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Immunohistological Features in Adenomatoid Odontogenic Tumor: Review of the Literature and First Expression and Mutational Analysis of β-Catenin in This Unusual Lesion of the Jaws

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Purpose: To investigate for the first time the immunohistochemical and mutational status of β-catenin in a mandibular case of adenomatoid odontogenic tumor (AOT) and to review the immunohistochemical expression data of various markers (cytokeratins, metalloproteinases, etc) in such a lesion.

Materials and Methods: A case of follicular-type AOT in a young male patient was analyzed in regard to the immunohistochemical expression of β-catenin and mutations of the β-catenin gene *(CTNNB1)*. Its expression is altered in some odontogenic tumors.

Results: We found a strong cytoplasmic expression of β-catenin, but no molecular anomaly within the exon 3 of *CTNNB1*. β-catenin is considered to play a role in cell differentiation processes.

Conclusion: Our results were consistent with previous findings in ameloblastoma and malignant odontogenic tumors. However, β-catenin alterations had not been explored in AOT so far. Further studies are necessary to understand the specific regulation of β-catenin in the AOT pathogenesis.

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The adenomatoid odontogenic tumor (AOT) is a rare lesion of the jaws that accounts for approximately 2.2% to 7.1% of all odontogenic tumors.[1] This slow-growing benign lesion of odontogenic epithelial origin was first described in 1905 by Steenlands[2] under the name of epithelioma adamantinum. Harbitz[3] in 1915 and Ghosh[4] in 1934 later called it cystic adamentoma or adamantinoma. Therefore, this tumor has long been considered as a variant of ameloblastoma. Generating considerable confusion, various classifications, such as ameloblastic adenomatoid tumor, pseudoadenomatoid ameloblastoma, adenoameloblastic odontoma, and cystic odontoma, are still used, contributing to the difficulties in distinguishing it from other odontogenic tumors, especially from ameloblastoma. In 1948, Stafne[5] acknowledged AOT as a distinct histological entity among the odontogenic tumors, and in 1969, Philipsen and Birn[6] dubbed it adenomatoid odontogenic tumor to distinguish it from ameloblastoma. The term AOT appeared to be the most appropriate and was eventually adopted in 1971 by the World Health Organization (WHO) in its first edition of the classification of odontogenic tumors. Indeed AOT is a benign tumor that usually does not recur, in contrast to ameloblastoma. According to the 1992 WHO

