

Topical 5-aminolevulinic acid photodynamic therapy improved refractory acne conglobata and perifolliculitis capitis abscedens et suffodiens rather than hidradenitis suppurativa

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Acne conglobata (AC), perifolliculitis capitis abscedens et suffodiens (PCAS) and hidradenitis suppurativa (HS) are uncommon refractory chronic, inflammatory, scarring diseases but cause serious damage to the quality of life. These three diseases are associated with follicular occlusion. Several studies indicated topical 5-aminolevulinic acid photodynamic therapy (ALA-PDT) improved follicular occlusion besides acne treatment. So we attempted to apply ALA-PDT to medicine resistant AC, PCAS and HS. Topical ALA-PDT was applied to 10 patients with AC, seven patients with PCAS and three patients with HS for more than three sessions. All the patients completed the dermatology life quality index (DLQI) questionnaire and were assessed for the efficacy at the baseline and on two weeks after each treatment. Adverse effects were recorded at each visit. The results showed 25.5% (5/20, two cases of AC and three cases of PCAS) of patients achieved excellent improvement after three sessions of PDT and another 60.0% (12/20, eight cases of AC and four cases of PCAS) of patients achieved good improvement. 15.0% (3/20, three cases of

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HS) got poor response (< 20% lesions clearance). Another five cases (three cases of AC and two cases of PCAS) also achieved excellent response after 5–7 sessions of PDT. We also found that papular/nodular, cyst/abscess showed higher clearance rate than sinus/fistula (88.5%, 86.1% versus 11.1%). DLQI was reduced after three sessions of PDT in AC and PCAS patients rather than HS patients. 5-ALA-PDT could improve refractory AC and PCAS but could not lead to improvement in late stage of HS. The efficacy increased with more treatment sessions.

Keywords: Acne conglobata; perifolliculitis capitis abscedens et suffodiens; hidradenitis suppurativa; aminolevulinic acid; photodynamic therapy.

1. Introduction

Acne conglobata (AC), marked by suppuration, cysts, sinuses, and scarring on face and back, is a severe form of cystic acne that is most difficult to manage. Perifolliculitis capitis abscedens et suffodiens (PCAS) is characterized by perifollicular pustules, suppurative nodules and fluctuating abscesses, as well as by intercommunicating sinus tracts on the scalp. Hidradenitis suppurativa (HS) is a recurrent, inflammatory, debilitating, skin follicular disease that usually presents after puberty with painful inflamed lesions in the axillary, inguinal, and anogenital regions. Yu and Cook¹ showed that follicular occlusion was the primary event in HS. The early and primary common event in AC, PCAS and HS was follicular occlusion in histology.² In 1956, Pillsbury, Shelley and Kligman coined the term “follicular occlusion triad” for the common association of AC, PCAS and HS.³ This implied that the pathogenesis of these three diseases is similar and they can be treated with similar methods. Mostly, these three types of diseases happened independently and a very small number of patients suffered from all of them. At the early stage the “follicular occlusion triad”, follicular orifice hyperkeratosis causes pilosebaceous metabolites accumulation and follicular occlusion and then leads to inflammation around the hair follicle. At the late stage, the inflammation destroys the folliculitis and other appendages including apocrine glands. So, at the early stage it manifests as inflammatory papule, nodules, cyst, abscess and at the late stage it manifests as sinus, fistula and scar. The key point of the differential diagnosis of these three diseases is the location: AC often occurs in the back, chest and buttocks, PCAS often occurs on scalp and HS often occurs in the armpits, groin and other apocrine gland rich areas.⁴ The three diseases often cause scar and even damage the patient’s physical and

