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Plane Warts: Clinical Features, Pathogenesis, Diagnostic Modalities, and Emerging Immunotherapeutic Approaches

El-Sayed Mohammed Galal Khater, Heba Essam-Eldeen Ibrahim Shehata Redwan, Basma Magdy Elkholy

Dermatology, Venereology and Andrology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Heba Essam-Eldeen Ibrahim Shehata Redwan

Email: Hebaredwan1990@gmail.com ,

Abstract

Plane warts (verrucae plana) are benign cutaneous lesions caused by infection with specific types of human papillomavirus (HPV), most commonly affecting children, adolescents, and immunocompromised individuals. They typically present as multiple, flat-topped papules distributed on the face, neck, and extremities, often following lines of trauma due to the Koebner phenomenon. Diagnosis is usually clinical and may be supported by dermoscopic and histopathological findings, including hypergranulosis, koilocytosis, and mild acanthosis. Although numerous treatment modalities are available, no definitive therapy eradicates HPV infection completely, and recurrence remains a major challenge. Conventional management includes destructive therapies, virucidal agents, antiproliferative drugs, and occlusive techniques. In recent years, immunotherapy has emerged as a promising strategy because of its ability to enhance cell-mediated immunity against HPV-infected keratinocytes. Various topical, systemic, and intralesional immunotherapeutic agents, including imiquimod, diphenylcyclopropenone, Candida antigen, purified protein derivative, Bacillus Calmette–Guérin vaccine, measles–mumps–rubella vaccine, and vitamin D3, have demonstrated favorable efficacy and safety profiles. This review summarizes the epidemiology, pathogenesis, clinical presentation, diagnostic methods, and currently available therapeutic options for plane warts, with particular emphasis on the evolving role of immunotherapy in achieving sustained clinical clearance and reducing recurrence.

Keywords: Plane Warts, Verruca Plana, Human Papillomavirus (HPV).

Introduction:

Plane warts (verrucae plana) or flat warts, are smooth, flat-topped or slightly elevated papules, usually skin-colored, pink or may be slightly pigmented. They are round or polygonal in shape, measuring 1–5 mm that typically present as multiple lesions, often following lines of trauma, as shaving or friction, due to the Koebner phenomenon **(1).**

Plane warts predominantly affect children and adolescents, but may occur in adult women and individuals with HIV. This type of warts is caused mainly by HPV types 3, 10, 27, 28, 29, 38, 41, and 49 **(2).**

Histopathology of plane warts:

The histopathology of plane warts (verrucae plana) reflects a benign HPV-induced epidermal proliferation with relatively subtle architectural changes compared with other wart types. Microscopically, the epidermis shows mild acanthosis with slight elongation of rete ridges, accompanied by orthokeratosis and minimal or absent parakeratosis, which helps distinguish it from verruca vulgaris where parakeratosis is more prominent **(3).**

Papillomatosis is either absent or only mild, contributing to the clinically flat surface of these lesions. A key diagnostic feature is prominent hypergranulosis with enlarged keratohyalin granules, particularly in the upper epidermis, along with numerous koilocytes, keratinocytes exhibiting perinuclear vacuolization and nuclear pyknosis, representing the cytopathic effect of HPV infection. These viral changes are most evident in the granular and upper spinous layers, where infected cells may show cytoplasmic pallor and vacuolization **(4).**

The dermis is typically unremarkable, lacking significant inflammatory infiltrate, although regressing lesions may exhibit lymphocytic infiltration and keratinocyte apoptosis. Overall, the combination of subtle epidermal hyperplasia, hypergranulosis, and koilocytic change with minimal papillomatosis forms the characteristic histological pattern of plane warts and correlates with their smooth, flat clinical morphology. There is no inflammatory infiltrate in the normal dermis **(Figure 1) (5).**

