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# Oral inverted ductal papilloma: not related to HPV

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## Abstract

Oral inverted ductal papilloma (OIDP) is a rare, non-recurrent, benign lesion of salivary glands. The etiology is still poorly understood; the correlation with human papilloma virus (HPV) is controversial. Herein we present a 74-year-old man with a tumor in lower lip. Incisional biopsy was performed and the histological diagnosis was OIDP. Inno-LiPA assay, based on polymerase chain reaction and in situ hybridization was used to assess for HPV with no detection of viral DNA. Surgical excision was performed without any recurrences after two years of follow-up.

*Keywords: oral inverted ductal papilloma, salivary glands tumors, HPV*

## Introduction

Inverted papilloma is a common alteration seen in upper airway (nasal cavity and paranasal sinuses), cervix, urinary tract, and lacrimal sac [1]. Oral inverted ductal papilloma (OIDP) was first described by White et al. in 1982 [2], and graded as a papillary salivary gland tumor, along with intraductal papilloma and sialadenoma papilliferum [1, 3]. This tumor is a rare benign neoplasm derived from the duct system of the minor salivary glands [1-3]. OIDP affects mostly middle-aged men and the differential diagnosis includes mucocele, squamous papilloma, fibroma, and some malignant processes such as mucoepidermoid carcinoma [1, 3, 4].

Histologically, OIDP exhibits an inversion of the proliferating epithelium, represented by an endophytic proliferation of the duct epithelium associated with a nodular mass. Owing to this appearance, the typical clinical aspect resembles a submucous nodule associated with an increase in volume and mucosal erythema instead of a warty appearance, which is clearly evidenced in oral papilloma [5]. The real incidence of OIDP is not clear, owing to the rarity of the lesion and the variation in terminologies used to describe this entity. It is also named papillary cystadenoma [5]. Anatomically, lip and buccal mucosa are the most affected sites in the oral mucosa [1, 3, 5].

Although the etiopathogenesis of the lesion is still obscure, some authors discuss a possible role of



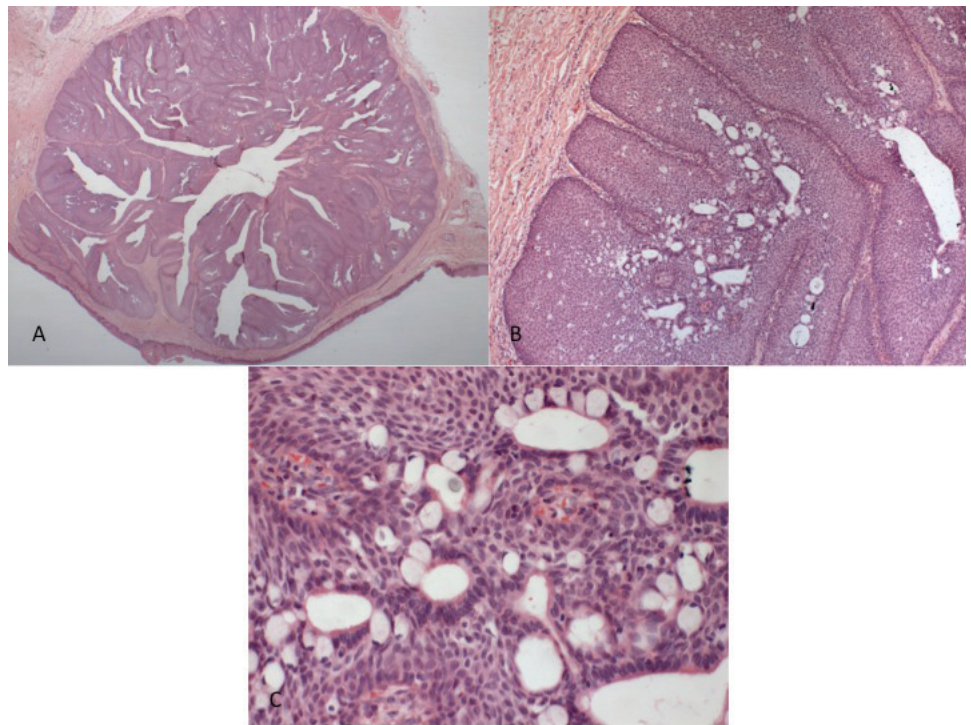
**Figure 1.** Submucosal nodule with ulcerated surface in the lower lip

human papilloma virus (HPV) in the pathogenesis of OIDP [6, 7].

