Sialadenoma Papilliferum: With Clinicopathologic, Immunohistochemical, Molecular Analysis, and Review of the Literature

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Research

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Abstract

Background

Sialadenoma papilliferum (SP) is an extremely rare benign neoplasm of salivary glands. To explore and define the clinicopathological features of SP, we retrospectively analyzed 65 cases previously reported and five new cases.

Materials and methods

The clinical features, histopathology, immunohistochemistry and molecular analysis of our cases were further performed and the related literatures were reviewed and analyzed.

Results

Combining 65 cases from the literature with our cases, the hard palate was the most common locations for SP. However, two of our cases were rarely located in the esophageal mucosa. Among all cases, the male gender was more affected, with the average age and median age of 58 and 59 years, respectively. Conventional histomorphologically, SP was characterized by complex papillary structures with a biphasic growth pattern of exophytic squamous component and endophytic glandular component. The glandular structures were lined by a double layer epithelium composed of flattened or cuboidal basal cells and a cuboidal or columnar luminal cells formed papillary infoldings into the ductal lumina. Immunohistochemically, the luminal epithelial configurations showed strong expression of CK7 along the luminal cell membrane, while the basal myoepithelia displayed strong nuclear p63 expression. In both the glandular and squamous tumor components showed BRAF V600E-positive immunostaining and BRAF V600E mutation.

Conclusion

For the first time, we have comprehensively aggregated and analyzed 66 cases sialadenoma papilliferum from almost all previous publications, and further explored the clinicopathological features of SP; concordantly, this study demonstrated that SP shows a papillomatous growth pattern with exophytic and endophytic proliferation of ductal epithelium composed of double-layered cells harboring BRAF V600E mutation. Additionly, adequate treatment for SP is surgical excision, with a favorable prognosis in patients.

Introduction

Sialadenoma papilliferum (SP) is a rare benign neoplasm \(^1\), estimated to account for less than 1% of all minor salivary gland tumours and 3-5% of head and neck tumours \(^2\). It was described initially in 1969 by Abrams and Finck, because of its histomorphology closely resembling that of the syringocystadenoma papilliferum of cutaneous adnexal origin, and a total of only 66 cases were reported by 2020 \(^2\). SP is characterized by coexisting papillary and glandular configurations, which occurs mainly in the palate, especially the hard palate. It can also occur in the soft palate, buccal mucosa, nasal cavity, upper lip, parotid glands, and rarely in the bronchus and esophagus \(^7\). SP usually presents as a painless exophytic papillary mass with the peak incidence in the fifth and sixth decades of life \(^2\). The prognosis of SP is mostly good; and in single cases may have recurrence \(^8\) or malignant transformation \(^10\). Given the rareness of SP and difficulty in distinguishing it from other malignant tumours, the experience gained from the present cases and thorough analysis of medical literature are a useful addition to the current knowledge on the correct diagnosis and appropriate treatment of disease.
Materials And Methods

Patients and samples

With Institutional Board Review approval, the Department of Pathology of the Affiliated Hospital of Jining Medical University and consultation archives from 2017 to 2019 were searched for cases of SP and analyzed for their clinicopathological features. In addition, all available hematoxylin and eosin-stained sections were reviewed and confirmed by two pathologists with expertise in head and neck tumour pathology, and the relevant case literature was retrospectively reviewed.

Immunohistochemistry

The immunohistochemistry analysis was performed on paraffin-embedded sections using the EnVision two-step method. Primary antibodies used in the study were displayed as follows: CK7 (MAB-0828, MX053), CK5/6 (MAB-0744, MX040), P63 (MAB-0694, MX013), CK8 (MAB-0670, MX004), S-100 (Kit-0007, 4C4.9), and Ki-67 (MAB-0672, MX006), Ready-to-use, Maixin Bio, Fujian, China. Anti-BRAF V600E (VE1, Ventana) antibody was performed on Ventana BenchMark GX autostainer (Ventana) followed by the Optiview DAB Detection Kit (Ventana). Appropriate positive and negative controls were performed coincidentally for all the markers tested.

