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ORIGINAL PAPER

Canalicular Adenoma: A Clinicopathologic and Immunohistochemical Analysis of 67 Cases with a Review of the Literature

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Abstract There is a lack of a comprehensive immunohistochemical (IHC) analysis of canalicular adenoma (CanAd), especially when combined with a description of the unique histologic features. Given the usual small biopsies, IHC may be useful in distinguishing CanAd from other tumors in the differential diagnosis. Retrospective. The patients included 54 females and 13 males (4.2:1), aged 43–90 years, with a mean age at presentation of 69.9 years. Clinical presentation was generally a mass (n = 61) slowly increasing in size (mean 38.5 months), affecting the upper lip (n = 46), buccal mucosa (n = 17) or palate (n = 4), involving the right (n = 29), left (n = 24) or midline (n = 9), *without* any major salivary gland tumors. The tumors ranged in size from 0.2 to 3 cm (mean 1.2 cm). Most tumors were multilobular or bosselated (76 %), often surrounded by a capsule. Histologically, the tumors were characterized by cystic spaces, tumor cords with beading, tubule formation, and by the presence of luminal squamous balls (n = 41). The cells were cuboidal to columnar with stippled chromatin. Mitoses were inconspicuous. A myxoid stroma (n = 64), sclerosis (n = 42), luminal hemorrhage (n = 51), and luminal microliths (calcifications) (n = 33) were characteristic. Nine (13.4 %) were multifocal. CanAd showed the following characteristic immunohistochemistry findings: CK-pan and S100 protein (strong, diffuse reaction); peripheral or luminal GFAP reaction; CK5/6 and p16 luminal squamous ball reaction; SOX10 nuclear reaction; cytoplasmic p63 reaction. CanAd are unique minor salivary gland tumors showing a distinct architecture and phenotype. They predilect to older women, with the majority multilobulated and affecting the upper lip, multifocal in 13 %; *no* major salivary gland tumors were identified. S100 protein, CK-pan, GFAP and SOX10 are positive, with luminal squamous balls highlighted by CK5/6 or p16.

Keywords Canalicular adenoma · Lip · Buccal · Palate · Luminal ball · Immunohistochemistry

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Introduction

Canalicular adenoma (CanAd) is an uncommon benign salivary gland neoplasm. Originally thought to be derived from terminal duct origin [1, 2], there has been controversy about origin and separation from other salivary gland neoplasms. These tumors have undergone taxonomic drift, with many terms used to describe these tumors over the years (Table 1). However, it is now agreed that CanAd are a unique salivary gland tumor, separated from other monomorphic adenomas in the last two editions of the World Health Organization. Many minor salivary gland

Table 1 Terminology used to describe canalicular adenoma

Year	Author	Term applied
1942	McFarland [109]	Canalicular tumor
1947	Ash [110]	Canalicular form of mixed tumor
1953	Bauer and Bauer [111]	Canalicular adenoma[a]
1955	Bhaskar and Weinmann [112]	Canalicular adenoma
1965	Calhoun et al. [113]	Papillary cystadenoma of the upper lip
1966	de la Pava [12]	Multifocal carcinoma of accessory salivary gland
1970	Rauch et al. [114]	Monomorphic adenoma: Basal cell adenoma: Canalicular type
1973	Nelson and Jacoway [34]	Monomorphic adenoma (canalicular type)
1976	Crumpler et al. [59]	Monomorphic adenoma: Canalicular
1977	Sarangapani [42]	Cystic adenoma
1977	Åhrén and Lindström [3]	Adenomatosis of accessory salivary glands of the lip
1981	Batsakis et al. [115]	Monomorphic adenoma: distal (terminal) duct origin: basal cell or basaloid adenoma: canalicular
1983	Gardner and Daley [83]	Canalicular adenoma

[a] First use of the term canalicular adenoma

Table 2 Literature summary of canalicular adenoma [3–58]

Clinical characteristics[a]	Number n = 456
Gender[a]	
Females	250
Males	168
Age (in years)[a]	
Range	33–91
Mean	65.6
Symptom duration (in months)[a]	
Duration (range)	2–180
Duration (mean)	31
Symptoms	
Asymptomatic	2
Mass	291
Pain	7
Anatomic site[a]	
Upper lip	323
Lip (not otherwise specified)	9
Buccal mucosal	68
Palate (hard or soft)	4
Other (mandible, esophagus)	2
Size (cm)[a]	
Range	0.3–4
Mean	1.6

[a] Results are incomplete, as value was not always stated

tumors (MSGTs) are frequently sampled by small or limited biopsies, and so the differential with other tumors can be challenging, resulting in incorrect classification and inappropriate management.

The English literature contains many case reports, small series, and a few larger series, all of which focus on a particular feature. A review of the English literature (1966–2014) reveals 456 well defined cases of CanAd, although these tumors are often presented as part of a clinical series of minor salivary gland tumors in general, within all benign salivary gland tumors, as part of a differential diagnosis presentation, a single institution's experience or as a regional incidence report of salivary gland neoplasms in general (Table 2) [3–58]. In a literature review by Pires et al. [38], there were a total of 7,746 intraoral minor salivary gland tumors: 3,988 benign and 3,758 malignant tumors. There were 249 CanAds, representing 6.2 and 3.2 % of benign tumors and all tumors, respectively.

It is the intention of this study to provide a comprehensive analysis of CanAd incorporating the use of clinical features, histologic findings, and immunohistochemical results applied to a group of 67 patients with this tumor, combined with a comprehensive review of the literature.

Methods

Eighty-seven cases of salivary gland tumors diagnosed as "canalicular adenoma" were selected from the clinical files of the authors between 1986 and 2012. Re-examination of the cases was performed in a blinded fashion, with 20 cases reclassified as basal cell adenoma (n = 16; 13: parotid; 2: upper lip; 1: buccal), pleomorphic adenoma (n = 3; 1 each, upper lip, palate and parotid) or chondroid syringoma (n = 1, upper lip). The remaining 67 cases were evaluated further. Materials within the files were supplemented by a review of the patient demographics (gender, age, race) and symptoms at presentation (asymptomatic, mass, pain) including duration. In addition, we reviewed the medical history, surgical pathology and operative reports, specifically noting exact tumor location, lateralization and tumor size (greatest dimension in centimeters). Follow-up data, available for 27 patients, included information regarding the specific treatment, the presence or absence of recurrent or persistent disease, and the current status of the disease and patient. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of an Internal Review Board authorization (#5968) performed under the direction of Southern California Permanente Medical Group relating to human subjects in research.

