

Bullous pemphigoid

Author: Professor Philippe Bernard

Service de Dermatologie, Hôpital Robert-Debré, Avenue du Général-Koenig, 51092 Reims cedex, France. pbernard@chu-reims.fr

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Abstract

Bullous pemphigoid (BP) is an autoimmune subepidermal bullous dermatosis defined immunologically by the existence of autoantibodies directed against 2 structural proteins found in the hemidesmosomes of the dermal-epidermal junction. These proteins, called BP antigen 1 (BPAG1 or AgBP230), and BPAG2 (or AgBP180 or collagen XVII) have respective molecular masses of 230 and 180 kDa. The disease is characterized clinically by tight bullae, with clear content, often large, developing primarily on the edge of erythematous plaques. Intense itching is common. BP is the most common of the autoimmune bullous dermatoses, with an annual incidence of more than 400 new cases in France. It affects primarily the elderly. However, it has also been described in children. It occurs within the first year after birth and presents as bullous lesions on erythematous skin or on normal acral skin. Very rare familial cases have been reported. Studies conducted in France demonstrated that the prognosis of survival of BP patients was very poor, with a death rate exceeding 30% after 1 year of treatment. Prognosis of infantile BP is favourable. Systemic corticotherapy (prednisone: 1 mg/kg/day) remains the standard treatment for many authors whereas, the treatment of choice for localized, paucibullous and/or slightly evolving forms of pemphigoid is topical corticotherapy with class I dermatocorticoids.

Key words

erythematous plaques, bullae, auto-immune disease, corticotherapy

Disease name and synonyms

- Bullous pemphigoid (BP),
- Pemphigoid,
- Lever's pemphigoid.

Definition

BP is an autoimmune subepidermal bullous dermatosis defined immunologically by the existence of autoantibodies directed against 2 structural proteins found in the hemidesmosomes of the dermal-epidermal junction. These proteins, called BP antigen 1 (BPAG1) or AgBP230, and BPAG2 (or AgBP180 or collagen XVII) have respective molecular masses of 230 and 180 kDa [8, 14]. The autoantibodies are localized *in vivo* along the epidermal basement membrane. BP is mostly found in the elderly. However, cases have also been reported in children.

Epidemiology

BP is the most common of the autoimmune bullous dermatoses, representing 70% of these diseases, with an annual incidence of more than 400 new cases in France [2]. It affects primarily the elderly (mean age in France: between 75 and 80 years). Very rare familial cases have been reported.

BP is very rare in children. About 50 cases have been reported [5].

Diagnostic criteria

In typical cases, the diagnosis of BP can be made based on 3 presumptive elements:

- clinical features (bullae developing on erythematous skin predominantly located on the flexor sides of the limbs);
- histological aspect (subepidermal cleavage);
- direct immunofluorescence (IF) of the affected skin (linear IgG and/or C3 deposits all along the epidermal basement membrane).

A recent French study validated the following clinical criteria for the diagnosis of BP:

- age over 70 years;
- absence of mucosal involvement;
- absence of atrophic scars;
- absence of preferential involvement of the head, neck and the upper half of the trunk [15].

The presence of 3 of these 4 criteria allows the diagnosis of BP with a probability of better than 90% for an autoimmune, subepidermal bullous dermatosis with linear IgG and/or C3 deposits seen on direct IF.

The diagnosis is confirmed by:

- indirect IF detection of serum antibodies, of IgG class, directed against the epidermal basement membrane of normal human skin separated by molar NaCl, that bind to the roof of the cleavage zone [4];

- the characterization of specific circulating autoantibodies by immunoblotting, detectable in ~ 80% of pemphigoid patients; they react with at least one of the 2 target antigens of the hemidesmosome: AgBP230 and/or AgBP180 [8, 14];
- immunoelectron microscopy of a skin biopsy showing immune deposits (IgG, C3) in the upper part of the lamina lucida [4].

Serological techniques to detect antibodies to BP230 and, especially, BP180 by enzyme-linked immunosorbent assay (ELISA) have been developed recently. This latter method detects anti-BP180 antibodies in more than 90% of the sera from patients with BP, particularly antibodies reacting with the NC16a domain of AgBP180. The epitopes seem to be numerous, particularly on the extracellular domain of AgBP180. These highly sensitive techniques are still experimental.

Differential diagnosis

In atypical cases, *i.e.* those with predominant mucosal involvement, with unusual topography or scarring of bullous lesions, other autoimmune subepidermal bullous dermatoses with linear IgG and/or C3 deposits (cicatrical pemphigoid, acquired bullous epidermolysis) can be eliminated by more sophisticated immunological techniques (immunoelectron microscopy, indirect IF on skin separated by molar NaCl, immunoblotting, immunoprecipitation).