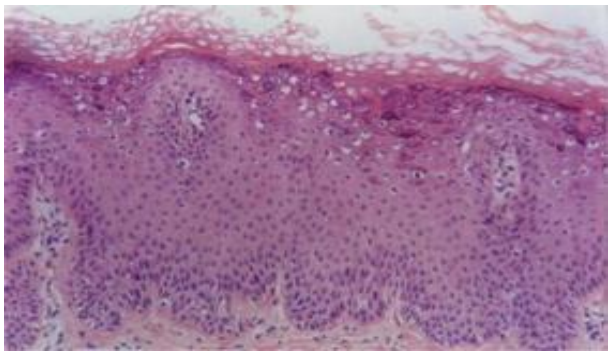

Figure (1): Histopathology of verruca plana: Verruca plana or flat wart, showing basket-weave hyperkeratosis, hypergranulosis, acanthosis with fusion of rete ridges and koilocytosis in the upper third of the epidermis **(5).**

Dermoscopy of plane warts:

Dermoscopy of plane warts (verruca plana) shows a relatively subtle and uniform pattern reflecting their flat, minimally keratinized nature. Lesions typically appear as homogeneous, structureless light brown to yellowish areas with a smooth surface, lacking the papillomatous features of common warts **(Figure 2) (6).**

The hallmark vascular feature is regularly distributed dotted vessels (pinpoint red dots), corresponding to dilated capillary loops, while thrombosed capillaries (black dots) are usually absent **(7).**

Skin lines are often preserved or only slightly disrupted, and a faint erythematous or yellow-brown background may be present **(8).**

Overall, the pattern is monomorphic, and recognition of these features, especially the combination of flat morphology, uniform coloration, and dotted vessels, helps in differentiation of plane warts from other conditions such as seborrheic keratosis, lichen planus, and melanocytic lesions, thereby reducing the need for biopsy **(9).**

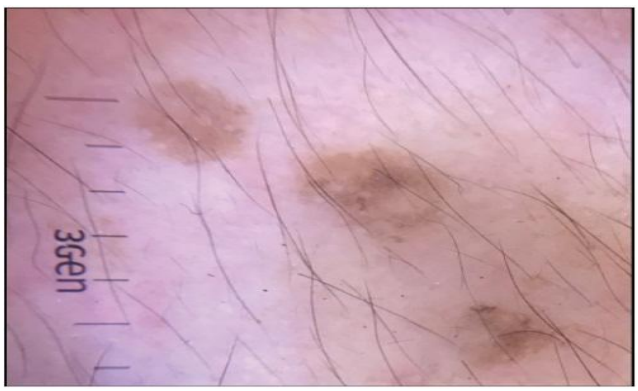

Figure (2): Dermoscopy of verrucae plana: showing ill-defined margins, even brown background and absence of vascularity **(6).**

Treatment of warts

Currently, there is no definitive cure for HPV infection, and available treatments do not prevent transmission of the virus. As a result, the primary goal of therapy is to relieve the visible signs and symptoms. Since no single treatment works for all patients, management often depends on the type and location of the wart, and may require a combination of therapies **(10).**

The ideal wart treatment would completely or significantly clear the lesions, be painless, require treatment of only part or all of the wart, involve just one to three sessions, leave no scars, provide lifelong immunity to HPV, and be accessible to all patients **(11).**

The American Academy of Dermatology established key indications for the treatment of cutaneous warts, emphasizing both patient preference and clinical necessity. Treatment is warranted when patients request removal; when symptoms such as discomfort, pruritus, pain, burning, or bleeding occur; or when lesions cause functional impairment or cosmetic concern. Additional indications include the risk of autoinoculation or transmission to others, the presence of immunosuppression that may predispose to persistent or progressive disease, and the occurrence of large or multiple warts. These criteria provide an evidence-based framework for determining the need for therapeutic intervention **(12).**

Current therapies for cutaneous warts primarily aim to either remove visible lesions or exert cytotoxic effects on HPV-infected cells **(Table 1) (13).**

1) Destructive therapies:

These treatments target the wart tissue itself without directly eliminating the virus. This approach aim to damage or destroy the infected epithelium. This can also induce cell death and antigen exposure and presentation, thereby potentially inducing an immune response. By reducing epidermal proliferation, or more specifically DNA replication, the wart should become less thick and production of new virus inhibited **(14).**

