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Under the surface: Understanding and managing bullous pemphigoid

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Abstract

Bulous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease in Western populations, and typically occurs in the elderly. Immunologically, BP is characterized by both tissue-bound and circulating autoantibodies against the BP antigen 180 (also referred to as BPAG2), BP antigen 230 (also referred to as BPAG1e), or both. These antigens are components of hemidesmosomes that are involved in dermal–epidermal adhesion. The following are risk factors for BP: advanced age, dementia, Parkinson's disease, cerebrovascular illness, and some medications, such as spironolactone, loop diuretics, and neuroleptics. In the early stages of the disease or in atypical, non-bullous variations, only excoriated, eczematous, or urticarial lesions are seen. Strong topical corticosteroids being an effective first-line treatment for BP, there is ongoing debate regarding their long-term viability. Future substitutes for traditional immunosuppressive medications for maintenance therapy include more recent therapeutic medicines that target molecules implicated in the inflammatory cascade linked to BP.

Keywords: Antibodies; Autoimmunity; Hemidesmosomes; Pemphigoid; Bullous; Skin diseases; Vesiculobullous

1. Introduction

BP is a subepidermal bullous acquired autoimmune disease in which autoantibodies target constituents of the skin's basement membrane zone. Autoantibodies mainly IgG (rarely IgA, IgM, and IgE) bind to the BP230 and BP180 antigens, which are components of the hemidesmosome adhesion complex. In animal models, the antigen–antibody interaction has been demonstrated to trigger the formation of subepidermal blisters.[1]

Lever originally used the name pemphigoid in 1953 to distinguish it from pemphigus, an intraepidermal blistering disorder caused by acantholysis, and to describe a disease characterized by bullous development due to subepidermal detachment. Then, through direct and indirect immunofluorescence techniques, Jordan and Beutner demonstrated that patients with bullous pemphigoid (BP) had autoantibodies.[2]

Bullous pemphigoid (BP), the first autoimmune bullous disease, mainly affects elderly patients and is strongly associated with neurological diseases, which are also significant predictors of prognosis.[3]

2. Clinical manifestations

Bullous pemphigoid (BP), the first autoimmune bullous disease, mainly affects elderly patients and is strongly associated with neurological diseases, which are also significant predictors of prognosis.

BP is an acute condition that typically results in flexural distribution of skin lesions and does not scar. However,the disease can be localized or generalized. In approximately 50% of patients, there is some form of mucous membrane

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involvement, and the oral mucosa is most commonly affected. Either normal-looking or erythematous skin can develop tense blisters. Oral lesions are typically composed of small blisters or erosions, predominantly on the palatal mucosa. An urticarial or eczematous rash can predate the formation of blisters. Itching is mild to very severe and often precedes blisters by weeks, months, or even years. [1]

3. Pathophysiology

Tissue-bound and circulating gG autoantibodies against BP 230 kD (BPAg1) and BP 180 kD (BPAg2, COL17), two constituents of the hemidesmosome within the stratified epithelia, are characteristic of the pathophysiology of BP. A cytoplasmic protein, BPAg1 facilitates the intermediate filaments to attach to the cytoskeleton. Several collagenous extracellular domains occur in the transmembrane adhesion protein, BPAg2. Antibodies to BPAg2 appear to be responsible for the development of subepidermal blisters. The exact role of BPAg1 in pathophysiology remains obscure and potentially plays a passive role. [4] In addition, autoantibodies against two more components of the skin basement membrane, namely, alpha 6 integrin and laminin-5, are associated with BP.[5] The fixation of IgG autoantibodies to the basement membrane leads to activation of the complement and inflammatory mediators. Most dependence has been established as being between complement system activation and the attraction of inflammatory cells toward the basement membrane. Proteolytic cleavage of these components by the secreted proteases from the blisters produces their formation due to the degradation of hemidesmosomal proteins. Histopathologically, it appears that the inflammation is accompanied typically by the presence of eosinophils; again, it isn't considered sufficient for the purposes of diagnosis. Chemokines and cytokines of the types-eotaxin, IL16, and IL2-play roles as well. IgE autoantibodies against COL17 (BP180Kd Ag) are present in 86% of untreated BP patients, implying that IgE is associated with the early urticarial phase of BP. IgE autoantibodies against COL17 were associated with a severe type of BP according to Iwata et al.[6] These patients required a higher dose of prednisolone and a more aggressive and long-term treatment regimen to attain remission.[6]

