

# Extensive Papillomatosis of the Palate Exhibiting Epithelial Dysplasia and HPV 16 Gene Expression in a Renal Transplant Recipient

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## ABSTRACT

We report a unique case of extensive papillomatosis of the palate in a renal transplant recipient. The condition resembled inflammatory papillary hyperplasia; it exhibited severe epithelial dysplasia and concurred with generalized gingival hyperplasia. We document and discuss the probable multifactorial etiology of the lesions, including evidence for human papillomavirus (HPV) type 16 expression, as detected by in situ reverse transcription polymerase chain reaction. This report illustrates the need for careful clinical investigation and follow-up of immunosuppressed individuals presenting with apparently benign, common oral lesions.

**MeSH Key Words:** adult; papillomavirus, human; renal transplantation; tumor virus, infections/virology

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An increasing body of molecular-epidemiological evidence indicates that some types of oncogenic human papilloma virus (HPV) are associated with intraepithelial neoplasia. The causal relation between HPV 16 and subgroups of squamous cell carcinoma of the head and neck has been established,<sup>1</sup> and HPV 16 gene expression has been reported as frequent in distinct types of oral mucosal lesions, such as koilocytic dysplasia<sup>2</sup> (including lesions described as bowenoid)<sup>3</sup> and proliferative verrucous leukoplakia.<sup>4</sup> Nevertheless, a distinct classification of HPV-associated lesions according to unique histopathologic features or clinical behaviour is yet to crystallize. In some recurrent exophytic lesions suspected of being virally induced, such as that described by Brown and others<sup>5</sup> as atypical papillomatosis, HPV infection could not be detected despite state-of-the-art laboratory testing.

Here we illustrate a case of extensive papillomatosis of the palatal mucosa, concurring with general gingival enlargement in a renal allograft recipient. The microscopic features of an initial incisional biopsy of the palatal lesion were consistent with inflammatory papillary hyperplasia, but the excised lesion was found to harbour HPV 16 and to exhibit severe epithelial dysplastic changes.

## Case Description

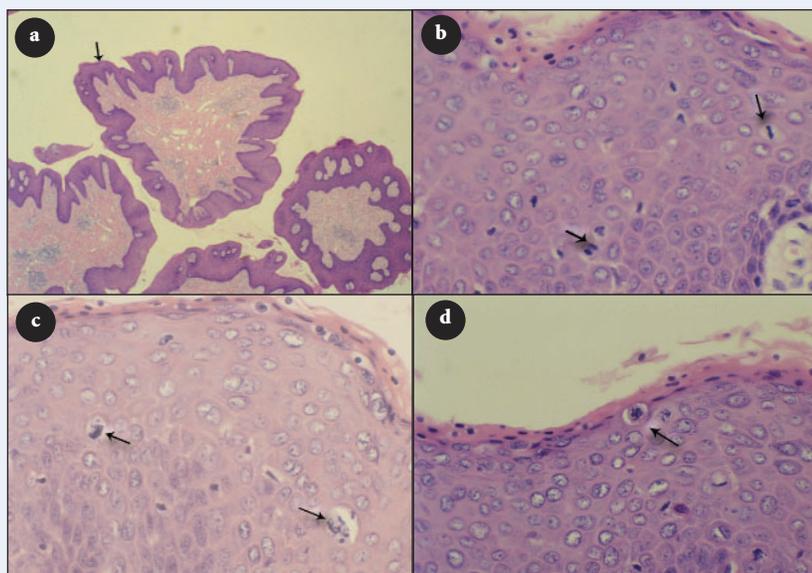
A 45-year-old man was referred for periodontal consultation for generalized enlargement of the maxillary and mandibular labial gingiva. His history included hypertension, parathyroidectomy for hyperparathyroidism, papillary carcinoma of the thyroid gland and renal transplantation for end-stage renal disease. In the 5 years since transplantation, his medications consistently included immuno-



**Figure 1a:** The palatal lesion at the initial presentation.



**Figure 1b:** Labial gingivae at initial presentation.



**Figure 2:** Photomicrographs of sections from the excised palatal lesion. **a.** The arrow indicates the epithelial area shown at higher magnification in images b to d. **b.** Note frequent mitotic figures (arrows). **c and d.** Note the distribution of atypical nuclei in the upper third of the epithelium (arrows).

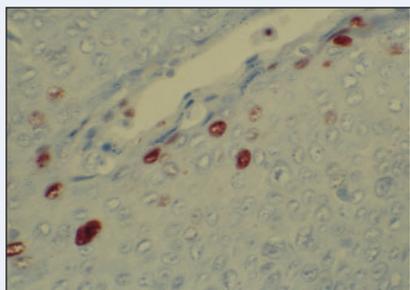
suppressant drugs (cyclosporine, prednisone and azathioprine) and antihypertensive medication (nifedipine and furosemide). At the time of presentation, he was also taking ranitidine for the treatment of gastritis. He reported having smoked half a pack of cigarettes a day for 20 years and having consumed moderate amounts of alcohol.

Intraoral examination revealed generalized gingival enlargement, which appeared typical of that defined as drug-induced, as well as a diffuse, erythematous, papillated lesion of the hard palatal mucosa exhibiting a superficial, white pseudomembrane (Fig. 1a). The onset of the gingival lesion (Fig. 1b) was uncertain and its progression slow. According to the patient, the palatal lesion had been present for approximately 3 months and had been increasing in size. The patient had not worn a maxillary denture and his general oral hygiene was fair.

