

Clinical Features and Practical Diagnosis of Bullous Pemphigoid

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KEYWORDS

- Autoantibody • BP180 • BP230 • ELISA
- Immunofluorescence microscopy

Bullous pemphigoid (BP) belongs to the group of autoimmune subepidermal blistering diseases, which are characterized by an autoantibody response directed against distinct components of the dermoepidermal junction of skin and adjacent mucous membranes. Besides BP, this group, which has overlapping clinical and immunopathologic features, also comprises pemphigoid gestationis (also called gestational pemphigoid), mucous membrane pemphigoid, linear IgA disease, anti-p200/laminin γ 1 pemphigoid, and epidermolysis bullosa acquisita.

Pemphigoid diseases were first differentiated from pemphigus in 1953 by Lever¹ who described intraepidermal split formation and loss of cell adherence between keratinocytes (acantholysis) as the histopathologic hallmark of pemphigus, whereas he coined the term pemphigoid for conditions in which a subepidermal split formation was typically present. A decade later, Jordon and colleagues² showed that patients with BP had tissue-bound and circulating autoantibodies directed against the dermoepidermal junction. Further milestones in the understanding of BP included the immunochemical characterization of

the hemidesmosomal target proteins BP180 (also called BPAG2 or type XVII collagen) and BP230 (BPAG1-e), the cloning of their genes, and the demonstration that autoantibodies to BP180 are pathogenic.^{3–7}

EPIDEMIOLOGY

The incidence of BP has been estimated at between 4.5 and 14 new cases per million per year.^{8–13} In a recent prospective study encompassing the entire Swiss population, the incidence was found to be 12.7 new cases per million per year.¹⁴ These data are consistent with a recent prospective study in Lower Franconia, a well-defined region in southern Germany, where the incidence of BP was estimated to be 13.4/1 million/y.¹⁵ A higher incidence of 42.8/1 million/y has recently been reported in Great Britain based on a data registry established on the general practitioner level. However, the British study, in which the immunopathologic criteria used were not specified, did not differentiate the various pemphigoid diseases and most likely also included bullous drug eruptions.¹⁰ In Lower Franconia,

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Germany, and Great Britain the incidence of BP has considerably increased within the last 10 years (twofold and 4.8-fold, respectively),^{10,15,16} an observation that may be related to either the increasing age of the general population or a better knowledge of the disease with proper diagnosis.

BP is probably the only autoimmune diseases of which the incidence increases with age. BP is typically a disease of the elderly and its diagnosis is usually made in patients aged between 75 and 81 years.^{9,14,15,17–19} In the population older than 80 years of age, the incidence is 150 to 180 new patients/1 million/y.^{14,15}

CLINICAL FEATURES

The name BP itself is a pleonasm. Pemphigoid is derived from Greek and means a form of blister (pemphix, blister, and eidos, form). Hence, from a purely etymologic point of view, the adjective bullous should not be added to designate the blistering in pemphigoid. However, the spectrum of clinical presentations is extremely broad (**Boxes 1 and 2**).

Characteristically, BP is an intensely pruritic eruption with widespread blister formation. In this bullous stage, vesicles and bullae develop on apparently normal or erythematous skin together with urticated and infiltrated plaques with an occasionally annular or figurate pattern (**Fig. 1**). The blisters are tense with a clear, sometimes hemorrhagic, exudate; the Nikolsky sign is negative. Pruritus, which may be invalidating, is almost constantly present.¹⁷ Blisters are typically symmetrically distributed and may persist for several days, leaving eroded and crusted areas. Predilection sites involve the flexural aspects of the limbs and abdomen. In our own prospective Swiss cohort of patients encompassing 164 patients with BP for a 2-year period, the clinical presentation at time of diagnosis consisted of typical blisters localized on the trunk and on the extremities in about 80% of cases. In the intertriginous spaces, vegetating plaques may occur, and oral lesions develop in

Box 1
Clinical manifestations suggestive of BP in elderly patients with chronic pruritic skin eruptions

