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CURRENT UPDATE ON PRESENTATION, PATHOGENESIS AND PROGNOSTIC MARKER OF BULLOUS PEMPHIGOID: A REVIEW

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ABSTRACT
Over the centuries, blistering skin disorders have been described under a variety of terms, such as pemphigus, plyctainia, phlyzakion. However, it is only about 40 years since Lever (1956), based on distinctive clinical and histological features, recognized bullous pemphigoid as a distinct disorder within the large group of blistering disorders, including the pemphigus group. Bullous pemphigoid is uncommon autoimmune subepithelial blistering diseases that most frequently arise in older adults and are characterized by the presence of cutaneous bullae and erosive mucosal lesions. Over the past few years due to advancement of markers and microscopes significant progress has been made in understanding the underlying pathogenesis of these diseases. Several factors including immunoglobulins, complement system and the migration of inflammatory cells into the subepithelial tissue, likely contribute to the clinical manifestations of bullous pemphigoid. This review will aid in understanding current concepts involved in presentation, pathogenesis, prognostic markers, diagnosis and treatment modalities bullous pemphigoid.

KEYWORDS: Autoimmunity, Bullous pemphigoid, BP180, BP230, Hemidesmosome.

INTRODUCTION
Bullous Pemphigoid (BP) is the most common autoimmune bullous disease affecting primarily the skin and is an example of organ-specific autoimmune disease. BP occurs most frequently in the elderly (60-80 years of age) and affects men and women equally. In contrast to most autoimmune diseases, men have a higher risk of suffering from BP than women. Although BP is usually a disease of the elderly, it may rarely occur in children.[1,2,3]

The skin lesions usually begin as urticarial plaques or erythematous papules, which evolve into large, tense bullae filled with clear fluid. Histologic examination of these lesions shows detachment of the epidermis from the dermis producing subepidermal blisters. The upper dermis exhibits an inflammatory infiltrates, including eosinophils, neutrophils, lymphocytes, and monocytes/macrophages. The predominant inflammatory cells in early lesions are usually eosinophils. Histologic evidence of mast cell degranulation has also been reported.[4,5,6] Current article focuses on concepts involved in pathogenesis and clinical presentation of Bullous pemphigoid.

Clinical Features
The lesions are frequently distributed symmetrically and predominate on the flexural aspects of the limbs, and abdomen. In the intertriginous spaces, vegetating plaques can be observed. Involvement of the oral cavity is observed in 10–30% of cases. The mucosae of eyes, nose, pharynx, esophagus and ano-genital areas are more rarely affected. Several *clinical variants* of BP have been described. Lesions remain occasionally localized, such as on the pretibial area ("pretibial pemphigoid"), around stomas, on the vulvar region ("vulvar pemphigoid"), on irradiated areas or confined to a paralyzed limb. Palmo-plantar involvement mimicking dyshidrosiform eczema ("dyshidrosiform pemphigoid") might be observed. Several other variants, such as a prurigo nodularis – ("pemphigoid nodularis"), and an erythroderma-like form have been described.[1,2,3,4,6]

PATHOGENESIS
1. Autoimmune Features
Autoantibodies
BP patients have circulating and tissue-bound IgG autoantibodies directed against two hemidesmosomal proteins known as the BP230 (BPAG1) and the BP180

(BPAG2, type XVII collagen) antigens. The autoantibodies to BP180 are predominantly of the IgG1 and IgG4 subclasses. In addition to IgG autoantibodies, IgE autoantibodies to BP180 are found in the majority of untreated BP patients. Only antibodies to BP180 have been demonstrated to be pathogenic in neonatal mice.[1,4,6]

