The Management of Oral Human Papillomavirus With Topical Cidofovir: A Case Report

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Cidofovir, a purine nucleotide analog of cytosine, has showed significant promise against a number of DNA viruses. In 1997, the US Food and Drug Administration approved the use of cidofovir intravenously in the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. Recent studies and reports suggest that a topical form of cidofovir may be useful for treating viral cutaneous lesions recalcitrant to traditional treatments. We report the case of a 36-year-old man with human immunodeficiency virus (HIV) and recalcitrant human papillomavirus (HPV) lesions on the gingiva that were successfully treated with cidofovir gel 1%.

Cutis. 2004;73:191-193.

The human papillomavirus (HPV) is a member of the *Papillomavirus* genus of the family Papovaviridae.[1] Based on their DNA, about 100 specific HPV types have been fully cloned and characterized.[2] HPV is a DNA virus that can cause lesions anywhere on the cutaneous surface, including the extremities, genitalia, and oral mucosa. Lesions involving the oral cavity can be transmitted sexually or by nail-biting in patients with periungual warts. Compared with immunocompetent patients, immunocompromised patients often present with HPV infections that are atypical or more extensive, recurrent, and recalcitrant to therapy.

HPV has a double-stranded, circular DNA genome, is nonenveloped, and has icosahedral virion.[1] Specific subtypes are found within certain lesions based on location and diagnosis. Antigenic determinants exist on the virion surface of HPV, are subtype specific, and can elicit a serologic response.[1] HPV genomes consist of 3 regions: early, late, and regulatory. The role of certain subtypes of HPV in promoting dysplasia, verrucous carcinoma, and squamous cell carcinoma on the oral mucosa has been shown by the detection of HPV DNA in malignant tissue. Oncogenic HPV subtypes (ie, early gene E6) facilitate the degradation of the p53 tumor suppression protein.[1] HPVs cause proliferative lesions on the squamous epithelium. HPV infection can be associated with various benign and malignant neoplasms, including anogenital and cervical dysplasias, carcinoma in situ, and invasive carcinoma.[3] Various studies report that 50% to 90% of oral squamous cell carcinomas contain HPV types 16 or 18.[2-8] More important, strains of HPV frequently are found on the oral mucosa without evidence of lesions.

Clinically, HPV-related lesions are often asymptomatic, soft, exophytic, cauliflowerlike, pedunculated in appearance, and vary in color from white to barely red or normal. The largest lesion is usually limited to less than 1 cm.[2] Oral HPV lesions tend to present more often on the vermilion border of the lip, hard and soft palates, and uvula than on other intraoral mucosal sites.[2] Head and neck lesions associated with HPV include oral squamous papilloma, common warts, oral and cutaneous verruca vulgaris, condyloma acuminatum, laryngeal papillomatosis, conjunctival papillomatosis, focal epithelial hyperplasia, and squamous dysplasia or neoplasia, or both.[2] The main route of transmission is direct genital and orogenital sexual contact with infectious lesions.

Current treatment of HPV infections depends on the area involved and the extent of the lesions but can include surgical excision, laser ablation, cryosurgery, immunostimulants (eg, interferon), and application of caustic agents (eg, podophyllotoxin, retinoic acid). With HPV recurrence, however,

Accepted for publication November 7, 2003.
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The authors report no conflict of interest.
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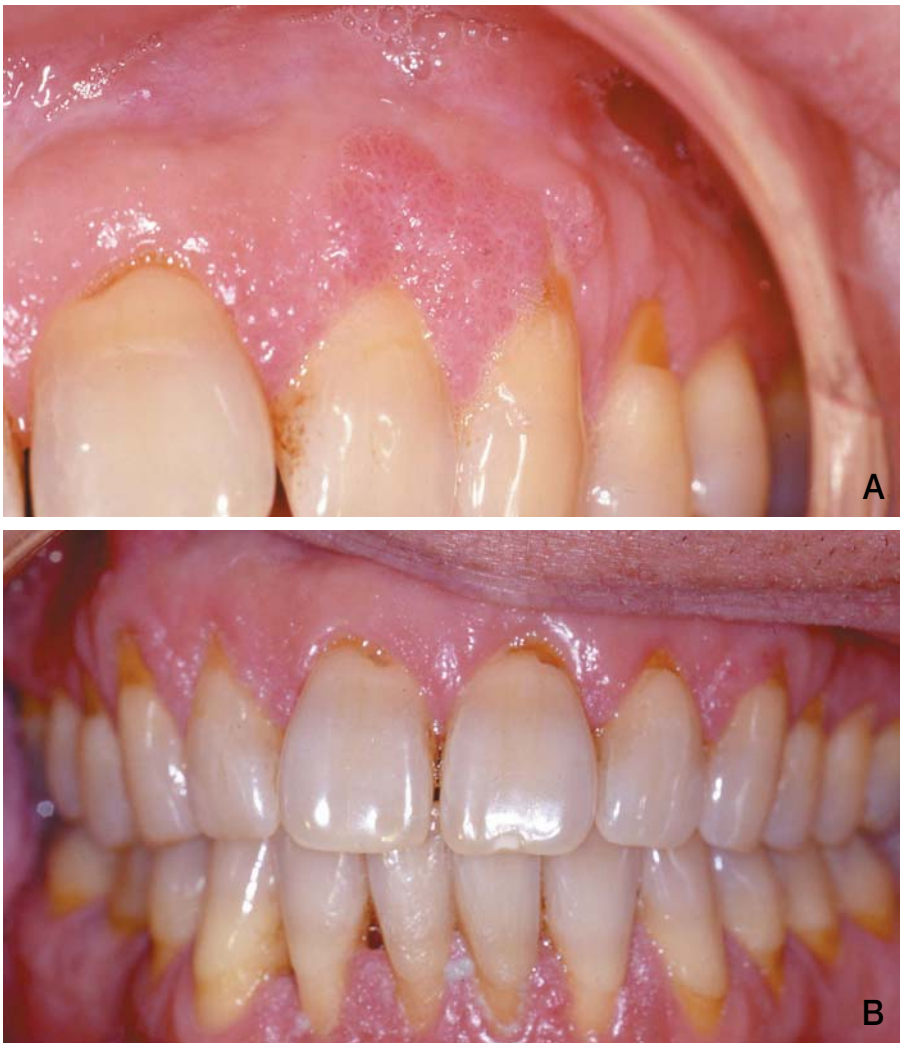

