

Differential Diagnosis of Bullous Dermatoses

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Introduction

Blister formation is the result of the breakdown of tissue integrity and fluid accumulation in a specific compartment of the skin (epidermal, dermal-epidermal junction or upper dermis). This can either be a primary or a secondary event.

In some cases blister formation is caused by localized bacterial (for example, impetigo) or viral (for example, herpes simplex or herpes zoster) infection. Blisters can also develop after a chemical or physical burn or after necrosis of the skin due to thrombosis of cutaneous blood vessels (for example, disseminated intravascular coagulation). Occasionally, blisters might arise as a presentation of an underlying dermatologic disease, such as lichen planus or lupus erythematosus. These groups of blistering diseases are formed secondary to another cutaneous disease.

Another group of blistering diseases has the formation of blisters as the primary skin disorder. The speaker highlighted a few examples of these, including epidermolysis bullosa lethalis, epidermolysis bullosa dystrophica, Stevens-Johnson syndrome, pemphigus vulgaris and bullous pemphigoid. They can also be further divided into genetic and acquired bullous dermatoses. As a consequence of the work of various investigators, remarkable advances have been made in elucidating the pathogenesis of these diseases and in developing new diagnostic tools and therapeutic approaches. The speaker spent the rest of the time on primary blistering disorders.

Evolution of the diagnostic criteria of blistering disorders

In 1943, the differential diagnosis of pemphigus vulgaris and bullous pemphigoid was made by light microscopy using H&E stain. This elucidated the differentiation between intraepidermal and subepidermal blisters. Subsequently, with the use of electron microscopy, a new form of blistering disorder, the junctional type, was defined. Later in the 60's, with the help of immunofluorescent stain, some patients with acquired blistering disorders were found to possess autoantibodies bound to intercellular substances as in pemphigus vulgaris and pemphigus foliaceus. Furthermore, granular IgA antibodies are found to bind to the basement membrane in patients with dermatitis herpetiformis and in a linear fashion in patients with linear IgA disease. Nowadays, the pathogenetic criterion is applied in the evaluation of patients with blistering disorders and molecular biological techniques are used to make the precise diagnosis for some genodermatoses.

The epidermal molecular structure

The epidermal molecular structure is highlighted in order to enhance the understanding of the pathogenetic criteria.

The keratinocyte cytoskeleton, composed of intermediate filaments (keratins), microfilaments (actin and associated proteins) and microtubules (tubulin), represents a structural component that is important in blister formation. The molecular components of the cytoskeleton and its associated proteins link the nucleus with the cell periphery, providing the framework structure of the epidermis. It has been demonstrated that keratins 5 and 14 are expressed by basal keratinocytes and that keratins 1 and 10 are expressed by keratinocytes of the suprabasal layers of the epidermis.

At the ultrastructural level, the desmosome appears as an organelle that is shared by two neighboring keratinocytes, each providing half of the structure. Two

parallel proteinaceous plaques are located just beneath the membrane of each cell and represent the site of insertion of intermediate filaments. The cell membrane of each keratinocyte is separated by a narrow space, the desmosomal core, which is contiguous with the epidermal intercellular spaces. The hemidesmosome also contains an intracellular attachment plaque in which intermediate filaments of the basal cells are inserted. The desmosomal plaque contains plakoglobin; desmoplakins 1 and 2, plakophilins 1a and keratocalmin. The hemidesmosomal plaque contains the BP230 antigen (a protein recognized by autoantibodies in patients with bullous pemphigoid) and plectin. The desmosomal core contains desmogleins 1, 2, and 3 and desmocollins. The hemidesmosomal transmembrane glycoproteins are BP180 and integrin $\alpha 6\beta 4$. The relevant components of the lamina lucida are laminin and fibronectin. The major component of the lamina densa is type IV collagen, and the anchoring fibers are composed of type VII collagen.

