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CLINICAL STUDY

Clinical manifestation variability of bullous pemphigoid

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ABSTRACT
BACKGROUND: Bullous pemphigoid (BP) is a rare autoimmune blistering disease predominantly affecting the elderly population.
OBJECTIVES: The present study aims to identify clinical factors that may influence outcomes of BP, including skin phenotype, serology, mucosal involvement, pruritus, and triggers.
METHODS: A retrospective analysis was conducted on 70 cases with BP registered from January 2019 to December 2022. The Bullous Pemphigoid Disease Activity Index (BPDAI) score was used to assess disease intensity. The BPDAI-Pruritus score and a modified Brest questionnaire were used to document pruritus. Anti-BP180 and anti-BP230 autoantibodies were regularly recorded. Peripheral blood eosinophil counts were documented during flare-up and remission phases of BP.
RESULTS. Of the cases, 81.4% were identified with bullous BP, 12.9% with nonbullous BP and 5.7% with localized BP. Oral involvement was documented in 17.1% of cases. Increased peripheral eosinophilia was prominent in the nonbullous phenotype and returned to normal level during remission in both phenotypes.
CONCLUSION: The outcomes of BP depended on the disease phenotype and trigger types. Bullous BP showed more intense disease activity, while nonbullous BP demonstrated more intense pruritus. BP associated with diabetes mellitus (DM) or psoriasis manifested as a more severe disease, predominantly with the bullous phenotype and pruritus, compared to cases without comorbidities. New triggers, including SARS-CoV-2 infection and vaccination, were documented *(Tab. 6, Ref. 43)*. Text in PDF www.elis.sk
KEY WORDS: bullous pemphigoid, nonbullous pemphigoid, pruritus, comorbidity, eosinophilia, new triggers.

Introduction

Bullous pemphigoid (BP) is a rare autoimmune blistering disease predominantly afflicting the elderly population. Various comorbidities may play a role in the pathogenesis of BP, including neurologic diseases, certain drugs, infections, and physical stimuli. The presence of antigen BP230 in the central nervous system may support the development of BP in cases with some neurological disorders (1). Several drugs were documented to trigger BP, with vildagliptin and aldosterone being confirmed triggers (2). On the other hand, malignancy in the elderly is considered a comorbidity and is not seen as a triggering factor of BP. However, some studies report potential associations with hematologic malignancies (3). The most frequent phenotype of BP is the bullous phenotype which has a polymorphous clinical appearance that includes blisters, urticarial plaques, erythematous patches, erosions, and crusts. The nonbullous phenotype does not induce blisters and typically manifests as urticarial plaques and erythematous patches. The localized phenotype afflicts one location on the body, often asymmetrically, with a preference for legs. In all phenotypes, BP180 and BP230 autoantibodies are detected in serum and tissues. Histopathologically, a typical subepidermal split is seen only in bullous and localized phenotypes. The nonbullous BP does not show this split, although other histological characteristics are similar (4). Diagnosing BP can be challenging and may lead to misdiagnosis at the onset of the disease. All pruritic diseases with a heralding symptom of pruritus should be suspected of developing into BP, as many dermatologists are still unaware of the nonbullous phenotype of BP. The heterogeneous clinical appearance of BP may mimic various conditions including allergy to drugs, scabies, nummular dermatitis, other blistering diseases, etc. The incidence of BP is rising worldwide, potentially due to changing lifestyles, introduction of new drugs, and increasing age of population in developed countries (5). The mortality of BP is higher than that of the general population (6) but lower than that of individuals with pemphigus vulgaris (PV) (7). The therapeutic management of BP differs from that of PV. In BP, systemic immunosuppressive drugs are used in lower doses than those used in PV (8). However, there is a higher risk of drug interaction, adverse events, and comorbidity restriction. In mild cases, the topical administration of strong corticosteroids may show good efficacy. Moreover, tetracyclines may be effective owing to their immune modulatory efficacy.

The objective of the study was to identify clinical factors that may influence the outcome of BP, including skin phenotype, serology, mucosal involvement, pruritus, relapses, and triggers.

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Material and methods

A retrospective analysis was conducted on cases of BP registered in the Dispensary Bullous Center at University Hospital in Bratislava. Cases were recruited from January 2019 to December 2022. Inclusion criteria comprised a clinical diagnosis of BP confirmed by histopathology, direct immunofluorescence (DIF), and circulating anti-BP180 and anti-BP230 autoantibodies detected by enzyme-linked immunosorbent assay (ELISA). Anti-BP autoantibodies were evaluated at the onset of the disease, and at regular 6-month intervals. A detailed review of the patient's clinical history, and clinical parameters, including age, sex, onset of the disease, completion of treatment, relapses, comorbidities, and triggers, was conducted. Clinical status at the onset of BP was evaluated using Bullous Pemphigoid Disease Activity Index (BPDAI) score (9).The severity scores categorized BP into three levels of disease intensity: mild BP (0-19), moderate BP (20-56) and severe BP (57≥) (10). Visual Analog Scale (VAS) was used to self-evaluate itching over the last 24 hours, the past week, and past month (9). In addition, a modified Brest Questionnaire was used to evaluate characteristics of pruritus (11). Peripheral blood eosinophil counts were evaluated in absolute and relative numbers during flare-ups and remission.

