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Anogenital warts: an update on human papilloma virus, clinical manifestations and treatment strategies

Anogenital siğiller: İnsan papilloma virüsü, klinik bulguları ve tedavi stratejileri üzerine bir güncelleme

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Abstract

Anogenital warts is a major health problem caused by human papilloma virus (HPV). To date, more than 200 subtypes of HPV exist. Depending on the type of HPV and the immune status of the patient, various clinical forms may appear. The most detected types are HPV-6 and 11 which are responsible for approximately 90% of anogenital warts. High oncogenic strains HPV types 16 and 18 are responsible not only for cervical cancer, but also other cancers such as vagina, vulva, penile, anus, head and neck. Besides, anogenital warts impact the individual's quality of life leading significant psychosocial problems. Treatment options for anogenital warts include cytodestructive, immune-mediated and surgical therapies. Treatment choice depends on the location, number, and size of the warts; patient situation (eg. pregnancy, ability to comply with therapy, immunosuppression); availability of clinical expertise; and patient preferences, cost, and convenience. This article updates the epidemiological, etiological, clinical features and therapeutic choices in anogenital warts.

Key words: *anogenital warts, human papilloma virus, treatment*

Özet

Anogenital siğiller insan papilloma virüsünün (HPV) neden olduğu önemli bir sağlık sorunudur. Bugüne kadar, 200'den fazla HPV alt tipi saptanmıştır. HPV tipine ve hastanın bağışıklık durumuna bağlı olarak, anogenital siğillerde çeşitli klinik formlar gözlenebilir. En çok tespit edilen tipler HPV-6 ve HPV 11 olup anogenital siğillerin yaklaşık% 90'ından sorumludur. Yüksek onkojenik suşlar HPV tip 16 ve 18 sadece servikal kanserden değil, vajina, vulva, penis, anüs, baş ve boyun gibi diğer kanserlerden de sorumludur. Ayrıca, anogenital siğiller, bireyin yaşam kalitesini etkileyerek önemli psikososyal sorunlara neden olur. Anogenital siğiller için tedavi seçenekleri arasında destrüktif, immün modülatör ve cerrahi tedaviler bulunmaktadır. Tedavi seçimi siğillerin yeri, sayısı ve büyüklüğüne; hastanın durumuna (örneğin, hamilelik, tedaviye uyma yeteneği, immün baskılama); klinisyenin tecrübesine; ve hastanın tercihleri ve rahatlığına bağlıdır. Bu makale anogenital siğillerdeki epidemiyolojik, etiyolojik, klinik özellikleri ve tedavi seçeneklerini güncellemektedir.

Anahtar kelimeler: *anogenital siğiller, insan papilloma virüsü, tedavi*

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Introduction

Anogenital warts (AGW) are one of the common sexually transmitted infections (STI)s in the world and are caused by human papillomavirus (HPV). AGWs also called as genital warts, anogenital condylomas or condylomata acuminata-are lesions that develop on the skin and mucosa due to infection with some types of HPV.[1-4] In this article, the epidemiology, etiology, clinical features of anogenital warts and treatment choices are reviewed in the light of current literature.

Epidemiology

Approximately 60% of sexually active people have been infected with genital HPV at any time during their life. There are more than 500,000 new cases of AGWs annually. Peak prevalence of HPV infection typically occurs after sexual activity, between the ages of 15 to 25 years. Today it is known that sexual intercourse is not necessary for the development of HPV infection. Skin-to-skin or mucosa-to-mucosa contact is enough for the transmission of the virus.[1-7]

Human papilloma virus is the cause of not only benign diseases (anogenital condylomas) but also pre-malignant lesions and different cancers.[2-3] High-risk HPV subtypes (HPV 16 and HPV 18) are the causes of approximately 70% of invasive cervical cancer and it is estimated that 500,000 cases of cervical cancer occur each year worldwide.[6-9] Risk factors for the development of AGWs and oral warts include young age, early onset of sexual activity, multiple sexual partners, a history of sexual transmitted disease, tobacco use, failure to use condom, being uncircumcised.[2,4] Epidemiologic data and prevalence in childhood genital warts are still limited.[10]

