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Original Article

Special AT-rich sequence binding protein 2 (SATB2), β-catenin, and CD10 immunohistochemistry provides insights into the histopathologic features and cellular differentiation of adenomatoid odontogenic tumor

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Abstract *Background/purpose:* Adenomatoid odontogenic tumor (AOT) is an odontogenic tumor histologically characterized by duct- and rosette-like structures. Although having distinct histologic features, AOT may show whorled cellular masses resembling morules seen in WNT pathway-altered odontogenic tumors (WNT-OTs). This study aimed to investigate the expression of morular markers in AOT.
Materials and methods: Twenty-four odontogenic tumors, consisting of 11 AOTs, 6 developing odontomas, and 7 WNT-OTs, were included. Special AT-rich sequence binding protein 2 (SATB2), β-catenin, CD10, and CDX2 immunohistochemistry was performed and evaluated for each histologic component by tumor type. Whole-exome sequencing was performed in 3 AOTs.

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Results: In AOT, a nodular growth pattern was highlighted by CD10 positivity in circumferential cells, and aggregates of small duct-like structures composed of cuboidal cells were revealed by β-catenin immunohistochemistry. Duct- and rosette-like structures in AOT were both positive for SATB2 and β-catenin, showing similar immunohistochemical profiles to ameloblast-lineage cells in developing odontoma. Two immunohistochemically distinct cell types were identified in nodules in AOT, and both cell types showed different immunohistochemical profiles from morules in WNT-OTs. The fibrous capsule of AOT showed similar SATB2 and CD10 expression patterns to the dental follicle in developing odontoma. In AOTs associated with a large cyst, the change in SATB2 expression was found in the basal layer of the cystic lining connected to the tumor. All 3 AOTs studied harbored the *KRAS* G12V mutation without other pathogenic mutations.
Conclusion: SATB2, β-catenin, and CD10 immunohistochemistry provides novel insights into the histopathologic patterns, cellular differentiation, and tumor development of AOT and may aid in its diagnosis.

Introduction

Adenomatoid odontogenic tumor (AOT) is a benign epithelial odontogenic tumor characterized by its unique histopathologic features. AOT is mainly surrounded by a thick fibrous capsule and consists of variably sized nodules of epithelial cells. Neoplastic epithelial cells are cuboidal, columnar or spindle in shape. Cuboidal and columnar cells may form duct- or rosette-like structures, imparting an "adenomatoid" appearance, and spindle cells are usually observed between these structures. Anastomosing strands of epithelial cells are mostly located at the periphery of nodules. Some AOTs contain cystic lining composed of non-keratinized stratified squamous epithelium, as seen in dentigerous cyst.[1–4] These diverse histologic components may be seen to varying degrees in individual cases.

Several immunohistochemical studies have been conducted in AOT, primarily focusing on its expression of intermediate filament proteins, including cytokeratins and vimentin, and extracellular matrix proteins, including enamel and dentin matrix proteins.[3,4] In duct- or rosette-like structures, cytokeratin 19 was strongly positive in columnar ameloblast-like cells but negative in other cells.[4,5] Vimentin was generally negative in nodular cells but consistently expressed in the periphery of nodules, including anastomosing strands.[3,4] This intratumoral heterogeneity of immunohistochemical markers may highlight underrecognized histopathologic patterns and demonstrate the process of tumor development. In addition, immunohistochemical profiling may provide insights into the cellular differentiation of AOT if tested along with its possible tissues of origin, including tooth germ, odontogenic epithelial rests, and cystic lining.[1,2,5]

WNT pathway-altered odontogenic tumors (WNT-OTs) represent a genetically distinct group of odontogenic tumors that harbor mutations in WNT pathway genes and share histologic features, such as ghost cells, dentinoid, and whorled cellular condensations known as morules.[1,6–8] It has been recently demonstrated that several morular markers, including special AT-rich sequence binding protein 2 (SATB2), caudal type homeobox 2 (CDX2), and CD10, may be useful in differentiating WNT-OTs from their histologic mimics, ameloblastoma or ameloblastic carcinoma.[9] Intriguingly, AOT may also show "whorled cellular masses" consisting of neoplastic epithelial cells,[2] warranting further investigation into its possible expression of morular markers. β-catenin is another morular marker, and its nuclear translocation, a classic hallmark of WNT pathway activation, is consistently observed in all types of WNT-OTs; however, nuclear β-catenin expression has also been frequently identified in odontogenic tumors without WNT pathway mutations (non-WNT-OTs), including ameloblastoma and odontoma.[9–12] Thus, further studies on other types of non-WNT-OTs, such as AOT with a higher prevalence of *KRAS* G12 mutations,[13] are needed to determine the diagnostic value of β-catenin immunohistochemistry.

In this study, we investigated the immunohistochemical expression of SATB2, β-catenin, CD10, and CDX2 in AOT, compared to other odontogenic tumors, to identify its histopathologic patterns and cellular differentiation.

Materials and methods

Tissue specimens

A total of 24 odontogenic tumors, consisting of 11 AOTs, 6 developing odontomas, and 7 WNT-OTs, were included in this study. The 7 WNT-OTs consisted of 5 dentinogenic ghost cell tumors (DGCTs) and 2 adenoid ameloblastomas (AAs), which were previously studied.[9] Non-decalcified, formalin-fixed, paraffin-embedded (FFPE) tissues were retrieved from the pathology archives of the authors' institutions. All diagnoses were confirmed according to the World Health Organization (WHO) classification.[1] This study was performed in accordance with the Declaration of Helsinki and

was granted exemption by the Institutional Review Board of Seoul National University Dental Hospital (No. ERI22030).