The destructive methods include: surgical removal, application of caustic chemicals or physical methods. Chemical therapies for warts include: Salicylic acid, Silver nitrate, phenol, monochloroacetic acid, trichloroacetic acid, glycolic acid, cantharidin, pyruvic acid, citric acid or formic acid with or without preceding curettage. Also Warts can be treated physically by the use of Co2 laser, electrocautery, cryotherapy, pulsed dye laser and photodynamic therapy and heat-based (hyperthermic) approaches **(15). (Table 1)**

While surgical removal of warts is best avoided at sites of pressure, such as the soles, as the resulting scar may be equally uncomfortable, and reinfection of the healing scar is a possibility as surgery does not always remove all virus-infected tissue **(16).**

The type, size, location, and number of warts all influence the choice of treatment. Additionally, the physician's experience and the patient's cooperation are important factors **(17).**

Many of these treatments require repeated sessions and carry a significant risk of scarring and recurrence. Moreover, since they act only on the treated area and lack a systemic effect, they are less suitable for patients with widespread or multiple distant lesions **(18).**

2) Virucidal agents:

The formaldehyde soaks (formalin) and the glutaraldehye 10% paint (glutaral) are effective virucidal agents in the treatment of warts **(19).**

3) Antiproliferative (Antimitotic) agents:

They include vitamin D analogue, podophylin, podophyllotoxin, 5-fluorouracil, bleomycin, topical and systemic retinoids **(20).**

4) Occlusion therapy:

The use of occlusion for the treatment of cutaneous warts has been practiced for some time, with a suggestion of 47% of patients cleared at 2 months, the exact mechanism is occluding the blood supply **(21).**

Algorithm for treatment of cutaneous warts is shown in **Figure 3**.

Table (1): Available treatment options for cutaneous warts **(12)**:

A) Destructive treatments:	**B) Antimitotic drugs:**
• Salicylic acid (15–40%) • Cryotherapy • Cantharidin • Tri/Monochloro-acetic acid • Surgery • Laser • Phototherapy	• 5-Fluorouracil • Bleomycin • Cidofovir • Podophyllin • Retinoids
C) Immunotherapy:	**D) Other treatments:**
• Topical e.g. imiquimod • Systemic e.g. Zinc Sulphate • Intralesional e.g. *C*andida antigen	• Local hyperthermia • Duct tape • Garlic extract • Hypnosis • Pottasium Hydroxide (KOH) • Bee Venom

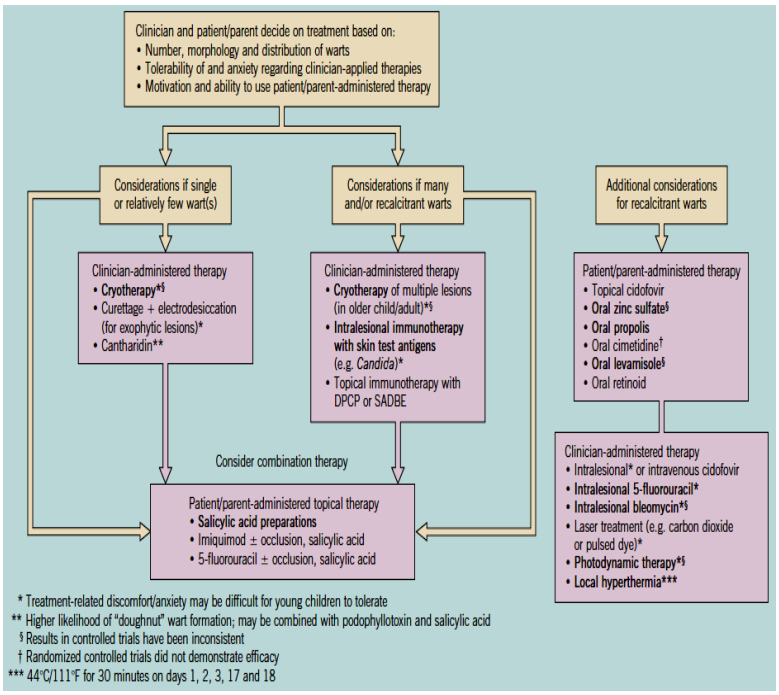

Figure (3): Algorithm for treatment of cutaneous warts. Therapies in bold are found to be effective in controlled trials. Adapted from: **(12).**

