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Recalcitrant oral squamous cell papilloma lesions in two HIV-infected patients successfully treated with topical imiquimod

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Abstract

Background: Squamous cell papilloma is a benign mucosal disease associated with human papillomavirus. Its presence in human immunodeficiency virus (HIV)-infected patients has rarely been reported. Therapeutic modalities for oral squamous cell papilloma have limited success and recurrences are frequent in HIV-infected subjects. Imiquimod, is a topical immunomodulator successfully used in some human papillomavirus-related oral lesions. However, its use for oral squamous cell papillomas in HIV-infected individuals has never been described.

Observations: We report two male adult patients with HIV-infection, B2 and C3 stage respectively, undergoing antiretroviral therapy, with multiple recalcitrant oral squamous cell papillomas, predominantly affecting the masticatory mucosa. These lesions were successfully treated with daily topical imiquimod 5% cream for a few weeks, with only mild and well-tolerated side effects. No recurrences were observed after a follow-up period of over 20 months.

Conclusions: Our cases highlight the value of imiquimod for the non-invasive treatment of multiple persistent oral squamous cell papillomas in two HIV-infected patients. (*J Dermatol Case Rep*. 2015; 9(1): 19-22)

Introduction

Human papillomaviruses are DNA viruses of medical importance, which selectively infect cutaneous and mucous membrane epithelia in human subjects.[1,2] Human papillomavirus (HPV)-related lesions in mouth can be divided into two distinct groups on the basis of their biological behavior. The first group includes benign lesions, such as squamous cell papilloma (SCP), focal epithelial hyperplasia (FEH), condyloma acuminatum and verruca vulgaris; the second group includes premalignant and malignant oral lesions, such as HPV-related leukoplakia, verrucous carcinoma and squamous cell carcinoma.[1,3]

Oral SCP is primarily related to HPV types 6 and 11, and archetypically manifests as a single lesion. However, atypical and/or severe clinical findings are often encountered amongst immunocompromised patients.[3] Recent evidence indicates that HPV-related oral diseases are more frequent in human immunodeficiency virus (HIV)-infected patients.[4,5] The prevalence of oral SCP in patients under treatment with highly active anti-retroviral therapy (HAART) has dramatically increased from 5% in the pre-HAART era to 23%. High rates of oral warts associated with long-term use of HAART and old age have also been reported.[5] Additionally, the likelihood of oral HPV-infections increased in HIV-patients undergoing HAART, after adjusting for CD4-lymphocyte count and HIV-viral load; and specifically, the incidence of oral SCP increases with logarithmic decline in the HIV-viral load after institution of HAART.[5,6]

Oral SCP-lesions in HIV-patients are frequently multiple, larger, and commonly widespread; triggering chronic functional and aesthetic disturbances.[1] Several therapeutic modalities have been used in order to manage oral HPV-related lesions in HIV-patients; however, persistence of lesions and/or recurrences are commonly observed.[7,8] The purpose of this paper was to describe the successful treatment

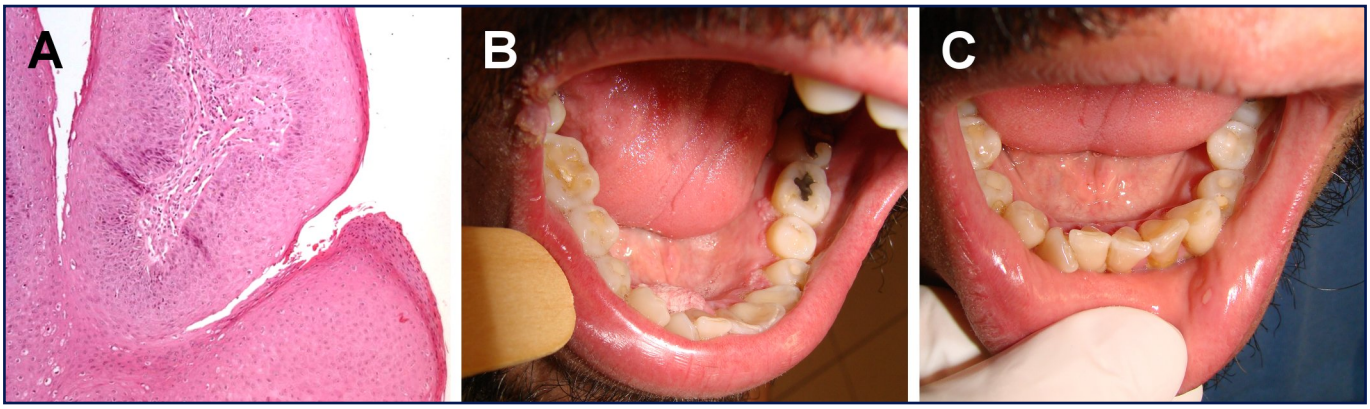

Figure 1

Patient 1. Sections stained with hematoxylin and eosin (10X) showing an oral squamous cell papilloma, characterized by an acanthotic and papillomatous epithelium with mounds of parakeratosis (A). The image depicts multiple papillomatous growths located on the attached and marginal lingual gingiva as well as in the right commissure. A large lesion, sized 10 mm approximately, is seen contiguously to the lower incisors (B). Clinical presentation after treatment. Note the clearance of all lesions and a small residual ulcer of traumatic origin, on the lower labial mucosa (C).

