




## ORIGINAL ARTICLE

# Diagnoses of hospitalized patients with skin abnormalities prompting biopsy by consulting dermatologists: A 3-year review from a tertiary care center

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## Abstract

**Background:** Dermatologists play an important role in diagnosing and managing hospitalized patients with cutaneous abnormalities. Skin biopsies remain an indispensable tool for aiding dermatologists in accurate diagnosis and treatment. We aimed to determine the range of conditions, and the most common conditions, prompting skin biopsy by dermatology hospital consultation (HCON) services to aid in evaluation of hospitalized patients.

**Methods:** All hospitalized patients seen by a single tertiary care center dermatology HCON service between 2015 and 2018 who had associated skin biopsies were identified. Histologic features and clinical diagnoses of each patient were classified into 13 histologic reaction pattern categories.

**Results:** Eight hundred and thirty one inpatients evaluated by our dermatology HCON service had 914 skin biopsies. The most frequent diagnostic categories prompting biopsy were vasculopathic (17.6%), interface dermatitis (16.5%), infectious (12.6%), and spongiotic dermatitis (10.9%). The most frequent diagnostic categories included drug reaction (13.2%), leukocytoclastic vasculitis (8.5%), skin cancer (5.4%), graft-vs-host disease (3.5%), connective tissue disease (3.3%), and calciphylaxis (3.0%).

**Conclusion:** Our study suggests a variety of serious diseases affecting inpatients prompts biopsy by dermatology consultation services. Educational curricula for dermatology and pathology residents, fellows, and staff designed with these data may enhance knowledge that improves the quality of inpatient dermatology care.

## KEYWORDS

dermatology hospital consultation, dermatopathology, inpatient dermatology, skin biopsy

**Abbreviations:** HCON, dermatology hospital consultation service; LCV, leukocytoclastic vasculitis; GVHD, graft-vs-host disease; CTD, connective tissue disease; ESRD, end-stage renal disease; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug rash with eosinophilia and systemic symptoms; AGEP, acute generalized exanthematous pustulosis; LABD, linear IgA bullous dermatosis; DIF, direct immunofluorescence; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; ACD, allergic contact dermatitis; ICD, irritant contact dermatitis.

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## 1 | INTRODUCTION

Dermatologists and pathologists/dermatopathologists play critical roles in diagnosing and managing hospitalized patients with primary cutaneous diseases and cutaneous manifestations of systemic diseases.<sup>1-4</sup> Hospitalized patients represent a unique subset of patients seen by dermatologists, as they are typically more ill and often have more comorbidities compared to outpatients. Thus, prompt and accurate diagnosis and treatment can affect outcomes. Skin biopsies are an indispensable tool for aiding dermatologists in making accurate diagnoses and recommending appropriate treatments for hospitalized patients.<sup>5-8</sup> While a broad spectrum of dermatologic findings is seen in hospitalized patients, little is known about the conditions most commonly prompting skin biopsy to aide in diagnosis. Given the importance of clinicopathologic correlation in this population, it would be valuable for dermatologists and pathologists to be aware of and especially knowledgeable about the most frequently biopsied conditions. Such knowledge could translate into much needed educational initiatives that help dermatologists more precisely develop a differential diagnosis and choose an appropriate area to biopsy in any given patient, and dermatopathologists more accurately interpret histopathologic findings.<sup>9,10</sup>

We reviewed clinical charts and biopsy results of hospitalized patients evaluated by the dermatology hospital consultation (HCON) service at a single, tertiary care academic center over a 3-year period. Our primary goal was to describe the most frequently biopsied diagnoses in hospitalized patients formally evaluated by dermatology consultation. Our secondary goal was to provide up-to-date knowledge concerning which conditions dermatologists and pathologists should feel adequately educated about to optimize care in this patient population.

## 2 | METHODS

An Institutional Review Board-approved retrospective review of inpatient dermatology consultations performed at our main campus from September 2015 to September 2018 was conducted. Electronic Medical Records were searched to identify hospitalized patients who had dermatology hospital consultations associated with documented skin biopsy during the above period. Patients without skin biopsies were excluded.

Medical charts of included patients were reviewed, and data were extracted from inpatient notes and pathology reports. Both clinical and histopathologic findings were utilized to determine a final diagnosis, which was classified into 1 of 13 major histopathologic (reaction) patterns: vasculopathic, interface dermatitis, infectious, spongiotic, neoplasms, ulcer/wound, vesicobullous, neutrophilic dermatosis, urticarial, psoriasiform, panniculitis, granulomatous, and "other." Diagnoses were further broken down into subcategories. Questionable cases were reviewed by a board-certified dermatologist/dermatopathologist to determine a final diagnosis using clinicopathologic correlation. Cases in which a final diagnosis could not be reached were categorized as "other." Analyses included calculating means, confidence intervals, overall counts, and percentages.

## 3 | RESULTS

Between September 2015 and September 2018, our dermatology HCON service performed 3279 inpatient consultations on 2861 unique patients. Three hundred patients had more than one unique consultation (418 total consultations in this subset), typically related to separate hospitalizations. Of the 2861 unique patients, 1472 were male and 1389 were female.

A total of 831 inpatients (29%) evaluated by our dermatology HCON service were biopsied during this period. Mean age of patients biopsied was 55.2 years (range: newborn to 93-years-old). Of 831 patients, 447 (53.8%) were female and 384 (46.2%) were male. During the 3-year study period, 914 biopsies were performed in these 831 patients. All but six skin biopsies were performed by the dermatology HCON service. The other six skin biopsy specimens were collected by plastic surgery (n = 2), otolaryngology (n = 2), vascular surgery (n = 1), and orthopedic surgery (n = 1) based upon dermatology HCON service recommendations. Approximately 19% of all biopsies (n = 172) were performed during weekend encounters. An additional biopsy for direct immunofluorescence (DIF) accompanied 147 of our 914 biopsies (16.1%). The results of DIF were positive in 47 biopsies (32%), non-specific in 48 biopsies (33%), and negative in 52 biopsies (35%).

