Dermatologic Urgencies and Emergencies
What Every Pathologist Should Know

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Context.—Fatal dermatologic diseases and ones with high morbidity can occur in the inpatient setting. In such cases, prompt and accurate assessment of a bedside skin biopsy is required. This may be challenging for many pathologists who are not familiar with the complexity of skin pathology and skin terminology within the fields of dermatopathology and dermatology.

Objective.—To provide the pathologist with a practical, up-to-date, and “must-know” reference guide on dermatologic urgencies and emergencies from a real-world perspective, highlighting diagnostic pearls, diagnostic pitfalls, and commonly encountered practice gaps. This review will focus on key diseases with which every pathologist should be familiar, including angioinvasive fungal infections, Stevens-Johnson syndrome/toxic epidermal necrolysis, staphylococcal scalded-skin syndrome, acute graft-versus-host disease, bullous pemphigoid, calciphylaxis, Sweet syndrome and its histiocytoid variant, pyoderma gangrenosum, and leukocytoclastic vasculitis, as well as those in their clinical and histopathologic differential.

Data Sources.—This review is based on peer-reviewed literature and our personal experiences with these diseases at major academic institutions, including one where a large number of hematopoietic stem cell transplants are performed. This review is unique as it represents collaborative expert opinion from both a dermatopathology and a dermatology standpoint.

Conclusions.—This review outlines the critical role that the pathologist plays in the outcomes of patients with dermatologic urgencies and emergencies. Improved patient care will result from prompt and accurate histopathologic diagnoses as well as an open line of communication with the dermatologist.


Inpatient dermatologic diseases are quite different from those in the outpatient setting. In the inpatient setting, life-threatening diseases can occur. Because skin manifestations may be the presenting sign of systemic disease and as the skin is readily accessible to bedside procedures, skin biopsy serves as a primary diagnostic tool that guides immediate treatment decisions and, ultimately, patient outcomes. Thus, the pathologist’s prompt and accurate assessment of the inpatient skin biopsy can have life-or-death consequences. Given that dermatology is commonly viewed as an outpatient field, increased awareness of the seriousness of these diseases and the pathologist’s role is needed. Even with increased awareness, many practicing pathologists may not be familiar with the complexity of skin pathology or how to approach an urgent skin biopsy in a timely manner. Further, differences in terminology and lack of communication between dermatologists and pathologists create detrimental practice gaps. Thus, an all-encompassing educational and practical resource geared toward the nondermatopathologist is needed. Here we have performed an up-to-date literature review, intertwined with our own expert opinion, in order to create a practical, must-know, and what-not-to-miss pathology reference guide for some of the most commonly encountered dermatologic urgencies and emergencies, namely angioinvasive fungal infections, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), staphylococcal scalded-skin syndrome (SSSS), acute graft-versus-host disease (aGVHD), bullous pemphigoid (BP), calciphylaxis, Sweet syndrome and its histiocytoid variant, pyoderma gangrenosum (PG), and leukocytoclastic vasculitis (LCV). For each of these diseases we have outlined key diagnostic pearls and pitfalls whose application can be used in an array of clinical scenarios. This review is the collaborative effort of dermatologists and dermatopathologists, all from major academic centers, including one where a large number of hematopoietic stem cell transplants (HSCTs) are performed.

ANGIOINVASIVE FUNGAL INFECTIONS

High-yield points for angioinvasive fungal infections include the following:

1. Rapidly progressive in immunosuppressed or trauma patients with high mortality.
2. Hematoxylin-eosin (H&E) reveals fungal hyphae in the dermis and/or vessels +/- epidermal and/or dermal necrosis.

3. Periodic acid–Schiff (PAS) or Gomori methenamine silver (GMS) is performed in all suspicious cases.

4. Speciation cannot be performed based on histopathology alone.

Angioinvasive fungal infections are true dermatologic emergencies because of their very high morbidity and mortality. They are considered opportunistic pathogens as they cause infection almost exclusively in the immunosuppressed. The classic patient is one with profound neutropenia status post HSCT. Other common risk factors include neutropenia secondary to chemotherapy, systemic immunosuppression (eg, high-dose steroids), diabetic ketoacidosis, and major trauma (eg, motor vehicle accident, natural disaster), with the latter being now recognized as the leading cause of angioinvasive fungal infections in previously healthy trauma patients. These filamentous molds are ubiquitous in the environment and cause skin infection via direct inoculation (eg, intravenous catheter site, soil contamination of trauma wound) or hematogenous spread from the lungs or other foci of infection. Skin lesions are manifestations of blood vessel invasion and tissue necrosis, ranging from small eschars to large, dusky purple plaques, sometimes with bulla formation (Figure 1). Because of the increased number of HSCTs and prolonged survival of these patients posttransplant, the incidence of angioinvasive fungal infections has exponentially increased over the years. Unfortunately, delayed and inaccurate diagnoses are major causes of mortality, and it is imperative for dermatologists and pathologists to close this practice gap.

Angioinvasive fungi are classically separated into septate versus nonseptate molds. The list of species is broad, but prototype septate molds include *Aspergillus*, *Fusarium*, and *Scedosporium*, whereas the prototype nonseptate species are those of the class *Mucormycetes* (previously *Zygomycetes*), with the most common human pathogens being *Rhizopus* spp, *Absidia* (*Lichtheimia*) spp, and *Mucor* spp. *Aspergillus* is known for its thin, septate hyphae with acute-angle branching, whereas the *Mucormycetes* are known for their more bulbous, ribbonlike, asceptate hyphae with wide-angle branching. In our experience, biopsies performed in the center of the lesion have the highest yield for hyphae. Biopsies should be performed down to the subcutaneous fat and submitted for both histopathology and fungal tissue culture. The specimen should be rushed and the pathologist should be called. Microbial tissue is to be chopped, not wiped-out, to preserve the hyphae, which can be difficult to culture. In our experience, multiple biopsies for tissue culture increase the chance of positive growth. On histopathology, hyphae are seen in the dermis and/or blood vessels, usually with associated tissue necrosis. In the setting of severe immunosuppression, the appearance on low magnification is often that of a pink, amorphous, “wiped-out” dermis because of the combination of dermal necrosis and hemorrhage without any associated inflammatory response (Figure 2, A). The appearance can be very similar to that seen in severe forms of coagulopathy, such as disseminated intravascular coagulopathy. Careful examination, with particular focus on the areas of hemorrhage and/or thrombosed vessels, is essential when this scenario is encountered to ensure that fungal hyphae are not overlooked. Hyphae are often visible on routine H&E, but special stains, such as GMS or PAS, can be used to confirm the diagnosis when fungi cannot be visualized on H&E (Figure 2, B and C). If hyphae are not visible on H&E, we recommend performing additional microbial stains (eg, Gram and acid-fast stains) to rule out other infectious etiologies. As a practical observation, Gram stain can also highlight *Mucormycetes*. Some fungi, like *Fusarium* and *Acremonium*, may produce both yeasts and hyphal forms in tissue (Figure 2, C and D). Use of polymerase chain reaction–based assays for identification of mold species is growing, but is only available in specialized centers and thus has a relatively long turnaround time. We have sent tissue for polymerase chain reaction identification in cases where fungal cultures were negative and identification of the species was desired for academic purposes. Repeat tissue cultures are often not possible because of rapid fatality. Of note, because of lack of sensitivity for these molds, blood cultures are usually negative, except in cases of disseminated fusariosis.

Treatment includes systemic antifungals in combination with surgical debridement or even amputation in some cases. Despite treatment, mortality rates are exceedingly high, up to 87% in HSCT patients with invasive aspergillosis, 96% in patients with disseminated mucormycosis, and essentially 100% in HSCT patients with prolonged neutropenia and disseminated fusariosis.

Because angioinvasive fungal infections are true emergencies, pathologists are often asked to classify, or make their best guess, as to whether the examined angioinvasive hyphae are septate or nonseptate. The significance of this delineation lies in the choice of empiric antifungal therapy. For example, first-line treatment for *Mucormycetes* is liposomal amphotericin B, as these organisms are resistant to voriconazole, the first-line treatment for *Aspergillus*. Histologic mimickers of *Aspergillus*, are relatively resistant to all antifungals and often require aggressive combination therapy. Choice of empiric therapy is multifactorial and takes into account various factors such as local fungal epidemiologic patterns and susceptibility profiles as well as prior history of antifungal use.

However, pathologists should also be aware of limitations in the ability to accurately identify fungal species in tissue...
Another well-described diagnostic problem occurs with the misdiagnosis of Aspergillus. Although Aspergillus is the most common pathogen, in cases in which a septate organism is strongly favored, it is important to include other morphologically similar fungi in the comment (eg, Fusarium, Scedosporium) in order to avoid inappropriate pharmacotherapy. Thus, the best approach is to give a 1-line diagnosis of “angioinvasive fungal infection” followed by a histologic description, with instructions to correlate with microbial cultures for speciation in the comment. Despite the inherent pitfalls in characterizing fungal species on histopathology alone, the pathologist’s role in these cases cannot be underestimated. The prompt institution of empiric antifungals, which are critical for any chance at survival, is often tailored by the pathologist’s best assessment of the fungal morphology while awaiting culture results.

