



Risk Factors of Giant Condyloma Acuminata in Immunocompetent Adult Woman

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ABSTRACT

Giant condyloma acuminata, or Bushke-Lowenstein tumor, is a rare clinical form of large anogenital warts that usually occur due to the patient's immunosuppressed condition. This case report aims to describe the risk factors of a rare case of giant condyloma acuminata in an immunocompetent patient. A 24-year-old female with lumps around her vagina and buttocks for two months. Initially, the mung bean size was enlarged and multiplied within one month. The patient had regular sexual intercourse with a single sexual partner for the past six months, and the last had sexual intercourse two months ago without using a condom. In the dermatovenereological status of the labia minora-vulva-labia majora-perineum-anus region, there are verrucous masses, multiple, well-defined, irregular edges, varied shapes and sizes, acetowhite test (+). The biopsy results showed a piece of papillomatosis-shaped tissue that appeared hyperkeratosis, showing images of corrosive cells with raisinoid nuclei that support condyloma acuminata. Based on anamnesis, physical examination, and supporting examinations, the patient was diagnosed with anogenital giant condyloma acuminata. The patient was then consulted with Digestive Surgery for a pro-wide excision treatment plan. The main risk factor for genital warts is having multiple sexual partners.

Meanwhile, immunosuppression is the main risk factor for developing giant condyloma acuminata. However, many other risk factors need to be considered and reviewed in immunocompetent patients, including genetic influences on HLA type, age, homosexuality, prostitution, chronic genital infection or irritation, poor hygiene, smoking, history of other sexually transmitted infections, simultaneous infection with another type of HPV, also pregnancy and hormonal contraception. The risk of Giant condyloma acuminata cases occurring in immunocompetent patients needs to be reviewed for other risk factors that may be present in the patient or their sexual partner, especially considering the high recurrence rate.

INTRODUCTION

Giant condyloma acuminata (GCA) or Bushke-Lowenstein tumor is a rare and slow-growing verrucous tumor in the penile and anogenital region that can grow up to 20 cm in size and damage surrounding structures but does not metastasize. Giant condyloma is a rare clinical form of genital warts that is large and usually occurs due to the patient's immunosuppressed condition. This tumor is most common in the glands of the penis, prepuce, and perianal region, but can also occur in the anogenital such as the vulva, vagina, and urinary vesica. In rarer cases, these tumors can also be found in the axilla.⁷ In the United States, the incidence of genital warts is 1.1 cases for men and 1.2 cases for women per

1000 people per year.^{6,8} Giant condyloma acuminata has a worldwide incidence rate of 0.1% in the general population, with a recurrence ratio of 50%.⁹ Chen et al stated that the incidence of human Papillomavirus (HPV) infection is highest in the age range of 18 – 28 years. The most common strains causing GCA are HPV strains type 6 and 11, with the highest rate in HPV type 6 strains at 43.59%. Meanwhile, at Dr. Saiful Anwar Hospital in 2017-2020, there were 9 cases of GCA with 6 Human Immunodeficiency Virus (HIV) co-infections among them.¹⁵

Condyloma acuminata (singular; plural: condyloma acuminatum) also called anogenital warts caused by HPV virus types 6 and/or 11. HPV interferes with cell



cycle regulation to become abnormal and neoplastic transforms in the affected local area by preventing cells from entering the G0 cycle or resting.¹⁰ In rare cases, this type of viral infection may also escalate into GCA or Buschke and Lowenstein tumors. In immunocompetent cases, this tumor will develop more slowly than in immunocompromised cases.^{5,6}

Giant condyloma acuminata more often attacks men than women, especially in men who do not have circumcision.⁷ The main risk factor for genital warts is changing sexual partners, with a transmission rate between sexual partners of 60%. The genetic influence of the type of human leukocyte antigens (HLA) also plays a role in a person's tendency to get genital warts.⁷ Other risk factors for giant condyloma acuminata include age, immunosuppression conditions (HIV infection, post-organ transplant, post-bone marrow transplant, etc.), homosexuality, prostitution, chronic genital infections, poor hygiene, smoking, a history of other sexually transmitted infections, and simultaneous infection with other types of HPV.^{11,12}

This report aims to describe rare cases of GCA in immunocompetent patients and possible associated risk factors. The benefit of this case report is learning material about factors that can trigger the emergence of GCA, especially in immunocompetent woman patients.

