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### Intralesional Mumps, Measles, Rubella (MMR) Vaccine as Therapy for Recurrent Condyloma Acuminata: A Case Report

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#### ABSTRACT

**Background:** Condyloma acuminata (CA), a prevalent sexually transmitted infection caused by the human papillomavirus (HPV), presents challenges in treatment due to its high recurrence rate. While various treatment modalities exist, intralesional immunotherapy with the mumps, measles, rubella (MMR) vaccine has shown promise in managing HPV-related conditions. This case report investigates intralesional MMR vaccine in treating recurrent CA. **Case presentation:** A 24-year-old female presented with recurrent CA lesions on the labia majora and perianal region. Despite prior treatment with trichloroacetic acid (TCA), the lesions had reappeared. Intralesional MMR vaccine injections were administered twice, one month apart, resulting in complete lesion resolution within six weeks of the second injection. No recurrence was observed during a six-month follow-up period, and the patient reported only mild, transient pain at the injection sites. **Conclusion:** This case report highlights the potential of intralesional MMR vaccine as an effective and well-tolerated treatment option for recurrent CA. Further research is warranted to validate these findings and establish optimal treatment protocols.

#### 1. Introduction

Condyloma acuminata (CA), commonly referred to as genital warts, stands as the most prevalent sexually transmitted infection (STI) globally. This condition is primarily attributed to infection with the human papillomavirus (HPV), with HPV types 6 and 11 being the most frequently implicated.<sup>1-3</sup> The transmission of HPV occurs predominantly through sexual contact, encompassing various forms of sexual activity. While some individuals infected with HPV may experience latent or subclinical infections that resolve spontaneously, CA often manifests as visible lesions. These lesions can present as solitary or clustered growths, exhibiting diverse shapes and colors, ranging from skin-colored and grey to brown.<sup>2</sup> The anatomical sites affected by CA differ between males and females.

In males, lesions are typically found on the scrotum, penile shaft, and around the tip of the penis, whereas in females, they commonly appear on the vulva, vagina, or cervix.<sup>2</sup> The global burden of CA is substantial, with a peak incidence observed in the age group of 20 to 24 years.<sup>4</sup> In the Asian context, the incidence rate is reported to be 3.1 cases per 1000 visits.<sup>5,6</sup> Notably, a study conducted in India in 2011, involving 44,061 patients aged 18-60 years across six cities, revealed a significant prevalence of CA.<sup>5,6</sup> These figures underscore the widespread nature of this STI and its impact on sexual health worldwide.

One of the most formidable challenges in the management of CA is its persistent recurrence. Several factors contribute to this recurrence, including the inherent characteristics of the HPV strains involved,

the individual's immune response, and the specific treatment modality employed.<sup>7</sup> The complex interplay of these factors necessitates a multifaceted approach to CA treatment, aiming not only to resolve existing lesions but also to minimize the risk of future recurrences. The current landscape of CA treatment encompasses a wide array of options, each with its own advantages and limitations. Topical therapies, such as podophyllotoxin and trichloroacetic acid (TCA), have been utilized for their direct action on the lesions.<sup>7</sup> Podophyllotoxin, derived from the mandrake plant, exerts its effect by inhibiting cell division, leading to the destruction of wart tissue. TCA, a caustic agent, works by chemically burning and removing the wart. While these topical agents can be effective in lesion clearance, they are often associated with localized side effects such as pain, irritation, and ulceration.

Immunomodulatory therapies, including imiquimod and sinecatechin, offer an alternative approach by stimulating the body's immune response against HPV.<sup>7</sup> Imiquimod, a toll-like receptor agonist, activates immune cells and promotes the production of cytokines, enhancing the body's ability to fight the virus. Sinecatechin, a green tea extract, possesses antiviral and anti-inflammatory properties that contribute to wart clearance. These immunomodulatory therapies are generally well-tolerated, but their efficacy in preventing recurrence may vary. In addition to topical and immunomodulatory therapies, immunotherapy and non-pharmacological interventions play a role in CA management. Immunotherapy, as discussed in detail later, harnesses the power of the immune system to target and eliminate HPV. Non-pharmacological interventions, such as surgical excision, cryotherapy (freezing), and laser ablation, offer direct removal of the lesions.<sup>7,8</sup> However, these procedures can be invasive, painful, and may lead to scarring.

