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Anogenital HPV

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Abstract

Human papilloma virus (HPV) is the most common sexually transmitted infection in the world. HPV is associated with various oral, genital and cutaneous conditions, both benign and malignant. HPV infection can be asymptomatic, but it may persist and cause lesions such as warts, dysplasia and cancers depending on low or high risk type of HPV infection. Anogenital warts are the most common clinical presentation of HPV infection. Despite the high incidence of HPV infections, vaccines, precaution methods and treatments are still matters of debate.

Keywords: HPV, anogenital, warts, condyloma acuminata, cancer, vaccines

1. Introduction

Human papilloma virus (HPV) can reside in epithelial basal cells of skin and mucosa. More than 200 genotypes have been identified; nearly 40–50 of these types cause genital infections. HPV 6, HPV 11 and HPV 16 are the most associated with genital warts. The transmission of the virus is by direct contact, but their infectivity is variable due to the number and the type of virus particles and the immune system of the infected human. Trauma, microabrasions and microdefects on the skin and mucosa promote the contagion. Less than 1–2% of infected people have clinically apparent anogenital warts [1, 2].

2. Epidemiology

HPV infection is a common sexually transmitted infection worldwide. HPV may cause several reproductive tract diseases, including genital warts and cervical cancer. The incidence of HPV

infections has been steadily increasing especially in the second decade of life. Genital warts affect both males and females, although slightly higher in men according to latest data [3].

The prevalence of HPV infection is estimated currently at 10–15%, with substantial regional variation [4]. The most common benign genital HPV infection is genital warts, caused in about 90% of the cases by nononcogenic HPV types such as 6 and 11. HPV infection is detected for more than 90% of the cases of cervical cancer [3, 4].

3. Etiology and pathogenesis

HPVs are small, circular, double-stranded DNA viruses. The capsid is made up of 72 icosahedral structures. Different types of HPV come from their variable L1 code. L1 encodes primary structural protein in the virus capsid. Genital HPV is associated with a high risk of carcinogenesis, as the viral DNA integrates into the hosts' DNA [5]. All HPVs target epithelia tissues and link their productive life cycles to differentiation of the infected host cell. HPVs are associated with a spectrum of manifestations ranging from unapparent infections to malignant neoplasias. The alpha-papillomaviruses contain viruses that infect mucosal epithelium, some of which are considered high risk (HR) and others low risk (LR) based on their association with cancers. The LR-HPVs can cause benign hyperproliferative lesions such as warts, and the High-risk HPV (HR-HPV) has been linked with progress to high-grade neoplasia and invasive malignant cancer [6, 7]. Low-risk HPV types include HPV 6 and 11 that have been associated with benign anogenital warts. At least 12 HR-HPV types, HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, have been associated with anogenital cancers as well as precursor neoplastic lesions [8]. It is now established that HPV 16 and 18 are the major papillomavirus types responsible for cervical cancer. Two viral proteins, E6 and E7, are essential for the integration into host chromosomes during malignant progression. They interact with p53 protein that regulates DNA damage repair [6, 7]. The high-risk mucosal HPVs, such as HPV 16, 18, 31 and 33, appear to have relation to the function of the E5, E6 and E7 gene products and the regulatory mechanisms that govern their expression. The cellular tumor suppressor gene p16 is an important biomarker for HPV-associated intraepithelial neoplasia. The overexpression of p16 is found in examined LSIL (CIN) lesions, except for those being caused by "low-risk" HPV types. There was no expression in healthy cervical epithelium [7].

Direct genital mucosa contact during sexual intercourse is the classical way of HPV transmission. The risk of male-to-female transmission is lower than that of female-to-male transmission. Five prospective studies have reported a significantly higher female-to-male transmission rate of any type of HPV than that of male-to-female. This may be explained by: (a) more transient infections in men; (b) lower HPV viral load in men; and (c) lower seroconversion rate for HPV infection in men [9]. Concordance of HPV infection between sexual partners is 40–60%. Length of sexual relationship, frequency of intercourse, condom use and number of sexual partners may play a role for the transmission. There is also vertical transmission to newborn from the mother. Contact with vaginal and cervical mucosa, transmission by placental or by amniotic fluid is the way of vertical infection to newborn. The rate of vertical transmission changes between 20 and 30% [10].

HPV enters epidermis through small defects on the skin or mucosa and proceeds to the basal layer of keratinocytes. The infected cells cannot undergo terminal differentiation. After the viral replication, multinucleation, nuclear enlargement, parakeratosis and koilocytes are seen in the upper layer of the epidermis. As the infected cells cornify and are shed, virus particles lead to further infection or transmission [2, 10].

