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Symmetric drug-related intertriginous and flexural exanthema: 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 7 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.

KEYWORDS

baboon syndrome, drug reaction with eosinophilia and systemic symptoms, histopathology, symmetric drug-related intertriginous and flexural exanthema, toxic erythema of chemotherapy

1 | 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.

2 | MATERIALS AND METHODS

This study was conducted according to previously approved Institutional Review Board protocols (HUM00064315, 2011P002524). 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.

3 | RESULTS

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

TABLE 1 Summary of clinical 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%)

Abbreviation: SDRIFE, symmetric drug-related intertriginous and flexural exanthema.

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[a]	17 (89%)[a]
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%)

[a]Includes one case (5%) with a "flame figure."

3.1 | Clinical data

Clinical history and findings of our cases are summarized in Table 1 and listed in detail in Table S1. 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 1 to 120 days after initiation of the inciting medication; median and average were 7 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.

3.2 | 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.

3.3 | 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 Table S2. 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, nonsteroidal anti-inflammatory drug (NSAID), anti-gastroesophageal reflux (GERD), intravenous radiocontrast, antihypertensive, antiepileptic, and antitumor necrosis factor-alpha medications. Average latency period was 5 days (range, 1 hour to 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.

4 | 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

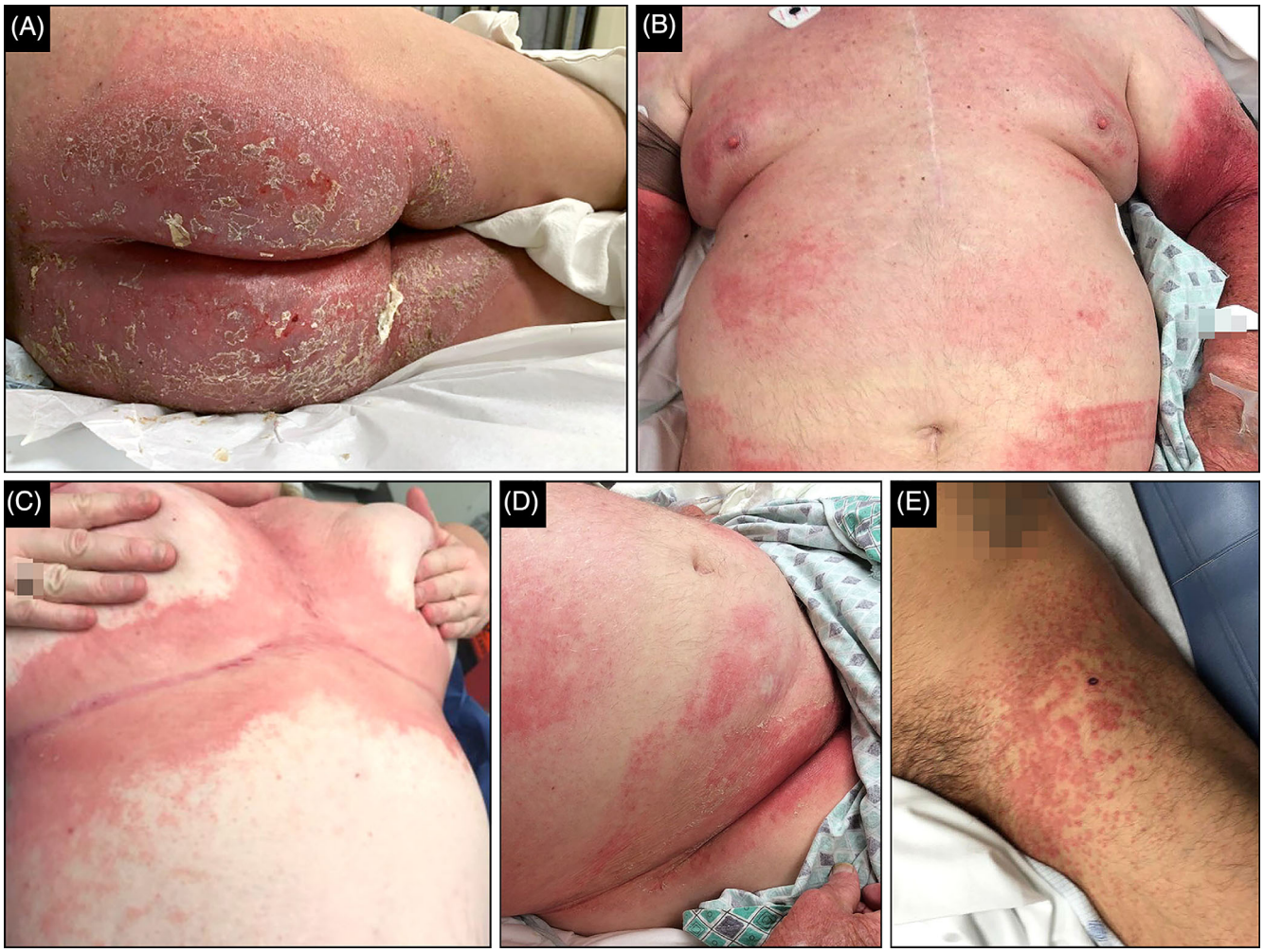

FIGURE 1 Representative clinical images of SDRIFE. A, Well-demarcated erythematous plaques with overlying scale involving bilateral buttocks and inner thighs. B, Marked erythema of bilateral antecubital fossae. C, Symmetric erythematous plaques on inframammary folds with surrounding papules. D, V-shaped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

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.

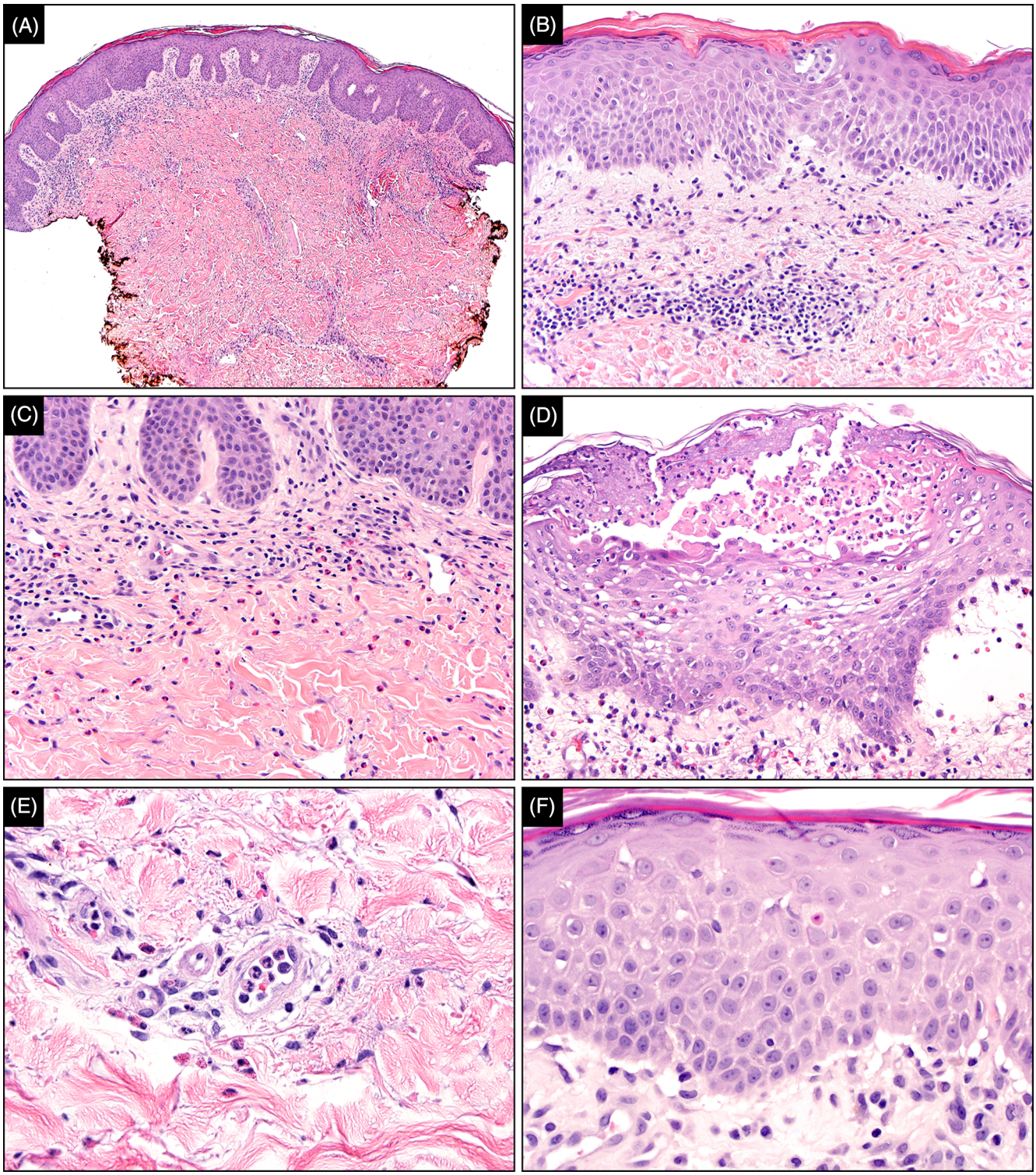

FIGURE 2 Characteristic histopathologic features of SDRIFE. A, Irregular acanthosis with overlying hyperkeratosis. B, Mild epidermal spongiosis with a small Langerhans cell microabscess. C, A superficial perivascular lymphocytic and eosinophilic infiltrate. D, A subcorneal pustule and a few intraepidermal 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, ×40; B, C, ×200; D, ×100; E, F, ×400). SDRIFE, symmetric drug-related intertriginous and flexural exanthema