mental health. Adverse effects on the quality of life for patients with these diseases were more severe than acne vulgaris, atopic dermatitis, psoriasis and other chronic diseases.⁵ Although many treatment methods including retinoic acid, glucocorticoid, antibiotics, hormones, tumor necrosis factor antagonist, dapsone and operation have been explored, the therapeutic effects are unsatisfactory. No matter what kind of method, frequent relapse and long-term treatment often make patients lose confidence for treatment. In recent years, 5-aminolevulinic acid photodynamic therapy (ALA-PDT) was successfully used for treating moderate and severe acne vulgaris.^{6–9} The mechanism of topical ALA-PDT is that the ALA is concentrated in hair follicle sebaceous gland unit through the skin and converts to light sensitive protoporphyrin IX and causes the photodynamic reaction when irradiated by 630 nm red light to kill *Propionibacterium acnes*, destroy sebaceous gland structure^{7,8} and improve follicular hyperkeratosis.¹⁰ The early common cause of follicular occlusion triad is follicular hyperkeratosis. Theoretically, ALA-PDT could improve the follicular occlusion triad. There are only a few reports about topical ALA-PDT on all these three kinds of follicular occlusion diseases. Here we treated 10 cases of AC, seven cases of PCAS and three cases of HS and summarized our experience.

2. Patients and Methods

2.1. Patient enrollment

We totally enrolled 20 cases of follicular occlusion disease treated by ALA-PDT in Shanghai Skin Disease Hospital from January 2009 to August 2011. All the cases were diagnosed by two doctors and fit the clinical and pathological criteria of AC, PCAS or HS and were resistant to previous treatment. All patients were informed about treatment

benefits, risks and adverse reactions, and other treatment options. All patients were voluntarily choice of PDT and signed the informed consent. All the patients ceased other treatments one month before ALA-PDT. All the patients completed at least three sessions of PDT and followed up at least for six months from the last treatment. Patients with PDT contraindication, diabetes mellitus or own high expectations were excluded. All patients agreed for clinical photos usage for academic communication. The treatment protocol was approved by the Shanghai Skin Disease Hospital Ethics committee.

2.2. ALA-PDT

The lesion surface was gently cleaned with saline. ALA cream (5%, wt/wt) was freshly prepared using ALA powder (Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co. Ltd., Shanghai, China) and applied evenly to target lesions. The ALA-applied area was occluded with cling film and covered with a black cloth for light protection for 4 h. After removing the excess cream, the target area was irradiated with a red LED device (633 nm \pm 6 nm, energy 126 J/cm²) (Omnilux Revive, Photo Therapeutics Ltd., Manchester, UK). The untreated area was protected by tin foil during irradiation. The similar PDT protocol was repeated at two-week intervals. Patients were advised to stay away from bright light for at least one day after ALA application.

2.3. Evaluation of therapeutic outcomes

Lesion types, location, and numbers were documented by visual examination and digital photographs before treatment and two weeks after each session of ALA-PDT. The primary outcome, defined as the change in lesion counts relative to baseline, was visually assessed blindly by two dermatologists at two weeks after each session. The numbers of inflammatory papule/nodular, cyst/abscess and sinus/fistula were recorded while the atrophy scar lesions were not recorded because the PDT did not improve it. Based on the lesion clearance rate, clinical responses relative to the baseline were rated as follows: Excellent response (\geq 90% improvement); Moderate response (50–89% improvement); Slight response (20–50% improvement); No response (< 20% improvement or worse). Recurrence

referred to new lesions developed after the excellent response. New lesions referred to new lesions developed after the last session of PDT. After the last session of treatment, monthly follow-up was carried out by visual examination for up to 6 months. Then we followed up once 3 months after 6 months.

2.4. Evaluation of DLQI and patient's satisfaction level

We evaluated the dermatology life quality index (DLQI) and patient's satisfaction level before treatment and two weeks after each session via a questionnaire. DLQI questionnaire includes 10 questions about how the skin disease affects day life or social activity. Each question scored 0 to 3 and the higher score means greater damage of life quality. The total score was 30. Patient satisfaction based on a self-evaluation was divided as "not so good", "ordinary", "good" and "excellent".

