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## Condyloma acuminata - the review of the treatment methods

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Summary of review paper:

Introduction and purpose:

Condyloma acuminata, a benign manifestation of HPV infection, is a common sexually transmitted disease. Condyloma acuminata most commonly affects the anogenital area, but can also occur in the oral cavity. Macroscopically the lesions present as raised, fleshy papules, sometimes flat and broad, pedicled or cauliflower-like. Generally, the lesions are multiple, and as they grow, tend to coalesce into larger ones. Due to the lack of symptoms, condyloma acuminata are often found incidentally during routine medical appointments, e.g. in gynecologist's offices. Additional symptoms and signs are pain, minor bleeding and pruritus. Patients suffering from condyloma acuminata are often in psychological and psychosexual distress.

This work aims to provide a summary of the currently available treatment options based on scientific reports to date.

A brief description of the state of knowledge:

Among the factors that increase the risk of the HPV infection are age, lifestyle, promiscuity, smoking, HIV infection, a history of chlamydia or gonorrhea infections. To date, no treatment algorithm has been developed for condyloma acuminata. Two vaccines are on offer as primary prevention, Gardasil and Cervarix. The available treatment options are divided into two main groups: patient-administered and physician administered. Surgical methods

have the highest therapeutic efficacy. Condyloma acuminata has a high recurrence rate. Usually, a multi-session combination treatment is needed to reach total remission.

Summary (conclusions):

The treatment of condyloma acuminata includes personalized targets due to their diverse clinical picture and the limitations of certain patient groups. The available treatment options do not exhaust the needs of patients suffering from condyloma acuminata. Further research into the effectiveness of specific treatments is advisable.

Key words: condyloma acuminata; anogenital warts; papillomavirus infections; human papillomavirus vaccine; podophyllin; Mohs surgery

## INTRODUCTION

Condyloma acuminata (CA) are a manifestation of human papillomavirus (HPV) infection in the anogenital area. An often-used synonym for CA is anogenital warts. HPV is a double-stranded DNA virus from the papillomavirus family. There are over 200 strains of HPV. Condyloma acuminata are generally caused by HPV type 6 and 11. An individual can be infected with more than one type of virus. [1] Most commonly HPV spreads through sexual contact. Non-sexual transmission may occur through skin-to-skin, mucosa-to-skin, or mucosa-to-mucosa contact. Oral condyloma acuminata may also be caused by autoinoculation from cutaneous lesions, kissing, or bathing. [2] Both conservative and surgical treatment methods are mentioned among the possible therapeutic options. Physician-administered treatment is preferred due to the location of the lesions; self-application of medication can be challenging for the patient. Patient education on safe sex practices should take place both at the first visit and during follow-up appointments. It is important to remember the common phenomenon of coinfection with several sexually transmitted pathogens. Findings of condyloma acuminata in children should always raise suspicion of sexual abuse. [3]

## ETIOLOGY

HPV is a representative of the Papillomaviridae family. To date, more than two hundred types of HPV have been discovered, of which about 40% attack the anogenital area. Dozens of types have oncogenic properties, the most commonly listed types include HPV-16, 18, 31, 33, 45, 66, 68, 82. HPV infection has been cited as a cause of cervical cancer, penile cancer, anal cancer and cancer of the mouth and the throat. Condylomas follow infection with HPV

types 16 and HPV 18, which have a low risk of oncogenicity. Cutaneous warts result from infection with HPV types 1, 2, 4, 27, 57. [1]

## EPIDEMIOLOGY

The aetiological agent of condyloma, HPV, is the most commonly sexually transmitted pathogen. Lysogenicity in the general population is estimated at a rate of 9-13%. [1] The largest number of infections is observed in the age group comprising those between 20-39 years of age. The risk of infection increases with the number of sexual partners, age, the patient's history of other sexually transmitted diseases e.x gonorrhoea or chlamydia infections, smoking, and HIV infection. Prevalence is difficult to determine due to lack of reporting of cases. Estimates of the incidence in the United States were in 2023 1.1-1.2 per 1000 person-year. In the pediatric population, there has been an increasing trend in the incidence of CA over recent decades. [3]