STEVEN’S-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

High-yield points for SJS and TEN include the following:

1. Life-threatening skin disorder with full-thickness epidermal sloughing of the skin and mucous membranes.
2. First step in treatment is immediate identification and withdrawal of causative drug.
4. Differentiated from SSSS both clinically and histologically because of the more superficial level of blistering in SSSS.

Stevens-Johnson syndrome and TEN exist on a disease spectrum with SJS representing body surface area involvement less than 10%, TEN representing body surface area greater than 30%, and involvement 10% to 30% best classified as SJS/TEN overlap. For simplicity, we will refer to diseases within this spectrum broadly as SJS/TEN. It is a life-threatening disorder characterized by widespread epidermal detachment and prominent mucous membrane involvement. As a rule, involvement of the lips and oral mucosa is present. Initially, the skin often appears erythematous and dusky with atypical targetoid lesions predominate in EM, in comparison with the dusky patches and atypical targetoid lesions seen in early SJS/TEN. Although mucous membrane involvement may be seen in more severe cases of EM, epidermal detachment is not a feature, and patients have a favorable prognosis. Recently, a new disorder named M pneumoniae–induced rash and mucositis has been described, and is best considered a variant of EM with greater oral mucosal involvement and less cutaneous involvement. It is important for pathologists to remember that EM can show areas of full-thickness epidermal necrosis (particularly in bullous lesions) and that SJS/TEN can lack full-thickness necrosis (particularly in early lesions or in skin at the leading edge of involvement). Full-thickness necrosis does not allow distinction among EM, SJS, and TEN. In our opinion, there is no reliable definitive way to distinguish among these 3 entities on histology alone.

Staphylococcal scalded-skin syndrome can be on the differential diagnosis for SJS/TEN, especially in the pediatric population, as SSSS is frequently seen in children as well as nonsteroidal anti-inflammatory drugs, cephalosporins, amnopenicillins, and quinolones. Mortality is reported to be as high as 30%, but varies greatly depending on the degree of body surface area involvement, age of the patient, heart rate, presence or absence of underlying malignancy, and laboratory values, which include blood urea nitrogen, glucose, and bicarbonate. These factors have been compiled into a scoring system that has been validated as a mortality predictor in SJS/TEN, called the severity-of-illness score for TEN (often abbreviated as SCORTEN). In addition to affecting the skin and oral mucosa, SJS/TEN can have involvement of ocular, gastrointestinal, genitourinary, and respiratory mucosa, leading to serious long-term sequelae of corneal scarring, esophageal stricture, genital adhesions, and chronic bronchitis, respectively. In the short term, the gravest manifestations of SJS/TEN are gastrointestinal bleeding, pulmonary embolism, myocardial infarction, pulmonary edema, and sepsis with multi-organ failure. The most important initial step in management is identification and discontinuation of all possible offending drugs. Many patients require prompt transfer to the burn unit. Beyond medication withdrawal and supportive care, numerous treatment modalities have been tried with mixed results, leading many institutions to not pursue adjunctive therapy. The most commonly used adjunctive therapies include systemic corticosteroids, intravenous immunoglobulin, cyclosporine, and tumor necrosis factor inhibitors. More recently, cyclosporine has been found to have mortality benefit over other systemic treatments in meta-analyses.

Features of SJS/TEN in its early stage include basal layer liquefaction (vacuolar interface change), scattered necrotic keratinocytes, and interface lymphocytes, which can be identical to EM (or other interface dermatoses) histologically, requiring clinical differentiation (Figure 3, E). In more developed cases, a subepidermal split with full-thickness necrosis of the epidermis and a sparse underlying lymphocytic inflammatory infiltrate is seen (Figure 3, F). There has been some diagnostic confusion in the past regarding the relationship of EM and SJS/TEN, but today most agree that the 2 are distinct entities despite their very similar, if not identical, histologic features. In contrast to SJS/TEN, EM is seen mostly in children, and infectious causes, such as herpes simplex and Mycoplasma pneumoniae, represent the most likely precipitating factors. Clinically, ringed targetoid lesions predominate in EM, in comparison with the dusky patches and atypical targetoid lesions seen in early SJS/TEN. Although mucous membrane involvement may be seen in more severe cases of EM, epidermal detachment is not a feature, and patients have a favorable prognosis. Recently, a new disorder named M pneumoniae–induced rash and mucositis has been described, and is best considered a variant of EM with greater oral mucosal involvement and less cutaneous involvement. It is important for pathologists to remember that EM can show areas of full-thickness epidermal necrosis (particularly in bullous lesions) and that SJS/TEN can lack full-thickness necrosis (particularly in early lesions or in skin at the leading edge of involvement). Full-thickness necrosis does not allow distinction among EM, SJS, and TEN. In our opinion, there is no reliable definitive way to distinguish among these 3 entities on histology alone.
Figure 2. Angioinvasive fungal infections. A, Fungal hyphae seen throughout the dermis with associated tissue ischemia and necrosis, giving the dermis a "wiped-out" appearance, in a patient with Aspergillus. Note that definitive vascular invasion was not evident on this section. B, Periodic acid–Schiff (PAS) confirms numerous hyphae within a large dermal vessel in a patient with Mucormycetes. C and D, Gomori methenamine silver (C) and PAS (D) highlight both hyphal and yeastlike forms in a patient with Fusarium. E and F, These hyphae have the ribbonlike, nonseptate appearance that is classic for Mucor, Rhizopus, or related species, yet this fungus was actually Aspergillus niger by microbial culture. Culture or molecular analysis is required for accurate species identification of fungal hyphal infections; the species cannot be reliably identified via microscopic
adults with renal failure.\textsuperscript{14} Staphylococcal scalded-skin syndrome results from skin cleavage by exfoliative toxins that are produced by \textit{Staphylococcus aureus} of a distant source; thus, the causal bacteria are not seen on routine histology unless there is secondary skin infection, which is not uncommon in any patient with open erosions and chronic \textit{S aureus} colonization.\textsuperscript{15} Both SJS/TEN and SSSS have a positive Nikolsky sign, wherein application of lateral pressure leads to shedding of the epidermis from the dermis.\textsuperscript{10,16} Clinical features of SSSS include lack of mucosal involvement, predilection for the skin folds, and perioral edema and dependency. Further, morbilliform drug eruptions can sometimes be in the clinical differential diagnosis for SJS/TEN. Notably, mucous membrane involvement is rare in aGVHD and absent in morbilliform drug eruptions, and morbilliform drug eruptions do not progress to widespread sloughing.\textsuperscript{9} In reality, however, the clinical distinction can be quite challenging in cases of aGVHD with epithelial detachment or in severe cases of morbilliform drug eruption that demonstrate widespread involvement, sometimes with development of bullae in areas of inflammatory edema and dependency. Further, morbilliform drug eruptions share common drug culprits with those of SJS/TEN, and patients with aGVHD often have a complex medication history. The pathologist should be aware that SJS/TEN and EM. However, if the clinical picture is unclear or consistent with SJS/TEN and the patient has been exposed to a known culprit medication, we do not routinely perform a second punch biopsy for DIF, as DIF is negative in SJS/TEN and EM. However, if the clinical picture is unclear or there is sufficient concern for an autoimmune blistering disorder, an additional punch biopsy for DIF can easily be obtained from perilesional skin.\textsuperscript{14}

Despite the urgent need for rapid diagnosis, we do not routinely use frozen section histology for diagnosis, as it has a high sensitivity but a low specificity.\textsuperscript{19} We find that overnight processing or rush (4-hour) processing of specimens does not significantly delay patient care and provides more robust histologic images for accurate diagnosis as compared with frozen sections. For cases consistent with SJS/TEN, we provide a 1-line diagnosis of “vaccular interface dermatitis” accompanied by a thorough histologic description and comment that SJS and TEN are on a spectrum that is differentiated on a clinical basis and that other interface dermatoses, including \textit{aGVHD} and EM, would have similar histologic features (comment varies depending on the clinical scenario and clinical differential diagnosis).

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\textit{examination of tissue sections (hematoxylin-eosin, original magnification \times 400 [A]; original magnifications \times 200 [B and C] and \times 400 [D]; PAS, original magnification \times 200 [E and F]).}
Figure 3. Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). A and B, Extensive hemorrhagic erosions and crusting of the lips and oral mucosa were seen on presentation in both this adult and this pediatric patient with SJS/TEN. C and D, Widespread erythema and dusky macules give rise to areas of epidermal separation and fragile bullae in a case of early TEN prior to skin sloughing. (Photos C and D are courtesy of Matthew Clark, MD, Saint Louis University, St Louis, Missouri.) E, Vacuolar interface alteration with dying keratinocytes should always be present in SJS/TEN provided there is some viable intact epidermis present in the biopsy to examine. F, The degree of epidermal necrosis can vary greatly in SJS/TEN depending on the area biopsied and when the biopsy is taken; E shows interface alteration but only superficial epidermal necrosis whereas F shows full-thickness necrosis with epidermal detachment (hematoxylin-eosin, original magnifications ×400 [E] and ×100 [F]).
ACUTE GRAFT-VERSUS-HOST DISEASE

High-yield points for aGVHD include the following:

1. Nonspecific morbilliform eruption in HSCT patients.
2. Hematoxylin-eosin reveals vacuolar interface dermatitis.
3. In early stages it can be histologically indistinguishable from other common rashes like viral exanthems or drug eruptions in the posttransplant period.

