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ORIGINAL ARTICLE

Pleomorphic Adenoma versus Basal Cell Adenoma: An immunohistochemical analysis with β-catenin

Adenoma Pleomorfo versus Adenoma de células basais: Análise imunohistoquímica com β-catenina

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ABSTRACT

Objective: The objective of this study was to investigate the distribution of β-catenin in pleomorphic adenomas and the basal cell adenomas to clarify its possible role in the etiopathogenesis of these two lesions. **Material and Methods:** The expression of β-catenin (BD Transduction Laboratories) was analyzed by immunohistochemistry in formalin-fixed, paraffin-embedded specimens by the avidin-biotin-peroxidase complex method in 10 pleomorphic adenomas and 2 basal cell adenomas. The specimens were analyzed taking into account intensity, distribution and association with myoepithelial cells. **Results:** The results showed that all cases of pleomorphic adenomas exhibited membranous and cytoplasmic immunostaining and the 2 cases of basal cell adenomas displayed nuclear staining. Higher β-catenin index rates were seen mainly in ductal structures of pleomorphic adenomas and in the nuclei of myoepithelial stromal and myoepithelial cells of solid clusters in basal cell adenomas. **Conclusion:** In conclusion, this immunohistochemical study may suggests the different degree of differentiation of the myoepithelial cells in these two tumors.

KEYWORDS

β-catenin; Basal Cell Adenoma; Immunohistochemistry; Pleomorphic Adenoma.

RESUMO

Objetivos: O objetivo deste estudo foi investigar a distribuição da β-catenina em adenomas pleomorfos e os adenomas de células basais para esclarecer o seu possível papel na etiopatogenia dessas duas lesões. **Material e Métodos:** A expressão de β-catenina (BD-Transdução Laboratories) foi analisada por imunohistoquímica em espécimes parafinados fixados em formalina pelo método avidina-biotina-peroxidase em 10 adenomas pleomórficos e 2 adenomas de células basais. Os espécimes foram analisados levando-se em conta a intensidade, quantidade de células marcadas e distribuição em estruturas morfológicas. **Resultados:** Os resultados mostraram que todos os casos de adenomas pleomorfos exibiram imunomarcação membranosa e citoplasmática e os 2 casos de adenomas de células basais exibiram coloração nuclear. Marcação mais intensa de β-catenina foi vista principalmente em estruturas ductais de adenomas pleomorfos e nos núcleos de células mioepiteliais de estruturas tubulares e trabeculares em adenomas de células basais. **Conclusão:** Concluindo, este estudo imunohistoquímico sugere distintos graus de diferenciação das células mioepiteliais em cada um destes dois tumores.

PALAVRAS-CHAVE

Beta Catenina; Adenoma Basocelular; Imuno-Histoquímica; Adenoma Pleomorfo.

INTRODUCTION

Pleomorphic adenomas are the most frequent type of salivary gland neoplasms. The World Health Organization's (WHO) latest histological classification of salivary gland tumors defined the pleomorphic adenoma as a tumour of variable capsulation characterized microscopically by architectural rather than cellular pleomorphism. Epithelial and modified myoepithelial elements intermingle most commonly with tissue of mucoid, myxoid or chondroid appearance. Basal cell adenoma is

a rare benign neoplasm characterized by the basaloid appearance of the tumour cells and the absence of the myxochondroid component present in pleomorphic adenoma [1]. Four cellular patterns may occur: solid, trabecular, tubular and membranous. The basal cell adenoma is relatively rare and may sometimes be misdiagnosed because of partial histological similarities to other parotid gland tumors, such as pleomorphic adenoma, adenoid cystic carcinoma, and canalicular adenoma [2,3].

