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."[11]

The expansion of specific antibodies for immunohistochemistry has produced substantial growth during the past few years helped us understand the histogenesis of this tumor. A detailed discussion on the immunohistochemical features has been included in the later part of the discussion of this article.

Here, we present an unusual presentation of this lesion in the mandible causing extensive jaw swelling.

CASE REPORT

A 15-year-old female patient, with an asymmetrical anterior mandibular swelling, reported to clinics. On examination, the face appeared asymmetrical with a swelling seen in the front region of the lower jaw, approximately 2.5 cm × 3.5 cm in size, extending from the lower lip to 1 cm below the lower border of the mandible. The overlying skin was tense, normal in color with no draining sinuses. The swelling was nontender, noncompressible, nonfluctuant, firm to hard in consistency with diffuse margins. There was no palpable lymphadenopathy, and there was apparent deviation of the jaw to the left side on opening of mouth [Figure 1a].

Intraoral examination revealed the presence of a solitary unilateral swelling in the lower jaw, extending from the distal aspect of central right mandibular incisor; crossing the midline up to left mandibular second premolar region with missing or impacted permanent canine. Superoinferiorly, it extended from the gingival margin obliterating the lower left facial vestibule. The left mandibular canine and premolars were lingually inclined [Figure 1b].

Radiographic features

Orthopantomogram showed [Figure 2a] a well-defined unilocular radiolucency extending anteroposteriorly from 31 to mesial aspect of 36 and superoinferiorly from gingival margin/inferior to roots of the inclined canine and from premolars to inferior border of the mandible. Radiopacities in the form of flecks suggestive of calcifications and a single large radiopaque mass suggestive of tooth are appreciable.

Computed tomography revealed an irregular thick cystic lesion with areas of calcification in the left parasymphyseal region [Figure 2b].

Microscopy

Fine needle aspiration cytology from the lesion showed proteinaceous fluid with few red blood cells, polymorphonuclear lymphocytes, and macrophages. No definitive diagnosis could be made.

The microscopic picture of the lesion revealed the presence of a single large cystic space and odontogenic epithelium in scanty connective tissue stroma surrounded by thick fibrous capsule. The odontogenic epithelium is arranged in sheets, duct-like and convoluted/whorled patterns. The ductal patterns are peripherally lined by single layer of ameloblast-like cells with nuclei away from the central space and clear cystic spaces. The convoluted patterns show spindle-shaped cells surrounded by amorphous eosinophilic material [Figure 3].

After carefully analyzing the clinical, radiographic, and histopathological findings, we reached to a final diagnosis of AOT. The patient was referred to the department of oral surgery for excision of lesion. Excision of the lesion from the mandible caused no problems.

A follow-up of 3 and 6 months was recorded; there were no signs of recurrence of the lesion till date. The wound healed uneventfully, and radiographically, no suspicious activity was observed.

DISCUSSION

A review of the literature on AOT was performed, the database used was PubMed interface of MEDLINE, only the case reports with confirmed histopathological diagnosis were included and collision tumors were excluded, the case series reported by authors were also included. The #MeSH words used were adenomatoid odontogenic tumor, odontogenic, and case report. We reviewed the data associated with AOT from 2000 to 2014,[3-8,13-93] and it was found that in the last 14 years, there was a record of 255 reported cases.

Out of 255 cases reviewed, 108 cases belonged to the mandibular anterior quadrant, 52 cases belonged to the mandibular posterior quadrant, 45 cases belonged to the maxillary anterior quadrant, and only 4 cases belonged to the maxillary posterior quadrant [Graph 1]. The age of occurrence of this lesion ranged from 2 to 44 years. An analysis of the mean age was performed separately in each quadrant and found it to be 19.5 years in the maxillary anterior quadrant, 19 years in the maxillary posterior

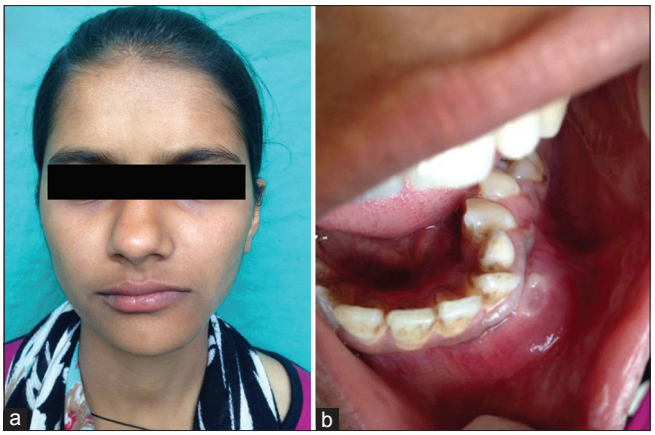


Figure 1: (a) Extraoral appearance of the patient. (b) Intraoral appearance of the lesion in patient.