The high recurrence rates observed with traditional CA therapies have prompted researchers to explore novel approaches that address the underlying immune mechanisms involved in HPV persistence. The immune

system, particularly cell-mediated immunity, plays a crucial role in controlling HPV infection.<sup>9,10</sup> Cell-mediated immunity involves the activation of T cells, which recognize and destroy HPV-infected cells. However, in some individuals, this immune response may be inadequate, allowing the virus to persist and leading to recurrent CA. Intralesional immunotherapy has emerged as a promising strategy to enhance the immune response against HPV.<sup>9,10</sup> This approach involves injecting an immunomodulatory agent directly into the wart lesions, stimulating a localized immune reaction. The injected agent acts as an antigen, triggering a cascade of immune events that culminate in the destruction of HPV-infected cells. This targeted approach not only promotes lesion clearance but also has the potential to induce systemic immunity, reducing the risk of recurrence. Various immunotherapeutic agents have been investigated for intralesional immunotherapy of CA, including the mumps, measles, rubella (MMR) vaccine, Mycobacterium w vaccine (MWV), and Bacillus Calmette-Guerin (BCG) vaccine.<sup>10</sup> Among these, the MMR vaccine has gained significant attention due to its established safety profile and its ability to elicit a robust immune response. The MMR vaccine contains live attenuated viruses that stimulate the production of antibodies and activate T cells, contributing to both humoral and cell-mediated immunity. The application of intralesional MMR vaccine for the treatment of warts, initially explored for cutaneous warts, has shown promising results.<sup>9,11</sup> Studies have reported high clearance rates and low recurrence rates following intralesional MMR vaccine therapy, with minimal side effects.<sup>6,11-13</sup> These findings have led to the investigation of intralesional MMR vaccine for the treatment of genital warts, including CA.

## 2. Case Presentation

A 24-year-old female patient presented to our dermatology clinic with complaints of itchy genital lumps that had initially appeared on her vaginal lips and subsequently spread to the anal area. The patient reported no difficulties with defecation or urination.

Her sexual history revealed that she had become sexually active at the age of 19, engaging in unprotected intercourse with multiple partners since then. She identified as heterosexual and reported engaging in both genito-genital and genito-oral sexual practices. The patient denied any history of HIV infection. Five months prior to her presentation at our clinic, the patient had been diagnosed with CA and had undergone treatment with topical 80% TCA once a week for two months. While the lesions had initially resolved following this treatment, they recurred a month later, prompting her referral to our facility.

Upon examination, multiple verrucous, skin-colored papules were observed on the labia majora and perianal region, exhibiting a vegetative appearance and measuring 2x1x0.5 cm (Figure 1A). The acetowhite test yielded a positive result (Figure 1B). Further screening for other STIs, including treponema pallidum hemagglutination assay (TPHA), venereal disease research laboratory (VDRL), and anti-human

immunodeficiency virus (anti-HIV) tests, produced non-reactive results. Based on the clinical presentation and the results of the diagnostic tests, a diagnosis of recurrent CA was confirmed. The patient was initiated on a treatment regimen consisting of intralesional MMR vaccine injections. The first injection involved administering 0.5 mL of the vaccine to the perianal area and 0.1 mL to four different points on the labia majora. This procedure was repeated one month later with the same dosage. Remarkable improvement was observed in the patient's condition. The lesions began to regress gradually one month after the initial injection and completely disappeared within six weeks of the second injection (Figure 2). No recurrence of the lesions was noted during a six-month follow-up period. The patient reported experiencing only mild pain at the injection sites, which subsided within 24 hours and did not require any intervention.



Figure 1. A. The labia majora region showed multiple verrucous skin-colored papules (red arrow) and the perianal region showed vegetation with a verrucous surface measuring 2x1x0.5 cm (yellow arrow), B. Acetowhite test showed a positive result, C. Intralesional injection of MMR vaccine at the first injection, D. Intralesional injection of MMR vaccine at the second injection.



