

Bullous pemphigoid: a retrospective analysis of 45 cases

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ABSTRACT

Introduction: Bullous pemphigoid (BP) is an autoimmune disease that most frequently affects older people.

Objectives: To identify the age of onset, sex and clinical variants of BP. Establish associations with other diseases, therapeutic response and compare the results with published statistics.

Materials and Methods: We performed a retrospective descriptive analysis of 45 patients with BP diagnosis evaluated at Hospital Policlínico Bancario between August 1995 and August 2010. The database was obtained from histologic records and their corresponding medical histories.

Results: 45 patients were recorded: 25 (55.5%) female and 20 (44.4%) male. The mean age at diagnosis was 75.9 years. Clinical variants: 35 patients (77.7%) classical; 5 (11.1%) localized; 1 (2.2%) vesicular; 2 (4.4%) nodular. Association with diabetes, 15 patients (33.3%); hypertension, 29 (64.4%); other systemic diseases, 19 (42.2%); dermatological diseases, 7 (15.5%). The therapeutic response was good.

Conclusions: The average age at diagnosis was advanced. We found no marked difference in gender distribution. The typical form of presentation predominated over other clinical variants. The association with systemic diseases could have been due to the fact that these pathologies occur more frequently in the same age group. Psoriasis was the most frequent skin disease association. The therapeutic response was highly satisfactory. In general our data are similar to published statistics (Dermatol. Argent., 2011, 17(5): 387-395).

Keywords

bullous pemphigoid, bullous disease, diabetes, psoriasis

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Introduction

Bullous pemphigoid (BP) is an acquired autoimmune subepidermal disease characterized by the circulation of antibodies directed against the highest BP antigen of 230 kDa (Ag 1 BP) and the lowest antigen of 180 kDa, located at the basement membrane zone. It is frequent in elderly people, shows no predilection for sex and it rarely affects mucosae¹. Our knowledge of BP is an example of the development of research into blistering diseases, whose most significant breakthrough are Walter Lever's studies, in which in 1953 BP was classified as an independent form of pemphigoid with distinct histologic and clinical features². Year later, its immunopathological profile would be established by Jordon, who proved IgG adhesion to the basement membrane zone, and by Beutner et al, who found circulating IgG antibodies directed against the basement membrane^{3,4}. The onset of BP may be acute or subacute: typical lesions are tense blisters which occur on normal or erythematous-looking skin, generally with serous content, though they are haemorrhagic at times, and the eroded skin tends to reepithelize and does not expand⁵. Among the clinical variants is the classic form, in which the bullae are distributed symmetrically on the lower abdomen, on the inner aspect of thighs and on flexural areas of limbs. Oral or ocular mucosal involvement is rare and, when it occurs, it has little clinical relevance. The bullae heal without scarring or with the formation of milia⁶. The classic form is the most frequent but other clinical variants have been described, namely:

- **Localized:** a predilection for lower limbs⁵.
- **Dyshidrosiform:** located on palms and soles⁵.
- **Vesicular:** mimicking dermatitis herpetiformis⁵.
- **Vegetating:** on intertriginous skin areas⁵.
- **Erythrodermic:** mimicking exfoliative erythroderma¹.
- **Nodular:** mimicking prurigo nodularis⁶.
- **Childhood:** the blisters are located on palms, soles and face⁵.

Diagnosis is clinical, histopathological and immunopathological. Many cases of coexistence of BP with malignant tumors have been reported but there are no case-control studies which support this association. BP has been observed to be associated with lichen planus, autoimmune diseases, neurologic disorders and dermatological diseases, among others⁵. Systemic corticoids is the treatment of choice, with good response, but cyclophosphamide, methotrexate, mycophenolate, mofetil, dapsone, tetracycline, nicotinamide and, exceptionally, biological therapy have also been used^{1,5}. It is a self-limited disease but its course and prognosis will depend on the patient's general condition.