Human papillomavirus lesions on the maxillary left anterior gingiva before (A) and 4 weeks after (B) treatment with cidofovir gel 1%.

these various treatments fail. Even if success is achieved, recurrences are common. Vaccines have been shown to neutralize certain HPV antibodies in human studies.[9,10] Over the last several years, new and exciting information has been elucidated regarding novel pharmacologic approaches in the treatment of viral diseases. We report the case of a 36-year-old man with human immunodeficiency virus (HIV) and recalcitrant HPV lesions on the gingiva that were successfully treated with cidofovir gel 1%. The patient remained symptom free for more than 12 months.

Case Report

A 36-year-old white man was referred by his physician for growths on his gingiva. The patient reported growths on his gum tissue, with concurrent recession. Genital and perianal HPV had been diagnosed between 1996 and 1998. Results of colonoscopies were negative, and no oral lesions were present during this period. In December 2000, a biopsy of asymptomatic oral lesions was performed, with subsequent diagnosis of HPV-related squamous papilloma. The oral lesions remained stable. Recently, however, increasing signs and symptoms appeared and included bleeding with toothbrushing and sensitive gum tissue. The patient became concerned about his appearance when the lesions gradually increased in size.

The patient's medical history was significant for HIV disease; oral, genital, and perianal HPV; functional heart murmur; hypercholesteremia; gastroesophageal reflux disease; hepatitis B virus; and prolonged chronic depression. The patient had been diagnosed with HIV in 1990 and had a recent CD4 count of 900 and an undetectable viral load. His current medications included efavirenz, didanosine, stavudine, pantoprazole, gemfibrozil, and zolpidem. A comprehensive review of systems revealed no other skin, eye, nasal, genital, or rectal lesions. The patient did report wrist pain, however,

and was currently undergoing psychiatric therapy. His social history was significant for 15 years of cigarette smoking but no current alcohol use.

Findings from the physical examination revealed mild, bilateral cervical lymphadenopathy, no enlargement of the salivary gland, no thyromegaly, no conjunctivitis, and no lesions on the exposed skin. The oral mucosa was dry, pink, and without masses or lesions. Furthermore, multiple, exophytic, cauliflowerlike, pink projections were present on the maxillary and mandibular buccal gingivae (Figure 1A). Based on the clinical presentation, a diagnosis of HPV was made.

Treatment options were discussed with the patient and included no treatment, surgery, interferon alfa, and cidofovir gel 1%. A trial of cidofovir applied every night was initiated. The patient was instructed to apply the gel with a cotton swab once a day for 4 weeks. Subsequently, he reported that the viral lesions had begun to flatten within 3 days of treatment and nearly completely resolved after 14 days. The patient returned for a 4-week follow-up visit with considerable improvements in the gingival lesions (Figure 1B); he reported no local or systemic side effects while using cidofovir. Findings from the physical examination revealed no lymphadenopathy and no enlargement of the salivary gland. The oral mucosa was moist, pink, and without lesions. Clinically, there was significant improvement of the papillomatous lesions on the gingiva, with 95% resolution. Topical therapy was continued for an additional 4 weeks, which completely resolved the lesions. No recurrence was observed at the 12-month follow-up visit.

Comment

Cidofovir, a nucleoside analog to deoxycytidine monophosphate, is effective against a number of DNA viruses. After its phosphorylation into its active metabolite, cidofovir selectively inhibits DNA polymerase, blocking viral DNA synthesis and replication. Intravenous administration of cidofovir has been approved by the US Food and Drug Administration in the treatment of cytomegalovirus retinitis in immunocompromised patients. Systemic treatment of cidofovir requires hospitalization and is known to cause nephrotoxicity. Topical application of cidofovir for treating recurrent herpes viruses, Kaposi sarcoma, molluscum contagiosum, and HPV-related lesions has been described.[4-11] To our knowledge, this is the first case described in the dermatologic literature where topical cidofovir was used for intraoral HPV.

When applied locally, the treatment can be administered on an outpatient basis and is well tolerated. The topical use of cidofovir appears to cause significant shrinkage and resolution of gingival HPV recalcitrant to traditional therapies. In this case, the topical formulation of cidofovir had no side effects in the short-term. Local side effects of topical cidofovir may include hyperpigmentation, reversible alopecia, and irritant dermatitis.[11] It is important to note that a special consultation with the hospital pharmacy was necessary to procure and formulate the topical gel. The cost of topical cidofovir is rather significant and must be taken into account when prescribing it. Topical cidofovir should be considered as an alternative therapy for gingival HPV lesions that do not respond to conventional therapy. A randomized, controlled, double-blind study is necessary to evaluate fully the efficacy of cidofovir in the treatment of intraoral HPV.

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