Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2019;28:21-26
doi: 10.15570/actaapa.2019.5

Pulsed-dye laser versus intralesional *Candida albicans* antigen injection in treatment of genital warts

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Abstract

Introduction: Genital warts are a troublesome therapeutic issue. Pulsed-dye laser (PDL) is a non-ablative therapeutic tool for viral warts. Intralesional *Candida albicans* (*C. albicans*) immunotherapy has yielded promising results in treatment of various types of warts. We aimed to evaluate the effectiveness of PDL versus *C. albicans* immunotherapy for treatment of genital warts.
Methods: Forty adult patients with genital warts were divided into two equal groups; the first was treated using PDL and the second using intralesional *C. albicans* antigen injection. Treatments were performed at 3-week intervals until complete lesion resolution or for a maximum of three sessions.
Results: PDL yielded higher complete clearance rates (95%) than *C. albicans* antigen (50%; $p = 0.001$), which in turn had the advantage of treating distant and internal genital warts. Apart from pain during the session in PDL, both modalities were well tolerated with no recurrence in cured patients during the 16-week follow-up period.
Conclusions: PDL and *C. albicans* antigen injection are safe and effective treatment alternatives for genital warts. PDL yielded better frequencies of clearance, but *C. albicans* antigen has additional advantages, including a single injection site and treating distant and internal mucosal uninjected warts, which are usually difficult to treat.

Keywords: genital warts, immunotherapy, laser

Received: 25 September 2018 | **Returned for modification:** 12 December 2018 | **Accepted:** 25 December 2018

Introduction

Genital human papilloma virus (HPV) infections are widely prevalent worldwide. Genital warts are associated with a negative impact on the wellbeing of infected men and women as reflected by poorer quality-of-life scores. Moreover, anogenital HPV is the leading cause of cervical cancer, especially with oncogenic high-risk HPV types 16 and 18, in addition to other benign and malignant genital neoplastic lesions (1, 2). HPV types 6 and 11 are low-risk subtypes that are responsible for 90% of the cases of genital warts and rarely give rise to cervical cancers, but they have been associated with some types of verrucous carcinomas such as oral florid papillomatosis and Buschke–Löwenstein tumor (2, 3).

Many different therapeutic options for genital warts currently exist, including imiquimod, podophyllin, interferons (IFNs), cryotherapy, intralesional bleomycin, laser vaporization, electrocautery, and surgical removal. Unfortunately, none of these modalities offer a guarantee of cure, in addition to the common risk of recurrence (4, 5).

Flash-lamp pumped pulsed-dye laser (PDL) emits a wavelength from 585 to 595 nm, consistent with the hemoglobin absorption peak, and it is therefore used for the treatment of vascular lesions. It has shown promising results in the treatment of viral warts because it destroys the characteristically dilated superficial dermal capillaries that supply the warts, thereby starving the epidermal cells harboring viral particles, resulting in wart regression. Furthermore, HPV is heat-sensitive, and that makes it vulnerable to the thermal destructive effect of PDL. PDL is thought to be a safe and effective modality for treatment of warts that can be applied to most body areas (6–8).

Immunotherapy has been tried for warts with oral immune modulators such as cimetidine and levamisole. Several intralesional immunotherapeutic antigens have also been tried, such as *Candida albicans* (*C. albicans*) antigen, tuberculin antigens (including purified protein derivative, *Mycobacterium w* vaccine, and Bacillus Calmette–Guérin), and *Trichophyton* in addition to measles, mumps, and rubella (MMR) (9). The first antigen that was tried for immunotherapy of warts was that of *C. albicans*, and the investigators reported success in the majority of patients treated with this test antigen (9, 10).

Intralesional immunotherapy stimulates the host immune system to trigger a delayed-type hypersensitivity response to a multitude of antigens, including the wart tissue. This therapy is associated with the production of a Th1 cytokine milieu and activation of cytotoxic and natural killer (NK) cells to fight HPV infection, not only in the local warts, but also affecting distant warts, unlike traditional wart therapies (11). It should be noted that these distant warts, especially if hidden (intravaginal, cervical, intraurethral, or intraanal), are a major therapeutic challenge in HPV affecting the genital area.

Moreover, some cases of genital warts might be associated with dysplasia or carry the risk of future transformation into intraepithelial carcinomas (12), and it should be noted that Buschke–Löwenstein tumors, with invasive growth, recurrence, and possible malignant transformation, are always preceded by condyloma acuminatum (13).

