

Inverted papilloma (Schneiderian papilloma) with involvement of the oral cavity: report of an unusual case *

Papiloma invertido (Papiloma Schneideriano) com envolvimento da cavidade oral: relato de caso incomum

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Abstract: Inverted Schneiderian papilloma (ISP) is a neoplasm of epithelial lining origin which arises in the respiratory mucosa that lines the nasal cavity and paranasal sinuses. The inverted Schneiderian papilloma frequently appears as a unilateral lesion in the nasal septum and extends secondarily to the nasal and paranasal sinuses. This paper reports an unusual case of this pathology with involvement of the oral cavity in a 61-year-old white man. Clinical evaluation revealed a vegetating mass in the alveolar ridge of the right maxilla that had been present for approximately 4 months. After radiographic evaluation, involvement of the maxillary sinus was detected. Microscopic evaluation, in situ hybridization and immunohistochemical analysis of the specimen led to a diagnosis of ISP moderate dysplasia associated with HPV infection.

Keywords: Immunohistochemistry; In Situ Hybridization; Papilloma, inverted; Pathology, oral

Resumo: O papiloma invertido schneideriano é uma neoplasia de origem no epitélio de revestimento que surge da mucosa respiratória revestindo a cavidade nasal e os seios paranasais. Frequentemente, surge como uma lesão unilateral no septo nasal e estende-se secundariamente para o nariz e os seios paranasais. Este trabalho relata um caso incomum desta patologia, com o envolvimento da cavidade oral em um homem branco, de 61 anos de idade, cuja avaliação clínica revelou uma massa vegetante no rebordo alveolar direito da maxila, com duração de aproximadamente 4 meses. Após avaliação radiográfica, constatou-se o envolvimento do seio maxilar. A análise microscópica, hibridização in situ e análise imunoistoquímica da peça cirúrgica levaram a um diagnóstico de displasia moderada em PIS associado à infecção por HPV. **Palavras-chave:** Hibridização In Situ; Imuno-histoquímica; Papiloma invertido; Patologia bucal

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INTRODUCTION

Inverted Schneiderian papilloma (ISP) is a neoplasm of epithelial lining origin, with onset on the respiratory mucosa that lines the nasal cavity and paranasal sinuses, also known as Schneiderian membrane.¹ Three morphologically distinct forms of Schneiderian papilloma may be detected: inverted papilloma, oncocyctic papilloma and exophytic papilloma. The oncocyctic papilloma has not been associated with the human papillomavirus (HPV), in contrast with the inverted papilloma and the exophytic papilloma, which may undergo squamous metaplasia and verrucous proliferation. Approximately 20% of the ISP may present several degrees of epithelial dysplasia, which confers a malignant potential to this type of tumor.² The ISP frequently appears as a unilateral lesion on the nasal septum that extends secondarily to the nasal cavity and paranasal sinuses.³ The present study reports an unusual ISP case with oral cavity involvement. Furthermore, the immunohistochemical profile of this type of tumor and its association with HPV were evaluated.

CASE REPORT

A 61-year old white man, with no signs of nasal obstruction, presented an exophytic mass on the right alveolar border of maxilla for approximately 4 months, with two recurrence episodes after surgical removal (Figure 1). The lesion was white-reddish and of vegetating aspect, bleeding after palpation. The patient reported history of dental extraction from the site that had taken place 5 months before. The panoramic X-ray revealed a radiodense image that occupied the entire right maxillary sinus (Figure 2). Surgery was performed through the oral cavity, under general anesthesia. A reddish mass was removed, mea-

suring around 6 cm in diameter, which apparently was not adhered to the sinus cavity walls. The sample was sent to the oral pathology laboratory and analyzed by routine procedure, with slides stained using the hematoxylin-eosin technique. The histopathological analysis revealed papilliferous projections lined by keratinized and nonkeratinized squamous epithelium, with invagination areas directed to the stroma (Figure 3A) and koilocytes in the superficial layers (Figure 3B). In some of the basal and parabasal layer areas, hyperchromatic cells could be observed, with voluminous nuclei and scarce cytoplasm and mitotic figures. The connective tissue was edematous. Vascular congestion and discreet mononuclear inflammatory infiltrate were also observed (Figures 3 and 4A). On this occasion, the mass was diagnosed as moderate epithelial dysplasia associated with infection by HPV. The case was analyzed and diagnosed as ISP.

