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Case Report

Case Report: Combination Therapy of Electrocautery and Zinc Sulfate in Perianal Giant *Condylomata Acuminata* with Human Immunodeficiency Virus (HIV)

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ABSTRACT

Introduction: Giant *Condylomata Acuminata* (GCA) or Buschke-Lowenstein tumours are rare variations of anogenital warts. Immunocompromising conditions are closely related to the development of GCA. There is no standard therapy in the management of GCA. Its large size allows malignant transformation and high recurrence.

Case Presentation: A male, 26 years old, with a complaint of wart in the anal in the last 11 months. The lump was getting bigger and sometimes bleed. The patient had been diagnosed with HIV 1 year ago and had received routine antiretroviral therapy (ARV). On physical examination of the perianal region showed stalked vegetation which was hypopigmented, partly erythema, verrucous surface, in the form of cauliflower, multiple, measuring 1.5x1.5x4 cm. A positive acetowhite test and histopathological examination showed condylomata acuminata. Patients were given combination electrocautery therapy and zinc sulfate 5-10 mg/kg/day for 2 months. Significant improvement appears and GCA disappears entirely.

Conclusion: Electrocautery and zinc sulfate as an immunomodulator can be considered as a treatment of GCA with HIV because they can work synergistically to achieve resolution of the lesion and prevent recurrence of GCA.

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INTRODUCTION

Giant *condylomata acuminata* (GCA) is a rare variant of *condylomata acuminata* (CA), which is a sexually transmitted infection caused by the human papillomavirus (HPV), associated with immunocompromised conditions. This CA infection is transmitted through sexual intercourse by 50-80%. Giant condylomata acuminata affects the quality of life due to this disease can transform into a malignant form called squamous cell carcinoma (SCC) with a 30-56% probability and has a chance for recurrence and high mortality rate of 2.3% [1,2,3].

Coinfection of GCA is frequently found among patients with Human Immunodeficiency Virus (HIV) infection. Based on the medical record of dermatology and venerology (DV) clinics at RSUD. Dr Saiful Anwar (RSSA) Malang, for the period 2017-2020, there were 9 cases of GCA with 6 of them having coinfection with HIV. Human Immunodeficiency Virus (HIV) is one of the risk factors for changing the progression of CA to invasive CA due to a decrease in the cellular immune system, which causes an increase in susceptibility to HPV with a prevalence is 31-57% [4]. Patients with HIV infection have decreased amounts of Langerhans cells, CD4+ cells, Neutrophils and Natural Killer (NK) cells, causing changes in local immunity that modulate HPV infection in tissues [5].

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Therapy of GCA is often associated with surgical excision, which is the main option, but it still has a high recurrence rate of 50%. Non-invasive surgical therapy that can be considered is electrocautery. GCA condition with HIV can affect the therapy selection because the immunodeficiency condition will affect HPV transcription and cell proliferation. Therefore, an immunomodulator is given with the aim of increasing the immune system so that it results in suppressing the growth of HPV. Immunomodulators are biological therapies that use a substance to stimulate the immune system to help the body fight cancer, infections, and other diseases. Zinc is one of the immunomodulators that contains mineral micronutrients that needed for the immune system, contributing to various biological processes of cell development and metabolism. The condition of zinc deficiency often occurs in GCA, accompanied by HIV infection, due to low food intake and digestive disorders. Giving zinc medication can help to suppress the proliferation of HPV [6].

A study reported a case of perianal GCA in a 26-year-old man with HIV who was given a combination therapy of electrocautery and zinc sulfate oral. This case report aims to assess the effectiveness of combination therapy against GCA. In addition, this case report can give additional knowledge about the therapeutic options that can be considered for GCA.

CASE PRESENTATION

Case Report

A 26-years-old man presented to the outpatient dermatology and venerology (DV) clinic at RSSA Malang with a chief complaint of warts on the anus since 11 months ago. Initially, small warts then rapidly grow and multiply to cover part of the anus. Warts are painless but slightly itchy (VAS 2/10). Warts sometimes bleed for the last 2 months, especially when the patient wears tight underwear. There are no complaints of red spots scattered on the body, genital sores, and discharge of pus from the genitals.