Final diagnoses were classified into 1 of 13 categories based on histologic (reaction) patterns. The most frequent diagnostic categories were vasculopathic (n = 161, 17.6%), interface dermatitis (n = 151, 16.5%), infectious (n = 115, 12.6%), spongiotic dermatitis (n = 100, 10.9%), other (n = 93, 10.2%), and neoplasms (n = 91, 10.0%). Less frequently encountered categories included ulcer/wound (n = 65, 7.1%), vesicobullous (n = 50, 5.5%), neutrophilic dermatosis (n = 23, 2.5%), urticarial (n = 19, 2.1%), psoriasiform (n = 18, 2.0%), panniculitis (n = 17, 1.9%), and granulomatous (n = 11, 1.2%) (Tables 1 and 2). We identified 39 biopsies within our cohort that were performed on

**TABLE 1** Diagnostic categories of biopsies performed by the dermatology hospital consultation service

Final diagnosis	Total (n)	Percentage (%)
Vasculopathic	161	17.61
Interface dermatitis	151	16.52
Infectious	115	12.58
Spongiotic dermatitis	100	10.94
Other	93	10.18
Neoplasm	91	9.96
Ulcer/wound	65	7.11
Vesicobullous	50	5.47
Neutrophilic dermatosis	23	2.51
Urticarial	19	2.08
Psoriasiform	18	1.97
Panniculitis	17	1.86
Granulomatous	11	1.20
<b>Total</b>	<b>914</b>	<b>100</b>

**TABLE 2** Diagnoses of patients biopsied by the dermatology hospital consultation service (n = 914)

Diagnosis	Diagnosis, n (%)
<b>1 Vasculopathic</b>	<b>161 (17.61)</b>
Leukocytoclastic vasculitis (non-IgA)	52 (5.69)
Calciphylaxis	27 (2.95)
Noninflammatory purpura	27 (2.95)
IgA vasculitis	25 (2.74)
Thrombotic vasculopathy	22 (2.41)
Livedoid vasculopathy	2 (0.22)
Septic vasculitis	1 (0.11)
Granulomatosis with polyangiitis	1 (0.11)
Lymphocytic vasculitis	1 (0.11)
Purpura fulminans	1 (0.11)
Coumadin necrosis	1 (0.11)
Type 1 cryoglobulinemia	1 (0.11)
<b>2 Interface dermatitis</b>	<b>151 (16.52)</b>
Drug rash	51 (5.58)
Graft-vs host-disease	32 (3.50)
Stevens-Johnson syndrome/toxic epidermal necrolysis	16 (1.75)
Dermatomyositis	13 (1.42)
Erythema multiforme	11 (1.20)
Lupus erythematosus	9 (0.98)
Still disease	4 (0.44)
Interface dermatitis	6 (0.66)
Morphea	3 (0.33)
Bullous fixed drug eruption	3 (0.33)
Toxic erythema of chemotherapy	2 (0.22)
Scleroderma	1 (0.11)
<b>3 Infectious</b>	<b>115 (12.58)</b>
<b>A Bacterial</b>	<b>66 (7.22)</b>
Folliculitis	21 (2.30)
Superficial Staphylococcal/Streptococcal infection	16 (1.75)
Abscess	11 (1.20)
Cellulitis	10 (1.09)
Mycobacterium	3 (0.33)
Pseudomonas	2 (0.22)
Erysipelas	1 (0.11)
Toxic shock syndrome	1 (0.11)
Septic emboli	1 (0.11)
<b>B Fungal</b>	<b>29 (3.17)</b>
Candidiasis	7 (0.77)
Tinea infection	6 (0.66)
Pityrosporum folliculitis	4 (0.44)
Angioinvasive fungal infection	3 (0.33)

(Continues)

**TABLE 2** (Continued)

Diagnosis	Diagnosis, n (%)
Pityriasis versicolor	3 (0.33)
Seborrheic dermatitis	2 (0.22)
Onychomycosis	1 (0.11)
Zygomycosis	1 (0.11)
Mucormycosis	1 (0.11)
Non-specific fungal infection	1 (0.11)
<b>C Viral</b>	<b>18 (1.97)</b>
Herpes simplex virus	5 (0.55)
Viral exanthem	4 (0.44)
Varicella zoster virus	4 (0.44)
Verruca vulgaris	4 (0.44)
HIV-associated lichenoid dermatitis	1 (0.11)
<b>D Infestation</b>	<b>2 (0.22)</b>
Scabies	2 (0.22)
<b>4 Spongiotic dermatitis</b>	<b>100 (10.94)</b>
Non-specific spongiotic dermatitis	42 (4.60)
Allergic/irritant contact dermatitis	12 (1.31)
Drug reaction with eosinophilia and systemic symptoms (DRESS)	12 (1.31)
Stasis dermatitis	9 (0.98)
Arthropod bites	4 (0.44)
Grover disease	3 (0.33)
Injection site reaction	3 (0.33)
Eczematous drug eruption	3 (0.33)
Atopic dermatitis	2 (0.22)
Prurigo nodule	2 (0.22)
Lichen simplex chronicus	2 (0.22)
Acneiform	2 (0.22)
Blepharitis	1 (0.11)
Actinic dermatitis	1 (0.11)
Pityriasis lichenoides chronicus	1 (0.11)
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)	1 (0.11)
<b>5 Neoplasms</b>	<b>91 (9.96)</b>
<b>A Benign</b>	<b>24 (2.63)</b>
Seborrheic keratosis	5 (0.55)
Actinic keratosis	5 (0.55)
Hemangioma	2 (0.22)
Pyogenic granuloma	2 (0.22)
Benign lichenoid keratosis	1 (0.11)
Poroma	1 (0.11)
Sclerosing blue nevus	1 (0.11)
Fibroepithelial polyp	1 (0.11)
Collagenoma	1 (0.11)
Recurrent/persistent nevus	1 (0.11)

(Continues)

TABLE 2 (Continued)

Diagnosis	Diagnosis, n (%)
Sebaceous adenoma	1 (0.11)
Atypical compound nevus with mild dysplasia	3 (0.33)
<b>B Malignant</b>	<b>67 (7.33)</b>
Squamous cell carcinoma	24 (2.63)
Basal cell carcinoma	19 (2.08)
Melanoma	3 (0.33)
Sebaceous carcinoma	1 (0.11)
Cutaneous large B-cell lymphoma	1 (0.11)
Cutaneous T-cell lymphoma	1 (0.11)
Cutaneous angioimmunoblastic T-cell lymphoma	1 (0.11)
Peripheral T-cell lymphoma not otherwise specified	1 (0.11)
Leukemia cutis	1 (0.11)
Cutaneous myeloid leukemia	1 (0.11)
Chronic myelomonocytic leukemia	1 (0.11)
Cutaneous plasmablastic myeloma	1 (0.11)
Breast carcinoma en cuirasse	1 (0.11)
Metastatic lung adenocarcinoma	1 (0.11)
Metastatic neuroendocrine tumor	1 (0.11)
Metastatic esophageal squamous cell carcinoma	1 (0.11)
Kaposi sarcoma	1 (0.11)
Indeterminate dendritic cell tumor	1 (0.11)
<b>6 Ulcer/Wound</b>	<b>65 (7.11)</b>
Ulcer, non-specific	18 (1.97)
Ulcer, venous stasis	17 (1.86)
Ulcer, infected	10 (1.09)
Healing ulcer	7 (0.77)
Hypertensive ulcer (Martorell)	3 (0.33)
Ulcer, thrombotic vasculopathy	3 (0.33)
Pressure ulcer	2 (0.22)
Tongue ulcer	2 (0.22)
Ulcer, neuropathic	1 (0.11)
Ulcer, mixed venous and arterial	1 (0.11)
Pauci inflammatory ulcer	1 (0.11)
<b>7 Vesicobullous</b>	<b>50 (5.47)</b>
Acute generalized exanthematous pustulosis (AGEP)	17 (1.86)
Bullous pemphigoid	10 (1.09)
Linear IgA bullous dermatosis	7 (0.77)
Edema bulla	5 (0.55)
Blister, non-specific	5 (0.55)
Coma bullae	3 (0.33)
Pemphigus foliaceus	2 (0.22)
Pemphigus vulgaris	1 (0.11)