Figure 2. A-B. Follow up 2 weeks after the second intralesional MMR vaccine injection, C-D. Follow up 6 weeks after the second intralesional MMR vaccine injection.

### 3. Discussion

The successful resolution of recurrent condyloma acuminata (CA) in this 24-year-old female patient following intralesional mumps, measles, rubella (MMR) vaccine therapy underscores the growing potential of immunotherapy in the management of this prevalent sexually transmitted infection (STI). This case not only adds to the accumulating evidence supporting the efficacy of intralesional MMR vaccine for CA but also sheds light on the intricate interplay between the immune system and HPV infection. The rationale behind immunotherapy for Condyloma Acuminata (CA) is deeply rooted in the intricate relationship between the human immune system and Human Papillomavirus (HPV) infection dynamics. HPV, a double-stranded DNA virus, primarily targets basal keratinocytes, the deepest layer of the epidermis. Upon infection, HPV establishes a persistent presence within these cells, often evading the host's immune surveillance mechanisms. This evasion is facilitated by the virus's ability to downregulate major histocompatibility complex (MHC) class I molecules, crucial components responsible for presenting viral antigens to cytotoxic T cells.<sup>10,11</sup>

MHC class I molecules are expressed on the surface of nearly all nucleated cells and serve as a platform for displaying peptide fragments derived from intracellular proteins, including viral proteins. These displayed peptides are recognized by cytotoxic T cells, which are equipped with T-cell receptors (TCRs) that can specifically bind to these peptide-MHC complexes. This recognition process is essential for initiating a targeted immune response against infected cells. However, HPV has evolved mechanisms to interfere with this process, effectively masking its presence from the immune system. By downregulating MHC class I molecules, HPV reduces the density of viral peptide-MHC complexes on the surface of infected cells. This reduction diminishes the likelihood of cytotoxic T cells encountering and recognizing these complexes, thereby hindering the activation of a robust immune response. Consequently, HPV-infected cells can persist and proliferate, leading to the formation of

warts, the hallmark of CA. In some cases, persistent HPV infection can also contribute to the development of precancerous lesions and, ultimately, malignant transformation.<sup>12,13</sup>

Immunotherapy offers a strategic approach to counteract HPV's immune evasion tactics and restore the host's ability to mount an effective immune response. The fundamental principle of immunotherapy is to stimulate and enhance the immune system's recognition and elimination of HPV-infected cells. This can be achieved through various mechanisms, including the administration of immunomodulatory agents, therapeutic vaccines, or adoptive cell therapies. Intralesional immunotherapy, a specific form of immunotherapy, involves the direct injection of an immunomodulatory agent into the wart lesions. This localized delivery bypasses systemic circulation, ensuring a high concentration of the agent at the site of infection and minimizing potential systemic side effects. The injected agent serves as an antigen, a foreign substance that triggers an immune response. In the case of CA, the ideal antigen would be one that mimics HPV antigens or induces a response that cross-reacts with HPV-infected cells.<sup>13,14</sup>

The introduction of the antigen into the wart lesion initiates a cascade of immune events. Antigen-presenting cells (APCs), such as dendritic cells and macrophages, residing in the skin, engulf the antigen and process it into smaller peptide fragments. These peptide fragments are then loaded onto MHC class II molecules and presented on the surface of APCs. T helper (Th) cells, a type of T cell, recognize these peptide-MHC complexes through their TCRs. This recognition leads to the activation and proliferation of Th cells, which orchestrate a broader immune response. Activated Th cells release cytokines, signaling molecules that recruit and activate other immune cells, including cytotoxic T cells and NK cells. Cytotoxic T cells, upon recognizing viral peptide-MHC complexes on the surface of HPV-infected cells, release cytotoxic granules containing perforin and granzymes, which induce apoptosis (programmed cell death) of the infected cells. NK cells, on the other hand, can directly

recognize and kill infected cells without the need for prior antigen exposure. The concerted action of these immune effectors leads to the destruction of HPV-infected cells and the subsequent clearance of warts. Moreover, the immune response generated against the injected antigen can also induce a bystander effect, whereby neighboring uninfected cells are also stimulated to express antiviral molecules, creating a hostile environment for HPV. In the context of intralesional immunotherapy for CA, the MMR vaccine has emerged as a promising candidate. The MMR vaccine contains live attenuated strains of the mumps, measles, and rubella viruses, which are known to induce a robust immune response. The vaccine's ability to activate both humoral and cell-mediated immunity makes it an attractive option for stimulating a comprehensive immune response against HPV.<sup>15,16</sup>