SATB2, β-catenin, CD10, and CDX2 immunohistochemistry

Immunohistochemical staining for SATB2, β-catenin, CD10, and CDX2 was performed using a Leica BOND-MAX autostainer (Leica Biosystems, Newcastle Upon Tyne, United Kingdom) and in vitro diagnostic antibodies against SATB2 (clone EP281; 1:200; 384R-14, Cell Marque, Rocklin, CA, USA), CDX2 (clone EP25; ready-to-use; PA0375, Leica Biosystems), CD10 (clone 56C6; ready-to-use; PA0270, Leica Biosystems), and β-catenin (clone 14; 1:100; 224M−14, Cell Marque) as previously described.[9]

Immunohistochemically stained slides were evaluated for each histologic component by tumor type. Cells showing strong/clear nuclear (SATB2, β-catenin, CDX2) or membranous (CD10) staining were considered positive, whereas weak/faint staining was considered negative. The histologic components in each slide were scored based on the percentage of positive cells as follows: 0 (negative), $<$ 1 %; 1 (rare), 1 %−9%; 2 (focal), 10 %−49 %; 3 (diffuse), $\geq$ 50 %. Each histologic component by tumor type was finally scored based on the percentage of positive cases (score $\geq$ 1, rare to diffuse) as follows: − (negative), $<$ 10 %; $\mp$ (occasionally positive), 10 %−49 %; $\pm$ (frequently positive), 50 %−89 %; + (mostly positive), $\geq$ 90 %.

Next-generation sequencing

To determine the presence of *KRAS* mutations and the independence between nuclear β-catenin expression and WNT pathway mutations in AOT, whole-exome sequencing was performed to identify somatic mutations in 3 AOT cases with sufficient tissue available, as previously described.[6,7] Genomic DNA was extracted from FFPE tissue sections using the QIAamp DNA FFPE Tissue kit (Qiagen, Hilden, Germany) according to manufacturer's instructions. Exome capture was performed using the SureSelect Human All Exon V8 (Agilent Technologies, Santa Clara, CA, USA), and libraries were sequenced on an Illumina Hiseq platform (Illumina, San Diego, CA, USA). Sequence reads were aligned to the hg38 human reference genome using the Burrows-Wheeler Aligner (BWA-0.7.19). Variants were called and filtered using the Genome Analysis Toolkit (GATK v4.0.5.1) and annotated using SnpEff (v.5.0e).

Sanger sequencing

To further validate the presence of *KRAS* mutations, Sanger sequencing was performed as previously described.[14] Primers for polymerase chain reaction (PCR) and sequencing were designed to amplify exon 2 of the *KRAS* gene (forward: 5′-GTGTGACATGTTCTAATATAGTCA-3'; reverse: 5′-GAATGGTCCTGCACCAGTAA-3′). PCR was performed as follows: initial denaturation at 95 °C for 5 min, 35 cycles of amplification (denaturation at 95 °C for 30 s, annealing at 58 °C for 30 s, and extension at 72 °C for 60 s), and final extension at 72 °C for 7 min. PCR products were sequenced using the Applied Biosystems 3730XL DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Sequencing results were analyzed using Variant Reporter Software version 2.1 (Applied Biosystems).

RAS G12V immunohistochemistry

To identify the expression of KRAS G12V protein in *KRAS* G12V-mutant AOTs, immunohistochemistry was performed using a Leica BOND-MAX autostainer and a rabbit monoclonal RAS (G12V mutant) antibody (clone HL169; GTX635623; GeneTex, Irvine, CA, USA) according to the manufacturer's instructions. To further validate the specificity of the antibody to RAS G12V proteins, a *KRAS* G12D-mutant ameloblastoma[15] and a wild-type *KRAS* oral squamous cell carcinoma were used.

Results

The results of SATB2, β-catenin, CD10, and CDX2 immunohistochemistry studied are summarized in Table 1.

Table 1 Results of Special AT-rich sequence binding protein 2 (SATB2), β-catenin, CD10, and CDX2 immunohistochemistry in this study.

	SATB2	β-catenin	CD10	CDX2
Adenomatoid odontogenic tumor				
Central nodular cells	+	−	−	−
Large duct-like structures	+/−	+/−	−	−
Small duct-like structures	+	+	−	−
Rosette-like structures	+	+	−	−
Circumferential nodular cells	−	−	+	−
Peripheral anastomosing strands	+	−	+/−	−
Cystic lining	+ (basal)	−	+ (upper)	−
Fibrous capsule	+	−	+ (inner)	−
Developing odontoma				
Inner enamel epithelium	−/+	+	−	−
Preameloblasts	−	+	−	−
Presecretory ameloblasts	+	+	−	−
Reduced enamel epithelium	−	+/−	−	−
Odontoblasts	+	−	−	−
Dental papilla	+	+/−	+/−	−
Dental follicle	+	−	+ (inner)	−
Adenoid ameloblastoma & dentinogenic ghost cell tumor				
Morules	+	+	+	+/−
Around ghost cells	−/+	+	−/+	−
Clear cells	+/−	+	−	−
Dentinoid cells	+	−	−	−

−, negative; −/+, occasionally positive; +/−, frequently positive; +, mostly positive.