Etiopathogenesis

Human papilloma virus is a double-stranded, non-enveloped DNA virus. To date more than 200 different genotypes have been identified. Over 40 mucosal HPV genotypes can infect the genital tract. HPVs are categorized as high or low risk according to their oncogenic potential. HPV types 6 and 11 are responsible for approximately 90% of genital warts while HPV types 16 and 18 are responsible for cervical cancers. HPV has a high tropism for squamous epithelium. Basal keratinocytes are thought to be the primary target for infection, by this way they can induce cellular proliferation.[2-4, 11-15] After infection, HPV typically requires an incubation period ranging from a few weeks to 8 months before the appearance of clinical manifestations. Lesions appear approximately 2 to 3 months after initial contact. HPV has the ability of lying dormant within epithelial cells for a prolonged time. Infection may be subclinical during the individual's life with no clinically apparent warts. Only about 10 to 15% of infections persist, and approximately 10 to 15% of these persistent infections result in cancer.[11-15]

Clinical Manifestations

Warts are typically small, discrete, smooth papules/plaques that can occur both separately or in groups. They are especially localized in anogenital areas, such as the vulva, penis, groin, perineum, perianal skin and/or mucosal surfaces. Due to the varieties in sexual behaviours, they may also occur on the lips and/or mucosa including anus, pharynx and larynx. The lesions may demonstrate various morphological features such as filiform, exophytic, papillomatous, verrucous, hyperkeratotic, cerebriform, fungating, or cauliflower-like and the color is also variable ranging from skin-colour to erythematous, and/or brown-hyperpigmented. After their initial appearance, AGWs may increase in number and size or silently regress over time.[1-4,6,8]

Buschke-Lowenstein tumors are slow-growing giant condylomata accuminata of the anogenital region. They are locally destructive, low grade in situ epithelial cancer with a low rate of metastasis.[4,16]

Bowenoid papulosis and erythroplasia of Queyrat are two conditions both of which are carcinoma-in-situ histopathologically and they are characterized clinically by small flat pigmented papules and erythematous plaques on the external genitalia, respectively. When encountered with pigmented, erosive, bleeding cases, biopsy

from the lesions should be taken in order to rule out carcinoma.[4,6,8]

Special conditions

Anogenital warts in children is another major issue to be discussed in depth. The physicians should suspect for sexual abuse when they encountered with anogenital warts in children.[10,17]

Anogenital warts in pregnancy: Due to the reduced cellular immunity and increased vascularity in genital tractus in pregnancy, AGWs tend to grow more rapidly, to be more in number and friable. Besides, HPV can be transmitted vertically from the mother to the child during delivery which may result in neonatal and congenital, oral, or conjunctival lesions.[18,19]

Anogenital warts in immunsupression: Immuncompromised individuals have a higher risk of malignant transformation and higher risk of coinfection with more than one HPV type and also have a higher viral load. AGWs are larger and more treatment resistant with higher recurrence rates.[20]

Comorbidities

Physcosocial problems and sexual dysfunction: Warts can bring about significant anxiety or distress for the patient and her/his sexual partner because of the disfiguring appearance of the warts. Patients usually have concerns about risk of cancer, and transmission of other STDs. The disease has negative psychological and social effects both for males and for females, and it affects life quality adversely. The patients usually have feelings of embrassment and guilty.[21,22]

Presence of other sexually transmitted diseases: It is estimated that 20-34% of affected patients have concomitant STDs.[23]

Neoplasia:

Cervical cancer: High-risk HPV subtypes (HPV 16 and HPV 18) are the causes of approximately 70% of invasive cervical cancer and it is estimated that 500,000 cases of cervical cancer occur each year worldwide.[9-24]

A study of paraffin-embedded samples of 10,575 cases of cervical cancer demonstrated that the most common HPV types were 16, 18, 31, 33, 35, 45, 52, and 58; HPV types 16 and 18 represented 71% of the cases overall.[25]

Other anogenital cancers: Vaginal, vulvar, penile and anal cancers and their precancerous precursors such as vulvar intraepithelial neoplasia (IN), penile IN, anal IN are other associated neoplasies. Individuals with AGWs are at increased risk for head, and neck cancers.[26-30]