The BP230 antigen is an intracellular hemidesmosmal plaque protein belonging to the plakin family, whereas the BP180 antigen is a hemidesmosomal transmembrane protein belonging to the collagen family. The BP180 protein shows a type II orientation, with its N-terminal region toward the intracellular hemidesmosomal plaque and its C-terminal half projecting into the extracellular milieu of the BMZ. The anti-BP180 autoantibodies from BP patients recognize multiple epitopes that cluster within the noncollagen 16A (NC16A) domain of the BP180 ectodomain. It has been reported that the serum levels of autoantibodies to BP180 NC16A in patients are directly correlated to disease severity.[1,6]

T-Cell Activation

It has been reported that BP180-specific autoreactive T cells recognize epitopes located predominantly on the NC16A domain of the molecule. These T lymphocytes express CD4+ memory T-cell surface markers and exhibit a Th1/Th2 mixed cytokine profile.

2. Genetic Features

HLA studies involving American, Japanese, and British BP patients showed no significant association between the disease and HLA-A, -B, -C, and -DR loci, while a marked increase in the HLA-DR5 allele was found in BP patients from France. Studies have demonstrated that HLA-DQB1*0301 is associated with BP in white patients. Whereas DRB1*0403, 0406, or DRB1*1101 have high frequency in Japanese patients.[7,8,9]

3. Humoral and Cellular Immune Response and Tissue Damage

Almost all BP patients have autoantibodies binding to an immunodominant region of BP180, the NC16A domain, which is located extracellularly close to its transmembrane domain. Memory B cells specific for the NC16A domain have been identified, that can be induced *in vitro* to synthesize autoantibodies. Nevertheless, additional antigenic sites exist on both the extracellular and intracellular domain of BP180, which is recognized by up to 40% of the BP sera.

As the result of an "epitope spreading" phenomenon besides BP180 and BP230 BP patients also exhibit IgG autoantibodies against distal 704-residues stretch of the BP230 tail. And NH2-terminal half of BP230 in at least 30% of the cases also against plectin and laminin 5. BP patients exhibit a specific reactivity pattern and binding to intracellular epitopes may be detectable at an early clinical stage.[10]

Since they are critical for driving autoantibody production Autoreactive T cell responses to the ectodomain of BP180 have been found in patients with BP, gestational pemphigoid and in healthy individuals. Strikingly, epitope recognition appeared to be restricted by certain HLA class II alleles, such as the HLA-DQβ1*0301 allele, that are prevalent in BP. CD4 T cell lines and clones derived from BP patients were shown to produce both Th1 and Th2 cytokines. Since Th1 cytokines (such as IFNγ) are able to induce the secretion of IgG1 and IgG2, while Th2 cytokines (such as IL-4, IL-5, and IL-13) have been shown to regulate the secretion of IgG4 and IgE. The detection of anti-BP180 and anti-BP230 antibodies of the IgG1, IgG4 and IgE isotype in BP patients suggest that both autoreactive Th1 and Th2 cells are involved in the regulation of the response to the BP target antigens. This idea is further supported by the analysis of the cytokine expression profile in lesional tissue and patient's serum, that shows an increase in most cytokines with significant correlations betweeen their level and skin lesions number. Nevertheless, the relative low concentrations of IFNγ and IL-2 compared to those of IL-4, IL-5 and IL-10 suggest a predominance of a Th2 response.[11,8]

The mechanisms by which autoantibodies are thought to be pathogenic include complement activation, recruitment of inflammatory cells and liberation of proteases, such as matrix metalloproteinase (MMP)-9 and neutrophil elastase, which are detected in lesional skin and blister fluid. Specifically, these proteinases, which are strongly expressed by neutrophils and eosinophils, are thought to proteolytically degrade various extracellular matrix proteins as well as the extracellular domain of BP180.[12]

