Original Article

Retrospective Analysis of Treatment of Cutaneous Warts with Measles, Mumps, and Rubella Immunotherapy Over 8 Years

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Abstract

Introduction: Warts are benign lesions caused by human papilloma virus. Various types of cutaneous warts include verruca vulgaris, genital warts, and palmoplantar warts. Various therapeutic modalities are available for warts with varying response. These include destructive therapies, cytotoxic agents (Bleomycin), and immunotherapy (measles, mumps, and rubella [MMR], candida antigen, etc.). We have analyzed the efficacy of intralesional MMR immunotherapy in patients with different kinds of cutaneous warts. **Aim:** The purpose of this study was to retrospectively analyze the effectiveness and safety of MMR immunotherapy in the treatment of different kinds of cutaneous warts. **Materials and Methods:** We included all the patients with cutaneous warts receiving MMR vaccine between March 2014 and March 2022. Demographic data were recorded. MMR vaccine was given for four doses at 3 weeks interval or till there was complete clearance, whichever was earlier. Clearance and reduction of wart sizes and potential side effects were recorded. **Results:** A total of 184 patients were enrolled, and 45% patients were women. Predominant age group of patients was 21–40 years. Most common types of warts observed was palmoplantar warts. Complete resolution was seen in 66% patients and partial response in 22% patients. Palmo-plantar and warts on extremities responded completely to immunotherapy, whereas 43% of genital warts had no improvement. Pain at injection site was observed in all patients, and 32% patients had flu-like symptoms. **Conclusions:** Immunotherapy with MMR vaccine shows a promising response in the treatment of palmo-plantar warts and warts on extremities, without any serious adverse effect, whereas the genital warts and verruca plana respond variably to immunotherapy.

Keywords: Cutaneous warts, immunotherapy, MMR, verruca, verruca plana, verruca vulgaris

New Learning Points

1. Immunotherapy with intralesional MMR vaccine is a safe and effective mode of therapy for cutaneous warts over palmo-plantar aspects and the extremities.
2. Genital warts respond poorly to the immunotherapy.

Introduction

Cutaneous warts occur commonly in children and young adults and are more common among certain occupations such as handlers of meat, poultry, and fish.[1] Human papillomaviruses (HPV) infect epithelial tissues of skin and mucous membranes and manifest as warts.[2] There are over 150 distinct HPV subtypes; some tend to infect specific body sites and produce characteristic proliferative lesions at those sites. Spontaneous remission of warts occurs in up to two-thirds of patients within 2 years.[3] In patients with intact cellular immunity, warts tend to regress without therapy; however, recurrence is common.[4] Current therapies for HPV are not virus-specific. Some treatments work by enhancing innate immunity or by local chemotherapeutic effect, and some by tissue destruction, with the goal of destroying the virus-containing epidermis and preserving as much uninvolved tissue as possible. Many researchers have recently shown that cell-mediated immunity affects virus

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multiplication in the wart. As a result, contact sensitizers, imiquimod, intralesional interferons, and oral drugs such as cimetidine have been used as immunotherapies. Little success has been demonstrated with the use of intralesional injections of vaccines and organic antigens. Antigens like *Candida albicans*, trichophyton, measles, mumps, and rubella (MMR), and tuberculin antigens such as purified protein derivative and Bacillus Calmette-Guerin have been injected intralesionally with varied results.[4] This study is aimed at studying the therapeutic effect of MMR vaccine in patients with different types of cutaneous warts.

Materials and Methods

Study design and sampling

In this observational study, we enrolled all the patients who visited the outpatient department in the Department of Dermatology, in a tertiary care hospital in North India from March 2014 to March 2022. We included all the patients diagnosed with warts by two independent dermatologists and treated with MMR immunotherapy (Tresivac). All the demographic data were recorded before starting the treatment. We excluded all the patients with a past history of allergic reaction to MMR vaccine, those on immunosuppressive therapy, pregnant or lactating women, children less than 12 years age, patients with active tuberculosis, and past history of seizures. Patients' demographic and clinical information was obtained from the hospital medical records. Patients were explained the purpose of the study and an informed written consent was obtained from them. Those refusing to consent for the study were excluded from the study and their management was not affected in any way.

Treatment protocol

For treating warts with MMR immunotherapy, the patients received 0.5 mL of reconstituted MMR vaccine into the same single wart, or maximum five large warts in the cases of multiple warts, at 3 weeks intervals until complete response was obtained or for a maximum of four doses. The response of treatment was assessed by a decrease in wart size or number and by a photographic comparison. For this study, complete response was considered if there was complete clearance of the warts, partial if the warts reduced in size by 50%–99%, and no response if there was 0%–49% decrease in wart size. Immediate and late adverse effects of MMR vaccine were also noted for each patient after the treatment session. All the patients were followed up monthly for 6 months to detect any recurrence of warts.