Acute graft-versus-host disease is a complex immune-mediated multisystem disorder involving the skin, liver, and gastrointestinal tract that develops as a serious complication of allogeneic HSCT. Historically separated from chronic graft-versus-host disease by its onset within 100 days posttransplant, aGVHD is now defined by the combination of rash, gastrointestinal and/or liver dysfunction, and the absence of distinctive features of chronic graft-versus-host disease, regardless of time of presentation. A widespread morbilliform eruption is characteristic (Figure 5, A). The skin is usually the first manifestation of aGVHD and precedes liver and gastrointestinal involvement, which is why the dermatologist is asked to perform a skin biopsy for early diagnosis. Because of the growing number of HSCTs, pathologists need to be well versed in the diagnosis of aGVHD and its implications.

Advanced cases of aGVHD are relatively easy to recognize both clinically and histologically. This is not the case for early disease, when most dermatologic consultations occur. In the authors’ opinion, a definitive clinical diagnosis or exclusion of aGVHD is not possible in the majority of cases with morbilliform rash without evidence of other organ involvement. This is because there is significant clinical and histologic overlap between aGVHD and other common rashes that occur status post HSCT, namely viral exanthems, drug eruptions, and eruption of lymphocyte recovery. Each can be clinically indistinguishable in an immunocompromised patient with recovering lymphocyte counts and history of exposure to numerous antibiotics, drugs, and combination chemotherapy. Well-described histologic features include interface dermatitis, basal vacuolization, dyskeratotic keratinocytes, and a generally sparse superficial perivascula

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Figure 4. Staphylococcal scalded-skin syndrome (SSSS). A, Perioral crusting/fissuring and involvement of the folds of the neck are predominant features. This patient also had shallow erosions on the forehead (inset). B, The superficial nature of the split in SSSS (in comparison with Stevens-Johnson syndrome) is evidenced by the superficial, subcorneal erosions. Note how the erosions show a strong predilection for the skin folds as well as sites of local trauma. C, Blister formation is due to a split at the level of the stratum granulosum, which causes the stratum corneum to detach from the rest of the epidermis. There is no inflammation and no bacteria are seen (this is a toxin-mediated process). D, In some cases, the stratum corneum entirely detaches and may either be lost during processing or found elsewhere on the slide. E, The result is a relatively normal-looking epidermis at
Immunofluorescent studies are not indicated. In cases where histology could be consistent with a diagnosis of early or low-grade aGVHD, we recommend a 1-line diagnosis of “vacuolar interface dermatitis” followed by a thorough histologic description and comment noting that findings could be consistent with early aGVHD, but that other common rashes in the posttransplant period like viral exanthem and drug eruption can have identical histologic findings and thus clinical correlation is essential. In cases that do not show obvious features of aGVHD, we recommend describing any other inflammatory pattern that may be present (eg, spongiform dermatitis, perivascular inflammation without epidermal changes), as well as making particular note of the absence of vacuolar interface change or dying/apoptotic/dyskeratotic keratinocytes. Trusted dermatologic assessment, knowledge of relevant laboratory studies (such as liver tests or other organ biopsies), and medication history may allow pathologists to be somewhat more or less suspicious of the likelihood of aGVHD in their reporting. Thus, alternatively, based on known clinical parameters coupled with history, a tiered approach to diagnosis may be reasonable.

**BULLOUS PEMPHIGOID**

High-yield points for BP include the following:

1. Subepidermal blistering disease most commonly seen in the elderly.
2. Characterized by tense bullae clinically, which correlate to cleavage along the basement membrane zone histologically.
3. Definitive diagnosis is made by immunofluorescence studies.

Bullous pemphigoid is the prototypical subepidermal bullous dermatosis and is classically characterized by the development of widespread inflammatory bullae. Although several clinical variants have been described, the classic bullous form is by far the most common presentation encountered in the inpatient setting. Generally considered a disease of the elderly, BP is only rarely diagnosed before the age of 60, and carries significant morbidity and mortality, with the 1-year mortality rate reported as high as 40%. Two well-recognized exceptions have been observed that do not follow the classic epidemiologic pattern: BP in the setting of pregnancy (termed pemphigoid gestationis) and BP precipitated by medications (drug-induced BP). These variants generally resolve after parturition or withdrawal of the offending agent, respectively.

The pathogenesis of BP has been well characterized and is mediated by the development of autoantibodies targeting structural components of the hemidesmosome, a multicomponent adhesion complex found along the dermal-epidermal junction (DEJ). The pathogenic targets are BP antigen 180 (BP180/BPAG2/collagen type XVII) and BP antigen 230 (BP230/BPAG1). Once formed, these autoantibodies (predominantly IgG1 and IgG4) are deposited along the DEJ and initiate a cascade of events, most importantly involving complement activation and inflammatory cell recruitment. This results in subepidermal cleavage along the DEJ, clinically manifesting as the hallmark tense bullae seen on clinical examination.

As previously stated, the classic clinical presentation is typified by a widespread eruption of intact, tense bullae on an erythematous base, often accompanied by eczematous or urticarial lesions and intense pruritus (Figure 6, A and B). Lesions tend to favor the distal extremities, lower trunk, and intertriginous regions. Mucous membrane involvement is uncommon, and when present is usually not a major feature. A significant portion of patients may present with only widespread urticarial or eczematous lesions, further complicating clinical identification. Of note, several very rare clinical variants have been described, but they are beyond the scope of this review.

In the acute setting, the clinical differential diagnosis for widespread blistering diseases can be quite extensive, and given the spectrum of dermatologic emergencies that can present with widespread blisters, prompt evaluation is imperative and correct diagnosis is essential. Other subepidermal autoimmune bullous diseases (including epidermolysis bullosa acquisita [EBA], linear IgA bullous dermatosis, dermatitis herpetiformis, and bullous systemic lupus erythematosus [SLE]) can occasionally be more difficult to differentiate clinically, but proper pathologic evaluation generally allows for correct diagnosis based on a combination of H&E and DIF findings. An important entity requiring prompt exclusion is the SJS/TEN spectrum, which is generally differentiated clinically based on the presence of prominent mucous membrane involvement, predominance of targetoid lesions, flaccid (rather than tense) blisters that easily rupture, epidermal detachment, and erosions (Figure 3, A through D), as well as distinct pathologic features (Figure 3, E and F). Other entities that should be considered include bullous drug eruptions (particularly bullous fixed drug eruption), bullous cellulitis, bullous cutaneous small vessel vasculitis, and bullous arthropod bite reactions. Again, these can usually be ruled out with thorough history, careful clinical examination, and pathologic evaluation.

Histopathology should be performed on a fresh (24-48 hours old), intact blister, either by shave biopsy if the entire lesion can be included, or by a 3- to 4-mm punch biopsy at the edge. Hematoxylin-eosin classically reveals a dense, mixed inflammatory infiltrate predominated by eosinophils, but also with lymphocytes and neutrophils, with overlying subepidermal cleavage along the DEJ (Figure 6, C and D). The blister cavity of BP is often filled with eosinophils, fibrin strands, and serum, and the underlying papillary dermis can demonstrate marked edema. Although eosinophils are usually prominent, some cases may be rich in neutrophils. Conversely, some cases of BP have minimal inflammation (“cell-poor” BP) and histologically resemble EBA. Of note, older blisters may show degeneration (resembling dyskeratosis) of the blister roof due to prolonged ischemia, but this is not a prominent feature. Although these findings are characteristic of BP, diagnosis must be made in conjunction with the clinical picture and DIF studies, as H&E alone cannot reliably differentiate BP from other subepidermal blistering disorders. Thus, H&E is primarily used to identify...
Figure 5. Acute graft-versus-host disease (aGVHD). A, Characteristic morbilliform eruption of the trunk in a patient with aGVHD. B, Erythema, bullae, and epidermal detachment is a relatively rare and severe manifestation of aGVHD and would have high-grade histologic features. (Photos A and B are courtesy of Andrew Johnson, MD, Summit Dermatology, Colorado Springs, Colorado.) C, Early aGVHD with a pauci-inflammatory dermis, basal vacuolization, and few necrotic keratinocytes. D, Acute graft-versus-host disease with basal vacuolization, necrotic keratinocytes, and lymphocytes with prominent exocytosis into the epidermis. E, Higher-power image demonstrating prominent basal vacuolization. Note the interface
the site of cleavage, to characterize the inflammatory infiltrate, and to determine if any other relevant findings are present that would point toward a different disease process (eg, interface alteration with dying keratinocytes). Of note, histology in early urticarial lesions (which are typically seen in the outpatient setting) may lack blister formation and have less characteristic H&E findings, limited to eosinophilic spongiosis with a less pronounced dermal infiltrate and/or with eosinophils lining up along the dermal side of the DEJ. Also, the dermal inflammatory infiltrate in urticarial BP is usually limited to the superficial dermis without involvement of the deep dermis, which can be a useful clue in distinguishing BP from arthropod bite reactions and other urticarial dermatoses. Stevens-Johnson syndrome/TEN can be readily differentiated histologically by the presence of interface alteration with prominent dying keratinocytes that often result in confluent, full-thickness epidermal necrosis. Additionally, SJS/TEN typically has relatively sparse dermal inflammation (Figure 3, E and F). Of note, PV falls into the pemphigus family of diseases (separate from pemphigoid), which is outside the scope of this review. Pemphigus vulgaris and BP are clinically and

