



# Treatment of Refractory Condylomata Acuminata with 5-Aminolevulinic Acid-Photodynamic Therapy Combined with Tretinoin: Report of 66 Cases

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## Abstract

Condylomata Acuminata (CA) is an infectious disease caused by Human papillomavirus (HPV) presenting as epidermal hyperplasia. CA is characterized by a long course of disease, easy recurrence after treatment and a potential risk for skin cancer. Traditional treatments for CA include topical remedies and surgical treatments. In addition to being painful and possible scarring, most conventional treatments are accompanied by a high rate of recurrence. And it is difficult to achieve the desired therapeutic effects with traditional treatment strategies. 5-Aminolevulinic Acid (ALA)- mediated Photodynamic Therapy (ALA-PDT) can selectively destroy CA in the epidermis and ensures a better efficacy with fewer side effects such as scarring, which is important for the anogenital region. We report here a series of 66 cases of refractory anogenital CA treated with ALA-PDT combined with tretinoin and all lesions were completely cured without recurrence. We believe that ALA-PDT combined with tretinoin can be used as an efficient and safe option to treat refractory anogenital CA.

**Keywords:** Condylomata acuminata; ALA-PDT; Tretinoin

## Introduction

Condylomata Acuminata (CA) is a very common sexually transmitted disease that occurs mainly in external genitalia and anal mucous membrane regions, which leads to psychological and physical burdens for patients. Traditional treatments for CA include topical drugs (trichloroacetic acid and imiquimod) and surgical treatments (carbon dioxide laser, photodynamic therapy and surgical resection). Compared with those methods, surgical treatment has a higher clearance rate but has the risk of infections, scarring and ulcerations [1]. 5-Aminolevulinic Acid (ALA)-mediated Photodynamic Therapy (ALA-PDT) is a promising technique for the treatment of proliferative diseases, not only for treating skin cancers and/or precancerous lesions but also for treating non-malignant skin diseases, such as psoriasis, viral infections and epidermal attachment diseases [2]. ALA is selectively absorbed by tumor cells and by rapidly proliferating cells and is transformed to endogenous Protoporphyrin IX [3]. Protoporphyrin IX is then activated by red light to form singlet oxygen, which leads to the killing or destruction of targeted cells. Studies have shown that ALA-PDT can effectively treat latent and subclinical infections of CA, thereby preventing their recurrence. A meta-analysis of 1,903 patients with CA showed that treatment with ALA-PDT significantly reduced the relapse rate within 12 weeks showing that ALA-PDT is an effective treatment for CA [4]. Tretinoin can inhibit cell proliferation and can induce cell differentiation and/or apoptosis. By regulating the growth and differentiation of a variety of cell types, tretinoin plays a vital role in cervical development and homeostasis [5]. We report here a case series of 66 patients with refractory anogenital CA who were successfully treated with ALA-PDT combined with tretinoin.

## Clinical Series

Sixty-six patients with CA who attended the Department of Dermatology and Venereology, the Third Affiliated Hospital of Soochow University during the period from January 2017 to August 2019 were included in this study. All patients provided written informed consent. Those patients had been diagnosed with CA for more than three months and conventional treatments had been ineffective. The diagnosis of CA was made based on clinical examination in addition to the acetowhitening test or pathologic diagnosis. Those patients met at least one of the following criteria:

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**Received Date:** 27 Jan 2022