Statistical analysis

Data were compiled into EXCEL files and analyzed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). Frequency tables were used for statistical analysis of numerical and categorical variables. Descriptive statistics were utilized for numerical variables, including the mean, median, CI, SD, IOR, 95% confidence interval for mean, minimum, maximum, and range. The normal distribution was tested using the Levene's test. For normally distributed data, an independent sample t-test was employed to compare two datasets, while ANOVA was employed to compare more than two datasets. For multiple comparisons, Scheffe´s method was applied. Numerical data with abnormal distributions were evaluated using the non-parametric Mann–Whitney test for comparing two datasets and the Kruskal–Wallis test for comparing more than two datasets. Associations between categorized variables and outcomes were assessed using Fisher's exact test. A $p<0.05$ was considered statistically significant.

Tab. 1. Demographic data and BPDAI score in various phenotypes of bullous pemphigoid (n=70).

Variables	Mean ±SD	Median±IQR	Min–Max
Age at presentation, years (n=70)	73.5±12.2	74.5±18.8	41.0–94.0
Age at onset BP in female patients	71.5±12.3	74.5±17.8	46.0–91.0
Age at onset BP in male patients	66.7±13.1	69.0±17.0	36.0–90.0
Bullous phenotype of BP (n=57)			
BPDAI Erosion/Blister score	17.5±10.9	14.0±12.5	4.0–47.0
BPDAI Urticaria/Erythema score	9.6±8.2	7.0±6.5	2.0–45.0
BPDAI Damage score	2.1±1.0	2.0±1.9	0–6.0
BPDAI Mucosal score	0.6±1.4	0±0	0–6.0
BPDAI Pruritus score	11.9±7.4	12.0±11.9	0–28.0
BPDAI Total score	29.7 ±16.9	24.0 ±20.0	11.0–96.0
Nonbullous phenotype of BP (n=9)			
BPDAI Erosion/Blister score	0	0	0
BPDAI Urticaria/Erythema score	24.8±10.6	27.0±22.3	10.0–35.0
BPDAI Damage score	2.0±1.6	2.0±3.5	0–4.0
BPDAI Mucosal score	0	0	0
BPDAI Pruritus score	22.8±4.2	22.0±13.8	18.0–28.0
BPDAI Total score	26.8 ±11.7	29.5 ±23.8	10.0–38.0
Localized phenotype of BP (n=4)			
BPDAI Erosion/Blister score	3.8±2.2	5.0±3.8	0–5.0
BPDAI Urticaria/Erythema score	0.8±1.3	0±1.1	0–3.0
BPDAI Damage score	0.8±0.4	1.0±0.5	0–1.0
BPDAI Mucosal score	3.8±1.8	0±15.0	0–15.0
BPDAI Pruritus score	3.7±2.9	11.0±4.0	0–15.0
BPDAI Total score	10.0 ±4.6	9.0 ±7.0	6.0–15.0

Results

Demographic data and phenotypes of BP

Demographic data and BPDAI score for 70 study cases are summarized in Table 1. The male-to-female sex ratio in the cohort was 1:1.6 (38.5% and 61.4%, respectively). Women were older at the onset of BP than men, although the difference was not statistically significant (p=0.06). Notably, 8.8% of cases were younger than 50 years. The highest age at BP onset (80.0±9.2 years) was recorded in the localized phenotype of BP. The mean follow-up time was 4.1±2.7 years (median 3.0, range 1–7). The bullous, nonbullous , and localized phenotypes of BP were recorded in 81.4%, 12.9% and 5.7% of cases, respectively. Moderate disease intensity was most frequently documented (61.4% of cases), followed by mild intensity (32.9% of cases). Severe BP was recorded in 5.7% of cases, with the highest BPDAI score of 96.0 in one patient. The bullous phenotype of BP was associated with a more severe disease compared to the nonbullous and localized phenotypes. Cases with DM and psoriasis showed significantly higher BPDAI total scores than those without these comorbidities (31.4±17.3; 31.0±24.2; p=0.04, p=0.05). The bullous phenotype of BP was documented in all cases with psoriasis and in 75% of cases with DM.

None of the cases had a family history of BP. However, other autoimmune diseases were recorded in family relatives in 27.1% of cases. Table 2 shows comorbidities in BP cases. Autoimmune diseases were documented in 32.9% of cases, with psoriasis vulgaris recorded in 11.4% of cases, preceding BP by an average of 11.6±3.5 years. The most frequent comorbidity was hypertension, affecting 51.4% of cases. Allergies, including drug allergy, food allergy and bronchial asthma were documented in 30.0% of cases. Malignant neoplasms were recorded in 28.6% of study patients. The most frequently documented malignancies included carcinoma of the prostate (12.9%), carcinoma of the urinary system (12.9%), followed by carcinoma of the skin (4.3%), malignant melanoma (1.4%), lung carcinoma (1.4%), colon

carcinoma (1.4%), breast carcinoma (1.4%), and chronic myeloid leukemia (CML) (1.4%).