RESULT AND DISCUSSION

Result

Case Report

The 24-year-old woman complained of lumps around the buttocks for 2 months. Initially, a lump as big as a green bean in the buttocks area then enlarges and multiplies to the vaginal lip area within 1 month. There are no complaints of pain, itching, or easy bleeding. Then the patient checked the complaint to a Dermatovenereologist and was then referred to Dr. Saiful Anwar Hospital. Patients also complain of vaginal discharge since 1 week ago, fishy smell, milky white discharge, minimal vaginal discharge not to stick to underwear, not itchy, and not hot. Pain during bowel movements and urination is denied, menstruation is normal, no low back pain. Complaints of fever, wounds in the genitals, red patches

on the body, weight loss, diarrhoea, and sore throat are denied by patients. There were no similar complaints before, and no history of diabetes mellitus and hypertension. The patient has never been treated using anything for his wart complaints. Family members have no complaints like patients. Patients routinely bathe twice a day with cold water and non-antiseptic soap and change underwear twice a day.

The patient has no history of transfusion, transplantation, or cancer. The patient is unmarried, the patient has a partner of 1 person (boyfriend), and started having sex regularly 6 months ago. The patient last had sex 2 months ago without using condoms anogenital only and never through oro-genital or genito-genital. During 6 months of active intercourse, the patient took birth control pills to prevent pregnancy. History of changing sexual partners is denied. The patient's partner had no complaints of genital warts. The history of gonorrhoea (-), genital sores (-), history of HIV, and syphilis in the couple is unknown (has never been checked because until now the couple has not been willing to come).

The patient is the first of 2 children, currently working as a grocery store keeper. The patient lives at home with her parents and younger brother. The patient has no history of smoking, consumption of alcoholic beverages, or use of illegal drugs. In the last education of patients at the high school level, during school patients often had difficulties in learning but never stayed in class, when they were toddlers patients experienced febrile seizures and this repeated 2 times. The patient bathes 2 times a day using anti-therapeutic soap, changing underwear with each bath. The history of feminine hygiene soap use is denied.

Generalist status, general condition appears mild pain with GCS 456, temperature 36.6°C, no enlarged lymph nodes colli and inguinal region. Dermatovenereological status of the labia minora-vulva, labia majora, perineum dan anus region there are verrucous masses, multiple, firm borders, irregular edges, varying shapes and sizes, and acetowhite test (+). There are no visible lesions in other areas of the body. in patients refuse to perform anoscopy.



Figure 1. Dermatovenereological Status : verrucous masses, multiple, firm borders, irregular edges, varying shapes and sizes, and acetowhite test (+) on labia minora-vulva, labia majora, perineum dan anus region

The labia minora-vulva, labia majora, perineum, and anus region contain verrucous masses, multiples, firm borders, irregular edges, varying shapes and sizes, and acetowhite (+). Laboratory examination results obtained non-reactive VDRL, non-reactive TPHA, and non-reactive anti-HIV. The results of histopathological examination with samples taken from the perianal region is pieces of papillomatosis-shaped tissue that appeared hyperkeratosis, showing images of corrosive cells with raisinoid nuclei. So this supports condyloma acuminata. Based on the history, physical examination, and supporting examination, the patient is diagnosed with anogenital giant condyloma acuminata. The patient is then planned for Wide Excision with a Digestive Surgery colleague. Patients and her sexual partner are also given education to maintain hygiene and ABCDE such as avoid sexual contact (abstinence), being faithful to partners, condom use (using condoms during sex), avoiding drugs, and sexual education. The patient lost to follow up without any information.

Discussion

Condyloma acuminata (singular; plural: condyloma acuminatum) also called genital warts is a proliferative benign lesion that is 90% caused by human papillomavirus (HPV types 6 and 11).^{3,4} Giant condyloma acuminata or Bushke-Lowenstein tumor is a rare verrucous tumor and has slow growth in the penile

and anogenital region that can grow to a size of 10-15 cm and damage surrounding structures such as forming cutaneous fistulas, but do not metastasize to other organs. Giant condyloma acuminata is a rare form of genital warts that most often occurs in the glades of the penis, prepuce, and perianal region, but can also occur in the anogenital such as the vulva, vagina, and urinary vesica.^{3,7,10} In this patient a verrucous tumor with a size of 12 cm in the perianal region.

