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Human Papillomavirus High-risk Type Infection on Perianal Giant Condyloma Acuminatum

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A B S T R A C T

Background: Giant condyloma acuminatum (GCA) is a large form of condyloma acuminatum that become locally invasive, destructive, but non-metastasizing, caused by human papillomavirus (HPV). Giant condyloma is a rare disease, with only 0.1% incidence in the general population. Most commonly caused by HPV type 6 and 11 infections, in this case, reported HPV high-risk type. **Case presentation:** A 20-years-old man, the main complaint is enlarging, easy bleeding perianal tumor with pruritus and constipation for 2 months. Physical examination found a skin-colored, verrucous surface. Some have a smooth surface, a cauliflower-like tumor on the perianal region, size 7x4x2cm. Syphilis and HIV Serology laboratory tests are non-reactive. Koilocytes appear on histopathologic examination. High-risk HPV type detected on HPV genotyping. This patient was diagnosed with GCA. Topical agent 25% podophyllin tincture applied to the lesions once a week. Improvement appears after eighth-time therapy. **Discussion:** High-risk type HPV infection, detected in the patient, have an important role in GCA development. Decreased immune systems and other risk factors also have a role in GCA. **Conclusion:** The high-risk type of HPV infection in GCA increases the risk of recurrence and malignancy in patients.

1. Introduction

Condyloma acuminatum (CA), or genital warts, is a proliferative disease of the genital epithelium caused by human papillomavirus (HPV) infection.[1,2] Giant condyloma acuminatum (GCA) is a clinical form of extensive, locally invasive, destructive but not metastatic CA. Giant condyloma acuminatum was first published by Buschke in 1925. Condyloma acuminatum is generally caused by human papillomavirus (HPV) types 6 and 11, sometimes also found with HPV 16 and 18.[2,3,4]

The annual global incidence of CA is estimated at 160 to 289 cases per 100,000 people. The estimated incidence in European countries ranges annually from 0.13 to 0.16% of the general population. The prevalence of CA in the sexually active male sex male (MSM) population in 2016 in the United States was 2.9%.[5] Men are more prevalent than women. The initial clinical picture of GCA is a warts-like papule. It then enlarges to form a white or yellowish papillomatous tumor-like cauliflower with an irregular surface that grow up to 10 cm.[2,4,6] Predilections are most often found on the penis anorectal and urethra in males, while women are in the vulva and anorectal.[7]

The risk factors for HPV transmission are multiple sexual partners, prostitution, MSM, poor hygiene, and chronic genital infections. On histopathological examination, the appearance was a benign tumor consisting of condylomatous tissue.[1] Histopathological examination was performed to confirm the diagnosis of GCA. The treatment is determined by the patient's

consent, ability to adhere to treatment, location, number of lesions, and the doctor's knowledge.[1] The treatment of choice for the management of GCA is wide excision of the tumor, although the recurrence rate of GCA is still high after the procedure. Other therapies include frozen surgery and topical cytotoxic chemotherapy, such as podophyllin or interferon-α injection.[2,7]

In this paper, we report a rare case of perianal GCA in a male caused by a high-risk type HPV infection, which was treated with a 25% tincture of podophyllin with the result of lesion repair.

2. Case Presentation

A 20-year-old man came to Dermatology and Venereology Clinics at Dr. Mohammad Hoesin, Palembang, with a perianal tumor as the main complaint that enlarged to the size of a chicken egg 1 month before the examination. The patient also feels pruritus on perianal and constipation. One week before the examination, the perianal tumor can easily bleed when defecating.

Based on his sexual history, the patient started having sex with a man for 7 months before examination with multiple sexual partners. This patient has anal-receptive sexual habits 1-2 times a week without a condom. Last sexual intercourse was 1 month before the examination. His sexual partners also had bean-size genital warts.

Based on physical examination, the patient has a normal general condition. On venereological examination, it showed a cauliflower-like verrucous surface, skin-colored, solitary tumor, size 7x4x2 cm, painful on palpation, supple, mobile, and easy to bleed (Figure 1).

Figure 1. Clinical appearance before therapy.

