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**Title:** Symmetric drug-related intertriginous and flexural exanthema (SDRIFE): clinicopathologic study of 19 cases and review of literature

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**Abstract**

***Background:*** Symmetric drug-related intertriginous and flexural exanthema (SDRIFE) is a cutaneous drug reaction characterized by gluteal/anogenital erythema and symmetric involvement of other intertriginous location(s) without systemic signs. Clinicopathologic characterization has been limited to case reports and small series. We describe 19 new cases and review the literature to better define the clinical and histopathologic spectrum of SDRIFE.

***Methods:*** Pathology archives were searched for “SDRIFE” and “baboon syndrome”. Cases meeting clinical criteria were included. Clinical and histopathologic features were recorded. Previous reports of SDRIFE with histopathologic descriptions were reviewed.

***Results:*** Nineteen new cases were included, over half triggered by antibiotics. Six new causative medications were identified. Median onset was seven days. Typical lesions were erythematous plaques or papules with or without scale. The most common histopathologic finding was superficial perivascular lymphocytic infiltrate followed by dermal eosinophils, spongiosis, and orthokeratosis. Basal vacuolization and apoptotic keratinocytes were less common. Interstitial histiocytes were present in almost half of our cases. Other findings included atypical lymphocytes and “flame figure”.

***Conclusions:*** Appreciation of the range of inciting medications and clinicopathologic features in SDRIFE will improve recognition of this condition. Although many histopathologic features overlap with other common dermatitides, biopsy may assist in excluding key clinical mimics.

## Introduction

Symmetric drug-related intertriginous and flexural exanthema (SDRIFE) is a rare cutaneous drug reaction characterized clinically by marked erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area, symmetric involvement of at least one other intertriginous or flexural area, and the absence of systemic signs or symptoms.[1] It is induced by administration of a systemic agent at first or repeated exposure.[1] Contact allergens should be excluded. Latency between exposure to the offending agent and development of the rash varies but is usually within hours to days.[2]

SDRIFE was historically described under the moniker “baboon syndrome” due to the characteristic bright erythema that often affects the bilateral buttocks.[3] Also grouped under “baboon syndrome” was systemic contact dermatitis, which was later distinguished from SDRIFE by its requirement for prior sensitization. The term baboon syndrome was ultimately dropped to avoid lumping of SDRIFE and systemic contact dermatitis.[1,3]

Despite progress in refining the clinical criteria of SDRIFE, histopathologic features have only been reported in isolated case reports and small case series. When Hausermann et al reviewed 18 cases of SDRIFE with accompanying histopathology in

the literature, the most common finding was a superficial perivascular lymphocytic infiltrate often with accompanying eosinophils or neutrophils.[1] Subsequent reports have described a variety of other histopathologic features such as subcorneal or intraepidermal pustules, apoptotic keratinocytes, spongiosis, papillary dermal edema, and vacuolar interface change.[2,4–7] Despite the more recent addition of several small case series on this topic, to our knowledge, no group has systematically reviewed all reported cases of SDRIFE with histopathology in the literature.[2,6,8] Here we report 19 new cases of SDRIFE and review the existing cases in the literature in order to better characterize the clinical and pathologic features of this rare cutaneous drug eruption.

**Materials and Methods**

This study was conducted according to previously approved Institutional Review Board protocols. Institutional pathology databases were queried for cases in which “SDRIFE” or “baboon syndrome” was mentioned in the pathology reports between 2010 and 2019. Clinical history and findings were obtained from electronic medical records. Only cases meeting clinical criteria for SDRIFE proposed by Hausermann et al[1] were included in the study. Key clinical features including patient age and sex, distribution and morphology of the skin lesions, inciting medications, latency period between initiation of the drug and the skin eruption, and follow-up data (complete list in Table 1) were recorded. Hematoxylin-eosin stained slides were reviewed for various histopathologic features listed in Table 2. Specifically, “basal vacuolization” was defined as vacuolar degeneration of multiple contiguous basal keratinocytes.

PubMed was queried using the terms “SDRIFE” and “baboon syndrome”. Cases meeting clinical criteria for SDRIFE with accompanying histopathologic descriptions were reviewed. Relevant clinical and histopathologic features described in these reports were recorded.

## Results

A total of 19 cases meeting clinical criteria for SDRIFE were identified in our archives and underwent further clinical and histopathologic review.

### *Clinical data*

Clinical history and findings of our cases are summarized in Table 1 and listed in detail in Supplemental Table 1. The average age of the 19 patients was 63 years. Male-to-female ratio was 3.8:1. The majority (53%) of cases were triggered by antibiotics, with trimethoprim/sulfamethoxazole being the most frequent culprit (16%). Onset of the rash ranged from one to 120 days after initiation of the inciting medication; median and average were seven and 21 days, respectively. Pruritus was a common symptom (89%). No one exhibited systemic signs or symptoms. Five (26%) patients had a concomitant malignancy at the time of diagnosis, including four with hematologic malignancies and one with a solid tumor. Primary morphology ranged from plaques (89%), papules (68%), to patches (11%); some with overlying scale (47%). Coloration of the lesions was described as erythematous (89%), dusky (21%), hyperpigmented (11%), or violaceous (5%). Vesicles/bullae, erosions, and pustules were relatively

infrequent. Representative clinical findings are shown in Figure 1. In all cases the eruption resolved upon cessation of the causative medication and/or use of steroids.

*Histopathologic features*

Histopathologic findings observed in our cases are summarized in Table 2. The most consistent feature was a superficial perivascular lymphocytic infiltrate (100%) followed by dermal eosinophils (89%), spongiosis (79%), orthokeratosis (79%), and a mid-dermal perivascular lymphocytic infiltrate (74%). Interstitial histiocytes were present in nine (47%) cases; one of these patients had a history of autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis). Sparse dermal neutrophils were seen in seven (37%) cases. Intraepidermal eosinophils in a background of spongiosis (eosinophilic spongiosis) were seen in four (21%) cases; two of these cases also displayed a subepidermal split, and one had an accompanying direct immunofluorescence study that was negative. Other less common findings included apoptotic keratinocytes (21%), basal vacuolization (16%), and subcorneal or intraepidermal pustules (16%). Two (11%) cases contained atypical lymphocytes imparting a “lymphomatoid” appearance. A “flame figure” was observed in a single (5%) case. Representative histopathologic features are shown in Figures 2 and 3.

*Literature review*

Seventy-three cases of SDRIFE with accompanying histopathologic data were identified in the literature.[4–57] Relevant clinical features and representative histopathologic features are summarized in Table 3 and listed in detail in Supplemental Table 2. The average age of patients was 51 years (range, 1.5-88 years). There was a slight male

predominance (male-to-female ratio of 1.5:1). Antibiotics were the most common culprits, reported in 33% of cases. Less common culprits included chemotherapy, antifungal, non-steroidal anti-inflammatory drug (NSAID), anti-gastroesophageal reflux (GERD), intravenous radiocontrast, antihypertensive, anti-epileptic, and anti-tumor necrosis factor-alpha medications. Average latency period was five days (range, 1 hour - 60 days). Similar to our observations, a superficial perivascular lymphocytic infiltrate was most common (99%), followed by dermal eosinophils (66%) and spongiosis (44%). Orthokeratosis and parakeratosis (19%) were much less commonly described than in our series, while basal vacuolization (33%) and apoptotic keratinocytes (30%) were reported more frequently.