Fig. 1. Dermatovenereological Status of Perianal

In medical history, the patient had similar complaints as small warts on the anus and fistula, he had surgical closure of the fistula and removal of the warts was performed at Jember Hospital 5 years ago. The patient had no other complaints of sexually transmitted infection (STI). He was diagnosed with HIV 1 year ago at Jember Hospital and regularly receives antiretroviral (ARV) treatment. The patient is a teacher in Malang and he is an immigrant from outside Malang city who currently lives in a boarding house. He is a man who has sex with men (MSM), not married, had sexual intercourse for the first time at the age of 20 years and had sex with 3 men anogenitally. His sexual partners are coworkers and girlfriends. The most frequent position is from the bottom and not using a condom. The patient's girlfriend had HIV and tuberculosis then died 14 months ago. Three months later, the patient was diagnosed with HIV. Since being diagnosed with HIV, the patient has not had sex until now.

Investigation

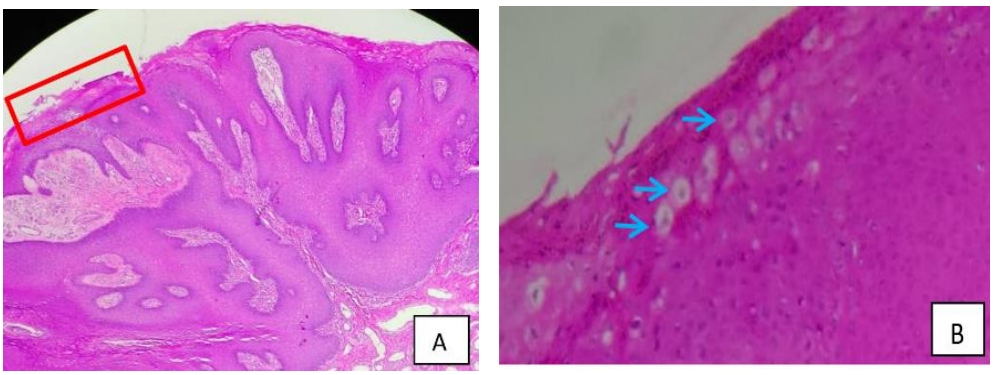


Fig 2. Histopathological Examination. (A) Papillomatosis, hyperkeratosis, and elongated rete ridge (H&E; X40 magnification); and (B) Coilocytes cells are polygonal round with oval nuclei with dysplasia and para nuclear clearing (→) (H&E; X400 magnification).

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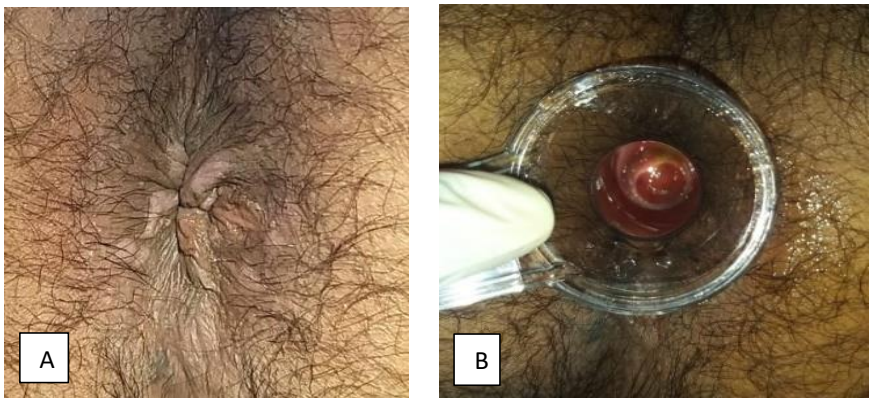


Fig. 3. (A) Dermatovenereological status of the perianal region after the combination therapy; and (B) Anoscopy examination after combination therapy

On the general examination, he looks mildly ill. Vital sign obtained blood pressure of 110/80 mmHg, pulse 80x/minute, respiratory rate of 18 x/minute, axillary temperature 36.3ºC, and body weight is 60 kg. No enlarged colli, axillary, and inguinal lymph nodes were found.

