Exacerbation of Seborrheic Dermatitis by Topical Fluorouracil

Fluorouracil effectively destroys clinical and subclinical actinic keratoses (AKs) by targeting rapidly proliferating cells while sparing normal skin. This effect was initially reported in patients treated with systemic fluorouracil for solid internal malignant neoplasms.[1] Subsequently, topical fluorouracil was demonstrated to clear AKs while minimizing the internal adverse effects associated with systemic treatment.[2] Topical fluorouracil can also produce an intense inflammatory response in areas of seborrheic dermatitis.[3] The purpose of this small, nonrandomized, open-label study was to determine if this inflammatory response could be confirmed prospectively.

Methods. This study was approved by the Northeastern Ohio Universities College of Medicine and Pharmacy institutional review board. All patients provided written informed consent.

Twenty-one consecutive patients with 5 or more facial AKs were recruited to join a prospective, nonrandomized, open-label study of topical fluorouracil, 5%, field treatment twice daily for 2 weeks. Subjects were enrolled from between October 2008 and March 2009. Visible or palpable AKs were counted at baseline, and the presence or absence of seborrheic dermatitis noted. When present, the seborrheic dermatitis was graded as "mild" or "marked" by a dermatologist certified by the American Board of Dermatology (R.T.B.).

After 2 weeks, the clinical response to topical fluorouracil at the sites of AK was judged based on the presence of erythema, pruritus, and pain or burning. The presence or absence of an inflammatory response in areas of seborrheic distribution was also tabulated. Following discontinuation of fluorouracil treatment, a topical, water-based emulsion (Biafine; Ortho Dermatologics, Skillman, New Jersey) was applied twice daily to treated areas. At a final visit, the degree of inflammation in areas of AK and seborrheic dermatitis was again documented. Statistical analysis was performed using the Fisher exact test to compare the proportions of the 2 independent groups.

Exclusion criteria included known allergy or intolerance to topical or systemic fluorouracil; pretreatment with ketoconazole cream, hydrocortisone cream, or other therapy for seborrheic dermatitis; known dihydropyrimidine dehydrogenase enzyme deficiency; or treatment with chemotherapy during the study period. None of the recruited patients were excluded based on these criteria.

Results. The ages of the 21 patients enrolled in the study (16 men and 5 women) ranged from 52 to 87 years (mean age, 72.9 years). One patient failed to return for the second visit and was excluded from the study.

All 20 patients who completed the study (16 men and 4 women; aged from 52 to 86 years) developed inflammation at the sites of AK and had excellent resolution of most AKs. At baseline, 1 patient was judged to have mild seborrheic dermatitis, and 11 patients were judged to have marked evidence of seborrheic dermatitis. Eight patients had no seborrheic dermatitis. Eleven of the 12 patients with seborrheic dermatitis at baseline (92%) developed an inflammatory response at these sites after 2 weeks of treatment with topical fluorouracil (**Figure 1** and **Figure 2**). None of the eight patients without seborrheic dermatitis demonstrated inflammation in the seborrheic distribution (0%). The Fisher exact test demonstrated that the difference between these data sets was statistically significant ($P < .001$). The severity of the reaction in the seborrheic distribution was quite variable. The patient with seborrheic dermatitis who did not develop an inflammatory response to topical fluorouracil was judged to have a mild case of seborrheic dermatitis

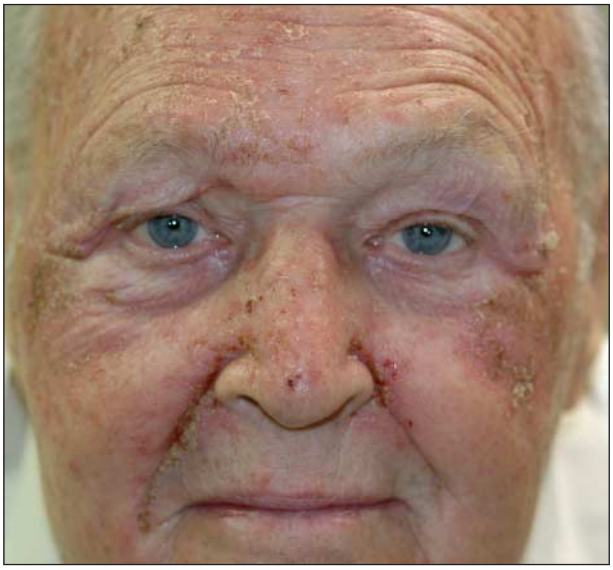

Figure 1. A 72-year-old man with actinic keratoses and seborrheic dermatitis was treated with topical fluorouracil for 2 weeks. Erythema, scaling, and crusting are noted at the sites of actinic keratoses on the cheeks and forehead with diffuse moist erythema and edema in the mesolabial fold.

