REVIEW ARTICLE

Human papillomavirus: Manifestations, prevention and treatment: An overview

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ABSTRACT

Human papillomavirus (HPV) is an epitheliotropic virus that can infect and cause disease of skin or mucosa at any site. HPV associated lesions can be broadly divided into cutaneous and mucous membrane lesions. Cutaneous lesions include: warts, Butcher's wart and epidermodysplasia verruciformis. The anogenital diseases, include warts (condyloma), dysplasia (cervical, vaginal, vulvar, anal), and squamous cell carcinoma. A number of treatment modalities are available including electrosurgical techniques, cryotherapy, lasers, trichloroacetic acid, podophyllin and imiquimod. Bivalent and quadrivalent vaccines are approved to prevent HPV infection. Both are indicated to prevent cervical cancer, as well as genital warts in males and females

INTRODUCTION

Human papillomavirus (HPV) is an epitheliotropic virus that can infect and cause disease at any site in stratified squamous epithelium, either keratinizing (skin) or non-keratinizing (mucosa).[1] HPV associated lesions can be broadly divided into cutaneous and mucous membrane lesions,[2] that may be either benign or malignant.[3] The widespread hazards of HPV are significant, especially with respect to anogenital warts and cervical cancer, as malignant lesions are often detected at later stages. Genital HPVs are grouped into high risk types (16, 18, 31, 33, 35, 39, 45, 51, 52,56, 58, 59, 68, 73 and 82), probable high-risk types (26, 53 and 66) and low risk types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108).[4] There is currently no definite cure for HPV infection,[5] and the available methods of treatment can only eliminate signs and symptoms of HPV infections. Given the worldwide burden of HPV infection, prevention of infection could provide relief from an important public health threat. This has led to the development of HPV vaccines.[6]

Virology

Human papillomaviruses are members of the family Papillomaviridae. They are small, epitheliotropic, non-enveloped, double stranded DNA viruses.[7] Over 100 HPV (HPV 1, 2, etc.) types have been identified and are grouped according to their genotype.[8] HPV's are a major cause of infection in humans; they infect mucosal or squamous epithelia in a site-specific fashion.[9] Although the majority of these infections are benign, a subset of these infections is the instigating factor in a variety of malignancies, particularly cervical and anogenital cancers.[10]

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Structure

Independent of the site or the type of lesion, the PV virion has a constant morphology and structure.[11] The virion is a non-enveloped 8 Kb long icosahedral structure of 55–60 nm diameter. Which forms paracrystalline arrays in the nucleus of infected cells.[12] The genome can be roughly divided into three regions: a long control region (LCR), that is noncoding and controls transcription of the adjacent open reading frames (ORFs), or coding sequences; the early region, consisting of the E1, E2, E4, E5, E6, and E7 ORFs; and a late region, encoding the L1 and L2 viral capsid structural proteins.[13] The early genes encode proteins which are necessary for viral DNA replication and transcription and can subvert cellular proliferation, ultimately leading to cell transformation.[14]

The E1 protein functions in viral DNA replication, and the E2 protein is involved in both control of transcription and viral DNA replication. The E3 ORF does not contain a start codon and is unlikely to be transcribed. The E4 ORF encodes a family of small proteins that are generated by alternative splicing and post-translational modifications.[15] It codes for protein E1-E4 that disrupt the cytoplasmic keratin network.[16] The E4 protein is also found to contribute to regulation of host cell cycle control.[13] The E4 proteins are abundant in HPV lesions.[17] E5 protein is known to aid in cellular transformation and plays a significant role in viral replication. E6 and E7 proteins play a major role in the malignant transformation of cervical cells.[18] E1 and E2 are viral regulatory genes, and E6 and E7 are considered the major transforming genes responsible for oncogenes. It is because of their interference with human tumor suppressor genes p53 and Rb, respectively.[19]

The late proteins L1 and L2 make up the viral outer icosahedral capsid.[20] They code for the major and minor capsid proteins respectively, which make up the mature virion. Both proteins encode virus-neutralizing epitopes.[21] The C-terminus of L1 is exposed on the surface of the virion and is thus likely to have a role in infection and immunogenicity.[22] Capsid proteins L1 and L2 are produced during early infection when complete virion assembly occurs so they are considered as ideal targets for HPV vaccines.[23]

Life cycle

HPV's are exclusively epitheliotropic, and their replication is intimately linked to the differentiation.[12] Productive papillomavirus infection are initiated when the virus enters proliferating basal epithelial cells, probably through micro-wounds because this layer of cells is not normally accessible to the virus.[24] The receptor(s) that mediate virus binding to epithelial cells have not been definitively identified, but binding appears to depend on the L1 major capsid protein, and cell surface heparan sulfate is necessary for efficient infection in vitro.[25] The early HPV genes El and E2 support viral DNA replication and its segregation, such that the infected cells can be maintained in the lesion for a long period. As infected daughter cells migrate towards the epithelial surface, viral late gene products are produced to initiate the vegetative phase of the HPV life cycle, resulting in the high-level amplification of the viral genome.[26]

The first genes to be expressed following infection are the E1 and E2 genes, which are responsible for controlling the transcription of the viral genes and replication of the viral genome.[27] Other early genes, E6 and E7 are required to coordinate the host cell environment so that it is suitable for viral DNA replication. In the suprabasal post-mi-

totic cells, E6 and E7 induce unscheduled re-entry into S-phase of the cell cycle, activating the host replication machinery needed for amplification of viral genomes.

In combination with other cellular proteins, E6 from high-risk mucosal HPV causes degradation of the cellular protein p53. Elevated levels of p53 arrest cells in the G1 phase of the cell cycle or induce apoptotic cell death.[28] The E7 protein drives cells into S-phase largely by associating with, and causing the degradation of the members of the Rb family. As a result, E7 disrupts the association between pRb and the E2F family of transcription factors, irrespective of the presence of external growth factors. E2F subsequently transactivates the expression of a large number of cellular proteins required for DNA replication, such as DNA polymerase and thymidine kinase.[29] For the low-risk types that cause warts, such E7- mediated degradation appears to be confined to pl30, whose degradation through E7-binding leads to S-phase entry in the upper epithelial layers of infected tissue.[30]

Capsid proteins L1 and L2 are then synthesized,[31] and the amplified genomes are then encapsulated by the L1 and L2 capsid proteins to generate infectious virions. The release of HPV virions is thought to be facilitated by the E1-E4 protein. The virus particles are observed in the granular layer of the epithelium and above. Virus assembly is not believed to lyse the cells but rather the virus is shed with the cornified layer as cells slough from the epithelial surface.[32]

Epidemiology

Generally, papilloma virus-associated infections are very frequent. Cutaneous warts are caused by a small group of specific HPV types, with an overall prevalence of 20% in schoolchildren and a decline thereafter with increasing age.[33] In fact, viral warts rank among the three most common dermatoses in children and occur with equal frequency in both sexes. Re-infection with the same HPV type appears uncommon after clearance, suggesting the development of protective type-specific immunity.[34]

