

Systemic drug-related intertriginous and flexural exanthema from radio contrast media: A series of 3 cases

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INTRODUCTION

Systemic drug-related intertriginous and flexural exanthema (SDRIFE) is a cutaneous reaction, characterized by 5 diagnostic criteria (Table I).¹ We report on 3 patients with SDRIFE induced by radio contrast media (RCM) and describe the dermatologist's role in the treatment and prevention of SDRIFE.

CASE SERIES

Patient 1

A 41-year-old African-American woman with a history of uncontrolled hypertension, diabetes mellitus type II, and chronic kidney disease secondary to diabetic nephropathy was admitted for a progressive pruritic eruption shortly after undergoing computed tomography angiography using intravenous (IV) iodinated dye for evaluation of pulmonary thromboembolism. A painful pruritic eruption developed within 12 hours of the procedure with erythematous plaques on the pannus, inframammary, and inguinal folds along with vesicles on the back and edematous palms. She had a similar rash 7 years ago from IV iodinated RCM. During the current admission, a very similar eruption developed despite her being premedicated with systemic steroids (oral prednisone, 50 mg, and IV hydrocortisone, 200 mg), diphenhydramine, and cimetidine.

Patient 2

A 64-year-old white woman with history of hypertension, diabetes mellitus type II, and hyperlipidemia

Abbreviations used:

DTH:	delayed hypersensitivity
IV:	intravenous
RCM:	radio contrast media
SDRIFE:	systemic drug-related intertriginous and flexural exanthema

presented with a worsening rash that initially started as mild pruritus on her hips approximately 8 hours after computed tomography scan with IV RCM. Physical examination found bright red, erythematous plaques with overlying vesicles that extended across the buttocks, lower back, thighs, inguinal folds, and abdomen.

Patient 3

A 53-year-old white woman with an unknown autoimmune disorder was admitted for a posterior communicating artery aneurysm after clipping. She presented with a 2-day history of severely pruritic rash after receiving computed tomography angiography with RCM 5 days earlier. She received IV contrast in the past without a reaction. Physical examination found bright red, erythematous plaques with overlying vesicles that extended across the buttocks, lower back, thighs, inguinal folds, and abdomen (Fig 1, A and B).

Medications

None of the patients' regular medications, which they all had been taking for at least 8 months, were

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Table I. Five diagnostic criteria for SDRIFE

Occurrence after exposure to systemic drug at first or on repeated doses
Sharply demarcated erythema of buttocks or V-shaped erythema of thighs
Involvement of at least one other flexural fold
Symmetry of affected areas
Absence of systemic symptoms and signs

Adapted with permission from Hausermann P, Harr T, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? *Contact Dermatitis*. 2004; 51(5-6):297-310.

considered to be associated with the SDRIFE reaction. The regular medication list by patient consisted of the following: patient 1—hydralazine, furosemide, lisinopril, carvedilol, amlodipine, atorvastatin; patient 2—metformin, atorvastatin hydrochlorothiazide, lisinopril, paroxetine; and patient 3—conjugated estrogens and hydroxychloroquine. None of the patients had systemic symptoms or mucosal involvement.

Histopathology

Biopsy specimens from patients 1 (left inframammary) and 3 (left inguinal) showed hyperkeratosis, spongiosis, and superficial perivascular infiltrate composed mostly of lymphocytes and occasional neutrophils (Fig 2). There was also focal basal layer hydropic degeneration. One patient had papillary dermal edema with sparse intraepidermal eosinophils and more pronounced spongiosis. These histopathologic findings are compatible with systemic contact-type reaction to intravenous RCM in the appropriate clinical context.

Laboratory data

One patient had peripheral eosinophilia (11%; normal, 0% to 5%). Comprehensive metabolic panel and complete blood count results were within normal limits.

Treatment

All 3 patients were treated with topical steroids including triamcinolone 0.1% ointment (abdomen, back, and thighs) and hydrocortisone 2.5% cream or desonide 0.05% cream (inframammary and inguinal folds). The patients were also given a combination of various oral antihistamines including loratadine, hydroxyzine, and diphenhydramine as needed for pruritus. Two patients received prednisone for 1 week. The eruptions resolved in all patients in 3 to 4 weeks with residual hyperpigmented patches.

DISCUSSION

In 1983, Nikiyama et al reported the first case of an eruption in this flexural distribution attributable to inhalation of mercury vapor.² In 1984, the term *baboon syndrome* described this distribution localized to buttocks and inner thighs. Hausermann et al¹ coined the term *SDRIFE* in 2004 after noting cases of baboon syndrome related to drug exposure without prior sensitization. SDRIFE is a self-limited phenomenon defined by 5 clinical diagnostic criteria (Table I).¹ Risk factors for RCM reactions include past reactions to RCM or prior severe allergic reaction to any substance; ≥ 1 drug allergy; ≥ 4 allergens; history of asthma, heart, thyroid, or kidney disease; being elderly, and being females.³ Time of onset can vary from hours to days after exposure to the inciting agent.

