

Symmetrical drug-related intertriginous and flexural exanthema

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Purpose of review

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously termed drug-related baboon syndrome, is a benign and self-limiting type IV hypersensitivity reaction characterized by symmetrical erythema involving the gluteal and intertriginous areas in the absence of systemic involvement. It may also occur in the absence of previous drug exposure.

Recent findings

Antibiotics, in particular beta-lactams, comprise the majority of causes of SDRIFE. Other drugs which have been implicated include antihypertensives, radiocontrast media, chemotherapeutic agents, and biologics. Histology of lesional skin is variable with predominance of superficial perivascular inflammatory cell infiltrates. Outcomes of allergy tests are variable with positive delayed intradermal tests reported for penicillin V, allopurinol; positive patch tests for erythromycin, mitomycin, nystatin, pseudoephedrine; positive lymphocyte transformation tests for erythromycin; and positive drug provocation tests for clindamycin, cimetidine, corticosteroids, terbinafine, and valacyclovir.

Summary

Diagnosis of SDRIFE is dependent upon recognition of the clinical morphology and distribution of the rash, and its temporal relationship to the use of the suspected drug. Outcomes of in-vivo and in-vitro tests have been inconsistent, and thus may not be useful in the identification of the putative drug.

Keywords

baboon syndrome, drug-related, exanthem, intertriginous, symmetrical drug-related intertriginous and flexural exanthema, symmetrical

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Introduction

Baboon syndrome was first described by Andersen *et al.* [1] in 1984 as a specific cutaneous eruption, characterized by striking erythema of the gluteal region and thighs, linked to the systemic absorption of mercury, nickel and other agents after prior cutaneous sensitization with the same substance. Subsequently, baboon syndrome was classified as one of several variants within the spectrum of systemically induced allergic contact dermatitis. With time, it was recognized that drugs – especially beta-lactam antibiotics, in particular amoxicillin – played an increasingly important role in its cause. Over 100 cases of drug-related baboon syndrome have been reported to date.

In 2004, Häusermann *et al.* [2^{••}] proposed the use of the more culturally neutral term ‘symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)’ to distinguish cases of baboon syndrome that were linked to drug exposure from those caused by systemic absorption of contact allergens, as well as to reflect the full range of

clinical symptoms and signs, including involvement of other intertriginous areas such as the axillae, knees and elbows.

The diagnostic criteria for SDRIFE are as follows: exposure to a systemically administered drug with exclusion of contact allergens; characteristic well demarcated erythema involving the gluteal, perianal, inguinal or perigenital area; involvement of at least one intertriginous area; symmetry; and the absence of systemic involvement [2^{••}].

Clinical features

SDRIFE has been observed in patients of varying ages (ranging from 18 months to 84 years) and has been found to have a male preponderance. The latency period between exposure to the drug and onset of exanthem varies between hours to up to 2 days.

Diagnosis is made clinically from the highly characteristic and stereotypic appearance of the rash. The involvement

of the gluteal and intertriginous areas and symmetry of lesions remain consistent and key diagnostic features. SDRIFE typically does not present with mucosal involvement, and involvement of the face and palmoplantar surfaces is rare. As with all other drug-related eruptions, the rashes should abate once the culprit drug is discontinued – this may take up to 3 weeks for complete resolution.

Atypical features reported include the presence of pustules [3–6], papules or bullae [7] overlying the flexural exanthem; concurrent maculopapular exanthema in non-flexural areas [8]; and targetoid lesions on the palms and soles [9].

Although the absence of systemic involvement (such as pyrexia, transaminitis, or cytopenias) is a diagnostic criterion for SDRIFE, Chong and Lim [10•] described a single case of SDRIFE following consumption of oral cloxacillin in which fever was a presenting symptom. Infective causes were excluded and the fever lysed promptly with systemic corticosteroids.

