



RESEARCH ARTICLE

THE TREATMENT OF HPV ORAL LESIONS: REPORT OF 3 CASES

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ABSTRACT

In oral cavity, HPV can induce the formation of squamous cell papilloma, focal epithelial hyperplasia, condyloma acuminatum and verruca vulgaris. Currently, there is no doubt about the sexual transmission of this virus and it is recognized as the most frequent sexual transmitted disease. HPV is transmitted by direct contact from person to person, with incubation periods that goes from 50 to 150 days. We have reported three cases of different types of therapies for human papillomavirus (HPV) and it depends on the location, stage of growth and the possibilities of recurrence. The choice of therapy is based on the number, size, location and morphology of lesions, as well as patient preference, cost, convenience, side effects and clinical experience of the professional.

INTRODUCTION

Clinical manifestations of oral cavity human papillomavirus infection (HPV) have been little investigated by dentists. The oral cavity is considered by many authors as a source of this virus infection. HPV caused Infections usually have exophytic growth, which increase along time, and are, often, confluent, showing a "cauliflower" aspect and may or may not affect keratinized or not keratinized tissues (Stoopler and Balasubramaniam, 2011). HPV is transmitted by direct contact from person to person, with incubation periods from 50 to 150 days. Transmission persists during many years and less than 10 % manifest as subclinical infections (Gillison et al., 2012). The average prevalence of HPV in the oral cavity has been reported to be between 20 and 30% (Miller and White, 1996). Form more than 150 HPV types identified, 24 were associated with oral lesions (HPV-1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72, 73), and 16 and 17 types are much more prevalent in oral and genital lesions (Bouda et al., 2000) which could mean an orogenital transmission (Schlecht, 2012). In oral cavity, HPV is responsible for four types of the disease: squamous papilloma, verruca vulgaris, condyloma acuminatum and focal epithelial hyperplasia (Moura et al., 2005). Benign hyperplastic lesions at buccal mucosa, are often

caused by viruses. They usually show the same clinical aspect of the lesions located at the genital mucosa, although with less number of lesions than in other areas. This could be explained by a genital virus variant or mutant that could have difficulty to establish at buccal mucosa (Moura et al., 2005). It is believed that the most recommended treatment for localized lesions in the mouth is surgical removal, for it eliminates the problem and makes it possible to confirm clinical diagnosis by histopathology study. The use of keratolytic substances are indicated in cases where there is a presence of multiple or disseminated lesions (Castro et al., 2006). Other forms of treatment such as high frequency surgery, CO₂ laser surgery, 5 - fluorouacil cream 5 %, topical application of podophyllin solution at 25%, trichloroacetic acid 80-90%, cryotherapy, electrocautery can be considered.

Literature review

Condyloma acuminata is a proliferation induced by the virus of the stratified squamous epithelium of the genitalia, perianal region, mouth and larynx virus. It seems to be associated with HPV- 6, HPV -11, HPV-16, HPV-18, among others. It is considered a sexually transmitted disease (STD), with lesions developing at the site of trauma or sexual contact (Castro et al., 2006; Herrero et al., 2003). Oral lesions occur most frequently on the labial mucosa, soft palate and tongue brake (Herrero et al., 2003; Ritchie et al., 2003). Other sites in the mouth are the

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buccal mucosa, gums or alveolar ridge, dorsum of the tongue and hard palate (Castro and Bussoloti Filho, 2006) and may also be located in the tonsils, uvula and floor of the mouth. In the floor of the mouth is found high quantity of saliva, where carcinogenic agents such as alcohol and tobacco are dissolved and allow greater opportunity for viral deleterious action (Ang *et al.*, 2010). The typical condyloma presents a sessile and short surface projections, purple mucosa and exophytic growth (Herrero *et al.*, 2003; Ritchie *et al.*, 2003). Clinically presents as multiple small nodules. Pinkish or whitish, which spread in papillary projections and can be pedunculated or sessile. The surface contour in most cases looks more like cauliflowers than papillomas (Ang *et al.*, 2010). The process of transmission of this virus is well known when occurs in the oral cavity, admitting that occurs through self-inoculation (Castro and Bussoloti Filho, 2006; Saini *et al.*, 2010) and through oral sex. In this region the tongue is the most frequent site affected by HPV, with an incidence of 55 % (Saini *et al.*, 2010). Regardless of the method used condyloma should be treated due to its venereal transmission and the possibility of malignant transformation (Castro and Bussoloti Filho, 2006). It is contagious and can spread to other oral surfaces and for other people through the normally direct sexual contact (Ritchie *et al.*, 2003; Machado *et al.*, 2010).