There are several subgroups of genetic defects in pleomorphic adenomas mainly characterized by structural deviations and, in particular, reciprocal translocations. The largest subgroup is characterized by rearrangements involving the band 8q12. The gene on chromosome 8q12 is a novel, developmentally regulated zinc fingers gene, designated PLAG1 [4]. Some genetic alterations results in promoter swapping between PLAG1 and the constitutively expressed gene for β-catenin (CTNNB1) [4]. β-catenin is defined as the protein that specifically co-immunoprecipitates with cadherin and forms the cadherin-catenin complex, which participates in intercellular adhesion. Now it is also recognized as an essential element of the wingless WNT signaling cascade [5]. β-catenin is significantly associated with the invasion and metastasis of several human cancers: carcinomas of the head and neck (esophagus), stomach, colon, liver, lung, breast, female genitalia, prostate, bladder, pancreas and melanomas [6-11]. Gastric adenomas have previously been reported to strongly express β-catenin [6]. CD9, another cellular adhesion molecule [12], has been investigated in parotid gland tumors because it can play an important role in cell proliferation, metastasis and poor prognosis in some types of cancers. Among the salivary gland tumors, adenoid cystic carcinoma and mucoepidermoid carcinoma were also immunohistochemically stained by β-catenin [13,14], and the immunoactivity of β-catenin showed significant correlation with the grade and stage of mucoepidermoid carcinoma [14].

The immunohistochemical features of basal cell and pleomorphic adenomas have been extensively studied to elucidate the tumor's origins, as well as for clinical application [15-24]. There is continued interest in defining the myoepithelial cell participation in salivary glands tumors and its association with the cancer pattern [18,25-27] however, there are no reports in the literature associating the myoepithelial nature and the immunoreactivity for adhesion molecules. The immunohistochemical expression of β-catenin has been previously reported in basal cell and pleomorphic adenomas [28,29] but independently. In normal epithelial tissues it stains cellular surface; in carcinomas, β-catenin marks the cell's malign nucleus and in mesenteric fibromatosis its expression is also nuclear [7-11]. The objective of this study was to compare the extent of β-catenin immunoreactivity in these tumors and discuss this expression, particularly in myoepithelial cells.

MATERIALS & METHODS

The samples analyzed in the study were obtained from the Department of Pathology at Bauru Dental School, University of Sao Paulo. The cases (10 pleomorphic adenomas and 2 basal cell adenomas) were obtained from the archives of the Department. The procedures were in accord with the ethical standards established by the Ethics Committee in Research of the Bauru Dental School. The tissue samples were fixed in 10% formalin solution and embedded in paraffin. The hematoxylin- and eosin-stained slides were independently reviewed by 2 experienced pathologists. The pathologists used accepted criteria according to the World Health Organization's international histological classification of tumors section on histological typing of salivary gland tumors, to reach agreement in all cases included in this study.

Information was obtained about gender, age, tumor location and histopathological features in pleomorphic adenomas and basal cell adenomas. The percentage of cells staining positively for the antibody was assessed and

graded: - , negative; + (0 - 33% of cells with mild staining); ++ (0 - 33% of cells with moderate to intense staining and 33 - 100% of cells with mild staining); +++ (33 - 100% of cells with moderate staining); ++++ (33 - 100% of cells with intense staining). Formalin-fixed, paraffin-embedded specimens were used for immunohistochemical analysis by the avidin-biotin-peroxidase complex method. Briefly, 3-μm sections of tumors were dewaxed and rehydrated prior to antigen retrieval, which was performed in a steamer at 100 °C for 40 min. These preparations were incubated in H_2O_2 for 5 min to block the endogenous peroxidase. Then, they were incubated overnight at 4 °C with primary mouse monoclonal antibody β-catenin (Clone β-Catenin-14, BD Transduction Laboratories - USA) 1/125 dilution. Chromogenic detection was performed with 3,3-diaminobenzidine (DAB). Counterstaining was briefly performed with Mayer's hematoxylin. Negative controls for immunostaining were obtained by substituting PBS for the primary antibodies. Gastric fibromatosis was used as a positive control. When present, ducts of remaining salivary glands and stratified squamous epithelium were used as an internal positive control.

RESULTS

The present investigation included 1 woman and 1 man with basal cell adenomas. The mean age was not available. Both affected the parotid glands. In the group of pleomorphic adenomas, there were two men and eight women with a mean age of 44.5 yrs (range: 28 - 63 yrs) Age was not available in one case. Five tumors were located in the palate, two in the parotid gland, two other in the oral mucosa and one in the submandibular gland. The immunohistochemical findings of β-catenin in pleomorphic adenomas and basal cell adenomas are summarized in Table 1.