3. Results

3.1. Patient demographic data

We evaluated 10 cases of AC, seven cases of PCAS and three cases of HS (two cases also suffer from atrophy scar caused by pervious AC and PCAS) treated by ALA-PDT in Shanghai Skin Disease Hospital from January 2009 to August 2011. All the patients were males from 17 to 38 years old with the average age being 30 years. The average course of disease was six years (ranging from 1 to 10 years duration) (Table 1). There were 15 cases with smoking history. Before PDT, 12 patients had received oral use tretinoin and topical treatment

Table 1. Patient demographic data.

Patient demographic data	
Sex, F/M	0/20
Age (yr), range (mean)	17–38 (30)
Length of history (mo),	12–120 (72)
Lesion counts, range (mean)	
Inflammatory papule/nodular	0–40 (20.2)
Cyst/abscess	0–20 (8.1)
Sinus	0–30 (2.5)
Diseases subtypes, cases	
Acne conglobata	10 (50.0%)
Perifolliculitis capitis abscedens et suffodiens	7 (35.0%)
Hidradenitis suppurativa	3 (15.0%)

Table 2. Previous treatment and previous outcome of the patients.

Patient No.	Disease type	Previous treatment	Outcome of previous treatment
1	AC	Oral use tretinoin, Chinese traditional medicine, topical antibiotics	partially remission
2	AC	Oral use tretinoin, traditional medicine, topical antibiotics, topical benzoylperoxid	partially remission
3	AC	Oral use tretinoin, Chinese traditional medicine, topical antibiotics	partially remission
4	AC	Oral use tretinoin, Chinese traditional medicine, topical antibiotics	partially remission
5	AC	Oral use tretinoin, Chinese traditional medicine, topical antibiotics	partially remission
6	AC	Oral use tretinoin, topical antibiotics	partially remission
7	AC	Oral use tretinoin, topical antibiotics, and topical retinoid	partially remission
8	AC	Minocyclin, Chinese traditional medicine, topical antibiotics and topical retinoid	Relapse
9	AC	Minocyclin, topical antibiotics and topical retinoid	Relapse
10	AC	Minocyclin, topical antibiotics and topical retinoid	Relapse
11	PCAS	Oral use tretinoin, Chinese traditional medicine, topical antibiotics	partially remission
12	PCAS	Oral use tretinoin, Chinese traditional medicine, topical antibiotics	partially remission
13	PCAS	Oral use tretinoin, topical antibiotics	partially remission
14	PCAS	Oral use tretinoin, topical antibiotics	partially remission
15	PCAS	Minocyclin and Chinese traditional medicine, topical antibiotics	partially remission
16	PCAS	Minocyclin and Chinese traditional medicine, topical antibiotics	partially remission
17	PCAS	Minocyclin, oral corticosteroids, topical antibiotics	partially remission
18	HS	Oral use tretinoin and topical antibiotics	no remission
19	HS	Minocyclin and Chinese traditional medicine, topical antibiotics and fistulectomy	no remission
20	HS	Minocyclin and Chinese traditional medicine, topical antibiotics	partially remission

(seven patients received Chinese traditional medicine at the same time), eight patients received minocycline and topical treatment (five patients received Chinese traditional medicine at the same time) (details seen in Table 2). One patient with HS received anal fistulectomy one year before PDT. All the patients achieved partial remission and they expected a better response.

3.2. Clinical outcome

In general, all the patients with PCAS and AC achieved improvement while the patients with HS did not relieve. After three sessions of PDT, 25.0% (5/20, including two cases of AC and three cases of PCAS) of patients achieved excellent response with more than 90% of lesion clearance, 60.0% (12/20, including eight cases of AC and four cases of PCAS) of patients achieved moderate response with

Table 3. Lesion types of AC, PCAS and HS.

	Lesion type
AC	Many papules, cysts and abscesses, small amount of sinus/fistula; some scar formed at late stage.
PCAS	Many papules, cysts and abscesses, some sinus/fistul; some scar formed at late stage.
HS	Papules, cyst and abscess at early stage, many sinus/fistula and scars formed at late stage.

