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Letter

5-Fluorouracil-induced exacerbation of rosacea

Ellen S. Haddock[1] AB, MBA, Philip R. Cohen[2] MD

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[1] School of Medicine, University of California San Diego, San Diego, California

[2] Department of Dermatology, University of California San Diego, San Diego, California

Correspondence:

Ellen S. Haddock, AB, MBA
230 Prospect St.; #31
La Jolla, CA 92037
Email: ehaddock@ucsd.edu

Philip R. Cohen, MD
10991 Twinleaf Court
San Diego, CA 92123
Email: mitehead@gmail.com

Abstract

Background
Topical 5-fluorouracil (5-FU) is an antineoplastic antimetabolite used for the treatment of actinic keratosis.

Purpose
A 66-year-old man with erythematotelangiectatic rosacea and biopsy-confirmed actinic keratoses who experienced a rosacea exacerbation after initiating topical 5-FU treatment of his actinic keratoses is described and this adverse event associated with 5-FU is reviewed.

Materials and methods
Using PubMed.gov the following terms were searched and relevant citations were assessed: rosacea and 5-fluorouracil. 5-FU drug label information and data sheets also were reviewed.

Results
Erythematous facial papules developed within a week of starting topical treatment of his actinic keratoses with 5-FU. The lesions resolved within two weeks of discontinuing the medication. Albeit rarely, exacerbation of rosacea by topical 5-FU treatment has been described when 5-FU was introduced as a topical treatment for actinic keratosis.

Conclusion
Topical 5-FU has been associated with several adverse cutaneous events, including accentuation of rosacea. Although rosacea flares due to topical 5-FU may be uncommon, the incidence may be greater than reflected in the literature. Physicians should be aware of this potential adverse effect in patients in whom they plan to initiate 5-FU therapy.

Key words: actinic, adverse, drug, event, 5-fluorouracil, keratosis, reaction, rosacea

Introduction

5-fluorouracil (5-FU) is a uracil analog that inhibits both RNA and DNA synthesis by preventing uracil incorporation into RNA and inhibiting thymidylate synthase, an enzyme required for converting deoxyuridine monophosphate to deoxythymidine monophosphate, a component of DNA [1,2]. Rosacea, an inflammatory skin disorder characterized by colonization with *Demodex folliculorum*, is known to flare with several factors including exercise, heat, spicy foods, stress, and ultraviolet light [3]. Additionally, drug-exacerbated or drug-induced rosacea or rosacea-like dermatitis has been reported with administration of acetazolamide, 5-FU, metformin, oral vitamin B complex, and phosphodiesterase-5 inhibitors [4-10]. We describe a 66-year-old man with baseline untreated erythematotelangiectatic-type rosacea who experienced a severe exacerbation of the condition after treatment of his actinic keratoses with topical 5-FU. We also review the literature on this adverse event.

Case synopsis

A 66-year-old man presented for evaluation of several non-healing lesions on his nasal bridge for more than a year. He also had redness of his cheeks, consistent with rosacea, for which he had never sought treatment (Figure 1).

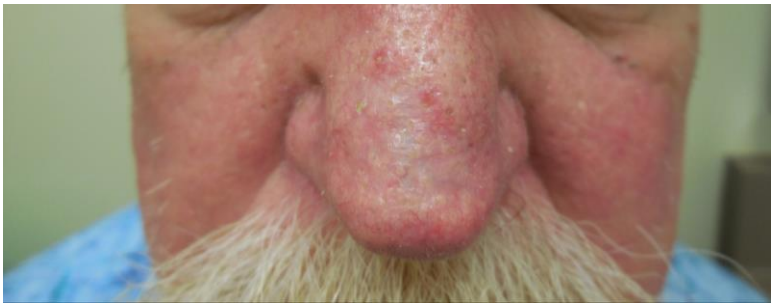

Figure 1. A 66-year-old man with erythematotelangiectatic rosacea presenting as mild malar erythema.

Clinical examination of his face revealed several 2 mm erythematous papules surrounding a central atrophic area on the nasal bridge (Figure 2).

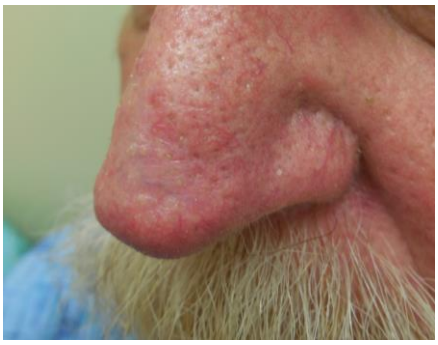

Figure 2. Biopsy-confirmed actinic keratoses presenting as red papules surrounding a white atrophic patch on his distal nose bridge and accompanying rosacea appearing as mild erythema.

Microscopic examination of shave biopsy specimens from two nasal bridge papules both showed similar findings. There were atypical keratinocytes in the basal layers of the epidermis. Solar elastosis and lymphocytic inflammation were present in the dermis. Correlation of the clinical features and pathologic changes established the diagnosis of actinic keratosis for both lesions.

The residual actinic keratoses were treated with 5-FU 5% cream daily for one week and twice daily thereafter. The patient applied the medication to his nose before going to sleep. His nose contacted the pillow, sometimes spreading the cream elsewhere on his face. Within a week of beginning the 5-FU treatment he began to develop asymptomatic erythematous papules on the left cheek and right nasal bridge. These became more prominent with continued therapy.

After three weeks of treatment, follow-up examination showed not only that his actinic keratoses had cleared but also several new red papules on the left cheek and one on the right nasal bridge (Figure 3). Correlation of clinical morphology and history established a diagnosis of rosacea exacerbated by 5-FU. The 5-FU cream was discontinued, and within two weeks all papules resolved, leaving only the patient’s baseline erythema.