Epidemiologic studies show genital warts to be among the most common sexually transmitted diseases, after chlamydia and gonorrhea. The incidence of condyloma acuminatum has been steadily rising over the past three decades.[35] W.H.O. estimates that 630 million people are infected with genital HPV, resulting in a worldwide prevalence of 9–13%.[7] There is an inverse relationship between age and HPV prevalence in many countries. But in some of the poorest areas, studied HPV prevalence was high across all age groups.[36] In some countries, cross-sectional and cohort studies have shown a U-shaped curve with a first peak in women under 30 years of age and a second peak in women aged 55–64 years.[37]

It is believed that many sexually active adults are infected with HPV, but only 1±2% of them are found to have clinical lesions. Rest of the infections remain subclinical, with the latent HPV residing in the epithelial basal cells.[38]

The transmission of infection to the anogenital area takes place mainly from human-to-human and animal-to-human. Generally, the infection is transmitted by genital skin-to-skin contact but not necessarily during sexual intercourse.[37] HPV can be transmitted among technical virgins via non penetrative sexual skin-to-skin contact.[39] Autoinoculation can also frequently cause multiple manifestations of HPV-associated lesions in the anogenital area. The possibility of contamination by

a highly transmissible material of the anogenital area in the respective predisposed groups must not be excluded.[40] Although genital warts in children may be a sign of child abuse and require a sexual abuse evaluation, such lesions may result from virus inoculation through nonsexual contact.[41]

The most important risk factor for genital warts are decreasing age of first sexual intercourse, multiple sexual partners and clinical history of other venereal diseases.[42] Other possible risk factors include age of first pregnancy, previous abnormal Papanicolaou (PAP) smear, cigarette smoking, excessive alcohol intake, poor diet, poor hygiene, and impairment of cell-mediated immunity (CMI).[41] Human immunodeficiency virus (HIV)-positive patients are at increased risk of contracting condylomata acuminate which are notoriously difficult to treat and commonly recur. Besides the heterosexual way of sexual transmission, the homosexual transmission is also possible.[43]

Although, some studies found no evidence of a reduction in HPV prevalence through condom use, others found a lower HPV prevalence. A protective effect against HPV infection and cervical cancer incidence has also been reported for women with circumcised partners.[44] The incubation period varies from 3 weeks to 8 months or years.[45] In most infected individuals, the virus is carried subclinically and never produces apparent lesions.[46] A Center for Disease Control (CDC) report concurred that women were affected more frequently than men.[47]

Most genital papillomavirus infections resolve spontaneously, and HPV DNA becomes undetectable by PCR. The median duration of high-risk HPV infections in women is reported to be 8 months and persistence is observed in 30% after 1 year and in 9% after 2 years of observation.[48] Recent evidence demonstrates the clearing of non-oncogenic HPV infections more quickly in older women than younger women, perhaps partially accounting for the higher prevalence of HPV infection among the younger population.[49]

Cervical cancer is caused by high-risk HPV infection, and development of cancer often takes decades after initial infection.[50] It is second most common cancer among women in the developing world. Worldwide, in 2002, an estimated 493 000 cases of cervical cancer were diagnosed, resulting in 274 000 cancer deaths.[51] Estimates of the mortality rate for cervical cancer are 11.2 deaths per 100,000 patients in less-developed regions of the world.[52]

The incidence of cervical as well as anal precursor lesions and cancer is markedly higher in HIV-positive men and women compared with HIV-negative men and women[53] By analyzing anal swabs, up to 93% of HIV positive homosexual male were found to be positive for HPV DNA, as compared to 60% of HIV-negative.[54] The introduction of antiretroviral therapy in the mid-nineties restored immune responses to several AIDS defining opportunistic infectious agents, thus significantly changing the prognosis and mortality rates of HIV-infected subjects. However, the longer survival of highly active antiretroviral therapy (HAART)-treated subjects led to a high incidence and steady increase in HPV-related malignancies both in women and men.[55] Laryngeal papillomatosis, caused by HPV 6 and 11, is a rare but potentially life-threatening complication in infants and children. Although generally benign, a recent report of laryngeal papilloma associated with HPV 11 demonstrated malignant transformation to a verrucous carcinoma.[56]

CLINICAL MANIFESTATIONS

HPV infection is usually asymptomatic.
(Table 1, 2)

Table 1 HPV associated with different skin warts

Clinical Types	Location and Characteristics	Associated HPV
Deep plantar wart	Bottom surface of the feet (single)	HPV-1
Common warts	Mostly on hands (multiple)	HPV-2, 4
Mosaic wart	Feet and Hands	HPV-2
Flat warts	Arms, face, around knees (multiple)	HPV-3, 10, 28, 41
Epidermodysplasia verruciformis	In light exposed areas	HPV-5, 9, 12,14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 49
Butcher's warts	Common warts on hands of Butchers and meat handlers	HPV-7

Table 2 Common HPV types associated with benign and malignant diseases

	HPV Types	Manifestations
High Risk	- Most common: 16, 18 - Others: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 - Likely: 26, 53, 66, 68, 73, 82	- Low grade cervical changes - High grade cervical changes - Cervical cancer - Anogenital cancers - Head and neck cancers
Low Risk	- Most common: 6, 11 - Other: 40, 42, 43, 44, 54, 61, 70, 72, 81, 89	- Benign low grade cervical changes - Condyloma accuminata - Respiratory papillomatosis

CUTANEOUS INFECTIONS

Warts

They are papillomas of viral origin. They are sometimes referred to in the literature as viral papillomas, verrucae or viral warts. They may vary in pigmentation from yellow to pink to dark brown or even black. The clinical picture of cutaneous warts differs by specific location on the body.[57]

Verruca vulgaris (common warts)

Verruca vulgaris are the most common warts, and are produced by serotypes 2 and 4. They are asymptomatic hyperkeratotic, exophytic and dome-shaped papules or nodules.[57] They may form large masses by coalescence. Although they may be found in any part of the skin, they are especially located on fingers, hands, knees, elbows or any other sites of trauma.[58] Characteristic features are punctate black dots representing thrombosed capillaries, and capillary bleeding that follows shaving of the hyperkeratotic surface. Autoinoculation by scratching may cause a linear arrangement of

warts.[59] Periungual warts occur anywhere along the nail margins, including the proximal nail fold and hyponychium. Nail biters commonly exhibit multiple periungual warts involving several nails. Verrucae of the lids may become quite large and often become keratinized. A large over time; associated cutaneous horns are not uncommon. Verrucae of the conjunctiva are less common and tend to maintain a more "fleshy" appearance.[60]

Verruca filliformis

As the name implies, present with numerous "finger-like" projections, present mainly on the face, neck and periorificial areas. They generally have an elongated shape with a small fixation base.[58] Digitate warts, often in small groups, also occur on the scalp in both sexes, where they are occasionally confused with epidermal naevi.[61]

Verruca plana

These are associated with types 3 and 10 HPV. They are generally round, flat-topped, slightly elevated small papules, skin colored, grey or yellowish, and are less than 5 mm in diameter. They are found in the peripheral areas of the face, back of the hands and pretibial areas in children and youths. Linear grouping is typical following scratch lines (isomorphism). Intermediate warts can show features of both common warts and flat warts.[62]