**Discussion**

SDRIFE is a rare but increasingly recognized cutaneous drug eruption characterized by the clinical criteria proposed by Hausermann et al: exposure to a systemically administered drug at first or repeated dose (excluding contact allergens); sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; involvement of at least one other intertriginous/flexural location; symmetry of the affected areas; and absence of systemic symptoms or signs.[1] Applying these strict criteria, we were able to identify 19 patients with SDRIFE who had undergone biopsies allowing for histopathologic characterization. We also performed a comprehensive literature review of 73 reported SDRIFE cases with available histopathologic descriptions, most of which were isolated case reports.

Clinically, our series largely mirrors the literature, including a wide age range and male predominance. Antibiotics were by far the most common culprits, accounting for over half of our cases and one-third of the previously reported cases. Less common culprits included chemotherapeutic agents, NSAIDs, antifungals, among others. Notably, we identified six medications which have not been previously associated with SDRIFE (ciprofloxacin, metoprolol, dapsone, lenalidomide, methylphenidate, and enfortumab vedotin). Onset of rash typically occurred several hours to days after intake of the offending drugs. In our series, the most frequent sites of involvement were the inguinal creases and the axillae, and the typical morphologies were erythematous plaques and/or papules. Interestingly, almost half of our cases were scaly, a clinical feature that was described in only 12% of the published cases. Lichenification and hyperpigmentation were also more common in our series, suggesting that our cases may have been biopsied in later stages compared to those in the literature.

Prior case reports and small series have painted a rather heterogeneous picture of the histopathologic features of SDRIFE. While superficial perivascular lymphocytic infiltrate, dermal eosinophils, and spongiosis were commonly reported, a variety of other features such as subcorneal/intraepidermal pustules, apoptotic keratinocytes, papillary dermal edema, extravasated erythrocytes, and dermal neutrophils have been inconsistently described.[4,6,45,47–57] Examination of our cases confirmed frequent findings of superficial perivascular lymphocytic infiltrate, dermal eosinophils, and spongiosis. Most cases were microscopically indistinguishable from a common eczematous dermatitis. Over one-third of our cases demonstrated urticarial features in the form of scattered dermal neutrophils; this finding closely matched the literature review in which 38% of SDRIFE

cases contained dermal neutrophils. Concordant with the frequent clinical observation of scale in our series, a vast majority of cases displayed orthokeratosis which may be attributable to the chronicity of the eruption at the time of biopsy.

Basal vacuolar change and apoptotic keratinocytes were prominently featured in a recent study by Muresan et al,[6] however these changes were less common in our series despite careful histopathologic review. While our criterion for basal vacuolization is likely more stringent than that adopted by Muresan et al, our lower frequency of apoptotic keratinocytes likely was not attributable to differing criteria. We believe the discrepancy simply reflects the wide histopathologic spectrum of SDRIFE. Of note, Muresan et al illustrated a cytotoxic immunophenotype in most of their biopsies, as expected for cases with interface changes. Such immunophenotypes may not be extrapolatable to other SDRIFE cases lacking interface changes. Additional immunohistochemical studies are needed to further elucidate the immunologic mechanism involved in SDRIFE.

A few interesting microscopic findings should be highlighted. First, interstitial histiocytes were identified in almost half of our cases, suggesting an element of interstitial granulomatous dermatitis (IGD). To our knowledge, this feature has only been reported in one SDRIFE case in the literature.[6] One of our patients with this feature had a history of autoimmune diseases, which are known to be associated with IGD.[58] IGD classically presents as symmetric erythematous to violaceous plaques affecting the superolateral trunk, proximal upper extremities, and medial thighs.[59,60] Although sole involvement of intertriginous sites is uncommon, IGD has occasionally been reported to involve the buttocks and symmetric intertriginous areas.[59,60] In such settings, clinical correlation is key in rendering the most appropriate diagnosis.

Eosinophilic spongiosis, a feature frequently associated with allergic contact dermatitis, urticarial bullous pemphigoid, and early pemphigus,[61] was observed in one-fifth of our cases. Importantly, some of these cases also displayed a subepidermal split, potentially necessitating direct immunofluorescence study to exclude bullous pemphigoid when clinically indicated. Another remarkable finding was a “flame figure” formed by abundant degranulated eosinophils, simulating the appearance of Wells syndrome. Two other cases imparted a “lymphomatoid” appearance. Similar atypical lymphocytes have been reported in SDRIFE once in the literature.[62] It is known that atypical or activated lymphocytes, often CD30 expressing,[63,64] may be seen in various drug reactions including acute generalized exanthematous pustulosis (AGEP)[65] and drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity (DIHS).[66]

The clinical differential diagnosis for SDRIFE is broad and includes common entities such as candidiasis, tinea, inverse psoriasis, contact dermatitis, as well as other cutaneous drug eruptions such as the intertriginous form of toxic erythema of chemotherapy (TEC), or an early presentation of exanthematous (morbilliform) drug reaction, DRESS, or AGEP.[2,67] While the timing and the type of medication implicated, distribution and primary morphology of skin lesions, and the absence of systemic signs, symptoms, or lab abnormalities may be sufficient for a diagnosis of SDRIFE, given its wide range of clinical morphologies, histopathologic examination may be required to exclude other entities in the differential diagnosis.[67] Based on our findings and most other reports, the absence of psoriasiform hyperplasia would readily exclude inverse psoriasis. However, when psoriasiform changes are present, as rarely described in the literature,[6] evaluation for other features such as eosinophils, as well as careful clinical

correlation, would be necessary in distinguishing SDRIFE from inverse psoriasis. Histologic examination revealing lack of intracorneal neutrophils and a negative fungal special stain would also help exclude superficial fungal infections.

Histologic distinction of SDRIFE from other types of drug reactions tends to be more challenging. While distinguishing SDRIFE from exanthematous drug reaction and AGEP is of little clinical significance, confusion with DRESS and TEC will have greater ramifications. Common features of SDRIFE, such as superficial perivascular lymphocytic infiltrate, dermal eosinophils, spongiosis, mild basal vacuolization, and apoptotic keratinocytes, are also commonly seen in DRESS.[66] However, DRESS may sometimes display confluent keratinocyte necrosis or leukocytoclastic vasculitis, findings that are extremely rare in SDRIFE; only one isolated SDRIFE case in the literature has described leukocytoclastic vasculitis.[18] Conversely, we have identified interstitial histiocytic infiltrates in almost half of our cases, which to our knowledge has not been described in DRESS. Ultimately, correlation with any clinical signs and laboratory findings of systemic involvement is required to exclude DRESS before a diagnosis of SDRIFE is rendered.

Another drug-induced condition that may enter the differential diagnosis is TEC, particularly its intertriginous variant known as intertriginous eruption of chemotherapy or “malignant intertrigo”.[68] While SDRIFE is a hypersensitivity reaction, TEC is a result of localized accumulation of cytotoxic agents[1,69] which likely explains the common complaint of pain or tenderness associated with the rash.[68] Our study indicated chemotherapy as the offending medication in 5-8% of SDRIFE cases. Histopathologically, epidermal dysmaturation and eccrine squamous syringometaplasia

are frequent findings in TEC[69,70] but have not been reported in SDRIFE, and hence may serve as useful discriminators of these two conditions in patients undergoing chemotherapy.

The histopathologic finding of intracorneal, subcorneal, or intraepidermal pustules in a small subset of SDRIFE cases may raise consideration for AGEP.[71] Interestingly, clinical pustules were seen in fewer cases, suggesting that some pustules observed microscopically were too small to appreciate clinically, and thus were less likely to invoke a clinical impression of AGEP.