Histopathologic patterns highlighted by immunohistochemistry in adenomatoid odontogenic tumor

A nodular growth pattern in AOT was highlighted by CD10 immunohistochemistry, which was negative in central cells but positive in circumferential cells surrounding the central nodular cells (Fig. 1A and B). Morphologically, CD10-positive circumferential cells were spindle in shape, while $CD10^{-}$ central cells were generally cuboidal. Duct- and rosette-like structures, consisting of cuboidal or columnar cells, were also negative for CD10 (Fig. 1C—F).

In AOT, β-catenin immunohistochemistry revealed aggregates of small duct-like structures composed of cuboidal cells with nuclear staining, in contrast to adjacent central or circumferential nodular cells with only cytoplasmic staining (Fig. 2). Although small duct-like structures containing eosinophilic material were recognizable in hematoxylin and eosin-stained slides by thorough histologic examination (Fig. 2A and C), these characteristic histopathologic patterns were more easily detectable by β-catenin immunohistochemistry (Fig. 2B and D).

Cellular differentiation of the histologic components in adenomatoid odontogenic tumor

In AOT, large duct-like structures (Fig. 3A and B), rosette-like structures (Fig. 3C and D), and small duct-like structures (Fig. 3E and F) were distributed within nodules in AOT, all of which were positive for SATB2 and β-catenin but

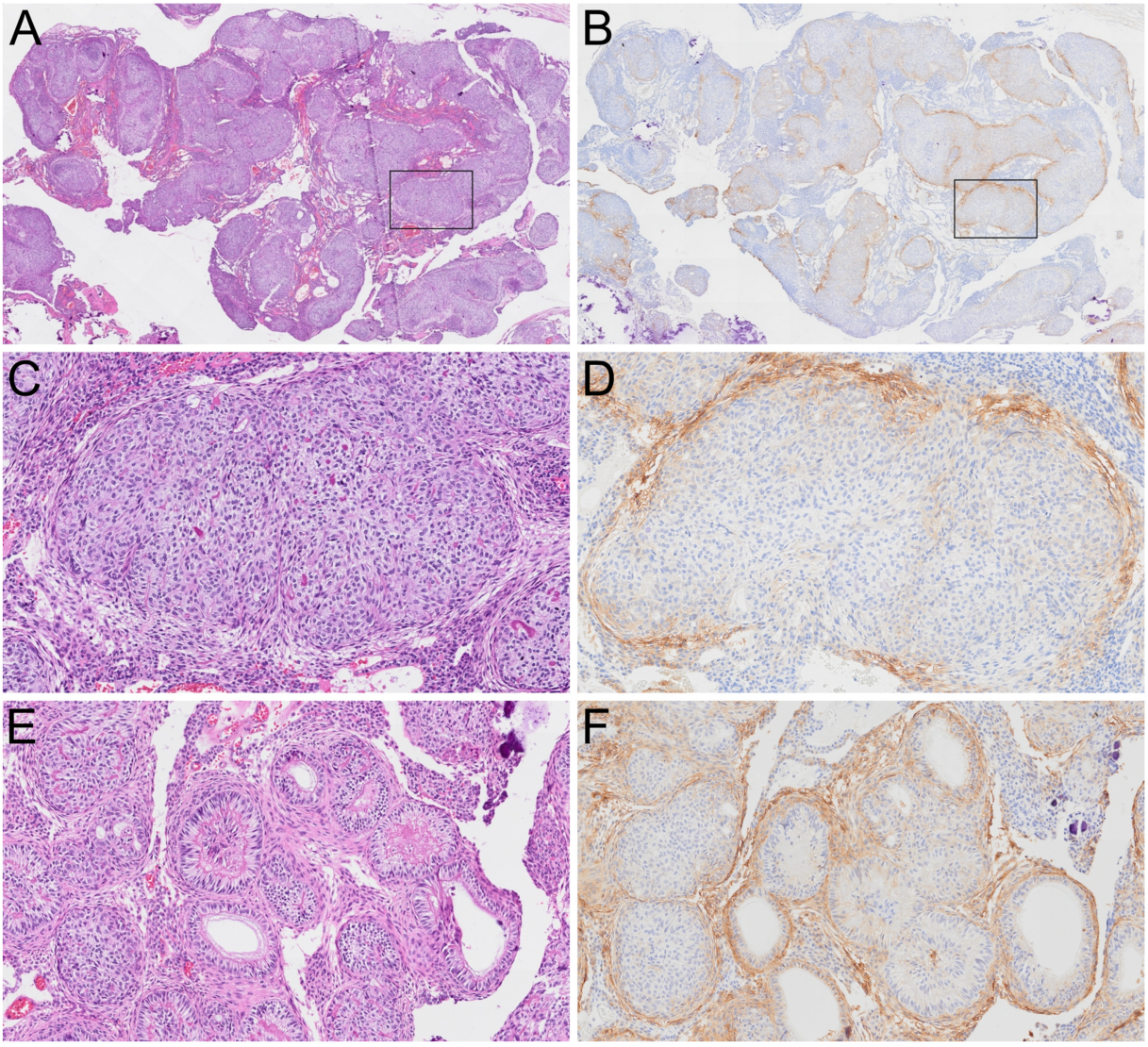

Figure 1 Nodular growth pattern in adenomatoid odontogenic tumor observed by hematoxylin and eosin (A, C, E) and CD10 (B, D, F) staining. (A, B) Nodules of varying sizes and shapes are surrounded by CD10-positive circumferential cells. (C—F) Spindle-shaped circumferential nodular cells are positive for CD10, whereas central nodular cells and duct- and rosette-like structures are negative or only weakly/faintly positive for CD10. C and D are the high-magnification images of the boxed areas in A and B, respectively. Original magnification × 40 (A, B); × 200 (C—F).

