

Successful Treatment with a Combination of Oral and Topical Glycyrrhizinic Acid in an Immunocompetent Anogenital Warts Patient

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Introduction: Anogenital warts (AGW) are benign proliferative diseases caused by human papillomaviruses (HPV), characterized by verrucous papules on the genital or anal region. In line with these findings, the prevalence of AGW is high among males and increasing in Indonesia, and most patients seek treatment because warts are cosmetically disfiguring and itchy. Self-applied treatments may cause local adverse effects such as irritation or burning. Oral and topical administration of glycyrrhizinic acid (Gly) has been observed to have antiviral and anticancer properties.

Case Report: A 21-year-old immunocompetent patient presented with multiple verrucous lesions on the anal region. Histopathological results showed condyloma acuminata type of AGW, and polymerase chain reaction results showed HPV type 11. The patient was treated with a combination of 10 mL oral Gly thrice daily and self-applied topical Gly three to four pumps thrice daily. The lesions gradually resolved after the first week of the combination of treatments. Subsequently, after 12 weeks of treatment, the wart decreased to one verrucous lesion, and the patient showed no adverse effects.

Discussion: Gly exhibited broad-spectrum antiviral effects against HPV, herpesviruses, hepatitis viruses, and others. Oral and topical applications are considered safer than intravenous administration. Previous studies on Gly-based topical treatment showed effectiveness in the treatment of AGW with minimal side effects. Oral Gly supplements also have been found to enhance immune response and aid in HPV treatment, particularly when combined with topical Gly. According to the results, a combination of oral and topical Gly leads to high HPV clearance rates, making it a promising non-invasive treatment option.

Conclusion: The combination of topical and oral Gly appears to be a promising self-applied treatment of AGW. However, the potential for recurrence warrants further observation and long-term follow-up studies.

Keywords: anogenital warts, condyloma acuminata, glizigen, glycyrrhizinic acid, viusid

Introduction

Anogenital warts (AGW) are sexually transmitted infections (STIs) caused by human papillomaviruses (HPV) infection that manifest as benign proliferative diseases in the form of single or multiple papules on the genital or anal region. AGW are the most common STIs worldwide with a higher prevalence among individuals engaging in anal intercourse, particularly men who have sex with men (MSM). In Indonesia, AGW recorded the highest cases of STIs found in teaching hospitals in 2016.¹ Most patients seek treatment as warts are cosmetically disfiguring and itchy as well as painful.² The treatment for AGW generally involves tissue destruction and the use of topical immune-modulating, antimitotic, antiviral, and anticarcinogenic medications.³ These processes are classified based on patient-applied or provider-administered. The most common patient-applied treatment is podofilox 0.5% solution or gel and imiquimod 5% cream. However, these two procedures have not been approved for the treatment of perianal, rectal, urethral, vaginal, and cervical warts, and also in pregnant women.⁴

Glycyrrhizinic acid (Gly) is a natural triterpene saponin found in the root and rhizomes of plant species, which has been observed to have antiviral and anticancer properties.^{5,6} The administration of Gly both topically and orally has been evaluated in the form of Glizigen[®] spray and Viusid[®] syrup. The combined treatment showed complete elimination of AGW in 87.5% of cases with mild adverse effects.⁵ Therefore, a case of perianal warts was successfully treated with patient-applied Glizigen[®] spray and Viusid[®] syrup as one of the procedures is an effective method for self-applied treatment of AGW.

Case Report

A 21-year-old homosexual male presented at Venerology Clinic Dr. Hasan Sadikin General Hospital (RSHS) with multiple brownish papules on the perianal region. The skin lesions initially appeared 1 month before the patient's visit as a single papule, gradually multiplied, itchy, but never bled, and no form of medication was used. The last sexual intercourse was 3 months ago with a male friend as the receptive, without using a condom, anogenitally and orogenitally. The patient had been circumcised, and did a coitarche at the age of 20 with a male friend anogenitally, without a condom as the receptive. The total sexual partners were two males and were unaware of the partners' HIV status or diseases, although there was no history of STIs.

