

Complete Regression of Anogenital Warts Following Intralesional Measles-Mumps-Rubella (MMR) Vaccine: A Case of Two

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Introduction: Anogenital warts (AGW) are benign proliferative lesions on the epithelium or mucosa caused by *human papilloma-virus* (HPV) types 6 and 11. HPV infection occurs when viral particles enter the basal cells through microtrauma in the epithelium. AGW demonstrate a predilection for involvement of any region of the genitalia, anal or perianal area, inguinal, pubic region, and is very common in the traumatized area during sexual intercourse. Immunotherapy is one of the therapeutic modalities for AGW. The measles, mumps, and rubella (MMR) vaccine given by intralesional injection can be a promising therapeutic option for multiple AGW, particularly those located hard to reach areas.

Case Presentation: We described two cases of anogenital wart type condyloma acuminata in a 19-year-old female and 21-year old female patient, who presented to Dermatology, Venereology, and Aesthetic Department. On physical examination, both cases have multiple skin-colored papules appeared with a verrucous surface in the labia majora and vagina. The patients received 0.5 mL of MMR vaccine, which was injected intralesional into the largest wart without a pre-sensitization test. The injections are planned to be administered every three weeks, with a maximum of three injections. The warts resolved completely and left no scars. The side effect when the injection is mild pain in the injection site.

Conclusion: Intralesional MMR vaccine can be considered one of the treatments for AGW because it has been proven safe and effective, but more research is needed as a therapy for AGW.

Keywords: anogenital warts, condyloma acuminata, immunotherapy, measles-mumps-rubella, MMR vaccine

Introduction

Anogenital warts (AGW) are a form of benign proliferation of the epithelium in the skin or mucosa caused by *Human papillomavirus* (HPV) infection.^{1,2} More than 200 types of HPV have been identified,³ with types 6 and 11⁴ being responsible for 90.2–95% of AGW cases.^{1,5} According to the Centers for Disease Control and Prevention (CDC), AGW ranks as the most common sexually transmitted infection (STI) in the United States, with an incidence of 13 million cases and a prevalence of 42.5 million cases in 2018.⁶ In Indonesia, the prevalence of AGW in 2009 was between 5% and 19%.⁷ Data from 12 teaching hospitals in Indonesia showed that AGW was the third most common STI from 2007 to 2011.⁸

HPV infection occurs when viral particles enter the basal cells through microtrauma in the epithelium. This attachment process is mediated by L1 and L2, allowing the viral genome to integrate into the host cell DNA, where the virus then replicates.³ The clinical manifestations of AGW may include benign epithelial proliferative lesions in the genital, anal, or perianal areas, as well as the inguinal and pubic regions, typically involving areas exposed during sexual activity with asymptomatic, include itching, easy bleeding, and dyspareunia.⁵

Currently, there is no specific or ideal therapy for AGW.¹ Various therapeutic modalities are available, including topical medications, destructive methods, and immunomodulators.⁹ The choice of therapy depends on the location, type, and severity of the disease, as well as the expertise of the treating physician.¹⁰ Treatment generally focuses on removing

warts without eradicating the virus.¹ Immunotherapy can be a therapeutic option. The principle of immunotherapy is to activate delayed-type hypersensitivity reactions and humoral immune responses against the antigen and virus causing AGW. Immunotherapy aims to destroy warts, including those located far from the injection site, while also preventing recurrence and eradicating the virus.^{11,12} The measles, mumps, and rubella (MMR) vaccine can be considered an alternative immunotherapy for multiple AGW, especially located in distant and difficult to access locations with minimal sessions of therapy. Here we present two cases of AGW involving the labia majora and vagina in sexually active women. The aim of this case series is to present of AGW successfully treated with MMR vaccine injection.

