

Prevalence and clinical features of Thai patients with bullous pemphigoid

Kanokvalai Kulthanan¹, Leena Chularojanamontri¹, Papapit Tuchinda¹, Wararat Sirikudta¹ and Samruay Pinkaew¹

Summary

Background: Bullous pemphigoid (BP) is a rare, subepidermal autoimmune blistering disease. Studies from different regions show discrepancies in clinical features and courses.

Objectives: To reveal clinical characteristics, investigations and clinical outcomes of Thai patients with BP and to evaluate the association of BP with malignancy, diabetes mellitus and neurologic diseases.

Methods: Patients diagnosed as BP who had visited the autoimmune skin clinic at Siriraj Hospital between 1991 and 2009 were retrospectively studied.

Results: Fifty-eight patients were enrolled. Mean age of onset was 69.3 years. The female to male ratio was 2.7:1. Fifteen percent of the patients had mucosal involvement and 38.9% showed peripheral blood eosinophilia. The sensitivity of the direct and indirect immunofluorescence test in the diagnosis of BP was 95.7% and 73.5%, respectively. The frequency of diabetes mellitus in BP patients was significantly higher than that in the general population ($p < 0.001$). BP patients had a significantly higher chance of having neurologic diseases compared with other autoimmune vesiculobullous disease patients (adjusted odd ratios 4, 95% confidence interval 1.2-13.3). Disease control was achieved in 89.7% of the patients. One-year and three-year remission rate was 6.4% and 66.3%, respectively.

Conclusions: BP usually occurred in the seventh and eighth decade of life and affected females more than males. BP is associated with diabetes mellitus and neurologic diseases.

Corticosteroids are the mainstay of the treatment. Two-thirds of patients are likely to be in remission within three years. (*Asian Pac J Allergy Immunol* 2011;29:66-72)

Key words: clinical features, clinical course, bullous pemphigoid, Thai, treatment

Introduction

Bullous pemphigoid (BP) is an autoimmune blistering skin disease usually affecting elderly people. The presence of subepidermal blisters in skin biopsies and linear deposition of IgG and/or C3 along the basement membrane from the immunofluorescence are the characteristic of BP.¹

BP was reported to be the most common autoimmune vesiculobullous disease (ABD) in Western Europe and less common in the Far Eastern countries.² However, a report from Singapore shows that BP is the commonest bullous disease in that region and affects females twice as often as males.³ As BP occurs in the elderly who often have underlying diseases, the association between BP and other diseases such as malignancy, diabetes mellitus (DM) and neurologic diseases has been studied in many centers. Nevertheless, whether those diseases correlate with BP or the increased age is still controversial.⁴⁻⁷

Systemic corticosteroids are widely used for the treatment of BP⁸, however, Joly et al.⁹ reported that topical corticosteroids alone were beneficial in the treatment of moderate to severe disease. Adjuvant drugs such as azathioprine, antibiotics together with nicotinamide, cyclophosphamide and methotrexate are also used in the treatment of BP.⁸ Piamphongsant¹⁰ studied the clinical outcomes of 28 Thai patients with BP treated with dapsone alone, and revealed that dapsone was effective in controlling the disease in 13 patients (45.4%).

Although there are many publications about the epidemiology, investigations and treatment of BP from many countries, data from Thailand have not yet been published. Thus, the aim of this study was to evaluate the clinical characteristics,

From the ¹Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Corresponding author: Kanokvalai Kulthanan

Email: sikkt@mahidol.ac.th

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investigations and clinical outcomes of patients with BP in Thailand and also to investigate the association of BP with other diseases such as malignancy, DM and neurologic diseases.