DPCP (Diphenylcyclopropenone), SADBE (Squaric Acid Dibutyl Ester)

5) Immunotherapy:

Immunotherapy has emerged as a cornerstone in the management of cutaneous warts, including plane warts, based on the growing recognition that CMI plays a pivotal role in controlling and eliminating HPV infection **(22).**

Evidence indicates that an effective host immune response, particularly involving T-cell–mediated mechanisms, is essential for wart regression. Immunotherapeutic approaches aim to enhance this immune response and include a wide spectrum of modalities such as topical agents, systemic therapies, and intralesional injections **(23)**.

These therapies function by stimulating a Th1-dominant immune response, characterized by increased production of cytokines such as IFN-γ, IL-2, IL-12, and TNF-α, which activate cytotoxic T lymphocytes and NK cells to target HPV-infected keratinocytes **(24).**

Topical immunotherapeutic agents include imiquimod and contact sensitizers such as diphenylcyclopropenone (DPCP) and squaric acid dibutyl ester (SADBE). Imiquimod is a well-established immune response modifier that induces the production of IFN-α, TNF-α, IL-1, and IL-6, while also promoting NK cell activation, thereby exerting antiviral and antitumor effects. It is widely used for genital and cutaneous warts and is particularly suitable for small, non-keratinized lesions **(25).**

Contact immunotherapy, on the other hand, works through induction of a type IV delayed hypersensitivity reaction, in which hapten-protein complexes trigger a localized immune response against HPV-infected cells. DPCP has demonstrated superior efficacy and safety compared to earlier agents such as dinitrochlorobenzene (DNCB), with studies reporting clearance rates as high as 88% and minimal recurrence **(26).**

Systemic immunotherapy also contributes to wart management. Oral zinc sulfate, for example, enhances immune competence by stimulating the production of antiviral cytokines such as IFN-α and IFN-γ. A placebo-controlled trial demonstrated complete clearance in 87% of patients treated with zinc compared to none in the placebo group **(27).** Other systemic agents, including cimetidine, levamisole, and various natural products such as echinacea and propolis, have been explored with variable efficacy **(28).**

Intralesional immunotherapy represents one of the most promising modalities, particularly for multiple and recalcitrant warts. This approach utilizes the host's immune system to mount a DTH response against injected antigens, leading to both local and distant wart resolution **(29).** Unlike destructive therapies, intralesional immunotherapy can induce clearance of untreated lesions, making it particularly advantageous for patients with multiple or difficult-to-access warts **(30). Figure 4,5.**

Various antigens have been employed, including MMR vaccine, BCG vaccine, purified protein derivative (PPD), Mycobacterium welchii (also known as *Mycobacterium indicus pranii* or MIP) (Mw) vaccine, Trichophyton antigen, and IFNs. These agents stimulate Th1 cytokine production and enhance systemic immune surveillance against HPV **(31).**

Intralesional IFN-α has shown superior efficacy compared to placebo and systemic interferon in achieving complete clearance and reducing recurrence rates in genital warts **(32).** Similarly, intralesional MMR vaccine has demonstrated favorable outcomes, with complete clearance reported in 63% of patients and minimal adverse effects **(33).**

Other modalities such as autoimplantation further highlight the role of antigen-specific immunity by reintroducing autologous wart tissue to stimulate a targeted immune response against HPV serotypes **(34).**

