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Successful in situ 5-aminolevulinic acid photodynamic therapy (5-ALA PDT) in 53-year-old female presented with cutaneous squamous cell carcinoma

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Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cutaneous SCC, cSCC), as certain forms of non-melanoma skin cancer (NMSC) or keratinocyte carcinoma (KC), are the most common forms of malignant neoplasm worldwide (Sharp et al., 2004). BCC and cutaneous SCC have been identified as two major components of NMSC, comprising one-third of all malignancies (Burton et al., 2016). Generally speaking, patients with NMSC tend to have relatively favorable survival outcomes, while different histopathological subtypes of NMSC exhibit distinct biological behaviors (Stătescu et al., 2023). Keratinocyte carcinoma, though not considered as deadly as melanoma, tends to metastasize if left untreated (Civantos et al., 2023; Nanz et al., 2024). Cutaneous squamous cell carcinoma can evolve locally, then aggressively metastasize, invade, and even lead to fatal consequences in a subset of patients (Winge et al., 2023). A solid, pigmented, smooth plaque, or a hyperkeratotic papule with or without central ulceration and hemorrhage appears to be characteristic of cSCC (Thompson et al., 2016; Zhou et al., 2023). Of note, a rare type of intraepidermal cSCC in situ often appears as a velvety, demarcated, slightly raised erythematosus plaque on the genitalia of men (Yamaguchi et al., 2016). Accounting for approximately 16.0% of scalp tumors and with a rising incidence, cSCC is now the second most frequent non-melanoma skin cancer in humans (Verdaguer-Faja et al., 2024). According to the latest statistics, up to 2-5% of cSCC in situ may gradually progress into invasive cSCC in the final step (Rentroia-Pacheco et al., 2023). Several risk factors for the carcinogenesis and development of cSCC have been listed, including age, accumulative exposure to ultraviolet light radiation A and B, human papillomavirus infection, arsenic ingestion, chronic scarring, xeroderma pigmentosa, relevant history of ionizing radiation, androgenetic alopecia in males, and immunosuppression therapy (Mortaja et al., 2023; Martinez et al., 2001; Welsch et al., 2012).

In clinical practice, for well-defined, low-risk tumors measuring less than 2 cm in diameter, a 4-6 mm marginal area of uninvolved skin around the tumor is highly recommended for resection by the National Cancer Care Network guidelines as first-line treatment (Chong et al., 2023). In recent years, radiotherapy has emerged as an alternative treatment choice in patients who are not amenable to curative surgical excision (Alvarez et al., 2024). Topically applied drugs including imiquimod and 5-fluorouracil (5-FU), though not routinely approved

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by the U.S. Food and Drug Administration (FDA), are also appropriate alternatives for superficial squamous cell carcinoma in situ (Borella et al., 2023; Li et al., 2024). In the treatment of skin tumors, the novel 5-aminolevulinic acid photodynamic therapy (5-ALA PDT) integrating the merits of various modalities has proven to be an effective therapeutic approach. As a tissue-sparing modality, the exploitation of non-surgical 5-ALA PDT carries a promising value in enhancing therapeutic clinical outcomes.

A 53-year-old female was admitted to the Dermatology Department of our hospital, who complained of "a papule on the left nasal bridge for more than one year". The painless papule on her nose appeared to be bean-sized, without any obvious itching, spontaneous bleeding or ulceration at its initial presentation. Since the patient had no facial discomfort and symptoms such as nasal hypertrophy, erythema or pustules in the nasal tissue, she did not resort to medications. Furthermore, there was no history of rapid morphological or pigmental change of this papule, and the lesion did not progressively spread. However, she reported slight pain and a gradual enlargement of the indolent papule, as she once accidently broke it by eyeglasses. She subsequently visited the local hospital and received a combination of treatment interventions including the use of bacteriostatic agent fusidic acid cream, mometasone furoate cream and Kanfuxin solution. The patient did not benefit from these treatments and therefore came to our dermatology clinic for further examination on Feb 12th, 2021. She was in good physical health, and denied any medical history of cutaneous malignancies. Histories of trauma, chronic sun damage burn, arsenic, radiation exposure or immunosuppressive therapy were also irrelevant. Furthermore, she did not have a family history of similar diseases and other chronic diseases (e.g., diabetes, hypertension, tuberculosis, chronic kidney disease) regarding this papule. Visual inspection revealed a red patch about 1.5 cm×1 cm in size located on the left nasal bridge, with central rupture, superficial erosive surface, and mild capillary dilatation (Figs. 1a and 1b).