Evaluation of pruritus in various phenotypes of BP

Pruritus is the major symptom that may herald the onset or recurrence of BP. It was documented as the first symptom in 65.7% of bullous BP cases, 100% of nonbullous BP cases, and in none of the localized BP cases. The BPDAI-Pruritus score indicated more intense pruritus in nonbullous BP compared to bullous BP, with the difference being statistically significant (p=0.001). The BPDAI-Pruritus scores for mild, moderate, and severe BP are shown in Table 4. In mild BP, 4.4% of cases did not report pruritus. Excoriations were significantly associated with severe and moderate BP (p=0.003) but did not differ significantly between bullous and nonbullous BP study groups (p=0.097). Cases with DM or psoriasis reported significantly more intense pruritus than those without comorbidities (p=0.023, p=0.05, respectively).

Characteristics of pruritus in BP cases obtained by modified Brest Questionnaire are summarized in Table 5. Cases with nonbullous BP experienced more intense pruritus than those with bullous BP. However, some characteristics of pruritus did not show differences between these two BP phenotypes. Cases with localized BP did not show relevant pruritus at all.

BP patients described pruritus with several types of sensations. Most frequently, pruritus evoked stinging (52.1%) followed by burning (22.4%), tickling (7.1%) and crawling (5.5%), while 12.93% of patients described pruritus simply as itching without any precise characteristics.

Evaluation of skin and mucosal afflictions

The characteristics of the clinical appearance of BP are manifold, which may complicate the clinical diagnosis. The bullous phenotype of BP was correctly diagnosed at the initial evaluation only in 30.0% of cases. However, 100% of cases with nonbullous phenotype of BP were misdiagnosed as scabies (55.6%) or urticaria (44.4%). The most frequent incorrect diagnosis was microbial eczema in 15.7%. Other incorrect initial diagnoses are documented in Table 5. The duration of clinical symptoms of BP up to the diagnostic assessment was prolonged in nonbullous phenotype with a mean time of 14.3±13.9 months. The dura-

Tab. 2. Comorbidities in 70 cases with bullous pemphigoid.

Comorbidity	n (%)
Other autoimmune diseases	23 (32.9)
Hypothyroidism	17 (24.3)
Psoriasis vulgaris	8 (11.4)
Rheumatoid arthritis	3 (4.3)
Crohn disease	2 (2.9)
Rheumatic fever	1 (1.4)
Vitiligo	1 (1.4)
Other comorbidities	59 (84.3)
Hypertension	36 (51.4)
Other cardiovascular disease	16 (22.9)
Diabetes mellitus	28 (40.0)
Hepatopathy	16 (22.9)
Chronic renal disease	13 (18.6)
Hemodialysis	2 (2.9)
Neurological diseases	16 (22.9)
Alzheimer disease	4 (5.7)
Stroke	3 (4.3)
Dementia	2 (2.9)
Parkinson disease	2 (2.9)
Malignant neoplasia	20 (28.6)

Tab. 3. Characteristics of pruritus in 70 cases with bullous pemphigoid.

Characteristics of pruritus	n (%)	p
Pruritus as the first clinical symptom	47 (67.1)	
Duration		NS
Almost always	20 (28.6)	
Weeks	7 (10.0)	
Months	43 (61.4)	
Frequency		0.001
Permanent	13 (18.5)	
Intermittent	50 (71.4)	
Daily occurrence		NS
Almost always	34 (48.6)	
Often	20 (28.6)	
Seldom	11 (15.7)	
Night occurrence		NS
Almost always	18 (25.7)	
Often	23 (32.8)	
Seldom	15 (21.4)	
Frequency of occurrence		0.048
Almost always	26 (37.1)	
Often	22 (31.4)	
Weekly	7 (10.0)	
Seldom	11(15.7)	
Difficulty of falling asleep		0.016
Almost always	18 (25.7)	
Often	23 (32.8)	
Seldom	15 (21.4)	
Difficulty of walking up from sleep		0.012
Almost always	22 (31.4)	
Often	28 (40.0)	
Seldom	4 (6.0)	
Use of sleeping drugs		NS
Almost always	18 (25.7)	
Often	24 (34.2)	
Seldom	3 (4.3)	
Localization		NS
Blisters	9 (12.9)	
Erythema, urticarial lesions	46 (65.7)	
Healthy skin	15 (21.4)	
Scratching		0.003
Almost always	18 (25.7)	
Often	31 (44.3)	
Seldom	13 (18.5)	
Feeling after scratching		NS
Relieve	46 (65.7)	
Neutral	13 (18.5)	
Unpleasant	1 (1.4)	

Tab. 4. BPDAI Pruritus score in various disease severity and comorbidities.