An *in situ* hybridization was requested to obtain additional data for discussion and positive results were obtained for HPV of the types that present low (6/11) and high risk (16/18) for malignancy (Figure 4B). In addition, an immunohistochemical study was carried out for detection of p53, p21, Ki-67 and CD44v6. Ki-67 is a cell proliferation marker, p53 and p21 verify if cell transformation is taking place and CD44v6 verifies whether there is cell adhesion alteration.

Positive staining was classified as weak, moderate and strong, according to the positive cells rate (<20%, 20-40% and > 40%, respectively). Immunohistochemistry was negative for p53, weakly positive for p21, moderately positive for Ki-67 in the several layers in the lower third of the epithelium (Figure 5) and strongly positive for CD44v6 in nondysplastic epithelial areas (Figure 6A). The dysplastic areas



FIGURE 1: White-reddish verrucous mass located on the right alveolar border of maxilla



FIGURE 2: Panoramic X-ray revealing increased radiodensity in the right maxillary sinus

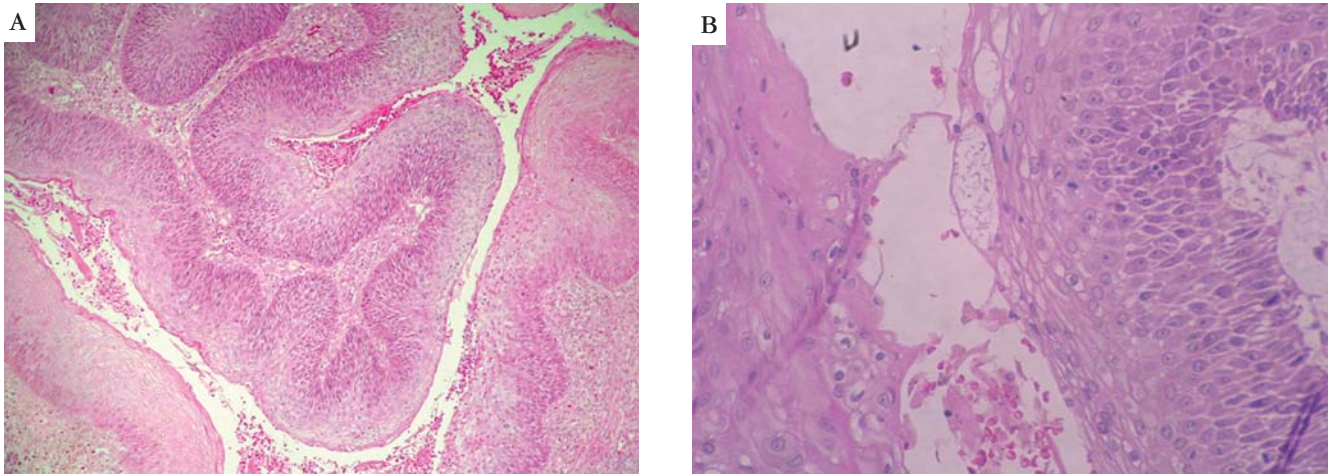


FIGURE 3: A. Papilliferous projections spread over the entire tumor (hematoxylin and eosin, 100x); B. Presence of koilocytes in the more superficial layers (hematoxylin and eosin, 400x)

of the neoplasm presented reduced CD44v6 expression (Figure 6B). The patient had not shown any signs of recidivism in two years after surgery.

DISCUSSION

The ISP case here described had its onset in the paranasal sinuses and grew toward the oral cavity, possibly due to buccosinusal communication resulting from dental extraction in the region. The X-ray image of the maxillary sinus lesion, as well as the histological analysis of the sample removed defined the ISP diagnosis.

The dysplastic areas in the epithelium lining the lesion and the confirmation of presence of high-risk HPV through *in situ* hybridization corroborate its malignization potential. According to Depprich et al.⁴, ISP may evolve into a verrucous carcinoma or a squamous-cell carcinoma, with possible involvement of HPV in the malignant transformation process.

According to the WHO, the malignization potential of ISP may also be related to keratinization of lesions, since in most cases its lining epithelium is keratin-free.⁵ The keratinized squamous epithelium areas found in our case may result from communication of the lesion with the oral cavity. According to Nair et al.⁶, the squamous metaplasia undergone by ISP in some situations and the clinical acquisition of a verrucous aspect may be reasons for diagnostic error, as the lesions are easily mistaken for verrucous carcinoma.