IgE anti-BP180 autoantibodies may also stimulate degranulation of basophils and/or mast cells. Eosinophils play an important role in mediating tissue injury. High levels of IL-5 and eotaxin have been detected in blister fluid of BP patients. IL-5 promotes growth and activation of Eosinophils and eotaxin is an eosinophil specific chemokine regulating eosinophil migration produced by fibroblasts and probably keratinocytes. It contributes to the local inflammation by releasing both pro-inflammatory cytokines as well as proteases. Autoantibodies to BP180 have been shown to directly modulate the expression of IL-6 and IL-8 as well as tissue-type plasminogen activator by cultured keratinocytes.[1,6,12]

4. ANIMAL MODELS

IgG Passive Transfer Model

Early studies on passive transfer of human BP IgG containing anti-BP180 and anti-BP230 autoantibodies to neonatal mice were unsuccessful as the murine BP180 protein did not react with human anti-BP180 antibodies due to differences at the amino acid level of the NC16A of the molecule. This problem was overcome by raising rabbit antibodies against a segment of murine BP180

homologous to the human epitope. It was demonstrated that these anti-BP180 antibodies were pathogenic if passively transferred into neonatal mice. The animals recapitulated the key clinical and histologic features of the human disease.[1,2,6]

Sub-epidermal blistering is an inflammatory process that develops in the following steps.

1. Anti-BP180 IgG binds to the pathogenic epitope of BP180 antigen in basal keratinocytes (BK).
2. The molecular interaction between BP180 antigen and anti-BP180 IgG activates the complement system (C).
3. C activation products C3a and C5a cause mast cells (MC) to degranulate.
4. Proinflammatory mediators released by MC recruit neutrophils (PMN).
5. Infiltrating PMNs release proteolytic enzymes, including neutrophil elastase (NE) and gelatinase B (MMP-9).
6. Proteolytic enzymes degrade BP180 and other extracellular matrix proteins, leading to subepidermal blistering.

In contrast to the PV and PF mouse models, the sub-epidermal blistering in mice induced by anti-BP180 anti-bodies depends on complement activation and a subsequent cascade of inflammatory events, including mast cell degranulation and neutrophil infiltration. Proteolytic enzymes (neutrophil elastase and gelatinase B) released from recruited neutrophils are the final effector molecules that cause the epidermal-dermal separation seen in skin lesions.[1,2,6]

5. Active Immunization Model

The BP animal model developed by active immunization of adult C57BL/6J mice with a recombinant murine BP180 antigen shows subepidermal blisters and a dermal inflammatory neutrophilic infiltrate three weeks after the boosting immunization. Perilesional skin of these animals showed *in vivo* deposition of IgG and C3 at the BMZ. The autoimmune response in these animals is an MHC class II-restricted T-cell response. Though BALB/c and SJL mice were unable to mount a pathogenic autoantibody response upon immunization with the murine BP180 antigen.[11,13]

Diagnosis

Because of the clinical and immunopathological overlap with other autoimmune subepidermal blistering disorders, diagnosis of BP relies on the characterization of the targeted antigens. However, immunofluorescence microscopy studies are very useful for an initial classification. The approach needs confirmation, a work-up including IF microscopy studies in elderly patients with itch with or without skin manifestations exclude a prodromal, non-bullous phase of BP.[1,2,3,4]