Plantar warts

These are associated with HPV types 1, 2 and 4. They are observed in two forms: endophytic and exophytic. Endophytic plantar warts are generally unique, deep, painful and are manifested by a circumscript keratinous plaque, with a black pointed central area (thrombosed capillaries), and thick whitish keratinous ring with gently sloping sides and a central depression, resembling an anthill (hence the term myrmecia, meaning anthill). On the sole, these are found in weight bearing areas of the foot, particularly on the front plantar arch.[63]
The exophytic plantar verrucae or mosaic plantar verrucae are formed by coalescence of large plaques in a tile-like pattern.[63] Inclusion warts of the sole are plantar cysts from which HPV types 4, 60, 63 and 65 have been isolated.[59]

Pigmented warts

Warts with pigmentation have been reported mainly on palms and soles. Melanosomes are increased within the lesions, which are associated with HPV-65, HPV-4 and HPV-60 (13%).[64]

Butcher's warts

They owe their name as they are observed in occupational handlers of meat, poultry or fish. They appear as extensive verrucous papules or in the shape of a cauliflower-like lesions on the back, palm or periungual borders of the hands and fingers. HPV-2 (the cause of common warts) is frequently found in butcher's warts, but HPV-7 is present in up to one-third of lesions.[65]

Epidermodysplasia verruciform (Levandowsky-Lutz)

This is a rare hereditary disease, transmitted as autosomal recessiv disorder. It is mainly related to HPV 5 and 8, but also with 3, and to a lesser extent, with 9, 12, 14, 15, 17, 19-25, 36-38, 46, 47, 49, 50 etc. Family consanguinity is often observed. It is more frequent in women. The disease usually manifests in childhood with highly polymorphic, widespread lesions.[66] Lesions on the face and neck are generally indistinguishable

from plane warts, but on the trunk and limbs they tend to be larger and of two main types; scaly macular lesions closely resemble pityriasis versicolor, showing depigmentation or varying degrees of brown pigmentation, thicker plaques are dull pink to violet in color and may resemble seborrhoeic keratoses. Typical common warts are often present.[67]

Because it may be difficult to differentiate flat warts from EV-associated lesions based on histology alone, in situations with clinical suspicion of the latter, the presence of EV-specific HPV DNA (e.g. HPV-5, -8, etc.) may establish the diagnosis. In a third of the cases, starting from the second or third decade of life, there is a malignant transformation of the lesions, especially in areas exposed to the sun.[68]

Psoriasis

HPVhas been associated closely with psoriatic skin. The use of sensitive PCR amplification has revealed HPV sequences in patients with psoriasis and it is speculated that the virus may have a role in the disease process.[69]

MUCOSAL INFECTIONS

Anogenital warts

Asymptomatic warts: The majority of patients with genital HPV have no symptoms or physical findings.[38] These are extremely important as they are invisible to the human eye. They may be observed by application of a solution of acetic acid followed by viewing using a magnifying glass or colposcope.

Classic genital warts

Condyloma accuminata appear as verrucous or cauliflower-like papules. But thick, horny keratotic warts and flat warts may also occur.[70] In the mucous membranes, the CA are observed with the aspect of a hyperplastic lesion, fleshy and humid, with a pink or white color. These clinical signs vary when the condylomas are found in surrounding skin, with an aspect of dry and keratotic lesions being possible or even as pigmented papules. The second clinical aspect of CA is their appearance as small, multiple papules which vary between 1 and 6 mm in diameter. They are generally indurated to the touch and are found on the edges of the mucous membrane with the skin (papular condylomas).

Genital warts may cause pain, irritation, pruritus, dysuria, or bleeding. Large internal warts may cause obstructive symptoms such as painful intercourse (vaginal or anal), urinary retention, or rectal pain.[71] Condylomas are nearly always benign, although 5% may contain oncogenic virus. High-grade intraepithelial neoplasias are usually caused by high-risk HPV types, mainly -16, -18 and -31. Whereas, low-grade lesions may contain low-risk as well as high-risk HPV types.[57]

In men, the main affected sites are the frenulum, balanopreputial fold as these areas are frequently traumatised during coitus. The urethra, scrotum and anus may also be affected. However in female, condyloma accuminata can appear on the fourchette, but due to the humid conditions of the female genital apparatus and possible associated infections it generally rapidly propagates to all the vulva, and even the perineum and perianal area.

Buschke–Löwenstein tumor (giant condylomata acuminata)

Giant condyloma of Buschke and Lowenstein, first described in 1925, is a rare tumor of the anorectum and the external genitalia associated with

the low-risk HPV types 6 or 11.[72] Lesions usually present as large, foul smelling, cauliflower-like masses, which grow slowly and often recur. It could infiltrate deeply into underlying tissues and may form fistulas and abscesses. Histologically, it appears similar to condyloma, but grows both upward and downward suggesting local invasion.[73] Focal malignant transformation may occur spontaneously or following X-irradiation. It is considered as a low-grade, well differentiated squamous cell carcinoma. Verrucous carcinoma should be considered in the differential diagnosis of lesions measuring greater than 1 cm in diameter. Radical surgical extirpation is the treatment of choice although recurrences are frequent, resulting in a high morbidity rate.[74]

Oral warts

Oral warts, including those which appear to have been sexually transmitted, appear as small, soft, pink or white, slightly elevated papules and plaques on the buccal, gingival or labial mucosa, the tongue or hard palate. They usually contain HPV-6 or HPV-11[75] and may result from digital or oral-genital sexual transmissions.

Conjunctival and nasal papillomas

HPV antigen is frequently identified in conjunctival papillomas.[76] Two childhood cases, presenting at about 1 year of age, had genital HPV types suggesting intrapartum infection.[77] HPV-11 and HPV-57 have been detected in nasal papilloma and in papilloma of the maxillary sinus.[78]

Focal epithelial hyperplasia (Heck's disease)

It appears in the form of multiple circumscribed papules on the gingival, buccal or labial mucosa, resembling flat warts or condylomata. HPV-13 and HPV-32 seem to be almost specific for this condition.[79]

Bowenoid papulosis

Bowenoid papulosis is a neoplasia that occurs predominantly in young, sexually active adults.[80] It represents a severe form of penile, perianal, and vulvar intraepithelial neoplasia (VIN-3, PIN-3, and PAIN-3).[43] It is clinically characterized by multiple and sometimes pigmented, present on cutaneous and mucosal surfaces of the anogenital region in both sexes, often resembling simple warts, seborrhoeic keratoses or cellular melanocytic naevi. There may be areas of erythematous thickening or small erosions or ulcers. The lesions may become confluent and coalesce. There is often a history of preceding genital warts and the disease is more common in smokers. Histologically it resembles squamous cell carcinoma in situ.