Variables	Mean±SD	Median±IQR	Min–Max	p
Mild BP (n=23)				
BPDAI Pruritus score	8.0±7.3	7.0±6.3	0–22.0	
Moderate BP (n=43)				
BPDAI Pruritus score	14.9± 7.5	12.0±11.8	1.0–28.0	0.017
Severe BP (n=4)				
BPDAI Pruritus score	19.8±5.9	17.5±15.5	15.0–28.0	0.001
Diabetes mellitus (n=28)				
BPDAI Pruritus score	15.5±7.4	15.5±11.3	13.0–28.0	0.023
Psoriasis vulgaris (n=8)				
BPDAI Pruritus score	15.7±3.8	14.0±6.0	15.0–22.0	0.050

tion was shorter in the bullous phenotype with a mean time of 5.1±5.5 months. In the localized phenotype, the mean duration was the longest, at 20.3±17.8 months. The typical clinical lesions including blisters, erosions, urticarial plaques, and erythematous patches were recorded in 50.0% of cases with the bullous phenotype. Table 5 depicts special lesions or configurations in 18.6% of cases. Oral involvement in BP is rare, observed in 17.1% of cases, predominantly in severe-to-moderate course of BP in the bullous phenotype. Moreover, a single case of localization in the oral cavity was documented (1.4% of cases with localized BP). In this case, the diagnosis was confirmed by histopathology, DIF and ELISA. The thighs were the most frequently involved area of the body (80.8%), followed by the legs (75.0%), thorax (72.1%), arms (70.6%), forearms (69.1%), and abdomen (50.0%). Affliction of the hands and feet was less common (23.5% and 16.1%, respectively), as well as involvements of the head, neck, and scalp (14.7%, 10.3%, and 10.3%, respectively). There were no significant differences in the localization of lesions between bullous and nonbullous phenotypes of BP. However, affliction of the genital and nasal mucosa was documented only in cases with bullous phenotype, accounting for 7.3% of cases. Cases with localized BP most frequently exhibited lesions on the legs (75.0%).

Tab. 5. Clinical assessment in 70 cases with bullous pemphigoid.

Clinical diagnosis	n (%)
Bullous pemphigoid	21 (30.0)
Microbial eczema	11 (15.7)
Scabies	7 (10.0)
Urticaria	6 (8.6)
Impetigo	6 (8.6)
Aphthae	7 (10.0)
Drug allergy	4 (5.7)
Pruritus/Prurigo	4 (5.7)
Dyshidrosis of palms/soles	2 (2.9)
Erythema exudativum multiforme	2 (2.9)
Special lesions and configurations	13 (18.6)
Papules/nodules	6 (8.6)
Figurate	2 (2.9)
Gyrate	1 (1.4)
Annular centrifugal	1 (1.4)
Dishydrosiform-like	2 (2.9)
Dermatitis herpetiformis-like	1 (1.4)

Treatment of bullous pemphigoid

Systemic corticosteroids were used as initial therapy in 88.6% of cases while topical corticosteroids were employed in 8.6% of cases. Prednisone was administered at doses in the range of 0.25–0.50 mg/kg or 0.6–1.0 mg/kg in severe cases. The mean initial daily dose was 48.6±15.1 mg (median 40.00, range 20.00–80.00). The mean maintenance dose was 8.1±5.1 mg (median 5.00, range 1.00–30.00). Systemic corticosteroids were administered as monotherapy in 57.1% of cases, and in combination with adjuvant therapy in 34.3% of cases. Azathioprine was used in 11.4% of cases, followed by sulfone, methotrexate, and cyclosporine (2.9% each). Adjuvant therapy was administered to support the immunosuppressive efficacy of corticosteroids to reduce the risk of side effects of systemic corticosteroids. Intravenous immunoglobulin (IVIG) therapy was used in 4.2% of cases and rituximab in 1.4% of cases, both yielding very good responses. These therapies were reserved for cases with intense and recalcitrant bullous phenotype and/or for those experiencing adverse side effects from systemic corticosteroids and/or adjuvant therapies such as azathioprine or sulfone. Tetracycline, valued for its antibacterial and immunomodulatory properties, was administered in 22.9% of cases, most frequently in combination with systemic or topical corticosteroids. Topical corticosteroids were employed in maintenance therapy to decrease systemic corticosteroid doses in 42.9% of cases. The dosage of immunosuppressive therapy was adjusted to the severity of BP. Antihistamines were prescribed to alleviate pruritus in 85.7% of cases, with high doses administered in 52.1% of cases to manage severe pruritus, mostly in nonbullous phenotype. In 38.6% of cases, the administration of antihistamines was deemed necessary as part of the maintenance therapy, mostly in the nonbullous phenotype. At the conclusion of the clinical study, 25.7% of cases were in complete remission with no need of prolonging the systemic immunosuppressive therapy. Minimal therapy (prednisone 5 mg/day) was administered in 42.9% of cases for maintaining remission. The maintenance therapy consisting of prednisone at 10–15 mg/day with adjuvant therapy was reduced to half the initial dose in 31.4% of cases. The mean time to achieve the maintenance therapy in bullous BP was 2.0±1.6 years, compared to 0.7±0.3 years in nonbullous BP. Statistical analysis revealed that the time to achieve maintenance therapy was significantly shorter in nonbullous BP than in bullous BP (p=0.001). In 24.7% of cases with bullous BP, the mean duration of off-therapy remission was 2.8±2.7 years. In nonbullous BP, the mean duration was 2.5±2.4, documented in 33.3% of cases. In localized BP, the mean duration was 2.5±0.1 years, observed in 25.0% of cases. The differences in remission duration across all BP phenotypes were not statistically significant.