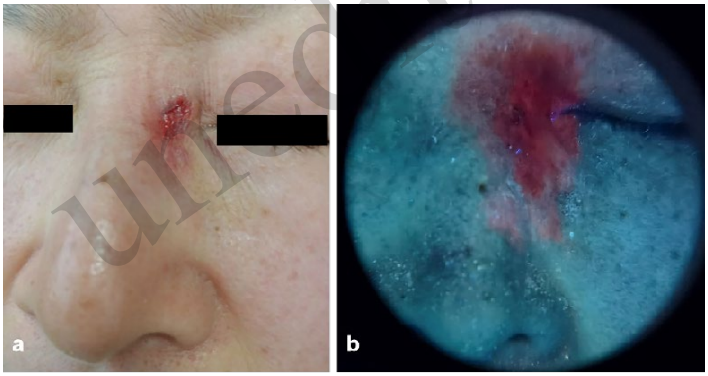

Fig. 1 Digital color photographs were taken at baseline before treatment: (a) A red patch about 1.5*1 cm in size located on the left nasal bridge, with central rupture, superficial erosive surface, and mild capillary dilatation; (b) Wood's light indicated a strong fluorescence intensity of the lesion before treatment.

Upon arrival to the hospital, the patient was in active position and was mentally healthy. She received a series of routine check-ups afterwards, and vital sign assessment was performed. The monitoring of body temperature, pulse rate, respiration rate, and blood pressure indicated relatively normal results. Based on thorough physical examinations, the patient did not have any palpable or swollen superficial lymph nodes. General medical examination of her heart, lung and abdomen organs exhibited no abnormality. Other auxiliary examinations were conducted. Observations of the mechanical properties of body muscles (e.g., muscle tone and muscle strength) were also normal. Furthermore, she exhibited physiological neurological responses without indicators of positive pathological reflex such as Hoffman sign, Babinski sign and Gordon sign. Subsequently, she underwent a serial of routine check-up for detailed laboratory examinations. Generally, the serum biochemistry, urinalysis, coagulation testing, liver and kidney function tests yielded negative results. Preoperative surgical testing did not detect HBsAg, HCV, HIV, and TP. There were no abnormal perturbations of serum electrocytes. Besides, classic cancer-associated biomarkers AFP, CA125 and CA153, specific immunologic

antibodies, namely IgG, IgM, IgE and IgA, exhibited normal concentrations. The heart's sinus rhythm was confirmed on the electrocardiogram, suggesting no presence of cardiovascular disorders. Furthermore, ultrasonography was performed for regular screening surveillance and found no morphological changes in cervical, submandibular, clavicular as well as occipital lymph nodes, confirming that the patient did not suffer from palpable lymphadenopathy. Usually, cSCC is presumptively diagnosed based on distinctive clinical features of the patients and dermosopic examination. As a noninvasive auxiliary diagnostic technique, dermoscopy promotes diagnostic accuracy as it assists physicians in inspecting subsurface skin structures such as little pigment and vascular pattern in the epidermis and the upper dermis, as well as the interface changes along the dermoepidermal junction. Dermoscopy revealed several brownish pigmented patches and globules surrounded the reddish plaque, with mild dilatation of arborizing capillaries at the periphery (Fig. 2).

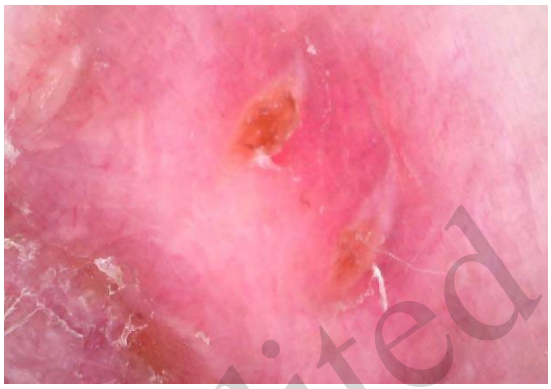

Fig. 2 Dermoscopic imaging revealed that the red-pigmented patch was crusted by a brownish scab. A whitish, structureless zone appeared in the central lesion, with arborizing telangiectatic surface vessels at the periphery. No obvious pigment structure was observed (×50).

Skin histopathological biopsy showed significant thickening of acanthosis cell layer and cytological atypia of the spinous cells, which could be exemplified by variably shaped nuclei with disorganized arrangement. Inflammatory cell infitrates were found in the superficial dermis. Taken together, the histopathological examinations were compatible with cSCC in situ. This form of NMSC is mostly presented in a non-invasive form in its initial status, manifesting as a solitary, reddish, scaly, well-demarcated plaque that is commonly detected on sun-exposed sites such as the head, lips, nose, eyelids, scalp, neck, trunk and extremities. A representative pathophysiological image of our case was shown in Fig. 3.