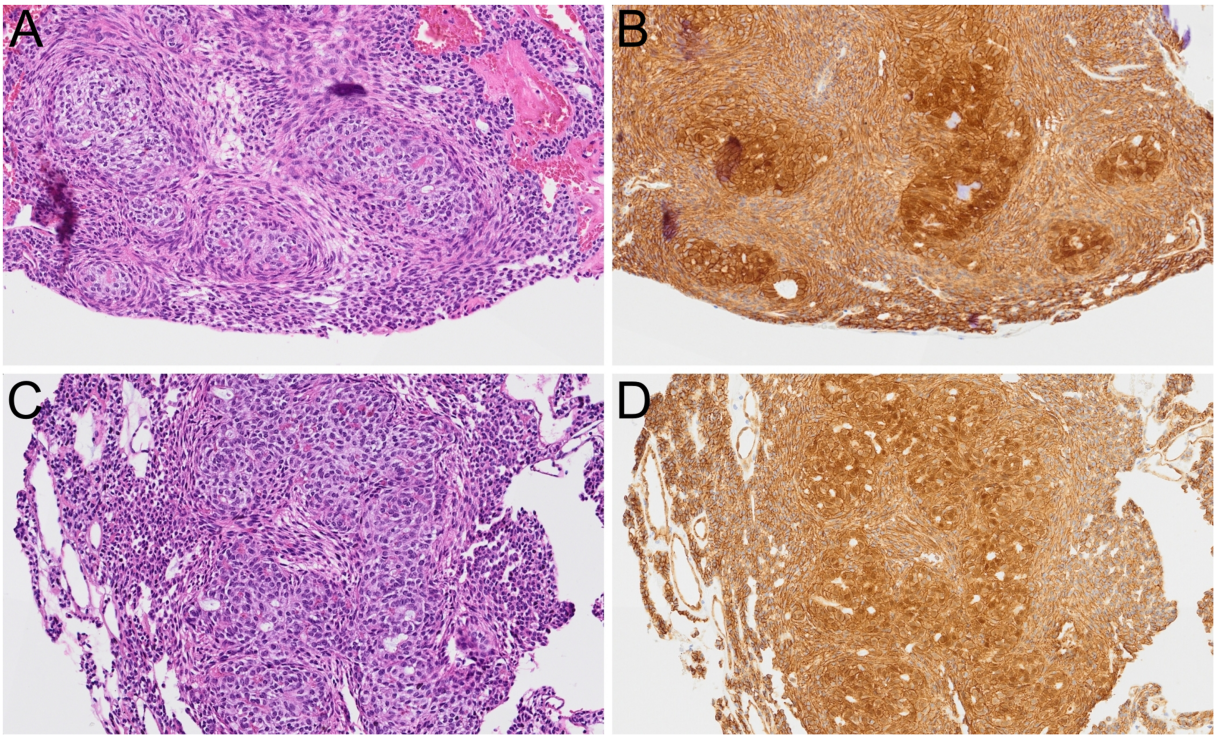

Figure 2 Small duct-like structures in adenomatoid odontogenic tumor. Aggregates of small duct-like structures are more easily detectable by β-catenin immunohistochemistry (B, D) than by routine hematoxylin and eosin staining (A, C). Nuclear β-catenin expression is found in cells forming duct-like structures, whereas adjacent nodular cells show only cytoplasmic staining (B, D). Original magnification × 200.

negative for CD10 and CDX2, demonstrating shared immunohistochemical profiles between these histologically distinct structures. In addition, similar immunohistochemical features (SATB2 +/β-catenin +/CD10 − /CDX2 −) were also seen in presecretory ameloblasts in developing odontoma (Fig. 3G and H). These immunohistochemical findings suggest that duct-like structures, regardless of their size, and rosette-like structures may share cellular differentiation into ameloblast-lineage cells.

Nodules in AOT consisted of two immunohistochemically distinct cell types: central nodular cells (SATB2 + /β-catenin − /CD10 − /CDX2 −) and circumferential nodular cells (SATB2 − /β-catenin − /CD10 +/CDX2 −) (Fig. 4A–E). On the other hand, morules in WNT-OTs (DGCT, AA) showed different immunohistochemical profiles (SATB2 +/β-catenin +/CD10 +/CDX2 ±) from the two types of nodular cells in AOT (Fig. 4F–J). These findings indicate that nodular structures in AOT and morular structures in WNT-OTs represent two distinct processes of tumor cell differentiation.

The fibrous capsule of AOT was positive for SATB2, and its inner part, adjacent to neoplastic epithelial cells, was positive for CD10 (Fig. 5A and B). Likewise, the dental follicle observed in developing odontoma was positive for SATB2 and CD10, the latter of which was also limited to the inner part (Fig. 5C and D). These findings suggest that the fibrous capsule of AOT may show cellular differentiation similar to the dental follicle, in the same context with the well-known radiological and macroscopic characteristics of the tumor.[1]

Tumor development from the cystic lining in adenomatoid odontogenic tumor

In 4/11 (36.4 %) AOT cases examined, a large cyst histologically identical to dentigerous cyst was observed in close association with the tumor (Fig. 6A–C). CD10 was expressed in the upper layers of the cystic lining (Fig. 6D), including the areas in close proximity to the AOT tissue (Fig. 6E). On the other hand, while SATB2 was negative in all layers of the cystic lining located away from the tumor portion (Fig. 6F), the basal layer connected to the AOT tissue showed SATB2 staining, indicating the change in protein expression to the immunohistochemical profile of the tumor (Fig. 6G). These findings suggest that a subset of AOTs may develop from a pre-existing odontogenic cyst.

