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ORIGINAL PAPER

Papillary Cystadenoma of Minor Salivary Glands: Report of 11 Cases and Review of the English Literature

Kellen C. Tjioe · Heliton G. de Lima · Lester D. R. Thompson · Vanessa S. Lara · José H. Damante · Christiano de Oliveira-Santos

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Abstract Papillary cystadenoma is a rare, benign salivary gland tumor which is well-circumscribed, containing cystic cavities with intraluminal papillary projections. Only 19 cases arising within minor salivary glands (MnSG) from the oral cavity sites have been reported in the English literature (PubMed 1958–2014). We report 11 new cases of MnSG papillary cystadenomas in conjunction with a review of the literature. Demographic information, clinical and histologic features, treatment and prognosis are compiled and discussed for all 30 cases reported in the English literature.

Keywords Papillary cystadenoma · Oncocytic · Benign neoplasm · Minor salivary gland

K. C. Tjioe (✉) · H. G. de Lima · V. S. Lara
Department of Stomatology, Area of Pathology, Bauru School of Dentistry, University of São Paulo, Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, São Paulo CEP 17012-901, Brazil
e-mail: kellentjioe@gmail.com

L. D. R. Thompson
Department of Pathology, Woodland Hills Medical Center, Southern California Permanente Medical Group, Woodland Hills, CA, USA

J. H. Damante
Department of Stomatology, Bauru School of Dentistry, University of São Paulo, Bauru, São Paulo, Brazil

C. de Oliveira-Santos
Department of Stomatology, Public Oral Health, and Forensic Dentistry, Ribeirão Preto School of Dentistry, University of São Paulo, Bauru, São Paulo, Brazil

Introduction

The papillary cystadenoma (PC) of salivary glands is a rare benign epithelial tumor characterized by predominantly multicystic growth [1], intraluminal papillary proliferation, and duct-like structures [2], frequently exhibiting an oncocytic appearance. The World Health Organization (WHO) classifies PC as a tumor that closely resembles Warthin tumor but without the lymphoid component [3]. It is constituted by multiple papillary projections and a great variety of epithelial lining cells [1]. Due to its well-circumscribed nature and indolent behavior, the recurrence rate of PC is low and the prognosis is good [2, 4].

The occurrence of minor salivary gland papillary cystadenoma (MnSG PC) is rare, with the majority of cases involving major salivary glands, and about 45 % of all cases developing in the parotid gland [1]. Further, PC comprises between 0.6 to 4 % of all MnSG tumors [5–7], although a PubMed database search from 1958 to 2014 revealed only 19 cases of oral PC in the English literature [2, 4, 8–24] (Table 1).

Herein, we report eleven new cases of MSG PC, presented in conjunction with a review of the 19 previously reported cases in the literature.

Case Series

Conducted as a retrospective collaborative study by the Southern California Permanente Medical Group, California, USA (seven cases) and Bauru School of Dentistry, University of São Paulo, Bauru, Brazil (four cases), the medical records were reviewed, histologic slides examined and follow-up data obtained on all patients with a diagnosis of MnSG PC between 2001 and 2013. The microscopic

Table 1 Reported cases of minor salivary gland papillary cystadenoma (1958–2014)

