Sialadenoma Papilliferum: Analysis of Seven New Cases and Review of the Literature

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Abstract Sialadenoma papilliferum (SP) is a rare benign salivary gland neoplasm that comprises from 0.4 to 1.2% of all salivary gland tumors. The tumor is so named because of its microscopic resemblance to the syringocystadenoma papilliferum, an uncommon benign tumor of sweat gland origin. The purpose of this paper is to report the clinical and microscopic features of seven new cases of SP and combine them with cases previously reported in the English language literature to further define this unusual lesion. Combining our cases with acceptable cases from the literature, the palate (especially the hard palate) was the most common site, with 80% of the cases occurring in this location. Other locations in decreasing order were buccal mucosa, upper lip, retromolar pad, and parotid gland. Age at diagnosis ranged from 18 to 87 years with a peak in the 6th decade and an average age of 56.4 years. Microscopically, the lesions demonstrated a papillary surface morphology, and the papillary projections varied from long and pointed to short and blunted. The supporting connective tissue contained a variable number of convoluted ductal structures, which often fused with the overlying surface epithelium. The ductal structures exhibited papillary infoldings and were lined by a double layer of epithelium consisting of basal cell layer and a luminal layer of cuboidal-to-columnar ductal cells. Immunohistochemical reactivity with p63 and p40 indicated that the basal cell layer was comprised predominantly of neoplastic myoepithelial cells. The luminal cells were immunoreactive with epithelial membrane antigen characteristic of ductal cell differentiation. Conservative surgical treatment

was accomplished in most cases and appears to be adequate treatment as only two recurrences were documented. Several case reports of purported malignant transformation in SP have been reported in the literature, but in our opinion, there is insufficient evidence in the publications to unequivocally determine whether any of the malignancies truly originated within a pre-existing SP.

Keywords Sialadenoma papilliferum · Salivary gland neoplasm · Syringocystadenoma · Papilliferum

Introduction

Sialadenoma papilliferum (SP) is a rare benign salivary gland tumor that most often arises from oral minor salivary glands, especially on the palate. Past reviews indicate that this tumor is perhaps the least common of all salivary gland tumors, comprising 0.4% of all minor salivary gland neoplasms accessioned at the Armed Forces Institute of Pathology [1] and 0.8 and 1.2% of all minor salivary gland neoplasms in two other large series [2, 3]. Sialadenoma papilliferum was described initially in 1969 by Abrams and Finck [4], who reported two cases, one in the parotid gland and the other at the junction of the hard and soft palate. The tumor is so named because of its microscopic resemblance to the syringocystadenoma papilliferum, an uncommon benign tumor of sweat gland origin that has a predilection for the scalp and forehead [5]. The purpose of this paper is to report seven new cases of SP accessioned at the University of Kentucky College of Dentistry and to review the English language literature with regard to this rare salivary gland neoplasm.

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Materials and Methods

The files of the oral pathology laboratory at the University of Kentucky College of Dentistry (UKCD) were reviewed from 1996 to 2016. Paraffin blocks, hematoxylin and eosin-stained microscopic slides, and clinical information were available for review in each case. Patient privacy was maintained in accordance with institutional review board approval. New sections of each case were cut and immunoreacted for p63 (Biocare Medical, 1:150 dilution), p40 (Biocare Medical, 1:100 dilution), S-100 protein (Biocare Medical, 1:600 dilution), smooth muscle actin (SMA) (Biocare Medical, 1:150 dilution), and epithelial membrane antigen (EMA) (Dako, 1:50 dilution). These immunoreactants were selected in order to verify the cell types in SP and to perhaps aid in determining a cell of origin. In addition, the English language literature was reviewed for single case reports and short series of SP. Publications without microscopic images or those with questionable histopathologic features were excluded from our review. The case by Nakahata et al. did not include any clinical information, but photomicrographs were available for review [6]. Also excluded from our study were extraoral cases involving the sinonasal tract, bronchus, and esophagus.

Results

Seven new cases of SP were found from review of UKCD files. Forty-two acceptable cases of SP were retrieved from the literature [4, 6–31]. The clinical findings for UKCD cases are summarized in Table 1 and are combined with the literature review cases in Table 2. Case reports alleging malignant transformation [8, 32–35] were excluded from our review because, in our opinion, there was insufficient evidence in the publications to support origin from a pre-existing SP.