Methods

Ethical approval was granted by Siriraj Institute Review Board, Siriraj Hospital, Mahidol University, Bangkok, Thailand. The study was conducted on patients with BP treated and followed up at the autoimmune skin clinic at Siriraj Hospital between January 1991 and December 2009. The diagnosis of BP was made based on the following characteristics: clinical manifestations, such as tense blisters on both normal and erythematous bases; histopathologic findings, such as subepidermal blisters and immunological findings of positive direct immunofluorescence (DIF) tests (deposition of IgG and/or C3 along the basement membrane zone) or indirect immunofluorescence (IIF) test (presence of circulating anti-basement membrane zone autoantibodies), 1 M NaCl direct or indirect-split skin study (staining of IgG and/or C3 at the roof or at both the roof and the floor of the blister), as previously reported.²

Data were obtained by reviewing outpatient records and autoimmune skin clinic files. The case record form included age of onset, sex, presenting symptoms, characteristic of skin and mucosal lesions, laboratory investigation results, treatment outcome and clinical course. The evaluation of therapeutic outcome of our patients with BP was based on criteria from the International Pemphigus Committee.⁽¹¹⁾ For instance, disease control is the time at which no new lesions develop and existing lesions begin to heal. Remission (on therapy) occurs when patients are lesion-free for at least two months while receiving prednisolone \leq 10 mg/day and/or adjuvant drugs at half of the full therapeutic doses. Remission (off therapy) is defined as being free of lesions for at least two months while patients are off all systemic therapy. Relapse is the time at which patients have \geq 3 new lesions/month that do not heal spontaneously within one week.

Statistical analysis was carried out by using the SPSS software version 17.0. Descriptive statistics were used to report demographic data, clinical characteristics and laboratory investigation results. Moreover, the prevalence of DM among

patients with BP, patients with other autoimmune vesiculobullous diseases and general population was compared using the Chi-squared test, Fisher's exact test or Z-tests. The association between neurologic diseases and BP was assessed by multiple logistic regression. The duration from treatment to each therapeutic outcome was analyzed by using Kaplan-Meier method of survival analysis.

Results

In total, 58 patients with BP who had visited the autoimmune skin clinic at Siriraj Hospital from 1991 to 2009 were studied. Among 196 patients with ABD, BP was the second most common disease diagnosed (29.6%) compared to pemphigus (63.3%). Considering the 72 patients with subepidermal autoimmune bullous diseases, BP was the most frequent diagnosis (58 cases; 80.6%) followed by epidermolysis bullosa acquisita (4 cases; 5.6%) and bullous systemic lupus erythematosus (4 cases; 5.6%). Additionally, linear IgA bullous dermatosis was diagnosed in 3 cases (4.2%) and the rest were cicatricial pemphigoid (1 case; 1.4%), dermatitis herpetiformis (1 case; 1.4%) and lichen planus pemphigoid (1 case; 1.4%).

The female to male ratio was 2.7:1. The peak age of onset was between 60 and 80 years. Hypertension was the most common associated disease, followed by cerebrovascular disease (CVD) and DM. Malignancy was presented in five patients as shown in table 1.

Table 1. Demographic data of patients with bullous pemphigoid (BP)

Character	BP patients n=58
Sex; number of patients (%)	
Male	16 (27.6)
Female	42 (72.4)
Age of onset; mean \pm SD, year	
	69.3 \pm 14.7
Underlying disease; number of patients (%)	
Hypertension	24 (41.4)
Cerebrovascular disease (CVD)	14 (24.1)
Diabetes mellitus (DM)	11 (19)
Malignancy	5 (8.6)
Cervical cancer	2
Breast cancer	1
Bladder cancer	1
Meningioma	1
Dyslipidemia	4 (6.9)
Others	16 (27.6)

