Case Report

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Melanoma Promotion after Photodynamic Therapy of a Suspected Bowen's Disease Lesion

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Key Words
Photodynamic therapy · Melanoma, de novo carcinogenesis · Bowen's disease · Tumorigenesis

Abstract
We report on a 61-year-old male patient who developed a melanoma at the site of a suspected Bowen's lesion on the right cheek. This lesion had evolved for years and had been treated using photodynamic therapy (PDT) in an outpatient facility. Only a couple of months after a single PDT treatment, a melanoma was histologically diagnosed. After excision, multiple metastases were found. The therapeutic strategy comprised re-excision, neck dissection and lateral parotidectomy – due to a metastasis – as well as subsequent α-interferon injections. The possible role of PDT in the promotion of melanoma is discussed.

Introduction

For many years, photodynamic therapy (PDT) has been in use as a therapeutic option for actinic keratoses, superficial and nodular basal cell carcinomas [1]. During PDT, reactive oxygen species are produced upon illumination of a topically or systemically applied photosensitizer. These reactive oxygen species exert cytotoxic effects with subsequent tissue necrosis or apoptosis [2]. Besides the classical form of 5-aminolevulinic acid PDT, its methyl ester is in use [3]. Since 2006, PDT has also been approved for use in the treatment of Bowen's disease [1]. PDT is often the treatment modality of choice for Bowen's disease because of its superior cosmetic results. Apart from side effects like pain and hyperaemia, only few severe side effects have been published to date. These severe adverse events comprise the development of keratoakanthoma, and until now there has been only one report of malignant melanoma following PDT in the literature [4].

S.S. and S.G. contributed equally to this paper.

Case Report

In July 2008, our male 61-year-old patient presented with a light brownish hyperkeratotic plaque on the right cheek. The lesion was 2.5 cm in diameter. Bowen's disease was clinically diagnosed. The suspected Bowen's lesion was treated with PDT in an outpatient facility once. The resulting erythema lasted for a few days, and an ulceration of 2 mm occurred in the treated area. Over a couple of weeks the small ulceration persisted, bled sometimes and exhibited dark pigmentation.

In October 2008, a biopsy of the lesion (fig. 1a) showed an ulcerated malignant melanoma with a Breslow thickness of at least 3.2 mm and Clark level IV. A re-excision with a safety margin of 1.5 cm and plastic surgical wound closure were performed. The final histological evaluation showed a melanoma with a Breslow thickness of 0.4 mm and Clark level III, which had microscopically been excised in sano. Taking the initial histopathological findings into account, it was a pT3b melanoma. Subsequent staging methods included chest X-ray, abdominal ultrasound and cranial computed tomography, which showed a lesion suspected to be a metastasis in the lower portion of the right parotid gland (fig. 1b).

In December 2008, a lateral parotidectomy and selective neck dissection on the right side were performed. Histological analysis showed two (1.2 and 1 cm in diameter) lymph node macrometastases within the periglandular adipose tissue of the right parotid gland. Lymph node status was pN2b. No distant metastases were found so that cM0 was clinically diagnosed. Due to the fact that the Breslow thickness of the initial biopsy of the lesion was 3.2 mm and the Clark level IV, stadium IIIB according to the American Joint Committee on Cancer was found for the initial pT3b pN2b cM0 melanoma.

In January 2009, high-dose α-interferon was initiated starting with 15 million IE per day over the first 2 weeks. During

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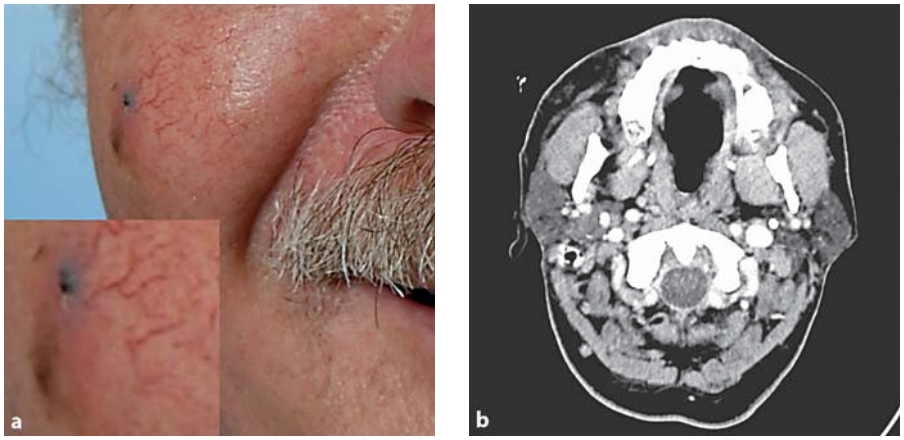