We evaluated the efficacy and safety of PDL versus intralesional *C. albicans* antigen injection for treatment of genital warts.

Materials and methods

Forty adult patients complaining of genital warts (32 females, 80%; eight males, 20%), whose mean age was 31.92 ± 11.31 (standard deviation [SD]) completed the study. A thorough local genital

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examination was performed, including the skin of the lower abdomen, perineum, perianal area, and upper thighs. In males, the penis, scrotum, and urethral meatus were examined. In married females, a cervico-vaginal examination using a Cusco speculum was performed to exclude internal genital warts. Patients with perianal warts underwent proctoscopy for detection of intraanal lesions. All patients included provided signed written informed consent, and the study protocol was approved by the institutional review board of the ethics committee at Tanta University's Faculty of Medicine.

Patients were divided into two equal groups; the first group was treated with PDL (Deka Synchro VasQ, Italy) using the following parameters: pulse duration 450 microseconds, spot size 7 to 10 mm (regarding the size of the lesions), and fluence ranging from 7 to 10 J/cm². Up to seven to 10 overlapping pulses were applied to each wart, covering the lesion and 1 mm of surrounding unaffected skin. When necessary, the treatment areas were locally infiltrated with 2% lidocaine hydrochloride before the PDL session. Group II patients were treated using intralesional *C. albicans* antigen injection (specific hyposensitizing vaccine, *C. albicans* Allergica; concentration 1:10). The oldest and usually the largest wart (the "mother wart") was injected intralesionally with 0.3 ml *C. albicans* antigen solution. In both groups, treatment sessions were performed at 3-week intervals until complete lesion resolution or for a maximum of three sessions. Patients with active local infection, immunosupression, pregnant females, lactating mothers, and children under 12 were excluded from the study. Patients with a history of photosensitive diseases, active vitiligo, active psoriasis, and keloidal tendency and those on isotretinoin treatment were excluded from PDL group, and those with a history of hypersensitivity to *C. albicans* antigen and those on beta blockers (because they may become unresponsive to epinephrine in the event of anaphylaxis) were excluded from the *C. albicans* antigen group.

Evaluation of efficacy

Patients were examined and digitally photographed at baseline, at each session of treatment with a notation for the number and size of warts, and after 16 weeks from the last session to assess any recurrence.

The degree of improvement was graded as excellent improvement = total resolution of all warts, marked improvement = 76 to 100% decrease in the number and/or apparent wart size, moderate = 51 to 75%, mild = 26 to 50%, and no improvement = ≤ 25% decline in the number or size of the warts treated. Patients that did not achieve complete clearance after three sessions were offered other treatment options in the form of cryotherapy or trichloroacetic acid.

Table 1 | Clinical characteristics, treatment outcome, and adverse effects of patients with genital warts treated by pulsed-dye laser (group I) or intralesional *Candida albicans* antigen immunotherapy (group II).

Characteristics	Group I (n = 20)	Group II (n = 20)	Statistical test	p-value
Age (years), mean ± SD	31.9 ± 11.6	31.95 ± 11	Student's t 0.014	0.99
Sex			Fisher's exact	
Female	19 (95%)	13 (65%)	5.6	0.04
Male	1 (5%)	7 (35%)		
Number of lesions			Fisher's exact	
1–5	10 (50%)	6 (30%)	2.07	0.35
6–10	3 (15%)	6 (30%)		
› 10	7 (35%)	8 (40%)		
Duration of current lesions, months, mean ± SD	4.3 ± 3.9	5.9 ± 6.3	Student's t 0.97	0.33
Distribution of current lesions			MC	
External genital	20 (100%)	20 (100%)	11	0.03
Perianal	4 (20%)	4 (20%)		
Intraanal	0	0		
Internal genital	0	3 (15%)		
Vaginal	0	2 (10%)		
Cervical	0	1 (5%)		
Other partner affected			Fisher's exact	
Yes	5 (31%)	6 (40%)	1.201	0.6
No	11 (69%)	14 (60%)		
Previous treatment			MC	
No	18 (90%)	18 (90%)	2	1.0
Ablative CO_2 laser	1 (5%)	0 (0%)		
Cryotherapy	1 (5%)	1 (5%)		
Electrocautery	0	1 (5%)		
Number of sessions needed for best results, mean ± SD (median)	2.1 ± 0.9 (2)	2.7 ± 0.7 (3)	MC 12.5	0.001*
Response to treatment after three sessions			MC	
Excellent improvement	19 (95%)	10 (50%)	13.3	0.001*
Marked improvement	1 (5%)	2 (10%)		
Moderate improvement	0 (0%)	1 (5%)		
Mild improvement	0 (0%)	2 (10%)		
No/poor improvement	0 (0%)	5 (25%)		
Side effects (present/absent)				
Pain	15 (75%) / 5 (5%)	9 (45%) / 11 (55%)		
Edema	–	17 (85%) / 3 (15%)	–	–
Dyspigmentation	1 (5%) / 19 (95%)	1 (5%) / 19 (95%)		
Flu-like symptoms	–	17 (85%) / 3 (15%)		

SD = standard deviation, MC = Monte Carlo correction method, p-value = level of significance, * = significant at $p < 0.05$.

