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CASE REPORT

Recurrent p16-Positive Human Papillomavirus (HPV) Associated Oral Lesions Treated with a Diode Laser: A Case Report

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ABSTRACT

Human papillomavirus (HPV) family comprises approximately 150 known subtypes of viruses that can infect humans and other animals. Among these, HPV-16 has been shown to be associated with oral squamous cell carcinoma, particularly within the oropharynx. Here we describe the case of a patient with recurrent p-16 positive papillomatous lesions, which were successfully treated via a diode laser (445 nm) surgery. Radical treatment of HPV-related lesions can be difficult to achieve. Notably, some viruses may infect multiple oral sites and spread throughout the whole mucosa. Even after the supposed radical intervention, HPV particle remnants may lead to recurrences and new lesions. A new laser approach allows radical surgery to be performed, providing an effective method for the treatment of widespread lesions, similar to those reported here. **Objective:** To report a recurrent p-16 positive oral papillomatous lesion treated with a diode laser. **Case report:** A 26-year-old man with multiple p-16 positive oral papillomatous lesions was referred for recurrences after treatment with conventional surgery (cold knife). The lesions were successfully treated via diode laser (445 nm) surgery with no recurrence observed during the 6-month follow up. Histological examination showed immunohistochemical positivity for p16. **Conclusions:** Radical surgical treatment of HPV-related lesions is important to prevent recurrence and malignant transformation. Laser surgery represents an innovative treatment option.

Key words: oral HPV lesions, diode laser surgery, papilloma

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INTRODUCTION

Human papillomaviruses (HPVs) are a group of DNA viruses characterized by epithelial tropism. To date, over 150 HPV subtypes have been identified. HPVs are ubiquitous and can infect humans through several routes, most frequently by sexual transmission.¹ It has been shown that there is a strong correlation between the frequency of infection and both the typology of sexual activities and the number of partners.^{1,2}

HPV infection is associated with a variety of benign, precancerous, and malignant lesions of the cutaneous and mucous squamous epithelium. The following are some examples of benign lesions: squamous papilloma, verruca vulgaris, condyloma acuminata, and focal epithelial hyperplasia.³ HPV 11, 16, and 18 are strongly

associated with malignant transformation, especially in the oropharynx.⁴ HPV 11, 16, and 18 are found within the neoplastic cells. Of note, the hypothesis of their oncogenic potential is supported by several observations: the virus's epithelial tropism, the well-known etiologic role of HPV in almost all squamous cell carcinomas (SCC) of the uterine cervix and in approximately 40% of the cases of other SCCs, and the histological similarities between the epithelium of the uterine and oral mucous membranes.⁵ As a consequence, all HPV-related lesions should be cured owing to the risk of the virus spreading to other anatomic sites and HPV 16 inducing malignant transformations.

The gold standard for the treatment of HPV lesions is surgical excision; however, this technique faces the possibility of multiple recurrences.⁴ Radical excision using a cold blade may be somewhat difficult, particularly for widespread lesions and for lesions in anatomical sites (e.g., the hard palate) where a first intention closure would be either difficult or induce scars which could potentially limit oral functionality. Laser surgery represents a better surgical approach compared to a traditional approach. Specifically, laser surgery allows the achievement of good hemostasis and lower post-surgical morbidity. The histopathological examination, possibly accompanied by viral genotyping, is crucial for a definitive diagnosis of HPV-induced papilloma.²

Here we report the case of a 26-year-old man with multiple, recurrent p-16 positive papillomatous lesions. The patient was successfully treated through diode laser (445 nm) surgery.

CASE REPORT

A 26-year-old male was referred by his dentist to the Department of Oral Medicine and Surgery of the University of Parma (Italy), due to recurrent exophytic lesions in the hard palate. The patient reported that the lesions had appeared one year ago and that they had been treated by surgical removal twice. Nevertheless, the lesions recurred on both occasions. A histopathological report was not available. The ethics guidelines of the University of Parma were followed for the development of the present case report. Informed consent was obtained from the patient for the use of his data.

