

A Systematic Approach to Systemic Contact Dermatitis and Symmetric Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)

A Closer Look at These Conditions and an Approach to Intertriginous Eruptions

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Contents

Abstract	171
1. Systemic Contact Dermatitis (SCD)	172
1.1 Introduction and History	172
1.2 Presentation	172
1.3 Causes	172
1.3.1 Metals	172
1.3.2 Medications	173
1.3.3 Plants and Herbals	173
2. Symmetric Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)	174
3. Diagnostic Testing in SCD and SDRIFE	175
4. Clinical Approach to the Patient with an Intertriginous Eruption	176
4.1 Adverse Cutaneous Drug Reactions	176
4.2 Infection	177
4.3 Other Dermatoses	177
4.4 Baboon Syndrome and SDRIFE	178
5. Conclusion	178

Abstract

Systemic contact dermatitis is a condition that occurs when an individual sensitized to a contact allergen is exposed to that same allergen or a cross-reacting molecule through a systemic route. Systemic exposure to allergens can include transcutaneous, transmucosal, oral, intravenous, intramuscular, and inhalational routes. Baboon syndrome is perhaps the most recognizable form of systemic contact dermatitis, presenting with diffuse, well demarcated erythema of the buttocks, upper inner thighs, and axillae. Other forms of systemic contact dermatitis include dermatitis at sites of previous exposure to the allergen such as at a previous site of dermatitis or at sites of previous positive patch tests, dyshidrotic hand eczema, flexural dermatitis, exanthematous rash, erythroderma, and vasculitis-like lesions.

The most common causes of systemic contact dermatitis consist of three groups of allergens: (i) metals including mercury, nickel, and gold; (ii) medications including aminoglycoside antibacterials, corticosteroids, and aminophylline; and (iii) plants and herbal products including the Compositae and Anacardiaceae plant families and Balsam of Peru.

Baboon syndrome caused by systemic medications without a known history of previous cutaneous sensitization in the patient has been termed drug-related baboon syndrome (DRBS) or symmetric drug-related intertriginous and flexural exanthema (SDRIFE). Criteria for SDRIFE include exposure to systemic drug at first or repeated dose, erythema of the gluteal/perianal area and/or V-shaped erythema of the

inguinal area, involvement of at least one other intertriginous localization, symmetry of affected areas, and absence of systemic toxicity. The most common causes are aminopenicillins, β -lactam antibacterials, and certain chemotherapeutic agents, though the list of etiologic agents continues to grow. Baboon syndrome and SDRIFE should be strongly considered in a patient presenting with a symmetric intertriginous eruption involving multiple body folds. With the knowledge of the most frequent causes of these conditions, a detailed history and review of exposures will guide the clinician in the search for the most likely etiologic agent.

Systemic contact dermatitis (SCD) is a fascinating and likely under-recognized condition that occurs when an individual sensitized to a contact allergen is exposed to that same allergen or a cross-reacting molecule through a systemic route. Sensitization to contact allergens in the population at large is quite common. Two large Danish cross-sectional population studies reported rates of 15.2% and 18.6% for positive patch tests to a European standard series.^[1] Allergens that can cause SCD are present in a variety of forms in our environment and can be presented to a sensitized individual through many different routes. SCD is likely being under-diagnosed due to a lack of knowledge among dermatologists of the many presentations of this condition. Here we review the different presentations and causes of SCD with a focus on baboon syndrome and the recently described drug-related form of baboon syndrome coined symmetric drug-related intertriginous and flexural exanthema (SDRIFE).^[2] Finally, a clinical approach to intertriginous eruptions is presented.

A literature search in December 2010 using the MEDLINE database was performed to obtain relevant articles for this review. The search terms 'systemic contact dermatitis,' 'baboon syndrome,' 'symmetric drug-related intertriginous flexural exanthema,' and 'intertriginous rash' were used.

1. Systemic Contact Dermatitis (SCD)

1.1 Introduction and History

SCD occurs when individuals sensitized to a contact allergen by skin contact are systemically exposed to the same allergen or a cross-reacting molecule. Routes of systemic exposure reported include oral, intravenous, intramuscular, and inhalational.^[3-5] It is important to note that systemic exposure can also occur via a transcutaneous or transmucosal route, including transrectal, if systemic absorption of the molecule through the skin is significant.^[3-5]

The first example of what was later to be called SCD was described by Dr Thomas Bateman in the 1970s as 'eczema rubrum' or mercury dermatitis.^[6] Patients presented with a symmetric erythema on major flexural areas as well as inverted

triangular or V-shaped erythema on the upper antero-medial thighs after contact with mercury through broken thermometers. Nakayama et al.^[7] reported 15 such patients in 1983, with most having a history of allergic contact dermatitis to topical antiseptics containing mercury (i.e. merbromin or Mercurochrome™) with positive patch testing for several mercurials.

In 1984, Andersen et al.^[8] first coined the term 'baboon syndrome' to describe a pattern of diffuse, well demarcated erythema of the buttocks, upper inner thighs, and axillae. They reported three cases of baboon syndrome due to ampicillin, nickel, and mercury. Of interest, the ampicillin in this report was a topical solution, which was presumably absorbed transcutaneously during surgery.

1.2 Presentation

Although baboon syndrome may be the most recognizable form for dermatologists, SCD can have many different presentations. This includes dermatitis at sites of previous exposure to the allergen, such as at a previous site of dermatitis (recall reaction) or at sites of previous positive patch tests.^[3,9] Other presentations include dyshidrotic hand eczema, flexural dermatitis, exanthematous rash, erythroderma, as well as vasculitis-like lesions.^[3] Some allergens are more likely to cause certain forms of SCD.