lymphocytes at the dermal-epidermal junction and resultant hydropic degeneration of the basal keratinocytes, which are becoming vacuolated and disorganized. F, More advanced aGVHD with additional feature of subepidermal clefting. G, Severe aGVHD with diffuse subepidermal clefting leading to dermoepidermal separation and blister formation. H, High-power image demonstrating prominent satellite cell necrosis (epidermal lymphocytes adjacent to necrotic keratinocyte), a classic feature of aGVHD. Note the randomly enlarged atypical keratinocytes; this is epidermal dysmaturation due to chemotherapy effect. I, Prominent lymphocyte exocytosis seen in a case of aGVHD with hair follicle involvement (hematoxylin-eosin, original magnifications ×200 [C, G, and I], ×400 [D, E, and F], and ×600 [H]).
histologically distinct. Pemphigus is more commonly seen in a younger adult population, with an age peak between the fourth and sixth decades of life.\textsuperscript{31} In comparison with the tense bullae of BP, the blisters of PV are very flaccid, and patients commonly present with erosions and crusting due to the blisters having already ruptured. Further, in PV, mucous membrane involvement is a key feature. Histologically, PV is characterized by intraepidermal acantholysis resulting in a tombstone pattern of retained basal layer keratinocytes adherent to the floor of the blister. Direct immunofluorescence of PV demonstrates intercellular (net-like) deposits.\textsuperscript{32}

Immunofluorescence microscopy is used for definitive diagnosis in BP and other autoimmune bullous diseases, via either direct (DIF) or indirect techniques. Direct immunofluorescence should be performed on a separate, perilesional skin specimen submitted in Michel medium or normal saline. Ideally, DIF should be performed within 2 days for specimens submitted in saline and within 5 days for specimens submitted in Michel medium (although some studies have shown Michel medium to preserve DIF viability in tissue for up to 6 months).\textsuperscript{33} Perilesional skin is the normal-appearing skin just adjacent to an active blister but not involving the blister itself. Sampling from a perilesional location for DIF is key because immunoglobulins and complement factors are susceptible to degradation by the inflammatory reaction within the blister cavity itself, rendering them falsely undetectable on DIF.\textsuperscript{32} If the skin biopsy is inadvertently placed in formalin, DIF is no longer possible. In our anecdotal experience, even short exposure to formalin of an hour or less is enough to damage the tissue so that DIF will no longer work correctly on the specimen. Bullous pemphigoid characteristically demonstrates linear deposition of C3 and IgG immunoreactants along the DEJ, which differentiates it from linear IgA bullous dermatosis (linear IgA deposition along the DEJ) and dermatitis herpetiformis (granular IgA deposition in the tips of the dermal papillae). Of note, 2 other diseases can also show linear IgG and C3 deposition along the DEJ: EBA and bullous SLE. In EBA, the deposits usually have an identical pattern to BP. In bullous SLE, the deposits may be more “shaggy” (thick and irregular) or granular in contrast to the crisp linear pattern of deposits in BP; IgA and/or IgM may also be present at the DEJ. Although routine histologic and DIF examination are usually sufficient to establish a diagnosis of BP, in some cases indirect immunofluorescence studies may be required to differentiate BP from some of its histologic mimics. This may be accomplished by combining the patient’s serum with salt-split skin to demonstrate localization of circulating autoantibodies to the epidermal side (“roof”) of the split. This allows differentiation of BP from EBA and bullous SLE, which demonstrate localization of IgG (±IgA in EBA) autoantibodies to the dermal side of salt-split skin.\textsuperscript{32,34} Newer techniques, including enzyme-linked immunosorbent assay and immunoblot, are increasingly being used to identify circulating IgG anti-BP180 and anti-BP230 antibodies, with reported combined diagnostic sensitivity approaching 90% in some studies.\textsuperscript{29} However, the presence of subepidermal blister with eosinophils on H&E and linear deposition of IgG and C3 along the DEJ on DIF are usually sufficient to suggest a diagnosis of BP to the dermatologist in the acute inpatient setting. More advanced analysis can be sent out later upon request from the dermatologist as needed.

Prompt identification is essential for appropriate institution of therapy, as further blistering can result in burn-unit transfer and/or death in some patients. Although the mainstay of treatment for BP in the acute setting is high-dose corticosteroids, this can lead to devastating consequences in the setting of SJS/TEN or underlying infection. Additionally, bullous drug eruptions require prompt discontinuation of the offending drug, and misdiagnosis could lead to a delay in identification of the causative agent. As always, if there is uncertainty, discussion between the pathologist and dermatologist is often extremely helpful in identifying the severity of the clinical situation and developing a plan for working up the case in a way that will be most helpful to the dermatologist in deciding how to best treat the patient acutely.

In summary, the diagnosis of BP relies upon accurate pathologic evaluation in the appropriate clinical context. To that end, an algorithmic approach should be used to correctly diagnose a patient with clinical findings concerning for BP. Ideally, the dermatologist will obtain a biopsy of both lesional and perilesional skin simultaneously when any bullous dermatosis is suspected. Generally, the requisition form should specify the type of bullae observed (intact/tense versus flaccid), presence or absence of erosions, and description of additional lesions (urticarial or eczematous), when present. The differential diagnosis will often include the most clinically relevant autoimmune bullous dermatoses, as well as other causes of acute-onset blistering, as previously mentioned. Although pathologic evaluation is generally straightforward, it is important for the pathologist to assess for underlying infectious etiologies, presence of LCV, and—most importantly—interface alteration that would suggest SJS/TEN or other forms of bullous interface dermatitis. Once routine histopathology has been performed and is suggestive of BP, immunofluorescence studies should be performed. DIF results should specify the immunoreactants identified (ie, IgG, IgA, C3, etc), as well as the pattern of deposition (linear).

**CALCIPHYLAXIS**

High-yield points for calciphylaxis include the following:

1. Tissue ischemia that develops as a serious complication in patients with end-stage renal disease (ESRD) on dialysis.
2. Hematoxylin-eosin reveals thrombotic vasculopathy in small (often subcuticular) vessels, with basophilic calcium deposits in the deep dermis and subcutis, associated inflammation, and/or tissue necrosis.
3. Von Kossa or alizarin red should be performed in all suspicious cases.

Cutaneous calciphylaxis (calcific uremic arteriolopathy) is a rare but serious phenomenon well known to both dermatologists and nephrologists. It is seen most commonly in hospitalized patients with ESRD on dialysis. It can rarely be seen in patients without renal disease but with other risk factors such as primary hyperparathyroidism, malignancy, alcoholic liver disease, connective tissue disease, and warfarin use.\textsuperscript{35,36} The exact pathogenesis remains poorly understood and is likely multifactorial. Ultimately, calcium is deposited in and around the subcutaneous blood vessels, which results in restriction of blood flow and subsequent ischemia and thrombosis in the skin.\textsuperscript{36,37} Clinically, this manifests as indurated, purpuric plaques and eschars with a
predilection for adipose tissue (ie, abdomen, thighs, buttocks, breasts) and the distal lower extremities (Figure 7, A and B). Affected skin is exquisitely painful and may ulcerate. A diagnosis of calciphylaxis has important prognostic and treatment implications, as the 1-year mortality is approximately 50% to 80% and prompt institution of therapy may slow disease progression.36-38 Because there are no established diagnostic criteria and skin biopsy remains the gold standard, it is important for the pathologist to be familiar with the histologic spectrum of features that might be seen.

In general, the pathologist is looking for fractured basophilic deposits representative of calcium deposition within and around the small to medium-sized blood vessels of the deep dermis and fat (Figure 7, C). Additional features of intravascular fibrin thrombi, panniculitis, and fat necrosis can be seen (Figure 7, D). The presence of small, deep dermal or hypodermal thrombi leads to tissue ischemia, resulting in dermal and epidermal ischemic necrosis, corresponding to what is seen clinically (Figure 7, E). In a 2017 study by Chen et al.,36 significant findings in cases of calciphylaxis in patients with ESRD as compared with patients with ESRD but without calciphylaxis included the increased incidence of diffuse thrombi and diffuse calcification (both intravascular and extravascular) in cases of calciphylaxis. Dermal angioplasia, also known as diffuse dermal angiomatosis or reactive angioendothelialomatosis, refers to the small, often lobular vessels that sprout in the dermis in response to chronic tissue ischemia (Figure 7, F). This feature of reactive vascular proliferation is also more frequently seen in cases of calciphylaxis and has been suggested to be a relatively specific feature and certainly a histologic clue.36 Perieccrine calcification has been described as a highly specific feature in calciphylaxis and can occasionally be seen in the absence of vascular calcification; however, it is not seen in all cases.36,38 Pseudoxanthoma elasticum–like changes (calcification of small elastic fibers) have also been reported as a helpful histologic feature, particularly in nonuremic cases.36,40 In the authors’ experience, the calcifications may be very focal and/or very small, often with a stippled appearance, and they may be scattered in the necrotic subcutis rather than around vessels. If the clinical scenario is consistent with calciphylaxis and there is microscopic evidence of ischemia, then we regard the presence of any calcifications in the subcutaneous adipose tissue (even if not in vessels) as strongly suspicious for calciphylaxis. Patients with suspicious but not totally diagnostic findings on a first biopsy should have a repeat biopsy if clinically feasible. Radiologic imaging has recently been shown to be a useful diagnostic tool when skin biopsy is contraindicated.37