- Papular and/or urticarial lesions
- Eczematous lesions
- Prurigo-like lesions
- Excoriations, hemorrhagic crusts
- Localized vesicles or erosions

Box 2
Unusual clinical variants of BP

- Dyshidrosiform pemphigoid
- Intertrigo-like pemphigoid
- Prurigo-nodularis-like pemphigoid
- Papular pemphigoid
- Lymphomatoid papulosis–like
- Vesicular/eczematous pemphigoid
- Erythrodermic pemphigoid
- Localized forms
 - pretibial
 - peristomal
 - umbilical
 - stump pemphigoid
 - on paralyzed body sites
 - on irradiated/traumatized body sites
- Brunsting-Perry form (variant of cicatricial pemphigoid)

10% to 20% of cases.²⁰ The mucosae of eyes, nose, pharynx, esophagus, and anogenital areas are rarely affected (reviewed in Refs.^{21,22}).

However, before the development of tense generalized blisters, BP is typically preceded by a prodromal nonbullous phase. In this stage, diagnosis is difficult. Mild to intractable pruritus, alone or in association with excoriated, eczematous, popular, and/or urticarial lesions are found that may persist for several weeks or even months (see **Box 1**; **Fig. 2**). These unspecific skin findings may remain the only signs of the disease. In this same context, several clinical variants of BP (see **Box 2**) (reviewed in Ref.²²) have been described with a variety of different denominations, such as prurigo nodularis–like, prurigo-like,²³ erythrodermalike, ecthyma gangrenosum–like,²⁴ intertrigolike, and toxic epidermolysis–like lesions. Localized forms have been described confined to areas affected by radiotherapy, surgery, trauma, and burns, as well as lesions limited around stomata, hemodialysis fistulae,²⁵ the pretibial (**Fig. 3**) or umbilical area,²⁶ the palmoplantar region (mimicking dyshidrotic eczema), and the genital area.

TRIGGER FACTORS AND ASSOCIATED DISEASES

Several triggers have been implicated in the disease onset of individual patients, including

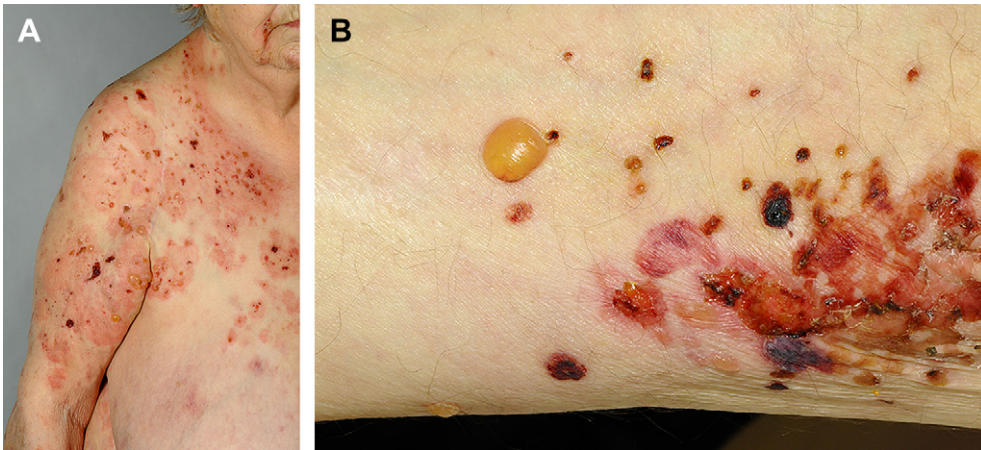


Fig. 1. Bullous pemphigoid. (A) Confluent urticated plaques and eczematous lesions with tense blisters on the trunk and right arm. (B) Close-up view.

