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Mini review

Bullous pemphigoid autoantibodies

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Abstract: Autoimmune blistering skin disorders are rare. According to direct immunofluorescence studies, three categories are described: pemphigus group, pemphigoid group and dermatitis herpetiformis. Among these diseases, bullous pemphigoid is the most common. Patients with typical bullous pemphigoid disease are usually elderly and have many comorbidities. Considering that topical and systemic corticosteroids are the first choice therapy, these patients also have increased morbidity and risk of death. The main characteristic of bullous pemphigoid as an acquired autoimmune blistering disease is the formation of autoantibodies against hemidesmosomal antigens BP180 and BP230. Although IgG autoantibodies predominate within the plasma and skin of BP patients, some features of the disease cannot be explained solely by IgG-mediated mechanisms. Epitope spreading phenomena, immunoglobulin class switch and the relevance of IgM and IgE autoantibodies are discussed in this article.

Keywords: bullous pemphigoid; autoantibodies; autoantigens

1. Introduction

Bullous pemphigoid (BP) is not only the most common disorder within the pemphigoid group, but also the reported incidence of BP in Europe is continuously increasing. An important aspect of this disease is that it affects older people with many comorbidities and chronic drug intake. The clinical picture typically presents with generalized crops of tense, pruritic cutaneous blisters and/or mucosal erosions. In up to 1/5 of the cases, the clinical picture may initially mimic other pruritic skin disorders. The non-bullous phase may dominate the clinical appearance, composed by eczematous, excoriated, urticarial-like or nodular lesions, and occasionally remains the sole clinical manifestation. Relative with the clinical picture, an inflammatory and non-inflammatory phenotype are described as an expression of different pathogenic mechanism. The histopathological assessment of a recent

blister is not pathognomonic, but it is necessary for the diagnosis. The dermal-epidermal split with a dermal inflammatory infiltrate, usually consisting of lymphocytes and eosinophils, and more rarely neutrophils, are highly suggestive. The immunologic criteria remain the corner stone of the definite diagnosis and include the linear deposition of antibodies and/or complement at the epidermal site of the basal membrane zone and circulating cutaneous autoantibodies confirmed via indirect immunofluorescence or ELISA.

2. The particularities of humoral response in BP

The immunological events events in BP begin with the humoral and cellular response directed against two self-antigens, BP 180 and BP230, both hemidesmosome proteins. Although BP180 remains the main BP autoantigen, other four autoimmune subepidermal blistering diseases are associated with immune response to BP180, including pemphigoid gestations, cicatricial pemphigoid, lichen planus pemphigoides and linear IgA disease. For the moment, the link between these diseases, the immunoglobulin class observed in each one, and the restricted expression of BP180 (BPAg2, BP180 or collagen XVII) to stratified, pseudostratified and transitional epithelia [1], remain insufficiently explored. The widely expressed throughout the body tissue-specific isoforms of BP230 (BPAg1, BP230, also called dystonin), including skeletal muscle and brain [2], accounts for less than 10% of all BP. While both serum autoantibodies are useful for diagnosing BP in patients with suspicious clinical features, only anti-BP180 IgG allowed prediction of disease activity over time [3]. Antibodies of the IgG isotype reacting against BP230, combined or not with anti-BP180 antibodies, are usually found in a smaller proportion of BP patients [4]. BP180, as a transmembrane glycoprotein, consists of a globular cytoplasmatic N-terminal domain, a short transmembrane stretch and a large extracellular C-terminal domain. The extracellular part contains 15 collagenous repeats interrupted by non-collagenous (NC) domains, with the largest and most immunogenic NC16A domain located in the immediate neighborhood of the epithelial cell membrane. However, several studies demonstrated that, in addition to the NC16A domain, other epitopes of BP180 and BP230 are the target for both autoaggressive B and T cells, and IgG recognition of the BP180 ectodomain is an early event, followed by intra- and intermolecular epitope spreading events [5]. The above immune-related procedure seems to be crucial for the individual course of any BP type, including drug-associated BP.