Case #	Authors	Year	Age	Sex	Location	Symptom duration[a]	Size (cm)	Treatment	Recurrence	Follow-up (in years)
1	Collins [11]	1958	74	F	Left cheek	1	1.5[b]	Excision	Yes	6.5
2	Chaudhry [10]	1960	64	M	Left buccal	n/r	n/r	Excision	n/r	n/r
3	Calhoun [9]	1965	51	F	Upper lip	0.3	2.5[c]	Excision	n/r	n/r
4	Parnes [20]	1966	53	M	Right buccal mucosa	60	2[c] and 0.7[b]	Excision	No	~3
5	Wilson [24]	1974	77	M	Right inferior gingiva	n/r	3[c]	Excision	n/r	n/r
6	Kerpel [15]	1978	72	F	Buccal mucosa	1	n/r	Excision	No	2
7	Kameyama [14]	1985	73	M	Left lower lip	n/r	1.8[c]	Excision	No	n/r
8	Martin [17]	1993	76	M	Right lower lip	180	0.5[c]	Excision	n/r	n/r
9	Alexis [8]	1995	73	F	Buccal mucosa	n/r	1.2[b]	Excision	No	2
10	Guccion [13]	1997	62	M	Palate	3	1[b]	Excision	No	3
11	Mahler [16]	1999	39	F	Buccal mucosa	18	1.5[c]	Excision	No	n/r
12	Tsurumi [23]	2003	80	F	Hard palate	n/r	1[c]	Excision	No	2.5
13	Matsuzaka [19]	2003	35	M	Left upper lip	1	n/r	Excision	n/r	n/r
14	Ribeiro [21]	2004	54	M	Lower lip	n/r	0.8[b]	Excision	No	2
15	Gallego [12]	2008	74	M	Upper lip mucosa	60	1.2[c]	Excision	No	2
16	Lim [2]	2008	91	M	Hard-soft palate junction	1.6	3[c]	Excision	No	2
17	Halbritter [4]	2009	46	M	Lower lip	6	1.5[c]	CO_2 laser	No	1
18	Stathopoulos [22]	2013	58	F	Lower vestibular sulcus	n/r	1.5[c]	Excision	No	2
19	Martins-Filho [18]	2014	53	F	Upper lip	n/r	0.5[c]	Excision	n/r	n/r
20	Tjioe	2015	28	M	Lip	3	1.2[c]	Excision	No	1.3
21			34	M	Palate	12	1[c]	Excision	No	0.5
22			29	F	Oral	2	0.7[c]	Excision	No	3
23			70	F	Palate	2	0.5[c]	Excision	No	3.5
24			76	M	Tonsil	0	1.1[c]	Excision	No	4
25			56	F	Lip	39	2[c]	Excision	No	3.4
26			66	M	Tongue	8	1.5[c]	Excision	No	7
27			60	F	Upper lip	12	6[c]	Excision	No	2
28			14	M	Upper lip	n/r	0.9[b]	Excision	n/r	n/r
29			n/r	M	Palate	n/r	1.7[b]	Excision	n/r	n/r
30			55	F	Buccal mucosa	n/r	6[c]	Excision	n/r	n/r

F Female, *M* male, *n/r* not reported

[a] In months

[b] Gross dimension

[c] Clinical dimension

analysis was performed by two experienced pathologists (L.D.R.T. and V.S.L.) following the WHO criteria for diagnosis [1].

The demographic data is summarized in Table 1. The mean age at clinical presentation was 48.8 years (range 14–76 years), with five females and six males. Tumors were identified in the lip (two upper and two not specified), three in the palate, and one each: tonsil, tongue, buccal mucosa, and "oral cavity." In addition to noticing an intraoral nodule, one patient reported itching and another experienced pain (Table 1). Interestingly, the patient with a tonsillar tumor reported a history of oral squamous cell carcinoma. The tumors measured on average 2.1 cm (range 0.5–6 cm) in greatest dimension and all were described as well-circumscribed swellings (Fig. 1).

The microscopic features included fibrous connective tissue capsule surrounding cystic spaces lined by one to three layers of columnar to cuboidal epithelial cells, all of them containing oncocytic cells. Simple to multiple papillary projections into the cyst lumen were observed. Adjacent minor mucoserous glands showed focal fibrosis and a mild mononuclear cell infiltrate. Pleomorphism, increased mitoses, necrosis and invasion were absent. Pyknosis of the epithelial cells was focally present, but true geographic tumor necrosis was not seen. Luminal secretions were focally present, but mucinous differentiation was not observed (Figs. 2, 3).

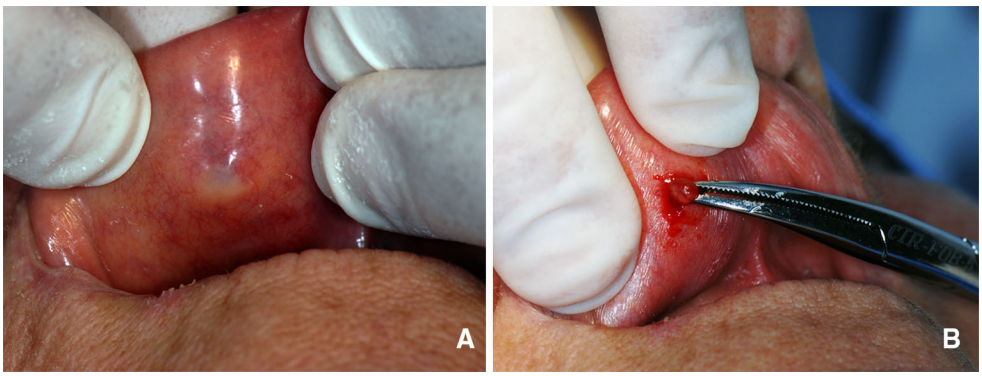

Fig. 1 Clinical appearance of the papillary cystadenoma. **a** Small and translucent nodule located in the right upper lip. **b** Trans-surgical view of the excisional biopsy. Note the well-circumscribed nature of the neoplasm