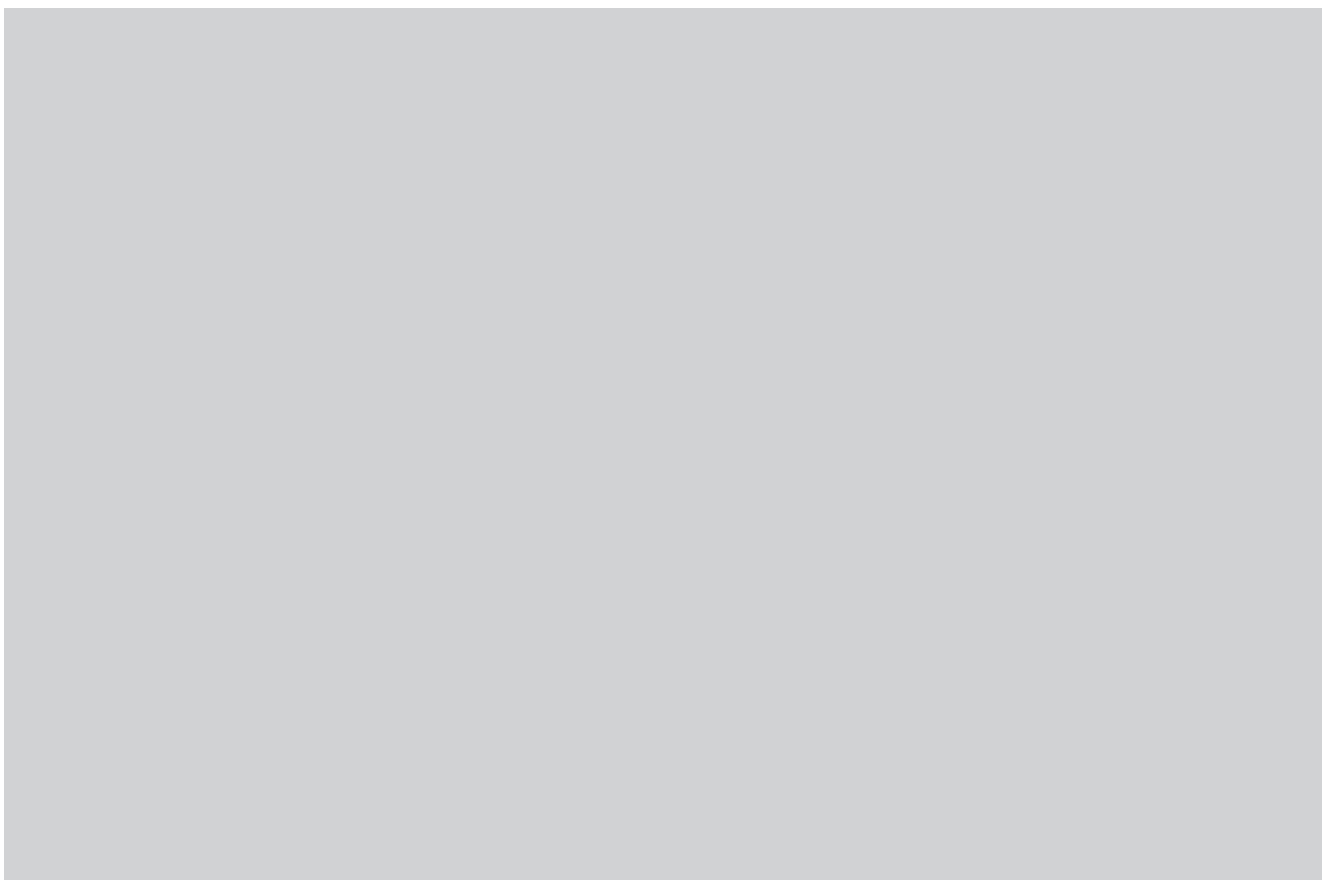


Photo 1: Bullous pemphigoid with oral, eye and vulvar mucosal involvement in 3 patients.

Material and methods

Study population: we have included all patients, male and female, with diagnosis of BP evaluated between August 1995 and August 2010 at the Dermatology Department at Policlínico Bancario.

Study design: a retrospective and descriptive analysis was carried out. A record of the following data was kept: age; sex; location of lesions; clinical variants; association with diabetes (DBT), arterial hypertension (AHT) and other systemic and dermatological diseases; therapeutic regimens and three-month therapeutic follow-up. Data collection was obtained from the histological records of the Dermatology Department at the Policlínico Bancario and from the corresponding medical histories.