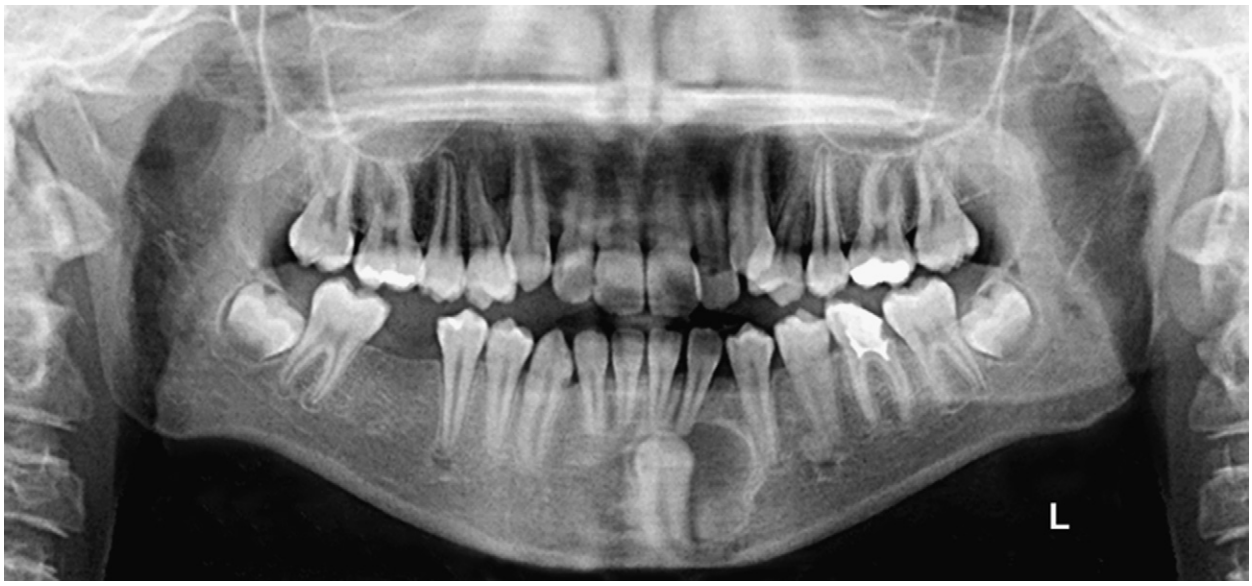

FIGURE 1. Panoramic radiograph showing a unilocular well-circumscribed radiolucency with radiopaque foci involving the left mandibulary impacted canine. Displacement of the mandibulary left lateral incisor.

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

Classification, AOT belongs to benign tumors related to the odontogenic apparatus, with odontogenic epithelium and odontogenic ectomesenchyme, with or without dental hard tissue formation. In 2005, the histological typing of the WHO defined AOT as a tumor composed of odontogenic epithelial wall presenting a variety of histoarchitectural patterns, and characterized by a slow but progressive growth.[1] Despite these advances for a better characterization of this tumor, the histogenesis of AOT is still under debate. Because the Wnt-signaling pathway is crucial in the formation of human teeth, alterations of the β-catenin gene (*CTNNB1*) sequence and of its protein product expression have been investigated in some odontogenic tumors[7-11]. However, to our knowledge, the status of β-catenin has not been explored in AOT so far. In this study, we present a clinicopathological description of this infrequent benign tumor in a young male patient.

The tumor belonged to the intra-osseous follicular type and affected the anterior area of the mandible. It was associated with an impacted lower left canine. We evaluated the mutational status and expression pattern of β-catenin.

Materials and Methods

CLINICAL CASE REPORT

A 14-year-old boy was referred to the Department of Oral Surgery, Faculty of Dentistry, University of Nice Sophia-Antipolis (France) in February of 2009 for an impacted lower left canine. Intraoral examination showed a 0.5 cm in diameter single swelling, without any other related symptoms, perceptible only on palpation. The overlying mucosa of that area of the mandible was normal. There was no history of trauma or pain. Facial symmetry was maintained. A panoramic radiograph revealed a circumscribed unilocular radiolucent area with fine calcifications, involving impaction of the left lower permanent canine (Fig 1). Several diagnostic hypotheses were considered preoperatively: *1)* dentigerous cyst, because of the radiolucency containing a tooth crown; *2)* AOT, because of a radiolucency containing an impacted tooth in association with radio-opacities; and *3)* calcifying epithelial odontogenic tumor (Pindborg tumor), which presents the same radiological characteristics as AOT. The patient was admitted for surgical treatment with local

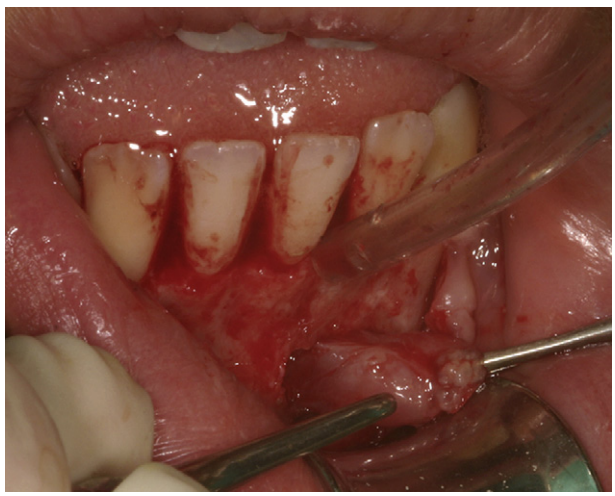

FIGURE 2. Intraoperative photographs showing the tumoral enucleation.

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

anesthesia. The tumor was enucleated (Fig 2) before extraction of the impacted tooth and curettage of bone cavity. Macroscopic examination showed a single thick well-encapsulated cystic lesion, measuring 2.5 cm × 1 cm. Healing was uneventful 8 months after the surgery.

HISTOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSES

The 4-μm-thick and 2-μm-thick sections of formalin-fixed, paraffin-embedded tissue were processed for light microscopic examination and immunohistochemical (IHC) analysis, respectively. Four-μm-thick sections were prepared and stained by hematoxylin and eosin (H-E), and periodic acid-Schiff (PAS) reaction, which was performed for completing H-E staining examination (better visualization of basal lamina and potential infiltration).

Deparaffinization and antigen retrieval were made using the pretreatment module PT Link (Dako, Glostrup, Denmark) at 97°C for 20 minutes. Immunostaining was performed using the EnVision Flex, High pH Mini kit (Dako). Incubation was performed using the polyclonal rabbit β-catenin antibody (clone C-2206; SIGMA, San Francisco, CA) at a dilution 1:2000 for 20 minutes at room temperature.

The binding antibody was visualized with diaminobenzidine (DAB), and the slide was lightly counterstained with hematoxylin. Expression of β-catenin was assessed in the nucleus, membrane, and cytoplasm separately. The staining was classified as positive when more than 70% of the tumor cells were positively stained. The positive and negative external controls consisted in detection of β-catenin expression in membrane but not in nucleus and cytoplasm of epithelial cells from a normal gingival epithelium. The same method was applied for E-cadherin using HECD-1 (Invitrogen, Camarillo, CA), a mouse monoclonal antibody that reacts with human epithelial cadherin.

MOLECULAR ANALYSIS

DNA extraction from ten 4-μm-thick formalin-fixed and paraffin-embedded tissue tumor sections was performed using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). Detection of mutations within the exon 3 of *CTNNB1* gene was performed using both pyrosequencing and DNA direct sequencing reactions. For pyrosequencing, a sequence within exon 3 was amplified by polymerase chain reaction (PCR) using forward and reverse primers β-catenin-F-pyro (5'-CAAC AGTCTTACCTGGACTCTGG-3') and β-catenin-R-pyro (5'-CAGGATTGCCTTTACCACTCA-3'; 5' biotinylated), designed using Pyromark Design Assay SW (Qiagen). The PCR was performed using the following conditions: 10 minutes at 95°C for initial denaturation, followed by 35 cycles of 30 seconds at 94°C, 30 seconds at 50°C, 30 seconds at 72°C and a final extension at 72°C for 10 minutes. The pyrosequencing reaction was performed according to the manufacturer's recommendations using a Q24 Pyromark (Qiagen). The primer sequence β-catenin-S (5'-CCATTCTGGTGCCACT-3') was designed using the Pyromark Design Assay SW (Qiagen).

DNA direct sequencing reaction was performed using PCR with forward and reverse primers ß-cat-1F (5'-TCCAATCTACTAATGCTAATACTGTTTCGTA-3') and ß-cat-1R (5'-AGGTATCCACATCCT CCT CCTC AG-3'). PCR was performed under the following conditions: 10 minutes at 95°C for initial denaturation, 35 cycles at 30 seconds at 94°C, 30 seconds at 51°C, 30 seconds at 72°C and final extension at 72°C for 10 minutes. The PCR products were subjected to electrophoretic migration in a 2% (w/v) agarose gel, visualized under UV light with ethidium bromide staining and recovered using the High Pure PCR Product Purification Kit (Roche Diagnostics, Mannheim, Germany). Direct sequencing was performed using the above primer (β-cat-1F) with the kit Big Dye Terminator v1.1 Cycle sequencing (Applied Biosystems, Foster City, CA) and ABI Prism 3100 Genetic Analyser (Applied Biosystems).

Results

HISTOLOGICAL FINDINGS

The histological examination showed ameloblast-like epithelial cells forming solid nodules and duct-like structures (Fig 3). Columnar and cuboidal cells that contained oval nuclei were part of these solid nodules that formed rosette-like patterns and sometimes single-row duct-like spaces. Elongated cells surrounded these 3 structures and spindle-shape cells,

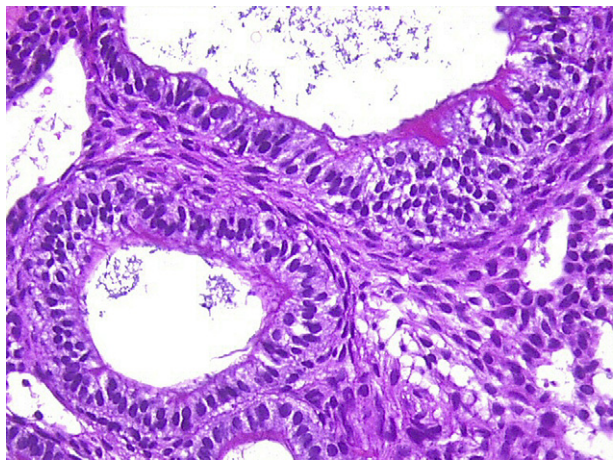

FIGURE 3. Photomicrograph (H/E 400×) showing duct-like structures.

