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Case Report

Imiquimod 5% Cream for Treatment of Actinic Keratosis of the Eyelid

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Abstract

A 61-year-old male presented with 20 x 15 mm diffuse, hyperpigmented lesion that covered the right upper eyelid and which had been present for 2 years. Lesion was diagnosed as actinic keratosis (AK). Since the patient refused surgery and reconstruction, he was treated with imiquimod (IMQ) 5% cream once a day, 5 times per week for 6 weeks. Lesion gradually reduced in size and no clinically evident residual keratosis was observed after treatment. No post-therapy excision was performed to assess histological clearance of AK for cosmetic reasons. Although surgery is first-line treatment for these lesions, in case of refusal to undergo surgery, when lesion is superficial and diffuse and in region where reconstruction would be difficult, treatment with IMQ may be preferred.

Keywords: Actinic keratosis, Aldara, imiquimod.

Introduction

Actinic keratosis (AK) is localized area of dysplasia with malignant potential, progressing to invasive squamous cell carcinoma in approximately 10% of cases within about 2 years (1, 2). Actinic keratosis evolving in the basal layer becomes clinically evident as coarse, erythematous patches and hyperkeratosis, most commonly in areas exposed to UV radiation (3). Surgery, cryotherapy, curettage with or without electrosurgery, topical chemotherapy, chemical peeling, dermabrasion, laser therapy, photodynamic therapy, intralesional steroid injection, and retinoid therapy are current treatment modalities (1, 4).

Imiquimod (IMQ) 5% cream (Aldara; Meda AB, Solna, Sweden) is an immunomodulatory and antitumorigenic agent. It acts by stimulating both innate and cell-mediated immunity pathways, activates antigen-presenting cells through toll-like receptor 7, and stimulates cytotoxic T-cells, Langerhans cells, and natural killer cells to produce interferon-gamma and other cytokines, which cause apoptosis (5). US Food and Drug Administration (FDA) approved IMQ for anogenital warts in 1997, and for superficial basal cell carcinoma (BCC) and AK in 2004 (6, 7). Other clinical indications are lentigo maligna, extramammary Paget's disease, Bowen's disease, xeroderma pigmentosum, and molluscum contagiosum (8). Case of patient with AK on the upper eyelid that was treated with IMQ is presented in this study.

Case Report

A 61-year-old male presented with 20 x 15 mm diffuse, hyperpigmented lesion that covered the right upper eyelid and which had been present and increasing in size for 2 years. Lesion was diagnosed as AK by incisional biopsy (Figure 1). Visual acuity was 20/20 in both eyes. Other ophthalmic examinations were normal. The patient preferred medical treatment of the lesion with topical IMQ 5% cream

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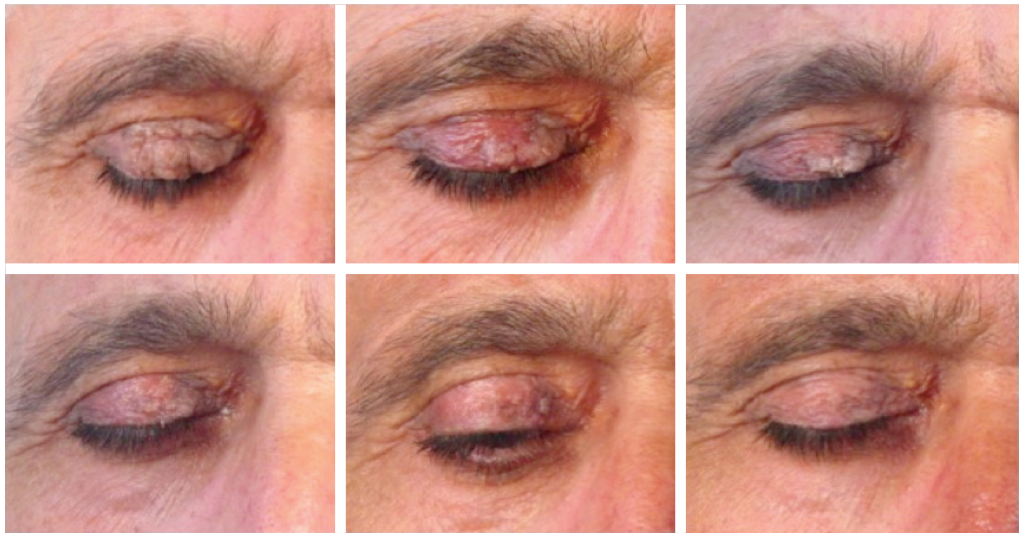

Figure 1. Images of the patient before, during, and after treatment with imiquimod 5% cream.

therapy to surgical excision and reconstruction.

After incisional biopsy was performed on the lesion, informed consent that included off-label usage and potential side effects of IMQ therapy was obtained from the patient in accordance with the Helsinki Declaration. The study was approved by the local ethics committee.