SD, standard deviation

Table 2. Clinical manifestations and laboratory investigations of BP patients

Character	Number (%) n=58
Presence of itching symptoms	46 (79.3)
Morphology of skin lesions	
Vesicle/bullae	58 (100)
Base : Erythematous base	50/58 (86.2)
Normal skin base	34/58 (58.6)
Wheal/urticarial plaque	23 (39.7)
Erosion/ulcer	33 (56.9)
Site of involvement at onset	
Skin involvement alone	51 (87.9)
Both oral mucosa and skin	7 (12.1)
Site of involvement during clinical course	
Skin involvement alone	49 (84.5)
Both oral mucosa and skin	9 (15.5)
Complete blood count; n=54	
Anemia (Hematocrit \leq 35%)	15 (27.8)
Leukocytosis (WBC \geq 12,000 cell/ μ L)	13 (24.1)
Neutrophilia (Neutrophil $>$ 80%)	8 (14.8)
Eosinophilia (Eosinophil $>$ 600 cell/ μ L)	21 (38.9)
Tzanck's smear; n=29	
Neutrophil predomination	5 (17.2)
Eosinophil predomination	13 (44.8)
Direct immunofluorescence (DIF); n=47	
Positive	45 (95.7)
Indirect immunofluorescence (IIF); n=49	
Positive circulating anti-basement membrane zone IgG	36 (73.5)

Itching symptoms were common among patients with BP. Moreover, blisters either on normal or erythematous bases were frequently found. The majority of patients had lesions on the skin and mucosal involvement occurred in 15% of the patients. The full blood count showed eosinophilia in 21 of 54 patients (38.9%). The percentage of eosinophils and the absolute eosinophil count ranged from 5.1 to 72 and 713 to 15,624 cells/ mm^3 , respectively. Tzanck's smear revealed eosinophil predomination in nearly half of BP patients as shown in table 2. Similarly, histopathologic sections demonstrated predominant eosinophil infiltration in approximately half of BP patients.

DIF studies showed linear staining of IgG in 33 of 47 cases (70.2%) and C3 in 44 of 47 cases (93.6%). Table 3 shows the diagnostic value of DIF and IIF in patients with BP. DIF yielded higher sensitivity but lower specificity than IIF. The IIF titer ranged from 1:10 to 1:10,240 (mean 1:509).

Considering the clinical characteristics between BP patients with and without malignancy or DM, there were no significant differences in the mean age of onset, mucosal involvement and IIF results as illustrated in table 4.

Table 3. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of DIF and IIF in diagnosis of BP in this study

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DIF	95.7	69.9	59.2	97.3
IIF	73.5	96	87.8	90.3

Among BP patients with malignancy, the malignancy was diagnosed prior to BP being diagnosed in three patients, and simultaneously diagnosed in the other two patients as shown in table 5. Furthermore, the associated malignancy in BP patients was not different from those in ABD patients (Fisher's exact test, $p = 0.58$).

On the other hand, all patients with DM were non-insulin dependent and BP occurred at an average duration of 15.2 years after DM was documented (range 3-40 years). Moreover, the prevalence of DM among BP patients was significantly higher than that among ABD patients and general population ($p = 0.026$ and $p < 0.001$, respectively), as shown in table 6.

Table 7 shows that CVD was the most common neurologic disease among patients with BP and ABD. The prevalence of neurologic diseases and CVD among patients with BP was significantly higher than that among patients with other ABDs (adjusted odd ratios (OR) for neurologic diseases, 4; 95% confidence interval (CI), 1.2-13.3; adjusted OR for CVD, 5.3; 95% CI, 1.3-21.8).

Prednisolone was used as a single agent in 19 of 58 patients (32.8%) whereas the combination of prednisolone and adjuvant drugs was prescribed to 33 of 58 patients (55.2%). The most common prescribed adjunctive drug was dapsone followed by cyclophosphamide. However, nicotinamide together with tetracycline was used in one patient and disease control was achieved. Three patients received only topical treatment and one of them went into remission (off therapy). The mean total dose of prednisolone required to achieve remission was 0.05 g/kg.