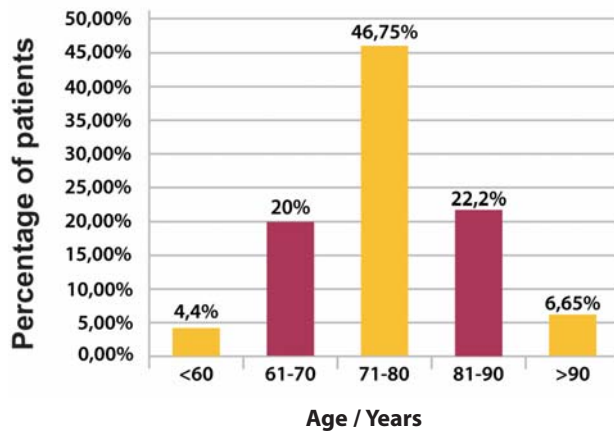
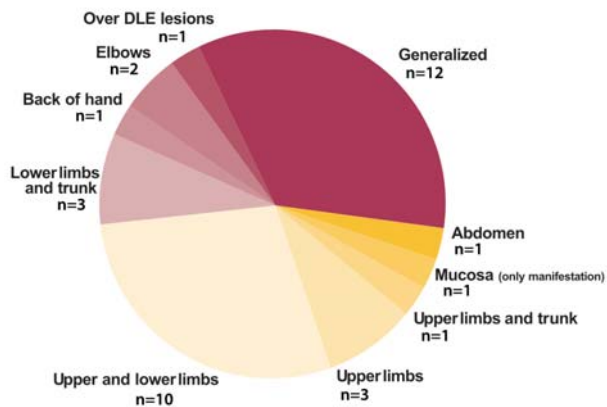
Objectives: to identify onset age, sex and clinical variants of BP in our population. To establish its association with other diseases, therapeutic response and to compare results with published statistics.

Results

Epidemiology: a total of 45 patients with BP diagnosis was included in this trial: 25 (55.5%) females and 20 (44.5%) males. Their ages ranged from 55 to 95 years with a mean onset age of 75.97 years (Graph 1).

Clinical presentation: of the recorded population, 35 patients (77.7%) had a typical presentation form (Graph 2). Within this variant, ocular mucosal involvement was seen in 1 patient (Photo 1) as the only manifestation of the disease; the oral mucosa was involved in 2 patients and the vulva in 2 patients. In the two latter cases, there were also lesions in other areas of the body. 2 patients (4.4%) evidenced BP mimicking erythema multiforme (Photo 2).

Among the clinical variants, there were 5 patients (11.1%) with localized BP (Photo 3), 1 patient (2.2%) with vesicular BP (Photo 4) and 2 patients (4.4%) with nodular BP (Photo 5) (Graph 3).

GRAPH 1: Distribution by onset age**GRAPH 2: Distribution of lesions in the classic presentation. The mucosal involvement as the only expression of the disease was observed in only one patient. The rest of the patients with mucosal involvement also presented cutaneous lesions.**

Healing with milia was observed in 2 patients (4.4%) (Photo 6).

Associations: BP was found in association with DBT in 15 patients (33.3%); with AHT in 29 patients (64.4%); with neurological diseases in 5 patients (Parkinson's disease (n=1), cerebrovascular accident (n=1), depression (n=1) and dementia (n=2)); with previous neoplasias in 5 patients (rectal cancer (n=1), breast cancer (n=2), lung adenocarcinoma (n=1) and chronic lymphocytic leukemia (n=1)); with cardiorespiratory diseases in 5 patients (heart failure (n=2), COPD (n=2), asthma (n=1)); with renal

diseases in 1 patient (CRF(n=1)); and with metabolic diseases in 3 patients (morbid obesity (n=1) and hypothyroidism (n=2)). BP was reported to co-exist with psoriasis in 3 patients (6.6%), in one of them during the treatment with PUVA. BP cases were recorded in patients with antecedents of melanoma (n=1), basocellular epithelioma (n=1), discoid lupus erythematosus (n=1) and pathomimesis (n=1) (Table 1).