SCD usually appears within hours to 2 days after systemic exposure to the allergen and is only rarely associated with systemic symptoms. Patch tests should be positive in cases of SCD as cutaneous sensitization has occurred as part of the definition of this entity.^[3-5]

1.3 Causes

The most common causes of SCD consist of three groups of allergens: metals, medications, and plants and herbals (table I).^[3-5]

1.3.1 Metals

The most common group historically has been the metals. This includes the previously mentioned mercury, which exists as a topical antiseptic (i.e. merbromin or Mercurochrome™) that is still used in some parts of the world, though not in North

Table 1. Common causes of systemic contact dermatitis

Metals
Mercury
Nickel
Gold
Medications
Aminoglycosides
Corticosteroids
Ethylenediamine/aminophylline
Plants and herbals
Compositae family
Anacardiaceae family (<i>Toxicodendron</i>)
Balsam of Peru
Other
Formaldehyde
Propylene glycol

America. Sensitized individuals are then exposed again to mercury vapor, for example, from broken mercury thermometers.^[3] Reactions to mercury are still being reported in certain European countries, especially in the pediatric population.^[10] A case of SCD due to mercury present in a skin lightening cream applied to the cheek and upper lip was recently reported. As expected, patch tests were positive to ammoniated mercury and thiomerosal.^[11]

Another common cause of SCD is exposure to nickel.^[12] Patients are topically sensitized by costume jewellery, coins, clothes, and nickel-plated objects. Routes of systemic exposure include oral (diet, utensils, orthodontic appliances),^[13,14] intravenous (catheters),^[15,16] and metal implants/stents.^[17,18] Another important route of exposure for this allergen in particular is transcutaneous exposure from pant buckles and belts in the peri-umbilical region, which is exacerbated in hot, humid climates.^[12] In a characteristic series of events, the patient develops a peri-umbilical pattern of allergic contact dermatitis to nickel in pant buckles/belts, which progresses to a generalized eczema in areas of the body not being exposed to nickel. This is believed to be due to SCD from transcutaneous systemic absorption of nickel particles. Nickel is also present in many foods including tea, cocoa, canned fruits and vegetables, and certain seafood.^[19-21] The most common form of nickel-induced SCD from oral intake is vesicular hand eczema.^[3,13] Some authors have advocated a trial of a nickel-free diet for patients with recalcitrant hand eczema who test positive to nickel on patch testing.^[20,21] In the hospital setting, patients have developed baboon syndrome due to intravenous catheters or surgical staples that unknowingly contained nickel.^[15,16]

Other metals reported to cause SCD include gold, cobalt, copper, chromium, and zinc.^[5] Cobalt exposure includes diet as well as intramuscular injections of vitamin B₁₂.

1.3.2 Medications

The second group causing SCD is medications. These are medications that have both topical and systemic forms, or at least have other systemic drugs with which they cross-react. This includes medications such as aminoglycoside antibacterials,^[22] corticosteroids,^[23-26] aminophylline,^[27,28] and fusidic acid.^[29] Neomycin is a very common cutaneous sensitizer and patients exposed to other aminoglycoside antibacterials, such as gentamicin, by systemic routes can develop SCD. In fact, 50% of patients reactive to neomycin will react to gentamicin.^[22] Corticosteroids are also a commonly reported cause of SCD as they exist in many topical and systemic forms. Patients can become sensitized to corticosteroids by application of topical corticosteroids and then can react to a systemically administered corticosteroid in the same or a cross-reacting group. SCD has been reported to group A corticosteroids such as prednisone and group C corticosteroids such as dexamethasone.^[23,26] One patient sensitized to triamcinolone developed SCD from budesonide in an intranasal corticosteroid spray.^[25] Patients reacting to ethylenediamine can develop SCD from aminophylline or piperazine antihistamines including hydroxyzine and cetirizine.^[27,28]

Other more recent medication causes have included SCD from oral estradiol in a patient with allergic contact dermatitis from transdermal estradiol,^[30] baboon syndrome from mesalazine (5-aminosalicylic acid; 5-ASA) in a foam enema,^[31] and from phenylephrine present in an eyedrop solution.^[32]

Many other systemic medications have been reported to cause baboon syndrome without the classic history of prior cutaneous sensitization, though previous sensitization by oral or parenteral routes is a possibility. These cases have been referred to as drug-related baboon syndrome and SDRIFE and will be discussed in section 2.^[2]

1.3.3 Plants and Herbals

The third and very important group of causative agents is plants and herbals.^[33-41] This includes the Compositae (or Asteraceae) family whose allergen is sesquiterpene lactones, the Anacardiaceae family including the *Toxicodendron* genus whose allergen is urushiol (pentadecylcatechol), Balsam of Peru, and garlic. The Compositae family is vast and includes plants such as the chrysanthemum, daisy, ragweed, chamomile, feverfew, wild feverfew (*Parthenium hysterophorus*), sunflower, and marigold, and vegetables including endive, artichoke, and

lettuce. The Anacardiaceae family includes poison ivy, poison oak, poison sumac, mango tree, cashew nut tree, Indian marking nut tree, Japanese lacquer tree, and Brazilian pepper tree. The Anacardiaceae family cross-reacts with the *Ginkgo biloba* tree.^[33-36] It is important to be aware that many of these plant products are used in topical and oral homeopathic preparations and SCD to such products has been reported. One such product containing *Rhus toxicodendron* from poison ivy resulted in a diffuse eczematous reaction.^[37] Ingestion of *Rhus* lacquer is common practice in some cultures and, in one series of 31 patients, resulted in serious skin reactions including erythroderma.^[38] Patients reacting to Balsam of Peru can develop SCD from ingestion of spices (cinnamon, cloves, vanillin, curry, ketchup), flavored foods (teas, ice cream, cola, wines, liqueurs), citrus and tomato-based products, cough syrup, lozenges, and toothpaste.^[39,40] A case of SCD to garlic has been reported, with eczematous cheilitis and dermatitis localized to elbow flexures, lower back, and periorbital regions. Patch testing was positive to diallyl disulfide, the allergen in garlic.^[41]

Other causes of SCD have included propylene glycol, formaldehyde, and enteral nutrition.^[42-44] Propylene glycol is present as a vehicle in many topical, oral, and injectable medications as well as a preservative in certain foods.