In addition to confirming the findings of previous reports, our series, which is the largest to date, has expanded the list of causative medications and histopathologic spectrum in SDRIFE. Combining our results with the literature, we found that antibiotics, chemotherapeutic agents, NSAIDs, antifungals, and anti-GERD medications accounted for the majority of cases. While SDRIFE is largely a clinical diagnosis, biopsy may be helpful in excluding other entities in the clinical differential diagnosis. Importantly, clinicians should convey their consideration for SDRIFE to the pathologist, as histopathologic overlap with various common dermatitides may result in misdiagnosis in the absence of clinical correlation. Dermatopathologists should keep a broad differential diagnosis when clinical information is inadequate or unavailable.

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Table 1. Summary of clinical and histopathologic data in the current SDRIFE series

| **Clinical findings** | **Number of cases (n=19)** |
|---|---|
| Inciting medications: | |
| Trimethoprim/sulfamethoxazole | 3 (16%) |
| Naproxen | 2 (11%) |
| Amoxicillin | 1 (5%) |
| Amoxicillin/clavulanate potassium | 1 (5%) |
| Ampicillin | 1 (5%) |
| Cephalexin | 1 (5%) |
| Clindamycin | 1 (5%) |
| Ciprofloxacin | 1 (5%) |
| Unknown antibiotic | 1 (5%) |
| Metoprolol | 1 (5%) |
| Gabapentin | 1 (5%) |
| Enfortumab vedotin | 1 (5%) |
| Methylphenidate | 1 (5%) |
| Lenalidomide | 1 (5%) |
| Dapsone | 1 (5%) |
| Intravenous immunoglobulin | 1 (5%) |
| Distribution: | |
| Bilateral axillae | 15 (79%) |
| Bilateral inguinal creases | 15 (79%) |
| Bilateral buttocks | 7 (37%) |
| Intergluteal cleft | 4 (21%) |
| Bilateral antecubital fossae | 4 (21%) |
| Bilateral inframammary folds | 3 (16%) |
| Bilateral popliteal fossae | 3 (16%) |
| Flanks | 3 (16%) |
| Neck | 2 (11%) |
| Other | 8 (42%) |
| Morphologies: | |
| Plaques | 17 (89%) |
| Erythematous | 17 (89%) |
| Papules | 13 (68%) |
| Scaly | 9 (47%) |
| Edematous | 7 (37%) |
| Dusky | 4 (21%) |
| Patches | 2 (11%) |
| Vesicles/bullae | 2 (11%) |
| Urticaria | 2 (11%) |
| Hyperpigmented | 2 (11%) |
| Macules | 1 (5%) |
| Erosions | 1 (5%) |
| Pustules | 1 (5%) |
| Lichenified | 1 (5%) |
| Violaceous | 1 (5%) |

Table 2. Summary of histopathologic findings in the current series

| **Histopathologic features** | **Number of cases (n=19)** |
|---|---|
| Epidermal changes: | |
| Spongiosis | 15 (79%) |
| Orthokeratosis | 15 (79%) |
| Irregular acanthosis | 9 (47%) |
| Langerhans cell microabscess | 6 (32%) |
| Intraepidermal eosinophils | 4 (21%) |
| Apoptotic keratinocytes | 4 (21%) |
| Subcorneal pustule | 3 (16%) |
| Basal vacuolization | 3 (16%) |
| Parakeratosis | 2 (11%) |
| Subepidermal split | 2 (11%) |
| Spongiotic vesicle | 1 (5%) |
| Intraepidermal pustule | 1 (5%) |
| Psoriasiform acanthosis | 0 (0%) |
| Dermal changes: | |
| Superficial perivascular lymphocytes | 19 (100%) |
| Dermal eosinophils* | 17 (89%)* |
| Mid dermal perivascular lymphocytes | 14 (74%) |
| Extravasated erythrocytes | 11 (58%) |
| Papillary dermal edema | 10 (53%) |
| Interstitial histiocytes | 9 (47%) |
| Dermal neutrophils | 7 (37%) |
| Lymphomatoid cells | 2 (11%) |
| Deep perivascular lymphocytes | 1 (5%) |

*Includes one case (5%) with a “flame figure”.

Table 3. Summary of previously reported cases of SDRIFE with histopathologic descriptions in literature

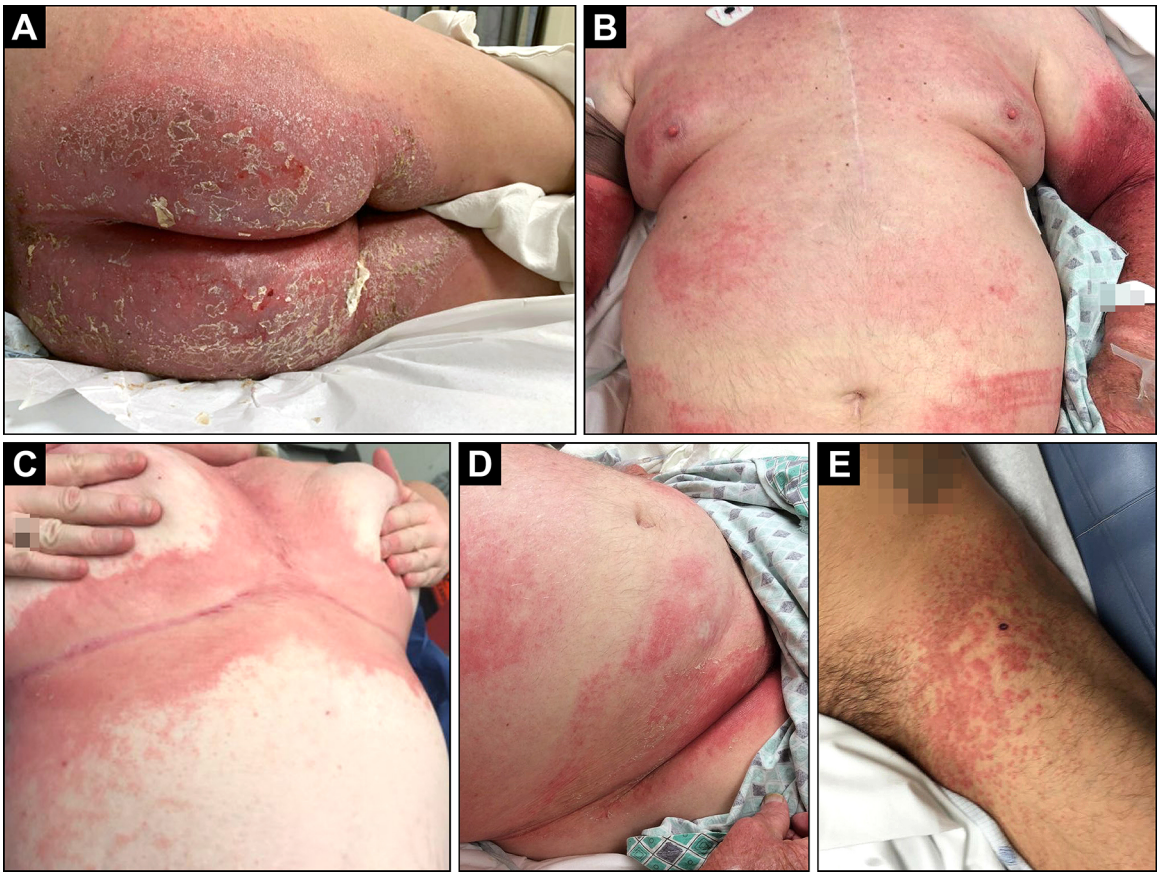
| **Clinical and histopathologic features** | **Number of cases (n=73)** |
|---|---|
| Inciting medications: | |
| Antibiotic | 24 (33%) |
| Chemotherapy | 6 (8%) |
| Antifungal | 5 (7%) |
| NSAID | 4 (5%) |
| Anti-GERD | 3 (4%) |
| Intravenous radiocontrast | 2 (3%) |
| Antihypertensive | 2 (3%) |
| Anti-epileptic | 2 (3%) |
| Anti-TNF-alpha | 2 (3%) |
| Other | 23 (31%) |
| Clinical morphologies: | |
| Erythematous | 63 (86%) |
| Plaques | 19 (26%) |
| Papules | 17 (23%) |
| Vesicles/bullae | 11 (15%) |
| Scaly | 9 (12%) |
| Pustules | 8 (11%) |
| Erosions | 5 (7%) |
| Edematous | 4 (5%) |
| Hyperpigmented | 1 (1%) |
| Microscopic epidermal changes: | |
| Spongiosis | 32 (44%) |
| Basal vacuolization | 24 (33%) |
| Apoptotic keratinocytes | 22 (30%) |
| Ortho-/parakeratosis | 14 (19%) |
| Subcorneal/intraepidermal pustules | 11 (15%) |
| Microscopic dermal changes: | |
| Superficial perivascular lymphocytes | 72 (99%) |
| Dermal eosinophils | 48 (66%) |
| Dermal neutrophils | 28 (38%) |
| Papillary dermal edema | 20 (27%) |
| Extravasated erythrocytes | 19 (26%) |
| Deep perivascular lymphocytes | 11 (15%) |