Genetic alterations in adenomatoid odontogenic tumor

All of the 3 AOT cases studied using whole-exome sequencing harbored the *KRAS* p.G12V (c.35G > T) mutation (Supplementary Table 1). No other pathogenic mutations were observed in MAPK (including *BRAF*, *NRAS*, *HRAS*, *FGFR2*), WNT (including *CTNNB1*, *APC*, *NEDD4L*, *SMURF1*),

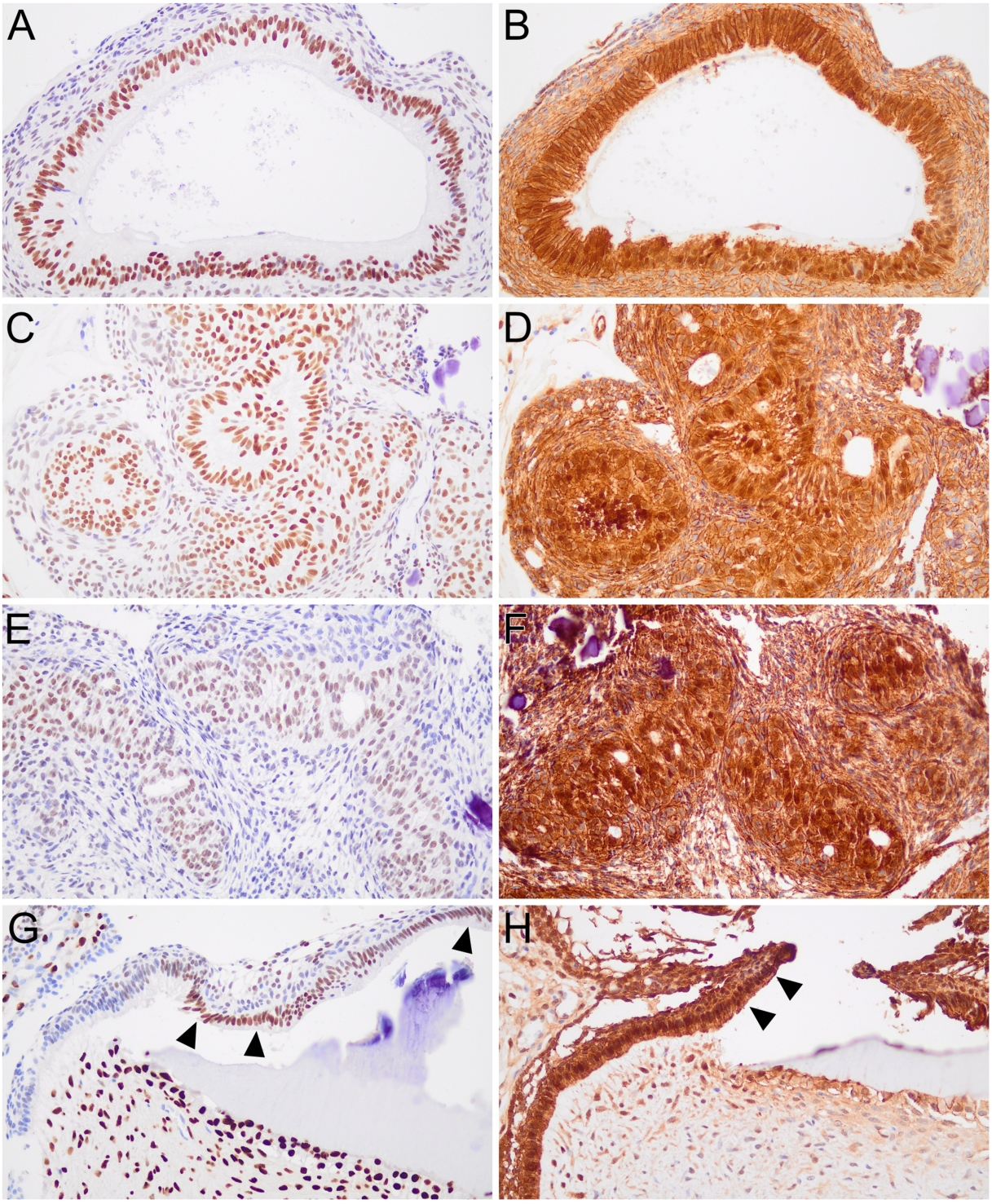

Figure 3 Special AT-rich sequence binding protein 2 (SATB2) (A, C, E, G) and β-catenin (B, D, F, H) staining in adenomatoid odontogenic tumor (A–F) and developing odontoma (G, H). Cells forming large duct-like structures (A, B), rosette-like structures (C, D), and small duct-like structures (E, F) are all positive for SATB2 and β-catenin. (G, H) Similar immunohistochemical profiles are observed in ameloblast-lineage cells, especially in presecretory ameloblasts (arrowheads). SATB2 is also expressed in odontoblasts producing dentin matrix and dental papilla mesenchymal cells (G), and β-catenin shows strong/clear staining in a subset of dental papilla mesenchymal cells and weak/faint staining in odontoblasts (H). Original magnification × 400.

and SHH (including *SMO*, *PTCH1*) pathway genes, reported to be altered in other types of odontogenic tumors.[1,6,7,16,17] The presence of the *KRAS* p.G12V (c.35G > T) mutation was also identified by Sanger sequencing in all of the 3 AOTs (Fig. 7). The results of RAS G12V immunohistochemistry are summarized in Supplementary Fig. 1.