2. Symmetric Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)

In 2004, Hausermann et al.^[2] examined more closely the subset of drug-related baboon syndrome. They found that 50 of 100 published cases of baboon syndrome were drug induced. Of these 50, eight were considered true SCD due to systemic absorption of a molecule to which the patient had previously been sensitized, including cases resulting from absorption of topical substances. These included ampicillin, 5-ASA, neomycin, aminophylline, bufexamac, and dibucaine (cinchocaine).^[8,31,45-50] The remaining 42 reported cases of baboon syndrome were due to systemically administered drugs where there was no known history of previous cutaneous sensitization.^[51-77] The list included a wide range of causative drugs (table II) but most common were β -lactam antibacterials such as amoxicillin and chemotherapeutic agents such as mitomycin. They proposed that these two types of reaction, the first being systemically induced cases with previous cutaneous sensitization and the second being systemically induced drug-related baboon syndrome without known previous cutaneous sensitization, be separated into two distinct groups.^[2]

Hausermann et al.^[2] coined the acronym SDRIFE to account for the 42 cases in the second group that deviated from the traditional definition of SCD. In their view, such flexural

Table II. Reported causes of symmetric drug-related intertriginous and flexural exanthema (SDRIFE)

Cause	No. of reported cases
Allopurinol	1
Ambroxol	1 ^[78]
Amoxicillin	13
Amoxicillin/clavulanic acid	1
Ampicillin	2
Barium sulfate contrast media	1
Brentuximab vedotin (monoclonal antibody-auristatin E conjugate)	1 ^[79]
Ceftriaxone	1
Cefuroxime	2
Cefalexin	2
Cetuximab	1 ^[80]
Cimetidine	1
Clindamycin	1
Cloxacillin	1
Deflazacort	1
Erythromycin	1
Ethyl loflazepate	1 ^[81]
Heparin (intravenous)	1
Hydrochlorothiazide	1 ^[82]
Hydroxycarbamide (hydroxyurea)	1 ^[68]
Iodinated radio contrast medium	2 ^[83]
Intravenous immunoglobulin	1
Mitomycin	3 ^[70]
Naproxen	1
Nystatin	1
Oxycodone	1
Penicillin	2 ^[84]
Piritramide	1 ^[85]
Pseudoephedrine	2
Risperidone	1 ^[86]
Rivastigmine	1 ^[87]
Roxithromycin	1
Salsalate	1
Telmisartan	1 ^[82]
Terbinafine	1
Valaciclovir	1 ^[88]

eruptions due to systemic medications should be viewed as a distinct type of adverse cutaneous drug eruption. This may be a preferential term as it reflects a pathogenesis distinct from SCD and is a more culturally sensitive term than baboon syndrome, which many find offensive.

Features of SDRIFE form the criteria as proposed by Hausermann et al.^[2] and include:

- exposure to systemic drug at first or repeated dose (contact allergens excluded);
- erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perianal area;
- involvement of at least one other intertriginous/flexural localization;
- symmetry of affected areas;
- absence of systemic symptoms and signs.

Small papules, pustules, vesicles, and rarely bullae may be present in the flexures.^[2] Palmoplantar surfaces, face, and mucosa are rarely involved. Onset of the eruption is from hours to 2 days after exposure to the causative agent. Overall, SDRIFE is an uncommon and benign type of hypersensitivity reaction with no systemic symptoms. Key differences between baboon syndrome and SDRIFE are outlined in table III. Notably, patch tests are only positive in up to 50% of patients with SDRIFE.

Since the article by Hausermann et al.^[2] in 2004, further cases of symmetric flexural exanthemas using the term SDRIFE have been published to iodinated radio contrast media,^[83] valaciclovir,^[88] penicillin,^[84] risperidone,^[86] ethyl loflazepate,^[81] telmisartan/hydrochlorothiazide,^[82] and rivastigmine (see the report by Allain-Veyrac et al.^[87] on pages 210-213) of this issue of the *American Journal of Clinical Dermatology*). Other cases using the terms systemic contact dermatitis or baboon syndrome have been reported to cetuximab,^[80] aminocaproic acid,^[89] piritramide,^[85] and ambroxol.^[78] These cases can be added to the growing list of causal agents reported for this distinct flexural drug eruption to date (table II).

3. Diagnostic Testing in SCD and SDRIFE

In the 2004 review by Hausermann et al.,^[2] epicutaneous patch tests were performed in 24 of the 42 patients (57%) with presumed SDRIFE. Of these, 12 (50%) patients had positive patch test results, one had an 'angry back' reaction and the remaining 11 patients had negative patch tests to the triggering drug. Oral provocation testing was performed in five cases and

was positive in four patients (80%). Prick testing was performed for nine patients and was negative in all. Delayed prick testing was performed in three cases and was positive in two patients. Lymphocyte transformation test was performed in five cases and was positive in only one of the five patients.

In the group of eight patients with baboon syndrome and a history of previous cutaneous exposure, patch tests were performed in seven patients with all being positive.^[2] Patch tests or other tests for delayed-type hypersensitivity should be positive in all patients with SCD.

Recent case reports of SDRIFE provide further insight into the usefulness of diagnostic testing. In a case of SDRIFE induced by penicillin, prick, intracutaneous, and patch tests yielded negative results.^[84] Oral provocation testing with a cross-reactive compound, phenoxymethylpenicillin, resulted in an identical flexural rash in a few hours.^[84] In a recent case of SDRIFE caused by valaciclovir, patch tests performed with aciclovir and valaciclovir, as well as a drug-induced lymphocyte stimulation test to aciclovir were all negative. However, oral provocation tests performed with valaciclovir reproduced an identical rash in the flexures within 1 hour of taking valaciclovir.^[88] A case report of SDRIFE due to risperidone described negative patch testing results to risperidone, but rechallenge with risperidone produced a recurrence of the skin findings in the patient.^[86]

In baboon syndrome and SDRIFE, histopathology most commonly demonstrates a superficial perivascular lymphohistiocytic infiltrate sometimes including neutrophils, eosinophils, or mast cells. This may or may not be accompanied by epidermal spongiosis. Hydropic degeneration of the basal cell layer with scattered necrotic keratinocytes can also be observed. Rarely, a peri-adnexal inflammatory infiltrate may be present.^[2,82,88,90]

A recent case of an intertriginous drug eruption resulting from a chemotherapeutic regimen demonstrated a lymphomatoid drug eruption that could mimic a lymphoma.^[91]

In conclusion, epicutaneous patch testing, though initially described as being positive in up to 50% of cases by Hausermann et al.,^[2] has been found to be negative in more recent reports of SDRIFE. Perhaps this could be due to reduced

Table III. Differences between baboon syndrome and symmetric drug-related intertriginous and flexural exanthema (SDRIFE)^[2]

Characteristic	Baboon syndrome	SDRIFE
Etiology	Metals, medicaments, plants, herbals	Antibacterials, predominantly aminopenicillins and β -lactams
Previous cutaneous sensitization	Yes	Not found
Patch test results to allergen	Should be positive	Negative in up to one-half of cases
Nature of reaction	Systemic allergic contact dermatitis	Adverse cutaneous drug reaction with distinct presentation

absorption of systemically administered drugs when applied to the skin by patch testing. Oral provocation testing or re-challenge is positive in almost all reported cases of SDRIFE and at this time is the most reliable way to confirm a diagnosis of SDRIFE. Histopathology is nonspecific and cannot be used alone to confirm a diagnosis of baboon syndrome or SDRIFE. Prick testing and lymphocyte stimulation testing are negative in the majority of reported cases of SDRIFE.