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

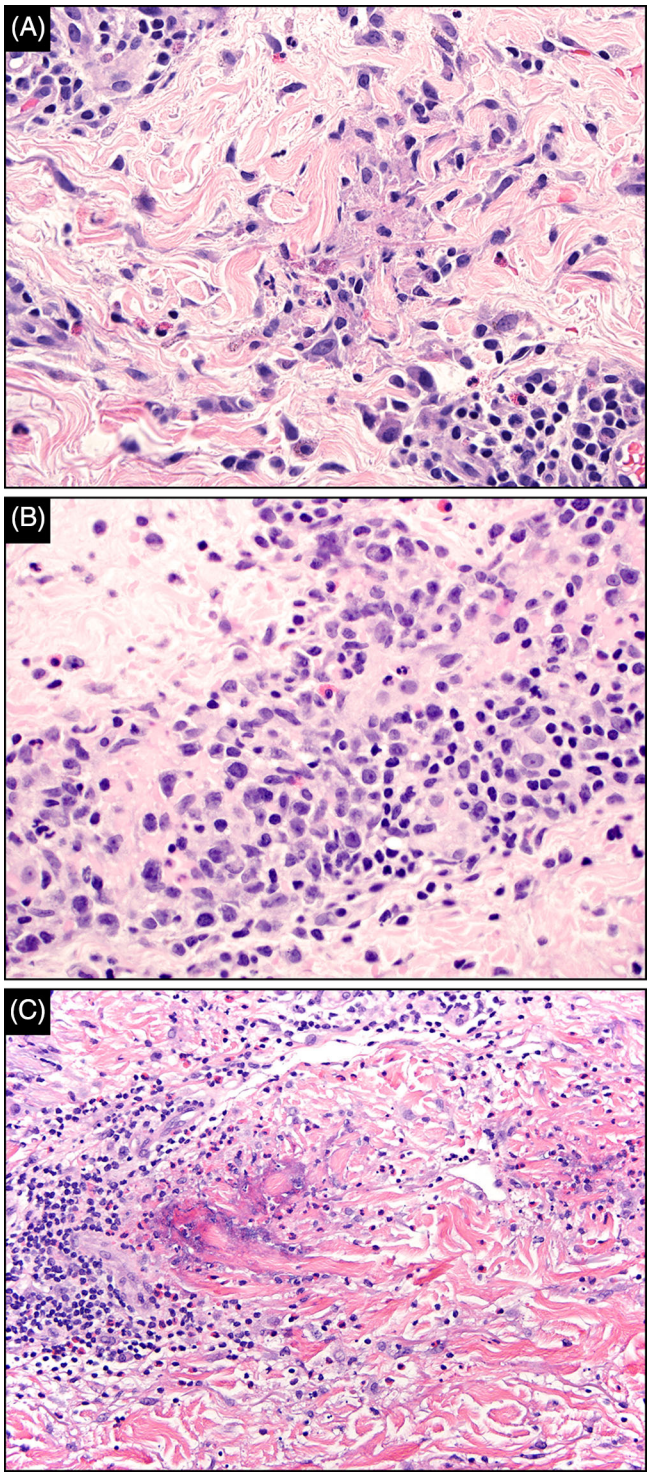

FIGURE 3 Relatively new histopathologic features of SDRIFE. A, An interstitial histiocytic infiltrate suggestive of an element of interstitial granulomatous dermatitis. B, Presence of large atypical lymphocytes giving rise to a lymphomatoid appearance. C, A "flame figure" noted in one case (hematoxylin-eosin stain; original magnifications: A, B, ×400; C, ×200). SDRIFE, symmetric drug-related intertriginous and flexural exanthema

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

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%)
Orthokeratosis/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%)

Abbreviations: GERD, gastroesophageal reflux; NSAID, nonsteroidal anti-inflammatory drug; SDRIFE, symmetric drug-related intertriginous and flexural exanthema; TNF, tumor necrosis factor.

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 expressing CD30,[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.[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. Histopathologic examination revealing lack of intracorneal neutrophils and a negative fungal special stain would also help exclude superficial fungal infections.

Histopathologic 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% to 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.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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