REVIEW

Doi: 10.4274/jus.galenos.2023.2023-6-8
J Urol Surg, 2023

The Effectiveness of Genital Wart Treatments

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Abstract

Human papillomaviruses (HPV) are a family of DNA viruses that infect the epithelium. They cause benign proliferative lesions called anogenital warts. HPV infection is common in men and women and is the most common sexually transmitted infection. HPV infection can cause cervical, penile, anal, vaginal, vulvar and oropharyngeal cancers. Genital warts adversely affect the quality of life. It may cause anxiety, guilt, anger, and loss of self-esteem and may cause anxiety about the cancer risk. For the diagnosis, generally, visual inspection is enough. Different kinds of treatments have been reported. Genital wart treatments are generally painful, prolonged, hard for the patient to apply, and unfortunately often recurrence of the lesions seen after treatment. Although many treatment methods are used, their superiority to each other is unclear. In this review, we investigate self-application treatments, clinical-based treatments and alternative treatments.

Keywords: Anogenital warts, condyloma acuminata, HPV

Introduction

Human papillomaviruses (HPV) are a family of DNA viruses that infect the epithelium (1). HPV infection is common in men and women and is the most common sexually transmitted infection. They cause benign proliferative lesions that called anogenital warts (AGW) (genital warts, condyloma acuminate, condylomas) (2,3) (Figures 1-3). There are more than 200 hundred variants of HPV (4). HPV is divided into two groups as low-risk noncarcinogenic and high-risk oncogenic types. HPV infections can cause cervical, penile, anal, vaginal, vulvar and oropharyngeal cancers (1). Ninety-nine percent of cervical cancers, 90% of anal cancers, 65% of vaginal cancers, 50% of vulvar cancers, 45-90% of oropharyngeal cancers are thought to be caused by HPV (4).

HPV can be transmitted through skin or mucosa contact. The most documented way of HPV infection is sexual transmission, but there are nonsexual courses reported for transmission. Fomites, fingers, mouth, skin contact, and self-inoculation are the reported ways of transmission. The transmission from mother to child is called a vertical transmission, and it is another way of transmission. Genital HPV in children and female virgins (without

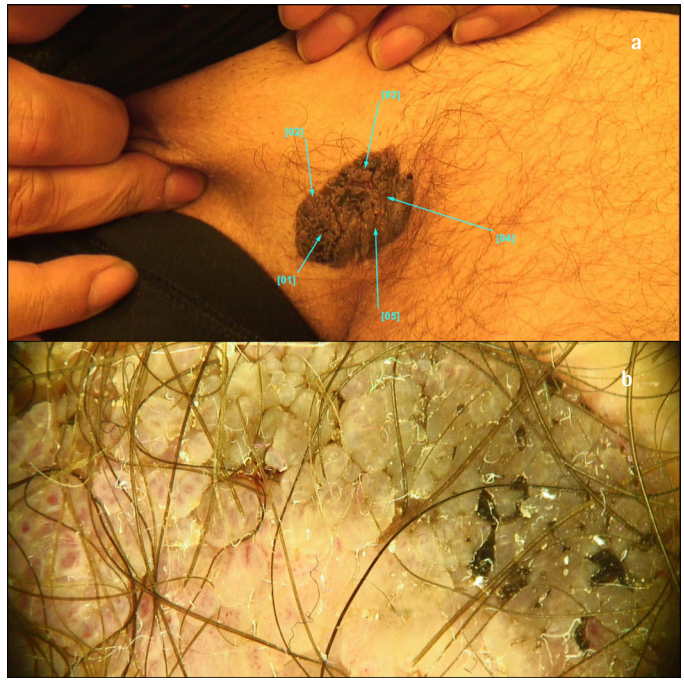

Figure 1a, b. Anogenital wart, dermoscopy

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Received: 20.06.2023 **Accepted:** 16.07.2023

Cite this article as: Bıyık Özkaya D, Erfan G, Çıtamak B. The Effectiveness of Genital Wart Treatments.

sexual abuse, with low-risk HPV types) has also been reported in studies. In a study, HPV DNA samples were collected from gynecological equipment. Gloves and copposcopy rooms may have a risk of HPV transmission (5). Condoms cover transvaginal ultrasound probes, but the risk of condom rupture may cause HPV transmission (6). Two gynecological laser surgeons were reported with HPV (+) tonsillar cancer that may show that particles in the air have transmission risk (7).

