



## Correspondence

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# Successful in situ 5-aminolevulinic acid photodynamic therapy in a 53-year-old female with cutaneous squamous cell carcinoma

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Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), as certain forms of non-melanoma skin cancer (NMSC) or keratinocyte carcinoma, are the most common forms of malignant neoplasms worldwide (Sharp et al., 2024). BCC and cSCC 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, although not considered as deadly as melanoma, tends to metastasize if left untreated (Civantos et al., 2023; Nanz et al., 2024). cSCC 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 erythematous 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 common NMSC in humans (Verdaguer-Faja et al., 2024). According to the latest statistics, up to 2%–5% of cSCCs in situ may gradually progress into invasive cSCCs in the final step

(Rentroia-Pacheco et al., 2023). Several risk factors for the carcinogenesis and development of cSCC have been identified, including age, accumulative exposure to ultraviolet light radiation A and B, human papillomavirus infection, arsenic ingestion, chronic scarring, xeroderma pigmentosa, a relevant history of ionizing radiation, androgenetic alopecia in males, and immunosuppression therapy (Martinez and Otley, 2001; Welsch et al., 2012; Mortaja and Demehri, 2023).

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 and Sevilla, 2024). Topically applied drugs including imiquimod and 5-fluorouracil (5-FU), although not routinely approved by the U.S. Food and Drug Administration (FDA), are also appropriate alternatives for superficial SCC 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 has promising value in enhancing therapeutic clinical outcomes.

A 53-year-old female who complained of “a papule on the left nasal bridge for more than one year” was admitted to the Dermatology Department of The First Affiliated Hospital, Zhejiang University School of Medicine. The painless papule on her nose appeared to be bean-sized, without any obvious itching, spontaneous

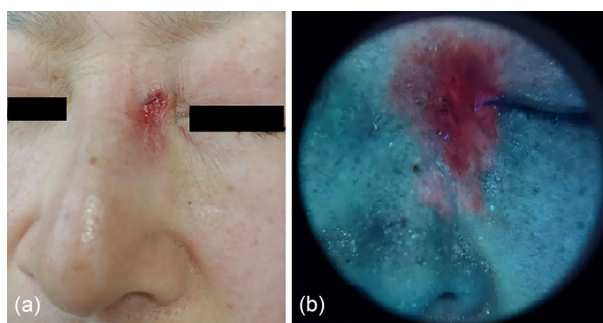
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bleeding, or ulceration at its initial presentation. Since the patient had no facial discomfort or symptoms such as nasal hypertrophy, erythema, or pustules in the nasal tissue, she did not resort to medications. Furthermore, there was no history of rapid morphological or pigmental changes in 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 accidentally broke it with her 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. 12, 2021. She was in good physical health and denied any medical history of cutaneous malignancies. Histories of trauma, chronic sun damage, burn, arsenic exposure, radiation exposure, and immunosuppressive therapy were also irrelevant. Furthermore, she did not have a family history of similar diseases or other chronic diseases (e.g., diabetes, hypertension, tuberculosis, or chronic kidney disease) associated with this papule. Visual inspection revealed a red patch about 1.5 cm×1.0 cm in size located on the left nasal bridge, with central rupture, superficial erosive surface, and mild capillary dilatation (Fig. 1).



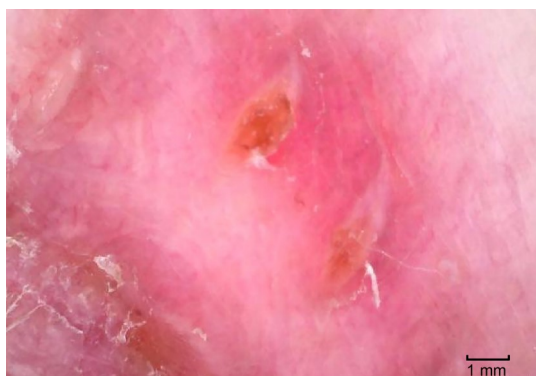
**Fig. 1** Digital color photographs at baseline before treatment. (a) A red patch about 1.5 cm×1.0 cm in size located on the left nasal bridge, with central rupture, superficial erosive surface, and mild capillary dilatation; (b) A strong fluorescence intensity of the lesion before treatment indicated by Wood's light.

