

## Combination treatment with photodynamic therapy and laser therapy in chronic hyperplastic candidiasis: A case report

Wenqing Zhang, Shuangshuang Wu, Xu Wang, Pan Wei<sup>\*</sup>, Zhimin Yan<sup>\*</sup>

Department of Oral Medicine, Peking University School and Hospital of Stomatology and National Center of Stomatology and National Clinical Research Center for Oral Diseases and National Engineering Laboratory for Digital and Material Technology of Stomatology, No.22, Zhongguancun South Avenue, Haidian District, Beijing, China

### ARTICLE INFO

#### Keywords:

Chronic hyperplastic candidiasis  
Photodynamic therapy  
Laser therapy

### ABSTRACT

Chronic hyperplastic candidiasis (CHC) is a rare subtype of oral candidiasis. Due to the malignant transformation potential of this disease, its treatment deserves attention. Here we report a refractory case of an 85-year-old female with chronic hyperplastic candidiasis treated with combined photodynamic therapy and laser therapy with a superior clinical result. The patient had a two-months history of thick white plaque on her upper inner lip. Conventional antifungal therapy and repeated photodynamic therapy contributed slightly improvement to the hyperkeratosis lesion, and then it was removed by laser therapy. Recurrence was found at the follow-up visit of eighth-week, and the recurrent lesion was removed again by laser therapy and prophylactic photodynamic therapy was performed. The patient is still under follow-up.

### 1. Introduction

Chronic hyperplastic candidiasis (CHC) is a rare subtype of oral candidiasis. Different from other types of oral candidiasis, CHC has its own particularity since its lesions may progress to various degrees of epithelial dysplasia and even malignant transformation if they are not treated timely and effectively [1]. In our cohort study, it was found that despite various treatments had been attempted for the management of CHC, there is lack of evidence as to the definite effectiveness [2]. 5-aminolevulinic acid (ALA) mediated PDT has been reported successful treatment of CHC in previously case report [3]. Here, we report a refractory case of CHC treated with combination of photodynamic therapy (PDT) and laser therapy with a superior clinical result.

### 2. Case report

An 85-year-old female presented at our department with chief complaint of thick white plaque on her upper inner lip for two months. The patient also felt obvious pain, which got worse when eating spicy food. In addition, the patient wore complete denture for more than 40 years and had a 45-year history of smoking. Her medical history included mild Alzheimer's disease, hypertension, diabetes and coronary heart disease under regimented control.

Intraoral examination revealed the presence of a 4 × 3 cm<sup>2</sup>

irregularly shaped thick white verrucous plaque on the inner side of the upper lip (Fig. 1A), and extensive lingual papilla atrophy of the dorsum of the tongue. Smear test with 10% KOH showed fungal hyphae under the microscope. Saliva mycological culture showed positive of *Candida albicans*. A biopsy of the white lesion was performed and histopathological examination revealed hyperkeratosis of the epithelium, with inflammatory cell infiltration and exudation, and significant proliferation of the spinous layer (Fig. 2A). Periodic acid-Schiff staining revealed abundant hyphae extending vertically into the epithelial layer and micro-abscesses formation in the subepithelium (Fig. 2B). Eventually, a diagnosis of chronic hyperplastic candidiasis was established based on clinical manifestation, mycological and histopathological findings.

The patient was initially instructed to quit smoking and keep denture clean by sodium bicarbonate tablets. However, she could not fully follow the advice to quit smoking because of the cognitive impairment caused by Alzheimer's disease. Besides, she was treated with fluconazole for two weeks and nystatin for four weeks, but the thick white plaque improved slightly. Considering the unsatisfactory antifungal effect, photodynamic therapy was considered as an alternative therapy. Plum-blossom needle was used to pre-treat the thick white plaque, then 20% ALA (Fudan Zhangjiang Co., Ltd., Shanghai, China) gel was applied topically to the thick white plaque for two hours, followed by irradiation with a 632 nm laser (LH-600, Leiye Technology Co., Ltd, Tianjin, China, spot diameter 1 cm, power density 500 mW/cm<sup>2</sup>, dosage 90–180 J/cm<sup>2</sup>,

<sup>\*</sup> Corresponding authors.