SDRIFE has been reported with multiple medications including antiasthma treatments (aminophylline, terbutaline), antibiotics (erythromycin, penicillins, aminoglycosides, and antifungals), and allopurinol.^{4,5} Arnold et al⁶ described cases of recurrent SDRIFE from 2 iodinated RCMs, iomeprol and iopromide, both nonionic monomers. Histopathology of SDRIFE finds superficial perivascular infiltrates of mononuclear cells; however, some cases have also shown extravasated erythrocytes, neutrophils, and eosinophils with mild dermal edema and slight spongiosis.²

The exact mechanism for SDRIFE is unknown. Based on positive patch tests, positive delayed skin tests, and lymphocyte transformation tests, T-cell-mediated type IV delayed hypersensitivity (DTH) immune response is the most plausible pathogenesis of SDRIFE.^{2,7,8} The pathomechanism of type IV DTH (a, b, c, and d) is determined by the primary T-cell subtype resulting in the release of specific inflammatory mediators. SDRIFE likely involves both a DTH type IVa reaction with CD4⁺ Th1 cells and macrophages as well as a type IVc reaction involving cytotoxic CD4 and CD8 T cells.^{9,10} For RCM-induced SDRIFE, Arnold et al⁶ noted that oral potassium iodide and skin test-negative contrast media were administered and both tolerated, indicating that antigen may be related to molecules in RCM and not iodine itself. These findings support a novel pathologic mechanism, the p-I concept (pharmacologic interaction with immunoreceptors), which suggests direct recognition of some chemically inert molecules that can bind directly and noncovalently to a fitting T-cell receptor without first being presented to the major histocompatibility complex.² This p-I hypothesis could help account for the rapid onset

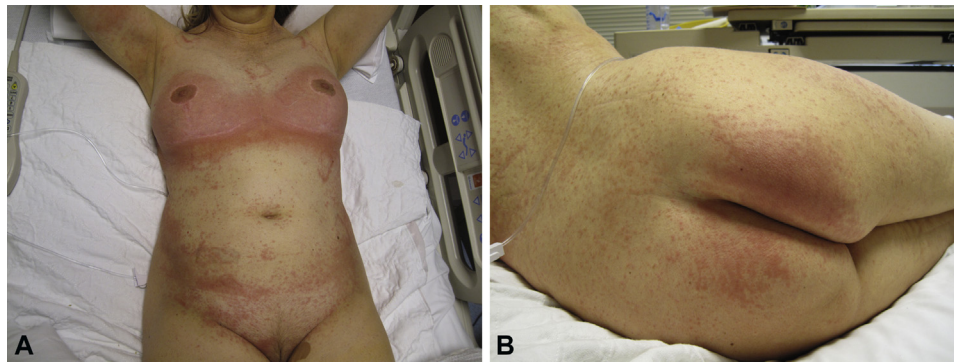


Fig 1. Patient 3. SDRIFE. Frontal view (A) and right lateral view (B) with erythema and blanching papules coalescing into plaques with vesicles on back, abdomen, and bilateral inframammary and inguinal folds.

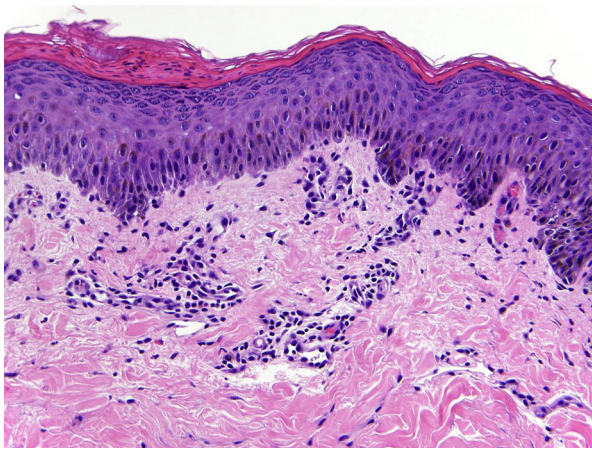


Fig 2. Patient 3. Biopsy specimen from the left inguinal area shows slight spongiosis and superficial perivascular infiltrate with occasional neutrophils and focal basal layer hydropic degeneration. (Hematoxylin-eosin stain; original magnification: $\times 40$.)

of the RCM SDRIFE reactions, which can occur within hours.

Our 3 patients meet the 5 criteria for SDRIFE in the absence of a known prior sensitizing agent. Treatment is directed toward symptomatic relief with topical or systemic steroids and antihistamines. We observed premedication prophylaxis was not effective, as one of our patients had multiple episodes of the same reaction after undergoing an unavoidable “rechallenge” from the same iodinated RCM despite premedication with systemic steroids, diphenhydramine, and cimetidine.

However, Arnold et al⁶ showed that his patient had positive delayed skin test results to 2 different

nonionic monomer RCMs but had negative skin test results for ionic dimer RCM. Hence, the dermatologist can help choose a different class of RCM for each patient to help prevent recurrence of SDRIFE in future procedures.

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