Treatment: a therapeutic regimen with glucocorticoids was initiated in 100% of patients, 95.5% (n=43) were treated systemically and the remaining 4.4% (n=2) were treated topically. The drugs of choice were meprednisone and clobetasol, respectively. Topical clobetasol was indicated for patients presenting the classic form of the disease with a distribution on the back of the hand and upper limbs with minimal clinical expression. Regarding the systemic treatment with meprednisone, the dosage was: 8 mg/day (2.32%) for a localized variant; 10 mg/day (9.30%) for a typical presentation form with little lesional expression; 20 mg/day (9.30%) for 2 patients with a classic presentation with little lesional expression and 2 patients with the localized variant; 40 mg/day (51.16%) mostly indicated in classic presentation forms and 2 patients with the localized variant. The 60 mg/day doses (27.90%) were mostly indicated in classic presentations and for 2 patients with the nodular and herpetiform variants respectively (Graph 4).

Therapeutic follow-up: the patients who initiated topical treatment went without medication after three months of follow-up. Of those patients who received steroids systemically, 4.65% went without medication after three months, 4.65% were getting the same dose as at the initiation of treatment and 81.38% were taking a lower dose than the initial one. None of the patients required an increase in the initial dose after three months or adjuvant medication. The evolution of 4 of the patients (9.30%) at month 3 is unknown as they discontinued follow-up (Graph 5).

Discussion

Bullous pemphigoid is a disease of autoimmune pathogenesis characterized by the appearance of subepidermal bullae. It does not show any predilection for ethnicity or sex⁵.

Between August 1995 and August 2010, 9,155 biopsies were performed at the Dermatology Department at our hospital. A total of 45 patients were diagnosed with BP during that period. The BP male/female ratio was 0.8:1. The slightly higher occurrence in females does not have any statistical significance and is consistent with the literature^{5,7}. Onset age of the disease is between 60 and 80 years⁵. A study of 20 BP cases carried out at this hospital between 1984 and 1994 shows that mean age was 70

years⁸ whereas in the current study, mean onset age was 75.97 years. We consider this variation could be due to the significant increase in life expectancy among the population of Argentina from 1985 (71.03 years) to the present (72.24 years), according to the Instituto Nacional de Estadística y Censos (INDEC)⁹.

According to the literature, the most frequent presentation form is the so-called classic^{1,5,10}. Our cases are consistent with such data. In a retrospective study of 53 patients with BP, erythema multiforme-like lesions are described in 1.9% of cases¹¹, which is a lower value than the one observed in our study. Between 10 and 30% of patients present lesions in the oral cavity and, less frequently, on the mucosae of the eyes, nose, pharynx and anogenital region^{7,10}. These data are comparable to our statistics. The healing process may cause post-inflammatory changes such as hyper- or hypo-pigmentation and, at times, milia¹⁰, as in the case of 2 of our patients. Different clinical presentations have been reported, among which is the localized variant, occurring in between 15 and 30% of cases. It has been posited that previous trauma or local factors could be responsible for the induction of lesions in immunologically susceptible individuals^{12,13}. In one of the cases, we found out that treatment with PUVA was the BP triggering factor. In 1979, Provost first referred to pemphigoid nodularis as a rare disease with features similar to pemphigus but with nodular prurigo^{5,14}, presenting lesions which may be persistent or heal with scarring. Some authors suggest that persistent scratching of the pruriginous nodules might modify the antigenicity of the basement membrane zone and release altered antigens responsible for the formation of antibodies against the basement membrane zone^{15,16}. We have reported some such cases in our study. Vesicular pemphigoid is characterized by small bullae or tense vesicles that tend to cluster together, as in dermatitis herpetiformis. It may at times evolve into typical bullous pemphigoid and heal without scarring⁵. It has been demonstrated that the circulating antibodies in this variant produce immunoprecipitation of the 230 kD bullous pemphigoid antigen, so this is why it is considered a separate clinical variant of generalized bullous pemphigoid¹⁷. We have observed this presentation form in only one patient.