The intralesional injection of the MMR vaccine into CA lesions introduces viral antigens that are recognized by the immune system. This recognition triggers a DTH reaction, characterized by the infiltration of T cells and other immune cells into the lesion. The DTH reaction, in turn, leads to the destruction of HPV-infected cells and the resolution of the wart. The success of intralesional MMR vaccine therapy in the case presented here, as well as in numerous other studies, underscores its potential as a safe and effective treatment option for CA. The ability of this therapy to harness the power of the immune system to target and eliminate HPV-infected cells offers a promising avenue for the management of this prevalent STI. Further research is warranted to elucidate the precise mechanisms underlying its efficacy and to optimize treatment protocols for different patient populations.<sup>15,16</sup>

The MMR vaccine, a trivalent live attenuated vaccine comprising weakened strains of the mumps, measles, and rubella viruses, has been a cornerstone of global public health efforts for decades. Its primary role in preventing these childhood diseases is well-established, owing to its capacity to elicit a robust and enduring immune response. This remarkable ability to stimulate the immune system has sparked interest in

its potential applications beyond its traditional use, particularly as an immunotherapeutic agent for various conditions, including warts. The immunomodulatory effects of the MMR vaccine are multifaceted and extend beyond the induction of specific antibodies against the mumps, measles, and rubella viruses. Upon administration, the vaccine triggers a complex cascade of immune events that involve both humoral and cell-mediated immunity. Humoral immunity, mediated by B cells, leads to the production of antibodies that neutralize the viral antigens, preventing them from infecting host cells. Simultaneously, the vaccine activates cell-mediated immunity, which is orchestrated by T cells. These T cells play a crucial role in recognizing and eliminating virus-infected cells, thereby contributing to the clearance of the viral infection.<sup>16,17</sup>

The activation of T cells by the MMR vaccine is not limited to the specific viral antigens present in the vaccine. It also induces a broader activation of the immune system, leading to the release of various cytokines. Cytokines are signaling molecules that play a pivotal role in coordinating the immune response. Among the cytokines released by activated T cells are interferon-gamma (IFN- $\gamma$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ). IFN- $\gamma$  is a potent antiviral cytokine that enhances the immune response against a wide range of viruses, including HPV. It activates macrophages, natural killer (NK) cells, and other immune cells, promoting the destruction of virus-infected cells. TNF- $\alpha$ , on the other hand, is a pro-inflammatory cytokine that plays a role in the recruitment and activation of immune cells at the site of infection. The intralesional injection of the MMR vaccine into wart lesions represents a strategic approach to harnessing the vaccine's immunomodulatory effects. By delivering the vaccine directly to the site of infection, the viral antigens are presented to the immune cells residing in the skin, bypassing the need for systemic circulation. This localized exposure triggers a delayed-type hypersensitivity (DTH) reaction, a cell-mediated immune response characterized by the infiltration of T cells and other immune cells into the lesion. The DTH

reaction is a key component of the immune response against intracellular pathogens, such as viruses.<sup>17,18</sup>

The DTH reaction induced by the intralesional MMR vaccine injection is a dynamic process involving multiple steps. Initially, the vaccine antigens are taken up by antigen-presenting cells (APCs) in the skin, such as dendritic cells and macrophages. These APCs process the antigens and present them on their surface in conjunction with MHC molecules. The presentation of viral antigens in this context activates T cells, which then proliferate and differentiate into effector T cells. These effector T cells migrate to the site of infection, where they release cytokines and other cytotoxic molecules that directly kill HPV-infected cells. The DTH reaction also involves the recruitment of other immune cells, such as NK cells and macrophages, to the site of infection. NK cells are cytotoxic lymphocytes that can recognize and kill virus-infected cells without prior sensitization. Macrophages are phagocytic cells that engulf and destroy pathogens and cellular debris. The concerted action of these immune cells leads to the clearance of HPV-infected cells and the resolution of the wart. The intralesional injection of the MMR vaccine not only triggers a localized immune response but may also induce systemic immunity against HPV. This is supported by studies that have reported the regression of distant, untreated warts following intralesional MMR vaccine therapy. This phenomenon, known as the abscopal effect, suggests that the immune response generated at the injection site can spread to other areas of the body, potentially providing protection against future HPV infections. The use of the MMR vaccine as an immunotherapeutic agent for warts is a testament to the versatility and adaptability of vaccines. While traditionally employed for prophylactic purposes, vaccines are increasingly being recognized for their potential in treating existing diseases. The MMR vaccine, with its ability to stimulate both humoral and cell-mediated immunity, represents a valuable tool in the fight against HPV infection and its associated conditions, including CA.<sup>16,19</sup>