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

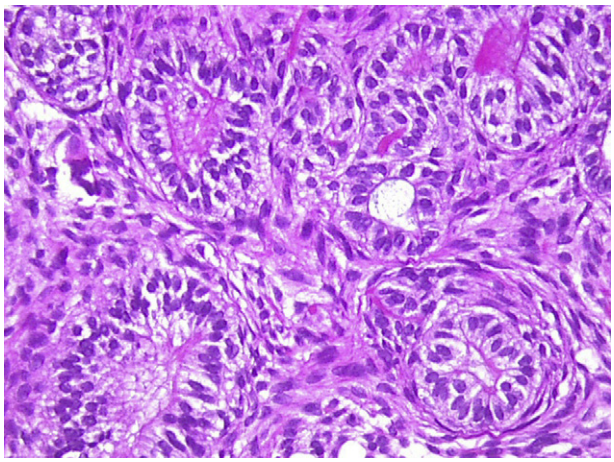

FIGURE 4. Photomicrograph (H/E 400×) showing rosette-like structures with eosinophilic amorphous material.

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

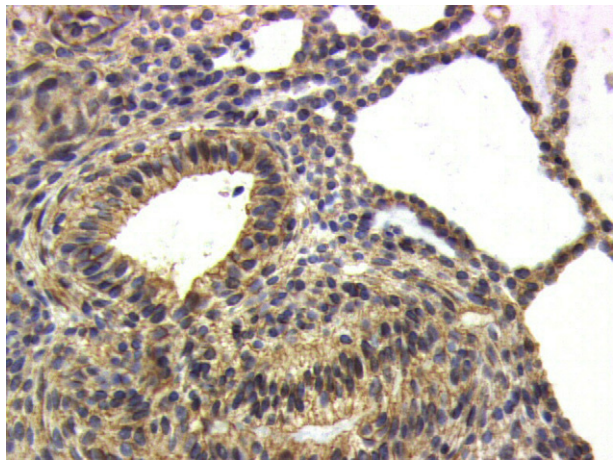

FIGURE 6. Representative immunohistochemical staining (400×) of ß-catenin protein localized in the cell membrane and cytoplasm.

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

toward peripheral portions of the tumor, formed trabecular patterns (Fig 4). Hyaline eosinophilic bodies (eosinophilic drops), PAS-positive diastase resistant, were observed at the intercellular level in the proliferative nodules and in luminal duct-like structures. Irregular displaced odontogenic calcification areas were seen among the epithelial cells (Fig 5). According to these features, the diagnosis of AOT was made.

IMMUNOHISTOCHEMICAL AND MOLECULAR ANALYSIS FOR DETECTION OF β-CATENIN EXPRESSION AND MUTATIONS

A strong cytoplasmic and membranous expression was detected in columnar and cuboidal cells of duct-like structures and solid nodules for β-catenin (Fig 6) and only membranous expression for E-cadherin (Fig 7).

Using pyrosequencing, we did not detect the following specific mutations of *CTNNB1* gene: c. 121A > G; p.T41A (cosmic id : 5664) / c. 133T > C; p.S45P (cosmic id : 5663) / c. 134C > T; p.S45F (cosmic id : 5667). Using DNA direct sequencing reactions, we did not detect any mutation or deletion within the whole exon 3 of the *CTNNB1* gene.