An incisional biopsy of the palatal lesion was performed. The microscopic features of the specimen were consistent with inflammatory papillary hyperplasia; they included typical architecture, pseudoepitheliomatous epithelial hyperplasia, the presence of densely collagenous subepithelial connective tissue and infiltration by chronic (predominantly lymphoplasmacytic) inflammatory cells. The superficial epithelium was colonized by fungal hyphae consistent with candidiasis. Initial treatment with topical nystatin cream caused the erythema to abate, but the palatal lesion persisted and continued to cause discomfort. The patient was referred to an oral maxillofacial surgery clinic, where the palatal lesion was excised by scalpel, and the palatal and labial maxillary and mandibular gingivae were recontoured by looped-wire cautery.

Microscopic examination of the excised specimen confirmed that the general architecture of the lesion was consistent with that of inflammatory papillary hyperplasia, but revealed a focal area exhibiting epithelial dysplasia, including frequent mitotic figures and atypical nuclei (Fig. 2) involving the full thickness of the epithelium. As the dysplastic features were reminiscent of HPV-associated bowenoid changes that we had observed previously,<sup>4</sup> HPV-typing by DNA in situ hybridization (with test probes for type-groups 6/11, 16/18 and 31/33/35), immunohistochemistry (with a genus-specific anti-HPV antibody), as well as reverse transcription polymerase chain reaction (with HPV 16 E6 gene-specific primers) were performed as described in detail previously.<sup>6</sup> Taken together, the test results confirmed the presence of HPV type 16 in the lesion. The results of in situ hybridization with the type-group 16/18 probe are shown in Fig. 3. As neither the clinical nor the microscopic features were consistent with Kaposi's sarcoma, testing for Kaposi's sarcoma-associated herpesvirus (KSHV) was not performed.

The patient was referred for further follow-up at a head and neck cancer treatment centre. By the second month post-surgery, the palatal excision site was almost completely healed with minimal papillomatosis still discernible (Fig. 4). The entire oral mucosa was normal in



**Figure 3:** Positive staining revealed by in situ hybridization with the HPV type-group 16/18 probe.



**Figure 4:** View of the palate in the second month after surgery.

appearance. The findings of indirect laryngoscopy were normal. At subsequent follow-up examinations (every 2–3 months for the following 2 years), no recurrence of the palatal lesion or neck lymphadenopathy was found on visual inspection or by palpation. The patient was lost for oral follow-up thereafter.

### Discussion

We document a case of in situ epithelial dysplasia–carcinoma presenting initially as inflammatory papillary hyperplasia. The clinical presentation and the general architecture of the biopsy specimens were congruent with the classical definition of inflammatory papillary hyperplasia of the palate, except that the most usual causative factors, i.e., ill-fitting dentures and poor oral hygiene, were absent.

The usual treatment of inflammatory papillary hyperplasia is surgical excision, complemented by antifungal therapy when fungal infection is identified as a cofactor. Mucocutaneous, HPV-associated wart-like lesions, including those of the gingiva,<sup>7</sup> have been treated with some success with the nucleotide analogue cidofovir; and immune-response modifiers, such as imiquimod, singly or in combination with antiviral agents, appear promising in the reversal of early intraepithelial neoplasias.<sup>8</sup> We considered, but did not carry out, antiviral therapy for our patient, as surgery yielded adequate clinical results.

In the case presented here, the laboratory findings were in keeping with our previous data suggesting that immunosuppressed individuals are at heightened risk of premalignant and malignant exophytic epithelial changes in oral lesion associated with HPV 16 infection.<sup>6</sup> Furthermore, the atypical nuclei seen in the excisional biopsy specimen were reminiscent of those reported previously in HPV-associated bowenoid dysplasia.<sup>4</sup>

A general propensity for oral epithelial neoplasia is apparent in immunosuppressed allograft recipients. One

interesting example is reported by Regev and others.<sup>9</sup> We could not exclude the mere coincidental association between the diffuse papillary lesion and HPV 16 expression, as the presence of HPV is found in a significant proportion of normal biopsy specimens. Nevertheless, in light of our knowledge of HPV 16 oncogenicity and considering previous studies, it would be more reasonable to assume that HPV 16 gene expression in inflammatory papillary hyperplasia may induce intraepithelial neoplasia.

Further arguments in favour of a role for various types of HPV in the pathogenesis of AIDS-associated oral mucosal lesion are presented in a report by Anderson and others.<sup>10</sup> However, prospective molecular–epidemiological studies are needed to prove or disprove the potential role of HPV infection in progression to malignancy in oral exophytic lesions of immunosuppressed individuals. Furthermore, in the case presented here, one cannot dispute that cyclosporine, singly or in combination with nifedipine, contributed to the collagenous connective tissue buildup of the palatal lesion by contiguity with the gingival lesion as, individually, each of these drugs is known to induce gingival hyperplasia. Interestingly, HPV is frequently detectable in cyclosporine-induced gingival overgrowth in immunosuppressed transplant recipients<sup>11</sup>; therefore, HPV infection may be a cofactor in such cases. Unfortunately, in the current case, sufficient gingival tissue was not available for HPV testing, as the gingival lesion was reduced by cautery.

This case is presented not merely as an argument for the probable role of HPV infection in atypical papillary hyperplasia of the palate, but also as an example of the probable multifactorial etiology of concurrent exophytic lesions. Unfortunately, the patient was lost for long-term oral follow-up. Nevertheless, in transplant recipients, strict adherence to the principles of the management of the immunosuppressed, including “frequent oral health assessments for interception of emerging oral problems, maintenance, and reinforcement of good oral care,”<sup>12</sup> is imperative. In such cases, laboratory screening for HPV expression is essential, considering new emerging antiviral treatment modalities. The reporting of new cases would further demonstrate the need for careful clinical follow-up of organ transplant recipients presenting with apparently common oral lesions, and would contribute to the identification of appropriate target populations for anti-HPV vaccination. ♦

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