Upon arrival at the hospital, the patient was ambulatory and exhibited normal mental status. She received a series of routine check-ups afterwards, and a vital sign assessment was performed. The monitoring of body temperature, pulse rate, respiration rate, and

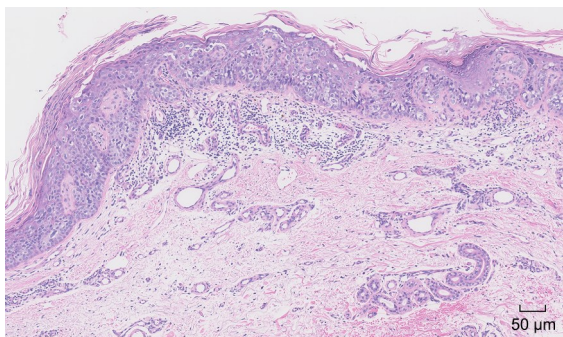
blood pressure indicated relatively normal results. Based on thorough physical examinations, the patient did not have any palpable or swollen superficial lymph nodes. General medical examinations of her heart, lung, and abdomen revealed no abnormalities. Other auxiliary examinations were also conducted. 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, or Gordon sign. Subsequently, she underwent a series of routine check-ups for detailed laboratory examinations. The serum biochemistry, urinalysis, coagulation, and hepatic/renal function tests were all within normal limits. Preoperative surgical testing did not detect hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), or *Treponema pallidum* (TP). There were no abnormal perturbations in the serum electrolytes. Besides, classic cancer-associated biomarkers  $\alpha$ -fetoprotein (AFP), cancer antigen 125 (CA125), and CA153, and specific immunologic antibodies, namely immunoglobulin G (IgG), IgM, IgE, and IgA, exhibited normal concentrations. The sinus rhythm of the heart was confirmed via the electrocardiogram, suggesting no presence of cardiovascular disorders. Furthermore, ultrasonography was performed for regular screening surveillance and revealed no morphological changes in the cervical, submandibular, clavicular, or occipital lymph nodes, confirming that the patient did not suffer from palpable lymphadenopathy. Usually, cSCC is presumptively diagnosed based on distinctive clinical features of patients and dermoscopic examination. As a noninvasive auxiliary diagnostic technique, dermoscopy promotes diagnostic accuracy, as it assists physicians in inspecting subsurface skin structures, such as fine pigment and vascular patterns in the epidermis and upper dermis, as well as interface changes along the dermoepidermal junction. Dermoscopic imaging revealed several brownish pigmented patches and globules surrounding the reddish plaque, with mild dilatation of arborizing capillaries at the periphery (Fig. 2).

Skin histopathological biopsy showed significant thickening of the acanthosis cell layer and cytological atypia of the spinous cells, which could be exemplified by variably shaped nuclei with a disorganized arrangement. Inflammatory cell infiltrates were found in the superficial dermis. Taken together, the histopathological

examinations were compatible with cSCC in situ. This form of NMSC is mostly non-invasive 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 pathological image of our case is shown in Fig. 3.



**Fig. 2** Dermoscopic imaging revealing 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.



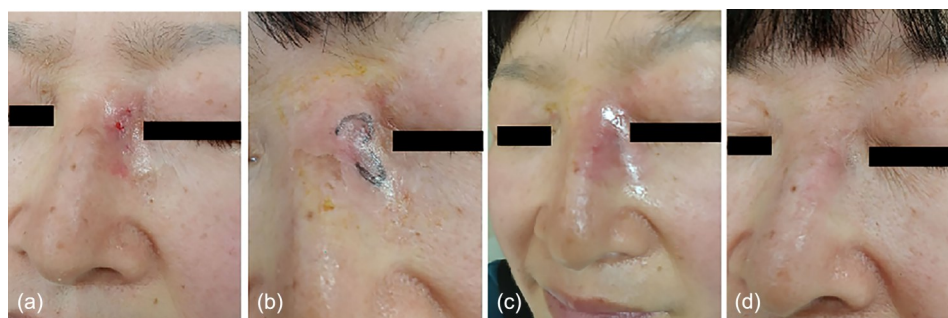
**Fig. 3** Pathological examination of the biopsy specimen. Representative image revealed significant hyperkeratosis, mild parakeratosis, acanthosis, and cytological atypia of keratinocytes. Disordered maturation of atypical keratinocytes with pleomorphic nuclei, prominent nucleoli, and mitosis could be seen in the epidermis. Moreover, we detected lymphohistiocytic infiltrates with different inflammatory immune cells located in the dermis. Hence, histopathological examination revealed the presence of a well-differentiated cutaneous squamous cell carcinoma (cSCC) in situ (hematoxylin and eosin (H&E) staining).