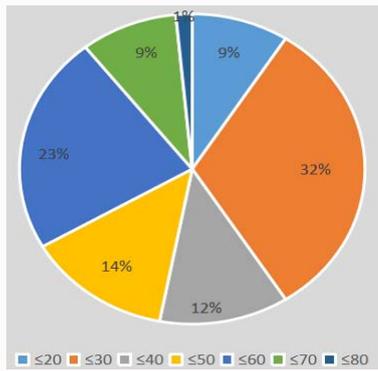
**Accepted Date:** 07 Mar 2022

**Published Date:** 15 Mar 2022

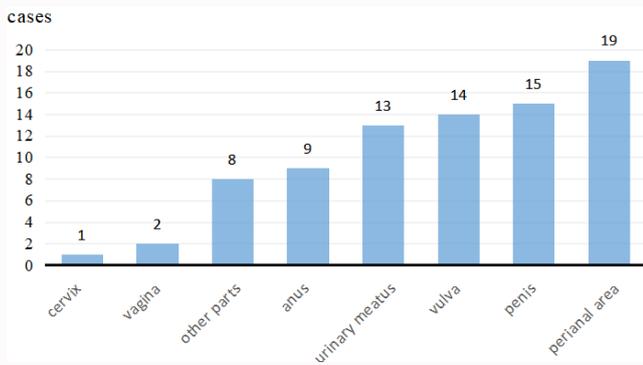
### Citation:

Li Y, Ge K, Zhang R-Z. Treatment of Refractory Condylomata Acuminata with 5-Aminolevulinic Acid-Photodynamic Therapy Combined with Tretinoin: Report of 66 Cases. *Clin Surg*. 2022; 7: 3448.

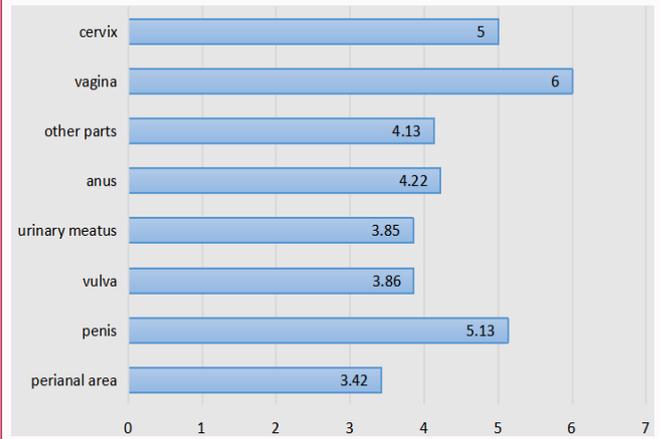
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**Figure 1:** Age distribution of the 66 patients with CA. The 20 to 29 year old age group accounted for the largest share (32%, 21/66) followed by the 50 to 59 year old age group (23%, 15/66).



**Figure 2:** Distribution of lesion locations. The perianal area was the most common location (19 cases), followed by the penis (15 cases), vulva (14 cases) and urinary meatus (13 cases).



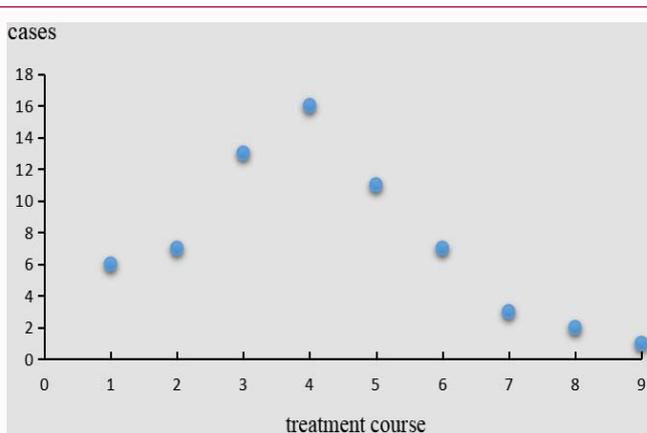
**Figure 3:** Mean treatment cycles. The mean treatment cycles varied in different locations. The vagina required the longest treatment cycles and the perianal area required the shortest treatment cycles.

