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Everolimus-Induced Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)

To the Editor:

A 76-year-old man presented with a severely pruritic flexural eruption. Just weeks before its onset, he initiated chemotherapy, which included everolimus for adenocarcinoma of the lung. Physical examination revealed erythematous plaques involving the inferior abdominal skin fold, medial thighs, perineum, and inguinal creases (Fig. 1). Eczematous plaques were also noted in his axillae and posterior neck fold. Apart from his rash, the patient was well and afebrile. Lesional biopsies were performed revealing a subacute spongiotic dermatitis with prominent eosinophils.

The combined clinical, historical, and histopathologic features of his presentation were consistent with a diagnosis of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). Concerted efforts were made to discontinue everolimus. Therapeutically, the patient improved with daily



Figure 1. Symmetrical drug-related intertriginous and flexural exanthema. Scaly plaques on the medial thighs and suprapubic abdomen.

application of triamcinolone acetonide cream. He resumed chemotherapy without everolimus and had a sustained remission of his eruption.

First described by Anderson et al,¹ SDRIFE is a systemic contact dermatitis characterized by a patterned, symmetrical erythema of the skin folds. Diagnostic criteria for SDRIFE were proposed by Tan et al² and require 4 of the 5 elements: exposure to a systemically administered agent; distinct erythema of the gluteal, inguinal, or axillary area; involvement of at least 1 intertriginous site; symmetry; and the absence of internal organ dysfunction. The exanthem usually occurs several days following ingestion of the inciting medication. Microscopically, a superficial perivascular infiltrate with or without eosinophils is seen; spongiosis may be a prominent feature. After discontinuation of the causative agent, the eruption subsides within weeks. Topical or systemically administered corticosteroids may hasten disease resolution, but because SDRIFE is a benign, self-limiting dermatosis, intervention apart from discontinuation of the instigating medication is not necessary.³

The most common culprit medications responsible for SDRIFE are the aminopenicillins and β -lactam antibiotics. Ingested metals, including nickel and mercury, as well as exposure to plant parts of the Compositae and Anacardiaceae families may rarely produce the exanthem.⁴

The pathogenesis underlying SDRIFE is incompletely understood, but as with allergic contact dermatitis, the condition appears to be a T-cell-mediated delayed-type hypersensitivity reaction. The higher density of eccrine sweat glands in body folds may explain its strict localization to intertriginous sites, where drug excretion precipitates the dermatosis.

Our patient experienced an episode of SDRIFE after initiation of a multidrug chemotherapeutic regimen. Based on

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TABLE 1. Mucocutaneous Reactions to mTOR Inhibitors

Common

Aphthous stomatitis
 Morbilliform rash
 Acneiform (papulopustular) rash
 Folliculitis
 Pruritus

Uncommon

Exfoliative dermatitis (erythroderma)
 Onychodystrophy
 Onycholysis
 Splinter hemorrhages
 Leukonychia
 Longitudinal ridging
 Paronychia

Rare

SDRIFE
 Cutaneous small vessel vasculitis

SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

his oncologist's suspicion, everolimus, a macrolide immunosuppressant that selectively inhibits mTOR, was discontinued and resulted in disease remission. After resuming chemotherapy without everolimus, his exanthem remained quiescent, which confirmed everolimus as the culprit medication.

A variety of mucocutaneous reactions may complicate treatment with everolimus and other mTOR inhibitors (Table 1).⁵ The majority of these are benign and require minimal intervention. As far as we are aware, our case represents the first report of SDRIFE complicating mTOR inhibitor therapy. Because it is a benign dermatosis, the development of SDRIFE should not preclude the use of an mTOR inhibitor if it is a requisite component of a treatment regimen. In rare instances, use of this class of medications may be complicated by erythroderma or cutaneous small vessel vasculitis, which may necessitate treatment cessation and more aggressive management.

Toxic erythema of chemotherapy must be distinguished from SDRIFE in patients receiving chemotherapy. Toxic erythema of chemotherapy is a nonspecific designation that has been proposed to simplify the nomenclature describing the variety of cutaneous eruptions noted during chemotherapy administration. Conventional chemotherapeutic drugs that exhibit nonselective mechanisms of cell injury, such as alkylating agents, antimetabolites, and mitotic inhibitors, are responsible for this heterogeneous group of disorders. In contrast to SDRIFE, toxic erythema of chemotherapy is often

painful and exhibits purpura or skin necrosis. Histopathology reveals keratinocyte apoptosis, dermal edema, and eccrine squamous syringometaplasia.

Our report is the first to describe SDRIFE occurring in association with everolimus, a selective mTOR inhibitor used as a treatment for solid tumors and as an immunosuppressant in organ transplant recipients. As the use of this class of medications is increasing, recognition of SDRIFE as a potential complication of mTOR inhibitor therapy is necessary. The clinical picture of a symmetric, pruritic eruption localized to skin folds in the absence of systemic signs or symptoms after drug administration should suggest the diagnosis. Proper management requires identification and discontinuation of the inciting medication. Supportive care with topical or systemic corticosteroids hastens resolution. A treat-through approach may be considered when the culprit medication is indispensable. Symmetrical drug-related intertriginous and flexural exanthema is likely an underdiagnosed condition with a benign, self-limiting course. Ongoing characterization of medications that induce the syndrome will assist with greater recognition and improved management of this uncommon dermatosis.

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