Molecular Analyses

The unstained paraffin-embedded sections were collected for DNA extraction (QIAamp DNA FFPE Tissue Kit, Qiagen, Hilden, Germany). And then DNA was amplified by polymerase chain reaction using primers for exon 15 of BRAF (HotStarTaq Master Mix kit (Qiagen), 5'-TCA TAA TGC TTG CTC TGA TAGGA-3' (BRAF-Exon15-F), 5'-GTC CAA AAA TTT AAT CAG TGGA-3' (BRAF-Exon15-R)). The amplified products were purified using a QIAquick Spin Kit (Qiagen), and then purified products were sequenced with a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Bio-systems, Foster City, CA, USA) on an ABI Prism 3700 instrument (Applied Biosystems). The confirmed assay was repeated for mutational specimens.

Results

Clinical features

There were five cases of SP from our hospital, including three males and two females, and age at diagnosis ranged from 50 to 78 years with an average age of 62 years. Four patients were found by accident in physical examination, only with slight local numbness but no obvious pain. In addition, one patient was treated for palatal tumors because of pain for one month. Two of the five cases occurred in the palate, one in nasal cavity and two in esophagus. All patients underwent tumour resection and were sent to the pathology department for pathological examination, with size of the mass ranging from 0.5 to 1.0 cm. Patients were followed for 6 to 22 months, and their prognosis was good without recurrence and worsening progression.

Combining 70 cases from the literature with our cases, the hard palate was the most common location, accounting for 60%, and others included the junction of the hard and soft palate, soft palate, buccal mucosa, nasal cavity, upper lip, parotid glands, etc (Fig. 1 and Table 1). Moreover, one of our cases was rarely located in the esophageal mucosa. There were 45 men and 25 women, showing preference for males, and age at diagnosis ranged from 15 to 96 years, with mean age and median age were 58 and 59 years, respectively (Fig. 2). Duration of the lesions ranged from 1 month to over 8 years, with 49.8 months of average duration. The misinterpreted clinical diagnosis included
squamous papilloma, fibroma, mucocele, salivary gland neoplasm, warty dyskeratoma, cystadenoma, cystadenocarcinoma or verrucous carcinoma.

**Macroscopy**

The tumour varied in sizes, from 0.3 to 3.0 cm in 46 cases known, with an average size of 0.93 cm, excluding two cases from the parotid gland (7.5 cm) and another two cases from the palate and left lower gingiva (4.0 cm). Gross observation showed that the cut surface of the lesion was slightly solid with grey-white to grey red colour, clear margins, and the papillary surface.

**Histopathology features**

Histologically, the tumors in our cases were characterized by biphasic differentiation, consisting of exophytic papillary structures covered by stratified squamous epithelium and endophytic glandular structures below the mucosa (Fig. 3a). The surface of papillary structures was covered with multiple layers of squamous epithelium, and the squamous epithelium was locally contiguous with a proliferation of papillomatous ductal epithelium located underneath the mucosal surface and extending downward into the deeper stroma (Fig. 3b). These papillas supported by fibrovascular connective tissue core often protruded into the lumen (Fig. 3c). These glandular structures were lined by double layers of columnar ductal epithelium and cubic basal cells. The luminal cells had round to oval, bland nuclei and inconspicuous nucleoli. The nuclei of regional tumors were enlarged with clear nucleoli, but without atypia. Inflammatory cell infiltration, including plasma cells, lymphocytes and neutrophils, was seen around the lumen and the connective tissue. Enlarged cysts with eosinophilic deposits (Fig. 3d) and accidental areas of oncocytic metaplasia (Fig. 3e) can be seen in the ductal structures of 3 cases, and mucinous cells and necrosis were seen locally in 2 cases. In addition, The tumor area showed normal cell morphology and mucinous cells can be seen in some tumor areas: Fig. 3f.