Biopsy by an experienced dermatologist is important in order to provide the pathologist with an adequate amount of subcutaneous adipose tissue for evaluation, as calcification and thrombi may only be seen deep in some cases. Thus, a diagnosis of calciphylaxis cannot be excluded if the biopsy does not sufficiently sample the subcuts. Traditional wedge excisions have now fallen away to deep punch biopsies, which have a lower risk of complications, as many of these are performed at bedside. We routinely perform a double-punch biopsy by first using a larger, 6- to 8-mm punch biopsy, followed by a second, smaller (ie, 4–6 mm) punch biopsy within the base of the initial punch. Others may refer to this as a telescoping biopsy or a punch within a punch. We recommend sampling the edge of the necrotic plaque for the highest yield. By this technique the specimen is submitted as 2 pieces, in formalin, for routine H&E. As adipose tissue falls apart relatively easily on the deeper punch biopsy, the dermatologist may be forced to submit multiple small fragments of fat. Thus, multiple pieces of adipose tissue in the specimen container often indicate that the dermatologist is trying to give the pathologist as much additional deeper tissue as possible, and each of these pieces should be reviewed. Care should be taken to ensure that the entirety of the specimen is submitted during gross examination, as these small fragments of fat may have the highest diagnostic yield; straining the contents of the biopsy container through a mesh bag may be helpful. Alternatively, the more traditional wedge excision may be submitted, but this has not been shown to affect the histopathologic yield.36

Special stains for calcium include von Kossa, which stains calcium black, and alizarin red, which stains calcium orange-red. Alizarin red is more specific for calcium as compared with von Kossa, but von Kossa is more commonly used. A 2013 retrospective histopathologic analysis of cutaneous calciphylaxis by Mochel et al.38 found the 2 stains overall comparable, but noted increased detection in a few cases using alizarin red. We recommend staining all cases in which calciphylaxis is suspected, particularly if calcium is not evident on routine H&E. Staining for calcium may not be necessary if all the histologic features (vascular calcification, small luminal thrombi in the fat, and dermal ischemia) are visible on H&E-stained sections.

The pathologist should always be on the lookout for calcification within the subcutis of any skin biopsy. However, it is important to remember that calcification of vessels may be seen in other circumstances, such as diabetes, atherosclerosis, and patients with ESRD without calciphylaxis (especially those on hemodialysis), and in the dermis as a dystrophic phenomenon. Calcification of the fat can also be seen in certain panniculitides, such as lupus panniculitis and pancreatic panniculitis. Thus, the diagnosis of calciphylaxis absolutely requires clinicopathologic correlation. The presence of diffuse thrombi and diffuse calcification of the capillaries can be helpful histologically.38 Calcification of capillaries has the highest specificity, given that greater statistical significance has been reported with smaller vessel size.38 We recommend a 1-line descriptive diagnosis such as “fat necrosis with perivascular calcification and diffuse thrombi” with a comment noting that the findings are consistent with a diagnosis of calciphylaxis in the correct clinical setting. Microbial special stains, including Gram, GMS or PAS, and acid-fast stains (Kinyoun, Ziehl-Neelsen, or Fite) should generally be performed and are expected by the dermatologist in cases where the clinical diagnosis of calciphylaxis is uncertain, an infectious etiology is listed on the clinical differential, or necrosis or panniculitis is seen by the pathologist on histology. This is because the clinical differential diagnosis for calciphylaxis can also include serious infectious etiologies such as purpura fulminans and angioinvasive fungal infection. Further, deep lesions of calciphylaxis can easily become secondarily infected, and sepsis can be a fatal complication. Other histologic differential diagnoses of deep dermal and subcutaneous thromboses include cholesterol emboli, warfarin necrosis, and autoimmune vasculopathies, such as antiphospholipid antibody syndrome and cryoglobulinemia.37 These entities typically lack the vascular calcification seen in calciphylaxis.

Warfarin necrosis (which by name lacks calcification) is technically a separate entity from warfarin-associated
Figure 7. Calciphylaxis. A, Lower extremity retiform purpura with induration and secondary bullae and erosions in a patient with end-stage renal disease (ESRD). B, Large atrophic, adherent eschar overlying a deep ulceration on the thigh in another patient with ESRD. C, Characteristic basophilic calcium deposits within and around blood vessels and adipocytes. D, Fibrin thrombi within vessels in the subcutis. E, Low-power image demonstrating diffuse tissue ischemia and thromboses. F, Note the proliferation of small lobular vessels in response to tissue ischemia (dermal angioplasia) (hematoxylin-eosin, original magnifications ×200 [C], ×400 [D], ×20 [E], and ×100 [F]).
calciphylaxis in which calcification is seen. Warfarin can induce cutaneous necrosis in various settings, all of which have been gaining significant attention across the literature, warranting brief mention here. Long-term use of warfarin is now believed to accelerate atherosclerosis and calcification via the inhibition of anticalcification activity of matrix Gla protein that is normally activated by vitamin K, suggesting that warfarin may play a pivotal role in the pathogenesis of calciphylaxis, as many ESRD patients with calciphylaxis are in fact on warfarin. Further, warfarin alone has been reported to cause calciphylaxis outside the setting of ESRD, an entity newly termed warfarin-induced calciphylaxis.

SWEET SYNDROME (ACUTE FEBRILE NEUTROPHILIC DERMATOSIS)

High-yield points for Sweet syndrome include the following:

1. Erythematous “juicy” papules on the head, neck, and upper extremities.
2. May be associated with underlying malignancy, infection, or medications.
3. Hematoxylin-eosin reveals marked papillary dermal edema with abundant neutrophils.
4. Despite clinical presentation and histopathology that may suggest an infectious etiology, all infectious workup will be negative.
5. Excellent response to corticosteroids.
6. A diagnosis of histiocytoid Sweet syndrome should be made with caution and leukemia cutis must be excluded.

Sweet syndrome (also called acute febrile neutrophilic dermatosis) is an acute inflammatory skin condition that presents with tender, nonpruritic, erythematous “juicy” papules favoring the head, neck, upper extremities, and dorsal hands (Figure 8, A). Patients commonly appear quite ill, with systemic symptoms that include fever, leukocytosis, arthralgias, arthritis, myalgias, and conjunctivitis. There are reported cases in the pediatric population, but the majority of cases occur in adults.

Diagnostic criteria for Sweet syndrome have been outlined. Abrupt onset of typical skin lesions and histopathology consistent with Sweet syndrome make up the major diagnostic criteria. Minor criteria include diagnosis of a known Sweet-associated malignancy, inflammatory disor-
der, drug exposure, or pregnancy; fever and constitutional symptoms; leukocytosis; and excellent response to systemic corticosteroids. Both major criteria and 2 of 4 minor criteria are required for diagnosis. The pathogenesis is unclear but thought to be due to a hypersensitivity reaction to an underlying condition. Sweet syndrome has often been reported in association with hematologic malignancy, most commonly with acute myeloid leukemia. Underlying infectious causes (i.e., upper respiratory tract and gastrointestinal tract infections), pregnancy, and inflammatory bowel disease have also been associated. Granulocyte colony-stimulating factor is the most common cause of medication-induced Sweet syndrome.

Histopathologically, Sweet syndrome falls under the broader category of sterile neutrophilic dermatoses and is characterized by prominent papillary dermal edema with marked infiltration by mature neutrophils (Figure 8, B through D). Notably, a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and rare eosinophils may be present in the background and can become more predominant in later stages. In the setting of hematologic malignancy, lesions may concurrently demonstrate leukemia cutis, posing a diagnostic challenge (see below on histiocytoid Sweet syndrome and myeloid leukemia cutis). Historically, frank vasculitis was not considered a feature of Sweet syndrome. However, a 2007 retrospective histopathologic analysis of the relationship between Sweet syndrome and LCV revealed that the majority of cases of Sweet syndrome demonstrated histologic evidence of vasculitis, such as fibrinoid necrosis, nuclear dust, and extravasated erythrocytes, suggesting that the 2 diseases are not mutually exclusive. The histopathologic differential diagnosis of Sweet syndrome is broad and includes other neutrophilic dermatoses, leukemia cutis, erythema elevatum diutinum, exaggerated arthropod bite reactions, and infection. In the inpatient population, especially in those undergoing treatment for hematologic malignancy where we encounter Sweet syndrome most often, leukemia cutis and infection must first be excluded. We routinely stain for microbial cultures as they have overlapping histologic features.

In cases where infection is not favored clinically, we recommend a 4-mm punch biopsy of a well-formed, representative lesion submitted for routine H&E. If the patient is immunosuppressed or if there is suspicion for infection, we generally perform 2 separate 4-mm punch biopsies for both H&E and tissue culture. Alternatively, a 6-mm punch biopsy can be bisected for culture and H&E. When the histology is consistent with Sweet syndrome, we typically provide a 1-line diagnosis of “neutrophilic dermatosis” followed by a thorough histologic description and comment that in the correct clinical setting the histology would be consistent with Sweet syndrome but that infection and other neutrophilic dermatoses such as PG, Behçet disease, bowel-associated dermatitis and arthritis syndrome, etc., are best differentiated clinically and through correlation with microbial cultures as they have overlapping histologic features.

