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Review Article

Updates on Etiopathogenesis and Management of Planter Warts.

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Abstract:

Cutaneous wart is a benign skin growth brought on by the human papillomavirus (HPV), plantar wart is that type of wart occurring in plantar aspect of the foot, To date, over 400 variants of HPV, HPV 2,4,27,57, and 60 are the most common serotypes causing plantar warts. The formation of a successful cell-mediated immune response is necessary for wart regression. Plantar warts typically present clinically by discomfort, oedema, or a stone sensation under the foot. Upon examination, plantar warts manifest as thickened (cobblestoned) plaque or rough, flesh-colored to yellow or grey-brown, hyperkeratotic papules. Dermoscopic features of viral warts include homogeneous black to red spots and globules, papilliform surfaces, and interrupted conspicuous skin lines. The histopathology of viral warts exhibits papillomatosis, acanthosis, and hyperkeratosis together with the distinctive koilocytosis in higher keratinocytes. Numerous therapeutic approaches have also been tr ied and tested to find the best results with the fewest negative effects. In order choose the optimum strategy of treatment that would yield the most satisfying results, we have compiled the most up-to-date and widely recognized ideas on etiopathogenesis, clinical manifestations, and dermoscopic presentations in this review paper.

Keywords: Plantar wart, HPV, clinical presentation, dermoscopy, histopathology.

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Introduction:

A benign skin growth called a cutaneous wart is brought on by the human papillomavirus (HPV), plantar wart is that type of wart occurring in plantar aspect of the foot [(1)]. To date, over 400 genotypes of HPV can infect humans.[(2)] These types are classified into species. Species are categorized into 1 of 5 genera, including α, β, γ, m, and ν [(3)]. HPV 2, 4 , 27, 57, and 60 are the most common serotypes causing plantar warts. [(4)]

The non-enveloped HPV virus is made up of circular, double-stranded DNA that is encased in an icosahedral capsid.[(5)] The three areas that make up the HPV genome are the upstream regulatory region (URR), the late (L) region, and the early (E) early region.[(6)] The URR (upstream regulatory region) contains the origin of DNA replication (ori) along with the transcription-factor binding sites necessary for the regulation of RNA-polymerase-II-dependent transcription, polyaden-ylation sites early and late (PAE and PAL, respectively), and nine ORFs (open reading frames): six were found in the early region (E1, E2, E1^E4, E5, E6, E7, and E8), and two in the late region (L1 and L2).[(7)]

Immunity to the wart:

A successful cell-mediated immune response is necessary for wart regression. The viral antigen is

initially detected by the epidermis's Langerhans cells, which then present it to T cells in a lymph node via the regional lymphatic drainage system. T cells are then activated and produce an antigen-specific immune response at the site of viral penetration. [8]

A host can become infected by direct touch with virus particles or indirect interaction with objects like towels, socks, shoes, flooring, and sporting goods.[9] The virus enters the body through recurring microtrauma to the skin of the plantar aspect of the foot; there is neither viremia nor systemic dissemination associated with HPV infection. [10]

In the general population, cutaneous viral wart prevalence ranges from 7 to 12%, of which common wart (42%), palmo plantar wart (20%), and plane wart (18%). [11]

Clinical presentation of planter wart:

Plantar warts typically manifest clinically as discomfort, swelling under the foot, or a stone-like sensation.[9] It can be observed as thickened (cobblestoned) plaque or rough, flesh-colored to yellow or grey-brown, hyperkeratotic papules. A mosaic wart is made up of several plantar warts that have joined together. [12]

Plantar warts can be seen as rough, flesh-colored to yellow or grey-brown, hyperkeratotic papules or as thickened (cobblestoned) plaque, Multiple plantar warts that have united to form a mosaic wart.[12]

Dermoscopy of planter wart:

Dermoscopy would be a useful diagnostic tool in this lesions since the clinical features are similar to those of other skin lesions such dermal nevus, seborrhoeic keratosis (SK), acne, and comedones, calluses, corns, acne, and folliculitis. [13] Papilliform surfaces, interrupted conspicuous skin lines, and homogeneous black to red spots and globules are all regarded as dermoscopic characteristics of viral warts.[14]

Histopathology of planter wart::

Histopathology is very useful for diagnosis. Acanthosis and hyperkeratosis are observed in viral warts, together with the distinctive koilocytosis observed in higher keratinocytes. There is also papillomatosis in the majority of warts. Basophilic nuclear inclusion bodies, which are observed ultrastructurally to be made of arrays of viral particles, may be present in koilocytes and other granular layer cells. Eosinophilic inclusions resembling uneven, clumped keratohyaline granules are observed in these top epidermal cells. [15]