Table (2): Various agents used as immunotherapy for warts **(35).**

Agents	Indication, dosage & administration
Topical agents:	
Imiquimod	For genital and cutaneous warts, 5% cream, 3 times a week, for 16 week
Sinecatechins	For cutaneous warts, 10% ointment 3 times a day for maximum 16 weeks
BCG	For cutaneous and genital warts, applied topically on the warts in normal saline or salicylic acid, washed after 2 hours, weekly treatment for 6 to 12 weeks
Intralesional agents:	
Mw vaccine	For cutaneous warts, 0.1 ml intradermal into 3-5 warts or all warts, followed by 0.1 ml intralesional, 2- 4 weekly, maximum 10 sessions
BCG vaccine	For cutaneous and genital warts, 0.1-- 0.5 ml intralesional injection in the largest wart, in 2 weeks interval in 5 sessions.
PPD	For genital warts, 0.1 ml weekly intradermal injection in the forearm for 12 weeks
MMR vaccine	For cutaneous warts, 0.3- 0.5 ml into the largest wart fortnightly for up to 5 sessions
***Candida*l extract**	For cutaneous warts, 0.1- 0.3 ml injected into the largest wart at first session, then 0.3 ml every 2 weeks
Trichophyton antigen	For cutaneous and genital warts, 0.3 ml injected into the largest wart every 3 weeks, maximum of 5 sessions
Tuberculin	For cutaneous warts, 2.5 units into few warts every 2 weeks
Vitamin D3	For cutaneous warts, 0.2 ml of 7.5 mg/ml, Vitamin D intralesional, 2 sessions 4 weeks apart
IFN alpha 2B	For genital warts, 1-2 million units 3 days/week for 3 weeks
Systemic:	
Zinc	For cutaneous warts, 10mg/kg/day (2.5 mg/kg/day elemental zinc) for 2 months
Cimetidine	For cutaneous warts, 20- 40 mg/kg/day for 3- 4 months
Levamisole	For cutaneous warts, 2.5-5 mg/kg/day, 2-3 consecutive days every 2 weeks for 4-5 months.
Echinacea	For cutaneous warts, 600 mg single oral dose (single study)
Propolis	For cutaneous warts, 500 mg single oral dose (single study)
HPV vaccines	For cutaneous warts, 0.5 ml intramuscularly, at 0, 2 and 6 months (2 dose or 3 dose regimen) may be followed