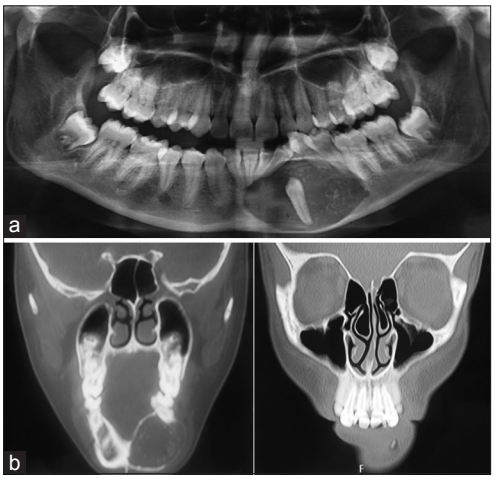


Figure 2: (a) Orthopantomogram of the lesion in the patient. (b)Computed tomography of the lesion in the patient.

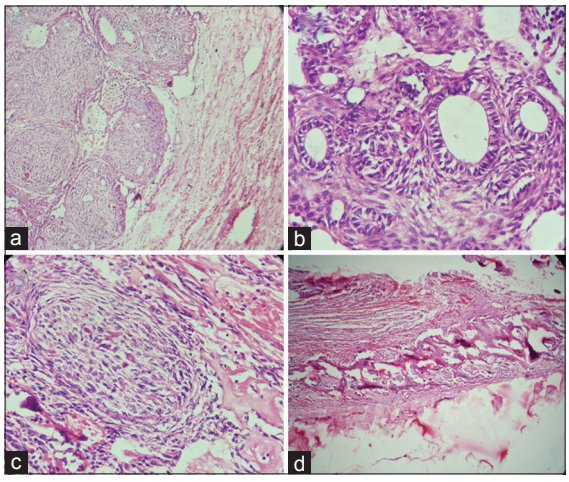


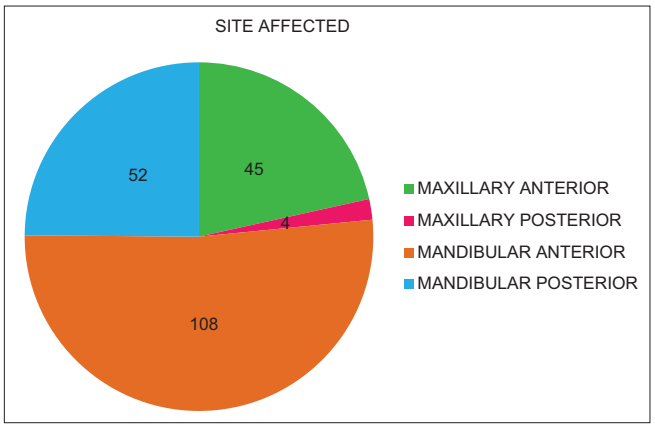
Figure 3: Microscopic appearance of the lesion.(a) showing a fibrous sheath encapsulating islands of tumor cells (b) Tumor cells arranged to form duct-like structures and rosettes (c) Tumor cells arranged to form characteristic whorls (d) Section of tissue showing normal bone with surrounding connective tissue stroma.

quadrant, 20.5 years in the mandibular anterior quadrant, and 17.8 years in the mandibular posterior quadrant [Graph 2]. Another comparison of site predilection was evaluated in males and females in each quadrant, which showed only 32% of maxillary anterior quadrants were associated with males and 68% were females, whereas in the maxillary posterior quadrant, 44% were males and 56% were females; in the mandibular anterior quadrant, 40.5% were males and 59.5% were females; in the mandibular anterior quadrant, 35% were males and 65% were females [Graph 3]. An overall female predominance was observed (62.12%) in the present study, with a female to male ratio of 1.45:1.