The condyloma treatment includes a research and the treatment of lesions of infected partners (Castro and Bussoloti Filho, 2006). The confirmation of condyloma lesions in the mouth can also suggest possible HIV infection (Castro and Bussoloti Filho, 2006) when patient informations are suggestive of it (Moura *et al.*, 2005). It is usually treated by conservative surgical excision (Gillison *et al.*, 2012; Ritchie *et al.*, 2003). Topical application of podophyllin not always give satisfactory results beyond the technical difficulties related to its implementation and also because it is a keratolytic, causing hepato-nephrotoxicity besides being totally contraindicated in pregnant patients. The laser treatment has been used but it has raised some issues, such as HPV air transportation by aerosolized microdroplets, created by the vaporization of the lesional tissue. In cases of extensive damage trichloroacetic acid from 70% to 90% has been used (Gillison *et al.*, 2012). The choice of therapy is based on the number, size, location and morphology of lesions, as well as patient preference, cost, convenience, adverse effects and clinical experience (Moura *et al.*, 2005). The immune system plays a relevant role in determining the extent of involvement. Patients on immunosuppressive therapy or those with AIDS often suffer great proliferation of injuries (Castro and Bussoloti Filho, 2006). The predisposition to get infected and severity of the condyloma acuminata in the following cases: infected partners, local trauma, diabetes mellitus and immunosuppression (Castro and Bussoloti Filho, 2006). In an article published in The New England Journal of Medicine (2007), the authors report that oral HPV infection is strongly associated with oropharyngeal cancer in patients with or without the established risk factors such as tobacco and alcohol. A study on 100 men and women with newly diagnosed disease and 200 healthy individuals was performed, found that a common strain of HPV-16 was found in 72% of tumors. Those whose blood or saliva patients indicated prior HPV infection were 32 times more likely to develop oropharyngeal cancer which affects the throat, tonsils and the back of the tongue (D'Souza *et al.*, 2007). The objective of Anaya - Saavedra *et al* in 2008, was to determine the association of high-risk human papillomavirus (HR- HPV) in Mexican patients with oral squamous cell

carcinoma (OSCC) and its association with various risk factors. The authors concluded that the high risk of oral human papillomavirus (HR- HPV) was strongly associated with oral squamous cell carcinoma (OSCC), suggesting that HPV-16 and -18 are risk factors for oral cancer in Mexican patients. A significant association of tobacco and alcohol was confirmed. In addition, family history of cancer was associated with oral squamous cell carcinoma (OSCC). The results show the important role of HPV in oral squamous cell carcinoma (OSCC) and their multifactorial etiology (Anaya-Saavedra *et al.*, 2008). There are different types of therapies for human papillomavirus (HPV) and it depends on the location, stage of growth and the possibilities of recurrence. The removal of the infected area can heal it, but if there is involvement of the hair attachments, recurrences may occur from the hair shaft and the sweat glands. There are some methods for treatment of HPV lesions, such as chemicals substances, surgical procedures and antiviraltherapies (Beutner and Ferenczy, 1997; Jayaprakash *et al.*, 2011; Chaturvedi *et al.*, 2011; Baker and Tyring, 1997). The treatment of different types of HPV is a challenge, it is a mix of simple treatments, with less skin aggression, including the possibility of spontaneous disappearance (Baker and Tyring, 1997). There are situations of extreme difficulty of resolution due to the location, extension, resistance to usual therapies, immunosuppression and the possibility of cancerization in the presence of oncogenic virus strains. However, the authors aim is solving those difficult situations and find a way to prevent cancer (Lingen *et al.*, 2013). The diagnosis and treatment of HPV are described in different ways, but the most important is the elimination of condyloma lesions.