Table 6 summarizes medications used to treat multiple comorbidities in BP cases.

Relapses and triggers in BP

Relapse of BP was defined as the appearance of three or more new lesions per month that did not heal spontaneously within one week or as the extension of existing lesions in a patient who had previously achieved disease control (9). In bullous BP, relapse was recorded in 22.8% of cases, in nonbullous BP in 2.9% of cases. No patient with localized BP showed relapse during the clinical study. In the first year of the BP diagnosis, 14.3% of cases were documented to experience relapse of BP. After two years, relapse of BP was documented in 8.6% of cases. Moreover, after 11 and 13 years, relapse of BP was observed in 1.4% of cases (in both instances). Among cases with documented relapse of BP, 14.3% were in off-therapy remission and 11.4% were in complete remission on minimal immunosuppressive therapy.

In our cohort we identified relapse-inducing triggers of BP in 22.8% of cases. These triggers included UV radiation (1.4%), vildagliptin (5.7%), pembrolizumab (2.9%), hematologic malignancy (1.4%), bacterial infection (1.4%) and SARS-CoV-2 infection (5.8%) or SARS-CoV-2 vaccination (10.0%).

In the study cohort, 7.1% of patients died. Cardiovascular failure was the cause in 5.7% of cases and neurologic stroke in 1.4% of cases. Among these, 2.9% of cases died from complications of SARS-CoV-2 infection, both having pre-existing cardiovascular comorbidities. Notably, neither of these patients had been vaccinated against SARS-CoV-2 virus. The mean time between the onset of BP and death was 23.9±12.9 months.

Evaluation of anti-BP autoantibody and peripheral eosinophilia

At the onset of BP, the anti-BP180 autoantibody was proved positive in 91.4% and the anti-BP230 antibody in 28.6% of cases. The mean time to achieve negativity for anti-BP180 and/or anti-BP230 autoantibodies was 8.6±9.4 months. Statistical analysis did not show significant difference in the reduction of autoantibody levels according to the phenotype or intensity of BP (p=0.116; p=0.500). Increased eosinophilia was observed in 48.6% of cases at the onset of BP. The absolute eosinophil count was $0.7\pm1.0x10^9$/L, and the relative eosinophil count in complete blood count was 7.8±8.2%. Statistical analysis showed, significantly higher absolute and relative eosinophil counts in the nonbullous phenotype of BP (p=0.034, p=0.003), compared to the bullous phenotype. In addition, cases with normal eosinophil values tended to have atypical BP localization, including mucosal, head and neck involvements. The increased values of eosinophil counts were correlated with the BPDAI rotal score, showing statistically significant differences across intensity levels of BP (p=0.020; p=0.048). In remission, both absolute and relative eosinophil counts dropped to normal values (means of $0.1\pm0.1x10^9$/L and $1.4\pm1.3x10^9$/L).

Tab. 6. Comorbidities medication in 70 cases with bullous pemphigoid.

Variable	n (%)
Calcium channel blocker	19 (27.1)
ACE inhibitor	26 (37.1)
Beta-blocker	33 (47.1)
Angiotensin receptor blocker	12 (17.1)
Statine	18 (25.6)
Diuretic loop	9 (12.9)
Tiazide diuretic	7 (10.0)
Antiepileptic	6 (8.6)
Antidepressive	8 (11.4)
Neuroleptic	10 (14.3)
Opionid	4 (5.7)
Salicylates	19 (27.1)
Antidiabetics	28 (40.0)
Antibiotics	24 (34.2)
Nilotinib	1 (1.4)
Bevacizumab	1 (1.4)
Pembrolizumab	1 (2.9)
Antihistamine	60 (85.7)

Discussion

Clinical studies worldwide have consistently reported the typical age range of BP onset between 63 and 83 years with an overage onset age of 73.4 years and the female-to-male ratio between 1.0 and 5.8 (12). In our current study, the average age was 73.5±12.2 years, with a female preponderance noted by ratio of 1.6, aligning with findings from previous research (5, 6, 13). It is worth noting that BP is uncommonly reported in individuals younger than 50 years (13), yet in our study, 5.7% of cases fell within this age group. The underlying rationale for this relatively high frequency in young individuals remains elusive to our current understanding. Various autoimmune disorders are linked to BP, and our study corroborates this association, with autoimmune disorders documented in 32.9% of BP cases and other comorbidities present in 84.3% of cases. Hypertension was the most frequent comorbidity, documented in 51.4% of cases, in concordance with findings from previous studies (14, 15). However, our study documented a lower frequency of neurological diseases (22.9%) and chronic renal diseases (18.6%) compared to later investigations. It is worth noting that DM was identified in 40.0% of our study cases, which is consistent with findings from a Moroccan study (43.0%) (15) but notably higher than the prevalence reported in a US study (18.5%) (16). A recent meta-analysis documented a significant correlation between DM and BP, showing a strong heterogenicity (17). We also documented a more severe manifestation of BP in diabetic cases than in those without DM (p=0.04). The bullous BP was the most frequent phenotype in cases with DM. This is in concordance with other authors who reported a more severe erosive BP phenotype in diabetic patients (18). Conversely, some authors did not observe a more severe course of BP in diabetic patients, particularly in cases induced by dipeptidyl peptidase-4 inhibitor use. Moreover, these cases showed lower urticarial and erythematous plaques than those with idiopathic BP (19).