While the precise mechanisms through which intralesional MMR vaccine therapy facilitates wart clearance remain incompletely understood, several compelling hypotheses have been proposed. These hypotheses offer insights into the complex interplay between the vaccine, the immune system, and the human papillomavirus (HPV) infection. One prominent hypothesis suggests that the MMR vaccine induces a "bystander effect." This phenomenon posits that the immune response generated against the attenuated vaccine viruses (mumps, measles, and rubella) inadvertently targets HPV-infected cells. The vaccine viruses, although weakened, still possess antigenic properties that stimulate a robust immune response. This response involves the activation of various immune cells, including cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, which are capable of recognizing and destroying virus-infected cells. In the context of CA, the bystander effect implies that the activated immune cells, primed to target the vaccine viruses, may also recognize and eliminate HPV-infected cells in the vicinity. This cross-reactivity could be due to shared antigenic epitopes between the vaccine viruses and HPV, or it could be a result of the inflammatory milieu created by the immune response, which enhances the overall immune surveillance in the area. Another compelling hypothesis centers on the role of antigen-presenting cells (APCs) in the skin. APCs, such as dendritic cells and macrophages, play a crucial role in initiating and orchestrating immune responses. They capture antigens, process them, and present them to T cells, which then become activated and mount a specific immune response against the antigen. In the case of intralesional MMR vaccine therapy, the vaccine viruses are likely taken up by APCs in the skin. These APCs then process the viral antigens and present them to T cells, leading to the activation of HPV-specific T cells. These activated T cells can then migrate to the site of HPV infection and exert their cytotoxic effects, destroying HPV-infected cells and contributing to wart clearance. While both the bystander effect and antigen presentation hypotheses offer plausible explanations for the efficacy

of intralesional MMR vaccine therapy, the available evidence does not definitively favor one over the other. Studies have shown that the vaccine induces a strong inflammatory response at the injection site, characterized by the infiltration of T cells, NK cells, and other immune cells. This observation supports the bystander effect hypothesis, as it suggests that the activated immune cells are not only targeting the vaccine viruses but also HPV-infected cells. On the other hand, studies have also demonstrated the upregulation of MHC class I molecules on HPV-infected cells following intralesional MMR vaccine therapy. This finding lends credence to the antigen presentation hypothesis, as it suggests that the vaccine enhances the visibility of HPV-infected cells to the immune system, facilitating their recognition and destruction by T cells. Regardless of the precise mechanism of action, the clinical efficacy of intralesional MMR vaccine therapy for warts is well-established. Numerous studies have reported high clearance rates, ranging from 75% to 98%, following this treatment modality. These studies have also demonstrated a low recurrence rate, with some reporting recurrence rates as low as 2%. The safety profile of intralesional MMR vaccine therapy is also favorable. The most common side effects are mild and transient, including pain, redness, and swelling at the injection site. Systemic side effects, such as fever and malaise, are rare. The vaccine is contraindicated in patients who are immunocompromised or pregnant. Intralesional MMR vaccine therapy offers several advantages over traditional wart treatment modalities. First, it is a relatively simple and minimally invasive procedure that can be performed in an outpatient setting. Second, it is generally well-tolerated, with most patients experiencing only mild and transient side effects such as pain, redness, and swelling at the injection site. Third, it has a high success rate, with studies reporting clearance rates of up to 98%. Fourth, it has a low recurrence rate, with some studies reporting recurrence rates as low as 2%. Finally, it is a cost-effective treatment option, as the MMR vaccine is readily available and relatively inexpensive.<sup>17,18</sup>