On physical examination, no lymphadenopathy was found, and the dermatological examination was within normal limits. Venereological examination showed multiple verrucous papules on the perianal region (Figure 1), and the acetowhite test indicated a positive result. The rectal examination and anoscopy showed the anal canal to be free of the disease. Laboratory examination showed negative results for anti-human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), *Treponema pallidum* hemagglutination assay (TPHA), and venereal disease research laboratory (VDRL) titer. Histopathology examination showed hyperplastic, acantholytic, hyperkeratotic, and parakeratotic keratinized epithelium with normal nuclei, and some cells showed koilocytosis. On the dermis layer was shown fibro-collagenous connective tissue with lymphocyte inflammatory cells accompanied by vascular dilatation and hemorrhage. The results were consistent with condyloma accuminata in the perianal region (Figure 2). The polymerase chain reaction (PCR) genotyping showed that HPV 11 was found. Based on the patient's history, physical examination, and histopathological results, a diagnosis of AGW was established. Self-treated method with three to four pumps was applied thrice daily of Glizigen[®], containing Gly, spray and 10 mL thrice daily of Viusid[®] as an immunostimulant. The treatment's effectiveness was evaluated by measuring the quantity of warts every week. There were no signs of redness, swelling, blisters, or scales on the site after the spray. The lesions showed improvements as they reduced in number and

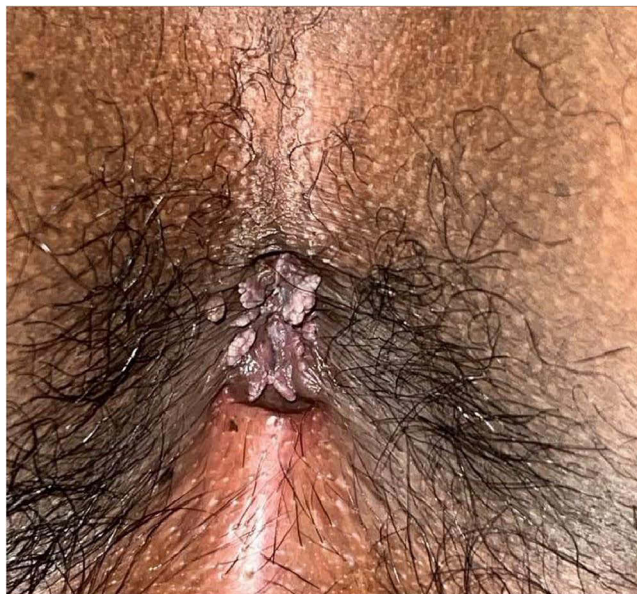


Figure 1 Multiple verrucous papules on anal region on the first consultation.

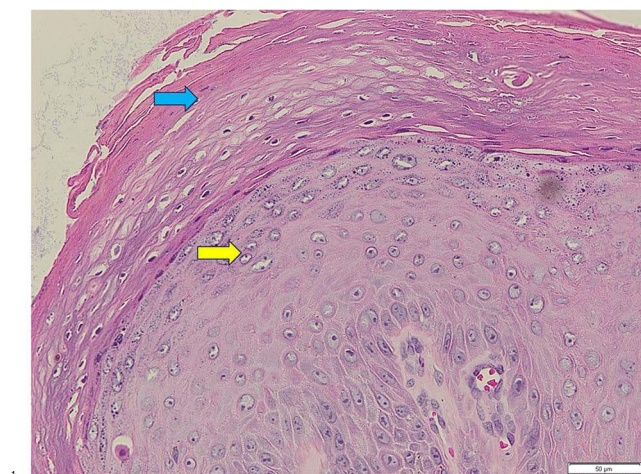


Figure 2 Histopathological result showed keratinized stratified epithelium that are hyperplastic, hyperkeratosis and parakeratosis (blue arrow) with koilocytosis (yellow arrow), that consistent with condyloma acuminata.