Genetic mutation vs breakdown of immune tolerance as causes of blister formation

Certain structural molecules of the skin might cause blistering disease by two unrelated mechanisms: genetic mutation and autoantibody formation. For example, patients born with a mutation of the BP180 antigen might develop generalized atrophic benign epidermolysis bullosa during the early years of life. However, in patients who become sensitized to this same molecule, diseases such as, herpes gestationis, cicatricial pemphigoid, or linear IgA disease might develop later in life. The mechanisms that modulate the phenotypic expression of a particular disease remain unknown. Similarly, mutation of laminin 5 is associated with epidermolysis bullosa lethalis (Herlitz syndrome) and an autoantibody response to this molecule leads to a form of cicatricial pemphigoid and bullous pemphigoid-like disease. Finally, mutation of type VII collagen results in epidermolysis bullosa dystrophica, whereas epidermolysis bullosa acquisita is a consequence of sensitization to this molecule. It seems that under normal circumstances a strict equilibrium is maintained between the function of these structural proteins and the immunologic tolerance to antigenic sites of the same molecules. Genetic mutation and a loss of function of the respective protein might trigger blister formation (genodermatoses). Similarly, a breakdown in immune tolerance to these antigens might trigger autoantibody formation, which, in turn, might induce blisters. In these

patients, the blistering eruption would be acquired and manifested later in life.

Pathogenetic classification

Bullous genodermatoses

These are divided into epidermolytic, junctional and dermolytic dermatoses. Epidermolytic hyperkeratosis, autosomal dominantly inherited, is an example of the epidermolytic type. It is due to the mutation of keratin 1 or 10. Epidermolysis bullosa simplex (EBS) is another example. There are many variants of EBS. In one of the variants, the defect is due to mutation of keratin 5 or 14. It is autosomal dominant and the blisters form through the basal layer. Another variant of EBS, being autosomal recessive, is associated with muscular dystrophy. The defect is due to mutation of plectin. Plakophilin deficiency syndrome is a new condition in this group of epidermolytic bullous genodermatoses. Plakophilin makes up the plaque of the desmosomes. Patients suffering from this syndrome present with suprabasal neonatal blisters.

There are mainly three forms in the junctional group, namely the Herlitz form, the junctional epidermolysis bullosa with pyloric atresia and the generalized atrophic benign epidermolysis bullosa (GABEB). The respective defects are due to mutation of laminin 5, integrin $\alpha 6\beta 4$ and BP180. All are autosomal recessive.

Both recessive and dominant epidermolysis bullosa dystrophica belong to the dermolytic group and the defect is due to mutation of collagen VII.

Autoimmune bullous dermatoses

Some of the examples of this group are the pemphigus foliaceus, pemphigus vulgaris, bullous pemphigoid (BP) and epidermolysis bullosa acquisita. Patients suffering from pemphigus foliaceus develop autoantibodies to desmoglein 1. When these antibodies are injected into mice, they develop features of pemphigus foliaceus. Fogo Selvagen is a form of pemphigus foliaceus endemic in Brazil. Autoantibody against desmoglein 3 is responsible for the development of pemphigus vulgaris.

In the bullous pemphigoid animal model, it is demonstrated that anti-BP180 antibody-mediated subepidermal blister formation depends on activation

of complement and recruitment of neutrophils. Results of more recent studies further suggest that neutrophil elastase and gelatinase B are key elements in the sequence of events leading to blister formation in this BP model. Other investigators demonstrated that antilaminin antibodies could induce subepidermal blisters demonstrated by passive transfer studies in neonatal mice. The results of these studies suggest that anti-laminin 5 autoantibodies associated with a subset of patients with cicatricial pemphigoid and with a BP-like disease might indeed be pathogenic. The pathogenic autoantibodies in EBA act against collagen VII of the anchoring fibers. To differentiate between BP and EBA, sodium chloride salt split test is employed. In BP, the antibodies bind to the epidermal side whereas in EBA the antibodies bind to the dermal side. The speaker also remarked that the test is not difficult to perform.

Conclusion

With better understanding of the complexity and pathogenesis of these blistering disorders, perhaps there will be new strategies to tackle them in the future. For example, gene therapy to correct the mutations in blistering genodermatoses or a new method to control the immune breakdown in autoimmune blistering disorders.

Learning points:

The pathogenetic criteria at the molecular level play a sophisticated role in the differential diagnosis of bullous dermatoses nowadays.