4. Laboratory

A clinical diagnosis can be made in apparent infection. If the lesion is suspicious, biopsy is possible for the differential diagnosis. To detect the HPV in subclinic infections, variable methods are used. HPV testing plays an important role adjunct to the cervical cytology after the Pap-smear categories. Serological tests have been developed for the early diagnosis of cervical cancer and to detect high risk HPV types. HPV-DNA testing includes PCR, southern blot hybridization and fluorescent in situ hybridization (FISH). PCR is highly sensitive in identifying small amounts of viral nucleic acids. The specimen can be taken from cervicovaginal area, vulva, urethra and anal anogenital area for PCR analysis [11]. Cytology and HPV testing are important for detecting cervical dysplasia. Because there is no treatment for asymptomatic HPV in men, routine HPV testing is not recommended in men [10, 11].

5. Clinical presentation

Anogenital warts are the most common clinical presentation of HPV infection. Although warts are benign lesions, they cause a lot of stress and discomfort in patients' social life. Itching, bleeding, discomfort and pain are the rare symptoms, usually they are asymptomatic. Genital warts are highly infectious, and approximately 65% of people whose sexual partner has genital warts will develop warts themselves. The incubation period of HPV infection is estimated 2 weeks to 8 months, with the majority of genital warts appearing 2–3 months after an HPV infection. Approximately 20–30% of genital warts will spontaneously regress within 1 year; however, recurrence of warts is common [12].

5.1. Anogenital warts (condylomata acuminata)

Lesions may be single or multiple, of varying sizes, and are usually asymptomatic. Condylomata acuminata are pale pink papules or nodules with a smooth and velvety surface. The difference from other warts is the lack of hyperkeratosis. They may grow exophytic and cauliflower-like mass. They are highly contagious. HPV 6–11 are the most common types detected in condylomata acuminata. These are low risk types. Many other types have also been described including HPV 2, 30–33, 35, 39, 41–45, 51–56 and 59, many of which are intermediate and high risk types. HPV 16–18 are the most common high risk types and can be found isolated or with HPV 6–11 [1, 13, 14]. The HR-HPV types, most often HPV 16 and 18, are considered to be the primary etiologic agents for cervical cancer and precancerous lesions in women (CIN, VIN, VaIN) [15]. HPV 16 is

the main virus type to be associated with the development of VAIN. Also, HPV 16 infection, VIN or condylomata acuminata in the past medical history seemed to be significant factors for early relapse [16]. Multiple studies verified that persistent HPV infection is considered to play a key role in the development of cervical cancer. Cervical intraepithelial neoplasia (CIN) is the prelesion of cervical cancer, and high-grade squamous intraepithelial lesions (HSIL) with HPV infection can develop and progress to cervical cancer over a period of 8–12 years. HPV 16, 58, 52 and 18 are the predominant high risk types correlated with cervical lesion. The distribution of dominant HPV genotypes showed obvious regional differences. HPV 16 is more prevalent in Europe and North America, HPV 31 is more prevalent in South/Central America, HPV 33 and 45 are more prevalent in Africa and HPV 52 and 58 are more prevalent in Asia [17]. In male anogenital area, HPV is responsible for a subset of squamous cell carcinomas and associated precursor lesions (penile intraepithelial neoplasia, Bowenoid papulosis, erythroplasia of Queyrat (EQ)) [15]. The most typical locations in women are the external genitalia, but lesions can also be in the cervix and labia minor. In men, condylomas usually involve the coronal sulcus, glans penis and the penile shaft. Circumcision is reported to reduce HPV prevalence in men; however, the efficacy remains imprecise. Recurrences occur in up to one-third of cases [14, 18]. The warts may coalesce in the rectal and perianal area without practicing anal sex. In this region, cauliflower-like shape is the most typical. Since HPV thrives in the rectum, all patients with anal lesions should undergo anoscopy or proctoscopy [2, 13]. Differential diagnosis should be made with condylomata lata, nevi, acrocordon and pemphigus vegetans [2]. If there are anogenital warts in children, sexual abuse should be considered. It should also be reported to the authorities. However, most of the cases in children warts are caused by nongenital HPV types. The mechanism for perinatal and postnatal transmission includes vertical transmission, autoinoculation, sexual transmission and indirectly through contaminated objects and surfaces. This can be explained by mother with hand warts, or child can transfer warts from his/her hand to his/her own genital or anal area [1, 14].

Histopathological findings in warts are hyperkeratosis with parakeratosis, papillomatosis and marked acanthosis. Keratohyalin granules and koilocytes in the granular layer are characteristic for condylomata acuminata. Rete ridges tend to be elongated and point inward toward the center of the wart, and the dermis will often display an increased vascularization with the presence of thrombosed capillaries [14]. Cytoplasmic vacuolization is specific for condyloma when located within deeper portions of the epidermis such as the stratum spinosum, given that the upper portions of the epithelia of mucosal surfaces normally have some degree of cytoplasmic vacuolization already [15].

