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Multiple Resistant Plane Warts Successfully Treated by Photodynamic Therapy Mediated by Transfersomal Methylene Blue Gel: A Case Report

Ghada Yassin [1], Kawser Kassab[2], Nevien Samy[3] and Maha Fadel[1]

[1]Pharmaceutical Nanotechnology Unit, Department of Medical Laser Applications, National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt; [2] Photobiology and cell photosensitization unit, National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt; [3] Dermatology Unit, Department of Medical Laser Applications, National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt

Abstract

Purpose: In the view of failure of conventional treatment modalities used for multiple resistant viral warts to achieve satisfactory results, new treatment modalities are needed. Recently, photodynamic therapy demonstrated its efficacy and safety for such indication especially when combined with nanotechnology which maximize its benefits.
Methods: In this case report, photodynamic therapy (PDT) mediated by transfersomal Methylene blue (TMB) gel was used for treatment of bilateral multiple resistant plane warts in the dorsum of feet in a 53-year-old woman.
Results: After two treatment session applied for her right foot, complete healing was achieved. Surprisingly, the left foot showed great spontaneous improvement without receiving any treatment. The patient was followed up for one year and did not show any signs of recurrence.
Conclusion: This case not only highlights the ability of PDT to treat multiple resistant plane warts but also focus on its ability to boost immune response and help body to eradicate viral infection.

Keywords— methylene blue, transfersomes, photodynamic therapy, plane warts, clinical

I. Introduction

Viral warts are cutaneous contagious lesions caused by infections with human papilloma viruses (HPV). HPV are two-stranded DNA viruses that is characterized with its persistence and resistant to a wide range of treatment drugs. Absence of envelope, high viral replication and its ability to escape from immune system account for the persistence of HPV infection. HPV includes a diverse group of approximately 120 genotypes with different clinical types and its associated lesions range from benign warts to malignant lesions [1–3].

Plane warts is a common skin manifestation of HPV, most frequently caused by types 3 and 10 and most commonly occurring on face and extremities. They often appear as slightly raised, smooth papules with skin colour, slightly erythematous but may be pigmented [1, 4, 5]. Despite their benign nature, warts are cosmetically unacceptable and might cause psychological, functional and physical troubles [6–9]. Most warts may spontaneously disappear, however multiple persistent warts that fail to resolve after several treatments present a therapeutic challenge [10, 11].

Several treatment modalities are available for viral warts, including repeated topical application of medical agents (e.g., retinoids and salicylic acid), physical destructive methods (e.g., cryotherapy and electrocautery), surgical excision and immunotherapy (e.g., *Candida* antigen and HPVs vaccination). However, none of these modalities is fully significant for every patient and most of them target the destruction of infected cells without direct effect against virus. Low cure rate and frequent recurrence are the main limitations. The need for long periods of application, pain during destructive therapy and risk of scarring are other drawbacks that make most of modalities inconvenient for patients [1, 5, 7, 12].

Recently, Photodynamic therapy (PDT) have demonstrated its value as an effective minimally invasive treatment modality for localized microbial infections including fungal bacterial, and viral infections [13–15]. It combines the effect of nontoxic dye called photosensitizers (PS) and light at a specific wavelength in presence of oxygen to induce generation of reactive oxygen species and singlet oxygen that destroy microbial cells. As a treatment modality for viral warts, PDT has showed several advantages including: high efficacy, low recurrence rates, minimal pain and good aesthetic prognosis [16, 17]. In addition, PDT was reported to have positive effects on host tissues, such as growth factor stimulation and immune response enhancement [18]. Nanotechnology was proved to optimize the photodynamic effect of PS and improve its penetration through skin [17, 19].

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Corresponding author: Ghada Yassin Email: ghada_yasin@cu.edu.eg

Herein, we report a case of resistant bilateral plane warts in the dorsum of her feet who was successfully treated with PDT mediated by transfersomal Methylene blue (TMB) gel that was previously prepared by our group and have shown promising results for treatment of resistant planter warts [17]. These results inspired our team to apply such promising nano-formulation for treatment of multiple resistant plane warts in the presented case. Surprisingly, the results not only highlight the efficacy of PDT in combination with nanotechnology as treatment modality for plane warts but also revealed its ability to boost immune response and help body to eradicate viral infection.

II. Case Presentation

A 53-year-old woman was referred to our department with a two-year history of bilateral multiple persistent plane warts in the dorsum of her feet which had been resistant to multiple topical products, cryotherapy and Candida antigen injection. In view of the resistance to first line therapies, a referral was made to trial photodynamic therapy (PDT). On review, she was not taking any current medications, had no drug allergies, and had no relevant medical history. The patient read and signed the consent term that explain all the clinical procedure and was instructed not to use any concomitant therapies.