with topical imiquimod, of multiple recalcitrant oral SCP lesions, in two HIV-infected subjects, undergoing medical care at the Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran" (INCMNSZ), which is a tertiary referral center in Mexico City.

Case Series

Patient 1

A 44-year-old male patient was referred to the Oral Pathology Consultation Service on July 2009, due to multiple oral papillomatous lesions, first noticed in March 1998. The patient had a history of heavy tobacco use (aproximately 40 cigarettes per day, for 25 years, till 1996), had been diagnosed with HIV-infection in 1992 (B2 stage), had initiated antiretroviral therapy with zidovudine and didanosine in 1997; and his last CD4+ lymphocyte count and HIV viral load were 300 cells/mm^3 and 16 700 copies/mL, respectively.

At oral examination, a verrucous growth in the right labial commissure angle and multiple papillomatous lesions affecting the palate, right lateral border of the tongue, free margin & attached area of the upper & lower gingiva involving both the lingual and vestibular aspects of it, were noted. The lesions which interfered with eating and phonation, were predominantly pedunculated, some of them had a white keratinized surface, and ranged in size from 3 to 13 mm.

A clinical diagnosis of SCP was done and confirmed histopathologically (Fig. 1A&B) from all intraoral specimens, which were surgically removed. By contrast, the lesion located on the right labial cutaneous commissure was diagnosed as verruca vulgaris. Following surgical excision, recurrences developed for all lesions and topical retinoids were administered as second-line treatment, but discontinued in November 2009 due to persistence of the lesions and mucosal irritation manifested as burning sensation.

Imiquimod 5% cream (Aldara™) was administered nightly on all lesions following meals and oral hygiene. The patient noticed a substantial reduction of the lesions from the first week of treatment and decided to continue such therapeutic scheme twice daily. After four weeks of treatment, a mild erosion on the labial mucosa was detected along with clearance of most SCPs (Fig. 1C; photographs were taken using a camera Sony Cyber-shot™ DSC-H5). Complete resolution of the lesions and the erosion referred previously were achieved after five weeks of treatment.

A viral load of 12 000 copies/mL and a CD4-lymphocyte count of 240 cells/mm^3 were documented after completing imiquimod therapy, and thus, HAART treatment was modified to atazanavir and ritonavir. The patient was otherwise well and had no other significant findings. No recurrences of HPV-oral lesions developed after a 20-months follow-up period.

Patient 2

A 40-year-old male patient with a 26-year history of HIV-infection was referred to the Oral Pathology Consultation in September 2009, because of multiple HPV-related oral lesions, which were first noticed in February 2008.

His medical chart revealed a history of molluscum contagiosum, disseminated herpes virus infection, vacuolar mielopathy and a recent diagnosis of anal squamous cell carcinoma.

HAART (lopinavir/ritonavir, abacavir and lamivudine) was administered since 2006, with a recent undetectable (<40 copies/mL) viral load and a CD4-lymphocyte count of 130 cells/mm^3.

Upon clinical oral examination, the patient presented numerous small and persistent papillomatous growths on the palate, upper and lower gingiva, clinically diagnosed as SCP (Fig. 2A); and multiple papules on the buccal, upper and lower labial mucosa were also observed, which were presumptively diagnosed as FEH. (Fig. 2B) Furthermore, countless cutaneous flat warts affecting the face, trunk, arms and hands (Fig. 2C) were noted. The largest oral growths were removed surgically, but recurrences followed in a short interval. The diagnoses of oral SCP and FEH were confirmed histologically and thus, topical imiquimod 5% cream (Aldara™)

