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Journal
Dermatology Online Journal, 27(6)

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Publication Date
2021

DOI
10.5070/D327654060

Painful scrotal dermatitis secondary to topical 5-fluorouracil

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Abstract

5-Fluorouracil (5-FU) is an antineoplastic agent that is used topically to treat actinic keratoses. Although topical 5-FU frequently causes irritant contact dermatitis at the site of application, distant skin reactions are rare and could relate to accidental transfer or systemic absorption of the drug. We present a patient who developed a painful scrotal dermatitis after applying the topical cream to actinic keratoses on his chest. Upon discontinuation of topical 5-FU, the reaction resolved over a four-week period with oral prednisone and topical betamethasone ointment. The patient was re-challenged with topical 5-FU one year later and again developed scrotal pain and erythema similar to the initial reaction. Scrotal dermatitis is a rare adverse effect of topical 5-FU therapy that can be associated with significant distress and disruption of daily activities.

Keywords: 5-fluorouracil, actinic keratosis, adverse effect, contact dermatitis, histology, interface change, scrotum, systemic toxicity

Introduction

5-Fluorouracil (5-FU) is a pyrimidine antimetabolite that disrupts DNA and RNA synthesis [1]. Topical 5-FU is widely used for the treatment of actinic keratoses, whereas systemic 5-FU is used as a chemotherapeutic agent. Common adverse effects of the topical drug include erythema, burning, and erosions at the site of application. Rarely, topical 5-FU can cause allergic contact dermatitis as well as distant or systemic skin reactions, including seborrheic dermatitis-like eruptions, symmetrical drug-related intertriginous and flexural exanthema, and generalized pustular drug eruption [2-4]. We present a patient who developed a painful scrotal dermatitis after using the topical cream to treat actinic keratoses on his chest.

Case Synopsis

A 70-year-old healthy man presented to our clinic with a painful rash on his scrotum. The rash appeared eight days after he began applying topical 5-FU 5% cream twice daily to his chest for the treatment of actinic keratoses. He subsequently experienced worsening scrotal erythema, pain, burning, and itching. He reported having difficulty sitting in a chair and sleeping at night owing to exquisite scrotal tenderness. This was the patient's first time using 5-FU and he denied any direct contact of the topical cream with scrotal skin. He was not on any other medications prior to symptom onset. Past medical history was negative for contact dermatitis or drug reactions. On physical examination, the entire scrotum was markedly erythematous.

Topical 5-FU was discontinued. Over the next two weeks, the patient trialed topical triamcinolone, zinc oxide ointment, and doxycycline 100mg twice daily without improvement in symptoms. A punch biopsy was taken of the scrotal skin one week after discontinuing 5-FU (**Figure 1**). Histopathology showed an interface dermatitis with parakeratosis, epidermal atrophy, interface vacuolopathy, and occasional basal layer necrotic keratinocytes (**Figure**

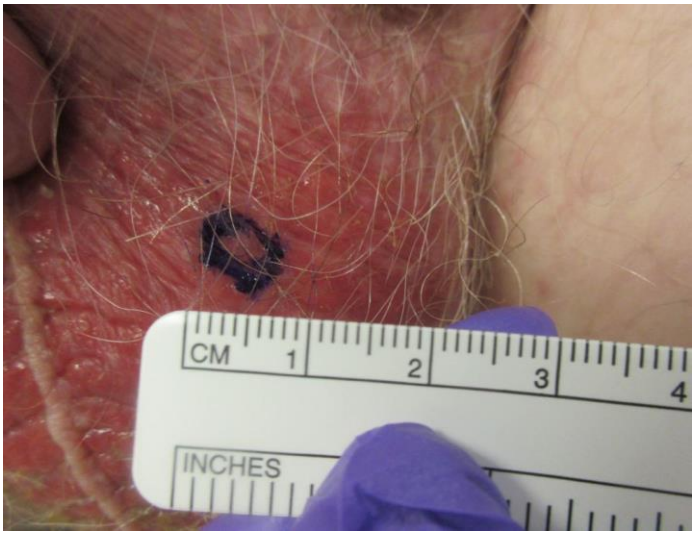

Figure 1. *Physical examination one week after discontinuation of topical 5-FU revealed erythema involving the entire scrotum without blistering or erosions. A punch biopsy was taken from the scrotal skin (circled).*

2). The dermis contained a sparse superficial lymphocytic infiltrate with rare eosinophils and neutrophils (**Figure 3**).