Statistical analysis

Qualitative data were described using numbers and percentages. Quantitative data were described using median and range (minimum and maximum) or mean and SD. Comparison of continuous variables was made using Student's *t*-test if normally distributed and the Mann–Whitney test if abnormally distributed, and categorical variables were compared using a chi-square test and, if more than 20% of the cells had an expected count less than 5, correction for chi-square was conducted using Fisher's exact test or Monte Carlo correction using IBM statistical software package SPSS, version 21. A *p*-value of less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the baseline clinical characteristics and treatment outcomes of the patients included. The median number of sessions needed for the best results was two sessions for group I and three sessions for group II ($p = 0.001$). There was statistically significant variation between both groups regarding the degree of clinical response after the third session. In group I an excellent response with complete resolution of the lesions was achieved in five patients (25%) after a single session, in nine patients (45%) after two sessions, and in five patients (25%) after three sessions (Fig. 1). On the other hand, after the three injection sessions in group II, 10 patients (50%) were completely cured with excellent improvement, one patient (5%) showed moderate improvement, two patients (10%) showed mild improvement, and seven patients (35%) showed poor or no improvement. All patients in group II with internal genital warts, either vaginal or cervical, showed clearance of their internal warts due to injection of the external genital mother wart with C. albicans antigen (Fig. 2).

Regarding recurrence, all cured patients in both groups showed no recurrence within the 16-week follow-up period after the last treatment session. Regarding the side effects of PDL therapy in group I, five patients (25%) experienced marked burning pain that required infiltration anesthesia during sessions, and only three patients (15%) developed post-procedural hyperpigmentation. In group II, one patient (5%) developed hypopigmentation at the injection site; three patients (15%) showed flu-like symptoms within 24 hours after the injection, which were relieved by non-steroidal

