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ORIGINAL ARTICLE

Marianne de Vasconcelos Carvalho[1]
Juan Manuel Arteaga Legarrea[2]
Ana Carolina Prado Ribeiro[3]
Felipe Paiva Fonseca[2]
Bruno Augusto Benevenuto de Andrade[4]
Oslei Paes de Almeida[5]
Márcio Ajudarte Lopes[5]
Pablo Agustin Vargas[5,*]

Clinicopathological and immunohistochemical study of canalicular adenoma

Abstract:

Objective: To evaluate the clinicopathological and immunohistochemical features of an original series of canalicular adenoma. **Methods:** Cases diagnosed as canalicular adenoma from a single center were retrospectively retrieved and clinical data collected from patients' charts. The histopathological features of all cases were reviewed and a large immunohistochemical panel carried out. **Results:** Eleven cases were collected, and no gender predilection was seen. A painless upper lip nodule was the most frequent clinical presentation. All cases presented the single-layer epithelial arrangement of tumor cells in a loose stroma. It was found an increased expression of low-weight cytokeratins, absence of myogenic markers, variable positivity for vimentin, S100 and GFAP, cytoplasmic and membrane reactivity for β-catenin and a strong CD34 positivity, whereas no lymphatic vessel was identified using D2-40 antibody. **Conclusion:** Canalicular adenoma is composed of luminal epithelium with strong expression of low-weight cytokeratins, and peripheral expression of β-catenin may be involved in the architectural maintenance of the tumor.

Keywords: Salivary gland tumors; Canalicular adenoma; Immunohistochemistry.

INTRODUCTION

Canalicular adenoma is an uncommon benign epithelial salivary gland tumor that characteristically affects minor salivary glands of the upper lip, with a suggested excretory duct origin[1-4]. Although initially recognized as a variant of basal cell adenoma and therefore grouped together with this entity in many older epidemiological studies, its frequency has been shown to range from less than 2% up to 11% of all salivary gland tumors[5-7].

Statement of Clinical Significance
This study highlights the clinicopathological relevance of canalicular adenoma, a rare salivary gland tumor favoring the superior lip, typically presenting in the seventh decade without gender bias. Molecular markers like vimentin, S100, and GFAP indicate cellular heterogeneity, with β-catenin likely important for tumor integrity, offering insights for diagnosis and treatment.

It typically exhibits indolent clinical behavior with no tendency for local recurrence, which, when reported, is usually associated with the tumor's multifocal nature or inaccuracies in treatment[8]. The differentiation of canalicular adenoma from basal cell adenoma, striated duct adenoma, and intercalated duct adenoma is supported by clinical, epidemiological, histopathological, and immunohistochemical characteristics; however, this distinction does not significantly impact patient prognosis, as all these neoplasms exhibit benign and indolent behavior. However, its differentiation from other salivary

[1]University of Pernambuco – Recife (PE), Brazil.
[2]Universidade Federal de Minas Gerais, Oral Surgery and Oral Pathology – Belo Horizonte, Brazil.
[3]Universidade de São Paulo, Faculdade de Medicina, Instituto do Câncer do Estado de São Paulo, Dental Oncology Service – São Paulo (SP), Brazil.
[4]Universidade Federal do Rio de Janeiro, Oral Diagnosis and Pathology – Rio de Janeiro (RJ), Brazil.
[5]University of Campinas, Oral Diagnosis – Piracicaba (SP), Brazil.
Corresponding author: Email: pavargas@fop.unicamp.br
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gland malignancies like adenoid cystic carcinoma (AdCC) and polymorphous adenocarcinoma gives to canalicular adenoma diagnosis an especial importance and a better understanding of the molecular features of this benign tumor could represent an adjunct tool for improving its correct identification, especially in cases with only small incisional biopsies available for analysis[3,8,9].

The purpose of the current study is to investigate the clinicopathological features and the immunohistochemical profile of a large panel of molecular markers in a series of canalicular adenomas.

MATERIAL AND METHODS

A 15-year retrospective review from January 1998 to December 2012 was done in the files of the Department of Oral Diagnosis (Pathology) of the Piracicaba Dental School, University of Campinas (Piracicaba/Brazil) and all cases diagnosed as canalicular adenoma were retrieved. Clinical information including gender, age, affected site, clinical presentation and symptomatology were collected from the patients' charts. The diagnoses were confirmed by 3 independent oral pathologists by reviewing the original 5μm histological sections stained with H&E following the current World Health Organization (WHO) guidelines for classification of salivary gland tumors[10].