## PATOPHYSIOLOGY

HPV attacks primarily the differentiated squamous cellular epithelium and basal keratinocytes. After entering the keratinocytes of the stratum spinosum of the skin, the HPV virus attacks the cell nucleus. Inside the nucleus HPV forms a double-stranded DNA episome. At this stage, the infection can progress to the latent phase, which can last from one month to several years. The process of integration of the HPV genome to the host genome occurs through the viral proteins E1 and E2, which bind to DNA, stimulating replication and mRNA synthesis. With these proteins, the virus can replicate using the host DNA polymerase. As the number of infected cells increases, the basal, squamous, and granular layers thicken leading to acanthosis, which is macroscopically visible in the form of a papilla. Following increased keratinization, infected cells are pushed to the skin surface. Subsequently, the virions are released from the dead cells, ready to infect others. Condylomas are macroscopically visible 3-4 months after the infection. In healthy individuals with a properly functioning immune system, the immune response can stop viral replication. Prolonged infection with HPV may lead to the malignancy of the lesions, which is usually a consequence of high-risk oncogenic HPV infection. [1, 3]

## HISTOPATHOLOGY

The characteristic clinical picture of condyloma usually allows the diagnosis to be made without additional examinations. The histopathological picture of condyloma is characterised

by the presence of hyperkeratosis, koilocytes and hyperplasia. Koilocytes are large keratinocytes with the presence of a small, pyknotic cell nucleus with translucent cytoplasm around it. Koilocytes are usually observed in the superficial layers of the lesion. Distinguishing condyloma from common warts on the basis of the microscopic image is possible by the presence of different types of hyperplasia in both entities. Papillomatosis is present in condyloma, whereas spiked verrucous hyperplasia is observed in common warts. In lesions CD8+ T cell count is low, which may contribute to the high recurrence rate of CA. [4]

#### CLINICAL PICTURE

Most of the anogenital HPV infections have subclinical character. In addition, the HPV virus appears to maintain a commensalism/mutualism relationship with human cells, as it is most commonly found in the unaltered skin and mucous membranes. Condyloma acuminata typically are found in the anogenital region, but may also occur in the oral cavity. Reports indicate the tongue and lips as the most common location in the oral cavity. [5] In the anogenital region typically engaged are cervix, vagina, vulva, penis, perineum, anal region. In children, condyloma acuminata typically affect the perianal and vulvar regions. [3] Generally, the lesions are multiple, however, cases of patients with single lesions have been described. Lesions as they grow tend to coalesce into larger ones.

Macroscopically condyloma acuminata presents as raised, fleshy papules, sometimes flat and broad, pedicled or cauliflower-like. The diameter may vary from one to five millimeters. Buschke-Lowenstein tumor is a malignant implication of condyloma acuminata, and so it should be taken into consideration when a large lesion covers the entire anogenital region. Pregnancy may lead to significant enlargement of the lesions, presumably given the physiological changes as the downregulation of the cell-mediated immunity. [6] Clinical picture of condyloma acuminata usually is reduced to the patient's concentration on the presence of lesions. Due to the lack of symptoms, lesions are often detected incidentally during routine examinations, e.g. in gynecologist's offices. Additional symptoms and signs which are not always present are pain and pruritus. Sometimes there may be minor bleeding from the lesions. In addition, patients suffering from condyloma acuminata are in psychological and psychosexual distress. History taking and physical examination require special attention by the reason of the patient's mental state.

## EVALUATION

Condyloma acuminata as a skin condition with typical clinical picture may be diagnosed throughout the following patient's history and clinical examination. A proper test is colposcopy, which allows accurate visualization of lesions located in the vagina and cervix. Clinicians may support their decision by running the additional testing, e.g. DNA detection in PCR or the acetic acid test. The acetic acid test is performed by applying the five percent solution of acetic acid to the lesion. The appearance of white spots suggests dysplasia. The high rate of false positives does not allow the acetic acid test to be used as a screening tool. Therefore, if a clinician suspects dysplasia, the biopsy should be undertaken as the most appropriate form of follow-up.

