

CONTACT POINT

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) associated with pristinamycin, secnidazole, and nefopam, with a review of the literature

Laurence Nespoulous¹  | Ioana Matei¹ | Aurélie Charissoux² | Christophe Bédane¹ | Safaë Assikar¹

¹Department of Dermatology, University Hospital Centre, Limoges, France

²Department of Pathology, University Hospital Centre, Limoges, France

Correspondence

Assikar Safaë, Dupuytren Hospital, Department of Dermatology, 2 Avenue Martin Luther King, 87042 Limoges, France.

Email: safae.assikar@chu-limoges.fr

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In 1984, Andersen et al¹ introduced the term “baboon syndrome” to describe a systemic contact dermatitis characterized by exanthema with involvement of the buttocks and flexure regions after the systemic absorption of a contact allergen (nickel, mercury, or ampicillin) in a sensitized patient. The rash looked like the red buttocks of a baboon. In 1983, Nakayama et al² published a report of 15 patients with symmetrical erythema predominantly on major flexural sites, which occurred 1 or 2 days after the breaking of a mercury thermometer. The non-contact allergic variant of baboon syndrome is also referred to as symmetrical drug-related intertriginous and flexural exanthema (SDRIFE).

Since 1984, ~100 cases of baboon syndrome or SDRIFE have been reported. We report 3 cases of SDRIFE, 1 each caused by pristinamycin, secnidazole, and nefopam.³

CASE REPORTS

Case 1. A 60-year-old man presented with an erythematous rash of the inguinal and axillary folds and gluteal area (Figure 1). He had been treated with candesartan for many years. He had recently been diagnosed with a bronchial infection, and was prescribed pristinamycin. The cutaneous rash appeared 2 days later. The results of laboratory tests were within normal limits, except for a mild biological inflammatory syndrome probably attributable to the infection. Histopathological analyses of a skin biopsy showed an orthokeratotic epidermis without keratinocytic necrosis, discrete spongiosis, and a lymphocytic infiltrate of the dermis with some eosinophils (Figure S1). The clinical and histopathological signs confirmed the diagnosis of SDRIFE caused by pristinamycin, which was discontinued. The skin

lesions completely regressed within 7 days. Two months later, the patient was patch tested with pristinamycin 30% pet. and 30% aq. on the back and in an inguinal fold. The results were negative on day (D) 2 and D3. The patient refused an oral provocation test.

Case 2. A 44-year-old woman was treated with secnidazole for vaginitis caused by *Trichomonas vaginalis*. After 2 days, she developed a pruritic eczema-like eruption in the axillary, inguinal and submammary folds, with no other signs (Figure S2). She denied taking any other medication, and had a history of maculopapular exanthema caused by metronidazole and acetylsalicylic acid. Secnidazole was stopped, and topical betamethasone treatment was initiated. The lesions resolved within 4 days. SDRIFE caused by secnidazole was diagnosed, and patch tests were performed with secnidazole 30% pet. and 30% aq. These gave negative results on D2 on the back and in 1 affected area (breast), but a positive reaction on D4 on the breast (+), although the result remained negative on the back. Metronidazole and secnidazole may potentially cross-react, because both are sulfonamides.

Case 3. A 68-year-old woman was referred with an erythematous V-rash of the buttocks, perineum, and axillary folds, which appeared a few hours after intravenous administration of nefopam and oxycodone (Figure S3). The patient had developed the same type of rash after taking nefopam a few years earlier. There was no mucosal or other involvement. A skin biopsy showed lichenoid dermatosis (Figure S4). SDRIFE caused by nefopam was suspected. The lesions resolved within 5 days. No patch tests were performed, because the intrinsic imputability of nefopam was strong with recurrence of the same lesions.