trauma, burns, radiotherapy, and ultraviolet radiation. In addition, various autoimmune disorders, psoriasis, and neurologic disorders have also been described in association with BP. A large variety of drugs have been anecdotally reported to induce BP. A weak association with aldosterone antagonists and neuroleptics was found²⁷ and,

most recently, with spironolactone and phenothiazines with aliphatic side chains.²⁸ Based on these data, the use of latter drugs should be carefully evaluated in BP. In 2 case-control studies including more than 1700 patients with BP and age-matched controls in Sweden and Japan, a low association with gastric cancer was identified in the Japanese

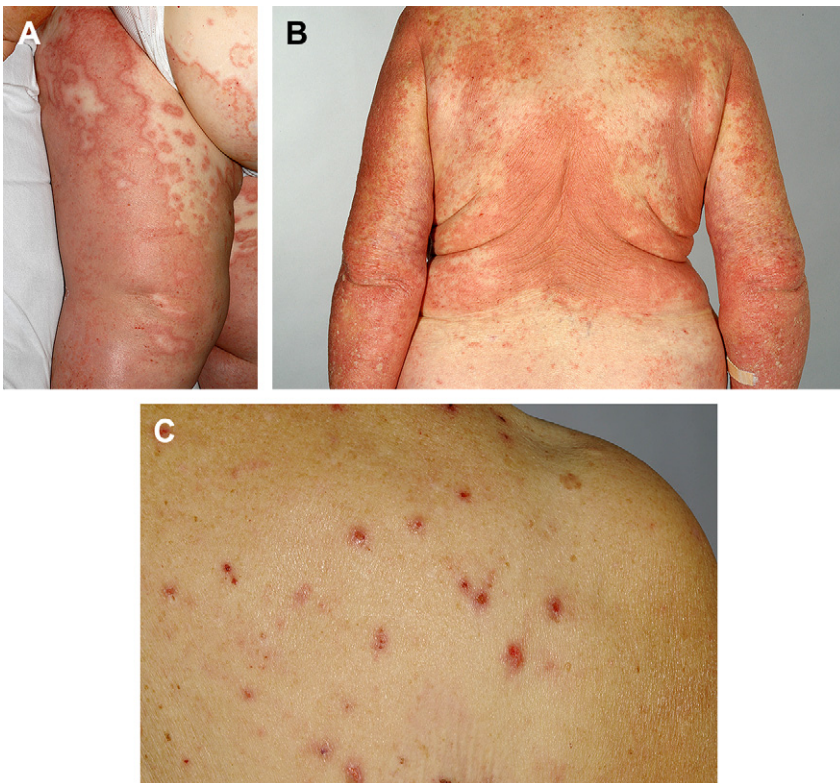


Fig. 2. Bullous pemphigoid. (A) Erythematous urticarial infiltrated plaques on the abdomen and legs with a figureate distribution. (B) Extensive eczematous and urticarial lesions on the trunk and arms. (C) Prurigo nodularis-like lesions and excoriated lesions on the shoulder.



Fig. 3. Localized bullous pemphigoid: pretibial form. Postbullous erosions and eczematous lesions on the right lower leg.

cohort.^{29,30} The previously described higher incidence of malignancies in patients with BP was probably biased by the lack of appropriate age-matched controls and the intensive work-up of affected patients in an hospital setting. Nevertheless, patients who develop BP at less than 60 years of age may be at higher risk for an underlying malignancy.³¹ We usually perform an age-related cancer screen based on patient's history and clinical examination without a systematic and extensive cancer screening.

Several autoimmune disorders, such as rheumatoid arthritis, Hashimoto thyroiditis, dermatomyositis, lupus erythematosus, and autoimmune thrombocytopenia, have been reported in BP. However, a case-control study did not find any increased risk for autoimmune disorders in BP,³² but a genetically determined susceptibility to develop autoimmune diseases is likely. BP has also been found in association with certain inflammatory dermatoses, such as psoriasis and lichen planus^{33,34}; a statistically significant link has not been provided. It is conceivable that the inflammatory process at the dermoepidermal junction in these disorders raises a secondary immune response

leading to autoimmunity against the target antigens of BP (epitope-spreading phenomenon).