In cases of significant lesions and high risk of malignant transformation, CT imaging of the abdomen and pelvis with contrast may be used for diagnosis. CT provides information on the local progression and vascularisation. In the diagnosis of malignancy, CT is of lesser value relative to histopathology examination and can be used as an adjunctive test. Lymphadenopathy in the inguinal region may accompany cases of condyloma acuminata and does not determine the malignant nature of the lesions. MR imaging can be helpful in the assessment of soft tissues before surgical treatment. Imaging studies are a valuable additional follow-up, however, there are no established guidelines on how often they should be performed. [7]

Condyloma acuminata of anal canal can be overlooked during routine physical examination, especially if they are asymptomatic. Endoscopic examinations, e.g. anoscopy, can be helpful during the diagnostic process. [8]

## TREATMENT AND MANAGEMENT

There are many possibilities for treatment for anogenital warts. An acceptable approach in young and healthy people is the observation and control of lesions, which may resolve spontaneously within a few months or years. Indications for treatment are asymptomatic lesions lasting more than two years and any symptomatic case. Possible therapeutic options include topical treatment, procedures e.g. cryotherapy and surgical methods. To date, no treatment algorithm has been developed for condyloma acuminata. The treatment plan should be selected individually, depending on the morphology of the lesions, symptoms, location and patient preference. Topical treatment is usually the first choice. Patients should be aware of the fact that only surgical treatment has recurrent rates of nearly zero percent. [9]

## TOPICAL TREATMENT

Fleshy papules may be treated with podophyllin, or its purified antiward compound podophyllotoxin. Podophyllin is a plant-derived cytotoxic agent, it disturbs the cell cycle and mitosis, leading to necrosis of the tissue. Various forms of podophyllotoxin, with a good safety profile, are available on the market, such as 0.5% solution and 0.15% cream. The medicine should be administered twice daily for three days. After 4 hours the drug has to be cleansed. This should be followed by a four-day break in the use of the drug. The effects of treatment are usually visible after a 4-week cycle. [10] Podophyllin is contraindicated during pregnancy, due to its teratogenicity. [11] The local adverse effects include skin irritation. Systemic side effects, such as neurotoxicity and suppression of the bone marrow, may occur as the medicine can be absorbed into the blood. [12]

Imiquimod is a drug with a lower risk of condyloma acuminata recurrence compared to podophyllotoxin. Imiquimod is applied once a day every other day. Improvement follows 16 weeks of treatment. [13] There are reports of the efficacy of imiquimod 5% cream therapy in a regimen of three times per week for five weeks. [14] In a group of children aged 12 and older imiquimod 5% is the first line treatment. There are cases of efficacy in younger children from 6 months of age. [3]

Another topical treatment option is administration of sinecatechins, available in 15% ointment and 15% cream form. Sinecatechins is a plant extract derived from *Camellia sinensis*. Mechanism of action is not yet understood, it is presumed that active agents deflect the inflammatory response via modulation of expression of cyclooxygenase-2 (COX-2) and inhibiting the transcription factors. An ointment containing 15% sinecatechins, 3 times a day for up to 16 weeks. If any sign of improvement is not visible after a few weeks of treatment, the physician should try another method. Clearance rates are up to 58%, recurrence rates range between 6 to 9%. The local adverse effects include pruritus, pain, rubefaction, and burning sensation. Severe side effects, e.g. balanitis, lymphadenitis, are rare. [15]

## PROCEDURES

Condyloma acuminata may be treated with cryotherapy, liquid nitrogen or trichloroacetic acid. The popularity of using cryotherapy is based on its low cost, minimal invasiveness, minimal risk of bleeding and high clearance rate in small, multiple lesions located on the penile or vulva. Cryotherapy is the first-line therapy in pregnant women, due to the lack of need for anesthesia and the optional outpatient setting. [16] The cooling agent, e.g., liquid nitrogen or nitrous oxide, is administered on the entire lesion, the base of the lesion, and 1-2 mm of surrounding unaltered tissue to cause permanent damage. The application time is a



maximum of 2 min. As a result, necrotic tissue activates the immune response. Treatment with liquid nitrogen consists of three to five 20-second applications of the drug. Procedures can be administered once weekly for up to ten weeks. Disadvantages of this method are limited efficacy and local adverse effects that occur more often than in other treatment options, such as discoloration, painful blistering, infection, and permanent scarring. TCA may cause significant pain at the time of administration. Recurrence rate of 25-40% is associated with non-radical damage of subclinical lesions. [15]

Trichloroacetic acid (TCA) at a concentration of 80-90% is cost-efficient, safe and high-effective drug used to treat small lesions. TCA causes erosion and cauterization of the skin and mucous membrane. An ulceration is formed at the site of the acid application, which heals without scarring. Clearance rate of 70-80% are due to the penetrating properties of the drug, affecting the infected cells lying at the skin level. Therapies with TCA can be performed once a week for a period of 8-10 weeks. Generally, a series of treatments is required to complete the healing, however, with small lesions, a single treatment may be sufficient. TCA can be used during pregnancy. Chief complaints in the course of therapy are pain and burning sensation. Systemic side effects are extremely rare, due to low absorption. [15]

#### SURGICAL TREATMENT

In cases of refractory lesions and those with a significant degree of progression, surgical treatment should be considered. Surgical methods are highly effective, with the clearance rates close to a hundred percent. Surgical methods effective in the treatment of condyloma acuminata include scissors excision, curettage, electrosurgery and laser therapy.