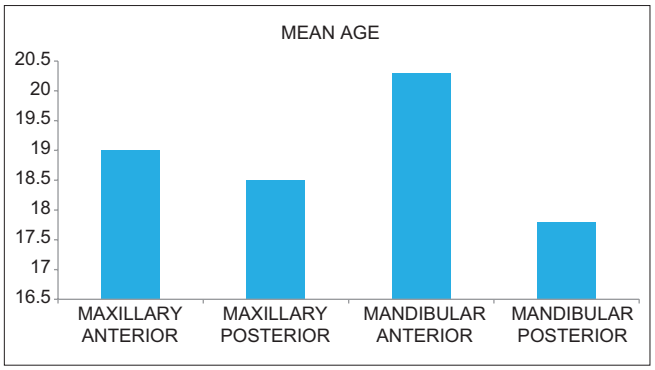
Our data were compared with the comprehensive analysis performed by Reichart and Philipsen[5] and a few striking points were noted [Graph 4]. Out of the 532 cases, 341 were associated with permanent unerupted teeth, in which 209 cases were recorded in the maxillary anterior quadrant (61.2%), 112 cases in the mandibular anterior quadrant (32.3%), 12 cases in the maxillary posterior quadrant (3.51%), and 8 cases in the mandibular posterior quadrant (2.34%). The mean age range recorded by them was 3–82 years; in contrast to our findings, the range of age of occurrence of the lesion to be 2–44 years. The mean ages recorded by both studies were apparently similar. The gender incidence of each decade was calculated and compared by the similar analysis performed by Reichart and Philipsen[5] [Graph 5]. The females and males in the 0–9 years age decade were 3.3% and 1.5% according to Reichart and 4.2% and 2.8% in our study; the female and male incidence in 10–19 year age decade was 43.7% and 24.8% according to Reichart and 47% and 20.2% in the present study; the female and male incidence in 20–29 year age decade was 15.2% and 4.1% according to Reichart and 14.5% and 3.6% in our study; in all cases above 30 years of age, female and male incidence was 2.8% and 4.3% according to Reichart and 3.5% and 4% in the present study.

Various terminologies have been used to describe this lesion and many have been discarded in the process; Table 1 shows the evolution of the term "AOT" in a chronological manner; Table 2 depicts the various terminologies which have been used to describe this lesion.

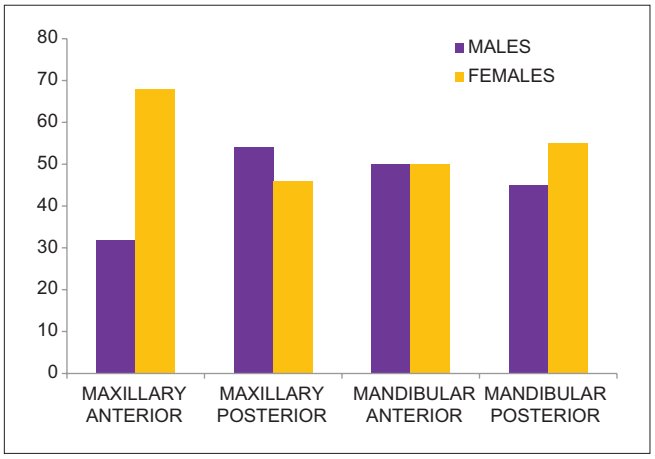
Microscopically, AOT presents an array of unique and distinctive features. This tumor is almost always delimited by a fibrous capsule which is usually well developed. The primary tumor cells are cuboidal or polygonal epithelial cells, sometimes spindle-shaped cells which are arranged in a characteristic variety of histomorphologic patterns.[7] They can form duct-like spaces with fluctuating diameter, but this pattern is not



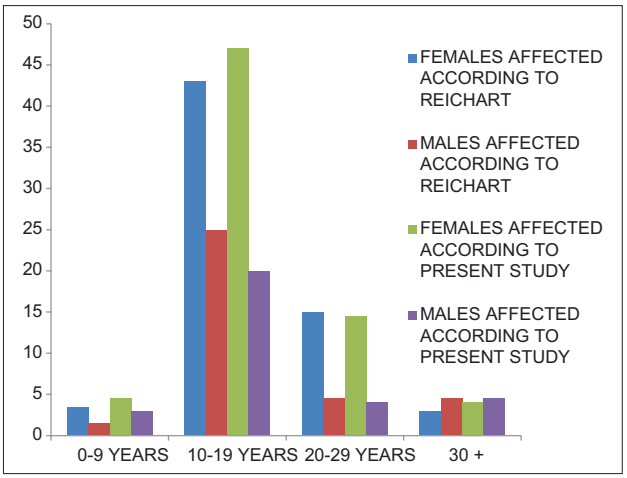
Graph 1: Graphical representation of the number of cases affected according to the site.