Giant condyloma acuminata has a worldwide incidence rate of 0.1% in the general population with a recurrence ratio of 50%.⁹ Chen et al stated that the incidence of HPV infection is highest in the age range of 18 – 28 years. The most common strains causing GCA are HPV strains type 6 and 11, with the highest rate in HPV type 6 strains at 43.59%. Meanwhile, at Dr. Saiful Anwar Hospital in 2017-2020, there were 9 cases of GCA with 6 HIV co-infections among them.¹⁵ Other studies state that genital warts can occur in both men and women who have a history of sexual intercourse, especially those who have sexual intercourse through the anal, without a tendency to one particular sex. GCA was more common in middle-aged men (reported at age 43) with a male-to-female ratio of 2.7:1, with no association with race.² Giant condyloma acuminata accounts for 5%-24% of perianal tumors, while in other regions it is much less common. Further research on tumor region distribution data is needed.^{13,16} In comparison, an Indonesian study described the



distribution of regions in condyloma acuminata patients in 2016-2020 where 53.5% of male respondents had tumors in the perianal region, 5.6% in the anogenital region, 38.1% in the genital region, and 2.8% in the extragenital region. In the female sex, 88.6% occurred in the genital region, 9.1% in the anogenital region, and 2.3% in the extragenital region.¹⁷ This patient was a 24-year-old woman who developed a verrucous tumor in the anogenital region.

The main risk factor for genital warts is changing sexual partners because the majority of transmission routes are through sexual intercourse with a transmission rate between partners of 60%.^{3,4} the main risk factors for progression of giant condyloma acuminata are immunosuppression conditions (HIV infection, post-organ transplant, post-bone marrow transplant, diabetes, and so on).² Other risk factors for genital warts infection include age, smoking, certain HLA genes, contraceptive use, chronic genital infections, and immunodeficiency. Age has a significant correlation with the recurrence of genital warts where the incidence is 5.83 times more common in reproductive age associated with more active sexual activity.¹⁸ A younger age of first-time coitus is also associated with an increased incidence of genital warts and other HPV infections. A younger coitus age causes HPV-infected cells to be more prone to dysplasia.¹⁹ In the study, a male/female ratio of 2.7:1 was reported, with an age range between 24 to 77 years, a median age of 43.9 years (42.9 years in men and 46.6 years in women), and a tendency to come at a younger age. Another study by Chen et al stated that the incidence of HPV infection is highest in the age range of 18-28 years. The incidence of giant condyloma acuminata in women is rare.¹⁷

Human leukocyte antigen (HLA) or allele of the human major histocompatibility complex (MHC) is concerned with the presentation of foreign antigens to immune cells. Specific genes influencing the increased incidence of GCA are the presence of DRB1 and DQB1 alleles acting on the induction of T-cell-mediated immune responses against bacteria and other pathogens. HPV peptides known as T lymphocytes activate the T helper 2 response (anti-inflammatory cytokines), triggering the development of genital warts in this population.²⁰ Cellular immune responses play an important role in controlling lesions caused by HPV. Patients on immunosuppressant treatment and having autoimmune diseases such as HIV have a higher risk of severe HPV infection. The incidence of genital warts is associated

with lower CD4+ counts in HIV patients.²¹ Several cases associated with immunodeficiency conditions have been described. Gungor et al reported the case of a 22-year-old female smoker with type 1 diabetes, who was not monitored. Indicates the growth of verrucous tumors later diagnosed with aggressive GCA associated with immunosuppression conditions.²²

Bastola et al describe the case of a 61-year-old man with a history of well-controlled HIV infection who experienced rapid growth of GCA. Histopathological results showed no signs of neoplasia, but there was evidence of HPV subtype 16 infection. The study showed deep tissue invasion, and these patients were unable to undergo surgical treatment or radiotherapy due to extensive soft tissue infiltration and the presence of multiple fistulas. The patient later died from sepsis.²³ In both sexes, smoking is associated with an increased incidence and prevalence of HPV infection. Smoking also increases the persistence of high-risk HPV infection but is still a matter of debate on low-risk HPV infection. Smoking has an adverse impact on systemic and local immunity because it suppresses both cellular and humoral immune responses, which can then increase susceptibility to HPV infection and trigger the development of genital wart lesions.²⁴ Individuals who have multiple sexual partners are more likely to have multiple HPV infections as well as other sexually transmitted infections. So if these habits are not changed, infection with various types of HPV will continue to occur as well.²⁵ Chronic genital infections, other sexually transmitted infections, and smoking are associated with increased immune reactions that promote the development of genital warts. Some studies have also linked pregnancy and the use of hormonal contraceptives that allow the role of the hormones estrogen and progesterone to the high incidence of genital warts.^{3,11,12} These patients had a history of oral contraceptive use since 6 months ago (sexually active).