Data collection and data analysis

Approval of the institutional ethics committee was taken before starting the study. Data were entered, checked for completeness, and analyzed using Statistical Package for the Social Sciences (SPSS) software version 23 (Windows, Version 19 Armonk, NY: IBM Corp). Data were expressed as number and percentage for qualitative variables and mean and standard deviation for quantitative variables. Associations between clinical response and patient related variables were established using the χ^2 test. All the results were considered to be significant at the 5% critical level.

Results

During the study period, a total of 184 patients were included in the study. Table 1 describes the distribution of patients according to their baseline characteristics. Approximately half of the patients were from 21 to 40 years age group and 45% of all patients were women. The most common site of warts was palmo-plantar (29%), followed by extremities (26%) and face and neck (22%). Majority of the patients had single warts (48%), whereas approximately one in four patients had more than 10 warts [Table 1]. Four injections were given in 58% of the patients. Complete resolution of symptoms was observed in 66% of the patients, partial response in 22%, and no response or worsening was observed in 12% of the patients [Figures 1–4] On analyzing the clinical

Table 1: Distribution of patients according to their baseline characteristics

Variable	*n* (%)
Age distribution of the patients	
≤20 years	48 (26%)
21–40 years	94 (51%)
41–60 years	34 (19%)
>60 years	08 (04%)
Gender distribution of the patients	
Female	83 (45%)
Male	101 (55%)
Site of warts	
Extremities	48 (26%)
Palmo-planter	54 (29%)
Face and neck	41 (22%)
Genitals	28 (15%)
Periungal	08 (04%)
Scalp	05 (03%)
Number of warts	
Single	89 (48%)
2–5	42 (23%)
6–10	10 (05%)
>10	43 (24%)
Number of injections given	
1	22 (12%)
2	37 (20%)
3	18 (10%)
4	107 (58%)
Clinical response	
Complete	122 (66%)
Partial	41 (22%)
No response/worsening	21 (12%)

response in association with patient-related variables, age group 21–40 years was found to be significantly associated with complete clinical response (P = 0.03) [Table 2]. Furthermore, warts situated on palmo-plantar surfaces and extremities were also significantly associated with complete clinical resolution of symptoms (P = 0.01), whereas 43% (12/28) of the warts situated on genitals had no clinical response or worsening. Gender of the patients or number of warts was not significantly associated with the clinical response of the treatment given. Pain at injection site was reported by all the patients, whereas flu-like symptoms were reported by 32% of the patients.

Discussion

Warts are the exophytic hyperkeratotic papules or plaques caused by the HPV. Spontaneous resolution maybe observed in a few warts; however, as the warts proliferate in the keratinized epithelium, lack of local immunity makes it difficult for spontaneous resolution.[5] The MMR vaccine has been used as an intralesional injection to treat

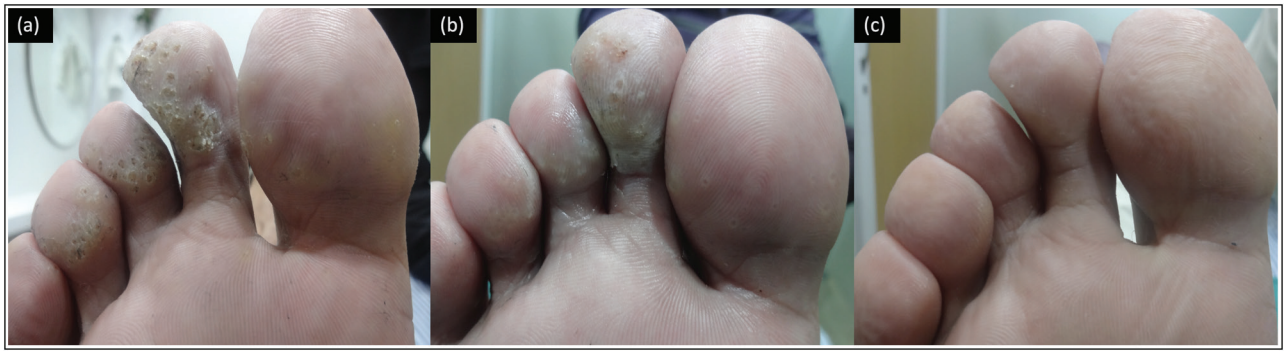

Figure 1: Plantar warts. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing complete response