Clinical Findings: UKCD Cases

For the UKCD cases, all occurred on the hard palate. Age at diagnosis ranged from 48 to 76 years with an average age of 58.7 years. Four cases occurred in males, and three cases occurred in females. Duration ranged from 1 month to over 15 years. The size of the lesion was known in five cases and ranged from 0.3 to 1.3 cm, with an average size of 0.7 cm. The most common provisional clinical diagnosis was squamous papilloma, but other considerations included fibroma, hemangioma, mucocele, salivary gland neoplasm, and carcinoma.

Clinical Findings: All Cases

The palate was by far the most common anatomic site, with 80% of the cases occurring in this location. Lesions involving the hard palate comprised most of the palatal cases, followed by the junction of the hard and soft palate, and buccal mucosa (Fig. 1). Age at diagnosis ranged from 18 to 87 years. The average age was 56.4 years with a peak in the 6th decade (Fig. 2). 63% of the cases occurred in males resulting in a male-to-female ratio of 1.7 to 1. Race was known in only 26 cases, with 81% of those cases occurring in Caucasians. The duration of the lesions prior to diagnosis ranged from 1 month to over 15 years. The average duration was 45 months, based on 18 cases in which the specific length of time was listed. The size of the lesion was known in 37 cases. Excluding the one case from the parotid gland, which measured 7.5 cm in greatest dimension, the size of the remaining intraoral lesions ranged from 0.3 to 2.0 cm with an average size of 0.8 cm. The most common provisional clinical diagnosis was squamous papilloma, but it is noteworthy that malignancy was considered in 3 cases.

Table 1 Clinical features of sialadenoma papilliferum (UKCD cases)

Case no.	Age (yrs)	Sex	Race	Location	Duration	Size (cm)	Clinical diagnosis	Clinical features	Follow-up
1	55	F	W	Hard palate	Several months	0.3	Papilloma	Exophytic pebbly pink with stalk	N/A
2	50	M	W	Hard palate	>15 years	0.8	Papilloma, fibroma, hemangioma	Exophytic pink/red	N/A
3	62	M	W	Hard palate	N/A	N/A	Papilloma	Papilloma-appearing lesion	N/A
4	63	M	W	Hard palate	N/A	N/A	Mucocele, fibroma	Raised mass	N/A
5	57	M	W	Palate	1 month	0.4	Papilloma	Red with stalk, fingerlike	N/A
6	48	F	W	Hard palate	N/A	0.5	Fibroma, salivary gland neoplasm	Red, slightly elevated	N/A
7	76	F	N/A	Hard palate	2.5 months	1.3	Carcinoma	White rough lesion	N/A

N/A information not available

Table 2 Clinical features of sialadenoma papilliferum (all cases)