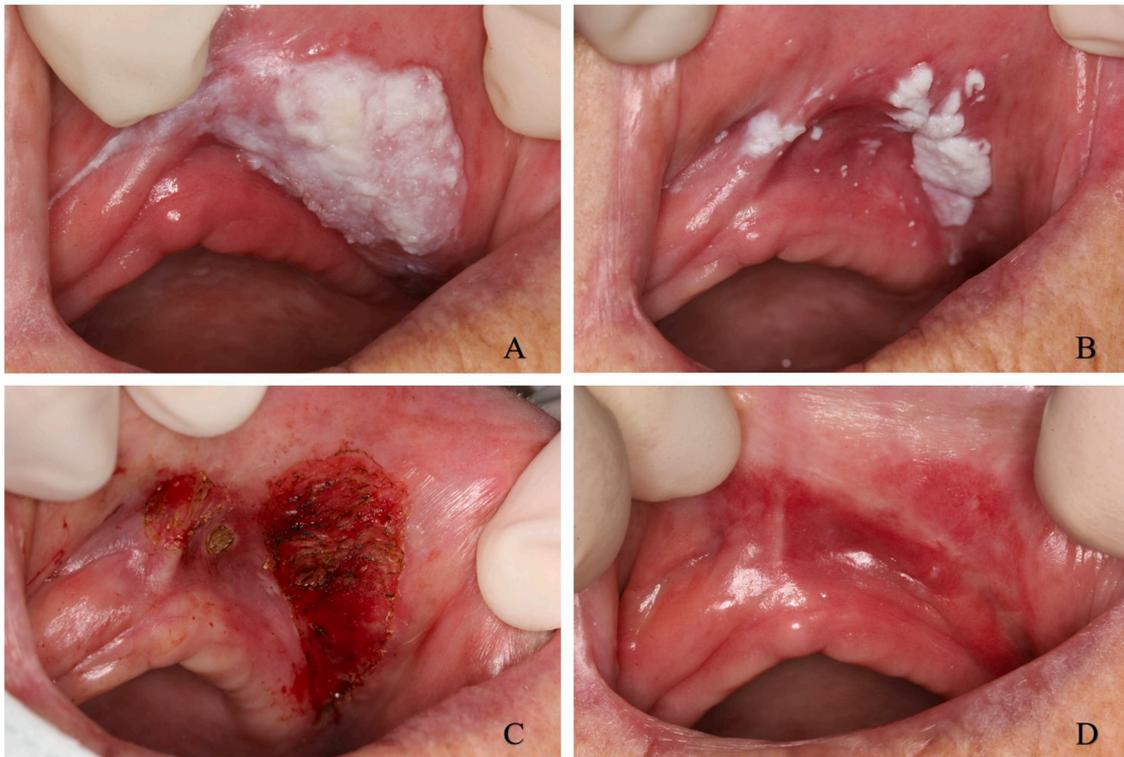
E-mail addresses: [dent\\_wei@163.com](mailto:dent_wei@163.com) (P. Wei), [yzhimin96@163.com](mailto:yzhimin96@163.com) (Z. Yan).

