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Prevention of Actinic Keratosis with Topical Imiquimod 3.75% Cream

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ABSTRACT

Background: Imiquimod 3.75% is licensed in the USA (FDA) and Europe (EMA) for the treatment of actinic keratosis (AK).

Objective: This case report shall show that subclinical actinic keratoses can originally be detected by the use of imiquimod cream in uv-exposed areas even if no lesions are clinically present.

Material and Methods: A 59-year old female without visible clinical signs of uv-damage like acitinic lentigines or actinic keratoses on the face applied imiquimod 3.75% cream twice daily on the entire face for two weeks.

Results: At the end of the treatment phase distinct signs of inflammation appeared, followed by a period of ten days for healing without sequalae. Conclusion: Thus, opening the discussion whether the use of imiquimod 3.75% cream should be recommended preventively in uv-exposed skin areas to obviate a later development of actinic keratoses and squamous cell carcinoma, a non melanoma skin cancer.

INTRODUCTION

Depending on age, lifestyle, and skin type, Sqaumaous Cell Carcinoma (SCC), a Non Melanoma Skin Cancer (NMSC) may develop in sun- exposed skin. Predominantly nasal and fronto-temporal areas, and bald male scalps are affected. Actinic Keratosis (AK) represents an early or in situ SCC [1-3]. The pathogenesis of AK can be derived from potentially carcinogenic UV light interacting with keratinocyte DNA where DNA repair mechanisms fail. AK evolve slowly in the basal layer until they become thicker and clinically evident as coarse erythematous patches in early stages which may become hyperkeratotic later on [4-6]. Topical imiquimod has been shown to be useful in clearing AK lesions [7-11]. Imiquimod as a Toll-Like Receptor 7 (TLR-7) agonist induces cytokines, starting an inflammatory skin reaction directed primarily against malignant or virus-infected cells, but has virtually no effect on normal skin.

Imiquimod 5% cream is licensed in the USA (FDA) and Europe (EMA) for the treatment of external genital warts, superficial basal cell carcinoma, and AK, and is being experimentally used in various other dermato- oncological conditions [12-14]. A lesser concentration of imiquimod 3.75% cream is licensed for the treatment of actinic keratoses on face and scalp [15]. Imiquimod binds to TLR-7 on monocytes and macrophages indirectly activating intrinsic and acquired immunity due to induction of cytokines with antiviral and antineoplastic abilities. Pro-inflammatory cytokines subsequently start an inflammatory reaction inducing apoptosis of skin cancer cells. In addition, imiquimod has a direct cytochrome- mediated pro-apoptotic effect [16,17].

In photo damaged skin featuring AK, these actions of imiquimod are not restricted to visible AK lesions, but often include their vicinity, suggesting that the neoplastic processes are in fact more frequent at cellular level and not confined to clinically evident lesions, supporting the concept of "Field Cancerization" [10]. Thus, subclinical actinic keratoses do exist in an early, macroscopically invisible state and may be rendered visible by imiquimod. At this stage Ak are being treated before they can be diagnosed by usual clinical means, and well before potential progression to invasive SCC/NMSC [18]. Our objective was to investigate the ability of imiquimod in making invisible subclinical AK visible. Such early detection and "preventive" treatment might be easier, more effective, and less burdensome than later treatment of clinically evident cancer [1].

MATERIAL AND METHODS

A 59-year old female without obvious clinical signs of uv-damage like acitinic lentigines or actinic keratoses on the face (photoaging: Glogau score 1) 20 applied imiquimod 3.75% cream twice daily on the entire face for two weeks for experimental reasons with the purpose of demonstrating that in uv-exposed skin even without clinical appearance of lesions uv-induced photo damage in subclinical state of AK may be present.

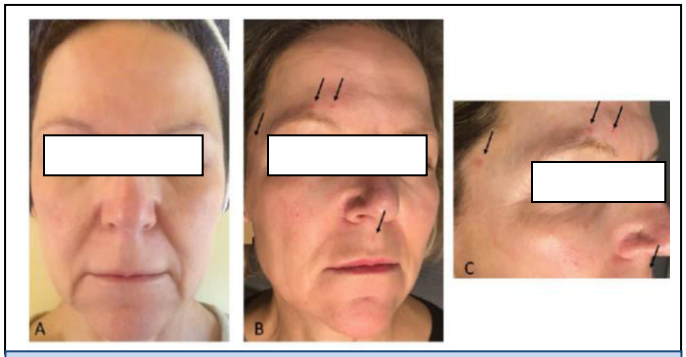

Figure 1: A: uv-exposed facial skin of a 59-year old without obvious signs of photodamage. B: day 13 of Imiqimod treatment showing erythematous inflammatory lesions (arrows). C: close up: inflammatory lesions on the upper lip, temporally right and above the right eyebrow (arrows).

RESULTS

There was no skin reaction visible until day twelve. On day 13 to 15 small erythematous lesions with a diameter of 5 mm to 7 mm appeared on the upper lip, temporally right and above the right eyebrow (Figure 1). Consequently there was a faint burning sensation. Within ten days all lesions healed without sequalae.

DISCUSSION

Uv-exposed skin may present mottled pigmentation, thinning, dryness, wrinkling and also AK as signs of photodamage and can be graded according to the Glogau score. Chronic UV exposure leads to cumulative DNA alterations overwhelming physiological DNA repair mechanisms. Consequently carcinogenic transformation in photodamaged skin occurs sooner or later, its extent depends on the skin type and on the amount of accumulated UV exposure. Our case demonstrates that the experimental use of Imiquimod 3.75% cream in uv-exposed facial skin led to faint but appearent inflammation as sign of Imiquimod binding to TLR-7 on monocytes and macrophages indirectly activating intrinsic and acquired immunity due to induction of cytokines with antineoplastic abilities. It caused a skin reaction directed against early, clinically invisible, malignant cells.

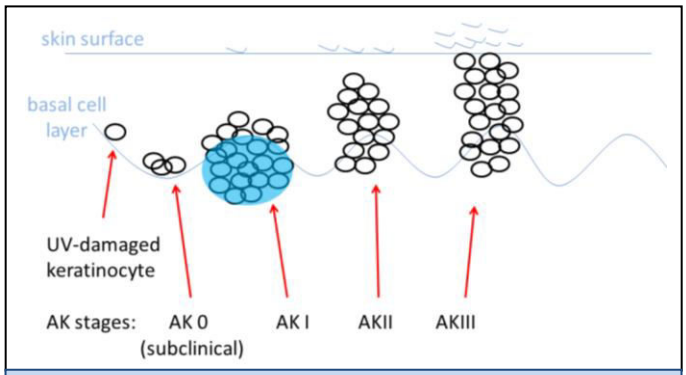

Figure 2: Progression of AK to invasive SCC (NMSC) [1].

In prior studies the term "Subclinical Actinic Keratoses" (SAK) was coined for these clinically, yet non-evident, precursors of AK [19]. In 2015 we posed the question at what stage AK progress on to NMSC (Figure 2) [20]. Now we have two more challenges, "What may be the most advantageous moment for the treatment of subclinical AK?", and, "Would it make sense to apply imiquimod as a preventive treatment avoiding AK/SCC/NMSC- formation." Thus, opening the discussion whether the use of imiquimod 3.75% cream could be recommended preventively in uv-exposed skin areas to obviate the presumptive development of actinic keratoses.

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CONTRIBUTIONS

Dr. Kopera had full access to all of the data in this work and takes responsibility for the integrity of the data and accuracy of the data analysis.

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FINANCIAL DISCLOSURE

The author has no relevant financial interest to report, list "None reported".

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