Dermatovenerological status of the pubic area, gland penis, body or the penis, coronary sulcus, external urethral meatus, and scrotum were no findings of abnormalities. The perianal region showed some erythematous hypopigmented papules, verrucous surface, multiple in number, stemmed, cauliflower-shaped with a size of 1.5 x 1.5 x 4 cm (**Fig. 1**).

Acetowhite examination using 5% acetic acid obtained positive results; warts changed colour to whitish. Blood examination showed complete blood count and liver and kidney function within normal limits. The results of the HIV test were reactive, with a CD4 cell count is 191/µL and zinc levels are 48 g/dl. The result of the rapid test antibody total anti-SARS-CoV-2 was non-reactive. The patient agreed to the next treatment in the form of a biopsy for histopathological examination and electrocautery by signing the informed consent.

Outcomes and Follow Up

Histopathological examination of the perianal lesion using Hematoxylin and Eosin (H&E) staining showed papillomatous tissue, minimal parakeratosis with acanthosis of the epidermis. There were round, polygonal cells with oval nuclei with dysplasia and para-nuclear clearing. The dermis showed minimal lymphocyte inflammatory cell and blood vessel dilatation. The conclusion is condylomata acuminata (**Fig. 2**).

Based on the history, physical examination, and other examinations, the patient was diagnosed with GCA and HIV on ARV. The patient received combination therapy of electrocautery once per week for 2 months and zinc sulfate orally 5-10 mg/kg every day for 2 months. To reduce pain, the patient was given mefenamic acid 3 x 500 mg (prn). ARV treatment is continued routinely. The patient was given education not to have sex to maintain anogenital hygiene and routine control at the clinic. Provide education to patient that recurrence can occur in new or old areas with a recurrence rate of 20-30% and GCA lesions can transform malignantly into SCC.

Patients come to the outpatient dermatology and venerology (DV) clinic at RSSA Malang every two weeks to continue the therapy and evaluate the presence of subjective complaints, such as nausea, vomiting, and indigestion. Electrocautery was performed in stages until the lesion was clean (**Fig. 3A**). An anoscopy examination was performed after the GCA lesions in the perianal area were clean. Anoscopy showed no verrucous papules inside the anus (**Fig. 3B**).

DISCUSSION

Giant condylomata acuminata is a clinical form of genital warts or CA, which are large and very rare, characterized by growth extending to the underlying dermal structure. The lesions are cauliflower-shaped, locally invasive, not metastatic and can be single or solitary, but mostly 5-10 lesions with a diameter of 1-5 mm [4,7,8]. It is a rare sexually transmitted infection, the incidence in the general population is about 0.1% [3,4,7,9]. Anal GCA cases have a high higher prevalence in men who have sex with men (MSM) at 57%, the anal area is used to get sexual satisfaction [10,11]. Special conditions immunocompromaised such as HIV, encourage HPV type 6 and 11 infections to grow and develop into GCA. Malignant transformation into squamous cell carcinoma (SCC) may occur in more than half of cases, and co-infection with CA is more frequent in patients with HIV [4,6]. Factors that can affect the decrease in plasma zinc levels in HIV are

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gastrointestinal disorders such as decreased appetite, nausea, and vomiting [5,6].

There are no standard guidelines for GCA therapy because these cases are still rare. Management depends on the size, depth, location, state of immunity, tissue transformation, facilities and skills of the treating doctor [13,14]. GCA therapy that has been proposed includes tumour removal (surgery, cryotherapy, electrocautery, and CO_2 laser), topical therapy (imiquimod, podophyllotoxin, trichloroacetic acid, sinecathechins), and immunotherapy or immunomodulators [14,15]. There is a challenge in a patient's clinical condition with various therapies is the high recurrence rate after a long-term follow-up period. In randomized controlled trial studies, data showed that surgical treatment provides a 100% cure rate, and relapse still will occur in all of these treatment modalities. The recurrence can occur as new lesions at new sites or old sites with a recurrence rate of 20-30% or more [13].