5.2. Condylomata plana

Condylomata plana are large flat warts mostly found on the cervix and prepuce. Identification of these warts often was possible only after applying acetic acid or colposcopic procedures. HPV 16–18 are usually responsible, and it is possible to progress in SCC of the genitalia [2].

5.3. Bowenoid papulosis

Bowenoid papulosis is characterized by multiple flat papules, plaques or macules less than 1cm in size in the genital area that may or may not be pigmented. The surfaces of the lesion mostly

are flat, dome-shaped, papillomatous and verrucous. The color of the lesions can be shiny flesh-colored, reddish-brown, violaceous or black [19, 20]. It resembles clinically viral wart and histopathologically Bowen's disease. The most common sites affected are the penis and vulva. In females, it is referred to as multifocal vulvar intraepithelial neoplasia [20]. Bowenoid papulosis is associated with HPV 16–18, but in a small number, HPV 31, 33, 35, 39 and 53, or mixed infections, have also been detected. Clinically, it should be differentiated from genital warts, seborrheic keratosis, lichen planus, molluscum contagiosum, Bowen's disease (BD) and melanocytic nevus. Younger age and multiple lesions differentiate it from Bowen's disease, but histologically it can be sometimes impossible to differ. Bowenoid papulosis and Bowen disease are clinical entities with similar histological findings of intraepithelial neoplasia. Bowenoid papulosis shows acrotrichial sparing, less pronounced cellular dysplasia and mitotic figures, which helps its differentiation [13, 20, 21]. The histopathological findings revealed full thickness epidermal atypia, acanthosis, papillomatosis, dyskeratotic cells and clumping cells with mild atypical nuclei [22, 23]. Bowenoid papulosis has a variable course, the lesions can stay for a few weeks or over 10 years, with a median of 8 months, but usually spontaneously resolves. Transformation to invasive carcinoma is rare occurring in <1% of cases, especially in immunocompromised [20, 22]. Women with BP have a risk of cervical dysplasia.

5.4. Buschke-Löwenstein tumor

Buschke-Löwenstein tumor (BLT), also known as giant condyloma acuminatum, was first described by *Buschke* and *Löwenstein* in 1925. It is a slow-growing, locally destructive tumor of the anogenital region, while the characteristic feature of tumor is benign appearance on histopathology [24, 25]. It is a sexually transmitted disease that it is thought to be induced by HPV 6 and 11. The estimated incidence of BLT is about 0.1% in the general population [26]. BLT is clinically seen as expansive, destructive exophytic fungating masses, sometimes with a cauliflower-like morphology. The tumor is located mostly (81–94%) on the penis in men, and the anorectal area is the second common area for BLW and in the urethral lesion is found in 5% of cases in men. In females, vulva is the most affected area (90%) and an anorectal location is less frequent. Suprapubic localization is rarely involved [27]. For the histological diagnosis, large and deeper biopsy should be performed to ensure that no malignant cytological characteristics are missed in superficially biopsied specimens. Microscopic features are thick stratum corneum, marked papillary proliferation, tendency to deep invasion, with displacement of surrounding tissues, negligible cellular atypia and a low mitotic rate [25, 28]. Similar features are also seen in verrucous carcinoma. As distinction between verrucous carcinoma and BLT is difficult, BLT is often regarded as a variant of verrucous carcinoma. Some authors also consider BLT as an intermediate lesion between condyloma acuminatum and VC, referring to it as a condyloma-like precancerous lesion [24, 27]. Although several etiologic factors are implicated in the malignant transformation, the etiology of BLT is not known. HPV type 6 or 11 subtypes that are normally lack of malignant potential have been frequently identified in typical cauliflower-like lesions, suggesting the pathogenic role of the virus in the initiation and progression of the tumor. It remains unknown if viral or host risk factors are the determinant factor. Increased viral gene expression or inability to mount a cytotoxic immune response may change the oncogenic potential of HPV types 6 or 11, causing progression of benign condyloma

acuminatum to the invasive giant condyloma phenotype. It is also believed that malignant transformation can be caused by the release of free oxygen radicals by activated inflammatory cells, inducing genetic damage and neoplastic transformation. Regular follow-up is necessary because of the frequent recurrences and possible malignant transformation of BLT [28].