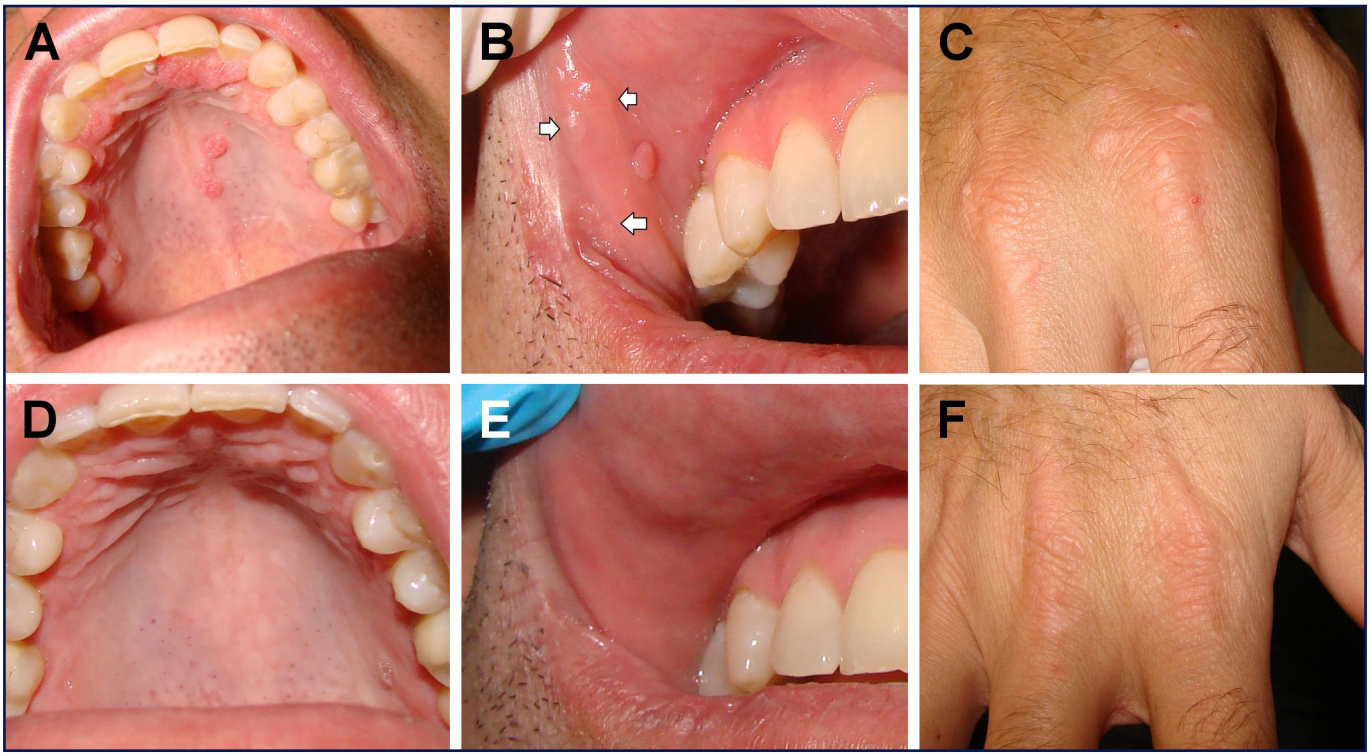

Figure 2

Patient 2. Numerous squamous cell papilloma lesions, predominantly affecting the hard palate (A). Arrows signal the presence of lesions consistent with focal epithelial hyperplasia affecting the right upper labial mucosa (B). Several flat warts on the dorsum of the right hand (C). Clinical resolution of the lesions on the palate (D), labial mucosa (E) and dorsum of the hand (F), following therapy with imiquimod.

was indicated nightly for both for oral and cutaneous lesions, starting in October 2009. Clinical clearance of oral SCP and FEH lesions was noted by the end of third week, but the patient continued applying the drug for three additional months until the clearance of cutaneous warts (Figs. 2D-F).

Following imiquimod therapy, the CD4-lymphocyte count was 246 cells/mm^3 and the viral load remained undetectable. Surgery and multi-agent chemotherapy (cis-platinum, dexamethasone and 5-FU) were instituted at the end of 2009 as oncologic treatment for his anal squamous cell carcinoma and the patient remained with the previous HAART scheeme. After 22 months of follow-up, no recurrences of HPV-oral or cutaneous lesions were observed. The patient was otherwise well without additional complaints.