Note: Scars were not evaluated in this study.

Table 4. Lesion clearance rate after three sessions of PDT. Lesion clearance rate means remission lesion counts relative to baseline.

Lesion clearance rate	Excellent response $\geq 90\%$	Moderate response 50–89%	Slight response 20–49%	Poor response $< 20\%$
Session 1	1 (5.0%)	7 (35.0%)	9 (45.0%)	3 (15.0%)
Session 2	2 (10.0%)	11 (55.0%)	4 (20.0%)	3 (15.0%)
Session 3	5 (25.0%)	12 (60.0%)	0 (0.0%)	3 (15.0%)

Table 5. Lesion clearance rate of different lesion types after each session of PDT.

Lesion clearance rate	Popular/nodular	Cyst/abscess	Sinus
Session 1	43.4 ± 5.7%	43.0 ± 5.3%	5.6 ± 5.0%
Session 2	73.8 ± 12.8%	75.0 ± 11.7%	8.9 ± 5.1%
Session 3	88.5 ± 10.0%	86.1 ± 10.7%	11.1 ± 2.2%

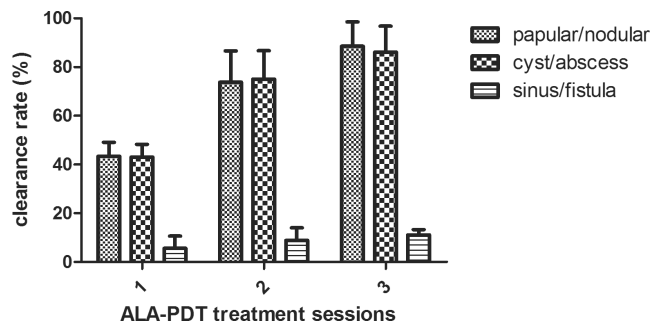


Fig. 1. Lesion clearance rate of different lesion types after each session of PDT. With more sessions of treatment, the clearance rate was increased. The clearance rate of popular, nodular, cyst and abscess was higher than sinus/fistula.

50–90% of lesion clearance, 15.0% (3/20, three cases of HS) of patients got poor response with less than 20% of lesion clearance (Table 4). With more sessions of PDT, it achieved higher lesion clearance rate and five more cases including three cases of AC and two cases of PCAS also achieved excellent response after 2–4 more sessions of PDT. Totally, 10 cases (50%, six cases of AC and four cases of PCAS) achieved excellent response ($\geq 90\%$ lesion clearance rate) after 3–7 sessions of ALA-PDT. Although the lesion counts of the patients with HS did not decrease, the patients felt better because the hard lesions became softer than before.

Meanwhile, we evaluated the clearance rate of different types of lesions and found that popular, nodular, cyst and abscess showed higher clearance rate than sinus/fistula (Fig. 1 and Table 3). Some of the clinical pictures before and after PDT are shown in Fig. 2.

3.3. DLQI evaluation

After completion of treatment, 25.0% (5/20) cases felt “excellent”, 50.0% (10/20) cases felt “good” and 10.0% (2/20) cases felt “ordinary”. The DLQI score



Fig. 2. Clinical pictures before and after PDT. (a)–(b) A 35 years old male with AC achieved more 90% lesions cleared after six sessions of PDT. (c)–(d) A 30 years old male with PCAS achieved all lesions cleared after three sessions of PDT. (e)–(f) A 32 years old male with HS achieved less than 20% lesions cleared after three sessions of PDT but he felt the stiffness of the axillary region relieved a lot.