The pathogenesis of giant condyloma acuminata is related to the HPV 6 and 11 genomes whose DNA sequences translate to produce E (early) 6 and E7 proteins. E6 and E7 bind to tumor suppressor protein p53, causing accelerated degradation of p53 resulting in chromosomal instability of epithelial cells. While from the other side chronic irritation of the anogenital regional skin, poor hygiene, ulcerative colitis, or perianal fistula also cause chromosomal instability and can worsen the growth of giant condyloma acuminata.⁷ Under certain conditions, genetic factors affect the development of



GCA, namely the presence of DRB1 and DQB1 alleles that act on the induction of immune responses mediated by T cells against bacteria and other pathogens. HPV

peptides known as T lymphocytes activate the T helper 2 response (anti-inflammatory cytokines), triggering the development of genital warts in this population.²⁰

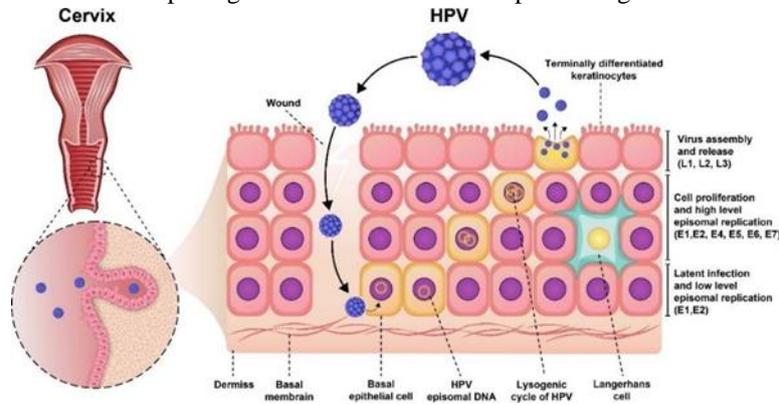


Figure 2 Pathogenesis of HPV10 Infection

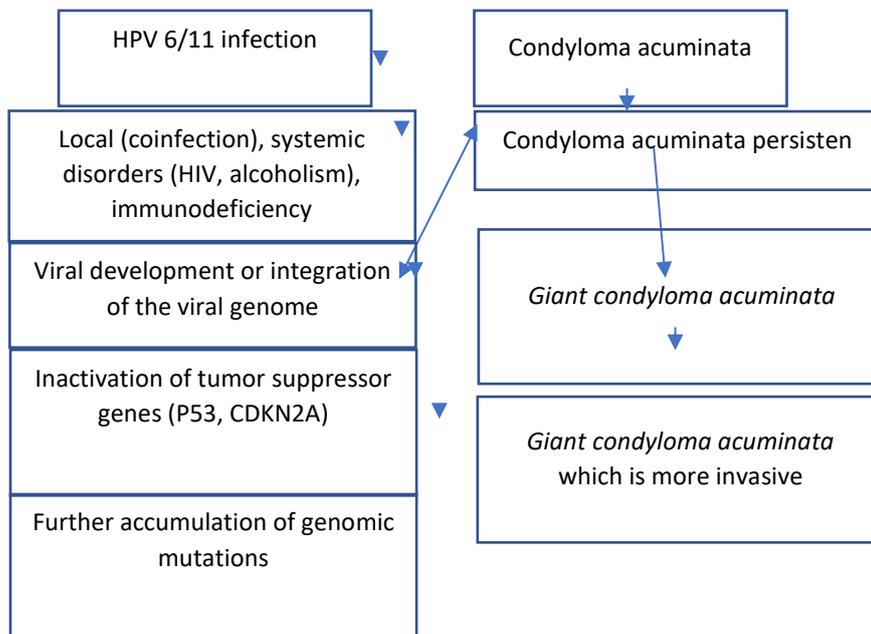


Figure 3 Pathogenesis of Giant Condyloma Acuminata

Genital warts are usually asymptomatic, but this is influenced by the size and location of the infection. Complaints can also be accompanied by pain or pruritus. The typical lesions of genital warts are usually flat, papular, or pedunculated (verrucous) exophytic tumors resembling cauliflower that grow on the genital mucosa. Genital warts often occur at the anatomical location of the vaginal introitus, below the prepuce on the uncircumcised penis, on the penile glans on the circumcised penis, the anogenital epithelium, or on the anogenital tract (e.g. cervix, vagina, urethra, perineum, perianal skin, anus, or scrotum).^{4,1} Genital warts

generally occur multiple on one lesion area and are often found on areas exposed during sexual intercourse.³

