

New Insights in The Treatment of Recalcitrant Plantar Warts

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Background: Warts are very common benign tumors caused by human papilloma virus (HPV) infection, which is acquired from direct contact with an infected individual or from the environment. Plantar warts are mostly refractory to treatments and represent a therapeutic challenge. Immunotherapy has been used as a promising alternative therapeutic option in such warts. Different agents have been used as Candida albicans antigen, measles, mumps, rubella (MMR) antigen, tuberculin antigens like purified protein derivative (PPD), mycobacterium indicus pranii (formerly known as mycobacterium welchii) (Mw) vaccines and Bacillus Calmette- Guerin (BCG) vaccine and Trichophyton. The intralesional injections are thought to work by inducing a systemic T-cell mediated response inducing principal increase in the release of cytokines from Th1 cells such as IL-2 and IFN- γ . Interleukin-2 stimulates the maturation of the natural killer T cell and promotes its cytotoxicity.

Keywords: Human papillomavirus ,recalcitrant plantar warts, topical treatment, intralesional immunotherapy.

1. Introduction

Warts are a common dermatological problem that is caused by HPV. Plantar warts represent great source of frustration for both practitioners and patients, as no single treatment is completely effective in all patients. Recalcitrant plantar warts referred to warts that are persistent for more than two years and or failed to respond to at least two modalities of treatment. Immunotherapy has been used successfully in treating recalcitrant ones and preventing its recurrence.

1.1 Epidemiology of plantar warts:

It is estimated that 40% of the population is infected with HPV. Plantar warts represent an annual incidence of 14% in the general population. Plantar warts are more common in adolescents and young adults, may be as a consequence of inadequate maturity of the immune system, repetitive microtrauma as in sports, the use of public showers and excessive perspiration.

(8)

1.2 Human papilloma virus (HPV):

HPV are double-stranded DNA viruses, which are associated with a spectrum of diseases, from benign verrucae vulgares and condylomata acuminata to the malignancies of the cervix, vulva, anus, and penis. Its capsid lacks an envelope, making HPV very stable and impervious to many therapeutic agents. Up to 226 HPV genotypes that cause both cutaneous and genital warts have been totally classified. (7).

1.3 Pathogenesis:

Human papillomavirus can establish a persistent infection through developing mechanisms to evade the host immune system. There is no systemic immune response that is elicited as there is no viremic phase. Moreover, the highest production of virion proteins tends to be in the terminally-differentiated layers of the epithelium, which are subsequently shed. Several cell types, receptors, inflammatory mediators and transcription factors involved in the antiviral immune response are viral targets and participate in tumorigenesis.

1.4 Clinical features:

Plantar warts may appear as a singular rough, flesh-colored to yellow or grey-brown, hyperkeratotic papule, or a thickened “cobblestoned” plaque, termed a mosaic wart and characterized by the presence of verrucous, yellowish structureless areas with multiple irregularly distributed red-brown to black dots or linear streaks due to hemorrhages. Presence of thrombosed capillaries and pinpoint bleeding along with the loss of normal dermatoglyphics differentiate a plantar wart from other cutaneous lesions, such as calluses or corns. They are mostly asymptomatic, but sometimes may be painful.(12)

2. Diagnosis:

The diagnosis of cutaneous warts is usually based on typical clinical appearance.

1) Histopathological characteristics:

Cutaneous warts show variable amount of acanthosis, papillomatosis, and hyperkeratosis. The presence of elongated and tortuous vessels as well as hemorrhages/extravasation of erythrocytes corresponds to the dotted, linear, hairpin, and coiled vessels and reddish/black dots seen at dermatoscopy, respectively.(19)

2) Dermoscopy:

Palmoplantar warts are characterized by the presence of verrucous, yellowish structureless areas with multiple irregularly distributed red - brown to black dots or linear streaks due to hemorrhages. Skin lines are typically interrupted in palmoplantar warts. (11)

3. Treatment:

The primary therapeutic option in the treatment of plantar warts is the conventional destructive and aggressive method, which includes topical salicylic acid in high concentration, topical or intralesional 5-fluorouracil, bleomycin, cantharidin, cryotherapy, surgical excision, electrocautery, laser therapy, and combination of these agents.

A Combination therapy with 1% cantharidin, 5% podophyllotoxin, and 30% salicylic acid has been reported to achieve complete clearance of plantar warts in 95.8% to 100% of patients. The preparation (CPS) was applied with a swab; surpassing the margins of the wart by up to 2 mm and the solution was allowed to dry for few seconds after that the zone was covered with nonporous dressing that was removed after 24 hours. The subsequent applications were repeated every 2 weeks or after the lesions have completely healed to allow skin to epithelialize and regenerate for a maximum of five sessions. (5)

Intralesional bleomycin has been used for the treatment of warts since the 1970s with a wide range of cure rates (14–99%). It has antitumor, antiviral, and antibacterial activities related to its ability to bind DNA and cause strand scission. Intralesional injection of (1 mg/ml) bleomycin was expeminted every 2 weeks for a maximum of four sessions for plantar warts and has shown a cure rate reaching 69.3% with minimal and tolerable side effects. (3)