There is no evidence that available treatments eliminate or alter the natural course of HPV infection. Even without treatment, the lesions can disappear, remain unchanged or even increase in size and number, but there are factors that can influence the choice of treatment. Those factors are the size, number and location of the lesion, morphology, patient preference, costs, the resource available, convenience, side effects and professional experience (Lingen *et al.*, 2013; Cardamakis *et al.*, 1997). There are several pharmacological and surgical treatments available, but no treatment is indicated for all patients. It should be emphasized that other therapeutic options should be evaluated if there is no substantial improvement after three applications or if the lesions do not disappear after six sessions (Beutner and Ferenczy, 1997). In clinical treatment, caustic agents can be used and cause tissue destruction, the most used is trichloroacetic acid (50 to 90%), once a week, for 4 weeks. The other one is a 25% podophyllin in alcoholic solution or 0.5 % applied 2 or 3 times a week. Surgical treatment with electrical or laser excision may be used for lesions with the advantage of preserving the sample for clinical pathology study (Beutner and Ferenczy, 1997; Baker and Tyring, 1997). The treatment of oral HPV lesion aim is the clinical cure with removal of visible injury, because it cannot eliminate it. Is possible to occur lesion recurrence in previously treated and in other places, with an incidence between 20 to 30 % of cases, which depends on the immune status of each patient (Beutner and Ferenczy, 1997; Cardamakis *et al.*, 1997).

Case reports

This study aim is to report three cases of condyloma acuminata in the oral cavity and evaluate the recommended treatment protocols.

Case study 1

Patient JS, male, 37 years old, HIV + since 1993, CD4 386 cells / mm³ and blood and viral load undetectable. In the anamnesis reported that their partner had similar lesions on genitals, later confirmed by the urologist and gynecologist. The patient reported lesion in the oral cavity, and the intra-oral clinical examination was observed a single lesion in the right lower lip, measuring approximately 1 cm in diameter, exophytic, pedunculated, with appearance of cauliflower (Fig. 1), consistent with clinical diagnosis of condyloma acuminata. Nothing was detected on the oral clinical examination of the partner. Total removal of the lesion (Fig. 2) and the material (Fig. 3) processed in the Pathology Laboratory was performed. Reading the biopsied and processed material was found koilocytotic cells with papillomatous aspect suggestive of HPV (Fig. 4).