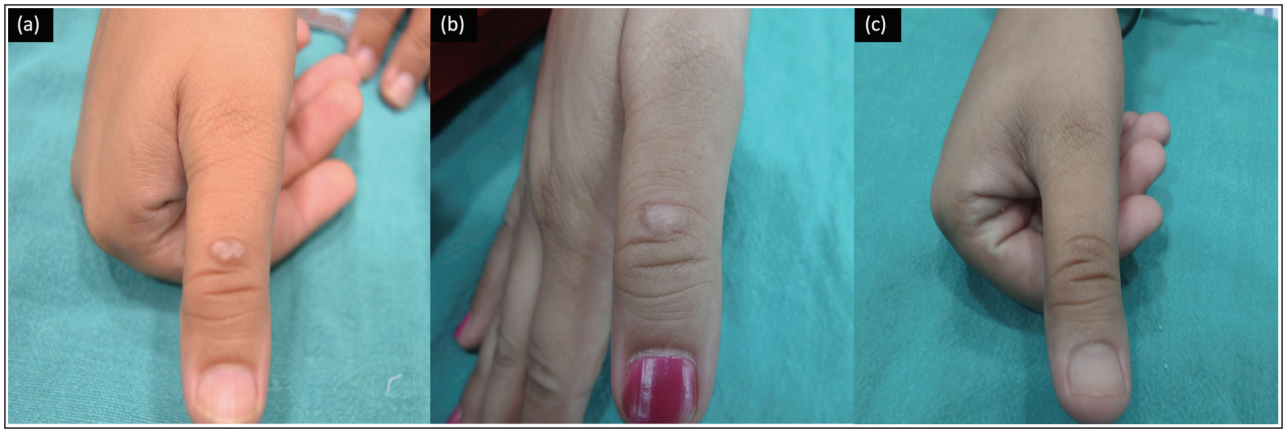

Figure 2: Verruca vulgaris. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing complete response

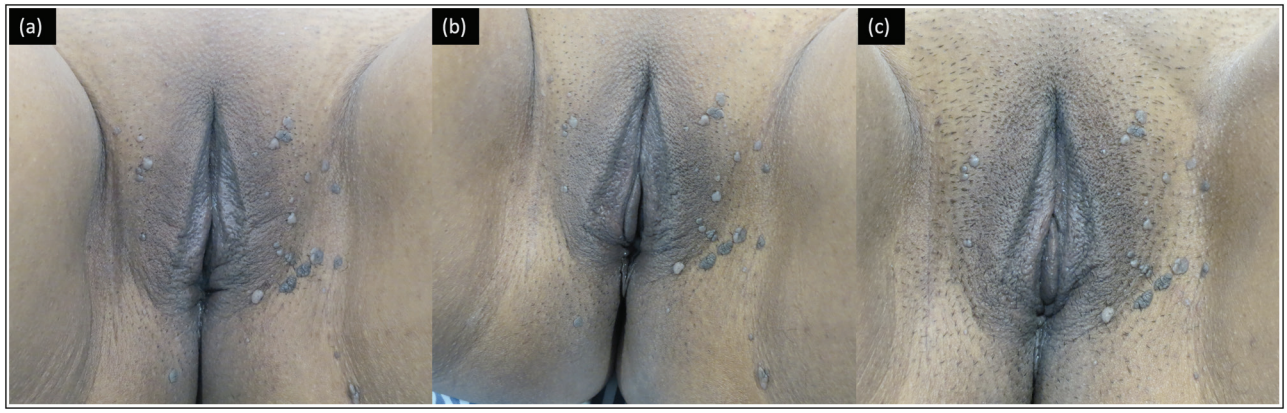

Figure 3: Genital warts. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing no response

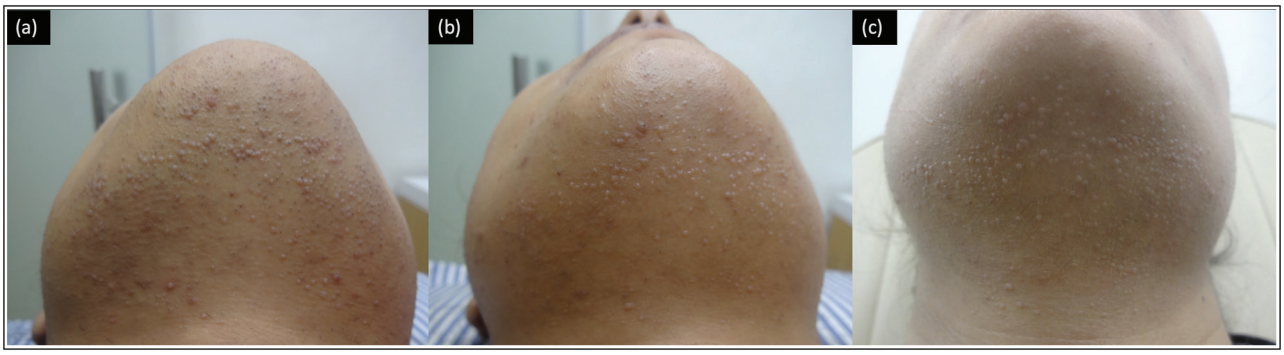

Figure 4: Verruca plana. (A) Baseline, (B) 2nd visit, and (C) 4th visit showing worsening of warts

