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## Histopathological findings of pleomorphic adenomas of the salivary glands

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### Abstract

**Objectives:** To describe the histopathological features of pleomorphic adenoma (PA) with special reference to the epithelial and mesenchymal components. **Study design:** 189 PA were selected and classified as myxoid or stroma-rich, cellular or cell-rich and classic (balanced amount of epithelial and stromal components). The epithelial component was analyzed according to the presence of plasmacytoid, spindle, clear, squamous, basaloid, cubic, oncocytoid and mucous cells and the morphological pattern (trabecular, ductal, cystic and solid). The stromal component was analyzed according to the presence of myxoid, hyaline, chondroid or calcified tissue. **Results:** Plasmacytoid cells were the most commonly found cellular type followed by fusiform and cuboidal cells. Trabeculae and duct-like structures were the most frequent patterns formed by the epithelial cells. Myxoid and chondroid stroma were the most frequently found mesenchymal-like tissue usually forming the so called myxochondroid stroma. **Conclusion:** The knowledge of the immense variety of cells, architectures and morphological characteristics present in PA of the salivary gland is essential for a correct diagnosis.

**Key words:** Histopathology, pleomorphic adenoma, salivary gland neoplasms.

### Introduction

Salivary gland tumors are rare, comprising less than 3% of all neoplasms of the head and neck region (1) and are known by their complex microscopical features. Pleomorphic adenoma (PA) is the most common salivary gland tumor and represents 60% to 73% of the parotid gland tumors, 40% to 60% of the submandibular and minor salivary glands tumors (2-4). It is a benign neoplasm composed of epithelial and myoepithelial cells arranged in a great variety of morphological patterns, with areas of mesenchymal differentiation (5,6). Epithelial cells typically form duct-like structures associated with non-

ductal cells presenting variable shapes and forms. The stromal element demonstrates varying degrees of myxoid, hyaline, cartilaginous, or osseous differentiation (5). In this paper we describe the histopathological characteristics of 189 cases of PA with special reference to the morphology of the epithelial cells and stromal components.

### Material and Methods

Four hundred ninety-six cases of salivary gland tumors were retrieved from the files of the Department of Pathology, Londrina Cancer Institute, Paraná State, Brazil, including the period from 1972 to 2001. PA was the most

frequent tumor with 269 cases, comprising 54.2% of all tumors and 80.3% of the benign (4). Considering the presence of representative amount of the tumor and discarding biopsy cases, 189 out of 269 were used in this study. The tumors were classified as myxoid or stroma-rich, cellular or cell-rich and classic (balanced amount of epithelial and stromal components) as described by Seifert et al. (7). The epithelial component was analyzed taking into consideration the presence of plasmacytoid, spindle, clear, squamous, basaloid, cubic, oncocytoid and mucous cells and the morphological pattern (trabecular, ductal, cystic and solid). The stromal component was analyzed according to the presence of myxoid, hyaline, chondroid or calcified tissue.

### Results

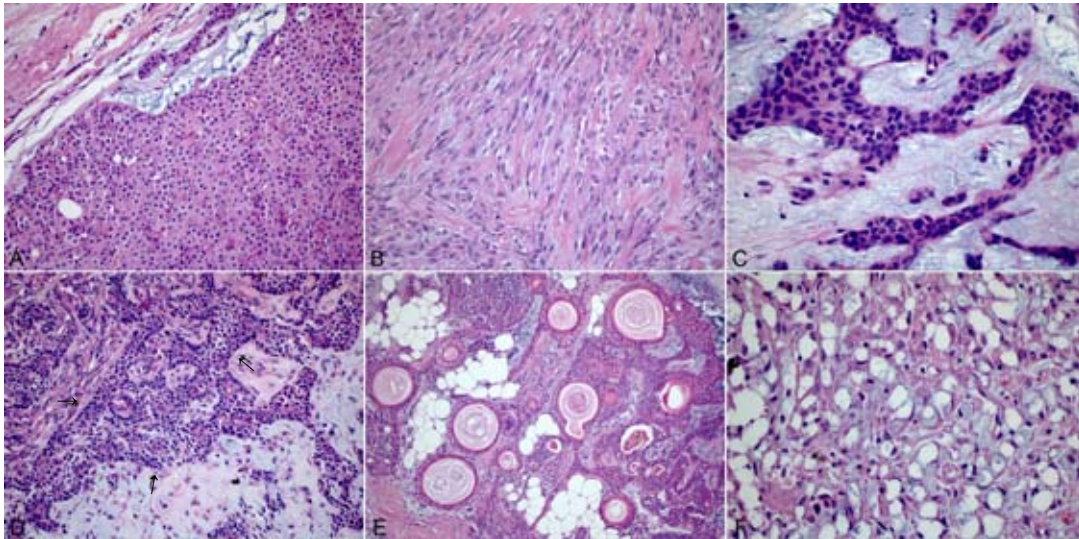
The majority of cases were located in the parotid gland (70.9%) followed by minor salivary glands (18%) and submandibular gland (11.1%). No cases were found in the sublingual gland. The mean age was 42.9 ( $\pm$ 16) years ranging from 13 to 90 years and the peak of incidence was in the fourth and fifth decades. 124 cases (65.6%) were in females while 65 (34.4%) in males. PA were classified as stroma-rich in 99 cases (52.4%), cell-rich in 69 (36.5%) and classic in 21 cases (11.1%) (Table 1). Plasmacytoid cells (Fig. 1a) were the most commonly found cellular type, being present in all studied tumors and were the predominant cellular type in 32 cases