The patient in the case complained of a lump with a surface around the buttocks since two months ago measuring 12 cm. and from the physical examination of the dermatovenereological status of patients of the labia minora-vulva region there are verrucous, multiple, firm borders, irregular edges, varying shapes and sizes, acetowhite test (+). Labia majora there are verrucous masses, multiples, firm borders, irregular edges, varying shapes and sizes, and acetowhite test (+). Perineum and anus there are verrucous masses, multiple, firm borders,



irregular edges, varying shapes and sizes, and acetowhite test (+).

Initial supporting examination of genital warts can be confirmed by an aceto white test, by dripping 3%-5% acetic acid solution (vinegar) on the lesion area which will cause discoloration to white due to increased nuclear protein and cytokeratin coagulation. In this case, all lesions that have an acetowhite (+) test are lesions that indicate papillomavirus infection, which is the etiology of condyloma acuminata.^{3,14}

In patients, syphilis serological examination was carried out and non-reactive VDRL was obtained, non-reactive TPHA, and non-reactive anti-HIV. Anti-HIV laboratory tests are intended to detect immunosuppression risk factors that may occur as the main risk factor for the occurrence of giant condyloma acuminata.^{1,3}

HPV tests such as HPV DNA are not recommended for the diagnosis of genital warts because they do not confirm and do not affect the management of genital warts. However, if further HPV subtype or genotype examination is carried out, 90% of giant condyloma acuminata cases will give positive results on HPV subtype 6 and 11 examinations, while some are also related to high-risk HPV subtypes such as types 16, 18, 52, and 56. HPV DNA genotype examination can be used with the reverse dot blot flow through the hybridization method.^{6,26}

Patients in this case have non-reactive anti-HIV results and have no history or symptoms of other

immunosuppressed diseases so this is a rare case where the incidence of giant condyloma acuminata in young female patients who are immunocompetent patients at a young age. Not many studies have studied specifically the risk factors for condyloma acuminata in immunocompetent status. In immunocompetent patients, risk factors other than patient immunity need to be reviewed. The influence of age, genetics, chronic genital infection or irritation, hygiene factors, smoking, contraceptive use, and history of other sexually transmitted infections can also cause condyloma acuminata infection.^{3,11,12} The patient's sexual partners also need to be reviewed because a history of changing partners that the patient may not do but is done by his sexual partner can be a source of transmission of HPV infection.

The diagnosis of giant condyloma acuminata is established by biopsy. Histopathological features generally show acanthosis, papillomatosis, hyperkeratosis, and sometimes granular cell vacuolization (koilocytosis), with local infiltration into the underlying dermis structures.³ In this case, the results of the perianal biopsy examination showed papillomatosis-shaped pieces of tissue appearing hyperkeratosis, showing a picture of corrosive cells with raisinoid nuclei. The conclusion of the biopsy results showed Condyloma Acuminata.

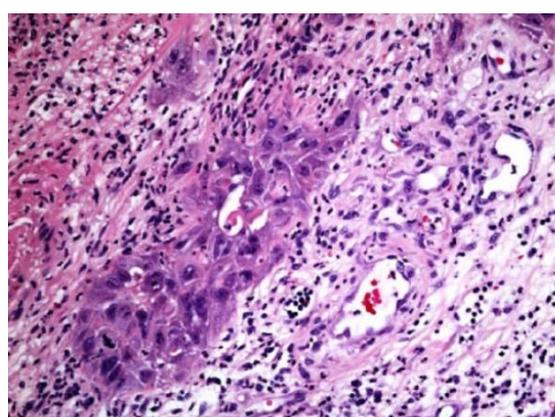
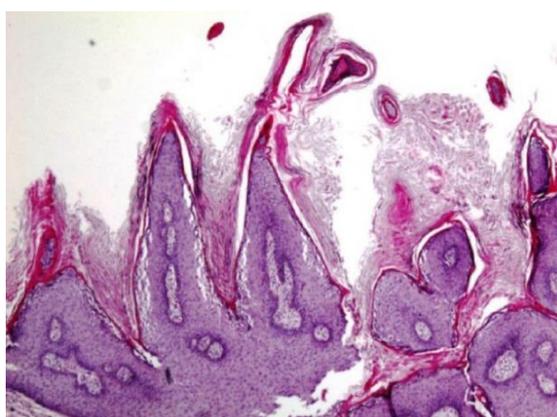