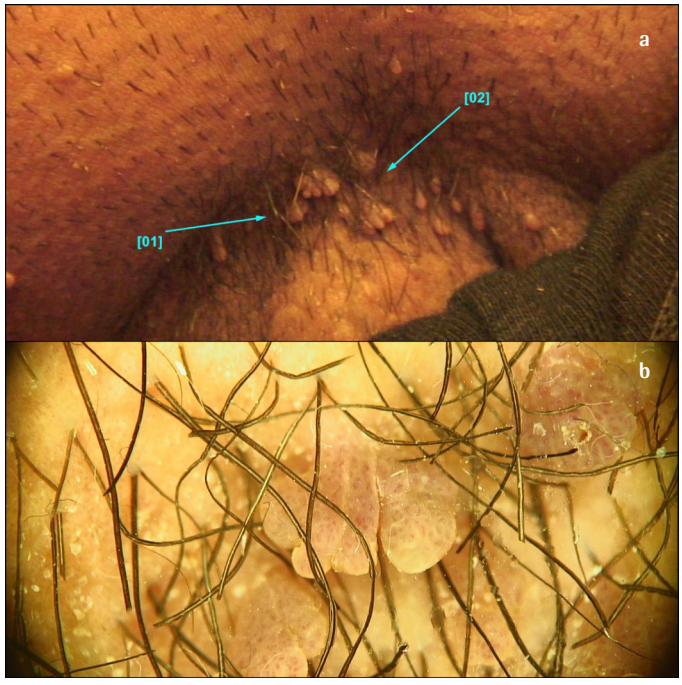

Figure 2a, b. Anogenital wart, dermoscopy

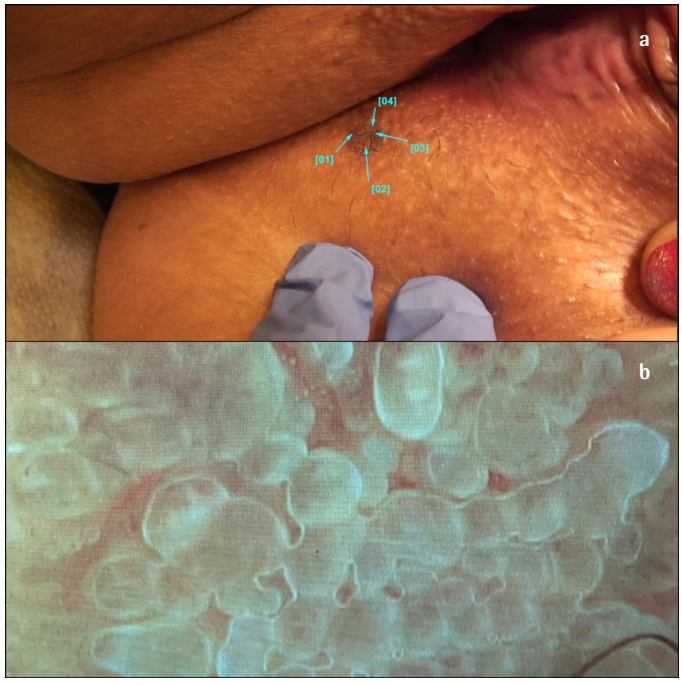

Figure 3a, b. Anogenital wart, dermoscopy

The most common HPV types seen in angenital verruca are HPV types 6 and 11. After HPV transmission, clinical presentation of symptoms is nearly 11-12 months among males and 5-6 months among females (8). In months, HPV infections mostly resolve spontaneously and are generally asymptomatic. The clearance time is approximately 6-24 months (Cervical HPV in 9.4 months, genital HPV in men 7.5 months with oncogenic and non-oncogenic types) (9). HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 are carcinogenic (8).

The genital warts negatively affect health-related quality of life outcomes. It may cause anxiety, guilt, anger, and loss of self-esteem and causes anxiety about the cancer risk (10). Multiple partners, early start to sexual activity, smoking, sexually transmitted diseases, lack or delayed treatment, and disruption of skin integrity are risk factors for HPV infection.

Generally, visual inspection is enough for diagnosis. A good light is important for examination. Urethral meatus examination, vaginal examination, perianal area examination, and if the suspected rectal examination must be performed. If lesions are atypical, there is resistance to treatment, and the diagnosis can be confirmed by biopsy (3,11).

Treatment

A wide range of treatment options are reported in the literature. Genital wart treatments are generally painful, prolonged, hard for the patient to apply, and unfortunately often recurrence of the lesions seen after treatment. Treatments generally depend on the physical destruction of the lesion because this recurrence can be easily seen. A treatment that has antiviral effects on human papillomavirus would give more success and lower recurrence rates. One more problem for the patient is several visits to the hospital for treatment. This makes the treatments not cost effective and sparing time may be hard for the patient too. Here, the treatments are discussed in three groups: self-application treatments, treatments applied in the hospital, and alternative medical wart treatments.