**Figure Legends**

Figure 1. Representative clinical images of SDRIFE. A, Well-demarcated erythematous plaques with overlying scale involving bilateral buttocks and inner thighs. B, Marked erythema of bilateral antecubital fossae. C, Symmetric erythematous plaques on inframammary folds with surrounding papules. D, V-shaped erythema affecting the inguinal folds. E, Numerous erythematous papules coalescing into plaques in the inguinal area.

Figure 2. Characteristic histopathologic features of SDRIFE. A, Irregular acanthosis with overlying hyperkeratosis. B, Mild epidermal spongiosis with a small subcorneal collection of neutrophils. C, A superficial perivascular lymphocytic and eosinophilic infiltrate. D, A subcorneal pustule and a few intraepidermal eosinophils. Marked papillary dermal edema results in focal subepidermal split. E, Scattered perivascular and interstitial neutrophils and eosinophils compatible with urticarial features. F, A small subset of cases demonstrate mild basal vacuolization. (Hematoxylin-eosin stain; original magnifications: A x40; B, C, E x200; D x100; F x400)

Figure 3. Relatively new histopathologic features of SDRIFE. A, An interstitial histiocytic infiltrate suggestive of an element of interstitial granulomatous dermatitis. B, Presence of large atypical lymphocytes giving rise to a lymphomatoid appearance. C, A “flame figure” noted in one case. (Hematoxylin-eosin stain; original magnifications: A, B x400; C x200)

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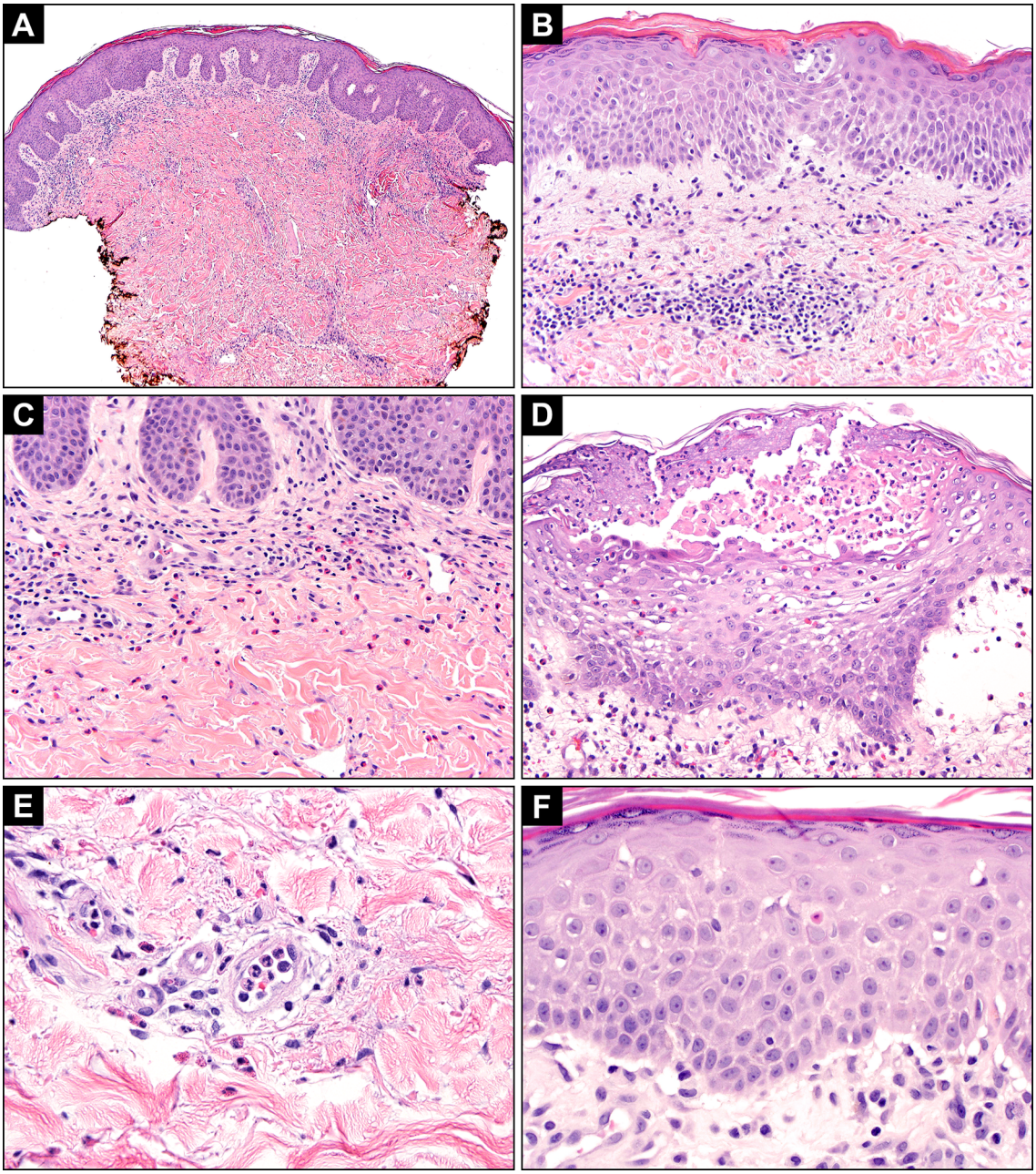


