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Review

Diagnosis and classification of pemphigus and bullous pemphigoid

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ABSTRACT

Pemphigus and bullous pemphigoid represent the two major groups of autoimmune blistering diseases. Pemphigus has three major variants: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus and is characterized by autoantibodies directed against the cell surface of keratinocytes, producing acantholysis that in turn leads to intraepithelial blisters in the skin and/or mucous membranes. In bullous pemphigoid, the autoantibodies are present at the dermo-epidermal junction and attack the hemidesmosomes, causing subepidermal blister formation. The classification of the major variants of both the pemphigus group and bullous pemphigoid can be based on the combination of clinical, histopathological and immunopathological criteria. Many tools are available for the diagnosis of these entities including biopsy, direct and indirect immunofluorescence, immunoprecipitation, immunoblotting and ELISA. However, currently there are no generally accepted criteria for the diagnosis of these disorders. The present review provides a proposal for diagnostic criteria.

Contents

1. Introduction

Pemphigus and bullous pemphigoid are part of a large group of cutaneous autoimmune blistering disorders of unknown etiology.

Pemphigus encompasses a group of life-threatening diseases of which there are three major variants: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. The pemphigus group is characterized by autoantibodies directed against epidermal surface proteins leading to acantholysis, which is the loss of cell-to cell adhesion [1] resulting in intra epidermal separation.

Bullous pemphigoid represents the most common type of autoimmune blistering disorder, and is characterized by autoantibodies located at the dermo-epidermal junction against specific antigens in the hemidesmosomes [2] thus causing complete separation of the epidermis from the dermis.

2. History

Both pemphigus and bullous pemphigoid have served as models for studying and understanding autoimmune diseases. Acantholysis in pemphigus patients was first described by Civatte in 1943 [3]. However, it was not until 1964 that Beutner and Jordan utilized indirect

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immunofluorescence (IIF) in discovering that the sera of pemphigus vulgaris patients contained IgG autoantibodies against the cell surface of keratinocytes [4]. This finding provided the first evidence for the autoimmune nature of pemphigus. Meanwhile, it was Lever who in 1953 first described bullous pemphigoid as a sole entity distinct from other bullous disorders [5]. Again the teams of Jordan and Beutner were the first to discover through indirect and direct immunofluorescence (DIF) that the autoantibodies in bullous pemphigoid patients were localized in the basement membrane [4].

3. Epidemiology

Pemphigus vulgaris is the most frequent form of pemphigus [6]. The incidence worldwide ranges from 0.7 to 5 new cases per million per year. Although the disease can affect anyone, the incidence in Ashkenazi Jews can reach up to 16–32 cases per million per year. The mean age of onset is 50–60 years of age, although many cases have been described in the elderly and children [7]. The male to female ratio is 1:1. To date there is no substantial data regarding the incidence of pemphigus foliaceus and paraneoplastic pemphigus. However, there is a well supported association between the latter and underlying neoplasms, such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease [8], and thymoma [9] amongst others.

Bullous pemphigoid represents the most common type of autoimmune blistering disorder, with an incidence of 6–7 new cases per million per year which rises to 150–330 per million per year in those over 80 years old [10].

4. Pathogenesis

It is well established that IgG plays a pivotal role in pemphigus, not only as a diagnostic marker but also as the main pathogenic agent acting against the cell surface of keratinocytes producing acantholysis and thus the clinical presentation of blisters. This has been described by the two main studies into the condition conducted in human skin by Schiltz and Michael [11] and by Anhalt and Diaz in neonatal mice [12].

Desmosomes, which are composed of desmosomal cadherins, plakoglobin, plakophilin and desmoplakin, are molecular complexes specialized for cell-to-cell adhesion by anchoring intermediate filaments.

The target antigens identified in pemphigus vulgaris and foliaceus are part of the cadherin family. They are Desmoglein 1 (DSG1) – with a molecular weight (MW) of 165 kD – [13–16] and Desmoglein 3 (DSG3) – MW 130 kD – [17,18].