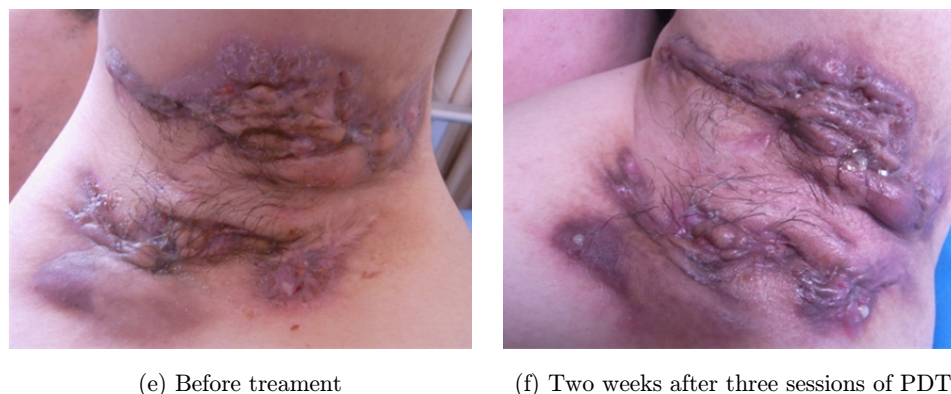


Fig. 2. (Continued)

decreased after PDT treatment except for the patients with HS. With more sessions of PDT, the DLQI score decreased more and the life quality improved more (Table 6). The DLQI score of two patients increased at the first session of PDT because of cyst rupture and exudation but decreased with more sessions.

3.4. Adverse reactions

All the patients suffered from itching, pain and edematous erythema of different levels within 1–7 days post PDT. All these responses were alleviated over time and disappeared in the second week post ALA-PDT. We did cool spray to relieve pain and edematous erythema. Pain killers were used when necessary. Within two weeks after the first session of PDT, some of the cysts and abscesses ruptured with exudation and crust. On the treatment day, two cases of AC had fever and were relieved the next day.

3.5. Follow-up

We followed up all the patients at least for one year after the last treatment. The patients achieved

excellent response ($\geq 90\%$ lesion clearance rate) including five cases of AC and five cases of PCAS (3–7 sessions PDT) kept remission without relapse for one year. In the patients with the moderate response (50%–89% lesion clearance rate), all the seven cases (five cases of AC and two cases of PCAS) developed new lesions during one year follow up. Among the seven cases, two cases were treated by ALA-PDT again and achieved remission. The other three cases were treated by topical Tazarotene Gel with oral minocycline or isotretinoin. The lesions in HS patients did not get worse nor were there remissions during one year.

4. Conclusion

5-ALA-PDT could improve AC and PCAS but could not lead to improvement in HS. The efficacy increased with more treatment sessions. During ALA-PDT, there were few side effects.

5. Discussion

AC, PCAS and HS are uncommon chronic, inflammatory, scarring diseases causing serious damage to the quality of life but are very hard to manage. Hair follicular occlusion has the same pathogenesis of these three diseases. These three diseases all manifest as inflamed nodular, cyst at the beginning and fibrous sinus at the late stage. In recent years, 5-ALA-PDT has been widely used in acne vulgaris. Topical use of 5-ALA on the surface of the skin can concentrate in the hair follicle sebaceous gland and convert to the light sensitizer protoporphyrin IX, then produce the photodynamic reaction by a specific wavelength light irradiation. The photodynamic reaction would kill

Table 6. Score of DLQI.

	HS ($n = 3$)	PCAS ($n = 7$)	AC ($n = 10$)
Baseline	26.67 \pm 1.15	8.14 \pm 2.79	12.9 \pm 3.48
Session 1	24.67 \pm 1.15	5.71 \pm 2.29	8.70 \pm 4.37*
Session 2	24.33 \pm 1.53	4.14 \pm 2.73*	5.70 \pm 3.59*
Session 3	24.33 \pm 1.53	1.00 \pm 0.82*	4.1 \pm 1.97*

Note: AC: acne conglobata; PCAS: perifolliculitis capitis abscedens et suffodiens; HS: hidradenitis suppurativa. (* $p < 0.05$, Paired-Sample T Test, compared with baseline).

