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Case Report

Case Report: The Effect of 25% Podophyllin Tincture in *Condylomata Accuminata*

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ABSTRACT

Introduction: *Condylomata accuminata* (CA) is one of the most common sexually transmitted infections in the genital area caused by Human Papilloma Virus (HPV) variants 6 and 11. This disease is also known as genital warts. The potential for recurrence is relatively high and the risk for malignancy is high, therefore it requires appropriate treatment and therapy. There is no clear evidence regarding the best treatment choice for patients with CA.

Case Presentation: Female, 24 years old with complaints of genital warts that have grown bigger since one month before. Physiological examination of the labia minora showed multiple papules with mucosal-like color and verrucous surfaces, varying in shape and size. The acetowhite test result was positive. Patients were treated with 25% podophyllin tincture, with an interval of one week one time.

Conclusion: Podophyllin usage as a therapy for CA provides excellent therapeutic response and is relatively affordable, simple, and has minimal side effects. Patients treated with 25% podophyllin tincture, with an interval of one week one time, for two weeks showed significant improvement of the lesions.

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INTRODUCTION

Condylomata accuminata (CA; singular*: condylomata acuminatum*), also known as genital warts, is a sexually transmitted infection in the genital area caused by the Human Papilloma Virus (HPV). The most common strains of HPV that often manifest on the genitals are HPV types 6 and 11. CA usually appear on the genitals as papules or cauliflower-like nodules in the vulva area, vaginal introitus, perianal, and cervix. Clinical manifestations are often found in women with a percentage of 38.6% compared to men [1]. Around 20 million people are infected each year, with an incidence rate of 6.2 million cases and more likely to increase. HPV cases increased from 0.78% to 3.09% from 2011 to 2014 at Dr. Soetomo Hospital. Most cases occur in the age range of 25 to 44 years old [2].

Human Papilloma Virus has a relatively high recurrence potential. In addition, the apparent risk of HPV malignancy in CA makes appropriate treatment and therapy indispensable. There is no absolute evidence regarding the best therapy options for patients with CA. Various modalities of CA therapy consist of cyto-destructive therapy (surgical excision, cryotherapy, laser, trichloro acetic acid, and podophyllin), anti-metabolic therapy (5-fluorouracil (5FU), antiviral therapy (cidofovir and IFNs), and immunomodulating therapy (imiquimod) [3]. Combinations of these various therapies are also often used. Podophyllin usage results in cell destruction and damage to the cell structure exposed by HPV. Various levels of podophyllin are used in the treatment of genital warts. The use of podophyllin 10-25% is suggested in multiple studies [4]. Recent network meta-analysis have shown that surgery is more effective than other treatments for CA; nonetheless,

other local treatments should be attempted in the event of surgical approach difficulties [5].

This case report presents a CA patient treated using 25% podophyllin tincture. Our case report is expected to add new insight for healthcare workers, especially dermatovenereologist, to consider the therapeutic modality in patients with CA. This report has been approved by the local ethical committee for publication.

CASE PRESENTATION

A 24-year-old woman presented to the dermatology and venereology (DV) clinic of Dr. Saiful Anwar Hospital (RSSA) Malang with genital warts. The patient had a history of visiting a dermatovenereologist two weeks before she came to the hospital and was diagnosed with genital warts. She was treated with two sessions of trichloroacetic acid (TCA) 10%. The patient had similar past complaints of genital warts two months ago but then disappeared. She reported no warts or lesions in another body region and had no history of genital ulcers.

The patient was married for one month and was sexually active with her husband inter-genitally, without using contraception. The patient had a history of having sexual intercourse with another man two years ago without using contraception. The patient's husband had no complaints of warts and had sex only with the patient. The patient has no child.

Investigation

General stated revealed consciousness level of *compos mentis* with mild illness. The vital sign was unremarkable. No enlarged lymph nodes were found in the *colli*, *axilla*, or *inguinal* region. There was no edema or hyperemia in the extremities, and capillary refill time was less than two seconds. Dermatovenereology status on the labia minora showed multiple papules with mucosal-like color and verrucous surfaces, varying in shape and size (**Fig.1A**). There was no tenderness, and the papules did not bleed easily. The acetowhite test showed a positive result. There were no visible lesions on the vaginal wall on inspection.