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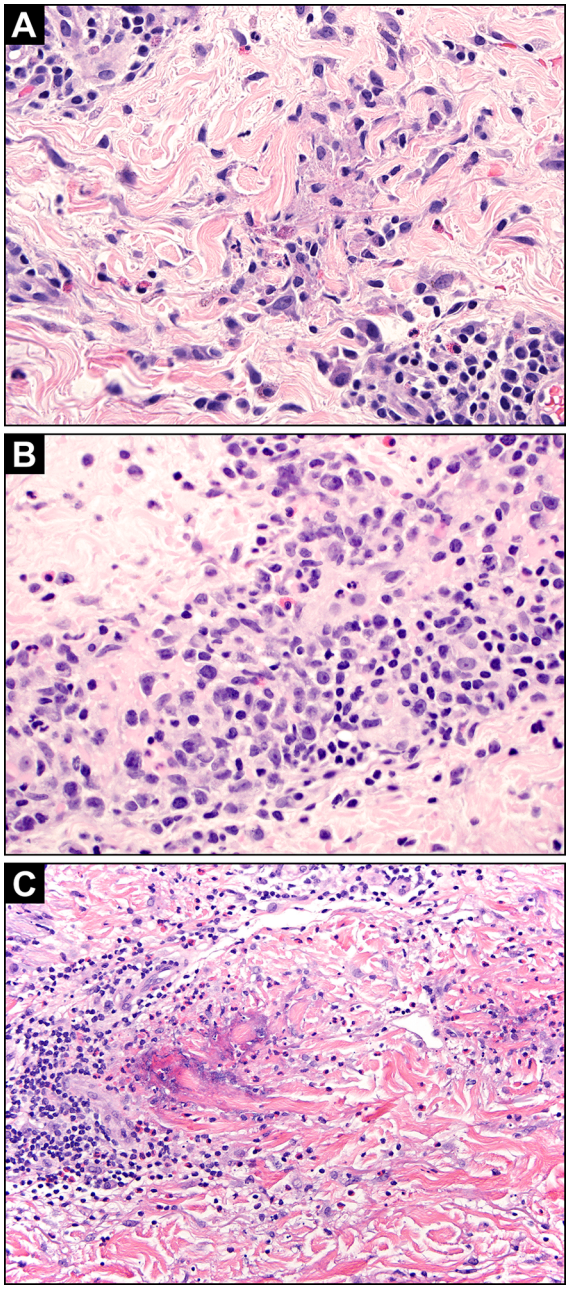


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Supplemental Table 1. Clinical data from the current series

| Case | Age (years) /Sex | Inciting medication | Latency (days) | Distribution | Morphology | Concomitant malignancy | Follow-up |
|---|---|---|---|---|---|---|---|
| 1 | 65/M | Naproxen | 4 | Bilateral inguinal areas and axillae | Dusky plaques with faint overlying desquamation | -- | Resolved within 2 weeks after strict avoidance of naproxen and application of topical steroids. |
| 2 | 58/M | Cephalexin | 7 | Inguinal folds, antecubital fossae, abdomen | Erythematous, edematous papules | -- | Resolved within 1 week with use of triamcinolone 0.1% ointment twice daily and fexofenadine 180mg once daily. A month after initial presentation, patient reported recurrence of rash on right arm and thigh that was amenable to topical desoximetasone 0.05% ointment twice daily for 2 weeks. |
| 3 | 26/M | Naproxen | 3 | Bilateral axillae, posterior neck, inguinal regions, buttocks | Erythematous to dusky edematous papules coalescing into plaques | -- | Resolved with strict avoidance of naproxen, 4 week 1mg/kg prednisone taper, topical triamcinolone 0.1% ointment twice daily for 2 weeks. |
| 4 | 63/M | Metoprolol | 90 | Bilateral axillae and groin | Eczematous rash | -- | Resolved with strict avoidance of metoprolol and topical triamcinolone 0.1% ointment twice daily for 2 weeks. Subsequent recurrence of rash 1 month after initial presentation that |

| | | | | | | | |
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| | | | | | | | remitted with 1mg/mg oral prednisone tapered over 3 weeks and topical clobetasol 0.05% ointment twice daily. |
| 5 | 61/M | Ampicillin | 3 | Bilateral intertriginous areas and buttocks | Morbilliform maculopapular rash | -- | Resolved 1 week after cessation of ampicillin during inpatient admission. |
| 6 | 55/M | Amoxicillin/ clavulanate potassium | 7 | Bilateral flexural areas, including inguinal regions and buttocks | Thin eczematous plaques | -- | Improved with use of topical triamcinolone 0.025% ointment to face and folds and triamcinolone 0.01% ointment to trunk and extremities twice daily for 2 weeks. Rash recurred and worsened after re-administration of amoxicillin / clavulanate, about 2 months after initial presentation; this resolved with admission for modified goeckerman therapy and 0.5mg/kg oral prednisone tapered over 4 weeks. |
| 7 | 56/F | Gabapentin | 21 | Bilateral axillae, inner thighs, buttocks, flanks | Erythematous to violaceous patches with fine superficial vesicles, bullae, and erosions | -- | Resolved with cessation of gabapentin and use of topical triamcinolone 0.1% ointment twice daily for 2 weeks. |
| 8 | 80/M | Clindamycin | 10 | Bilateral inguinal creases, antecubital and popliteal fossae, neck flexure | Erythematous to dusky plaques with peripheral desquamation and early superficial bullae | -- | Resolved with strict avoidance of clindamycin and use of topical triamcinolone 0.1% ointment twice daily for 2 weeks in addition to |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 0.5mg/kg oral prednisone tapered over 3 weeks. |
| 9 | 78/M | Trimethoprim/ sulfametho-xazole | 21 | Bilateral inguinal creases, axillae, forearms, chest, abdomen, lower back | Erythematous and edematous papules coalescing into plaques, some with overlying pustules | Multiple myeloma | Resolved with strict avoidance of bactrim and use of 1 mg/kg oral prednisone tapered over 3 weeks. |
| 10 | 59/M | Trimethoprim/ sulfametho-xazole | 1 | Bilateral axillae, infra-mammary creases, buttocks, forehead, lower back, bilateral flank, lower extremities | Erythematous papules and plaques | Multiple myeloma | Resolved with cessation of trimethoprim-sulfamethoxazole, IV solumedrol 2mg/kg for 2 days, with subsequent taper to oral prednisone 1mg/kg over 2 weeks, in addition to topical triamcinolone 0.01% and 0.025% ointment applied twice daily for 2 weeks. |
| 11 | 52/M | Trimethoprim/ sulfametho-xazole | 13 | Bilateral groin, axillae, and left calf | Erythematous, edematous papules coalescing into plaques with scant scale. | -- | Resolved with strict avoidance of trimethoprim-sulfamethoxazole, use of 0.5mg/kg oral prednisone tapered over 3 weeks and use of triamcinolone 0.1% ointment twice daily for 1 week. |
| 12 | 75/M | Intravenous immuno-globulin (IVIG) | 7 | Bilateral axillae and buttocks | Erythematous scaly maculopapules coalescing into plaques | -- | Resolved with triamcinolone 0.1% cream twice daily for 2 weeks. Rash recurred 1 month after presentation with subsequent administration of IVIG. |
| 13 | 73/M | Unknown | 5 | Bilateral inguinal | Erythematous | -- | Resolved with over the |

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|---|---|---|---|---|---|---|---|
| | | antibiotic | | areas, thighs, popliteal fossae, lower abdomen, lower back | plaques | | counter antihistamines in 1 week. |
| 14 | 69/F | Dapsone | 42 | Bilateral proximal thighs, inguinal creases, axillae | Erythematous, scaly patches and thin plaques | -- | Resolved in 2 weeks with cessation and strict avoidance of dapsone and use of fluocinonide 0.05% cream twice daily for 2 weeks. |
| 15 | 71/M | Lenalidomide | 5 | Bilateral inguinal folds, perineum, posterior legs, axillae, lower abdomen | Erythematous papules coalescing into plaques | Mantle cell lymphoma | Resolved in 2 weeks with cessation and avoidance of lenalidomide and with oral prednsione 0.5 mg/kg tapered over 2 weeks in addition to fluocinonide 0.05% cream twice daily for 2 weeks. |
| 16 | 81/M | Methyl-phenidate | 120 | Bilateral axillae, inguinal creases, flanks, anterior thighs | Small papules coalescing into plaques | Central nervous system B-cell lymphoma | Resolved in 2 weeks with cessation and avoidance of methylphenidate and with use of fluocinonide 0.05% solution and triamcinolone 0.1% ointment twice daily for 2 weeks and as needed hydroxyzine 25mg every 8 hours. |
| 17 | 79/M | Enfortumab vedotin | 2 | Bilateral inguinal creases, axillae, medial thighs | Erythematous to hyperpigmented plaques | Metastatic urothelial carcinoma | Resolved in 1 week with use of triamcinolone 0.1% ointment twice daily for 1 week; recurrences of rash with subsequent infusions of this drug as part of a clinical trial for metastatic urothelial carcinoma. |