Treatment of viral warts of planter wart::

1.The "wait-and-see" strategy:

This good option in many situations, particularly with young patients, Specially for lesions that not painful , hinder function, or cause psychological distress. [16]

2. Destructive methods:

a- Physical methods:

- **Electrosurgery**

It was suggested that the success rate of cryotherapy treatments is similar to that of electrosurgery. Pain during infiltrating local anaesthetic occured in all patients with electr-osurgery; whereas, in cryotherapy, some indivi-duals during procedure had brief pain or discomfort resembling stinging/burning feeli-ng. When electrosurgery was used instead of cryotherapy, there was a significant increase in pain, wound infection, and delayed wound healing after four weeks. Electrosurgery is not a viable method for warts on the plantar aspect because of its high rate of pain. Due to open wounds and lesions that became infected, electrosurgery had a higher rate of delayed wound healing in lesions than cryotherapy. [17]

- **Cryotherapy:**

The most widely utilized technique in medical practice is the application of liquid nitrogen using a cotton bud or cryospray, Compressed-gas is dimethyl ether and propane [18], Depending on the location and size of the wart, we typically freeze until a halo of frozen tissue forms around it. This halo is maintained for 5 to 30 seconds. Typically, we repeat the therapy every two to three weeks until the warts disappear, for a total of no more than six sessions.[19]

- **Curettage and surgical excision:**

Remission rates for chemotherapy and surgical excision range from 65-85%. [20], typically linked to a significant risk of scarring.[16]

- **Laser and photodynamic therapy:**

Both the carbon dioxide laser and the pulsed dye laser cause non-selective thermal tissue destruction. However, the pulsed dye laser is more targeted, producing intralesional ischemia and coagulating blood vessels to kill the wart. [21]

b- Chemical procedures:

- **Salicylic acid:**
  Salicylic acid breaks down intercellular cohesions in the corneal layer, which results in keratolytic effects, also induce mild irritant effects that induce an immune response.[22]

- **Potassium hydroxide:**
  When compared to salicylic acid therapy, KOH therapy demonstrated a significantly better treatment response and fewer side effects, as well as increased patient satisfaction.[23]

- **Monochloroacetic acid:**
  Monochloroacetic acid has caustic effects, although there is a chance of really harmful reactions.[24]

- **Topical treatment with formic acid:**
  The giant stinging nettle (Urtica dioica) and the red ant (Formica rufa) create formic acid [25], Although its precise mode of action is still unknown, formic acid mostly destroys tissue by having a drying effect that is comparable to formalin.[16]

- **Cantharidin:**
  Keratinocytes absorb cantharidin, it is a blistering chemical that present in the oral secretions of oil beetles (Meloidae),[26] It causes acantholysis by activating neutral serine proteases, which disrupts desmosomal connections between epithelial cells.[21]

- **Silver nitrate:**
  The best way to cure warts is to use silver nitrate 95% in a solid formulation, which can be obtained through a caustic antiseptic and astringent pen. may result in skin discoloration that is greyish and localized inflammation.[26]

- **Vitamin A derivatives:**

Vitamin A acts by affecting keratinocyte growth and keratinization.[21]

c- Topical immunotherapy

- **Diphencyprone(DCP):**

When compared to dinitrochlorobenzene (DNCB) at the same concentration, DCP is a more powerful contact sensitizer. [27]

- **Squaric acid dibutylester**
  Squaric acid dibutylester acts by causing an HPV-infected tissue to undergo a type IV hypersensitivity reaction.[28]

- **Imiquimod**
  A synthetic immune response modulator with antiviral and anticancer properties is called imiquimod.

- **Sinecatechins**
  Sinecatechins acts as a scavenger of reactive oxygen-free radicals. Also, it has an inhibitory effects on transcription factors.[29]

d- Intralesional immunotherapy

- **Fluorouracil**
  By preventing DNA synthesis, the fluorinated pyrimidine antimetabolite fluorouracil functions as an antitumor agent, [30] may result in bullae, moderate to severe pain, and onycholysis, or nail detachment (particularly when used for warts close to the nails).[31]

- **Activated vitamin D**
  Analogues of vitamin D3 control cytokine synthesis, cell proliferation, and differentiation. It affects angiogenesis, tumour invasion, and cell death. [32]

