CORRESPONDENCE

Skin Changes Following Organ Transplantation: An Interdisciplinary Challenge

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Anogenital Area Should Also Be Examined

Admittedly, the anoderm (the lining of the lower part of the anal canal) and the perianal skin account for only a minute proportion of the body's 2 m² skin surface. We missed in the interesting article (1) any mention of the fact that especially HPV-associated cancers and precancerous lesions (anal [AIN] and vulval [VIN] intraepithelial neoplasias) in the anogenital region are notably more common in immunosuppressed patients (not only medication-induced immunosuppression, but also infection-related immunosuppression [HIV]) (2–4). Since one generally gets the impression, that nowadays many diseases are treated with biological medications that affect the immune system, an increasing incidence of such skin tumors (cancers and precancerous lesions) might be expected in such diseases as well (Crohn's disease, psoriasis, multiple sclerosis, rheumatoid arthritis, etc). As has been suggested for HIV patients (2), otherwise immunosuppressed patients should also have regular proctologic, urologic, and gynecologic examinations if these were not done at the dermatologic examination.

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Conflict of interest statement

The authors declare that no conflict of interest exists.

Surgical-Mechanical Procedures

The article (1) seems exclusively focused on photodynamic therapy (PDT) for the purpose of minimizing cutaneous carcinomas. Surgical-mechanical interventions, such as curettage, topical cutaneous excisions, or shave excisions were not mentioned. Studies have been conducted in this setting, one of which included 1300 patients (2). The references cited by the authors relate to studies with small case numbers—8, 12, 17, 27 patients (e11–e13, e15 in the article)—and follow-up periods of 6 weeks to 12 months. What happens afterwards? In one study, PDT was applied for 2 years, at intervals of 4–8 weeks. A 95% reduction in actinic keratoses (AK) was achieved by means of an extremely high use of resources.

In some of the cited studies, curettage was used on actinic keratoses before PDT, but it was not used in the alternative treatment arm (e9, e11, e15 in the article). The study with the longest follow-up period compared cryotherapy—a non-optimal therapeutic modality for precancerous lesions—with photodynamic therapy (e9 in the article). The difference between the two failed to reach significance after 27 months. In a case-control study including 40 organ-transplant patients (e16 in the article), photodynamic therapy did not prevent the development of squamous cell carcinoma. PDT entails a risk of superficial treatment that may conceal invasive tumors, especially in the highly aggressive, desmoplastic type, which is more common in these patients (3).

Tübingen University Hospital's Department of Dermatology does not use PDT for such patients. Sun protection, the necessary self-examination by patients, and, depending on the condition of the skin, follow-up with a doctor every 3, 6, or 12 months are the foundation pillars of treatment. All hyperkeratotic AKs or those with clinically suspected cancer are shave-excised and subjected to histological analysis. The latter measures are useful as early therapy, since the rate of metastasis for squamous cell carcinoma is low and tumors of up to 2 mm thickness do not metastasize at all (3). In the individual case, adapted multimodal therapy of the cutaneous carcinomas can be administered. Is the fact that the costly PDT was promoted in the article due to the lead authors' competing interests?

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In Reply:

The studies by Scholefield and Steele, that Dr Jongen and Professor Kahlke referred to in their letter to the editor, underline the necessity to consider interdisciplinary follow-up care strategies the development of anal cancers, especially in immunosuppressed risk patients. This idea is supported by a study that was published in December 2013—after we had already submitted our manuscript to *Deutsches Ärzteblatt*—which included 187 649 organ-transplant patients, and which compared with the non-transplant general population described a rise in the incidence (standardized incidence ratio, SIR) of so-called HPV related cancers by a factor of 3.3–20.3 for in-situ cancers and 2.2–7.3 for invasive cancers (1). Similar to the finding of squamous cell carcinomas of the peripheral skin a continual increase in the incidence of vulval, anal, and penile squamous cell cancers was observed under transplant-associated immunosuppression (incidence rate ratio [IRR] 2.1–4.6 for >5 years versus <2 years after transplantation).

The authors explain the rare occurrence of invasive squamous cell cancers of the uterine cervix that was documented in this study (with an SIR of 1.0) with the success of gynecologic screening in the cohort under study and therefore recommend that analogous screening investigations should also be used to for the early detection of other HPV associated squamous cell cancers in immunosuppressed patients (1). We agree with this idea.

Professor Breuninger's contribution to the discussion questions the value of photodynamic therapy (PDT) beyond its previously described value in immunosuppressed patients. In addition to pondering—in principle—the question of whether a modern skin cancer center should keep from its patients a therapeutic modality that has been described in the literature with a sound evidence base, we wish to point out that for most dermatologists the curettage—recommended as “monotherapy” in this letter — is obviously an already

intrinsic part of the preparation for PDT. Our recommendation of PDT in immunosuppressed patients with pronounced actinic cutaneous carcinoses is based on the sound data for this small group of patients and is supported by others (2).

Obviously, in our outpatient clinic, many immunosuppressed patients, especially those with milder actinic keratoses (AK), are also treated successfully with topical diclofenac in hyaluronic acid or topical 5-FU, or—with a very strictly refined indication—off-label with imiquimod. Because of the wide spread and clinical intensity of actinic cutaneous carcinoses in immunosuppressed patients, we think that, for these tumors, reactive surgical management alone is hard to explain to high-risk patients, and in the meantime, cases have become known where patients explicitly refused repeated surgery for squamous cell cancer after dozens of preceding excisions, in full awareness of what the subsequent clinical course would be.

We wish to express our support for the undisputed value of complementary, mechanically destructive treatment for hyperkeratotic lesions, embedded into stringent topical treatment, as well as the absolute necessity of biopsy confirmation and excision of potentially invasive skin tumors (2).

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