Treatment

Based on history and physical examination, this patient was diagnosed with *condylomata accuminata*. The patient was treated with 25% podophyllin tincture two times at two-week intervals. The patient was prohibited from having any sexual intercourse during the treatment. A week later, post-treatment evaluation showed there were still multiple papules with mucosal-like color and verrucous surfaces, varying in size but smaller than before treatment. No new lesions were found. The patient had no complaints of burning sensation, itching, and redness of the genitals during the 25% podophyllin tincture usage.

Outcome and Evaluation

On evaluation in the 2nd-week post-treatment, no papules or lesions were found **(Fig.1B)**. The patient remains in stable condition after one month. She had no complained about new lession, however longer follow up might be needed in this case.

DISCUSSION

Condylomata accuminata (CA) is a sexually transmitted infection in the genital area caused by the *Human Papilloma Virus* (HPV). Currently, there have been over 120 types of HPV identified. HPV types 6 and 11 are the most prevalent types that cause CA (about 90% of all CA cases) [6]. The number of HPV infection cases has been increasing globally in the last 35 years. Recent estimates report the incidence of HPV infections at 160 to 289 per 100,000 people per year. The prevalence of CA in Indonesia itself ranges from 5-19%. A retrospective study at RSDS Surabaya found a total of

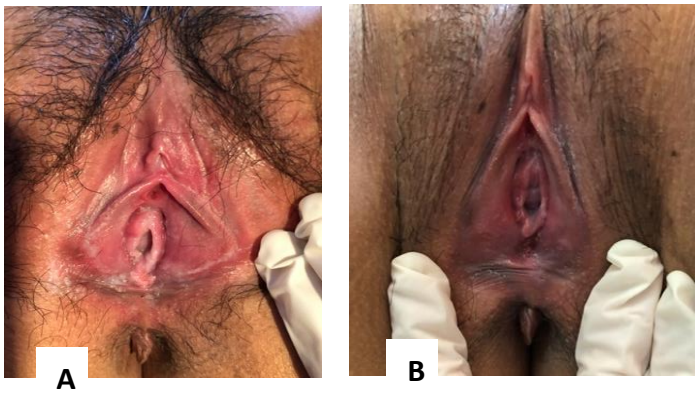

Fig. 1 (A) Dermatovenereology Status of Labia Minora; and (B) Dermatovenereology Status of Labia Minor 2nd Week Post-treatment Evaluation

318 cases of CA in 2011-2014. The researchers state that CA is the second most common infection of all sexually transmitted infections [2].

Approximately 81% of CA cases occur in the age range of 25 to 44 years old [6,7]. The prevalence of CA is higher in females than in males, with a percentage of 38.6% [2]. In this case report, a female patient aged 24 years had an HPV infection in the form of CA. This corresponds with literature suggesting that CA infection most often occurs in women, with an age range of 25 to 44 years old. *Human Papilloma Virus* is easily transmitted through physical contact. Most transmission occurs through oral and anal sexual habits in the young adult population [8]. A person infected with HPV has a 75% probability of spreading the virus through sexual intercourse which leads to CA. In this case, the patient was suspected of being infected by CA through sexual contact, in line with the literature that stated sexual contact is the main transmission route of HPV infection that could evolve into CA [9].

HPV infection is differentiated based on its tissue tropism (dermotropic or mucosotropic) and its malignancy potential (low risk or high risk). HPV infection can appear in genital and non-genital areas as genital warts and non-genital warts. Genital warts appear as papules or nodules in the vulva, vaginal, perianal, and cervical introitus. It can be considered a low-risk type if the causative agent is HPV type 6 and 11 [10]. On the contrary, the high-risk type of CA that tends to be malignant is caused by HPV type 16 and 18. The majority of patients with HPV types 6 and 11 will recover spontaneously. Meanwhile, in high-risk types, there will be progression changes in normal cells into malignant *squamous cell carcinoma* (SCC). The definite pathomechanism of malignant HPV is still not fully understood. Recent evidence suggests that the transformation of HPV into malignant lesions requires the integration of viral DNA into host DNA [11].