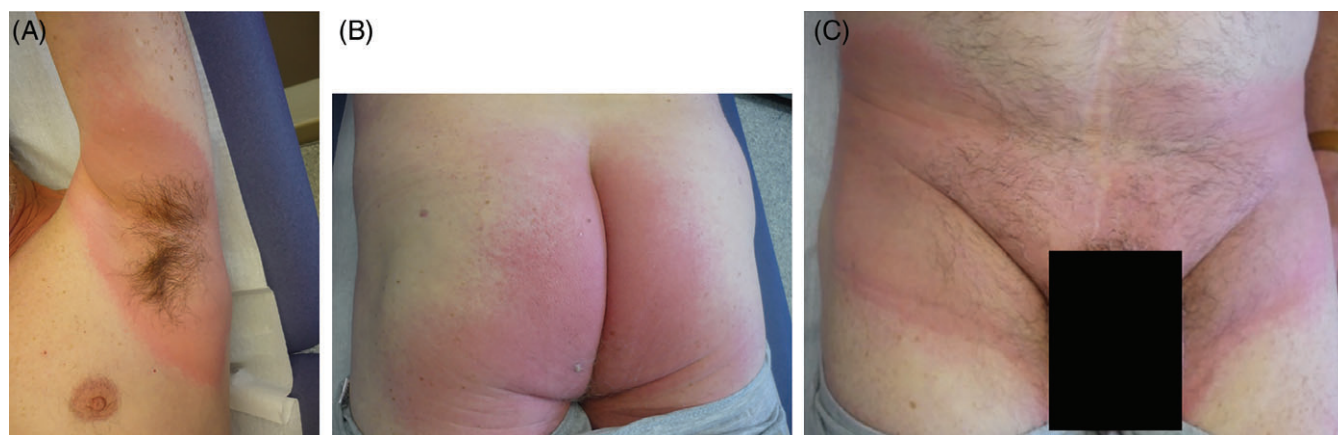


FIGURE 1 Patient 1. (A), Symmetrical erythema of axillary folds. (B), Sharply demarcated erythema of the gluteal region. (C), Erythematous squamous exanthema of inguinal folds

DISCUSSION

In 2004, Häusermann et al⁴ proposed the term SDRIFE for reactions that occur after exposure to systemic drugs. We have reported 3 typical cases of SDRIFE. The diagnosis involves the 5 criteria shown in Table S1 in File S1.⁴ Clinically, there is V-erythema of the inguinal folds and in various regions of the integument, for example, axillary folds. There are no systemic signs.⁵ The differential diagnosis includes intertrigo, seborrheic dermatitis, allergic contact dermatitis caused by a textile dye or fragrances, and other specific drug reactions, such as a fixed drug eruption, acute generalized exanthematous pustulosis, and drug rash with eosinophilia (Table S2 in File S2).^{4,6} SDRIFE affects patients of any age, but is rare in children (Table S3 in File S1). Both sexes are affected, with a male predominance (male/female ratio of 3:1). The latency is from a few hours to a few days after the causative drug has been taken.^{7,8} SDRIFE is most commonly associated with β -lactams, particularly amoxicillin, which is responsible for half of all cases. However, it is also associated with other drugs, such as chemotherapeutic agents and anti-tumour necrosis factor- α (Table S3 in File S1). The histological features are non-specific: a superficial mononuclear perivascular infiltrate, primarily composed of mononuclear cells, in some cases including neutrophils and eosinophils; other rare findings are subcorneal pustules, vacuolar changes, and necrotic keratinocytes.⁹

The diagnosis is based mostly on clinical presentation and history, and exclusion of other causes for a rash. A patch test gives a positive reaction in only up to 50% of patients, probably because of the reduced absorption of the drugs by the skin. Skin patch tests on the previously affected areas are preferred. Controlled drug-provocation testing is the gold standard clinical test, and gives a positive result in most patients with SDRIFE. The exact immune and pathophysiological mechanisms of SDRIFE have not yet been elucidated; it apparently corresponds to a type IV hypersensitivity immune response. This notion is supported by immunohistochemical evidence for CD4⁺ T cell infiltration and increased endothelial and keratinocyte expression of CD26P-selectin, which recruits type 1 helper T cells to sites of inflammation.

The postulated reasons for the flexural predilection are occlusion, sweating, or the excretion of certain drugs or metabolites from the eccrine glands.^{10,11}

CONCLUSION

To the best of our knowledge, these are the first published cases of SDRIFE caused by pristinamycin, secnidazole, and nefopam, respectively. The prognosis is good when the drug is discontinued. Different treatments can be used, including antihistamines and topical and systemic corticosteroids for severe forms. SDRIFE is considered to be a benign rash with characteristic clinical signs.

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Conflict of interest

The authors declare no potential conflict of interests.