Most recently, the association between BP and neurologic disorders has been highlighted, such as stroke (odds ratio 2.1), Parkinson disease (odds ratio 3.0 and 2.2), major cognitive impairment (odds ratio 2.2), psychiatric disorders such as unipolar and bipolar disorders (odds ratio 5.3), epilepsy (odds ratio 1.7), and most strongly with multiple sclerosis (odds ratio 6.7 and 10.7).^{28,35–37} These findings are particularly intriguing because some evidence has been provided suggesting that both antigens BP180 and BP230 are expressed in the central nervous system,^{38–40} and mice with either target disruption of or inherited mutations in the dystonin (DST) gene encoding for various isoforms of BPAG1 (including the epithelial isoform BP230/BPAG1-e) develop severe dystonia and sensory nerve degeneration.⁴¹

TARGET ANTIGENS

In BP, autoantibodies recognize BP180 (also known as type XVII collagen or BP antigen 2) and BP230 (also known as BPAG1-e or BP antigen 1). These proteins are components of junctional adhesion complexes called hemidesmosomes, which are expressed in stratified and complex epithelia, such as skin, mucous membranes, and the ear, nose, and throat area. BP180 is a transmembrane glycoprotein of about 1500 amino acids. Ultrastructurally, it spans the lamina lucida before kinking back from the lamina densa into the lamina lucida (reviewed in Refs.^{42,43}). The juxta-membrane domain of the extracellular portion of BP180 called NC16A was identified as the immunodominant region of BP180 in BP.^{44,45} BP180 interacts with the $\beta 4$ chain of $\alpha 6\beta 4$ integrin, plectin, BP230, and most likely with laminin 332⁴⁶). It provides a structural link between the intermediate filaments of the cytoskeleton and dermal collagen fibers. The importance of BP180 for the structural integrity of the skin is attested to by the observation that pathogenic mutations in its gene, COLXVII, lead to nonlethal junctional epidermolysis bullosa.⁴⁷

In contrast, BP230 is an intracellular constituent of the hemidesmosomal plaque and belongs to the plakin family of cytolinkers. Its globular C-terminal domain mediates the anchorage of keratin filaments to the cell membrane.⁴⁶ Targeted inactivation of the DST gene encoding BP230 in mice resulted in mild skin fragility. Unexpectedly, affected mice developed neurologic defects with sensory neuron degeneration.⁴¹ The phenotype was identical to those observed in mice suffering

from dystonia musculorum, with a spontaneous mutation in the so called DST gene.^{48–50} Better understanding of the phenotype of these animals has led to characterization of several tissue-specific isoforms of BP230, including at least a neuronal and a muscle-specific variant. These findings, together with the recently highlighted increased association between BP and neurologic disorders,^{28,35–37} may suggest that autoimmunity to BP230 is involved in the development of neurologic diseases. Recently, mutations in the DST gene have been identified in a patient with epidermolysis bullosa exhibiting mild, localized blistering.⁵¹

DIAGNOSIS

Diagnosis of BP is based on a combination of clinical features and immunopathologic findings (Fig. 4).^{43,52} In atypical and nonbullous variants, diagnosis of BP critically relies on the findings of

direct immunofluorescence (IF) microscopy together with the characterization of the specificity of circulating autoantibodies and/or findings from other approaches (Fig. 4).

Clinical Criteria

The typical patient with BP is older than 75 years and presents with a pruritic eczematous, urticarial eruption with or without frank blistering. Mucous membranes and the face and neck region are usually not affected. In many patients, there are simply excoriated lesions. Knowledge of the wide spectrum of clinical presentations and atypical variants is important to consider the diagnosis of BP. Vaillant and colleagues⁵³ showed that the diagnosis of BP can be made with high specificity and sensitivity in patients with linear immunoglobulin G (IgG) and/or C3 deposits along the dermoepidermal junction when 3 of the 4 clinical criteria are present: age greater than 70 years, absence