Immunohistochemistry was performed following the methods of Andrade et al.[11] and Table 1 depicts the antibodies, dilutions and antigen retrieval methods used. Briefly, the reactions were conducted in 3 μm histological sections that were de-waxed with xylene and then hydrated in an ethanol series. The antigen retrieval was done and the endogenous peroxidase activity was blocked using 10% hydrogen peroxide in five baths, 5 minutes each. After washing in PBS buffer (pH 7.4), slides were incubated overnight with primary antibodies. All slides were subsequently exposed to avidin-biotin complex and horseradish peroxidase reagents (LSAB Kit – DakoCytomation, USA) and diaminobenzidin tetrahydrochloride (DAB, Sigma, St. Louis, MO, USA), and subsequently counterstained with Carazzi hematoxylin. Adequate positive control sections were used for each antibody, whereas the negative control was obtained by omitting the primary specific antibody. Semi-quantitative analysis of the immunohistochemical reactions was carried out by two independent observers, where those stainings limited to 20% of all neoplastic cells were considered as focal and above this value considered as diffuse[12].

RESULTS

During the period investigated, 11 cases diagnosed as canalicular adenoma were retrieved. Clinical features are detailed described in Table 2. In summary, individuals in the seventh decade of life were more commonly affected, with a mean age of 66,3 years ranging from 49 to 73 years. No gender predilection could be seen (male:female ratio of 1:1) and superior lip was affected in 10 cases (Figure 1A and B), whereas in only one case the palate was involved. Multifocal tumors were seen in one case affecting the upper lip. All cases presented as

Table 1. Antibodies used in the immunohistochemical analysis of canalicular adenoma.

Antibodies	Clone	Source	Dilution	Antigen retrieval
CK7	OV-TL 12/30	DAKO	1:300	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
CK8	Polyclonal	Novocastra	1:500	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
CK13	KS-1A3	Novocastra	1:400	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
CK14	LL002	Novocastra	1:200	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
Vimentin	Vim3B4	DAKO	1:400	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
GFAP	6F2	DAKO	1:400	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
S100	Polyclonal	DAKO	1:10.000	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
αSMA	1A4	DAKO	1:400	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
Calponin	CALP	DAKO	1:600	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
SMA	HHF35	DAKO	1:800	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
D2-40	D2-40	DAKO	1:100	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
CD34	QBEnd10	DAKO	1:50	Citrate buffer (pH 6.0); 3 minutes of pressure cooking
β-Catenin	17C2	Novocastra	1:200	Citrate buffer (pH 6.0); 3 minutes of pressure cooking

CK: Cytokeratin; GFAP: Glial Fibrilary Acid Protein; αSMA: α Smooth Muscle Actin; SMA: Specific Muscle Actin.

Table 2. Clinical features of 11 cases of canalicular adenoma.

No.	Sex/Age	Site	Size (cm)	Clinical presentation	Color	Symptoms
1	M/53	Upper lip	1.5x1.5x1.0	Single nodule	Normal colored	Painless
2	F/71	Upper lip	1.0x1.5x1.0	Single nodule	Normal colored	Painless
3	F/71	Upper lip	3.0x1.0x1.0	Single nodule	Bluish	Painless
4	F/73	Palate	NS	Single nodule	Bluish	Painless
5	M/49	Upper lip	NS	NS	NS	Painless
6	M/72	Upper lip	1.0x1.0x0.7	Single nodule	Reddish	Painless
7	F/58	Upper lip	1.0x1.0x1.0	Single nodule	Reddish	Painless
8	M/73	Upper lip	1.0x1.0x1.0	Single nodule	Normal colored	Painless
9	F/71	Upper lip	0,9x,0,9x0,7	Single nodule	Normal colored	Painless
10	M/71	Upper lip	2.0x1.0x1.0	Multiple nodules	NS	Painless
11	F/72	Upper lip	3.0x1.0x1.0	Single nodule	Normal colored	Painless

M: male; F: Female; NS: Not specified.