- **Bleomycin**
  An antibiotic medication developed from Streptomyces verticillus, that has antiviral, anticancer, and pyrimidine and purine base elimination because of its capacity to bond with DNA and cause bleomycin strand scission,[33]. The most common way to apply bleomycin was by injecting it into the lesion using a syringe, although alternative techniques such a dermojet, prick method, and dermatographic approach can also be employed Follow up is usually weekly during the first month, and then every 3 months.
  Routine investigation when it is necessary to perform chest radiography, liver function testing, and renal function testing before and after 3 months of treatment [34]. local side effect as necrosis, pain, scaring, pigment

change, Raynaud's phenomenon, and nail dystrophy may occur**.** [35]

- **Interferon (α and γ)**

Low-molecular-weight glycoprotein interferon-α is produced by various cell types and functions by blocking the growth of tumor and the reproduction of viruses. For best results, apply IFN-a-2b, an intralesional IFN FDA-approved for genital warts, twice weekly for three weeks.[36] Activated T cells produce IFN-γ, which has a stronger antiproliferative effect than IFN-a and IFN-b. [37] Additionally, it causes macrophages and natural killer cells to become cytotoxic. [38]

- **Measles, mumps, and rubella vaccine**

The measles, mumps, and rubella vaccine eliminates warts that have been treated and those that are far away and untreated, with no side effects and a low chance of recurrence. Although the exact mechanism of action of intralesional injection of MMR vaccination and antigens is uncertain, it has been postulated that the primary immunotherapy mechanism is nonspecific inflammatory response to the injected antigens. [39] Flu-like symptoms and injection site soreness are the most frequent side effects. [40]

- **Mycobacterium *w***

Mycobacterium w is created from an unusual, fast-growing, nonpathogenic Mycobacterium that is a member of Runyon class IV. It is an antigenic agent that triggers the T-cell response and the cytokine (IL-2, IFN-g) production. [41] Fever, discomfort, sterile pustule at the injection site, and paraesthesia in limbs far from the injected warts are possible side effects. [42]

- **Bacillus Calmette–Guérin vaccine (BCG):**

BCG is used as a prophylaxis against tuberculosis also used in the management of recurrent oral stomatitis and alopecia areata [43]. The main mechanism of action of the immunotherapy is via increasing cytokines including interleukin (IL)-1, IL-2, and tumour necrosis factor a (TNF-a) and activating CD4 cells. [44]

- **HPV vaccine**

By strengthening the immune system's defence against HP viruses, HPV vaccinations are primarily offered as a preventative measure against cervical cancer. Two vaccines are available, per the SI-RL immunization guidelines: a nonavalent vaccine (Gardasil® 9) and a bivalent vaccine (HPV 16 and 18; Cervarix®). The latter took the position of its quadrivalent predecessor in 2016 (HPV 8, 11, 16 and 18). [45]

- **Intralesional *Candida albicans* antigen**

The primary mechanism by which Candida antigen functions is immune system stimulation, causing a delayed-type hypersensitivity reaction against both the wart tissue and other antigens. In order to completely remove HPV infection, it also works by producing Th1 cytokines, which stimulate cytotoxic and natural killer cells. This helps with distant and localised warts. [46]

When injecting, two distinct techniques are employed. Either an intradermal candida antigen injection is administered to the patient on the volar aspect of the forearm to cause a delayed hypersensitivity reaction, which is measured 48–72 hours later as erythema and induration. Patients who have 5 mm in diameter induration and erythema are deemed Responders and are eligible to get the therapy. [47]

Another approach omits the intradermal testing step and involves injecting the antigen straight into the largest wart, injected using an insulin syringe. The syringe's bevel should be facing upward and positioned parallel to the skin's surface. This treatment is continued every two to three weeks until the warts completely disappear, or up to three sessions if there is no improvement [48]. The most frequent adverse effects of candida immunotherapy include myalgia, painful purple digit syndrome, fever responses, and discomfort, erythema, and edoema at the injection site. [49]

- **Acyclovir**

Acyclovir is an antiviral drug act as purine analogue, used mainly Oral, injectable, and topical treatments are available for the treatment of herpes simplex virus (HSV) and herpes zoster virus (HZV) infections. [50]

The selective suppression of herpes virus DNA replication is the primary mechanism of action.

