Zagazig University Medical Journal
www.zumj.journals.ekb.eg
Doi: 10.21608/zumj.2019.16153.1443
Microbiology & Immunology

ORIGINAL ARTICLE

Efficacy of Intralesional Candida Antigen Immunotherapy in Treatment of Recalcitrant Warts.

Ayman Marie, Ghada Boghdadi, Rehab El said, Eman Salah*.
Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University. Zagazig. Egypt

Corresponding author
Eman salah*
Instructor of medical microbiology and immunology
purity_2010@hotmail.com

Submit Date	**2019-08-26**
Revise Date	**2019-09-20**
Accept Date	**2019-10-04**

ABSTRACT

Background Despite existence of numerous therapeutic approaches, treatment of warts especially recalcitrant one still represent a real challenge as there is no treatment modality exhibited high efficiency and low recurrence rate. Recently, intralesional immunotherapy via various types of antigens has proved high efficiency in the treatment of warts. This work aimed to evaluate the efficacy of intralesional injection of Candida antigen in treatment of recalcitrant warts. **Methods** The study included 24 patients with recalcitrant warts. Injection with 0.1 ml of 1/1000 solution of *C. albicans* antigen was done at 2-week intervals until complete clearance or for a maximum of six treatment sessions. Follow-up was done every month for six months to detect any recurrence. **Results** 14 patients (58.3%) showed complete response, 6 patients (25%) showed partial response and 4 patients (16.7%) showed no response with no change in warts size throughout treatment sessions. Side effects were mild and no recurrence of warts was detected. **Conclusion** Intralesional Candida antigen immunotherapy is a safe, promising and efficient treatment approach for recalcitrant warts.
Keywords Candida antigen; immunotherapy; recalcitrant warts.

INTRODUCTION

Warts are benign papillomas, caused by infection of mucosal or epidermal cells with the human papillomavirus (HPV)[1]. Although seemingly harmless, warts cause quite a lot of morbidity. They are estimated to affect up to 7-12% of the population. They can greatly affect the patients' quality of life by causing disfigurement, discomfort and social embarrassment because they are cosmetically unacceptable. Also, warts affect patients' confidence, especially if they cover a wide area of body in addition to pain, tendency to spread, persistence and recurrence[2].

Treatment of warts is challenging issue because ideal treatment with good efficacy and low recurrence rate has not been detected [3].

Multiple treatment modalities are available for different types of warts. Most of them directly destroy the visibly infected tissue such as salicylic acid, cryotherapy, surgical interventions and lasers. The burdensome nature of the traditional therapies and increase recurrence rate (up to 30%) make immunotherapeutic modalities are the most important therapeutic approach [4].

Intralesional antigen immunotherapy is a promising therapeutic modality for the treatment of various kinds of warts, especially recalcitrant ones which are defined as those lasting greater than two years with no response to two or more treatment modalities [5].

Different types of antigens have been utilized, either alone or as a combination of antigens. These include bacterial antigens such as BCG (Bacillus Calmette Guerin) vaccine, viral antigens such as MMR (Mumps, Measles and Rubella) and fungal antigens such as Dermatophytes and Candida [6].

Complete clearance of both treated and untreated warts, either near the injected wart or at distant anatomic sites, has been documented (7).This may be mediated through induction of strong cell mediated immune response altering

the balance between Th1 and Th2 responses in favor of the former, leading to elimination of the HPV-infected cells(8). Also, release of different cytokines such as IL-2, IL-5, IL-8, IL-12, IL-18, and INF-gamma that induce a strong immune response against HPV has been reported after intralesional antigen immunotherapy[7].

In view of the above we tried to evaluate the efficacy of intralesional injection of Candida antigen in treatment of recalcitrant warts.

METHODS

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. A cross-sectional study was done in Medical Microbiology & Immunology Department, Faculty of Medicine, Zagazig University. The study was approved by the Institutional Reviewer Board (IRB), Faculty of Medicine, Zagazig University.

Twenty-four patients with recalcitrant warts were enrolled into this study. They were recruited from the Outpatient Clinic of Dermatology, Venereology and Andrology Department at Zagazig University Hospitals. A written informed consent was taken from all participants before the beginning of the study. Each participant was primarily subjected to clinical history taking and dermatological examination. Exclusion criteria included immuno-compromised patients, concomitant intake of immunosuppressive or immune modulatory drugs, allergic reaction to injected antigen, past history of allergic skin disorders, acute febrile illness, pregnancy and lactation.

All patients were injected with 0.2 ml of 1/1000 solution of *C. albicans* antigen; *C. albicans* 1:20 w/v 10 ml vial (Allergy Laboratories, INC. Oklahoma City, USA.).

Injections at 2-week intervals for six treatment settings were done.[9]

Evaluation of response to treatment was done by photographic comparison at baseline and at each visit and the decrease in size of warts. Immediate and late side effects were evaluated after each setting. Complete disappearance of the warts and return of normal skin markings was identified as complete response, but regression of warts size by 50–99% or 0–49% was identified as partial or no response respectively.[10]

Every month for 6 months after end of the treatment, follow up evaluation was done to detect any wart recurrence.

Statistical Analysis:

Data were checked, entered and analyzed using Statistical Package for the Social Sciences software SPSS version 25 (SPSS Inc., Chicago, IL)

used in Windows 10 for data processing and statistic. Data were expressed as number and percentage for qualitative variables and mean ± standard deviation for quantitative one.

