Symmetrical Drug-Related Intertriginous and Flexural Exanthema Secondary to Topical 5-Fluorouracil

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We report the case of a 56-year-old man who developed a distinctive skin eruption after treating actinic keratoses on the dorsal aspects of his right and left hands with topical 5-fluorouracil (5-FU). The distribution of his rash was characteristic of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), also known as baboon syndrome.

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Case Report

A 56-year-old man with a history of diabetes mellitus, hypertension, hyperlipidemia, reflux, squamous cell carcinoma in situ of his right hand, and actinic keratoses of the right and left hands presented with a painful, burning, pruritic, erythematous, and blistering rash on his medial thighs, scrotum, penis, antecubital fossae, axillae, and dorsal hands. The patient had a successful history of treatment of actinic keratosis on his right hand with topical 5-fluorouracil (5-FU) 8 years prior to presentation. Two months prior to presentation, electrodesiccation and curettage were performed on a squamous cell carcinoma in situ on the dorsum of his right hand. One month prior to presentation, he initiated treatment of actinic keratoses on the dorsal aspects of his right and left hands with 5-FU twice daily and tretinoin cream 0.1% once daily. Approximately 2 weeks after initiation of therapy, the patient reported that he broke out with itchy, painful, red spots and blisters on his hands, right and left medial thighs, genitalia, and bilateral antecubital fossae and axillae. His dermatologist stopped the 5-FU and started prednisone, erythromycin, hydrocortisone ointment, and fexofenadine hydrochloride. Over the next week, the areas became eroded and the pain worsened. A biopsy was performed. The hydrocortisone was discontinued and he was referred for a second opinion.

Medications at presentation included erythromycin, fexofenadine hydrochloride, acetaminophen-codeine, prednisone, petrolatum ointment, metformin hydrochloride, enalapril maleate, ranitidine hydrochloride, simvastatin, triamterene/hydrochlorothiazide, aspirin, and omeprazole. He reported no known allergies.

Physical examination revealed an overweight man who appeared agitated and reported substantial discomfort. He had well-demarcated, violaceous, red erosions on his medial thighs (Figure 1), scrotum, and penis; erythematous denuded patches in the antecubital fossae (Figure 2) and axillae; and crusty erosions on the dorsum of his hands (Figure 3).

His differential diagnosis included an intertriginous toxic drug eruption versus bullous pemphigoid. A punch biopsy of his right thigh revealed epidermal ulceration with occasional necrotic keratinocytes and vacuolar changes of the basal layer accompanied by a superficial perivascular lymphocytic infiltrate and rare eosinophils. Direct immunofluorescence revealed perivascular and subepithelial deposition of fibrinogen, IgG, C3, and IgA, but the degree of positivity was not as striking as would be expected in bullous pemphigoid.

He was diagnosed with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), or baboon syndrome, resulting from systemic absorption of 5-FU. He was treated with triamcinolone acetonide ointment 0.1%, white petroleum jelly, doxycycline hyclate, and gabapentin, in addition to prednisone. The rash gradually cleared over the next month but healed with scarring.

Drs. Powers and Kovach are from West Virginia University School of Medicine, Morgantown. Dr. Gordon is from the Center for Clinical Studies, Houston, Texas. Dr. Roberts is from private practice, Cumberland, Maryland.

The authors report no conflict of interest.

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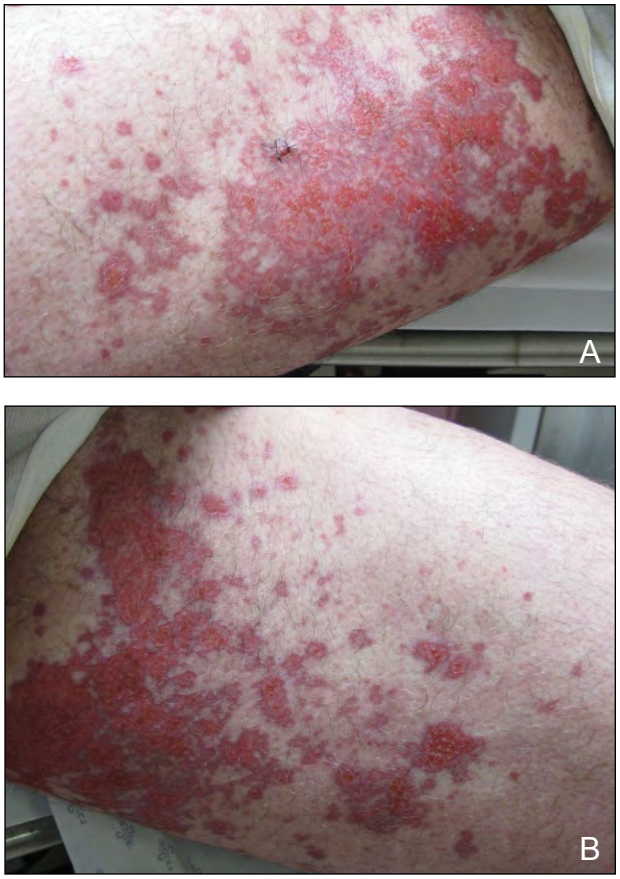

Figure 1. Violaceous and red erosions of the right (A) and left (B) medial thighs.