Surgical scissor excision is the physical removal of lesions using a scalpel or scissors, following suturing. The procedure is typically performed under local or general anesthesia. It is a remedy for large lesions, cases unresponsive, or ineligible to other treatments. When the malignant character of the lesions is suspected, surgical excision is the only possible treatment. The specimens must undergo histopathological evaluation. Pain, bleeding, and scarring are the most often reported side effects. The alternative to classical surgical excision is the Mohs surgery. The procedure consists of successive excision of thin skin fragments that are at once undergoing microscopic evaluation. The skin sections are taken until clear margins are achieved. Mohs surgery in condyloma acuminata qualifies for maximum removal of the lesions while preserving as much area of healthy tissue as possible and minimal scarring. The ground rationale for the low popularity of this method is the high cost. In cases of large lesion resection, consideration should be given to extending the procedure to include

a skin graft or skin flap. This reduces recovery time, and decreases the risk of infection and postoperative anal stricture. [17]

Carbon dioxide laser therapy is a method involving a focused beam of infrared light energy to heat up with the aim of vaporization of the lesions. The vessels up to 1 mm in diameter at the targeted area are immediately cauterized, therefore laser treatment is a nearly bloodless procedure. Furthermore, laser therapy causes minimal pain sensation due to sealing the nerve endings. Patient comfort during the procedure is so advanced that some centers offer laser therapy as an outpatient procedure. In laser therapy, the influence of the energy beam is not only limited to the surface of the lesion but also affects the deeper cells. After the process, the tissues heal quickly, with minimal or no scarring. The CO<sub>2</sub> laser can be used during pregnancy, the previous reports have not confirmed an association of laser therapy with spontaneous abortions, fetal malformations, and preterm delivery. [18] Reports of adverse effects are mainly confined to mild irritation of the surrounding tissues and a burning sensation in the perioperative period. CO<sub>2</sub> laser therapy is a particularly recommended treatment for immunosuppressed patients, pregnant women, and individuals with extensive lesions unresponsive to topical treatment such as TCA or cryotherapy. A particular advantage of this method is that all lesions can be treated simultaneously and it can be used in cases of lesions of significant size. Treatment results with CO<sub>2</sub> laser are inferior compared to other methods, the clearance rates stand at approximately 50%, and the recurrence rates are 77%.

#### NEW METHODS

Among the most recent reports of condyloma acuminata treatment methods the novel is photodynamic therapy (PDT) with the 5-aminolevulinic acid (ALA). There are reports with complete response of 63-100% after scheme of several photodynamic therapy procedures. The effect of PDT is due to the physical destruction of lesions, the stimulation of the immune response, and the reduction of the local viral load. This therapy appears to have a higher efficacy with a lower risk of recurrence compared to CO<sub>2</sub> laser. [19] Side effects are minimal. Furthermore, photodynamic therapy is a simple procedure and can be used as an element of the combined treatment of condyloma acumina, reports specify the combination of PDT with laser therapy as a highly effective method.. [20]

#### DIFFERENTIAL DIAGNOSIS

Condyloma acuminata should be differentiated with a number of diseases, e.g: condyloma lata, lichen planus, psoriasis, pearly penile papules, sebaceous cyst and more.

## PROGNOSIS

The prognosis is good; however, treatment can be prolonged, requiring multiple methods. Recurrence rate is estimated as 20-30%. Condyloma acuminata may relapse after every type of treatment. CA treatment is associated with a high rate of recurrence due to the characteristic features of HPV: high replication and mechanisms to deceive the immune system. The highest clearance rate is achieved in surgical methods.

In severe cases, such as Buschke-Lowenstein tumor, the prognosis is poor, and the risk of recurrence is significantly higher. The mortality rate is up to 21%. [7]

## COMPLICATIONS

In condyloma acuminata, complications are usually size-related. Anogenital warts may cause urinary obstruction, fistulas in the anogenital region, abscess, ulceration, and difficulty defecation.