Obstruction: External AGWs invading anal canal and/or urethra may cause defecation problems, bleeding and mixion problems as a result of obstruction.[31]

Differential Diagnosis

Other cutaneous conditions including normal skin variations, other infectious and inflammatory diseases may mimic AGWs. Differential diagnoses include pearly penile papules, Fordyce spots, acrochordons, condylomata lata of syphilis, molluscum contagiosum, granuloma annulare, lichen nitidus, lichen planus, seborrheic keratosis, epidermal nevus, lymphangioma circumscriptum, lymphogranuloma venereum, scabies, syringomas, traumatic neuromas, schwannomas, and squamous cell carcinoma.[4,8]

Treatment

The basic indication for treatment of AGWs is reducing of symptoms (pruritus, bleeding, burning, tenderness, vaginal discharge, pain, obstruction of the vagina, dyspareunia) or psychologic anxiety.[32,33] There is no medical indication for treatment of asymptomatic warts incidentally noted on physical examination, but patients should be made aware of the presence of these lesions. Warts do not pose serious risks to health or fertility. In placebo controlled treatment trials, spontaneous regression occurred in up to 40% of cases. Patients should be informed that prolonged treatment with frequent follow-up is often necessary. They should also understand that medical and surgical therapies lead to clearance of warts in 35 to 100 percent of patients in 3 to 16 weeks,[34] but do not necessarily eradicate all HPV infected cells.[33,35,36] The likelihood of recurrence is variable depending on the patient's medical condition, im-

mune status, and the extent of disease, but 20 to 30% of patients have a recurrence within a few months.[37] Nevertheless, most HPV infections associated with genital warts in immune competent patients are cleared within two years.[38]

Both medical and surgical options are available for treatment (Table 1). There is no high quality evidence that any treatment is significantly better than others or suitable for whole patients and all types of warts; therefore, treatment choice depends on the location, number, and size of the warts; patient situations (eg, pregnancy, ability to comply with therapy, immunocompromised); availability of resources and clinical expertise; and patient preferences after considering side effects, cost, and convenience.[39,40]

Medical therapies are generally tried first; if the patient has not responded to the initial medical treatment after 3 weeks or total clearance has not happened by 6 to 12 weeks, a different medical therapy can be administered.[41] Surgical therapy is typically reserved for patients with extensive and/or bulky lesions and those who have failed to respond adequately to medical therapy. Surgery results in high initial clearance rates (90 to 100%), but recurrence rates are similar to those with medical therapy.[34]

Medical therapy

All medical therapies are most useful for patients with limited disease (eg, ≤5 small warts).[41] Podophyllotoxin (podofilox), imiquimod, sinecatechins, and topical interferon can be self-administered. Vaginal warts can only be treated with trichloroacetic acid (TCA), bichloroacetic acid (BCA), and interferons. TCA has no systemic absorption and no fetal side effects reported; therefore, it is the preferred treatment for pregnant women. In general, if the patient has not responded to the initial treatment after approximately 3 weeks or total clearance has not occurred by 6 to 12 weeks, it is appropriate to use another treatment.[42]

1. Cytodestructive therapies

Podophyllotoxin (podofilox): Podophyllotoxin (podofilox) consists of the biologically active component of podophyllum resin. The patient applies a 0.5% gel or solution to external genital warts by a cotton swab twice daily for three sequential days, then stops treatment for four days, and repeats this phase weekly up to four times.[33,43] No more than 0.5 mL of podofilox should be applied in one day. Broad areas (10 cm^2 or more) should not be treated at one time because pain is likely when the area becomes necrotic. Podophyllotoxin is avoided in pregnancy.

