

Bullous Pemphigoid Seen at the National Skin Centre: A 2-year Retrospective Review

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Abstract

Introduction: Bullous pemphigoid (BP) is the most common immunobullous disorder in Western Europe, affecting mainly the elderly. Previous reports have suggested that it is rarer in the Far East. We report on the clinico-epidemiological features of BP seen at our centre. **Materials and Methods:** This is a 2-year retrospective study of patients seen at the National Skin Centre who were diagnosed to have BP. **Results:** Fifty-nine patients were newly diagnosed with BP over a 2-year period between January 1998 and December 1999. The minimum estimated incidence was 7.6 per million population per year, with mean age of onset of 77 years, and a male to female ratio of 1:2. There was a predilection for Chinese but not Indian. Localised disease was found in 34% and mucosal involvement in only 1.7%. Direct immunofluorescence was positive in almost all patients, and 94% of those tested had positive indirect immunofluorescence. 'Roof' pattern was present in 95.8% and 'roof and floor' pattern in 4.2%. Prednisolone was the treatment of choice in most patients (78%). Anti-inflammatory agents were more commonly used than a decade ago (13.5%). **Conclusions:** BP is the most common immunobullous disease locally, with an incidence at least equal to that in Western Europe. There was a predilection for ethnic Chinese rather than Indian. Apart from the rarity of mucosal involvement, the clinical features are similar to those of Western nations.

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Introduction

Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disorder affecting mainly the elderly. It is characterised by autoantibodies to the basement membrane zone (BMZ), which are detectable on immunofluorescent studies. These are chiefly of the IgG isotype, and target the BP180 and BP230 antigens in the hemidesmosome, activating complement and setting off an inflammatory cascade which culminates in disruption of the hemidesmosome and blister formation.

Although it is the commonest autoimmune blistering disorder in Western Europe,¹ the few studies from Asia have suggested that it is less common than pemphigus in this region, with a predilection for Indians.²⁻⁴ However, in our experience, there are many more cases of BP than pemphigus diagnosed and on follow-up at our Bullous Clinic.

The aims of this 2-year retrospective study were to study the clinico-epidemiological features of BP seen at the National Skin Centre (NSC), determine the number of new cases seen per year and compare them with reports from other countries.

Patients and Method

The case records of all patients newly diagnosed with BP at NSC during the period from January 1998 to December 1999 were examined. The absolute inclusion criterion was the confirmation of diagnosis of BP on immunofluorescence (IF), either with linear deposits of IgG and/or complement along the BMZ on direct immunofluorescence (DIF), or positive serum indirect immunofluorescence (IIF) with 'roof' or 'roof and floor' pattern when performed on human saline-split skin. Patients who had negative IF or a 'floor' pattern on saline-split skin immunofluorescence (SSSIF) were excluded from this study.

The following data were extracted from the records: patient demographics, clinical presentation, referring diagnosis, investigation results and treatment required for initial control of disease.

Results

Patient Demographics

There were 59 new cases of BP diagnosed during the 2-year period study period. There was a female preponderance with a female to male ratio of 2:1 (39 females, 20 males).

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The average age of onset was 77 (range 51 to 101) years. The racial distribution was: 54 Chinese (92%), 4 Indians (7%) and 1 Malay (2%) (Table I).

Clinical Presentation

The average duration of symptom onset to presentation at NSC was 10.3 (range 0.5 to 104) weeks. Fifty-five (93%) had bullae or vesicles on presentation but in 4 patients (7%), blisters were not seen. Of these, 2 had erosions and papules, 1 had erosions and urticarial lesions, and 1 had erosions only. There were 39 (66%) cases of generalised BP, involving trunk and limbs. Only 1 had oral mucosal non-scarring involvement. The distribution of lesions in the remaining 20 (34%) with localised BP is shown in Table II.

Associated Diseases and Precipitating Factors

Nineteen (32%) had associated hypertension, 17 (29%) had type 2 diabetes mellitus, 4 (7%) had associated malignancies and 3 (5%) had peptic ulcer disease. Other less common associations are listed in Table III. The majority of patients could not identify any precipitating factor. Three had preceding pneumonia and 5 were associated with recent ingestion of drugs: 1 diltiazem, 1 hydro-chlorthiazide, 1 antibiotics, 1 Nuelin/cough mixture and 1 Chinese herbal medicine.