### Case Synopsis

A 74-year-old man was referred to our clinic for evaluation and treatment of a painless tumor of 3 months duration located in the left lower lip. The patient reported alcohol consumption and tobacco use. In addition, a medical history of diabetes and a recent cardiovascular surgery were report during the consultation. Oral examination revealed an asymptomatic, firm, submucosal nodule with ulcerated surface of 2.0 cm in diameter in the lower lip (**Figure 1**). Based on clinical aspects, the differential diagnosis was squamous cell carcinoma and mucoepidermoid carcinoma. An incisional biopsy was performed and the histological analysis revealed a well-circumscribed luminal papillary proliferation filling the superficial lumen of an excretory duct of the minor salivary gland. The tumor was continuous with the superficial squamous epithelium of the oral mucosa, growing in an inverting pattern and consisting of immature squamous or basaloid epithelium, showing no evidence of cytological atypia. In addition, numerous mucinous goblet cells and microcysts were found (**Figure 2**). Immunohistochemistry was positive for cytokeratins 7, 13 and 14. Based on these histopathological findings, the final diagnosis was OIDP. The treatment was the complete surgical excision of the lesion (**Figure 1**). No signs of recurrence were observed after 2 years of follow-up.

In order to identify the presence of HPV, the inno-LiPA assay (Innogenetics, Gent, Belgium) was performed. This assay utilizes the SPF10 consensus primer system to amplify a 65-bp fragment of the L1 region of HPV, followed by reverse line blot hybridization to HPV type-specific immobilized probes for 18 high-risk/possibly high-risk and 7 low-risk HPV types. The lesion was negative for HPV.



**Figure 2.** Histopathological features of the oral inverted ductal papilloma. A, B. Papillary proliferation in an inverted pattern of immature squamous or basaloid epithelium. H&E, original magnification A, 25x; B, 100x. C. Numerous intermixed mucinous goblet cells and multicystic region. H&E, original magnification 400x.

### Case Discussion

Inverted ductal papilloma is a rare benign tumor of the minor salivary glands, mainly affecting both buccal mucosa and lower lip. The tumor exhibits a slight predominance among middle-aged males. Clinically, the lesion arises as an asymptomatic, submucous nodule, usually not exceeding 1.5 cm in diameter. This case fits the classic description of the lesion, except for the ulcerated surface, which in our case is likely to be related to secondary trauma [4, 8, 9].

Macroscopically, these nodules may or may not appear as papillary masses and occasionally exhibit cystic spaces after sectional incision. Histologically, the OIDP can resemble a non-encapsulated endophytic epithelial mass; this squamous epithelium can be surrounded or not by a fibrous stroma. A microcystic space also can be seen within the fibrovascular connective tissue stroma, presenting mucous, columnar, and cuboidal cells in the luminal surface [4, 10].

The differential diagnosis includes other tumors of the minor salivary glands such as intraductal papilloma,

inverted oral papilloma, sialadeloma papilliferum, and mucoepidermoid carcinoma [6, 11]. The main characteristics differentiating these lesions are the presence of exclusively endophytic sub-epithelial components (which do not surpass the mucous surface), origin from the excretory duct close to the mucous surface, and epidermoid cells and mucosa with mixed-architecture. Normally, the lesions do not exhibit multinodular and multicystic areas as seen in the mucoepidermoid carcinoma [1].

Some studies have suggested an association between cells of the excretory duct glands and cells of the mucous surface [9]. Immunohistochemical studies have demonstrated positivity for some epithelial markers in these tumors and for cytokeratins in the duct lumen [1, 5, 7, 8, 10, 13, 14, 19]. These results support the theory that the excretory duct close to the oral mucosal surface accounts for the emergence of such a neoplasm [6, 9].

For many authors the pathogenesis of inverted ductal papilloma was considered controversial [6-14]. Some studies point to an association between the lesion and HPV. In a series of 6 cases of inverted ductal papilloma, 50% were positive for HPV-6 and HPV-11 by means of in situ hybridization [7]. Other authors have described the presence of HPV-11 in cases of inverted ductal papilloma associated with condyloma acuminatum in the oral cavity of a HIV-positive woman [6]; this association could be attributed to the presence of the latter lesion. Other case reports using different techniques found no positivity for the HPV [9, 12]. In the present case, no positivity was found for the 25 subtypes (high and low risk) analyzed by using the Inno-Lipa technique, which is very sensitive and specific for the detection of HPV.

For this reason, the literature has not shown any conclusive evidence regarding the participation of HPV in the etiopathogenesis of inverted ductal papilloma, with most of the cases presenting negativity for the virus [9, 13]. In a recent report, the authors retrospectively evaluated 36 consecutive patients diagnosed with nasal inverted papilloma, with just one case positive for HPV (2.7%) by in situ hybridization for low-risk HPV (5 genotypes) and high-risk HPV (13 genotypes). This further substantiates

the lack of evidence for HPV participation in the pathogenesis of inverted papillomas. These findings were also corroborated by our case report. Trauma was considered a possible etiological factor in two more recently published case reports [9, 12].

## Conclusion

In conclusion, there is no conclusive evidence of HPV participation in the etiopathogenesis of OIDP. The correct diagnosis of OIDP is extremely important, since mucoepidermoid carcinoma is in the differential diagnosis. Total excision of the lesion is the preferred method of treatment, with no reports of recurrence or malignant transformation.

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