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Successful treatment of chronic hyperplastic candidiasis with 5-aminolevulinic acid photodynamic therapy: A case report

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ABSTRACT

Chronic hyperplastic candidiasis (CHC) is a chronic oral mucosal infection caused by *Candida*. Refractory hyperplastic lesions may lead to epithelial dysplasia and carcinogenesis. Traditional surgical resection may cause irreversible damage and effect the patient's quality of life. This paper reports the case of a 63-year-old man with CHC. After routine treatment, local hyperplastic lesions remained. Photodynamic therapy with ALA was applied to the hyperplastic lesions and yielded satisfactory results, with no recurrence at 1 year. This case report describes a promising, effective method for the treatment of CHC.

1. Introduction

Chronic hyperplastic candidiasis (CHC) is a chronic oral mucosal infection caused by *Candida*. It is characterized mainly by *Candida* leukoplakia and hyperplasia with a nodular or speckled appearance. Most lesions involve the cheeks, tongue, and palate, often accompanied by angular stomatitis [1–3]. CHC is more likely to develop in middle-aged men who smoke [4]. Persistent hyperplastic lesions may lead to epithelial dysplasia and malignant transformation [5]. Up to 15% of CHC lesions show dysplasia, necessitating close monitoring of hyperplastic lesions [2]. The treatment of candidiasis entails the elimination or treatment of any underlying cause or identifiable risk factor [2,3,6]. Common CHC treatments include the removal of causes, control of infection, and surgical resection of hyperplastic lesions [2,4,7]. Antifungal treatment has no obvious effect on most hyperplastic lesions; [3] surgical resection is required. Wide surgical resection of large lesions inevitably affects patients' quality of life and tissue function [2,8]. Thus, the exploration of new disease-control methods that maintain the appearance and function of soft tissues as much as possible is needed.

Photodynamic therapy (PDT) involves the use of photosensitisers that produce reactive oxygen species when exposed to specific light wavelengths and damage specific abnormal tissues, cells, or microorganisms to achieve therapeutic effects. This cytotoxic effect is highly selective for diseased tissues, such as inflamed and cancer tissues, and causes few adverse reactions [8]. PDT has been used widely to treat local inflammatory diseases, epithelial dysplasia, and cancer [9–11].

PDT also has anti-*Candida* effects, inhibiting *Candida albicans* plaque biofilms *in vitro*. [12] In a mouse model of *C. albicans* infection, manifestations disappeared after 5 days of PDT. [6] PDT was also used to treat a case of cutaneous granuloma caused by *C. albicans*. [13] To our knowledge, however, no report describes the use of PDT for oral CHC. We report the application of PDT in the treatment of CHC.

2. Case report

A 63-year-old man with a 40-year smoking history was referred to the Department of Oral Medicine, Peking University Hospital of Stomatology. He complained of a red patch at the center of his tongue dorsum, which had been present for 2 years. It had enlarged gradually, and the patient felt pain when eating spicy food. His medical history was non-contributory. He also denied any other symptom, such as a skin, nail, or genital lesion.

Physical examination revealed a $2 \times 2.5\text{-cm}^2$ red patch at the center of the tongue dorsum, with nodular hyperplasia and atrophy of the lingual papilla, surrounded by white keratotic lesions (Fig. 1). The initial clinical impression was fungal infection. Saliva culture showed positive of *Candida albicans*. Histopathological examination of a biopsy sample from the dorsal tongue lesion revealed mild to moderate abnormal

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Fig. 1. Photograph of the lesion before treatment

epithelial hyperplasia, with microabscesses and chronic inflammatory-cell infiltration in the lamina propria. Periodic acid–Schiff staining of tissue sections showed fungal invasion of the epithelium (Fig. 2A, B). A comprehensive review of the patient's medical history, current clinical manifestations, and histopathological results led to the diagnosis of CHC with mild to moderate epithelial dysplasia.

The patient was instructed to quit smoking and was given local antifungal treatment, including nystatin and sodium bicarbonate tablets and miconazole nitrate cream. One month later, the discomfort at the back of the tongue had been relieved slightly, but the nodular hyperplasia, lingual papilla atrophy, and surrounding white lesions on the tongue dorsum persisted (Fig. 3). Given the poor improvement after 1 month of medication, we applied PDT to the hyperplastic lesions. First, 20% 5-aminolevulinic acid (ALA) was prepared as a fresh thermosensitive hydrogel, and a piece of medical cotton containing the 20% gel was placed on the tongue dorsum for 2 hours. The area was then irradiated with a 632-nm laser (600 mW) for 10 minutes. The patient underwent three PDT sessions at 2-week intervals. After treatment, the atrophic area of the tongue dorsum had improved significantly, and the hyperplastic lesions had disappeared (Fig. 4).