Detailed studies on nonimmediate drug reactions have demonstrated increased expression of cutaneous lymphocyte-associated antigen (CLA) and CD25 and production of Th1 cytokines and other cytotoxic markers (perforin/ granzyme B and FasL) as well as various interleukins, which correlate with the severity of the reaction [11]. It is likely that the fever was a result of intense inflammation brought about by the release of cytokines, including interleukins and tumour necrosis factor α (TNF- α), and may just represent a more severe form of SDRIFE.

Histology

Histology of lesional skin typically demonstrates superficial perivascular infiltrate of inflammatory cells (typically lymphocytes or eosinophils, though neutrophils and monocytes have been seen). Other features reported include subcorneal pustules [12], or vacuolar changes and hydropic degeneration in the basal cell layer with subepidermal bullae [7] and necrotic keratinocytes (these changes are usually found in bullous drug eruptions).

Wolf *et al.* [13•] also described a case of SDRIFE to chemotherapeutics (cisplatin and gemcitabine) with histology consistent with lymphomatoid drug eruption, evidenced by large atypical lymphocytes with prominent nuclei staining positive for CD30.

Given the emergence of drug eruptions diagnosed as SDRIFE presenting with atypical clinical and histological features, we feel that this condition may be more

Key points

- Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is a drug eruption characterized by symmetrical gluteal and intertriginous erythema with no other systemic involvement following systemic exposure to a drug.
- The most common causative drugs are beta-lactam antibiotics, although SDRIFE has also been reported following exposure to corticosteroids, biologic, and chemotherapeutic agents.
- Diagnosis is made clinically, although the clinical presentation may show atypical features. Outcomes of allergological tests are highly variable.
- The condition is self-limiting, and treatment involves withdrawal of the offending agent and supportive management. Topical or parenteral corticosteroids may hasten recovery.

heterogeneous than originally described, and with time perhaps the original five diagnostic criteria may need to be revised further.

Cause

Pichler [14] had previously subdivided type IV drug hypersensitivity reactions into four categories which correlated the specific clinical manifestations with particular effector T-cell and chemokine profiles.

Type IVa reactions involve the production of interferon- γ (IFN- γ) with the manifestation of eczema. Type IVb responses involve the production of interleukins IL-4 and IL-5 inducing mast cell and eosinophil responses, with the manifestation of maculopapular exanthema and drug rash with eosinophilia and systemic symptoms (DRESS). Type IVc responses involve the production of cytotoxic mediators by CD4+ and CD8+ T cells, resulting in keratinocyte apoptosis in toxic epidermal necrolysis (TEN) and maculopapular exanthems. In type IVd responses, neutrophil recruitment is mediated by IL-8 resulting in acute generalized exanthematic pustulosis (AGEP). There is some degree of heterogeneity within this classification and between conditions, and different T-cell subtypes may be involved in different nonimmediate reactions (NIRs).

In SDRIFE, immunohistological findings on skin biopsies have shown an infiltration of CD3+ and CD4+ T cells (and to a lesser extent, CD20 and CD50 positive T cells) in the dermis [3,12], suggesting a similar pathological mechanism to type IV reactions. Other authors have reported an expansion of CD26P (P-selectin), which normally plays a role in recruitment of memory or effector Th1 cells to sites of inflammation, in the endothelial and keratinocyte layers [12].

To date, in-vitro cytokine profiling and lymphocyte responses in SDRIFE have been rarely described. However, given that baboon syndrome was originally described in the context of systemically induced allergic contact dermatitis, one may infer that similar immunological mechanisms to contact dermatitis are involved.

Studies on lymphocyte participation in biopsies following a systemic contact dermatitis reaction to nickel [15] have shown an infiltration of CD4+ and CD8+ T cells in the skin. CD3+, CD4+ and CD8+ T cells were found to be reduced in the peripheral blood of patients who were previously nickel-sensitized and then orally challenged [16]. Plasma levels of TNF- α and IL-1 have been found to be elevated in patients previously sensitized to gold who had subsequent systemic exposure [17]. IL-2 and IL-5 levels were elevated in patients with systemic contact dermatitis to nickel.