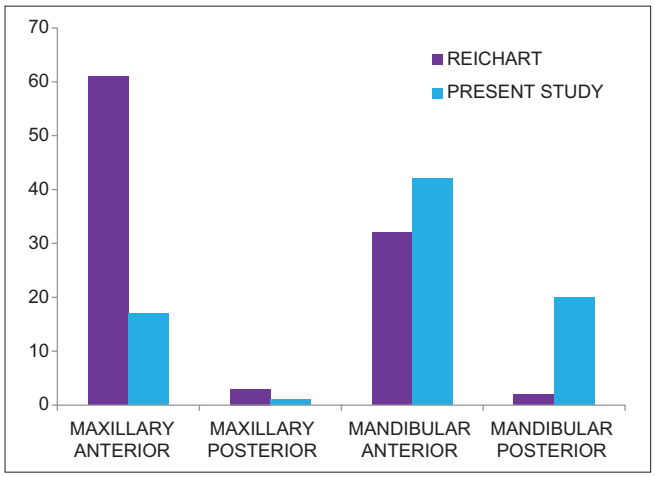
Graph 2: Graphical representation of incidence of adenomatoid odontogenic tumor, with respect to mean age of occurrence in each quadrant.



Graph 3: Graphical representation of the number of males and females affected by adenomatoid odontogenic tumor in each quadrant.



Graph 4: Graphical comparison of data collected in the present study and Reichart study on the basis of sex and age groups affected by adenomatoid odontogenic tumor.



Graph 5: Graphical representation of comparison between Reichart and the current study on the basis of site affected.

predominantly seen. The ducts are lined by a single layer of cuboidal to columnar epithelial cells that have nuclei that frequently are polarized away from the lumen.[12] These duct-like structures are frequently lined by an eosinophilic rim of varying thickness called as the hyaline ring. Anastomosing strands of basaloid epithelial cells which resemble cell rests of the dental lamina, arranged in a plexiform, cribriform, trabecular, or lattice-like configuration.[112]

Amorphous homogenous material which is eosinophilic (tumor-droplets) is usually seen in the core of these rosettes.[12] Furthermore, darkly staining dystrophic calcifications in inconsistent amounts is also a feature observed in the histological examination of these lesions. Other materials which are associated with degraded enamel, mostly, due to

Table 1: List of terms proposed by many authors but were rejected

Cystic complex composite odontome[107]
An unusual pleomorphic adenoma-like tumor in the wall of dentigerous cysts[108]
Tumor of enamel organ epithelium[109]
Adenomatoid ameloblastoma [110]
Adenomatoid odontome [111]

Table 2: Chronological insight to adenomatoid odontogenic tumor

Year	Evolution
1905	Steensland introduced this uncommon odontogenic tumor[94]
1907	Dreibaldt described it as pseudoameloblastoma[95]
1909	James and Forbes, from England, coined the term, "Epithelial Odontome"[96]
1915	First irrefutable case from Norway by Habitz called as, "Adamantoma"[97]
1916	First acceptable American Case, "tooth germ cyst of jaw" by Wohl of Omaha, Nebraska[98]
1916	Gorlin *et al.* introduced the term, "ameloblastic adenomatoid tumor"[99]
1948	Stafne reported the first case series of AOT (three cases) – "epithelial tumors associated with developmental cysts of the maxilla"[100]
1950	Bernier and Tiecke – first published case of AOT. Used the term "Adeno-ameloblastoma"[101]
1951	Simple ameloblastoma and adenoameloblastoma were included in the classification of odontogenic tumors but not accepted at the 5th American Academy of Oral Pathology meeting[102]
1963	Shafer *et al.* adopted the same term in his 2nd ed.ition of the Textbook of Oral Pathology[103]
1968	Abrams *et al.* suggested the term "odontogenic adenomatoid tumor"[104]
1969	Philipsen and Birn proposed the term "AOT"[105]
1970	Adenomatoid odontogenic tumor was accepted by WHO's Histological typing of odontogenic tumor, jaw cysts, and allied lesions[106]

AOT: Adenomatoid odontogenic tumor

a metaplastic process and not an induction incident, such as hyaline, dysplastic, or calcified osteodentin, are other uncommon findings in AOTs.[2] The presence of cystic areas in AOTs mimics odontogenic cysts, such as dentigerous cyst, has been reported in the literature (Leon *et al.*, 56.4%).[45,113]

These tumors present a minimal mature connective tissue stroma, which is generally loosely structured and contain thin-walled congested vessels with peripheral hyalinization rather apparent. According to el-Labban and Lee,[114] an estimate of 70–90% of the blood vessels found in the stroma shows degenerative changes affecting both the endothelial lining and the perivascular connective tissue. These authors attribute these vascular and perivascular changes to the multiplying

basal lamina which is associated with the collagen surrounding the blood vessels undergoing degenerative changes.[114] Philipsen and Reichart emphasize the easy detection of these changes at light microscopic level as they the degeneration is significantly evident.[7] a few cases of AOT have also exhibited melanocytes which can be attributed to the interaction of neural crest cells with developing odontogenic epithelium.[115,116]

