Exuberant inflammatory reaction to occlusion of topical 5-fluorouracil (FU) under a continuous positive airway pressure (CPAP) mask: A warning to dermatologists and patients

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Key words: 5-fluorouracil; actinic keratosis; adverse effect; continuous positive airway pressure mask; inflammatory reaction; occlusion.

INTRODUCTION

Actinic keratoses (AKs) are precancerous cutaneous lesions with a prevalence of 11% to 25%.[1] Fair skin (Fitzpatrick type I and II) with light eyes and hair along with increased age, male gender, excessive ultraviolet light exposure, and immunosuppression increase the risk of AKs. AKs are most commonly found in ultraviolet-exposed sites, such as the head, neck, and upper extremities.[2] They present as erythematous gritty macules, patches, papules, or plaques. Induration, ulceration, hemorrhage, rapid growth, or pain may indicate malignant transformation to squamous cell carcinoma. This transformation can be attributed to ultraviolet-induced mutation of the p53 gene and subsequent clonal proliferation of squamous cells in the epidermis.[3,4] Mutations in p53 are seen in approximately 53% of AKs and 70% to 90% of squamous cell carcinomas, and the progression of AKs to squamous cell carcinomas is estimated at 0.1% to 10%.[2,4] Hence, the treatment of all AKs is recommended and considered an important step in preventative dermatology.[1,2]

The treatments for AKs are myriad and depend on the extent of disease (ie, number, location, and depth). All therapeutic interventions have advantages and disadvantages, and it is paramount to balance them with the patient's preference. For few, well-defined AKs, lesion-directed therapy is often preferred and cryotherapy is the treatment of choice. Other options include electrodessication and curettage and laser surgery. For numerous, ill-defined AKs, field therapy is typically recommended as it treats both clinically apparent and subclinical lesions. Field-directed therapies include 5-fluorouracil (FU), diclofenac, imiquimod, ingenol mebutate, chemical peels, and photodynamic therapy.[1]

Abbreviations used:

AKs:	actinic keratoses
CPAP:	continuous positive airway pressure
FU:	fluorouracil

Topical 5-FU is an antineoplastic medication that has been used to treat AKs since the 1970s when it was first approved by the Food and Drug Administration for topical dermatologic use.[3] It is a pyrimidine analog that irreversibly binds and inhibits thymidylate synthetase and leads to a reduction in DNA and RNA synthesis.[3] It preferentially targets AKs over normal epidermis. Topical 5-FU can cause an erosive dermatitis, pain, pruritus, hypopigmentation, and hyperpigmentation, which can result in poor medication compliance. Occlusion and extensive exposure to sunlight can precipitate these reactions.[3,5] Patient education about expected reactions and precipitating factors should be considered standard of care.

CASE REPORT

A 72-year-old Caucasian man presented to the dermatology clinic of a tertiary care center for evaluation of several dry spots on his nose and

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Funding sources: None.
Conflicts of interest: None declared.
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JAAD Case Reports 2016;2:278-80.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2016.05.011

Fig 1. Continuous positive airway pressure mask apparatus.

cheeks present for approximately 2 years. He had no personal or family history of skin cancer, but he endorsed several blistering sunburns. His medical history was significant for obstructive sleep apnea, for which he used a continuous positive airway pressure (CPAP) mask (Figs 1 and 2).

Physical examination revealed numerous pink, gritty papules on his scalp, temples, and nose, as well as a 1 cm erythematous, gritty plaque on his left cheek. He was given a diagnosis of multiple AKs. The thicker, well-defined lesions were treated with cryotherapy, and the thinner, ill-defined lesions were treated with topical 5-FU 5% cream twice a day for 3 weeks. The expected reaction of AKs treated with topical 5-FU was discussed.

Eighteen days into treatment, he discontinued therapy because of a severe, tender eruption on his nose and cheeks. He had applied topical 5-FU under occlusion of his CPAP mask. He ultimately discontinued the use of his CPAP device because of his severe discomfort. He denied any fevers, chills, night sweats, or other systemic symptoms. Physical examination revealed erythematous plaques with erosions and thick honey-colored, yellow crust over his bilateral cheeks (Fig 3). He was also noted to have injected sclera. Given the distribution and timing of his eruption, he was given a diagnosis of an exuberant inflammatory reaction from occlusion of topical 5-FU under his CPAP mask. There was no evidence of systemic toxicity, such as fatigue, malaise, alopecia, or diarrhea. The patient was advised to discontinue 5-FU and apply desonide 0.05% ointment twice a day to the affected areas for 2 weeks given his extensive inflammation. He was also given a 10-day course of oral doxycycline for possible secondary infection although no cultures were obtained. He was advised to clean his CPAP mask before future use to remove any residual 5-FU. Within 3 days of therapy, his rash started to improve and his pain subsided. At 1 month follow-up, his facial rash had resolved completely.

Fig 2. Patient wearing continuous positive airway pressure mask in correct position as indicated by device instructions.

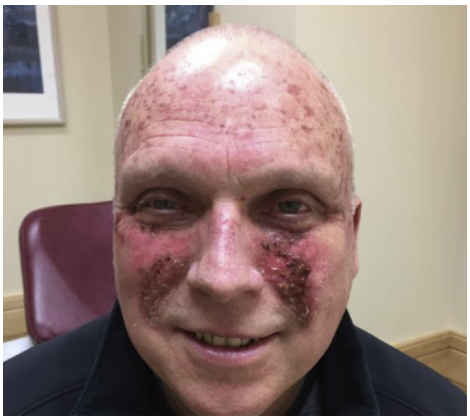

Fig 3. Follow-up evaluation 22 days after initial consultation.

DISCUSSION

To our knowledge, this is the first reported case of an exuberant inflammatory reaction to topical 5-FU under occlusion of a CPAP mask. The increased efficacy and subsequent exuberant inflammatory reaction of occluded topical 5-FU is well known in the dermatology literature. Multiple studies have shown that topical 5-FU under occlusive dressings increases its absorption and potency, resulting in a robust inflammatory response and increased risk of systemic absorption.[5-7] There is 1 case report of severe systemic toxicity from topical 5-FU in a patient deficient in dihydropyrimidine dehydrogenase, the key enzyme in 5-FU metabolism. Fortunately, our patient showed no clinical signs of systemic absorption or toxicity.

Obstructive sleep apnea affects approximately 2% to 7% of the general population[8] and 30% of the elderly population. Compliance with CPAP devices is estimated at 63%.[9] Subsequently, it is important to provide proper patient education about the adverse effects of occluded topical 5-FU, specifically under a CPAP mask. Of note, severe inflammatory reactions from topical 5-FU can occur without occlusion. Exuberant dermatoses are also seen with other topical antineoplastic medications (±occlusion), such as imiquimod, diclofenac, and ingenol mebutate. The treatment for these severe inflammatory reactions includes a reduction or discontinuation of the topical medication with or without the addition of topical steroids. We hope to urge our fellow colleagues to inquire about CPAP mask use before prescribing topical therapies for facial AKs to avoid patient dissatisfaction and unexpected exuberant results.

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