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ALA-PDT combined with holmium laser therapy of postoperative recurrent extramammary Paget's disease

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ABSTRACT

Extramammary Paget's disease (EMPD) is a rare intraepithelial neoplasm arising in apocrine rich area of the skin. Surgery is the standard treatment but relapse is common. The postoperative skin defects, penile reconstruction, functional effects and old age are also challenges for curing disease. Herein, a case of postoperative recurrent EMPD, which was treated by combination therapy of non-invasive repeatable ALA-PDT and deep penetrated holmium laser is reported. Ultrasonography monitor of lesions showed light vascularity and the formerly hypoechoic lesion disappeared after treatment.

1. Introduction

Extramammary Paget's disease (EMPD) is an uncommon cutaneous malignancy originating in areas rich in apocrine glands and accounting for approximately 1–2% of vulvar cancers [1]. Traditional treatment including surgical resection, radiotherapy and chemotherapy would do great damage to the normal tissue in patients and recurrence rate is high; extended resection is difficult and skin grafting or skin flap prosthesis is needed for large lesions, which would greatly affect patients' quality of life [2,3]. To date, non-invasive ALA-PDT with its unique ability to maintain tissue integrity and reduce the recurrence rate, have been exploited for repeatable treatment in skin tumors and other skin diseases [4–6]. The penetration ability of light source of PDT is limited and there are also some refractory skin tumors treated with repeated PDT with recurrence in the clinic [7]. Holmium laser therapy has high efficacy in vaporization, cutting tissues, coagulation and strong penetration capability which suitable for deep or large skin tumors [8,9]. This case report presents the treatment and clinical outcome of EPMD-suffering patient where a combination therapy of ALA-PDT and holmium laser was applied and a skin ultrasonography was used to monitor the invasion of lesion to direct therapy.

2. Case report

A 71 years old male patient was presented with erythema on his right perineal region with itch for 4 years. The lesion gradually became larger and was ulcerated with exudates, he went to the hospital for treatment on May 2018. In 2006, the patient had a coin-like erythema on his right perineal region and was diagnosed as EMPD on a pathological level. The lesion was surgically resected and the further immunohistochemical assays reported Ki67 25%+, P53+, CK+, CerbB2 + . Previous history showed that the patient has been suffering from coronary artery stenosis and a coronary artery stent was implanted in 2014. On dermatological examination, erythema found on right perineal region was measured about 5*5 cm in diameter, with central thick but unclear boundary. The lesion was ulcerated and had some exudation on the surface (Fig. 1a). On palpation, the lesion was hard and adhered firmly to the underlying layer. Dermoscopy (MoleMax HD, Derma Medical Systems Handels-und Entwicklungs GmbH, Vienna, Austria; polarized light source, 30x-100x magnification) showed that there was pulp on the lavender background and white-pink structure, as well as a large number of linear blood vessels and topical globular pigments (Fig. 1b). The ultrasonography (MD-300S high frequency ultrasound, MEDA Co., Ltd., Tianjin, China; ultrasound frequency: 50 MHz, resolution: 50 μm) of the lesion areas showed a