Although the classification of SDRIFE as a NIR implies that the onset of the eruption occurs from 24 to 48 h after drug exposure, numerous cases have been reported in which the exanthema appears within hours. This may be accounted for by the model of pharmacologic interaction of drugs with immune receptors (the P-i concept) proposed by Pichler *et al.*'s [18] group. In this model, the causative chemically inert drug binds directly to T-cell receptors, without prior presentation by major histocompatibility complex (MHC) molecules or conjugation to form haptens, resulting in direct T-cell activation.

The reason for a particular predilection of the flexural areas is unknown, though two hypotheses have been proposed. The first is that SDRIFE and baboon syndrome may represent a form of recall phenomenon from previous mechanical stimulation or intertrigo of flexural areas [8]. The second possibility is that certain drugs or drug metabolites may be preferentially excreted from the eccrine gland [19] (the intertriginous and flexural areas being sweat-rich areas). However, this does not account for the exanthema in the gluteal region which is a main diagnostic criterion for SDRIFE.

In summary, although the cause of SDRIFE has yet to be elucidated, in view of similar clinical manifestations (pustulation, bullae, maculopapular exanthema in other nonflexural regions), histological features (subepidermal bullae and necrotic keratinocytes) and immunologic profiles with the other type IV drug reactions, it may be seen as another subtype of NIR, with the T cell playing a central role in its pathogenesis.

Causative drugs

A variety of causative drugs have been described, the majority from amoxicillin (with over 15 cases reported).

Other putative drugs reported include intravenous immunoglobulins, chemotherapeutic agents, and biologics. A clinical diagnosis of SDRIFE has also been made to roxithromycin [20], ceftriaxone [8], cefalexin [8], barium sulphate [8], mitomycin C [21], and oxycodone [8] but there were no corresponding confirmatory skin or oral provocation tests in these cases. SDRIFE may also occur on re-exposure to a cross-reactive drug [22].

Additionally we note a report of a patient receiving TNF- α inhibitor (adalimumab) injections for treatment of refractory seropositive rheumatoid arthritis [23] developing erythematous plaques involving the axillae, antecubital fossae and wrists. Skin biopsy showed epidermal hyperplasia and spongiosis, a neutrophilic and eosinophilic infiltrate, as well as intraepidermal pustules. This eruption recurred upon subsequent injections of adalimumab. The drug eruption was termed as a pustular eruption to adalimumab. SDRIFE would have been a consideration if not for the lack of gluteal or perineal involvement.

Differential diagnoses

Other common dermatoses affecting the flexural areas (e.g. fungal infections, inverse psoriasis, granular parakeratosis, Darier disease and Hailey-Hailey disease) should be excluded before a drug eruption is to be diagnosed. However, very few of these conditions produce such striking erythema of the gluteal area which earned SDRIFE its original moniker of baboon syndrome.

Rarely, infections have been reported to cause cutaneous eruptions mimicking SDRIFE. Yamada *et al.* [24] described a case of parvoviral infection presenting with fever, arthralgia, and follicular papules involving the axillae, chest, abdomen, inner thighs, and popliteal fossae. Skin biopsy revealed an epidermal lymphocytic infiltrate. Similarly, another case reports similar findings of diffuse erythema on the neck, axillary, antecubital, and popliteal fossae resembling baboon syndrome following a streptococcal throat infection, though this case was confounded by prior ingestion of oral cefaclor [25].

Diagnosis and investigations

Histology of the lesional skin is nonspecific and often variable, with predominantly perivascular mononuclear cell infiltrate, occasionally with neutrophils or eosinophils [22]. Laboratory investigations have a role in excluding systemic involvement (such as cytopenias and transaminitis), but are otherwise not indicated in the diagnosis of SDRIFE. As with most other NIRs, currently available tests, including skin patch and delayed intradermal tests

