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Rosacea Flare - Up after Photodynamic Therapy (PDT) for Field Cancerization and a Review on Adverse Events with PDT in General

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Abstract

BACKGROUND: Actinic keratoses (AKs) are precancerous epidermal lesions induced by chronic exposure to ultraviolet light. Several topical and surgical treatments are available. For field cancerization, photodynamic therapy (PDT) is a very effective noninvasive treatment with excellent outcome and cosmesis. The management of treatment-associated adverse events, however, is crucial to achieve the treatment aims and to ensure patients adherence to PDT.

CASE REPORT: We report on adverse events and their management related to PDT. We conducted literature research on PUBMED (R). Also, we present a case of an uncommon adverse event-PDT-induced rosacea flare-up on scalp and eyes. The patient was treated successfully by submicrobial slow-release doxycycline orally.

Conclusions: PDT is an excellent treatment option for multiple AKs such as in bald scalp field cancerization. The management of adverse events during and after PDT is an essential part of a successful treatment plan.

Introduction

Actinic keratoses (AKs) are common dysplastic intraepidermal lesions induced by chronic exposure to ultraviolet radiation (UVR). The prevalence of AKs in the United States has been estimated at nearly 40 million in 2004. AKs have the ability to progress to cutaneous squamous cell carcinoma (SCC) rate a yearly rate of 0.6% in the elderly population [1]. Multiple AKs often develop on the bald scalp in patients with an outdoor profession such as farmers, construction workers, or sailors. Such a situation has been described as field cancerization since the affected area is at higher risk to develop cutaneous squamous cell carcinomas (SCC) [2]. Recently, the AK area and severity index (AKASI) has been developed as a new quantitative tool for assessing AK severity on the head and to monitor outcomes of different treatments [3].

For the treatment of AKs, various pharmacological, surgical and phototherapeutic approaches are available. One of the highly preferred methods to treat field cancerization is photodynamic therapy (PDT) [4], [5].

PDT is a non-invasive method that combines a photosensitizer that accumulated in preneoplastic and neoplastic epidermal keratinocytes with subsequent irradiation. Protoporphyrin IX (PpIX) is the photosensitizer most commonly used in dermatological PDT. Soluble precursors to PpIX such

as 5-aminolevulinic acid (ALA) or methyl-aminolevulinate (MAL) are used in topical ointments. These compounds are absorbed by the skin and enzymatically converted into PpIX within the keratinocytes. In contrast to normal keratinocytes, preneoplastic and neoplastic cells accumulate more PpIX more rapidly than normal cells because their heme biosynthesis is elevated. The most effective way to activate intracellular PpIX is an irradiation with 635 nm [6]. By irradiation, the photosensitizer becomes activated and leads to oxidative stress in mitochondria and membranes, resulting in cell death [7].

Case Report

A 70-year-old Caucasian male patient present with a field cancerization with multiple actinic keratoses (AKs) on the forehead and scalp (Figure 1). His medical history was remarkable for facial and scalp rosacea, but the disease was in remission.

In the past, actinic keratoses were treated topically with diclofenac sodium 3% in hyaluronic acid 2.5% gel and 0.015% ingenol mebutate gel. However, this did not result in complete remissions but showed a rather rapid relapse. Therefore, photodynamic treatment (PDT) was suggested.

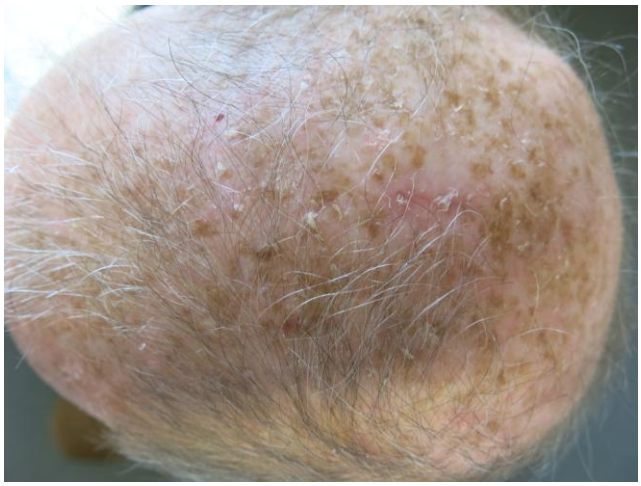

Figure 1: Field cancerization of the bald scalp

He underwent a single PDT. The session started with roughing of the actinically damaged skin with a mono-filamentous fibre pad (Debrisoft®, Lohmann & Rauscher GmbH & Co. KG, Neuwied, Germany). The area was disinfected with Octenisept® solution (SCHÜLKE & MAYR GmbH, Norderstedt, Germany). After that, a gel containing 78 mg 5-aminolaevulinic acid nanoemulsion (Ameluz®, Biofrontera AG, Leverkusen, Germany) was applied. The area was covered by the aluminum foil for 3 hours. Before irradiation, the gel residues were removed with a wet gauze compress. Irradiation was performed with a narrow-band red light with a peak wavelength of 635 nm and a total light intensity of 37 J/cm^2 (BF-RHODO LED®, Biofrontera). During PDT, skin surface was treated by cooled air and an ice-spray. After PDT, skincare with a cream containing an extract of *Mahonia aquifolium* (Beliox® cream, Biofrontera AG) for at least two weeks was recommended.