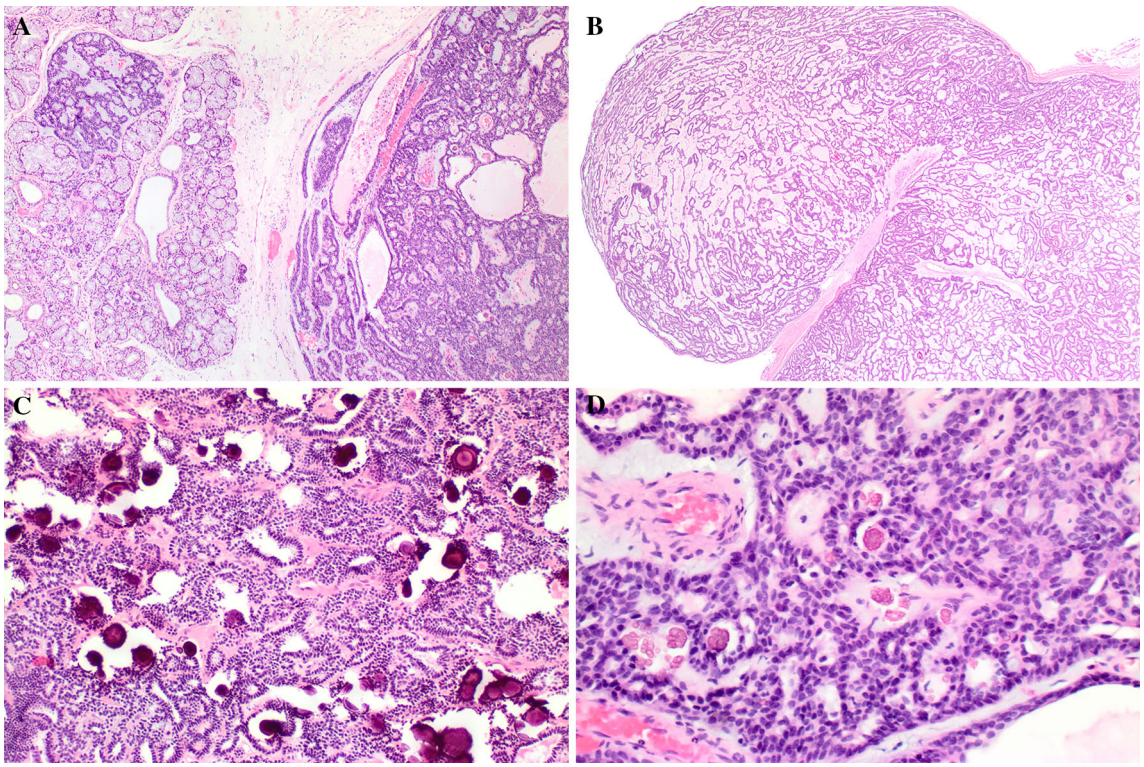

Fig. 1 Canalicular adenoma with: **a** Multifocal tumor growth, with a topographically separate nodule (*left side*). **b** Multinodular pattern, with a nodule of tumor adjacent to the main mass. **c** Microliths (calcifications) without adjacent necrosis. **d** Tyrosine crystals within the lumen

Hematoxylin and eosin-stained slides from all 67 cases were reviewed, with a range of 1–5 slides reviewed per case (mean 1.2 slides), with each slide often containing multiple sections. The following specific macroscopic and histologic observations were recorded for each tumor: surface epithelium (present or absent); surface origin or involvement; surgical margin status; tumor bosselation or lobulation (Fig. 1); tumor multifocality (Fig. 1); capsule; cystic appearance (Fig. 2); beading of the neoplastic cells (Fig. 2); tubule formation (Fig. 2); nuclear chromatin distribution (stippled, coarse, vesicular or hyperchromatic); nuclear to cytoplasmic ratio; cell shape (columnar or cuboidal); presence of intraluminal squamous ball or morule (Fig. 2); reduplicated basement membrane; sclerosis; intraluminal hemorrhage; myxoid stroma (Fig. 3); histiocytes (luminal or stroma; foamy or hemosiderin/lipofuscin laden; Fig. 3); microliths (psammoma bodies, calcifications; Fig. 1); necrosis (present or absent); mitotic figures (number of mitotic figures per 10 high power fields [magnification at 40× with a 10× objective lens using an Olympus BX41 microscope]; Fig. 3); atypical mitotic figures (present or absent, and defined by abnormal chromosome spread, tripolar or quadripolar forms, circular forms, or indescribably bizarre); and the presence of other microscopic pathologic findings.

Immunophenotypic analysis was performed in all cases with sufficient suitable material by a standardized Envision^{TM} method employing 4 μm-thick, formalin fixed, paraffin embedded sections using a tissue microarray constructed using 2 mm cores from each case block with available material (n = 52). Table 3 documents the commercially available immunohistochemical antibody panel used (Figs. 4, 5, 6). Epitope retrieval was performed, as required by the manufacturer guidelines. Standard positive controls were used throughout, with serum used as the negative control. The antibody reactions were catalogued by *location* (nuclear, cytoplasmic, membrane, luminal, ball, canalicular); *tumor distribution* (stromal, cellular, peripheral); *fraction of positive cells* (focal, diffuse); and *graded*: absent to weak (0–1+), moderate (2+ to 3+) and strong (4+) staining. The proliferation marker was separated into ≤5 and >5 %. In situ hybridization for high-risk HPV was performed using an automated benchmark XT system (Ventana Medical Systems, Inc., Tucson, AZ). The INFORM HPV III family 16 probe cocktail, with affinity for high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66), was applied and the reaction was developed using a Hybrid Ready Detection Kit (Ventana Medical Systems, Inc., Tucson, AZ). Positive signals included punctate or diffuse reactivity within tumor nuclei. Periodic acid Schiff (PAS) with and without diastase,