**Immunohistochemical features**

Immunohistochemical studies of our cases have shown that CK7 (Fig. 4a) and CK8 were strongly expressed in the luminal cells, while p63 (Fig. 4b), CK5/6 and S-100 (Fig. 4c) were strongly expressed in the basal cell layer but were negative in the luminal cells. Ki67 decorated less than 30% lesional cells in all cases (Fig. 4d and Table 2). BRAF V600E in both the glandular and squamous tumor components showed a moderate or weak staining (Fig. 4e, f).

**Molecular features**

Molecular analysis revealed that *BRAF* mutation was confirmed in three of four cases, because of one case lacking sufficient tissue for testing (Fig. 5).

**Treatment and Follow up**

Our patients were followed for 6 to 22 months, and their prognosis was good without recurrence and worsening. According to the literature review, conservative surgery was documented in 56 cases and treatment was not specified in 6 cases. And one case from the left lower gingiva with malignant transformation invading the mandible was treated by partial mandibular resection and cervical lymph node dissection. Another case from the parotid gland, considering the preservation of the facial nerve, only superficial parotidectomy was performed. In addition, the follow-up information of 37 cases was available, in which the length of follow-up period of the patients ranged from 1 month to 96 months, with an average length of 31 cases. Three cases with malignant transformation of SP have been
recognized, and only two recurrences were recorded, each at 36 months after initial treatment, which indicated a recurrence rate of 6.5%.

**Discussion**

SP is a subtype of intraductal papilloma, a rare benign tumor commonly found in middle-aged men with hard palate, accounting for approximately 80 percent. It can also occur in the parotid gland, submandibular gland, nasopharynx and esophagus. Clinically, there are generally no obvious clinical symptoms with mostly painless growth, but sometime papillary erythema or pedicled lumps, occasional ulcers. Grossly, most of the lesions presents as a round to oval mass with white-colored and papillary surface, sharing about 80 percent.

Histologically, SP is formed by mucosal surface epithelium and ductal epithelium of the salivary gland which proliferate outward and inward simultaneously, with the characteristics of biphasic proliferation of squamous and ductal epithelium. Generally, SP has two components: (1) superficial papillary structure: stratified squamous epithelium covered with incomplete keratinization, in addition to acanthosis or acanthosis cell edema; (2) ductal structure: the lumen-like structure lined by two layers of columnar and cuboidal cells is formed under the mucosa, and the ductal lumina can be mesh-like, fissure-like or expanded into a large cystic cavity. In addition, there are numerous inflammatory cells in the epithelial space, such as plasma cells and lymphocytes. Immunohistochemistry showed that CK7 and CK8 were strongly expressed in columnar cells, and p63 was strongly positive in basal cells, but was negative in columnar cells from Table 2 and reported literatures, and some cases were positive for S-100 and GFAP, which indicate the convoluted ductal structures of SP include two cell types at least.

The Histogenesis of SP is still not fully understood. There are several viewpoints as follows. Freedman, Lumerman, and Anuradha et al proposed that it may originate from the excretory tube cell, which is supposed to be a primitive precursor cell capable of multi-directional differentiation. According to Abrams and Finck, the lesion was of pleuripotential myoepithelial origin because the tumor cells revealed the immunoreactivity for SMA. Moreover, Asahina and others suggested that the lesion derived from the intercalated duct cell due to the presence of the tumour cells coexpressing cytokeratin, vimentin, and desmin. Conversely, Eversole and several authors considered SP as the result of focal hyperplasia after salivary duct obstruction rather than a true neoplasm. However, in our limited series of SP, BRAF V600E immunoreexpression presented in both the proliferative ductal and squamous tumor elements, which confirmed by molecular analysis, suggested the neoplastic nature of both components, and the transition of ductal epithelium to squamous epithelium seen in SP indicated this tumour may originate in the excretory ducts. Although the cells of origin are not entirely clear at present, the histopathological, immunohistochemical and molecular features of the fusion of the duct components with the surface epithelium seem to favor the origin of the excretory ducts.