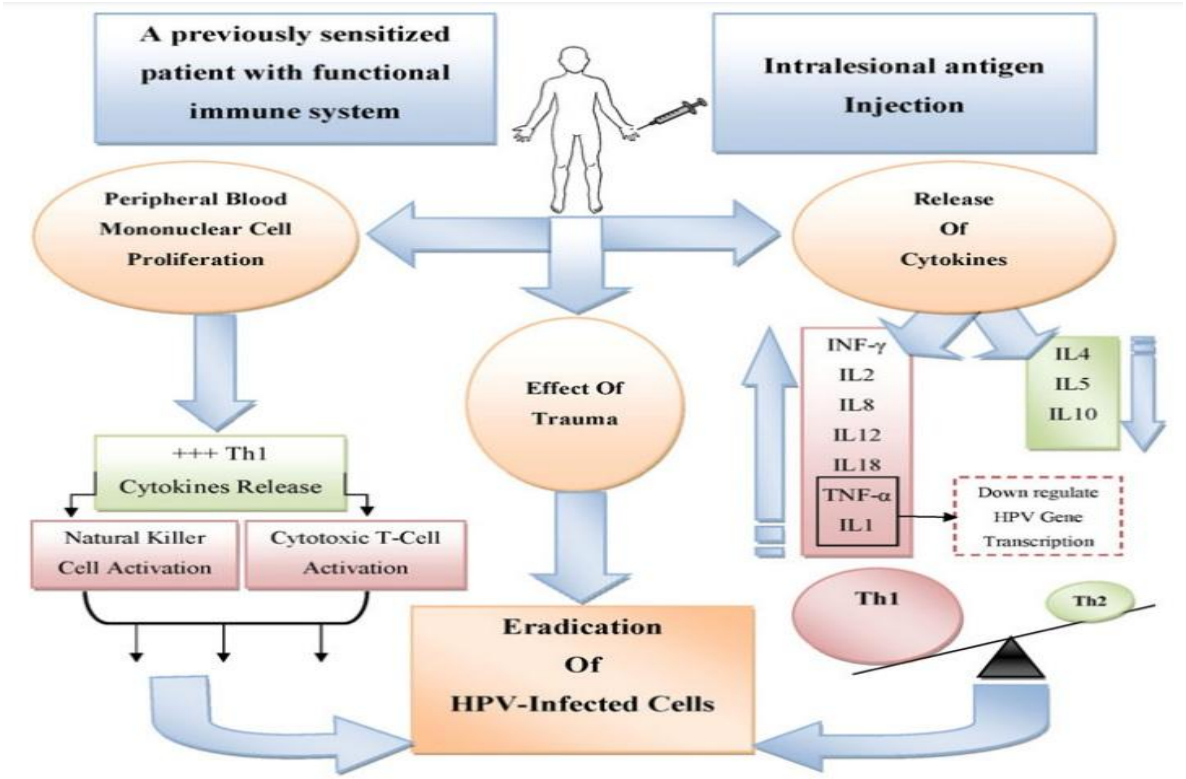

Figure (4): Mode of action of intralesional antigen immunotherapy. HPV human papillomavirus, IFN interferon, IL interleukin, Th1 T helper 1, Th2 T helper 2, TNF tumor necrosis factor **(30).**

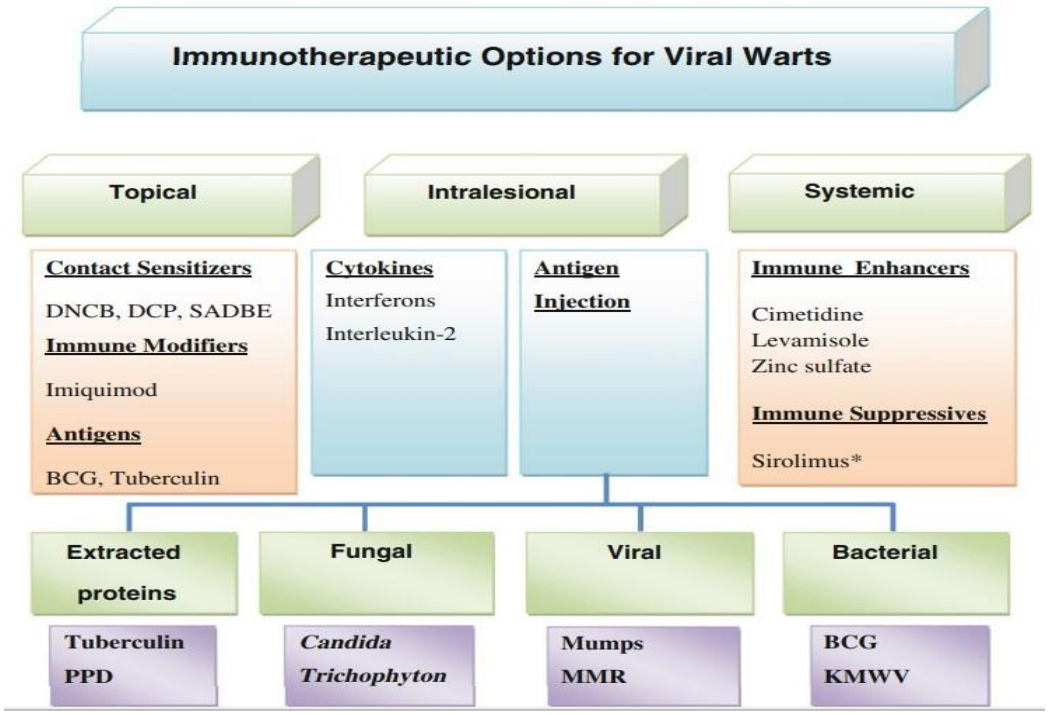

Figure (5): Immunotherapeutic options for viral warts **(30).** Asterisk sirolimus is used for treatment of warts in organ transplant patients. DNCP dinitrochlorobenzene, DPC diphencyprone, SADBE squaric acid dibutylester, MMR measles, mumps, rubella, BCG Bacillus Calmette Gue´rin, KMWV killed Mycobacterium w vaccine, PPD purified protein derivative.

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