Case Presentation

Case One

A 19-year-old female presented to the Dermatology and Venereology Department at Hasan Sadikin Hospital Bandung in 2022 with multiple papules over the labia majora that sometimes felt itchy for more than two months. She noted that lesions were increasing in size and number. The patient has not yet treated the AGW and seeks a therapy with minimal side effect. She admitted a history of frequent sexual intercourse with their partner without using condoms. Similar complaints in the partner are unknown. The patient has a history of smoking and alcohol consumption, but she denied ever using any drugs. The patient is not pregnant, is not currently taking immunosuppressive medications, and has no previous history of an allergic reaction to the MMR vaccine.

On physical examination, the patient had multiple skin-colored, flat, and verrucous papules—some discrete, others confluent—on the labia majora, perineum, and vagina ranging from 0.2×0.4×0.2 cm to 2×1.2×0.3 cm (Figures 1A and 2A), with no lymphadenopathy, discharge, or ulceration. Laboratory tests were negative for HIV, VDRL, TPHA, and hepatitis B surface antigen. Genotyping with PCR showed positive results for HPV type 6.

She was treated with 0.5 mL of intralesional MMR vaccine (M-M-R[®] II, Merck Sharp & Dohme, USA) into the largest wart in labia majora sinistra, without prior sensitization, once every three weeks and without additional therapies. After only a single session, the lesions began to regress, as evidenced by a reduction in both size and number of lesions in the labia majora and perineum (Figure 1B), with complete resolution and no scarring at three weeks after single session (Figures 1C and 2B). Follow-up at three months showed no recurrence (Figure 1D).

The diagnosis of genital warts was supported by clinical presentation, dermoscopic, histopathological, and molecular findings. Dermoscopy revealed a characteristic finger-like pattern, while histopathological analysis showed stratified squamous epithelium with hyperplasia, papillomatosis, hyperchromasia, parakeratosis, and partial koilocytosis (Figure 3). Polymerase chain reaction (PCR) confirmed the presence of HPV type 6.

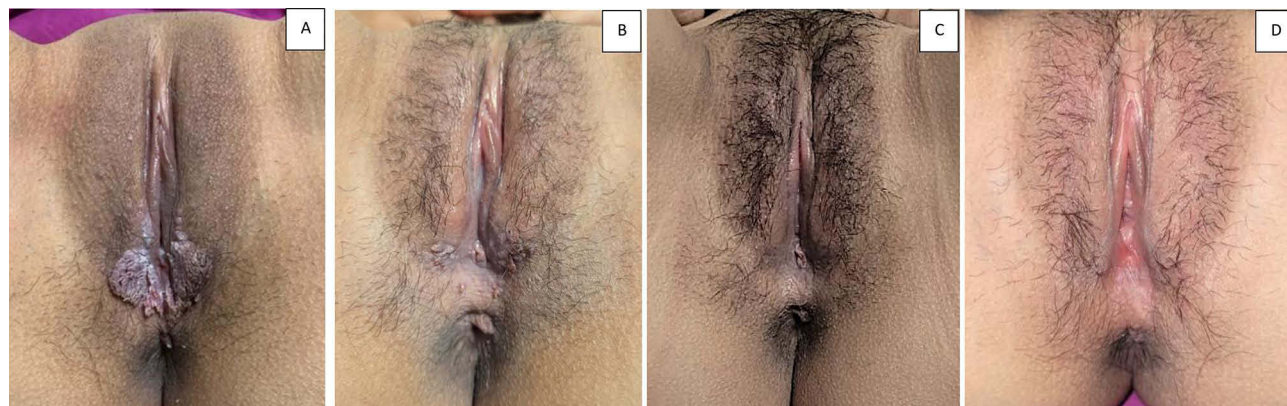


Figure 1 AGW in the case one at labia majora. (A) Before injection MMR; (B) 1 week after injection MMR; (C) 3 weeks after injection MMR; (D) 3 months after injection MMR.



Figure 2 AGW in case one at introitus vagina. (A) Before injection MMR; (B) 3 weeks after injection MMR.