Although SP has been proposed as a distinct entity, it also needs to be differentiated from the following neoplasms. First of all, papillary squamous cell carcinoma, a papillary subtype of squamous cell carcinoma similar to the histopathological characteristics of SP, is characterized by an exophytic and papillary growth pattern. However, there is no glandular component with mucous cells in the lesion, and the squamous cell papilloma is mainly composed of the squamous epithelium, which manifests highly differentiated squamous cell carcinoma with keratinized beads structure, without downward extension of SP. Inverted ductal papilloma is another candidate for differential diagnosis, mainly composed of hyperplastic squamous epithelium under the mucosa that protrudes into connective tissue and connects with duct, but unlike SP with characteristic papillary surface configuration. Another antidiastole is highly differentiated mucoepidermoid carcinoma, which is rich in mucous cells, often forming a glandular cavity, and sometimes hyperplastic mucous cells form the papillary structure resembling that of SP, while mucoepidermoid
carcinoma usually composed of epidermal-like cells, intermediate cells, mucus cells and other cell components. Wathin tumor shares papillary adenoid structure with characteristic double layer epithelium lining the glandular cavity resembling SP should also be considered, but the interstitial of it is a lymphoid component associated with lymphoid follicle formation. Also papillary cystadenocarcinoma is a rare malignant tumour characterized by predominantly cystic growth and cell types that comprise the lining epithelium of cysts include most often cuboidal and columnar cells, which though resemble SP, neither exhibits squamous elements.

The current treatment of SP is conservative surgical resection. In addition, oral robotic surgery (TORS) is a novel technique for head and neck surgery in some centers around the world. Atarbashi-Moghadam proposed the first successful removal of SP tumors by TORS. The use of TORS provides better control of surgical procedures and reduced morbidity compared to traditional oral surgical procedures.

Although there have been a few reports of recurrence and malignant transformation, in which SP has reported that it can transformed into epithelial-muscle epithelial carcinoma, squamous cell carcinoma, and mucoepidermoid carcinoma, but malignant transformation is rare and not entirely convincing. As the results of the statistics show that the prognosis of this lesion is very good, we believe that SP does not have malignant potential.

Summarily, SP is a rare, benign and exophytic tumor of salivary gland neoplasm that commonly occurs in the hard palate in middle aged males with a painless and slow growing lesion. Characteristic of this tumor is its exophytic growth pattern, with multiple papillary surface fronds and deeper ductlike structures, which may be continuous with the surface epithelial component. In this study, we added another five cases of SP to the literature and discussed the clinicopathologic features of the 70 described cases of this unusual neoplasm. Although to identify the cell of origin of SP is difficult, we conclude that SP is a neoplastic lesion arising from the excretory ducts by immunophenotypic feature and molecular analysis, and virtually has no potentially malignant features mostly with good prognosis, which should be distinguished from other malignant tumours and avoided resultant overtreatment.

Declarations

Acknowledgments

None.

Author contributions

YS and RYZ designed the research study. SC, JP and LS performed the research. YS, PJ, CTY and RYZ analyzed the data and made the diagnosis. SC wrote the manuscript and YS revised the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Ethical Approval

Ethical approval was obtained from the ethical committee from Affiliated Hospital of Jining Medical University.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Tables**