Patient was instructed to apply IMQ 5% cream treatment once a day, 5 times a week for 6 weeks. Patient was instructed to prepare conjunctival sac with lubricant gel and swab IMQ cream onto lesion with safety margin of 5 mm beyond lesion edge at bedtime, and then to rinse lesion with soap and water in the morning. Lesion was to be in contact with the drug for sleep period and was not to be covered unless necessary due to weeping or bleeding. Lubricating eye drops and ointments were administered 4 times a day to overcome corneal problems. In case of contact with the eye, it was recommended that the patient rinse with 0.9% saline solution. Five-day treatment regimen was followed by 2-day drug-free period.

The patient was seen weekly for visual acuity and biomicroscopy testing and photographs.

Erythema and erosion were observed on the surface of the lesion, and significant inflammatory reaction started 1 week after initiation of local treatment, which progressed in following weeks. Conjunctiva developed itching, burning sensation and epiphora. In follow-up period, ulceration and crusting with decrease in diameter of lesion was seen. Ophthalmic side effects were managed with topical lubricating eye drops and the patient continued the treatment. Inflammatory reaction resolved within 1 month after cessation of therapy. Lesion gradually reduced in size and eventually no clinically evident residual keratosis remained (Figure 1).

Conclusion

Imiquimod 5% cream (1-(2-methylpropyl)-1H-imidazol [4, 5-c] quinolin-4-amin) is a low-molecular-weight synthetic compound with antitumor and antiviral activity (9, 10). Recently, 3.75% IMQ cream (Zyclara; Valeant Pharmaceuticals International, Inc., Quebec, Canada) was approved by the FDA for the treatment of AK (9). However, periocular use of this drug is not recommended (6).

Surgery remains the choice of treatment that permits histopathological margin assessment. Decision to use IMQ should be made on case-by-case basis. In study conducted by Tinelli it was reported that patients are usually more concerned with cosmetic outcomes and side effects they might experience over and above their chance of clearance or cost (11).

Reported complete clearance rate of AK with topical IMQ has ranged from 45% to 84% (12). In studies comparing clinical and histological outcomes of use of topical 5% IMQ, topical 5-fluorouracil, and cryosurgery, it has been reported that percentage of clinical clearance, histological clearance, sustained clearance of cleared lesions, and acceptable cosmetic outcome were highest among those 3 treatment groups in the patients who used IMQ (12, 13).

Several regimens with varying application frequency and duration of AK treatment have been reported in the literature (2, 12, 13). Stockfleth et al. indicated that patients were treated 3 times per week for 12 weeks (14). Del Rosso reported treatment regimen of 3 times per week for 4 weeks followed by 4 weeks off therapy (12). In case of persistent lesion, they repeated same regimen. However, these treatment regimens were valid for areas of the body other than eyelid. Because lesion in our case was diffuse over the upper eyelid, our patient treated lesion once a day, 5 times per week for 6 weeks.

Drug manufacturer does not recommend use of IMQ in periocular area as cream base includes stearyl and benzyl alcohol (6, 15, 16). However, several studies in recent years have reported beneficial IMQ treatment of eyelid. Cannon et al. described ophthalmic side effects of IMQ therapy in patients with AK, Bowen's disease, and BCC (16). Erythema, itching, and scaling at application site were the most common side effects seen in patients. Mild to severe conjunctivitis, ocular stinging, diffuse punctate keratitis, preseptal cellulitis, microbial keratitis (Staphylococcus aureus keratitis, which responded to topical antibiotics), and cicatricial ectropion were reported by Cannon et al. (16). Erythema and crusting were seen in our patient, but were tolerable and healed after cessation of therapy. Discontinuing treatment for rest period has been recommended to manage ophthalmic side effects (16). Rest periods were permitted when side effects were severe in our patient. Concurrent artificial drops, as reported by Blasi et al., were also prescribed for the patient (6). Brannan et al. suggested that reducing dosing regimen might reduce side effects (17). Local inflammatory reaction noted in our patient was acceptable in treatment of premalignant condition. We preferred to allow the patient a rest period rather than reduce dosing regimen in order not to decrease efficacy of treatment. Ocular side effects resolved during 1-week rest periods and our patient did not discontinue therapy. Lesion was resolved after 6-week period. Systemic side effects such as flu-like symptoms, nausea, headache, myalgia, fatigue, and fever that have been reported in the literature (18, 19) were not observed in our patient.

In the present case, post-treatment follow-up time was 2 years, which was relatively short. We will continue close follow-up at frequent intervals to manage any recurrent lesion without delay. Surgical excision of diffuse AK can be difficult without causing damage to the eyelid, and reconstruction with grafts or flaps is required. Although surgery is first-line treatment for these lesions, in case of refusal to undergo surgery, when lesion is superficial and diffuse and in region where reconstruction would be difficult, treatment with IMQ may be preferred.

Larger study groups with longer follow-up term are required to confirm efficacy of IMQ administration in periocular AK.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (GOK, KF, CO, BB, MT, PK); preparation and review of the study (GOK, KF, PK, MT); data collection (GOK, KF, CO, BB).

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