5.5. Bowen's disease

Bowen's disease is an in situ squamous cell carcinoma that rarely progress to invasive carcinoma. The disease is associated with the high-risk HPVP types, mostly HPV 16. Clinically, usually a single, sharply demarcated plaque without spontaneous regression is seen in the genital area. The lesions are generally asymptomatic; however, they may cause pruritus or burning pain. Genital BD usually is found in elderly men, especially on the mucosa of the penis (glans or prepuce). Some authors consider mucosal BD equal to the erythroplasia of Queyrat; however, some of them accept them as different histological patterns [13, 29]. Histological characteristics are atypia and anaplasia of cells from the mucous malpighian body with cellular loss of polarity and presence of some dyskeratotic cells, in both the basal and squamous layers [29].

5.6. Erythroplasia of Queyrat

Erythroplasia of Queyrat is an in situ carcinoma that mainly occurs on the glans penis, the prepuce or the urethral meatus of elderly males. In females, vulva is the common area that is affected. The cause of erythroplasia of Queyrat is largely unknown. But in one study some HPV DNAs are detected; all patients were infected with the carcinogenic EV-associated cutaneous HPV type 8. HPV 16, 39 and 51 are other types that are found [30]. Sharply demarcated, erythematous, velvety and bright reddish plaques are characteristics for EQ. Progression to squamous cell carcinoma is more than 30% and is higher than the BD [13].

5.7. Cervical cancer

Cervical carcinoma, which is caused by malignant transformation of cervical epithelial cells following persistent HPV infection, is one of the most common malignant cancer among women, approximately 10% of all cancers in the female population [31]. The relationship between HPV and cervical cancer is observed in many studies, and the persistent infection of the HPV carcinogenic types is found to be the cause in about 90–100% of the cases. HPV 16 and 18 are the two most common types that are responsible for about 70% of cervical carcinomas and 50% of intraepithelial neoplasia grade 3 [13].

6. Prevention methods

Condoms can be a protective method from HPV infection in a limited way. It can lower the chance of transmitting HPV, but it may not be totally safe because of the infected areas that are not covered by condom. Avoiding sexual intercourse or reducing the number of sex partners

can lower the risk for HPV. Abstaining from sexual activity is the most reliable method for preventing genital HPV infection. Pre-exposure vaccination is one of the most effective methods for preventing transmission of HPV. The Cervarix (bivalent) and Gardasil (quadrivalent) vaccines protect against most cases of cervical cancer. These vaccines are safe and effective [32]. Cervical cancer and its precursor lesions can be detected by screening women with screening technologies such as cytology-based screening, application of acetic acid during the inspection and HPV DNA test. By using these methods, cancer or precursor lesion is detected at an early stage, thereby improving the survival. The disease can also be prevented by HPV vaccination against oncogenic HPV types [33].

6.1. Vaccines

HPV infections and associated diseases remain a serious burden worldwide. The incidence of HPV-related carcinomas has been increasing every year. Vaccines have been used for over a decade, but widespread vaccine administration is still problematic for multiple reasons in some countries and areas. Many socioeconomically developed countries have been applying the vaccine programs for females and some of the countries are also starting to include the males between the ages of 9–26 for vaccine programs [34].

In 1991, Zhou et al. were the first to develop an innovative vaccine technology based on noninfective recombinant virus-like particle (VLP) of L1, the so-called major papillomavirus virion protein. The VLPs do not contain the viral DNA, and they are completely noninfectious and nononcogenic. Three HPV vaccines are available on the market: bivalent HPV vaccine, quadrivalent HPV and nine-valent HPV vaccine. In bivalent HPV vaccine, there are the VLP form antigens of oncogenic HPV types 16 and 18. Quadrivalent HPV vaccine contains HPV types 6, 11, 16 and 18 L1 proteins. Antigens of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 types are in the nine-valent HPV vaccine [35]. According to the recent 58 studies in nine countries from 2007 to February 2016, it is found that a nearly 90% decrease in HPV infection, anogenital warts and cervical lesions in countries with the highest vaccination rates is seen [36]. Gardasil (quadrivalent) is European Medicines Agency (EMA)-approved for males and females, whereas the EMA-approval for Cervarix (bivalent) is currently limited to females only. Gardasil-9 (ninevalent) is a newly EMA-approved nonavalent vaccine in 2015 [37]. All HPV vaccines are administered as three doses i.m. injections in a 6-month period, with the second and third doses given 2 and 6 months after the first dose. The same vaccine product should be used for the three injections. Vaccine is applied in the age of 11–12 for girls and also can be administered at 9-year-old girls. But if the girls or women aged 13–26 years have not been administered the vaccines, they should receive the vaccine as it is possible. The quadrivalent or 9-valent HPV vaccine is also recommended routinely for boys aged 11–12 years. For the unvaccinated, immunocompromised patients, vaccination is recommended through age 26 years. HPV vaccines cannot be used in pregnant women. Women who have received HPV vaccine should continue cervical cancer screening routinely after 21 years of age [32]. Common adverse effects of HPV vaccines are pain, redness, swelling, syncope, dizziness, nausea, headache, fatigue and fever. Life-threatening side effects are very low with autoimmune responses [34, 35].