Pleomorphic Adenomas

The cases of pleomorphic adenomas usually exhibited a wide variety of types of epithelial cell, including cuboidal, spindle, squamous, and plasmacytoid, clear and spindle-shaped myoepithelial cells. There was some metaplastic keratinization within tumor nests. Epithelial elements proliferated in several combinations with ducts, cords, sheets or individual cells seen within any given tumor (Figure 1). The pleomorphic adenomas were encapsulated and presented a tendency towards bosselation of the tumor into and slightly beyond the limits of the capsule. Pleomorphic adenomas only have cytoplasmic and membranous staining patterns. All pleomorphic adenomas reacted positively with β-catenin, with variable intensity, on the surface and cytoplasm of the outer and luminal cells of the tubular and trabecular structures. Some samples also showed expression of the molecule in the internal non-luminal cells of clusters. The spindle-shaped stromal cells were negative in all cases (Table 1 and Figure 2).

Basal Cell Adenomas

Microscopic features of the two cases of basal cell adenomas studied showed remarkable similarities. The neoplastic component consisted of uniform and monotonous epithelial cells, which tended to form duct-like structures or appeared to undergo anastomosis in either trabecular strands or in more solid basaloid nests (Figure 3). Tumor nests frequently had peripheral palisading epithelial cells that were cuboidal or low columnar in morphology. The central cells were large and polyhedral, with abundant cytoplasm and pale nuclei, frequently showing eosinophilic material inside the ducts. The tumor stroma was sparse, and neither myxomatous nor chondromatous components could be found. A distinct basement membrane differentiated the tumor cells from the surrounding stroma, which was generally pale-stained and poorly collagenized. Focal stromal areas appeared edematous, hypocellular, with abundant fibrin precipitate. Numerous thin-walled vessels were seen in close proximity to the tumor nests. The tumors were well-

encapsulated, with no evidence of invasion into the capsule or surrounding normal stroma. Immunohistochemical reactions showed that basal cell adenomas expressed nuclear, cytoplasmic, membranous β-catenin. Some internal non-luminal cells of the solid areas were positive for the antibody. Higher cytoplasmic and nuclear β-catenin index rates were seen in the outer cells of the tubular and trabecular structures and in the spindle-shaped stromal cells of the two cases of basal cell adenomas (Table 1 and Figure 4).

Table 1 - Immunohistochemical findings of β-catenin in pleomorphic adenomas and basal cell adenomas

Lesion/Structure	Outer cells of bilayered neoplastic tubules/outer-most cells of the trabeculae (myoepithelial cells)	Luminal cells (epithelial cells)	Internal non-luminal cells of clusters (epithelial cells)	Spindle-shaped stromal cells (myoepithelial cells)
Pleomorphic Adenoma(1)	++	++	++	-
Pleomorphic Adenoma(2)	+	+	+	-
Pleomorphic Adenoma(3)	+	+	-	-
Pleomorphic Adenoma(4)	++	++	+++	-
Pleomorphic Adenoma(5)	+++	+++	+++	-
Pleomorphic Adenoma(6)	+	+	+	-
Pleomorphic Adenoma(7)	++++	++++	++++	-
Pleomorphic Adenoma(8)	+	+	-	-
Pleomorphic Adenoma(9)	+++	+++	+++	-
Pleomorphic Adenoma(10)	+	+	-	-
Basal cell adenoma(1)	++++*	-	++*	++++*
Basal cell adenoma(2)	++++*	-	++*	++++*

