# Metastasizing Squamous Cell Carcinomas in a Patient Treated With Extracorporeal Photopheresis for Cutaneous T-cell Lymphoma

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### Sir,

Extracorporeal photopheresis (ECP) is described as effective and safe in the treatment of erythrodermic cutaneous T-cell lymphoma (CTCL) (1). It is thought that ECP acts mainly through the induction of apoptotic cell death in leukocytes; this apoptotic cell death may cause subclinical immunosuppression.

Actinically derived squamous cell carcinoma (SCC) are usually found in patients with an extensive lifetime sun exposure and are typically not aggressive. Moreover, CTCL patients are not known to have an increased incidence of SCC, not even in those who have undergone multiple psoralen plus UVA (PUVA) photochemotherapies (2, 3). Here we describe a patient with CTCL in whom multiple SCC with rapid growth and metastatic lymph node involvement developed shortly after ECP treatment.

#### CASE REPORT

A 53-year-old otherwise healthy woman, skin type II, presented in 1989 with a generalized eczema-like skin disease of 2 vears' duration. Cutaneous T-cell lymphoma, patch-stage, was diagnosed (stage IB). Treatment with topical corticosteroids and PUVA (total cumulative dose 10.1 J/cm<sup>2</sup>) was initiated; however, PUVA therapy had to be stopped after one month due to severe phototoxicity. A UVB therapy over one month followed (total cumulative dose 0.6 J/cm<sup>2</sup>). In 1993 she received UVA/ UVB radiation (total cumulative dose UVA 3.93 J/cm<sup>2</sup>; UVB 0.16 J/cm<sup>2</sup>), followed by topical miltefosine, an anti-neoplastic drug that acts mainly by inhibiting tumour cell growth, and corticosteroid therapy (4), under which CTCL was stable for 7 years. By June 2001 the patient's condition had progressed to generalized erythrodermic mycosis fungoides with mucinosis follicularis, but there was no Sezary syndrome or any detectable blood involvement of the CTCL. ECP therapy over the next 2 years was initiated with a total of 27 cycles (total cumulative dose 54 J/cm<sup>2</sup>), under which the generalized erythroderma resolved with solitary eczema-like skin lesions remaining (<10% of body surface). In 2003 another attempt with PUVA radiation was started, but again had to be discontinued after two treatments due to extensive photosensitivity (total cumulative dose 1 J/cm<sup>2</sup>). Further therapeutic attempts included short-term interferon-alpha treatment for one month and oral bexarotene for 4 months, which had to be stopped due to depression and therapy-resistant hyperlipidaemia.

In January 2004, 8 months after the last ECP cycle, the first cutaneous neoplasm, an actinic keratosis appeared on the left arm. The patient was 68 years old at that time. Between September and November 2004 two well-differentiated SCC on the abdomen were excised with tumour-free margins. The tumour thicknesses were 2 and 4 mm, respectively. The patient was followed up regularly in our department at 6-month intervals. In

June 2005, she presented with a purulent node in the left groin. Histology revealed a lymph node metastasis from a SCC. A total lymph node dissection followed by postoperative radiation of the left groin (50 gray) was performed. Computed tomography scan and sonography of the abdomen and pelvis showed no evidence of further lymphadenopathy or metastasis. In February 2006, a rapidly growing ulcerated plaque, 3×5 cm in diameter, appeared on the abdomen, and was excised with tumour-free margins. Histopathology revealed nests of squamous epithelial cells extending from the epidermis into the reticular dermis with frequent central keratinization typical for SCC; tumour thickness was 4.5 mm (Fig. 1A). Additionally, a compact node was palpable in the right groin. Histological specimen of the removed inguinal node displayed a moderately differentiated SCC lymph node metastasis (Fig. 1B). Three months after surgery the patient died due to severe wound infection with consecutive incontrollable sepsis.



*Fig. 1.* (A) Histological evaluation of a section from one of the squamous cell carcinomas. Nests of squamous epithelial cells extending from the epidermis into the entire dermis with frequent central keratinization (original magnification  $\times$ 50). (B) Lymph node largely infiltrated by nests of squamous epithelial cells with central keratinization (inset, original magnification  $\times$ 100).

## DISCUSSION

Multiple aggressive SCC with metastatic lymph node involvement are rarely observed other than in patients receiving long-term systemic immunosuppressive therapy or with underlying lymphoproliferative disorders (5).

Besides our report, only three cases of aggressive SCC in patients with CTCL under ECP treatment have been described previously (6, 7). An increased risk for the development of secondary cutaneous malignancy has not been demonstrated in patients with CTLC due to their disease (2, 3). However, all patients, including ours, additionally had received PUVA therapy, which is known to be associated with an increased incidence of SCC (8–10). Yet, PUVA-related SCC do not metastasize more often or behave more aggressively than usual SCC (9, 11, 12). Importantly, PUVA therapy is not associated with an increased incidence of SICC at a total cumulative dose of 11.1 J/cm<sup>2</sup>. The risk only increases significantly after 200 treatments (8).

Although it is thought that ECP induces apoptosis in treated lymphocytes, this phenomenon alone cannot account for the immunomodulatory effects, as only approximately 5% of the total lymphocyte population are targeted during ECP treatment. Various other mechanisms have been suggested, including the generation of regulatory T-cells, the release of tumour necrosis factor, and shifting of T-cell phenotype (13, 14). Interestingly, recent reports have demonstrated that ECP-treated dendritic cells are kept in an immature state with regard to phenotype and function and produce large amounts of interleukin-10 (15). Thus, it seems possible that longterm application of ECP might harm the immunosurveillance function of dendritic cells.

Given the diverse immunomodulatory effects of ECP, it may be possible to cause chronic subclinical immunosuppression, which might be at least partly responsible for the rapid development and aggressive behaviour of cutaneous malignancies in PUVAdamaged skin. Our patient may have been particularly susceptible to this immunosuppression as she had several additional risk factors for cutaneous malignancies, including appropriate age, fair complexion resulting in incompatibility of PUVA radiation and treatment with immunosuppressive and immunoregulatory compounds (topical miltefosine and corticosteroids; systemic bexarotene and interferon-alpha). Furthermore, CTCL itself can be immunosuppressive. However, it should be noted that no systemic involvement (Sezary syndrome, lymphadenopathy) was detected at any time.

In view of its beneficial therapeutic efficacy, ECP should still be considered in the treatment of CTCL.

However, patients should be monitored carefully and frequent skin examinations should be performed.

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