Vesiculobullous Skin Disease

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KEYWORDS

• Autoimmune bullous disease • Bullous pemphigoid • Pemphigus vulgaris
• Corticosteroid

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Learn the differential diagnosis of vesiculobullous skin disease.
2. Understand the workup of vesiculobullous disease.
3. Identify the 2 most important autoimmune bullous diseases—bullous pemphigoid (BP) and pemphigus vulgaris (PV)—and their associations.
4. Know the first-line treatment for BP and PV.

DEFINITION

What is vesiculobullous skin disease?

Vesiculobullous skin disease is a group of diseases that cause blistering of the skin. The differential of skin diseases that can cause vesicles ($\leq$1 cm in diameter) and bullae (>1 cm in diameter) is broad and includes multiple causes including, but not limited to, infection (impetigo, staphylococcal scalded skin syndrome [SSSS], herpes simplex viruses, varicella zoster virus), allergic reaction (Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], erythema multiforme [EM]), physical trauma (friction blisters, burns, edema), and autoimmune disease (dermatitis herpetiformis [DH], pemphigus vulgaris [PV], bullous pemphigoid [BP]). Autoimmune bullous diseases are those caused by dysregulation of the immune system, leading to autoantibodies against protein components of the skin and mucous membranes. In turn, this causes disruption of the integrity of these crucial areas, leading to bullae formation. The 2 most common autoimmune bullous diseases are PV and BP.

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Why is diagnosing these diseases so important?

Treatment of infectious, drug-mediated, and autoimmune-mediated blistering disease differs dramatically. Correct diagnosis potentiates appropriate therapeutic choices. Left untreated (and to a lesser degree with appropriate treatment), disseminated varicella, PV, BP, and TEN can be fatal. PV, BP, and TEN can result in widespread cutaneous erosions, compromising the skin's barrier function, leading to superinfection and bacteremia. Erosions can also lead to immobility from pain, with associated deep vein thrombosis and pneumonia. Therapy for BP differs from that for PV in some instances.

EPIDEMIOLOGY

How common is vesiculobullous skin disease?

Although impetigo and herpes simplex virus are relatively common, many causes of vesiculobullous disease are rare. SJS/TEN occurs in up to 7 patients per million per year.[1] Between 4.5 and 14 new cases of BP occur per million per year in Europe.[2] PV is the most common type of pemphigus and occurs in 1 to 5 per million, but is much more common in certain populations, including Ashkenazi Jews and some populations in Asia (India, China, Japan, Malaysia).[3]

At what age do patients contract autoimmune bullous disease?

Different diseases have different age distributions. Bullous impetigo occurs most commonly in neonates and children. SSSS is also more common in younger patients but can be seen in adults. PV is most common in those between 40 and 60 years of age and occurs equally in both sexes. BP generally occurs in those older than 60, with an increase in incidence as patients age. In one study, the incidence was greater than 400 per million in patients older than 90 years.[4]

PATHOGENESIS

What causes the bullae in bullous disease?

Most autoimmune bullous diseases involve autoantibody formation to protein components holding keratinocytes to each other or keratinocytes to the basement membrane. Different proteins are targeted in different diseases.

Autoantibodies in BP target the BP180 and BP 230 proteins in the cutaneous basement membrane zone.[5] Once bound, these autoantibodies trigger complement activation, triggering mast cell activation, attraction of other inflammatory cells and their accompanying proteolytic enzymes, and finally, a loss of cell-cell adhesion at the dermal-epidermal junction and formation of subepidermal bullae.

Autoantibodies in PV target the calcium-dependent cell-cell adhesion molecules, desmoglein 1 and desmoglein 3, resulting in acantholysis, or loss of cellular adhesion within the epidermis. Some hypothesize a contribution to acantholysis by antibodies targeting keratinocyte acetylcholine receptors.[6] Clinical manifestations may depend on the ratios of such antibodies.

In contrast to PV, the bullae in SSSS and bullous impetigo are caused by the cleavage of the desmoglein 1 complex by a bacterial exotoxin rather than by autoantibodies.[7] Unlike autoimmune bullous disease, bullae caused by allergic bullous disease (ie, SJS and TEN) occur through a cytotoxic T-cell mechanism. The cytolytic protein