4. Clinical Approach to the Patient with an Intertriginous Eruption

4.1 Adverse Cutaneous Drug Reactions

When a patient presents with a rash predominantly affecting the major body folds or flexures the first step would be to assess for toxicity related to an adverse drug reaction with an intertriginous predilection such as acute generalized exanthematous pustulosis (AGEP) [table IV]. A patient with early AGEP would have an abrupt onset of non-follicular pustules on an erythematous base beginning in intertriginous sites. There would be associated fever and leukocytosis.^[92,93] Other cutaneous clues would include edema of the face and hands, occasional purpuric or targetoid lesions, and erythroderma. Also, AGEP would not be confined to the intertriginous sites. The most commonly implicated medications include β -lactam and macrolide antibacterials, and calcium channel blockers. Though vesicles or pustules are uncommonly present in SDRIFE, they would not be as numerous or confluent as in AGEP. Furthermore, SDRIFE lacks the systemic toxicity and other cutaneous features of AGEP.

Table IV. Differential diagnosis of intertriginous eruptions

Irritant contact dermatitis
Allergic contact dermatitis
Intertrigo (<i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Corynebacterium</i> , <i>Candida</i>)
Tinea cruris
Inverse psoriasis
Hailey-Hailey disease
Pemphigus vegetans
Acute generalized exanthematous pustulosis (AGEP)
Systemic contact dermatitis (baboon syndrome)
Symmetric drug-related intertriginous and flexural exanthema (SDRIFE)
Intertriginous eruption associated with chemotherapy in pediatric patients ^[92]
Eccrine squamous syringometaplasia
Neutrophilic eccrine hidradenitis
Staphylococcal scalded skin syndrome



Fig. 1. Patient presenting with a symmetric intertriginous eruption compatible with symmetric drug-related intertriginous and flexural exanthema following a course of chemotherapy. Symmetric erythema of the left axilla is shown.

A distinct chemotherapy-induced eruption with a predilection for intertriginous sites in pediatric oncology patients was described by Webber et al.^[94] in 2007. They reported 16 pediatric patients who developed dusky, red papules evolving towards confluent erythematous dusky patches in intertriginous sites due to a variety of chemotherapeutic agents used in combination. Onset of the eruption ranged from 1 to 25 days and fever on the first day of the eruption was reported in five of the patients. Some patients had lesions on other areas of the body including the palms and soles, the trunk, and the face. In all cases, the eruption followed a benign course with spontaneous resolution. It could be argued that some of the patients described in this paper could fulfill the criteria for SDRIFE as described in section 2. However, the onset of the eruption following drug exposure was longer than the 2 days described for SDRIFE in the majority of the patients and the eruption involved sites other than the flexures in most patients.

Neutrophilic eccrine hidradenitis and eccrine squamous syringometaplasia are two other entities described primarily

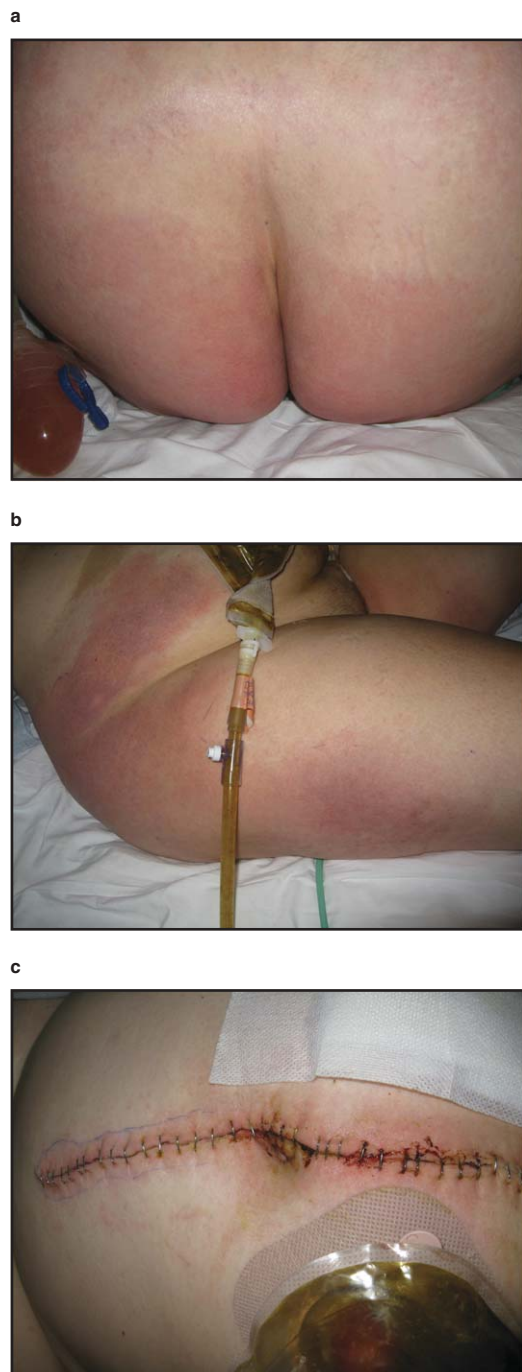


Fig. 2. Patient presenting with baboon syndrome following surgery for colorectal carcinoma. Resolving symmetric erythema of the (a) buttocks and (b) right inguinal area are shown. Circumscribed eczematous reaction around the (c) surgical staples on the abdomen along with a strong history of allergic contact dermatitis to nickel favors a diagnosis of nickel-induced systemic contact dermatitis.

in the context of adults receiving chemotherapy that can present with intertriginous lesions.^[95] Both conditions are thought to represent a spectrum of chemotherapy-related toxic effects

on eccrine sweat glands.^[96] Often, lesions will be present concurrently in other body sites (including the palms in neutrophilic eccrine hidradenitis) and will not have the strikingly symmetric involvement of multiple body folds as in SDRIFE.