Table 1. Treatment modalities of anogenital warts

Medical therapy	Surgical therapy
Cytodestructive therapies	**Ablative therapies**
Podophyllotoxin (podofilox)	Cryoablation (Liquid nitrogen, Nitrous oxide)
Podophyllum resin	Laser ablation
Trichloroacetic acid	Electrocautery
Bichloroacetic acid	Ultrasonic aspiration
Fluorouracil	
Immune-mediated therapies	**Excisional therapies**
Imiquimod	
Sinecatechins	
Interferons	
Bacillus Calmette-Guerin	
HPV vaccine	

Podophyllum resin: Podophyllum resin is a plant-based resin that arrests cell division at metaphase and induces apoptosis. A 25% solution applied directly on the warts with a cotton swab by the clinician. No more than 0.5 mL should be used in each treatment period and wide areas (10 cm^2 or more) should not be treated in a single application because of potential pain and destructive area. The area should air-dry before the patient dresses. Podophyllum resin is avoided in pregnancy. In contrast to podophyllotoxin, systemic absorption and toxicity have been documented. A dilute solution (10%) should be applied when treating broad warts to minimize total systemic absorption, and application to open lesions/wounds should be avoided. The treatment is repeated weekly for four to six weeks, or until the lesions have cleared.[33,43]

Trichloroacetic acid and bichloroacetic acid: Both TCA and BCA are corrosive acids that damage the wart by chemical coagulation of tissue proteins. TCA is used most commonly, and can be used on the vulva and vagina, and during pregnancy. An 80 to 90% TCA solution is applied carefully to the wart with a cotton swab; the wart turns white as the solution dries. Application of an ointment or gel to the normal area surrounding the wart can prevent the destruction of unaffected tissue. TCA treatment is suitable for small area of vaginal warts (eg, ≤5 small warts).[41] If excess TCA is applied, it can be antagonized by washing with soap or sodium bicarbonate solution. The patient should not sit, stand or dress until the treatment area has dried. The treatment should be applied weekly for four to six weeks, or until the lesions disappeared. The only study evaluating the use of TCA in women reported a 70 percent clearance rate.[44]

Fluorouracil: Fluorouracil (FU) is a pyrimidine antimetabolite that hinder methylation of deoxyuridylic acid in DNA synthesis, causing to apoptosis. Topical FU is often less tolerable due to side effects (burning, pain, inflammation, edema, or painful ulcerations). It should not be used during pregnancy. A gel consisting of FU is injected intradermally directly under the wart. Injections are performed once per week for up to six weeks. Clearance rates of 65% after treatments have been reported.[45] Preferably, a thin layer of 1 or 5% cream has been applied on vulvar or vaginal warts to make a chemical desquamation.[46-48] Several dosing protocols have been suggested, ranging from twice daily application to once weekly for several weeks. Zinc oxide cream or petroleum jelly can be applied to unaffected areas as a barrier to help protect against ulceration.[47,48]

2. Immune-mediated therapies

Both imiquimod and interferon initiate a local immune response at the site of the wart that ultimately may clear the lesions. Imiquimod and topical interferon may be self-administered; injectable interferon is given in the office. Experience with these agents is more limited than for other medical therapies.[49-53]

Imiquimod: Imiquimod is a toll-like receptor 7 agonist, which acts as a positive immune response modifier, and stimulates local cytokine induction. Two formulations are available, Aldara (5% imiquimod) and Zyclara (3.75% imiquimod). There are no comparative data available between the two dosing regimens. The manufacturers recommend against vaginal administration. The patient applies imiquimod cream directly to the clean dry warty tissue at bedtime, rubbing it in until the cream is no longer visible; this area is washed with mild soap and water 6 to 10 hours later. Sexual contact should be avoided while the cream is on the skin. The cream can weaken condoms and diaphragms. Aldara is applied three days per week for up to 16 weeks.[49] Zyclara is applied daily for up to 8 weeks. Forty to 50% of women will have complete clearance of the warts and most of the remainder will have partial clearance, but up to 30% will experience a recurrence within 12 weeks.[50] The use of imiquimod in pregnancy should be avoided[33] and its higher cost is a disadvantage.