1.Self-application Treatments

1. a. Podophyllotoxin

Podophyllotoxin is a product prepared by separating nontherapeutic lignans and the mutagenic agent quercetin from podophyllin (12). Podophyllotoxin inhibits the proliferation of human skin keratinocytes by its antimitotic effect and cures genital HPV by inhibiting the proliferation of HPV-infected cells and destroying infected tissue (12,13). Podophyllotoxin has different forms: 0.15% cream, 3% cream and 5% solution and 5% gel. Cream form is suggested for vulval and perianal warts because of its easy application (12). Side effects are itching, burning, tenderness, erythema, and erosion. Podophyllotoxin is contraindicated during pregnancy. Podophyllotoxin is a

stable and safe product. Treatment is applied by the patient topically twice in a day at home for 3 consecutive days and after a 4 day break. If the treatment is not enough, it can be repeated for 4 weeks. Claesson et al. (12) compared the clinical efficacy of 0.3%, 0.15% cream forms of podophyllotoxin versus 0.5% solution. They found that the efficacy is similar and the tolerance is better with 0.15% cream. Strand et al. (14) compared 0.3%, 0.15% cream forms of podophyllotoxin with 0.5% solution. They found similar response rates but they also found that the effect of %0.15 cream is slower than other forms. Lacey et al. mentioned that in the original warts treatment, podophyllotoxin solution 5% is superior to podophyllin and podophyllotoxin 0.15% cream. For all warts, podophyllotoxin solution was significantly better than podophyllin and similar to podophyllotoxin cream (15). The clearance rates of warts have been reported to be 36-83% for podophyllotoxin solution and 43-70% for podophyllotoxin cream. The recurrence rates with podophyllotoxin treatment were reported as 6-100% within 8-21 weeks after clearance (16).

1. b. Imiquimod 5% cream

Imiquimod is a non-nucleoside heterocyclic amine, immune response modifying agent. Imiquimod induces several proinflammatory cytokines including interferon alpha, interleukin 1,6,8,12, tumor necrosis factor alpha, and other cellular proteins. It also induces the production of monocytes and macrophages. Imiquimod has antiviral and antitumor effects by enhancing the immune system without tissue destruction (17-19). Side effects are listed as itching, erythema, burning, irritation, tenderness, ulceration, erosion, pain, headache, upper respiratory tract infections. In reports; the complete response rate with imiquimod is 40% and the recurrence rate is 19% (18,19). Komericki et al. (20) compared imiquimod 5% cream with podophyllotoxin 5% solution. There was no statistically significant difference in the treatment results. In comparison with podophyllotoxin; the major disadvantage of imiquimod is the long treatment period (4 months-4 weeks). Due to this fact, in the study of Komericki et al. (20); 6 (5 from imiquimod group) of the patients left the study and they believe that this is not only because of the side effects, long treatment period of imiquimod favors podophyllotoxin.

Edwards et al. (17) compared imiquimod 5%, 1% cream and vehicle. They found in their study imiquimed 5% cream was effective and safe. In this study 50% of patients using imiquimod 5% cream had total clearance and the recurrence rate was 13%.

Another study compared treatment options with 5% imiquimod cream 3 times a week, once daily, twice daily, and three times a day and found the optimal dosing 3 times a week. Although the other options were also effective, the side effects increased in these options and these applications showed no association with increased total wart clearance (21). In Arican et al. (22) study; 69.7% of the patients healed totally and female patients displayed earlier improvement than male patients. Garland et al. (23) compared the treatment durations with imiquimod 5% in female patients. They compared 4,8,12,16 weeks of treatment. The clearance rates were not significantly different (40.0%, 48.4%, 39.3% and 51.6%). They suggest that women with genital warts should be treated for 4 weeks and then followed for 12 to 16 weeks. This would help to decrease side effects, drug costs, and clinic visits. They suggest that following the cessation of treatment by a T-cell memory-mediated immune response, the effect of treatment goes on (23). In a meta-analysis of Elana et al. (24); they investigated the optimal application schedule for imiquimod 5% cream. They found that effect size was significantly higher in women than in circumcised men regardless of the drug application frequency, and the optimal application frequency of 5% imiquimod cream for all groups (women, circumcises and uncircumcised men) was 3 times a week. The drug penetration is the best in a keratinized and moist environment (24).

In a report of 7 women who used imiquimod cream during their pregnancy; all patients gave live births with no major complication and the mean birth weight was 3528 grams. Besides this, systemic absorption is reported as minimal (0.25-2.5%) in animal studies (25). Audisio et al. (26) reported 17 pregnant women treated with 5% imiquimod cream during pregnancy. In this retrospective case series 13 (76.4%) of 17 pregnant women provided a complete response. There is not enough data for recommending imiquimod cream during pregnancy, and imiquimod cream is category B during pregnancy.