* Nuclear location in most cells

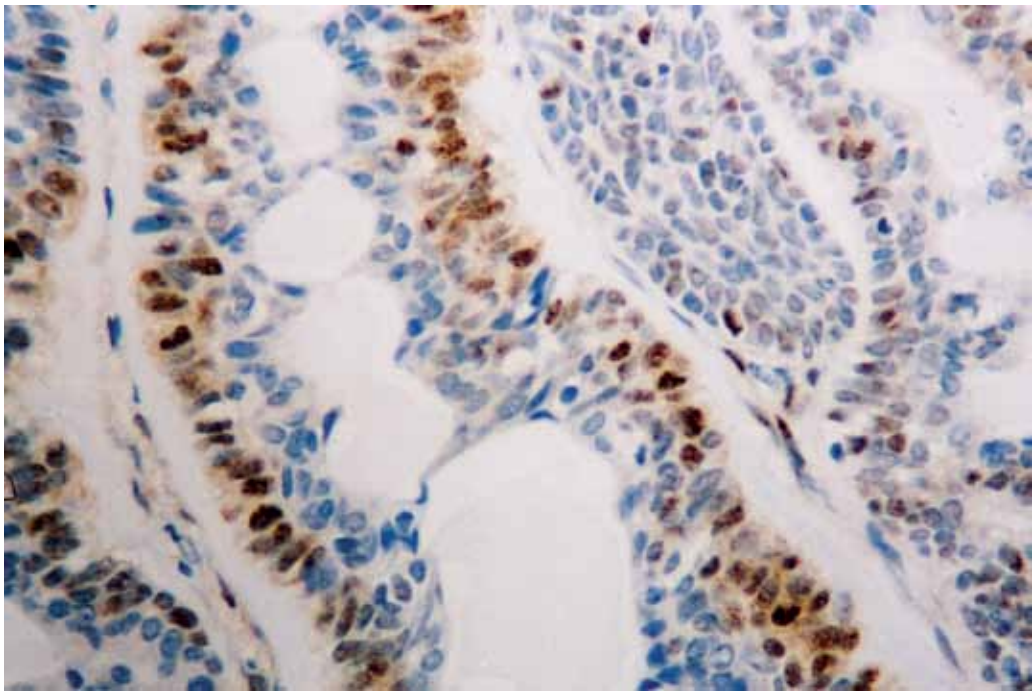

Figure 1 - Pleomorphic adenoma. The epithelial and myoepithelial cells form anastomosing ductal structures of varying thickness in a fibrohyaline or fibrous connective tissue stroma. (H&E staining, original magnification X100).

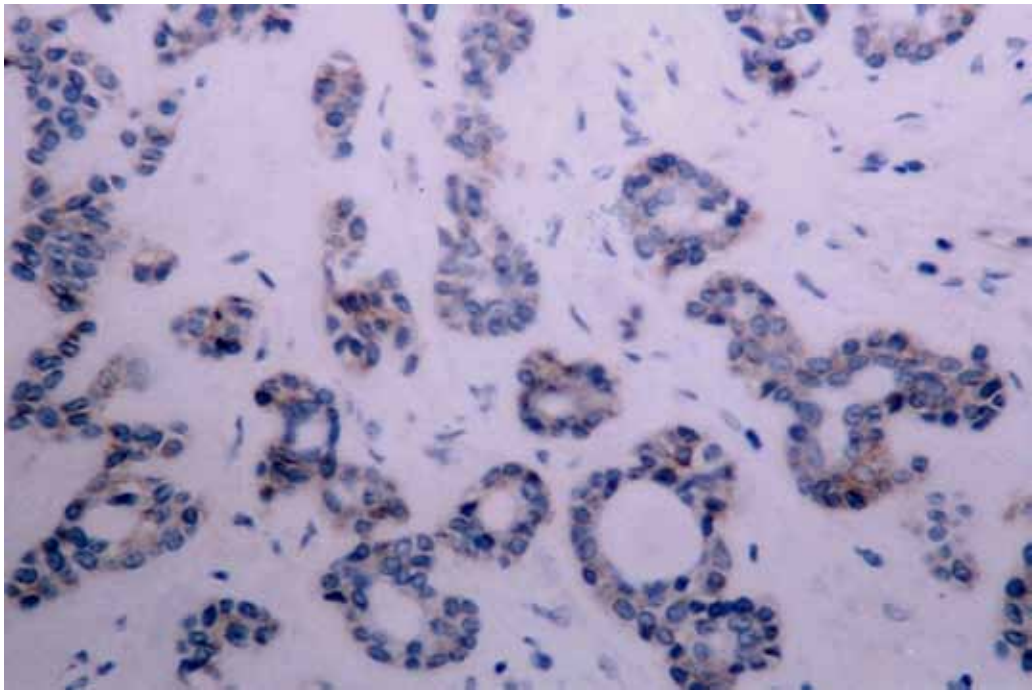

Figure 2 - Pleomorphic adenoma. Moderate multifocal surface and cytoplasmic positive staining for β-catenin in neoplastic cells of duct-like structures. A few peripheral cells also stained. (β-catenin, original magnification X400).