Table 8 shows the clinical courses of BP patients. Disease control was reached in almost all patients, whereas remission (off therapy) was achieved in only 10 of 58 patients (17.2%). Since some patients were lost to follow-up, the Kaplan Meier survival curve was used to determine time to remission (off treatment) and is shown in figure 1. One-year and three-year remission rate was

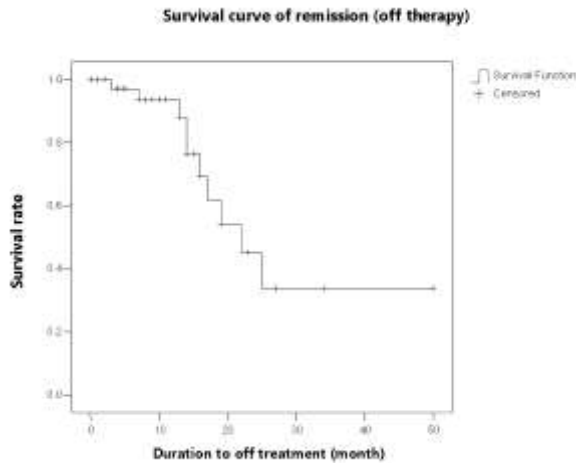


Figure 1. Kaplan Meier survival curve of remission (off therapy) in BP patients. One-year and three-year remission rate is 6.4% and 66.3%, respectively.

6.4% and 66.3% respectively. The mean follow-up period was 14.4 months and almost all patients had clinically improved at their last hospital visit. Five patients, however, died during the follow-up period. Four of them died of serious infection which resulted from complications of BP treatment, the other died from upper gastrointestinal bleeding related to his underlying cirrhosis. The one-year Kaplan-Meier survival rate was 87.7%.

Adverse drug reactions occurred in 10 of 58 BP patients (17.2%). The most common side effect was infection (46.2%), followed by a Cushingoid appearance (30.8%) and anemia (23.1%). One patient had dapsone hypersensitivity.

Discussion

BP is the most common ABD reported in European countries such as France, Germany and England.¹²⁻¹⁴ However, our data show that BP is the second most common ABD after pemphigus,

which is in concordance with reports from Malaysia and Romania.^{15, 16} The mean age of onset in our patients was in the seventh decade of life and females were affected more than males. The same findings are also observed in many reports; however, the mean age of onset is higher (in the eighth decade) in studies from Singapore, Romania, Greece, England, Italy and Scotland.^{3, 14, 16-21}

Skin lesions in the non-bullous phase of BP can be polymorphic and ulcers can occur following blister rupture. In our study, 39.7% of patients had wheals/urticarial plaques and 56.9% had erosions/ulcers at the first presentation. The variation in the duration from onset of disease to hospital visit may account for this (median 30 days, range 1-730 days). Although the lesions of BP are mainly on skin, 15.5% of our patients also had lesions on the oral mucosa which is comparable to data from Taiwan, Poland and Italy.^{18, 20, 22} On the contrary, the mucous membrane involvement is higher in reports from Greece (24.3%) and Kuwait (37%) and much lower in the report from Singapore (1.7%).^{3, 17, 19}

Bushkell et al.²³ reported that one-half of BP patients had peripheral blood eosinophilia, ranging from 5% to 43% at the first test, with an increase during follow-up to 56% in one patient. Our data indicate blood eosinophilia in approximately 40% of patients, but with a greater range than reported elsewhere (5% to 72%). Durdu et al.²⁴ studied the value of Tzanck’s smear test in diagnosis of bullous skin lesions and stated that Tzanck’s smear results in 7 out of 9 BP patients (77.7%) showed eosinophils without acantholytic cells. In our study, 44.8% of BP patients had Tzanck’s smear result compatible with BP. The technique of obtaining Tzanck’s smear and discrepancies in the stages of lesions may be the reason for this variation.