Thus, it is important to emphasize that the term epithelial dysplasia is employed when there are morphological and architectural alterations that may involve some layers or the entire epithelium, characterizing the lesion as potentially malignant. In accordance with the findings in this case, we may consider ISP as an epithelial hyperplasia induced by HPV, that may present alterations ranging from dysplasia to carcino-

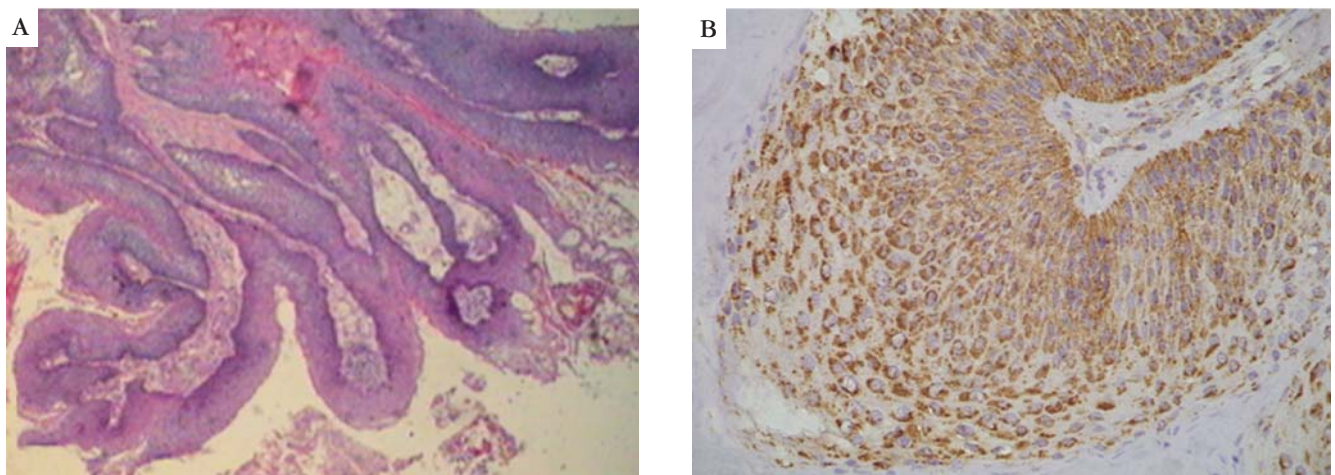


FIGURE 4: A. A view with small increase showing a papilliferous epithelial proliferation with central areas of edematous connective tissue (hematoxylin and eosin, x100); B. Hybridization in situ revealing positivity for HPV (original x400)

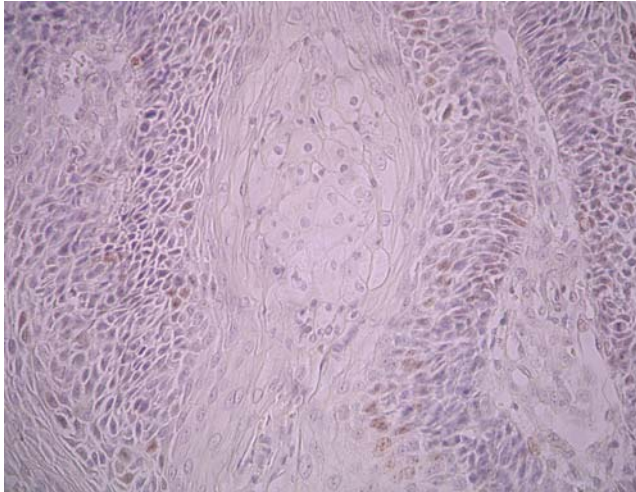


FIGURE 5: Neoplastic basal and suprabasal cells exhibiting positivity for Ki-67 (streptavidin-biotin complex, 400x)

ma. The epithelial dysplasia was evidenced by epithelium disorganization, as well as by immune reactions of the markers utilized.