**Table 1 Clinical features of sialadenoma papilliferum (71 cases, but 70 cases available)**
| Reference       | Age | Sex | Location            | Duration | Size (cm) | Clinical diagnosis       | Clinical features                     | Follow-up |
|-----------------|-----|-----|---------------------|----------|-----------|---------------------------|---------------------------------------|-----------|
| Case 1          | 78  | M   | Hard palate         | 1 mo     | 0.5       | Squamous papilloma        | Yellow-brown mucosa                   | NED-19 mo |
| Case 2          | 56  | F   | Hard palate         | 5 mo     | 1.0       | Squamous papilloma        | Hard and clear tubercle               | NED-15 mo |
| Case 3          | 72  | M   | Nasal cavity        | 2 mo     | 1.0       | Squamous papilloma        | Hard and clear tubercle               | NED-9 mo  |
| Bobos et al.    | 53  | M   | Bronchus            | 4 mo     | 2.2       | N/A                       | Exophytic papillary yellowish tumour  | N/A       |
| Campisi et al.  | 66  | M   | Bronchus            | N/A      | 1.5       | N/A                       | Pulmonary nodule                      | N/A       |
| Fowler et al.   | 55  | F   | Hard palate         | Several mo| 0.3       | Papilloma                 | Exophytic pebbly pink with stalk      | N/A       |
| Fowler et al.   | 50  | M   | Hard palate         | >15 yrs  | 0.8       | Papilloma, fibroma, hemangioma | Exophytic pink/red                    | N/A       |
| Fowler et al.   | 62  | M   | Hard palate         | N/A      | N/A       | Papilloma                 | Papilloma-appearing lesion            | N/A       |
| Fowler et al.   | 63  | M   | Hard palate         | N/A      | N/A       | Mucocele, fibroma         | Raised mass                           | N/A       |
| Fowler et al.   | 57  | M   | Hard palate         | 1 mo     | 0.4       | Papilloma                 | Red with stalk, fingerlike            | N/A       |
| Fowler et al.   | 48  | F   | Hard palate         | N/A      | 0.5       | Fibroma, salivary gland tumour | Red, slightly elevated               | N/A       |
| Fowler et al.   | 76  | F   | Hard palate         | 2.5 mo   | 1.3       | Carcinoma                 | White rough lesion                    | N/A       |
| Gera et al.     | 96  | F   | Nasal cavity        | Almost 30 yrs | 0.8       | N/A                       | Yellow-brown mucosa                   | NED-9 mo  |
| Loehn et al.    | 65  | M   | Parotid             | 8 yrs    | 7.5       | Sialadenoma papilliferum  | Pink, exophytic, fungating tumor      | NED-14 mo |
| Oze et al.      | 67  | F   | Nasal cavity        | 2 yrs    | 0.8       | Sialadenoma papilliferum  |                                        | NED-4 mo  |
| Pimentel et al. | 67  | F   | Buccal mucosa       | 12 mo    | 2         | N/A                       | Recurrent epistaxis                   | Rec-36 mo |
| Reis de et al.  | 20  | M   | Upper lip           | N/A      | 1.6       | Mucocele                  | Sessile mass; recurrence              |           |
|                 | 30  | M   | Upper lip           | N/A      | 1.5       | Mucocele                  |                                        |           |
| Author et al. | Age | Gender | Location | Age | Duration | Lesion Type | Description | Follow-Up |
|--------------|-----|--------|----------|-----|----------|-------------|-------------|-----------|
| Ponniah et al. | 10 | F | Floor of the mouth | N/A | 4 | Sialadenoma papilliferum | Nodular mass, asymptomatic, exophytic, slightly papillary lesion | NED-21 mo, NED-8 mo |
| Shimoda et al. | 79 | F | Hard/soft palate | N/A | 4 | Sialadenoma papilliferum | Exophytic pink-white papillary mass | NED-1 mo |
| Abrams and Finck | 71 | M | Parotid | 10–12 yrs | 7.5 | Low-grade malignancy | Fungating cauliflower-like mass | NED-18 mo |
| Abrams and Finck | 57 | M | Hard/soft palate | 3 mo | 1.5 | N/A | Verrucous lesion | NED-19 mo |
| Mahajan et al. | 18 | M | Upper lip | 12 yrs | 0.8 | Infected hemangioma | Firm tumour | NED |
| Kubota et al. | 62 | M | Hard palate | 3 mo | 1 | N/A | White, exophytic | NED-13 mo |