TABLE I: RACIAL DISTRIBUTION OF PATIENTS WITH BP COMPARED WITH RACIAL COMPOSITION OF THE GENERAL POPULATION, AND COMPARISON WITH PREVIOUS LOCAL STUDY IN 1984 (IN PARENTHESES)⁴

Race	No. of patients with BP	Proportion of patients with BP	Proportion of general population
Chinese	54 (26)	92% (70%)	77% (76.7%)
Indian	4 (6)	7% (16%)	7.6% (6.4%)
Malay	1 (4)	2% (11%)	17% (14.7%)
Others	0 (1)	— (3%)	1.4% (2.2%)

TABLE II: MAJOR CLINICAL FEATURES

Clinical feature	No. of patients	Percentage of total
Blisters present	55	93%
Blisters absent	4	7%
Erosions and papules only	2	
Urticarial lesions only	1	
Erosions only	1	
Generalised involvement	39	66%
Mucosal involvement	1	
Localised involvement	20	34%
Proximal and distal limbs	14	
Distal limbs	1	
Hands and feet (acral)	2	
Legs only	2	
Chest only	1	

Histology and Immunopathology

Histology showed subepidermal blistering in all but 1 patient. This was likely due to sampling error, as this patient had bullae on clinical examination, with positive DIF as well as IIF. DIF was performed on all patients. Fifty-one (86%) had linear deposits of C3 and IgG along the dermo-epidermal junction and 6 (11%) had C3 alone (Table IV). DIF was negative in 1, while the epidermis was absent in another: the diagnosis in these 2 cases was based on clinical features, histology and IIF. Serum IIF was positive in 48 of 51 patients (94%) tested. Forty-six (95.8%) had antibodies binding to the epidermal aspect of the induced blister on SSSIF in the so-called 'roof' pattern, with the remaining 2 (4.3%) showing binding to both epidermal and dermal aspects in the 'roof and floor' pattern.

Treatment (Table V)

Forty-four (74.6%) received corticosteroid monotherapy with an average dose of 31.2 (range 15 to 60) mg/day of prednisolone required for initial control. One had received

TABLE III: ASSOCIATED DISEASES

Disease	No. of patients	Percentage of total
Hypertension	19	32%
Type 2 diabetes mellitus	17	29%
Malignancies	4	6.8%
Colonic carcinoma	2	
Lung carcinoma	1	
Breast carcinoma	1	
Peptic ulcer disease	3	5.1%
Fractures	3	5.1%
Neck of femur	2	
Vertebrae	1	
Osteoporosis	2	3.4%
Alopecia areata	1	1.7%
Psoriasis	1	1.7%

TABLE IV: IMMUNOPATHOLOGY

Immunofluorescent study	Positive	Negative	Not done
DIF	57 (97%)	2	0
Linear C3 and IgG	51 (86%)	—	—
Linear C3 only	6 (11%)	—	—
Serum IIF	48 (94%)	3	8
SSSIF	—	—	8
Roof pattern	46 (95.8%)	—	—
Roof and floor	2 (4.3%)	—	—

DIF: direct immunofluorescence; IIF: indirect immunofluorescence; SSSIF: saline-split skin immunofluorescence

TABLE V: TREATMENT PRESCRIBED FOR INITIAL CONTROL OF DISEASE

Treatment	No. of patients	Percentage of patients	No. with generalised disease	No. with localised disease
Steroid monotherapy	44	74.6%	29	15
Prednisolone	43		28	15
IM betamethasone dipropionate	1		1	0
Prednisolone + dapsone	2	3.4%	2	0
Anti-inflammatory agents	8	13.6%	6	2
Doxycycline + nicotinamide	4		2	2
Tetracycline + nicotinamide	3		3	0
Doxycycline alone	1		1	0
Topical steroids	2	3.4%	2	0
No treatment	3	5%	0	3

IM: intramuscular

intramuscular betamethasone dipropionate from the referring physician and no further medications were required. Two (3.4%) more patients with generalised bullae had prednisolone initially, with dapsone added as adjunctive treatment. Anti-inflammatory agents were the mainstay of treatment in 8 (13.6%) patients, of which 2 had a history of peptic ulcer disease. Doxycycline and nicotinamide combination therapy was used in 4 cases, tetracycline and nicotinamide in 3, and doxycycline monotherapy in 1 patient. Of these 8 patients, 6 had generalised and 2 localised involvement. Two (3.4%) patients received topical steroids only, while 3 (5%) patients with mild and localised disease had no treatment at all.

