CASE REPORT

In situ photodiagnosis is ineffective in treating deeply invasive squamous cell carcinoma

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ABSTRACT

In situ photodiagnosis (ISPI) can be a treatment option for selected cutaneous malignancies in patients who are not surgical candidates. We herein report the case of a large, ulcerating poorly differentiated squamous cell carcinoma (SCC) affecting the foot of an elderly woman with chronic arsenicism. The tumor failed radiotherapy, intratumoral methotrexate, and 5-aminolevulinic acid photodynamic therapy (PDT). Because the patient was reluctant to undergo amputation, the recurrent tumor was treated with ISPI using topical imiquimod application followed by PDT. Despite some initial improvement in the superficial part of the tumor, tumor invasion to the underlying bone was detected. This case illustrates the lack of efficacy of ISPI in treating a high-risk invasive SCC.

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Introduction

Squamous cell carcinoma (SCC) in patients with chronic arsenicism is believed to be more invasive.1 The treatment of choice is surgical excision.2 However, alternative treatments may be needed for patients who cannot tolerate or refuse surgery. Imiquimod is a topical immune modifier acting mainly by exhibiting agonistic activity toward Toll-like receptors 7 and 8.3 Initially, it was approved to treat genital and perianal warts. In recent years, imiquimod has been used as a safe and effective treatment option for a variety of skin cancers including actinic keratosis, basal cell carcinoma, SCC in situ (Bowen’s disease), lentigo maligna, and extramammary Paget’s disease.4 Although studies of imiquimod in treating invasive SCC are limited, some case reports showed encouraging outcomes.5–7 For example, Hengge and Schaller3 treated a 65-year-old man with a 4 cm × 3 cm SCC on the temple area. The tumor was treated by applying 5% imiquimod cream overnight three times a week. At week 16, the tumor was cured completely, which was also confirmed by a histopathological analysis. There was no tumor recurrence at the 16-month follow-up examination.5

Photodynamic therapy (PDT) destroys tumor cells by activating a photosensitizer by a specific wavelength of light after selective accumulation of the photosensitizer in cancer cells.8 In situ photodiagnosis (ISPI), which comprises PDT and topical imiquimod, has shown promising results in patients with highly aggressive cancers including metastatic melanoma9,10 and angiosarcoma.11 A patient with cutaneous metastasizing melanoma preserved his left foot after ISPI.12 Although there is no report concerning ISPI in treating invasive SCC, these results encouraged us to treat our patient with ISPI as a limb-sparing approach.

Case report

An 85-year-old female with chronic arsenicism visited our clinic in 2005 with an 8-year history of chronic nonhealing ulcer over her right dorsal foot. A physical examination revealed a large ulcer (7.2 cm × 5 cm; Figure 1A), which proved to be a poorly differentiated SCC with minimal dermal invasion histopathologically. She refused surgical intervention or chemotherapy but accepted radiation therapy. There was approximately 90% improvement of the tumor (Figure 1B) with re-epithelialization after radiotherapy with a total dose of 4000 cGy over 4 months. However, local recurrence with ulceration occurred 3 months later. Both the radiologist and surgeon suggested amputation but the patient refused. She...
preferred less invasive approaches, such as local chemotherapy and/or PDT. Since then, she has received weekly or biweekly injections of 0.5 mL intratumoral methotrexate (Emthexate, 25 mg/mL; ASTA Medica Pty Limited, Auckland, Australasia) and PDT. The PDT was done by occluding the ulcer with 4% 5-aminolevulinic acid for 6 hours prior to exposing it to 120 J/cm² at 120 mW/cm² red light (PDT 1200 lamp; Waldmann, Villingen-Schwenningen, Germany). The ulcer showed a partial response (Figure 1C) after she