Discussion

Innate and/or adaptive immunity appear to provide some control of HPV-infection and/or replication, since HPV-induced oral warts are considerably more common in HIV-infected patients and other immunocompromised subjects.[3,9] Surprisingly however, in contrast to most oral complications that have decreased after the beginning of the HAART area, the incidence of oral warts seems to have increased in HIV-patients undergoing HAART,[5] a treatment that leads to the reconstitution of the peripheral immune system.[5,6]

Reported treatments for HPV-oral lesions include caustic/acid agents, cantharidin, podophyllin resin, tretinoin, intralesional bleomycin, topical 5-fluorouracil, surgical modalities (cryosurgery, CO2 slush, electrosurgery and curettage, blunt dissection, excision, CO2 laser), imiquimod, vitamin A (oral etretinate), cimetidine, zinc sulphate, x-ray, heat and tape occlusion, or a combination of the above.[7,10] However, a very limited number of case reports have addressed treatments specifically targeted to intraoral warts in HIV-patients. These have included pharmacotherapy (cidofovir, bleomycin, cimetidine, podophyllum, or interferon), surgery, or a combination of the above. The treatment of some HPV-related oral lesions such as SCP in HIV-patients is frequently a challenge due to the often widespread distribution of such lesions and the high recurrence rate. Besides, therapeutic procedures may lead to the possibility of spreading lesions to other surfaces; for example, cauterization may seed other mucosal surfaces with HPV, such as the nasal mucosa. Currently, surgery is still the most common therapy for lesions that interfere with function or are of esthetic concern in immunocompetent patients; however, recurrence is frequent in immunosuppressed subjects, and to date, there are no highly-effective treatments for intraoral SCP-lesions in HIV-patients.[7]

Imiquimod has been used to treat some mucosal HPV-related lesions. Imiquimod is an imidazoquinoline amide derivative with a low molecular weight, which acts as an immunomodulator. This drug is a novel immune response modifier which induces the secretion of cytokines such as interferon-α, tumor necrosis factor-α and interleukin-1, -6,

-8, -12 and -18. Imiquimod binds to the toll-like receptor-7 from the group of toll-like receptors present in humans and increases the output of this receptor.[10,11] A decrease in HPV-viral load after the use of imiquimod has been noted along with a reduction in the expression of p16ink4a, Ki67, minichromosome maintenance protein and proliferating cell nuclear antigen; biomarkers of high-grade lesions.[12]

Imiquimod was approved for the treatment of actinic keratosis, superficial basal cell carcinoma and external anogenital warts; and more than 60 anecdotal reports have been published regarding its use in diverse pathologies.[11]

The use of imiquimod for some HPV-related oral lesions has been described;[10] but to our knowledge, imiquimod had never been attempted in oral SCP. In this manuscript, we report two HIV-patients with SCP-lesions confined to mouth mucosa, which disappeared after a short course of topical imiquimod.

In our first patient, HPV-related oral lesions spectacularly resolved in a few weeks, despite previous failures to different therapeutic modalities; in our second patient, an important decrease in the size and number of the multiple, different HPV-related oral lesions was also noted after 4 weeks of treatment. No clinical evidence of new lesions or recurrences was noted after 20 and 22 months of follow-up, respectively. Remarkably, the clinical resolution of these lesions was observed in a shorter time than previously described for other HPV-related oral lesions (12-16 wk/three times a week) occurring in immunocompetent hosts; even though, the CD4-lymphocyte count and HIV-viral load remained unchanged in our patients during the period of treatment with imiquimod.[10]

During imiquimod application, several side effects have been reported to occur on the lesional site, including erythema, edema, itching, burning sensation, bleeding, vesicles, excoriations, crusting, induration, tenderness, pain, eczematization, erosion, ulceration and induction of some other dermatoses. These side effects, typically resolve after cessation of treatment. Rarely, systemic side-effects such as headache, upper respiratory tract infection, flulike syndrome (fatigue, fever, chills, arthralgias and myalgia) sinusitis, gastrointestinal symptoms (nausea and diarrhea) or some non-dermatologic disorders (neuropathic pain, thyroiditis, abnormal liver function, etc.) have been mentioned.[11] In our patients, only a mild erosion was seen in the labial mucosa in one patient. However, despite the absence of severe complications in our patients, it is important to consider the need to analyse the administration of imiquimod for long-term periods and its safety in other type of patients, with diverse systemic diseases or deleterious conditions. Also, a careful interpretation of the results to imiquimod therapy in these patients should be made, because of the multiple inherent biases when dealing with isolated cases; for example, characteristics of the patients and the lesions themselves. On the other hand, even if there are no available data suggesting clinically relevant long-term side effects of imiquimod,[11] patients should be monitored carefully, due to the risk of potential side effects such as increased carcinogenesis, and especially due to the known relationship of some HPV-types and squamous cell carcinoma.[2,13] In consequence, periodic reassessment of all HIV-patients with HPV-oral lesions is recommended.

In summary, this is an initial approach to imiquimod as a potential treatment of some oral HPV-infections in HIV-patients. Topical imiquimod may be a safe, noninvasive, and successful therapeutic alternative for HIV-patients with oral SCP; however, further research is mandatory in order to fully evaluate its genuine efficacy in the clearance of oral SCP-lesions.

Additional contributions

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