(1) Six or more lesions were located in an anatomical area; (1) 3 to 6 lesions were located in an anatomical area, and at least one lesion was larger than 1 cm in diameter; (3) Rashes occurred in more than 3 anatomical sites at the time of consultation; (4) After using ALA-PDT alone more than 3 times, the rashes did not subside or relapsed soon after they had disappeared. Of these 66 cases with CA, 33 patients had other skin diseases, including psoriasis, dermatitis, urticaria, etc. and 24 of them had background diseases, including hypertension, insomnia, diabetes, respiratory tract infections, pharyngitis, etc. The number of patients with both forms of the diseases was 13. The exclusion criteria for patients were as follows: (1) Patients who are allergic to light; (2) Patients with liver injury or related liver disease; (3) Patients who have fertility requirements within two years. All 66 patients signed informed consent prior to treatment. Before the ALA-PDT combined with tretinoin, the lesions were first treated with skin cryotherapy. This step achieves the effect of local edema, so that the tretinoin has a better effect on the skin lesions. In addition to being safer than traditional treatments, the freezing process is more like a pre-treatment process, making it more effective in areas with severe skin lesions or where laser treatment is not possible. Following receipt of signed informed consent, a gel containing 16% ALA was applied topically to the lesions, which were then covered with a polyethylene dressing. A transvaginal probe was used for application on internal lesions. After 3 h, the application sites were irradiated with 120 mJ/cm<sup>2</sup>/s red light with a peak emission at 630 nm to a total dose of 150 J/cm<sup>2</sup>. For the treatment of intravaginal disease, a translucent plastic speculum was used to separate the vaginal wall. Follow-up treatments

with ALA-PDT were performed every 15 days until the lesions disappeared completely. In addition to treatment with ALA-PDT for these refractory CA, we also used a small dose of tretinoin for oral treatment, 10 mg/dose, twice a day for 45 to 90 days. For patients with fertility needs in the future, we replaced tretinoin with isotretinoin, at the same dosage as tretinoin. Among the 66 patients, 41 were male and 25 were female and they ranged in age from 17 to 73 years, with an average age of 39.7 years. The 20 to 29 year old age group (32%, 21/66) had the most patients, followed by the 50 to 59 year old age group (23% 15/66) (Figure 1). In males, the lesions involved the penis, urinary meatus, perianal area and anus. In females, the vulva, urinary meatus, vagina, cervix and perianal area were involved. The statistics of the 66 patients revealed that the perianal area was the most common lesion location (Figure 2). We also found that the mean treatment cycles were different in various locations (Figure 3). Side effects of the ALA-PDT treatment combined with tretinoin were tolerable and short-lived. Almost all patients experienced mild burning pain during the irradiation. There were no reports of serious complications such as infections, scarring or stenosis. Each patient received ALA-PDT treatment combined with tretinoin once a week and effects were observed one week after each treatment to confirm whether it was necessary to continue treatment. Patients were followed up for 3 months after confirming the clearance of their lesions (Figure 4). All 66 patients had complete clinical remission (no visible warts on the perianal or genital areas three months after the last treatment) after 1 to 9 ALA-PDT treatments combined with tretinoin (average of 4.0 times). Of those, 13 patients (19.7%) only needed to receive one or two treatments, most patients (60.6%) needed 3 to 5 treatments, and a few patients (19.7%) needed more than 5 treatments to completely clear their lesions (Figure 5). Interestingly, we found that older patients required fewer ALA-PDT treatments combined with tretinoin to obtain clinical remission. We speculate that this may be related to inactive epidermal hyperplasia in older patients and the easy removal of viruses. Our results show that a complete response was achieved in all 66 cases of refractory anogenital CA treated with ALA-PDT combined with tretinoin. No recurrences were registered and the treatments were very well tolerated by the patients. Most patients achieved remission after 4 to 9 treatments with ALA-PDT combined with tretinoin, and we found that older patients responded better to ALA-PDT combined with tretinoin.



**Figure 4:** Pre- and post-treatment images of some cases. A: CA of the perianal area; B: complete resolution after treatment. C: CA of the vulvar and perivulvar area; D: complete resolution after treatment. E: CA of the vaginal area; F: complete resolution after treatment.