Commonly, Bowenoid papulosis can be mistaken for lichen planus, psoriasis, seborrheic keratoses, or condylomata acuminate. It is strongly associated with HPV-16.[81]

In men, lesions appear on the glans or shaft with a benign clinical course. In women, lesions are found around the labia minora and majora, inguinal folds, and perianal areas. Low-grade and some high-grade lesions resolve spontaneously despite marked histologic atypia. But untreated, VIN-III may carry a high risk of progression to invasion.[82]

Erythroplasia of Queyrat

Erythroplasia of Queyrat is a distinct entity, affects the middle-aged and elderly. It presents clinically as a well-demarcated, velvety erythematous plaque of the glabrous skin of the penis and vulva. Erythroplasia contains high-risk HPV types, pre-

dominantly HPV-16.[57] It shows more advanced dysplasia, and carries a significant risk of invasive malignancy. Prevalence only in the uncircumcised males indicates a locally acting cause.[83]

Oral florid papillomatosis (Ackerman tumor)
It occurs as multiple, confluent warty or verrucous lesions in the oral cavity or the nasal sinuses. It is strongly associated with HPV-6 or -11. Smoking, irradiation and chronic inflammation are the main predisposing causes. It may progress to verrucous carcinoma.[84]

Epithelioma cuniculatum of the sole
Verrucous carcinoma occurring uncommonly on the sole of the foot. It belongs to a group of 'semi-malignant' verrucous carcinomas that are locally invasive and destructive but rarely metastasize.

Recurrent respiratory papillomatosis (RRP)
It is considered the most common benign tumor affecting the larynx.[85] Recurrent respiratory papillomatosis (RRP) has a bimodal age distribution, which forms the basis of their classification as juvenile- (JO) or adult-onset (AO). Juvenile-onset RRP (JO-RRP) presents in prepubertal children usually before 5 years of age, while in adults the typical age is 20-40 years.[86] The younger the age of onset, the more severe is the disease.[87] HPV type is the most important factor affecting the severity degree of this disease. It is well accepted that HPV could be transmitted from the mother's anogenital site to the infant's respiratory tract during delivery, and even before delivery through infected placenta and amniotic fluid. Resulting in juvenile-onset RRP after months or years of latency.[88]
RRP may arise anywhere in the respiratory tract with a predilection to the so-called transformation area where squamous epithelia and ciliated columnar epithelia meet. The most common lesion site anatomically is the laryngeal area[89] (benign exophytic laryngeal papillomas) the common clinical symptoms of RRP include hoarseness, cough, wheeze, voice change, chronic dyspnea, choking and syncope.[88] RRP is potentially life-threatening as it has the tendency to grow in size and number, causing complete airway obstruction. Endoscopy is the main method to make a definite diagnosis.
In some patients, RRP lesions have been seen to regress spontaneously, but prone to recur even after years of regression. In other patients, such as pregnant women,[90] these are prone to aggravation. Under some conditions such as smoking, irradiation, cytotoxic drugs, p53 mutation, HPV11 infection, high severity score or high activity of 2′, 5′-oligoadenylate synthetase, RRP lesions may undergo malignant transformation.[4]
Endoscopic surgical removal is still the fundamental treatment. And the most extensively used approaches in recent years are laser ablation and microdebrider removal. Other available approaches include electrocautery and cryotherapy. Adjuvant medical treatment is required in approximately 20% of patients with RRP. Repeated treatment is usually required because recurrence is very common after cure or spontaneous regression. Latent virus is the main cause of recurrence[91] because HPV may persist latently in the morphologically normal tissue adjacent to lesions, and eradication is usually impossible.

DIFFERENTIAL DIAGNOSIS

The diagnosis of skin and genital warts is uncomplicated if typical clinical features are present. Nevertheless, various differential diagnoses have

to be considered and a biopsy may be required for confirmation or to identify dysplastic lesions. Seborrheic keratoses, actinic keratoses, cornu cutaneum, keratoacanthoma, lesions of acrokeratosis verruciformis, angiokeratoma and amelanotic melanoma may resemble common warts, and even tuberculosis verrucosa cutis or a psoriasis lesion may have a similar clinical appearance.

Flat, wart-like periungual plaque of the finger may rarely represent Bowen's disease. Similarly, amelanotic melanoma can masquerade as persistent periungual warts and should be clinically suspected if erosion or pigmentation is present. Lichen planus (including the verrucous type) may resemble flat warts and either lesion may occur in a linear array. The net-like pattern of reticulated white streaks (i.e. Wickham's striae) of lichen planus may help to distinguish between the diseases.[57]

Plantar warts are often confused with callosities or corns, with which they may indeed be associated. Callosities have a uniformly smooth surface across which the epidermal ridges continue without interruption. In cases of doubt the horny layer should be gently pared. Plantar warts may rarely be confused with the discrete horny papules of punctate keratoderma of genetic origin, which develop during childhood or early adult life, are irregularly scattered over the palms and soles, and are often largest in pressure areas.[92]

The clinical differential diagnosis of genital warts includes pearly penile papules, vulvar papillomatosis (the female equivalent of pearly penile papules), Fordyce spots, skin tags (fibroepithelial polyps), seborrheic keratoses, nevi, and microglandular hyperplasia (progesterone-induced glandular units lined with eosinophilic epithelium that form small polypoid growths on the cervix).[7] Condylomata acuminata are rarely confused with condylomata lata of secondary syphilis.

A clinically similar oral disease with the descriptive name 'verrucous proliferative leukoplakia' does not contain HPV DNA and has a high risk of progression to metastatic squamous cell cancer and thus represents a distinct entity.[93]

LABORATORY DIAGNOSIS

The diagnosis of warts is usually made by careful inspection. The use of a magnifying lens may aid in diagnosis. The majority of sub-clinical lesions are found on the mucous membranes and are seen as white colored stains, which appear after the application of acetic acid and should be interpreted by a specialist[94] but these findings may be seen in non-HPV-related cases of inflammation or microtrauma.[7] Biopsy is indicated when genital lesions are atypical in appearance; pigmented, indurated, or fixed; resistant to standard treatments; or occurs in patients who are older (>40 years of age) or immunocompromised.[70]

Screening with a Pap test is used to identify any high grade squamous intraepithelial lesions, which are associated with an increased risk of invasive cervical cancer. Screening should occur annually with the conventional Pap test Cytology. However, it is only 50% to 75% effective in identifying glandular neoplasm. This screening do not apply to immunosuppressed or immunocompromised women.[17]

There is no routine infectivity assay available to detect virions in clinical samples, and diagnostic tests are therefore based on the molecular detection of papillomavirus DNA, e.g. by in-situ hybridization. Sensitive PCR protocols have been described that use degenerate primers to detect a broad range of genital and skin HPV types.[95] Sero-

conversion to L1 major capsid protein is common following infection with genital HPV types, and ELISA's using L1 VLP as the antigen have been useful in many epidemiologic studies. However, due to low antibody titers and variable intervals between infection and seroconversion, this assay is not used for diagnosis in individual patients.[96]

HISTOPATHOLOGY

The histopathologic changes induced by HPV infection are quite variable, according to the clinical presentations at different anatomic sites. Characteristically, there are epithelial cells with cytoplasmic vacuoles isolating the nucleus from the cytoplasmic membrane, known as koilocytotic (hollow) cells. The presence of koilocytosis can distinguish verrucae from other types of papillomas.[97]

Common warts are well circumscribed from the surrounding skin, and characteristically have steeply sloping 'church spire' papillomatosis heaped with ortho- and parakeratosis. There is also marked acanthosis, and elongation of rete ridges. The papillary dermis underlying the elongated rete ridges is highly vascular, with thrombosis of some vessels that correspond to the 'black dots' detected clinically in some warts.

