Human papillomaviruses are members of the *Papovaviridae* family of viruses and are classified as members of the *Papillomavirus* genus. They are circular, double-stranded DNA viruses containing approximately 8,000 base pairs. Based on cross-hybridization DNA studies, human papillomaviruses are classified into more than 75 subtypes. Dermatologic manifestations of human papillomaviruses are initiated by infection of keratinocytes found in the stratum corneum and stratum granulosum layers of the epidermis. Human papillomavirus infection of keratinocytes induces a tissue reaction resulting in the formation of benign epidermal neoplasms, known as verrucae or warts.

Clinical classification of verrucae is determined by the appearance and location of the lesion. The appearance varies depending on the local environment of the lesion and the human papillomavirus subtype of the infection. Verrucae on the feet can appear at five major sites: plantar, dorsal, interdigital, periongual, and subungual. The most common human papillomavirus subtypes found at these sites are 1, 2, and 4.

Many factors are considered before choosing a treatment modality for verrucae. These factors include size, number of lesions, location, presence of pain, previous treatment, and immunologic status of the patient. Clinical management of verrucae includes such modalities as topical 5-fluorouracil, salicylic acid, lactic acid, liquid nitrogen, and injection of bleomycin sulfate. The general function of these treatments is to induce and augment the patient's immune system, ultimately resulting in the disappearance of the verrucae and the clearing of the virus from the keratinocytes. When these treatments prove insufficient for clearance, more aggressive surgical procedures are implemented including blunt enucleation, full-thickness dissection, and laser surgery.

Statistics regarding immunocompetent individuals indicate a cure rate for treatments involving salicylic acid and lactic acid of 80% within 12 weeks for single plantar warts and 50% for multiple lesions. Even though it has been reported that approximately 35% to 65% of lesions spontaneously resolve within 2 years in healthy individuals, these figures appear to differ extensively when the patient is immunocompromised. It has been reported that up to 45% of patients treated with immunosuppressant drugs during renal transplantation develop warts in their lower extremities. Furthermore, in 20% of these patients, it is reported that the warts transform into squamous cell carcinoma, epithelioma cuniculatum, or verrucous carcinoma of the sole.

Human immunodeficiency virus (HIV) is the causative agent of AIDS, a disease characterized by the progressively immunocompromised state of the patient. Progression is marked by a continuous decline of peripheral blood CD4+ T lymphocytes, which are one of the targets for infection with HIV. These cells are important in coordinating the events of the immune system and thus, the patient’s immune system progressively loses the ability to respond to new invaders and the reactivation of previous infections.

Common podiatric manifestations associated with HIV infection can be classified into four groups: vascular, neurologic, musculoskeletal, and dermatologic. Vascular complications include lower extremity edema and a few reported cases of pseudothrombophlebitis. Neurologically, complications of the lower extremity include motor neuropathy, myelopathy, and peripheral sensory neuropathy, which is often described as progressive paresthesia or pain in a stocking-glove-type distribution. The most common musculoskeletal complications observed are polymyositis, Reiter's syndrome, psoriatic arthritis, myopathy, tenosynovitis, and nonspecific arthritis. Dermatologically, fre-
quent lower extremity complications consist of onychomycosis, tinea pedis, impetigo, cellulitis, and other bacterial or fungal infections. Of other dermatologic importance is the endothelially derived, multifocal tumor, Kaposi’s sarcoma. Finally, reports indicate that there is a high incidence of both singular and mosaic plantar verrucae caused by human papillomavirus.

Case Report

A 26-year-old HIV-positive male presented in May 1992 to Pacific Coast Hospital in San Francisco with a complaint of painful plantar warts bilaterally. He stated that the plantar verrucae had been present since 1990 and previous treatments included mechanical debridement of lesions, liquid nitrogen, salicylic acid, and over-the-counter medications. None of the modalities had proven effective. The patient denied any history of previous trauma to the affected area.

The patient’s medical history indicated that he tested positive for HIV in 1989. His medications included azidothymidine (AZT), acyclovir, Desyrel®1, and multivitamins. The patient indicated allergies to codeine and Septra®2. He denied the use of alcohol and tobacco. The patient indicated a previous history of HIV-related eczema and dermatitis. His CD4+ T-cell count on the day of his first visit was 525 cells/mm³ of peripheral blood.

Dermatologic examination revealed the presence of large, multiple hyperkeratotic lesions in several locations on the plantar surface of both feet. Areas affected included the first, second, and fourth submetatarsal heads bilaterally and the plantar aspect of the hallux and the third and fourth interspaces of both feet. The lesions were circumvented by skin lines and showed pin-point bleeding with mechanical debridement. Other aspects of the physical examination were unremarkable.