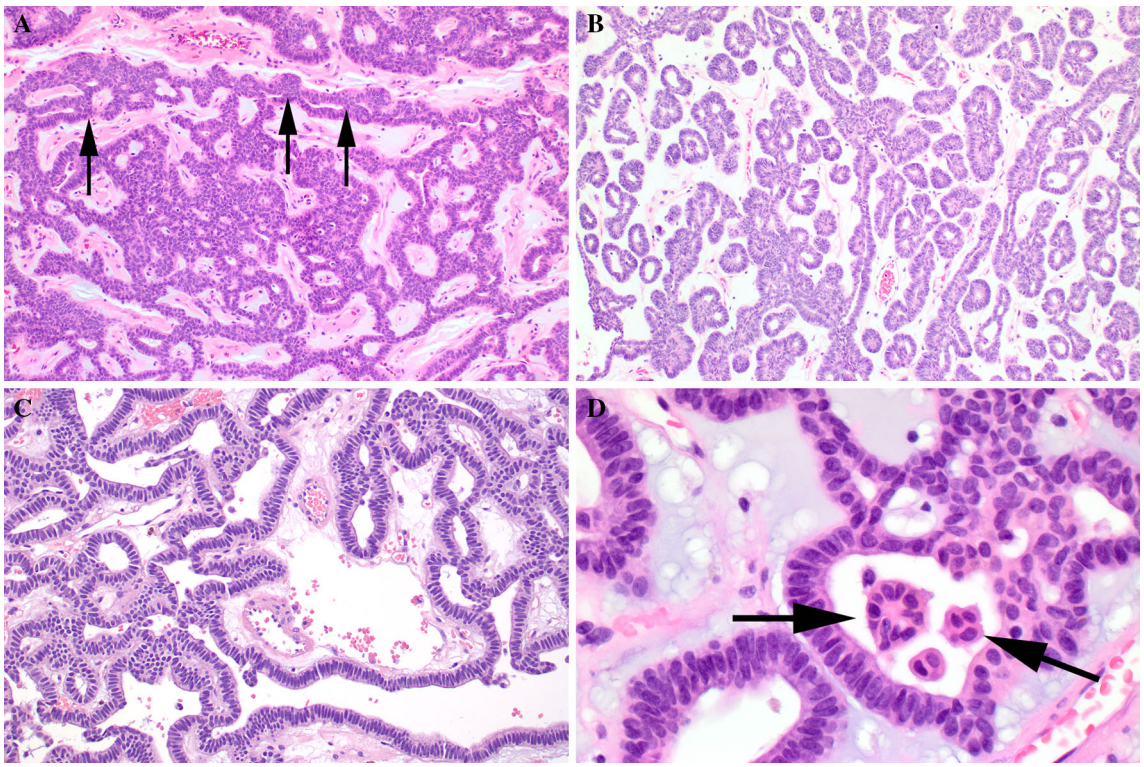

Fig. 2 Canalicular adenoma showing: **a** Characteristic beading (*arrows*), with parallel rows joining. **b** Tubular growth with club-ended cords with small lumina, set in a loose stroma. **c** Cyst formation with edematous stroma. **d** Intraluminal squamous balls or morules (*arrows*). Note they may be free in the lumen or attached

mucicarmine and alcian blue (Fig. 6) were performed on standard automated stainers.

A review of publications in English (MEDLINE 1966–2014) was performed, with all cases reported with clinical, histologic, immunophenotypic and/or follow-up information on CanAd evaluated and included in the review, but excluding "Quiz" or "Case of the Month" type reports. Several studies were excluded if no specific or separable information was given about CanAd or if the illustrations were not characteristic [23, 51, 55, 59–78]. Several of the cases seemed to have been included multiple times in different series reports [9, 10, 40, 79–83].

Statistical evaluation was performed using a standard statistics software package with categorical variables analyzed using Chi square tests and Fisher's Exact tests to compare observed and expected frequency distributions. Comparison of means between groups was made with unpaired *t* tests or one-way analysis of variance, depending on whether there were two groups or more than two groups, respectively. Multiple comparisons were analyzed using the Tukey method and log-rank analysis. Confidence intervals of 95 % were generated for all positive findings. The alpha level was set at $p < 0.05$.

Results

Clinical

The patients included 54 women and 13 men (Table 4) who ranged in age from 43 to 90 years, with a mean age at presentation of 70 years. There was no difference in mean age at presentation between men and women, nor was there a difference in anatomic site of involvement between the genders. The majority of patients presented with a painless mass (n = 61), while 6 were discovered incidentally during dental examination. If symptomatic, symptoms were present for an average of 3 years. Multifocal tumors were identified in 9 patients, 5 of whom had another surgery at a later time to manage the tumor. The upper lip was the most common site affected (n = 46). No cases were identified in major salivary glands in this series.

Pathologic Features

Macroscopic

The tumors ranged in size from 0.2 up to 3 cm, with a mean of 1.2 cm. Tumors of the lip were on average smaller

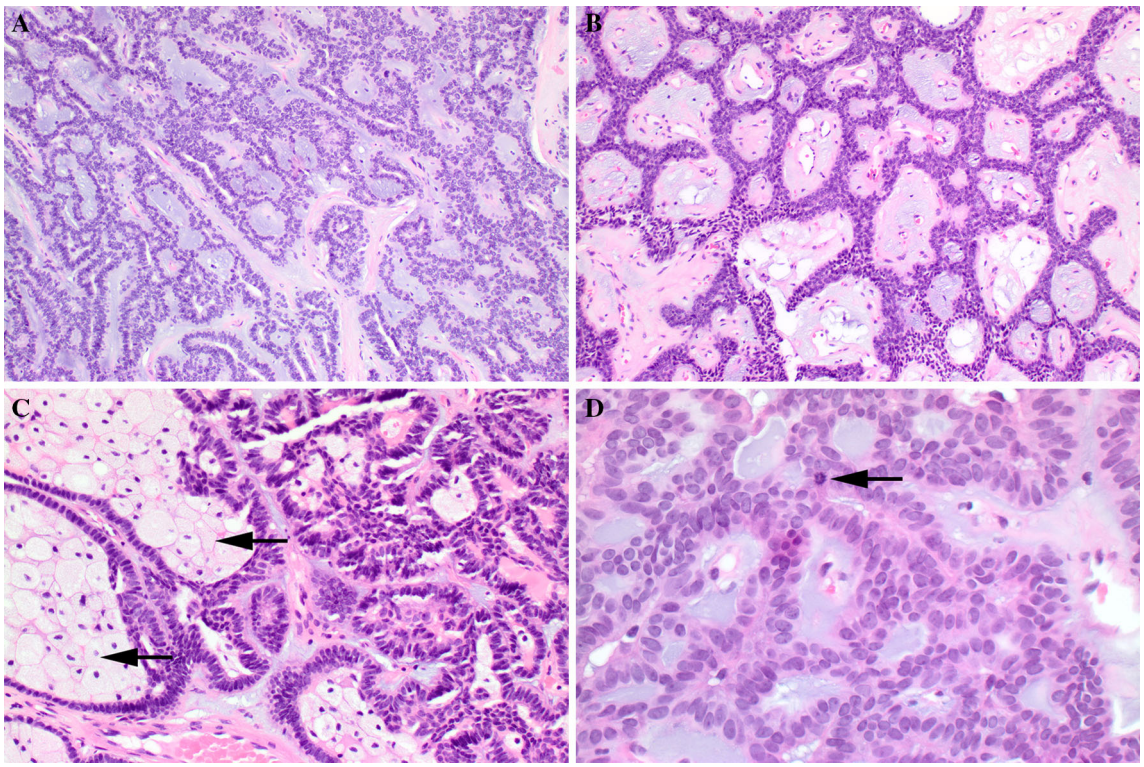

Fig. 3 Canalicular adenoma will often show: **a** Bluish myxoid stroma; **b** Fibrovascular stroma with edema and collagen; **c** Luminal clusters of foamy histiocytes. **d** Infrequently, mitotic figures (*arrow*) may be identified

than those of the buccal mucosa or palate ($p = 0.027$). There was no difference in tumor size between genders. On gross examination, the tumors were partially to completely encapsulated, with a yellow-tan to brown, homogenous cut surface. The firm masses had a mucoid to gelatinous appearance, with cyst formation.

Microscopic

Microscopically, the tumors were bosselated or lobulated at the periphery (Fig. 1; Table 5), well circumscribed, occasionally showing a well developed fibrous connective tissue capsule (especially if the lesions were >1 cm). Separate tumor islands (multifocality) were noted in nine cases (Fig. 1). There was no tumor necrosis. The majority of the cases showed cyst formation (Fig. 2), frequently accompanied by intraluminal hemorrhage (n = 51) and hemosiderin/lipofucsin laden macrophages (n = 20). In a few cases the cyst was the dominant finding. Laminated calcifications, psammoma bodies, or microliths were seen in 33 cases (Fig. 1). The microliths were associated with viable cells and identified in the stroma or the lumen, often in areas with papillae. Mitoses were only found in 24 cases (Fig. 3), ranging from 1 to 4, with a mean of 0.5 per 10 high power fields, without any atypical forms. Three tumors were degenerated or had undergone infarction. One case showed tyrosine crystals (Fig. 1). The surgical margins were positive (i.e., tumor cells on ink) in 28 cases. This was not related specifically to multifocality, but rather to the lobulation or bosselations of the tumor.