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**Figure 1** (A) A large squamous cell carcinoma presented as a chronic ulcer on the dorsal foot of an 85-year-old female. (B) The ulcer reduced by >90% after she received 4000 cGy over 4 months. (C) The tumor regrew despite repeated photodynamic therapies (PDTs; 660 J/cm²) and intratumoral methotrexate (62 mg) injections. (D) The tumor improved with a shallower ulcer and flat edge within a month after 12-day imiquimod occlusion and 120 J/cm² PDT (in situ photoinmunotherapy or ISPI). (E) The intact metatarsal bone prior to ISPI. (F) The bone underneath was invaded by the tumor after ISPI. ISPI—in situ photoinmunotherapy; PDT—photodynamic therapy.
received 62 mg methotrexate and 660 J/cm² over 4 months, but it relapsed soon after. In an attempt to stimulate host immune response against the tumor, 250 mg (5%) imiquimod cream (Aldara; 3M Pharmaceuticals, St. Paul, MN, USA) was evenly applied on the ulcer, which was subsequently occluded with an air-permeable water-resistant membrane (Tegaderm; 3M Pharmaceuticals) for 12 hours daily over 12 days. One additional PDT (120 J/cm²) was performed on Day 6 during imiquimod therapy. She tolerated the treatments well and the tumor improved clinically (Figure 1D). Regrettably, a follow-up radiographic examination showed evidence of tumor invasion to the underlying metatarsal bone, which was intact 5 months prior to ISPI (arrows, Figure 1E and F). She finally underwent below the knee amputation and was disease free at a 4-year follow-up after surgery.

**Discussion**

It is well documented that both arsenic and human papillomavirus (HPV) are strong carcinogens in humans. A history of arsenic exposure and HPV seropositivity were associated with increased nonmelanoma skin cancer risks. However, the mechanisms by which HPV and arsenic interact remain to be established. Even though we did not examine HPV titer in this patient, it is of interest to investigate the role of HPV in skin cancer arising in patient with chronic arsenicosis.

Topical imiquimod without PDT has shown significant efficacy in treating superficial skin cancers. However, there is a risk of incomplete eradication of the deeper penetrating portion of the tumor. This can result in the invasion of the underlying bone and cause bone fracture and bone pain. A similar case of SCC invading the bone of a digit was reported previously.

ISPI is a new anticancer therapy, which intends to boost the host immune response against cancer. This is achieved by the activation of innate and cellular immune responses with imiquimod when tumor antigens have been generated by tumor cell destruction with PDT. The tumor antigens are strong and specific. A systemic immune response specifically against a distant tumor can be elicited by treating a tumor locally with PDT and imiquimod. The failure of ISPI in our patient might be attributed to the following reasons. (1) The tumor was naturally less responsive to ISPI. (2) The absorption peak (635 nm) of the photosensitizer protoporphyrin IX, the active metabolite of 5-aminolevulinic acid, only penetrates the superficial dermis leaving the deeper part of the tumor untouched. By comparison, the infrared absorption peak of indocyanine green used in treating melanomas can penetrate deeper tissues. The immune responses elicited by ISPI may depend on the dose and strength of the antigens generated from tumor destruction. The insufficient destruction of the tumor might have limited the release of tumor antigens in our patient. It is well known that tumor antigens of malignant melanoma are highly immunogenic. Melanoma-associated vitiligo is the best studied example of the linkage between tumor immunity and autoimmunity. The tumor antigens of SCC released after ISPI might not be as immunogenic as in melanoma. The patient had three small Bowen's diseases (SCC in situ) on her trunk. The lesions were treated with cryotherapy and healed without recurrence prior to ISPI. Otherwise, we could observe the systemic effects of ISPI.

(3) The amount of imiquimod absorbed might not be sufficient to initiate antitumor immunity. Naylor et al did not quantify the amount of imiquimod they used in ISPI. Nevertheless, they applied 20 cm² × 20 cm² imiquimod on their patient’s skin, an area that was approximately three times larger than our patient.

In conclusion, though ISPI may have significant efficacy on the treatment of metastatic melanoma, physicians should be aware of the limitations of ISPI in treating aggressive or deeply invasive SCCs in which the deeply invasive part of the tumor may be beyond the penetration limit of ISPI despite positive treatment response in the superficial part of the tumor.

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**References**