Duration of efficacy is a key question when discussing the HPV vaccines. All three vaccines provide very high immunogenicity with antibody titers that are higher than the natural infections and remain high enough to prevent new infections. Booster doses' necessity is still unknown. Up to now, it has been shown that the duration of vaccines may last 5–9 years. But more studies are needed about these important issues [35, 38]. The development of HPV vaccine is a milestone in the prevention of HPV-related infections and probably in the prevention of cervical cancer. But HPV screening still has a major role in cancer prevention and should be improved in low-income countries. It is clear that early vaccination before exposure provides the best results. The Global Alliance for Vaccination and Immunization (GAVI) has demonstrated that a reasonable price and wide distribution can be achieved. Projects in Rwanda and Bhutan have showed that a well-organized, school-based program can achieve excellent coverage. In countries with screening programs, the prevention of abnormal Papanicolaou tests and treatments for precancerous lesions will lower costs [39].

7. Treatment

Anogenital warts can potentially heal without treatment. Waiting a period of time before starting treatment is an option. However, there is uncertainty around the frequency of spontaneous resolution of lesions, with reports of rates of clearance without treatment ranging between 0 and 50% of people affected. A delay in treatment could result in a worsening of anogenital warts and increase the transmission rates. First-line treatment is not always successful in achieving complete clearance of warts and repeated treatments might be required to eradicate large or persistent lesions. Treatment of the warts does not mean to clear the HPV deoxyribonucleic acid (DNA). Cells that remain infected with HPV DNA can stay dormant (latent) for prolonged periods of time, and there can be a recurrence after months, or even years, after initial infection. Thus, those who do not become HPV DNA negative can also pass on the virus, even after treatment or clearance of lesions. These are the important information that should be given and explained in detail to the patients. A wide range of therapies are presently in use, which are highly variable and can differ dramatically with respect to effectivity, cost, side effects, dosing schedules and duration of treatment [32, 40].

7.1. Topical treatment

7.1.1. Patient-applied treatments

Imiquimod: Imiquimod is a non-nucleoside heterocyclic amine, which acts as an immunomodulator. It increases the cellular levels of interferon alpha (IFN- α), tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) by binding to toll-like receptor 7, which leads to strong antiviral and antitumor effects [41]. It is available as a 5% cream. Its pregnancy category is C. Imiquimod is licensed by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the topical treatment of external genital and perianal warts (condylomata acuminata) in adults. Patients should apply imiquimod cream a thin layer onto the affected area every other night for three nights weekly. The cream should be left in place for

6–10 hours, and after that the treated area should be washed with soap and water. Application of an excess of cream or prolonged contact with the skin might result in a severe application site reaction. The treatment can be continued until the warts resolve or for up to 16 weeks [42, 43]. Common side effects are itching, erythema, burning, irritation, tenderness, erosion, ulceration and pain. Occasionally, patients may experience systemic side effects such as headaches, muscle aches, fatigue, and general malaise. In the pivotal clinical study, wart clearance was achieved in 56% of patients with imiquimod. More women (77%) than men (40%) cleared their warts, with the male study population comprising predominantly circumcised men. Females had a shorter median time to clearance (8 weeks) compared to males (12 weeks). A low recurrence rate (13%) was found [40].

In 2010, the FDA approved imiquimod 3.75% cream for the treatment of anogenital warts in patients 12 years of age or older. Imiquimod 3.75% should be applied to warts daily for 2-weeks and then with repeat of 2-weeks treatments after a 2-weeks rest period. The cure rates for the 3.75% imiquimod are not as high as the 5% imiquimod; however, the newer product has fewer side effects and is more appropriate for patient compliance [44].

Podofilox: Podofilox is an anti-mitotic drug that causes tissue necrosis. It is purified from podophyllin. This product is available as 0.5% gel or solution. Patients should apply the solution to affected areas twice daily for 3 days, followed by 4 days of no therapy. This weekly cycle can be repeated for up to 4 weeks. Clearance rates (45–77%) are similar to imiquimod, and recurrence rates range from 4 % to 33%. Most common adverse effects are burning, pain, erosion, itching and inflammation. Podofilox is contraindicated in pregnancy [32, 42].