The predilection areas of genital warts in women are the cervix, perineum, vagina, periurethral, clitoris, and labia [10]. In this case, the patient had warts on her labia minora and no lesions were found in the vagina, clitoris, or cervix. The patient had just experienced a complaint of CA for 1 month and had received previous therapy. The literature stated that the most common site of initial lesions is in exposed mucosal areas such as the labia. The lesions then can spread to other parts of the body such as the vagina, periurethral, cervix, and clitoris over time [12].

Genital HPV infection clinically manifests as papules or nodules that develop on stalks or are directly attached to the base of the lesion. There are also granular papillae that have verrucous surfaces. The initial lesion will appear small, with a diameter of 2-5 mm. The lesion then may increase in size and become confluent over time [3]. In this case, a pedunculated papular lesion with verrucous surfaces was found. The patient also complains of small warts appearing at first and getting more prominent over time.

The clinical and histological features of HPV appear within one to eight months after the initial HPV infection. The most common histological features are the thickening of the epidermis, hyperplasia of the stratum spinosum, and hyperkeratosis [16]. The lesions that are not promptly treated will progress into benign lesions in low-risk HPV and pre-cancerous or cancerous lesions in high-risk HPV types. The patient's clinical condition was worsened by the evidence of the inadequate number of Langerhans cells in the lesion, indicating a low adaptive immune response [13,14].

The diagnosis of CA is often made clinically by history and physical examinations. Additional testing such as *acetowhite test*, colposcopy, and pathology examinations can be done to aid in the diagnosis. *Acetowhite test* is used for the initial screening of HPV suspicion. It is done by dripping 3-5% acetic acid on the lesion, which will result in the coagulation of the *cytokeratin* cells. A positive result of this test will show whitish lesions that indicate the occurrence of infection from HPV. The additional use of colposcopy in this test increases its final sensitivity as a diagnostic value [18]. In this case report, the *acetowhite test* was performed to objectively evaluate the lesions suspected due to HPV infection. Although previous studies have explained that the sensitivity value of this test is only 44%, the test still can increase objectivity in the diagnosis of CA. Pathology examination is required when the diagnosis is uncertain, the lesion does not improve or worsens during therapy, or the lesion is atypical. The hallmark pathological appearance of HPV-infected cells is *koilocytes*. *Koilocytes* are cells that have eccentrically enlarged, pyknotic nuclei surrounded by a perinuclear halo. Other findings such as acanthosis, hyperkeratosis, parakeratosis, and epidermal thinning with loss of granularity can appear on the epidermis. Findings on the dermis can show *rete ridges* that extend towards the dermis and increased vascularity with thrombotic capillaries [15]. In this case, a pathology examination was not done as the diagnosis could be defined sufficiently through the appropriate history and physical examination, and the *acetowhite test* also showed positive results.

To date, there is no clear evidence regarding the best treatment choice for patients with CA. Adequate and prompt therapy is highly needed in HPV patients because of the high recurrence rate and high malignancy risk development of HPV infection. In addition, CA can have physical and psychosexual implications for the patient, causing anxiety, guilt, anger, loss of self-esteem, and fertility concerns. Factors that influence the therapy selection include size, number, morphology, location of the lesions, side effects, convenience, cost of treatment,

patient preference, operator experience, and the availability of therapeutic modalities at the health facilities. Other factors to consider include immunocompromised condition and adherence to therapy [4,16].

In wide scope, treatment modalities in HPV-infected patients are divided into *cyto-destructive* therapy (surgical excision, *cryotherapy*, laser, *bi-chloroacetic/ trichloroacetic acid,* and podophyllin), anti-metabolic therapy (5-*fluorouracil* (5FU), antiviral therapy (cidofovir and IFNs), and immunomodulators (imiquimod). The combination of these therapies is still often used. There is no proof that one type of treatment is notably better than the other or even acceptable for all types of warts. According to the data, only surgical treatments have a primary clearance rate that is almost 100%, and recurrence occurs in all treatments at a rate of 20% to 30% or more [17]. Excision of the lesion is the main modality in eradicating CA lesions. However, the recurrence rate after excision is high, presumably due to the presence of the living HPV virus in the surrounding tissues. The most common side effects of excision therapy are scar tissue formation, bleeding, and infection. The use of *electrocautery* during excision provides better results than excision alone. Dissection of the lesion should be done thoroughly until the surgical margins are clean. The recurrence probability of CA is approximately 31.9% to 47% in excised patients with lesions remaining at the operative margin [4].