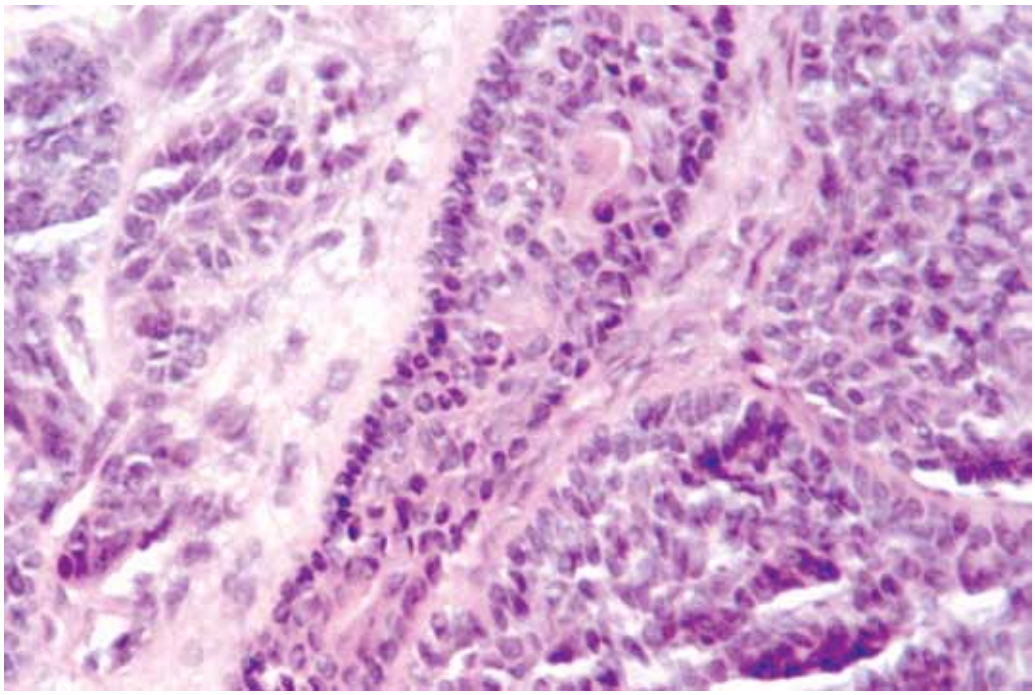

Figure 3 - Basal cell adenoma. Basaloid cells are arranged in cords and islands exhibiting peripheral palisading in a fibrous connective tissue stroma. (H&E staining, original magnification X400).

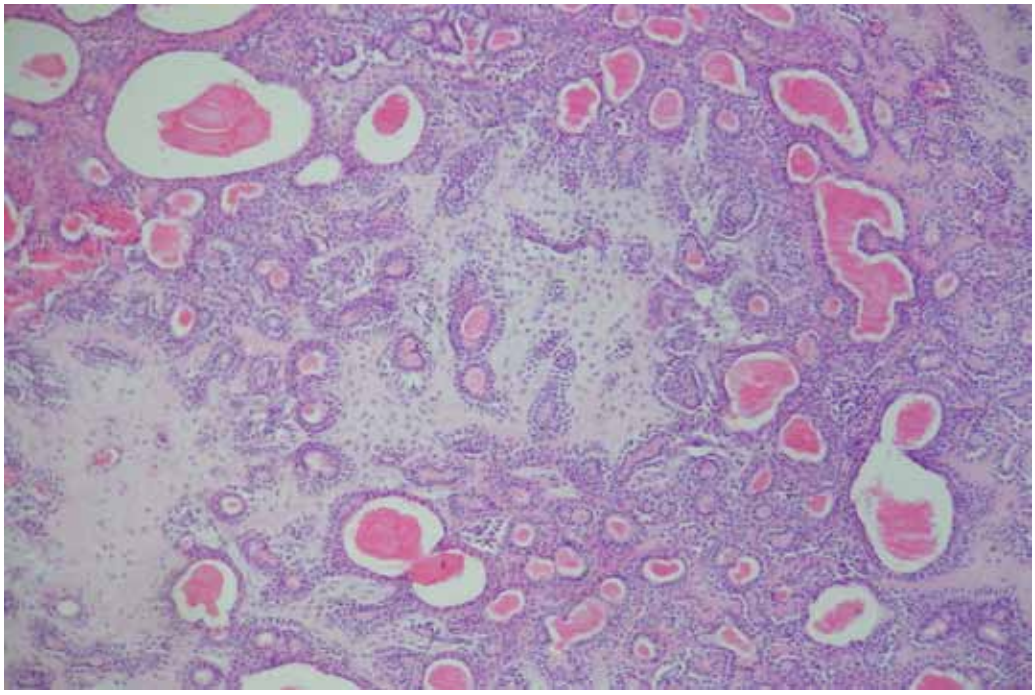

Figure 4 - Basal cell adenoma. Intense nuclear β-catenin immunoreactivity, mainly in the outermost myoepithelial cells of tubular-trabecular structures. (β-catenin, original magnification X400).