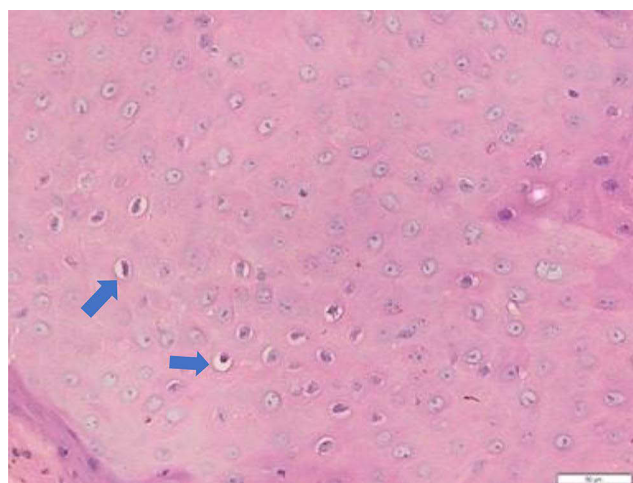


Figure 3 Histopathological findings of the AGW showed koilocytosis in case one (blue arrow).

Case Two

A 21-year-old female presented to the Dermatology and Venereology Department at Hasan Sadikin Hospital Bandung in 2022 with multiple papules over the labia majora that sometimes felt itchy for more than three months. The patient reported progressive enlargement of lesions in size and number, but has not yet treated the AGW and sought a rapid therapy with minimal side effect. The patient admitted a history of frequent sexual intercourse with their partner without using condoms. Similar complaints in the partner are unknown. The patient has no history of smoking, alcohol consumption, and drugs. She also complained of vaginal discharge. The patient is not pregnant, is not on immunosuppressive medications, and has no prior history of an allergic reaction to the MMR vaccine.

On physical examination, there were multiple skin-colored flat and verrucous papules, some discrete and some confluent, over the labia majora and vagina ranging from $0.3 \times 0.2 \times 0.2$ cm to $1.8 \times 0.5 \times 0.4$ cm (Figures 4A and 5A). There was no lymphadenopathy and ulceration on the genital. From the vaginal discharge examination, Gram-negative diplococci were identified, and cervical erosion was observed. HIV status along with serological test for syphilis, and hepatitis B were normal.

She was diagnosed with gonococcal cervicitis and treated with Cefixime 400 mg single dose and Azithromycin 1-gram single dose. For AGW, she received 0.5 mL of MMR solution (M-M-R[®] II 0.5 mL vial, Merck Sharp & Dohme Corp., New Jersey, USA) intralesional into the largest wart in perineum without a pre-sensitization test, once every three weeks with no other modalities. The lesion started to decrease in size and number at three weeks after the initial injection