**Figure 5:** Treatment course of 66 patients with CA. A few patients (19.7%, 13/66) only needed to receive one or two treatments. The course of treatments for most patients was 3 to 5 weeks (60.6%, 40/66).

## Discussion

CA is characterized by verrucous lesions caused by human papillomavirus infections. In men, CA lesions are commonly found in the coronal sulcus of the penis as well as the prepuce. In women, CA lesions mainly appear at the labia majora, labia minora and the introitus vagina. Multiple therapies have been used to treat CA, including drugs, carbon dioxide lasers, photodynamic therapy and surgical resection [6,7]. However, CA has a high recurrence rate. The main factor resulting in CA recurrence is the continued existence of latent HPV and subclinical infections. In addition, the relapse of CA may be closely related to the abnormal function of an individual’s local immunity, as well as insufficient and/or inefficient treatment. ALA-PDT was developed in the 1990s and has been used to treat nonmalignant skin diseases. In recent years, ALA-PDT has been gradually applied to the treatment of CA. Grebenova et

al. [8] studied the mechanism of the cytotoxic effects of ALA-PDT on HL60 leukemia cells, and the results showed that ALA-based PDT initiates several intracellular signaling processes that lead to rapidly progressing apoptosis followed by slow necrosis. Another study showed that ALA-PDT seems to trigger both the apoptotic process and necrosis in HPV-infected keratinocytes according to the histological results. ALA-PDT is very selective and causes minimal damage to surrounding healthy tissues [9]. Moreover, compared with other methods, treatment with ALA-PDT has a low recurrence rate. ALA-PDT treatment can stimulate local immunity to treat CA. Studies have found that the numbers of CD4+ T lymphocytes and CD123+ plasmacytoid dendritic cells were increased and migrated to the superficial dermis within 24 h after treatment with ALA-PDT. In addition, treatment with ALA-PDT effectively reduced the HPV viral loads, which may be a reason for the significant reduction in the recurrence rate of CA [10]. Treatment of CA with ALA-PDT is usually associated with burning and/or stinging sensations after treatment. In our study, the side effects were slight and tolerable and no serious complications were reported. There was no evidence that less pain was associated with treatment failure, but some studies have suggested that more intense pain seems to be related to larger lesions and subsequently more pronounced swelling [11]. Combination therapies are effective for treating genital CA and preventing the recurrence of CA [12]. In this study, we used a combined tretinoin therapy. Retinoids are synthetic vitamin A derivatives that act on target cells by binding and/or activating nuclear receptors that lead to the expression of genes regulating cell growth and differentiation. A randomized placebo-controlled trial showed the effectiveness and safety of tretinoin to treat refractory cervical CA. The mechanism by which tretinoin has beneficial effects in HPV infections is still unknown, but it may be related to its endogenous antiproliferative effect. There is an inverse relationship between the concentration of retinoids and HPV-DNA in infected epithelial cells [13], indicating that retinoids downregulate viral replication. In addition, their strong

induction of apoptotic activity may also play a role. Studies have shown that combined treatments for CA are effective in the short term, with faster skin healing and fewer scars. In the long term, the risk of recurrence is greatly reduced. Because of the photosensitivity of tretinoin, we speculate that some complications or side effects may occur during ALA-PDT. However, compared with mono-tretinoin treatment, the combination therapy did not have other adverse reactions, and obtained better treatment results.

## Conclusion

In this study, the combination of ALA-PDT and tretinoin was used to treat refractory CA of 66 patients. Our results show that after 3 months of evaluation, the lesions of all 66 patients were completely cured without recurrence. We conclude that ALA-PDT combined with tretinoin is an effective and well-tolerated treatment for refractory CA that is associated with a low recurrence rate.

## Funding

The work was supported by the Foundation of the National Natural Science (No: 81673078).

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