1. c. Sinecathecins

Green tea (leaves of Camellia sinensis, Theaceae) has many favorable effects such as anti-inflammatory, anti-oxidative, anti-mutagenic, anti-carcinogenic, and cardioprotective effects. Preventing type 2 diabetes and osteoblast differentiation are other effects of green tea extracts. Green tea extract contains polyphenols (e.g., catechin, epicatechin, epigallocatechin (EGC), and their gallates), teanin, caffeine, and polysaccharides, many of which are thought to be responsible for the beneficial health effects. By blocking the mitotic signal transduction pathway, it has antitumor effects. With these effects and anti-inflammatory properties, green tea extracts have been successful for treating warts. The ointment should be used 3 times a day until the lesions heal for a maximum of 16 weeks. Sinecathecins are not suitable for use on internal warts and during pregnancy (27,28). Side effects such as local skin reactions (itching, erythema), intensity, balanitis, herpes simplex, lymphadenitis, dysuria, rash, hyperkeratosis, skin discoloration, pain, and allergic dermatitis have been reported (28,29). Gross et al. (28) found that the 15% ointment preparation was more effective than the 10%

cream formulation and both of them were superior to placebo. They found higher clearance rates in uncircumcised men and suggested that the lower degree of keratinization and semi-occlusive effect of may cause these higher clearance rates. They found clearance rates 61% and recurrence rate of 10.6% for 15% ointment (28). Tatti et al. (30) found clearance rates higher in women, but the difference was small. They associated this with higher keratinization of the penis. Tzellos et al. (31) found both forms of Polyphenon E (15%,10%) effective, safe, cost-effective and well tolerated. Both forms have low recurrence rates (31).

2. Clinical Based Treatments

2. a. Cryotherapy

Cryotherapy (CRYO) destroys warts by cold-induced cytolysis. It is liquid nitrogen and can be used as a spray or cryoprobe, and it is a very common treatment technique (32). The adverse effects are pain, erythema, swelling, exudation, blistering, ulceration, and post-inflammatory pigmentation (32,33).

In a review that discussed the efficacy and safety of CRYO for patients with AGW, it was mentioned that CRYO has a similar effect as trichloroacetic acid (TCA), imiquimod, and podophyllin and slightly less effect than electrosurgery (32). The disadvantage of CRYO is that the treatment effectiveness depends on the user, and this is a limitation for deciding the effectiveness of the treatment (32). Pontini et al. (33) investigated the efficacy of topical nitriding complex solution (NZCS) versus cryotherapy for treating AGWs. They found that the treatment efficacy in NZCS was slightly higher, and this difference was statistically significant. Not only was the efficacy higher but also the number of recurrences after one month was lower in the NZSC (18.4%) than the CRYO group (38.1%) (p=0.0356) and tolerability to NZCS was better (33). Rodriguez et al. (34) investigated cryotherapy plus low dose oral isotretinoin vs cryotherapy treatment. In their study with the isotretinoin group, both faster treatment success was achieved and recurrence was less frequent. Cryotherapy is safe during pregnancy. An important advantage of cryotherapy is that anesthesia is unnecessary (35). In clinical studies clearance rates reported as 44-87% and recurrence rates reported as 12-42% in 3 months of follow-up. CO_2 laser was found to be more effective than CRYO; electrosurgery was found to be slightly more effective than CRYO and TCA and podophyllin showed similar effects with CRYO (32-38).

2. b. Trichloroacetic acid (TCA)

TCA treats AGW by causing chemical coagulation, protein denaturation, and cell death of tissue proteins. TCA can be used in different concentrations between 60 and 90%. TCA treatments are generally performed in hospitals up to 3 times weekly and the applications go on until the warts heal (39,40).

Sodium bicarbonate 5% is a neutralizing agent for TCA and it should stay with TCA for safeness. Generally, a superficial ulcer occurs and it heals without scarring. With TCA, clearance rates are reported as 56-94% and recurrence rates as 36% (36,41,42). The side effects are pain, itching, irritation, erythema, erosion, and ulceration. Anggraini et al. (43) compared 1%, 5 5%-fluorouracil creams and 90% TCA and found that the effectiveness was similar. The response was earlier (at week 2) in the TCA group in their study. Recanati et al. (44) compared cantharidin versus TCA and found that cantharidin was more effective (100%, 66%), the cantharone group healed with less scar and needed less treatment for heeling. Trichloroacetic acid is not absorbed from the mucous membranes and skin, so it can be safely used for pregnant women (35).

2. c. Surgical Treatment

There are several different surgical techniques for the treatment of AGW. Excision, electrosurgery, and laser treatments are the most recommended surgical treatments.

2.c1. Laser treatment

In a review, both ablative lasers (CO2 and Erbium YAG (Er yag)) and nonablative lasers were mentioned as effective, but the number of treatment sessions was found to be lower with ablative lasers than nonablative (Pulsed Dye (PDL) and NDYag) lasers. When nonablative lasers are compared, patients with neodymium-doped yttrium aluminum garnet (NDYag) laser treatments need lower sessions for clearance. Combining keratolytic agents with laser treatments may help in rapid clearance times (45). The combination of PDL with interferon alpha or bleomycin may cause higher efficacy but because of side effects this combination can be used as second-line treatment (46,47). On the other hand; applying a moisturizing cream before NDYag laser treatments may lead to deeper penetration and higher response rates (48). For patients with darker skin types; NDyag would be a better choice. Among lasers; PDL seems safer and can be preferred first choice if possible (49). The side effects of laser treatments are listed as pain, hemorrhage, crust formation, blisters, hyperpigmentation, hematoma, second bacterial infection, persistent erythema, hypertrophic or atrophic scar formation, ulceration, recurrent anal fissures, and perianal dermatitis (45-49). In pregnancy, the studies did not show adverse effects related to laser therapy (35). The advantage of laser treatment is that widespread warts can be treated in a single session with laser treatment. With PDL treatment response rates are 0-100% and recurrence rates are 0-30%, with NDyag treatment complete remission rates vary between 9.1% and 100%, recurrence rates vary between 0 and 10, with CO_2 laser treatment complete remission rates are different between 59.15% and 100%, and recurrence rates are between 0and 40.8% (45-49).