Buschke-Lowenstein tumor or giant condyloma acuminata is considered to be the intermediate point in the spectrum of malignant transformation from classic condyloma acuminata to squamous cell carcinoma. Lesions form exophytic cauliflower-like growth, size more than 10 cm. Buschke-Lowenstein tumors differ from classic condyloma acuminata on a histological level, in giant condyloma acuminata are observed features that are absent in the classic type. The distinctions are papillomatosis, acanthosis, and elongation of the ridges. Furthermore, the mitotic activity in giant condyloma acuminata is increased more explicitly. On a histological level, Buschke-Lowenstein tumors differ from squamous cell carcinoma, intact basement membrane, polarity is preserved and no lymphatic invasion or metastasis is observed. The management of giant condyloma acuminata requires the combination of various treatment methods. Surgical resection, as the technique with the highest clearance rate, is considered as the gold standard. The alternative treatment, such as topical agents or radiotherapy, may be put in scheme as neoadjuvant or adjuvant. [22]

Patients suffering from condyloma acuminata may be psychologically burdened, presenting e.g. feelings of guilt, anxiety, and aggression. As the lesions may mimic or become malignant over time, patients' concerns about cancer are in place. Sometimes patients have concerns about their reproductive health.

Obstetric complications include increased risk of neonatal HPV infection, obstruction of birth canal and hemorrhage-related compromised wound cicatrising. Prophylactic cesarean section has limited benefits as though it does not eliminate the risk of vertical mother-to-child transmission of HPV. [6] An example of neonatal HPV infection is juvenile-onset recurrent

respiratory papillomatosis. The primary lesion in this disease entity is a benign neoplasm located in the larynx or trachea. The etiological agent is HPV type 6 and 11. The first line of treatment is surgical. Repeated operations are usually necessary. [16]

## PATIENTS EDUCATION

In the case of condyloma acuminata, patient education has a great impact on the compliance effect and on the success of the therapeutic process. From the first visit to the doctor's office, patients should be informed about their disease. After the consultation, patients should know what is the cause of the infection and how to prevent it. Furthermore, patients should receive the data of clearance and recurrence rates of various treatment options. The importance of follow-up consults and avail of multiple treatment methods should be mentioned at the very first appointment to avoid disturbances during the time of healing.

Patients should contact all sexual partners, both present and in the past six months. Primary prevention methods of condyloma acuminata include following the public and personal hygiene principles and vaccination. Condom usage is highly effective and due to broad-spectrum operation against sexually transmitted diseases, it is recommended in protection against HPV infection. Safe sex practice counsel includes information on avoidance of anal intercourse and promiscuity. Patients should be aware of the possibility of other sexually transmitted diseases contagion and also be encouraged to test. The circumcision procedure is associated with a lower risk of HPV infection, as the prepuce is considered a reservoir of pathogens. [17]

The presence of condyloma acuminata is not an indication to modify cervical cancer screening. [3]

## VACCINES

HPV vaccines, Gardasil® and Gardasil9®, protect against not only oncogenic types of HPV but also types 6 and 11, which are the causative agents in the majority of cases of condyloma acuminata. Cervarix® provides protection only against HPV types 16 and 18, therefore it does not affect the development of condyloma acuminata. The highest efficacy is obtained when the vaccine is administered before exposure to the HPV. The recommendation is to perform the vaccination in children 11-12 years of age. In children with a history of sexual abuse, earlier vaccination is advisable at the age of 9. [3] Vaccination results in a 63% reduction in the risk of developing condyloma acuminata in contrast to unvaccinated women. It is thought that sexual initiation before vaccination nullifies its protective effect. It is likely

that incomplete vaccination already has a protective effect, as there are no differences in incidence between groups of fully vaccinated women and women with partially completed vaccination schemes. [22]

## CONCLUSIONS:

### Summary (conclusions):

In addressing condyloma acuminata, the individualized nature of treatment plans is crucial given the diverse clinical presentations and unique considerations within certain patient groups. Despite the available treatment modalities, the complex nature of the disease often necessitates a more comprehensive understanding of patient-specific factors. The available treatment options do not exhaust the needs of patients suffering from condyloma acuminata. This ongoing exploration into the effectiveness of specific interventions will not only enhance our therapeutic arsenal but also contribute to a more nuanced and effective management of condyloma acuminata. Further research into the effectiveness of specific treatments is advisable.

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