Fig 1. Injury clinic in lower edge



Fig 2. Surgical removal of the lesion



Fig 3. Surgical specimen

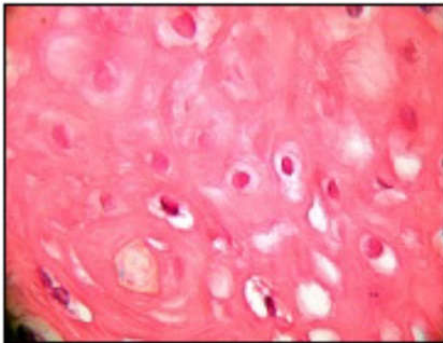


Fig 4. High-power light microscopy displaying koilocytes



Fig 5. Interdentary Papilla injury



Fig 6. Application of Alcoholic Solution of 25% podophyllin

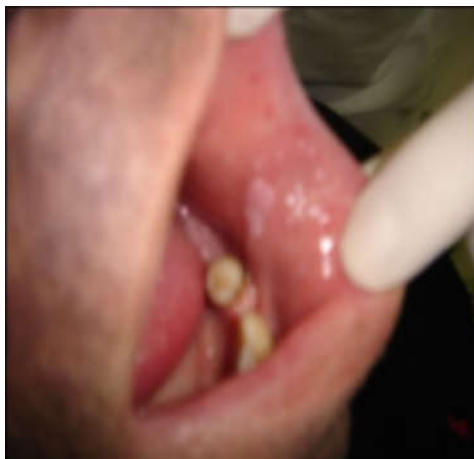


Fig 7. Clinical lesions in retrocommissura

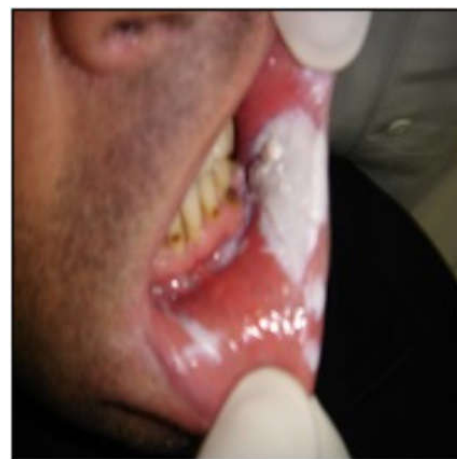


Fig 8. Application of acid = 90% trichloroacetic whitish

Case study 2

Patient DS, male, 33 years old, MSM, HIV+ since 1998, CD4 123 cells / mm³, blood viral load = 11 000 cells / mm³ blood, complained about a lesion in the oral cavity. The intra-oral clinical examination detected right lower lip lesions, measuring approximately 1.5 cm in diameter, with exophytic growth, pedunculated, whitish and with cauliflower shape (Fig. 5), consistent with a clinical diagnosis of condyloma acuminata. The alcoholic solution Podophyllin to 25% was the chosen treatment (Fig. 6), applied topically with a swab, with a light touch, once a week until complete regression of the lesion (5 sessions). The coloring of benzoin (brownish) facilitates the visualization of the application if the same was done to the entire extent of the injury, otherwise the patient might complain about unpleasant taste.

Case study 3

Patient MC, male, 40 years old, MSM, HIV+ since 2001, CD4 224 cells / mm³ and blood viral load undetectable. The clinical examination of oral cavity detected multiple lesions in the unapparent commissure and lower lip (Fig. 7), exophytic growth, pedunculated, whitish, cauliflower shape, compatible with a clinical diagnosis of condyloma acuminata. The patient was treated with ATA at 90% (Fig. 8) applied topically with a swab, with a light touch, once a week until complete regression of the lesion (4 sessions), reminding the patient's localized pain caused at the time of application.

DISCUSSION

The treatment of many types of HPV presents us a challenge, with a variety of mixed simple treatments, with less skin aggression (Beutner and Ferenczy, 1997; Baker and Tyring, 1997; Cardamakis *et al.*, 1997). There are situations of extreme difficulty of resolution because of the location, extension, resistant to usual therapies, immunosuppression and the possibility of cancerization in the presence of oncogenic strains of virus (Cardamakis *et al.*, 1997). There are different types of therapies for human papillomavirus (HPV), which depend on the location, (Beutner and Ferenczy, 1997; Jayaprakash *et al.*, 2011; Chaturvedi *et al.*, 2011; Baker and Tyring, 1997) number, size, morphology and the growth stage of the lesions, taking into account the patient's opinion, costs, resources, (Cardamakis *et al.*, 1997) convenience, adverse effects and clinical experience (Moura *et al.*, 2005) and the possibilities of recurrence (Beutner and Ferenczy, 1997; Jayaprakash *et al.*, 2011; Chaturvedi *et al.*, 2011; Baker and Tyring, 1997) that depend on the immune status of each patient (Ang *et al.*, 2010). There are pharmacological and surgical treatments available, but no treatment is ideal for all warts or for all patients (Cardamakis *et al.*, 1997). For the clinical treatment is used caustic agents, tissue destruction are used, the most used is trichloroacetic acid (50 to 90%) in the lesion, once a week, for 4 weeks. Another is a 25 % podophyllin in alcoholic solution or 0.5 % in the lesion applied 2 or 3 times a week. The surgical treatment with surgical excision can be used with the advantage of preserving the sample for clinical pathology study (Ang *et al.*, 2010). Despite the treatment of oral HPV lesions adopted, the aim is the clinical cure with removal of visible lesions, (Ang *et al.*, 2010; Cardamakis *et al.*, 1997) because there is no definitive eradication of the virus (Ang *et al.*, 2010). There is no evidence that available treatments eliminate or alter the natural course of HPV infection. Even without treatment, the lesions can stay unchanged, disappear, or even increase in size and number (Cardamakis *et al.*, 1997). Podophyllin has been used as an adjunct to surgical excision, because it reduces the size of the lesions, minimizing the extent of surgery. Its application to large areas of mucosa should be avoided, as there may be systemic toxicity or local (Castro and Bussoloti Filho, 2006) in addition to its teratogenic effect which prevents its use during pregnancy (Cardamakis *et al.*, 1997).