The neoplastic cells were a relatively monotonous, isomorphic population of high cuboidal to columnar cells, 1–2 cell layers thick arranged in anastomosing, branching or budding cords, tubules, rows, strands, columns or canaliculi (Figs. 2, 3). Solid nests were occasionally seen. Papillary projections were common in areas of cyst formation. The rows or ribbons of cells, arranged parallel to each other, would frequently merge, creating the characteristic "beading" phenomenon (Fig. 2). Stated differently, knots of cells can be seen joining together two parallel tracks of epithelial cells that are separated by a narrow lumen or cystic space. A pseudostratification of the nuclei or vaguely palisaded appearance was seen in most cases, where there was a preferential placement of the nucleus towards the base or mid-zone of the cells (not at the lumen). This pseudostratification results from different nuclei heights and plane of section. Intraluminal squamous morules or balls were seen in 41 cases (Fig. 2). This is a unique finding not identified in other salivary gland tumors, and specifically not in basaloid neoplasms. These balls were attached or free floating, showing a "metaplastic" squamous appearance. The cells showed a moderate

Table 3 Immunohistochemical panel and results

Antigen/antibody	Company	Dilution	Reaction	Reaction pattern
Cytokeratin-pan (AE1/AE3:M3515)	Dako	1:40	100 % (52/52)	S, D, Cytoplasmic
CK5/6 (D5/16 B4)	Dako	1:25	75 % (39/52)	S, F, Specifically ball
S100 protein	Dako	1:2,000	100 % (52/52)	W-S, D, Nuclear and cytoplasmic
Glial fibrillary acidic protein (GFAP)(6F2)	Dako	1:200	81 % (42/52)	S, F, Periphery or luminal
SOX10 (N-20)	Santa Cruz	1:200	100 % (52/52)	S, D to patchy, Nuclear
p63 (7jul)	Leica	1:40	73 % (38/52)	S, F, Cytoplasmic and nuclear (balls)
CK7 (OV-TL-12/30)	Dako	1:200	100 % (52/52)	S, D, Membrane
CAM5.2	Covance	1:8	100 % (52/52)	S, D
E-Cadherin (36B5)	Leica	1:50	100 % (52/52)	S, F-D, Membrane
CD15 (MMA)	Ventana	Neat	98 % (51/52)	S, D, Stromal
CK903 (34βE12)	Axxora	Neat	92 % (48/52)	S, F, Luminal
CD117 (C-Kit)	Dako	1:400	92 % (48/52)	W-S, F-D, Luminal
p53 (DO-7)	Dako	Neat	85 % (44/52)	W, F
Vimentin (V9)	Ventana	Neat	83 % (43/52)	S, D, Basal
Epithelial membrane antigen (EMA)(E29)	Ventana	Neat	79 % (41/52)	S, F, Luminal and/or ball
CK19 (RCK108)	Dako	1:20	75 % (39/52)	S, F-D
Calponin	Abcam	Neat	63 % (33/52)	W, F-D
p16INK4a (E6H4)	Ventana	Neat	31 % (16/52)	S, F, Ball (nuclear & cytoplasmic)
bcl-2 (124)	Dako	1:40	29 % (15/52)	W-S, F-D
Mammaglobin (304-1A5)	Zeta	1:2	19 % (10/52)	W-S, F
CD10 (56C6)	Leica	1:25	12 % (6/52)	S, F, Canalicular
CEA (p)	NeoMarkers	1:250	4 % (2/52)	S, F, Luminal
Ki67 (MIB1)	Dako	1:100	1–5 %	S, N
DOG1 (1.1)	Zeta Co	1:50	0 %	None
CK20 (KS20.8)	Ventana	Neat	0 %	None
Smooth muscle actin (asm-1)	Leica	1:200	0 %	None
Muscle specific actin (HHF35)	Enzo Life Sciences	1:100	0 %	None
Smooth muscle myosin heavy chain (SMMS-1)	Dako	1:100	0 %	None
Desmin	Dako	1:400	0 %	None
p40	CalBiochem	1:2,000	0 %	None
HPV (ISH)(Y1404)	Dako	n/a	0 %	None
β-Catenin	Millipore	1/100	0 %	None
CD34 (QBEnd/10)	Ventana	Neat	0 %	None
CD43 (DFT-1)	Ventana	Neat	0 %	None
CD56 (123C3.D5)	Lab Vision	Neat	0 %	None
Androgen Receptor (AR441)	Dako	Neat	0 %	None
Her-2/neu	Dako	1:800	0 %	None
Mucicarmine			0 %	No reaction in epithelial cells; weak stromal reaction
Alcian Blue-PAS 2.5			96 % (50/52)	S, D, stromal (blue)

S Strong, *W* Weak, *D* Diffuse, *F* Focal

nuclear to cytoplasmic ratio, limited to absent pleomorphism, and lacked prominent nucleoli. The nuclei were round to oval, regular and smooth, with stippled nuclear chromatin, while focal nuclei may be vesicular or show coarse chromatin distribution (Fig. 3). The cytoplasm was moderate to scant, eosinophilic, with granules noted (highlighted with PAS-D but not mucicarmine), while rare oncocytes or mucous cells were noted (3 cases). The cells