First, only in infected cells can viral thymidine kinase phosphorylate acyclovir into acyclovir monophosphate; it has no effect on uninfected cells. Cellular guanosine monophosphate (GMP) kinases (human) and other kinases convert acyclovir monophosphate to acyclovir triphosphate. [51]

As a result, compared to normal, uninfected cells, the concentration of Acyclovir triphosphate produced in virally infected cells was 40–100 times higher. Acyclovir triphosphate completely and irreversibly inhibits viral DNA polymerase by competing with normal deoxy adenosine triphosphate. [51]

As regard adverse effect acyclovir is well tolerated. The main risk is renal tubular crystallization with rapid intravenous administration, must be cautious with high doses and in the dehydrated patient. Interstitial nephritis also reported in some cases. Central nervous system affection is uncommon, but may occur as lethargy, tremors, or seizures. Specially in Patients with underlying diseases involving the central nervous system .[52]

e- microwave therapy

Most long-standing plantar warts disappear after three to four sessions of carefully heated, keratinized skin treated with microwave therapy. [53] In contrast to other widely used treatments, which can cause ulceration, discomfort, bleeding, and secondary infections. [54] Patient receiving microwave therapy required no post-treatment recovery period. Although participants reported considerable pain during the application of microwave therapy. [53]

f- Systemic immunotherapy

- **Cimetidine**

The H2 receptor blocker cimetidine is used to treat stomach acidity and duodenal ulcer disease. In cutaneous diseases, it is used in conditions that are characterized by increase of histamine release as an adjuvant therapy as allergic, urticaria, mastocytosis, and different eosinophilic dermatoses, Additionally, it suppresses T cells by preventing H2 receptors from doing their job. [55]

Cimetidine's immunomodulating action stimulates the immune system of individuals with T-cell immunodeficiency, as seen in the case of cutaneous viral infections such as herpes simplex, molluscum contagiosum, epidermodysplasia verruciformis, zoster, and warts, as well as skin cancers such as malignant melanoma. [56] primarily used for numerous warts, vaginal warts, periungual warts, adult recalcitrant warts, and childhood warts. [57]

- **Levamisole**

Levamisole is an anti-helminthic medication used to treat animal and human worm infestations. Due to its immunomodulatory properties, it was taken off the market in the USA and Canada but is still in use in other nations. Levomisol is used to treat bacterial, viral, and parasite infections in cutaneous illnesses. Additionally, it can be used in conjunction with other medications, such as prednisolone, to treat aphthous ulcers, lichen planus, and erythema multiforme. [58]

Levomisole typically has modest side effects, such as rash, nausea, cramping in the abdomen, change in taste, alopecia, arthralgia, and a feeling similar to the flu. Agranulocytosis is the most dangerous side effect of levamisole. [59]

- **Zinc sulfate**

Zinc is one of the most important micronutrients for humans. It is available in both topical and oral forms. In cutaneous diseases , It is used to treat inflammatory problems including acne vulgaris, psoriasis, and eczema, as well as infections like leishmaniasis, leprosy, and dermatophytosis. Hair and nail disorders include alopecia, seborrhoeic dermatitis, and erosive pustular dermatosis of the scalp. [60]

It is used to treat infections such as dermatophytosis, leishmaniasis, and leprosy, as well as inflammatory issues such as psoriasis, eczema, and acne vulgaris. Alopecia, seborrhoeic dermatitis, and erosive pustular dermatosis of the scalp are examples of illnesses affecting the hair and nails. [61]

- **Systemic retinoids**

Treatment for cutaneous viral wart with topical and systemic retinoids is safe and efficient. Systemic and topical retinoids were not less effective than one another.[62]

- **Hydroxychloroquine**

notable reaction that was temporally connected with hydroxychloroquine treatment The antiviral property of hydroxychloroquine may have a

connection to the patient's experience. Also comforting is the lack of recurrence.[63]

f- Autoimplantation therapy :

The modified technique of autoimplantation using the pared stratum corneum tissue of the wart instead of the subcutis deep wart tissue for autografting is a safe, efficacious, less traumatic and rapid procedure for the treatment of multiple, recurrent and palmoplantar warts. This technique also scores over the autowart injection method of treatment.[64]

g- Acupuncture

In the United States, Europe, and numerous Asian nations, acupuncture is a widely accepted alternative medical practice. It modulates the immune system and provides acupuncture-like analgesic effects. That might work well for a number of immune-related conditions, such as immunodeficiency syndromes, autoimmune illnesses, infections, and allergy disorders. [65]

Conclusion:

A prevalent problem in dermatology practice is plantar wart. Its pathophysiology is complex, making treatment difficult. The best course of treatment with the most efficacy and the fewest side effects may require more investigation and clinical trials

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