Table 1 Summary of drugs reported to have caused SDRIFE

Drug	Delayed IDT	Patch test	Lymphocyte transformation test	Drug provocation test	Skin biopsy
Allopurinol [27]	Positive	Negative	Not done	Not done (history of similar exanthema with previous ingestion of allopurinol)	Superficial perivascular infiltrate with eosinophils; necrotic keratinocytes
Amoxicillin [2**]	Negative	Negative	Negative	Positive at 1000 mg	Not done
Amoxicillin [22]	Negative (amoxicillin 50 mg/ml)	Negative at 24 and 48 h	Not done	Not done to amoxicillin Positive to penicillin	Not done
Betamethasone [28]	Positive at 1:10 dilution at 48 h	Not done	Not done	Positive 12 h after cumulative dose of 5.87 mg	Not done
Cimetidine [3]	Not done	Negative	Negative	Positive (200 mg)	Spongiosis, superficial perivascular infiltrate with mononuclear cells
Cetuximab [5]	Not done	Negative	Not done	Not done	Subcorneal pustule with neutrophils and mixed cellular infiltrate in dermis
CR011-vcMAAE [7]	Not done	Not done	Not done	Positive. drug continued with antihistamine and corticosteroid comedication	Subepidermal bulla; basal vacuolar alteration. Dermal infiltrate of lymphocytes, neutrophils and eosinophils
Cefuroxime [8]	Not done	Negative at 30% concentration	Not done	Not done	Not done
Clindamycin [31]	Not done	Positive	Not done. Mast cell degranulation test positive	Positive	Superficial perivascular mononuclear infiltrate with hyperkeratosis
Cloprednol [28]	Not done	Negative	Not done	Positive at cumulative dose of 9.375 mg	Not done
Dexamethasone [28]	Positive at 1:10 dilution at 48 h	Not done	Not done	Positive at cumulative dose of 13.5 mg	Not done
Erythromycin [26]	Positive at 1:10 000	Not done	Positive	Not done	Perivascular lymphocytic dermatitis
Hydrocortisone [28]	Not done	Negative	Not done	Positive at cumulative dose of 78.75 mg	Not done
Methylprednisolone [28]	Positive at 1:10 dilution at 24 and 48 h	Not done	Not done	Not done	Not done
Prednisolone [28]	Not done	Positive	Not done	Not done	Not done
Heparin [29]	Positive	Not done	Not done	Not done	Not done
Hydroxyurea [38]	Not done	Not done	Not done	Not done	Perivascular upper dermal and epidermal lymphocytic infiltrate; focal degeneration of the granular layer
Intravenous immunoglobulin [34]	Not done	Not done	Not done	Not done	Superficial perivascular infiltrate with CD4+ lymphocyte cells, granular deposits of C1q along the dermo-epidermal junction and expression of CD26P on keratinocytes
Loflazepate ethyl [35]	Not done	Negative on lesional and nonlesional skin	Negative	Positive	Focal liquefaction degeneration in the epidermal basal layer with lymphocytic exocytosis and infiltration of perivascular lymphocytes and eosinophils in the upper dermis
Naproxen [8]	Not done	Negative up to 96 h at concentrations of 1, 2, 5, 10 and 20%	Not done	Not done	Consistent with erythema multiforme
Nystatin [39]	Not done	Positive	Not done	Not done	Spongiosis and superficial perivascular infiltrate with mononuclear cells
Pseudoephedrine [32]	Not done	Positive	Not done	Negative	Superficial perivascular infiltrate with mononuclear cells and eosinophils. Subcorneal pustule
Radio-contrast media (RCM) [30]	Positive for culprit agent iomeprol (at 300 mg/ml) at 48 h as well as all other nonionic monomer RCM at fixed dilutions	Positive for culprit agent iomeprol (at 300 mg/ml) at 48 h as well as all other nonionic monomer RCM at fixed dilutions	Not done	Positive; additionally patient had same reaction to another cross-reactive, nonionic RCM (iopromide)	CD3/ CD4 positive lymphocytic infiltrate of dermis; scattered CD8, CD20 and CD50 positive cells
Risperidone [40]	Not done	Negative	Not done	Not done	Superficial perivascular lymphocytic infiltrate
Salasate [4]	Not done	Not done	Not done	Not done	Consistent with leukocytoclastic vasculitis
Telmisartan-hydrochlorothiazide [6]	Not done	Negative in both lesional and nonlesional skin	Not done	Not done	Acanthosis; intraepidermal pustule; perivascular lymphohistiocytic infiltrate in dermis, with eosinophils and mast cells
Terbinafin [41]	Not done	Negative	Not done	Positive (250 mg)	Not done
Valacyclovir [36]	Not done	Negative to acyclovir (20% in petroleum) and valacyclovir (20% in petroleum) on nonlesional skin	Negative at 0.5–50 ng/ml acyclovir	Positive at 50 mg valacyclovir (one-fifth of regular dose)	Epidermal spongiosis, liquefaction degeneration in dermoepidermal junction, perivascular eosinophilic infiltrate in the dermis