Table 4. Clinical parameters of BP patients with and without malignancy and DM

Variable	BP with malignancy	BP without malignancy	p value	BP with DM	BP without DM	p value
Mean age of onset; year	71 ± 8.2	69.2 ± 15.2	0.79*	72.6±9.6	68.6±15.6	0.43*
Mucosal lesions; number of patients (%) , n=58			0.58 [†]			1.00 [†]
Presence of mucosal lesions	0 (0)	10 (18.9)		2 (18.2)	8 (17)	
Absence of mucosal lesions	5 (100)	43 (81.1)		9 (81.8)	39 (83)	
IIF studied; number of patients (%) , n=49			0.31 [†]			0.71 [†]
Positive IIF	5 (100)	31 (70.5)		8 (80)	28 (71.8)	
Negative IIF	0 (0)	13 (29.5)		2 (20)	11 (28.2)	

*t-test,
[†] Fisher’s exact test



Table 5. Clinical features and course of BP patients with malignancy

No.	Age (yr)	Sex	Underlying malignancy	Duration from onset of malignancy to BP (month)	Malignancy activity at onset of BP	Course of BP		Last visit	
						Control	Remission (off therapy)	Status	Follow-up duration (month)
1	78	F	Breast cancer	65	inactive	yes	no	loss F/U	14.8
2	60	M	Petroclival meningioma	60	inactive	yes	no	loss F/U	7.2
3	70	F	Recurrent cervical cancer	24	active	yes	no	loss F/U	4.3
4	80	F	Bladder carcinoma	7	active	yes	yes	during F/U	24.5
5	67	F	Cervical cancer	6	active	yes	yes	during F/U	18.0

yr, year; F, female; M, male; F/U, follow-up

Immunofluorescence studies are useful tools in the diagnosis of BP. The DIF studies showed deposition of IgG and/or C3 along the basement membrane zone in almost all BP patients, and the IIF studies revealed the presence of anti-basement membrane IgG auto-antibodies in about 70% to 80% of BP patients.^{25, 26} Our results also show the higher sensitivity of DIF in diagnosis of BP as compared to IIF (95.7% and 73.5%, respectively).

Concerning the association of BP and malignancy, Venencie et al.²⁷ reported that the frequency of malignancy in BP patients was not higher than in the general population, but the frequency of malignancy was higher in BP patients with negative IIF tests than that with positive IIF tests. In contrast, Ogawa et al.⁷ stated that the association ratio of malignancy and BP was significantly higher than that of controls aged over 70 years old and the percentage of negative IIF tests was lower in BP patients with malignancy. Our data show that the prevalence of malignancy in BP patients was not higher than that in other ABD patients. Moreover, none of BP patients with malignancy had negative IIF tests. However, the number of BP patients with malignancy in our study is limited. Further studies with larger sample size should be conducted.

In the present study, the overall prevalence of DM in BP patients was significantly higher than that in the general Thai population²⁸, which is similar to reports from Chuang et al.⁴ and Rosina et al.⁶ In contrast, Taylor et al.²⁹ found no discrepancy between the frequency of DM in BP patients and in controls. Additional studies are needed to confirm whether these two diseases are related.

Taghipour et al.³⁰ conducted a case-control study in 90 patients with BP and 141 controls and concluded that BP is associated with CVD and dementia. Furthermore, Bastuji-Garin et al.³¹ reported that dementia and Parkinson's disease were the risk factors for BP. In addition, our results revealed that the prevalence of neurologic disease particularly CVD was significantly higher in BP patients compared with other ABD patients. We cannot draw a conclusion about the association between other neurologic diseases and BP because of the small number of patients.

Systemic corticosteroid treatment is effective and seems to be the best initial treatment in BP patients.⁸ Surprisingly, a randomized, multicenter trial in 341 BP patients found that topical corticosteroid alone is effective for moderate and severe diseases.⁹ Almost all BP patients in our study were treated with oral prednisolone. However, three patients received only topical corticosteroids and all of them achieved disease control. Moreover, remission (off therapy) was also reached in one out of these three patients.

The use of dapsone either as a single treatment or as an additional drug to prednisolone was reported to be effective in approximately 45% of BP patients.^{10, 32} Fivenson et al.³³ reported that nicotinamide together with tetracycline was beneficial as an alternative therapy to systemic corticosteroids. In our study, about one-half of the patients were prescribed adjunctive drugs concurrently with prednisolone, moreover dapsone was the most frequently used adjunct drug.