Immunohistochemical studies have provided us with confirmatory evidence supporting the odontogenic origin of this lesion [Table 3].[117-126]

- Two distinct varieties of cells (duct and nonduct) have been identified, where none of the enamel matrix proteins such as enamelin, amelogenin, and sheathelin showed positivity by duct forming cells although the nonductal cells were positive for amelogenin[127-130]
- The periluminal and intraluminal material were found to be positive with laminin, type IV collagen, heparan sulfate, proteoglycans, fibronectin, amelogenin, and enamelin[116,127,129,131]
- A cytoplasmic expression of sheathelin has been observed by the cells in the vicinity of the hyaline droplets[129]
- Calcifications were positive for amelogenin, enamelin, and enamelysin and negative for sheathelin[128-130,132,133]
- A variety of spindle cells is observed in the intranodular and internodular spaces and the juxta-tumor spindle cells showed no expression with the enamel matrix proteins similar to ductal cells, suggesting it to be a predecessor of this variety of cells.[134]

CONCLUSION

To summarize, we reviewed 255 reported cases of AOT from 2000 to 2014 and observed a striking paradigm shift with respect to prevalence of location.

Table 3: Immunohistochemical findings by various authors

Marker	Cells (positivity)	Author
Collagen IV	Basement membrane of cribriform, areas and hyaline materials (+++), epithelial whorls, mineralized foci (+)	Nagatsuka *et al.*[117]
Versican	Connective tissue stroma (++), epithelial cells (+)	Ito *et al.*[118]
CK8	Intense expression	Larsson *et al.*[51]
CK5	Peripheral cells (+)	
CK17	Peripheral cells (+)	
CK19	Peripheral cells (+)	
OPG	(+++), stromal cells	Andrade *et al.*[119]
RANKL	(++) stromal cells	
Integrin α2β1, α3β1, α5β1	(+) tumor cells	de Souza Andrade *et al.*[120]
MMP1	Stroma and parenchyma (++)	Ribeiro *et al.*[121]
MMP2	60% tumor cells (++), 80% stromal cells (++)	
MMP9	Parenchymal and stromal cells	
AE1/AE2	Superficial (+), ductal (++), basaloid (++), fusiform (++), cyst basal (++), syst superficial (++)	Friedrich *et al.*[19]
CK18	Cyst basal (+), cyst superficial (+)	
CK14	Duct like (+++), basaloid (+++), fusiform (+++), cyst basal (+++), cyst superficial (+++)	
CK5/6	Duct like (+++), basaloid (+++), fusiform (+++), cyst basal (+++), cyst superficial (+++)	
CK19	Superficial (+++), ductal (+++), basaloid (+), cyst basal (+), syst superficial (+++)	
P63	Duct like (+++), basaloid (+++), fusiform (+++), cyst basal (+++)	
VIMENTIN	Basaloid (+), fusiform (+)	
SMA	Duct-like (++)	
EMA	Superficial (++), duct like (++), cyst superficial (+++)	
Osteonectin	Epithelial cells	Modolo *et al.*[122]
Osteopontin	Calcification foci	
Cyclin D1	Whorls, nuclear stain	Kumar *et al.* (2011)[92]
PCNA	Mild staining all tumor cells	Salehinejad *et al.*[123]
P53	Mild staining all tumor cells	
Podoplanin	Spindle cells positive	Tsuneki *et al.*[124]
c-met	Cytoplasm of epithelial tumor cells	Crivelini *et al.*[125]
HGF	Cytoplasm of epithelial tumor cells	
c-myc	Tumor cells (80%)	Moosvi *et al.* (2013)[126]
B-catenin	Tumor cells (cytoplasmic expression – [+++])	Harnet *et al.*[74]

Reichart and Philipsen[5] concluded that maxillary anterior area is the most common site for AOT occurrence, whereas our data revealed that in the last 14 years, there is more incidence of AOT in the mandibular anterior quadrant. The origin of AOT is still debatable as to whether AOT is a hamartoma or neoplasm has not been clarified. The lesion has struggled throughout for its name and origin, and an evaluation of the immunohistochemical data also shows us no specific diagnostic marker for this particular odontogenic lesion. Therefore, further detailed studies are required to unveil the secrets of AOT.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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