Immunotherapy or immunomodulator is defined as a type of biological therapy that uses a substance to stimulate or suppress the immune system to help the body fight cancer, infections, and other diseases. Some types of immunotherapy target only specific cells of the immune system, while others affect the immune system in general. The use of immunotherapy is well applied in cases of malignancy, and its role in infection has been found. Human papillomavirus is a DNA virus, which is neoplasia that can be both benign and malignant [5].

Zinc is needed for the immune system function, and its deficiency affects the function of immune cells, especially T cells [18,19]. Zinc can inhibit the formation of Reactive Oxygen Species (ROS), if ROS is inhibited, NF-κB activation does not continue, so it will inhibit the activation of several growth factors, including Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor Receptor (EGFR), cyclin D1 protein and several anti-apoptotic molecules including B-cell lymphoma 2 (Bcl2), B-cell lymphoma-extra large (BclXL), cellular inhibitor of apoptosis protein 2 (cIAP-2). Low plasma zinc levels can cause a decrease in immunity and dysregulation of cell apoptosis, resulting in an uninhibited increase in the proliferation of HPV-infected epithelial cells [5].

According to study Read et al., both topical and oral zinc supplementation has been shown to be effective for skin and genital warts. However, some researchers have found that it is most effective for warts on the skin. Approximately 78% of patients in the study showed improvement in lesions in response to zinc sulfate 10 mg/kg to 600 mg/day [6]. zinc levels in the plasma of CA patients with HIV were significantly lower than those without HIV. Recommendations that can be given to CA patients with HIV co-infection are zinc supplements to enhance the immune system and regulate cell apoptosis [5]. Zinc is one of the minerals needed for immune system function and contributes to various biological processes of cell development and metabolism. In the majority of patients, zinc deficiency is associated with persistent, progressive or recurrent HPV [16]. According to Thappa et al., the use of zinc sulfate at a dose of 10 mg/kg/day for 2 months showed improvement of CA. Zinc sulfate can be used in combination with other therapeutic modalities such as imiquimod, podophyllin, and cryotherapy [22]. According to Stefani et al., in a randomized, double-blind trial study in 18 patients comparing zinc sulfate therapy (10 mg/kg/day) and cimetidine therapy (35 mg/kg/day) for 3 months of resistance CA. The study concluded that zinc sulfate was more effective than the use of cimetidine, but the side effect are nausea, vomiting, and epigastric pain [17].

Prognosis of GCA depends on the patient's adherence to medication, lifestyle changes, immunological condition. The recurrence rate itself is quite high, namely among the total cases, both treated and self-limited. Immunocompromised patients have a higher risk of malignant metaplasia when infected with high-risk HPV strains. Recurrent infections from sexual partners and being immunocompromised can cause condyloma acuminata to respond poorly to therapy, require longer treatment cycles, and have a higher chance of relapse.

CONCLUSION

GCA therapy is still a challenge due to the possibility of malignant transformation and the high recurrence rate after receiving therapy. HIV patients with low immune status are very susceptible to various infections, one of which is GCA. There is an association between zinc levels in HIV patients, which is with low levels, patients are more prone to the recurrence of condylomata acuminata. Therefore, in cases of GCA with HIV co-infection, low plasma zinc levels were also found, and therapy was given was gradual electrocautery and zinc sulfate (5-10 mg/kg/day) for 2 months, showing satisfactory results with resolution of GCA lesions. Electrocautery is a minimally invasive technique that may be considered. Giving zinc sulfate as an immunomodulator is expected to help to heal and increase immune response so it could prevent a recurrence. At 6-months evaluation, no recurrence was found. Patient is advised to be vigilant and re-examind if similar complaints reappear due to the high rate of recurrence of this disease.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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