A short oral prednisone taper was initiated, followed by betamethasone ointment twice daily. The reaction cleared four weeks after discontinuing topical 5-FU. One year after the initial reaction, the patient used topical 5-FU and calcipotriene to treat actinic keratoses on his forearms. After five days of treatment, he again developed scrotal pain and erythema similar to the initial reaction. The reaction resolved days after discontinuing topical 5-FU.

Case Discussion

To our knowledge, five cases have been reported in the literature of scrotal dermatitis in association with topical 5-FU. Shelley and Shelley described four patients who developed an acute scrotal dermatitis after using the cream to treat lesions on the face, extremities, trunk, or penis [5]. Leung and Critchley additionally reported a patient who recalled inadvertently scratching his scrotum after applying topical 5-FU to actinic keratoses on his forearms [6]. He developed an erythematous scrotal rash that progressed into a severe, necrotic lesion. In these cases, symptoms resolved one to three weeks after discontinuation of the cream. Topical corticosteroid therapy was used in two patients who experienced symptom resolution. In another individual, the reaction persisted after seven days of topical fluocinolone treatment and cleared following an intramuscular injection of 40mg triamcinolone [5].

The pathophysiology of scrotal dermatitis secondary to topical 5-FU may related to several causes. Prior authors have hypothesized that the scrotal dermatitis is related to an irritant contact dermatitis from 5-FU [5,6]. However, the histopathologic findings of this eruption from prior cases have not been described. Irritant contact dermatitis classically manifests with spongiosis, epidermal cell necrosis, and neutrophilic infiltration of the epidermis. In contrast, the histology in our case demonstrated a pattern of interface change, which may represent a direct cytotoxic effect of 5-FU.

In a prior study, application of topical 5-FU to normal truncal skin produced epidermal edema and keratinocyte vacuolopathy predominantly in the lower third of the epidermis, even in the absence of clinical symptoms [7]. These changes were apparent after two weeks of 5-FU therapy. Biopsies of actinic keratoses treated with topical 5-FU similarly displayed vacuolar degeneration and widened intercellular spaces of the basal layer [8]. The greater degree of cellular alteration in this region is believed to relate to the effect of 5-FU on mitotically active basal cells [7]. Systemic 5-FU and its oral prodrug, capecitabine, are known to cause acral erythema (palmoplantar erythrodysesthesia or hand-foot syndrome), a chemotherapy-induced skin reaction

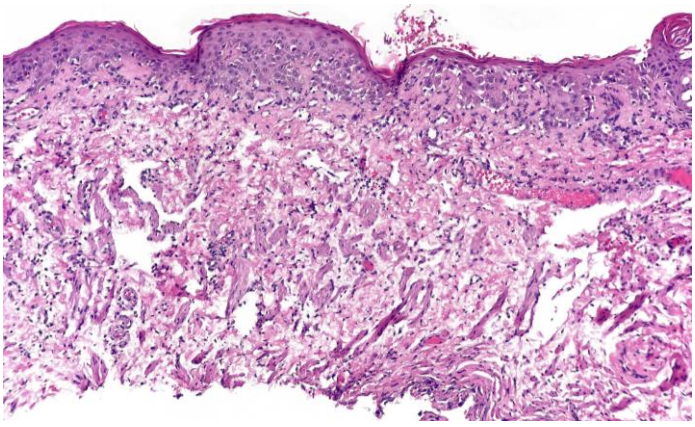

Figure 2. *Interface change with epidermal atrophy, interface vacuolopathy, occasional basal layer necrotic keratinocytes, and parakeratosis, H&E, 100×.*