The characteristic features of flat warts include orthokeratosis with a basket-weave appearance alternating with parakeratosis, acanthosis, no or minimal papillomatosis, a uniformly thickened granular layer, and vacuolization of cells in the granular and upper malpighian layers, termed 'bird's eyes'.[98] The histopathology of flat and pityriasis versicolor-like lesions of EV is closely similar to that of flat warts. Dysplasias and actinic keratoses may be evident, especially in sun-exposed areas.[97]

The most characteristic histologic features seen in genital warts are epidermal hyperplasia, parakeratosis, koilocytosis and papillomatosis, but all these features are not necessarily present in all patients. Mitotic figures are frequent. Prior treatment with podophyllotoxin, an antiwart agent may cause the appearance of aberrant mitoses. The Buschke–Löwenstein tumor shares many features with condylomata acuminata, but there is marked downward extension of characteristically bulbous rete ridges and less vacuolization of epidermal cells. While it is known to be associated only with extension into and destruction of local tissue, metastases to local lymph nodes from foci of squamous cell carcinoma arising in these tumors has been reported. Intraepithelial neoplasia can occur with HPV infection and it may progress to invasive carcinoma. Nuclear enlargement and hyperchromasia of the lower epithelial layers together with cytoplasmic halos (koilocytotic atypia) are the characteristic features of in cervical intraepithelial neoplasia (CIN) grade I. Atypia with abnormal differentiation of the keratinizing cell layers; start to appear in all layers of the epithelium in CIN II. CIN III shows features of evident squamous cell carcinoma. Vulva, vagina, penis and anus may show similar features and are termed VIN (vulvar intraepithelial neoplasia), VaIN (vaginal intraepithelial neoplasia), PIN (penile intraepithelial neoplasia) and AIN (anal intraepithelial neoplasia), respectively.[57]

PREVENTION

Given the worldwide burden of HPV infection (anogenital warts and neoplasia of several sites), prevention of infection could provide relief from an important public health threat.[6, 99] In the past, prevention of HPV disease was centered around

transmission prevention and cervical cancer screening. Organized cytologic screening programs with Pap smears have reduced the incidence of cervical cancer.[100] However, cervical cancer is more prevalent in developing countries, where Pap screening test is not widely available. Many studies have demonstrated that most patients are unaware of HPV and its association with genital warts and cervical cancer.[101] The advent of vaccines formulated to provide protection against the most common types of HPV causing disease represents a promising strategy in reducing the medical, financial, and psychological burdens associated with abnormal Pap test results.[102]

The inability to grow HPV in cell cultures is one major limitation for vaccine development. The goal of prophylactic vaccines is to create an immunological barrier at the entry portal.[103] Whereas most research suggests that antibodies raised against one kind of HPV are unlikely to offer strong protection against other types,[104] emerging results from vaccine trials suggest that some cross-protection might be possible. Therefore, preventing most cervical cancer cases is likely to require a multivalent vaccine effective against multiple types of HPV.[105]

Two HPV prophylactic vaccines have been developed. (Table 3)

The Advisory Committee on Immunization Practices (ACIP) recommended routine HPV4 vaccination of females aged 11 or 12 years, and catch-up vaccination for females aged 13 through 26 years.[47]

These are subunit vaccines based on L1, the major papillomavirus virion protein, which has an intrinsic capacity to assemble into VLP143 and contains the immunodominant neutralization epitopes of the virus. These VLP are morphologically indistinguishable from the outer shell of authentic virions. Given that only a single structural viral protein is involved in VLP production, they are noninfectious and nononcogenic particles. The formation of VLP is important for L1 vaccines because: (i) They can induce high levels of neutralizing antibodies;[106] (ii) The L1 epitopes recognized by neutralizing antibodies are conformation dependent and predominantly type specific. Therefore, denatured L1 does not induce neutralizing antibodies and does not protect against challenge with heterologous papillomavirus;[107] (iii) Compared with structurally simple antigens, the ordered repetitive arrangement of epitopes found on VLP surface induces exceptionally potent antibody responses.[4]

Table 3 HPV vaccines

	Quadrivalent	**Bivalent**
Manufacturer Product	Merck (Gardasil ®)	GSK (Cervarix ®)
VLP types	HPV6 20µg HPV11 40µg HPV16 40µg HPV 18 20µg	HPV16 20µg HPV18 20µg
Antigen source	Yeast technology	Recombinant Baculovirus technology
Adjuvant	Alum hydroxyphosphate sulfate	ASO4 (alum plus proprietary adjuvant MPL)
Schedule	0, 2, 6 months (0.5mg I.M.) (prime, boost, longer term titre)	0, 1, 6 months (0.5mg I.M.)
FDA clearance	June 2006	October 2009

Who and when to vaccinate[108]

ACIP recommends routine vaccination of females aged 11 or 12 years with 3 doses of either HPV2 or HPV4. The vaccination series can be started beginning at age 9 years. Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. If a female reaches age 26 years before the vaccination series is complete, remaining doses can be administered after age 26 years. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact. Vaccination in boys and men 9 through 26 years of age for the prevention of genital warts caused by HPV types 6 and 11.

Dosage, administration, and schedules[109]

The dosing and administration schedules are the same for HPV4 & HPV2. Each dose is 0.5 mL, administered intramuscularly, preferably in a deltoid muscle. The vaccines are administered in a 3-dose schedule. The second dose is administered 1 to 2 months after the first dose, and the third dose is administered 6 months after the first dose. The minimum interval between the first and second dose of vaccine is 4 weeks and between the second and third dose is 12 weeks. The minimum interval between the first and third dose is 24 weeks. Doses received after a shorter-than-recommended dosing interval should be re-administered. If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. Co-administration of a different inactivated or live vaccine, either simultaneously or at any time before or after HPV vaccine, is permitted because neither HPV vaccine is a live vaccine. Whenever feasible, the same HPV vaccine should be used for the entire vaccination series. However, if the vaccine provider does not know or have available the HPV vaccine product previously administered, either HPV vaccine can be used to complete the series to provide protection against HPV 16 and 18.

Special situations

Females who have abnormalities on their cervical cancer screening results are likely to be infected with one or more genital HPV types. With increasing severity of Pap findings, the likelihood of infection with HPV 16 or 18 increases, and benefits of vaccination decrease. Vaccination is still recommended for such females, because vaccination can provide protection against infection with HPV vaccine types not already acquired. Females should be advised that vaccination will have no therapeutic effect on an existing HPV infection or abnormal Pap test. However, prevaccination assessments (e.g., Pap testing or screening for high-risk HPV DNA, type-specific HPV tests, or HPV antibody) to establish the appropriateness of HPV vaccination are not recommended at any age. Lactating women can receive HPV vaccine. HPV2 and HPV4 are not live vaccines, and can be administered to females who are immunosuppressed (from disease or medications).