4.2 Infection

Also important to rule out when faced with an intertriginous rash is an infectious cause, especially in a pediatric patient with an intertriginous eruption (table IV). This includes bacterial causes such as intertrigo or perianal cellulitis due to Group A β -hemolytic *Streptococcus* or *Staphylococcus aureus*.^[97] Well demarcated, erythematous, and oozing plaques can present in the axilla, inframammary area, and inguinal folds as a result of these infections. In a pediatric patient, the early stage of staphylococcal scalded skin syndrome should be considered in a severely ill child with fever and intertriginous erythema.^[98]

Candidiasis could present with involvement of major body folds, with erythematous papules and pustules.^[99] Satellite pustules would be a clue along with the patient's underlying health status including diabetes mellitus and immunosuppressed state. Erythrasma due to *Corynebacterium minutissimum* presents with well demarcated, reddish-brown patches in the axilla and/or groin and would demonstrate coral-red fluorescence on Wood's lamp examination. Dermatophyte infection in the form of tinea cruris can present with erythematous and scaly plaques in the genitocrural crease and the medial upper thigh. There is often central clearing, and an advancing border present. Bacterial culture and fungal scraping can be performed to rule out infectious conditions.

4.3 Other Dermatoses

The next step would be to rule out dermatoses such as inverse psoriasis, Hailey-Hailey disease, or pemphigus vegetans, which also preferentially affect the body folds (table IV). Inverse psoriasis is characterized by shiny, pink-to-red, sharply demarcated plaques. There is much less scale than in untreated chronic plaque psoriasis and a central fissure can be seen. The most common sites of involvement are the axillae, the inguinal crease, the intergluteal cleft, the inframammary region, and the retroauricular folds.^[100] In Hailey-Hailey disease, flaccid blisters and erosions are seen on the neck and in intertriginous areas, especially the axillae and groin. Moist, malodorous vegetations and fissures can develop.^[101] This is similar to pemphigus vegetans, where vegetating plaques develop in flexures along with mucosal involvement.^[102] Vegetating plaques and erosions will not be present in baboon syndrome or SDRIFE.

Table V. Assessing the patient with a symmetric intertriginous eruption

Is the patient toxic (fever, edema, erythroderma, leukocytosis)? Rule out acute generalized exanthematous pustulosis (AGEP)?
Evidence of infection (satellite pustules, fiery red and painful, foul odor)?
History of prior cutaneous disease (allergic contact dermatitis, psoriasis, Hailey-Hailey disease)?
Exposure history (medications, procedures):
new medications, antibacterials, chemotherapy?
homeopathic preparations?
intravenous catheter or metal implant?
History of allergic contact dermatitis, positive patch tests, or metal sensitivity?
Establish timeline related to exposures and onset of rash

It is important to rule out a simple allergic contact dermatitis to a topical product that was being applied to the folds or an irritant contact dermatitis due to excessive friction and humidity.^[99] Most of these conditions can be ruled out based on clinical appearance and history of the lesions.

4.4 Baboon Syndrome and SDRIFE

A patient with baboon syndrome or SDRIFE will present with an abrupt onset of symmetric erythema of the buttocks and/or V-shaped erythema of the inguinal area as well as involvement of other skin folds such as the neck or axillae following systemic exposure to an allergen (figures 1 and 2).^[2,3] The characteristic rash will present within 2 days after exposure to the causative agent in most cases, though onset of the rash at 4 days after exposure has been described.^[82] It is then the task of the clinician to determine the most likely cause of the eruption, keeping in mind the most common causes of SCD and SDRIFE. Assessment should include history of allergic contact dermatitis, history of positive patch tests, metal sensitivity indicating possible allergic contact dermatitis to metals, and all known allergies to medications (table V). Then all recent exposures in the few days before the rash should be noted, including parenteral medications, intravenous catheters, surgical staples, and other metal implants. In a patient with known allergic contact dermatitis to a specific allergen, a careful history should be targeted towards identifying exposure to a systemic form of the allergen including cross-reacting molecules. In the hospital setting, it is not uncommon to have patients presenting with an intertriginous eruption who have had more than one suspect exposure. Clues to a SCD caused by nickel would be well demarcated erythema at the site of intravenous catheters or surgical staples along with a history of allergic contact dermatitis to metals in the past (figure 2). A diagnosis

of SDRIFE would be favored if the patient had received an aminopenicillin, other β -lactam antibacterial or chemotherapeutic agent in the 2 days prior to the eruption with no clear history of previous allergic contact dermatitis.^[2]

New causes of SDRIFE continue to be described and it is important to keep an open mind when assessing a patient who fulfills the criteria for this condition. Luckily, both SCD and SDRIFE are benign conditions without systemic toxicity. However, these eruptions can cause significant distress to the patient and identification of the etiologic agent is both academically satisfying and a great service to the patient and the medical team.

5. Conclusion

SCD is an under-recognized condition with a variety of clinical presentations including the characteristic baboon syndrome. Cases of baboon syndrome related to drugs without a history of previous cutaneous sensitization, recently given the designation SDRIFE, are being reported with a growing number of medications. With the nosologic debate of the proper use of terminology in describing these unique reactions aside, it is most important for the clinician to be aware of this type of reaction and its characteristic features. Knowledge of the variety of clinical presentations and etiologic agents of this condition will better arm the clinician to make a proper diagnosis of SCD or SDRIFE and to successfully assign causality to a particular culprit in the realm of systemic allergens.