The clinical examination revealed the presence of multiple diffuse sessile papillomatous lesions, covering an area of almost 2 x 2 cm (Figure 1a). Other lesions (size of approximately 1 mm) were evident on the left palatal molar area and on the dorsum of the tongue (Figures 1b and 1c).

The anamnesis did not disclose any medical problems. Additionally, the patient had a negative history of alcohol and/or tobacco habits. No allergies to food or drugs were recorded. Data on recent orogenital activity were not available. The patient reported the presence of a verrucous lesion on one hand; this was recently removed by a dermatologist.

Based on the possible presence of immunodeficiency, a thorough blood examination was performed. Laboratory tests included screening for viruses such as human hepatitis viruses B and C (HBV and HCV) and human immunodeficiency virus (HIV); all the results were negative.

An excision including 0.5 cm of the clinically healthy margins was performed around the palatal exophytic lesions. Additionally, the remaining oral lesions were removed. Surgery was performed under local anesthesia using a diode laser (445 nm–3.5 W, continuous wave) (Figures 2a-i)

The histopathological evaluation confirmed the diagnosis of a papilloma with mild epithelial dysplasia, probably of a viral origin (Figure 3). Immunohistochemical positivity to p16 and Ki67 proteins was found in the lesions (Figure 4). Neither HPV genotyping nor specific immunohistochemical markers were performed. While the P16 protein cannot thoroughly be used as a surrogate marker for HPV in oral lesions, generally its positivity indicates the presence of one or more HPV.¹⁹

After two weeks, complete mucosal healing was observed. No signs of inflammation were present. The post-operative course was reported as normal, without any significant pain. After six months, no recurrence of the lesions was observed (Figure 5).

DISCUSSION

Over the last decade, it has been shown that HPV infection represents a cause for a subset of oral squamous cell carcinoma (OSCC).^{1,4} A recent study found an increased incidence (ranging from approximately 50% to 225%) of HPV-associated OSCCs. HPV-16 is the most prevalent type, being present in at least 90% of HPV-associated OSCCs.⁶

Interestingly, such a trend in the incidence has been linked to an increase in the number of OSCC cases among young people (from 0.8 per 100,000 to 2.6 per 100,000), the latter are predominantly white men. These findings can be partially explained by changes in sexual activities in terms of the promiscuity and precocity of sexual experiences.⁷

The management of HPV lesions is important to prevent both the possible malignant transformation and the shed of viral particles to other anatomic subsites (autoinoculation). The latter is, most probably, the cause of recurrence in the present case. Specifically, despite the dentist's efforts to remove the main palatal lesion, we believe that the remaining tiny (most probably undiagnosed) lesions (molar area and tongue) represented reservoirs of the virus. By these means, the virus has re-infected the palatal mucosa.

The treatment of HPV consists mainly in the surgical excision of the lesion. The excision includes safety margins, and it is aimed at avoiding the recurrence of the lesion. Surgery is generally performed using a conventional scalpel, electric scalpel, or laser.^{8,9} Based

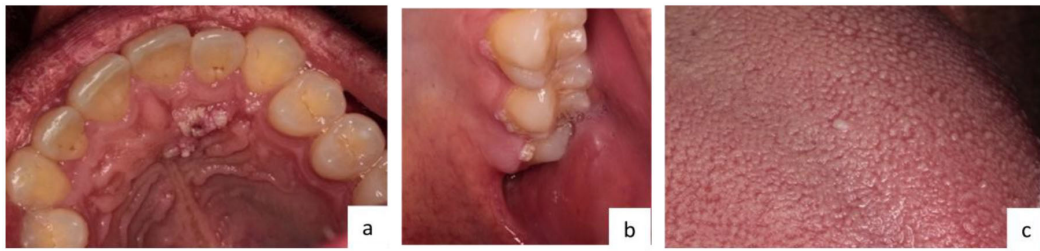


Figure 1. The clinical manifestation of multiple papillomatous lesions: (a) Palatal sessile widespread papillomatous lesions; (b) Tiny, multiple papillomatous lesions on the left palatal side, in the molar area; (c). Tiny, single papillomatous lesion on the dorsum of the tongue