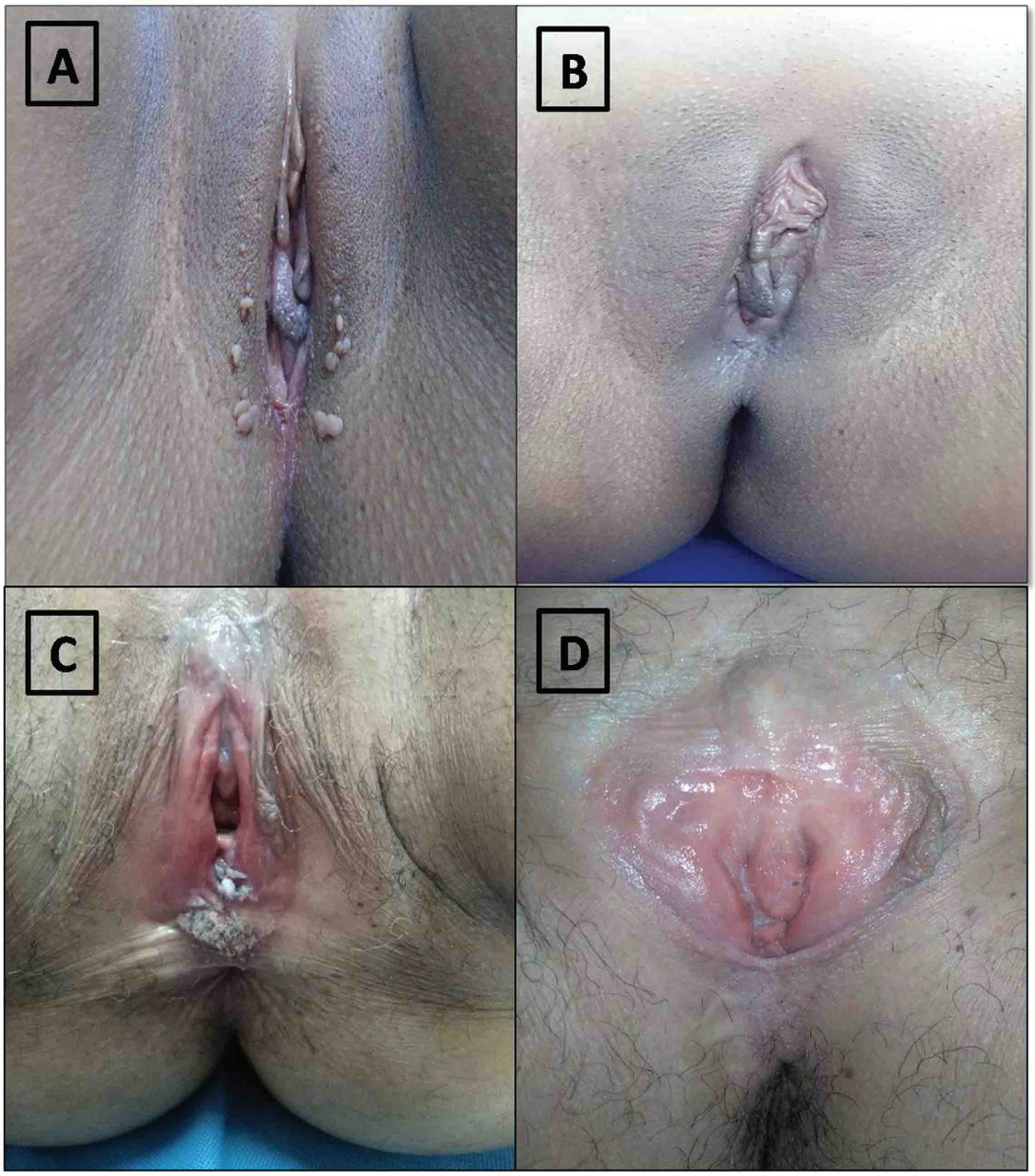

Figure 1 | A: a 22-year-old female patient with multiple genital warts involving both the labia majora and perineum. B: after two sessions of pulsed-dye laser (PDL) with excellent improvement. C: a 46-year-old female patient with multiple genital warts involving the perineum and vestibular fossa. D: after two sessions of PDL with excellent improvement.

anti-inflammatory drugs; 17 patients (87%) developed temporary edema at the injection site, which was relieved by cold compresses; and nine patients (45%) experienced transient mild pain during the day of injection, relieved by analgesics.

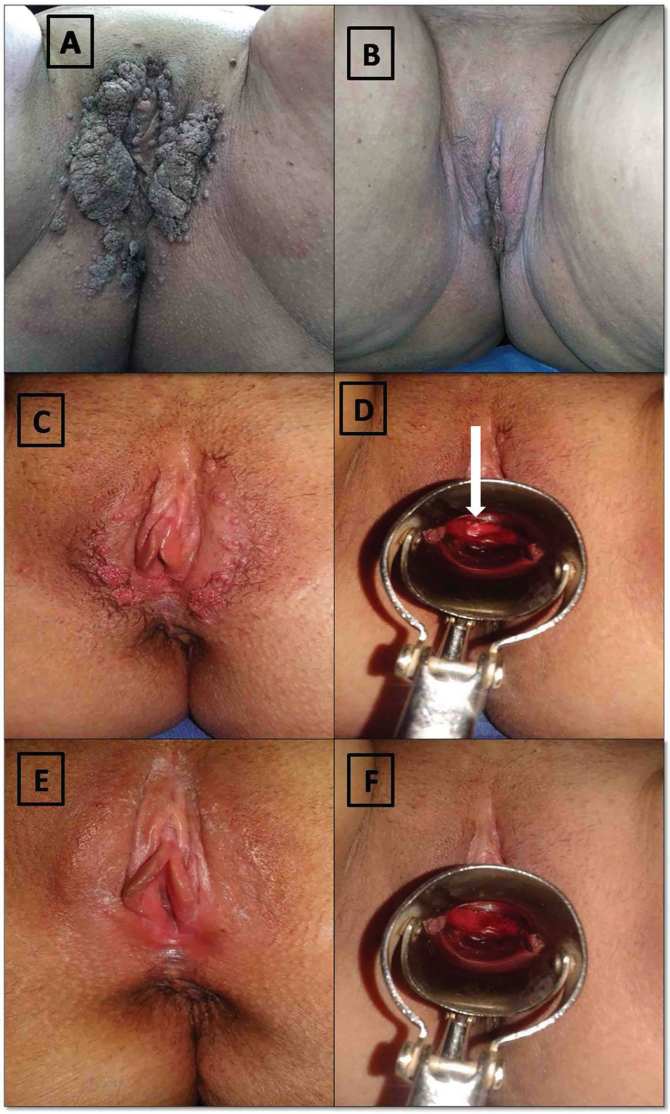

Figure 2 | A: a 51-year-old female patient with genital warts involving the entire vulva. B: after three injection sessions of *Candida albicans* antigen with excellent improvement. C: a 26-year-old female patient with multiple genital warts on the labia majora. D: wart on cervical os (arrow) in the same patient. E and F: after two injection sessions of *C. albicans* antigen with excellent improvement of both external and uninjected internal warts.