Sinecatechins: Sinecatechins are extracts of green tea leaves from *Camellia sinensis* that are compounded as a 15% ointment. It contains eight different catechins and other green tea components. The main catechin in sinecatechins ointment is epigallocatechin gallate (EGCG), which has the highest biological activity. Sinecatechins are thought to decrease viral replication. Also they have an anti-oxidant by inhibiting a number of proteins, including enzymes involved in oxidative stress, immunostimulatory activity by blocking the kinases needed in tumor cell signaling and induction of apoptosis. These mechanisms presumably contribute to the therapeutic effect of sinecatechins ointment [45]. Patients should apply a 0.5-cm strand of ointment onto each wart three times daily until the complete clearance of warts. But it should not be used for longer than 16 weeks. Common side effects are: erythema, pruritus, burning, pain, erosion, edema, induration and vesicular eruption. Sinecatechins should not be put on open wounds. Mucosal surfaces should be avoided because of the irritation by sinecatechins. The medication is not recommended for patients with HIV infection, other immunocompromised conditions, or genital herpes because the safety and efficacy of therapy has not been evaluated. The pregnancy category of this product is C [32, 44]. Ten percent of sinecatechins ointment is also effective against genital warts. It is also used three times a day like the 15% form. Efficacy rates from the Phase III trials of sinecatechins 10% ointment are higher than those achieved with podophyllotoxin 0.5% or imiquimod 5% and 3.75%. Sinecatechins 10% ointment has lower recurrence rates relative to other patient-applied therapies; therefore, it presents a botanically based alternative to currently available treatments for external anogenital warts [46].

7.1.2. Clinician-applied treatments

Podophyllin: Podophyllin is available as a 25% solution. The preparation causes wart regression and necrosis by stopping mitosis. The solution is typically applied once weekly until complete clearance up to 3–6 weeks. Because of the corrosive nature and the toxicity of the treatment, when podophyllin is overapplied or occluded, it is recommended to limit the application area to less than 10 cm² of warts per treatment, limiting the amount applied to less than 0.5 mL per treatment. Podophyllin should not be used in pregnant women or breastfeeding [42, 43].

Trichloroacetic (TCA): Trichloroacetic acid may be compounded in different concentration, generally 60–90%. It is a caustic that erodes the skin and mucous membranes, but generally is not absorbed systemically. TCA is applied in the office with a cotton tip applicator, with repeated applications up to three times weekly until the warts have resolved. It is more effective in few small, moist lesions. The initial response rate is 70–81%, but recurrence rate is up to 36%. TCA also can be used to treat vaginal and anal lesions. TCA treatment is delivered in a controlled manner to provide limited local destruction. A small amount should be applied only to the warts and allowed to dry until the white frosting develops. It destroys the warts by chemical coagulation of proteins. The application of TCA is accompanied by a burning sensation that lasts for 2–5 min. A neutralizing agent (sodium bicarbonate) should be at reach in case of excess application or spills. Dermal injury or scarring is rare. Common side effects are local and include pain, ulceration and crust formation [47, 48].

7.2. Ablative treatments

Cryotherapy: Cryotherapy is a process in which the abnormal tissue is frozen by using of a cooling agent such as through the use of a nitrous oxide or liquid nitrogen. Freezing causes permanent dermal and vascular damage. This leads to the initiation of an immune repair response which causes necrosis and clearance of the destroyed cells. This treatment is most effective when used for multiple small warts on the penile shaft or vulva. Treatment should be repeated every 1–2 weeks. Clearance rates range from 71 to 79%, with recurrence rates of 38–73% at 6 months. Cryotherapy has been used to treat external genital warts without adverse effects during pregnancy [40, 42]. Application of this treatment is easy, and it has a rapid destructive effect. It also has an 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. Common side effects include local tissue destruction, such as painful blistering, ulceration, infection, rarely scarring and loss of pigmentation. Another disadvantage of cryosurgery is that subclinical lesions cannot be treated in the surrounding skin. Multiple outpatient visits are required for the clearance of warts, and the pain associated with its application can limit its repeated use in certain patients and localizations [40, 47].

Electrosurgery: There are two types of electrosurgery: electrocautery and electrical surgery. Local anesthesia is needed to perform electrosurgery. In electrocautery, electricity flows only through the instrument producing heat that is applied to the lesion. In the alternating-current form of electrosurgery, electricity flows from the instrument through the patient to a grounding plate. The alternating current systems produce cutting, coagulation, or a blend of both. Electrotherapy

is particularly effective for treating smaller warts located on the shaft of the penis, the rectum or the vulva or for pedunculated lesions, but is not recommended for the larger warts because of the permanent scarring [43, 47]. Clearance rates with electrosurgery range from 90 to 96%, and recurrence rates of 18% have been reported. The smoke resulting from this procedure may contain HPV particles. To prevent the transmission to the oropharynx, use of smoke evacuation equipment and a mask is recommended [42].