4. Risk factors and associated disorders

4.1. Age

One of the most important, if not the most important, risk factors for the development of BP is old age. [7,9,11]This was first demonstrated in a retrospective study based on the age- and gender-specific incidences of BP in two German regions. The research concluded that above the age of 60 years, patients exhibited an increased possibility of BP and that at above 90 years of age, the relative risk seemed to approximately 300 fold than for below 60 or the younger people.[7] Other studies, conducted in European countries, confirmed that the risk of BP development increases steeply beyond age 80[9,11], with a rate of over 300 cases per million person-years in people aged 80 years or older. Actually, it would not be appropriate to label BP in elderly people as a rare condition.[11]

4.2. Neurologic disease

Over the last decade, numerous reports in either a hospital-based or community-based setting have pointed to a relationship between BP and any psychiatric or neurological disorder.[28-40] Neurologic conditions, including dementia (Alzheimer's disease), Parkinson's disease, and cerebrovascular disease, were reported in 22–46% of all BP patients.[28,31,33-35,37] Patients with an associated dementia were older and had a lower Karnofsky score.[28,39] BP was significantly related to neurological conditions in case-control studies and also in a recent meta-analysis.[40] The solitary population-based study, conducted in the UK, and also a meta-analysis reported a significant association with multiple sclerosis. In addition, several case reports and small case series have suggested an association of BP with Shy-Drager syndrome or amyotrophic lateral sclerosis, which has not been confirmed by case-control studies.[41,42] Thus, degenerative neurological diseases such as Parkinson's and Alzheimer's, which may involve autoimmune pathways, seem to be associated with BP. Both the central nervous system and the peripheral nervous system exhibit various forms of BP230. Therefore, an autoimmune reaction to the dystonin gene's neural isoform of BPAG1 (BPAG1-n) might result in a secondary autoimmune reaction to the epithelial isoform of BPAG1. In general, when considering all these biological and clinical data, they highly suggest that neurologic disorders could indeed be a significant risk factor for BP , perhaps through humoral inflammatory reactions in the nerve system that can then spread to the skin.

4.3. Drugs

Systemic drugs may also play a role in the etiology of BP in some patients.[35, 43-47] Many drugs have been reported to be associated with BP development, including diuretics (furosemide and spironolactone), analgesics, D-penicillamine, antibiotics (amoxicillin and ciprofloxacin), potassium iodide, captopril, tumor necrosis factor inhibitors, and more

recently, antidiabetic dipeptidyl peptidase-4 inhibitors, known as gliptins.[43,44] There have been anecdotal reports of BP lesions reappearing after drug rechallenge with some drugs (e.g. spironolactone). Therefore, to conclusively prove that dipeptidyl peptidase-4 inhibitors are linked to the development of BP, large, prospective, case-control studies are still required. Therefore, while some mechanisms through which these drugs lead to this autoimmune blistering skin condition remain obscure-including by altered antigenic features of the epidermal basement membrane or as modulators of the immune system-more study needs to be devoted to ascertaining mechanisms leading to BP when it has a suspected inducer such as the identified culprit drugs. [47]

4.4. Internal malignancies

Since both BP and cancer are diseases of old age, the association between intra-abdominal malignancies and BP is likely to be due primarily to the patient's advanced age. Indeed, for decades, thousands of case reports have associated BP with all sorts of cancers; but, in a few hundred of these, the clinical course of intra-abdominal cancer and BP result paralleled.[48] Case-control studies yielded inconsistent results regarding the association of BP with cancers of internal organs. Hematological and non-hematological malignancies were significantly higher in patients with BP than in controls (17% vs. 5.4; OR 3.6), a UK hospital-based case-control study reported.