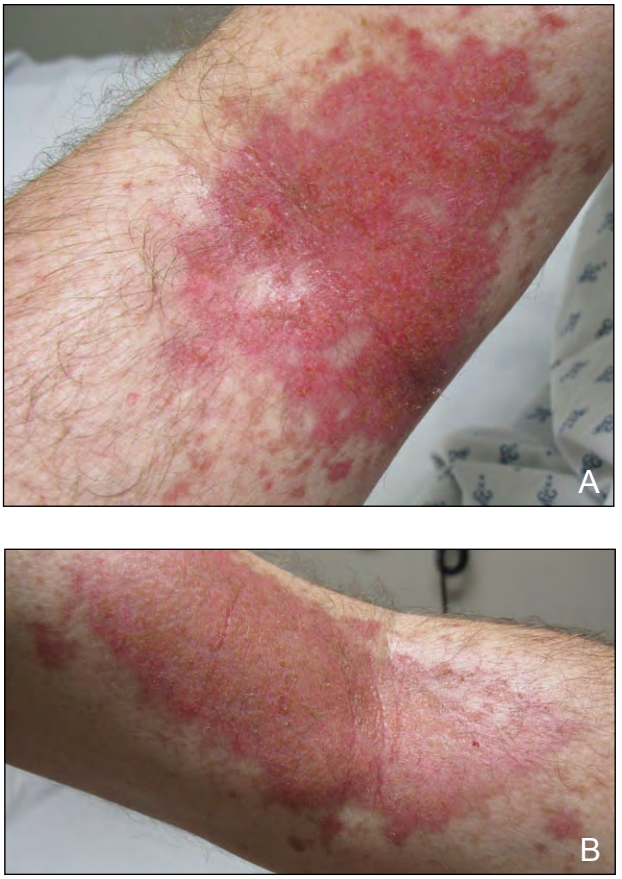

Figure 2. Erythematous denuded patches in the right (A) and left (B) antecubital fossae.

Comment

Cutaneous eruptions commonly occur secondary to systemic administration of drugs, topical administration of medications, and/or exposure to contact allergens. Although classic drug eruptions involve the trunk and extremities, unusual and specific distribution patterns have been reported. The term *baboon syndrome* was introduced in 1984 to describe a specific dermatologic response to systemic or local administration of contact allergens and certain drugs.[1] The name was coined due to the characteristic distribution of erythema on the buttocks and upper inner thighs, resembling the red buttocks of baboons. The rash also characteristically occurred in flexural and intertriginous areas such as the axillae and antecubital fossae.

The earliest description of this curious distribution pattern occurred after exposure to mercury.[2] Since the 1980s, more than 100 cases of baboon syndrome have been reported. Approximately half of the cases were attributed to exposure to systemic drugs, particularly amoxicillin and/or β-lactam antibiotics,[3] but the syndrome also has been reported after exposure to valacyclovir hydrochloride,[4] risperidone,[5]

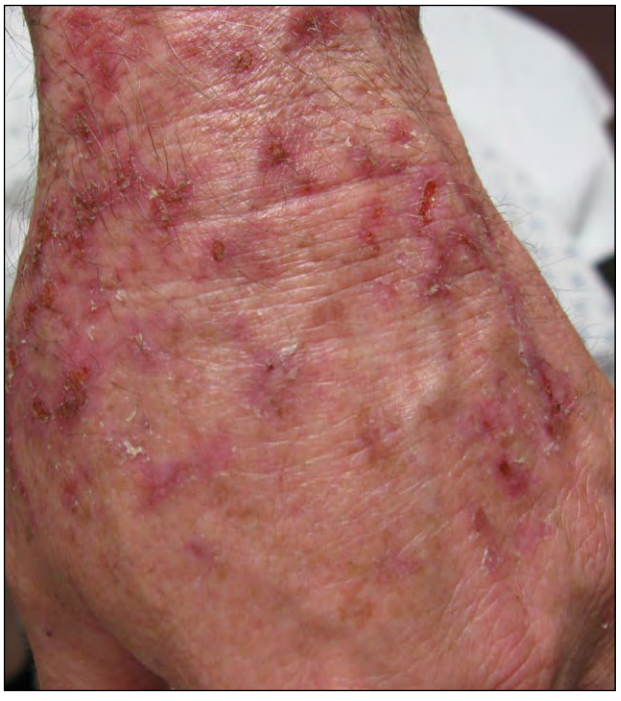

Figure 3. Crusty erosions on the dorsum of the hands.