Discussion

We have presented a complete and extensive clinical and histopathological report of a rare entity, AOT. Our findings are compared with those previously described in the literature. Moreover, we describe

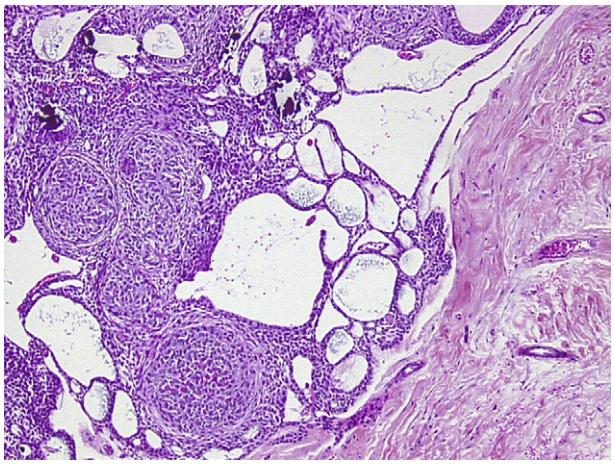

FIGURE 5. Photomicrograph (H/E 200×) showing elongated cells forming trabecular patterns and calcifications.

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

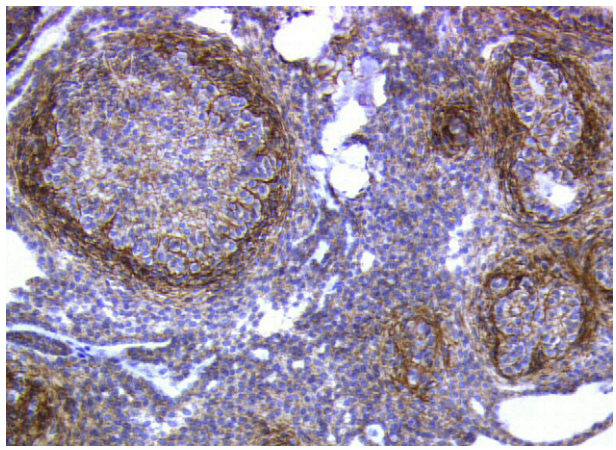

FIGURE 7. Representative immunohistochemical staining (200×) of E-cadherin protein localized in the cell membrane.

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

the first assessment of β-catenin status in AOT in regard to reported alterations of this member of Wnt-signaling pathway in other odontogenic tumors.

CLINICAL AND RADIOLOGICAL FEATURES OF AOT

Classically, 3 clinicopathologic variants of AOT are described. The intra-osseous follicular type is the most common form, accounting for approximately 70% of cases. It involves an impacted tooth and is often mistaken for a dentigerous cyst. The two other types are the intraosseous extra follicular and the peripheral AOT, respectively.

Our case was a follicular AOT, associated with an impacted lower left canine. The age of onset of the tumor in our patient, who was a 14-year-old boy, was concordant with the occurrence of most AOT during the second decade (69%), usually in the 13-year to 19-year age group,[12] or sometimes during the third decade.[13] To note, AOT mainly affect young women according to gender ratio reported in several series: 2/1,[14] 1.37/1,[15] or 2.31/1,[16] respectively. Clinical cases reported in Asian continent populations showed even higher gender ratio in favor of women.[17,18] The reason for such a female prevalence is unknown. AOT are more often located in the maxilla than mandible[13,19,20] with a ratio of 2/1. Most lesions are found in the anterior region of the upper jaw. The canine maxillary area is the predilection site of AOT.[8,21] In our case, the tumor was located in the left mandibular anterior region, which is a rare though previously described location.[22]

AOT are generally and typically asymptomatic lesions, but may cause cortical expansion. Displacement of the adjacent teeth can also be observed.[23] Swelling seems to be observed only at a more advanced stage of the lesion. This painless evolution often delays the consultation and increases the risk of complications, such as facial asymmetry or functional disorders.[24]

In our patient, we observed a well-defined unilocular radiolucent area with radiopaque foci and associated with an impacted canine. Computed tomography scans showed loss of cortical bone. Radiographically, AOT show a unilocular or multilocular radiolucent image associated with an impacted tooth[25] and including radiopaque foci. This last radiological feature constitutes a useful diagnostic criterion because it is observed in approximately 78% of cases of AOT.[22] The lesion is occasionally associated with divergence of adjacent roots, which can present resorptions.[26]

HISTOLOGICAL FEATURES OF AOT

The lesions consist of a proliferation of odontogenic epithelium, in a variety of architectural forms, solid nodules, and duct-like structures, the central cavity being lined partly by stratified squamous epithelium. According to Takahashi et al,[27] there are 3 epithelial cell types: *1)* cuboidal or columnar cells that form solid nodules with rosette-like or duct-like structures; *2)* elongated cells surrounding generally the solid nodules and duct-like structures; *3)* spindle cells arranged in trabecular network at the periphery of the epithelial tumor. Eosinophilic amorphous material and calcification areas may be present among these epithelial cells. In our case, we observed these 3 cell types, eosinophilic amorphous material, and calcifications.