Sweet syndrome is commonly encountered in the inpatient setting, especially in patients with known disease associations, like hematologic malignancies. It is important for pathologists to be aware of the clinical and histologic challenges in diagnosing Sweet syndrome as well as the treatment implications. An easy diagnostic pitfall is mistak-
to be aware of the immunophenotypic differences that exist between the bone marrow and skin. As an example, a 2009 study by Cronin et al. 52 studied the immunohistochemical characteristics of 33 cases of myeloid leukemia cutis and compared them with the corresponding bone marrow blast immunophenotype and found discordance in all cases. Notably, CD34 and CD117 were predominantly negative. Consistent with previous literature, Cronin et al. 52 confirmed that the immunophenotypic markers that are normally used to confirm blasts in the bone marrow (eg, CD34 and/or CD117) cannot be reliably used in the skin, even when flow cytometry of the bone marrow shows expression of these antigens.52,53 Several hypotheses for this discordance exist. Absence of CD34 and CD117 is common in monocytic leukemias. However, in myeloid leukemias without a primary monocytic origin, the reason for their absence of expression is not clear. Extramedullary involvement of the skin is more common in acute myeloid leukemias with monocytic differentiation, which typically show weak to no expression of CD34 and CD117. Thus, it is possible that there is some degree of monocytic differentiation that is taking place in the cutaneous leukemic infiltrates, regardless of a primary monocytic lineage.52 A second hypothesis for discordant antigen expression is related to clinical therapy. As a result of interim chemotherapy (systemic therapy administered between bone marrow biopsy and the diagnosis of leukemia cutis), the blasts manifesting as leukemia cutis may actually represent immunophenotypically distinct cell populations as selected for or altered by therapy. A third hypothesis is that the blasts in myeloid leukemia cutis actually do express CD34 and/or CD117, but immunohistochemical methods are insufficiently sensitive for their detection in the skin. In addition to discrepancies in CD34 and/or CD117, Cronin et al. 52 also noted discordant expression of MPO and CD56 in skin lesions as compared with the immunophenotype of the bone marrow, again with the hypothesis that extramedullary involvement of the skin may result in an immunophenotypically distinct blast population, warranting more research in this area. Given the immunophenotypic differences that exist between the bone marrow and skin, an updated approach to diagnosing myeloid leukemia cutis via immunophenotyping has been designed by Cronin et al. 52

**PYODERMA GANGRENOsum**

High-yield points for PG include the following:

1. A “neutrophilic dermatosis” that presents with rapidly progressive skin ulcerations.
2. Commonly misdiagnosed, which can result in devastating tissue loss.
3. Histology is nonspecific and the inflammatory infiltrate can vary with location of biopsy and duration of lesion.
4. Infection by bacteria, fungi, or acid-fast bacteria must be excluded by either special stains, microbial cultures, molecular techniques, or a combination of these.

Pyoderma gangrenosum, commonly referred to as PG by dermatologists, is another sterile neutrophilic dermatosis that is commonly encountered in the inpatient setting and can present in similar patient populations as Sweet syndrome. Pyoderma gangrenosum is a very morbid neutrophilic dermatosis, as it presents with rapidly progressive and often refractory skin ulceration. This presentation is quite different from the classic juicy erythematous nodules in Sweet syndrome; however, there are variants of PG and Sweet syndrome that can overlap, and some consider these 2 diseases to lie on a spectrum.54 The name PG is a misnomer, as it is not an infectious process, but is frequently misdiagnosed as such.55 Pyoderma gangrenosum is associated with an underlying systemic disorder in at least 50% of patients.56 Inflammatory bowel disease is most commonly associated, and was found in 35 of 103 patients (34%) in one study, with an equal incidence in Crohn disease and ulcerative colitis.57 Other associated systemic disorders include arthritis (both seronegative and rheumatoid), hematologic disorders, and hematologic malignancies. Immunoglobulin A monoclonal gammopathy is the most commonly encountered hematologic disorder. Up to 7% of cases of PG are associated with an underlying hematologic malignancy, with acute myeloid leukemia being the most common malignant subtype.56 The pathophysiology is poorly understood and likely dependent on the presence of an underlying systemic disease; it is thought to involve abnormalities of innate immune regulation and alternated neutrophil chemotaxis.56-57 The diagnosis of PG is a diagnosis of exclusion and a notoriously difficult one to make, requiring a systematic approach by both the clinician and the pathologist.

Classically, lesions begin as tender purple pustules and nodules that, during a period of days, quickly coalesce and break down to form deep cribiform ulcerations with undermined violaceous borders (Figure 10, A). Other less common clinical variants exist, such as bullous and vegetative/superficial granulomatous lesions, which are outside the scope of this review. Devastating tissue loss with extension to the muscle can be seen in aggressive and untreated cases. Pathergy is a feature of PG, meaning that lesions can appear or worsen at sites of trauma (including sites of surgical manipulation). This often means that surgical debridement can actually worsen rather than improve the condition; for this reason, it is imperative for pathologists and clinicians alike to be aware of PG and its manifestations. However, the pathergy phenomenon is not universally present; it occurs in only 31% to 50% of patients.55,56 Further, PG may develop at one site but not all sites of trauma in the same patient. Treatment involves combination of topical and systemic therapy and treating any underlying disease process. Cyclosporine or high-dose corticosteroids are first-line systemic treatments. However, PG can be refractory to treatment and may require a combination of systemic immunosuppressive therapies. Healing can take months to years, and relapses and the development of new lesions at other sites are common.

Diagnosing PG is largely clinical, as there are no pathognomonic histologic findings. Nonetheless, a biopsy may still be helpful, as some histologic features can help support the diagnosis, and a biopsy can exclude other etiologies of chronic nonhealing ulcers such as infection, carcinoma, vasculitis, vascular stasis/insufficiency, and coagulopathy. We recommend that biopsy (deep punch or incisional) be performed of an early active lesion (ie, a violaceous papulopustule) or at the edge of an actively advancing ulcer for routine H&E. A mixed, neutrophil-predominant inflammatory infiltrate extending deep within the dermis, sometimes with LCV, is characteristic of early lesions prior to ulceration.56 The infiltrate in early lesions may be centered around hair follicles, resembling folliculitis. Ulcers with active advancing borders may demonstrate undermining inflammation, meaning that the inflammatory
Histiocytoid Sweet syndrome and myeloid leukemia cutis. Erythematous “juicy” papules in a patient with histiocytoid Sweet syndrome (A) and myeloid leukemia cutis (B), which are clinically indistinguishable from one another, as well as from classic Sweet syndrome (Figure 8, A). Histiocytoid Sweet syndrome may have papillary dermal edema and a dense dermal infiltrate, similar to conventional Sweet syndrome (C and D), but high magnification shows that in addition to variable numbers of neutrophils (left) there are also larger histiocytoid cells (right) that likely represent immature myeloid progenitors (E). The blasts in some forms of myeloid leukemia cutis (F) may have very similar histiocytoid cytologic features to the...
cells extend underneath the more normal skin and are not just in the ulcer bed (Figure 10, B and C). A lymphocyte-predominant infiltrate with necrosis and thrombosis may be seen in specimens taken from the peripheral erythema of the ulcer, and biopsy of ulcer beds may show necrosis and hemorrhage. Lymphocytes may be seen within and around vessel walls.56,57 It is important to note that histology is quite variable in PG and neutrophils are not always seen, especially in fully developed and long-standing ulcers. Indeed, in the largest PG cohort study to date, which examined the histopathologic records to rule out other possible diagnoses, only 7% (8 of 103 patients with PG) had biopsy findings consistent with PG, that is, the classic neutrophilic infiltrate with early abscess formation.55 Thus, biopsies are useful to rule out other causes (ie, infection) but cannot definitively rule out PG.

A methodical approach for any PG biopsy is necessary to exclude other causes. The pathologist should routinely evaluate for vascular occlusion; vascular calcification; vasculitis of the larger, medium-sized vessels; malignancy; and any additional differentials specified by the dermatologist. The pathologist should then carefully look for any signs of infection. Microbial stains for bacteria, fungi, and atypical mycobacteria should be performed on all H&E specimens submitted to rule out PG unless otherwise specified. Notably, the classic H&E appearance of early neutrophil-predominant PG is very similar to that of an infectious abscess. The dermatologist will often simply write “infectious” or “infection” as the differential diagnosis on the requisition form, assuming that bacterial, fungal, and acid-fast stains will be performed. We routinely use Gram, PAS and/or GMS, and acid-fast stains. Any infectious studies that are needed in addition to these would normally be specified on the requisition form by the dermatologist. For example, in an HIV patient with an anogenital ulcer, the dermatologist’s clinical differential diagnosis might include something like “PG versus herpes versus cytomegalovirus versus syphilis versus granuloma inguinale versus other infectious/infection,” indicating to the pathologist that a broader panel of stains to evaluate for specific infectious etiologies may be advisable depending on the features seen on examined H&E-stained slides.