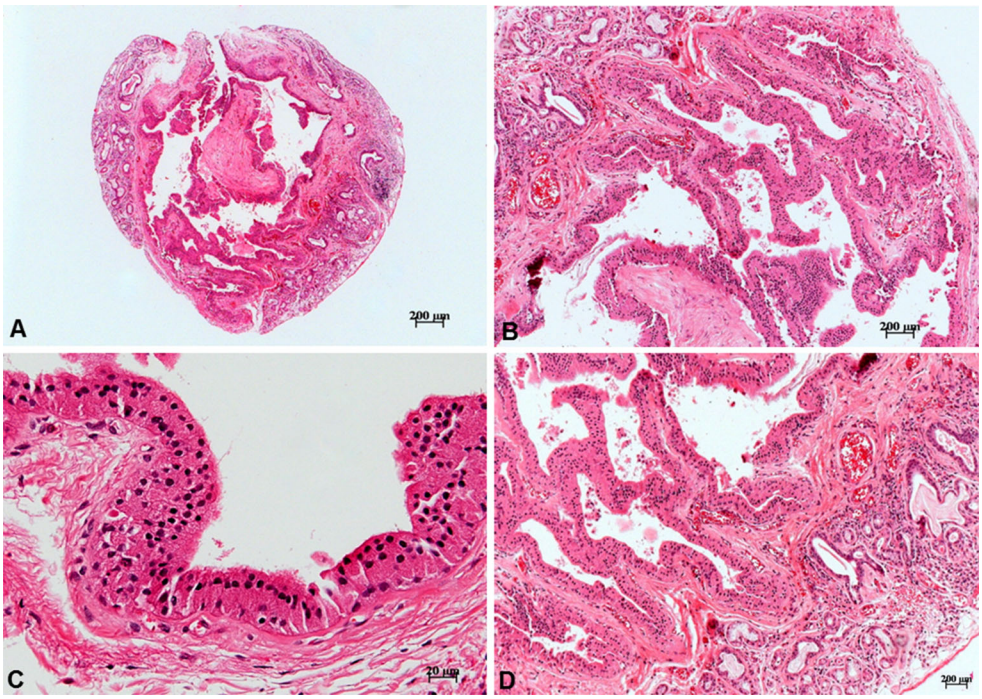

Fig. 2 Histologic features. **a** Low magnification showing cystic spaces with papillary projections. **b** Intraluminal papillary projections supported by fibrous connective tissue and underlying capsular connective tissue. **c** One to three layers of columnar to cuboidal oncocytic epithelial cells lining cystic spaces. **d** Adjacent fibrous connective tissue with ducts and acini of salivary glands and minimal lymphoplasmacytic infiltrate

All patients were treated by complete excision of lesions. They were followed-up for an average of 3.9 years (range 0.5–7 years) without recurrence, although no follow-up was available for three patients.

Review of the Literature and Discussion

The definition and nature of PC have been controversial. This tumor was classified as a subtype of monomorphic adenoma in the first edition of World Health Organization Histological Classification of Salivary Gland Tumors in 1972 [25]. However, from the second edition forward [3], cystadenoma became a distinct salivary gland benign tumor which was further subclassified into papillary and mucous types [23].

Many terms have been used to describe this tumor in the past, including: “PC”, “monomorphic adenoma”, “cystic duct adenoma”, “Warthin tumor without lymphoid stroma”, “intraductal papillary hyperplasia”, and “oncocytic cystadenoma.” Specifically, our search included “MnSG”, “oral”, “intra-oral”, “lip”, and “palate” using