IMMUNOHISTOCHEMICAL REACTIVITIES IN AOT

IHC proteins expressions in AOT have been widely described in the literature during the 10 last years and are summarized in Table 1.

Cytokeratins (CK)

Crivelini et al[28,29] showed that CK14 expression suggests the reduced dental epithelium to be a probable origin of AOT.

A positive staining with CK5, CK17, and CK19 was described by Larson et al[30] showing that the classical AOT phenotype is characterized by a CK profile similar to that of dentigerous cyst and/or oral or gingival epithelium. These results were confirmed by Leon et al,[31] suggesting also diffuse and strong positivity for AE-1-3 keratins.

Replication and transcription factors of DNA

Immunoexpression of PCNA and p53 was analyzed in 16 cases of ameloblastoma and 8 cases of AOT.[32] For the latter tumor, the results showed a higher PCNA expression in epithelial cells than p53 protein expression. Moreover, the quantitative analysis of staining observed in ameloblastomas contributed to establish the more proliferative and aggressive potential of these tumors. Moreover, the mildness of AOT was shown in the study of Sempere et al[33] because of low proliferation marker Ki67 expression and a nuclear reactivity of p63 antigen in almost all AOT tumoral cells.[31] This observation helped to demonstrate the initiator role of p63 in the stratification process and epithelial proliferation marked by the presence of AE-1-3 cytokeratins in the basal cells. These cells contribute efficiently to the formation of a benign tumor with low proliferation, but with a wide variety of morphological phenotype.

Extracellular matrix (ECM) components and metalloproteinases (MMPs)

Several authors analyzed the involvement of components of the extracellular matrix (ECM) in the AOT development. Positive reactions were observed for amelogenin, laminin, heparan sulfate proteoglycan

Table 1. IMMUNOHISTOCHEMICAL PATTERN OF PROTEIN EXPRESSIONS IN AOT

Authors	Cytokeratins (CK)	Replication and Transcription Factors of DNA	Metalloproteinases (MMP)	Extracellular Matrix Components
Murata et al (2000)				Amelogenin HSPG Laminin Type IV collagen
Abiko et al (2001)				Amelogenin
Nagatsuka et al (2002)				Type IV Collagen
Larson et al (2003)	CK5 / CK17, CK19			
Crivileni et al (2003, 2005)	CK 14	PCNA		
Leon et al (2005)	AE-1 / AE-3	P 63		
Barboza et al (2005)		PCNA P 53		
Ribeiro et al (2009)			MMP-1 / MMP-2 MMP-9	
Freitas et al (2009)			MMP-7 / MMP-26	
de Medeiros et al (2010)				Fibronectin Tenascin Type I Collagen
Modolo et al (2010)				Osteonectin

Harnet et al. Adenomatoid Odontogenic Tumor. J Oral Maxillofac Surg 2013.

(HSPG), collagen types I and IV, tenascin, fibronectin, and osteonectin[34-38].

In these studies, strong stainings have been reported in limited areas of AOTs, especially in the matrix of immature enamel present in duct-like structures and hyaline droplets, but the nature of amorphous eosinophilic material of AOTs is a matter of discussion: a dystrophic enamel-like tissue produced by neoplastic epithelial basal cells,[28] real enamel tissue,[39] or dentinoid tissue with ectomesenchymal component[40] have been evocated. Some recent studies evaluated the expression of matrix metalloproteinases (MMPs) that degrade certain ECM components. Under physiological conditions, the tissues do not express MMPs, although in pathological processes, they are overexpressed because of the imbalance between their activity and their inhibitors.[41] Then, it is accepted that MMPs play an important role in cell proliferation, angiogenesis, invasion, and metastasis in various malignancies in humans. Ribeiro et al[42] showed a very strong immunoexpression of MMP-1 in epithelial cells and stroma of ameloblastomas (20 cases) and AOTs (10 cases) revealing the importance of this collagenase in the degradation of ECM proteins and confirming its role in the growth and expansion of both odontogenic tumors, regardless of their aggressiveness. Souza Freitas et al[43] evaluated the expression of 2 other MMPs, MMP-7, and MMP-26 (matrilysins) in 2 series of 20 cases of ameloblastoma and 10 cases of AOT. In these tumors, the immunoexpression of MMP-7 and MMP-26 was easily observable in the epithelial cylindrical and cubic cells that form nodular and duct-like structures and in some endothelial cells and stromal fibroblasts. These results suggest the role of stroma in tumoral progression, showing an obvious synergy or cooperation between the neoplastic epithelial cells and stromal fibroblasts in MMPs production.