3. Discussion

CHC is a rare type of oral candidiasis characterized mainly by *Candida* leukoplakia or hyperplasia, which may be nodular or speckled in appearance. Up to 15% of CHC lesions become dysplastic, with a risk of malignant transformation [5]. Increased p53 in oral chronic hyperplastic candidiasis suggests an increased potential for malignant change in the epithelium, higher than that of normal tissues [14]. Thus, the surgical resection using laser or surgical scalpel of hyperplastic lesions is recommended [2]. In this way, CO2 laser can be the treatment choice, since it offers a number of both intra- and postoperative advantages [15]. However, when laser was used for large-area lesions, it also affect the appearance and function.

Here, we report on a patient with a large hyperplastic lesion on the dorsal tongue. After 1 month of antifungal drug treatment, the lesion remained. The lesion was suspected to be related to his 40-year smoking history. Smoking is an important risk factor for CHC [2,16,17]. In India, 98% of patients with *C. albicans* infection have smoked or chewed tobacco [18]. Smoking correlates with oral *Candida* colonization [19]. Active smoking can inhibit antibody responses and reduce T-lymphocyte proliferation and neutrophil phagocytosis [20]. It can also lead to epithelial changes, including epithelial keratosis and increased hydrophobicity [19], which are conducive to *Candida* colonization. The removal of extensive hyperplastic lesions on the tongue dorsum by conventional surgery affects patients' speech and swallowing functions. To preserve the greatest function and to control infection and eliminate proliferative lesions, we applied ALA-PDT in this case.

PDT has highly selective cytotoxic effects on inflammatory tissues and dysplastic cells, selectively destroys diseased tissues, and has few adverse effects [8]. It has been used to cure epithelial dysplasia. PDT induces an aseptic inflammatory response, increases systemic proinflammatory factors [21], and prompts the rapid accumulation of neutrophils, which fight abnormal proliferative cells [22]. PDT using ALA for dysplasia of the mouth produces consistent epithelial necrosis with excellent healing and is a simple and effective way to manage these patients [23]. ALA is an excellent photosensitizer whose small size enables its free entry into the stratum corneum of target cells [24]. Then, PDT can be applied to quickly remove ALA from the tissue. Compared with other photosensitizers, ALA has phototoxic and non-cumulative toxic effects, and a short service life [24,25]. Adverse reactions to ALA include pain, local erosions, and ulcers. Furthermore, PDT is an

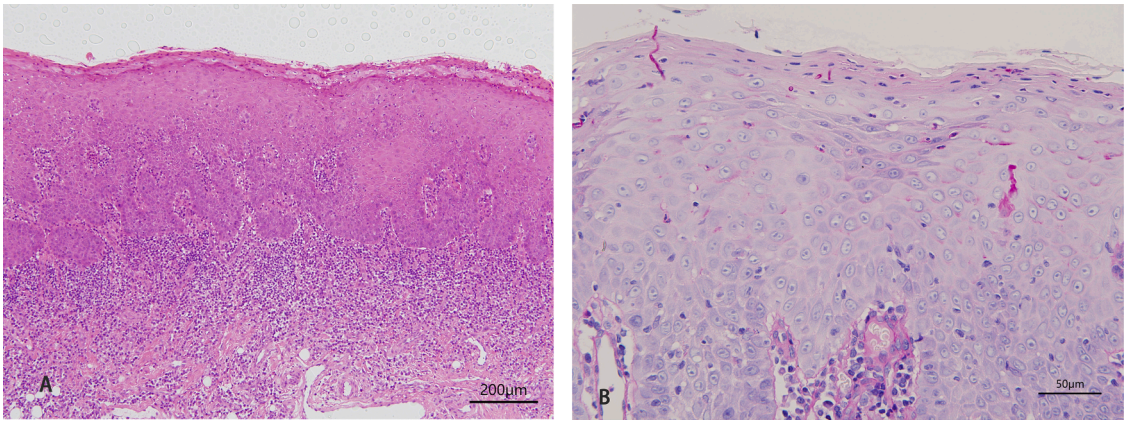

Fig. 2. Histopathological examination. A. Hematoxylin and eosin staining showed mild to moderate epithelial dysplasia. B. Periodic acid–Schiff–stained tissue sections showed *Candida* hyphae (+)

Fig. 3. Photograph taken after routine local antifungal treatment

Fig. 4. Photograph taken after three PDT sessions

alternative antimicrobial approach to infectious disease [26]. Wilson and others first discovered it in 1992 that PDT can be used to kill oral bacteria [27,28]. ALA-PDT affects drug-resistant *Candida* and inhibits *C. albicans* biofilms *in vitro* [12,29]. It also eliminates *Candida* on denture surfaces [30]. High concentrations of ALA metabolites generate free radicals in a variety of ways [31] to destroy *C. albicans*. In a mouse model of *C. albicans* infection, no *C. albicans* was detected after 5 days of PDT [6]. Another animal experiment showed that ALA-PDT affects innate immunity and promotes the host defense against *C. albicans* infection. And ALA-PDT is non-toxic to the host and can effectively inhibit the growth of C. albicans [32].