(Continues)

TABLE 2 (Continued)

Diagnosis	Diagnosis, n (%)
<b>8 Neutrophilic dermatosis</b>	<b>23 (2.52)</b>
Sweet syndrome	10 (1.09)
Pyoderma gangrenosum	7 (0.77)
Neutrophilic eccrine hidradenitis (NEH)	4 (0.44)
Subcorneal pustular dermatosis secondary to monoclonal gammopathy	1 (0.11)
Neutrophilic dermatosis	1 (0.11)
<b>9 Urticarial</b>	<b>19 (2.08)</b>
Dermal hypersensitivity reaction	14 (1.53)
Urticaria	4 (0.44)
Wells syndrome	1 (0.11)
<b>10 Psoriasiform</b>	<b>18 (1.97)</b>
Psoriasis	11 (1.20)
Erythrodermic psoriasis	3 (0.33)
Spongiotic psoriasiform dermatitis	2 (0.22)
Guttate psoriasis	1 (0.11)
Psoriasiform drug eruption	1 (0.11)
<b>11 Panniculitis</b>	<b>17 (1.86)</b>
Erythema nodosum	6 (0.66)
Lobular panniculitis	2 (0.22)
Lipodermatosclerosis	2 (0.22)
Pancreatic panniculitis	2 (0.22)
Cytophagic lobular panniculitis	1 (0.11)
Mixed panniculitis	1 (0.11)
Neutrophilic lobular panniculitis	1 (0.11)
Non-specific panniculitis	1 (0.11)
Palisaded granulomatous panniculitis	1 (0.11)
<b>12 Granulomatous</b>	<b>11 (1.20)</b>
Hidradenitis suppurativa	4 (0.44)
Granuloma annulare	2 (0.22)
Cutaneous sarcoidosis	1 (0.11)
Palisading granulomatous dermatitis with neutrophils	1 (0.11)
Cutaneous Crohn disease	1 (0.11)
Rheumatoid nodule	1 (0.11)
Granuloma gluteale	1 (0.11)
<b>13 Other</b>	<b>93 (10.18)</b>
Non-specific	44 (4.81)
Keloid/scar	9 (0.98)
Normal skin	6 (0.66)
Cyst	3 (0.33)
Nutritional deficiency dermatosis	3 (0.33)
Disseminated superficial actinic porokeratosis	2 (0.22)
Prurigo nodularis	2 (0.22)
Vascular ectasia	2 (0.22)

(Continues)

**TABLE 2** (Continued)

Diagnosis	Diagnosis, n (%)
Engraftment syndrome	1 (0.11)
Elephantiasis nostra verrucosa	1 (0.11)
Reactive process	1 (0.11)
Sunburn	1 (0.11)
Granulation tissue	1 (0.11)
Café au lait macule	1 (0.11)
Superficial telangiectasias	1 (0.11)
Kikuchi-Fujimoto disease	1 (0.11)
Sclerosing dermatosis	1 (0.11)
Edema	1 (0.11)
Reactive perforating collagenosis	1 (0.11)
Perforating disorder	1 (0.11)
Trichodystrophy	1 (0.11)
Dermatofibroma	1 (0.11)
Acute radiation dermatitis	1 (0.11)
Hypertrophic lichen planus	1 (0.11)
Ichthyosis-like condition	1 (0.11)
Sebaceous hyperplasia	1 (0.11)
Venous lymphatic malformation	1 (0.11)
Trichorrhexis nodosa	1 (0.11)
Lichen amyloidosis	1 (0.11)

**TABLE 3** Ten most frequent diagnoses of patients biopsied by the dermatology hospital consultation service

Diagnosis	Total (n)	Percentage (%)
Drug reaction	121	13.24
Leukocytoclastic vasculitis (LCV)	78	8.53
Primary cutaneous skin cancer	49	5.36
Graft-vs-host disease	32	3.50
Connective tissue disease (CTD)	30	3.28
Calciphylaxis	27	2.95
Noninflammatory purpura	27	2.95
Folliculitis	26	2.84
Thrombotic vasculopathy	24	2.63
Venous stasis ulcer	21	2.30
Total	435	47.59

pediatric patients (age < 18 years). The most frequent diagnostic categories within the pediatric population included infection (n = 10, 26%), vasculopathic (n = 7, 18%), other (n = 7, 18%), interface dermatitis (n = 5, 13%), and spongiotic dermatitis (n = 4, 10%).

The 10 most frequent specific diagnostic categories constituted 47.7% (n = 436) of biopsies (Table 3). These diagnoses included drug reaction (n = 121, 13.2%), leukocytoclastic vasculitis (LCV) (n = 78, 8.5%), primary skin cancer (n = 49, 5.4%), graft-vs-host disease

(GVHD) (n = 32, 3.5%), connective tissue disease (CTD) (n = 30, 3.3%), calciphylaxis (n = 27, 3.0%), noninflammatory purpura (n = 27, 3.0%), folliculitis (n = 26, 2.8%), thrombotic vasculopathy (n = 24, 2.6%), and venous stasis ulcer (n = 21, 2.3%).

In the vasculopathic group, LCV accounted for 48.4% of cases. Of LCV cases, 26.6% were attributed to infection, 11.4% were medication-induced, 6.3% were associated with autoimmune disease, and 55.7% had unclear etiologies. IgA-mediated LCV accounted for 15.5% of cases. Of patients with IgA-mediated LCV, 48% had renal involvement (only one under 18-years-old). Calciphylaxis accounted for 16.8% of cases in the vasculopathic group, with the majority having associated end-stage renal disease (ESRD; 66.7%).