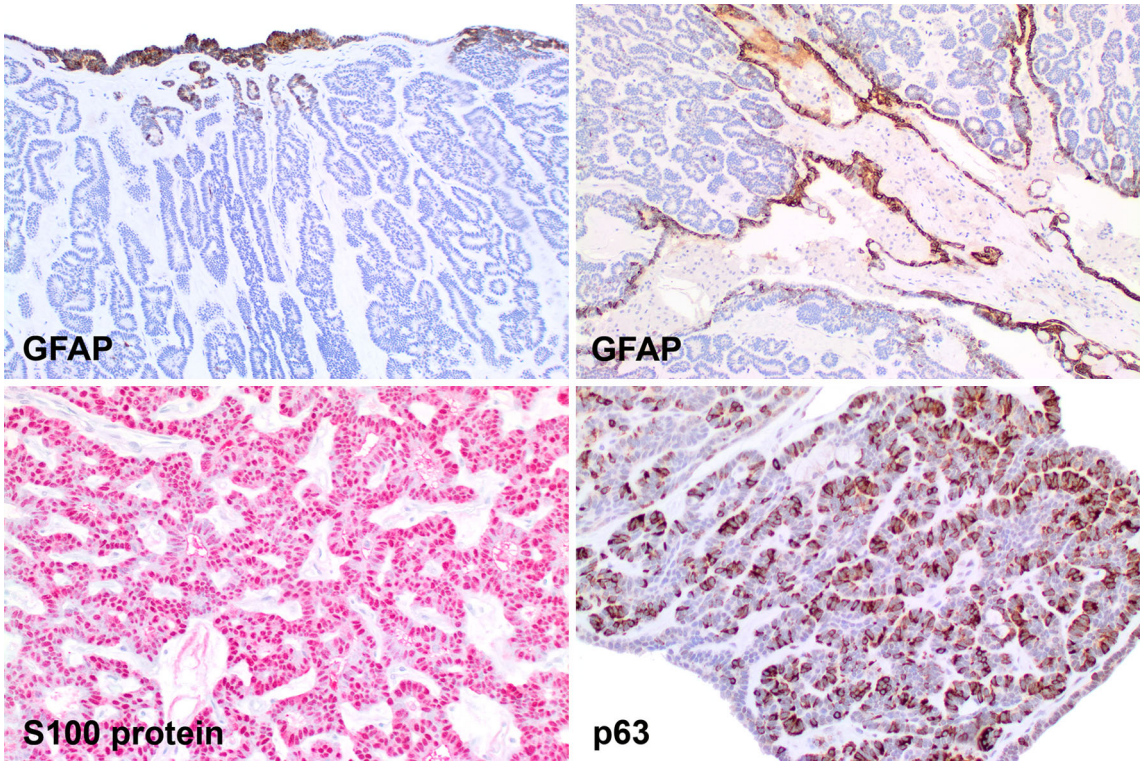

Fig. 4 The immunohistochemistry findings in canalicular adenoma show: GFAP: only at the periphery (*left*) or lining the cystic lumen (*right*). S100 protein shows a strong, diffuse nuclear and cytoplasmic reaction. p63 showing a cytoplasmic reaction without any nuclear reactivity in this field

appeared as a syncytium, with indistinct cell borders. Cytoplasmic hemosiderin or lipofuscin was present at the luminal surface of isolated tumor cells in most cases (apocrine-like cells). It is important to note that a basal layer or myoepithelial layer is not present by histology (or by immunohistochemistry). A supporting loose stroma was myxoid and often associated with a sclerosing to fibrillar collagen deposition. The stroma was richly vascularized, frequently (n = 51) associated with luminal hemorrhage. No chondroid matrix or stellate/bipolar epithelial cells were present. In general, the stroma was sparse, fibrillar and edematous (Fig. 3). This stroma stained with mucicarmine, alcian blue (Fig. 6), and periodic acid-Schiff, the latter both with and without diastase. Histiocytes were present in many cases, separated into foamy histiocytes and hemosiderin/lipofuscin laden histiocytes. The foamy histiocytes were usually luminal (n = 9; Fig. 3), with two cases showing a stromal location. The lipofuscin laden macrophages were usually luminal (n = 20), although also seen in the stroma (n = 11). Only two cases had both types of histiocytes.

Immunohistochemical Results

All tumors tested reacted with S100 protein (Fig. 4), pancytokeratin (Fig. 5), CK7, CAM5.2, and E-Cadherin (Table 3). Additional reactive epithelial markers included CK903, EMA (Fig. 6), and CK19 (Fig. 6). GFAP was present in the majority of cases, but stained only the periphery or luminal borders in an isolated and linear fashion (Fig. 4), similar to previously reported findings [72]. p63 was negative in the nuclei of the lesional cells, but with a peculiar cytoplasmic reaction (Fig. 4). The squamous balls/morules present in the lumen were highlighted with both CK5/6, p63 (nuclear), and p16 (nuclear and cytoplasmic) (Fig. 5). p16 positive cells were nonreactive with high risk HPV. SOX10 showed a strong, patchy to diffuse nuclear reaction, while DOG1 was negative in the lesional cells. Muscle markers were negative in the tumor cells. Many other markers (such as p40, β-catenin, androgen receptor, and Her-2/neu) were also negative, performed primarily as part of the potential differential diagnostic considerations raised by evaluating small biopsy specimens.

Treatment and Follow-up

All patients were managed by surgery, with biopsy, incisional biopsy and excisional biopsy the most commonly performed procedures, rather than a wide excision or resection-type procedures. Recurrences versus persistence or multifocality were difficult to determine with certainty.

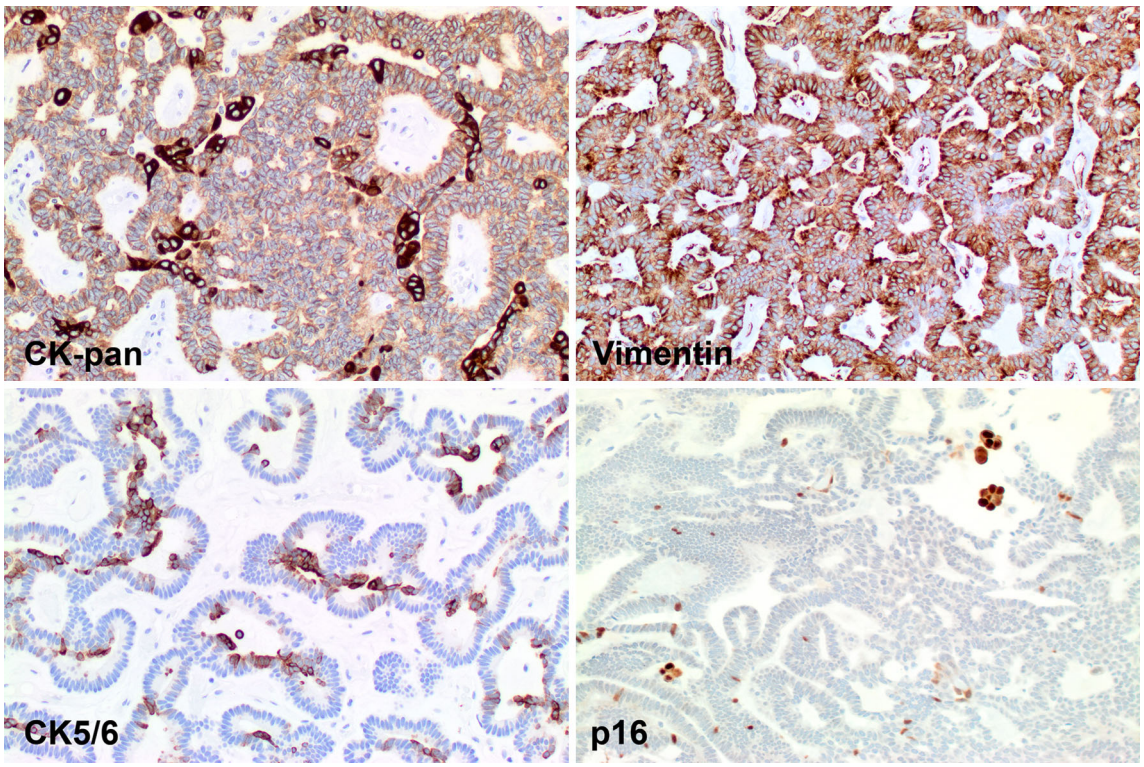

Fig. 5 Canalicular adenoma reacted with pan-cytokeratin, although the luminal balls/squamous morules show a stronger reaction. Vimentin highlights the cytoplasm, although in a graduated pattern. CK5/6 and p16 both react with the luminal balls