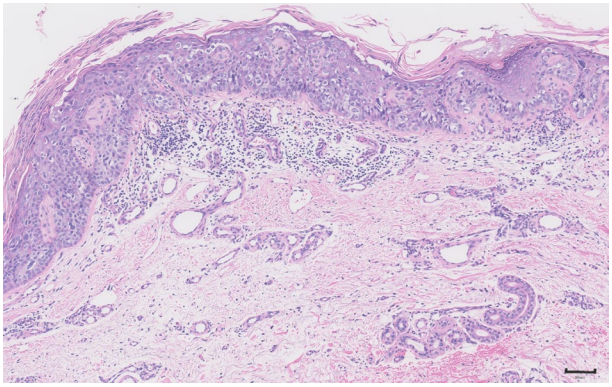

Fig. 3 The biopsy specimen was subjected to pathological examination. Representative pictures revealed significant hyperkeratosis, mild parakeratosis, acanthosis, and cytological atypia of keratinocytes. Disordered maturation of atypical keratinocytes with pleomorphic nuclei, prominent nucleoli and mitosis could be seen in the epidermis. Moreover, we detected lymphohistiocytic infitrates with different inflammatory immune cells located in the dermis. Hence, histopathological examinations corresponded to the presence of a well differentiated cutaneous SCC in situ (H&E staining, ×200).

Due to the elevated incidence and mortality rates of cutaneous SCC, devising novel preventive and treatment strategies is imperative. Treatment regimens for the primary site usually include surgical excision procedures. It has been confirmed that the external excision of low-risk primary cSCC could achieve complete histological clearance (Bander et al., 2019). Thus, an excisional surgery was initially proposed to the patient, whereas for cosmetic reasons, she preferred another therapeutic alternative, ALA-PDT, to minimize the risk of mutilation and its psychological repercussions. Reports have demonstrated that ALA-PDT is well-suited to the treatment of different cancer types and early-stage malignancies in the realms of dermatology, urology and gastroenterology (Cohen et al., 2016; Fukuhara et al., 2021; Deng et al., 2023). 5-aminolaevulinic acid is the precursor of protoporphyrin IX (PpIX), an endogenous photosensitizer. After ALA administration, emission of a strong red or blue fluorescence followed by the conversion of ALA to PpIX can be clearly visualized for detection of the surface tumor margins relative to normal para-tumor tissues (Rhodes et al., 2007). Aminolaevulinic acid hydrochloride powder (Shanghai Fudan Zhangjiang Bio-Pharmaceutical Co., Ltd., Shanghai, China) was first dissolved in normal saline at a concentration of 20% and 236 mg was used in a single dose. The nasal plaque was pretreated with CO_2 fractional laser and its solid crusting was gently removed by normal 0.9% saline. Incubated with an aminolevulinic acid hydrochloride solution-soaked sterile gauze pad, the lesion was then kept in the dark for 3 h. Next, exposure to a red LED light (wavelength of 633 nm, power intensity of 80 mW/cm^2) at approximately 10 cm above the wound was performed for a duration of 20 minutes. Aside from slight pain, burning or stinging sensation, mild redness and swelling of the radiated area, the female patient experienced no other kinds of discomfort. After ALA-PDT therapy, the patient was prescribed with erythromycin ointment for the protection of the wound surface. For photodynamic treatment, she received ALA-PDT at 7-d intervals over 4 weeks. To closely monitor the tumor remission process, visual inspections of the wound were evaluated carefully. As illustrated, the patient gained a satisfactory outcome after receiving a four-session ALA-PDT treatment (Figs. 4a-4d), without leaving residual hyperpigmentation in the left nasal lesion.