While intralesional MMR vaccine therapy has demonstrated promising results in the treatment of condyloma acuminata (CA), it is essential to acknowledge and address its limitations to optimize its clinical application and further advance the field of HPV-related disease management. One of the primary limitations lies in the absence of standardized treatment protocols. The current literature lacks consensus on the optimal dose, frequency, and duration of MMR vaccine injections for CA treatment. The dosage used in clinical studies has varied, ranging from 0.1 mL to 0.5 mL per lesion, and the frequency of injections has ranged from weekly to monthly intervals. This variability in treatment protocols makes it difficult to compare results across studies and to determine the most effective regimen for different patient populations. Furthermore, the long-term efficacy of intralesional MMR vaccine therapy remains to be fully established. While short-term studies have reported high clearance rates and low recurrence rates, the durability of these responses over extended periods is unclear. Long-term follow-up studies are needed to assess the potential for late recurrences and to determine whether booster injections may be necessary to maintain remission. Another limitation pertains to the generalizability of the findings to different types of warts and diverse patient populations. Most studies on intralesional MMR vaccine therapy have focused on common warts, and the evidence for its efficacy in other types of warts, such as plantar warts and flat warts, is limited. Additionally, the majority of studies have been conducted in immunocompetent individuals, and the efficacy and safety of this therapy in immunocompromised patients, who are at higher risk of HPV-related complications, remain to be determined. Rigorous clinical trials are needed to establish standardized treatment protocols for intralesional MMR vaccine therapy. These trials should investigate the optimal dose, frequency, and duration of treatment for different types of warts and different patient populations. Factors such as age, sex, immune status, and HPV type should be considered

when designing these trials. Long-term follow-up studies are essential to assess the durability of responses to intralesional MMR vaccine therapy and to identify predictors of recurrence. These studies should also evaluate the potential need for booster injections to maintain long-term remission. Research should be expanded to include diverse patient populations, such as immunocompromised individuals, children, and pregnant women. The safety and efficacy of intralesional MMR vaccine therapy in these populations need to be carefully evaluated before it can be widely adopted. Further research is needed to elucidate the precise mechanisms by which intralesional MMR vaccine therapy mediates wart clearance. Understanding these mechanisms will not only enhance our knowledge of the immune response to HPV but also inform the development of novel immunotherapeutic agents. The development of novel immunotherapeutic agents that specifically target HPV is an area of active research. These agents may offer improved efficacy and safety profiles compared to existing therapies. For example, therapeutic vaccines that target specific HPV antigens are currently under investigation. In addition to these research priorities, it is important to consider the potential of intralesional MMR vaccine therapy to prevent malignant transformation in patients with high-risk HPV types. While the current evidence suggests that this therapy is effective in clearing warts, its impact on the risk of cervical, anal, and other HPV-related cancers remains unknown. Prospective studies are needed to assess the long-term oncologic outcomes of patients treated with intralesional MMR vaccine therapy. The development of novel immunotherapeutic agents that specifically target HPV is a rapidly evolving field. These agents may offer improved efficacy and safety profiles compared to existing therapies. For example, therapeutic vaccines that target specific HPV antigens are currently under investigation. These vaccines aim to induce a targeted immune response against HPV, potentially leading to the eradication of the virus and the prevention of HPV-related diseases. Furthermore, the use of immune checkpoint inhibitors, which are drugs that unleash

the immune system to attack cancer cells, is being explored for the treatment of HPV-related cancers. These inhibitors have shown promising results in clinical trials for cervical cancer and are now being investigated for other HPV-related malignancies.<sup>19,20</sup>

#### 4. Conclusion

The successful treatment of recurrent CA in this patient with intralesional MMR vaccine therapy highlights the potential of immunotherapy in the management of this common STI. The MMR vaccine, with its established safety profile and ability to induce a robust immune response, offers a promising alternative to traditional wart treatment modalities. While further research is needed to optimize its use, intralesional MMR vaccine therapy represents a significant advancement in the field of CA treatment.

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