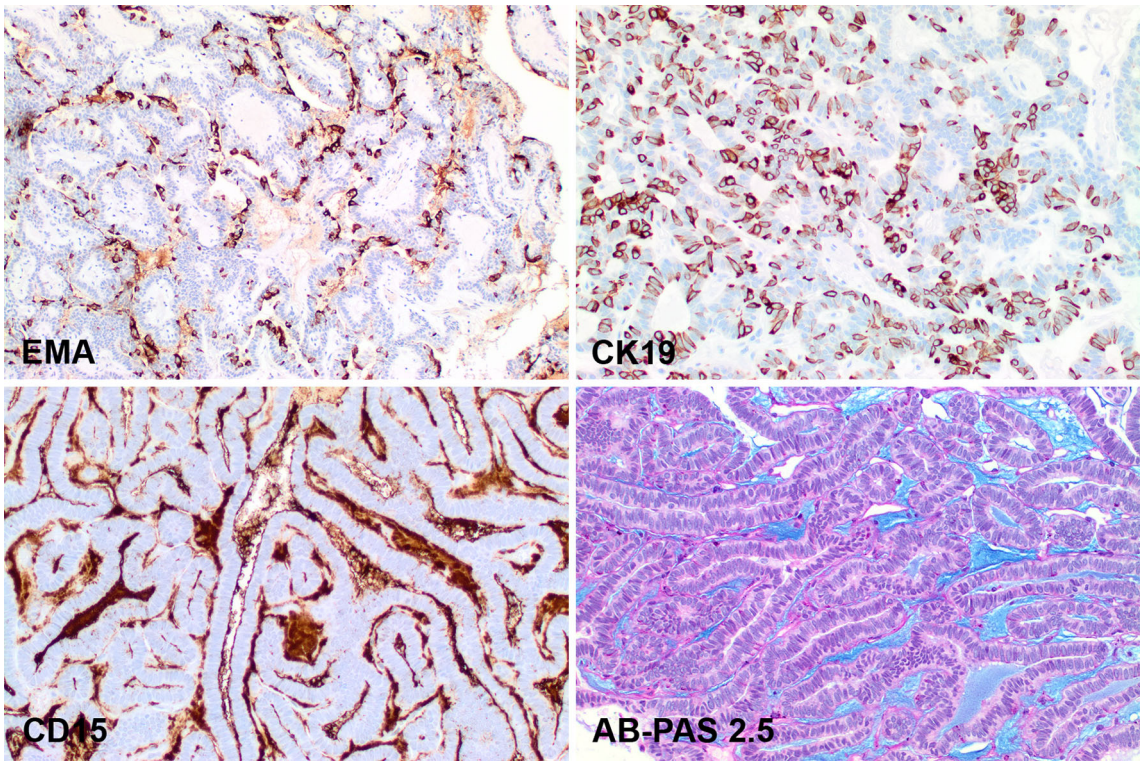

Fig. 6 The neoplastic cells showed variable reactivity with EMA (luminal cells) and CK19 (isolated cells). CD15 was positive in the stroma, which was also highlighted *blue* with the alcian blue-PAS 2.5

Table 4 Clinical characteristics of the current series

Clinical characteristics	Number (n = 67)
Gender	
Females	54
Upper lip	37
Buccal mucosa	13
Palate	4
Males	13
Upper lip	9
Buccal mucosa	4
Palate	0
Age (in years)	
Range	43–90
Mean	69.9
Women (mean)	69.4
Men (mean)	72.0
Upper lip	70.3
Buccal	69.6
Palate	65.5
Symptoms (in months)[a]	
Duration (range)	1–240
Duration (mean)	38.5
Duration (mean; women)	43.1
Duration (mean; men)	17.5
Mass	61
Pain (also had a mass present)	1
Asymptomatic	6
Anatomic site	
Upper lip	46
Buccal mucosa	17
Palate	4
Laterality	
Right[b]	29
Left	24
Midline	9
Size (cm)	
Range	0.2–3
Mean	1.2
Female (mean)	1.2
Male (mean)	1.0
Lip (mean) ($p = 0.027$)	1.1
Buccal (mean)	1.6
Palate (mean)	1.4
Recurrence or persistence (multifocal)	9
Current status (available in 27 patients)	
Alive, no evidence of disease (8.9 years, mean)	24
Dead, no evidence of disease (2.9 years, mean)	3

[a] More than one symptom may have been experienced by the patients

[b] Laterality was not reported for all cases

Table 5 Microscopic features of this clinical series

Microscopic characteristic	Number (n = 67)
Bosselated or lobulated	51
Multifocal	9
Cystic	62
Beading	67
Tubules	67
Luminal squamous ball/morule	41
Stromal sclerosis or collagen present	42
Myxoid stroma	64
Histiocytes	
Lipofucsin/hemosiderin laden, *luminal* location	20
Lipofucsin/hemosiderin laden, *stromal* location	11
Foamy, luminal and/or stromal location	11
Luminal hemorrhage	51
Microliths (calcifications; psammoma bodies)	33
Necrosis present	0
Mitotic figures	
Present (number of cases)	24
Mean (per 10 HPFs)	0.5
Range (per 10 HPFs)	1–4
Atypical figures identified	0
Other features	
Degenerated or infarcted	3
Tyrosine crystals	1
Oncocytic	2
Mucinous metaplasia	1
Surgical margin status	
Positive	28
Negative	39
Number of slides examined (mean)	1.2
Difference in features between surgical sample and TMA core	None

HPF high power field, *TMA* tumor microarray

Nine patients had multifocal tumors, five of whom had additional tumors removed at a later time, from a few months to decades later. No patients died of their disease and there was no malignant transformation (carcinoma ex-canalicular adenoma) (mean follow-up, 8.2 years).

Discussion

Etiology/Embryogenesis

Salivary glands contain a mixture of mucus or serous acini, which are surrounded by myoepithelial cells. The secretions are then carried by intercalated ducts to striated ducts

to interlobular ducts, which empty the contents into a cavity (oral cavity, sinonasal tract, larynx, etc.). The intercalated ducts are lined by cuboidal cells, with occasional myoepithelial cells noted. The luminal cells however are considered separate from the myoepithelial cells. Striated ducts are lined by columnar cells generally lacking myoepithelial cells. Finally, the interlobular ducts have both cuboidal and columnar cells, but also nearly always lack myoepithelial cells. Over the years, the specific origin of CanAd has been postulated to arise from each of these specific duct systems [7, 10, 17, 21, 33, 84–86]. Interestingly, as most CanAd arise from the labial glands or buccal mucosa, there are very few intercalated ducts in these locations, although most intralobular ducts in minor salivary glands resemble intercalated ducts [87]. A recent publication has highlighted what has been called a *striated duct adenoma*, a lesion that is morphologically distinct from CA [88]. Further, Triantafyllou et al. [49] have suggested that the phenotypes in CanAd may not reflect a histogenetic origin, but may derive from the interplay between an altered secretory product, the lack of neuroeffector relationships and different microenvironments throughout the tumor.