The administration methods of photosensitisers include systemic administration including oral and intravenous and local administration to penetrate the mucosa under occlusive dressing [33]. Considering this patient was outpatient, we chose local administration to penetrate the mucosa to avoid prolonged skin photosensitivity. The patient received PDT using ALA three times. Different photosensitisers can also be considered to treat in one session if the treatment effect is unsatisfactory.

Here, we report a promising, effective method for the treatment of CHC. To our knowledge, this case report is the first to describe the application of PDT to CHC with good clinical effect. Large clinical studies are needed to confirm the efficacy and safety of this treatment.

Conflict of Interest

The authors report that they have no conflict of interest related to this work.

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The patient and his family members consented to the publication of the case report details.

References

[1] PA Krishnan, Fungal infections of the oral mucosa[J], Indian J Dent Res 23 (5) (2012) 650–659, https://doi.org/10.4103/0970-9290.107384.
[2] MA Sitheeque, LP. Samaranayake, Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia)[J], Crit Rev Oral Biol Med 14 (4) (2003) 253–267, https://doi.org/10.1177/154411130301400403.
[3] JW Millsop, N. Fazel, Oral candidiasis[J], Clin Dermatol 34 (4) (2016) 487–494, https://doi.org/10.1016/j.clindermatol.2016.02.022.
[4] D Williams, M. Lewis, Pathogenesis and treatment of oral candidosis[J], J Oral Microbiol 3 (2011), https://doi.org/10.3402/jom.v3i0.5771.
[5] S Tamgadge, A Tamgadge, A Pillai, et al., Association of Candida sp. with the Degrees of Dysplasia and Oral Cancer: A Study by Calcofluor White under Fluorescent Microscopy[J], Iran J Pathol 12 (4) (2017) 348–355, https://doi.org/10.30699/ijp.2017.27991.
[6] F Freire, C Ferraresi, AO Jorge, et al., Photodynamic therapy of oral Candida infection in a mouse model[J], J Photochem Photobiol B 159 (2016) 161–168, https://doi.org/10.1016/j.jphotobiol.2016.03.049.
[7] PG Pappas, CA Kauffman, D Andes, et al., Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America[J], Clin Infect Dis 48 (5) (2009) 503–535, https://doi.org/10.1086/596757.
[8] I Khan, PR Arany, Photobiomodulation Therapy Promotes Expansion of Epithelial Colony Forming Units[J], Photomed Laser Surg 34 (11) (2016) 550–555, https://doi.org/10.1089/pho.2015.4054.
[9] M Pietruska, S Sobaniec, P Bernaczyk, et al., Clinical evaluation of photodynamic therapy efficacy in the treatment of oral leukoplakia[J], Photodiagnosis Photodyn Ther 11 (1) (2014) 34–40, https://doi.org/10.1016/j.pdpdt.2013.10.003.
[10] W Jerjes, T Upile, Z Hamdoon, et al., Photodynamic therapy outcome for T1/T2 N0 oral squamous cell carcinoma[J], Lasers Surg Med 43 (6) (2011) 463–469, https://doi.org/10.1002/lsm.21071.
[11] H Jajarm, R Asadi, E Bardideh, et al., The effects of photodynamic and low-level laser therapy for treatment of oral lichen planus-A systematic review and meta-analysis[J], Photodiagnosis Photodyn Ther 23 (2018) 254–260, https://doi.org/10.1016/j.pdpdt.2018.07.001.
[12] H Shi, J Li, C Peng, et al., The inhibitory activity of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) on Candida albicans biofilms[J], Photodiagnosis Photodyn Ther 34 (2021), 102271, https://doi.org/10.1016/j.pdpdt.2021.102271.
[13] Q Cai, L J Yang, J Chen, et al., Successful Sequential Treatment with Itraconazole and ALA-PDT for Cutaneous Granuloma by Candida albicans: A Case Report and Literature Review[J], Mycopathologia 183 (5) (2018) 829–834, https://doi.org/10.1007/s11046-018-0267-4.