Laboratory examination showed non-reactive anti-HIV, VDRL dan TPHA. Absolute CD4 is 392 cells/μL (32.1%), and anti-HIV is re-examined twice every 3 months and is still non-reactive. Histopathologic examination showed hyperkeratosis, papillomatosis, acanthosis, parakeratosis consisting of basal cells, parabasal-like hyperplasia of less than one-third of the thickness of the epithelium, cells with polygonal shapes, resinoid nuclei, perinuclear halo, superficial eosinophilic cytoplasm (koilocytes) are also found in the epidermis. Figure 2 showed intact subepithelial basement membrane in fibro collagenous connective tissue, densely packed plasma cells and lymphocytes, proliferative blood vessels, and hyperaemic dilatation (). No signs of malignancy were found. Anal swab was done for HPV genotyping examination, type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 HPV virus was detected.

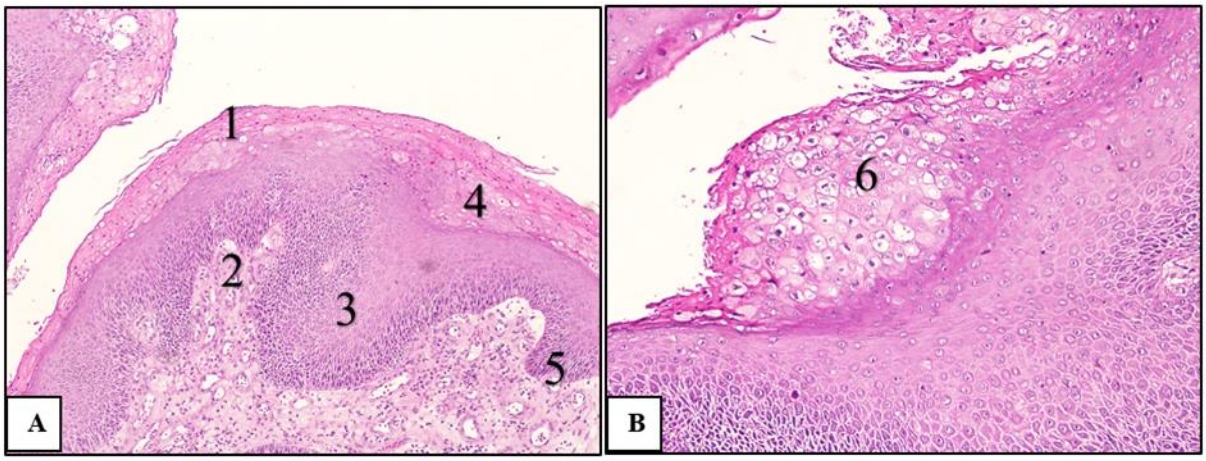

Figure 2. Histopathologic examination. A. Hematoxoxylin-eosin, 40x (1), papillomatosis (2), acanthosis (3), parakeratotic (4), intact basement membrane (5). B. Hematoxylin-eosin 200x. Koilocyte (6).

The patient was diagnosed with giant condyloma acuminatum of the perianal region and was differentially diagnosed with squamous cell carcinoma. The patient was educated to change the sexual habits, avoid sexual intercourse, use condoms if necessary, and be treated with 25% podophyllin tincture. This topical agent is applied to the lesions once a week. Improvement appears after eighth-time therapy.

Figure 3. Clinical appearance after 8 times therapy

3. Discussion

Giant condyloma acuminatum (GCA), also known as Buschke-Lowenstein tumor, is an effective form of CA that is locally invasive, destructive, and not metastasized.[1] Giant condyloma acuminatum, first published by Buschke in 1925, is a rare disease, with an estimated incidence of around 0.1% of the general population.[3,4] The number of new CA cases at the Sexually Transmitted Infections (STI) Division of Muhammad Hoesin General Hospital (RSMH) Palembang from July 2018 to July 2019 was 25 patients, 4 of them were GCA.

Based on the literature review of Spinu et al., the prevalence of GCA in males was higher than in females, with a ratio of 2.7:1. It is most common in the anogenital region, rarely in the urethra and bladder.[8] In the case series of Montana et al., seven cases of GCA were obtained from 2009 to 2013. Six of the patients were male, ranging from 19 to 53 years.[9] In this case, the patient is a male aged 20 years, with GCA lesions

in the perianal region following GCA's stated epidemiology.

Risk factors for GCA include poor hygiene, uncircumcised patients, multiple sexual partners, MSM, unprotected sex, chronic irritation, immunosuppression (by HIV infection, use of corticosteroids, immunomodulators, diabetes mellitus), sexual partners suffering from RA and warts, and regular recurrence.[1,3,7,9] In this case, the risk factors found in the patient were a history of MSM and anoreceptively frequent sexual activities with multiple sexual partners. His sexual partners also did not use condoms and had a history of warts on the penis.