[49] However, the rate of malignancy in controls was unexpectedly low, and the sample size was small.[51] In addition, a recent statewide English record linkage research found that BP patients did not have a higher risk of concomitant and subsequent malignant tumors than the reference cohort (relative risk of cancer). [52]Patients with BP should be closely monitored in clinical practice, both clinically and through the use of age-related cancer screening procedures that are advised for the general public.[53]

4.5. Other conditions

Bullae may be confined to psoriatic plaques or lichenoid papules, a Koebner phenomenon, and BP has been associated with a variety of dermatoses, including lichen planus and psoriasis. The term used to describe the coexistence of BP and lichen planus is lichen planus pemphigoides. [33] Other theories, such as the function of antipsoriatic medications like tar or psoralen plus ultraviolet A (PUVA) therapy [48], have been put out to try and explain the co-occurrence of psoriasis vulgaris and BP. Recent studies indicate that there may be a pathophysiological link between psoriasis and BP, with potential future treatment avenues for BP based on the possible role of T helper (Th) 17 cells in patients with psoriasis and interleukin (IL)-17 cytokine in BP [56]. In contrast to psoriasis, lichen planus has never been established as being significantly associated with BP, likely due to a lack of statistical power based on its rarity [50]. However, autoantibodies against the BP180 antigen may still suggest a pathogenic link [57]. Other autoimmune diseases include rheumatoid arthritis, Hashimoto's thyroiditis, dermatomyositis, Grave's disease, autoimmune thrombocytopenia or neutropenia, vitiligo, and lupus erythematosus also occasionally have been associated with high BP. These associations are thought to reflect an established genetic predisposition to develop autoimmune diseases rather than by chance. However, a case-control study showed no increased risk of autoimmune diseases in BP.[58] As glycation of dermal–epidermal junction proteins could enhance their immunogenicity, a relationship between BP and diabetes mellitus has been also assumed.[59] The increased prevalence of diabetes mellitus among BP patients is probably due to their older age because this association was not confirmed by other case-control studies. Lastly, trauma, burns, radiation therapy, or ultraviolet (UV) radiation, especially PUVA, appear to be the causes of BP in some individuals.[31,33,35,48,60]

4.6. Treatment

These aims include the prevention of blister development, support blister and erosion healing, and application of the minimum dose that is effective for disease process control. All patients require a unique treatment program designed with respect to their background condition as well as other personal circumstances. The primary and most often useful treatment for localized BP is topical steroids. Oral corticosteroids form the mainstay of treatment in more advanced cases, which is often more difficult to control. These include systemic anti-inflammatory and immunosuppressive drugs. The condition is usually managed within 1-2 weeks with oral prednisone/prednisolone at a dose of 0.3 to 1.25 mg/kg body weight/day; this is then tapered off. Morel and Guillaume [33]reported no statistically significant differences between the groups compared for effectiveness in evaluating various prednisolone dosages, 0.75 mg/kg/day vs. 1.25 mg/kg/day. Greater side effects were associated with the higher dose of prednisolone. Other pulsed corticosteroids include methylprednisolone (0.5–1 g intravenously over 2 hours each day for 5 days), dexamethasone (100 mg in 500 ml of 5% dextrose intravenously over 2–3 hours for 3 consecutive days), and suprapharmacological dosages of betamethasone. Dexamethasone is the steroid of choice for pulse treatment in India. It can be administered either alone (DP) or with cyclophosphamide (DCP). [34]To achieve a corticosteroid sparing effect, several studies have suggested the concomitant use of immunosuppressive drugs.[35] Azathioprine is the most widely used drug at a dose of 0.5–2.5 mg/kg body weight/day. Cyclophosphamide, methotrexate, cyclosporine A, tetracycline/minocycline combination with