The anoctamin-1 (ANO1, also known as DOG1) gene acts as a calcium-activated chloride channel and potentially has a role in salivary gland secretory activity. It has been recently described in normal salivary gland tissue, where DOG1 immunohistochemistry shows a strong membranous staining of normal serous acini, while intercalated ducts show an apical-luminal membranous pattern, stronger towards the distal portion as it approaches the acinus. However, striated ducts and excretory ducts are negative for DOG1 [89]. The CanAd cells were negative, without a difference seen between luminal, abluminal, peripheral or canalicular areas.

SRY-related HMG-box 10 (SOX10) protein is a transcription factor with positive expression in major salivary glands. SOX10 expression by immunohistochemistry was specific to the nuclei of normal acini and both luminal and abluminal cells of intercalated ducts, but was not identified in other sites (although positive in several tumors, such as acinic cell carcinoma, adenoid cystic carcinoma, and pleomorphic adenomas) [90]. The CanAd cells showed a strong, patchy to diffuse, nuclear reaction in nearly all of the lesional cells.

Therefore, overall, based on the histologic, immunophenotypic and ultrastructural findings, CanAd most closely approximates the phenotype of normal intercalated duct luminal cells.

Clinical Information

In many series, CanAd is the third most common minor salivary gland tumor of the oral cavity, with pleomorphic adenoma and mucoepidermoid carcinoma the most common [6, 38, 55, 91]. However, if all salivary gland tumors are taken into consideration (all sites, benign and malignant), then CanAd represent <1 % of all tumors [23, 65, 67].

The tumor is more common in women than men, although when the cases from the literature are combined with the present series, there is a female to male ratio of 1.7:1. Patients are middle age or older at presentation, with a range of 33–91 years. This tumor has *not* been reported in pediatric patients. While some patients are asymptomatic, most present with a painless, non-ulcerated mass, slowly growing, with an average duration of about 3 years. The clinical differential includes a mucocoele, thrombosed vessel, lipoma or other salivary gland tumor.

CanAd seems to occur exclusively in the oral labia, buccal mucosa and palate. Specifically, it occurs preferentially in the upper lip, as there are only 5 reported cases from the lower lip [25, 34, 38, 55] which are not illustrated or specifically highlighted. In general, is seems that CanAd *may not* develop in major salivary glands. Cases reported thus far in the major salivary glands (parotid, submandibular) are either not well illustrated or lack immunohistochemistry studies to confirm the diagnosis [25, 64, 69, 92–95]. Additional investigation is encouraged.

There is no well developed documentation of inherited or syndrome associated canalicular adenoma.

Pathology

CanAd are strikingly similar case to case. They are surrounded by a thin capsule, frequently showing lobulation or bosselations at the periphery. The capsule is better formed in larger tumors (>1 cm), and may be discontinuous. Multifocal tumors are observed infrequently (about 9 % of all cases), when combining the present series with those from the literature. Further, there can be a range from 2 to 22 separate tumors [24, 41, 42, 55]. These nodules are usually distinctly separate, several millimeters away from the main nodule of tumor. They have a similar histologic appearance to the main tumor. Some authors have referred to these as "adenomatous" growths, highlighting the lack of destructive or infiltrative growth [3, 24, 30], although they were interpreted to represent carcinoma by some [12, 45, 48]. Cyst formation of some degree is nearly always present, often containing extravasated erythrocytes, hemosiderin or lipofucsin laden macrophages, or foamy histiocytes.

Squamous balls or morules, a fairly specific feature of CA, are often present in the cystic lumen, but usually connect to the epithelium with serial sections (possibly the tips of papillae). These are thought to represent metaplasia, as these cells are uniquely CK5/6, p63, and p16 immunoreactive, findings distinctly different from the remaining tumor.

However, these balls were negative with p40, suggesting the cells may not be squamous, as p40 is more specific to squamous differentiation than p63 [96]. Other tumors undergo cyst formation but do not develop these areas of metaplasia. It may be that the luminal microliths result in epithelial irritation or injury, causing a metaplastic change. However, microliths were present in 33 cases, 22 of which had luminal squamous balls; but 19 cases with luminal balls did not have microliths and 11 cases with microliths did not have luminal balls. Alternatively, there may be remodeling of the cytoskeleton in response to an increased microenvironmental pressure within the lumen [49]. Microliths are similar to sialoliths (salivary gland stones), showing lamellar calcifications [49]. It is postulated they form in phagosomes of tumor cells, as part of degradation of mucosubstances enriched by calcium. As there is no cell death, the concept of a true psammoma body (calcified necrotic cells) should not be used in this setting [49]. Luminal calcifications were associated with histiocytes in 22 cases in this series. However, lipofucsin laden macrophages were present in 7 cases that did not have microliths and 11 cases had microliths without lipofucsin laden macrophages. Further, it is known that secretory glycoproteins and calcium complexes are found in microliths in normal salivary glands [97].

The canalicular architecture, with characteristic beading is nearly diagnostic. The joining of parallel epithelial rows is quite unique to CA. The lesional cells are columnar with very limited to absent pleomorphism. Nucleoli are only focally noted. The nuclear chromatin is delicate, stippled to focally hyperchromatic. The stroma is edematous, hypocellular, fibrillar to myxoid associated with collagen deposition (sclerosis) in most cases. By histochemistry (PAS, alcian blue, mucicarmine), the mucoid to stellate reticulum-like stromal material is probably of epithelial derivation rather than connective tissue origin, although others have postulated production by tumor cells as a result of epithelial-mesenchymal transition [49]. There are PAS-positive granules in the basal area cytoplasm, confirmed by ultrastructural exam [7, 21, 33], which may give rise to the myxoid stromal material. Mitoses are rare to absent. Necrosis is vanishingly rare. Further, conspicuous by its absence is any chondroid or cartilaginous matrix material, helping to separate this tumor from a pleomorphic adenoma.

Immunohistochemical Studies

The immunohistochemistry findings reported have been mixed without any definitive series thus far. Salivary gland parenchyma tissues comprise two lineages: one epithelial luminal lineage and one myoepithelial basal lineage. Based on the findings in this series and those reported earlier, this tumor is a luminal epithelial lineage. The tumor cells show a strong reaction with epithelial markers, including AE1/AE3, CK7, CAM5.2, CK903, EMA, and CK19; reactions with CK8 and CK13 are also reported [14, 15, 21, 29, 40, 79, 98, 99]. Further, the neoplastic cells are strongly and diffusely reactive with S100 protein [14, 100], despite earlier reports of negative reactions [40, 79]. The distinctive linear reaction of GFAP at the tumor to connective tissue interface previously reported [72], was reproduced in the current series. This may be a helpful finding in separating this tumor from others in the differential diagnosis, which do not possess this unique linear or peripheral distribution. Vimentin is positive, a finding different from that reported by others [15, 29, 98], although such a strong reaction cannot be discounted by differences in technique or fixation.

Myoepithelial and muscle markers (α-smooth muscle actin, muscle specific actin, smooth muscle myosin heavy chain, calponin, desmin) are all negative [14, 80, 98]. In this series, the calponin was a weak and focal reaction, and seemed to be a "blush" rather than a genuine positive finding. Nuclear p63 is negative in the tumor cells, although positive in the areas of squamous morule formation in the lumen [101–103]. There was an aberrant cytoplasmic reaction, but the significance of this finding is unknown [104, 105].

