MULTIPLE COMMON WARTS MANAGEMENT OPTIONS

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Abstract

Background: Warts constitute the commonest cutaneous manifestation of human papillomavirus (HPV) that infects epithelial tissues of the skin and mucous membranes. Despite the existence of many destructive and immunotherapeutic modalities, treatment of warts still represents a real challenge. Warts (verrucae vulgares) are common benign proliferations of the epidermis caused by several types of the human papillomavirus (HPV). They can be found throughout the human body are most commonly seen in the hands and feet, face, and anogenital region. Warts affect 7% to 10% of the dermatological departments around the world. Genital warts, in particular, are the most common sexually transmitted disease. Traditional therapeutic options for warts, such as topical salicylic acid, topical imiquimod, bleomycin injections, cryotherapy, surgical excision and electrocautery, have proven somewhat effective, but these approaches may offer incomplete and superficial results leading to high recurrence rates in addition to being destructive therapies with high risk of scarring.

Keywords: Multiple Common Warts

Background

Warts are benign skin growths that appear when a Human Papilloma virus (HPV) infects the top layer of the skin. Warts can spread by contact with the wart or something that touched it. They are often skin-colored and feel rough, but they can be dark (brown or gray-black), flat, and smooth.

Epidemiology:
Warts are a common medical problem, especially in Whites. The estimated global HPV prevalence is 11.7%. South Africa (17.4%), Eastern Africa (33.6%), Eastern Europe (21.4%), Western Europe (9%) and Caribbean (35.4%). They are more common among young people. Estimated rates of genital warts in sexually active women are 12%. Warts have been described at least as far back as 400 BC by Hippocrates.

- Frequency: Warts are common worldwide and affect approximately 10% of the population. In school-aged children, the prevalence is as high as 10% to 20%. They are more common among immunosuppressed patients and meat handlers.
- Age: Warts can occur at any age. Although rare in infancy and early childhood, prevalence increases among school-aged children and peaks at 12 to 16 years.
- Race: Warts are twice as common in Whites as in Blacks or Asians.
- Sex: The male-to-female ratio is approximately equal.

Diagnosis:
Symptoms:
Common warts usually occur on fingers or hands and may be:
• Small, fleshy, rough, grainy growth.
• Hard, thickened skin over a well-defined spot on the skin.
• Black pinpoints (warts seeds) which are clotted blood vessels.
• A lesion that interrupts the normal lines and ridges in the skin (4).

Dermoscopy:
Viral warts are keratinocytic lesions with a lobular structure, sometimes with a central thrombosed capillary within each lobule. The normal dermatoglyphics are interrupted. Some warts exhibit a papilliform structure, with or without red streaks implementing micro-hemorrhages. Warts may also show fingerlike, knoblike or mosaic patterns. Vascular forms include hairpin, glomerular, dotted or mixed forms (5).

Figure (1): Dermoscopy of different types of warts
Dermoscopy of plane wart revealing tiny dotted (pinpoint) vessels on a light brownish background. b Dermoscopy of verruca vulgaris. The dotted vessels are larger than in plane warts and located in the centre of the papillae (frogspawn). c Dermoscopy of verruca palmo-plantaris typically shows dots and brown to red streaks that correspond to hemorrhages. d Dermoscopy of callus. Note the central bluish to reddish structureless area, which can help in selected cases to distinguish callus from warts. Original magnification x10 (6).

Histopathology:
Common warts:
Histopathologic features include acanthosis, digitated epidermal hyperplasia, papillomatosis, compact orthokeratosis, hypergranulosis, tortuous capillaries within the dermal papillae, and vertical tiers of parakeratotic cells with red blood cells entrapped above the tips of the digitations. Elongated rete ridges may point radially toward the center of the lesion. In the granular layer, cells infected with HPV have coarse hyaline granules and vacuoles surrounding wrinkled-appearing nuclei. Koilocytic cells are pathognomonic (7).
2- Filiform:
Filiform warts appear similar to common warts, but they may have prominent papillomatosis. The paring of a wart often reveals tiny black dots which represent thrombosed capillaries. (8)

3- Deep Palmo-plantar:
Deep palmoplantar warts are similar to common warts except the lesion lies deep to the plane of the skin surface. The endophytic epidermal growth has the distinctive feature of polygonal, refractile-appearing, eosinophilic, cytoplasmic inclusions made up of keratin filaments, forming ring-like structures. Basophilic parakeratotic cells loaded with virions and basophilic nuclear inclusions and may be in the upper layers of the epidermis (9).

4- Flat:
Flat warts are similar to common warts in light microscopy. Cells with prominent perinuclear vacuolization around pyknotic, basophilic, centrally located nuclei can be in the granular layer. These are referred to as "owl's eye cells" (10).