The clinical picture of GCA, based on the case report of Buschke et al., reported three patients with clinical lesions. There was a soft mass in the distal penis in the first patient, enlarged to cover the external urethral ostium, and ulceration. After the incision was made, the tumor looked like cauliflower with the size of a small apple. The second patient had clinical lesions in the form of changes in the shape of the penis except in the right upper quadrant. Changes in the form of an irregular mass with a ridged surface raised edges with ulceration. The third patient-reported clinical lesions on the penis with a tumor the size of flat cherry fruit with induration and a ridged surface. When the prepuce is opened, a mass with a cauliflower appearance is seen in red-gray color.[10] In this case, a clinical appearance showed a cauliflower-like verrucous surface, skin-colored, solitary tumor, size 7x4x2 cm.

The histopathological examination of GCA based on the literature showed epithelial cell hyperplasia or acanthosis on the stratum spinosum and parakeratotic one to two layers of the stratum corneum, elongation of the dermal papillae with clear boundaries of the dermis and epidermis. There are scattered koilocytes in the outer layer of the epidermis, which are mature squamous cells with large perinuclear clear zones. Ultrastructural studies showed the virus in several cell nuclei. The koilocyte cells studied were a specific description of the cytopathological effect of HPV infection.[1,2,8] Histopathological examination of the patient followed the literature that showed hyperkeratosis, papillomatosis, acanthosis, parakeratosis, and koilocytes found in the superficial epidermis. The basement membrane was intact, and there were no signs of malignancy.

The human papillomavirus plays a significant role in the etiology of GCA, 66-100% of patients with GCA have type 6 HPV, and 33% have type 11 HPV. Types 1, 4, 16, 18, 31, 33 and 35 are rare.[11] Sarin A et al., study on 25 patients with CA, PCR examination was performed to determine the type of HPV, the results obtained were 10 patients (40%) with type 6 HPV infection, 8 patients (32%) with type 11, 1 patient (4%) type 16, 1 patient (4%)) types 6 and 16, and 1 patient (4%) types 11 and 18. Histopathological examination in 2 patients with HPV infection types 16 and 18 showed dysplastic changes in condyloma lesions.[12] Case report by Bhageerathy et al., on a female patient with GCA, with PCR examination, was found the infection of HPV type 16, on histopathological examination only CA was found.[13] In this case, HPV genotyping examination in patients, found high-risk types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, but histopathological examination showed no signs of malignancy. Patient education and regular follow-up are necessary because the patient has a high risk of recurrence and malignant transformation of the lesion.[13]

In the case series of Montana et al., the CD4 T cell count was examined in 7 GCA patients. The highest CD4 T cell count was 418 cells/mm^3, and the lowest was 195 cells/mm^3. The CD4 T cell count decreased due to the HIV test results. 5 out of 7 patients were reactive. A decrease in the number of CD4 T cells causes an increase in susceptibility to HPV infection and the severity of HPV infection, and can be an illustration of the relationship between GCA disease in immunosuppressed patients.[9,14,15] Absolute CD4, which is 392 cells/μL with a percentage of 32.1%, plays a role in the development of CA lesions by causing local immunodeficiency so that the host immune response is unable to control HPV infection. It is recommended that anti-HIV serologic examination 3 months after the initial assessment, considering the patient had a history of high-risk sexual activity.

Sexually transmitted infections are often

accompanied by other sexually transmitted diseases, especially in high-risk groups. Human papillomavirus enters through nonintact skin, and genital ulcers are one of the risk factors for CA.[1,2] Serological examination of the cause of Treponema pallidum genital ulcers was examined in this case. The results of the VDRL and TPHA examinations are non-reactive in these patients.

Case analysis by Chu et al. carried out on 42 cases of GCA in the anorectal and perianal region, obtained complications related to GCA in the anorectal and perianal area, fistula in 7 patients, abscess in 6 patients, easy bleeding in 4 patients, graft failure in 3 patients, a bacterial infection in 2 patients, chronic wounds in 2 patients, urethral obstruction in 2 patients, the others are failed colostomy, anorectal stricture, rectal incontinence, urinary tract infection, ileus infection and low blood pressure. In this case, the lesions bleed easily and make it challenging to defecate.