Direct immunofluorescence is uncommonly used in the diagnosis of PG, but may show IgM, C3, and fibrin deposition in dermal blood vessels in the majority of cases, attributes that are neither sensitive nor specific.56 We recommend a 1-line descriptive diagnosis followed by a more in-depth microscopic description that includes the results of the microbial stains. Notably, these ulcers can become easily colonized and secondarily infected, especially in long-standing lesions; thus, the location (superficial colonization versus deep dermal) and degree (diffuse versus focal) of microbial staining should be specifically described. In cases where a microbial stain is positive, instructions to correlate with microbial tissue cultures should be added, as the dermatologist also will have generally submitted a separate biopsy for tissue cultures. Alternatively, formalin-fixed, paraffin-embedded tissue can be sent for molecular analysis via polymerase chain reaction in an attempt to identify potential infectious organisms in select cases as needed. As mentioned previously, PG can sometimes overlap clinically and histologically with other diseases on the neutrophilic dermatoses spectrum, such as Sweet syndrome variants. Pyoderma gangrenosum is not to be confused with pyogenic granuloma (lobular capillary hemangioma); although both are abbreviated as PG by dermatologists, they are completely different, unrelated entities.

In summary, diagnosing PG based on histology is challenging given the lack of pathognomonic findings, rendering PG a diagnosis of exclusion. The frequent misdiagnosis of PG has important treatment implications. Pyoderma gangrenosum that is mistaken for infection can result in inappropriate use of antibiotics and wound debridement, the latter of which can incite pathergy and result in limb amputation. In turn, a missed infection could result in inappropriate treatment with steroids. Misdiagnosis by the pathologist can be avoided by following the above systematic approach and by discussing the clinical details of the case (and the implications of the pathologist’s diagnosis) with the treating dermatologist.

**CUTANEOUS LEUKOCYTOCLASTIC VASCULITIS**

High-yield points for cutaneous LCV include the following:

1. Represents a distinct histologic inflammatory pattern affecting small vessels of the dermis.
2. Corresponds to the clinical diagnosis of cutaneous small vessel necrotizing vasculitis and classically manifests as palpable purpura.
3. Can be seen in a variety of primary vasculitic dermatoses or as a secondary finding in nonvasculitic dermatoses; clinicopathologic correlation is required.

The term LCV refers to a distinct histologic inflammatory pattern affecting small blood vessels that can develop in any organ system. In the dermatologic setting, it refers to inflammation of the small vessels in the superficial and mid dermis—specifically, postcapillary venules—and corresponds to the clinical presentation of cutaneous small vessel vasculitis (CSVV). Cutaneous small vessel vasculitis encompasses an etiologically heterogeneous spectrum of disorders that present with similar clinicopathologic cutaneous findings. It is observed in 1 of 3 specific settings: a skin-limited vasculitis (most common), a primary cutaneous vasculitis with secondary systemic manifestations, or a secondary cutaneous manifestation of a primary systemic vasculitis.58,59 Thus, when diagnosing cutaneous LCV, it is important to first rule out any systemic involvement of the vasculitis, as well as any underlying causes and disease associations.

The majority of CSVVs result from the deposition of circulating immune complexes in the walls of postcapillary venules, initiating an inflammatory cascade that results in complement activation and neutrophil chemotaxis. Immune complex–mediated CSVV has numerous underlying etiologies, including infections, medications, underlying rheumatologic or connective tissue disease, and rarely malignancy. Importantly, CSVV is idiopathic in approximately 50% of cases, with some distinct clinical syndromes distinguished.
based on unique etiologic and clinicopathologic characteristics. The major CSVV syndromes include Henoch-Schönlein purpura/IgA vasculitis, the urticarial vasculitis spectrum, and cryoglobulinemic vasculitis (mixed-type cryoglobulinemia).58,59

Clinically, CSVV presents as palpable purpura of variable size favoring dependent areas and sites of trauma.58 Lesions often present acutely and in crops. Presentations can vary, and purpuric macules, patches, urticarial purpuric papules, and hemorrhagic vesicles may be admixed or predominate (Figure 11, A through C). However, the dermatologist will often simply write “palpable purpura” to indicate to the pathologist that skin findings are consistent with vasculitis. Absence of “palpable purpura” (or “purpura”) on the requisition form may signify that the dermatologist’s suspicion for CSVV is low or that the presentation is atypical. Lesions generally develop during 1 to 2 days, followed by gradual resolution during 2 to 3 weeks with residual postinflammatory hyperpigmentation. (Of note, postinflammatory hyperpigmentation is pigmentation in the skin that is left over from a previous insult [ie, from a rash, including vasculitis] but not representative of an active process. Thus, when the dermatologist uses the term postinflammatory hyperpigmentation, he or she is indicating that the rash seen is just residual pigmentation, and unlikely to reveal pathologic changes of a primary inflammatory process under the microscope.) Most cases of CSVV are limited to the skin without extracutaneous manifestations.58 Only rarely do patients experience a chronic, relapsing course, which, in the authors’ experience, is indicative of systemic involvement.

Approaching a patient with CSVV can be quite challenging. When dermatologists approach cases of CSVV in the hospital, we ask ourselves, “Is this a routine, isolated case of LCV limited to the skin? Or are there other signs that point toward something more serious?” In order to make this distinction, a thorough history, review of systems, and physical examination are warranted, particularly to identify any evidence of systemic involvement or disease associations. A skin biopsy is often performed in order to confirm the presence of LCV, as well as to identify any additional unique pathologic characteristics that may aid in diagnosis. Histopathology of an early lesion of CSVV (≤48 hours old) typically demonstrates the pathognomonic findings of LCV—perivascular neutrophilic infiltration with fibrinoid necrosis of dermal blood vessel walls, endothelial swelling, karyorrhexis with nuclear dust (leukocytoclasis), and erythrocyte extravasation, predominantly affecting postcapillary venules (Figure 11, D and E).59,60

As lesions of LCV age, histologic findings often become more nonspecific, with diminution of neutrophilic infiltrate and increased lymphocytic inflammation, highlighting the importance of appropriate timing of skin biopsy for accurate diagnosis.60 In general, a 3- to 4-mm punch biopsy should be taken from a fresh and well-developed lesion, ideally 24

Figure 10. Pyoderma gangrenosum. A, Violaceous pustules rapidly coalescing into cribiform ulcerations. B, There is ulceration of the epidermis (right). The dermis is replaced by a dense inflammatory infiltrate that undermines the nonulcerated skin adjacent to the ulcer (left), a classic feature of pyoderma gangrenosum. C, The infiltrate is composed mostly of neutrophils and debris. There is also background hemorrhage and edema (hematoxylin-eosin, original magnifications ×40 [B] and ×200 [C]).
to 48 hours old. This is of particular importance when the clinical differential diagnosis includes both vasculitis and microvascular occlusion, as a late lesion of vasculitis may resemble an early occlusive lesion and vice versa. Ideally, the age of the sampled lesion should be provided on the pathology report comment, but this information is rarely given. Discussion with the dermatologist may be helpful when there is difficulty in distinguishing vasculitis from microvascular occlusion. When there is any doubt, the authors usually add a comment that these 2 processes may resemble one another depending on the age of the lesion, with recommendation that the treating physician should pursue additional laboratory workup if there is any clinical concern for a coagulopathy or other microvascular occlusive disease process.

Although the histologic finding of LCV is not specific for any one type of CSVV, certain findings may be suggestive of a particular entity, and the authors recommend that the pathology report comment on the presence or absence of such findings. The presence of vasculitis in the deep dermal vessels raises the possibility of a systemic vasculitis. Thus, the depth of involvement should be specifically noted in the pathology report. The presence of eosinophils may suggest a drug-induced vasculitis or an urticarial vasculitis. Prominent lymphocytic infiltration can be seen in autoimmune connective tissue diseases, viral infections, and drug exposures.

Urticarial vasculitis with prominent dermal interstitial neutrophilic infiltrates is suggestive of the hypocomplementemic variant of urticarial vasculitis and should prompt investigation for underlying SLE. Of note, there is a normocomplementemic variant of urticarial vasculitis that is skin limited and more commonly demonstrates LCV with eosinophils, as opposed to the prominent dermal neutrophilic infiltrate in hypocomplementemic urticarial vasculitis. The presence of prominent thrombi and inflammation may also raise consideration of a septic vasculitis or levamisole vasculitis (described more in detail below), in the correct clinical setting.

Mixed-type cryoglobulinemia (types II or III) will display small vessel vasculitis with intraluminal bright pink PAS-positive hyaline material representing deposits of cryoglobulins, sometimes intermingled with fibrin thrombi. The cryoglobulin deposits will usually stain brightly with PAS. Importantly, it should be emphasized that findings of vascular damage resembling LCV can also be observed as a secondary finding in nonvasculitic processes, including infections, arthropod bite reactions, chronic ulcers, and PG. Therefore, it is imperative that the pathologist evaluate thoroughly for any findings suggestive of these disorders and comment accordingly. We perform special staining to evaluate for the presence of organisms, including Gram, PAS, and acid-fast stains in select cases when there may be concern for infection.