Propionibacterium acnes and destroy the structure of sebaceous gland and improve the follicular hyperkeratosis. For the treatment of severe acne vulgaris,⁷⁻¹⁰ ALA-PDT is especially suitable for nodular cystic acne. Therefore, we attempt to treat follicular occlusion diseases by PDT. In this study, more than half of AC and PCAS patients achieved excellent response ($\geq 90\%$ lesions cleared) by treatment of 3-7 times, one year follow-up showed no recurrence. The efficacy increased with more sessions of PDT treatment. Some patients achieved partial remission, there were new rashes during follow-up, but continuous PDT was found to be effective. For the patient of HS, although the counts of the lesion did not reduce, the subjective feelings of patients improved and they felt the stiffness of the original lesions had become softer after three sessions of ALA-PDT. Why is it that the effect of PDT for AC and the PCAS is good but invalid for HS in our cases?

There are three possible reasons: types of skin lesions, sites of lesions and stage of the disease. As our cases showed, inflammatory papules, nodules, cysts and abscesses displayed good response while sinus/fistula displayed poor response (Table 3 and Fig. 1). AC and PCAS mostly present as papule, cyst and abscess, which responded well to PDT. While, there were many sinus/fistula which responded poorly to PDT in HS patients. So for patient enrollment of PDT, lesion types should be considered as an important factor. During the late stage of disease, sinus and fibrotic scars may obstruct penetration of ALA. So it showed poor response. All the three cases of HS were present as stage III (Hurley defined HS as three stages, stage I means isolated or abscess; stage II means multiple abscess, with sinus and scar formation; stage III means fusion sinus, abscess and scar formation, accompanied by inflammation and chronic purulent discharge).¹¹ Although in our cases we found better effect on scalp, face, chest, back than groin, armpits, it is hard to declare that the lesion site influences the effects because the numbers of sinus/fistulas on groin and armpits were more than the other sites. That is the limitation of our cases. In future study, more cases of HS at different stages are needed.

In previous research, Guilan Yang reported high cure rate of AC with ALA-PDT. In her study, patients received oral vitamin capsules and doxycycline, zinc gluconate and topical metronidazole gel plus PDT.⁶ In our cases, mono ALA-PDT showed

good effect on AC. Also, our study first reported the good effect of ALA-PDT on PCAS. The previous study of ALA-PDT on HS showed converse results.¹²⁻¹⁵ Gold *et al.* reported an improvement of 75-100% in four patients.¹⁴ Schweiger *et al.* observed a 50% reduction in mean lesion count after four weeks and a 29% reduction after eight weeks.¹⁵ Strauss *et al.* report negative results similar with our study.¹² Strauss also mentioned the limited penetration of ALA and light in fistula and fibrotic lesions. The late stage may reduce the efficacy. Recently, Rodriguez-Prieto *et al.* used intralesional PDT for the treatment of HS and showed good effect.^{16,17} Intralesional PDT will be a good choice for late sinus/fistula lesions. Saraceno *et al.* reported a case of HS achieved 80% remission of skin lesions treated by nine times of Methyl aminolaevulinate PDT.¹⁸ Increase in treatment sessions may also achieve good response for the early stage of HS. Fadel *et al.* reported topical PDT using methylene blue niosomal gel improved HS and even for Hurley stage three of HS¹⁹ which means novel photosensitizer may increase the efficacy of PDT for HS.

In conclusion, topical ALA-PDT could improve AC and PCAS and keep long remission time. In addition, inflammatory papules, nodules, cysts and abscesses showed good response while sinus/fistula showed poor response. The efficacy increased with more treatment sessions.

The main side effect of topical ALA-PDT was acute inflammatory pain and swelling and topical surface anesthetic or cold spray could relieve it. The first session of treatment develops a burst cyst and abscess drainage, pre-appropriate measures may increase patient comfort.

Treatment with the use of other light sources, other photosensitizers at different concentrations, different incubation times and additional applications in case of recurrent lesions and the combination with other treatments will need to be analyzed for the future study.

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