DISCUSSION

The present study showed that both basal cell adenoma and pleomorphic adenoma have different immunohistochemical profile for β-catenin, thus confirming previous ultrastructural and histochemical studies [28,29].

Basal cell adenomas were included in the category monomorphic adenoma, it exhibited a regular, uniform cell structure, basement membrane and lobular structure [17]; It is distinguished from the pleomorphic adenoma by the absence of the chondroid or myxoid foci that typified the pleomorphic adenoma and facilitate its recognition [1]. However, not all pleomorphic adenomas contain myxoid or chondroid areas, and may also appear basaloid [30]. Pleomorphic adenomas are occasionally associated with cystic changes or hemorrhage necrosis [31].

The following conditions can bring about difficulties for the pathologist to differentiate these two salivary gland lesions:

1-basaloid appearance of pleomorphic adenomas without stromal matrix;

2-small incisional biopsy or curetted fragments resulting in the absence of an overall diagnostic architectural pattern.

The present investigation show a difference in β-catenin reactivity between pleomorphic adenoma and basal cell adenoma, because nuclear β-catenin immunostaining was observed only for the basal cell adenoma.

Several authors suggest the derivation of pleomorphic adenomas and basal cell adenomas from intercalated ducts [18,25,28,32-35]. Zarbo et al. [23] also showed an overlapping between the histomorphological and common cellular composition of the variants of basal cell adenoma with other recognized adenomas, such as pleomorphic adenomas and myoepithelioma; according to these authors, the relative differentiation toward 3 cell phenotypes (ductal luminal, basal and myoepithelial) and the character of the production of extracellular matrix in varying proportions by the neoplastic myoepithelial cells distinguish the spectrum of salivary gland adenomas identified in current classification schemes.

The myoepithelial nature of the stromal cells, outer cells of bilayered neoplastic tubules and outermost cells of neoplastic trabeculae in basal cell adenomas was suggested by Ogawa et al. [18], Ferreiro [27] and Edwards et al. [26] when some of these cells displayed an intense staining for vimentin, S100 protein and p63 protein.

The immunohistochemical findings of the basal cell adenoma closely resemble those of pleomorphic adenomas. There is a similar staining pattern with CEA (carcinoembryonic antigen) and EMA (epithelial membrane antigen), which stain luminal structures, and with vimentin and the S100 protein, which label myoepithelial stromal cells and the outer layer of epithelial nests [27]; however, analysis of the β-catenin expression reveals that all myoepithelial cells of different shapes (spindle-shape stromal cells, outer cells of bilayered tubules and trabeculae) that expressed the protein had nuclear immunoreactivity in the basal cell adenoma and cytoplasmic immunostaining in the pleomorphic adenoma. Even though the present sample of basal cell adenomas is limited, this can suggest a distinct degree of differentiation between the myoepithelial cells in these two tumors, which can be responsible for the production of extracellular matrix by these neoplastic myoepithelial cells.

There are groups of genetic defects in pleomorphic adenoma, such as the t(3;8) (p21;q12) translocation, resulting in promoter swapping between PLAG1 and β-catenin [4], which may impact on the concentrations of PLAG1 and β-catenin in pleomorphic adenomas; however, this is not enough to translocate the protein into the nuclei. Therefore, possibly there is an important mutation in basal cell adenoma

cells, especially in myoepithelial cells, which carried the molecule into the nuclei [28]. However, accumulation of nuclear β-catenin may be not only the result of mutation of the β-catenin gene, but also mutation of the APC or inactivation of GSK-3β (glycogen synthase kinase 3β), responsible for the proteolytic degradation of β-catenin. The membranous loss of the E-cadherin-catenin complex and nuclear translocation of β-catenin are early events of gastric carcinogenesis and progress through the adenoma-carcinoma sequence [6]. Further genetic studies are necessary to elucidate the specific role of β-catenin in the etiopathogenesis of these tumors.

In conclusion, this immunohistochemical study allows the differential diagnostic separation of basal cell adenoma and pleomorphic adenoma; moreover, it also suggested the distinct degree of differentiation of myoepithelial cells in these two tumors.

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