Reference	Age	Sex	Race	Location	Duration	Size (cm)	Clinical diagnosis	Clinical features	Follow-up
Case 1	55	F	W	Hard palate	Several mo	0.3	Papilloma	Exophytic pebbly pink with stalk	N/A
Case 2	50	M	W	Hard palate	>15 yrs	0.8	Papilloma, fibroma, hemangioma	Exophytic pink/red	N/A
Case 3	62	M	W	Hard palate	N/A	N/A	Papilloma	Papilloma-appearing lesion	N/A
Case 4	63	M	W	Hard palate	N/A	N/A	Mucocele, fibroma	Raised mass	N/A
Case 5	57	M	W	Palate	1 mo	0.4	Papilloma	Red with stalk, fingerlike	N/A
Case 6	48	F	W	Hard palate	N/A	0.5	Fibroma, salivary gland tumor	Red, slightly elevated	N/A
Case 7	76	F	N/A	Hard palate	2.5 mo	1.3	Carcinoma	White rough lesion	N/A
Kubota et al. [7]	62	M	J	Hard palate	3 mo	1.0	N/A	White, exophytic	NED-13 mo
Mahajan et al. [9]	18	M	N/A	Upper lip	12 yrs	0.8	Infected heman-gioma	Firm tumor	NED*
Gomes et al. [10]	53	M	W	Hard palate	3 yrs	1.0	Papilloma, vascular	Pedunculated red papillary mass	NED*
Gomes et al. [10]	52	F	W	Soft palate	4 yrs	0.5	Fibrous polyp	Firm pedunculated mass	NED*
Ubaidat et al. [11]	72	M	N/A	Hard palate	N/A	0.4	N/A	Exophytic growth (0.6 cm on gross)	NED-3 mo
Ubaidat et al. [11]	58	M	N/A	Hard palate	N/A	0.5	Melanoma	Ulcerated and pigmented	NED*
Brannon et al. [12]	69	F	N/A	Hard palate	N/A	N/A	Squamous papilloma	Slow growing exophytic mass	N/A
Brannon et al. [12]	53	F	W	Soft palate	3 mo	N/A	Squamous papilloma	Slow growing exophytic mass	N/A
Brannon et al. [12]	31	F	W	Hard palate	4 yrs	N/A	Squamous papilloma	Slow growing exophytic mass	N/A
Argyres [13]	50	M	N/A	Hard palate	Several mo	0.5	Squamous cell carcinoma	firm exophytic mass	N/A
Markopoulos et al. [14]	50	M	W	Hard palate	12 yrs	0.5	N/A	Papillary mass	N/A
Asahina [15]	50	M	J	Hard palate	6 mo	0.5	Fibrous polyp	Cauliflower like mass, white/pink	NED-24 mo
Maiorano et al. [16]	56	M	N/A	Hard palate	N/A	0.5	Squamous papilloma	N/A	NED-18 mo
Maiorano et al. [16]	37	F	N/A	Hard palate	N/A	1.0	Verrucous leukoplakia	N/A	NED-48 mo
Maiorano et al. [16]	60	M	N/A	Buccal mucosa	N/A	0.8	Squamous papilloma	N/A	NED-96 mo
Maiorano et al. [16]	46	M	N/A	Hard palate	N/A	1.4	Salivary gland tumor	N/A	NED-36 mo
Maiorano et al. [16]	50	M	N/A	Hard palate	N/A	1.8	Salivary adenoma	N/A	NED-6 mo
Pimentel et al. [17]	67	F	W	Buccal mucosa	1 yr	2.0	N/A	Sessile mass; 1 × 1 cm recurrence	Rec-36 mo
van der Wal and van der Waal [18]	46	M	W	Hard/Soft palate	10 yrs	0.5	Fibroepithelial polyp	Pedunculated firm exophytic mass	NED-12 mo
Nakahata et al. [6]	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Papanicolaou [19]	46	M	W	Hard palate	N/A	0.5	N/A	Red firm exophytic growth	N/A
Fantasia et al. [20]	87	F	N/A	Hard palate	Several mo	N/A	Irritated papilloma	Exophytic red papillary lesion	N/A
Fantasia et al. [20]	77	M	N/A	Buccal mucosa	N/A	N/A	N/A	N/A	N/A
Fantasia et al. [20]	48	F	N/A	Hard palate	N/A	N/A	N/A	N/A	N/A
Fantasia et al. [20]	45	M	N/A	Hard palate	N/A	N/A	N/A	N/A	N/A
Fantasia et al. [20]	60	F	N/A	Upper lip mucosa	N/A	N/A	N/A	N/A	N/A

Table 2 (continued)