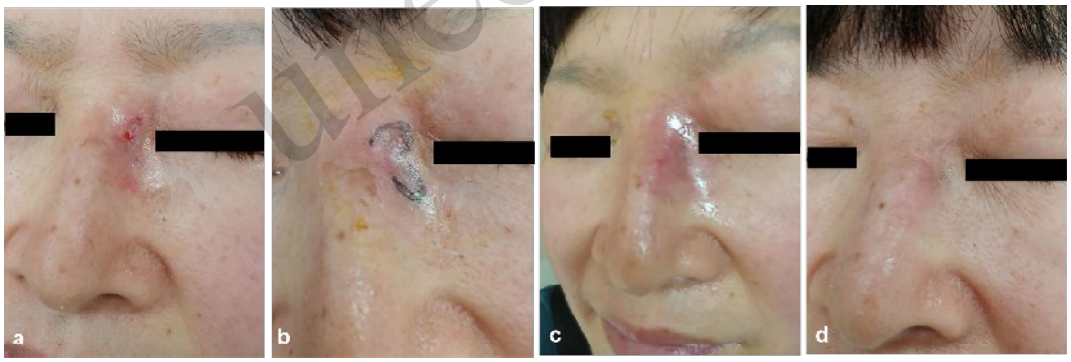

Fig. 4 Regular follow-up examinations of the female patient were conducted. Visual inspections were applied to monitor her condition following photodynamic therapy. Close-up views were illustrated in the image. (a) First week after receiving 5-ALA PDT treatment for the first time; (b) after receiving 5-ALA PDT treatment for a second time; (c) after a third session of 5-ALA PDT; (d) after a fourth session of PDT treatment.

Overall, the patient gained a satisfactory outcome after receiving a four-session ALA-PDT treatment**.** Clinical evaluation of a 2-year follow-up showed that there was no recurrence of the tumor in the female patient (Figs. 5a and 5b), indicating the good efficacy of ALA-PDT therapy in treating cutaneous squamous cell carcinoma in situ.

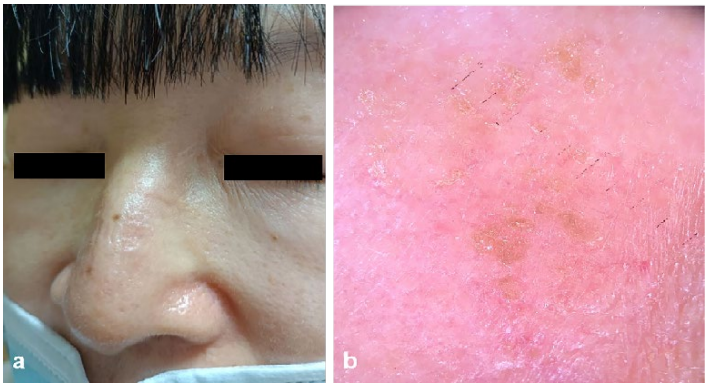

Fig. 5 This representative dermoscopic picture was taken at the 2-year follow up after ALA-PDT treatment. (a) A satisfactory treatment efficacy was achieved without leaving residual hyperpigmentation or scar in the left nasal lesion and no recurrence of the tumor; (b) upon dermoscopy, no dark dots/globules in linear arrangement or coiled vessels were found, except for slight hypergranulosis of the epidermis (×50).

As a heterogeneous disease, skin cancer can be delineated into two major subsets, melanoma and non-melanoma skin cancers, the latter of which encompass actinic keratosis (AK), basal cell carcinoma, and cutaneous squamous cell carcinoma (Kwiek, et al., 2016). The incidence of BCC and cSCC varies among different geographical regions and human populations (Eggermont et al., 2023). By far, BCC accounts for the most common carcinoma among Caucasians, with an estimated 2.5:1 BCC/SCC ratio (Woods et al., 2005). Admittedly, cSCC and BCC share many similarities while cSCC is biologically distinct from BCC. SCC of the skin arising from the malignant proliferation of epidermal keratinocytes is a prevalent form of skin cancers, second only to BCC. Whether patients with nevi have a greater probability of developing cSCC remains unknown due to a paucity of convincing evidences. The sun-exposed areas of the body are common anatomic sites where cSCC mostly occurs (Mortaja et al., 2023; Motaparthi et al., 2017). There has been a growing appreciation of the contribution of oxidative DNA damage in keratinocytes after ultraviolet light exposure, which can ultimately induce genetic mutation and therefore be involved in the development of SCC (Hufbauer et al., 2015). Additionally, other factors including age, ethnicity, human papillomavirus infection, ionizing radiation, androgenetic alopecia in males, and long-term immunosuppression also give rise to cSCC tumorigenesis, as demonstrated by a systematic review of the literature (Alam and Ratner, 2001; Kim et al., 2018; Brantsch et al., 2008). Despite the fact that the risk factors for cSCC development have largely included environmental elements, there is evidence of a gene mutational profile in patients with cSCC. The examination of skin pigmentation-related genes with association to cSCC development was previously reported (Scherer and Kumar, 2020; Sarin et al., 2020). Besides, it is worth noting that several genes predisposing to cSCC involved in cancer progression, immune modulation and keratinocyte differentiation were validated in previously unidentified cSCC susceptibility loci (Ioannidis et al., 2018; Xu et al., 2021; Asgari et al., 2016). These genetic perturbations ultimately cause the aberrant hyper-activation of classic RAS/RAF and PI3K-AKT/mTOR signaling pathways that are central to the pathophysiology of cSCC (Di Nardo et al., 2020).