Precautions and contraindications

HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. HPV vaccines can be administered to persons with minor acute illnesses. Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient

improves.[110]

Syncope can occur after vaccination and has been observed among adolescents and young adults. To avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after they are vaccinated. HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is produced in Saccharomyces cerevisiae (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast. Pre-filled syringes of HPV2 have latex in the rubber stopper and should not be used in persons with anaphylactic latex allergy.

Vaccine efficacy and tolerability

Both vaccines have generally been well-tolerated, and do not appear to be associated with severe adverse events following immunization (AEFIs). Injection site reactions such as pain, swelling, and redness are common.[111] Pain severity is mild to moderate and generally lasts for 1 to 2 days. Systemic symptoms such as fatigue, headache, rash, upset stomach, and temperature elevation and the occurrence of serious adverse events are infrequent.[111]

Both vaccines have been evaluated in randomized, placebo-controlled, clinical trials in women who have no evidence of exposure or infection to the HPV genotypes in the vaccine. Both vaccines show high efficacy, with more than 90% reduction in persistent infection and 100% reduction in high-grade cervical lesions.[112]

Second-generation prophylactic vaccines[113]

Although clinical trials of Gardasil and Cervarix have been extremely promising, these first generation VLP vaccines are not the ideal vaccine candidates, especially in low-resource setting. Researchers are actively working to develop other prophylactic HPV vaccines that may be: effective against a broader range of HPV types, have a long shelf life, effective and long-lasting with a single dose and no boosters, able to elicit a mucosal immune response, manufactured, distributed, and administered in developing countries, rather than being expensive imports, which would result in the vaccines being less expensive and easier to use, both prophylactic and therapeutic, stable at a wide range of temperatures so that a cold chain is not required, and administered orally or via nasal spray, thereby eliminating the need for sterile needles and highly trained providers. There are many trials to produce second generation vaccines either by *Refining* virus-like particle (VLP) vaccine, Protein and peptide vaccines, Recombinant live-vector vaccines, Plant-based vaccines or DNA vaccines.

Therapeutic vaccines

In addition to preventive vaccines, laboratory research and clinical trials are focused on the development of therapeutic HPV vaccines. These vaccines focus on the main HPV oncogenes, E6 and E7. Since expression of E6 and E7 is required for promoting the growth of cervical cancer cells (and cells within warts), it is hoped that immune responses against the two oncogenes might eradicate established tumours.[114]

TREATMENT

There is currently no cure for HPV infection, and there is also no drug that can change the infectivity of the patient.[5] Therefore, the available methods of treatment can only eliminate signs and symptoms

of HPV infections. Treatments usually aim at destruction of the warty growths, rather than elimination of the virus.[46] Single treatment is usually not satisfactory in many patients and combination of therapies might be required.

Destructive therapy

Destructive therapy should not be confused with virucidal therapy. Destructive therapies are designed to damage or remove the lesion, rather than to kill the virus.

Surgical excision

Surgical removal of genital warts can be performed either by scissor excision, tangential shave excision, or curettage.[7] It is appropriate for Large (>1 cm) keratinized warts and for any genital wart, but especially for large lesions causing obstruction.[161] Scissors or scalpel excision is best mode of treatment when a tissue specimen to be submitted for histopathological examination is needed to rule out malignancy. Surgical removal of warts by curettage followed by cautery was an early and still widely practiced method of treatment.[9] Scarring can be particularly problematic on the sole of the foot, so this technique is most commonly used for filiform warts on the limbs and face. Success rates of 65% to 85% have been reported, but scarring and recurrence can occur. Like any destructive therapy, there is no assurance that the wart will not recur. Recurrence rates can be as high as 30%. This gives another meaning to the therapeutic intervention, and leads to the application of new adjuvant methods.[116]

Electrosurgical techniques

Electrosurgery involves either thermal coagulation or electrocautery, to destroy HPV affected lesions. There are two forms of electrosurgery; the direct-current form of electrosurgery, termed electrocautery, and the alternating current.[38] Electric cauterization is an ideal method to remove big exophytic lesions (e.g. Buschke Lowenstein lesions). The patient can be wart- free in one visit, but treatment requires local anaesthesia.[117] It is not recommended as a standard therapy because it can be painful and cause scars that are difficult to treat.[118]

Cryotherapy

Cryotherapy involves application of nitrous oxide or liquid nitrogen (-196°C) to warts every 2–4 weeks,[7] inducing dermal and vascular damage and edema, and leading to both epidermal and dermal cellular necrosis. Cryosurgery in genital warts leads to necrosis of the epidermis and occasionally of the superior part of the dermis; microthrombi in the blood vessels are often visualized histologically.[119] It may be used for any anogenital wart that is accessible to treatment. It has many advantages; the treatment is performed on an ambulatory basis, is easy, the method is accessible, with rapid destructive effect and there are no serious complications. It may have special advantage in treating bulky lesions, grouped lesions, and lesions on hair-bearing areas. It does not have systemic side effects, and only affects tissue to which it is directly applied, scar formation is rarely significant. Pigmentary alterations in the short term are not uncommon but usually normalize.[117]

Most warts cleared with fewer than three treatments.[120] HPV can itself survive and be stored in liquid nitrogen for research purposes; thus, the treatment does not kill the virus, and one should exercise precautions against both the spread of virus from patient to patient by contaminated cryo-

probes or swabs.[121]

Laser therapy

Different types of lasers can be used for treatment of warts. Laser treatment may be useful in HIV-infected patients who have very large external genital warts or severe local symptoms.[117]

Carbon dioxide laser therapy

The CO2 laser utilizes focused infrared light energy to vaporize affected tissues. It permits precise tissue ablation by spatial confinement of thermal damage and effective vaporization, which promotes rapid healing without scar formation in most cases.[122] A focused CO_2 laser beam can be used as a scalpel to excise the wart down to the subcutaneous tissue after which the base of the wart is vaporized by a defocused beam until a clean surgical field is obtained. This treatment may be useful for periungual and subungual warts that are recalcitrant to other treatments.[123] It has also been found to be useful in immunosuppressed patients.[124]

CO2 laser is applicable to smaller lesions located on the transitional mucous membranes, for which the endophytic growth is characteristic (e.g. bowenoid papulosis). Adverse effects of this treatment in immunocompetent patients include postoperative pain, prolonged healing time, and scarring.[118]

The principal advantages of CO_2 laser therapy are precision (which results in sparing of normal tissue), probable elimination of the infective agent, and relatively good cosmetic result. Carbon dioxide laser can be used to treat extensive and thick warts quickly and without the drawing of blood, larger lesions, lesions resistant to other treatments, or obstructive lesions.[7] In using any laser, hazards may be associated with the laser plume, including pulmonary and infectious hazards from released bacterial, fungal or viral organisms. Recurrence rates range from 60 to 77 %.[125]

Erbium:Yttrium-Aluminum-Garnet(Er:YAG) laser

The Er:YAG laser emits a shorter wavelength infrared radiation (2940 nm). It has a smaller zone of thermal damage, thereby allowing more precise thermal ablation with minimal scarring. Warts in a variety of locations have been successfully eliminated in 75% of patients after a single treatment, with a 25% relapse rate within 1 year after treatment.[126] Postoperative healing occurred after 7 to 10 days, but erythema that occurred in all patients required 2 months to subside. A potential safety feature of this laser is that HPV DNA has not been detected in the laser plume.[127]