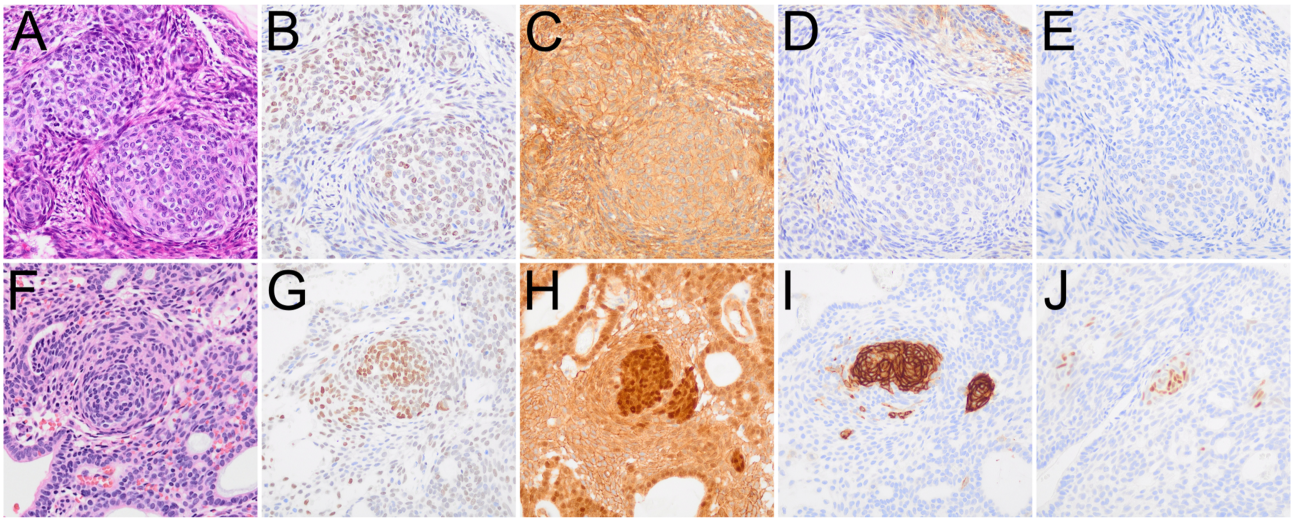

Figure 4 Comparison of hematoxylin and eosin (A, F), Special AT-rich sequence binding protein 2 (SATB2) (B, G), β-catenin (C, H), CD10 (D, I), and CDX2 (E, J) staining between adenomatoid odontogenic tumor (A–E) and adenoid ameloblastoma (F–J). (A–E) Central nodular cells (SATB2 +/β-catenin − /CD10 − /CDX2 −) and circumferential nodular cells (SATB2 − /β-catenin − /CD10 + /CDX2 −) are seen in adenomatoid odontogenic tumor. (F–J) Whorled cellular condensations called morules (SATB2 + /β-catenin +/CD10 +/CDX2 ±) are noted in adenoid ameloblastoma. Original magnification × 400.