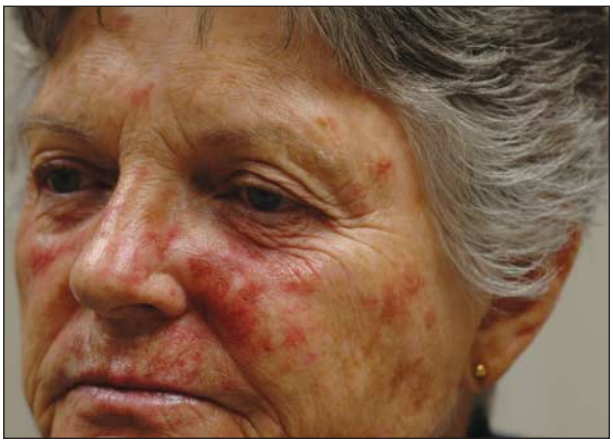

Figure 2. A 73-year-old white woman after 2 weeks of twice daily topical fluorouracil applications. She developed patches of erythema and scaling 2 to 4 mm in diameter at sites of actinic keratoses on the temples, cheeks, upper lip, and chin and confluent moist tender erythema in the mesolabial folds at sites of preexisting seborrheic dermatitis.

at baseline. The inflammatory response resolved in all patients 2 weeks after treatment was discontinued, leaving only mild postinflammatory erythema.

Comment. The epidermis in both AKs and areas of active seborrheic dermatitis proliferates rapidly. These keratinocytes serve as prime targets for the effects of topical fluorouracil, which inhibits DNA synthesis by inhibiting thymidylate synthetase.[2] In fact, anecdotal reports suggest that topical fluorouracil can inflame the skin of the nasomesial (nasolabial), retroauricular, eyebrow, and glabellar areas in patients with active seborrheic dermatitis just as it does in AKs.[3] Systemic fluorouracil has also been shown to exacerbate seborrheic dermatitis.[4] One textbook mentions that an intense irritant dermatitis is prone to occur in the chin, glabella, and nasolabial folds in patients exposed to fluorouracil.[5]

To our knowledge, this is the first prospective study to demonstrate that topical fluorouracil exacerbates preexisting seborrheic dermatitis when used to treat AKs. This is unlikely to be a nonspecific irritant reaction because inflammation is absent in the seborrheic distribution in patients without preexisting seborrheic dermatitis. Furthermore, irritants such as topical tretinoin do not preferentially affect the seborrheic distribution. Finally, reports of systemic fluorouracil inflaming seborrheic dermatitis confirm that this is not a local irritant effect.[4] Though delayed hypersensitivity to topical fluorouracil has been described, the presence of inflammation only in the seborrheic distribution and at sites of AK argues against an allergic contact dermatitis.

It is possible that pretreatment of seborrheic dermatitis with topical fungal "azole" drugs may minimize the inflammation that occurs in the seborrheic distribution in these patients. At a minimum, patients can be warned to expect inflammation to occur in areas of seborrheic dermatitis as well as in clinical and subclinical AKs.

The limitations are obvious in this observational study of 20 patients from a single office-based clinical practice. This study design was chosen because the presence or absence of inflamed AKs would have made it immediately obvious in a randomized, placebo-controlled study which group was being treated with a placebo.

Recognizing the possibility of bias in a nonblinded study, we assert that the validity of the results is strengthened because the findings were not subtle. There is a possibility that subjects developed inflammation at sites of preexisting seborrheic dermatitis following topical fluorouracil because of a confounding variable. However, all subjects denied the concurrent use of any other topical medications, and no other exposure unique to patients with seborrheic dermatitis was suspected. None of the patients had preexisting contact dermatitis or atopic eczema.

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Accepted for Publication: September 8, 2010.
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Financial Disclosure: Dr Brodell serves or has served on speakers' bureaus for Allergan, Galderma, GlaxoSmithKline, and Dermik and serves or has served as consultant for Galderma, Sirius Laboratories, and Medicis; he has conducted clinical trials for Galderma, Allergan, and Dow.
Previous Presentation: Preliminary data from this study were presented at the 51st Annual Meeting of the Noah Worcester Dermatological Society; March 30, 2009; Lake Las Vegas, Henderson, Nevada.
Additional Contributions: Michael Hewit, MS, and Denise J. Kropp, BS, performed the statistical analysis for this study.

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COMMENTS AND OPINIONS

Dilute Bleach Baths for *Staphylococcus aureus* Colonization in Atopic Dermatitis to Decrease Disease Severity

A commentary published recently in the *Archives*[1] addressed some omissions in methods and raised some questions about our group's recent article[2] describing the value of dilute sodium hypochlorite baths and intranasal mupirocin for moderate to severe atopic dermatitis in infection-prone patients. We are writing to provide clarification.

The study was a single-blind, randomized investigation using permuted blocks of size 4. All investigators