Intralesional Measles-Mumps-Rubella Vaccine for Genital Warts

A report of two cases with review of literature

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Abstract
Genital warts are caused by several strains of Human Papilloma Viruses (HPVs). Although asymptomatic in most cases, they can be psychologically and physically distressing for patients. Recently, Intralesional immunotherapy by different antigens like Bacille Calmette–Guerin vaccine, candida antigen, and measles, mumps, and rubella (MMR) vaccine has shown promising efficacy in the treatment of warts. Here we report two cases in Omani males who presented to the dermatology clinic at Barka Poly clinic with recalcitrant genital warts that resolved completely with intralesional injection of MMR vaccine.

Keywords: Genital Warts; immunotherapy; Measles-Mumps-Rubella Vaccine; Venereal Warts; Oman

Introduction
Genital warts, also known as anogenital warts and condylomata acuminata, are fleshy growths affecting the genital and anal area and are caused by the human papilloma viruses (HPVs). More than 200 HPV subtypes have been identified, with HPV subtypes 6 and 11 being considered low risk, while subtypes HPV 16 and 18 are considered high risk as they are associated with cervical dysplasia.1 Genital warts are
transmitted through sexual contact, but vertical transmission and autoinoculation have also been reported.\textsuperscript{2,3}

The treatments for genital warts focus on removing the warty growths, rather than eradicating the virus. Many treatment modalities are available: topical agents (such as imiquimod ointment); destructive methods (cryotherapy or lasers); and immunomodulators (e.g. interferon). Recently, immunotherapy with intralesional agents such as the measles-mumps-rubella (MMR) vaccine, purified protein derivative (PPD), and the Bacillus Calmette-Guérin (BCG) vaccine have been shown to be efficient with good tolerability in the treatment of warts, especially refractory ones.\textsuperscript{4} Here we report two cases of recalcitrant genital warts that were treated successfully with intralesional immunotherapy using the MMR vaccine, along with a review of literature for the use of this treatment method on genital warts.

Case One
A 23-year-old man presented to the skin clinic with multiple papules over the groin area lasting for more than 2 months. He noted that the lesions were getting bigger and increasing in size.

Upon examination, there were multiple skin-colored flat and verrucous papules coalescing into plaques over the pubic area and shaft of the penis (Fig. 1a). The Koebner phenomenon was also observed, some of the lesions appeared in a linear fashion due to hair removal with a razor. Laboratory investigations were negative for HIV, VDRL, TPHA, hepatitis C and hepatitis B surface antigen. The patient was diagnosed with genital warts based on the typical clinical presentation.

A plan of treatment was discussed with the patient and he agreed to try cryotherapy at 2 week intervals with KOH 5% solution application at home twice daily. After 6 sessions, there was no significant improvement and so the patient was offered ablative radiofrequency. Two sessions were performed one month apart but he had a recurrence after a few weeks. Finally, an intralesional MMR injection was offered considering prior vaccination with MMR as per the national program, and two biggest warts were chosen to be injected with 0.3ml of MMR solution (M-M-R\textsuperscript{®} II 0.5ml vial, by Merck Sharp & Dohme Corp., NJ, USA), once every 2 weeks with no other
modalities of treatment. A total of four sessions were required to achieve complete resolution of warts without any reported side effects (Fig.1b). To enhance the efficacy, the patient was given two sessions of cryotherapy after the 3rd session of intralesional MRR. There was no recurrence on follow up after 3 and 6 months.

Case Two
A 25-year-old man presented to the skin department with extensive anogenital warts for more than 18 months (Fig. 2a). He was seen in different skin clinics and had received multiple treatments, including topical imiquimod cream 5%, cryotherapy sessions, electrocautery and radiofrequency treatments with no successful results as the warts were reoccurring.

The patient was counselled on potential treatment using immunotherapy via MMR injections as he was already vaccinated with the same as per national program, and he agreed. Prior to the injection, he was investigated for HIV, HBsAg, HCV, ANA, TPHA and VDRL which were negative. The patient was given a total of 7 sessions of MMR injections (M-M-R® II 0.5ml vial, by Merck Sharp & Dohme Corp., NJ, USA), 2 weeks apart, 4 sites injected in each session, 0.3ml of MMR per site. In addition, the patient started cryotherapy after the 3rd session of MMR injections, once every 2 weeks, receiving a total of 5 sessions. The patient had significant improvement after completing the course of treatment with no reported side effects (Fig. 2b). There was no recurrence at 8 week follow up and most of the inflammation marks were resolved.

