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ORIGINAL ARTICLE

Candida Antigen Immunotherapy for Treatment of Cutaneous Warts: A one-Year Zagazig University-Dermatology Clinic Experience.

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ABSTRACT

Background: Warts are widespread cutaneous and mucosal infections caused by human papilloma virus. Resistance to treatment is the main concern while dealing with cutaneous warts. Previous research has defined an ideal wart therapeutic modality as the one that is able to clear all present warts painlessly with no recurrences. Current therapeutics are still far away from meeting this definition. The growing evidence of the role of cell mediated immunity in wart resolution supports the use of various immunotherapeutics in treating cutaneous warts especially the recalcitrant ones. *Candida* antigen injection has recently emerged as a potential effective therapeutic option that needs confirmatory research trials on a large scale. The aim of this work is to evaluate the efficacy of intralesional *Candida* antigen injection in treating resistant warts in patients attending our clinic over a period of one year.

Subjects &Methods: Ninety-two adult patients with recalcitrant warts were included in this study. All patients were subjected to adequate dermatologic examination of warts regarding site, type and number, presence of distant warts at baseline and at each follow-up visit. All patients included were injected with 0.3ml of 1/1000 *Candida* antigen solution into the largest wart for 5 sessions biweekly.

Results: out of the 92 patients,80 patients (92.3%) responded to therapy; 55 patients (59.7%) achieved complete resolution, 25 (27.1%) patients demonstrated partial response and 12patients (13%) showed no response.

Conclusion: Our results indicate *Candida* antigen is an efficacious treatment option of recalcitrant warts that can be adopted in clinical practice.

Keywords: Wart, Resistance, Candida

INTRODUCTION

Warts or *verrucae* are the known medical terms used to describe cutaneous and mucosal infections caused by Human Papilloma Virus (HPV). Addressing cutaneous warts as an old and seemingly everlasting clinical problem is mandatory due to several causes. First is the high incidence of cutaneous warts both in Egypt and worldwide. The lack of a specific antiviral therapy together with the varied untrusted efficiencies of current treatment options add more to the severity of the problem [1].

Although the great majority of warts are claimed to resolve spontaneously within no more than 2 years, about one third of cases persist despite treatment. There's no exact definition for resistance. However, it's been accepted to be defined as failure to respond to

five subsequent treatments over a period of 6 months [2].

Previous research has defined an ideal wart therapeutic modality as the one that is able to clear all present warts painlessly with no recurrences and with no scarring. Current therapeutic options are still far away from meeting this definition. Standard therapeutic modalities for warts, especially resistant ones, are usually destructive [3].

Destructive options include surgical procedures such as electrocautery, laser ablation, surgical excision and aggressive cryotherapy. They also include medical options such as high concentration trichloroactetic acid, Salicylic acid and anti-proliferative agents such as podophyllotoxin, 5-fluorouracil and bleomycin [4].

Most of these options require multiple sessions with high incidence of adverse effects as scarring and recurrence. The major drawback for those traditional treatments is that they are limited to local application and can't act systemically. Thus, they are not convenient for patients with distant and multiple warts. Hence, the need for an effective systemic therapeutic modality [5].

The growing evidence of the role of cell mediated immunity in wart resolution has supported the use of various immunomodulatory options in the treatment of cutaneous warts especially in patients with multiple and recalcitrant warts. Those include topical sensitizers e.g. diphenylcyprone, proinflammatory cytokines e.g. interferons, oral levimasol and intralesional antigen therapies e.g. BCG vaccine and *Candida* antigen therapy [6].

Back in 1990, Cenci et al. demonstrated on mice that *Candida* antigen treatment produced high levels of IFN-γ *in vitro*. Recently in 2017, Nofal et al., illustrated a significant correlation between the response of common warts to Candida antigen treatment and the levels of IFN-γ. Both studies support the mounting evidence on the effect of *Candida* antigen treatment through stimulating cell medicated immunity particularly a TH1 response [5].