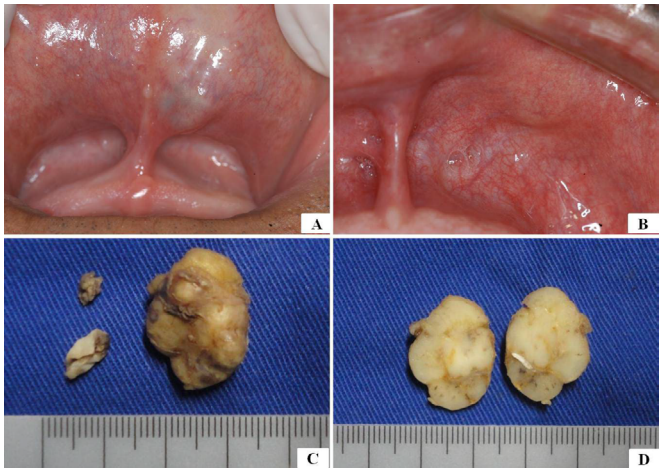

Figure 1. Clinical aspects and macroscopic features of canalicular adenoma. A and B) A painless fibroelastic bluish or normal colored nodule affecting the upper lip was the most commonly described clinical presentation in the cases evaluated. C and D) Although canalicular adenoma most frequently presented as small nodules, tumor as large as 3.0cm has been described, presenting a homogeneous brownish interior.

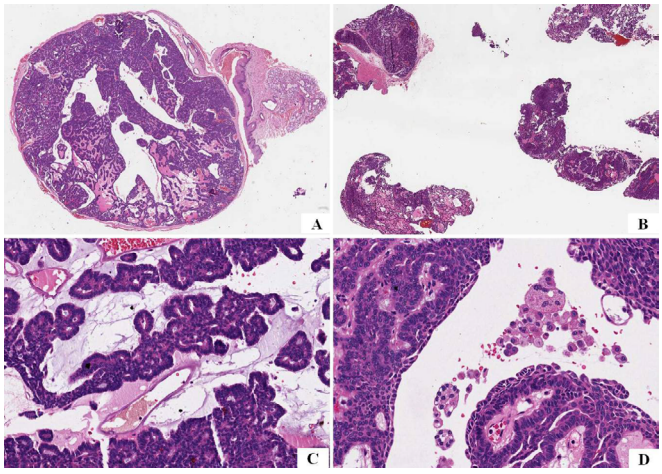

Figure 2. Histopathological features of canalicular adenomas. A) Most cases presented as well circumscribed neoplastic tissue (H&E, 50X), B) even though several cases presented very fragmented, in these cases the distinction from polymorphous adenocarcinoma and AdCC must be a special concern (H&E, 50X). C) All cases presented columnar epithelial cells in a loose stroma containing mucoid material (H&E, 100X). D) Foamy macrophages could be identified in neoplastic stroma of four cases (H&E, 20X).

asymptomatic fibroelastic nodules with intact overlying oral mucosa, ranging in size from 0.9 to 3 cm (mean of 1.7 cm) (Figure 1C and D).

Eight cases analyzed presented as well-circumscribed or encapsulated tumors, while 3 highly fragmented cases proved to be only partially encapsulated or even unencapsulated, this could possibly be an artifact of the processing or the surgical procedure performed (Figure 2A and B).

All cases were composed by uni or bilayer strands of epithelial cells, displayed opposed to each other or widely separated, leading to the classical canaliculi aspect of the tumor and the presence of pseudocystic spaces (Figure 2C). The cell ribbons frequently abut one another (termed "beading") with knots of cells joining parallel rows. The epithelial cells ranged from columnar to cuboidal in shape, displaying a moderate to abundant cytoplasm and uniformly sized ovoid nuclei containing inconspicuous nucleoli and absence of mitotic figures. In some cases, it could also be noted an increased cellular density and foci of basaloid cells. The stromal component of the neoplasia was always loosely arranged, frequently showing lightly fibrillar material and scarce collagenous tissue with few fibroblasts and a prominent vascular background. Papillary projections into cystic spaces were commonly observed in most of the cases. Foamy macrophages were found in four cases

(Figure 2D) and negative image of cholesterol crystals in another one.

Regarding immunohistochemical features of the neoplasm, Table 3 demonstrates the results obtained in this series. The investigation of cytokeratins expression showed a strong positivity for CK7 and a variable staining for CK8, CK13 and CK14. The expression of all cytokeratins was found not only in the periphery of neoplastic cords, but also in their central areas (Figure 3).

Myogenic markers calponin, HHF35 and αSMA proved to be negative in all cases evaluated, only reacting with stromal components like blood vessels and scarce myofibroblasts. Vimentin was positive in 72.7% of the cases, being expressed mostly in neoplastic cells located in the periphery of the strands (Figure 4A).

