emphasized that a drug reaction can lead to both a cutaneous eruption and a fever ("drug fever"), especially in the setting of DRESS, AGEP, or serum sickness–like reaction. Additional inflammatory diseases that are often associated with a fever include pustular psoriasis, erythroderma, and Sweet syndrome. Lyme disease, secondary syphilis, and viral and bacterial exanthems (see "Exanthems," above) are examples of infectious diseases that produce a rash and a fever. Lastly, it is important to determine whether or not the cutaneous lesions represent septic emboli (see "Purpura," above). Such lesions usually have evidence of ischemia in the form of purpura, necrosis, or impending necrosis (gunmetal-gray color). In the patient with thrombocytopenia, however, purpura can be seen in inflammatory reactions such as morbilliform drug eruptions and infectious lesions.



# 73 Immunologically Mediated Skin Diseases

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A number of immunologically mediated skin diseases and immunologically mediated systemic disorders with cutaneous manifestations are now recognized as distinct entities with consistent clinical, histologic, and immunopathologic findings. Clinically, these disorders are characterized by morbidity (pain, pruritus, disfigurement) and, in some instances, result in death (largely due to loss of epidermal barrier function and/or secondary infection). The major features of the more common immunologically mediated skin diseases are summarized in this chapter (Table 73-1), as are the autoimmune systemic disorders with cutaneous manifestations.

## AUTOIMMUNE CUTANEOUS DISEASES

### PEMPHIGUS VULGARIS

*Pemphigus* refers to a group of autoantibody-mediated intraepidermal blistering diseases characterized by loss of cohesion between epidermal cells (a process termed *acantholysis*). Manual pressure to the skin of these patients may elicit the separation of the epidermis (*Nikolsky's sign*). This finding, while characteristic of pemphigus, is not specific to this group of disorders and is also seen in toxic epidermal necrolysis, Stevens-Johnson syndrome, and a few other skin diseases.

Pemphigus vulgaris (PV) is a mucocutaneous blistering disease that predominantly occurs in patients >40 years of age. PV typically begins on mucosal surfaces and often progresses to involve the skin. This disease is characterized by fragile, flaccid blisters that rupture to produce extensive denudation of mucous membranes and skin (Fig. 73-1). The mouth, scalp, face, neck, axilla, groin, and trunk are typically involved. PV may be associated with severe skin pain; some patients experience pruritus as well. Lesions usually heal without scarring except at sites complicated by secondary infection or mechanically induced dermal wounds. Postinflammatory hyperpigmentation is usually present for some time at sites of healed lesions.

Biopsies of early lesions demonstrate intraepidermal vesicle formation secondary to loss of cohesion between epidermal cells (i.e., acantholytic blisters). Blister cavities contain acantholytic epidermal cells, which appear as round homogeneous cells containing hyperchromatic nuclei. Basal keratinocytes remain attached to the epidermal basement membrane; hence, blister formation takes place within the suprabasal portion of the epidermis. Lesional skin may contain focal collections of intraepidermal eosinophils within blister cavities; dermal alterations are slight, often limited to an eosinophil-predominant leukocytic infiltrate. Direct immunofluorescence microscopy of lesional or intact patient skin shows deposits of IgG on the surface of keratinocytes; deposits of complement components are typically found in lesional but not in uninvolved skin. Deposits of IgG on keratinocytes are derived from circulating autoantibodies to cell-surface autoantigens. Such circulating autoantibodies

**TABLE 73-1 IMMUNOLOGICALLY MEDIATED BLISTERING DISEASES**

| Disease | Clinical Manifestations | Histology | Immunopathology | Autoantigens[a] |
|---|---|---|---|---|
| Pemphigus vulgaris | Flaccid blisters, denuded skin, oromucosal lesions | Acantholytic blister formed in suprabasal layer of epidermis | Cell surface deposits of IgG on keratinocytes | Dsg3 (plus Dsg1 in patients with skin involvement) |
| Pemphigus foliaceus | Crusts and shallow erosions on scalp, central face, upper chest, and back | Acantholytic blister formed in superficial layer of epidermis | Cell surface deposits of IgG on keratinocytes | Dsg1 |
| Paraneoplastic pemphigus | Painful stomatitis with papulosquamous or lichenoid eruptions that may progress to blisters | Acantholysis, keratinocyte necrosis, and vacuolar interface dermatitis | Cell surface deposits of IgG and C3 on keratinocytes and (variably) similar immunoreactants in epidermal BMZ | Plakin protein family members and desmosomal cadherins (see text for details) |
| Bullous pemphigoid | Large tense blisters on flexor surfaces and trunk | Subepidermal blister with eosinophil-rich infiltrate | Linear band of IgG and/or C3 in epidermal BMZ | BPAG1, BPAG2 |
| Pemphigoid gestationis | Pruritic, urticarial plaques rimmed by vesicles and bullae on the trunk and extremities | Teardrop-shaped, subepidermal blisters in dermal papillae; eosinophil-rich infiltrate | Linear band of C3 in epidermal BMZ | BPAG2 (plus BPAG1 in some patients) |
| Dermatitis herpetiformis | Extremely pruritic small papules and vesicles on elbows, knees, buttocks, and posterior neck | Subepidermal blister with neutrophils in dermal papillae | Granular deposits of IgA in dermal papillae | Epidermal transglutaminase |
| Linear IgA disease | Pruritic small papules on extensor surfaces; occasionally larger, arciform blisters | Subepidermal blister with neutrophil-rich infiltrate | Linear band of IgA in epidermal BMZ | BPAG2 (see text for specific details) |
| Epidermolysis bullosa acquisita | Blisters, erosions, scars, and milia on sites exposed to trauma; widespread, inflammatory, tense blisters may be seen initially | Subepidermal blister that may or may not include a leukocytic infiltrate | Linear band of IgG and/or C3 in epidermal BMZ | Type VII collagen |
| Mucous membrane pemphigoid | Erosive and/or blistering lesions of mucous membranes and possibly the skin; scarring of some sites | Subepidermal blister that may or may not include a leukocytic infiltrate | Linear band of IgG, IgA, and/or C3 in epidermal BMZ | BPAG2, laminin-332, or others |

[a]Autoantigens bound by these patients' autoantibodies are defined as follows: Dsg1, desmoglein 1; Dsg3, desmoglein 3; BPAG1, bullous pemphigoid antigen 1; BPAG2, bullous pemphigoid antigen 2.

***Abbreviation:*** BMZ, basement membrane zone.