2.c.2. Excision

There are a smaller number of studies on scissor excision. When the lesions are small, exophytic, pedunculated, or single, scissor excision can be a choice. Handley et al. (50,51) found that scissor excision plus electrocautery of anogenital warts under general anesthesia were safe for prepubertal children. The side effects of this treatment are scarring, pain, and hypohyperpigmentation. For scissor excision 89-100% clearance rates were reported and 19-29% of recurrence rates were reported (50-52).

2.c.3. Electrocautery and surgery

Electrosurgical units show their effects of destroying the wart lesion by thermal coagulation and burning. The tissue that is desiccated is afterward removed by curettage. For small lesions on the penis shaft, vulva, or rectum, this technique is effective but for large lesions because of scar formation, this technique is not recommended. Electrosurgery is a painful procedure for local anesthesia of small lesions and general anesthesia is required for a large number of lesions (53). The side effects are pain and scar formation. Electrocautery treatment is contraindicated in patients who have cardiac pacemakers (54,55). In pregnancy, there are not enough reports about electrocautery or surgery. Electrocautery or scissor excision may be preferred primarily in cases where laser treatments cannot be reached or when the pathological investigation is required (35). The clearance rates of this procedure have been reported as 94-100%, whereas recurrence rates are 22% (56).

2.c.4. Transurethral resection

Urinary tract and bladder HPV infections may rarely be seen. Immunsuppression and anogenital condylomas are risk factors for isolated urinary tract infection (57-59). Sarier et al. (57) reported a case of HPV type 45 (+) condyloma acuminata of the bladder in a renal transplant recipient. By transurethral resection (TUR), they removed multiple warty lesions inside the bladder. They did control cystoscopy in the third and sixth postoperative months and did not see recurrence. Condyloma arising inside the bladder is a risk factor for developing squamous cell carcinoma (SCC) (58). For this reason, urological examination is important for patients who are immunosupressed and have anogenital condylomas (57-59).

Alternative Medical Wart Treatments:

3. a. 5-Fluorouracil

5-fluorouracil blocks thymidylate synthase and inhibits DNA synthesis. It is available in 5% cream form (60). The side effects of 5-fluorouracil treatment are pain, burning, inflammation, and ulceration (60). In a review with 988 patients 5% fluorouracil cream was found to be superior to placebo, but the authors found the evidence level for this treatment week in these studies (60). In pregnancy 5-fluorouracil treatment is not recommended (35).

3. b. Interferon

Interferon has immune-boosting effects and promotes the healing of virally infected cells. By this therapy not only the lesions seen by the naked eye but also infected cells can be treated, which may lead to lower recurrence rates (61,62). The side effects of interferon are flu-like symptoms, such as headache, nausea, vomiting, fatigue, and myalgia, elevated liver enzymes, bone marrow suppression, bronchospasms, and depression, and pain is also reported with intralesional injections (61-64). In a meta-analysis with 1500 patients' interferon therapy was found to be superior to placebo (61). In pregnancy, interferon is not recommended (35). Interferon therapy for anogenital warts is controversial and expensive; it can be a choice for resistant cases.

3. c. Photodynamic therapy

Using 5-aminolevunic acid (ALA) and photodynamic therapy (PDT) is a noninvasive technique. It is an effective treatment for proliferative diseases, inflammatory diseases such as psoriasis, acne, infectious diseases such as verruca vulgaris, condyloma acuminate, and cutaneous leishmaniasis (65). PDT uses photoensitizer, light, and oxygen to destroy the target tissue cells. 5-aminolevunicacid metabolizes to active protoporphyrin IX, which photoensitization. The 635 nm red light is clinically used because of its absorption rate and penetration depth. With photodynamic therapy, cell death occurs by apoptosis and necrosis and this causes the destruction of HPV-infected 65-67). The major side effects are pain, bleeding, and secondary infection. Xie et al. (65-67) concluded that ALA-PDT is a safe and effective treatment for condyloma acuminate with lower recurrence rates. ALA-PDT especially has advantages for threatening the urethra and anal canal warts. With ALA-PDT, subclinical latent infections around the lesions can be treated. PDT is expensive and it can be an option for resistant cases and for areas that are hard to treat such as the urethra and anal canal (65-67). There are insufficient data on the efficacy and safety of photodynamic therapy in pregnancy (35).