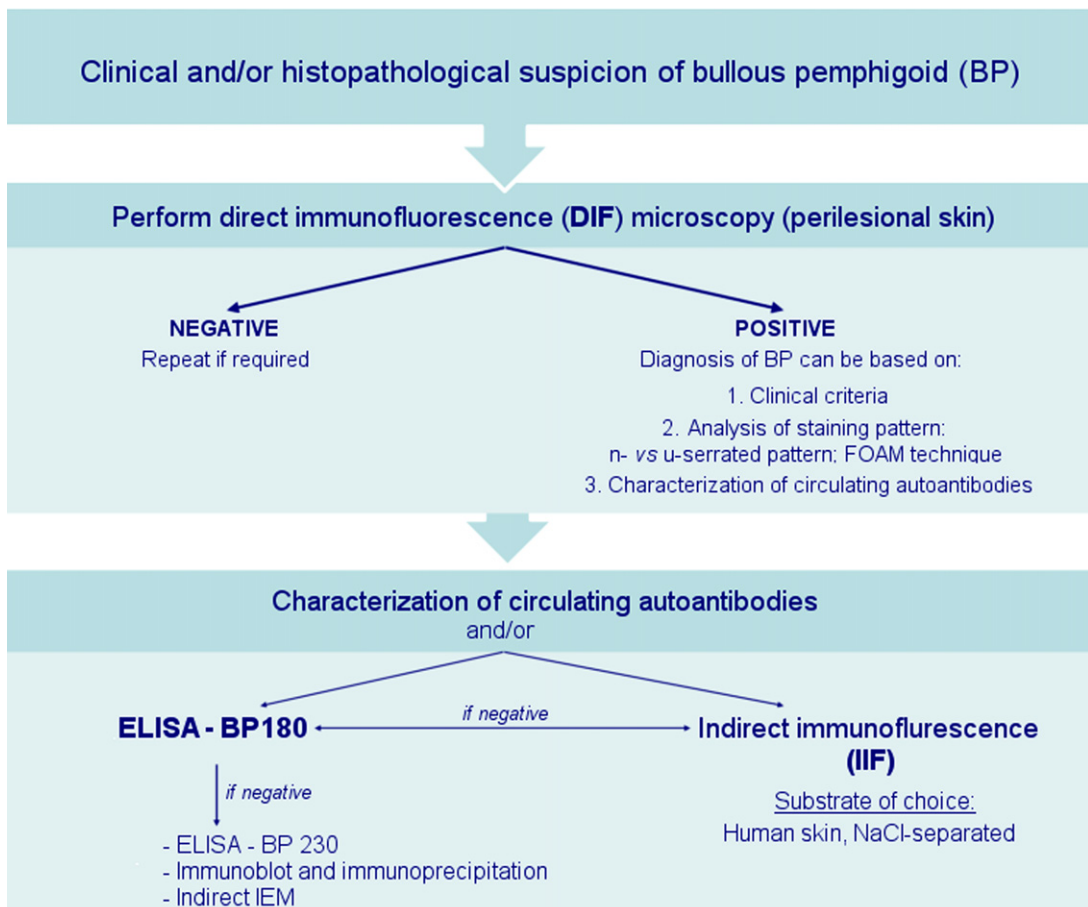


Fig. 4. Bullous pemphigoid. Diagnostic algorithm.

of atrophic scars, absence of mucosal involvement, and absence of predominant bullous lesions on the neck and head.⁵³

Histopathology and Immunohistochemistry

Histopathology is not essential for the diagnosis of BP. Findings may be either typical or suggestive, or at least useful, for the differential diagnosis. When BP is suspected, the biopsy specimen should ideally include a macroscopically visible vesicle, a bulla, or at least the edge of a larger bulla. Light microscopy studies of an early bulla typically reveal a subepidermal blister formation with a superficial dermal inflammatory infiltrate rich in eosinophils (**Fig. 5**). In early nonbullous phases, subepidermal clefts and eosinophilic spongiosis can be found. Recently, immunohistochemical studies have suggested that the detection of C3d deposits at the dermoepidermal junction in formalin-fixed tissue is useful for the diagnosis.^{54,55}