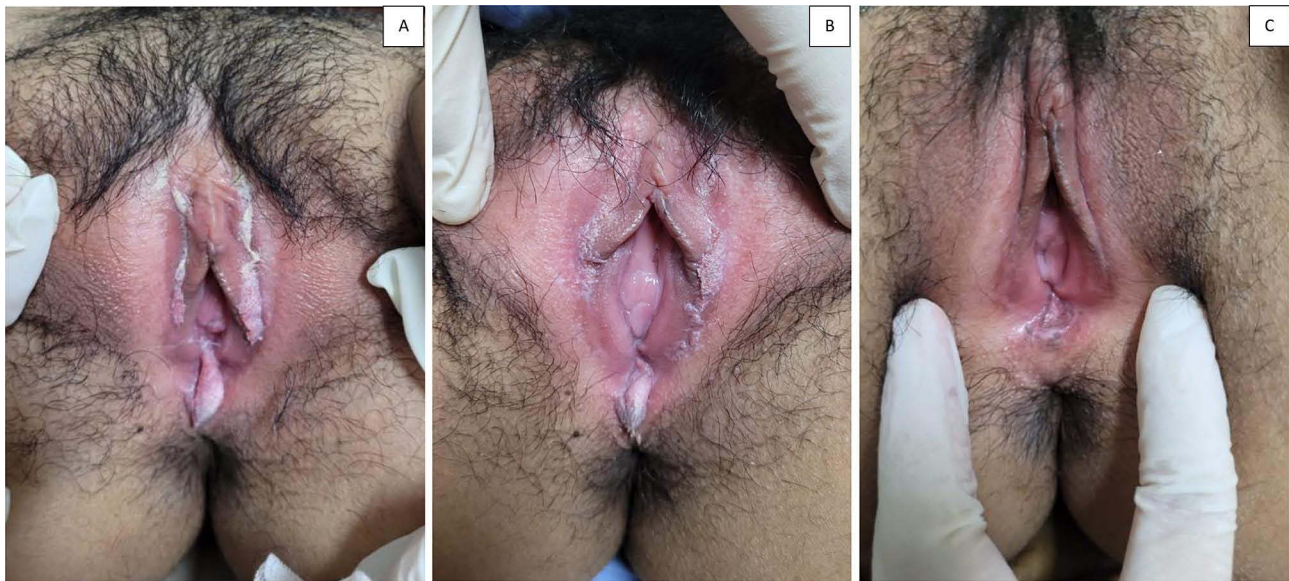


Figure 4 AGW in case two at labia majora and minora. **(A)** Before injection MMR; **(B)** 3 weeks after initial injection MMR; **(C)** 3 weeks after second injection of MMR.