Due to the elevated incidence and mortality rates of cSCC, developing 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

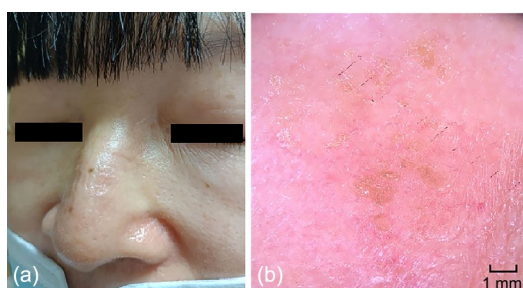
primary cSCC could achieve complete histological clearance (Bander et al., 2019). Thus, excisional surgery was initially proposed for the patient, whereas for cosmetic reasons, she preferred another therapeutic alternative, 5-ALA PDT, to minimize the risk of mutilation and its psychological repercussions. 5-ALA PDT is well-suited for the treatment of different cancer types and early-stage malignancies in dermatology, urology, and gastroenterology (Cohen and Lee, 2016; Fukuhara et al., 2021; Deng et al., 2023). 5-ALA is the precursor of protoporphyrin IX (PpIX), an endogenous photosensitizer. After 5-ALA administration, the emission of strong red or blue fluorescence, followed by the conversion of 5-ALA to PpIX, can be clearly visualized for the detection of surface tumor margins relative to normal para-tumor tissues (Rhodes et al., 2007). 5-ALA hydrochloride powder (Shanghai Fudan Zhangjiang Biopharmaceutical Co., Ltd., Shanghai, China) was first dissolved in normal saline at a concentration of 20% (0.2 g/mL) and 236 mg was used in a single dose. The nasal plaque was pretreated with a fractional CO<sub>2</sub> laser, and the solid crust was gently debrided with normal saline. After incubation with an aminolevulinic acid hydrochloride solution-soaked sterile gauze pad, the lesion was then kept in the dark for 3 h. Next, exposure to red light-emitting diode (LED) light (wavelength of 633 nm, power intensity of 80 mW/cm<sup>2</sup>) at approximately 10 cm above the wound was performed for a duration of 20 min. Aside from slight pain, a burning or stinging sensation, and mild redness and swelling in the radiated area, the female patient experienced no other kinds of discomfort. After 5-ALA PDT, the patient was prescribed erythromycin ointment for the protection of the wound surface. For photodynamic treatment, she received 5-ALA PDT at 7-d intervals over four weeks. To monitor the tumor remission process closely, visual inspection of the wound was performed carefully. As illustrated, the patient achieved a satisfactory outcome after receiving four sessions of 5-ALA PDT (Fig. 4), without leaving residual hyperpigmentation in the left nasal lesion.

Overall, the patient achieved a satisfactory outcome after receiving four sessions of ALA-PDT. Clinical evaluation at the 2-year follow-up showed that there was no recurrence of the tumor in the female patient (Fig. 5), indicating the good efficacy of 5-ALA PDT in treating cSCC in situ.

As a heterogeneous disease, skin cancer can be delineated into two major subsets, melanoma skin cancer



**Fig. 4** Regular follow-up examinations of the female patient. Visual inspection was performed to monitor her condition following photodynamic therapy. Close-up views are illustrated in the image. (a) After a first session of 5-aminolevulinic acid photodynamic therapy (5-ALA PDT); (b) After a second session of 5-ALA PDT; (c) After a third session of 5-ALA PDT; (d) After a fourth session of 5-ALA PDT.