Each of these proteins is more intensely expressed in different layers of the epidermis. For example DSG1 is located more superficially than DSG3, which is confined to the lower portions of the epidermis. On the other hand, in the mucosa both are expressed throughout the squamous layer, although DSG3 is more abundant than DSG1. On the basis of this antigen distribution, Mahoney has suggested the “compensation theory” to explain the different clinical presentations in these two types of pemphigus [19]: DSG1 and DSG 3 compensate for each other's loss of function in tissues where they are equally expressed [20]. For example, in patients with pemphigus foliaceus, who have antibodies against DSG1 alone, superficial blisters are formed due to an absence of DSG3 in the most superficial layers of the epidermis. Although the anti-DSG1 antibodies in these patients bind to the mucosa, no clinical blisters are formed due to the coexpression of DSG3.

In contrast, in mucosal dominant pemphigus vulgaris, in which there are antibodies to DSG3, there are generally no cutaneous blisters because DSG1 compensates for the loss of DSG3. However, in the mucosa the low levels of DSG1 will not be able to compensate for the loss of DSG3. In the mucocutaneous form of pemphigus vulgaris, in which there are antibodies to both DSG1 and DSG3, blisters will be present in both the skin and the mucosa.

The antigens described in paraneoplastic pemphigus patients are primarily those of the plakin family [21–23] these being envoplakin – MW 210 kD, desmoplakin I – MW 250 kD, desmoplakin II – MW 210 kD, plectin – MW 500 kD – and periplakin – MW 190 kD. However, other antigens have also been reported such as DSG3, DSG1, bullous pemphigoid antigen 1 (BPAG1) and, most recently, the alpha-2 macroglobulin-like-1 — MW 170 kD [24].

In bullous pemphigoid the antigens targeted by circulating autoantibodies have been described as BPAG1 – MW 230 kD and bullous pemphigoid antigen 2 (BPAG2) or type XVII collagen – MW 180 kD [25–27]. These are key components of the hemidesmosomes and play a major role in cell-matrix adhesion.

While both antigens are recognized and targeted by T and B cells in bullous pemphigoid, it has been demonstrated that the NCA16 region of BPAG2 is the main site [28].

These autoantibodies that bind complement lead to the disruption of the dermo-epidermal junction [29,30].

5. Clinical manifestations

Patients with pemphigus vulgaris are divided into two major subgroups: those with only mucosal lesions and those with both mucosal and skin involvement.

The primary eruption consists of flaccid blisters that easily rupture leaving large painful erosions. In the mucosa, blisters are rarely observed, since they are fragile and break easily, leaving erosions.

The most common affected mucous membrane is the oropharyngeal mucosa. However other sites, such as the genitalia and conjunctiva, may be involved as well. While skin lesions may involve any body area, the most commonly affected sites are the scalp, face, neck, trunk and groin.

Unlike patients with pemphigus vulgaris, those affected with pemphigus foliaceus very rarely develop mucosal lesions. These patients present with small flaccid blisters that almost immediately rupture leaving crusted erosions.

In both pemphigus vulgaris and foliaceus, Nikolsky's sign (the ability to split the epidermis on normal-appearing skin next to a lesion by applying pressure) is frequently positive and correlates with disease activity.

The clinical hallmark of paraneoplastic pemphigus is painful and persistent stomatitis which is extremely resistant to therapy. The cutaneous presentation is much more variable than that observed in the other types of pemphigus, manifested by a spectrum of lesions such as flaccid or tense blisters, lichenoid lesions, erythema multiforme-like lesions or confluent-erosive lesions resembling toxic epidermal necrosis [31].

Bullous pemphigoid is characterized by pruritic tense blisters localized to the trunk and flexural aspects of the extremities, which break after several days leaving eroded and crusted lesions. The vast majority of patients do not suffer from oral involvement. Unlike in pemphigus, Nikolsky's sign is negative.

Occasionally, bullous pemphigoid can be manifested as a pruritic non-bullous eruption consisting of polymorphic and nonspecific lesions such as erythematous, urticarial papules and plaques.

6. Histopathology

Pemphigus is characterized by the presence of acantholysis with the formation of intraepidermal blisters. In the vulgaris type these are suprabasilar, while in the foliaceus type they are located in the granular layer and therefore are more superficial.

When evaluating biopsies taken from the skin or mucosa in patients with paraneoplastic pemphigus, it is important to emphasize that the histology will vary depending on the morphology of the lesions. Biopsies taken from the stomatitis show nonspecific inflammation. However perilesional mucosa may show intraepithelial acantholysis; a biopsy from a skin blister will show suprabasilar acantholysis, while the