Associations with multiple diseases and BP have been described¹⁸. Some authors suspect the association with DBT to be due to complex changes caused by the glycosylation of proteins at the dermo-epidermal junction which could expose BP antigens to autoimmune responses. The trials do not show a higher prevalence of DBT in patients with BP¹⁹. We have observed this association, but it does not represent a relevant sample as there is no case-control group. AHT is prevalent in elderly patients and it was the most frequent association seen in our population. The literature does not reveal any significant differences between



Photo 2: Bullous pemphigoid with erythema multiforme-like clinical presentation.

GRAPH 3: Clinical variants of bullous pemphigoid

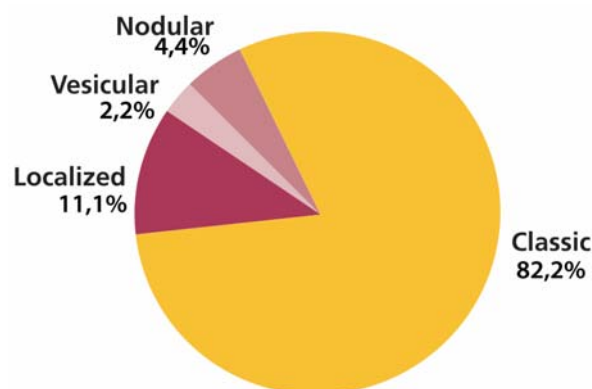




Photo 3: Localized variant of bullous pemphigoid.



Photo 4: Vesicular variant of bullous pemphigoid.

ween groups of patients with AHT and case-control groups¹⁹. Association with cardiorespiratory diseases was not significant, in coincidence with the literature¹⁸. We have observed associations with neurological diseases among our cases. BP has been found to be related to several neurological disorders such as multiple sclerosis, amyotrophic lateral sclerosis, dementia and Parkinson's disease²⁰. The link between BP and these neurological diseases could be due to the expression of a neuronal isoform of Ag1BP. The Ag1BP gene codifies the epithelial isoform (Ag1BP-e) and a neuronal isoform that expresses itself in the central and peripheral nervous systems (Ag1BPn)^{21,22}. The damage caused by these neurological diseases would expose the Ag1BP neuronal isoform and trigger an immunological cross-reaction with the epithelial variant²². The relation between neoplasias and BP can be explained by means of a number of theories. One of them posits the production of antibodies against tumoral specific antigens, which would result in a cross-reaction on with the basement membrane¹⁰. Another theory suggests that tumoral cells secrete a substance which could damage the basement membrane through secondary production of anti-basement membrane antibodies¹⁰. Still another proposal points to the possibility of the same external agent which gives rise to neoplasias damaging the basement membrane. Finally, there is a theory which postulates a genetic predisposition for both diseases¹⁰. Studies such as Rzany's²³ or Jedlickova's¹⁸ have demonstrated this association not to be statistically significant. We have observed in our patients that all neoplasias were diagnosed before the onset of BP. BP has also been reported to be associated with pernicious anaemia, rheumatoid arthritis, alopecia areata, primary biliary cirrhosis, ulcerous colitis, hypothyroidism, systemic lupus erythematosus and pemphigus vulgaris. We highlight the concomitance of BP with hypothyroidism and discoid lupus erythematosus.

BP has often been reported to associate with psoriasis and there are several theories regarding the coexistence of both dermatoses which suggest PUVA therapy, aggressive local treatments and psoriasis itself would generate changes at the basement membrane level in which cytokines would lead to the expression of an antigen triggering the immune response²⁴⁻²⁵. This association was observed in our population and, in one of the patients, after PUVA therapy. Finally, other associations found in our trial were associations with melanoma, basocellular epithelioma and pathomimesis.