| Atarbash Mogha dam et al. | 50 | F | Hard palate | 12 mo | 1 | N/A | Reddish mass with slightly papillary | NED-48 mo |
| Gomes et al. | 53 | M | Hard palate | 3 yrs | 1 | Papilloma, vascular | Pedunculated red papillary mass | NED |
| Gomes et al. | 52 | F | Soft palate | 4 yrs | 0.5 | Fibrous polyp | Firm pedunculated mass | NED |
| Ubaidat et al. | 72 | M | Hard palate | N/A | 0.4 | N/A | Exophytic growth (0.6 cm on gross) | NED-3 mo |
| Ubaidat et al. | 58 | M | Hard palate | N/A | 0.5 | Melanoma | Ulcerated and pigmented | NED |
| Brannon et al. | 69 | F | Hard palate | N/A | N/A | Squamous papilloma | Slow growing exophytic mass | N/A |
| Brannon et al. | 53 | F | Hard palate | 3 mo | N/A | Squamous papilloma | Slow growing exophytic mass | N/A |
| Brannon et al. | 31 | F | Hard palate | 4 yrs | N/A | Squamous papilloma | Slow growing exophytic mass | N/A |
| Argyres et al. | 50 | M | Hard palate | Several mo | 0.5 | Squamous cell carcinoma | Irregular exophytic mass | N/A |
| Author(s)                      | Age | Gender | Location        | Duration | Size | Diagnosis                      | Description                                      | Follow-up |
|-------------------------------|-----|--------|-----------------|----------|------|-------------------------------|--------------------------------------------------|-----------|
| Markopoulos et al.            | 50  | M      | Hard palate     | 12 yrs   | 0.5  | Papillary mass               | N/A                                              | N/A       |
| Asahina et al.                | 50  | M      | Hard palate     | 6 mo     | 0.5  | Fibrous polyp                | Cauliflower like mass, white/pink                | NED-24 mo |
| Maiorano et al.               | 56  | M      | Hard palate     | N/A      | 0.5  | Squamous papilloma           | N/A                                              | NED-18 mo |
| Maiorano et al.               | 37  | F      | Hard palate     | N/A      | 1    | Verrucous leukoplakia         | N/A                                              | NED-48 mo |
| Maiorano et al.               | 60  | M      | Buccal mucosa   | N/A      | 0.8  | Squamous papilloma           | N/A                                              | NED-96 mo |
| Maiorano et al.               | 46  | M      | Hard palate     | N/A      | 1.4  | Salivary gland tumour        | N/A                                              | NED-36 mo |
| Maiorano et al.               | 50  | M      | Hard palate     | N/A      | 1.8  | Salivary adenoma             | N/A                                              | NED-6 mo  |
| Van der Wal and van der Waal  | 46  | M      | Hard/Soft palate| 10 yrs   | 0.5  | Fibroepithelial polyp        | Pedunculated firm exophytic mass                 | NED-12 mo |
| Nakahata et al.               |     |        | N/A             | N/A      | N/A  | N/A                          | N/A                                              | N/A       |
| Papanicolaou et al.           | 46  | M      | Hard palate     | N/A      | 0.5  | N/A                          | Red firm exophytic growth                        | N/A       |
| Fantasia et al.               | 87  | F      | Hard palate     | Several mo| N/A  | Irritated papilloma          | Exophytic red papillary lesion                   | N/A       |
| Fantasia et al.               | 77  | M      | Buccal mucosa   | N/A      | N/A  | N/A                          | N/A                                              | N/A       |
| Fantasia et al.               | 48  | F      | Hard palate     | N/A      | N/A  | N/A                          | N/A                                              | N/A       |
| Fantasia et al.               | 45  | M      | Hard palate     | N/A      | N/A  | N/A                          | N/A                                              | N/A       |
| Fantasia et al.               | 60  | F      | Upper lip       | N/A      | N/A  | N/A                          | N/A                                              | N/A       |