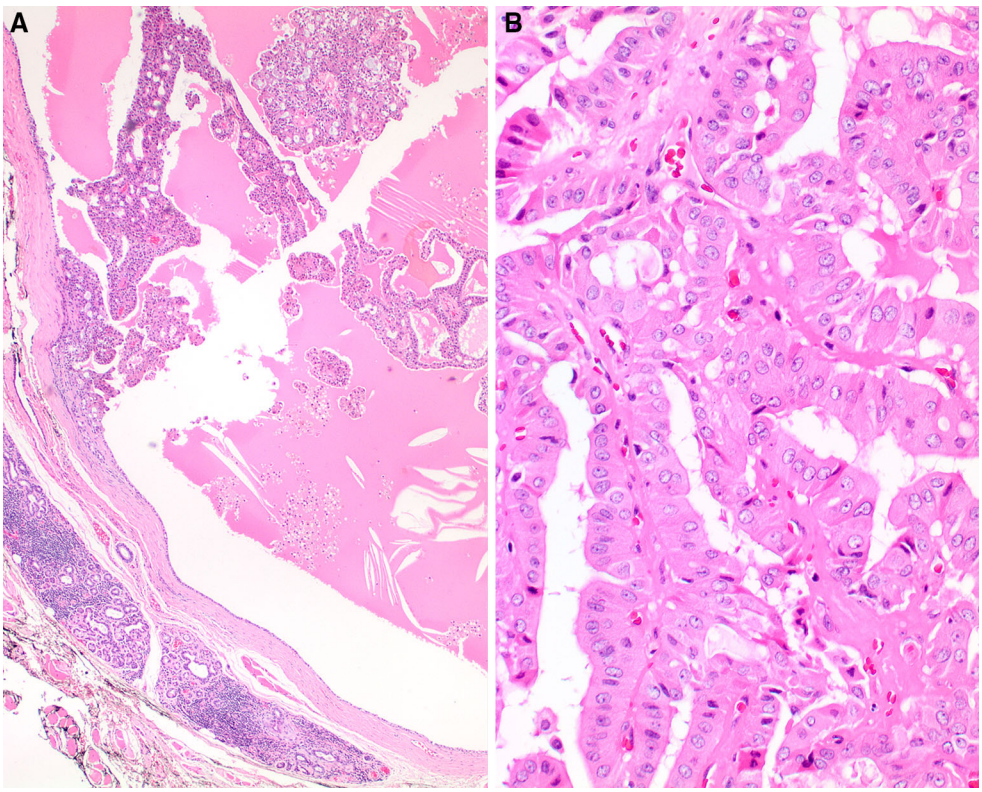

Fig. 3 Histologic features. **a** Low magnification showing unicystic papillary cystadenoma with intraluminal proliferation. The tumoral cells are intermixed by an eosinophilic material. Surrounding fibrous connective tissue and salivary gland tissue can be seen. **b** Prominent intracystic papillary growth with monolayer of cuboidal to columnar oncocytic epithelial cells devoid of atypia

Medline from 1955 to the present. Nineteen case reports had sufficient information to be included, while solely epidemiological retrospective studies and single case reports without good histologic images were excluded. The resulting evaluation was conducted on 30 total cases of MnSG PC involving the oral cavity.

The features of MnSG PCs reported in the literature are summarized in the Table 1. Combining all cases, there were 17 males and 13 females, ranging from 14 to 91 years (mean 58.4 years), with only seven patients younger than 50 years.

The most affected oral cavity site was the lip, with 12 cases (6 in upper, 4 in the lower lip, and 2 not specified), followed by buccal mucosa and palate (6 cases each). Wilson and MacEntee [24] reported an ectopic PC located midway between the right buccal sulcus and the crest of the edentulous ridge in the lower right premolar area, specifically stating that the gingiva is normally devoid of MnSG, the structures from which the PC originates [24].

The left side was affected more frequently (57.7 %) than the right (30.8 %) with a few cases in the midline (11.5 %) in the 26 cases including this information. Of the 19 patients in which symptom length was listed, it ranged from 10 days to 15 years (mean 21.6 months). Excluding the one tumor with 15 years disease duration, the mean was 13.5 months. In the vast majority, MnSG PC were asymptomatic (86.4 %). The patient treated by Halbritter et al. [4] reported a spontaneous rupture of a lower lip lesion a few weeks before consultation. Moreover, their case was the only one with reported symptoms (i.e. discomfort during eating) [4]. In our case series, two patients had symptoms, including pain and itching. All MnSG PC were clinically described as swelling, mass or tumefaction, with a benign appearance beneath an intact mucosa. Benign and malignant salivary gland tumors were included in the clinical differential diagnosis for the lesions located in the palate [2, 13, 23] due to the high frequency of neoplasms in this location. It is known that salivary gland tumors may be difficult to diagnose or interpret due to their wide variation in clinical presentation [26].