In the current study, psoriasis was documented in 11.4% of BP cases and showed a more severe disease course compared to those without psoriasis (p=0.05). Although we did not find any literature directly comparing disease severity in BP cases with and without psoriasis, a meta-analysis showed a significant association between BP and psoriasis, particularly noting a stronger correlation in men than in women (20). Notably, our study did not reveal any

differences in association of BP cases with psoriasis between the sexes. Furthermore, in line with another nationwide study on the association of psoriasis with BP, reporting a mean time-period between psoriasis and BP onset of 14.6 years (21), we found that psoriasis preceded the onset of BP by an average of 11.6 years.

A systemic data search review of nonbullous BP from several cohort studies showed that at least 20% of BP cases presented as the nonbullous phenotype BP (22).

In the current study, we documented nonbullous BP in 12.9% of cases. The duration between disease onset and the establishment of a firm diagnosis of nonbullous BP was 14.3 months. In contrast, two other studies reported longer periods between symptom onset and confirmation of nonbullous BP diagnosis, specifically 22.6 and 29.0 months, respectively (22, 23). The shorter diagnostic time demonstrated in our study may be attributed to our long-term clinical experience with pruritic dermatoses and the employment of a precise diagnostic algorithm, including anti-BP autoantibody ELISA test, aimed at identifying the underlying cause of pruritus. Pruritus is typically the predominant symptom which may herald the onset of BP or predict a flare of BP. In the analyzed cohort, pruritus was the initial symptom in 65.7% of cases with bullosus BP and in 100% with nonbullous BP. Daily experience of pruritus was documented in 77.2% of cases which is comparable to the incidence rates ranging from 78.1 to 85% reported by other authors (11, 24). In the current study, we found that pruritus was significantly more intense in nonbullous BP compared to bullous BP (p=0.001). Furthermore, BP patients with DM or psoriasis experienced significantly more intense pruritus than those without these conditions (p=0.02 and p=0.05, respectively). In the present study, the patients with BP described sensory symptoms associated with pruritus, such as stinging (52.1%), burning (22.4%), tickling (7.1%), crawling (5.5%) or itching alone (12.9%). Other authors also reported stinging as the most frequent sensation associated with pruritus, which was recognized in about 70% of cases. Additionally, their BP patients described sensations, including cold, pain, and crawling (11).

In the current study, urticarial and erythematous plaques were more intense in nonbullous BP than in bullous BP. In line with our study, Lambert et al (2018) reported urticarial and erythematous plaques as the most frequent skin lesions in nonbullous BP.

Several studies demonstrated a correlation of peripheral and dermal eosinophilia and pruritus with disease severity (25, 26). These findings are consistent with our observations. In the present study, peripheral eosinophilia was found in 48.6% of cases. In addition, absolute and relative eosinophilia values were significantly higher in nonbullous BP compared with bullous BP (p=0.03, p=0.003) and was associated with disease severity (p=0.02). Our results are consistent with those of other studies, which recorded different levels of peripheral blood eosinophils in nonbullous and bullous BP (27).

Several authors documented mucosal affliction in 10–30% of cases with the bullous phenotype of BP (28). In the current study, we reported oral involvement in 17.1% of bullous BP cases, with one patient (1.4%) experiencing exclusively oral lesions confirmed by histopathology, DIF and ELISA. To our knowledge, this single BP localization in the oral cavity is a unique finding not reported so far. Consistent with another study, mucosal afflictions were typically associated with severe disease, manifesting as intense blisters and erosions (29). The mechanism underlying the formation of mucosal lesions is not fully understood and warrants further research.

Special lesions or configurations were recorded in 18.6% of BP cases, aligning with 20.5% documented in another study (30). These miscellaneous characteristics are relatively common, challenging the diagnostic procedure and highlighting the need for precise diagnostic methods to confirm BP autoantibody in tissue (DIF) and peripheral blood (ELISA, IIF, etc.).

In general, corticosteroids are employed as the first-line therapy for all phenotypes of BP (31). In our study, 97.2% of cases were treated with systemic or topical corticosteroids. Adjuvant therapy was used in 34.3% of cases to enhance immunosuppression and reduce the risk of systemic corticosteroid side effects. Tetracycline was used in 22.9% of cases. In recalcitrant and severe cases, IVIG and rituximab were used in 4.2% and 1.4% of subjects, respectively, all of whom were diagnosed with the bullous phenotype of BP. These biologic drugs are used in a manner similar to their use in pemphigus vulgaris (PV). Several studies documented good efficacy and safety of both biologics in the treatment of autoimmune bullous disorders (32, 33). Consistent with these studies, we observed significant efficacy in disease outcomes. At the end of follow-up period, 25.7% of our study cases were in complete remission off therapy, including bullous, nonbullous, and localized phenotypes, In addition, the nonbullous phenotype required a shorter time to achieve maintenance therapy compared to the bullous phenotype (p=0.001).