In the interface dermatitis category, morbilliform drug rash was the most common (33.8%) diagnosis and these were mostly prompted by antibiotics. Other common interface dermatitides were GVHD (21.2%), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) spectrum reactions (10.6%), and dermatomyositis (8.6%). Of 13 dermatomyositis diagnoses, all were new and three were malignancy-associated.

In the infectious category, bacterial infections were the most common (57.4%), followed by fungal (25.2%), viral (11.9%), and infestations (1.3%). No single infectious diagnosis was strikingly common. However, a significant percentage were serious (27/115; 23.5%), including ecthyma gangrenosum, disseminated zoster, and angioinvasive fungal infections.

The spongiotic dermatitis category included mostly non-specific diagnoses (42.0%), although allergic/irritant contact dermatitis and drug reaction with eosinophilia and systemic symptoms (DRESS) each accounted for 12.0%. Antibiotics were the most common culprit of DRESS, with vancomycin being the most frequent causative agent.

In the neoplasm group, the majority were malignant (73.6%), suggesting our HCON service biopsied skin growths mainly if concerned for malignancy. The most common malignancies were squamous cell carcinomas (26.4%) and basal cell carcinomas (20.9%). Other neoplastic diagnoses each involved  $\leq 5$  biopsy specimens. Of the neoplasms biopsied, 82.4% were the primary reason for consultation while others were noted during physical examination.

In the ulcer/wound category, non-specific (27.7%), venous stasis (26.2%) and infected ulcers (15.4%) were most commonly biopsied. In the vesicobullous category, acute generalized exanthematous pustulosis (AGEP) was the most common diagnosis (34.0%), followed by bullous pemphigoid (20.0%) and linear IgA bullous dermatosis (LABD) (14.0%). The "other" diagnostic category accounted for 10.2% of specimens, with non-specific histologic findings (47.3%) and keloids/scars (9.7%) representing the most common diagnoses.

The remaining five categories each included less than 25 specimens. Of neutrophilic dermatoses, Sweet syndrome (43.5%) and pyoderma gangrenosum (39.4%) were most common. The urticarial category mostly included dermal hypersensitivity reactions (73.7%), and psoriasis was the most common psoriasiform diagnosis (61.1%). Finally, in the panniculitis category erythema nodosum was the most common (35.3%), and in the granulomatous category hidradenitis suppurativa (36.4%) and granuloma annulare (18.2%) were the most common.

## 4 | DISCUSSION

Hospitalized patients with dermatologic manifestations are often critically ill, requiring prompt and accurate diagnosis and treatment for recovery without permanent morbidity or death. Close and effective communication between dermatologists and dermatopathologists is critical to successful dermatology hospital consultations.<sup>10,11</sup> Educational programs aimed at dermatologists and pathologists that focus on precise clinicopathologic correlation of complex dermatologic conditions seen in hospitalized patients may promote prompt and accurate diagnosis, as well as optimal inpatient dermatology care.<sup>12</sup>

Furthermore, knowledge about commonly biopsied diagnoses in hospitalized patients can help drive efficiencies related to increasing financial pressures.<sup>12</sup> As prolonged biopsy turnaround times inherently delay diagnosis and treatment initiation, advanced knowledge may improve this by increasing the chances appropriate lesions are biopsied and adequate clinical information is provided to knowledgeable pathologists/dermatopathologists. All of the above could translate into improved outcomes, decreased morbidity and mortality, decreased lengths of hospital stay, and decreased hospital readmissions. Such improvements could result in significant healthcare cost savings, as hospital readmissions occurring within 30 days of discharge from index stays for skin disease alone cost the American health care system \$1.05 billion in 2014.<sup>13</sup>

Here we provide a comprehensive review of skin biopsies performed on hospitalized patients evaluated by a dermatology HCON service at a large, tertiary-care academic center over a 3-year period. Many groups have reviewed dermatology hospital consultations at their institutions and have found value in dermatology input in terms of guiding accurate diagnoses and treatments. These studies typically confirm that biopsy is an important adjunctive test used by dermatology hospital services, and have been reportedly performed in approximately 18% to 40% of all consultations.<sup>6,14-16</sup> When cohorts of hospital consultations related to patients with specific dermatologic disorders or underlying systemic diseases are reviewed, biopsies have been reported in approximately 5% to 48%.<sup>2,4,17,18</sup> However, we were unable to identify a single study that explored the diagnoses of patients who specifically underwent a biopsy procedure. Thus, we believe our study reveals unique information concerning diagnoses that dermatologists most commonly feel necessitate biopsy for information to help guide/confirm diagnosis, and that both dermatologists and dermatopathologists should be specifically educated about in order to provide optimal care of hospitalized patients with cutaneous abnormalities.

Our results suggest that dermatologists and pathologists who provide care for hospitalized patients should be particularly knowledgeable about clinicopathologic findings of several disease classes. Of 914 biopsies collected by our dermatology HCON service, vasculopathic diseases represented the most common category (17.6%). Vasculopathic diseases mainly include vasculitides and vasculopathies, both of which include subtypes that can manifest life-threatening involvement. In fact, 4 of the 10 most common diagnoses