Clinical description

The disease is characterized clinically by tight bullae, with clear content, often large, developing primarily on the edge of erythematous plaques [10]. Intense itching is common. The lesions are symmetrical with a predilection for the flexor sides of the limbs, the anterior-internal face of the thighs and abdomen. Mucosal lesions are rare, predominantly affecting the buccal mucosa (10-20% of the cases). Nikolsky's sign is absent. The disease progresses by successive bouts, the bullae healing without scarring. Affect on the patient's general status is variable; it depends on the extent of the lesions, and the severity and duration of itching.

Numerous clinical variants have been described like, for example, those with vesicular lesions suggestive of dermatitis herpetiformis, those with persistent lesions of the major folds, those with lesions resembling prurigo nodularis or erythroderma, or localized forms.

Diverse immune disorders have been described as isolated cases in association with BP (rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis, pemphigus vulgaris, etc.). Although sometimes included within the framework of a "multiple autoimmune disease", this kind of association is often coincidental. In contrast, the frequency of diabetes and psoriasis was shown to be significantly higher during the course of BP in two case-control studies.

The BP-cancer association has been explored in many studies. At present, it has been concluded that BP patients have no significantly increased risk of cancer compared to patients of comparable age.

Childhood BP occurs within the first year of life. It presents as bullous lesions on erythematous skin or on normal acral skin. In 2002, a classification of childhood BP was suggested by Fisler *et al.* [7] into two subtypes:

- Infantile BP
- Childhood localized vulval BP

Childhood localized vulval BP is self-limited and non scarring. Prognosis of infantile BP is also favourable. [7]

Etiology

BP is a specific autoimmune disease whose antigen targets are part of the normal human dermal-epidermal junction [13]. The mechanisms leading in the elderly subject to rupture of tolerance of hemidesmosomal proteins are still unknown. Within the hemidesmosome, the molecules recognized by the autoantibodies are 2 structural proteins normally present in the dermal-epidermal junction: AgBP230, strictly intracellular, and AgBP180, a transmembrane protein with a large extracellular domain. The pathogenic character of the antibodies to AgBP180, which has an extracellular domain directly accessible to the action of the autoantibodies, has been formally demonstrated in an animal (mouse) model [11]. In contrast, no definitive proof has yet been obtained supporting the direct pathogenicity of anti-AgBP230 autoantibodies directed against a strictly intracytoplasmic hemidesmosomal protein and thus, in principle, inaccessible to the direct action of the autoantibodies.

Isolated observations have suggested that the disease could sometimes be induced by PUVAtherapy (psoralen + UV-A irradiation, *i.e.*, photochemotherapy) or by certain drugs (spironolactone, bumetanide, fluoxetine, etc.). An epidemiological case-control study suggested a potential triggering role for spironolactone and, to a lesser degree, neuroleptics [1].

Etiology of childhood BP is also unknown. However, drug intake and vaccination have been incriminated in some cases [5].

Management including treatment

Studies conducted in France demonstrated that the prognosis of survival of BP patients was very poor, with a death rate exceeding 30% after 1 year of treatment [3, 12]. Although the pejorative impact of the presence of circulating anti-AgBP180 antibodies was suggested [3], age and Karnofsky score of 40 or less have been shown to significantly affect prognosis [12]. It is likely that co-morbidities and practice patterns (use of immunosuppressive drugs and/or systemic corticosteroids) also influence overall morbidity and mortality. Nevertheless, the cure can be achieved, in the absence of complications, in a time interval ranging from 1 to 5 years. For the severe forms of extensive and progressive pemphigoid, the first-line therapy consists of corticosteroid monotherapy. Systemic corticotherapy (prednisone: 1 mg/kg/day) remains the standard treatment for many authors, notably the English and Americans [6].

In France, topical corticotherapy tends to replace systemic steroids, provided that high doses of dermocorticoids are used as induction therapy (clobetasol propionate: 30-40 g/day). Regardless of the corticotherapy prescribed, the induction dose is maintained for about 1 month and until the post bullous lesions are completely healed. During the first month of therapy, the weekly evaluation of treatment efficacy is based on the number of new bullae per day. Then, the corticosteroid dose is progressively tapered over a period of 4-6 months until a maintenance dose (5-7 mg/day of prednisone or 20-30 g/week of clobetasol propionate) is reached. This dose is maintained for several months before complete withdrawal of steroids. In the case of corticoresistance or corticodependence, adjuvant immunosuppressive therapy (azathioprine: 100-150 mg/day) can be prescribed. In the case of initial corticoresistance in a patient with very severe pemphigoid, plasma exchanges can be tried.

The treatment of choice for localized, pauci-bullous and/or slightly evolving forms of pemphigoid is topical corticotherapy with class I dermatocorticoids. [9]

Treatment of the 2 infantile forms defined by Fisler *et al.* with systemic or topical corticosteroids is all the more effective as it is started early, before the disease becomes widespread [7]:

A [clinical trial on BP](#) is currently carried out in France. The aim is to evaluate the criteria for stopping corticotherapy.

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