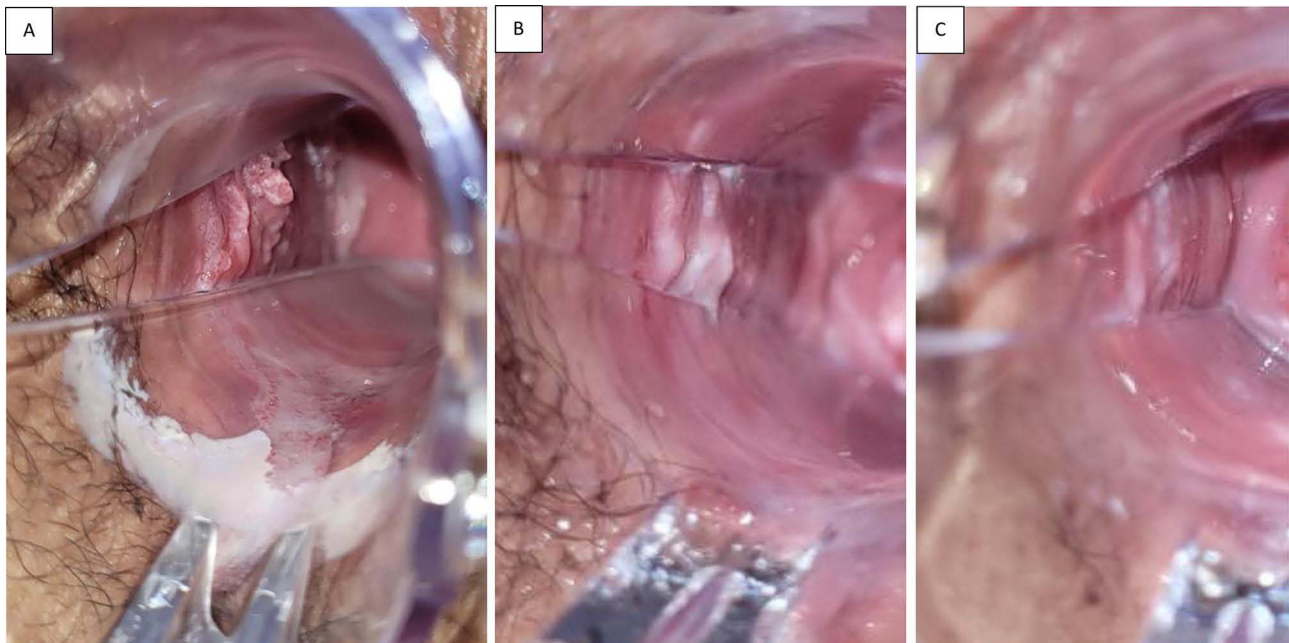


Figure 5 AGW in case two at introitus vagina. **(A)** Before injection of MMR; **(B)** 3 weeks after the first injection; **(C)** 3 weeks after the second injection.

(Figures 4B and 5B), and complete resolution was achieved three weeks after the second injection with no scar (Figures 4C and 5C).

Dermoscopy at the initial visit showed a finger-like pattern, while histopathological examination revealed stratified squamous epithelium with hyperplastic, papillomatous, parakeratosis, and koilocytosis (Figure 6), confirming the diagnosis of genital warts. The patient reported minimal side effects, consisting of mild pain (VAS 1/10) at the injection site. She no longer complained of vaginal discharge, and Gram-negative diplococci were no longer present. Unfortunately, the patient was lost to follow-up after the second injection.



Figure 6 Histopathological findings in case two, showing koilocytosis (yellow arrow).

Discussion

Anogenital warts are caused by a HPV infection.¹ More than 200 HPV types have been identified,³ with types 6 and 11⁴ being the cause in 90–95%¹ of AGW cases.⁵ HPV transmission can occur through both sexual and non-sexual routes. The sexual transmission routes include genito-genital, anogenital, and oral sex. HPV infection occurs when viral particles enter the basal cells through microtrauma in the epithelium. This attachment process is mediated by L1 and L2, allowing the viral genome to integrate into the host cell DNA and initiate viral replication.³

Currently, there is no specific and most ideal therapy for AGW. The MMR vaccine is one of the immunotherapies that can be considered as a treatment option. This vaccine is a live-attenuated vaccine primarily used to prevent measles, mumps, and rubella (German measles) with strong immunological stimulus. Mohta et al¹¹ suggested that the mechanism of action of the MMR vaccine as immunotherapy involves enhancing the T helper 1 (Th1) immune response, increasing tumor necrosis factor- α (TNF- α), interleukin-2 (IL-2), IL-4, IL-5, and interferon gamma (IFN- γ), as well as activating delayed-type hypersensitivity reactions to both MMR and HPV antigens, thereby stimulating the immune response to clear lesions even in distant areas from the injection site. In immunocompetent individuals, Th1 cells (CD4+) secrete various cytokines, including IFN- γ , IL-2, and IL-12. The IL-2 stimulates the maturation of cytotoxic T cells and enhances the cytotoxic activity of natural killer (NK) cells, which play a role in eliminating virus-infected cells.¹³

There are no established criteria for the indication of immunotherapy in AGW. Most immunotherapy is administered for recurrent, recalcitrant, extensive extragenital warts or for warts in difficult-to-treat locations, such as palmoplantar and periungual warts.¹⁴ Contraindications to MMR vaccination include hypersensitivity to MMR antigens, pregnancy, breastfeeding, active infections (ie herpes), tuberculosis, chronic diseases (ie diabetes mellitus), HIV infection, and patients on immunosuppressive drugs.¹⁵ A number of variables, including the duration, history, and active condition of the disease, as well as prior immunisations and the use of broad-spectrum antibiotics, may also affect how well the MMR vaccine works as a treatment. Achdiat et al¹⁶ reported a case of extensive anogenital and extragenital warts with a 5-year onset and a history of prior antibiotic use that showed a poor therapeutic response to 0.5 mL of MMR vaccine administered at three-week intervals. In another case, Achdiat et al¹⁷ also reported a case of AGW with a 6-month onset involving HPV type 16 (oncogenic) treated with 0.5 mL of MMR vaccine subcutaneously in the upper arm, which might contribute to the risk of therapy failure with the MMR vaccine.