(16.9%). They represented less than 30% of the tumor cells in 37.6% of the cases, 31% to 50% in 49.2% of the cases and more than 50% in 13.2% of the cases. Spindle cells (Fig. 1b) were present in 180 cases (95.2%), representing the second most frequent cellular type. It was predominant in 21.7% of the cases and corresponded to less than 30% of the tumor cells in 65.1% of the cases, 31% to 50% in 21.2% of the cases and more than 50% in 9% of the cases. Cuboidal cells (Fig. 1c) were found in 85.7% of the cases, in 48.1% it represented less than 30% of the tumor cells, in 34.9% it represented 31% to 50% of the tumor cells and in only 2.6% it corresponded to more than 50% of the tumor cells. On the other hand, cuboidal cells were the predominant cell type in 58 cases (30.7%). Basaloid cells (Fig. 1d) were the fourth most frequent cellular type, been present in 49.2% of the cases and in all of them corresponded to less than 50% of the tumor cells. Additionally, basaloid cells were most commonly found in cell-rich PA subtype. Squamous cells (Fig. 1e) were found in 40.2% of the cases, however in only 3 cases they represented more than 35% of the tumor cells. Clear cells (Fig. 1f) were present in only 69 cases (36.5%), representing less than 30% of the tumor cells in 33.3% of the cases and were the predominant cellular type in 6 cases. Mucous and oncocytic cells were considered occasional findings. They were present in 22.2% and 9.5% of the cases, respectively, but not in more than 15% of the tumor cells (Table 2). In 54 cases (28.6%) there was no predominance of a single cellular type, showing a balanced admixture of two or more cellular types. In general, nuclear features of all cell types were uniformly bland with small or absent nucleoli. Mitosis were rare, however, in 6 cases (2.6%) we found focal cellular atypia non related to infarcted tissue. Five cases demonstrated infarction with necrotic areas. In one case, disperse pigmented cells were found in the parenchyma of the tumor. Concerning the morphological patterns of the epithelial component, trabeculae formation (Fig. 2a) was found in 96.8% of the cases. It was present in all stroma-rich and classic subtypes and in 91.3% of the cell-rich subtype. Ductal, cystic and solid formations (Fig. 2a-2c) were seen in 92.6%, 37.6% and 60.3% of the cases, respectively. These three architectural configurations were most commonly found in cell-rich or classic variants than in stroma-rich tumors (Table 2). Myxochondroid stroma was present in 82.5% of the cases. Myxoid areas (Fig. 3a) were found in 94.2% of the cases corresponding to 44.6% of the stromal component. It was present in 92.9% of the stroma-rich tumors, 97.1% of the cell-rich subtype and in 90.5% of the classic form. The stroma-rich subtype demonstrated higher percentage of myxoid tissue when compared to other subtypes. Chondroid areas (Fig. 3b) were seen in 82.5% of the cases corresponding to 32.2% of