The typical direct immunofluorescence studies demonstrate the subepidermal splitting and linear IgG deposition along the epidermal basal membrane zone in an “n” serrated pattern. While IgG are usually predominant, sometimes along with IgM, IgA or IgE, the complement linear deposition alone or associated with IgG is also considered an immune diagnostic criteria for BP. Establishing the pathogenic relevance of each autoantibody isotype might be essential for guiding the therapeutic regimen. An important prospective multicenter study concludes that higher IgG reactivity with extracellular, but not intracellular epitopes of BP180, is directly related with the severity of the disease course [6]. Another study shows that higher levels of IgG anti-BP180 are associated with increased 1-year mortality [7].

IgG1 and IgG4 are the most frequent subtypes and sometimes IgM coexists. The exclusive IgM deposition in pemphigoid has rarely been described. The significance of only IgM presence is still a debate matter in the physiopathology of BP [8]. Over the last two decades, the IgG-based models were critical for understanding the fundamental pathomechanisms of BP. The itching, the erythema

and the eosinophilia remain specific features observed in human disease that this model failed to reproduce experimentally. While the role of IgA and IgM is still elusive and their deposits did not seem to effect the disease course, the role of IgE is controversial. Thus, the pathogenic contribution of IgE in BP was initially considered based on the early urticarial phase of BP and the established role of IgE in type I hypersensitivity responses. Despite the fact that some studies support the pivotal role of IgE in BP pathogenesis [9,10], there are still many questions to be asked about the way in which total or specific IgE determines the disease course. Cases where omalizumab, a recombinant DNA-derived humanized IgG1 monoclonal antibody that specifically binds to free human IgE, was successfully used in treating BP, represent a consistent proof that IgE might play a key role in BP pathogenesis, as well as a therapeutic target [11]. Blood eosinophilia, elevated total serum IgE levels, and different soluble inflammatory Th2 and Th1 response mediators have been described in cohorts of patients with classic clear-cut BP manifestations [9,12]. Clinical features and histological findings in BP support a predominantly Th2-oriented inflammatory reaction, especially in the early stages of the disease. Furthermore, in a recent study, Kridin et al. conclude that a history of atopic dermatitis and allergic rhinitis confers susceptibility to the development of BP [13]. Both IgE autoantibodies and a Th2-oriented immune response may play a role at least in the initial phases of BP and atypical cases of BP, such as severe erythematous and urticarial forms of BP, as well as blister formation [14]. Direct immunofluorescence and indirect immunofluorescence, as well as anti-BP230 and anti-BP180 IgE ELISA testing, show self-reactive IgE autoantibodies in a consistent number of BP patients, more often in patients with high total circulating IgE [15,16]. Recent observations suggest that IgE may have FcR-independent effects in BP [17]. Therefore, detection of bound IgE is complicated by the cross-binding of anti-IgE antibodies to IgG [18].

Drug-induced or drug-associated BP describes clinical, histological and immunopathological features identical to classic form of BP and is related with systemic ingestion of particular drugs, more frequently dipeptidyl peptidase inhibitors (DPP4i) [19]. Depending on the implicated drug, different pathogenetical mechanism are described. Finally, the elevated titre of anti-BP180NC16A auto-antibodies observed in patients receiving any systemic medications prior to the development of the disease, when compared to those receiving no medications [20], is occasionally observed this particular drug reaction. New data suggest that DPP4i-associated BP do not involve the NC16A domain [21], at least not at the beginning of the pathological process [22], supporting the epitope spreading theory along with immunoglobulin isotype switch.

3. Conclusions

In conclusion, BP is an organ-specific disease of the skin and mucous membranes characterized by circulating and tissue bound autoantibodies against BP180 and BP230 multiple epitopes. After binding of autoantigens to their targets, a series of immunological responses and enzymatic processes are activated. These responses are mostly intermediated by complement activation and inflammatory cell recruitment. IgG recognition of the BP180 ectodomain is an early event, followed by intra- and intermolecular epitope spreading events [5] and probably certain antibody deficiencies [23] related with immunoglobulin class switch, which determine the individual course of BP.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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