as well as in-vitro studies, lack sensitivity and specificity in identifying the putative drug.

Skin testing

Delayed intradermal tests were most commonly performed with amoxicillin. Results were inconsistent: even negative tests did not correlate with a positive oral provocation test [2^{••}]. Positive skin tests have been reported for erythromycin [26], allopurinol [27], various corticosteroids [28], heparin [29], and ionic and nonionic radiocontrast media [30]. Thus, the utility of intradermal tests in the specific setting of SDRIFE is unknown.

Positive patch tests have been reported with the following drugs: erythromycin [26], clindamycin [31], and pseudoephedrine [32]. The results of patch testing were again inconsistent as negative tests were reported in one-third to one-half of patients.

The likely causes of these highly variable results include technique (as test procedures and drug concentrations have been poorly validated for most drugs) and latency of the test (as some negative reactions were attributed to the patch test being performed too late after the initial reaction).

Padial *et al.* [33] recently evaluated the utility of intradermal and patch testing in a cohort of patients with maculopapular exanthema to beta-lactams and demonstrated skin test sensitivity to be lower than expected. Barbaud [34] reported positive patch testing to amoxicillin in only 50% of patients with SDRIFE. In certain cases, patch tests may only elicit positive responses if applied to sites that were affected by the initial reaction, though this has yet to be validated.

Lymphocyte transformation tests

The lymphocyte transformation test (LTT) measures the proliferation of T cells to a drug *in vitro* to determine whether there was previous sensitization to the drug *in vivo*. This test has the advantage of avoiding re-exposure to the culprit drug in patients. However, the usefulness of LTTs is questionable – LTT measures only the sensitization of lymphocytes, but does not measure the effector reaction, hence there may be positive results in exposed individuals without manifesting any clinical symptoms. Further limitations of LTTs include the availability and cost of the test. Results of LTTs in cases of SDRIFE have been variable and negative tests did not correlate with positive drug provocation in certain cases [35,36].

Recent research in the use of dendritic cells as an in-vitro assay to assess drug allergies is promising [37]. However, the role of dendritic cells in the pathogenesis of SDRIFE has yet to be explored.

Drug provocation tests

Although controlled drug provocation tests (DPTs) remain the gold standard for diagnosis, caution should be advised as a relapse can be elicited by a systemic exposure to the offending drug, possibly with a more severe generalized reaction. In a reported case of SDRIFE to pseudoephedrine, patch testing even induced a flare of the allergy [32].

In summary, intradermal skin tests with delayed reading, patch tests, and lymphocyte transformation tests have limited utility in diagnosis as the outcomes are not consistent and appear to be drug-specific. Drugs reported to have caused SDRIFE and their corresponding allergological work-up are summarized in Table 1 [2^{••},3–8,22,26–32,34–36,38–41].

Treatment

SDRIFE is self-limiting and has a benign prognosis. Treatment is symptomatic, the offending drug should be withdrawn and avoided, and the patient educated on drug avoidance. As there is no systemic involvement, corticosteroids are rarely used, although topical or systemic glucocorticoids may help to hasten recovery.

Conclusion

SDRIFE is a benign and self-limiting type IV drug hypersensitivity reaction. Atypical features include pustulation, bullae, pyrexia, other overlapping exanthams, and pyrexia. It may develop within hours of first exposure. Diagnosis remains clinical, with other causes of intertrigo requiring exclusion.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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