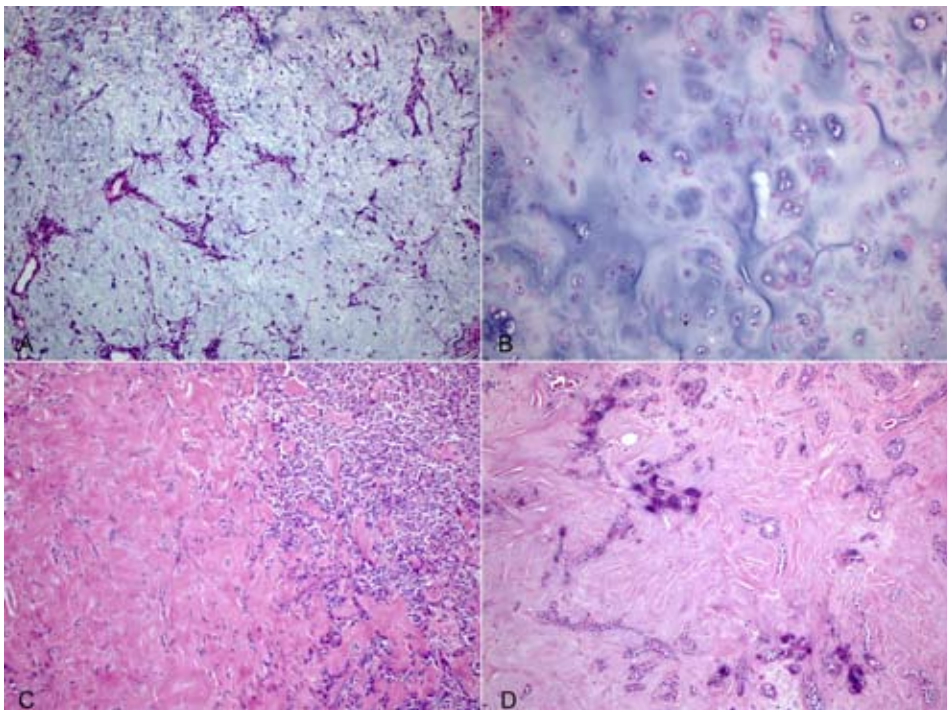
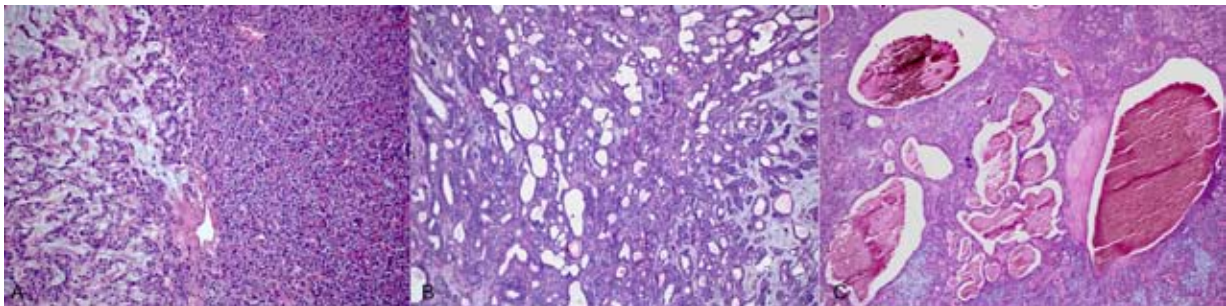
**Table 1.** Demographic data and histological classification of 189 cases of pleomorphic adenoma.

Variables	Patients, n (%)
<b>Location:</b>	
Parotid	134 (70.9)
Submandibular	21 (11.1)
Minor	34 (18)
<b>Age, y:</b>	
<20	8 (4.2)
21-30	39 (20.6)
31-40	41 (21.7)
41-50	43 (22.8)
51-60	28 (14.8)
61-70	18 (9.5)
>70	12 (6.3)
<b>Sex:</b>	
Females	124 (65.6)
Males	65 (34.4)
<b>Histological classification:</b>	
Stroma-rich	99 (52.4)
Stroma-poor	69 (36.5)
Classid	21 (11.1)

**Fig. 1.** Epithelial cell types present in pleomorphic adenomas. A: plasmacytoid cells (H&E, x200); B: fusiform cells (H&E,x200); C: cuboidal cells (H&E, x400); D: basaloid cells (arrows, H&E, x200); E: squamous cells (H&E, x100); F: clear cells (H&E,x400).



**Fig. 2.** Morphological patterns of the epithelial component. A: trabecular (left) and solid (right) (H&E, x100); B: ductal (H&E, x100); C:cystic (H&E, x50).



**Fig. 3.** Mesenchymal-like components of pleomorphic adenomas. A: myxoid (H&E, x100); B: chondroid (H&E, x100); C: hyaline (H&E, x100); D: calcifications (H&E, x100).

**Table 2.** Cellular types present in the epithelial component of pleomorphic adenomas and morphology of epithelial and stromal components of pleomorphic adenomas.