Table 2: Association of clinical response with patients' demographic and clinical variables

	Clinical response			*P* value
	Complete (n = 122)	Partial (n = 41)	No response/worsening (n = 21)	
Age of the patients				
≤20 years	30	12	2	0.03
21–40 years	76	17	8	
41–60 years	15	10	7	
>60 years	1	2	4	
Gender of the patients				
Female	54	16	14	0.41
Male	68	24	8	
Site of warts				
Extremities	38	8	2	0.01
Palmo-planter	44	8	2	
Face and neck	20	15	6	
Genitals	12	4	12	
Periungal	4	4	0	
Scalp	4	1	0	
Number of warts				
0–5	92	24	12	0.22
6–10	39	16	10	

cutaneous warts by stimulating nonspecific host immune response against HPV antigen by releasing IL-2, 4, 5, 8, 12, IFN-γ, and TNF-α.[6]

The present study observed the patients diagnosed with cutaneous warts and treated with MMR vaccine. A maximum of four treatment sessions were done at our clinic and the clinical response was assessed by the decreasing size of warts. Complete clinical response was observed in 66% of the patients, and it was significantly higher in younger patients and in those with warts situated on palmo-plantar surfaces and extremities. A double-blinded, randomized placebo-controlled trial by Zamanian *et al*.[4] found complete clinical response in 75% of the patients treated with MMR vaccine, with 29% reporting flu-like symptoms. In another randomized trial with similar methodology, Nofal and Nofal[7] studied 110 patients diagnosed with cutaneous warts and found complete clinical response in 81% of the patients and partial response in 10%. Unlike the present study, the authors determined the dose of MMR vaccine according to the extent of intradermal reaction. This method of dose calculation was described by Johnson *et al*.[8] Later, Nofal *et al*.[9] conducted an open label study of 65 patients using standard 0.3 mL dose of MMR vaccine and found that 63% of the patients had a complete response and 23% had a partial response. Furthermore, in the present study, one patient had a relapse at a different site within 6 months and two patients had relapse after 1 year. Na *et al*.,[10] retrospectively, studied 136 patients using the dosing methodology as described by Johnson *et al*.[8] Though only 27% of the patients were found to have a complete clinical response, 6% of these developed recurrence during the 6-month follow-up.

The exact underlying mechanism of intralesional immunotherapy is not completely understood. Intralesional immunotherapy has been shown to induce non-specific inflammatory signals attracting antigen-presenting cells, which further act upon HPV particles.[11] Previous studies

have demonstrated that intralesional immunotherapy with different types of skin antigens like mumps, Candida, or Trichophyton antigens may lead to resolution of warts.[12] Horn *et al*.[13] observed that patients who demonstrated at least a 5 mm response to a skin antigen and later received an a 0.3 mL dose of that antigen had a significantly greater resolution of the injected wart than those treated with interferon alone or saline. Additionally, some patients reported resolution of even those warts which were not injected. However, this trial was stopped prematurely as it involved an unblinded clinical assessment, and there appeared to be an increased rate of fever and myalgias in the patients treated with immunotherapy.

In our study, we found that among patients with genital warts, 43% (12/28) patients did not show any clinical improvement or showed worsening with the MMR immunotherapy. Meena *et al*.,[14] in their report, showed excellent response in two patients with genital warts treated with immunotherapy. A possible explanation to this varied response could be the type of HPV causing the genital warts. But there are no data in the existing literature regarding response of MMR vaccine to specific HPV types. Also, among patients with verruca plana, around 50% of the patient showed complete response with immunotherapy. Mohta *et al*.,[15] in their report, concluded that immunotherapy with MMR is superior to vitamin D3 in verruca plana.

There are a few limitations of this study. Firstly, this was an observational study, and no comparison groups were studied. Secondly, the treatment protocol is specific to the study setting. We performed a maximum of four treatment sessions, which might not be true for other patient settings. Moreover, the immunogenicity of MMR vaccine used in the present study might vary with vaccine used in other patient settings. Lastly, we did not collect immunization history of patients, and prior doses of MMR vaccine may influence the clinical outcome.

Conclusion

The findings of our study show that MMR appear to be an effective and safer option than traditional destructive treatments for cutaneous warts. Warts in younger patients and located on palmo-plantar surfaces and extremities responded favorably to MMR vaccine. The treatment was well tolerated by the patients as well. Future multi-centric, randomized, controlled, prospective trials are needed to evaluate the clinical effects and factors affecting the efficacy of this treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/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.

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Conflicts of interest

There are no conflicts of interest.

Author's contribution

RK and SS contributed to the initial conceptualization, critical revision of content, and final approval of the manuscript. RK and IA contributed to the initial draft of the manuscript and literature review. BS contributed in statistical analysis.

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