Oral Science International 9 (2012) 55–58

Oral Science International

journal homepage: www.elsevier.com/locate/osi

Case Report

Inverted ductal papilloma arising from the buccal minor salivary gland: A case report and immunohistochemical study

Hisashi Kato[a,*,1], Yoshihide Ota[b], Masashi Sasaki[b,2], Akihiro Kaneko[b], Yasutomo Sekido[c], Keiichi Tsukinoki[d]

[a] Department of Oral and Maxillofacial Surgery, National Hospital Organization Shizuoka Medical Center, 762-1 Nagasawa, Shimizu-cho, Suntou-Gun, Shizuoka 411-8611, Japan
[b] Department of Oral and Maxillofacial Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
[c] Department of Pathology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
[d] Department of Diagnostic Science Division of Pathology, Kanagawa Dental College, 82 Inaoka-cho, Yokosuka, Kanagawa 238-8580, Japan

ARTICLE INFO

Article history:
Received 16 January 2012
Received in revised form 13 February 2012
Accepted 17 February 2012

Keywords:
Inverted ductal papilloma
Minor salivary gland tumor
Cytokeratin
Epithelial membrane antigen
Immunohistochemistry

ABSTRACT

Oral inverted ductal papilloma is a rare, benign epithelial tumor that exhibits an endophytic growth pattern and is found almost exclusively in the minor salivary glands. We report on a case of inverted ductal papilloma in the buccal mucosa. We also performed an immunohistochemical study. The tumor cells were positive for cytokeratin and epithelial membrane antigen, while negative for calponin, S-100 protein, α-SMA, vimentin, and desmin. This result indicated that the lesion arises from the excretory duct near the oral mucosal surface but not the myoepithelial cells. In addition, Ki-67 labeling index of 3.96% indicated the low level of proliferation.

1. Introduction

Oral inverted ductal papilloma (IDP) is a rare, benign papillary epithelial tumor that exhibits an endophytic growth pattern [1–4]. The lesion resembles inverted papilloma of the urinary bladder, nasal cavity, and paranasal sinuses [5,6]. Similar lesions have also been described in the renal pelvis [7], the lacrimal sac [8], cervix, and the posterior pharyngeal wall [9]. However, oral IDP is a distinctive lesion with histological features similar to those of the more common sinonasal inverted papilloma [4]. In contrast to sinonasal inverted papilloma, which arises from the surface epithelium, oral IDP arises almost exclusively at the junction of the minor salivary gland duct and the oral mucosal surface epithelium [1,4]. Sinonasal inverted papillomas are associated with squamous cell carcinoma in 10–15% of the cases, while oral IDPs are benign [4,10].

IDP is a member of the triad of ductal papillomas that also includes sialadenoma papilliferum and intraductal papilloma. These three benign lesions derive from the ductal epithelium and exhibit unique histopathologic features that separate them as different entities [4].

Immunohistochemical studies assist in the diagnosis and possibly in the determination of the origin of the lesion. However, the immunohistochemistry of IDP has not been thoroughly studied. In this paper, we report an immunohistochemical study on an instance of IDP through an analysis of cytokeratin (CK7, CK14, CK19, AE1/AE3, CAM5.2, and 34βE12), epithelial membrane antigen (EMA), S-100, calponin, α-smooth muscle actin (α-SMA), vimentin, desmin, carcinoembryonic antigen (CEA), Ki-67, and p53.

2. Case report

A 71-year-old woman was referred to the Department of Oral and Maxillofacial Surgery at the National Hospital Organization Shizuoka Medical Center with a painless nodule on the left buccal mucosa of over 10 years' duration. There was no swelling of the left cheek and no associated lymph node enlargement. On intraoral examination there was a slightly firm, mobile nodule approximately 1.0 cm in diameter on the left buccal premolar area. The overlying mucosa appeared normal, but there was a central

* Corresponding author at: Department of Oral and Maxillofacial Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. Tel.: +81 463 93 1121; fax: +81 463 95 7567.
E-mail addresses: hisashi@tokai-u.jp (H. Kato), yotaorsg@ybb.ne.jp (Y. Ota), sasaki75@is.icc.u-tokai.ac.jp (M. Sasaki), akihiro@is.icc.u-tokai.ac.jp (A. Kaneko), aethyrk@gmail.com (Y. Sekido), ktsukino@kdcnet.ac.jp (K. Tsukinoki).
[1] Present address: Department of Oral and Maxillofacial Surgery, Tokai University, School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan.
[2] Present address: Department of Oral and Maxillofacial Surgery, National Hospital, Organization Shizuoka Medical Center, 762-1 Nagasawa, Shimizu-cho, Suntou-Gun, Shizuoka 411-8611, Japan.