Tumor cells	Cells of the epithelial component									
	Plasmacytoid	Spindle	Cuboidal	Basaloid	Squamous	Clear	Mucous	Oncocytic		
Absent n (%)	0	9 (4.8)	27 (14.3)	96 (50.8)	113 (59.8)	120 (63.5)	147 (77.8)	171 (90.5)		
<30% n (%)	71 (37.6)	123 (65.1)	91 (48.1)	80 (42.3)	67 (35.4)	63 (33.3)	42 (22.2)	18 (9.5)		
31-50% n (%)	93 (49.2)	40 (21.2)	66 (34.9)	13 (6.9)	9 (4.8)	3 (1.6)	0	0		
>51% n (%)	25 (13.2)	17 (9)	5 (2.6)	0	0	3 (1.6)	0	0		

	Epithelial Component					Stromal Component			
	Trabeculae	Ducts	Cysts	Solid	Myxoid	Chondroid	Hyalinization	Calcification	
Stroma-rich n (%)	99 (100)	90 (90.9)	28 (28.3)	47 (47.5)	92 (92.9)	89 (89.9)	75 (75.8)	2 (2)	
Cell-rich n (%)	63 (91.3)	65 (94.2)	34 (49.3)	51 (73.9)	67 (97.1)	49 (71)	61 (88.4)	2 (2.9)	
Classic n (%)	21 (100)	20 (95.2)	9 (42.9)	16 (76.2)	19 (90.5)	18 (85.7)	15 (71.4)	0 (0)	

the stromal component and they were less frequent in cell-rich tumors. Hyalinization (Fig. 3c) was found in 79.9% of the cases, mainly in the cell-rich variant, corresponding to only 18.1% of the stromal component. In only 22 cases (11.6%) hyalinization predominated over myxoid or chondroid stroma. Calcifications (Fig. 3d) were seen in only 4 cases (2.1%) and did not correspond to more than 5% of the stroma (Table 2).

**Discussion**

PA is a slow-growing benign salivary gland tumor, most commonly arising in the parotid gland. It accounts for 60% to 73% of the parotid gland tumors, 12% to 60% of the submandibular and 14% to 70% of the minor salivary glands tumors (2-4). Female patients are more affected than males (2,5,8,9) and the peak incidence occurs in the fourth and fifth decades (2,8,10,11). In the present study, PA was also more frequent in the parotid gland of female patients with age between 30 and 50 years. Regardless of the great variety of histopathological aspects the main diagnostic feature is the presence of both epithelial and mesenchymal-like tissues. The proportion of these tissues has been used to sub-classify PA, however, it does not have therapeutic or prognostic significance (5). In our study, stroma-rich subtype corresponded to 52.4% of the cases, cell-rich 36.5% and classic 11.1%, results interestingly close to those reported by Stennert et al.(12) and Paris et al. (13). In the current study, plasmacytoid cells were the most frequent cell type followed by spindle cells. Ellis and Auclair (5) related that these cells appear to be in transition from one form to the other. Additionally, in PA, plasmacytoid cells seem to originate from luminal rather than myoepithelial cells (14). The other cellular types, with the exception of the squamous cells that are commonly abrupt and organized in islands, also seem to be closed associated with one another and correspond to transition forms from one type to another (5). Cuboidal cells located in hypocellular areas were considered to have a pre-chondroprogenitor phenotype, they express cartilage-derived morphogenic protein (CDMP-1), that may play a role in the acceleration of the trans-differentiation from cuboidal neoplastic myoepithelial cells to lacunar cells in an autocrine manner (15). Acinar phenotypes such as mucous cells in PA could reflect either an abnormal line of differentiation or luminal cells with increased synthesis and/or retention of variably mature glycoproteins (16). Development of oncocytes has been associated with acinar and striated duct cells (17) and this metaplasia probably occurs in other cell types as well (18). In our study, cuboidal cells were the third most common cellular type. On the other hand, mucous cells and oncocytes were considered occasional, being present in few cases and in small amounts. It is known that benign PA may, in some cases, con-

tain focal areas of marked atypia and/or bizarre tumor cells (5,6). In addition, atypical cytomorphology could be found in tumors previously manipulated by biopsy or fine needle aspiration, especially within infarcted areas and necrotic tissue (6). We found 6 cases (2.6%) containing cellular atypia non-related to infarcted areas. These findings were similar to those previously reported by Takeda et al. (6). On the other hand, Ohtaké et al. (19) described 51% of the analyzed cases with cellular atypia, 6% focal, 15% sporadic and 30% singular. Mesenchymal-like elements of PA including chondroid and myxoid tissues were shown to be related to neoplastic myoepithelial cells migrating into the stroma (20). In the present study, the predominance of the myxochondroid stroma was clear. Hyalinization of the stroma was common, although in small quantities, nevertheless in 22 cases (11.6%), it predominated over myxoid or chondroid tissue. Prominent zones of hyalinization have been related to an aggressive behavior or malignant transformation of PA (21), however we believe that hyalinization as an isolated fact is not sufficient to predict this progression. In summary, these results emphasize the immense variety of cells, architectures and morphological characteristics present in PA of the salivary gland. Since PA is the most frequent salivary gland neoplasia and can resemble other salivary gland tumors, the knowledge about these variations is essential for a correct diagnosis.

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