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 γ1 pemphigoid, and epidermolysis bullosa acquisita.

Pemphigoid diseases were first differentiated from pemphigus in 1953 by Lever[1] 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 colleagues[2] 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 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.

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)

TRIGGER FACTORS AND ASSOCIATED DISEASES

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