Cryotherapy is a safe and comparatively painless procedure with less complications and success almost similar to electrosurgery making it more suitable for plantar warts. Unfortunately, pain, dyspigmentation, scar formation, delayed healing and relapses are potential side effects. Therefore, Intralesional Cryotherapy (ILC) is a new and alternative modality performed for deeply applying cryosurgery in recalcitrant plantar warts in a trial to overcome the disadvantages of conventional Cryotherapy spray (cryo-sp). ILC was studied in the treatment of recalcitrant plantar warts every 2 weeks and for a maximum of 5 sessions. Complete clearance was achieved in 83.3% of patients compared to 50.8% of patients treated with cryo-sp. It was found that ILC has a slower cooling rate of 20 °C/min while the thawing rate was faster allowing deep freezing of the entire core of the virally infected cells which is unique to ILC. When the liquid nitrogen flows through the needle, a lethal zone less than 22°C is created around the inserted probe within the dermis. Subsequently, the freezing starts from the center outwards which allow preservation of the superficial skin and provides rapid healing time and less pain. (1)

5-fluorouracil has been used intralesionally for treatment of plantar warts. However, its intralesional injection is painful and intolerable by the patients. Despite the IL5-FU injection provides a higher drug concentration inside the warts, using the microneedling followed by 5-FU solution application was reported to achieve a higher complete clearance in plantar warts up to 86.7% compared to 76.7% and 70% of intralesional 5-FU and microneedling alone groups respectively. Microneedling assisted topical 5-FU solution was associated with a higher cure rate as 5-FU inhibits DNA synthesis and the microneedling was reported to help in drug delivery so it

can facilitate 5-FU absorption, offer a less painful modality, potentiate the 5-FU effect and minimize the adverse effects as compared to the IL 5-FU therapy.(6)

Laser modalities, including carbon dioxide (CO₂), pulsed dye and neodymium-doped: yttrium-aluminum-garnet lasers (NdYAG), have also been used to treat recalcitrant plantar warts. CO₂ lasers have been used to treat warts since the 1980s. Seventeen patients with 30 lesions of recalcitrant plantar warts were enrolled in a study where they were treated by CO₂ laser with a computerized scanner under local anaesthesia. All 30 plantar warts were completely cleared with a single treatment session. Re-epithelialization was completed within 7–21 days (average 13.6), with almost no scar formation. The CO₂ laser with a computerized scanner generates a continuous focused beam of laser energy that moves rapidly across an area of skin with the aid of the computerized scanner. This system can vaporize a wart as deeply as the upper dermis in both the central and peripheral areas of the lesion. In addition, thrombus formation may suggest the induction of ischaemic damage in HPV-infected cells. These mechanisms may result in the remission of warts, even after a single treatment session. (9)

Topical application of 5-aminolaevulinic acid (ALA) followed by red light photodynamic therapy (PDT) is a well-known treatment for many proliferative skin diseases including treatment of plantar warts as it is noninvasive, specific to the target tissue, well tolerated, allows treatment of multiple lesions at the same time and has a low rate of adverse events. ALA-PDT has been studied in Twenty-Five patients with recalcitrant plantar warts where twenty-two of them (88%) showed a complete response. The most common adverse effects observed were pain and edema. The specific mechanism of ALA-PDT involves both necrosis and apoptosis of plantar wart keratinocytes. (19)

The second line in treatment of warts is immunotherapy, which is based on the activation of the immune system. Such therapy may be applied either topically or through intralesional injection or systemic administration. (18)

Various systemic immunotherapies such as interferons and contact sensitizers have been used to stimulate the host immune response. Intralesional injections of vaccines and organic antigens have also been studied extensively with some degree of success in the treatment of warts. Antigens studied include *Candida albicans*; MMR; *Trichophyton*; and tuberculin antigens such as PPD, *Mycobacterium w* vaccine, and BCG.(2)

Intralesional *Candida* antigen injection is considered a promising immunotherapeutic approach. This modality is associated with the production of Th1 cytokines such as IFN- γ and TNF- α , which activate cytotoxic and NK cells to eliminate HPV infection in both injected and non-injected lesions. Discomfort at injection, bulla, edema, desquamation, febrile reactions, intense pain, rash and constitutional symptoms such as fever, aches, and febrile reactions are the main side effects.(14)

Vitamin D3 has the property of regulating the epidermal cell proliferation, toll-like receptor activation of human macrophages, immunomodulatory and apoptotic activities that act synergistically and when used as an intralesional injection, serves as an immunotherapeutic agent. Vitamin D3 also has the advantages of better response on distant warts, minimal side effects, and low rate of wart recurrence.

Zinc sulfate has an immunomodulatory function that helps the elimination of HPV and plays a role in enhancing cellular and humoral immunity and thus has been used in treatment of warts.

In a comparative study in treating recalcitrant plantar warts in three groups using intralesional injection of 2% zinc sulfate solution, intralesional injection of vitamin D3 solution (600,000 IU, 15 mg/mL) and 0.2 ml of 1/1000 solution of Candida antigen. The results had revealed a higher therapeutic response in the intralesional vitamin D3 group (89.5 %) compared to (52.7%) and (65.7%) complete response in zinc sulfate and Candida antigen groups respectively. **(13)**

Human papillomavirus infection of the skin is a complex disease entity that creates a therapeutic conundrum for both patients and physicians. The aim of most treatments is to remove the affected epidermal cells, but, sometimes the cellular damage is not sufficient to produce the cytokines that would destroy the latent virus in adjacent cells. Host's immune status, the type of HPV involved, the anatomical location and the tolerance for a certain procedure from a lifestyle perspective should be considered. The ideal treatment should be simple, cheap, effective, and with a minimum of adverse effects. **(4)**

At this time, there are a variety of well-studied as well as brand new therapies that one can use as monotherapy or in combination to create a positive therapeutic outcome for patients dealing with plantar warts.

Recalcitrant warts are a real problem and emerging therapies are getting discovered every now and then.

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