Reference	Age	Sex	Race	Location	Duration	Size (cm)	Clinical diagnosis	Clinical features	Follow-up
Mitre [21]	42	F	W	Hard/soft palate	7 mo	0.4	N/A	Red warty lump	N/A
Rennie et al. [22]	78	F	W	Hard/soft palate	N/A	1.0	Squamous papilloma	Firm warty papule	Rec-36 mo
Puts et al. [23]	77	M	W	Hard palate	N/A	1.6	N/A	Exophytic papillary growth	NED*
Shirasuna et al. [24]	56	M	J	Hard palate	N/A	0.7	Squamous papilloma	Pedunculated papillary mass	NED-20 mo
Wertheimer et al. [25]	32	F	N/A	Hard palate	N/A	0.5	Papilloma	Dome-shaped mass	NED-18 mo
Wertheimer et al. [25]	43	M	N/A	Soft palate	8 yrs	0.5	N/A	Papillary mass, recently ulcerated	NED-30 mo
Nasu et al. [26]	61	M	N/A	Hard palate	6 mo	0.6	N/A	Papillary exophytic mass, slow growth	N/A
McCoy [27]	77	F	W	Buccal mucosa	N/A	0.7	N/A	Papillary growth, indurated	NED*
Drummond et al. [28]	71	M	W	Retromolar pad	N/A	0.5	N/A	Pink papillary pedunculated growth	NED-6 mo
Freedman and Lumerman [29]	68	M	N/A	Hard palate	N/A	0.3	N/A	Raised sessile papillary lesion	NED-21 mo
Freedman and Lumerman [29]	68	M	N/A	Hard palate	1 mo	0.5	N/A	Raised round papillary lesion	NED-19 mo
Whittaker and Turner [30]	65	M	N/A	Hard/soft palate	N/A	0.6	N/A	Area of hyperplasia	NED-36 mo
Whittaker and Turner [30]	50	M	N/A	Hard/soft palate	N/A	N/A	N/A	N/A	N/A
Jensen and Reingold [31]	48	M	W	Hard palate	10 yrs	0.8	Squamous papilloma	Pedunculated papillary lesion	N/A
Abrams and Finck [4]	71	M	B	Parotid	10–12 yrs	7.5	Low-grade malignancy	Fungating cauliflower-like mass	NED-18 mo
Abrams and Finck [4]	57	M	B	Hard/soft palate	3 mo	1.5	N/A	Verrucous lesion	NED-19 mo

N/A information not available, NED no evidence of disease, NED* no evidence of disease, length of follow-up not specified, mo month, yr year
Reported cases of SP with purported malignant transformation [8, 32–35] have been excluded (see explanation in “discussion” section)

Fig. 1 Anatomic location of SP (combined UKCD and literature cases) **Fig. 2** Age Distribution of SP (combined UKCD and literature cases)

Microscopic Features: UKCD Cases

The microscopic features in our cases fulfilled the criteria for SP as outlined by Ellis and Auclair [1]. The lesions were surfaced by hyperplastic stratified squamous epithelium

that displayed a papillary surface morphology. In most of our cases, the papillary projections were blunted rather than sharp (Fig. 3). The surface epithelium often exhibited a thickened layer of orthokeratin or parakeratin. No features of epithelial dysplasia were identified. The supporting

Fig. 3 Case 5. SP showing surface papillary projections overlying a proliferation of convoluted ductal structures. (H&E stain, orig mag $\times 40$)

connective tissue contained a variable number of convoluted ductal structures, which often fused with the overlying surface epithelium. At the point of fusion, a cleft or crypt usually was formed (Fig. 4). The ductal structures showed numerous papillary infoldings and were lined by a double layer of epithelium consisting of a basal layer of flat or low cuboidal cells and luminal layer of columnar cells (Fig. 5). In two cases, the columnar cells exhibited oncocytic metaplasia (Fig. 6a). In two cases, mucous cells lined a portion of the ductal structures (Fig. 6b). Although the ductal proliferation was unencapsulated, no infiltration into adjacent minor salivary glands was identified. A variable number of chronic inflammatory cells were seen in the connective tissue papillae as well as in the connective tissue surrounding the ductal structures.

Fig. 4 Case 4. SP showing cleft formation (*asterisk*) at the point of fusion of the surface epithelium with the underlying ductal structures. (H&E stain, orig mag $\times 200$)

Fig. 5 Case 4. SP showing ductal structures exhibiting papillary infoldings. The ductal structures are lined by a flattened basal cell layer and a cuboidal-to-columnar luminal layer. (H&E stain, orig mag $\times 200$)

Immunohistochemistry: UKCD Cases

In each of our cases, the basal cells within the ductal structures were similarly immunoreactive for p63 and p40, indicating a myoepithelial immunophenotype (Fig. 7a). p40, an isoform of p63, recently has been shown to be a more specific marker for basal, squamoid, and myoepithelial cells in salivary gland tumors [36]. Intermittent reactivity in the basal cell layer with smooth muscle actin (SMA) was also identified. In all cases, the luminal cells within the ductal structures were immunoreactive with EMA (Fig. 7b). S-100 protein reactivity was not as specific, and stained both basal cells and luminal cells. These results indicate two cell types comprising the convoluted ductal structures of SP: a basal layer of myoepithelial cells (p40+, p63+, and SMA+) and a luminal layer of ductal epithelial cells (EMA+).