ORCID

Laurence Nespoulous  <http://orcid.org/0000-0001-8187-2916>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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CRITERIA	
	SDRIFE FDE AGEP DRESS
1	Exposure to a systemically administered drug either at the first 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
5	Absence of systemic symptoms and signs

Table 1: Diagnostic criteria for symmetrical drug-related intertriginous and flexural exanthema proposed by Häusermann et al (1)

<i>Clinical manifestation</i>	Symmetrical intertriginous and flexural erythematous exanthematous with a predilection in the buttocks and inguinal regions, without facial and mucosal involvement, no erythroderma	A sudden onset of annular, edematous, dusky-red macules, or plaques on the skin and/or mucous membranes, along with burning sensation and/or itching. Characteristic residual hyperpigmentation will be seen after lesions subside. There is a characteristic recurrence at the same sites on the repeat administration of the offending drug.	Mostly generalized symmetrical non-follicular pustules exanthema (numerous, small (<5mm), sterile, non-follicular pustules) with possible erythroderma and facial involvement, rarely with mucosal involvement. Other rare skin signs are edema of the face, purpura, atypical target-like lesions, and vesicles.	Generalized symmetrical maculo-papular or morbiliform exanthema often with facial involvement (edema) and possible erythroderma. Other types of cutaneous lesions are also described as pustular lesions, purpura and more rarely vesiculobullous lesions. Mucosal involvement may be present and mainly affects the oral cavity
<i>Systemic symptoms</i>	None	None	Fever	Fever
<i>Organ involvement</i>	None	None	Normally none	Arthritis, nephritis, hepatitis, pneumonia, pericarditis and myocarditis
<i>Laboratory findings</i>	Normal	Normal	Leucocytosis with elevated neutrophil count, sometimes moderate eosinophilia	Eosinophilia, mononucleosis-like atypical lymphocytosis. some patients : a reactivation of the human herpes virus type 6
<i>Latency</i>	Hours to 2 days	1-2 weeks after exposure, after subsequent exposure regularly within 24 h	Hours to few days	2 to 6 weeks
<i>Histopathology</i>	Superficial mononuclear perivascular infiltrate, primarily composed of monuclear cells, in some cases including neutrophils and eosinophils, other rare findings subcorneal pustules, vacuolar changes and hydropic degeneration in the basal cell layer with subepidermal bullae, and necrotic keratinocytes were also reported	Predominantly lymphocytic inflammation, variable slights parakeratosis, slight focal oedema, rare dyskeratotic cells, vacuolarization along dermoepidermal junction, slight papillary fibrosis and scattered melanophages, especially between venules	Many individual necrotic keratinocytes surrounded by eosinophils especially prominent towards the basal layer, vacuolar alterations of the basal layer, extensive oedema of the papillary dermis, a superficial and deep perivascular lymphocytic infiltrate with many eosinophils. Spongiform subcorneal and/or intraepidermal pustules with papillary edema	Varying combinations of epidermal hyperplasia, spongiosis, parakeratosis and individually necrotic keratinocytes in the background of lymphocyte predominant dermal infiltrate (with some atypia)

Table 2: Comparison of distinct cutaneous drug eruption. Adpated from Hauserman et al. (1)

FDE: Fixed drug eruption; AGEF: acute generalized exanthematous pustulosis; DRESS: drug rash with eosinophilia and systemic symptoms; SDRIFE: symmetrical drug-related intertriginous and flexural exanthema

<i>FAMILY</i>	<i>NUMBER</i>	<i>TRIGGERING DRUG</i>	<i>COMEDICATION</i>	<i>AGE</i>	<i>SEX</i>	<i>LATENCY</i>	<i>PATCH TEST</i>	<i>REFERENCES</i>
<i>ANTIBIOTIC</i>	1	Amoxicillin	Nm	12	Male	12h	Negative	(2)
	2	Amoxicillin-Clavulanate	Nm	3	Male	2d	Nd	0/0/0000 0:00:00 AM (3)
	3	Amoxicillin-Clavulanate	Paracetamol	35	Female	1h	Negative	(4)
	4	Amoxicillin	Nm	30	Male	5d	Negative	(5)
	5	Penicillin	Nm	46	Male	1d	Nd	(6)
	6	Cefixime	Ampicillin	1	Male	3d	Negative	(7)
	7	Ceftriaxone	Clindamycin	64	Female	3d	Nd	(8)
			Daptomycin					
	8	Cephalexin	Nm	50	Male	20h	Negative	(9)
	9	Benzylpenicillin	Nm	40	Male	1d	/	(10)
	10	Cloxacillin	Nm	45	Male	3d	Nd	(11)
	11	Clindamycin intradermal test	Nm	72	Female	2d	Nd	(12)
	12	Sulfamethoxazole- Trimethoprim	Nm	64	Female	2d	Negative	(13)
	13	Clarithromycin	Ampicillin	1	Male	5d	Negative	(7)
	14	Clarithromycin	Nm	43	Male	7d	Positive	(14)
	15	Doxycyclin	Nm	51	Female	2w	Nd	(15)
	16	Doxycyclin	Nm	64	Female	4d	Nd	(16)