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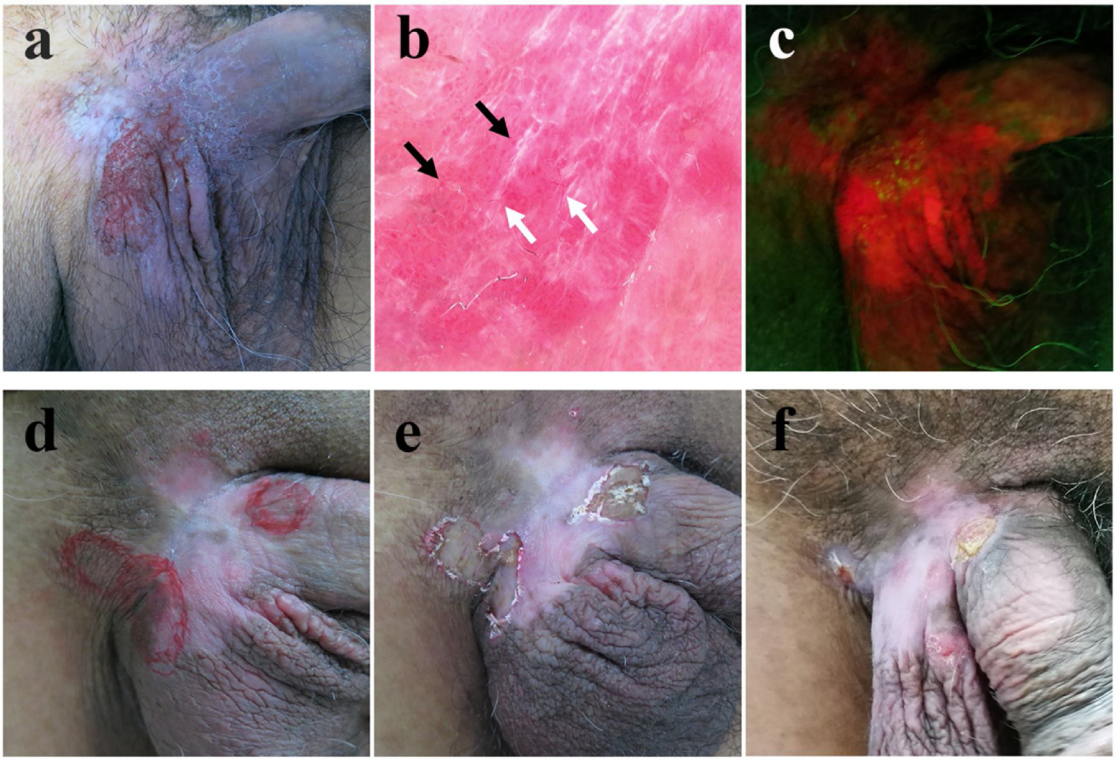

Fig. 1. a) Clinical image before treatment showed erythema and ulceration with exudates. b) Dermoscopy image before treatment with white-pink structure, linear blood vessels (white arrows) and globular pigments (black arrows). c) Fluorescence image after ALA incubated for 3 h. d) Clinical image of red-marked lesion under ultrasonography location before forth treatment of holmium laser. e) Clinical image after forth treatment of holmium laser. f) Clinical image 3 weeks after 9 sessions of ALA-PDT and 4 sessions of holmium laser irradiation showed scars and depigmentation but no ulceration or exudates.

hypoechoic lesion with a thickness of 2–2.5 mm, an irregular contour and obscured boundary showing cutaneous invasion and sub-cutaneous tissue involvement beyond the epidermis. The base was located in the shallow of dermis and echodoppler showed numerous intralesional vascularity. According to the previous history and clinical examination, a diagnosis of recurrent EMPD was made. Taking under consideration the location of lesion, old age, patient's refusal to undergo the surgical procedure, another surgery was not the best option. The US scan showed widespread and deep invasive neoplasm, a non-invasive combination therapy of ALA-PDT and holmium laser (holmium:yttrium-aluminum-garnet laser, VersaPulse P20, Lumenis Ltd., Yokneam, Israel; Energy: 0.5–2.5 J, Rate: 5–15 Hz) irradiation was then suggested. Freshly prepared 20% 5-ALA cream (Shanghai Fudan-Zhangjiang Bio-pharmaceutical Co., Ltd., Shanghai, China) was applied to the affected area and incubated for 4 h. Wood's lamp revealed a strong fluorescence suggesting the selectively absorption of ALA and explicitly showed the margin of the lesion (Fig. 1c). The lesion was then irradiated with 100 J/cm^2 635 nm red light using a semiconductor laser therapy machine (LD600-C, Wuhan Yage Optic and Electronic Technique Co., Ltd., Wuhan, China). There was a transient, mild burning sensation during the irradiation and no further adverse effects were observed. PDT was used to deal with the superficial lesion with involved large area. Then skin ultrasonography was used to search for the most deeply invaded lesions for guidance of the following holmium laser treatment (Energy: 0.5 − 0.9 J, Rate: 10 Hz, Fiber Diameter: 550 μm) (Fig. 2a–c). The patient received 9 sessions of PDT and 4 sessions of holmium laser irradiation at 2-weeks interval. Ulceration was healed and eroded surface faded after treatment with a mild hypopigmentation (Fig. 1f). The follow-up US examination showed light vascularity and the formerly hypoechoic lesion disappeared after treatment (Fig. 2d).