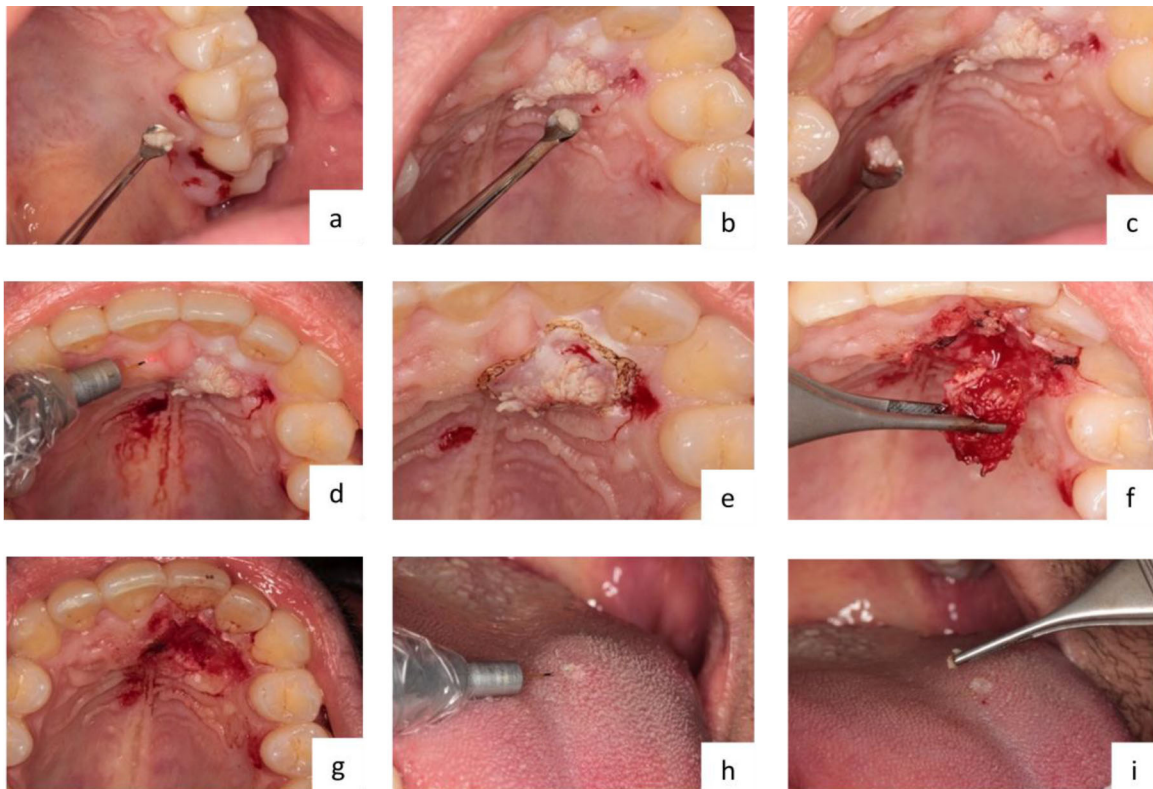


Figure 2. The removal of all the papillomatous lesions through a diode laser-assisted approach: (a-d) Removal of the small and scattered palatal lesions; (e-g) Removal of the main palatal lesion; (h-i) Removal of the tiny lesion on the dorsum of the tongue.

on this background, it becomes clear how the radicality of the excision is important.

To the best of our knowledge, only a few reports are available on the topic of laser surgery for HPV-related lesions. Of note, the majority of these studies are on patients carrying a possible immune dysregulation (e.g., pediatric and HIV infected patients).^{10,11} On the contrary, the present case has some relevance because it reports on a recurrent, widespread set of lesions in a young and healthy patient.