Several triggers were documented that may induce BP in genetically predisposed individuals, with triggers recognized in approximately15% of BP cases (34). In the present study, we identified triggers in 22.8% of cases, which is a higher rate that may be associated with the coronavirus pandemic outbreak. In concordance with other studies, we confirmed vildagliptin as a trigger of BP in 5.7% of cases. Vildagliptin, a dipeptidyl peptidase-4 inhibitor, is used to treat type 2 DM, and is the most frequently implicated gliptin drug potentially inducing BP (35). In the current study, vildagliptin exclusively induced the bullous phenotype of BP. Other gliptins such as linagliptin and sitagliptin can act as potential triggers of BP (36); however, they were not used in the current study. In addition, we recorded the PD-1 inhibitor, pembrolizumab, as a trigger in 2.9% of cases, inducing an intense course of bullous phenotype of BP. Checkpoint inhibitors were documented to induce both bullous and nonbullous BP phenotypes (37, 38). In the present study, we did not identify other medications that might trigger BP flares in patients with multiple comorbidities. Several studies investigated correlations between drugs and their potential to trigger BP, with meta-analytic studies confirming only aldosterone antagonists, dipeptidyl peptidase-4 inhibitors, anticholinergics, and dopamine medications as triggers (2). In our study, we observed an association between BP flare-ups and SARS-CoV-2 infection or vaccination in 5.8% and 10.0% of cases, respectively Among vaccinated patients, SARS-CoV-2

infection induced a mild course of bullous phenotype of BP which effectively responded to topical or systemic corticosteroid therapy. Additionally, we documented a fatal outcome of SARS-CoV-2 infection in 2.9% of cases; both individuals were not vaccinated and succumbed to complications related to their cardiovascular comorbidities. Furthermore, the administration of SARSCoV-2 vaccine triggered the first onset of bullous phenotype BP in 5.7% of cases. These findings align with other studies that reported associations between BP and SARSCoV-2 infection or vaccination, most of which were based on case reports or small case series (39, 40, 41). Maronese et a. (2022) described 21 cases of SARSCoV-2 vaccination-induced BP, all of which exhibited a benign course and responded appropriately to therapy. Further studies are required to elucidate the mechanism by which the SARS-CoV-2 vaccine induces BP and the impact of anti- SARS-CoV-2 antibody and cell immunity resulting from vaccination. In general, vaccination reduces the risk of poor clinical outcomes and hospitalization rates associated with SARS-CoV-2 infection. A review study on the efficacy, immunogenicity, and safety of vaccination in individuals with autoimmune diseases provides evidence-based recommendations for vaccination (43).

Limitations

The clinical study has some limitations including its retrospective design and the limited number of BP patients, all from a single medical center. However, this center provides healthcare to a large part of Slovakia. In addition, the follow- up period was short for some patients.

Conclusion

BP may pose a serious problem in the elderly population, who often suffer from various comorbidities requiring multiple medications. The most frequent phenotype is bullous BP which manifests as a more intensive disease compared to the nonbullous or localized phenotypes. However, pruritus can be most intense in the nonbullous phenotype of BP. Pruritus is a herald symptom of BP and may precede the clinical appearance, contributing to misdiagnosis, especially in the nonbullous phenotype. BP could be more severe and pruritic in patients with DM and psoriasis compared to those without these conditions. In both comorbidities, the bullous phenotype is more frequent than the nonbullous phenotype. Some drugs as well as new infections such as SARS-CoV-2 infection or vaccine may trigger BP. New stimuli may trigger the first flare of BP in genetically predisposed individuals or induce a flare in existing BP cases.

References

1. Chen J, Li L, Chen J et al. Sera of elderly bullous pemphigoid cases with associated neurological diseases recognize bullous pemphigoid antigens in the human brain. Gerontology 2011; 57: 211–6.

2. Liu SD, Chen WT, Chi CC. Association between medication use and bullous pemphigoid. JAMA Dermatol 2020; 156: 1–11.

3. Atzmony L, Mimouni I, Reiter O et al. Association of bullous pemphigoid with malignancy: a systemic review and meta-analysis. J Am Acad Dermatol 2017; 77: 691–699.

4. Meijer JM, Dierecks GF, de Lang EW et al. Assessment of diagnostic strategy for early recognition of bullous and nonbullous variants of pemphigoid. JAMA Dermatol 2019; 155: 158–165.

5. Kridin K, Ludwig RJ. The growing incidence of bullous pemphigoid: overview and potential explanations. Front Med (Lausanne) 2018; 5: 220.

6. Joly P, Baricaut S, Sparsa A et al. Incidence and mortality of bullous pemphigoid in France. J Invest Dermatol 2012; 132: 1998–2004.