S100 protein was also mainly present in these peripheral cells but in a much stronger way and not limited to them (Figure 4B). No nervous structures could be identified in the interior of the neoplasias. Interestingly, GFAP positivity was seen in 63.6% of the cases, always restricted to the neoplastic cells located in the interface with the tumor capsule (Figure 4C).

Considering the adhesion molecule β-catenin, all cases revealed membrane and cytoplasmic positivity (Figure 4D). CD34 evidenced the high number of intra- and peritumoral blood vessels present in the neoplastic stroma (Figure 4E). On the other hand, D2-40 revealed no lymphatic vessels in the tumoral stroma, but only few vessels situated peripherally in the fibrous capsule of the tumors (Figure 4F).

Table 3. Semi-quantitative results of the immunohistochemical reactions used in the molecular analysis of canalicular adenoma.

Antibodies	Negative		Focal		Diffuse	
	No. cases	%	No. cases	%	No. cases	%
CK7	0	0.0	0	0.0	11	100.0
CK8	2	18.2	3	27.3	6	54.5
CK13	2	18.2	3	27.3	6	54.5
CK14	1	9.1	6	54.5	4	36.4
Vimentin	3	27.3	1	9.1	7	63.6
GFAP	4	36.4	7	63.6	0	0.0
S100	0	0.0	1	9.1	10	90.9
SMA	11	100.0	0	0.0	0	0.0
Calponin	11	100.0	0	0.0	0	0.0
HHF35	11	100.0	0	0.0	0	0.0
D2-40	11	100.0	0	0.0	0	0.0
CD34	0	0.0	0	0.0	0	0.0
β-Catenin	0	0.0	4	36.4	7	63.6

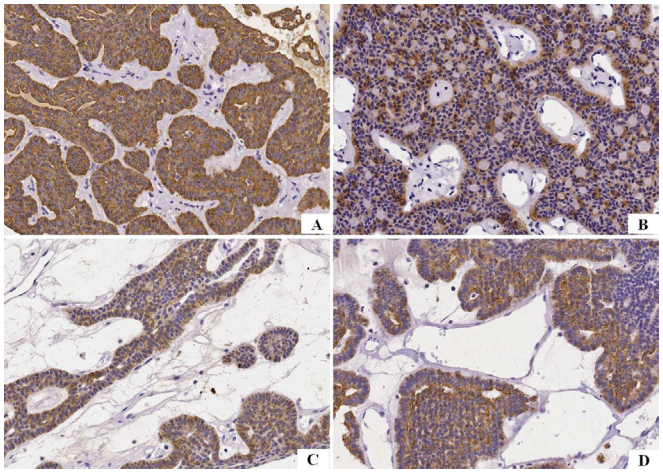

Figure 3. Cytokeratins expression in canalicular adenoma. A) CK7 presented a strong positivity in all cases evaluated both in peripherally and centrally situated cells of neoplastic strands (DAB, 100X). B) CK8 heterogeneously stained neoplastic cells (DAB, 100X), C) as well as CK13 (DAB, 100X). D) CK14 revealed the weaker staining, but could be found both peripherally and centrally situated (DAB, 100X).