PDT using 0.05% transfersomal Methylene blue gel (TMB) was administered to the patient's right foot. The gel was applied in a thin layer covering all lesions and the potentially subclinical affected areas, then the whole area was occluded for 30 minutes. After this period the sheet and residual gel was removed using cotton swap. This was followed by irradiation session with diode laser 670 nm of output power 90 mW for 15 minutes. The treatment sessions were provided once weekly until the complete clinical clearance. The patient denied any pain or adverse effects during the session. At the third week, after receiving two treatment sessions, examination of the patient's right foot revealed a dramatic clearance of warts with no active lesions (**Figure 1**). Surprisingly, the left foot, which had not received any PDT sessions showed great improvement. The Patient was followed up for one year, no recurrence was noticed, and the patient was embarrassed with treatment results (**Figure 2**).

Figure 1: Evolution of the clinical responses in the right leg before treatment (**a**), after first session (**b**) and after second session (**c**)

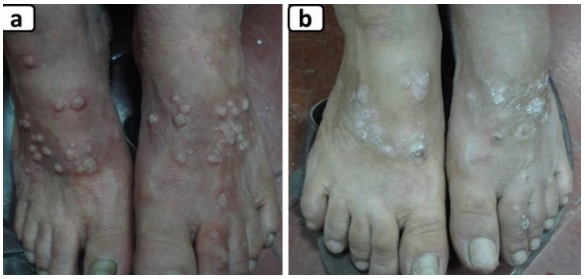

Figure 2: (**a**) Multiple plane warts in both right and left feet before photodynamic treatment session, (**b**) after two treatment photodynamic treatment sessions to the right leg.

Treatment of HPV-associated lesions is challenging. Despite their high prevalence, no antiviral medication against HPV is currently available. Most treatment protocols used for such viral lesions are cyto-destructive and mean to destroy lesions rather than eradication of virus. Thus, even with adherence to the evidence-based treatment protocols, a notable proportion of warts remain resistant to cure or tend to relapse, adding to the unsatisfactory cosmetic results. New treatment modalities that fight the virus not only the lesion are needed [2, 11, 20].

Lately, PDT has demonstrated its efficacy in fighting against viruses, showing a great potential in several applications including viral decontamination of fluids, clinical treatment of cutaneous viral lesions caused by herpes simplex virus (HSV), varicella zoster virus (VZV), and human papillomavirus (HPV). Recently, It have been also used for suppression of respiratory tract infections and management of COVID-19 [21–23].

Considering treatment of HPV associated lesion, several studies have shown that PDT could offer several therapeutic benefits that make it very appealing including efficacy, safety, non-invasiveness and selectivity. Moreover, PDT have shown much superior results in term of rate of recurrence [16, 22].

Regarding the case presented, PDT mediated with TMG gel were used for treatment for such multiple resistant plane warts. TMB gel was previously prepared where transfersomes were prepared using phosphatidylcholine from soybean and deoxycholic acid sodium salt in a ratio of 10: 1 by thin film hydration method. Such nano-vesicles showed a mean particle size of 712.4 nm, zeta potential of -58.7 mV, encapsulation capacity of 59.64 % and cumulative percentage release of 74.5 % after 3 hours. TMB gel (0.05 %Methylene Blue) was prepared using 5% Carboxymethyl cellulose sodium salt and 0.2% methylparaben sodium. TMB gel has proven to deliver MB into deep layers of skin through an animal study guided by histological examination. Moreover, TMB gel mediated photodynamic effect has showed great efficacy and safety in treatment of resistant planter warts in a single-blinded randomized placebo-controlled study [17].

Although the warts in the presented case were refractory after several treatment methods, PDT mediated by TMB showed high efficacy. The efficacy of PDT could be related to several mechanisms. Firstly, photodynamic inactivation of HPV, where the produced reactive oxygen species and singlet oxygen inactivate the virus and supress its replication. Secondly, the anti-proliferative effect of PDT,

where the HPV-infected keratinocytes are photodynamically destructed as PS is selectively accumulated in the rapidly dividing cells. Lastly, the immune-modulating effect of PDT, where PDT was proved to induce innate and adaptive immune responses and promote the release of pro-inflammatory proteins [6, 18, 20, 23].

It is believed that the use of transfersomes as nano-carriers for Methylene blue facilitate its transfer through skin and hence maximize its photodynamic effect. It was worth noting that only two treatment session were needed to achieve complete cure which was convenient for the patient. Moreover, it seems likely that use of PDT not only serve in cure of the treated warts in right foot but also improve the patient's immune response and help in eradication of the virus. This explains the great spontaneous improvement in the left foot that did not receive any treatment sessions.

The patient was very satisfied with treatment results, especially after one year of follow up free of any signs of recurrence. The ability of PDT to reduce recurrence is attributed to its ability to decrease the viral load as well as treatment of a larger area and thereby treating subclinical lesions [16, 20]. Minimal pain during treatment and good cosmetic outcomes increased patient satisfaction with the treatment. Based on these finding, PDT combined with nanotechnology is recommended as a first-line therapy for plane warts.

III. Conclusion

Our case suggests that PDT mediated by TMB gel could be an effective modality for treatment of resistant plane warts owing to its effectiveness and safety, in addition to its immune-modulating effect that help body to eradicate viral infection. Further studies in a larger population are required to determine the optimal regimen for resistant plane warts.

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