Treatment and Follow-up

All of the UKCD cases were treated by conservative surgical excision. For the literature review, conservative surgical excision was documented in 44 cases; treatment was not specified in 5 cases. The one case from the parotid gland was treated by superficial parotidectomy with preservation of the facial nerve. Follow-up information was available in 27 cases, all from the literature. Length of follow-up ranged from 2 months to 96 months. The average length of follow-up was 25 months for the 21 cases in which a specific length of follow-up was given. Two recurrences were recorded, each at 36 months after initial treatment, indicating a recurrence rate of 7.4%.

Fig. 6 Case 5. Ductal structures of SP exhibiting oncocytic metaplasia (a) and mucous goblet cells (b). (H&E stain, orig mag $\times 400$ [a], orig mag $\times 200$ [b])

Fig. 7 Cases 2, 5. SP demonstrating immunoreactivity to p40 in the basal cells of the ductal structures (a) and epithelial membrane antigen (EMA) in the luminal cells (b). (p40 immunostain, orig mag $\times 400$, EMA immunostain, orig mag $\times 600$)

Discussion

Sialadenoma papilliferum (SP) is a rare benign salivary gland neoplasm that occurs most often on the hard palate. Although the first published report of this lesion involved the parotid gland, [4] almost all subsequent case reports and short series have described intraoral lesions. Three additional cases of SP have been reported in the parotid gland, but the photomicrographs are not convincing and likely represent two examples of papillary cystadenoma and one example of Warthin tumor [37–39].

Histopathologically, SP is comprised of a papillary epithelial component that resembles squamous papilloma combined with a subjacent unencapsulated salivary gland ductal proliferation that is contiguous with the overlying papillary squamous mucosa. The ductal structures are lined by a double row of cuboidal or columnar cells that form small papillary infoldings into the ductal lumina. Scattered mucous cells and occasional areas of oncocytic metaplasia may be

seen in the ductal component. A variable number of inflammatory cells, most often lymphocytes and plasma cells, typically are identified in the surrounding connective tissue.

Numerous investigators have discussed or attempted to identify the cell of origin of SP based on light microscopy, immunohistochemistry (IHC), and electron microscopy (EM). These methods have yielded variable results with most investigators suggesting excretory duct or excretory duct reserve cell origin, [10, 11, 16, 20, 26, 27, 29, 40] while others have concluded that intercalated duct cells, [24, 26] myoepithelial cells, [4, 11] or primitive precursor cells of the ductal apparatus [6] may play a role in the histogenesis of SP. Langerhans cells have also been identified, [11, 16] but their specific role, if any, in the development of SP is unknown. To date, no association with HPV has been documented [13]. While the IHC and EM features in the literature cases aid in identifying cell types seen in SP, these studies are not particularly helpful in identifying the cell of origin. Most investigators favor excretory duct or excretory duct

reserve cell origin for two reasons based on light microscopic features: (1) Because SP has both a surface squamous and underlying ductal component, it likely arises from the portion of the ductal epithelium near the junction of the surface mucosa; i.e. excretory duct epithelium, (2) Because SP contains squamous cells, basal myoepithelial cells, and ductal cells, it likely arises from excretory duct reserve cells with the potential to differentiate into the three cell types.