5- Cystic:
A cyst wart is filled with horny material. The wall is composed of basal, granular, and squamous cells. Many epithelial cells have large nuclei and clear cytoplasm with eosinophilic inclusion bodies. The cyst may rupture causing a foreign body granuloma (8).

Figure (2): Histopathology of warts (Sanders, 2008)

Laboratory investigations:
The diagnosis of a wart is usually made on a clinical examination; however, some laboratory workup is needed to assure the diagnosis and etiology of warts. Immunohistochemical detection of HPV structural proteins confirms the presence of a virus, but this has a poor sensitivity. Viral DNA identification using Southern blot hybridization is more sensitive and specific for HPV type. Polymerase chain reaction (PCR) amplifies viral DNA for testing. Although HPV can be detected in younger lesions, it is not always present in older lesions (11).

Differential Diagnosis:
1- Epidermodysplasia verruciformis: Epidermodysplasia verruciformis (EV) is an inherited disorder in which there is a mild defect of cell-mediated immunity and widespread and persistent infection with HPV. The lesions vary considerably and may be flat, wart-like lesions, often pigmented, red or atrophic macules or branny pityriasis versicolor-like plaques (12).
Bowenoid papulosis: Also known as vulval, penile and anal intraepithelial neoplasia (VIN, PIN, AIN), Bowenoid papulosis presents as small papules, usually multiple, sometimes pigmented, on the cutaneous and mucosal surfaces of the ano-genital regions in both sexes (13).

Focal Epithelial Hyperplasia (Heck disease): Focal epithelial hyperplasia is characterized by acanthosis, blunting, hyperplastic mucosa with thin parakeratotic stratum corneum, anastomosis of rete ridges, and whiteness of epidermal cells due to intracellular edema. Some may have prominent keratohyaline granules, and vacuolated cells may be present (7).

Epithelioma cuniculatum and verrucous carcinoma: Epithelioma cuniculatum is a squamous cell carcinoma that appears as a soft bulbous mass with a squashy consistency on the sole of the foot. Multiple sinuses open onto the surface and when pressed. Verrucous carcinoma may develop in the oral cavity and on the genital mucosa and appear as cauliflower-like lesions (12).

Other lesions: Corn, callus, lichen planus and molluscum contagiosum are also clinically related to warts diagnosis (16).

Prevention and vaccination: HPV vaccines: HPV vaccines are prepared from empty protein shells called virus-like particles produced by recombinant technology. They do not contain any live biological product or DNA, so they are non-infectious. Current HPV vaccines are designed to protect against HPV 16 and 18; the quadrivalent vaccine also protects against low-risk genotypes 6 and 11 (14).

Gardasil, Gardasil 9, and Cervarix, the three vaccines used to prevent genital warts, are unable to prevent plantar warts as they target different HPV strains. To this end, patient need to reduce their risk by maintaining good foot hygiene and covering their feet in places where people walk barefoot (17).

Management: Once the diagnosis is made, the treatment depends on symptoms, patient preferences, and cost. There are many treatments for warts, but none is very effective, and recurrences are common. One should try the least expensive and least painful treatment first. The more expensive and invasive treatments are usually reserved for multiple recurrent warts. It is known that nearly two-thirds of warts spontaneously disappear within 24 months. There is a small risk that the wart can enlarge and may even spread to other areas (15).

The primary reasons for treating warts are to 1) alleviate symptoms associated with the warts; 2) prevent spread of the virus to adjacent anatomical sites or other people; and 3) removal of the wart, usually for aesthetic reasons. Treatment modalities are generally either immune modulating or ablative (18).

The focus of non-pharmacologic management is preventing the spread of HPV either through autoinoculation or spread to others. This includes hand washing before and after handling warts; avoiding picking, cutting, or shaving warts; keeping feet clean and dry; designating a towel to dry only specific body areas with warts; avoiding sharing towel, razors, or other objects capable of carrying the infectious agent; keeping warts covered; and avoiding walking barefoot (19).

Salicylic acid is considered the first-line agent for the majority of cutaneous warts. It is a keratolytic agent that slowly breaks down the HPV-infected epithelial tissues. It may also cause an immune response to be mounted in clearing the infective agent through mild irritation (18).

Cryotherapy is another nonprescription option that has been used for many years in physicians’ offices. It involves the use of liquid nitrogen at a temperature of −196°C to create an area of necrosis below and around the wart with a resulting tissue irritation that induces the immune system to clear the infection. Cryotherapy provides benefits with regard to certain aspects: cryotherapy brings about quicker results than salicylic acid; in general, only 3–4 applications (at 14-day intervals) are necessary. Aggressive cryotherapy (for 10–30 seconds) achieves a clearance rate roughly 20% higher than weak cryotherapy.
Cryotherapy should continue for at least three months, even if unsuccessful at first; this especially applies when treating hands and feet (20).