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doi:10.1016/S1348-8643(12)00024-9

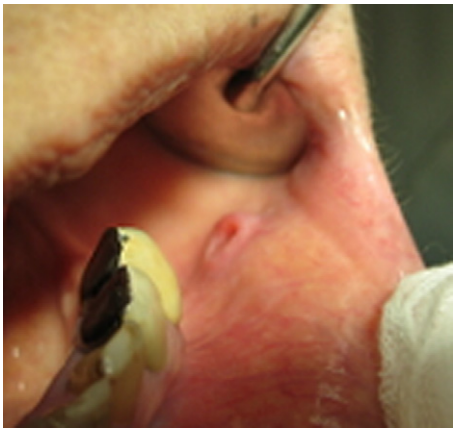

Fig. 1. An intraoral view of the inverted ductal papilloma on the left buccal mucosa. The tumor is approximately 1 cm in diameter. There is a submucosal swelling with a punctum on the mucosal surface. The lesion is slightly firm and mobile.

punctum that was continuous with the underlying mass (Fig. 1). There had been no growth or regression in the size of the tumor for several years. There was no history of prior trauma, dental problems, allergies, or other medical problems. The rest of the clinical and laboratory examination was within normal limits.

With the provisional diagnosis of a benign tumor, the lesion was excised under local anesthesia with a small margin of normal tissue. The tumor was then fixed and examined histologically. Histologic evaluation of the lesion confirmed the diagnosis of IDP. The healing of the excision site was uneventful, and there has been no recurrence after 1 year and 8 months of follow-up.

Microscopically, the neoplasm appeared as an unencapsulated, well-demarcated endophytic epithelial mass that was continuous with the mucosal epithelium. At the periphery, the tumor had a broad pushing interface with the connective tissue stroma. The mucosal epithelium had a central pore-like opening in the mucosal surface (Fig. 2). The lesion was filled with thin papillary structures lined by a thick layer of predominantly cuboid and columnar epithelia with numerous invaginations and cleft-like structures. The lesion contained scattered goblet cells and occasional microcysts (Fig. 3). No features of infiltration or invasion were appreciated.

We performed an immunohistochemical study to evaluate the character and origin of the lesion. Details concerning the primary antibodies, their application, and the results are presented in Table 1. The routine indirect immunoperoxidase method was used for immunohistochemistry. After deparaffinization, the sections were immunostained using an autoanalyzer (BenchMark® XT, Roche Diagnostics K.K., Tokyo, Japan). After activating the antigen, monoclonal and polyclonal antibodies were used as the primary antibody, and an iView DAB Detection kit (Roche Diagnostics K.K.) was used as the autoimmunostaining reagent. Dehydration and mounting were performed after nuclear staining with hematoxylin. The tumor cells reacted positively with CK and EMA antibodies. CK14 was predominantly expressed in the basal cells of the tumor, while AE1/AE3, CAM5.2, and CK7 were predominantly expressed in the luminal cells of the tumors (Fig. 4). EMA was expressed at low levels, 34βE12 was moderately expressed and CK19 was strongly expressed in all of the tumor cells. The tumor cells were negative for S-100, calponin, α-SMA, vimentin, desmin, CEA, and p53. In addition, Ki-67 was expressed only in the basal cells of the tumors with a labeling index of 3.96%.

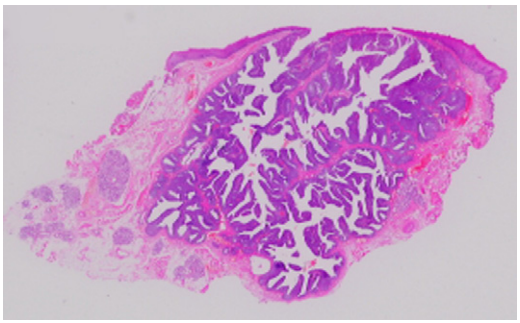

Fig. 2. A low-power view of the tumor. The tumor consisted of papillary proliferation of the epithelial tissue compressed, the surrounding connective tissue. The covering epithelium was continuous with the tumor at the opening, and minor salivary glands were observed in the vicinity of the tumor. (H&E, ×4.)