One of the most frequently used chemical *cyto-destructive* drugs is podophyllin. Podophyllin is an alcoholic plant extract obtained from the dried rhizomes of the *Podophyllum emodi* and *Podophyllum peltatum* plants. This substance is a cytotoxic drug that has been used widely since the 1940s, as a topical treatment for various lesions, especially warts, but it can also be used in the treatment of leukoplakia, molluscum contagiosum, keratoacanthoma, seborrheic keratosis, and actinic keratosis [5,18].

The available podophyllin solution level is 10% to 25%. This level is considered to provide the highest treatment efficacy. Podophyllin has been proven to be an effective, safe, and non-invasive method for treating superficial CA. The success rate for using podophyllin as monotherapy reaches 45% to 77%. The substance is also cost-effective [19]. The mechanism of action of 25% podophyllin tincture is conducting tissue necrosis by blocking cell mitosis. A recent study described the usage of podophyllin solution and cream can provide a therapeutic response of up to 63% [16]. In this case report, the patient was given a 25% podophyllin tincture solution, and clinical improvement was achieved.

As the first line therapy podophyllin has several side effects. The most common side effects are a burning sensation, inflammation, erosion, pain, and visible bleeding. This treatment is strictly prohibited in pregnant patients. The worst side effect ever reported was death event though it is very rare. Educating the patients is also important to reduce its side effects [18]. In this case report, there were no contraindications for the patient. Thus, the patient could be given podophyllin therapy. No side effects were found in this patient. As the first line therapy, the usage of podophyllin as CA treatment has also been preferred as it has much better efficacy than 5% imiquimod. A recent study conducted in an Asian population came to the conclusion that the utilization of podophyllin has level 1b of evidence. According to the asian guidelines, the only treatments with a greater level of evidence for treating cancer than podophyllin are surgery, photodynamic therapy, interferon, and 5-FU [20]. On the other hand, in recent times it has become common practice to provide a preventative care that consists of multiple types of HPV vaccine. If, on the other hand, the patient already had CA, there was no statistically significant difference in the effectiveness of the HPV vaccine and the podophylin treatment [21].

One of the preventive measures to reduce the possibility of infection in the future is the HPV vaccine. Currently, the *Food and Drug Administration* (FDA) recommends using the HPV vaccine in certain groups of people [12]. There are three groups recommended by the *Centers for Disease Control and Prevention* (CDC) to get the HPV vaccine, including children aged 9-26 years, women aged 27-45 years, and pregnant women. There is no clear evidence that a history of HPV infection is a contraindication to HPV vaccine usage to date. Recommendations for the HPV vaccine in women infected with HPV or with abnormal pap smear results were needed, considering that the vaccine itself can reduce the risk of high-risk HPV types infections [13]. In this case, we found a 24-year-old woman who had HPV infections and had never been vaccinated against HPV. The patient is advised to take HPV vaccines as it reduces the occurrence of HPV type 6 or 11 infections in the future. In addition, vaccines can also prevent infection from high-risk HPV types that usually cause cervical cancer. However majority of genital wart cases, especially individuals with repeated infections might be not respond to treatment. Verifying patient adherence to treatment, switching the therapeutic substance, and adding isotretinoin can all be beneficial [22].

CONCLUSION

Condylomata accuminata (CA) is one of the most prevalent sexually transmitted genital illnesses. This disease has a significant recurrence rate, necessitating timely treatment and control. In cases with *Condyloma accumoma*, Podophyllin tincture therapy is one of the

treatment modalities. In this study, the use of a 25% podophyllin tincture shown a promising therapeutic effect with minimal adverse effects. As a treatment for CA we recommend the usage of Podophyllin tincture as it has an excellent therapeutic response, relatively affordable, simple to use and has few adverse effects.

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CONFLICT OF INTEREST

The authors state that they have no conflicts of interest.

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