RESULTS

This study was performed on twenty-four patients (10 males and 14 females), their ages ranging from 9- 59 years. Different types of warts were included in the study. Plantar wart was the most prevalent subtype. The duration ranged from 2 to 10 years. Cryotherapy was the most common therapeutic modality used previously. The baseline characteristics of the studied group are demonstrated in Table 1.

Our study revealed that 14 patients (58.3%) showed complete response, 6 patients (25%) showed partial response and 4 patients (16.7%) showed no response with no change in warts size throughout treatment sessions. (Table 2)

No statistically significant association was found between response to Candida antigen immunotherapy and any of clinical variables, including age, sex, duration, site and previous therapy of warts.

Mild and transient side effects were reported, included tolerable pain during injection in all patients, erythema, edema /induration and flu-like symptoms in some patients.

No recurrence of warts was detected after the 6- month follow- up period.

Table 1. The baseline characteristics of the studied patients.

Variable	No (24)	
Age *Mean ± SD* *Range*	33.4±12.32 9-59	
Duration (years) *Mean ± SD* *Range*	5.6±2.8 2-10	
	No	**%**
Sex		
Male	10	41.7
Female	14	58.3
Type		
Plantar	10	41.7
Periungual	3	12.5
Genital	7	29.1
Common	4	16.7
Previous therapy		
Cryotherapy	12	50
Salicylic acid	4	16.7
Electrocautery	6	25
Surgery	2	8.3

Table 2. Therapeutic response to Candida antigen immunotherapy

Response	No	%
Complete response	14	58.3
Partial response	6	25
No response	4	16.7

(A) **(B)**

Fig. 1. Multiple recalcitrant warts at face

(A)Before treatment

(B)Decrease in warts numbers after six settings of intralesional Candida antigen immunotherapy.

DISCUSSION

Treatment of recalcitrant warts is considered a real challenge and often frustrating for both patient and physician in spite of existence of numerous traditional and immunotherapeutic modalities. **[11- 12]**

Many immunotherapies with variable efficacies have been used for the treatment of various kinds of warts. Intralesional immunotherapy has been shown to be safe and effective modality. It is characterized by clearance of both treated and untreated warts

without scarring, low recurrence rate and a high profile of safety. [13]

The result of this study showed that 58.3% of studied patients showed complete response. Candida antigen is the first antigen used for immunotherapy of warts [14]. A subsequent study by Johnson et al. [15] showed 74% complete clearance of wart among studied group.

Intralesional Candida immunotherapy has also been used in recalcitrant warts in children with a complete response in 34% of all body warts [16]. Treatment of genital warts by Candida antigen immunotherapy was described as well [8].

Further studies evaluate efficacy of other immunotherapeutic agents in treatment of warts. Nofal et al.[17] used MMR in treatment of recalcitrant warts with complete clearance observed in 63% of studied patients. Eassa et al.[18] reported 47.5% complete response of recalcitrant warts using PPD. Also, Sharquie et al.[19] achieved complete response in 39.7% of their patients using BCG.

The differences in the study subjects selected for treatment, the nature of injected antigen, the number of the studied participants and the duration, type and resistance of warts may be responsible for this difference [3]

Many authors demonstrated high efficacy of combined therapy using more than one treatment modality in treatment of recalcitrant warts in comparison to monotherapy.

Nofal et al.[5] proved that the combined therapy of Candida antigen injection and acitretin is more efficient than use of either of them alone in the treatment of recalcitrant warts. Also, Marie et al.[20] reported high efficacy of combined use of Candida antigen and Cervarix (bivalent HPV vaccine) compared to Candida antigen alone due to synergistic effect of the both in induction of cell–mediated immunity against HPV.

Intralesional injection of immunotherapeutic agent induce a delayed type hypersensitivity response to various antigens including the wart tissue leading to production of Th-1 cytokines, which activate natural killer and cytotoxic cells to get rid of HPV infection. This clears not only the injected warts but also distant warts unlike other conventional modalities [6]

Concerning side effects, pain was constant observation in all patients. Burning sensation, induration, erythema, edema and flu-like symptoms were reported. However, these side effects were insignificant, mild and did not indicate treatment stoppage. This is similar to that reported by Nofal et al. [11] and Sabry et al. [9]

No recurrence was observed after the 6-month follow-up period after Candida antigen immunotherapy. A similar observation of absent or low recurrence rates have also been found by similar related studies [7- 9-11-15-21].This finding reflects a promising benefit of intralesional immunotherapy that can be ascribed to the acquisition of long-term, continuous immunity to HPV.

CONCLUSION

Candida antigen immunotherapy is a promising, secure and efficient method for recalcitrant warts treatment. It is inexpensive and has the benefit of sustained immunity against HPV.

RECOMMENDATION

Use of Candida antigen immunotherapy in treatment of recalcitrant warts due its promising results. Comparison between effectiveness of Candida antigen immunotherapy and other treatment modalities as HPV vaccine in treatment of recalcitrant warts is also recommended.

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How to cite

Marei, A., Boghdadi, G., Tash, R., Elgharabawy, E. Efficacy of intralesional Candida antigen immunotherapy in treatment of recalcitrant warts.. *Zagazig University Medical Journal*, 2020; (769-774): -. doi: 10.21608/zumj.2019.16153.1443