Regarding the lesions size, some authors reported the gross pathology diameter while others related the clinically measured size. The gross pathology MnSG PC had an average of 1.7 cm [6 cases [8, 11, 13, 21] (2 belonging our series)], while the clinical measure presented a mean of 1.3 cm [21 cases [2, 4, 9, 12, 14–18, 22–24] (9 from our series)]. Both dimension were listed in one case [20]. Both macroscopically and clinically, the size was usually small.

Most cases of MnSG PC (96.3 %) were described as well circumscribed tumors. However, Collins [11] reported

a PC in the left cheek that did not appear to be well encapsulated and was quite adherent to the adjacent tissue. The patient experienced a recurrence of the tumor 6.5 years later.

By microscopy, all MnSG PC showed cystic spaces of variable size, exhibiting intraluminal papillary projections. The tumors were typically well circumscribed and surrounded by a rim of fibrous tissue. The lining of the cystic structures was composed by a double layer of flattened to columnar epithelium. The cells were cuboidal, mucous, and/or oncocytic, without atypia; in all our case series, oncocytic cells were found scattered in the cystic lining composed of cuboidal to columnar epithelial cells (Fig. 3). Focal variation in epithelial differentiation was common, but in an individual cystadenoma, a single cell type was characteristically predominant [8, 23, 26]. Considering the complexity and histomorphological diversity of salivary gland tumors, the differential diagnosis of PC would include intraductal papilloma, cystadenocarcinoma, low-grade mucoepidermoid carcinoma (especially the oncocytic type), Warthin tumor, oncocytoma, and cheilitis glandularis [26]. There is some confusion in the literature regarding the ductal papilloma (specially the intraductal type) and PC. This occurs because both represent well-circumscribed tumors with intra-luminal growths. The PCs are described as "predominantly" multicystic once about 20 % of them are unicystic, as stated in the last World Health Organization Histological Classification of Salivary Gland Tumors. However the reference cited in the book for this figure dates from 1988, 3 years before the publication of the 2nd WHO Histological Classification of Salivary Gland Tumors that classified the cystadenoma as a tumor itself. An unicystic tumor still points to ductal papilloma. Moreover, the papillary projections found in ductal papilloma tend to be more numerous and complex than those from PCs.

Another lesion that present cystic spaces and may contain oncocytic cells and simulate PC is the low-grade mucoepidermoid carcinoma. However, PC usually exhibits multiple large cystic structures lined, in most areas, by a thin layer of cuboidal cells while the cystic structures in mucoepidermoid carcinomas present variable sizes and are lined, at least focally, by proliferation of many cell types. Although both lesions show papillary projections, the cell type characteristic of each is maintained [26, 27]. In addition, the absence of invasion and in general a lack of transitional epithelium would eliminate the diagnosis mucoepidermoid carcinoma. PCs lack a lymphoid stroma and are classified within the minor mucoserous glands, making a Warthin tumor must less likely. There is no atypia, no increased mitoses and no invasion, which helps to exclude a cystadenocarcinoma.

All cases reported were successfully treated by simple excision, although laser resection was used in a single case [4]. Of the 19 patients with reported follow-up (mean 2.8 years; range 0.4–7 years), there were three cases of possible recurrence [11, 16, 17]. The first case presented a recurrence 6.5 years after the first lesion removal but it was from 1958 and it may be that improvements in surgical technique have helped to eliminate any risk of recurrence [11]. The second case was a PC developed in the same anatomical location as a previous lesion 14 years before diagnosed as a mucous retention cyst [16]. The third case was a PC at the same place of a "skin cancer" treated 15 before [17]. It is not possible to know if the two last cases were recurrences once the first specimens were not available for analysis.

In summary, MnSG PCs are rare and shows a benign and indolent course. These lesions are usually slow growing, with a mean diameter of 1.3 cm and a symptom duration average of 1.8 year. Malignant potential for PC has been suggested, especially in older publications [11, 14, 20, 24], based on the recurrence rates observed. However, they are confined to inadequate removed major salivary gland tumors [27]. In PC affecting MnSG, malignant transformation has not been reported and seems unlikely to occur due to its indolent behavior and low recurrence rate [13]. The characteristic papillary and oncocytic appearance of these tumors makes the clinical differential diagnosis more of a concern than the pathology differential diagnosis.

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