FAMILY	NUMBER	TRIGGERING DRUG	COMEDICATION	AGE	SEX	LATENCY	PATCH TEST	REFERENCES
ANTIBIOTIC	17	Ampicillin-Sulbactam	Nm	14	Male	2d	Nd	(17)
ANTIVIRAL	18	Valacyclovir	Nm	56	Female	1h	Negative	(18)
	19	Valacyclovir	Nm	79	Male	3h	Positive	(19)
ANTIFUNGAL	20	Terbinafine	Nm	60	Male	3d	Negative	(20)
	21	Terbinafine	Metfomin Glimepiride	62	Male	Nm	Positive	(21)
	22	Oral Fluconazole	Nm	66	Female	1d	Nd	(22)
	23	Itraconazole	Nm	43	Female	1d	Negative	(23)
CONTRACEPTIVE	24	Nuvaring®	Nm	33	Female	7d	Positive	(24)
ANALGESIC	25	Paracetamol	Nm	33	Male	Few days	Negative	(25)
	26	Paracetamol	Cefcapene Pivoxil	53	Male	1d	Negative	(26)
	27	Codeine	Paracetamol	60	Female	2d	Negative	(27)

FAMILY	NUMBER	TRIGGERING DRUG	COMEDICATION	AGE	SEX	LATENCY	PATCH TEST	REFERENCES
ANTI INFLAMMATORY BENZODIAZEPINE	28	Ibuprofen	Nm	2	Male	4h	Nd	(28)
	29	Loflazepate Ethyl	Nm	64	Female	3y	Negative	(29)
CORTICOSTEROID	30	Bethamethasone	Nm	58	Male	2d	Positive	(30)
	31	Prednisolone	Nm	50	Female	1d	Positive	(31)
NEUROLEPTIC	32	Clozapine	Nm	42	Male	6m	Nd	(32)
	33	Clozapine	Nm	56	Male	4m	Nd	(32)
	34	Risperidone	Nm	8	Male	2d	Negative	(33)
MTOR INHIBITOR SYSTEM	35	Everolimus	Nm	76	Male	Few weeks	Nd	(34)
PROTON PUMP INHIBITOR	36	Omeprazole	Nm	67	Female	17d	Negative	(35)
PROTON PUMP INHIBITOR	37	Omeprazole	Methotrexate	27	Female	6d	Nd	(35)

FAMILY	NUMBER	TRIGGERING DRUG	COMEDICATION	AGE	SEX	LATENCY	PATCH TEST	REFERENCES
COXIB	38	Etoricoxib	Ibuprofen	61	Female	6h	Positive	(36)
	39	Celocoxib	Nm	61	Female	4d	Negative	(37)
ANTIBIOTIC PEST CONTROL	40	Metronidazole	Nm	16	Female	5d	Negative	(38)
ANGIOTENSIN II RECEPTOR ANTAGONISTS - THIAZID DIURETIC	41	Telmisartan- Hydrochlorothiazide	Nm	28	Female	4d	Nd	(39)
IODINATED CONTRAST AGENT	42	Iodine-based contrast dye	Nm	57	Female	6h	Nd	(40)
	43	Radio contrast media	Nm	41	Female	12h	Nd	(41)
H2 BLOCKER MONOCLONAL ANTIBODY	44	Radio contrast media	Nm	64	Female	8h	Nd	(41)
	45	Radio contrast media	Nm	53	Female	2d	Nd	(41)
	46	Ranitidine	Cetirizine	8	Male	5d	Negative	(42)
	47	Golimumab	Nm	70	Female	1w	Nd	(43)
	48	Inflixumab	Nm	50	Male	2d	Nd	(44)

FAMILY	NUMBER	TRIGGERING DRUG	COMEDICATION	AGE	SEX	LATENCY	PATCH TEST	REFERENCES
H1 BLOCKER	49	Hydroxyzine	Meprobamate	60	Male	2d	Positive	(45)
STIGMINE	50	Rivastigmine	Nm	88	Male	3m	Nd	(46)
PROTEASOME INHIBITOR	51	Bortezomib	Talidomide/ Dexamethasone/ Bactrim/ Valaciclovyr	61	Male	2w	Nd	(47)
MONOCLONAL ANTIBODY AURISTATINE E CONJUGATE	52	Monoclonal antibody Auristatine E conjugate	Nm	72	Male	7d	Nd	(48)
BIPHOSPHONATE	53	Zoledronic	Nm	54	Female	1d	Nd	(49)
ALPHA BLOCKER	54	Terazosin	Nm	71	Male	Nm	Nd	(50)
IMMUNOSUPPRESSANT	55	Tacrolimus	Nm	41	Male	2y	Positive	(51)