Surgical excision: Surgical excision may be the most cost-effective treatment for genital warts. This method is more effective when warts are large, pedunculated or exophytic. The advantage of this method is to preserve intact tissue for histologic examination and offers quick results. Pain, scarring, slow healing and pigment changes are the disadvantages [42]. Especially for treatment of BLT, wide surgical excision by Mohs technique is recommended as the most important therapeutic intervention [25].

Carbon dioxide laser therapy: Carbon dioxide laser therapy relies upon the use of a concentrated beam of infrared light energy, which will heat and cauterize the affected area. The intense light energy has the added benefit of providing immediate cauterization of any ligated vessels, ensuring a virtually bloodless procedure. Side effects are generally mild and limited to the burning of tissue surrounding the lesion. The deep penetrating effect of the laser often allows for a greater and more complete viral attack than seen with other surgical treatment options. This makes the laser treatment a better choice for immunosuppressed individuals, and for pregnant women with extensive lesions which are unresponsive to TCA or cryotherapy. Laser therapy is typically considered to be less effective than other forms of surgical treatment, with clearance rates ranging between 23 and 52%. Recurrence rates are also high as 77%. Laser treatment is also more complex and costly than electrosurgery or cryotherapy. A CO₂ laser requires maintenance and additional training to perform correctly [40, 47].

7.3. Other treatments

Interferons: Interferons are a class of small (15–28 kDa) protein and glycoprotein cytokines (15–28 kDa) produced by T cells, fibroblasts and other cells in response to viral infection and other biologic and synthetic stimuli. Interferon has been used in the treatment of genital warts for its immunomodulatory, antiproliferative and antiviral properties. Interferon could be used either locally or systemically. Local administrations are mainly composed of intralesional injections and topical applications. Interferon tends to be a well-tolerated form of therapy. According to different administration, topical interferon appears to be much more effective than both systemically used interferon and placebo in either improving the complete response rate or reducing the recurrence rate for the treatment of genital warts [41, 49]. Combining interferon with other treatments increases the effectiveness of treatment. In one study, the addition of subcutaneously administered interferon α -2b to laser-treated patients with chronic therapy-resistant genital lesions significantly enhanced the chance of eliminating these warts, and it was fairly well tolerated. It is also suggested that gel form of interferon can help treat intravaginal warts. However, because of its high cost and inconsistent effect, interferon is best considered to the genital warts that are resistant to other treatments [47].

Cidofovir: Cidofovir is a monophosphate nucleotide analogue. Cidofovir is converted to the active cidofovir diphosphate that is a competitive inhibitor and an alternative substrate for viral DNA polymerases. As cidofovir acts directly on viral DNA, it has been found effective on immunocompromised people and thus could potentially afford greater clinical benefit for people with HIV infection than with other treatments available. Cidofovir has been formulated as a 1% gel and is applied topically to lesions overnight, three times a week for up to 16 weeks [43, 50].

5-Fluorouracil: Use of topical 5-FU is indicated for therapy-resistant condylomata. It can be applied to the affected extragenital area once or twice for 10 weeks. It appears to be as effective as continued regimens but better tolerated [51].

Zinc: Zinc is an immunoregulator that stimulates the leucocytes and natural killer cells. Oral and topical form of zinc has been found effective in the treatment of warts. It has been shown that there is a deficiency of zinc in patients with multiple or recurrent warts. Oral zinc sulfate given in a dose of 10 mg/kg/day has been used, with approximately 84–87% patients showing complete resolution of warts in 2 months in two randomized placebo-controlled trials [41]. In a study, the podophyllin-, imiquimod- and cryotherapy-treated patient is combined with 400 mg oral zinc sulfate for 8 weeks. And it is shown that oral zinc sulfate combination therapy appears to reduce the relapse rate of vulvar warts [52]. Topical 5 and 10% zinc solution has been used in cutaneous warts, three times a day for 4 weeks with only 5 and 11% responses [41].

H2 receptor blockers: Cimetidine is a H₂ receptor blocker that can be used in the treatment of warts especially in children. It blocks the type 2 histamine receptors on suppressor T cells and augments cell-mediated immunity. It increases mitogen-induced lymphocyte proliferation and the levels of IFN γ and IL-2 and inhibits suppressor T cells. It decreases the levels of IL-18. It has been used in a dose of 20–40 mg/kg/day for 3–4 months with response ranging from 30 to 87% [41]. In a study that included four children with extensive condylomata acuminata of the genital and perigenital areas, high doses of cimetidine have been found effective to eradicate the condyloma and avoid recurrence in two and as primary treatment in two. All patients were treated with 30–40 mg/kg cimetidine daily in three divided doses during a 3-month period. So it is suggested that cimetidine can be considered as first-line therapy and is useful for primary and adjunctive treatment of condyloma in young children [53].