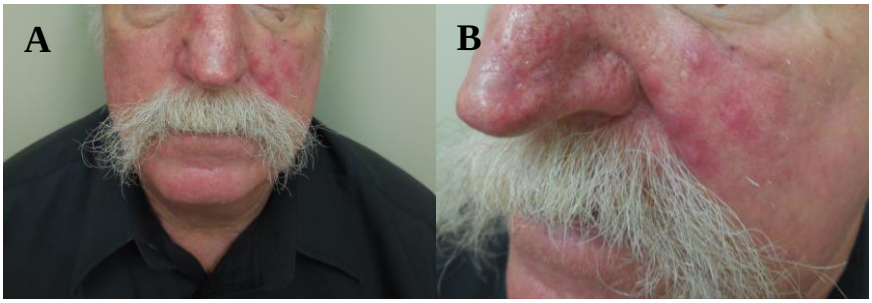

Figure 3. Distant (**A**) and closer (**B**) view after three weeks of topical treatment with 5-fluorouracil 5% cream. There is exacerbation of his rosacea that was induced by the 5-fluorouracil 5% cream presenting as increased malar erythema with numerous new erythematous papules on the right nasal bridge (**A**) and left malar cheek (**A** and **B**). The actinic keratosis on his distal nasal bridge has completely resolved.

Discussion

Topical treatments of actinic keratosis include diclofenac, 5-FU, imiquimod, and ingenol mebutate [11]. Each of these therapies may be associated with cutaneous adverse events. Cutaneous reactions associated with topical 5-FU include erythema, blistering, pruritus, necrosis, erosion, and pain [11]. Although rosacea is not listed as a cutaneous adverse effect on the drug label for Valeant's Efudex 5% fluorouracil cream sold in the United States [12], the data sheet for Bausch & Lomb's 5% fluorouracil cream sold as Efudix in New Zealand states, "Patients with chloasma and rosacea and other inflammatory dermatoses may encounter accentuation of their condition and should first be treated with appropriate therapy before using the medication" [2].

A comprehensive review of the literature, to the best of our knowledge, only includes a single report by Sams published in the Archives of Dermatology in 1968 in which exacerbation of rosacea with 5-FU is described [5]. The paper, titled "Untoward Response With Topical Fluorouracil," was originally delivered at the annual meeting of the American Dermatological Association in 1967. The introduction states, "Pre-existing dermatoses may be accentuated by the inflammatory response which ensues from this procedure. Patients with chloasma and rosacea are the most likely to encounter temporary accentuation of the underlying disorder." Sams also states that a "rather common result which is a source of annoyance is the persisting erythema which follows treatment of patients with rosacea," and, "I have had several patients with rosacea and seborrhea. They acquired a rather marked inflammatory reaction. This does subside, but they may remain unhappy because the erythematous component of the rosacea does not completely subside" [5].

Dinehart et al.'s review of treatment of actinic keratosis published in the Journal of the American Academy of Dermatology in 2000 references Sams' paper to support the statement that topical 5-FU can worsen cutaneous conditions such as acne rosacea [13]. There is also a paper that describes systemic 5-FU exacerbating previously undiagnosed ocular rosacea [14]. Additionally, systemic capecitabine, a chemotherapeutic agent metabolized to fluorouracil, has been associated with an acneiform eruption, which in severe cases can mimic rosacea [15]. Seborrheic dermatitis, which may occasionally coexist with rosacea, can also be exacerbated after treatment with either topical or systemic 5-FU [16, 17].

Our patient had erythematotelangiectatic rosacea, although his facial redness was not of clinical concern and he had never sought treatment. There was temporal association between initiation of topical 5-FU therapy and exacerbation of his rosacea. Furthermore, his rosacea flare spontaneously resolved after discontinuation of 5-FU.

The mechanism for 5-FU exacerbation of rosacea remains to be elucidated. By inhibiting DNA replication, 5-FU has greatest impact on rapidly dividing cells, resulting in their death. Density of saprophytic *Demodex* mites is increased in patients with rosacea [18], and one possible mechanism for the exacerbation of rosacea after treatment of the area with topical 5-FU may be that accelerated cell death causes an accumulation of dead skin cells and encourages proliferation of *Demodex* mites, which may feed on these keratinocytes [19,20].

An alternative hypothesis for 5-FU exacerbation of rosacea may possibly be related to toxic effects of the drug on the *Demodex* mites. The mites have short life cycles (14-18 days) [21]. Hence, they replicate rapidly, and uptake of 5-FU by replicating mites may lead to their death. Subsequent release of the mites' internal contents could trigger a local inflammatory reaction that secondarily causes a rosacea flare [22].

Conclusion

Topical 5-FU cream may be associated with cutaneous adverse events including exacerbation of rosacea. Our patient, with underlying non-treated rosacea, had an exacerbation of his condition within one week of initiating therapy with topical 5-FU 5% cream. All lesions resolved spontaneously within two weeks of discontinuing the medication. Similar observations were described previously when 5-FU was newly formulated for treatment of actinic keratosis. However, this unique adverse cutaneous event has not been reported subsequently. Disruption of RNA and DNA synthesis and subsequent cell death may promote the development of rosacea by boosting the *Demodex* mite population, which has been implicated in the pathogenesis of rosacea. Alternatively, possible 5-FU associated toxicity to the mites may result in their death; postmortem release of antigens from the mites may result in localized inflammation and rosacea. Although rarely described, clinicians should be aware of this potential cutaneous adverse event following initiation of topical 5-FU 5% cream to the face of individuals with active or subclinical rosacea.

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