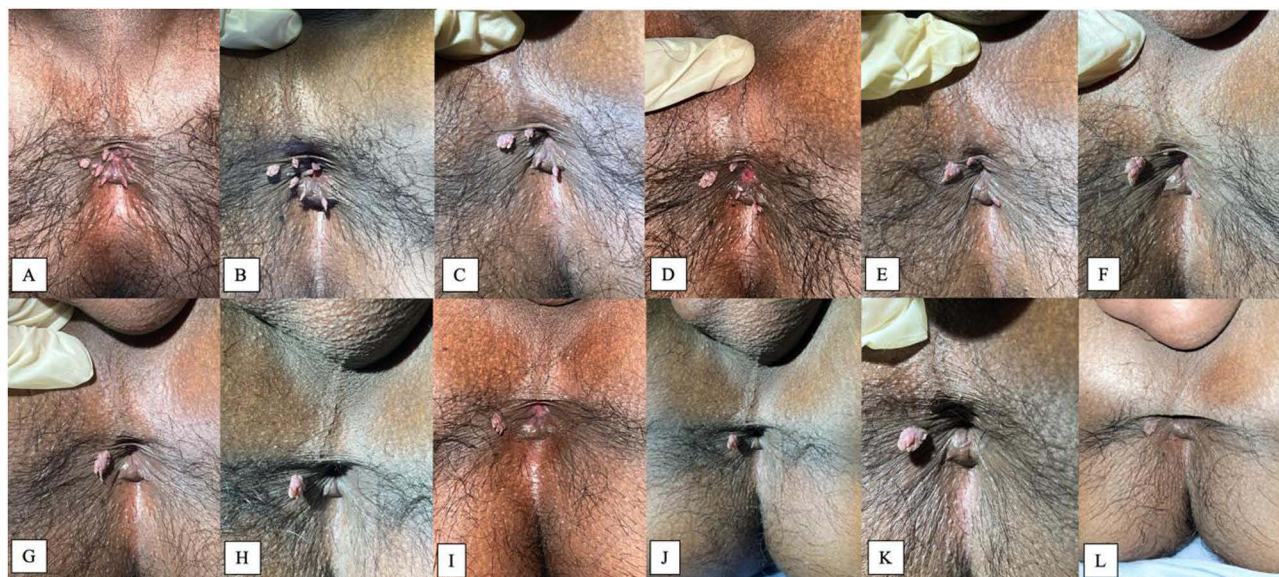


Figure 3 Multiple verrucous papules on anal region that gradually resolved after 1 week of therapy (A), after 2 weeks (B), after 3 weeks (C), after 4 weeks (D), after 5 weeks (E), after 6 weeks (F), after 7 weeks (G), after 8 weeks (H), after 9 weeks (I), after 10 weeks (J), after 11 weeks (K), and after 12 weeks (L).

size in the first week after treatment (Figure 3A) and the next follow-up weeks (Figure 3B–L). After 12 weeks of treatment, one wart remained, prompting the decision to discontinue the combination. Subsequently, electrocauterization was performed to remove the remaining wart.

Discussion

AGW are the most frequently transmitted infections in young adults with a peak age of 24 years in females and 25–29 years in males.⁷ The incidence of AGW is reported to be 2–6 times higher among MSM compared to heterosexual men and is recognized as one of the most frequently transmitted infections each year. Although benign, AGW can be distressing as the appearance and sometimes the symptoms may affect the patient's quality of life and relationships.⁸ The disease can also spread to other regions including the urinary tract and urinary bladder, causing serious complications.⁹ HPV infection imposes a significant socioeconomic burden because of the repeated occurrence of benign lesions.¹⁰ There is still no definitive and ideal treatment for AGW,^{4,10} with the goals being aesthetics, symptom

improvement, reducing transmission, and preventing lesion expansion through autoinoculation.⁴ The selection of treatment for AGW depends on factors such as wart size, number, anatomic location, patient preference, treatment cost, convenience, potential adverse effects, and the provider's experience.¹¹ The treatment option also varies between patient self-applied or provider-administered. Self-applied topical treatments are usually associated with local adverse effects such as irritation and burning and may be difficult to administer.⁸ A complete cure and the high cost of treatment, and another alternative from recent studies is Gly.^{6,12}