The literature mentions the use of potent topical corticosteroids for localized BP. A recent study suggests that they should even be considered for the treatment of generalized BP²⁶. However, most patients with generalized BP require systemic therapy. Corticosteroids are the systemic agents of choice, as they not only have anti-inflammatory effects but also immunosuppressive effects, which result in a reduction of circulating lymphocytes, eosinophils,

CHART 1: Associations with other diseases

Associated diseases	Patients (n)	Patients (%)
Diabetes	15	33.3
Arterial hypertension	29	64.4
Neurological diseases	5	11.1
Previous neoplasias	5	11.1
Cardiorespiratory diseases	5	11.1
Renal diseases	1	2.2
Metabolic diseases	3	6.6
Dermatological diseases	7	15.5

monocytes and basophils²⁷. According to the "Guide to handle BP" (*British Journal of Dermatology*, 2002), it is advisable to initiate treatment with 20 mg/day prednisolone for BP with mild clinical expression and increase to 40 mg/day in cases with moderate clinical expression, and administer 50-70 mg/day for conditions of extensive cutaneous involvement⁷. These regimens coincide with the ones applied on our patients.

As far as prognosis is concerned, unlike two studies carried out in Germany and France, which highlight the fact that old age in general and high doses of oral steroids could worsen prognosis³⁰⁻³¹, a study carried out in Greece and one carried out in Great Britain failed to identify any clinical features attributable to the prognosis of these patients²⁸⁻²⁹. We were not able to evaluate this aspect in our cases due to insufficient data in their clinical histories.

Conclusions

We have not found any significant differences as regards distribution by sex. The mean onset age was higher than the one published in a previous study carried out some years before at the same institution, but it is consistent with statistical data in recent publications. The classic presentation form was the most frequent but we highlight the erythema multiforme-like onset form and the BP cases with mucosal involvement. The associations with other systemic diseases could be due to the fact that these disorders are more frequent within the same age group, and the association with other dermatological diseases was less frequent in our cases, psoriasis being the most relevant. We have not found any data supporting the association of BP with malignant neoplasias and thus we do not consider tumor screening necessary, unless the patient presents symptoms or signs of neoplastic disease. Therapeutic response to the conventional regimen with corticotherapy was satisfactory. The patients did not require any alternative medication for their control and the doses were lower than 40 mg/day for most of them, which reduces the risk of complications and adverse effects derived from treatment.

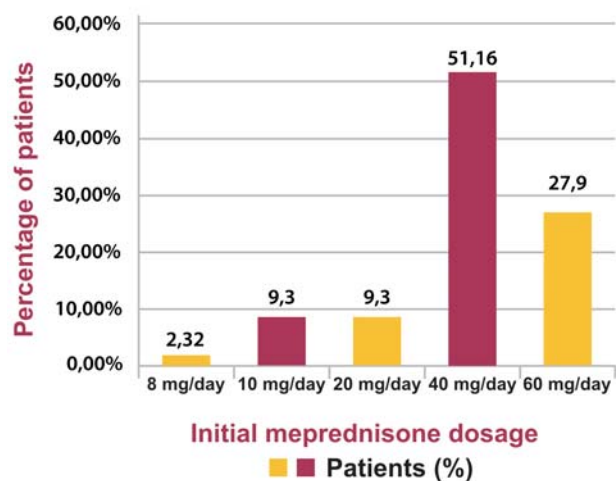


Photo 5: Nodular variant of bullous pemphigoid.

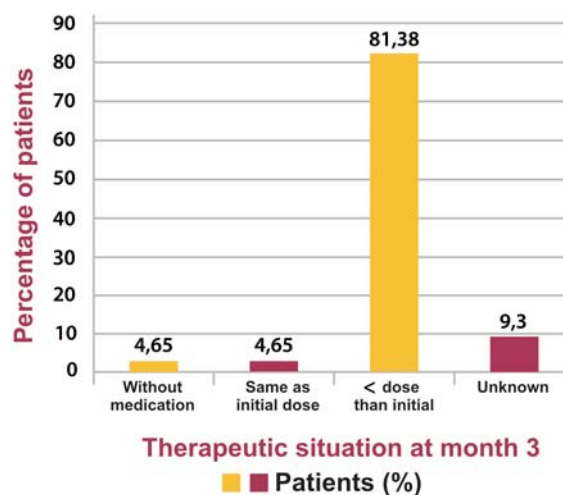


Photo 6: Bullous pemphigoid healing with milia.

GRAPH 4: Initial meprednisone dosage



GRAPH 5: Dosage control after three months



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