Direct immunofluorescence should also be performed whenever possible, and optimally should be performed on representative lesions between 8 and 24 hours old, as older lesions can often be falsely negative after 48 hours. We recommend that DIF be performed on the most proximal lesions, as areas of dependency (ie, the lower legs) can demonstrate nonspecific fluorescence even if the skin is uninvolved. Direct immunofluorescence of LCV most commonly demonstrates deposition of fibrin and granular C3 around vessels. In the correct clinical context, DIF can be suggestive, and in some cases diagnostic, for specific types of CSVV. Immunoglobulin A deposition around vessel walls is very sensitive for Henoch-Schönlein purpura, whereas IgA seen as one of multiple other immunoreactants can be nonspecific. As mentioned previously, Henoch-Schönlein purpura/IgA vasculitis is a subtype of CSVV and has unique clinical implications. For example, in adults, a diagnosis of IgA vasculitis warrants close monitoring of renal function, as it can be associated with severe renal impairment. The pathologist should carefully evaluate for IgA deposition in all cases of LCV in both adults and children. In our experience, IgA deposits may be very focal and granular in IgA vasculitis and thus may require careful examination at high power in cases where there is high clinical suspicion. Prominent IgM deposition is associated most closely with mixed-type cryoglobulinemia, monoclonal lymphoproliferative disease, and rheumatoid vasculitis. In mixed-type cryoglobulinemia, the cryoglobulin deposits within the vessel lumina may be composed of both IgG and IgM, consistent with rheumatoid factor. Deposition of immunoreactants along the basement membrane zone in addition to blood vessel walls—referred to as the lupus band—should raise suspicion for hypocomplementemic vasculitis and, possibly, underlying SLE. We recommend that the pathology report detail specific patterns and immunoreactants identified whenever DIF studies are positive.

Notably, granular perivascular IgM and/or C3 may be seen in biopsies from the lower extremities of patients without necrotizing vasculitis. Positive perivascular DIF findings may also be seen in several non-LCV diseases, some of which may clinically mimic vasculitis. Pigmented purpuric dermatosis (pigmented purpura) displays fibrin and C3 deposits (sometimes with immunoglobulins) around papillary dermal vessels. Atrophic blanche shows thick layers (“cuffs”) of fibrin deposited around dilated vessels in the papillary dermis (analogous to the changes seen on H&E in this disease). Perivascular fibrin may also be seen in stasis dermatitis or essentially any other nonvasculitic processes in which blood vessels are leaky, allowing blood to exit the vessel and enter the dermis. The authors have also personally observed one case of pernio/perniosis (chilblains) with perivascular deposits of fibrin and granular C3. We were unable to find any previous report of this in the literature. As mentioned above, nonspecific immunofluorescence may also be seen in normal skin.

Rarely, cutaneous vasculitis with severe and fatal systemic involvement can be encountered in the inpatient setting. In these cases, prompt diagnosis is necessary so that immunosuppression can be instituted without delay in order to avoid end-organ damage. There are various primary systemic vasculitides that exist, ranging from small vessel to medium vessel to large vessel vasculitis. Well-known examples of primary systemic medium and large vessel vasculitis include polyarteritis nodosa and Takayasu arteritis, respectively; however, diagnosis and classification of the systemic small vessel vasculitides or those with mixed vessel involvement (that is, involvement of both the small and medium-sized vessels) can be more complex, as their dermatologic and histologic features can overlap with skin-limited CSVV. As stated previously, this is why, when presented with palpable purpura and LCV, dermatologists must separate skin-limited CSVV from systemic involvement that warrants prompt immunosuppressive treatment. Cutaneous small vessel vasculitis with involvement of the small and medium-sized vessels may indicate an underlying connective tissue disease or an antineutro-
Figure 11. Leukocytoclastic vasculitis (LCV). A through C, Note the clinical spectrum of palpable purpura seen in various presentations of cutaneous LCV. A, Urticarial lesions predominate in a patient with urticarial vasculitis. B, Hemorrhagic vesicles are admixed with purpuric papules in a patient with immunoglobulin A vasculitis. C, Purpuric patches predominate among few palpable lesions in patient with LCV with systemic involvement. D, Neutrophils cluster around individual vessels with associated hemorrhage, a low-magnification clue for LCV. E, Pink fibrinoid necrosis within vessel walls, extravasated erythrocytes in the dermis, and neutrophils with associated nuclear debris are all characteristic features of vascular damage in LCV (hematoxylin-eosin, original magnifications ×100 [D] and ×400 [E]).
philic cytoplasmic antibody (ANCA)–associated vasculitis. It is important for pathologists to recognize that vasculitides are classified by the largest vessel they involve, but, because of the superficial nature of routine skin biopsies, only small vessel involvement may be seen in a mixed or even medium vessel vasculitis, sometimes requiring biopsy of other affected organs for a more definitive diagnosis. This can be a diagnostic pitfall in the realm of cutaneous vasculitides. The importance of this can be highlighted by the ANCA-associated vasculitides, which, despite having serious systemic involvement of medium-sized vessels, can merely demonstrate LCV histologically on skin biopsy.

The ANCA-associated vasculitides are rare, primary systemic vasculitides with high morbidity and mortality. They are characterized by mixed vessel involvement (of both small and medium-sized vessels), unique systemic manifestations, and prominent cutaneous involvement. The 3 major entities in this category include microscopic polyangiitis, granulomatosis with polyangiitis (previously termed Wegener granulomatosis), and eosinophilic granulomatosis with polyangiitis (previously termed Churg-Strauss syndrome). For simplicity, we will use the former, more universally familiar eponyms, Wegener granulomatosis and Churg-Strauss syndrome, when referring to granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis, respectively. In contrast to immune complex–mediated CSVV, vascular injury in the ANCA-associated vasculitides is mediated directly by neutrophils, hence the term pauci-immune vasculitis. Given that these are pauci-immune vasculitides, DIF is generally negative. An exception to this has been reported in cases of Wegener granulomatosis, in which DIF has been found to be positive during early, active disease states, raising question of an initial, transient role for immune complex deposition.

Histologically, LCV is often seen in the ANCA-associated vasculitides. Microscopic polyangiitis classically shows LCV on pathology, but may have involvement of the deeper reticular dermis, as compared with skin-limited CSVV, which is typically limited to the more superficial dermis. Wegener granulomatosis may also demonstrate LCV. In fact, true granulomatous vasculitis in the skin is rare as compared with histology of other involved organs. Churg-Strauss syndrome is characterized by LCV with a prominent eosinophilic infiltrate, with a variable degree of granulomatous inflammation present. Again, because shallow biopsies may not reveal additional diagnostic features of deeper vessel vasculitides, the pathologist must be aware of this diagnostic pitfall and clinicopathologic correlation must be applied. Clinical findings (which can occur in addition to palpable purpura) that point toward a diagnosis of an ANCA-associated vasculitis or other deeper vessel vasculitides include the presence of subcutaneous nodules, livedo reticularis, retiform purpura, and/or ulceration; characteristic multi-organ involvement; positive ANCA serology; and a chronic relapsing course.

Of note, levamisole toxicity can result in atypical ANCA patterns. Levamisole is often used in the production of cocaine, and levamisole toxicity from cocaine abuse is becoming more common, especially in the United States. Clinically, patients present with purpura, skin necrosis (particularly on the ears), and renal dysfunction in the setting of very high perinuclear anti-cytoplasmic antibodies (p-ANCA). However, antibody titers to MPO, the typical target of p-ANCA, are low to nonexistent. This discrepancy results from levamisole-induced atypical p-ANCA target antigens, known as an atypical ANCA pattern. Histologic features of levamisole toxicity include small vessel LCV in the superficial and deep dermis, often with prominent luminal fibrin thrombi.

In summary, the clinicopathologic spectrum of CSVV is quite expansive, and as such requires exhaustive investigation for diagnosis. Neither the clinical presentation nor pathologic findings alone provide sufficient evidence for definitive diagnosis. Rather, it is the combination of characteristic pathology demonstrating LCV occurring in the appropriate clinical context that allows for the definitive diagnosis of CSVV. The pathologist should be familiar with the spectrum of pathologic features associated with different CSVV entities to provide both diagnostic and prognostic information to the clinician, which in turn allows for optimal patient management.

**SUMMARY**

Here we have highlighted the pivotal role that pathologists play in dermatologic urgencies and emergencies and how timely and accurate histologic diagnoses can result in improved patient outcomes. This review thus serves as a practical, must-know reference guide for any pathologist approaching a rush inpatient skin biopsy. We would like to reemphasize that an open line of communication with the dermatologist or other treating clinician should always be established, ideally well in advance of the emergency scenario. In emergent cases, our practice is to have an initial discussion with the pathologist at the time of consultation regarding the physical examination findings, urgency of the case, and main differential diagnosis, which sets the stage for the pathologist. Once the slides have been processed, it is helpful to hear the pathologist’s initial impression of the biopsy as well as learn of any pertinent positive, negative, and pending stains. Continued conversation with the dermatologist can help narrow the differential diagnosis, allow for transmission of any additional valuable clinical information, and ultimately help the pathologist arrive at the diagnosis. Bidirectional communication between the pathologist and dermatologist will result in optimal patient care. Urgencies and emergencies do not have to elicit a sense of panic but can rather be approached systematically with the knowledge that a collaborative approach yields the best patient outcome.

**References**

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