Treatment

Treatment modalities initiated on presentation of the patient to the authors’ facility in 1992 included the following: 1) lesion debridement, 2) chemocautery, ie, use of keratolytic, 40% to 60% salicylic acid, 3) water soaks to dry the interspace, 4) topical 5-fluorouracil, and 5) occlusion. These were tried for the first 6 months and all failed to control the verrucae. Finally, it was decided to treat the plantar surgically. The plantar warts were anesthetized intralesionally with lidocaine and 2% epinephrine. Blunt enucleation was performed, followed by curettage and trimming debridement. The area was cleaned with hydrogen peroxide, and Silvadene®3 and dressing were applied.

Postoperative management included dry dressing for 48 hr to allow hemostasis. A Darco®4 shoe was used to take weight off of the area. A postoperative follow-up examination indicated signs of epithelialization, healing, and absence of any sings of infection. Two weeks postoperatively, the fourth interspace appeared macerated and wet. The patient was instructed to apply Betadine®5 solution as a drying agent to this area. Four weeks postoperatively, some hyperkeratotic areas were noted around the fourth interspaces bilaterally. Some small verrucous lesions were noted on the plantar aspect of the proximal phalanx of the hallux on the right foot. Debridement of hyperkeratotic lesions was performed and the patient was instructed to apply Betadine to the third interspace. Six weeks postoperatively, verrucous lesions were noted on the plantar aspect of the left hallux, on the second and fourth digits on the left foot, and on the fourth digit on the right foot. Treatment to this recurrence included debridement and salicylic acid.

Two years after the initial visit, the patient presented with more aggressive and extensive verrucae on the plantar aspect of his feet bilaterally. His CD4+ T-cell count was 420 cells/mm³. Treatment consisted of debridement and intralesional injection of bleomycin under local anesthesia for 2 months with no apparent resolution. It was then decided to perform partial thickness epidermal surgery (enucleation by blunt dissection) under local anesthesia. Postoperative results indicated signs of healing and no signs of infection. Two weeks postoperatively, signs of maceration appeared in the fourth interspaces bilaterally. Three weeks after surgery, hyperkeratotic lesions were noted in the third interspace and on the plantar aspect of the left hallux.

By May 1995, the patient’s CD4+ T-cell count was 330 cells/mm³ and most of the plantar lesions had reappeared (Figs. 1-3).

Discussion

As the second decade of AIDS begins, many developments have improved the clinical management

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61 Bristol-Myers Squibb, Princeton, NJ.
62 Burroughs Wellcome/Glaxo Wellcome, Inc, Research Triangle Park, NC.
of some of the serious complications of disease caused by HIV. Close monitoring of patients, prophylactic drugs against many opportunistic pathogens, new antiviral drugs, and lifestyle changes favoring healthier habits have greatly contributed to the increase in length and quality of life for patients infected with HIV. However, as the average life expectancy of HIV-infected patients increases, new clinical manifestations become of greater importance for patient care. As a result, podiatric medicine has assumed a new and increasing role in the management of HIV disease. Among the clinical complications of HIV observed in the lower extremities, plantar verrucae, caused by human papillomavirus, represent one of the most common podiatric manifestations of HIV.

This case report describes highly resistant lesions caused by human papillomavirus in an HIV-infected individual. It describes the recurrence of the lesions within 2 months of their complete surgical removal. The CD4+ count of the patient at the time of the first visit, when the verrucae lesions had already been treated for 2 years, was 525 cells/mm³. This range is indicative of an individual minimally, if at all, immunocompromised.

This highlights a crucial issue in the pathogenesis of human papillomavirus in HIV-infected individuals; namely, even when the patient is relatively immunocompetent, human papillomavirus can manifest itself aggressively with a high rate of recurrence. It is possible that the generalized immunocompromised state of the HIV-infected patient is the sole cause for the increased incidence of manifestations in this population. However, the presence of such aggressive lesions when the immune system of the patient appears to be intact (according to his CD4+ counts) suggests that there may be specific interactions between these viral agents. For example, soluble factors released at the local level by HIV-infected lymphocytes or macrophages could directly increase expression of human papillomavirus. A more direct mechanism may involve products from the HIV genome directly interacting with regulatory sequences of human papillomavirus.
Recent reports indicate that such a mechanism of interaction between HIV and human papillomavirus may exist. *In vitro* studies have shown that protein products from regulatory genes of the HIV genome, specifically the tat protein, when provided exogenously, can bind to and increase expression controlled by the upstream regulatory region of human papillomavirus. The interaction between tat and the human papillomavirus upstream regulatory region could point to a direct relationship that could help explain the aggressive nature of human papillomavirus in HIV-infected individuals. It should also be noted that the incidence of venereal warts caused by different types of human papillomavirus (other than types 1, 2, and 4) in HIV-infected females is markedly higher than that observed in HIV-negative controls.

Understanding the molecular mechanisms underlying pathogenesis of human papillomavirus in HIV-infected patients is critical in order to improve the management of plantar verrucae in this population. Elucidation of these mechanisms is also likely to advance understanding of the pathogenesis and clinical manifestations of other human papillomavirus infections observed in this and other patient populations, such as anal and cervical human papillomavirus infection.

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**References**