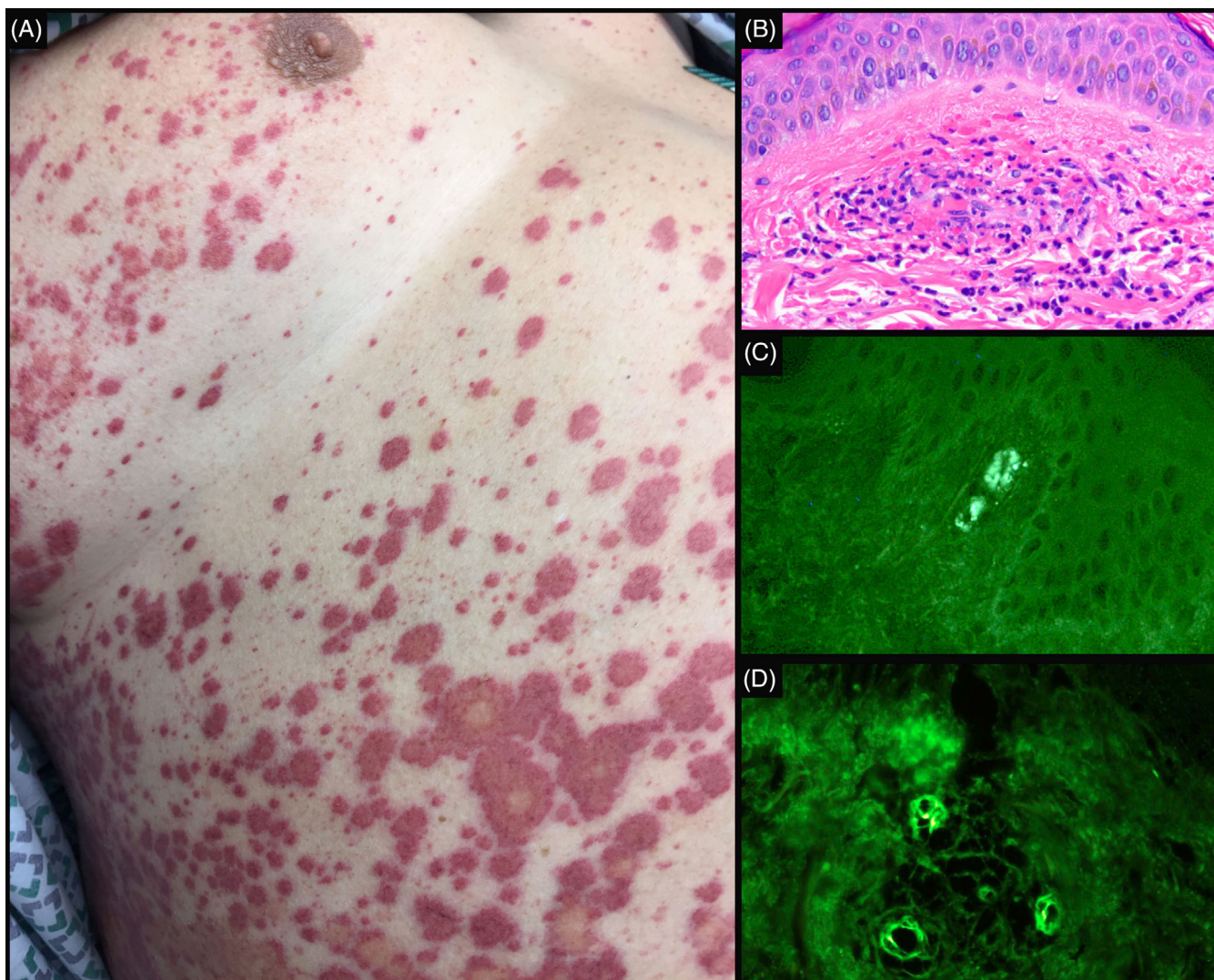
found in our cohort (LCV, calciphylaxis, noninflammatory purpura, thrombotic vasculopathy) reside within this histologic category. LCV and thrombotic vasculopathy can be further broken down into subtypes that may have differing optimal treatments, underscoring the importance of adequate knowledge concerning their distinguishing clinical and histopathologic features.

LCV may affect variably-sized vessels.<sup>19</sup> Small-vessel LCV is a relatively straightforward histologic diagnosis, but clinical and histologic details can help distinguish between subtypes. For example, IgA-mediated vasculitis often presents with palpable purpuric plaques and retiform purpura along lesion margins, and recognizing these clues can lead to consideration of this diagnosis.<sup>20</sup> Knowledge of these clinical details is also important because patients (especially adults) with IgA-mediated vasculitis may not present with the classic triad of purpura, abdominal pain, and nephritis.<sup>21</sup> Such knowledge can prompt additional biopsies of appropriately-aged lesions for DIF by clinicians, and pathologists must be knowledgeable about resulting DIF patterns to help solidify the diagnosis (Figure 1). Furthermore, establishing this diagnosis should lead educated clinicians to carefully monitor for renal involvement, which is particularly prevalent in adults.<sup>22</sup> Some studies suggest specific DIF patterns may be associated with an increased risk of underlying renal involvement, including perivascular IgM deposition or absence of perivascular fibrinogen.<sup>23,24</sup>

While classification systems for cutaneous vasculitides, such as the Chapel Hill Consensus Conference Criteria, are useful in delineating known vasculitides, many present with overlapping clinicopathologic features requiring expertise of both dermatologists and pathologists.<sup>25</sup> Common secondary LCV causes include infections, medications, CTD, and malignancy.<sup>26</sup> Although clinical lesions may be similar, histopathologic findings may help distinguish among etiologies. For example, drug-associated vasculitis may exhibit eosinophils within the inflammatory infiltrate, whereas eosinophils are typically rare-to-absent in CTD-related vasculitis.<sup>27</sup> Alternatively, biopsies of cutaneous vasculitis secondary to severe bacterial infections may commonly display tissue neutrophilia (neutrophils in the interstitial dermis).<sup>28</sup> While skin biopsy may not always confirm specific subtypes or etiology, findings also help distinguish LCV from mimickers like pigmented purpuric dermatoses.<sup>21</sup>

Other vasculopathic diagnoses frequently made were calciphylaxis and thrombotic vasculopathy. Calciphylaxis has a poor prognosis, with 1-year survival rates of approximately 50%.<sup>29</sup> Calciphylaxis generally presents with painful ulcers in patients with ESRD. However, it is important for dermatologists and dermatopathologists to recognize calciphylaxis patients may lack renal disease (nonuremic) and that calciphylaxis may present with livedo reticularis and/or indurated painful plaques without ulcers. Of 27 calciphylaxis cases we biopsied, 9 were nonuremic.

Histopathologic evidence remains the gold standard for calciphylaxis diagnosis, but findings distinguishing calciphylaxis from clinical mimickers requires knowledge by interpreting pathologists. For example, stippled extravascular calcification is seen significantly more often in calciphylaxis compared to mimics.<sup>30</sup> Additionally, calcification in smaller vessels has been found to more strongly correlate



**FIGURE 1** A, An adult patient with diffuse purpuric macules, papules, and small plaques. B, A lesional biopsy (200× magnification) reveals a perivascular infiltrate in and around small vessels with neutrophils, leukocytoclasia, endothelial wall damage, and intraluminal fibrin deposition consistent with leukocytoclastic vasculitis. An additional lesional biopsy for direct immunofluorescence revealed perivascular deposition of (C) IgA (200× magnification) and (D) complement C3 (200× magnification), consistent with IgA-mediated vasculitis