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|---|---|---|---|---|---|---|---|
| 18 | 34/F | Ciprofloxacin | 32 | Perineum, buttocks, breast folds, axillae | Erythematous desquamating plaques | -- | Resolved with cessation of ciprofloxacin. |
| 19 | 52/F | Amoxicillin | 4 | Intergluteal cleft, bilateral breast folds, axillae, upper extremities, chest | Scaly erythematous plaques | -- | Resolved within 2 months after cessation of amoxicillin, oral prednisone taper, and topical betamethasone 0.05% ointment. |

F, female; M, male; --, absent; Y, yes; N, no; NA, not applicable

Supplemental Table 2. List of previously reported cases of SDRIFE with histopathologic descriptions in literature

| Reference | Implicated agent | Latency (days) | Clinical descriptions | Histological features |
|---|---|---|---|---|
| 47 | Amoxicillin | 4 | 32-yo M with intertriginous rash initially thought to be toxic epidermal necrolysis | Hydropic degeneration of keratinocytes, necrotic keratinocytes, subepidermal separation, and superficial perivascular infiltrate |
| 9 | Amoxicillin | <1 | 52-yo M with flexural exanthem | Spongiosis, superficial perivascular infiltrate with mononuclear cells, edema and extravasation of erythrocytes |
| 10 | Amoxicillin | 1 | 60-yo F with symmetric eruption on buttocks and major flexures | Superficial perivascular infiltrate with mononuclear cells |
| 11 | Amoxicillin | <1 | 37-yo M with flexural and baboon-type drug eruption | Spongiosis, neutrophilic exocytosis, superficial perivascular infiltrate with mononuclear cells and eosinophils, edema |
| 48 | Amoxicillin | 1 | 62-yo M with baboon-type exanthem | Superficial perivascular infiltrate with mononuclear cells and eosinophils, edema |
| 11 | Ceftriaxone | 2 | 78-yo F with baboon-type exanthem and involvement of flexural folds | Superficial perivascular infiltrate with mononuclear cells and neutrophils, neutrophilic exocytosis, subcorneal neutrophilic pustules |
| 12 | Clindamycin | NA | 28-yo F with baboon-type exanthem and involvement of intertriginous areas | Superficial perivascular infiltrate with mononuclear cells, hyperkeratosis, acanthosis and elongation of rete ridges |
| 13 | Erythromycin | NA | 1.5-yo M with baboon-type exanthem and involvement of flexural areas | Superficial perivascular dermatitis with lymphocytes |
| 14 | Penicillin V | NA | 57-yo M with baboon-type exanthem with erosions, petechiae, and pustules | Pustular haemorrhagic drug exanthem |
| 15 | Intravenous immunoglobulin (IVIG) | 1 | 28-yo F with baboon-type exanthem | Superficial perivascular infiltrate with CD4þ lymphocytes, edema, granular depositis of C1q along dermoepidermal junction, expression of CD62P (p-selectin, GMP140) observed on keratinocytes mainly along dermoepidermal junction |

| | | | | |
|---|---|---|---|---|
| 48 | Naproxene | 1 | 60-yo M with erythematous, purpuric, erosive eruption confined to three intertriginous areas (inguinal, buttocks, and axillae) | Consistent with the mixed dermoepidermal type of erythema multiforme |
| 16 | Nystatin | 2 | 47-yo M with baboon-like erythema | Spongiosis, superficial perivascular infiltrate with mononuclear cells |
| 17 | Pseudoephedrine | <1 | 73-yo F with baboon-type exanthem | Superficial perivascular infiltrate with mononuclear cells and eosinophils, edema, subcorneal and suprabasal pustules |
| 18 | Salsalate | 14 | 36-yo M with baboon-type exanthem | Consistent with leukocytoclastic vasculitis |
| 19 | Allopurinol | <1 | 58-yo M with baboon-type exanthem with secondary spread | Superficial perivascular infiltrate with mononuclear cells and eosinophils, exocytosis of erythrocytes, necrotic keratinocytes, edema |
| 20 | Cimetidine | NA | 74-yo M with baboon-like erythema | Spongiosis, superficial perivascular infiltrate with mononuclear cells |
| 21 | Daflazacort | <1 | 27-yo F with baboon-like exanthem associated with fever, nausea, vomiting, malaise, and hypotension | Superficial perivascular infiltrate with lymphocytes and eosinophils, apoptotic keratinocytes (consistent with erythema multiforme), granular IgM deposits at dermoepidermal junction |
| 22 | Hydroxyurea | 6 | 81-yo F with baboon-type exanthem and pruritic rash on trunk, legs, and face | Superficial perivascular infiltrate with mononuclear cells |
| 23 | Brentuximab vedotin (monoclonal antibody-auristatin E conjugate) | NA | 72-yo M with erythematous plaques on neck, chest, antecubital fossae, axillae, and inguinal and gluteal folds | Subepidermal bulla due to basal vacuolar alteration, necrotic keratinocytes, epidermal dysmaturation, and increased mitotic figures, infiltrate of lymphocytes, neutrophils, and numerous eosinophils in the dermis and in the bullous cavity |
| 24 | Cetuximab | NA | 71-yo M with symmetric erythematous and painful eruptions studded with pustules on the neckline and axillary areas associated with perineal inflammatory edema | Subcorneal pustule with neutrophils and a mixed cellular infiltrate in the papillary dermis |

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| 25 | Ethyl lofazepate | NA | 64-yo F with non-scaled band-like erythema on abdomen, resolved with removal of loflazepate ethyl and reappeared with challenge of same drug | Focal liquefaction degeneration in the epidermis, lymphocytic exocytosis and infiltration of perivascular lymphocytes and eosinophils in the upper dermis |
| 26 | Telmisartan/Hydro -chlorothiazide | 4 | 48-yo F with sharply demarcated erythema on inferior cervical folds, axillae, and gluteal area | Dense perivascular and periadnexal lymphohistiocytic infiltrate in the superficial dermis, with some eosinophils and mast cells |
| 46 | Pencillin | <1 | 46-yo M developed well-defined erythematous areas at the right elbow flexure, inner thighs, inguinal region, and gluteal area; rash resolved spontaneously after a few days without treatment | Single dyskeratotic cells within the stratum spinosum, minimal vacuolization in the basal layer, mild dermal edema, a sparse dermal infiltrate composed of lymphocytes and eosinophils |
| 7 | Valaciclovir | 1 | 56-yo F with erythematous pruritic rash appeared symmetrically on the neck and in the axillary, inguinal, and intergluteal areas; experienced similar eruption 3 years ago about 1hr after acyclovir | Spongiosis, liquefaction degeneration of the dermoepidermal interface, and perivascular inflammatory infiltrate composed predominantly of eosinophils in the superficial dermis and around the eccrine secretory gland |
| 53 | Cisplatinum or gemcitabine | 2 | 76-yo M with maculopapular purpuric eruption confined to intertriginous areas (inguinal, gluteal, and axillary folds) that occurred after second round of chemotherapy; resolved after change in chemotherapy regimen | Superficial and deep perivascular lymphocytic infiltrate with sparse nuclear dust, interstitial eosinophils, and large atypical CD30+ lymphocytes, some of them showing prominent nucleoli |
| 27 | Metronidazole | 7 | 16-yo F with sharply demarcated V-shaped macular erythematous patches on the axillary regions, inner arms, gluteal area, thighs, and groin; resolved with discontinuation of metronidazole and starting antihistamine | Spongiosis and lymphocytic infiltration in the superficial dermis |
| 28 | Zoledronic acid | 1 | 54-yo F with asymptomatic flat red rash on left antecubital fossa (infusion site) and bilaterally groin areas, medial thighs, right antecubital fossa, both axillae and popliteal fossae without systemic symptoms; rash resolved with withdrawal of zoledronic acid | Mild spongiosis, variable superficial and deep perivascular infiltrate, and a focal periadnexal infiltrate comprised of lymphocytes and eosinophils |