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References

1. Nielsen NH, Linneberg A, Menne T, et al. Allergic contact sensitization in an adult Danish population: two cross-sectional surveys eight years apart (the Copenhagen Allergy Study). *Acta Derm Venereol* 2001 Jan-Feb; 81 (1): 31-4
2. 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 Nov-Dec; 51 (5-6): 297-310
3. Veien NK, Menne T. Systemic contact dermatitis. In: Frosch PJ, Menne T, Lepoittevin JP, editors. *Contact dermatitis*. 4th ed. Berlin: Springer, 2006: 295-305
4. Menne T, Veien NK, Maibach HL. Systemic contact dermatitis. *Am J Contact Dermatitis* 1994; 5: 1-12
5. Jacob SE, Zapolanski T. Systemic contact dermatitis. *Dermatitis* 2008 Jan-Feb; 19 (1): 9-15
6. Shelley WB, Crissey JT, Thomas Bateman. In: Shelley WB, Crissey JT, editors. *Classics in clinical dermatology*. Springfield (IL): Charles C. Thomas, 1970: 22
7. Nakayama H, Niki F, Shono M, et al. Mercury exanthema. *Contact Dermatitis* 1983; 9: 411-7

8. Andersen KE, Hjorth N, Menne T. The baboon syndrome: systemically-induced allergic contact dermatitis. *Contact Dermatitis* 1984; 10: 97-100
9. Torchia D, Capretti C, Pizzo B, et al. Patch test triggering recurrence of distant dermatitis: the flare-up phenomenon. *CMAJ* 2008 Aug 12; 179 (4): 341
10. Moreno-Ramírez D, García-Bravo B, Pichardo AR, et al. Baboon syndrome in childhood: easy to avoid, easy to diagnose, but the problem continues. *Pediatr Dermatol* 2004 May-Jun; 21 (3): 250-3
11. Ozkaya E, Mirzoyeva L, Otkur B. Mercury-induced systemic allergic dermatitis caused by 'white precipitate' in a skin lightening cream. *Contact Dermatitis* 2009; 60: 61-3
12. Dou X, Liu LL, Zhu XJ. Nickel-elicited systemic contact dermatitis. *Contact Dermatitis* 2003 Mar; 48 (3): 126-9
13. Nielsen GD, Jepsen LV, Jorgensen PJ. Nickel-sensitive patients with vesicular hand eczema: oral challenge with a diet naturally high in nickel. *Br J Dermatol* 1990 Mar; 122 (3): 299-308
14. Pigatto PD, Guzzi G. Systemic contact dermatitis from nickel associated with orthodontic appliances. *Contact Dermatitis* 2004 Feb; 50 (2): 100-1
15. Raison-Peyron N, Guillard O, Khalil Z, et al. Nickel-elicited systemic contact dermatitis from a peripheral intravenous catheter. *Contact Dermatitis* 2005 Oct; 53 (4): 222-5
16. Raison-Peyron N, Kluger N, Guillard O, et al. A new case of systemic contact eczema to nickel in a peripheral venous catheter. *Ann Dermatol Venerol* 2008 Nov; 135 (11): 769-72
17. Nosbaum A, Rival-Tringali AL, Barth X, et al. Nickel-induced systemic allergic dermatitis from a sacral neurostimulator. *Contact Dermatitis* 2008 Nov; 59 (5): 319-20
18. Gimenez-Arnau A, Rimbau V, Serra-Baldrich E. Metal-induced generalized pruriginous dermatitis and endovascular surgery. *Contact Dermatitis* 2000 Jul; 43 (1): 35-40
19. Lofgren SM, Warshaw EM. Dyshidrosis: epidemiology, clinical characteristics, and therapy. *Dermatitis* 2006 Dec; 17 (4): 165-81
20. Veien NK, Hattel T, Justesen O, et al. Dietary treatment of nickel dermatitis. *Acta Derm Venereol* 1985; 65 (2): 138-42
21. Veien NK, Hattel T, Laurberg G. Low nickel diet: an open, prospective trial. *J Am Acad Dermatol* 1993 Dec; 29 (6): 1002-7
22. Guin JD, Phillips D. Erythroderma from systemic contact dermatitis: a complication of systemic gentamicin in a patient with contact allergy to neomycin. *Cutis* 1989 Jun; 43 (6): 564-7
23. Quirce S, Alvarez MJ, Olaguibel JM, et al. Systemic contact dermatitis from oral prednisone. *Contact Dermatitis* 1994 Jan; 30 (1): 53-4
24. Chew AL, Maibach HI. Multiple corticosteroid orally elicited allergic contact dermatitis in a patient with multiple topical corticosteroid allergic contact dermatitis. *Cutis* 2000 May; 65 (5): 307-11
25. Poon E, Fewings JM. Generalized eczematous reaction to budesonide in a nasal spray with cross-reactivity to triamcinolone. *Australas J Dermatol* 2001 Feb; 42 (1): 36-7
26. Nucera E, Buonomo A, Pollastrini E, et al. A case of cutaneous delayed-type allergy to oral dexamethasone and to betamethasone. *Dermatology* 2002; 204 (3): 248-50
27. Walker SL, Ferguson JE. Systemic allergic contact dermatitis due to ethylenediamine following administration of oral aminophylline. *Br J Dermatol* 2004 Mar; 150 (3): 594