cetuximab,[6] ethylenediamine-aminophylline,[7] pseudoephedrine hydrochloride,[8] and iodinated radiocontrast media.[9] Baboon syndrome typically presents with sharply defined, *V*-shaped erythema in inguinal/genital and gluteal/perianal areas, sometimes with tiny papules, pustules, and vesicles, and often with exanthema in other flexural areas. Acral and mucosal sites usually are spared. Systemic symptoms are absent.[3] Histology is variable, with a reported predominance of superficial perivascular infiltrates of mononuclear cells and occasional neutrophils and eosinophils. Vacuolar alteration of the basal cell layer and the presence of necrotic keratinocytes have been mentioned in some cases.[3]

Hausermann et al[3] proposed that the term *baboon syndrome* be replaced with *SDRIFE* to include the occurrence of these reactions after exposure to systemic drugs. They proposed that certain criteria be met for the diagnosis of SDRIFE: (1) exposure to a systemically administered drug at the first dose or repeated dose, excluding contact allergens; (2) sharply demarcated erythema of the gluteal/perianal area and/or *V*-shaped erythema of the inguinal/perigenital area; (3) involvement of at least one other intertriginous/flexural localization; (4) symmetry of affected areas; and (5) absence of systemic symptoms and signs.[3]

The precise immunologic and pathogenetic mechanisms of SDRIFE have yet to be elucidated. Theorists propose that the inciting agent collects in eccrine or apocrine glands, areas of increased temperature or friction,[10] or areas of prior dermatitis (ie, recall phenomenon,[11] Wolf isotopic response[12]), and elicits a T-cell–mediated, delayed-type hypersensitivity reaction.[9]

Webber et al[10] reported the occurrence of an intertriginous eruption associated with chemotherapy in pediatric patients. Although not labeled as SDRIFE, the pattern and description of the rash were consistent with SDRIFE. Methotrexate and cyclophosphamide were the chemotherapeutic agents most frequently associated with the intertriginous eruption, but 5-FU was not among those reported.

Topical 5-FU is a pyrimidine analogue that inhibits RNA processing and thymidylate synthase. It is used both systemically and topically to treat a number of malignancies. A number of cutaneous reactions have been reported following systemic therapy with 5-FU, including hand-and-foot syndrome (palmar-plantar erythrodysesthesia or acral erythema),[13] exanthema, hyperpigmentation, photosensitivity, recall reactions,[14] and inflammation or exacerbation of other cutaneous conditions such as actinic keratosis or seborrheic dermatitis.[15]

Topical 5-FU, most commonly used for treatment of actinic keratosis, is frequently associated with a moderate to severe irritant contact dermatitis with erythema, pruritus, irritation, burning, inflammation, vesiculation, and crusting at the site of application.[16] Allergic contact dermatitis from topical 5-FU is thought to be uncommon but has been reported.[17]

Tretinoin, a topical retinoid used to enhance the uptake of 5-FU, can cause local irritation, erythema, peeling, burning, and pruritus. If systemically absorbed, it may be associated with xerosis and palmoplantar desquamation but has not been reported to cause a flexural exanthema.

Our patient was careful to wash his hands after applying the medication and denied the possibility that he transferred the 5-FU or tretinoin to areas of his body other than the dorsal surface of his hands.

Cutaneous reactions distal to the area of topical therapy with 5-FU have been rarely reported but could occur if there was increased systemic absorption secondary to the breakdown of the skin barrier.[18] Pretreatment of the area with a topical retinoid and electrodesiccation and curettage of his right hand may have led to barrier reduction and greater absorption of 5-FU. Our patient's distinctive skin eruption was consistent with a diagnosis of SDRIFE secondary to systemic absorption of topical 5-FU.

Conclusion

Topical 5-FU is commonly used by dermatologists. Local irritant contact dermatitis is expected and is considered to be a side effect of therapy. We present a case of a distant and distinctive eruption consistent with a diagnosis of baboon syndrome, or SDRIFE, caused by topical application of 5-FU to raise awareness of the possibility of this adverse reaction.

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