Assured conservative surgical excision appears to be adequate treatment for SP. Based on the 27 cases in the literature with follow-up information, the recurrence rate is 7.4%. Cases of malignant transformation of SP have appeared in the literature; [8, 32–35] however, in our opinion, there is insufficient evidence in the publications to unequivocally determine whether any of the malignancies truly originated within a pre-existing SP. Although the case reported by Ide et al. [8] may represent an SP with potentially malignant features, we could not entirely exclude a papillary cystadenocarcinoma with a surface papillomatosis based on the available photomicrographs. Surface papillomatosis (papillary epithelial hyperplasia) previously has been described overlying other malignant salivary gland neoplasms, most often polymorphous adenocarcinoma [41]. Of interest, rare examples of syringocystadenocarcinoma papilliferum on skin have been reported [42–45]. Basal cell carcinomas have also been reported in about 10% of cases of syringocystadenoma papilliferum along with rare examples of other benign and malignant adnexal tumors [5], but no such association has been reported in SP.

The microscopic differential diagnosis consists of exophytic ductal papilloma, intraductal papilloma, inverted ductal papilloma, and papillary cystadenoma. Table 3 shows a comparison of key features of these lesions and SP. Exophytic ductal papillomas originate from ductal epithelium and grow out through the ductal orifice (Fig. 8a). Like SP, they fuse with the surface epithelium, but do not demonstrate the multiple submucosal convoluted ductal structures seen in SP. Intraductal papillomas are characterized by a single dilated duct with an intraluminal papillary proliferation of ductal epithelium that partially fills the duct lumen (Fig. 8b). Unlike SP, they do not demonstrate any connection with the epithelial surface. Inverted ductal papillomas display only an endophytic growth pattern, and although some do fuse with the epithelial surface producing a pore-like opening, surface papillary projections characteristic of SP are not seen. In addition, the submucosal component of inverted ductal papillomas involves an excretory duct and is comprised primarily of epidermoid (squamous) cells, which are not seen in the submucosal component of SP (Fig. 8c). Papillary cystadenomas demonstrate multiple cystic compartments, some of which can display papillary infoldings, but do not possess the surface papillary squamous component characteristic of SP (Fig. 8d).

Table 3 Comparison of lesions in the differential diagnosis of sialadenoma papilliferum

	Sialadenoma papilliferum	Exophytic ductal papilloma	Intraductal papilloma	Inverted ductal papilloma	Papillary cystadenoma
<i>Gross appearance</i>					
<i>Exophytic papillary component</i>	Exophytic and papillary Yes, composed of surface squamous cells often with clefts	Exophytic and papillary Yes, composed of squamous, ductal, and transitional cells	Submucosal nodule No	Submucosal nodule No	Submucosal nodule No
<i>Histomorphology: submucosal component</i>	Small duct-like structures with papillary infoldings, merges with mucosal surface often forming a cleft or crypt	Single ectatic duct with papillary proliferation out through ductal orifice	Single ectatic duct with papillary proliferation into lumen	Endophytic bulbous papillary proliferation into and filling excretory duct, sometimes contiguous with mucosal surface	Multiple variably sized ectatic ductal and cystic structures
<i>Histomorphology: lining epithelium</i>	Double layer of flattened or cuboidal basal cells and luminal cuboidal or columnar cells	Cuboidal or columnar and transitional cells	Cuboidal or columnar cells	Squamous cells, transitional cells, and columnar cells	Cuboidal or columnar cells

Other cell types that are variably present: mucous cells and oncocytic cells

Fig. 8 Low-power photomicrographs illustrating the lesions in the microscopic differential diagnosis of SP. **a** exophytic ductal papilloma, **b** intraductal papilloma, **c** inverted ductal papilloma, **d** papillary cystadenoma. (All images are H&E stained, orig mag $\times 40$)

Conclusion

SP is a rare benign salivary gland neoplasm that almost always arises on the palate. The neoplasms appear to be slow growing with the average lesion having been present for almost 4 years prior to diagnosis. With the exception of the original case involving the parotid gland, the SP appears to have a limited growth potential with an average size at diagnosis of less than 1 cm. Although the lesions are not encapsulated microscopically, conservative excision is curative in most cases, with only two examples of recurrence recorded to date. In our opinion, malignant transformation has not been demonstrated convincingly. While the cell of origin is not entirely clear, the histomorphologic features showing fusion of the complex ductal component with the surface epithelium would seem to favor an origin from excretory duct reserve cells that possess the ability to differentiate into either a ductal or squamous phenotype.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The University of Kentucky IRB waived the requirement for informed consent.

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