Direct IF Microscopy

Studies of a biopsy specimen obtained from perilesional skin still represent the diagnostic gold standard. They show the presence of deposits of IgG and/or C3 along the dermoepidermal junction (**Fig. 6A**). IgM, IgE and fibrinogen may also be detected with variable frequency. The proper choice of the site for the skin biopsy is critical because lesional biopsies may give false-positive or false-negative results. Close analysis of the linear fluorescence pattern at the BMZ (n-serrated vs u-serrated pattern)⁵⁶ as well as examination of patient's skin after treatment with 1 M NaCl (referred to as salt-split skin of autologous skin)

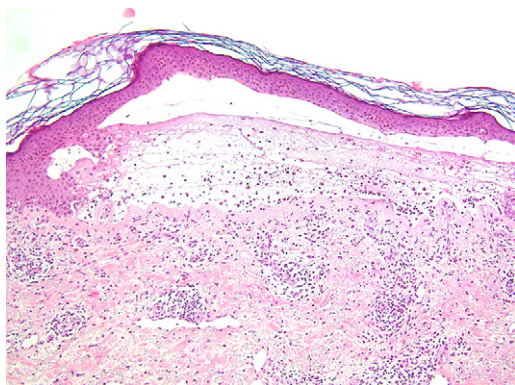


Fig. 5. Light microscopy of a fresh bulla from a patient with bullous pemphigoid (hematoxylin-eosin stain): subepidermal blister formation with discrete inflammatory infiltrate (eosinophils and neutrophils) in the blister cavity and in the dermis by light microscopy.

is also helpful for the diagnosis⁵⁷: In patients with BP, IgG localizes to the epidermal side of the split, whereas a dermal staining is seen in patients with anti-laminin 332 mucous membrane pemphigoid, anti-p200/laminin γ 1 pemphigoid, and epidermolysis bullosa acquisita, respectively. The distribution of C3 seems less reliable than that of IgG.⁵⁸

Indirect IF Microscopy

In up to 80% to 85% of patients, indirect IF microscopy studies show the presence of circulating IgG autoantibodies that typically bind to the epidermal side of 1M NaCl-split normal human skin, the substrate of reference (see **Fig. 6B**), differentiating BP sera from sera from patients with anti-laminin 332 mucous membrane pemphigoid, anti-p200/laminin γ 1 pemphigoid, and epidermolysis bullosa acquisita, which all bind to the dermal side.^{59,60} Additional circulating autoantibodies of the IgA, IgE, and IgM class can also be found. Isotype reactivity with the epidermal side of the artificial split appeared to be associated with age: sera from younger patients contained significantly more IgA reactivity, whereas IgG reactivity was predominantly found in older patients.⁶¹

Enzyme-linked Immunosorbent Assays

Enzyme-linked immunosorbent assays (ELISAs) using recombinant proteins of various portions of BP180 (such as the NC16A domain, the C-terminal portion, or its entire ectodomain) have been found to be highly specific and sensitive.^{62–73} The NC16A domain of BP180 has been identified as an immunodominant stretch in BP IgG. These anti-BP180 NC16A antibodies were found in between 75% and 90% of patients with BP^{44,45,68,69,71–73} and their level correlates with the disease activity of patients with BP.^{20,71,73–76} Two highly sensitive and specific ELISA systems for serum anti-BP180 antibodies are commercially available (Euroimmun, Lübeck, Germany and MBL, Nagoya, Japan).^{72,73}

Most patients with BP also develop, beside IgG, IgA anti-BP180 reactivity.⁷⁷ Sera from patients with linear IgA bullous disease also contain IgG and IgA antibodies against BP180,^{61,77} suggesting that these 2 diseases belong to the same group of disorders. IgE reactivity against BP180 NC16A is also found in most patients with BP.^{78–80} In recent studies, 10% of BP sera contained IgE but no IgG reactivity with the NC16A domain,⁸⁰ and IgE anti-BP180 antibodies were shown to contribute to tissue damage in mouse models.^{81,82}