3. Discussion

Extramammary Paget disease (EMPD) is a rare cutaneous carcinoma of apocrine gland-bearing skin that presents as an erythematous plaque, sometimes accompanied by hyper- or hypopigmented patches, typically involving the vulva, scrotum, penis, perianal region and axilla of elderly individuals with a peak age of 65 [1,10]. In this case, the patient previously suffered from a histopathologically-proven EMPD which was treated with surgery. Additionally, clinical characteristics and auxiliary examinations led to a diagnosis of recrudescent EMPD. Surgical treatment with wide local excision has been the standard therapy. Nevertheless, clinically ill-defined margins and microscopic extension of cancer cells often results in high recurrence rates of 20%–60%, and postoperative skin defects, penile reconstruction, functional effects are also challenges in treating the disease [11,12]. Therefore, a palliative, safe, non-invasive and effective treatment which could kill tumor cells to an extreme is needed.

PDT have been suggested for the treatment of EMPD and successively reported worldwide since the 1980′s. PDT is a relatively new therapy performed by light activation of photosensitizer and subsequent generation of singlet oxygen ($^1O_2$) which attacks tumor cells through oxidation [13]. PDT has many advantages such as non- or minimally invasive, better cancer selectivity, low toxicity and easy to repeat compared to conventional surgery and radiotherapy [14]. Topical ALA-PDT is an effective option for skin and mucosal lesions and treating non-melanoma malignant skin tumors including EMPD [12]. But the penetration of light source in PDT is limited, leading to unsatisfactory results for deeply infiltrated EMPD. Holmium laser therapy has better effect in vaporization, cutting tissues and coagulation as compared to traditional surgical therapy and it is simple to treat in special locations which are hard for skin grafting, as well as deep or large skin tumors. Operational depth of holmium laser is controlled by adjusting the output energy, thereby possessing the ability to cut

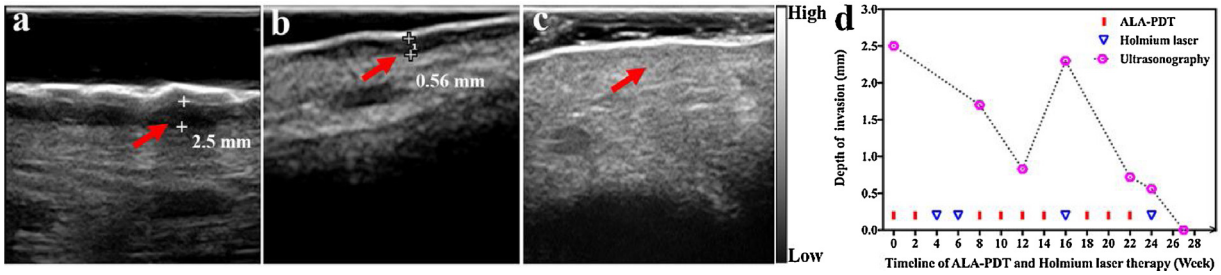

Fig. 2. Skin ultrasonogram of lesion: a) before treatment showed hypoechoic lesion with a thickness of 2.5 mm (red arrow), an irregular contour and obscured boundary, b) 2 weeks post 9 sessions of ALA-PDT and 3 sessions of holmium laser irradiation showed reduced hypoechoic lesion (0.56 mm), c) 2 weeks post 9 sessions of ALA-PDT and 4 sessions of holmium laser irradiation showed no hypoechoic lesion. d) Timeline of ALA-PDT combined holmium laser therapy and the line chart of depth of involved subcutaneous area during treatment.

accurately [15]. Ultrasound (US) is a useful primary imaging modality for soft tissue lesions including skin lesions [16]. A lower cost, better speed, easier availability and no exposure to ionizing radiation are the main assets of Ultrasound. It can be used for characterization of EMPD lesions and to assess the associated malignancies while determining the extent of disease, lateral margin of the lesion and the depth of invasion [17].

In this case, after a comprehensive evaluation of the patient's overall condition including confirmation of deep invasive extent of the lesion by US imaging, ALA-photodynamic and holmium laser combination therapy was chosen. After ALA-PDT of superficial lesion, deeply lesion invasiveness was located using skin ultrasonography, followed by eliminated through holmiun laser ablation. After 9 sessions of ALA-PDT and 4 sessions of holmium laser irradiation at 2-weeks interval, the patient's symptoms were basically relieved, the erosive surface subsided, the lesion area monitored by US imaging shrunk, the subcutaneous infiltration was cleared and the patient's quality of life was improved. Selective accumulation of photosensitizers in tumor cells and topical irradiation of lesions in PDT therapy, combined with deep penetrated holmium laser, may be a choice of non-invasive focal treatment for EMPD. The monitoring of the invasion of lesions with ultrasound imaging before and during treatment could effectively guide the treatment and assess its feasibility and efficacy.

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