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Bullous, pseudobullous, & pustular dermatoses

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ABSTRACT

Several dermatoses are typified by the formation of spaces (blisters; bullae) within or beneath the epidermis. These may be acellular or filled with particular species of inflammatory cells. Etiological categories include infectious, immune-mediated, genetic, drug-related, and idiopathic lesions. Examples of such disorders include impetigo, *Herpes* virus infections, pemphigus, bullous pemphigoid and pemphigoid gestationis, epidermolysis bullosa acquisita, IgA-related dermatoses, inherited epidermolysis bullosa variants, Hailey-Hailey disease, and porphyria cutanea tarda. Other conditions manifest microscopic acantholysis within the surface epithelium but are not associated with clinical bullae, such as Darier disease and Grover disease. Finally, both infectious and non-infectious causes exist for the development of neutrophilic pustules in the epidermis, as seen in pustular psoriasis, Sneddon-Wilkinson disease (subcorneal pustular dermatosis), and acute generalized exanthematous pustulosis. This review considers the clinical and histological features of all of these diseases.

Because of their relative rarity and a regular requirement for adjunctive diagnostic studies, lesions with bullous features are regarded as perplexing by many pathologists. Etiologic underpinnings for such conditions include various genodermatoses, infections, inflammatory dermatoses, drug reactions, and autoimmune blistering disorders. This brief review aims to provide a practical approach to the interpretation of vesicobullous cutaneous diseases.

Biopsies of vesicobullous clinical skin lesions

Dermatologists are trained to take at least 2 biopsy specimens from cutaneous lesions that are vesicobullous. One is submitted for histologic examination in formalin, and the other is placed in a non-fixative transport medium (*e.g.,* Michel's solution) or frozen in liquid nitrogen. The second sample can then be studied by direct immunofluorescence microscopy (DIFM) for the possible presence of bound immunoglobulins and complement fractions.[1] That form of analysis is not easily performed—if it can be done at all—using formalin-fixed, paraffin-embedded tissue sections.[2]

Non-dermatologists may not know of this routine. Accordingly, when specimens from their patients show vesicobullous morphological changes that may be autoimmune in nature, they should be prompted by the pathologist to do additional biopsies for DIFM.

Infectious vesicobullous disorders of the skin

Bacterial Infections

Selected bacterial cutaneous infections may cause vesicles and bullae to form. Two of them—**erysipleas** and **necrotizing fasciitis**—have been considered elsewhere in this issue of *Seminars* and will not be covered here. Another important disease in this category is **bullous impetigo**, a common condition in children and adolescents.[3] It is caused by mixed infections by *Staphylococcus aureus* and *Streptococcus pyogenes*, but only rarely can those organisms be demonstrated histologically within the lesions.

Clinically, impetigo takes the form of multiple grouped vesicles and bullae that contain yellowish fluid, usually on the face. They easily rupture, and the resulting exposed reddish plaques of tissue are then covered with crusts. Etiologically, impetigo is often seen in children and teenage athletes who have skin-to-skin contact with other individuals who carry the causal bacteria.[4]

This histologic hallmark of impetigo is the presence of a subcorneal intraepidermal blister that is filled with neutrophils.[3](Fig. 1). Differential diagnosis is limited, practically represented only by acute bullous cutaneous lupus erythematosus (a rare disorder).[5] The clinical presentation typically allows for an easy distinction between these conditions.

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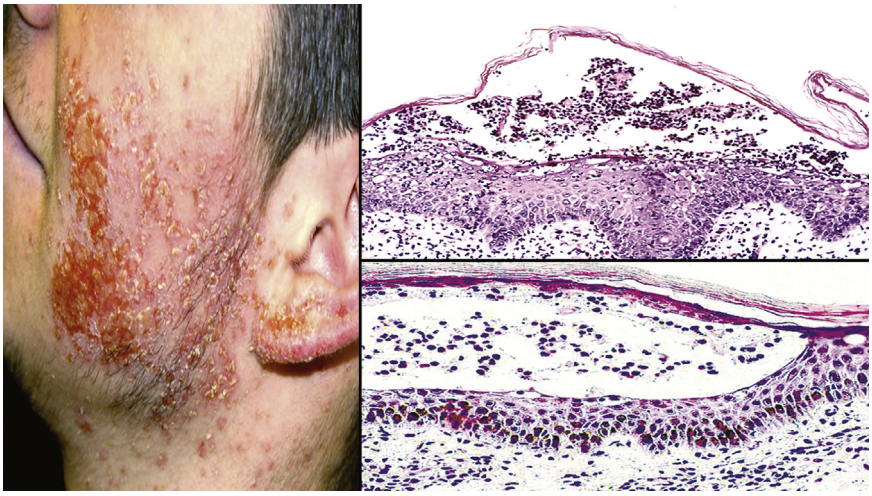

Fig. 1. Bullous impetigo is shown here. The bullae on this patient's face have ruptured, leaving scabs and open erosions (left). Histologically, the lesions are typified by subcorneal blisters filled with neutrophils (right panels).