| Mitre                        | 42  | F      | Hard/soft palate| 7 mo     | 0.4  | N/A                          | Red warty lump                                   | N/A       |
| Rennie et al.                 | 77  | M      | Hard/soft palate| N/A      | 1    | Squamous papilloma           | Firm warty papule                                | Rec-36 mo |
| Puts et al.                   | 78  | M      | Hard palate     | N/A      | 1.6  | N/A                          | Exophytic papillary growth                       | NED       |
| Authors            | Age | Sex | Site                        | Duration | Size | Diagnosis                  | Description                                      | Follow-up |
|--------------------|-----|-----|-----------------------------|----------|------|----------------------------|---------------------------------------------------|-----------|
| Sunil et al.       | 58  | F   | Hard palate                 | 1 mo     | 1    | Papilloma/fibroma           | Exophytic erythematous                            | N/A       |
| Shirasuna et al.   | 56  | F   | Hard palate                 | N/A      | 0.7  | Squamous papilloma          | Pedunculated papillary mass                       | N/A-20 mo |
| Wertheimer et al.  | 32  | M   | Hard palate                 | N/A      | 0.5  | Papilloma                   | Dome-shaped mass                                  | N/A-18 mo |
| Wertheimer et al.  | 43  | M   | Soft palate                 | 8 yrs    | 0.5  | N/A                        | Papillary mass, recently ulcerated                | N/A-30 mo |
| Nasu et al.        | 62  | F   | Hard palate                 | 6 mo     | 0.6  | Papilloma exophytic mass,   | slow growth                                       | N/A       |
| McCoy              | 77  | F   | Buccal mucosa               | N/A      | 0.7  | N/A                        | Papillary growth, indurated                       | NED       |
| Drummond et al.    | 71  | M   | Retromolar pad              | N/A      | 0.5  | N/A                        | Pink papillary, pedunculated                      | N/A-6 mo  |
| Whittaker and Turner | 65  | M   | Hard/soft palate            | N/A      | 0.6  | N/A                        | Area of hyperplasia                               | N/A-36 mo |
| Whittaker and Turner | 50  | M   | Hard/soft palate            | N/A      | N/A  | N/A                        | N/A                                               | N/A       |
| Jensen and Reingold | 48  | M   | Hard palate                 | 10 yrs   | 0.8  | Squamous papilloma          | Pedunculated papillary lesion                     | N/A       |
| Su et al.          | 70  | F   | Esophagus                   | 20 mo    | 1.0  | Adenocarcinoma              | Broad-based polypoid tumour                       | N/A-12 mo |
| Rouse et al.       | 81  | M   | Esophagus                   | 36 mo    | 1.5  | Esophageal adenoma          | Pedunculated polyp                                | N/A-12 mo |
| Honda et al.       | 75  | M   | Bronchus                    | 2 mo     | 0.5  | N/A                        | N/A                                               | N/A-8 mo  |
| Freedman and Lum erman | 68  | M   | Hard palate                 | N/A      | 0.3  | N/A                        | Exophytic papillary lesion                        | N/A-21 mo |
| Freedman and Lum erman | 65  | M   | Hard palate                 | 1 mo     | 0.5  | N/A                        | N/A                                               | N/A-19 mo |
| Freedman and Lum erman | 15  | F   | Floor of the mouth          | 12 mo    | 0.8  | Papilloma                   | N/A                                               | N/A       |
| Su et al.          | 72  | M   | Floor of the mouth          | 12 mo    | 3    | Salivary neoplasm           | Raised sessile papillary lesion                   | N/A       |
| Rouse et al.       | 81  | M   | Esophagus                   | 36 mo    | 1.5  | Esophageal adenoma          | Pedunculated polyp                                | N/A-12 mo |
| Honda et al.       | 75  | M   | Bronchus                    | 2 mo     | 0.5  | N/A                        | N/A                                               | N/A-8 mo  |