nicotinamide, and more recently, mycophenolate mofetil (MMF) have all been used successfully in other research. When Burton et al.[36] compared prednisone with prednisone and azathioprine, they found that the group treated with azathioprine took 45% less prednisone overall in a three-year period. Patients receiving methylprednisolone 0.5 mg/kg once daily plus 1000 mg of MMF given orally twice daily (2 g/day) or methylprednisolone 0.5 mg/kg once daily in combination with azathioprine sodium 2 mg/kg were treated in a double-blind, randomized controlled experiment. The same cumulative dosages of corticosteroids were required in both treatment arms to manage the disease, and MMF and azathioprine had similar efficacy.[37] In contrast to azathioprine, MMF had a much lower profile of liver injury. With low side effects and a tendency for a higher survival rate in patients with moderate to severe disease,[38] methotrexate was deemed the most effective treatment. The overall response rate for BP with the use of dapsone alone or in combination with immunosuppressive drugs or corticosteroids is around 81%. A randomized, open-label comparison of prednisone therapy alone versus 500 mg of nicotinamide three times a day and 500 mg of tetracycline four times a day yielded comparable response rates. All five of the continuation cases in the nicotinamide + tetracycline group were in remission and remained disease-free during drug tapering, while two of the three cases in the prednisolone group had repeated relapses at the 10th month. [39]Standard treatment fails for as many as 24% of BP patients. IVIg, plasma exchange, and biologicals (anti-TNF drugs,[40] rituximab) are also drugs used for treating high BP. For patients with severe BP whose condition is not responding to conventional therapy or who are at risk of suffering from severe or even life-threatening adverse effects from conventional immunosuppressive therapy, IVIg appears to be a potential option. IVIg may be especially useful if therapy is initiated early. A dose of 1–2 g/kg is recommended, usually given as a 5-consecutive-day course of 0.4 g/kg/day, but a 3-day course may be used.[42] The typical first dosing is one course every three to four weeks. The spacing of infusions is increased as the dose of high-dose IVIg is titrated down.Steroids, given orally or as pulses, are the most common therapeutic agent in India. [43]In addition, to enhance the efficacy and as steroid sparing adjuvants, the non-steroidal immunosuppressive agents are used. Prednisolone with azathioprine compared with prednisone alone in one trial; prednisolone plus azathioprine compared with prednisolone plus plasma exchange in one trial; prednisolone with either MMF or azathioprine in one trial; tetracycline plus nicotinamide compared with prednisolone in one trial was not found different in disease control. In one trial, clobetasol compared to standard regimen was no worse and did not differ in detectable differences in the healing process of patients. This study found significant improvements in both disease control with clobetasol and death and adverse effects with oral prednisolone against extensive and moderately ill patients.[44]

Table 1 Bullous Pemphigoid Summarized

Annual incidence	**Most frequent autoimmune blistering disease**	**2.5 TO 42.8 CASES/MILLION/Y (INCREASING)**
Age	Classic BP , Childhood BP	8th decade of life Two peaks: 4 months; 8 years
Antigens	Hemidesmosome	BP180 (180kDa) or collagen XVII or BPAG2 BP230 (230kDa) or dystonin or BPAG1
Associated diseases	Neurological disorders Thrombotic risk	Multiple sclerosis, dementia (including Alzheimer's disease), Parkinson's disease, stroke Increase in ischemic cardiovascular events
Clinical presentation	Classic BP Nonbullous BP Childhood BP Drug-induced	Tense hyaline or hemorrhagic blisters over an erythematous and edematous background on the trunk and extremities Rare mucosal involvement Pruritus, excoriation, urticariform, prurigo-like, erythema multiforme-like, exfoliative erythroderma Blisters and urticarial lesions on the face and acral sites Younger patients Onset at an average of 3 months after drug initiation Rapid control after drug withdrawal
Diagnosis	Histopathology DIF/IIF ELISA	Eosinophilic spongiosis Subepidermal detachment with eosinophils Linear IgG and/or C3 deposition at BMZ Anti-BP180 NC16A IgG and IgE Anti-BP230 IgG

First-line treatment	0.05% propionate clobetasol cream Prednisone	10-30g/day 0.5-1.0mg/kg/day
Prognosis	1-year mortality rate Risk factors of mortality	23.5% Age, neurological disorder, increased serum levels of anti-BP180 IgG

BULLOUS PEMPHIGOID IN SUMMARY [8]

5. Conclusion

In summary, neurological disorders such as dementia, Parkinson's disease, and stroke are strongly associated with Bullous Pemphigoid (BP), a severe autoimmune blistering disease that typically occurs in older individuals. Autoantibodies directed towards components of the basement membrane of the skin form part of the pathophysiology of BP, resulting in the formation of subepidermal blisters. Age, certain medications, neurological diseases, as well as even internal malignancies, are risk factors for blood pressure. Histopathology, immunofluorescence, and ELISA testing are utilized to establish the diagnosis, which typically presents as tight blisters with pruritus. Corticosteroids are the treatment of choice; in severe cases, immunosuppressive drugs are used. Although effective management strategies do exist, additional research into the mechanism and more targeted treatments is necessary to improve patient outcomes. Understanding the complex relationship between blood pressure and neurological disease may offer new therapeutic approaches and improve treatment of those affected.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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