It is a fact that HPV has oncogenic potential, since benign hyperplastic lesions induced by the virus may undergo neoplastic transformation. Moreover, the difficulty for histopathological and clinical delimitation of these lesions is well known, as there may be the beginning of incipient neoplasia in the borderline region of the hyperplasia.⁷ Thus, we point out to the importance of utilization of immunohistochemical markers in supplementation of morphological findings for verification of potential for cellular proliferation and lesion prognosis.^{8,9}

The removal of papilloma lesions by invasive methods, such as electrodissection, cryosurgery and/or laser therapy may be successful and could be

combined with topical application of podophyllotoxin, trichloroacetic acid, 5-fluorouracil gel, epinephrine, topical chemotherapy, cidofovir or interferon.¹⁰ In the present study, surgery was conservative and no sign of relapse was observed during two years of preservation. It should be emphasized that the nasal septum was not involved.

The absence of staining for p53 and the weak markings for p21 may be related to a possible inactivation of E6 and E7 viral proteins respectively, which would make the tissue more susceptible to malignant transformation, as it occurs in the presence of high-risk HPV, leaving the tissue susceptible to malignant transformation by additional mutations.¹¹ However, the tumors associated with HPV infection usually have better prognosis, since they rarely overexpress p53 and p21.¹² The moderate Ki-67 expression, involving the two lower thirds of the epithelium, mainly in nonkeratinized areas, is corroborated by report of Saegusa et al.⁹, who attributed a better prognosis to keratinized tumors, as Ki-67 expression is higher in nonkeratinized tumors and in little differentiated areas. Dysplastic epithelium areas showed reduced CD44v6 expression, while nondysplastic areas presented strong immunomarking. According to Ogawa et al.¹³, CD44 expression suggests a lower risk for metastasis, with indication of conservative treatment in cases of squamous-cell carcinoma.

These results suggest that HPV may be involved in the IPS malignant transformation process and it is an early event in tumor progression. The immunohistochemical panel presented in this report was adequate to verify the occurrence of cell proliferation and transformation in the affected tissue, as well as to study the prognosis for the case. □

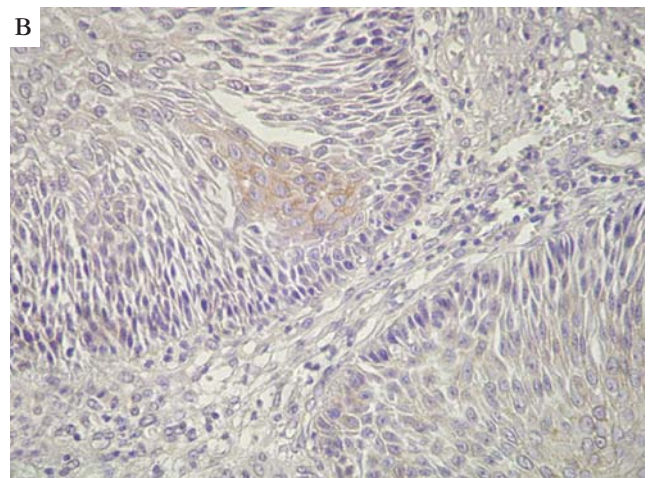
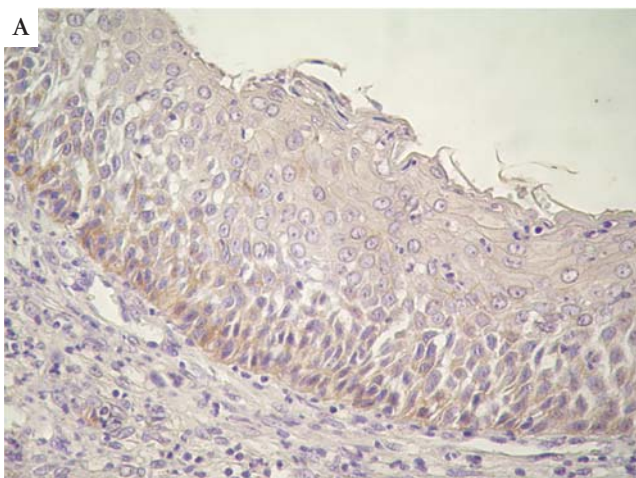


FIGURE 6: A. Reduced immunoreactivity for CD44v6 in areas with epithelial dysplasia (streptavidin-biotin complex, 400x); B. Strong immunoreexpression for CD44v6 in areas without epithelial dysplasia (streptavidin-biotin complex, 400x)

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