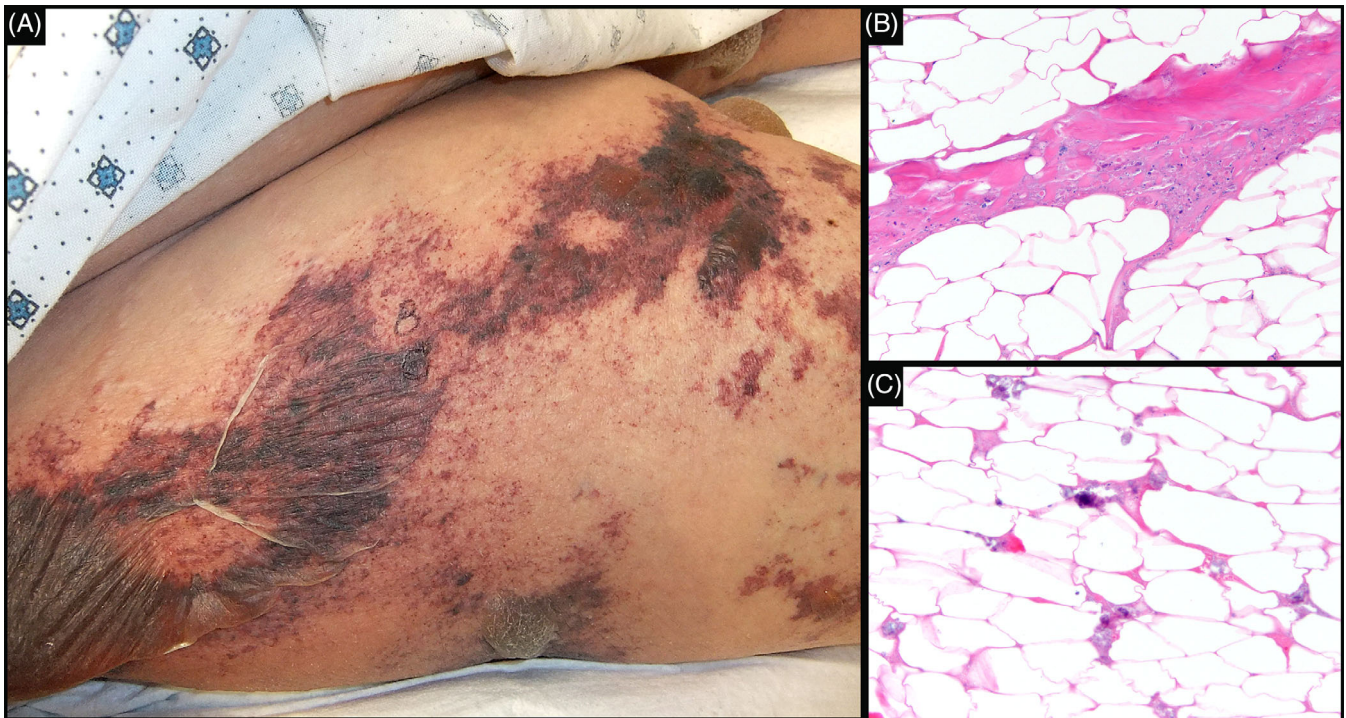
with a calciphylaxis diagnosis, with calcification of capillaries being most specific for calciphylaxis compared to clinical mimics (Figure 2).<sup>29</sup> Moreover, pathologists need to recognize that atherosclerotic calcification of distal vessels is a common incidental finding in patients with renal disease, diabetes, and peripheral vascular disease to avoid misdiagnosis/overdiagnosis as calciphylaxis.<sup>31</sup>

Thrombotic vasculopathy has various clinical manifestations and can lead to secondary infection, soft tissue destruction, and infarction of other organ systems.<sup>19</sup> Livedoid vasculopathy is a thrombotic vasculopathy that requires particular dermatologist/pathologist education to appropriately diagnose (Figure 3). Livedoid vasculopathy often occurs in young to middle-aged women with painful ulcerations, reticulate dyspigmentation and atrophic blanche on the lower extremities.<sup>32</sup> Importantly, abnormal serologic findings to aid in diagnosis are often absent. Histology reveals dermal vessels with intraluminal fibrin deposition. Studies have shown that DIF may be useful in diagnosis,

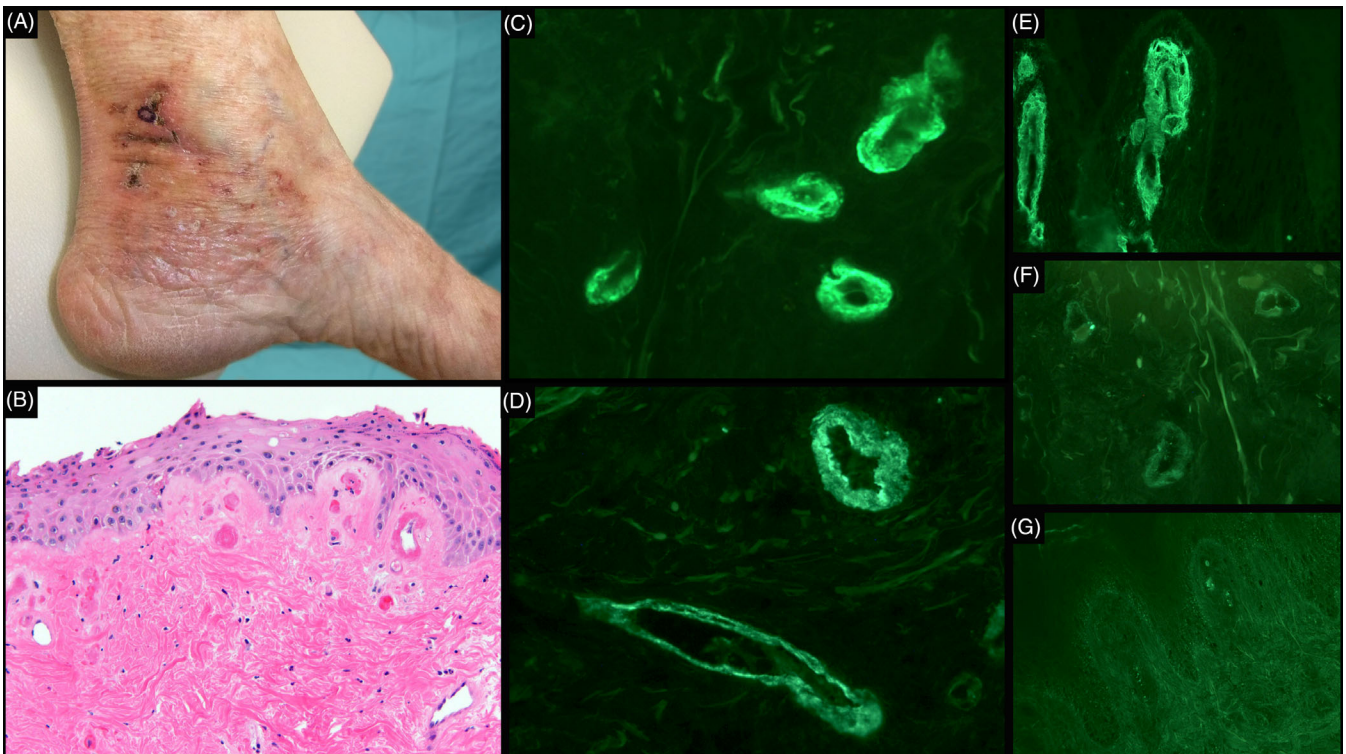
typically revealing strong IgM, C3, and fibrinogen perivascular staining without significant perivascular IgA or IgG.<sup>33</sup>

Interface dermatitis was the second most common category in our cohort. Three interface dermatitides ranked within the 10 most common diagnoses (drug reaction, GVHD, CTD). Adverse drug reaction was the single most common diagnosis in our cohort (13.2%). This diagnosis included numerous interface subtypes (morbilliform, erythema multiforme, SJS/TEN, lichenoid, toxic erythema of chemotherapy), as well as subtypes in other histologic categories (AGEP, DRESS, LABD, neutrophilic eccrine hidradenitis, symmetrical drug-related intertriginous and flexural exanthema). Of 121 drug reactions in our cohort, 45 (37.2%) were subtypes considered severe or potentially life-threatening.