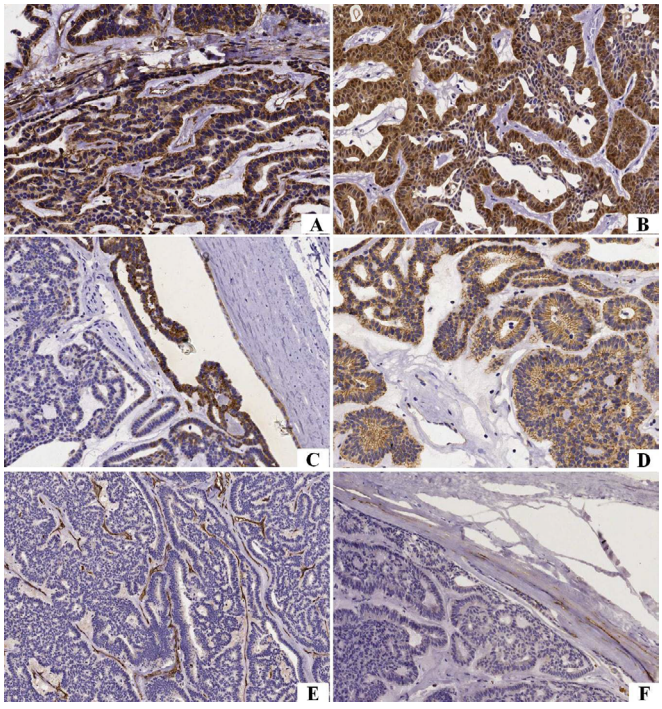

Figure 4. Immunohistochemical analysis of canalicular adenoma. A) Vimentin mainly stained the peripheral cells of neoplastic cords in the majority of the cases (DAB, 100X). B) S100 protein presented an intense cytoplasmic and nuclear staining in the peripheral cells of neoplastic cords, but could also be observed in central cells (DAB, 100X). C) GFAP staining was seen in neoplastic cells located in the interface with fibrous capsule (DAB, 100X). D) β-catenin was present in 10 cases mostly as membranous expression, but cytoplasmic staining was also observed (DAB, 100X). E) CD34 highlighted the highly vascularized stroma of canalicular adenoma (DAB, 100X), F) whereas no lymphatic vessel could be demonstrated in the interior of the tumoral stroma, with only scattered structures present in the capsule of the tumor (DAB, 100X).

DISCUSSION

Canalicular adenoma had long been considered a morphological variant of basal cell adenoma, representing its trabecular variant[1,13]. Although the term canalicular adenoma had been first used by Bhaskar and Weinmann in 1955, it was only in the second edition of the WHO histological classification of salivary gland tumors that this benign tumor was accepted as a distinct entity after some clinical and pathological features of both neoplasias had been proved to be different, despite their similar indolent behavior[14].

In contrast to the majority of minor salivary gland tumors that mainly occurs in the palate, canalicular adenoma predominantly affects the upper lip, as illustrated in the present study, what diverges from the anatomical preference of basal cell adenoma for the parotid gland[3,15,16]. Although no gender predilection was seen in our sample, a slight female preponderance is frequently reported in the literature[2,3,8], and patients in the seventh decade of life would be the most affected individuals, as shown in the present study[3,13,16]. As also described in our patients, pain and local recurrences are not expected in cases of canalicular adenomas, and when the latter is present, it may most probably indicate treatment inaccuracy or multifocality of the tumor, a clinical characteristic found in one case of our series[2,3,17,18].

To better understand the pathogenesis of salivary gland tumors and to obtain new molecular markers that could be used as adjunct tools in their diagnoses, many authors have attempted to determine the origin of these neoplasias from specific regions of the normal glandular structure. Canalicular adenoma is believed to be derived from excretory ducts, with an exclusive luminal cell origin, what has been supported by ultrastructural studies and the expression pattern of different cytokeratins[12,13,19]. As shown in the current research, canalicular adenomas presented an evident although heterogeneous expression of luminal cells-related cytokeratins 7, 8, and 13, and in a more focal and faintly expression pattern the CK14, a high-weight cytokeratin more usually observed in myoepithelial cells. These findings reinforce the results previously published in the literature that mainly correlate the luminal cell features to canalicular adenoma histogenesis[1,15,20]. Moreover, by investigating the expression of cytokeratins in the most important differential diagnoses of canalicular adenoma, it has been shown that high-weight filaments are strongly expressed in basal cell adenomas and in AdCC, what is explained by the presence of different amounts of myoepithelial cells in the composition of these tumors; therefore, the analysis of the cytokeratin profile has been proposed as an auxiliary tool in their differential diagnosis[15,20,21].

Interestingly, Triantafyllou et al.[17] described an increased expression of stratified epithelium-related cytokeratins in the periphery of the neoplastic strands of canalicular adenoma and an inferior staining in the central portions of these structures, suggesting that their expression would be determined by influences of the surrounding microenvironment. However, we failed to demonstrate this staining pattern and all cytokeratins investigated were peripherally and centrally distributed in neoplastic strands, suggesting that the expression of these molecules would be more probably histogenetically determined.

Further supporting the exclusive epithelial composition of canalicular adenomas, myogenic markers like calponin, HHF35 and SMA, commonly related to myoepithelial differentiation have been proved to be negative, whereas their expression is usually described in the peripheral layer of basal cell adenomas and AdCC[12,22,23]. In the current study, only stromal positivity was found in canalicular adenoma, highlighting its vascularized stroma and the presence of scattered myofibroblasts.