<https://doi.org/10.1016/j.pdpdt.2022.102819>

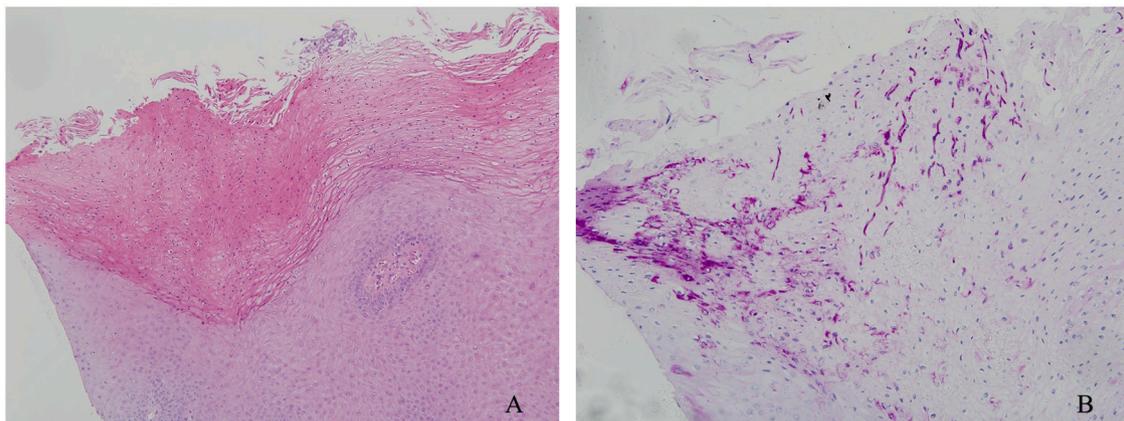
Received 2 March 2022; Received in revised form 9 March 2022; Accepted 17 March 2022

Available online 22 March 2022

1572-1000/© 2022 Elsevier B.V. All rights reserved.



**Fig. 1.** A. Thick white verrucous plaque on the inner side of the upper lip; B. Only part of the lesion subsided after three times of ALA-PDT; C, D. The remaining lesion was removed by the semiconductor laser.



**Fig. 2.** A. Histopathologic manifestations of the biopsy showed hyperkeratosis of the epithelium and no epithelial dysplasia (H&E,  $\times 10$  magnification); B. Numerous hyphae perpendicular to the stratum corneum (PAS,  $\times 20$  magnification).

three minutes per spot). The ALA-PDT was totally performed three times at two-week intervals, but only part of the lesion subsided (Fig. 1B). The semiconductor laser (4.5 W) was used afterwards to remove the remaining lesion (Fig. 1C, D). We followed up the patient and found that tiny white spotted lesions recurred at the eighth week, then laser was performed to remove the residual lesions and prophylactic photodynamic therapy was performed at the mean time. The only adverse event observed after PDT and laser therapy was local ulceration and pain, which subsided after application of topical lidocaine gel. So far, the patient is still under close follow-up.

### 3. Discussion

Chronic hyperplastic candidiasis (CHC) is a rare and refractory subtype of oral candidiasis. In our previous retrospective cohort study, it

was revealed that 20.83% of CHC patients had varying degrees of epithelial dysplasia and 4.17% had malignant transformation [2]. Although multiple methods were attempted for the management of CHC, including antifungal therapy, isotretinoin and surgical management, there is currently no evidence-based guideline for the management of CHC. Despite conventional photodynamic therapy (PDT) and ablative laser treatment could be considered as alternative options for the treatment of CHC, up to date little evidence are available from the clinical aspects. Therefore, it is essential to explore the management strategy with both effectiveness and safety in eliminating the lesions and in preventing malignant transformation and recurrence of CHC.

PDT is a promising minimal invasive therapeutic technique, which selectively destroys target tissues through the combination of photosensitizer and corresponding light source. In recent years, topical PDT has been used as a therapeutic regimen for oncologic and infectious

conditions, such as actinic keratosis, squamous cell carcinoma *in situ*, and human papilloma virus (HPV) and fungal-related lesions [3,4]. PDT has the potential to deliver antimicrobial treatment to a specific lesion and may therefore be of interest in the management of superficial fungal infections. However, it was reported that deeper cutaneous fungal infections such as cutaneous *Candida* granuloma are difficult to treat and treatment with antifungal drugs are associated with low cure and high relapse rate. Cai et al. reported a case with cutaneous granuloma caused by *C. albicans* that was refractory to itraconazole was successfully treated with two sessions of ALA-PDT [5]. However, some studies also found cases refractory to antifungal drugs with PDT treatment, which may partially be explained with limited penetration of both photosensitizer and the corresponding light [6].