The ATA has no side effects to the fetus regardless of gestational age, it can be used during pregnancy (Beutner and Ferenczy, 1997). When the injured area is too extensive to be associated with surgical excision (Baker and Tyring, 1997; Cardamakis *et al.*, 1997). The effectiveness of the solution of podophyllin in the treatment of oral lesions is discussed. Some authors report successful treatment for oral lesions, others claim that the solution of podophyllin was not effective,

because is hard to make the solution stay in contact with the lesion, in sufficient concentration for long periods of time, required for their action (Castro and Bussoloti Filho, 2006). The ATA is probably more effective in treating small residual lesions that often remain after other treatments (Beutner and Ferenczy, 1997). Despite being a painful treatment with extensive ulceration and destruction of normal tissue and the area treated, this therapy has no systemic effects and no teratogenic effects (Baker and Tyring, 1997; Cardamakis *et al.*, 1997). If ATA therapy is not successful, surgical removal of the lesion is required (Cardamakis *et al.*, 1997). It reaches therapeutic success rates of up to 80 %, which can be seen in the case of Castro (2004) that with the implementation of ATA in the tongue lesions of condyloma acuminata observed total regression of the lesion (Castro and Bussoloti Filho, 2006). Surgical excision is the method that brings benefits to patients with large number of injuries, big areas affected, or even resistant to other forms of treatment (Beutner and Ferenczy, 1997; Castro and Bussoloti Filho, 2006). This therapy is often indicated when all the other alternatives were not effective (Baker and Tyring, 1997). The oral squamous cell carcinoma (OSCC) is the most frequent malignant tumor in the mouth, and among the etiologic agents involved, the human papillomavirus (HPV) has been extensively studied in recent years in an attempt to establish an accurate correlation with HPV, similar to what happens with cancer of the cervix. The hypothesis of involvement of HPV in oral cancer is due largely to the increased diagnosis of sexually transmitted diseases in the oral cavity and the association of some types of HPV oncogenic anogenital malignancies, particularly with squamous cell carcinoma of cervix uterus, which displays similarities with the mucosa epithelium of the oral mucosa. (Miller and White, 1996; Bouda *et al.*, 2000; Herrero *et al.*, 2003; Ritchie *et al.*, 2003; Ang *et al.*, 2010; Saini *et al.*, 2010; Machado *et al.*, 2010; D'Souza *et al.*, 2007; Anaya-Saavedra *et al.*, 2008; Jayaprakash *et al.*, 2011; Chaturvedi *et al.*, 2011; Lingen *et al.*, 2013)

Conclusion

It was possible to conclude that according to the literature and case reports presented, the choice of therapy is based on the number, size, location and morphology of lesions, as well as patient preference, cost, convenience, side effects and clinical experience of the professional. Despite various treatment options, we observed that surgical removal is the recommended option, especially for single lesions, but in cases of multiple lesions the recommended option is to use the ATA 90 % applied as a therapeutic protocol, which has been evidenced good responses in the control of disease, clinical remission of manifestations occurring in up to about 3 sessions, and if the bigger lesions do not respond to ATA, we perform the resection of the lesion establishing a mixed protocol with great success. We should emphasize that in recent studies on papillomavirus, the literature indicates that HPV 16 and 18 are considered risk factors in the etiology of oral cancer development, so it is imperative to monitor patients regularly, even the already treated patients with remission of clinical manifestations.

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