Effective treatment of extensive and recalcitrant plantar warts associated with human papillomavirus-52 by oral acitretin

Case report

A healthy 27-year-old Taiwanese man presented with extensive and recalcitrant plantar warts on his right foot for more than 10 years. When he was 14 years old, three discrete coin-sized thick scaly hyperkeratotic plaques with warty rough surface were noted over his right sole. Skin biopsies had been performed twice in other medical institutes and verruca plantaris was diagnosed at that time. Various conventional therapies, including cryotherapy, electrocauterization, chemical cauterization, and local injection of interferon alfa-2b, were done; nevertheless, the cutaneous lesions were refractory and furthermore complicated with digital atrophy. Three years later, the skin lesions became diffuse hyperkeratotic whitish waxy plaques with involvement of the nonweight-bearing digits (Figure 1A). There was no family history of similar lesions.

On arrival at our hospital, the patient underwent a series of laboratory investigations. Complete blood count and antinuclear antibodies were found to be within normal limits, and human immunodeficiency virus antibody screen test was negative. Incisional skin biopsies were taken from the lesional skin of the right foot as well as normal skin of the left foot. Both of the specimens were sent for histological examination at our hospital. Consensus primers of human papillomavirus (HPV), MY11, and GP6þ were used for polymerase chain reaction assay. Then commercial EasyChip HPV blot (King Car Yuan Shan Institute, I-Lan, Taiwan) was used to determine specific genotype. The tissue from the nonlesional skin of the left foot was confirmed normal histopathologically, and no HPV DNA was detected. However, histopathologically, the skin taken from the lesional skin of the right foot revealed marked hyperkeratosis with parakeratotic columns over the tops of the papillae, acanthosis, papillomatosis, and elongation of rete ridge (Figure 2A). Some scattered vacuolated cells with condensed keratohyalin granules in epidermis were found (Figure 2B). There was no evidence of malignancy in the sections examined (Figure 2).

In addition, the product of polymerase chain reaction displayed the occurrence of HPV DNA (Figure 3) and was matched to genotype 52. Under the impression of verruca plantaris refractory to conventional treatments, oral acitretin (Neotigason, Actavis/Patheon Inc., Ontario, Canada) 0.5 mg/kg/d was prescribed for 6 months, subsequently tapered to half of previous dosage for one more month, and then discontinued. Marked improvement was observed after one month of treatment. The lesion was nearly clinically ameliorated after 6 months with few small residual hyperkeratotic areas (Figures 1B–D). The patient's triglyceride, cholesterol, and hepatic and renal function were checked every 3 months during the course of the treatment, and all results were within normal limits. Except for the presence of mild chelitis and xerosis, no other adverse drug events were noted. The lesions were stationary and no relapse was observed after a 1-year period of follow-up.

Discussion

Warts, an extremely troublesome but common affliction, are caused by HPV and pose therapeutic challenges for both patients and physicians. HPV is composed of a large family of small double-strand circular DNA viruses infecting epithelial cells and is host-specific. HPV-52 reference genome was first isolated from a cervical intraepithelial neoplasia. Hybridization analysis with restriction fragments of HPV-52 showed collinearity with the HPV-33 genome. Therefore, HPV-52 is considered a high-risk carcinogenic type and the sixth most common type in cervical cancer. Although cervical condylomata and anogenital warts are the most frequent clinical lesions associated with HPV-52, Fölster-Holst et al. first identified the presence of HPV-52 from the papillomatosus skin of a patient's groin. This indicates that HPV-52 could be found not only in mucosal areas but also in nonmucosal skin.

There are multitudes of conventional treatment opinions regarding the combative therapies of warts, such as topical keratolytic agents, antimitotic agents (podophyllin, bleomycin, retinoids), topical immunomodulators, electrocauterization, laser surgery, cryosurgery, and photodynamic therapy. The choice of therapy, however, will be determined by cost, pain, success rate, ease of use, side effects, cosmetics, compliance, and patient preference. One of the most common first-line therapeutic methods, for instance, is cryosurgery as it is relatively safe and easily available. Despite of wide acceptance, the clearance rate for plantar warts is only 50% after executing every 3 weeks for a 3-month duration. Furthermore, patients with plantar warts tend not to follow up owing to the high-relapse rate, persisting discomfort, and cutaneous secondary bacterial infection.

Retinoids exert diverse biological effects on cells, including the regulation of growth and differentiation. An inverse relationship was observed between concentration of retinoic acid and HPV DNA content within infected epithelial cells, suggesting an inhibitory effect on viral replication. Lutzner and Blanchet-Bardon proposed that the retinoids, by altering keratinization, are capable of inhibiting the replication and assembly of HPV within the affected cells, which requires human keratinocytes in an advanced state of differentiation.

In normal adult skin, keratin pairs K5/K14 and K1/K10 predominate in the basal layer and suprabasal compartment. Keratin K13 and K19 are usually expressed separately in adult epithelia. Retinoids have been proven to repress differentiation-specific keratins (K1/K10) and strikingly induce the expression of...
K13 and K19. Furthermore, by inducing K13 expression or directing keratinocytes toward nonkeratinizing differentiation, retinoids might be chemopreventive by “freezing” cells in this differentiated state. This is the reason why retinoids could lower the number of hyperkeratotic warty cutaneous lesions by inducing nonkeratinizing squamous epithelium.⁶

Worthy of note is the fact that retinoids reduce the bulk of hyperkeratotic warts and substantial clinical improvement is achieved. Choi et al⁷ treated a 25-year-old man suffering from multiple warts on both hands with oral acitretin 1 mg/kg/d. Almost total clearance was achieved after 2 months of therapy. Simone et al⁸ used acitretin 25 mg/d to remedy a 33-year-old HIV-positive man who manifested with multiple giant exophytic and hyperkeratotic lesions on his hands and feet. The lesions began to reduce within 2 weeks and were dramatically improved after 2 months. No sign of relapse was found after a 6-month period of follow-up.

In conclusion, oral synthetic retinoids can be a good alternative therapeutic method in treating extensive and recalcitrant viral warts that could bring about physical and psychosocial dysfunction in patients.

Figure 1 (A) Diffuse whitish hyperkeratotic waxy plaques with involvement of the nonweight-bearing sole and digital atrophy. (B, C, D) Dramatic improvement of cutaneous lesions after systemic acitretin treatment (time of follow-up: B = 1 mo; C = 2 mo; D = 6 mo).

Figure 2 (A) Microscopically, marked hyperkeratosis with parakeratotic columns over the tops of the papillae, acanthosis, papillomatosis, and rete ridge elongation. (B) Some scattered vacuolated cells with condensed keratohyalin granules in epidermis were found. There was no evidence of malignancy in the sections examined (H&E, 40×).

Figure 3 Human papillomavirus DNA in the skin biopsy paraffin specimen of right foot was displayed in polymerase chain reaction (M = an 100-bp DNA ladder marker; S = sample DNA isolated from patient’s skin; N = negative control; P = positive control).
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