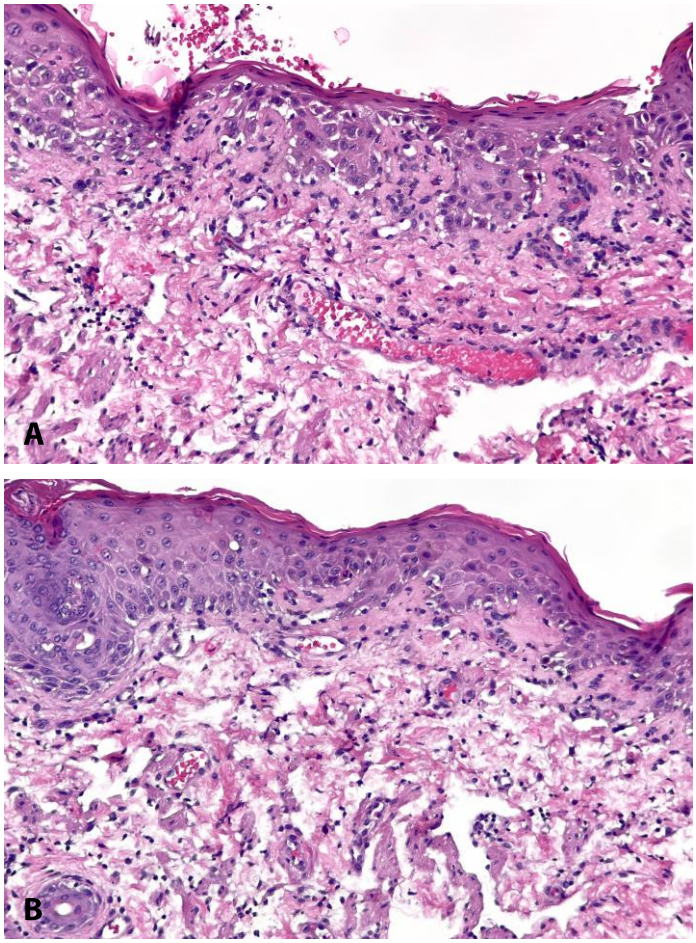

Figure 3. *High power H&E histopathology.* ***A)*** *View showed a sparse perivascular lymphocytic infiltrate surrounding the vessels, 200×. Vascular congestion and dilatation can be appreciated in the superficial dermis.* ***B)*** *Interface change of an eccrine sweat duct evident in the lower left corner of the figure, 200×.*

considered to be secondary to the direct cytotoxic effects of 5-FU [9]. Histologic examination of affected skin in patients with acral erythema demonstrated an interface dermatitis with hydropic degeneration of basal cells, necrosis in isolated basal keratinocytes, vascular dilation, and a mild infiltrate in the dermoepidermal junction. Interestingly, although acral erythema characteristically involves the palmoplantar skin, there have been rare reports of patients undergoing capecitabine therapy who developed painful scrotal erythema and erosions with absent or mild palmoplantar involvement [10].

Cutaneous reactions distal to the area of topical therapy with 5-FU are rare but could occur with systemic absorption of the drug [2-4]. Our patient was careful to wash his hands after applying the medication each time and denied direct contact of the cream with scrotal skin. Patients with abnormal variants of the gene encoding *dihydropyrimidine dehydrogenase* (*DPD*), an enzyme that metabolizes 5-FU, have been reported to a greater response to the drug [11]. *Dihydropyrimidine dehydrogenase* genotyping was not performed in our patient. The scrotal skin is highly permeable and vascular, making it particularly susceptible to a variety of irritant and toxic agents [12].

In addition to 5-FU-induced cytotoxicity and irritant contact dermatitis, the differential diagnosis includes fixed drug eruption. Fixed drug eruption characteristically recurs in the same location upon re-exposure to the culprit drug and commonly involves the anogenital region. However, these eruptions are typically asymptomatic and accompanied by post-inflammatory hyperpigmentation [13]. Histologically, fixed drug eruption is characterized by interface dermatitis with a band-like inflammatory infiltrate.

Conclusion

Scrotal dermatitis is a rare adverse effect of topical 5-FU that is associated with significant distress and disruption of daily activities. The histologic findings associated with this case suggest that the cause of scrotal dermatitis secondary to topical 5-FU relates to the direct cytotoxic effects of the drug. Dermatologists should be aware of this potential side effect of the topical cream, as early recognition and discontinuation of the drug may be warranted.

Potential conflicts of interest

The authors declare no conflicts of interest.

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