Sinecatechins: Sinecatechins (eg, Veregen) is a botanical drug product for self-administered topical treatment of external AGWs. The active ingredient is kunecatechins, which are a mixture of catechins and other components of green tea. They have both antioxidant and immune enhancing activity.[51] A 0.5 cm strand of ointment is placed on each wart and a finger is used to cover the wart with a thin layer of the ointment 3 times each day

for up to 16 weeks. It should not be used in the vagina or anus and should be washed off of the skin before sexual contact or before inserting a tampon into the vagina. Sinecatechins should be avoided in immunocompromised women and women with active genital herpes lesions. There is minimal information on the risk of use during pregnancy.[51]

Interferons: Interferons have antiviral, antiproliferative, and immune-stimulating effects, theoretically making them an ideal agent for treatment of anogenital warts. Interferon-alpha and -beta have been administered as a systemic therapy (intramuscular injection), topically, and as a subcutaneous intralesional injection. Placebo controlled randomized trials have generally found intralesional therapy to be most effective,[52] while evidence for the efficacy of systemic and topical therapy has been inconsistent.[53-56] Intralesional injection of 0.5 to 1.5 million international units per lesion is administered two to three times per week for up to three weeks. The course of therapy can be repeated 12 to 16 weeks from the initial treatment. Local anesthesia is recommended.[57] Interferon may be used as adjunctive therapy to surgical and cyto-destructive treatments, especially in patients with refractory lesions. Interferons are contraindicated in pregnancy.[53-56]

Bacillus Calmette-Guerin: Topical administration of bacillus Calmette-Guerin (BCG) has been used primarily for treatment of perianal warts in men and requires further study.[58-60]

HPV vaccine: HPV vaccines are effective in the primary prevention of HPV infection.[33]

3. Surgical therapy

Surgical management options consist of ablative and excisional procedures. Especially in patients with extensive or multifocal disease, surgical treatment modalities are used. Regardless of the method chosen, the surgeon should maintain control of the depth of tissue destruction due to the risk of fistula formation. An advantage of surgical management is that fewer visits for treatment are needed compared with medical therapy. A disadvantage of all surgical therapies is that they generally require anesthesia and often need to be performed in an operating room. Surgical therapy may result in hypopigmentation, hyperpigmentation and scarring, especially when the subdermal layer is destroyed.

Biopsy is recommended to rule out underlying intraepithelial neoplasia or cancer prior to surgical treatment of lesions that are refractory to medical therapy or appear atypical. If performed, biopsy must be done prior to using any ablative technique. All of the surgical options can be used in pregnant women and on both the vulva and vagina.[33,61-64]

Cryoablation: Cryoablation with either liquid nitrogen or nitrous oxide destroys wart tissue via cell lysis. Although it is an office procedure, cryoablation causes pain during application and variable localized inflammation afterward. Providing local anesthesia for the procedure is especially important when the area undergoing cryotherapy is extensive.[61]

Liquid nitrogen is most commonly used, and is applied directly to the vulvar or vaginal lesion with a cotton swab or a fine spray. The treatment is applied for 30 to 60 seconds, until an ice ball forms and encompasses the lesion and 1 to 2 mm surrounding area.[61] Repeated weekly application is required until the lesions have resolved.

Nitrous oxide is dispensed via a cryoprobe and generally gives a greater depth of freezing; therefore, it is not recommended for use in the vagina because of the risk of vaginal perforation and fistula formation.[33]

Laser ablation: Lasers produce light energy, which is absorbed by water within warty tissues, leading to thermal damage and resultant ablation. Carbon dioxide laser is the most commonly utilized type of laser for treatment of vulvar warts, but requires specific training and specialized equipment.[62] Laser ablation is the preferred therapy than the surgical knife for extensive or multifocal vulvar lesions to maintain normal vulvar anatomy. Laser is also useful for treating vaginal warts when surgical excision is technically challenging or not feasible. The risks of laser surgery include scar formation (up to 28 percent), pain, hypopigmentation and vulvodynia.[63,64]

The surgeon and operating room personnel should wear protective masks when performing laser ablation, as HPV DNA can be dispersed in the laser plume.[65] Patients are instructed to take sitz baths two to three times a day during the initial one to two weeks following the procedure for pain management. Antibacterial creams or ointments are suggested to prevent superficial infection, as well as to separate the vulvar folds and prevent agglutination of tissues.[62-65]

Electrocautery: Electrocautery can also be used for ablation of vulvar or vaginal lesions. An advantage of this approach over cryoablation is that a single treatment session is usually adequate for eliminating the warts. A disadvantage is that electrocautery requires administration of anesthesia and use of an operating room. If available, laser ablation is generally preferable to electrocautery because it is associated with less bleeding and discomfort following the procedure.[33]

Ultrasonic aspiration: The Cavitron ultrasonic aspirator (CUSA) technique utilizes ultrasound to fragment and aspirate warty tissue.[66] This allows removal of epithelium without damage to underlying tissue.