PATIENTS &METHODS

Ethical considerations

The protocols and informed consent forms used in this study were approved by the Institutional Review Board (IRB) of Zagazig University. All participants signed a written informed consent and filled a written survey including demographic and clinical data. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Sampling:

Ninety-two cases complaining of persistent warts, resisting at least one modality, were recruited from attending cases in the period from January 2017 to October 2017. Wart persistence was defined as persistence of warts despite being treated for more than one year.

Study design:

All patients were subjected to:

- Thorough history taking and a detailed questionnaire including obtaining their socio-demographic data (Age, Sex, Residence… etc), duration of wart presence, its course and previous therapies used.
- Adequate clinical dermatologic examination of warts regarding site, type and number, presence of distant warts at baseline and at each follow-up visit. Patients were advised not to use any other wart-directed therapy during the study period.
- ***Candida*** **antigen injection:** all patients included were injected, without prior sensitization, with 0.3ml of 1/1000 *Candida* antigen solution (Candida albicans 1:20 w/v 10ml vial, Allergy laboratories, INC, Oklahoma City, USA) into the largest wart, if multiple, using an insulin syringe. Injections were done biweekly for a total of 5 subsequent non-interrupted injections. Photographic evaluation and comparison from baseline photographs were done at each visit. Immediate and late adverse effects were recorded at each visit. All patients were followed for up to 6 months after completion of therapy to detect any recurrence.

Statistical Analysis:

The collected data were analyzed by computer

using Statistical Package of Social Services version 24 (SPSS), Data were represented in tables and graphs, Continuous Quantitative variables e.g. age were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage).

Suitable statistical tests of significance were used after checked for normality. The results were considered statistically significant when the significant probability was less than 0.05 ($P < 0.05$). P-value < 0.001 was considered highly statistically significant (HS), and P-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

Demographic characteristics of patients under study:

Our study included Ninety-Two (92) adult patients; Forty-Two (42) males and Fifty (50) females). Their ages ranged from Twenty to Forty-seven (47) years old with a mean of 33.37 ± 6.96.

Type &Duration of warts in patients under study

Table 1 shows that 39.2% of the patients under study suffered from warts for less than 2 years, while 60.8% of them had warts for 2 years or more. Results also show 26.1% had common warts only, 58.7% had only planter warts and that 15.2% of patients had both planter and common warts.

Results by Response

Table 2 demonstrates that out of the 92 patients,80 patients (92.3%) responded to therapy; 55 patients (59.8%) achieved complete resolution, 25 (27.2%) patients demonstrated partial response and 12patients (13%) showed no response.

Figure 1 demonstrates Multiple recalcitrant planter warts in a 21 year old female showing complete response after only 3 biweekly injection sessions. No recurrence upon follow-up.

Table 1: Type &Duration of wart among studied patients

Duration of warts	Studied patients (N=92)	
	No.	**(%)**
Duration of warts		
< 2 years	36	39.2
≥ 2 years	56	60.8
Wart Type		
Common warts	24	26.1
Planter warts	54	58.7
Both	14	15.2

Table 2: Response to *Candida* antigen immunotherapy among studied patients.

Response to *Candida* antigen	Studied patients (N=92)	
	No.	**(%)**
Non responder	12	13
Partially responder	25	27.2
Responder	55	59.8