SJS/TEN is arguably the most important drug reaction given high potential for mortality, and most dermatologists and pathologists are well-educated about findings in these patients (Figure 4). Several of

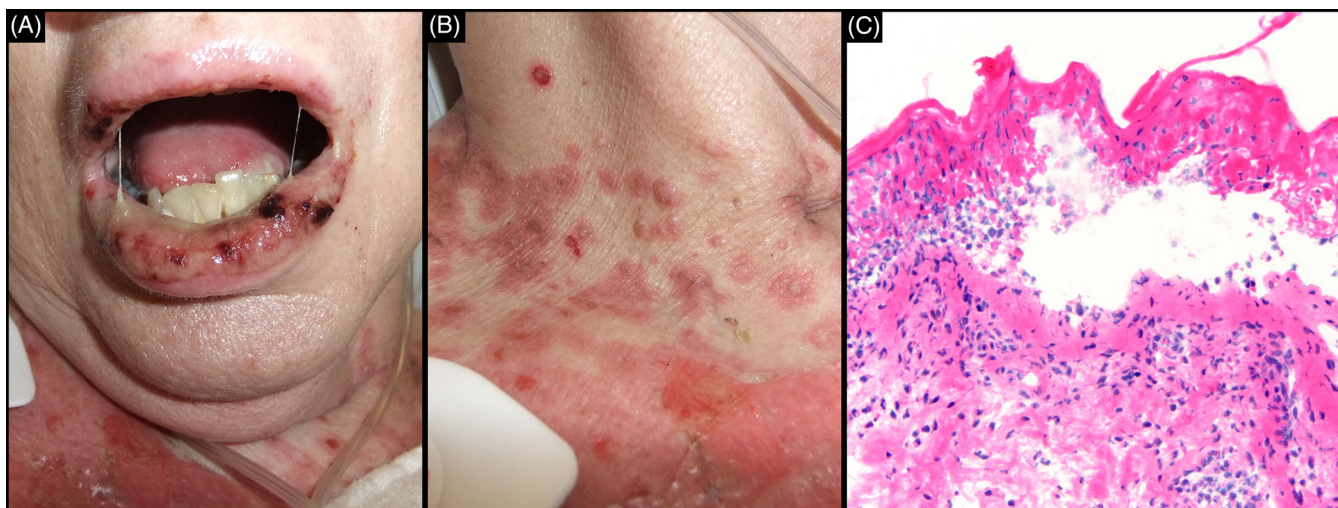


**FIGURE 2** A, A hospitalized patient with indurated, retiform purpura, and large bullae on her thigh. A lesional biopsy revealed (B) stippled calcification within subcutaneous septa (200 $\times$  magnification) and (C) calcific plugging of capillaries within the subcutis (200 $\times$  magnification), consistent with calciphylaxis

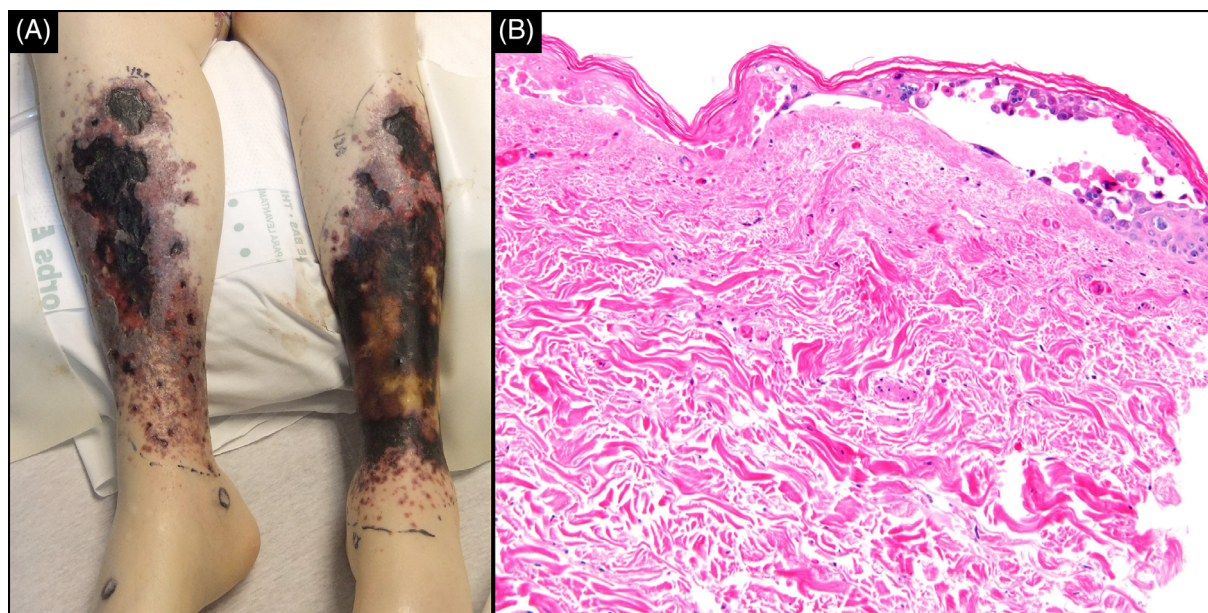


**FIGURE 3** A, A patient with small painful ulcers with surrounding retiform purpura and atrophic blanche involving the medial malleolar areas. B, A lesional biopsy (100 $\times$  magnification) reveals fibrin plugging of numerous vessels without significant inflammation. An additional lesional biopsy for direct immunofluorescence revealed thick, positive perivascular deposition of (C) IgM (200 $\times$  magnification), (D) complement C3 (200 $\times$  magnification), and (E) fibrinogen (100 $\times$  magnification). There was negligible deposition of (F) IgG (200 $\times$  magnification) and (G) IgA (100 $\times$  magnification). Clinicopathologic correlation was consistent with a diagnosis of livedoid vasculopathy