For chronic hyperplastic candidiasis, it is more similar to deep fungal infection since hyphae extending vertically into the whole epithelial layer and micro-abscesses forming underneath. Practically, the sensitizers have a limited penetration depth of 2 mm, so that PDT is only effective for superficial lesions limited in thickness. To overcome the limitations to the use of conventional PDT, various methods including plum-blossom needle, ablative laser and micro-needle puncture, have been used as a pre-treatment to debulk or drill the lesions to assist penetration of the photosensitizer [7]. In this case, ALA PDT has been shown to be effective in chronic hyperplastic candidiasis, but treatment can be limited with light attenuation by thick lesions and some adjunctive treatment is required. Considering the patient's age and to tolerance to retreatments, mono laser therapy was applied with shorter duration and less pain in the context of combined therapy, followed by prophylactic photodynamic therapy in combination to prevent the recurrence and enhances the efficacy.

To our knowledge, chronic hyperplastic candidiasis is frequently refractory to antifungal treatment and it lacks of effective treatment strategies. This case revealed that combination of photodynamic therapy with laser therapy has potential to be a practically safe and well-tolerated treatment alternative for chronic hyperplastic candidiasis, especially for the lesions with thick keratosis and deep infection. The patient is still being followed up, and the long-term efficacy remains to be observed.

## Funding

The work was supported by the grant from the Program for New Clinical Techniques and Therapies of Peking University School and

Hospital of Stomatology (PKUSSNCT- 20B08) and National Natural Science Foundation of China (81570985).

## Ethical approval

Informed consent was obtained from patient for publication and unidentified image.

## CRediT authorship contribution statement

**Wenqing Zhang:** Writing – original draft, Data curation. **Shuangshuang Wu:** Data curation. **Xu Wang:** Resources. **Pan Wei:** Writing – review & editing, Supervision. **Zhimin Yan:** Writing – review & editing, Supervision.

## Declaration of Competing Interest

No conflict of interest.

## References

- [1] M.A. Sitheeque, L.P. Samaranyake, Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia), *Crit. Rev. Oral. Biol. Med.* 14 (4) (2003) 253–267, <https://doi.org/10.1177/154411130301400403>.
- [2] W. Zhang, S. Wu, X. Wang, Y. Gao, Z. Yan, Malignant Transformation and treatment recommendations of chronic hyperplastic candidiasis—a six-year retrospective cohort study, *Mycoses* 64 (11) (2021) 1422–1428, <https://doi.org/10.1111/myc.13371>.
- [3] B. Li, X. Fang, X. Hu, H. Hua, P. Wei, Successful treatment of chronic hyperplastic candidiasis with 5-aminolevulinic acid photodynamic therapy: a case report, *Photodiagnosis Photodyn. Ther.* 17 (37) (2021), 102633, <https://doi.org/10.1016/j.pdpdt.2021.102633>.
- [4] M. Kim, H.Y. Jung, H.J. Park, Topical PDT in the treatment of benign skin diseases: principles and new applications, *Int. J. Mol. Sci.* 16 (2015) 23259–23278, <https://doi.org/10.3390/ijms161023259>.
- [5] Q. Cai, L.J. Yang, J. Chen, H. Yang, Z.Q. Gao, X.L. Wang, Successful sequential treatment with itraconazole and ALA-PDT for cutaneous granuloma by candida albicans: a case report and literature review, *Mycopathologia* 183 (5) (2018) 829–834, <https://doi.org/10.1007/s11046-018-0267-4>.
- [6] Y. Yang, Y. Hu, J. Zhang, X. Li, C. Lu, Y. Liang, L. Xi, A refractory case of chromoblastomycosis due to *Fonsecaea monophora* with improvement by photodynamic therapy, *Med. Mycol.* 50 (6) (2012) 649–653, <https://doi.org/10.3109/13693786.2012.655258>.
- [7] X. Wang, Y. Han, J. Jin, Z. Cheng, Q. Wang, X. Guo, W. Li, H. Liu, Plum-blossom needle assisted photodynamic therapy for the treatment of oral potentially malignant disorder in the elderly, *Photodiagnosis Photodyn. Ther.* 25 (2019) 296–299, <https://doi.org/10.1016/j.pdpdt.2019.01.011>.