28. Isaksson M, Ljunggren B. Systemic contact dermatitis from ethylenediamine in an aminophylline preparation presenting as the baboon syndrome. *Acta Derm Venereol* 2003; 83 (1): 69-70
29. De Castro Martinez FJ, Ruiz FJ, Tornero P, et al. Systemic contact dermatitis due to fusidic acid. *Contact Dermatitis* 2006 Mar; 54 (3): 169
30. Corazza M, Mantovani L, Montanari A, et al. Allergic contact dermatitis from transdermal estradiol and systemic contact dermatitis from oral estradiol: a case report. *J Reprod Med* 2002 Jun; 47 (6): 507-9
31. Gallo R, Parodi A. Baboon syndrome from 5-aminosalicylic acid. *Contact Dermatitis* 2002 Feb; 46 (2): 110
32. Tamagawa-Mineoka R, Katoh N, Yoneda K, et al. Systemic allergic contact dermatitis due to phenylephrine in eyedrops, with a long-lasting allergic patch test reaction. *Eur J Dermatol* 2010 Jan-Feb; 20 (1): 125-6
33. Sasseeville D. Clinical patterns of pyodermitis. *Dermatol Clin* 2009 Jul; 27 (3): 299-308
34. Rodríguez-Serna M, Sanchez-Motilla JM, Ramon R, et al. Allergic and systemic contact dermatitis from Matricaria chamomilla tea. *Contact Dermatitis* 1998 Oct; 39 (4): 192-3
35. Mahajan VK, Sharma NL, Sharma RC. Parthenium dermatitis: is it a systemic contact dermatitis or an airborne contact dermatitis? *Contact Dermatitis* 2004 Nov-Dec; 51 (5-6): 231-4
36. Oh SH, Haw CR, Lee MH. Clinical and immunologic features of systemic contact dermatitis from ingestion of Rhus (Toxicodendron). *Contact Dermatitis* 2003 May; 48 (5): 251-4
37. Cardinali C, Francalanci S, Giomi B, et al. Systemic contact dermatitis from herbal and homeopathic preparations used for herpes virus treatment. *Acta Derm Venereol* 2004; 84 (3): 223-6
38. Park SD, Lee SW, Chun JH, et al. Clinical features of 31 patients with systemic contact dermatitis due to the ingestion of Rhus (lacquer). *Br J Dermatol* 2000 May; 142 (5): 937-42
39. Pflutzner W, Thomas P, Niedermeier A, et al. Systemic contact dermatitis elicited by oral intake of Balsam of Peru. *Acta Derm Venereol* 2003; 83 (4): 294-5
40. Pflutzner W, Niedermeier A, Thomas P, et al. Systemic contact eczema against Balsam of Peru. *J Dtsch Dermatol Ges* 2003 Sep; 1 (9): 719-21
41. Pereira F, Hatia M, Cardoso J. Systemic contact dermatitis from diallyl disulfide. *Contact Dermatitis* 2002 Feb; 46 (2): 124
42. Lowther A, McCormick T, Nedorost S. Systemic contact dermatitis from propylene glycol. *Dermatitis* 2008 Mar-Apr; 19 (2): 105-8
43. Hill AM, Belsito DV. Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame? *Contact Dermatitis* 2003 Nov; 49 (5): 258-9
44. Watanabe T, Yoshida Y, Yamamoto O. Enteral nutrition induced systemic allergic dermatitis. *Contact Dermatitis* 2008 Dec; 59 (6): 374-5
45. Menne T, Weismann K. Hematogenous contact eczema following oral administration of neomycin. *Hautarzt* 1984; 35: 319-20
46. Guin JD, Fields P, Thomas KL. Baboon syndrome from i.v. aminophylline in a patient allergic to ethylenediamine. *Contact Dermatitis* 1999; 40: 170-1
47. Isaksson M, Ljunggren B. Systemic contact dermatitis from ethylenediamine in an aminophylline preparation presenting as the baboon syndrome. *Acta Derm Venereol* 2003; 83: 69-70
48. Proske S, Uter W, Schnuch A, et al. Severe allergic contact dermatitis with generalized spread due to buprenorphine presenting as the 'baboon' syndrome. *Dtsch Med Wochenschr* 2003; 128: 545-7
49. Marques C, Faria E, Machado A, et al. Allergic contact dermatitis and systemic contact dermatitis from cinchocaine. *Contact Dermatitis* 1995; 33: 443
50. Erdmann SM, Sachs B, Merk HF. Systemic contact dermatitis from cinchocaine. *Contact Dermatitis* 2001; 44: 260-1
51. Montag G, Weber L, Gall H. Baboon-syndrom auf Allopurinol. *Akt Dermatol* 1996; 22: 311-3
52. Wolf R, Brenner S, Krakowski A. Intertriginous drug eruption. *Acta Derm Venereol* 1992; 72: 441-2
53. Wolf R, Orion E, Matz H. The baboon syndrome or intertriginous drug eruption: a report of eleven cases and a second look at its pathomechanism. *Dermatol Online J* 2003; 9: 2
54. Herfs H, Schirren CG, Przybilla B, et al. Baboon syndrome: a particular manifestation of hematogenous contact reaction. *Hautarzt* 1993; 44: 466-9