Discussion

Primary treatment modalities for warts include destructive therapies such as cryotherapy, electrocautery, laser therapy, and surgical excision. They are designed to damage and remove an apparent skin lesion rather than to kill the virus, for which they lack any specific antiviral effect. This is a major drawback for patients in whom the adjacent, clinically normal skin harbors viral DNA, and thus they are at great risk of recurrence and transmitting the infection. In addition, these therapies are mostly associated with pain, incomplete cures, and disfiguring scarring in addition to the high rates of recurrence (14, 15). PDL showed efficacy in several non-vascular indications, including simple and recalcitrant verrucae vulgaris, on various sites of the body using various fluencies ranging from 6 to 10 J/cm² without ablation (16, 17).

The results of this study detected an overall response rate of 95% for all warts treated with PDL after three treatment sessions. The required number of sessions and the response rates varied by the size and surface area of the warts. Only one patient (5%) did not achieve complete clearance after the third session and needed an additional session to achieve a complete response.

In a previous study including 22 patients with genital warts using a 585 nm PDL with a fluence of 6 to 7 J/cm², all patients achieved complete resolution after an average of 1.59 treatment sessions (range: one to five sessions) with a 2- to 3-week interval. A single treatment session was sufficient in 59% of the patients (18).

Badawi et al. (19) used 585 nm PDL in the form of three to four overlapping pulses with higher fluencies (9 to 10 J/cm²) to treat 174 male patients with anogenital warts, and they reported a 96% complete clearance rate. This was achieved after one to three sessions with 2-week intervals between. In this study, seven to 10 overlapping pulses were applied at every site treated, based on the size and thickness of the warts, until the appearance of a faint livid color. This multi-pass technique makes possible greater target destruction while preserving laser selectivity.

It should be considered that pulse stacking makes it possible to apply cumulative heating of the dermal capillaries with concomitant epidermal cooling between pulses due to a shorter epidermal thermal relaxation time than that of dermal capillaries (20, 21).

In this study, the adverse effects of PDL treatment were minimal. Compared with other destructive modalities used to treat genital warts, there is better patient acceptance, less intense and shorter duration of pain, and minimal disruption in daily activities following PDL treatment. Moreover, no recurrence of genital warts was observed during the 16-week follow-up after the PDL treatment sessions. This lower risk of recurrence of genital warts after PDL treatment has been previously detected by other investigators (22, 23). On the other hand, the results of Komericki et al. (18) showed no recurrence in the treatment areas, but 22% of their patients developed new genital warts in other locations than those treated after PDL treatment. Badawi et al. (19) reported a recurrence rate of 5% in genital warts after one to three sessions of PDL treatment.

This low incidence of recurrence of warts after PDL sessions could be attributed to its mechanism of action based on laser interaction with wart vasculature and thermal injury to HPV. It has also been postulated that the resulting tissue damage is followed by a cell-mediated immune (CMI) response with up-regulation of lesional interleukin (IL) 2 and IL-4 (24–26). IL-2 plays fundamental roles in immunity through its direct effects on T cells. In addition, on antigenic stimulation IL-2 promotes T cell differentiation into effector and memory T cells, thus helping the body combat infections (27).

Regarding immunotherapy, it is a promising modality for recurrent and/or resistant warts that could lead to clearance of lesions without any local tissue injury or scarring (28).

It should be noted that intralesional *C. albicans* antigen has shown encouraging results for treatment of common warts in several previous reports (9, 29, 30), but unfortunately it has not been well investigated in genital warts. King et al. (31) studied mumps, *Candida*, and *Trichophyton* skin test antigens (0.1 ml each) as single therapies or in combination for treatment of 21 patients with genital warts. The number of sessions was high, reaching 10 sessions in some patients, and a complete response was only seen in those injected with *Candida* antigen in combination with other antigens (mumps or *Trichophyton*) (31).