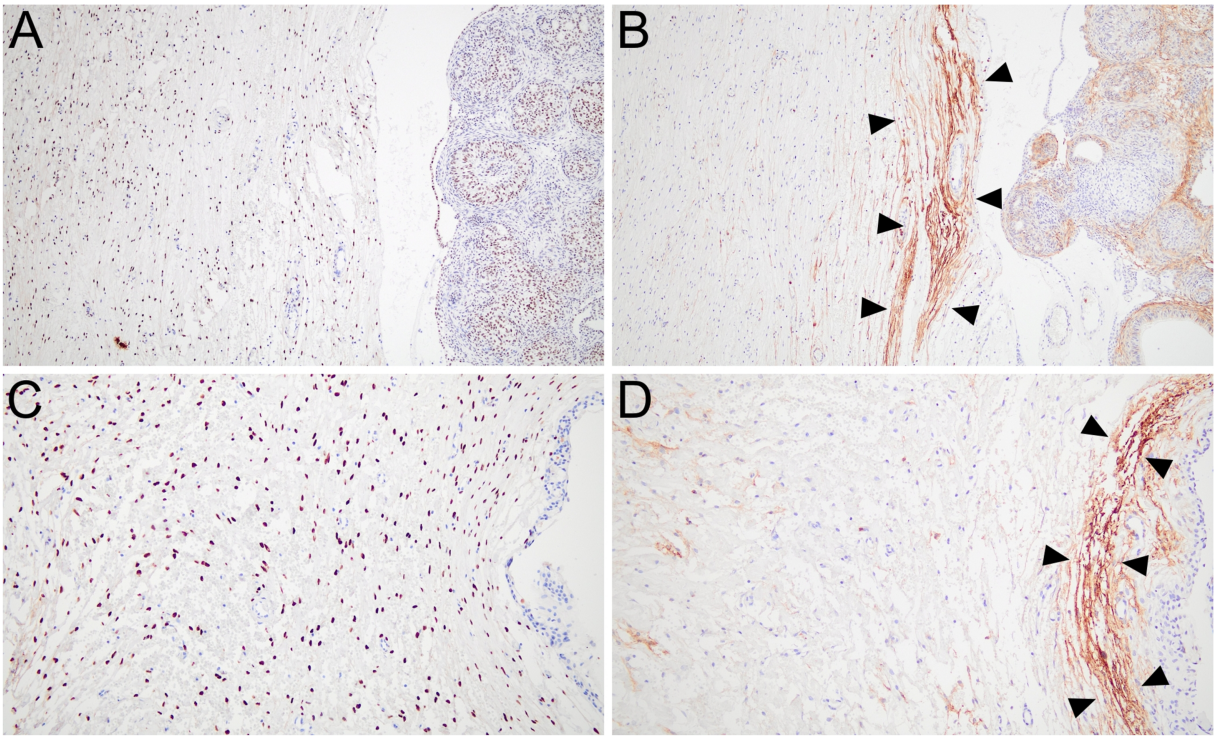

Figure 5 Special AT-rich sequence binding protein 2 (SATB2) (A, C) and CD10 (B, D) staining in adenomatoid odontogenic tumor (A, B) and developing odontoma (C, D). The fibrous capsule of adenomatoid odontogenic tumor is positive for SATB2 (A), and its inner part (arrowheads) is positive for CD10 (B). The dental follicle shows similar expression patterns of SATB2 (C) and CD10 (D). Original magnification × 100 (A, B); × 200 (C, D).

Discussion

Among the histologic components seen in AOT, duct- and rosette-like structures may be most representative of the tumor and, accordingly, are widely used for its definition.[1] Interestingly, the histologic transition between duct- and rosette-like structures has been demonstrated in a previous study by using serial sections.[3] In a similar context, the shared immunohistochemical features characterized by SATB2 and β-catenin positivity were also identified

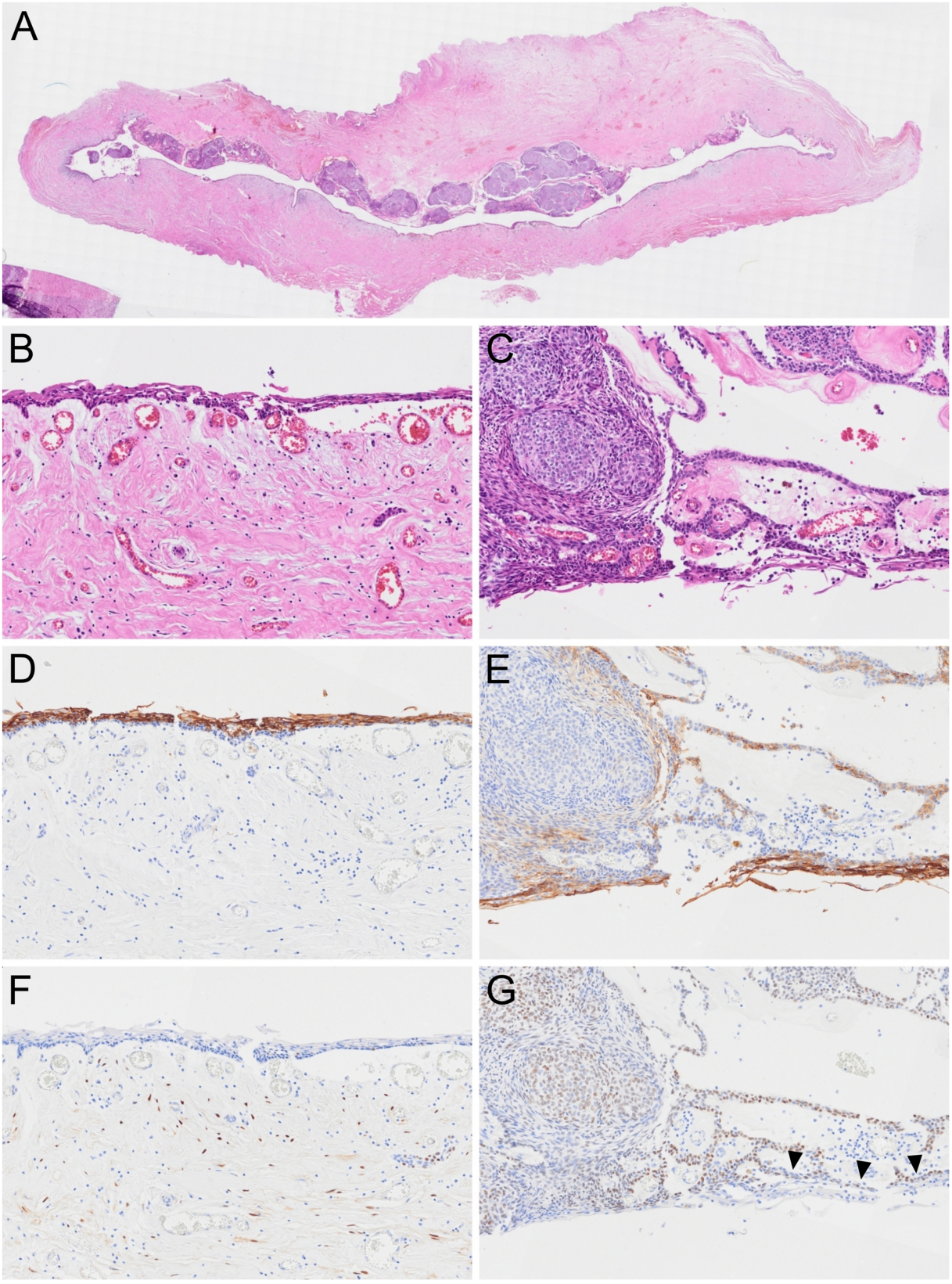

Figure 6 Adenomatoid odontogenic tumor arising in a dentigerous cyst. (A) A low-power histologic image shows a large cyst with focal epithelial proliferation. (B) The cystic lining consists of a thin layer of non-keratinized stratified squamous epithelium as seen in dentigerous cyst. (C) Adenomatoid odontogenic tumor is seen in close proximity to the cystic lining. (D, E) CD10 is positive in the upper layers of the cystic lining. Special AT-rich sequence binding protein 2 (SATB2) is negative in all layers of the cystic lining located away from the tumor (F) but positive in the basal layer of the cystic lining (arrowheads) connected to the tumor tissue, which also shows SATB2 positivity (G).