3. Discussion

When evaluating a nodular submucosal swelling with a punctum on the surface in the oral cavity, it is important to be able to recognize and differentiate neoplasms or inflammatory diseases from infections or injuries, such as masticatory trauma. The lack of inflammatory symptoms assists in identifying the difference between injuries and neoplasms. A differential diagnosis of a neoplasm must be considered along with several other entities, including epithelial tumors.

IDP is a rare, benign epithelial tumor occurring almost exclusively in the minor salivary glands. However, IDP has a set of common clinical features and typically presents as a painless, nodular submucosal swelling that often has a punctum on the surface of the swelling. The most common location of IDP is on the lower lip, followed by the buccal mucosa/mandibular vestibule. The tumors range from 0.5 to 1.5 cm in size, and the duration ranges from months to several years. The majority of the cases of IDP occur in the middle-aged and elderly [2,3]. Our case demonstrated the typical clinical features of IDP.

Histopathologically, IDP is a luminal papillary proliferation that exhibits an endophytic growth pattern. These proliferating masses of epithelial cells contain scattered goblet cells and occasional microcysts [4]. Typical IDPs show broader papillary projections predominantly composed of epidermoid and basal cells in tumor. However, this case showed the atypical histological feature that had narrow papillary projections composed of few epidermoid and basal cells. IDP can be easily differentiated from other ductal papillomas, such as intraductal papilloma and sialadenoma papilliferum. The intraductal papilloma is entirely confined within an encapsulated unicystic cavity, while sialadenoma papilliferum exhibits an exophytic growth pattern [4]. However, the most important lesion to distinguish from IDP is mucoepidermoid carcinoma because both IDP and this carcinoma contain epidermoid and mucous cells. However, IDP does not display the multicystic, multinodular, and infiltrative growth pattern of mucoepidermoid carcinoma [4].

Immunohistochemistry may help in the diagnosis and possibly in the determination of the origin of these lesions [11]. According to immunohistochemical studies, IDP most likely arises from the excretory duct near the oral mucosal surface where squamous differentiation occurs and the epidermoid cell component of IDP is the main feature [4,12]. Anti-CK and EMA antibodies are often a marker for cells of epithelial origin and are useful for evaluating the differentiation to the ductal epithelium. The expression of these CKs is frequently organ- or tissue-specific. For example, CK14 is found in the basal cells of the excretory ducts in the normal salivary gland [13], and it is also found in the basal cells of IDP. However, there is abundant expression of CK7 in normal luminal cells but only low expression levels in IDP. In our case, we observed the expression of CK and EMA in the tumor cells along with the moderate expression of CK7 and CK14 in the luminal and basal cells,

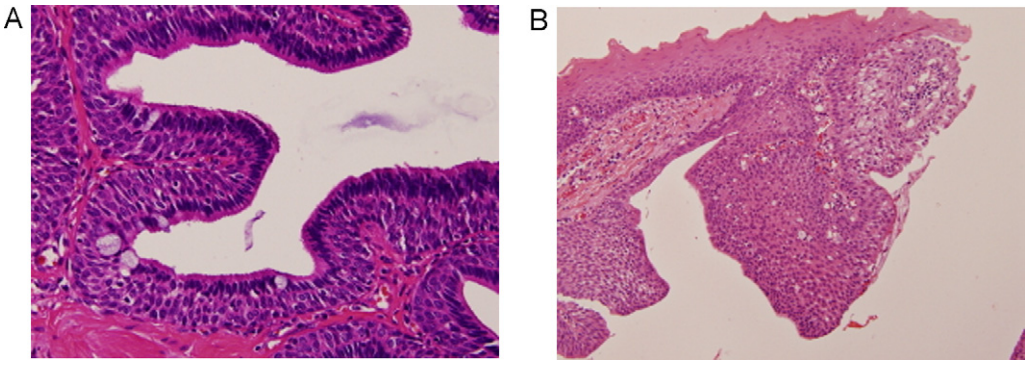

Fig. 3. A medium-power view of the tumor. (A) The tumor was mainly composed of basal epidermoid cells with no signs suggestive of malignancy, such as nuclear atypia. The luminal surface was lined with columnar epithelium with a few scattered mucinous goblet cells. (H&E, ×400.) (B) The covering epithelium was continuous with the tumor at the opening. (H&E, ×200.)

Table 1
Primary antibodies used immunohistochemical staining and immunoreactivity of tumor cells.