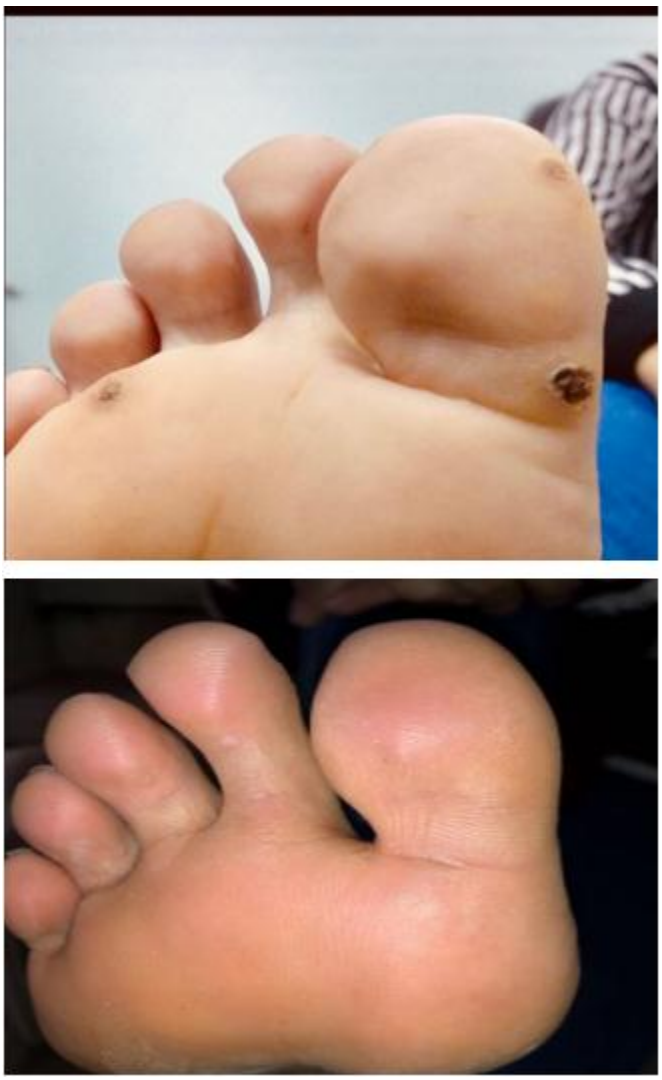

Figure (1): Complete response of planter warts to *Candida* treatment.

DISCUSSION

Warts represent one of the commonest troublesome dermatological problems for both dermatologists and patients. Even though most warts regress spontaneously within two years, many warts fail to resolve even with using more than one therapeutic modality. The recalcitrant nature and the frustrating recurrence pose a difficult therapeutic dilemma as no particular therapy has demonstrated a complete efficacy [7].

The growing evidence of the role of cell mediated immunity in wart resolution has supported the use of various immunomodulatory options in the treatment of cutaneous warts, especially in patients with multiple and recalcitrant wart, the most common of which is *Candida* antigen intralesional injection that has proven effective in treating warts since 1999 [2].

In the present study, *Candida* antigen was used to treat recalcitrant warts of different types and durations in adult patients. Overall, 59.8% of our patients were complete responders, 27.2% demonstrated partial response and 13% didn't show adequate response to the therapy employed. In general, our results are comparable to those of other studies. However, the efficacy is somewhat lower than many others.

Our results are can be said to be comparable to [8] where they applied Candida antigen injection

on eighty-seven adult and pediatric patients with recalcitrant warts and complete response was seen in 51% of patients, partial response in 41% and no response in 8%. Majid et al**.** used 0.1ml of intralesional Candida for a total of 3 weeks at a 3 week interval sessions in adults with recalcitrant warts and could achieve a complete response in 55.9% of included patients [9].

Nofal et al., in 2017 could achieve a complete response in 61.1% of patients under Candida treatment for five biweekly sessions [5]. Higher response rates could be seen with [10] where 72% of patients were complete responders. In 2001, Johnson et al. could, by using only 3 intralesional Candida injections, achieve complete response in 70% of patients [11].

CONCLUSION

Our data indicate that intralesional *Candida* antigen therapy for cutaneous warts is an efficacious option in a clinical practice setting. Our results add to the literature a large Egyptian retrospective series reported to date and treatment outcomes are similar to previously reported studies evaluating this therapeutic modality. *Candida* antigen injection should be considered in all patients with cutaneous warts, particularly those with multiple recalcitrant warts. Advantages include affecting distal warts, easy use and lack of scarring and systemic adverse effects.

Conflict of interest:
The authors report no conflict of interests. The authors alone are responsible for the content and writing of the paper.
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