Figure 3.3 Histopathology of Giant Condyloma Acuminata⁶: hyperkeratosis and papillomatosis along with mitotic features of invasion

As a rare form of genital warts, GCA is distinguished from condyloma acuminata by its histopathological results. In ordinary genital warts, hyperkeratosis cells do not infiltrate locally into the underlying dermis

structures. Histopathology can also distinguish giant condyloma acuminata against other differential diagnoses. In squamous cell carcinoma, hyperkeratosis cells can invade the mucosa or even metastasize.³



GCA management depends on the size, number, location, immunity, patient choice, and type of treatment available at the health facility. However, the choice of GCA therapy is wide excision surgery. Wide excision is a tumor resection technique accompanied by free margins surrounding which is then also followed by neoadjuvant therapy. Mohs surgery in wide excision is a technique in which the operator removes each thin layer of skin and then examines it under a microscope to confirm the presence of remaining tumor cells. This is the technique of choice for GCA because it maintains healthy tissue and simultaneously allows the operator to ensure tumor-free margins are important to prevent recurrence, there are no contraindications to giant condyloma acuminata, and defects can be reconstructed later when needed using split thickness grafts. The recurrence of giant condyloma acuminata is treated by radical surgery or laser resection of argon or carbon dioxide.⁷ In this case report the patient is consulted to Digestive Surgery for a pro-wide excision plan.

Topical, intralesional, or oral chemotherapy treatment with fluorouracil (5-FU), podophyllin, cidofovir, interferon, and imiquimod, and leucovorin has been used as a neoadjuvant or adjuvant to treat tumor recurrences after surgery. However, single chemotherapy did not show good results for treating giant condyloma acuminata. Radiation therapy as a neoadjuvant has been avoided because of the possibility of causing further anaplastic transformations.⁷ As mentioned earlier, the application of podophyllin as a topical therapy did not have good results on giant condyloma acuminata. Whereas in combination therapy after resection, topical podophyllotoxin and imiquimod as well as cryotherapy performed weekly have shown effectiveness without consequences on the area of surgery. Contraindications of this topical therapy include hypersensitivity and warts that are more than 10 cm² because the dose per day should not exceed 0.5 ml which then causes toxicity.^{7,26} Adjuvant topical therapy with imiquimod as an aminoquinoline modifier of the immune response has shown therapeutic benefit for residues of giant condyloma acuminata after resection. Total regression has been reported with administration of 5% imiquimod cream with application once daily for 12 hours for 6 months of use, without recurrence for 3 years. This therapy is contraindicated in mucous lesions due to the risk of severe inflammation and in hypersensitivity.⁷ Intralesional therapy is immunotherapy using Purified Protein Derivate injected 0.2-0.3 ml once every two

weeks distributed at two or three different sites, which are at least two centimeters apart. This therapy does not require topical anesthesia or injection. This therapy can also be an option for pregnant women who must delay resection until after delivery or to prevent the enlargement of lesions in patients who are still waiting for surgery. The contraindication to this therapy is an allergy to tuberculin components.^{7,26}

Complications that can cause giant condyloma acuminata include fistula formation, secondary infection, odorous fluid, recurrence, and transformation into malignant.⁷ Although giant condyloma acuminata is a benign tumor, the possibility of infiltrating surrounding tissue and transforming into squamous cell carcinoma is still possible at around 40-60%. The recurrence rate of this disease is quite high reaching 66%, therefore regular follow-up is needed.^{2,13}

CONCLUSION

Giant condyloma acuminata in immunocompetent adult female patients can occur due to genetic influences of HLA type, age, sexual orientation, chronic genital infection or irritation, poor hygiene, smoking history, history of other sexually transmitted infections, simultaneous infection with other HPV types, as well as pregnancy and hormonal contraceptives that allow the role of estrogen and progesterone hormones. Identification of these risk factors is important to prevent repeated infections resulting from the same and modifiable risk factors, given the high recurrence rate of giant condyloma acuminata. In these patients, the most likely predisposing factors are the influence of young age, chronic genital irritation, and the use of oral contraceptives.

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