Autoantibodies against BP230, the other targeted antigen in BP, can also be detected by ELISA.^{70,83–85} The globular C-terminal domain of BP230 is targeted by about 80% of the

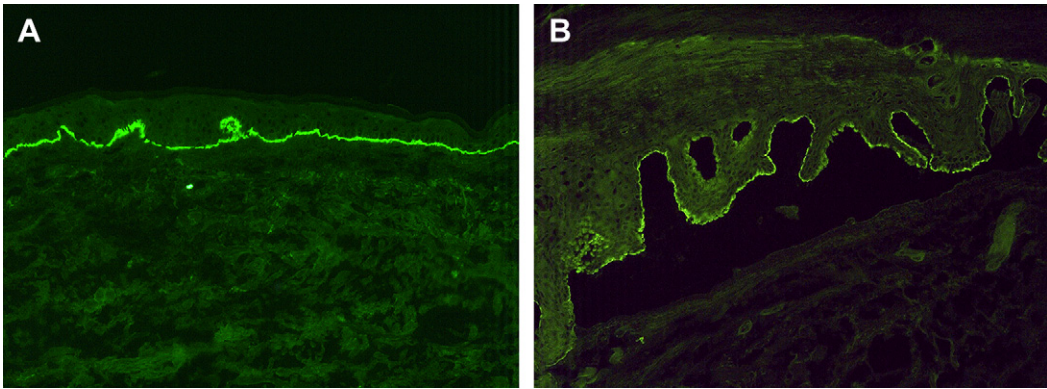


Fig. 6. (A) Direct immunofluorescence microscopy study of perilesional skin from a patient with bullous pemphigoid revealed linear, continuous deposits of C3 along the dermoepidermal junction. (B) Indirect immunofluorescence microscopy study using NaCl-split normal human skin as a substrate. Staining of the epidermal side of the split typical for autoantibodies in bullous pemphigoid.

BP230-reactive BP sera.^{20,86} Two ELISA kits have been commercialized (Euroimmun and MBL) and use a recombinant C-terminal stretch of BP230, whereas, in the MBL ELISA, an N-terminal fragment is also included. Both ELISA systems are less sensitive compared with the BP180 ELISA, with anti-BP230 reactivity in only 50% to 70% of BP sera.^{70,83–85} For routine analysis, a search for anti-BP230 antibodies is only helpful in patients with positive direct IF microscopy but negative BP180 ELISA reactivity.

Immunoblot and Immunoprecipitation

In the past, detection of anti-BP180 and anti-BP230 reactivity relied on immunoblot and immunoprecipitation studies using extracts of cultured keratinocytes or human epidermis,^{3,5,87,88} conditioned medium of cultured human keratinocytes, as well as various recombinant forms of BP180 and BP230 produced in different expression systems.^{45,66,77,78,89–91} The combination of various ELISAs with immunoblotting, as well as cell-based IF studies, allows the detection of autoantibodies in virtually all BP sera.^{20,90} Currently, immunoblotting and immunoprecipitation studies are only used for investigative studies.

REACTIVITY WITH BP180 AND BP230 IN INDIVIDUALS WITHOUT BP

In a large cohort of 337 patients with various dermatologic disorders, 4.2% of the tested sera showed low positive values for BP180 (range between 9.2 and 33.1; normal, <9.0) and BP230 (range between 9.1 and 15.2; normal, <9.0), independently of age or sex.⁹² Foureur and colleagues⁹³ confirmed this finding in a group of 138 dermatologic patients without evidence for

BP. However, anti-BP180 reactivity has also been reported in patients with a variety of pruritic disorders.^{94–96} At present, the detection of low-level anti-BP180 and anti-BP230 serum antibodies in patients without clinical signs of BP does not require further investigations. In patients with pruritic disorders and ELISA reactivity against BP180 or BP230, direct IF microscopy is required to differentiate between unspecific autoantibody reactivity and BP.