1. *Light microscopy studies:* In early non-bullous phases, subepidermal clefts and eosinophilic spongiosis are found. Nevertheless, in the early phase of the disease or in atypical cases of BP histological features are not diagnostic.
2. An early bulla shows a subepidermal blister with a dermal inflammatory infiltrate composed predominantly of Eosinophils and neutrophils.
3. *Direct immunofluorescence microscopy studies:* characteristically shows linear deposits of IgG and or C3, and more rarely, of other Ig classes along the epidermal basement membrane.
4. Testing of autologous patient's skin after treatment with 1 M NaCl can allow the distinction of patients with BP (deposits on the epidermal side of the split or on both side of the split) from those with epidermolysis bullosa acquisita or anti-epiligrin cicatricial pemphigoid (deposits on the dermal side).
5. *Indirect immunofluorescence studies:* demonstrates the presence of circulating IgG autoantibodies in 60 to 80% of patients, that typically bind to the epidermal side of saline separated normal human skin. The latter substrate has been found to be superior than intact skin and other substrates such as monkey esophagus.
6. In gestational pemphigoid, patients have IgG1 and IgG3 complement-fixing antibodies which are best detectable by a complement-binding indirect method.
7. *Immunoblot and immunoprecipitation studies:* of keratinocyte extracts show in 60% to 100% of patients' sera the presence of autoantibodies binding to a 180 kDa and 230 kDa protein, corresponding to the BP antigen 180 (BP180, also termed BP antigen 2, or type XVII collagen) and BP230 (also termed BP antigen 1), respectively. Recombinant forms of BP180 and BP230 expressed in prokaryotic or eukaryotic systems (such as baculoviruses, epithelial cell lines, and yeast) have been increasingly used for the detection of auto-antibodies.
   In gestational pemphigoid, patients' autoantibodies predominantly recognize BP180.
8. *Enzyme linked immunosorbent assays:* (ELISA) utilizing recombinant proteins encompassing various portions of either BP180 (such as the NC16A domain, the COOH-terminal portion or its entire ectodomain) or of BP230 have been found to be highly specific and sensitive. Antigens are tested under native conditions and, by this means, reactivities against conformational antigens are not missed.

Prognostic Markers

Serum levels of autoantibodies to BP180 are parallel to disease activity. The phenotype of the disease is relateed to the autoantibody profile. For example, reactivity with both the NH2- and COOH-terminal region of the ectodomain of BP180 was found to be more frequently detected by ELISA in patients with mucosal lesions. Furthermore, in a recent study, the presence of anti-BP230 IgG autoantibody was particularly associated with a less severe clinical manifestation of BP. There is

no data if assessment of antibodies to BP180 could guide treatment.

Therapy and Prognosis

BP is a chronic disease showing spontaneous exacerbations and remissions, that might be associated with significant morbidy and have serious impact on the quality of life (severe itch, bullous and eroded lesions, impetiginization). The majority of patients go into remission under treatment but the mortality rate is estimated between 12 to 40% in the first year, is considerable. It is likely that practice patterns (e.g., use of either systemic corticotherapy or immunosuppressive drugs) critically affect overall morbidity.

The treatment of BP is relatively well codified. Systemic corticosteroids have been widely utilized in clinical practice and their efficacy has been confirmed in uncontrolled and controlled studies. However, their use is associated with significant side effects. For patients with extensive disease, oral prednisone at the dosage of 0.5 to 1 mg per kg per day usually controls the disease within one or two weeks. This dose is then progressively tapered over a period of 6 to 9 months. The concomitant use of immunosuppressive drugs, such as azathioprine, chlorambucil, cyclophosphamide, ciclosporine, mycophenolate mofetil, and methotrexate, is a matter of debate. Some clinicians prefer to introduce them only when corticosteroids alone fail to control the disease, or if the latter are contraindicated. In addition, in certain treatment-resistant cases, pulse corticosteroid therapy, intravenous immunoglobulins, plasmaphereseis and photophoresis have been utilized. Finally, in all BP patients, it is important to undertake all measures aimed at preventing the complications of both the cutaneous lesions and of the treatment.[1-4,6]

SUMMARY

Our understanding of BP, a blistering disorder of the skin and mucosae, has greatly improved. BP has emerged as a paradigm of organ-specific autoimmune disease. Patients' autoantibodies are directed against the BP antigen 230 and BP antigen 180. These two autoantigens are components of hemidesmosomes, adhesion complexes in human skin that promote dermo-epidermal cohesion. Animal models have provided convincing evidence for the pathogenic significance of these autoantibodies as well as novel insights into the cascade of events leading to subepidermal separation. Improved knowledge of the pathophysiology of BP will hopefully allow the development of new immunomodulatory treatments for this potentially devastating disease.

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