| Freedman and Lum erman | 68  | M   | Hard palate                 | N/A      | 0.3  | N/A                        | Exophytic papillary lesion                        | N/A-21 mo |
| Freedman and Lum erman | 65  | M   | Hard palate                 | 1 mo     | 0.5  | N/A                        | N/A                                               | N/A-19 mo |
| Su et al.          | 70  | F   | Esophagus                   | 20 mo    | 1.0  | Adenocarcinoma              | Broad-based polypoid tumour                       | N/A-12 mo |
| Rouse et al.       | 81  | M   | Esophagus                   | 36 mo    | 1.5  | Esophageal adenoma          | Pedunculated polyp                                | N/A-12 mo |
| Honda et al.       | 75  | M   | Bronchus                    | 2 mo     | 0.5  | N/A                        | N/A                                               | N/A-8 mo  |
| Freedman and Lum erman | 68  | M   | Hard palate                 | N/A      | 0.3  | N/A                        | Exophytic papillary lesion                        | N/A-21 mo |
| Freedman and Lum erman | 65  | M   | Hard palate                 | 1 mo     | 0.5  | N/A                        | N/A                                               | N/A-19 mo |
| Su et al.          | 70  | F   | Esophagus                   | 20 mo    | 1.0  | Adenocarcinoma              | Broad-based polypoid tumour                       | N/A-12 mo |
| Rouse et al.       | 81  | M   | Esophagus                   | 36 mo    | 1.5  | Esophageal adenoma          | Pedunculated polyp                                | N/A-12 mo |
| Honda et al.       | 75  | M   | Bronchus                    | 2 mo     | 0.5  | N/A                        | N/A                                               | N/A-8 mo  |
| Freedman and Lum erman | 68  | M   | Hard palate                 | N/A      | 0.3  | N/A                        | Exophytic papillary lesion                        | N/A-21 mo |
| Freedman and Lum erman | 65  | M   | Hard palate                 | 1 mo     | 0.5  | N/A                        | N/A                                               | N/A-19 mo |
| Su et al.          | 70  | F   | Esophagus                   | 20 mo    | 1.0  | Adenocarcinoma              | Broad-based polypoid tumour                       | N/A-12 mo |
| Rouse et al.       | 81  | M   | Esophagus                   | 36 mo    | 1.5  | Esophageal adenoma          | Pedunculated polyp                                | N/A-12 mo |
| Anuradha et al.\(^{43}\) | 67  | M | Nasal cavity | Retromolar pad | 12 mo | 3 | N/A | lesion | NED-12 mo |
| Hamilton et al.\(^{45}\) |   |   | Retromolar pad |   |   |   | N/A | Soreness in mouth | NED-12 mo |
| Koc et al.\(^{46}\) |   |   | Retromolar pad |   |   |   | N/A | Chronic nasal obstruction | NED-12 mo |
| Ide et al.\(^{47}\) |   |   |   |   |   |   | Mass with a papillomatous hemorrhagic surface | N/A |

*mo* month(s), *yrs* years, *N/A* Not available, *NED* No evidence of disease.

**Table 2 Immunohistochemical findings of sialadenoma papilliferum (our five cases).**

|                      | Luminal layer of ductal epithelial cells | Basal layer of myoepithelial cells |
|----------------------|----------------------------------------|-----------------------------------|
| BRAF V600E           | ++                                    | -                                 |
| CK7                  | ++                                    | -                                 |
| CK8                  | ++                                    | -                                 |
| CK5/6                | -                                     | ++                                |
| P63                  | -                                     | ++                                |
| S100                 | -                                     | +                                 |
| Ki-67                | 5%                                    | 20%-30%                           |

(*) focal staining, (++) diffuse staining.