CD117 is positive in all CanAd [106], and does not seem to help separating between CanAd, polymorphous low grade adenocarcinoma, adenoid cystic carcinoma, basal cell adenoma or pleomorphic adenoma. CD43 and bcl-2 were negative in CanAd [68, 81], a finding essentially supported by the results of this series. In this series, E-cadherin showed a strong, focal to diffuse membranous staining, different from results reported in the literature [82]. However, different manufacturers and clones were used, which may account for the differences.

SOX10 and DOG1 do not necessarily provide a unique finding, but do support the luminal intercalated duct cell phenotype [89, 90]. The differences between expression may help with the differential, as polymorphous low grade adenocarcinoma (PLGA) and pleomorphic adenoma are usually negative with DOG1, although adenoid cystic carcinoma and epithelial–myoepithelial carcinoma are often positive. SOX10 is positive in adenoid cystic carcinoma, epithelial–myoepithelial carcinoma and pleomorphic adenoma, so it may not be as useful in this differential.

Differential Diagnosis

The histologic differential diagnosis encompasses primarily salivary gland neoplasms, including basal cell adenoma, pleomorphic adenoma (PA), PLGA, adenoid cystic carcinoma (ACC), ductal adenoma, and reticulated myoepithelioma, while ameloblastoma, adenomatoid odontogenic

tumor, paraganglioma, and skin basal cell carcinoma are also occasionally considered [16, 21, 25, 32, 88, 107].

Basal cell adenomas do not usually show a canalicular pattern of growth and usually show reduplicated basement membrane material. This tumor tends to occur much more commonly in the major salivary glands. In this clinical series, we identified several basal cell adenomas (subsequently excluded from further evaluation), 13 of which involved the parotid gland, with three involving the lip or buccal mucosa. Specifically, the trabecular variant is the tumor that may show morphologic similarity. Basal cell adenoma show a dual cell population with two layers, often showing cells oriented perpendicular to the basement membrane. While the tumor shows a monomorphic growth, there is strong S100 protein positivity, with p63, SMA, MSA, and SMMHC variably present. Two of the original cases from Daley et al. [10] are referred to as *atypical canalicular adenoma*, although not illustrated and without any reasons as to why they are atypical. However, as they were parotid gland tumors, they probably represent basal cell adenoma.

The lack of chondroid or myxochondroid matrix helps to exclude a PA. PA often shows plasmacytoid to spindled myoepithelial cells, especially in palate or buccal lesions. Further, by immunohistochemistry, the characteristic biphasic appearance is again highlighted by markers similar to basal cell adenoma. Ductal adenomas (striated duct adenoma) are usually encapsulated tumors (although multinodularity can be seen), composed of variably sized ducts without any intervening stroma and without an epithelial beading pattern or parallel tumor cords. Unlike CanAd, these tumors can be seen in the parotid gland. The cells usually have more eosinophilic (oncocytic) cytoplasm than CanAd. They are also negative with SMA, but usually positive with S100 protein, suggesting they are probably ductal adenomas [21, 88]. Reticulated myoepithelioma nearly always involve major salivary glands, may be cystic, and show polygonal to columnar cells arranged in cords and anastomosing trabeculae. Parallel cords and a beading pattern, characteristic of CanAd, are not usually found in reticulated myoepithelioma. While they overlap with S100 protein, keratin and CK7 immunoreactivity, they also show strong CK18, GFAP, calponin, p63 and SMA immunoreactivity [107]. All myoepithelial markers are negative in CanAd and are frequently positive in basal cell adenoma, myoepithelioma and PA, while the GFAP staining pattern is characteristic in CanAd.

PLGA grows in heterogeneous histologic patterns, entombing minor salivary glands and showing a characteristic perineural invasion. The neoplastic cells have more open and vesicular nuclear chromatin and show tumor cell spindling. Further, cystic change and squamous metaplasia are not features of a PLGA, and so separation from a CanAd can be achieved. ACC usually has a biphasic appearance, an infiltrative growth, significant perineural invasion, and pseudo-cystic spaces without a highly vascularized stroma. The nuclei are angulated with coarse chromatin. Mitoses are usually easily identified. This tumor also shows a strong patchy p63 reaction and a biphasic epithelial and myoepithelial phenotype.

Ameloblastoma may arise from mucosa overlying a tooth-bearing area or from the bone, although described in non-dentate sites [108]. However, most CanAd lack a stellate reticulum pattern, while also expressing a different immunohistochemistry profile.

Adenomatoid odontogenic tumors may arise peripherally from the anterior maxillary gingiva. The tumor tends to have minimal stroma, but shows cuboidal to columnar cells that may be arranged in duct-like or tubular structures, while occasionally arranged in very convoluted cords with invaginations or retiform patterns. Amorphous tumor droplets are characteristic, as is a reverse nuclear polarization away from the lumen.

Paraganglioma usually have a nested pattern, a rich vascularized stroma, tend to have significant, isolated pleomorphism, and show a characteristic neuroendocrine immunohistochemistry profile, with a delicate S100 protein sustentacular reaction. A skin basal cell carcinoma shows surface basal epidermal origin, tumor to stroma clefting or separation, a peripheral palisade, and usually easily identified mitoses. The neoplastic cell nuclei are more hyperchromatic.

Rare examples of hybrid tumors (CanAd and basal cell adenoma) may be seen. It would be important to document histologically and immunophenotypically the two tumor components. It is unclear whether they may be collision tumors (two separate tumors colliding) or true divergent differentiation tumors (such as a mixed follicular medullary carcinoma of thyroid gland). It is these authors' practice to suggest a composite-hybrid designation, with the first name the dominant histologic finding.

One of the only studies addressing specifically frozen section diagnoses, showed CanAd are usually diagnosed correctly [95].

Treatment and Prognosis

Patients included in this report were managed at more than 25 different hospitals by dentists, surgeons, and dermatologists. Enucleation, biopsy, and excision are the treatments proposed. However, with multifocal tumors and a periphery that is bosselated to nodular, a cure is best achieved by a surgical excision that has a small cuff of normal, uninvolved parenchyma. Follow-up of the patients is recommended, at least in the short term, to manage possible multifocal disease.

Conclusion

In conclusion, canalicular adenoma is a unique minor salivary gland tumor, arising from the luminal cells of the intercalated duct. Women are affected more often than men, with a marked predilection for the 7th decade. Tumors preferentially affect the upper lip, with buccal mucosa and palate also affected, and are usually small (mean 1.2 cm), presenting as a non-painful, non-ulcerated slowly enlarging mass. About 9 % of tumors are multifocal. Histologically, tumor cell beading and intraluminal squamous balls/morules are unique, while the myxoid stroma, cystic appearance and microliths are characteristic histologic findings. Other tumors in the histologic differential diagnosis can be eliminated by a pertinent immunohistochemical panel of S100 protein, p63, CK5/6 and GFAP, the results of which would be characteristic and discriminating.

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