3. d. Ingenol tebutate

Ingenol tebutate stimulates the inflammatory response and neutrophil infiltration and by this way stimulates cell death in proliferating keratinocytes. The major side effect reported is local skin irritation (68,69)

3. e. Injectable immunotherapy:

Intralesional antigens led to an immune response and by this way wart resolution becomes. The most common injectable immunotherapy agents are candida antigen, mumps-measles-rubella vaccines, mycobacterial antigen, and HPV vaccines.

Intralesional candida antigen and measles, mumps, and rubella vaccine (MMR) were found to be more effective than cryotherapy. They do not only treat the injected lesion but are also effective in distant lesions than the injected lesion. The side effects are reported as mild injection site pain, flu-like symptoms and within very few reports a short-term myalgia, erythema and local swelling (70-79).

3. f. Human Papilloma Virus (HPV)Vaccine

HPV vaccines target high-risk HPV types in the prevention of associated cancers. Although they do not target common warts, there are studies that found them effective for treating extragenital warts. Although there are not sufficient studies with a large number of patients, it may be an option for recalcitrant warts, even in immunosuppressed patients (80-85).

3. g. Vitamin D

Vitamin D analogs are used in the treatment of warts both topical and intralesional. In a study comparing intralesional vitamin D, candida antigen, and saline, intralesional vitamin D treatment was found to be superior. On the other hand; when compared with CRYO, the efficacy was found to be similar. There is not enough data on the use of topical vitamin D but it may be more comfortable in terms of side effects (86-90). The side effects are listed as injection site pain, redness, and swelling (86-90).

3. h. Bleomycin

Intralesional bleomycin treatment has been used on resistant warts. The most common dosing schedule was using 1 U/mL solution, up to 1-2 mL per treatment. It can be performed intralesionally up to 4 times at 2-3-week intervals. The side effects are eschar formation and hyperpigmentation and flagellate hypopigmentation (91).

3.ı. Retinoids

Retinoids are vitamin derivates. They have effects on epithelial differentiation and proliferation and may also have an immunomodulatory inhibitory effect on HPV replication. They can be used topically and systemically in HPV treatment. Even though oral etretinate was found to be the most efficient agent, oral isotretinoin studies are higher in number. In studies; topical tretinoin has the least efficiency. The side effects are cheilitis, xerosis, xerostomia, conjunctivitis, xeropthalmia, epistaxis, desquamation, retinoid dermatitis, photosensitivity, pruritus, local irritation, fatigue, hair loss, arthralgia, myalgia, hypertriglyceridemia, hypercholesterolemia, and elevated liver function tests. The retinoids are in category X during pregnancy. Clearence rates are reported as 100% with etretinate, and 56% with isotretinoin, and the patients in the studies were resistant cases (92).

Genital wart differential diagnosis

In differential diagnosis, 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, angiokeratoma Bowenoid papulosis, and squamous cell carcinoma can be listed (Figure 4-9) (93).