The clinical types of cSCC include invasive cSCC, cSCC in situ, and other specific subtypes. Cutaneous squamous cell carcinoma in situ was identified as an intraepidermal carcinoma. The presentation of cSCC was typified as a single, dark-pigmented, scaly patch or plaque arising in the sun-exposed site (Que et al., 2018). Usually, a presumptive diagnosis of cSCC is made on the basis of the general appearance, morphology and anatomic location of the lesion. Apart from the physician's self-interpretation of clinical information, clinical diagnosis is routinely validated by histological evaluation of the suspicious patch before treatment (Bichakjian et al., 2018). Parakeratosis and hyperkeratosis are the main histological features of cSCC. Disordered maturation of atypical keratinocytes with pleomorphic nuclei, prominent nucleoli and mitosis, can be seen at all layers of the epidermis. An infiltration indicated by inflammatory $CD4^+$ T cells, $CD8^+$ T cells and plasma cells can be often detected in the papillary dermis (Schmitz et al., 2019). Individuals diagnosed with cSCC often show a

favorable prognosis and are successfully treated with standard treatment modalities. Nevertheless, the metastatic potential of primary cSCC ranges from 0.3% to 3.7% and its local recurrence can be high if it is contraindicated, suggesting that regular monitoring for disease recurrence is of necessity considering the high risk of disease recurrence, metastasis and death (Bhandari et al., 2014). It should be noted that while most cutaneous SCC can be treated surgically, in light of the fact that the in situ cSCC shows a specific predilection for the nasal site, there is a growing cosmetic demand for a novel treatment of cSCC with regard to esthetic complaint (Casas, 2020). For in situ or low-risk cSCC, physicians can choose the topical 5-aminolevulinic acid-mediated photodynamic therapy, a multi-component modality encompassing the application of a photosensitizer and subsequent light source. Although not routinely recommended for the treatment of cSCC on the basis of existing available data or comparative studies, radiation can also be used in special situations when other therapies are contraindicated (Farberg et al., 2007; O'Connell et al., 2018). Over the years, PDT has evolved into a successful treatment option for NMSCs in dermatology. ALA-mediated PDT is now used for patients with superficial nodular BCC, SCC in-situ and actinic keratoses in dermatologic oncology clinics (Hasan et al., 2023; Baeza-Hernández and Cañueto, 2023; Love et al., 2009). Of note, the European Federation for Colposcopy (EFC) have recently developed consensus statements on pre-invasive vulvar lesions including vulvar squamous intraepithelial neoplasia, vulvar Paget disease in situ as well as melanoma in situ (Preti et al., 2022). Compared with conventional treatment, the feasibility of 5-ALA PDT in treating vulvar and vaginal condyloma and intraepithelial neoplasia markedly improved the healing of the lesion without causing erosions to the appearance of normal adjacent skin (Fehr et al., 2009). For an additive effect upon anti-tumor immune responses in these diseases, scientists have sought to exploit diverse neoadjuvant agents that potentiated the efficacy of PDT (Anand et al., 2024; Ahmady et al., 2024).

In our study, we presented a female case with cSCC in situ who received a 4-session-ALA-PDT regimen out of cosmetic demand. At the 2-year follow-up, her skin defect achieved complete lesion clearance without pigmentation or disease recurrence, reaffirming the current practice in treating cSCC in situ using this novel approach.

Data availability statement

Please refer to the detailed information in the following websites (https://www.springer.com/us/ editorial-policies/data-availability-statement; https://www.springernature.com/gp/authors/ research-data-policy/data-availability-statements)

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Author contributions

Limin Luo responsible for collecting, organizing, analyzing the case, and writing the majority of the content. Jianjun Qiao and Hong Fang provided professional opinions on the diagnosis and treatment of the case. Xiaoling Jiang participated in the revision of the article. Jun Li participated in the discussion and analysis of the case, providing important views and suggestions. All authors read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Limin LUO, Xiaoling JIANG, Jianjun QIAO, Hong FANG and Jun LI declare that they have no conflicts of interest.

The study design was carried out under the approval of Clinical Research Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine (No. 1.1, 20210314). Informed consent was obtained from the patient for being included in the study. Additional informed consent was obtained from the patient for whom identifying information is included in this work.

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