β-CATENIN DYSREGULATION IN ODONTOGENIC TISSUES AND TUMORS

The Wnt (Wingless integration site) pathway is crucial in the genesis of many organs. Notably, it plays an essential role in tooth development.[44] In particular, β-catenin dephosphorylation and nucleus translocation are dependent on a complex that includes adenomatous polyposis coli (APC) protein, axin, and GSK-3b. In addition to its transcription factor activity, β-catenin binds the cytoplasmic domain of E-cadherins, playing a role in epithelial cell-cell adhesion and maintenance of tissue architecture.[45] Abnormal activation or loss of certain components of this complex Wnt pathway are involved in many human tumors.[46,47]

So far, increase in β-catenin levels has been described to result either from activation mutations in the *APC* gene or the *CTNNB1*. *CTNNB1* is composed of 16 exons.

Somatic mutations have been described at the GSK-3b phosphorylation site within the exon 3. These mutations cause β-catenin stabilization by inhibiting proteosomal degradation. Such mutations have been described in a variety of benign and malignant tumors including desmoid tumor, pilomatricoma, hepatoblastoma, medulloblastoma, colorectal cancer, and ovarian carcinoma.

Ahn et al[7] considered that β-catenin expression and *CTNNB1* mutation were characteristics of benign

and malignant calcifying odontogenic cysts development. Sekine et al[9] showed also a high frequency of *CTNNB1* mutations and β-catenin accumulation in calcifying odontogenic cysts, whereas these anomalies were rare in ameloblastomas. This difference was in favor of distinct histogenesis for calcifying odontogenic cysts compared with ameloblastomas despite morphological resemblances. However, β-catenin immunohistochemical expression is not identical in ameloblastomas. Indeed, Miyake et al[18] reported β-catenin expression in 5 cases of follicular ameloblastoma and in a case of primary intraosseous odontogenic carcinoma. This expression was particularly marked in the nuclei and cytoplasms of tumor cells. A mutation at codon 40 of the exon 3 of the gene was found in one case of follicular ameloblastoma. Tanahashi et al[11] showed a significant nuclear accumulation of β-catenin in cuboidal cells of regions with a follicular appearance in 18 cases of ameloblastoma. Siriwardena et al[10] conducted a study to clarify the relation of β-catenin accumulation and mutations of *CTNNB1* and *APC* in the process of development of 6 ameloblastomas and 8 odontogenic carcinomas. Mutations of *APC* were detected in 3 ameloblastomas and 2 odontogenic carcinomas. Finally, Hakim et al[48] showed, in a recent publication, a significant alteration of the expression of β-catenin and E-cadherin in sporadic and syndromal keratocystic odontogenic tumors (KCOTs). These authors concluded that the results of their study could provide a new hypothesis explaining the development of KCOTs and a new therapeutic approach to these lesions. According to Philipsen et al's recommendations,[49] we have reported a clinical case of AOT with an original immunohistochemical and molecular analysis. To the best of our knowledge, ß-catenin alterations have not been explored in AOT.

We found no nuclear expression, but a strong cytoplasmic and the membranous ß-catenin staining of the epithelial cells. Similarly, we found a membranous expression of E-cadherin.

These results are in agreement with the benign clinical behavior of AOT when compared with the results of other similar studies of ß-catenin immunoexpression on ameloblastomas. Though no mutation of ß-catenin was detected, we think that a more specific gene inactivation scheme is required to dissect the functions of ß-catenin in the AOT pathogenesis.

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