The use of a diode laser instead of the traditional biopsy method has some advantages which are as follows: less bleeding during the procedure, allowing for a clearer surgical field; better tolerance of post-surgical pain; and a faster recovery time (complete healing in the first 30 days post-surgery).¹² Additional advantages are that hemostasis allows for a second intention healing process. The possibility of avoiding sutures, especially in the palate, can help to extend the surgical margins beyond those strictly needed. In the present case, the diode laser allowed the operator to reach 0.5 cm of free margins in all directions.

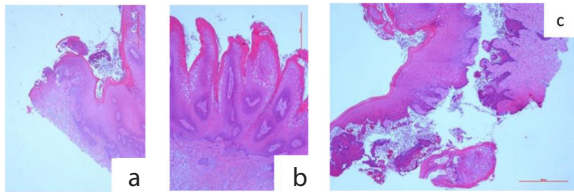


Figure 3. Histopathologic features of the main palatal lesion. (H&E staining section–4X magnification): (a) The surgical margins of the main lesion. Laser induced artifacts; (b) Histopathologic features of an HPV-related oral lesion, including viral-associated cytopathological alterations; (c) The surgical margins of the main lesion. Connective-epithelial detachment induced by a diode laser.

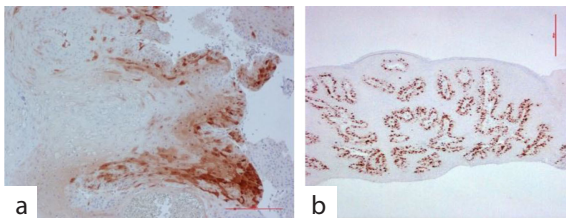


Figure 4. Immunohistochemical stainings: (a) p16 immunohistochemical staining. Most of the superficial epithelial cells show strong positivity (10X magnification); (b) Ki 67 immunohistochemical staining. A mild positivity is observed (4X magnification).



Figure 5. Clinical appearance on six-month follow up visit. Absence of recurrence lesion.

A limitation linked to the use of laser is that it induced some histopathological artifacts. Specifically, it may limit the histopathological evaluation due to the high temperature generated in the tissue hit by the laser ray. Of note, artifacts include epithelial changes (e.g., nuclei distortion) and connective tissue changes (e.g., carbonization). In the present case, although such artifacts were present, they did not limit the diagnostic accuracy.¹³

Compared to scalpel and electro surgery, laser surgery provides better results with regard to the recurrence rate. This is since it generates a high temperature in the surrounding tissues. Specifically, the carbonization of the tissue causes cell disruption at the margins of the lesion, avoiding new cell contamination.¹⁴

P16 protein is a cyclin-dependent kinase inhibitor. It has been shown that the loss of expression of p16 by deletion, mutation, or hypermethylation is common in both OSCC and esophageal cancer.¹⁵ HPV infection can lead to p16 overexpression through the production of HPV-oncogenes E6 and E7; therefore, p16 overexpression is a surrogate biomarker of HPV infection (in particular high-risk HPV types). This finding facilitates the evaluation of HPV-associated squamous neoplasia.¹⁶ Some studies have shown a better prognosis (lower recurrence and overall survivor) for p16-positive SCC vs. p16-negative cancers. Such results indicate that p16 expression represents a reliable prognostic marker for OSCC. Additionally, it may be a surrogate marker for HPV-positive OSCC.¹⁷⁻¹⁹ We believe that p16 protein evaluation may be important for the identification of a potentially malignant lesion and for treatment planning.

CONCLUSION

The radical surgical treatment of HPV-related lesions is important for the prevention of recurrence and malignant transformation. p16 and Ki67 protein positivity highlights a malignant potential of the lesions; therefore, a more radical treatment is needed. Taking into consideration the history of recurrences and the position and number of lesions, laser surgery appears as a preferable approach for this kind of surgery.

CONFLICT OF INTEREST

The authors declare that there were no conflicts of interest related to this case report.

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