55. Duve S, Worret W, Hofmann H. The baboon syndrome: a manifestation of hematogenous contact-type dermatitis. *Acta Derm Venereol* 1994; 76: 480-1
56. Kohler LD, Schonlein K, Kautzky F, et al. Diagnosis at first glance: the baboon syndrome. *Int J Dermatol* 1996; 35: 502-3
57. Wakelin SH, Sidhu S, Orton DI, et al. Amoxycillin-induced flexural exanthem. *Clin Exp Dermatol* 1999; 24: 71-3
58. Kick G, Przybilla B. Delayed prick test reaction identifies amoxicillin as eliciting baboon syndrome. *Contact Dermatitis* 2000; 43: 366-7
59. Loze I, Milpied-Homs B, Parent E, et al. Le syndrome babouin, une toxidermie particuliere: quatre observations. *Nouv Dermatol* 2001; 20: 624-5
60. Strub C, Bircher AJ. Exanthem with emphasis of body flexure points 10 hours after administration of amoxicillin 'baboon syndrome'. *Schweiz Rundsch Med Prax* 2002; 91: 232-4
61. Schultz ES, Diepgen TL. Clinical characteristics and the causes of the baboon syndrome. *Dermatosen* 1996; 44: 266-9
62. Rasmussen LP, Menne T. Systemic contact eczema in ampicillin allergy. *Ugeskr Laeger* 1995; 147: 1341-2
63. Helmbold P, Hegemann B, Dickert C, et al. Symmetric psychotropic and nonpigmenting fixed drug eruption due to cimetidine (so-called baboon syndrome). *Dermatology* 1998; 197: 402-3
64. Wolf R, Elman M, Brenner S. Drug-induced 'intertrigo'. *Int J Dermatol* 1993; 32: 515-6
65. Garcia-Bravo B, Repiso JB, Camacho F. Systemic contact dermatitis due to deflazacort. *Contact Dermatitis* 2000; 43: 359-60
66. Goossens C, Sass U, Song M. Baboon syndrome. *Dermatology* 1997; 194: 421-2
67. Pfeiff B, Pullmann H. Baboon-artiges Arzneiexanthem auf heparin. *Deutsch Dermatologe* 1991; 39: 559-60
68. Chowdhury MM, Patel GK, Inaloz HS, et al. Hydroxyurea-induced skin disease mimicking the baboon syndrome. *Clin Exp Dermatol* 1999; 24: 336-7
69. Barbaud A, Trechot P, Granel F, et al. A baboon syndrome induced by intravenous human immunoglobulins: report of a case and immunological analysis. *Dermatology* 1999; 199: 258-60
70. De Groot AC, Conemans JM. Systemic allergic contact dermatitis from intravesical instillation of the antitumor antibiotic mitomycin C. *Contact Dermatitis* 1991; 24: 201-9
71. Lechner T, Grytzmann B, Baurle G. Hematogenous allergic contact dermatitis after oral administration of nystatin. *Mykosen* 1987; 30: 143-6
72. Panhans-Gross A, Gall H, Peter RU. Baboon syndrome after oral penicillin. *Contact Dermatitis* 1999; 41: 352-3
73. Sanchez TS, Sanchez-Perez J, Aragues M, et al. Flare-up reaction of pseudoephedrine baboon syndrome positive patch test. *Contact Dermatitis* 2000; 42: 312-3
74. Sanchez-Morillas L, Reano Martos M, Rodriguez Mosquera M, et al. Baboon syndrome due to pseudoephedrine. *Contact Dermatitis* 2003; 48: 234
75. Amichai B, Grunwald MH. Baboon syndrome following oral roxithromycin. *Clin Exp Dermatol* 2002; 27: 523
76. Gordon E. Baboon syndrome caused by Salasate. *J Drugs Dermatol* 2002; 1: 66
77. Weiss JM, Mockenhaupt M, Schopf E, et al. Reproducible drug exanthema to terbinafine with characteristic distribution of baboon syndrome. *Hautarzt* 2001; 52: 1104-6
78. Monzon S, Del Mar Garces M, Lezaun A, et al. Ambroxol-induced systemic contact dermatitis confirmed by positive patch test. *Allergol Immunopathol* 2009 May-Jun; 37 (3): 167-8
79. Elmariah SB, Cheung W, Wang N, et al. Systemic drug-related intertriginous and flexural exanthema (SDRIFE). *Dermatol Online J* 2009 Aug 15; 15 (8): 3
80. Sans V, Jouary T, Hubiche T, et al. Baboon syndrome induced by cetuximab. *Arch Dermatol* 2008 Feb; 144 (2): 272-4
81. Watanabe T, Yamada N, Yoshida Y, et al. A case of symmetrical drug-related intertriginous and flexural exanthema induced by loflazepate ethyl. *J Eur Acad Dermatol Venereol* 2010 Mar; 24 (3): 357-8
82. Ferreira A, Mota A, Morais P, et al. Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) induced by telmisartan-hydrochlorothiazide. *Cutan Ocul Toxicol* 2010 Dec; 29 (4): 293-5
83. Arnold AW, Hausermann P, Bach S, et al. Recurrent flexural exanthema (SDRIFE or baboon syndrome) after administration of two different iodinated radio contrast media. *Dermatology* 2007; 214 (1): 89-93
84. Handisurya A, Stingl G, Wöhrl S. SDRIFE (baboon syndrome) induced by penicillin. *Clin Exp Dermatol* 2009 Apr; 34 (3): 355-7
85. Waltermann K, Geier J, Diessenbacher P, et al. Systemic allergic contact dermatitis from intravenous piritramide. *Allergy* 2010 Sep; 65 (9): 1203-4
86. Akay BN, Sanli H. Symmetrical drug-related intertriginous and flexural exanthem due to oral risperidone. *Pediatr Dermatol* 2009 Mar-Apr; 26 (2): 214-6
87. Allain-Veyrac GG, Lebreton A, Collonnier C, et al. First case of symmetric drug-related intertriginous and flexural exanthema (SDRIFE) due to rivastigmine? *Am J Clin Dermatol* 2011; 12 (3): 210-3
88. Daito J, Hanada K, Katoh N, et al. Symmetrical drug-related intertriginous and flexural exanthema caused by valacyclovir. *Dermatology* 2009; 218 (1): 60-2
89. Cunha D, Carvalho R, Santos R, et al. Systemic allergic dermatitis to epsilon-aminocaproic acid. *Contact Dermatitis* 2009 Nov; 61 (5): 303-4
90. Thyssen JP, Maibach HI. Drug-elicited systemic allergic (contact) dermatitis: update and possible pathomechanism. *Contact Dermatitis* 2008; 59: 195-202
91. Wolf R, Barzilai A, Davidovici B. Intertriginous lymphomatoid drug eruption. *Int J Dermatol* 2010 Oct; 49 (10): 1207-9
92. Guevara-Gutierrez E, Uribe-Jimenez E, Diaz-Canchola M, et al. Acute generalized exanthematous pustulosis: report of 12 cases and literature review. *Int J Dermatol* 2009 Mar; 48 (3): 253-8
93. Roujeau JC, Bioulac-Sage P, Bourseau C, et al. Acute generalized exanthematous pustulosis: analysis of 63 cases. *Arch Dermatol* 1991 Sep; 127 (9): 1333-8
94. Webber KA, Kos L, Holland KE, et al. Intertriginous eruption associated with chemotherapy in pediatric patients. *Arch Dermatol* 2007 Jan; 143 (1): 67-71
95. Valks R, Fraga J, Porras-Luque J, et al. Chemotherapy-induced eccrine squamous syringometaplasia: a distinctive eruption in patients receiving hematopoietic progenitor cells. *Arch Dermatol* 1997 Jul; 133 (7): 873-8
96. Hurt MA, Halvorson RD, Petr Jr FC, et al. Eccrine squamous syringometaplasia: a cutaneous sweat gland reaction in the histologic spectrum of 'chemotherapy-associated eccrine hidradenitis' and 'neutrophilic eccrine hidradenitis'. *Arch Dermatol* 1990 Jan; 126 (1): 73-7
97. Honig PJ, Frieden IJ, Kim HJ, et al. Streptococcal intertrigo: an under-recognized condition in children. *Pediatrics* 2003 Dec; 112 (6 Pt 1): 1427-9
98. Iwatsuki K, Yamasaki O, Morizane S, et al. Staphylococcal cutaneous infections: invasion, evasion and aggression. *J Dermatol Sci* 2006 Jun; 42 (3): 203-14
99. Janniger CK, Schwartz RA, Szepietowski JC, et al. Intertrigo and common secondary skin infections. *Am Fam Physician* 2005 Sep 1; 72 (5): 833-8
100. Meier M, Sheth PB. Clinical spectrum and severity of psoriasis. *Curr Probl Dermatol* 2009; 38: 1-20
101. Szigeti R, Kellermayer R. Autosomal-dominant calcium ATPase disorders. *J Invest Dermatol* 2006 Nov; 126 (11): 2370-6
102. Madan V, August PJ. Exophytic plaques, blisters, and mouth ulcers: pemphigus vegetans (PV), Neumann type. *Arch Dermatol* 2009 Jun; 145 (6): 715-20

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