In this case, the patient was differentially diagnosed with squamous cell carcinoma of the perianal region. The clinical picture of GCA is similar to that of verrucous carcinoma type squamous cell carcinoma in the form of growth of a verrucous surface tumor mass with an exophytic pattern. Still, in verrucous carcinoma, it is accompanied by the development of an endophytic tumor mass following the picture of squamous cell carcinoma. The three most common locations for verrucous carcinoma are oropharynx, anogenitalia, and plantar pedis. Cases of verrucous carcinoma mainly occur in men and generally over 50 years of age. Ackerman stated that a verrucous carcinoma is a well-differentiated form of squamous cell carcinoma with low or low-grade metastases despite having a large tumor size.[17] Literature review Chan MP et al. explained that histopathological examination of verrucous carcinoma found minimal dysplasia, epithelial cells experienced hyperplastic penetration into deeper tissues with bulbous growth extending downwards, mitotic cells up to the basal layer, dyskeratotic cells, and atypical cells.[17,18] Another difference with GCA is that verrucous carcinoma is not associated with HPV.[18] In this case, the differential diagnosis can be ruled out because the histopathological features include koilocytes, hyperkeratotic, parakeratotic, acanthosis, papillomatosis not forming a bulb, intact basement membrane, and no signs of malignancy were found.

The treatment of choice for GCA is extensive excision surgery. Wide excision can be carried out to the abdominoperineal region with lymph node dissection if metastases are present. Other treatment options for GCA are carbon dioxide laser therapy, frozen surgery, intralesional and topical chemotherapy.[7,17] In the case of patients refusing surgery, 25% podophyllin tincture was chosen with the patient's consent after education about GCA management, goals, procedures, risks, and side effects.

Tincture of podophyllin 20-25% has been used to treat CA since 1942. A comparative study by Reddy GS et al, comparing the efficacy of spotted podophyllin 10-25% with imiquimod 5% cream in 40 patients with CA, the mean clearance of condyloma lesions in the podophyllin group was 16, 7% at 4 weeks, 50% at 8 weeks with a mean total clearance of 66.7%. The imiquimod group had 0% clearance at 4 weeks, 26.3% at 8 weeks, 52.6% at 12 weeks, with a total mean clearance of 78.9%. It was concluded that podophyllin had a higher and faster mean lesion clearance than imiquimod cream, although it had a mean lesion recurrence of 11.1%.[19] The study of Kar PK et al. compared topical therapy with podophyllin and podophyllotoxin in 72 patients with CA. The results obtained a complete recovery in the podophyllin group of 82.8%, while in the podophyllotoxin group, 89.1% was achieved within 6 weeks of treatment.[20] In this case, the patient showed improvement with podophyllin therapy once a week. The eighth session of treatment significantly reduced the size of the GCA lesions.

Podophyllin is an antimitotic and cytotoxic agent that binds to cellular microtubules to inhibit cell metaphase and causes tissue necrosis.[21,22] podophyllin's side effects include erythema, swelling, burning, pain, and itching. Tissue necrosis causes erosions that can heal. The amount of each dose of podophyllin in the lesion is limited to less than 0.5 ml. The total surface area does not exceed 10 cm^2 in reducing the risk of systemic absorption, which can

cause enteritis, bone marrow suppression, and neurological deficits.[23] In this case, the patient was given petrolatum gel to the normal skin around the lesion before administration of podophyllin for protection. Podophyllin is administered with the tip of a cotton tip swab to prevent overfeeding of the lesion. Side effects in patients obtained pain, burning, and erythema after administration of podophyllin. During control, post-inflammatory hyperpigmentation and erosions were found in several post-spotted sites.

The expected prognosis in GCA patients is complete recovery, no skin function, and no impaired defecation. However, some patients have had recurrent lesions. Routine examination, mainly if new lesions are found because the GCA recurrence rate is high, namely 60-66%, and there is a risk of changing GCA lesions to become malignant in the range of 30-56%, especially in patients infected with high-risk HPV types.[3,24] It is recommended for periodic follow-up and avoiding risk factors to prevent GCA recurrency and malignancy.

4. Conclusion

One case of GCA has been reported in a male patient aged 20 years. High-risk sexual habits, immunosuppression, and high-risk type HPV infection play an important role in increasing the risk of GCA development. High-risk type HPV infection in GCA increases the risk of recurrence and malignancy in patients.

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