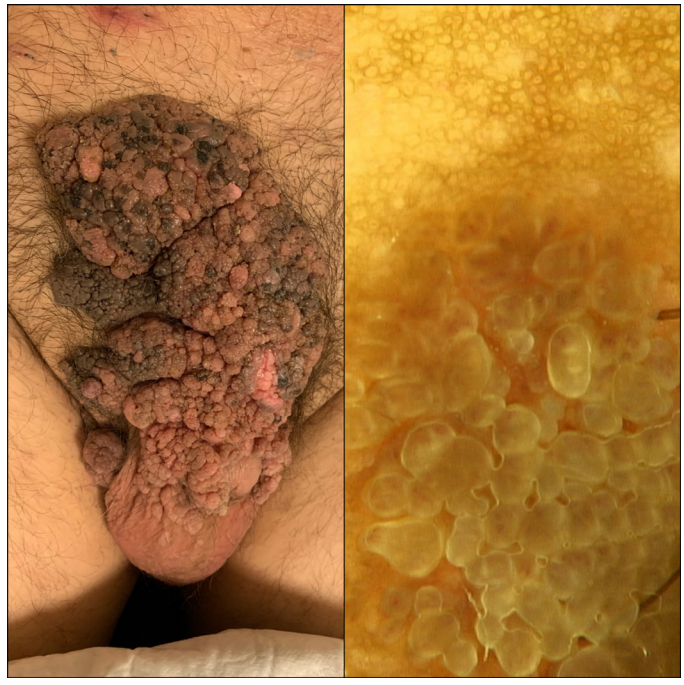

Figure 4. Buschke-Löwenstein, dermoscopies

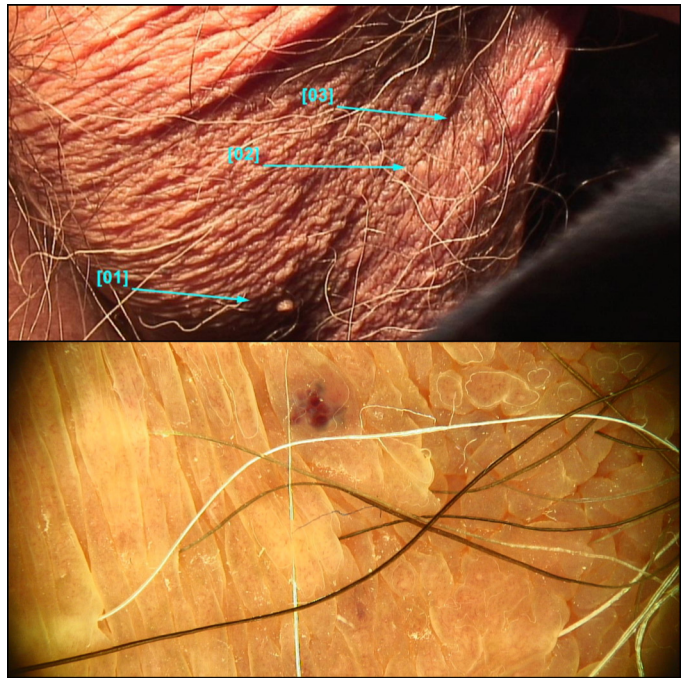

Figure 5. Angiokeratoma dermoscopy

Exophytic cauliflower-like growth lesion, which has a tendency to infiltrate adjacent tissue, is called Buschke-Lowenstein (94-96). It is generally associated with HPV 6,11 and is mostly seen in immunosuppressed patients. It is locally aggressive, has potential for destructive growth and malignant transformation. Computarised tomography and magnetic resonance imaging are necessary because of malignancy transferals and adipose tissue growth tendency. The gold standard treatment is excision.

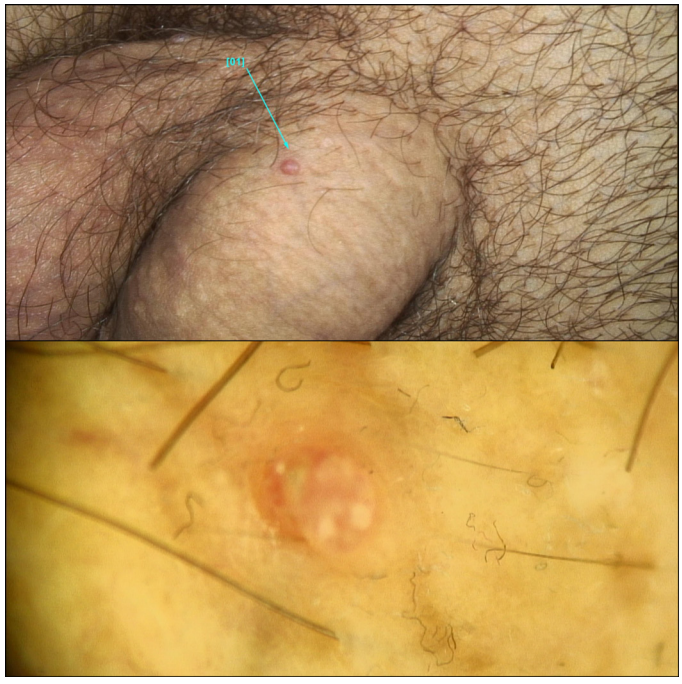

Figure 6. Molluscum contagiosum dermoscopy

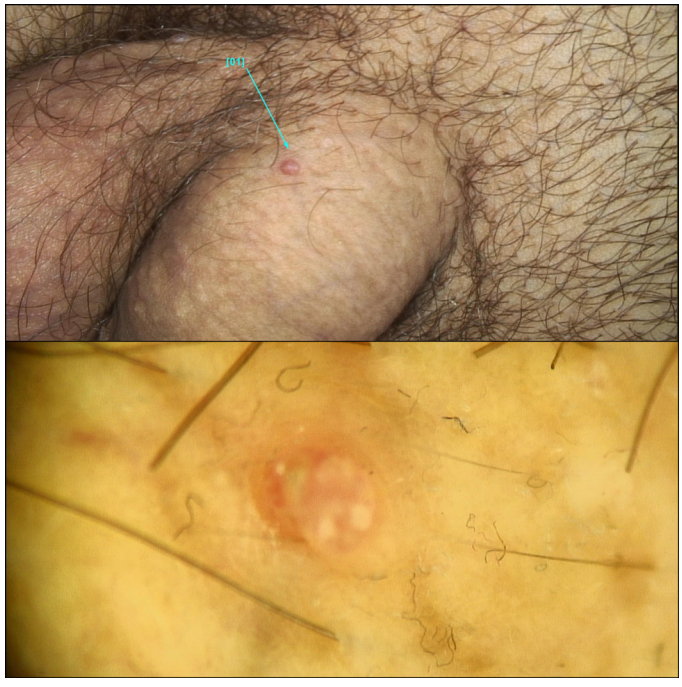

Figure 7. Pearly penile papules, dermoscopies

Cryotherapy, Co2 laser, electrocauterisation, intralesional bleomycin, intralesional 5-FU, radiation therapy, chemotherapy, imiquimod 5% cream are other treatment options (94-96).