Meanwhile, the previously described strong positivity for S100 was found in all cases analyzed in this series[12,15,24,25]. In addition, Curran et al.[9] described a specific staining pattern for GFAP in cases of canalicular adenoma if compared to polymorphous adenocarcinoma and pleomorphic adenomas, where a distinct row of GFAP-positive cells was present solely in the tumoral periphery, in the interface with the fibrous connective tissue. This staining pattern could also be demonstrated in seven cases of the current study, but it was evidently seen in only four; hence, in those tumors incisionaly biopsied with fragmented samples the observation of this feature would be very difficult and for this reason we believe that despite its distinctive staining pattern, the diagnostic use of GFAP must be kept with caution. We demonstrated a variable positivity for vimentin in the majority of the cases studied, mainly in the peripheral cells of neoplastic strands, what is in contrast to other studies[1,15].

Taken together, despite the absence of SMA, HHF35 and calponin confirm that canalicular adenoma is a tumor devoid of myoepithelial cells and mainly composed by luminal ones, the expression of vimentin, S100 and GFAP proteins mostly in peripheral cells of

neoplastic strands, would suggest that despite canalicular adenoma cells are committed to excretory duct differentiation as postulated by Panagiotis et al.[1], some of these cells would not be completely differentiated and would maintain some primitive molecular features; therefore, this tumor could also be composed of a cellular population with transitional features between myoepithelial/basal and luminal cells, what is supported by Guccion et al.[26] that showed ultrastructural evidences of myoepithelial differentiation in some cellular components of canalicular adenoma and by Aquino et al.[13] and Triantafyllou et al.[17] that highlighted the mucoid stroma of canalicular adenoma rich in glycosaminoglycans, resembling the stromal component produced by myoepithelial cells of pleomorphic adenoma.

Because of the typical morphological arrangement of canalicular adenomas we aimed to investigate the expression of the adhesion molecule β-catenin, known to interact with E-cadherin to maintain normal and neoplastic morphology[27,28]. When free in the cytoplasm, β-catenin is quickly phosphorylated and degraded through a proteic complex. The inactivation of one constituent of this complex would lead to cytoplasmic accumulation of β-catenin, allowing its migration to the nucleus, where it would promote the transcription of genes involved in cell proliferation[27,29]. As described by Chandrashekar et al.[27] before in one case of canalicular adenoma, in the present investigation the authors observed that β-catenin was present both in the cytoplasm and in the membrane of the cases studied, especially in the latter, suggesting that it would represent an important adhesion molecule for maintaining the morphological structure of canalicular adenomas. Meanwhile, it has been shown that in basal cell adenomas, the expression of β-catenin is mostly nuclear, suggesting its use as an adjunct diagnostic tool for differentiating both neoplasms in borderline cases[29].

The investigation of neoplastic stromal features has gained much attention since its characteristics are known to influence neoplastic characteristics. Therefore, we evaluated the vascular composition of the stroma of canalicular adenoma by determining the distribution of blood and lymphatic vessels. We could observe that all vascular spaces present in the interior of the tumor corresponded to blood vessels and that the neoplasia is devoid of intra-tumoral lymphatics, although few of them could be identified in the peripheral area of the neoplasia, this lack of lymphatic vessels is similar to the described previously for pleomorphic adenomas[30].

CONCLUSION

In conclusion, the current study demonstrated that although canalicular adenoma is primarily composed of luminal epithelial cells, some exhibit primitive molecular features, including the expression of vimentin, S100, and GFAP. Furthermore, β-catenin may play a crucial role in maintaining the tumor's structural integrity. Clinically, in this study 11 cases were identified, predominantly affecting individuals in their seventh decade of life, with no gender predilection, and the superior lip being the most frequently affected site.

AUTHORS' CONTRIBUTIONS

MVC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing original draft, Writing review & editing. JMAL: Conceptualization, Data curation, Methodology, Visualization, Writing original draft, Writing review & editing. ACPR: Conceptualization, Data curation, Methodology, Visualization, Writing original draft, Writing review & editing. FPF: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing original draft, Writing review & editing. BABA: Conceptualization, Data curation, Methodology, Visualization, Writing original draft, Writing review & editing. OPA: Conceptualization, Data curation, Methodology, Visualization, Writing original draft, Writing review & editing. MAL: Conceptualization, Data curation, Methodology, Visualization, Writing original draft, Writing review & editing. PAV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing original draft, Writing review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose..
Ethics approval: This study was approved by the Ethics Committee of the Piracicaba Dental School, University of Campinas, Piracicaba, Brazil (protocol

no. 08271813.5.0000.5418). All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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