Viral infections—Herpesviridae

Herpes simplex and ***Varicella-zoster*** are both members of the viral family *Herpesviridae*, and the clinical lesions that they produce are similar in appearance. *Herpes* is most often seen in the facial skin or the oral and anogenital mucosa, although selected cases—for example, those in which digital contact with an active lesion has occurred—may involve the extremities as well.[6] *Varicella-zoster* is primarily a disseminated skin infection in children, but susceptible adults also may develop that condition, especially if they are immunocompromised.[7] The lesions in both diseases are vesicobullous, grouped, and painful; they are often preceded by a prodrome of localized dysesthesia or pruritus. Zoster is typified by an anatomic distribution that follows the dermatomes.[6] Because *Herpes* family viruses are rarely if ever cleared by the host, they persist in occult clinical form in the sensory ganglia of the peripheral nervous system.[8] Under favorable clinical conditions, the viruses may again replicate actively and cause recurrent skin lesions.

The microscopic appearances of lesions caused by *H. simplex* and *V. zoster* are identical (Figs. 2 and 3). In classic form, they are respresented by intraepidermal or transepidermal vesicles and bullae, or by shallow ulcers. One sees keratinocyte ballooning, acantholysis, and necrosis. The infected epidermal epithelial cells are large and pale, with blue-gray nuclei, marginated chromatin, and, potentially, intranuclear inclusions. Multinucleation and nuclear molding are also common.[8] Additional helpful findings include cytopathic changes in dermal appendages, as well as intrabullous and periappendigeal infiltrates of neutrophils, lymphocytes, and plasma cells. In some instances, leukocytoclastic small-vessel vasculitis may be present as well.[9] The lymphoid cells may be enlarged and sufficiently cytologically-atypical that a diagnosis of lymphoma, leukemia, or plasmacytoma can be seriously considered.[8,9] Those misinterpretations are possibly furthered by the fact that the atypical mononuclear cells may be immunoreactive for CD30 or CD56, both of which can be associated with true hematopoietic malignancies in the skin.[8] However, additional immunostains [10] or in-situ hybridization studies will resolve diagnostic uncertainty by showing the presence of virus-related proteins and nucleic acids in infections with *Herpesviridae.*

Immunobullous dermatoses

Several bullous cutaneous diseases reflect the presence of autoimmune processes that involve, or are directly specifically at, the skin. These can be divided into two broad subcategories—intraepidermal bullous disorders and subepidermal bullous conditions.

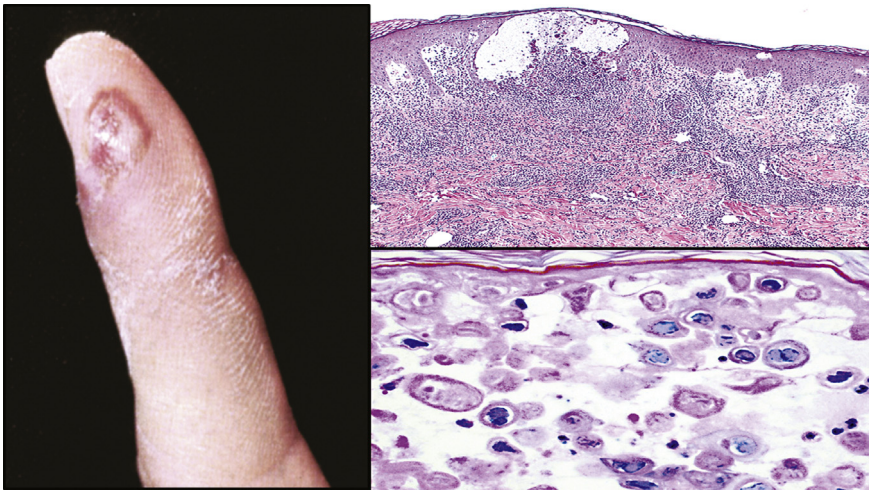

Fig. 2. *Herpes simplex* dermatitis is shown on the finger of a person who touched an active herpetic lesion on someone else (left). The lesion is represented by an inflammatory blister (top right), filled with dyshesive keratinocytes that show blue-grey nuclei, multinucleation, and margination of chromatin (bottom right).