Photodynamic therapy: Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) is a new technique based on the interaction of light, photosensitizer and oxygen. ALA is a topical used photosensitizer with few side effects. It is the first compound in the porphyrin synthesis pathway. ALA is selectively absorbed by tumor cells and rapidly proliferating cells and transformed to endogenous protoporphyrin IX (PpIX) after the exogenous application of ALA. The PpIX is then activated by red light, leading to the formation of singlet oxygen, which leads to the killing or destruction of tumor cells and proliferative cells. Cells infected by human papillomavirus are proliferative cells; ALA is selectively absorbed by these cells and can be killed by the radiation of red light. This means ALA-PDT treatment can destroy visible and invisible infected tissues and reduce the number of the viral load and the recurrence rate [54]. The common side effects in patients treated with ALA-PDT mainly include mild burning and/or stinging restricted to the applied area [41].

7.4. Treatments in pregnancy

Patients who have condyloma acuminata during pregnancy are a risky group. During pregnancy, vaginal secretions contacting the skin and mucous membranes are more abundant, meaning that the vulva will remain in a moist and immersed state. In pregnancy, hormones and reduced immunoresponsiveness can promote the growth of HPV-induced lesions. The warts are characterized by fast-growing and a reduced tolerance and poor compliance to treatment. Only a few treatments have been tested and recommended in pregnancy [55]. Podofilox (podophyllotoxin), podophyllin and sinecatechins should not be used during pregnancy. Trichloroacetic acid, cryotherapy, electrocautery and surgical excision, including laser treatment, are recommended treatments. But the resolution might be incomplete or poor until pregnancy is complete. Significant side effects have been observed for some of these methods, including local ulceration and scar formation, which may reduce a patient's compliance with treatment requirements. Medicine could potentially cause fetal malformation, and laser treatment and surgical excision may cause uterine contraction, or even abortion [32, 55]. The safety of imiquimod has not been established, but a small number of patients worldwide have been treated with imiquimod and found to be effective and promising. No adverse fetal outcomes or fetal and neonatal abnormalities were observed. No complications were observed in the postpartum and follow-up period [56]. Photodynamic therapy with topical ALA seems to be safe and effective in the treatment of condyloma acuminata in pregnancy. In case reports, it demonstrated high clearance rate of warts, was well-tolerated by patients and showed no adverse effects on mothers or fetuses [57]. Cryotherapy appears to be the best choice. During the cryotherapy procedure, liquid nitrogen freezes the tissue and thereby causes necrosis; the treatment also stimulates specific immune responses, such as an immunomodulatory action of T lymphocytes against the remaining viable wart tissue. It is also a simple and inexpensive procedure, rarely causes scarring or depigmentation, and is safe for use in pregnancy. The transmission (transplacental, perinatal or postnatal) of virus to the baby is not completely understood. So the necessity of cesarean section in the presence of genital warts is also unclear. Cesarean delivery is indicated for women with anogenital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding [32]. Prophylactic cesarean delivery is not recommended to prevent the respiratory papillomatosis in infants and children, because it is reported that only 7 infants of 1000 in mothers with external genital warts developed respiratory papillomatosis, and cesarean delivery did not reduce this risk [42].

7.5. Treatment in immunosuppressive patients

Patients with significant immunosuppression (patients with HIV infection, immunosuppressive therapy to suppress transplant rejection, or other concomitant disease) might have larger or more numerous lesions, might not respond to therapies and might have more frequent recurrences after treatment. They are also at increased risk of squamous cell carcinoma, which may be clinically similar to genital warts. Lesions that ulcerate, grow rapidly, or are atypical should be biopsied to rule out squamous cell carcinoma [32, 42]. Cryotherapy, electrosurgery, excision and laser therapy can be applied to these patients.

8. Conclusion

Genital warts, also known as condylomata acuminata, are one of the most common forms of sexually transmitted diseases affecting the general population. Most infections do not result in the manifestation of genital warts. Genital warts are not themselves cancerous, but warts caused by high risk types of HPV are predisposed to oncogenic transformation. Because of the contagiousness and the progression to precancerous lesions, HPV infections should be underestimated. Selection of a treatment modality may depend on the patient, all the appropriate choices should be explained to patients, and they should be informed what risks can be seen. Given the strikingly high prevalence of genital warts among the population, and the lack of adequate therapies, HPV vaccines may play a significant role in reducing the burden of disease by preventing viral infection and transmission.

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