Fig. 1. Clinical presentation and computed tomography. **a** Light brownish hyperkeratotic papule (2.5 cm in diameter) on the right cheek. Initially, Bowen's disease was clinically diagnosed and therefore no biopsy taken. After PDT in an outpatient facility, a small ulceration occurred and persisted. Histological analysis was performed showing an ulcerated malignant melanoma. The inset shows the lesion prior to biopsy as a close-up. **b** One month later, cranial computed tomography showed enhanced contrast medium uptake in the lower portion of the right parotid gland which was suspected to be a metastasis. Lateral parotidectomy and neck dissection were performed, and histological analysis showed two lymph node macrometastases within the periglandular adipose tissue of the right parotid gland.

the inpatient stay, a postoperative control check-up showed a submental tumour of 2.5 cm in diameter on the right side, which was excised in local anaesthesia and histologically identified as a lymph node metastasis. α-Interferon therapy was continued using 9 million IE per day on 5 subsequent days of the week over 2 more weeks and then set to 5 million IE α-interferon 3 times a week. Until the submission of the paper the patient has shown stable disease conditions.

Discussion

The main acute side effect of PDT is pain during and immediately after treatment. It could also be shown that low pain during the first treatment may be predictive of higher pain during follow-up PDT [5]. Besides acute side effects, chronic ones like hypo- and hyperpigmentation have often been described in the literature. PDT is mainly applied to non-pigmented skin tumours [3].

There is only one case report of de novo melanoma in the treatment area following multiple PDT over 4 years: a nodular malignant melanoma exhibiting a Breslow thickness of 0.4 mm and a Clark level of II had evolved 6 months after the last PDT session in the periphery of one treated lesion. In this case, PDT was used to treat 28 solar keratoses and 3 superficial squamous cell carcinomas. The authors mention that this could well be an incidental event [4].

However, in early studies on the effects of PDT, an immunosuppressive impact of PDT could be shown [6]. A variety of immunomodulatory factors seem to be involved. There is a case report on the exacerbation of systemic lupus erythematosus after PDT of laryngotracheal papillomatosis [7]. The authors mention a combination of sun exposure (immunosuppressive) and the simultaneous induction of an inflammatory local reaction by PDT as the most likely cause for the exacerbation of systemic lupus erythematosus. Furthermore, a mouse model of cancer (subcutaneous fibrosarcoma) treatment using PDT showed significantly elevated levels of acute-phase proteins like serum amyloid P, mannose-binding lectin A and C-reactive protein [7]. Interleukin 6 and glucocorticoids seem to mediate the inflammatory reactions which are triggered by the acute-phase reaction following PDT [8]. Of course, this inflammatory reaction could possibly trigger tumorigenesis [4]. However, as PDT does not lead to covalent DNA modifications, the risk of de novo carcinogenesis is thought to be low [3]. Besides, the porphyrin derivates in PDT have anti-oxidant and anti-mutagenic properties as well [9]. Novel findings also show that PDT only leads to a slight up-regulation of p53, but does not cause damage via p53 phosphorylation [10]. Apart from apoptosis, it could be proven that autophagy plays an important role in PDT-induced cell death as well. Bcl-2 protects against apoptotic but not autophagic cell death following PDT [11].

Taking everything into account, it has to be noted that PDT triggers both pro- and anti-tumorigenic reactions. The subtle balance of these pathways may be crucial for de novo tumorigenesis as well as for the promotion of pre-existing malignancies. However, large studies have shown that there is no increase in melanoma incidence among immunosuppressed organ transplant recipients whereas others have reported on a slight increase

in melanoma incidence [12]. These controversial studies suggest that the role of immunosuppression in melanoma development has yet to be established. In the case of our patient, it could not definitely be proven whether PDT led to de novo melanoma or rather promoted the progression of a pre-existing melanoma. Bowen's disease was only clinically diagnosed, but no biopsy was taken to confirm the diagnosis. Moreover, it can not be excluded that the melanoma occurred incidentally at the treatment site.

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