Electrocautery is a routine clinic procedure in treatment of warts. Electric current yields high amount of heat sufficient for tissue destruction and wart removal. The patient undergoes electric cauterization with or without local anesthetic according to the site and extent of the wart. Electrocautery usually has minimal side effects, but if any happens it includes pain, discomfort or slight bleeding (21).

CO₂ laser ablation is another effective option in treatment of warts with complete remission in 75 % of cases. A clearance rate of 75 % to 88 % in this ablative procedure signifies that not all HPV-infected keratinocytes have been destroyed. In order to achieve a high level of freedom from recurrence and nearly 100 % clearance, it is therefore crucial to maintain the required safety margins, while taking anatomical structures into account. This is the only way to ensure not missing any HPV-infected keratinocytes that are clinically not visible. Reported drawbacks of this procedure include occurrence of large wounds, long healing times (potentially entailing sick leaves from work), and scarring (22).

Photodynamic therapy (PDT), which involves treatment with aminolevulinic acid followed by phototoxicity, is considered likely beneficial, although it is expensive and not as readily available. It is applied to the wart for 3 to 8 hours, after which the treated wart is exposed to a range of light sources. Adverse effects associated with PDT are considered mild and include burning sensation, mild-to-moderate pain, pigmentation changes, and erythema (23).

Immunotherapy in treatment of warts include intralesional injection of measles, mumps and rubella (MMR) vaccine, candida albicans and tuberculin PPD. Intralesional immunotherapy stimulates the host immune system to trigger a delayed-type hypersensitivity response to a multitude of antigens, including the wart tissue. This therapy is associated with the production of a Th1 cytokine milieu and activation of cytotoxic and natural killer (NK) cells to fight HPV infection, not only in the local warts, but also affecting distant warts, unlike traditional wart therapies. Minimal side effects were observed in patients underwent immunotherapy, only slight fever and discomfort were noticed (24).

Cidofovir, (intralesional): A nucleoside analogue markedly effective against a wide range of DNA viruses, cidofovir has been approved for cytomegalovirus (CMV)-induced retinitis in HIV patients and is also effective against herpes simplex virus type 1 and 2, Epstein-Barr virus, papillomavirus and others. In 2012, Broganelli et al. published a retrospective analysis of 280 patients who had been treated with intralesional cidofovir over the period from 2003 to 2008. The maximum daily dose came to 140 mg for each site of infiltration. Two hundred seventy-six cases saw 100 % clearance, with no recurrence observed over a twelve-month period. There are, however, currently no more recent studies on the use of cidofovir.

Other treatment options with unknown efficacy include occlusion with duct tape, thought to act by causing local irritation that stimulates an immune response; intralesional bleomycin, which causes acute tissue necrosis that may stimulate an immune response (25); pulse dye laser, which destroys the dilated capillaries of a wart and is well tolerated but requires expensive equipment (26); intralesional interferon-α, a low-molecular weight glycoprotein that may be involved in inhibition of viral replication (28); imiquimod, which is well established for genital and perianal warts but lacks published evidence for use in cutaneous warts; and surgical removal of warts (27).
Table (1): Guidelines for cutaneous warts treatment (29)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Suggested method of use</th>
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</thead>
<tbody>
<tr>
<td>Salicylic acid (SA)</td>
<td>Daily application of 15±20% SA in suitable base. 25±50% SA may be used cautiously on plantar warts. 2 ±5% SA cream may be used for plane face wart</td>
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<tr>
<td>Cryotherapy</td>
<td>15±20 s single or double freeze of warts, every 3 ±4 weeks</td>
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<tr>
<td>Photodynamic therapy</td>
<td>3 treatments: 20% topical amino-levulinic acid + irradiation</td>
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<tr>
<td>Bleomycin</td>
<td>Single intralesional delivery</td>
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<tr>
<td>Retinoids</td>
<td>Topical: 0.05% tretinoin cream daily Systemic: 1 mg/kg/day acitretin for 3 months</td>
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<tr>
<td>Formaldehyde</td>
<td>Daily application of 0.7% gel or 3% solution as short soak for mosaic plantar warts</td>
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<tr>
<td>Thermocautery</td>
<td>Single surgical removal of wart; risk of scarring</td>
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<tr>
<td>Glutaraldehyde</td>
<td>Daily application of 10±20% in suitable base</td>
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<tr>
<td>Chemical cautery</td>
<td>Twice weekly application</td>
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<tr>
<td>CO2 and pulsed dye laser</td>
<td>Single treatment</td>
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<tr>
<td>Cimetidine</td>
<td>Up to 40 mg/kg/day for 3 months</td>
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<tr>
<td>Topical sensitization</td>
<td>Sensitization with 2% diphencyprone, then weekly application of appropriate dilution of the allergen.</td>
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References.