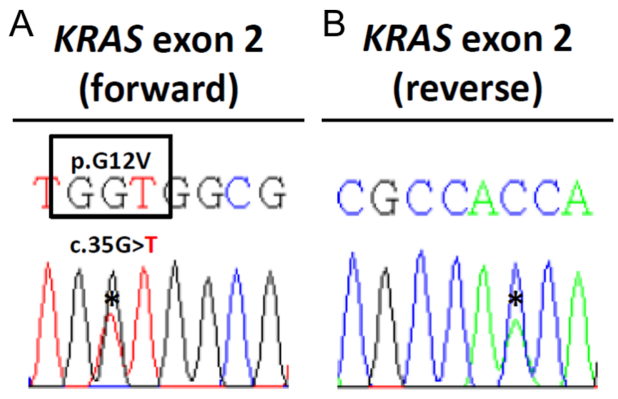

Figure 7 The *KRAS* c.35G > T (p.G12V) mutation is identified by Sanger sequencing in both forward (A) and reverse (B) directions.

between the two structures in this study. In addition, immunohistochemical staining highlighted aggregates of small duct-like structures composed of cuboidal cells, which were previously underrecognized in the literature,[2,4] as well as well-known large duct-like structures composed of columnar cells with polarized nuclei. It has been postulated that cells forming duct-like structures in AOT are derived from the inner enamel epithelium at the presecretory stage based on ultrastructural findings.[18] In support of this assumption, we demonstrated that ameloblast-lineage cells, particularly presecretory ameloblasts, show immunohistochemical profiles analogous to those observed in the duct- and rosette-like structures. Collectively, these results suggest that the formation of these distinctive histopathologic patterns in AOT may be attributable to the differentiation of tumor cells into ameloblast-lineage cells.

WNT-OTs generally show the histologic component known as morules, which are also referred to as "whorled cellular condensations,"[1,6,7] and a somewhat similar term "whorled cellular masses" is sometimes used in the literature to describe a nodular growth pattern in AOT.[2,19] In this study, however, the differences in immunohistochemical expression were confirmed between morules in WNT-OTs and nodular cells in AOT, representing two distinct differentiations of odontogenic tumor cells. In WNT-OTs, it has been speculated that the consistent expression of SATB2 by tumor cells may be involved in the formation of dentinoid, given its function in odontoblastic differentiation and association with WNT pathway activation.[9,20,21] In AOTs investigated in this study, SATB2 expression was observed in most histologic components except circumferential nodular cells. It is noteworthy that the expression of SATB1, comprising special AT-rich sequence-binding protein (SATB) family proteins along with SATB2,[22] has been reported in ameloblast-lineage cells in mouse teeth, with the highest intensity in presecretory ameloblasts,[23] which is similar to the expression pattern of SATB2 in ameloblast-lineage cells in developing odontoma observed in this study. As mentioned above, AOT shows differentiation into ameloblast-lineage cells in part, and its eosinophilic secretory material has a histologic resemblance to enamel matrix.[1,24] Consequently, it can be inferred that SATB2 may play a role in the production of enameloid by neoplastic epithelial cells in AOT.

It has been reported that nuclear translocation of β-catenin, a hallmark of WNT pathway activation, can be identified in the absence of WNT pathway mutations in odontogenic tumors. In ameloblastoma, β-catenin immunohistochemistry shows nuclear staining frequently in follicular islands and cystic structures.[9–11] A previous study on odontoma demonstrated nuclear β-catenin in odontogenic epithelial rests.[12] In this study, nuclear β-catenin expression was observed in epithelial cells, including ameloblast-lineage cells and reduced enamel epithelium, in developing odontoma and, additionally, in cells forming duct- and rosette-like structures in AOT, with no WNT pathway mutations detected. Taken together, WNT pathway activation, mediated by nuclear β-catenin, seems to be involved in the development of specific histologic components in some odontogenic tumors, not as a result of genetic alterations but rather in the context of tumor cell differentiation.

AOT has well-known radiological and macroscopic features characterized by a well-defined, unilocular radiolucency involving the crown of an unerupted tooth and a thick fibrous capsule easily identified during gross examination.[1,2] The results of this study demonstrated similarities in the expression patterns of SATB2 and CD10 between the fibrous capsule of AOT and the dental follicle, suggesting that the formation of the fibrous capsule may result from the proliferation of the odontogenic mesenchyme rather than adjacent non-odontogenic fibrous tissue. Whether this finding represents a neoplastic or reactive process remains to be elucidated. In our previous study, aberrant SATB2 expression has also been identified in the stroma of WNT-OTs and ameloblastomas.[9] Therefore, further studies are warranted to determine the biological nature of fibrous connective tissue seen in odontogenic tumors, which may be facilitated by evaluating the expression of proteins such as SATB2. In addition, although comprehensively analyzing the expression of morular markers in odontogenic neoplasms, this study is limited by the lack of normal odontogenic tissues, such as tooth germs, in the cases studied.

In conclusion, SATB2, β-catenin, and CD10 immunohistochemistry provides novel insights into the histopathologic patterns, cellular differentiation, and tumor development of AOT and may aid in its diagnosis.

Declaration of competing interest

The author has no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2025.11.003.

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