DIFFERENTIAL DIAGNOSIS

In our experience, BP is a great imitator. In either the nonbullous prodromal stage or in atypical presentations, it can bear close resemblance to a variety of dermatoses including localized or generalized drug reactions, contact and allergic dermatitis, prurigo, fixed urticaria, urticarial vasculitis, arthropod reactions, scabies, ecthyma, or even pityriasis lichenoides. Detailed patient history, clinical evaluation, histopathologic features, and, above all, direct immunofluorescence microscopy studies are essential to distinguish these disorders from BP. The development of specific and sensitive ELISA systems in recent years may now allow the serologic diagnosis of BP in most patients.

Diseases of the pemphigus group can be easily differentiated by distinctive clinical (positive Nikolski sign) and immunopathologic features. Mucous membrane pemphigoid is differentiated from BP by its predominant involvement of mucosal surfaces.⁹⁷ In contrast, the distinction of BP from linear IgA disease, epidermolysis bullosa acquisita, and anti-p200/laminin γ 1 pemphigoid based simply on clinical and histopathologic features is usually impossible and requires direct IF microscopy (for linear IgA disease) and serologic analyses (for the last 2 entities). Lichen planus pemphigoides is

clinically characterized by the presence of lichen planus lesions on otherwise unaffected skin in addition to tense blisters. In dermatitis herpetiformis, direct IF microscopy findings, and particularly the serologic profile (presence of anti-tissue and anti-epidermal transglutaminase as well as anti-IgA antibodies) are characteristic.

PROGNOSIS AND MORTALITY

BP frequently has a chronic evolution with remissions and relapses. It is associated with significant morbidity, such as severe itch, bullous and eroded lesions, and impetiginization. The impact on the quality of life is significant. In a recent prospective study encompassing, at entry, 114 patients with BP, 47% of the 96 evaluable patients experienced a disease relapse within 1 year after cessation of therapy, confirming the recurring nature of the disease. There have been some controversies about the prognosis and mortality of BP.^{98–104} It is likely that the reported diverging mortalities are related to the inclusion of populations of different mean age, in different general conditions (outpatients vs inpatients), and the use of different treatment protocols (oral corticosteroids, immunosuppressants) as well as diagnostic accuracy. For example, the 1-year mortality in 62 patients with a median age of 76 years, who were treated with methylprednisolone, dapsone, and clobetasol propionate cream, was as low as 6%,⁹⁸ whereas in a study of 312 patients with an average age of 82 years and treated by clobetasol propionate cream alone, the 1-year mortality was 39%.¹⁰⁴ The 1-year mortality after diagnosis of BP was reported to be 29%, 26%, 23%, and 19% in 369, 341, 223, and 869 patients with BP from Germany, France, the United States and the United Kingdom respectively.^{10,18,19,103} Langan and colleagues¹⁰ reported a 2.3-fold higher 1-year mortality risk for patients with BP compared with age-matched and sex-matched controls. In 2 large studies encompassing 369 and 177 patients, the following risk factors for lethal outcome in the first year after diagnosis were identified: (1) age greater than 82 and 80 years, respectively; (2) daily prednisolone dose of more than 37 mg after hospitalization; (3) serum albumin levels of less than 3.6 g/dL; (4) an erythrocyte sedimentation rate greater than 300 mm/h; and (5) a Karnofsky score of 40 or less.^{19,102}

CONCLUDING REMARKS

Recent animal models of BP have provided unequivocal evidence for the pathogenic effect of autoantibodies to BP180 as well as novel insights into the cascade of events leading to tissue damage in BP. Despite these advances, BP still represents

a clinical, diagnostic, and therapeutic challenge in our practice. The protean clinical features, the difficult diagnosis of early and atypical forms of BP, and the advanced age of affected patients with multiple comorbidities require a high degree of expertise and caution with the management of affected patients. Better knowledge of the pathophysiology of BP will hopefully facilitate the development of new immunomodulatory treatments with fewer side effects for this debilitating disease. The joint efforts by all international experts are required to improve the evaluation and treatment of these patients.

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