Prevention

Reducing the number of sexual partners, using condoms, and HPV vaccines (11-12 years for boys and girls) are important factors in the prevention of HPV infections. cigaret smoking

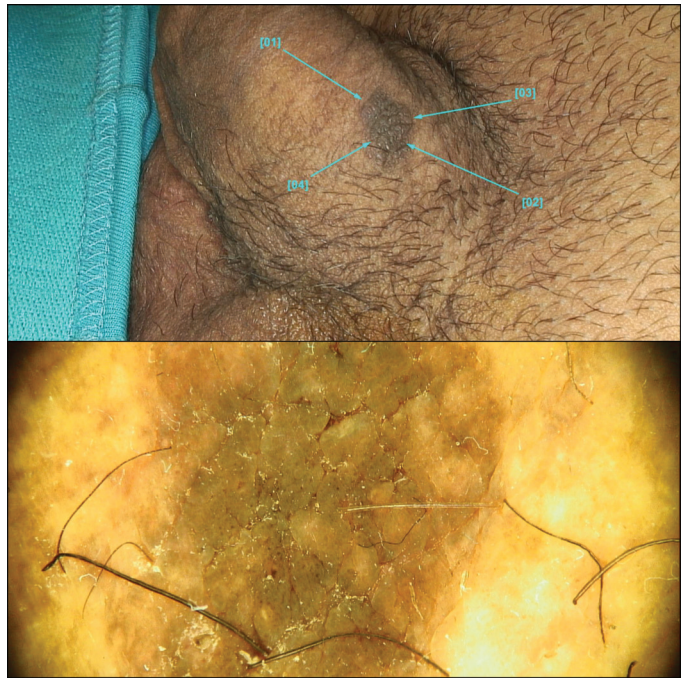

Figure 8. Seborrheic keratosis dermoscopy

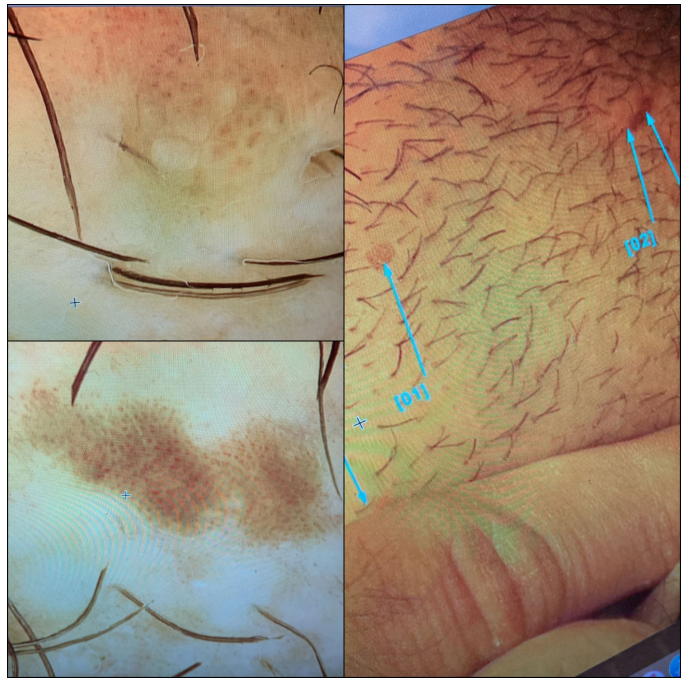

Figure 9. Genital melanosis, anogenital wart, dermoscopies

is associated with a high risk of genital warts, but there is no evidence that cigaret cessation improves treatment success (97,98).

Conclusion

HPV may cause cancers in the cervix, vagina, vulva, anus, penis, and oropharynx. Apart from the cancers it causes, the difficulties during the treatment also disrupt the psychology of the patient. Although many treatment methods are used, their superiority to each other is unclear. When deciding the treatment option, the patient's preference, the physicians' experience, access to the device, cost, localization, and size of the lesion should be evaluated. Although there are many treatment methods, it seems that the best way is to provide adequate training to teach prevention and vaccination. Large-scale studies are needed to determine treatment algorithms.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.B.Ö., G.E., B.Ç., Concept: D.B.Ö., G.E., B.Ç., Design: D.B.Ö., G.E., B.Ç., Data Collection or Processing: D.B.Ö., G.E., B.Ç., Analysis or Interpretation: D.B.Ö., G.E., B.Ç., Literature Search: D.B.Ö., G.E., B.Ç., Writing: D.B.Ö., G.E., B.Ç.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study received no financial support.

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