The MMR vaccine has several benefits over alternative forms of treatment, including a low rate of recurrence, few adverse effects, and ease of administration.⁹ Several studies have been conducted to evaluate and compare the efficacy of the MMR vaccine in treating anogenital warts. In an open-label study, Sharma et al¹⁵ evaluated the use of 0.5 mL MMR vaccine in 35 AGW patients at three-week intervals. The results showed 98% response rate after nine weeks, following the third injection. Al-Qassabi et al⁹ reported two cases of extensive anogenital warts treated with the MMR vaccine at

higher doses, with a total of 0.6 mL in one case and 1.2 mL in the other case, administered at two-week intervals, followed by cryotherapy after the third session. The AGW achieve complete resolution without any reported side effects. Several previous studies have also used the MMR vaccine for cases of recalcitrant extragenital warts. Rezai et al¹³ administered intralesional MMR vaccine with varying doses based on the immune response, which was assessed through an immunocompetence test by injecting 0.1 mL of MMR vaccine intradermally in forearm. The MMR vaccine dosage was administered based on the results of induration and erythema observed after the immunocompetence test, with diameters of less than 20 mm, 20–40 mm, and more than 40 mm, corresponding to doses of 0.3, 0.2, and 0.1 mL of MMR vaccine, respectively. However, no pre-sensitization test was carried out before MMR injections for resistant extragenital warts in the study by Mohta et al.¹¹ A maximum of four intralesional injections of 0.2–0.3 mL of MMR were given into the biggest wart at intervals of two weeks. In both case reports, both patients received 0.5 mL of intralesional MMR vaccine.

The side effects of MMR vaccine injections are generally mild and temporary, such as injection site pain, swelling, and flu-like symptoms.¹⁸ Flu-like symptoms, potentially caused by inflammatory cytokines triggered by the vaccine antigens, have been identified as the most frequent side effect in prior studies on immunotherapy for warts.¹⁹ Awal et al²⁰ reported the side effects of MMR vaccine injections for extragenital warts as injection site pain (90%), flu-like symptoms (6%), and edema/erythema/itching (4%). In both cases, pain at the injection site was reported, with a VAS score of 1–2/10, but no flu-like symptoms were observed following the injection. At the three- and six-month follow-up, the first patient showed no signs of recurrence, while the second patient was lost to follow-up.

Conclusion

This case series highlights the potential of intralesional MMR vaccine as a safe and effective treatment option for AGW. Both cases demonstrated complete regression of lesions with minimal side effects and no recurrence during follow-up in the first case. The treatment protocol involved administering 0.5 mL of MMR vaccine intralesionally at intervals of three weeks, with a maximum of three therapy sessions, and was applied to lesions with a minimum size of 1 cm. While these findings are promising, the small sample size limits the generalizability of the results. Further studies with larger cohorts and comparative analyses with other treatment modalities are needed to validate efficacy and establish standardized protocols for the use of MMR vaccine in AGW therapy.

Abbreviations

AGW, anogenital warts; CDC, Centers for Disease Control and Prevention; HIV, Human immunodeficiency virus; HPV, *human papillomavirus*; IFN, interferon; IL, interleukin; MMR, measles, mumps, and rubella; NK, natural killer; STI, sexually transmitted infection; Th, T helper; TNF, tumor necrosis factor; TPHA, treponema pallidum hemagglutination assay; VDRL, venereal disease research laboratory.

Ethical Approval

This study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practices, local regulatory requirements, and was approved by the Medical Ethics Committee of Hasan Sadikin General Hospital Bandung (approval number DP.04.03/D.XIV.6.5/79/2025).

Consent for Publication

Both patients signed informed consent forms. They also signed forms giving consent for the use of cases details and images for publication and for scientific purposes.

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Disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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