Discussion

With approximately 30 new cases of BP seen per year at NSC, BP is three times more common than pemphigus vulgaris in our local population (unpublished data, NSC), making it the major immunobullous skin disorder seen here as it is in Western Europe. This is in contrast to other reports from Asian countries where pemphigus was more common.^{2,3} The predominance of pemphigus in a neighbouring country could be due to referral bias; in that, only the more severe cases of blistering diseases were referred to the University Hospital and pemphigus is usually more severe or recalcitrant compared to BP. In the report from China, the exact incidence of BP and pemphigus were not known, but it was noted that there were many more reports in the Chinese literature of pemphigus than BP. This is also biased towards more severe or therapeutically challenging cases, which more often represent pemphigus than BP.

With the population of Singapore numbering 3.86 million in 1998, the incidence of BP in Singapore would be *at least* 7.6 per million population per year. Only a *minimum estimate* can be derived from this study, as patients with BP

may also present to the University department of dermatology, or to private dermatologists. This figure is comparable to the 7.4 and 6.6 per million population per year reported from France⁵ and Central Germany,⁶ respectively. This refutes the oft-quoted notion that BP is rarer in the Far East than in Western Europe.¹ The true incidence may in fact be even higher.

Our results corroborate with earlier observations that BP is a disease of the elderly, with a female preponderance, probably due to the higher female to male ratio in this subgroup, rather than a true predilection for females. In fact, a recent study showed that males were more predisposed to BP than females.⁷ There was a predilection for ethnic Chinese, who comprised 92% of patients with BP but only 77% of the general population in Singapore in 1998. There was no evidence of a predilection for Indian, as was reported in an earlier Malaysian study as well as a previous study from this centre.^{2,4} In our study, Indians made up only 7% of the patients with BP, while in 1984 they comprised 16% of the patients studied (Table I).

Although most had blisters on presentation, BP can also present with just erosions, with or without papules or urticarial lesions (Fig. 1). The possibility of BP should be considered in the latter situations in the elderly, particularly if the lesions are fixed, irritable and erythematous, with a careful search for blisters, and a skin biopsy for histology and IMF if the lesions persist. Localised BP is more common than first thought,⁸ representing about 34% in our series. Mucosal BP is rare in our population. They may have presented to other specialties instead.

The most frequently associated diseases were hypertension, diabetes mellitus and osteoporosis. At first glance, these may be attributable to age. However, a case-control study has found that the prevalence of diabetes before administration of corticosteroids was significantly higher in BP than that in controls.⁹ The reason is unknown.

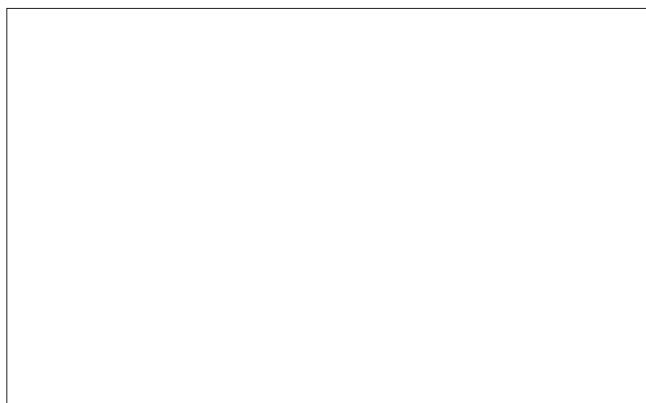


Fig. 1. Tense bullae on an urticarial base, typical of bullous pemphigoid, is seen over the trunk. An older flaccid bulla, as well as erosions, are also seen.

Four of our patients had associated malignancies. Whether BP is associated with a higher risk of malignancies is still controversial. A Swedish study found that the incidence of malignancy in BP was not significantly higher than that expected based on age and sex-standardised incidence data,¹⁰ while a Japanese case-control study showed an excess of malignancies, particularly gastric¹¹ in BP. Our findings should not be interpreted without age- and sex-matched controls. An association with autoimmune disease has been refuted by a case-control study,¹² but has been reported to be associated with psoriasis.¹³ Interestingly, one of our patients also had concomitant psoriasis. Although infections, diltiazem, hydrochlorothiazide and traditional Chinese medicine were possible precipitating factors in a few of our patients, they cannot be attributed as causal without case-control studies. A case-control study has suggested that neuroleptics and aldosterone antagonists are associated with the development of bullous pemphigoid, but not calcium channel blockers, captopril, frusemide or antibiotics.¹⁴

Histology was typical in all but 1 case, with subepidermal clefting and dermal eosinophilic infiltrate (Fig. 2).