Neodymium: YAG (Nd:YAG) laser

The Nd:YAG laser's principal emission wavelength is at 1064 nm, still in the infrared range. Hyperthermic treatment with this laser has been reported to cause remission with no recurrence in several case reports and case series.[128] A flexible probe can be used successfully to treat recurrent respiratory papillomatosis.[129]

Pulsed dye laser

The mechanism of action of the pulsed dye laser is through selective microvascular destruction of dilated capillaries in the warts. Thermal damage and a cell-mediated immune response are believed to contribute to wart healing usually within 2-4 weeks. It produces less pain and scarring than with CO_2 laser treatment and has been used for children.[130] Pulse dye laser has been reported to result in complete remission in 48% to 95% of cases.[131]

Potassium-Titanyl-Phosphate (KTP) laser

The KTP laser has been utilized in the treatment of recalcitrant cutaneous warts.[132]

Photodynamic therapy

Photodynamic therapy uses light of a wavelength absorbed by specific photosensitizing molecules that are exogenously administered to the target tissue. It has been applied to warts in sensitive mucosal tissues including venereal warts and cervical intraepithelial neoplasia, and to oral and respiratory tract papillomas.[133] Generally, results are equivalent to or superior to other treatment modalities with the advantage that little, if any, scarring results.[117]

Trichloroacetic acid

Trichloracetic acid (TCA) can be used effectively to treat warts.[134] It is a caustic that erodes the skin and mucous membranes, but generally is not absorbed systemically. TCA is suitable for treating few small, moist lesions, although it can be used for vaginal or anal lesions. It is topically applied in a solution concentration of 60-90% every 1–3 weeks.[117] A small amount of TCA can be applied to a wart and allowed to dry until a white frosting develops. The acid is associated with local burning that is immediate and lasts for a few minutes. Side effects are local and include pain, ulceration, and crust formation.

Salicylic acid

Salicylic acid is a first-line therapy that many patients choose, since it is available over the counter. It is a keratolytic therapy with a mechanism of action that slowly destroys virus-infected epidermis and may cause an immune response from the mild irritation caused by the salicylic acid. Over-the-counter preparations are available as 17% salicylic acid combined in a base of flexible collodion or as a 40% salicylic acid plaster patch. The advantages of over-the-counter salicylic acid include convenience, minimal expense, negligible pain and reasonable effectiveness. Disadvantages are that results require weeks to months of treatment, and the patient must strictly adhere to instructions. Side effects can include occasional contact dermatitis.[135] There is also a potential risk of systemic toxicity in children. Salicylic acid liquid should be applied every day, and patches must be reapplied every 48 hours. Acids are appropriate for plantar warts and sensitive body parts where cryotherapy would be painful.[136]

Podophyllin

Podophyllin resin is derived from the rhizome (underground root system) of the may apple (Podophyllum peltatum), a plant that grows wild in eastern North America.[137] Podophyllin resin has been used mostly in the treatment of anogenital warts. It (in tincture benzoin 10%-25%) should be applied in small amount to warts and then washed off with soap and water 1-4 hours after application. This should be repeated weekly. Wart area should not exceed 10 cm2 and volume should not exceed 0.5 mL/day.[138]

Podophyllin shouldn't be applied on open wounds or by occlusion. It shouldn't also be used on cervix, vagina or anal canal where squamocolumnar junction is prone to dysplastic changes.[71] The use of podophyllin is contraindicated in pregnancy.[139] The disadvantages of the use of podophyllin include unstandardized preparation, side effects, lower effectiveness, failure to induce lasting remission, and teratogenicity.

Podophyllotoxin

Podophyllotoxin (0.5 and 0.15%), in the form of solution or an ointment, is an easily applicable method providing good results. The substance represents a purified extract from the podophyllon plant.[137] Podophyllotoxin binds to microtubules and causes mitotic arrest in the metaphase of cell division. It is applied twice daily for 3 consecutive days followed by a 4 to 7 day medication intermission.[43] There is no evidence to suggest that more frequent application will increase efficacy, but additional applications do increase the rate of local adverse reactions and systemic absorption.[139] Side effects, in the form of erythema and erosions, are noticed during the initial application.[140] It is suitable for treatment of moist non-keratinized warts and wart area should not exceed 10 cm^2 and volume should not exceed 0.5 mL/day.[7] Podophyllotoxin solution could be used for penile lesions; cream or gel formulations are easier to use for anogenital and vaginal lesions.[140] It is contraindicated for use on mucus membranes due to toxicity. Although it is safer than podophyllin, podophyllotoxin is contraindicated during pregnancy.

Imiquimod

Imiquimod is a patient-applied imidazoquinolinamine derived, immunomodulatory topical treatment of genital warts.[141] Imiquimod was introduced for the treatment of anogenital warts in 1997.[48] It is more suitable for wart area 0.5–1.0 cm in diameter & moist non-keratinized warts.[142] It has more recently been approved for the treatment of non hypertrophic actinic keratoses and superficial basal cell carcinomas. Others have reported effective treatment of recalcitrant plantar, periungual and subungual warts.[143]

Imiquimod is a toll-like 7 receptor agonist, which stimulates a complicated cascade of reactions in the cytoplasm, leading to activation of nuclear factor kappa-beta, and eventually the production of cytokines and chemokines outside of the cell. The most important of these include interferon-alpha, interferon-gamma, interleukin-12, interleukin-8 and tumor necrosis factor-alpha. It is known that these inflammatory cytokines promote the innate immune system. The cell-mediated branch of the immune response is also stimulated, leading to an overall T-lymphocyte helper type-1 response, and may even inhibit Th-2 response.[144] A clinical response with imiquimod is accompanied by a decrease in the amount of HPV DNA and of messenger RNA for HPV proteins L1 and E7. It is applied 3 times a week at bedtime, followed by 4 days rest or every other day 3 times a week. It should be washed with soap & water 6-10 hours after application. Maximum duration of treatment is 16 weeks. It is more effective in women than men.[145]

The commonest side effect of imiquimod is the adverse local inflammatory reaction but it is usually mild and transient. Other side effects include erosions, pruritus, bacterial infection, fever and scarring.[146]

Interferon

Interferons are endogenous intracellular proteins possessing not only antitumor, but also an antiviral immunomodulating effect.[147] For genital warts that are recurrent or recalcitrant to other treatments, intralesional injection of interferon has been found to be effective.[148]

Intralesional IFNα is injected directly into the base of each wart. The procedure is painful; local anesthesia is recommended to minimize discomfort. It is suggested that interferon is able to protect the

basal keratinocytes from HPV infection, and the reason for this is likely due to its immunomodulating effect.[147] The activation of Th-1 cells and their cytotoxic effect is probably the basis of the effect.[149]