**Fig. 5** Representative dermoscopic images at the 2-year follow-up after 5-aminolevulinic acid photodynamic therapy (5-ALA PDT). (a) Satisfactory treatment efficacy was achieved without residual hyperpigmentation or scarring in the left nasal lesion or 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.

and NMSC, the latter of which encompasses actinic keratosis, BCC, and cSCC (Kwiek and Schwartz, 2016). The incidence of BCC and cSCC varies among different geographical regions and human populations (Eggermont and Eggermont, 2023). By far, BCC accounts for the most common carcinoma among Caucasians, with an estimated 5:2 BCC/SCC ratio (Woods et al., 2005). Admittedly, cSCC and BCC share many similarities, while cSCC is biologically distinct from BCC. cSCC of the skin arising from the malignant proliferation of epidermal keratinocytes is a prevalent form of skin cancer, second only to BCC. Whether patients with nevi have a greater probability of developing cSCC remains unknown because of a paucity of convincing evidence. The sun-exposed areas of the body are common anatomic sites where cSCC mostly occurs (Motaparathi et al., 2017; Mortaja and Demehri, 2023). 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 cSCC (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; Brantsch et al., 2008; Alam et al., 2018). Despite the fact that the risk factors for cSCC development largely include environmental elements, there is evidence of a gene mutational profile in patients with cSCC. The examination of skin pigmentation-related genes associated with cSCC development was previously reported (Scherer and Kumar, 2010; Sarin et al., 2020). Besides, it is worth noting that several genes predisposing to cSCC involved in cancer progression, immune modulation, and keratinocyte differentiation have been validated in previously unidentified cSCC susceptibility loci (Asgari et al., 2016; Ioannidis et al., 2018; Xu et al., 2021). These genetic perturbations ultimately cause aberrant hyper-activation of the classic rat aarcoma sarcoma viral oncogene homolog/Raf murine fibrosarcoma viral oncogene homolog (RAS/RAF) and phosphatidylinositol 3 kinase-protein kinase B/mechanistic target of rapamycin (PI3K-Akt/mTOR) signaling pathways, which 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. cSCC in situ was identified as an intraepidermal carcinoma. The presentation of cSCC is 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 observed in all layers of the epidermis. An infiltration indicated by inflammatory cluster of differentiation 4-positive (CD4<sup>+</sup>) T cells, CD8<sup>+</sup> T cells, and plasma cells can often be detected in the papillary dermis (Schmitz and Kanitakis, 2019). Individuals diagnosed with cSCC often have 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 rate can be high if it is contraindicated, suggesting that regular monitoring for disease recurrence is necessary, considering the high risk of disease recurrence, metastasis, and death (Bhandari and Pai, 2014). It should be noted that while most cSCCs can be treated surgically, in light of the fact that in situ cSCC shows a specific predilection for the nasal site, there is a growing demand for a novel treatment of cSCC with respect to aesthetic complaints (Casas, 2020). For in situ or low-risk cSCC, physicians can choose the topical 5-ALA PDT, 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 (O'Connell et al., 2018; Farberg et al., 2023). Over the years, PDT has evolved into a successful treatment option for NMSCs in dermatology. 5-ALA PDT is now used for patients with superficial nodular BCC, SCC in situ, and actinic keratoses in dermatologic oncology clinics (Love et al., 2009; Baeza-Hernández and Cañueto, 2023; Hasan et al., 2023). Of note, the European Federation for Colposcopy (EFC) has recently developed consensus statements on pre-invasive vulvar lesions including vulvar squamous intraepithelial neoplasia, vulvar Paget disease in situ, and melanoma in situ (Preti et al., 2022). Compared with conventional treatment, the feasibility

of 5-ALA PDT in treating vulvar and vaginal condylomas and intraepithelial neoplasia markedly improved the healing of the lesion without causing erosions to the appearance of normal adjacent skin (Fehr et al., 2002). For an additive effect on anti-tumor immune responses in these diseases, scientists have sought to exploit diverse neoadjuvant agents that potentiate the efficacy of PDT (Ahmady et al., 2024; Anand et al., 2024).

In our study, we present a female case with cSCC in situ who received a 4-session 5-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

The raw and processed data generated in this study are not yet publicly deposited but are available from the corresponding author upon reasonable request.

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#### Author contributions

Limin LUO was 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 have read and approved the final manuscript, and therefore, have 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 the 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 and published in this work.

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