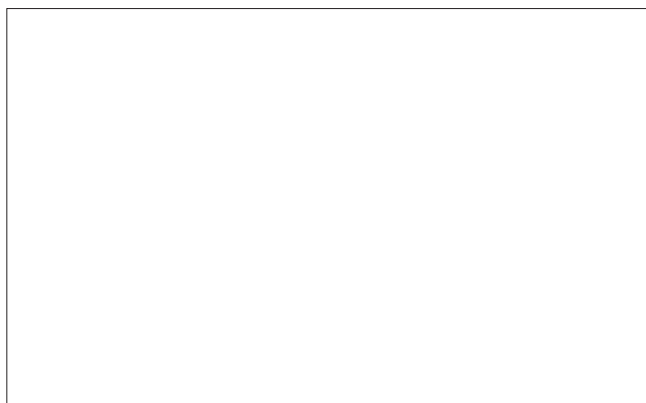


Fig. 2. There is clefting beneath the basal layer of the epidermis, with eosinophils seen within the blister as well as in the dermis (H&E, x40).

As mentioned, the 1 negative result was probably a sampling error. Careful sampling of blisters is required for optimal results.

DIF was almost always positive in our series, with most demonstrating IgG and C3, and a minority showing C3 alone, along the BMZ, where the target antigens are located. One was negative despite a positive IIF. False negatives occur if blisters are biopsied instead of perilesional skin, as immunoreactants are often lost from the roof of the blister, and the roof of the blister is often lost from the specimen.

The proportion of cases with circulating IgG autoantibody to the BMZ as detected on serum IIF was exceptionally high in our series, at 94% of those tested, compared to 70% to 80% reported in the literature.¹⁵ This makes it an attractive method of confirming the clinical diagnosis when patients decline skin biopsy.

As in previous reports, IIF using human skin split through the lamina lucida with saline showed a 'roof' pattern in most cases of BP, with 'roof and floor' pattern in a minority.¹⁶ The 'roof' pattern reflects the presence of anti-BP230 antibodies, which bind exclusively to the epidermal side, and is considered specific for pemphigoid.¹⁶ The 'roof and floor' pattern suggests the presence of autoantibodies binding to both the extra and intracellular epitopes of the 180 kD BP antigen, with the extracellular epitopes separated from the epidermis by the salt-splitting process. Rare cases of BP with 'floor' pattern on SSSIF have been reported. The 'floor' pattern has traditionally been used to denote the diagnosis of epidermolysis bullosa acquisita (EBA), another subepidermal immunobullous disorder that can be clinically indistinguishable from BP, but where the target antigen is collagen VII, a major component of anchoring fibrils present in the sublamina densa zone. However, on immunoblotting, only up to 50% of these dermal-binding serum samples react to the EBA antigen, with the rest reacting to BP180 or laminin-5, indicating the diagnoses of BP and cicatricial pemphigoid respectively.¹⁷ As immunoblotting and immunoelectronmicroscopy are not currently available for routine use here, our diagnostic criterion for BP currently excludes those rare cases with dermal-binding on SSSIF. Moreover, in 6% of our patients with negative IIF, a definite distinction from EBA cannot be made. Although these 'grey' cases make up only a small percentage of cases seen, they are nevertheless a reminder that epidemiological data may change as technology advances and boundaries are redrawn.

Prednisolone at about 0.5 mg/kg/day is the treatment of choice for BP at our centre. Dapsone has been useful as adjunctive treatment for more severe disease not responding to steroids alone. In recent years, there has been a resurgence of interest in the use of anti-inflammatory agents such as

tetracycline, doxycycline and nicotinamide in the treatment of BP,¹⁸⁻²⁰ and this is reflected in our series, particularly if a past history of peptic ulcer disease is elicited. The anti-inflammatory agents are thought to exert their effects by inhibiting neutrophil and eosinophil chemotaxis and secretion, thus reducing the inflammatory cascade that occurs after autoantibody binding and complement activation. However, the onset of action is slow with anti-inflammatory agents, requiring from 2 to 8 weeks for cessation of bulla formation.¹⁸⁻²⁰ As such, its use should be limited to localised disease of limited extent, with prednisolone as the preferred treatment in rapidly progressive or generalised disease.

Conclusion

In contrast to other Asian countries, BP is the most common immunobullous disease seen locally, with a predilection for ethnic Chinese. Apart from the rarity of mucosal involvement, the clinical features resemble those of Western nations. DIF is the most useful diagnostic test in BP, but the high rate of IIF positivity in our study population suggests that serum IIF may be a useful alternative in patients who decline skin biopsy.

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