Publications from Taiwan and Kuwait show that 30% of BP patients went into complete remission (off treatment).^{17, 22} However, only 17.2% of BP patients in the present study reached

Table 6. Prevalence of associated DM in BP patients, ABD patients and controls categorized by age group

Age (year)	Prevalence of DM (%)			p value	
	BP n=58	ABD n=138	Control† n=17,900	BP vs ABD	BP vs control
18-29	0	0	0.6	-	-
30-44	0	2.3	3.4	1.000	-
45-59	22.2	11.4	10.1	0.588	0.229
60-69	14.3	13.6	16.7	1.000	0.810
70-79	20.0	16.7	15.8	1.000	0.657
≥ 80	25.0	25.0	11.5	1.000	0.097
total	19.0	8.0	6.9	0.026*	< 0.001*

ABD, autoimmune vesiculobullous diseases other than BP

†Control is the general population²⁸

remission (off therapy). This may be due to the fact that the follow-up period in our study was shorter than the others. Additionally, our center is a tertiary care hospital so some patients were referred for follow-up at hospitals close to their residences when their symptoms improved.

Five of 58 BP patients in our study died during the follow-up period. The mortality rate was 8.6% which is lower than reported from France and the United State (26% and 23%, respectively).^{34, 35} The variety of mortality rates among studies may be due to the discrepancies in disease severity and treatment regimens.

Our data show that the most common adverse drug reaction was infection. Moreover, serious infection was also the major cause of death. This implies that BP patients should be closely monitored for side effects of treatment. Similarly, Wojnarowska et al.⁸ suggested that treatment in BP patients should be reviewed frequently to confirm that the current corticosteroid dose is not higher than needed.

Table 7. Prevalence of neurologic diseases in patients with BP and other ABDs

Variable	Number (%)		Odds ratio (95% CI)	
	BP* n=58	ABD n=138	Crude	Adjusted†
Any neurologic diseases	16 (27.6)	5 (3.6)	10.1 (3.5-29.3)	4.0 (1.2-13.3)
CVD	14 (24.1)	3 (2.2)	14.3 (3.9-52.2)	5.3 (1.3-21.8)
Dementia	2 (3.4)	0 (0)	-	-
Parkinson	1 (1.7)	1 (0.7)	2.4 (0.2-39.1)	-
Alzheimer	1 (1.7)	0 (0)	-	-
Epilepsy	0 (0)	1 (0.7)	-	-

CI, confidence interval

*Two patients had two neurologic diseases; one had CVD and dementia, another had CVD and Alzheimer's disease

†Adjusted for age, sex and other underlying diseases.

Table 8. Clinical courses of BP patients

Clinical courses	BP patients
Disease control; n=58	
Number of patients (%)	52 (89.7)
Duration between treatment and disease control; median (days)	34
Remission (on therapy); n=58	
Number of patients (%)	26 (44.8)
Duration between treatment and remission on therapy; median (months)	8
Remission (off therapy); n=58	
Number of patients (%)	10 (17.2)
Duration between treatment and remission off therapy; median (months)	22
Relapse; n=10	
Number of patients (%)	6 (60)
Duration between off treatment and relapse; median (months)	6

To summarize, BP is the second most common ABD among Thai patients and usually occurs in the seventh and eighth decade of life. Females are affected more than males. The frequency of DM in BP patients is significantly higher than in the general population, while there is no such correlation between malignancy and BP. The prevalence of neurologic diseases particularly CVD is higher among BP patients compared with other ABD patients. Peripheral blood eosinophilia can be seen in nearly half of the patients. DIF tests have a higher sensitivity but lower specificity than IIF tests. Prednisolone is established as the main treatment. Dapsone is the most common adjunctive drug prescribed either alone or together with prednisolone. Almost all patients achieve disease control. One-year and three-year remission (off treatment) rate is 6.4% and 66.3%, respectively. The major cause of death is serious infection which is a complication of treatment.

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