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|---|---|---|---|---|
| 49 | Hydroxyzine | 2 | 60-yo M developed symmetric erythema with few small pustules on both inner thighs, antecubital fossae, axillae, and gluteal area without systemic symptoms; resolved with removal of hydroxyzine, but reappeared when patient took hydroxyzine a week later | Perivascular lymphohistiocytic infiltrate with eosinophils and some neutrophils in the dermis, some subcorneal pustules |
| 29 | Everolimus | 14 | 76-yo M with erythematous plaques involving lower abdominal skin fold, medial thighs, perineum, and inguinal creases; eczematous plaques in axillae and posterior neck fold; no systemic symptoms; resolved with withdrawal of everolimus | Subacute spongiotic dermatitis with prominent eosinophils |
| 30 | Amoxicillin | 5 | 30-yo M with symmetric petechial, purpuric macules and plaques tending to coalesce on axillary, inguinal, and gluteal areas; also yellow-brown crusts on both lips | Extravasated erythrocytes, edema, and perivascular infiltration of lymphocytes, eosinophils in the upper dermis, mild exocytosis to the epidermis |
| 50 | Clindamycin | NA | 72-yo F with pruritic maculopapular rash in baboon-type distribution | Spongiosis, some necrotic keratinocytes in the epidermis, dermal edema, blood extravasation, perivascular inflammatory infiltrate with predominantly lymphocytes and some eosinophils |
| 5 | Infliximab | 2 | 50-yo M with macular erythematous rash on bilateral intergluteal, inguinal, abdominal, axillary, antecubital, and neck regions without systemic findings; eruption reappeared with subsequent infusions of same drug | Subcorneal pustules, vacuolar degeneration of dermoepidermal junction, perivascular infiltrate with some neutrophils and eosinophils, and slight epidermal spongiosis |
| 31 | Penicillin G benzathine | NA | 32-yo M with pruriginous erythema involving bilateral axillae, groin, and popliteal fossae; spontaneous resolution after 2 weeks | Superficial perivascular infiltrate of lymphocytes, histiocytes, eosinophils, and epidermal spongiosis |

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| 32 | Ranitidine | 5 | 8-yo M with sharply demarcated, pruritic, erythematous, scaly lesions involving the neck and groin, and scattered erythematous scaly papules and plaques over the chest and axillae; resolved with withdrawal of ranitidine in 1 week | Superficial perivascular dermatitis |
| 4 | Benzylpenicillin (intravenous) | NA | 40-yo M with macular rash over groin, buttocks, and axillae, and necrotic patches in groin | Extensive subcorneal pustule formation with necrosis of superficial epidermis and a moderately dense superficial perivascular and interstitial lymphohistiocytic infiltrate with neutrophils and scattered eosinophils |
| 33 | Fluconazole (oral) | 1 | 66-yo F with pruritic erythematous rash extending from bilateral inguinal folds to medial thighs, pruritus under breasts | Superficial perivascular infiltrate of lymphocytes and eosinophils in the dermis with mild spongiosis |
| 8 | Intravenous radiocontrast media | <1 | 41-yo F with erythematous plaques on the pannus, inframammary and inguinal folds, along with vesicles on back, and edematous palms; history of similar rash 7 years prior from IV iodinated radio contrast media | Hyperkeratosis, spongiosis, and superficial perivascular infiltrate composed mostly of lymphocytes and occasional neutrophils |
| 8 | Intravenous radiocontrast media | 3 | 53-yo F with bright red erythematous plaques with overlying vesicles that extended across buttocks, lower back, thighs, inguinal folds, and abdomen | Slight spongiosis and superficial perivascular infiltrate with occasional neutrophils and focal basal hydropic degeneration |
| 34 | Intravenous immunoglobulin (IVIG) | NA | 73-yo F with erythematous to hyperpigmented patches and plaques on face and erythematous patches, plaques, pustules, and fluid-filled vesicles on scalp, axillae, trunk, inguinal folds, medial inner thighs, sacral and gluteal areas and dorsum of the feet; resolved with fexofenadine | Subcorneal vesicle filled with necrotic keratinocytes, dense neutrophils and eosinophils |

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| 35 | Paracetamol (acetaminophen) | 1 | 53-yo M with symmetric erythema on buttocks, axillae, and both legs; rash resolved with steroids and discontinuation of paracetamol | Numerous lymphocytes, some eosinophils around papillary dermal small vessels, small subcorneal neutrophilic pustules |
| 36 | Fluorouracil (topical) | 14 | 56-yo M with burning, painful, erythematous, pruritic, and blistering rash on scrotum, penis, thighs, axillae, antecubital fossae, and dorsal hands | Epidermal ulceration with vacuolar changes of the basal layer and necrotic keratinocytes, perivascular lymphocytic infiltrate and rare eosinophils |
| 37 | Bortezomib | NA | 61-yo M with pruritic and symmetrically distributed intertriginous, maculopapular exanthema, localized to the axillae, antecubital fossae, groin, neck, and buttocks | Discrete, mixed pericapillary infiltrate |
| 38 | Clozapine | NA | 42-yo M with florid symmetric erythema affecting axillae and groin, extending to trunk and lower extremities | Epidermal hyperkeratosis, parakeratosis, and foci of subcorneal pustules filled with neutrophils alongside a mixed inflammatory infiltrate comprising lymphocytes, neutrophils and eosinophils in the dermis |
| 38 | Clozapine | NA | 56-yo M with symmetric erythema affecting axillae, groin, and antecubital fossae | Epidermal hyperkeratosis, parakeratosis, and foci of subcorneal pustules filled with neutrophils alongside a mixed inflammatory infiltrate comprising lymphocytes, neutrophils and eosinophils in the dermis |
| 39 | Ceftazadime | 1 | 9-yo M with developed symmetrical, erythematous rash confined to axillary and inguinal regions; similar reaction 1 year prior following administration of ceftazidime | Acanthosis and papillomatosis with focal vacuolar degeneration of basal layer, superficial and deep perivascular lymphocytic dermatitis with scattered eosinophils and neutrophils in the superficial dermis |
| 40 | Piperacillin/tazo-bactam | NA | 56-yo F with well demarcated patches of erythema and edema limited to axilla, groin and posterior neck, with small vesicles over the axilla | Spongiosis with intraepidermal vesicle formation, an interstitial and superficial perivascular chronic inflammatory infiltrate rich in eosinophils |