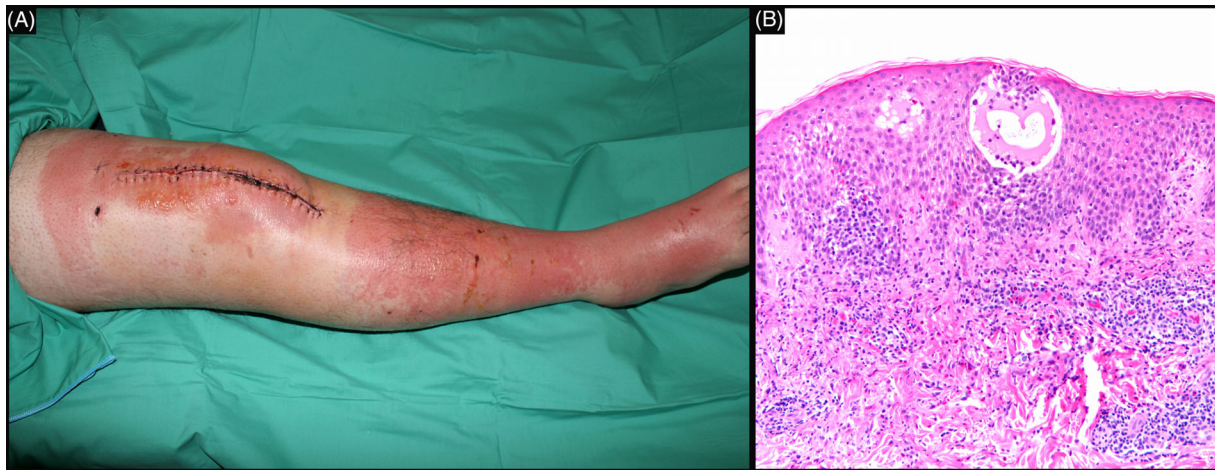
**FIGURE 4** A, A middle-aged woman with dermatomyositis who developed mucositis and (B) atypical targetoid lesions after initiation of IV antibiotics for an infection. C, A lesional biopsy for frozen section analysis (200× magnification) revealed full-thickness epidermal necrosis and a superficial dermal inflammatory infiltrate consistent with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)



**FIGURE 5** 76 year-old woman with rheumatoid arthritis treated with methotrexate, hydroxychloroquine, prednisone, and rituximab who developed a progressive rash. Biopsy at an outside hospital was interpreted as rheumatoid vasculitis and she was treated with intravenous cyclophosphamide and prednisolone. This resulted in worsening of the rash, revealing (A) necrotic ulcerations with peripheral smaller erosions, in addition to increased weakness, diarrhea, and inability to ambulate. Upon transfer to our hospital and examination by our hospital consultation (HCON) team, re-biopsy revealed (B) viral cytopathic changes (100× magnification) leading to diagnosis of disseminated herpes zoster. She improved with IV acyclovir and taper of prednisone

our patients with DRESS, however, were previously seen by outside dermatologists and treated with glucocorticoids, but then readmitted to our hospital due to recurrence because glucocorticoids were too quickly tapered. Thus, inadequate knowledge of DRESS has potential for unnecessary end-organ damage and unnecessary health-care costs. Alternatively, it is important to know when drug reactions are not serious and inciting medications, which are often important for optimal care, can be continued.

Cutaneous infections represent a large portion of inpatient dermatology and were the third most common category in our cohort (12.6%). Diagnosis is typically established utilizing a combination of clinical findings, skin biopsy, and tissue culture. Low threshold for suspicion of cutaneous infection by dermatologists and pathologists is important in hospitalized patients. Infections become increasingly challenging to diagnose in immunocompromised patients with atypical clinical findings (Figure 5).



**FIGURE 6** A, A middle-aged man who developed an erythematous rash surrounding his surgical incision site and lower leg following total knee arthroplasty surgery. The surgical team consulted our dermatology hospital consultation (HCON) service due to concern for cellulitis. Our HCON service was suspicious for allergic contact dermatitis (note the sharp demarcation of the erythema, which corresponded to areas underlying adhesive bandages). B, A lesional biopsy (100× magnification) revealed spongiotic dermatitis with intraepidermal Langerhans cell microabscesses and a dense superficial dermal inflammatory infiltrate with eosinophils, consistent with allergic contact dermatitis as opposed to cellulitis

Spongiotic dermatitis accounted for 10.9% of biopsies in our cohort. Most diagnoses in this category were non-specific, stressing the importance of improving clinicopathologic correlation to arrive at definitive diagnoses. When specific diagnoses were made, allergic/irritant contact dermatitis (ACD/ICD) was the most common. Accurately identifying ACD can ensure important procedures (including surgeries) or treatments (chemotherapy, etc.) are not delayed by other medical/surgical teams. Histologic clues to ACD include presence of Langerhans cell microabscesses, but not necessarily eosinophils, making pathologist interpretation/expertise important (Figure 6).<sup>34</sup> Other common diagnoses seen in our cohort require similar attention to detail by both dermatologists and pathologists.

Strengths of our study include a large population of biopsied hospitalized patients over a 3-year interval, and definitive diagnosis in the vast majority of cases. Limitations include the retrospective study design and potential variability in threshold for biopsy by staff rotating on our HCON service. Additionally, we are not certain all patients truly required biopsy for accurate diagnosis. Occasionally we perform biopsies to ensure that we have objective data that will drive compliance with our recommendations by other medical/surgical teams. Furthermore, because biopsies were collected at a tertiary care center that is a major international referral site, data may not be generalizable to all hospital systems.

## 5 | CONCLUSIONS

Our study suggests that a wide variety of serious diseases are biopsied in hospitalized inpatients. To optimize dermatology inpatient care, it would be valuable for dermatologists and pathologists/dermatopathologists to be knowledgeable about the detailed clinicopathologic features of specific diseases within vasculopathic, interface dermatitis, infectious and spongiotic dermatitis categories based on

our results. These data may be valuable for developing educational curricula for dermatology and pathology residents/fellows, and for practicing dermatologists and pathologists/dermatopathologists who care for hospitalized patients. With heightened expertise in these histopathologic (reaction) patterns coupled with greater knowledge of clinical findings, accurate diagnosis, management, and outcomes of hospitalized patients with cutaneous manifestations may be optimized.

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## CONFLICT OF INTEREST

The authors have no relevant conflicts of interest to disclose concerning this manuscript.

## AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of this manuscript.

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