Antgen (Antibody)	Clonality	Dilution	Source	Immunoreactivity of tumor cells	
				Luminal surface side	Basal cell side
Cytokeratin 7 (OV-TL)	Mouse IgG	1:1000	Dako	++	+
Cytokeratin14 (LL002)	Mouse IgG	1:40	Novocastra	±	+
Cytokeratin19 (Ks19.1)	Mouse IgG	1:50	Progen	++	++
Cytokeratin 8 (CAM5.2)	Mouse IgG	1:10	Becton Dickin	++	±∼+
Cytokeratin1 – 8, 10, 14–16, 19 (AE1/AE3)	Mouse IgG	1:1	Roche	+	±∼+
Cytokeratin 1, 5, 10, 14 (34βE12)	Mouse IgG	1:1000	Dako	+	+
Epithelial membrane antigen (E29)	Mouse IgG	1:200	Dako	±	±
Calponin (CALP)	Mouse IgG	1:100	Dako	–	–
S-100	Rabbit polyclonal	1:8000	Dako	–	–
Vimentin (V9)	Mouse IgG	1:1000	Dako	–	–
Desmin (6F2)	Mouse IgG	1:400	Dako	–	–
α-Smooth muscle actin (1A4)	Mouse IgG	1:20,000	Sigma Chemical	–	–
p53 (DO7)	Mouse IgG	1:2000	Diyatoron	–	–
Carcinoembryonic antigen	Rabbit polyclonal	1:160	Kyowa Medex	–	–
Ki-67 (MIB-1)	Mouse IgG	1:1000	Dako	Labeling index: 0%	Labeling index: 3.96%

++: strong-positive reaction., +: moderate-positive reaction., ±: weak-positive reaction., –: non-reaction.

respectively. These results support the theory that the excretory duct near the oral mucosal surface are responsible for the origin of this neoplasm. In addition, Ki-67 was expressed only in the basal cells of the tumors with a labeling index of 3.96%. This result was indicative of the low level of proliferation. CEA and p53 were not expressed in the tumor cells. The negative for p53 was indicative of the benign character of the lesion [14]. Anti-calponin, S-100 protein, α-SMA, vimentin, and desmin antibodies can assess the myoepithelial differentiation in this lesion [15]. The tumor cells that we analyzed were negative for staining by all of these antibodies. This result indicated that the myoepithelial cells are not the progenitors of this lesion.

The pathogenesis of IDP remains unknown. However, some studies have associated the lesion with the human papilloma virus (HPV) or with chronic inflammation, such as the inflammation associated with masticatory trauma [16,17]. The pathogenesis of some nasal inverted papillomas is associated with HPV, especially types 6 and 11 [18]. The results of numerous studies have documented the results of HPV testing over 1000 cases of sinonasal papillomas. Through the use of methods including polymerase chain reaction and hybridization techniques, HPV was identified in 33.3% of these sinonasal papillomas [19]. In contrast, the association between HPV and oral IDP has not been sufficiently studied. In a review of the literature, we found only 9 cases of oral IDP that had been tested for

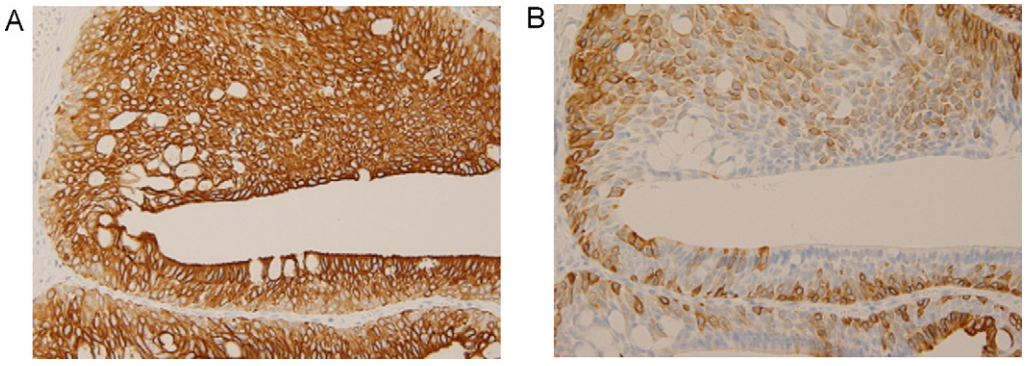

Fig. 4. Immunohistochemical staining of the tumor. (A) Positive immunoreactions for CK7. CK7 was predominantly expressed in the luminal cells of the tumors. (×400.) (B) Positive immunoreactions for CK14. CK14 was predominantly expressed in the basal cells of the tumors. (×400.)