Table 3: Cases of SDRIFE: review of literature

Nm: Not mentioned; Nd: not done; h: hours; w: weeks; d: days; m: months, y: years

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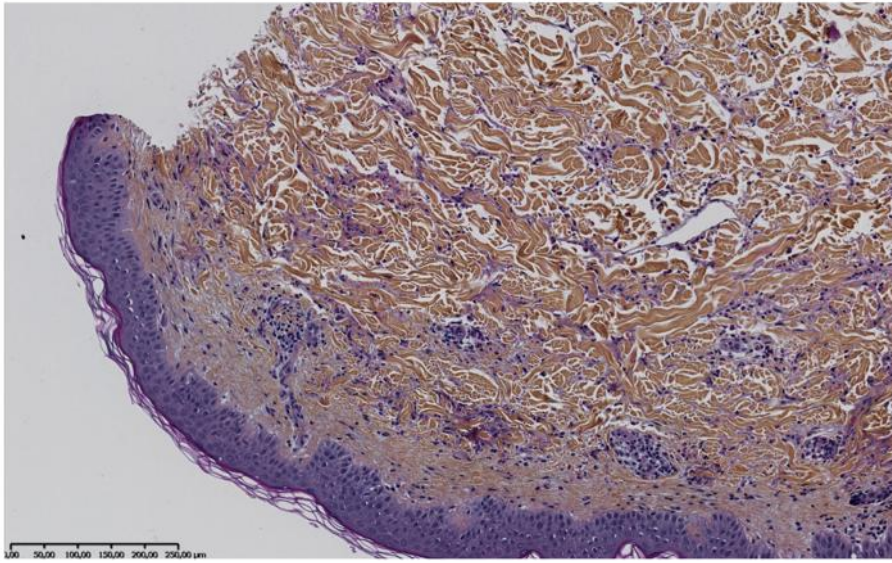
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Online supplemental figure 1. Orthokeratosis epidermis without keratinocytic necrosis, a very discrete spongiosis and in the dermis lymphocytic infiltrate with some eosinophils



A



B



C

Online supplemental figure 2. Patient 2

(A) Symmetrical erythematous squamous exanthema of inguinal folds; **(B)** Sharply demarcated erythema of perianal area and axillary folds; **(C)** Exanthema of axillary fold



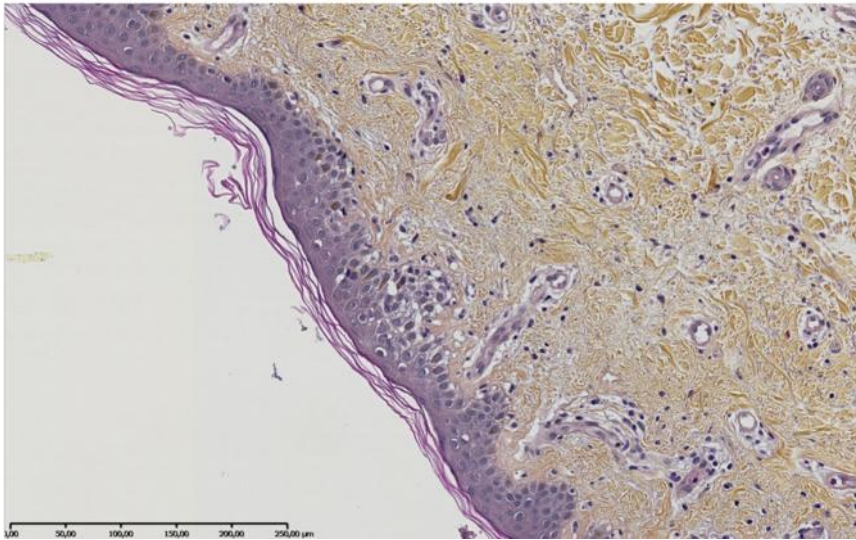
A



B

Online supplemental figure 3. Patient 3

(A) Erythematous V-rash of perineum ; **(B)** Eczematiform eruption on the folds' regions



Online supplemental figure 4. Vacuolation of the basal associated with exocytosis of some lymphocyte cells and a discrete spongiosis.