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| 41 | Omeprazole | 17 | 67-yo F developed symmetrical, confluent erythematopapular lesions on neck, groin, and inner gluteal areas | Slight spongiosis, small intra/subcorneal pustules, and vacuolar degeneration with moderate, mostly superficial, perivascular infiltrate and some eosinophils and neutrophils |
| 42 | Clarithromycin | NA | 22-month-old M with rash and pruritus of axillary, popliteal, and inguinal regions | Significant focal spongiotic foci with apoptotic keratinocytes, lymphocytes, edema and inflammation |
| 43 | Terbinafine | NA | 60-yo M with mildly painful erythematous eruption involving buttocks and flexural areas including axillae and groin | Mixed, predominantly mononuclear perivascular infiltrate in the dermis |
| 44 | Codeine | 2 | 60-yo F with pruritic macular rash in the gluteal, inguinal, popliteal, legs, neck, and inframammary areas without systemic symptoms | Spongiosis, eosinophilic and lymphocytic exocytosis in the epidermis, and a dermal perivascular infiltrate of inflammatory cells, predominantly eosinophils and lymphocytes |
| 6 | Rivastigmine transdermal patch | NA | 66-yo M with symmetric, gluteal, flexural, intertriginous erythematous macules papules and plaques | Spongiosis, dyskeratosis, lymphocytic exocytosis in epidermis, mild vacuolar interface, superficial and deep perivascular infiltrate |
| 6 | Benzocaine Cetylpiridinum chloride | NA | 32-yo F with symmetric, perigenitoanal, predominantly flexural, intertriginous, erythematous slightly scaly macules papules and plaques | Parakeratosis, spongiosis, dyskeratosis, lymphocytic extravasation, vacuolar interface, superficial perivascular infiltrate, infiltrate in papillary dermis |
| 6 | Cefuroxime | NA | 64-yo M with symmetric, perigenital, flexural and intertriginous erythematous macules papules plaques bullae and pustules | Parakeratosis, spongiosis, dyskeratosis (strongly present), intraepidermal neutrophils, vacuolar interface, bullae/clefting, papillary edema, superficial and deep perivascular lymphocytic infiltrate |
| 6 | Gabapentin | NA | 88-yo M with symmetric, gluteal, perigenital predominantly flexural and intertriginous, erythematous slightly scaly macules papules and plaques | Epidermal hyperplasia, parakeratosis, dyskeratosis, intraepidermal lymphocytes and neutrophils, vacuolar interface, fibrosis of papillary dermis, superficial perivascular lymphocytic infiltrate |

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| 6 | Gabapentin | NA | 88-yo M with symmetric, gluteal, perigenital predominantly flexural and intertriginous, erythematous slightly scaly macules papules and plaques | Epidermal hyperplasia, parakeratosis, spongiosis, dyskeratosis, intraepidermal neutrophils, papillary edema, superficial perivascular lymphocytic infiltrate |
| 6 | Metamizole | NA | 59-yo M with symmetric, anogenital region flexural intertriginous and extremities, bullae and erosions | Dyskeratosis prominent, vacuolar interface, bulla, superficial perivascular lymphocytic infiltrate |
| 6 | Clindamycin | NA | 70-yo F with symmetric, gluteal, perigenital, predominantly flexural, intertriginous, erythematous macules, papules and plaques | Parakeratosis, spongiosis, dyskeratosis, vacuolar interface, papillary edema, superficial perivascular lymphocytic infiltrate |
| 6 | Hydrochloro-thiazide | NA | 57-yo M with symmetric, gluteal, perigenital, predominantly flexural, intertriginous and extremities, erythematous scaly macules papules and plaques | Parakeratosis, dyskeratosis, vacuolar interface, superficial perivascular lymphocytic infiltrate |
| 6 | Hydrochloro-thiazide | NA | 57-yo M with symmetric, gluteal, perigenital, predominantly flexural, intertriginous and extremities, erythematous scaly macules papules and plaques | Parakeratosis, spongiosis, dyskeratosis, intraepidermal lymphocytes, neutrophils, vacuolar interface, superficial perivascular lymphocytic infiltrate |
| 6 | Ibuprofen | NA | 31-yo F with symmetric, gluteal, flexural and intertriginous erythematous macules and plaques | Vacuolar interface, dyskeratosis, spongiosis, papillary dermal edema, superficial and deep perivascular lymphocytic infiltrate |
| 6 | Ibuprofen | NA | 37-yo F with symmetric, perigenital, predominantly flexural, intertriginous erythematous macules, papules plaques, few pustules and few bullae | Vacuolar interface, dyskeratosis, spongiosis, papillary dermal edema, superficial and deep perivascular lymphocytic infiltrate |
| 50 | Tacrolimus | NA | 41-yo M with symmetric erythematous papules in the antecubital fossae, axillae, inguinal area, gluteal region and neck | Epidermal spongiosis, superficial perivascular lymphocytic infiltrate and dermal eosinophils |

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| 51 | Doxycycline | <1 | 38-yo M with symmetric erythematous patches and blistering over axillae, inframammary areas, inguinal areas and buttocks | Parakeratosis, acanthosis, subcorneal vesicle, superficial perivascular lymphocytic infiltrate and red blood cell extravasation |
| 52 | Gefitinib | 28 | 72-yo F, symmetric erythematous macules and papules in gluteal, inguinal axillary areas and inframammary folds. | Dermal papillary edema, superficial perivascular lymphocytic infiltrate, dermal neutrophils and eosinophils |
| 53 | Ampicillin sulbactam | 2 | 14-yo M with symmetric erythematous patches affecting anogenital region, inguinal area, flexures of wrists | Dermal papillary edema, superficial perivascular lymphocytic infiltrate and dermal neutrophils and eosinophils |
| 54 | Golimumab | 7 | 70-yo F with symmetric erythematous patches, bullae and erosions in bilateral inguinal areas as well as bilateral axillae | Vacuolar interface with few dyskeratotic cells, and superficial perivascular lymphocytic infiltrate and dermal eosinophils |
| 55 | Acetaminophen | 1 | 62-yo M with symmetric erythematous patches on the posterior neck, axillae, inguinal and inframammary areas | Spongiosis, dermal papillary edema, superficial perivascular lymphocytic infiltrate, eosinophils and neutrophils in the dermis as well as extravasated red blood cells |
| 56 | Berberine | 60 | 54-yo M with symmetric, erythematous macules in bilateral inguinal areas and axilae | Dermal papillary edema, superficial perivascular lymphocytic infiltrate, dermal neutrophils and eosinophils |
| 45 | Itraconazole | 3 | 35-yo M with symmetric erythematous patches in gluteal area, inguinal area, flexures and neck | Superficial perivascular lymphocytic infiltrate and extravasated red blood cells |
| 45 | Itraconazole | 3 | 31-yo F with symmetric erythematous patches in gluteal area, inguinal area, flexures and neck | Superficial perivascular lymphocytic infiltrate |
| 2 | Pristinamycin | 2 | 60-yo M with erythematosquamous rash of the inguinal and axillary folds and gluteal area | Orthokeratosis, spongiosis, superficial perivascular lymphocytic infiltrate with some eosinophils |

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| 2 | Nefopam | <1 | 68-yo F with erythematous rash in V-shaped distribution of buttocks, perineum, axillary folds | Vacuolar interface, spongiosis, superficial perivascular lymphocytic infiltrate |
| 57 | Cefuroxime | 6 | 64-yo M with symmetric, pruritic, erythematous patches with occasional pustules and blisters in the groin, axillae, and antecubital fossae | Superficial perivascular lymphocytic infiltrate, spongiosis, dermal eosinophils and neutrophils and focal necrotic keratinocytes |

F, female; M, male; NA, not available; yo, year-old

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**Title:** Symmetric drug-related intertriginous and flexural exanthema (SDRIFE): clinicopathologic study of 19 cases and review of literature

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