Excision: If tissue is needed for histological diagnosis, an excisional biopsy can be performed before an ablative procedure, or an excisional procedure can be performed. Typically, exophytic lesions are tangentially excised or shaved to the level of normal skin using scissors or a surgical knife, and then the base of the lesion is cauterized.[67] Curettage or electrosurgery can also be used for excision of lesions. Adverse sequelae of excisional therapy include pain, dyspareunia, scar formation, and infection.[61]

Treatment of AGWs in pregnancy

No studies have compared occurrence and course of clinical warts in pregnant and non-pregnant patients. Few studies have evaluated HPV in pregnancy and most showed an increase in prevalence.[68,69]

Indications for treatment of AGWs in pregnant women are similar to those for non-pregnant women. In addition, lesions that potentially obstruct the birth canal should be treated to avoid complications during vaginal birth. Treatment may not reduce the risk of vertical transmission. Treatment options are limited in pregnancy because podophyllin, podophyllotoxin, interferon, and FU are all contraindicated because of potential fetal harm. However, given the scarcity of data on use of imiquimod or sinecatechins in pregnancy, these drugs are generally not recommended.[33] TCA has no systemic absorption and no known fetal effects; therefore, it is the preferred medical treatment for pregnant women. Clearance rates are highest and recurrence rates lowest when TCA is used in the second half of the pregnancy.[70] Cryoablation is also considered a safe and effective treatment for use in pregnancy.[71,72] A number of case series have described use of laser ablation in pregnancy for bulky, potentially obstructive lesions, with success rates of 90 to 100%.[73,74] The risk of wart recurrence appears lowest when the treatment is delayed until the third trimester.[75]

Recommendations

- Imiquimod or podophyllotoxin (podofilox) is recommended for initial therapy of a small area of external genital warts (eg, ≤5 small warts),[41] as long as the patient can comply with home therapy.

- Podophyllotoxin (podofilox) has negligible systemic absorption/toxicity, and can be self-administered, and is more effective than podophyllum resin (podophyllin). Comparative studies have shown that podophyllotoxin is more effective than podophyllum resin for clearance of all warts.[76,77]

- Sinecatechins are a reasonable alternative, but the most costly approach.

- Trichloroacetic acid (TCA) and cryotherapy are recommended for initial office-based treatment of women who cannot comply with self-administered therapy or as a second-line approach for those who fail home therapy.[34,78] TCA can be used in combination with imiquimod for patients who fail monotherapy or cryotherapy.[78]

- TCA, BCA, and interferons are the only medications that can be used to treat vaginal warts, but many patients cannot tolerate intralesional interferons. Laser ab-

lation is our preferred surgical approach as it is possible to reach into the vagina and the depth of treatment can be controlled.

- For patients with extensive (>20 cm^2) and/or bulky disease, surgery as initial therapy is recomended because medical therapy alone often requires a prolonged course of treatment and is often inadequate and poorly tolerated. Laser ablation is less destructive and less technically challenging than excision, and better tolerated than electrocautery.

- For patients with multifocal or refractory disease, a combination of techniques is often effective. For these patients a surgical approach or a combination of intralesional interferon and TCA can be used. For patients with recurrent disease, the same treatment that resulted in initial clearance of warts may be used again and is likely to be successful.

- Postmenopausal women who present with warty-appearing lesions should be biopsied before initiation of therapy, as these women have a greater chance of having an underlying vulvar intraepithelial neoplasia or vulvar cancer than younger women.

Conclusion

HPV infection is a global public health problem leading to an economic burden accounting for the costs of the treatment of AGWs and HPV-associated neoplasies. The patient should be evaluated by a multidisciplinary approach including dermatologists, gynecologists, urologists, general surgeons and ear, nose, and throat specialists. The main goal dealing with this problem should primarily be to raise public awareness about HPV infection. Patients should be educated about transmission routes, prevention of transmission and the importance of vaccination.

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