HPV DNA with hybridization techniques. HPV types 6 and 11 were identified in 33.3% of these 9 cases of oral IDP [4,12,16,20]. Further studies are needed to determine the viral implications involved in the pathogenesis of this lesion [16].

IDP exhibits nonaggressive biologic behavior. No cases of malignant transformation or recurrence have been reported with IDP [21]. Therefore, simple local excision of the tumor is the most appropriate treatment [3].

When evaluating a nodular submucosal swelling with a punctum on the surface in the oral cavity, it may be difficult to provisionally diagnose the swelling as IDP because of the rarity of these lesions. However, IDP can be considered as a provisional diagnosis because of the typical clinical features.

References

[1] Clark DB, Priddy RW, Swanson AE. Oral inverted ductal papilloma. *Oral Surg Oral Med Oral Pathol* 1990;69:487–90.
[2] Hegarty DJ, Hopper C, Speight PM. Inverted ductal papilloma of minor salivary glands. *J Oral Pathol Med* 1994;23:334–6.
[3] Brannon RB, Sciubba JJ, Giulani M. Ductal papillomas of salivary gland origin: a report of 19 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;92:68–77.
[4] Cabov T, Macan D, Manojlović S, et al. Oral inverted ductal papilloma. *Br J Oral Maxillofac Surg* 2004;42:75–7.
[5] Suh KW, Facer GW, Devine KD, et al. Inverting papilloma of the nose and paranasal sinuses. *Laryngoscope* 1977;87:35–46.
[6] Caro DJ, Tessler A. Inverted papilloma of the bladder: a distinct urological lesion. *Cancer* 1978;42:708–13.
[7] Matz LR, Wishart VA, Goodman MA. Inverted urothelial papilloma. *Pathology* 1974;6:37–44.
[8] Fechner RE, Sessions RB. Inverted papilloma of the lacrimal sac, the paranasal sinuses and the cervical region. *Cancer* 1977;40:2303–8.
[9] Radclifee A. Transitional cell papilloma of the post-pharyngeal wall. *J Laryngol Otol* 1953;67:682–8.
[10] Hyams VJ. Papillomas of the nasal cavity and paranasal sinuses. A study of 315 cases. *Ann Otol Rhinol Laryngol* 1971;80:192–206.
[11] Regezi JA, Lloyd RV, Zarbo RJ, et al. Minor salivary gland tumors. A histologic and immunohistochemical study. *Cancer* 1985;55:108–15.
[12] Scolyer RA, Rose B, Painter DM. Test and teach. Number ninety six: Part 1. Inverted duct papilloma of minor salivary gland origin. *Pathology* 1999;31:423–4.
[13] de Sousa SO, Sesso A, de Araújo NS, et al. Inverted ductal papilloma of minor salivary gland origin: morphological aspects and cytokeratin expression. *Eur Arch Otorhinolaryngol* 1995;252:370–3.
[14] Terada T. Ductal adenoma of the breast: immunohistochemistry of two cases. *Pathol Int* 2008;58:801–5.
[15] Ren J, Liu Z, Liu X, et al. Primary myoepithelial carcinoma of palate. *World J Surg Oncol* 2011;9:104.
[16] Koutlas IG, Jessurun J, Iamaroon A. Immunohistochemical evaluation and in situ hybridization in a case of oral inverted ductal papilloma. *J Oral Maxillofac Surg* 1994;52:503–6.
[17] Rangel AL, Jorge JJ, Vargas PA. Oncocytic metaplasia in denture hyperplasia. Is it a rare occurrence? *Oral Dis* 2002;8:227–8.
[18] Kashima HK, Kessis T, Hruban RH, et al. Human papillomavirus in sinonasal papillomas and squamous cell carcinoma. *Laryngoscope* 1992;102:973–6.
[19] Syrjänen KJ. HPV infections in benign and malignant sinonasal lesions. *J Clin Pathol* 2003;56:174–81.
[20] Haberland-Carrodeguas C, Fornatora ML, Reich RF, et al. Detection of human papillomavirus DNA in oral inverted ductal papillomas. *J Clin Pathol* 2003;56:910–3.
[21] Kubota N, Suzuki K, Kawai Y, et al. Inverted ductal papilloma of minor salivary gland: case report with immunohistochemical study and literature review. *Pathol Int* 2006;56:457–61.