In this study, only 50% of patients with genital warts showed

complete clearance of their lesions after the third session of *C. albicans* antigen immunotherapy. The results of this study and several others revealed partial or no response in some subjects to *Candida* antigen immunotherapy, and the underlying cause is unclear. Many factors may explain the difference in response between the patients studied, including the degree of sensitivity to the antigen injected, the number, type, size, duration, and resistance of warts, the age and sex of the patients, the level and function of toll-like receptors, the difference in the degree of human leukocyte antigen (HLA) presentation of processed antigen, the difference in the distribution and function of antigen-presenting cells, and the difference in the immune cell response to the processed antigen (26, 30, 32).

In this study, edema after intralesional immunotherapy was the most common side effect (recorded in 85% of patients) and it improved with cold fomentation. King et al. recorded local erythema and edema in 14.28% of their patients; these were transient, lasting less than 24 hours (31).

Hypopigmentation was observed in one patient (5%) in this study at the injection site, which agreed with Wilmer et al. (2013), who reported the occurrence of vitiligo at the injection site of *Candida* antigen for verruca vulgaris in an 8-year-old girl (33). The concomitance of candidal antigen injection and the occurrence of vitiligo or hypopigmentation suggest a causal relationship in which immunotherapeutic antigen might either trigger a cytotoxic effect against melanocytes or induce Koebnerization (34, 35). In this study, no recurrence was observed among all cured patients that were treated with *C. albicans* antigen injection during the follow-up period, which is in line with previous studies performed on common warts (9, 30, 36). Antigen intralesional immunotherapy enhances virus recognition by the host immune system with advantageous clearance of both treated and untreated lesions and diminished risk of future recurrence or appearance of new lesions (11, 29). The clearance of untreated genital warts, including nearby and distant internal genital lesions (which are usually difficult to reach and treat) was an important advantage of *C. albicans* antigen immunotherapy reported in our study. This finding has also been reported by other investigators utilizing intralesional antigen immunotherapy for eradication of genital or non-genital warts (31, 32, 37). This could be attributed to the generation of widespread CMI attacking HPV as a response to antigen injection (30, 35).

It was proposed that intralesional antigen immunotherapy provokes proliferation of peripheral blood mononuclear cells and alteration in the T helper cells, favoring Th1 over Th2 responses with resultant activation of cytotoxic T cells and NK cells to eradicate HPV-infected cells (29, 35, 38). The release of various cytokines such as IL-2, IL-5, IL-8, IL-12, and IL-18 that induce a strong immune response against HPV has also been reported after intralesional antigen immunotherapy (30, 31).

Considering the oncogenic potential of some HPV strains affecting the genital area, an additional anti-oncogenic role of *C. albicans* antigen immunotherapy might be suggested. Because of the immune-enhancing capability of recall antigens such as the *C. albicans* antigen, which induces wart regression, some authors tried using it as a novel adjuvant to HPV therapeutic vaccine for biopsy-proven cervical intraepithelial neoplasia 2/3 (39, 40). Wang et al. (41) demonstrated significantly up-regulated CD40 and CD80 levels after *C. albicans* antigen injection, indicating maturation effects of the peptide on Langerhans cells with secretion of IL-12 in addition to T-cell proliferation. In a recent study, *C. albicans* antigen immunotherapy was found to induce a significant polarization of Th1 response with production of IFN-γ, which indicated that *C. albicans* antigen may be used solely as a potential immunotherapeutic reagent not only for HPV-associated lesions but also for other viral infection or even cancers (39).

This study is mostly limited by the relatively small sample size and the relatively short follow-up period. Furthermore, histopathological as well as cytological evaluation of the lesions was not carried out, and it would be informative to conduct future studies using these maneuvers for evaluation of results and for detection of the effects of those treatment modalities in cases associated with dysplasia and carcinomas in situ.

Conclusions

PDL and *C. albicans* antigen injection are simple, safe, and effective treatment alternatives for treatment of genital warts, even recalcitrant or multiple ones, with no post-procedural downtime and decreased risk of recurrence.

Although PDL resulted in much better cure rates, its cost, device availability, pain during the session, especially in massive large lesions, and difficult accessibility to internal genital warts might limit its use. *C. albicans* antigen injection might be helpful for treating distant uninjected warts, including troublesome internal genital ones.

This study recommends trying *Candida* antigen immunotherapy as an inexpensive and promising therapy in female patients with combined external and internal genital warts, in males with combined external and intraanal or intrauretheral warts, and in children before resorting to other destructive interventions.

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