Discussion
Several treatments for genital warts are available including medical agents (e.g. imiquimod cream and podophyllotoxin), destructive methods (e.g. cryotherapy, electrocautery, and lasers) or surgical excision. These options are limited by a high rate of recurrence and side effects, such as pain and scarring. Immunotherapy is becoming more popular for the treatment of warts, especially for genital and refractory warts. Commonly used agents include the MMR vaccine, PPD, the BCG vaccine and the Candida antigen. Among these, the MMR vaccine and PPD have been shown to be the most effective in achieving complete primary and long term recovery, reducing the recurrence rate at the same site compared with cryotherapy and other immunotherapeutic modalities. Additionally, combining intralesional immunotherapy
with a destructive method may enhance the efficacy and reduce treatment duration.\textsuperscript{6} There are no clear guidelines on when to use immunotherapy but it is generally used on extensive, recurrent and refractory warts in difficult to treat areas, such as the periungual area.\textsuperscript{4}

The exact mechanism of intralesional immunotherapy is not entirely understood. Postulated mode of action include release of different immunoregulatory cytokines such as interleukins 2 and 12 and interferon-c that stimulate a strong immune response against HPV.\textsuperscript{7} Furthermore, antigen injection is associated with proliferation of peripheral blood mononuclear cells that promotes T-helper 1 cytokine responses to eradicate HPV-infected cells.\textsuperscript{8} It is used to treat genital warts at a dose of 0.3 to 0.5ml, injected into the biggest wart at 3 weeks interval.

To date, there are no randomized clinical trials evaluating the efficacy of intralesional MMR vaccines in the treatment of genital warts nor clear guidelines as to when to use them. A review of the literature conducted in December 2020 showed a dearth of research evaluating the use of MMR vaccines to treat genital warts (table 1). In an open-label study, Sharma \textit{et al.} evaluated the use of the MMR vaccine on 35 patients using a 0.5ml dose given at 3 weeks interval.\textsuperscript{9} The treatment response rate was nearly 98\% after a period of nine weeks. Meena \textit{et al.} reported two cases of genital warts that had an excellent response to a 0.5ml intralesional injection of the MMR vaccine at a similar interval.\textsuperscript{10} Side effects were minimal and temporary, however, with flu-like symptoms being the most common side effect reported from studies of intralesional MMR vaccines to treat extra-genital warts.\textsuperscript{11} In the current cases, we used a slightly higher dose of the MMR vaccine, as the patients had extensive bilateral warts. We also used a combination of destructive methods with cryotherapy to enhance the resolution of stubborn lesions.

Till date intralesional MMR vaccine is not routinely used for genital warts. The present cases with previous few reports draws attention for further randomized clinical trials to establish the potential role of MMR vaccine immunotherapy in the management of anogenital warts. Compared with current modalities of treatments; MMR vaccines offers low recurrence, less side effects and an easy to use therapeutic method.
Conclusion
Intralesional immunotherapy with the MMR vaccine seems to be a safe and effective treatment modality for recalcitrant genital warts and can save the patients and doctors a long treatment time, noted using other methods. Further large sample studies are needed to establish this modality of treatment for genital warts.

Declaration of patient consent: The authors certify that they have obtained all appropriate patients’ consent. The patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgment: We would like to thank the patients for giving consent to publish the cases.

Conflict of interest: None

Authors’ Contributions
AQ and FF were involved in the literature review process. AQ wrote the manuscript. FF contributed with the evaluation of the cases. Both authors approved the final version of the article.

References


Figure 1: (A) A 23 years old male with genital warts before treatment with intralesional MMR. (B) After 4th session showing complete regression with post-inflammatory hypopigmentation.

Figure 2: (A) A 25 years old male with extensive genital warts. (B) Complete resolution after 7 sessions of intralesional MMR injection.

Table 1: Summary of published literatures for the use of intralesional MMR in genital warts

<table>
<thead>
<tr>
<th>Study type</th>
<th>No. of patients</th>
<th>Dose and number of MMR sessions</th>
<th>combination treatment used</th>
<th>Result</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Meena et al.⁹</td>
<td>Case report</td>
<td>2</td>
<td>0.5 ml into biggest wart every three weeks</td>
<td>Complete response for 1st patient after 2 sessions, 2nd patient had almost complete response</td>
<td>Pain during procedure</td>
</tr>
<tr>
<td>Sharma et al. ⁸</td>
<td>Open label study</td>
<td>35</td>
<td>0.5 ml into biggest wart every three weeks for a maximum of three injections</td>
<td>Nill</td>
<td>98% improvement at nine weeks</td>
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<tr>
<td>Present cases</td>
<td>Case report</td>
<td>2</td>
<td>Case 1: Total of 0.6 ml of MMR every two weeks</td>
<td>Cryotherapy</td>
<td>Complete resolution after 4 and 7 sessions for case 1 &amp; 2 respectively</td>
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