The additional application of subcutaneously administered interferon α-2b to laser treated patients with chronic therapy-resistant genital lesions significantly enhanced the chance of eliminating these warts. It has systemic side effects & toxicities in the form of myalgias, headaches, fever/chills, and decrease in platelet count.[7] Several studies have shown good results of systemic therapy with interferon in combination with a CO2 laser, surgical methods and electrodessication.[147] The subcutaneous application of interferon-α-2a and interferon-α-2b within three cycles of one week each, is recommended as a good preoperative procedure.[150] The intermission between each cycle lasts approximately 4 weeks. Its advantage compared to an intralesional application is the absence of pain and frequent visits to physicians. There are also data that suggest a gel containing interferon can help treat vaginal warts.[151]

VIRUCIDAL THERAPY

Glutaraldehyde

Glutaraldehyde is virucidal and available as a 10% water miscible gel or alcohol solution. Application of glutaraldehyde is typically applied twice a day. It can stain the skin brown, as well as cause contact sensitivity. Treatment has been reported to be as effective as with salicylic acid with cure rates over 70%. No randomized, controlled trials for glutaraldehyde treatment of warts have been published.[136]

Formaldehyde

Formaldehyde is also virucidal and works by disrupting the upper layer of epidermal cells and possibly damaging the virions. Available as 0.7% gels or 3% solutions are used to soak pared plantar warts to speed resolution. Formaldehyde can cause sensitization and should be avoided in patients with eczema and allergies.[152]

Formic Acid

In a non-randomized, placebo-controlled, open trial in 100 patients, a topical 85% formic acid/needle puncture technique resulted in a 92% complete clearance rate as compared with 6% in the placebo (water) group. The exact mechanism of action is not known, it may relate to the mode by which formaldehyde acts, or it may act in the series of caustic acids.[153]

Antiviral Drugs

Cidofovir is a nucleoside analogue of deoxycytidine monophosphate that inhibits DNA synthesis, induces DNA fragmentation, reduces epithelialization and enhances excoriation.[154] It has been used successfully in HIV-positive patients for the topical treatment of genital warts.[155]

Antimitotic Therapy

Bleomycin

Bleomycin, an antibiotic derived from Streptomyces verticillus, is reserved for recalcitrant warts that have failed to respond to other types of treatment. It selectively affects squamous cell and reticuloendothelial tissue.[156] It inhibits DNA and protein synthesis, and triggers apoptosis.[157] Bleomycin causes acute tissue necrosis that may stimulate an immune response, as evidenced by the fact that it is less effective as a treatment for wart

in immunosuppressed renal transplant patients.[158] Adverse effects include injection pain and burning, erythema, swelling and painwithin 24 to 72 hours after injection before a black thrombotic eschar forms. Raynaud's phenomenon is a definite concern in treated digits, and the nail may become dystrophic or be completely lost.[159]

Retinoids

Epidermal growth and differentiation are disrupted by retinoids, so wart growth is affected. Retinoids are also potent immune modulators.[160] There is some evidence that retinoids can downregulate HPV transcription in affected cells as well.[161] A great deal of interest has been expressed in the use of retinoids as a potential chemopreventive and/or therapy in HPV-related cervical cancer.[162]

IMMUNOTHERAPY

Contact Sensitizers

The mechanism of action for topical immunotherapy with contact sensitizers is proposed to be a type IV hypersensitivity reaction. Immunotherapy using dinitrochlorobenzene (DNCB) was first reported for common warts.[163] Diphencyprone (DCP), the standard sensitizer used for topical immunotherapy, is nonmutagenic and is available in acetone solution. Another nonmutagenic contact sensitizer, squaric acid dibutyl ester (SADBE), has been used in treatment of recalcitrant warts.[164] Adverse effects included painful blistering near the wart, blistering at the sensitization site, pompholyx-like or more generalized eczematous eruption, influenza-like symptoms, vesiculation elsewhere due to passive transfer of DCP and inguinal adenopathy.[163]

Cimetidine

Cimetidine, an H_2-receptor antagonist, is postulated to act as an immunomodulating agent at daily doses of 20 to 40 mg/kg by inhibiting suppressor T-cell function while increasing lymphocyte proliferation, thereby enhancing cell-mediated immune responses.[165]

Levamisole

Levamisole has been used effectively in the treatment of flat and common warts with moderate success.[166]

Bacillus Calmette-Guérin (BCG) therapy

Topical bacillus Calmette-Guérin treatment has been tried in the treatment of venereal warts. Complete response has been achieved in 60% to 92% of patients treated after 1 or 2 cycles, and they remained disease free after 6 to 9 months. Eight percent to 30% were unresponsive.[167] The mode of action is based on stimulation of the local immune response.

FOLKLORE AND ALTERNATIVE REMEDIES

Folklore

Historic folk remedies have included many variants: "Rub a dusty, dry toad on warts, and they will disappear. Before these remedies are scoffed at, they serve as a reminder that many warts resolve spontaneously regardless of the treatment.[168]

Hypnosis/suggestive therapy

For many years there have been sporadic reports of wart cures in both adults and children through hypnosis or autosuggestive therapy.[169] These are largely case reports or small case series with no controls for comparison with spontaneous regression rates.

Garlic extracts

Components of garlic (Allium sativum) have been shown to have antiviral activity and to inhibit cellular proliferation of infected cells.[170] In one placebo-controlled trial, the application of chloroform extracts of garlic was reported to result in the complete resolution of cutaneous warts with no recurrence after 3-4 months.[171]

Duct tape

Occlusive duct tape treatment has become popular due to a journal article in 2002 by Focht et al comparing duct tape treatment with cryotherapy. It involved applying a piece of duct tape the size of the wart directly to the wart and removing it 6 days later. An emery board or pumice stone was then used to scrub the wart after soaking it in water. The wart was left open to the air overnight. The 6-day cycle was repeated the following morning. This process was repeated for up to 2 months. Warts completely resolved in 85% of the duct tape arm of the study versus only 60% in the cryotherapy group. The mechanism by which duct tape acts remains speculative. Distant warts that were not treated with the duct tape also resolved, raising the possibility that the host's immune system was stimulated through local irritation produced by the duct tape. There were no reported side effects with using the duct tape.[172]

CONCLUSION

The Papillomaviruses are DNA viruses which belong to the Papova family, having a great affinity for epithelial tissue. They can produce proliferative lesions either in the skin or mucosa, The most common clinical manifestation is the verruca, with its different morphological forms: verruca vulgaris, verruca plana, anogenital warts or condylomata acuminate. Genital infection by HPV is very common in sexually active adults. Genital warts are not themselves cancerous, but warts caused by high risk types of HPV are predisposed to oncogenic transformation. Given the worldwide burden of HPV infection, prophylactic vaccines were introduced. Two HPV L1VLP vaccines have been developed: a quadrivalent HPV6/11/16/18 and a bivalent HPV16/18 product. Both of these vaccines have been shown to be safe and highly immunogenic. Therapeutic vaccines are also present. Treatment options for genital warts are numerous. Topical treatments include podophyllin resin, imiquimod, trichloroacetic acid, and podophyllotoxin. Surgical or destructive therapies include carbon dioxide laser, surgical excision, loop excision, cryotherapy, and electrodessication. Interferon can be injected locally or administered systemically to treat genital warts.

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