Gly is a substance found in *Glycyrrhiza glabra* root, commonly known as "sweet root", which was originally used for the treatment of respiratory infections and has anti-inflammatory properties. Additionally, this substance has been found to have anti-ulcerative and antiviral effects that lead to the inactivation of the extracellular free virus particles, the prevention of the intracellular decapsulation of infectious particles, and the deterioration of the component of the virus.¹² Gly is a broad-spectrum antiviral against different viruses such as human papillomavirus, herpesviruses, hepatitis viruses, influenza viruses, human immunodeficiency viruses, coronaviruses, rotaviruses, and coxsackievirus. Intravenous and oral administration has been observed to have antiviral and anticancer properties. However, the toxicity is higher in intravenous administration than in oral. Therefore, oral and local administration has more potential for treatment.⁵ Topical application of Gly has other benefits as this procedure does not cause skin irritation and no interactions with other pharmacological preparations have been reported.¹² Gly has also been found to have less complexity in application and control of dosage, making it easier and safer to self-application.¹³ The published studies on Gly has been conducted under the brand name Glizigen[®] spray. Monotherapy of Glizigen[®] spray has been observed to be more beneficial in treating AGW with minimal local and systemic adverse effects compared to other self-applied treatments.¹² Monteros et al observed 97 women who were diagnosed with low-grade squamous intraepithelial lesions on cervical and treated with Glizigen[®] spray for 10 days to be beneficial and showed normal cytology in 80% of the cases after 20 days after completion of the treatment.¹⁴ Moreover, Sandi et al conducted a trial of focal multi-epithelial hyperplasia in a total of 20 pediatric-age patients, which was divided into one group treated with topical Gly and one group treated with topical liquid nitrogen. Gly group showed 63% efficacy after 4 weeks, while the liquid nitrogen group showed 81% efficacy after 12 weeks, with the adverse effects observed in the liquid nitrogen group as erythema, edema, pain, nausea, and vomiting.¹⁵ Sakaniia et al further investigated the efficacy and safety of topical Gly in pregnant women, and the results showed 26 patients with positive HPV PCR, and the virus was detected at 30–34 weeks of pregnancy. The patient was then prescribed topical Gly in the form of spray three times daily, 1 week before the expected birth. As a result, from 25 children to 25 patients who had a natural birth, samples were taken on the oral and genital regions since the first day after delivery and showed negative HPV PCR. Meanwhile, one patient was scheduled for a caesarian section, and HPV PCR was also negative. Therefore, topical preparation of Gly is an effective method of HPV treatment in women and prevention of transmission of the virus to the child.¹⁶

Other published studies on Gly have been conducted for oral administration under the brand name Viusid[®], containing Gly, L-arginine, L-glycine, vitamin C, B5, B6, B9, B12, and zinc-based nutritional supplements. Viusid, a food supplement to balances and stimulates the functions of the immune system, contains antiviral agents, antioxidants, and anti-free radicals that are essential to boost the defenses of the immune system. The combination of Gly and Viusid was found to be effective in the treatment of external AGW compared to podophyllin.¹² Romo et al also conducted a study to compare the effectiveness of topical and oral Gly. Seventy-six AGW patients were treated with topical application of Gly together with oral supplement three times a day for 12 weeks. The lesions of 68.4% of the patients disappeared altogether, and the other 28.9% of the patients decreased by more than 75%, and no adverse reactions were observed.¹⁷ Valencia et al conducted a study on 62 women who presented with HPV infection and were treated with a combination of topical and oral Gly for a minimum period of 8 weeks. As a result, after 12 weeks of treatment, 74% of the cases were HPV negative, and after more than 13 weeks of treatment, 100% of the cases were HPV negative.¹³ Therefore, the patient in this case was observed with the combination of topical and oral Gly and showed a good result after the first week of the treatment. After a few weeks of treatment, the lesions started to resolve gradually. However, after 12 weeks of treatment, one wart remained, prompting the decision to discontinue the combination. Subsequently, electrocauterization was performed to remove the remaining wart.

Conclusion

In conclusion, the combination of Glizigen[®] spray and Viusid[®] syrup in immunocompetent AGW patients showed a good response to AGW even from the first week of treatment, and after 12 weeks there were no side effects. Therefore, the combination treatment seems to be a promising self-applied procedure of AGW. However, the risk for recurrence still needs to be observed.

Ethics Statement

The publication of images was included in the patient's consent for the publication of the case. Institutional approval was obtained to publish the case details from Dr. Hasan Sadikin Hospital Ethical Committee with ethical approval number DP.04.03/D.XIV.6.5/96/2025.

Consent Statement

The authors certify that they have obtained all appropriate patient consent forms. The patient signed a consent form for the publication of the case details and images.

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Disclosure

The authors declare no conflicts of interest in this work.

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