[14] M R Darling, C Mccord, L Jackson-Boeters, et al., Markers of potential malignancy in chronic hyperplastic candidiasis[J], J Investig Clin Dent 3 (3) (2012) 176–181, https://doi.org/10.1111/j.2041-1626.2012.00120.x.
[15] M Tamarit-Borrás, E Delgado-Molina, L Berini-Aytés, et al., Removal of hyperplastic lesions of the oral cavity. A retrospective study of 128 cases[J], Med Oral Patol Oral Cir Bucal 10 (2) (2005) 151–162.
[16] RG Sherman, L Prusinski, MC Ravenel, et al., Oral candidosis[J], Quintessence Int 33 (7) (2002) 521–532, https://doi.org/10.1067/moe.2002.123828.
[17] A Akpan, R. Morgan, Oral candidiasis[J], Postgrad Med J 78 (922) (2002) 455–459, https://doi.org/10.1136/pmj.78.922.455.
[18] DK Daftary, FS Mehta, PC Gupta, et al., The presence of Candida in 723 oral leukoplakias among Indian villagers[J], Scand J Dent Res 80 (1) (1972) 75–79, https://doi.org/10.1111/j.1600-0722.1972.tb00265.x.
[19] E S Shin, S C Chung, Y K Kim, et al., The relationship between oral Candida carriage and the secretor status of blood group antigens in saliva[J], Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 96 (1) (2003) 48–53, https://doi.org/10.1016/s1079-2104(03)00160-4.
[20] G Piaggeschi, S Rolla, N Rossi, et al., Immune Trait Shifts in Association With Tobacco Smoking: A Study in Healthy Women[J], Front Immunol 12 (2021), 637974, https://doi.org/10.3389/fimmu.2021.637974.
[21] SO Gollnick, SS Evans, H Baumann, et al., Role of cytokines in photodynamic therapy-induced local and systemic inflammation[J], Br J Cancer 88 (11) (2003) 1772–1779, https://doi.org/10.1038/sj.bjc.6600864.
[22] CM Brackett, JB Muhitch, SS Evans, et al., IL-17 promotes neutrophil entry into tumor-draining lymph nodes following induction of sterile inflammation[J], Journal of immunology (Baltimore, Md: 1950) 191 (8) (2013) 4348–4357, https://doi.org/10.4049/jimmunol.1103621.
[23] K F Fan, C Hopper, P M Speight, et al., Photodynamic therapy using 5-aminolevulinic acid for premalignant and malignant lesions of the oral cavity[J], Cancer 78 (7) (1996) 1374–1383, https://doi.org/10.1002/(sici)1097-0142(19961001)78:7<1374::Aid-cncr2>3.0.Co;2-l.
[24] M Ikeh, Y Ahmed, J Quinn, Phosphate Acquisition and Virulence in Human Fungal Pathogens[J], Microorganisms 5 (3) (2017), https://doi.org/10.3390/microorganisms5030048.
[25] PC Kousis, BW Henderson, PG Maier, et al., Photodynamic therapy enhancement of antitumor immunity is regulated by neutrophils[J], Cancer Res 67 (21) (2007) 10501–10510, https://doi.org/10.1158/0008-5472.CAN-07-1778.
[26] M R Hamblin, T. Hasan, Photodynamic therapy: a new antimicrobial approach to infectious disease?[J], Photochemical & Photobiological Sciences 3 (5) (2004) 436–450, https://doi.org/10.1039/B311900A.
[27] M Wilson, J Dobson, W. Harvey, Sensitization of oral bacteria to killing by low-power laser radiation[J], Curr Microbiol 25 (2) (1992) 77–81, https://doi.org/10.1007/bf01570963.
[28] M. Wilson, Photolysis of oral bacteria and its potential use in the treatment of caries and periodontal disease[J], J Appl Bacteriol 75 (4) (1993) 299–306, https://doi.org/10.1111/j.1365-2672.1993.tb02780.x.
[29] G Greco, S Di Piazza, J Chan, et al., Newly formulated 5% 5-aminolevulinic acid photodynamic therapy on Candida albicans[J], Photodiagnosis Photodyn Ther 29 (2020), 101575, https://doi.org/10.1016/j.pdpdt.2019.10.010.
[30] EG Mima, AC Pavarina, DG Ribeiro, et al., Effectiveness of photodynamic therapy for the inactivation of Candida spp. on dentures: in vitro study[J], Photomed Laser Surg 29 (12) (2011) 827–833, https://doi.org/10.1089/pho.2011.3022.
[31] EJ Bechara, Oxidative stress in acute intermittent porphyria and lead poisoning may be triggered by 5-aminolevulinic acid[J], Braz J Med Biol Res 29 (7) (1996) 841–851, https://doi.org/10.1515/botm.1996.39.1-6.401.
[32] X Huang, M Xu, W Pan, et al., Antimicrobial and immunomodulatory responses of photodynamic therapy in Galleria mellonella model[J], BMC Microbiol 20 (1) (2020) 196, https://doi.org/10.1186/s12866-020-01882-9.
[33] JS Mccaughan Jr., JT Guy, W Hicks, et al., Photodynamic therapy for cutaneous and subcutaneous malignant neoplasms[J], Arch Surg 124 (2) (1989) 211–216, https://doi.org/10.1001/archsurg.1989.01410020081013.