Immediately after the procedure, moderate erythema was noted. The following days, he developed the usual inflammatory reaction in the treated area, which improved after topical treatment with moisturiser.

After 2 weeks, however, he presented with a severe flare-up of preexistent rosacea with multiple papulopustules on the scalp (red scalp syndrome) and ocular involvement with blepharon-conjunctivitis (Figure 2). He received oral low-dose doxycycline (Oraycea 40 mg retard capsules 1 x d) with rapid improvement within 10 days.

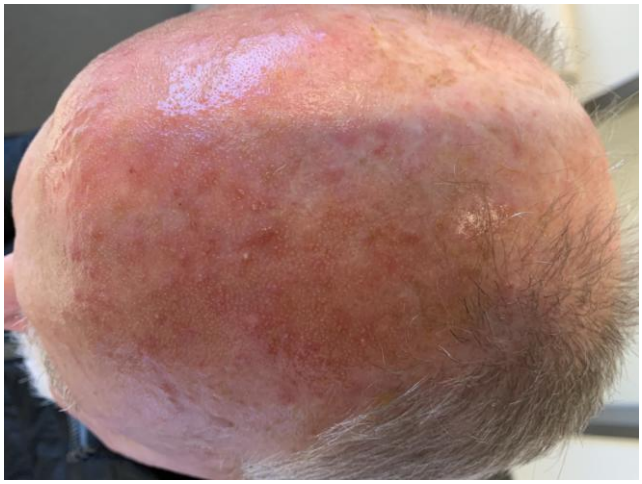

Figure 2: Rosacea eruption on the scalp after successful PDT. No actinic keratoses can be seen but erythematous papules

Literature review on adverse events of dermatological PDT

The major drawback of PDT is the strong pain experienced during the irradiation with 635 nm light that can sometimes become even intolerable for patients, requiring interruption or termination of the process [4], [5]. Reactive oxygen species, transient receptor potential channels and inflammatory reactions are mediators in pain. This type of pain does not respond to oral pharmacological pain killers. Topical anaesthesia is of limited value. In a comparative trial, the scalp nerve block was more effective than intravenous (IV) analgesia with piritramide 7.5 mg IV plus oral metamizole in combination with cold-air analgesia, and cold-air analgesia alone [8].

An alternative to classical red-light irradiation

is day-light PDT. The efficacy is slightly lower in particular in case of thicker AKs. On the other hand, low-irradiance light sources (such as variable pulsed light and daylight PDT) are currently the best analgesic option [9].

Other treatment-emergent adverse events are erythema, bullous reactions, transient oedema, and oozing. These cutaneous adverse events are experienced by 100% of treated patients in variable grades of severity. Sun-protection after PDT and moisturisers for skincare are highly recommended. Usually, these adverse events disappear within 2 weeks after PDT [10], [11].

Discussion

PDT is a versatile treatment option in dermatology to improve symptoms of extrinsic ageing, including actinic keratoses but also acne and rosacea [12],[13],[14]. Adverse events are temporary and include pain sensations and localised inflammatory reactions. Here we report a rather uncommon adverse event after successful PDT – a rosacea flare-up.

During the treatment of field cancerization, rosacea is a possible adverse event. In a trial with topical ALA-PDT and red light, 70 J/cm^2 for mild and moderate AKs rosacea occurred in 6.6% of cases [15]. In a series of 30 patients with field cancerization treated by 5-aminolaevulinic acid nano-emulsion and narrow-band red light, no rosacea was noted [12].

Our patient presented with a combination of papulopustular eruptions on his scalp, suggesting a red scalp syndrome and ocular rosacea. Red scalp syndrome is part of the rosacea spectrum and responds very well to oral low-dose doxycycline [16], [17]. Systemic treatment is also warranted in the case of ocular rosacea involvement [18].

An alternative for the treatment of actinic keratoses and rosacea would be the use of combined Q-switched KTP 532 nm and Nd: YAG 1064 nm laser [19], combined intense pulse light and Q-switched KTP 532 nm, or Q-switched KTP 532 nm laser alone [20]. All of these methods work on precancerous lesions. They also target telangiectasia (KTP) and erythema (Nd: YAG and IPL). However, none of these is efficient for papulopustular rosacea.

Rosacea is known to be aggravated by several endogenous and exogenous factors. Heat activates both TRPV1 and TRPV2 (transient receptor potential vanilloid), which are involved in rosacea pathogenesis. Inflammasome (NALP3) and TLR-2 are induced by sun-light exposure in rosacea. Last not least, cosmetics have been shown to induce TRPA1 (transient receptor potential ankyrin 1) [19]. Although not studied in detail, various pathogenetic pathways might have been involved in this rare adverse effect of PDT – red scalp and blepharon-conjuctivitis.

In conclusion, PDT is a versatile noninvasive method in dermatology. The major medial indication is the treatment of multiple AKs and field cancerization. Adverse events are common but of a temporary nature. While pain and inflammatory reactions are noted in almost all patients, rosacea is a rather uncommon unwanted side effect. Treatment is as in idiopathic rosacea.

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