7. Chmurova N, Svecova D. Pemphigus vulgaris: a 11–year review. Bratisl Lek Listy 2009; 110: 503–503.

8. Svecova D. Pemphigus vulgaris: a clinical study of 44 cases over 20-year period. Int J Dermatol 2015; 54: 1138–1144.

9. Murrell D, Daniel BS, Joly P et al. Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts. J Am Acad Dermatol 2012; 66: 479–485.

10. Masmoudi W, Vaillant M, Vassileva S et al. International validation of the Bullous Pemphigoid Disease Area Index Severity score and calculation of cut-off values for defining mild, moderate, and severe types of bullous pemphigoid. Brit J Dermatol 2021; 184: 1106–1112.

11. Briand C, Gourier G, Poizeau F et al. Characteristics of pruritus in bullous pemphigoid and impact on quality of life: a prospective cohort study. Acta Derm Venereol 2020; 100: adv00320.

12. Rosi-Schumacher M, Baker J, Waris J et al. Worldwide epidemiologic factors in pemphigus vulgaris and bullous pemphigoid. Front Immunol. 2023; 14: 1159351.

13. Chung JG, Ramji R, Coomarasamy C et al. Bullous pemphigoid: Its incidence, mortality and clinical outcome in New Zealand. Australas J Dermatol. 2022; 63: 197–203.

14. Lee S, Rastogi S, Hsu DY et al. Association of bullous pemphigoid and comorbid health conditions: a case- control study. Arch Dermatol Res 2021; 313: 327–332.

15. Titou H, Kerrouch H, Frikh R et al. The association between bullous pemphigoid and comorbidities: a case-control study in Moroccan patients. Acta Dermatovenerol Alp Pannonica Adriat 2022; 31: 7–11.

16. Lee S, Rastogi S, Hsu DY et al. Association of bullous pemphigoid and comorbid health conditions: a case-control study. Arch Dermatol Res 2021; 313: 327–332.

17. Jiirasutat N, Pongchareon P, Weschawalit S. Bullous pemphigoid and diabetes mellitus: a systematic review and meta-analysis. Int J Dermatol 2024. DOI: 10.1111/ijd.16970.

18. Ständer S, Schmidt E, Zillikens D et al. More severe erosive phenotype despite lower circulating autoantibody levels in dipeptidyl peptidase-4 inhibitor (DPP4i)-associated bullous pemphigoid: a retrospective cohort study. Am J Clin Dermatol 2021; 22: 117–127.

19. Chanprapaph K, Pratumchart N, Limtong P et al. Dipeptidyl peptidase-4 inhibitor-related bullous pemphigoid: A comparative study of 100 cases with bullous pemphigoid and diabetes mellitus. J Dermatol 2021; 48: 486–496.

20. Phan K, Goyal S, Murrell DF. Association between bullous pemphigoid and psoriasis: systemic review and meta-analysis of case-control studies. Australas J Dermatol 2019; 60: 23–28.

21. Furue K, Ito T, Tsuji G et al. Autoimmunity and autoimmune comorbidities in psoriasis. Immunology 2018: 154: 21–27.

22. Lamberts A, Meijer J M, Jonkman ME. Nonbullous pemphigoid: A systemic review. J Am Acad Dermatol 2018; 78: 989–995.

23. Lamberts A, Meijer J M, Pas HH et al. Nonbullous pemphigoid: Insights in clinical and diagnostic findings, treatment responses, and prognosis. J Am Acad Dermatol 2019; 81: 355–363.

24. Kalinska-Bienias A, Kowalczyk E, Jagielski E et al. Clinical characteristics of pruritus in cases with bullous pemphigoid: a preliminary questionnaire -based study. Postepy Dermatol Alergol 2020; 37: 938–942.

25. Hashimoto T, Kursewicz CD, Fayne RA et al. Pathophysiologic mechanisms of itch in bullous pemphigoid. J Am Acad Dermatol 2020; 83: 53–62.

26. Farnaghi F, Ehsani AH, Kamyab-Hesary K et al. Correlation of dermal and blood eosinophilia with bullous pemphigoid disease severity. Int J Womens Dermatol 2020; 6: 171–175.

27. Mordehai BY, Faibish H, Astman N et al. Characteristics of patients with bullous pemphigoid: comparison of classic bullous pemphigoid to nonbullous pemphigoid. J Eur Acad Dermatol Venereol 2020; 34: 161–165.

28. Della Torre R, Combescure C, Cortéz B et al. Clinical presentation and diagnostic delay in bullous pemphigoid: a prospective nationwide cohort. Brit J Dermatol 2012; 167: 1111–1117.

29. Clapé A, Muller C, Gatouillat G et al. Mucosal involvement in bullous pemphigoid is mostly associated with disease severity and to absence of anti-BP230 autoantibody. Front Immunol 2018; 9: 479.

30. Bernard P, Antonicelli F. Bullous pemphigoid: a review of its diagnosis, associations and treatment. Am J Clin Dermatol 2017; 18: 513–528.

31. Borradori L, Van Beek N, Feliciani C et al. Updated S2K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2022; 36: 1689–1704.

32. Svecova D. IVIG therapy in pemphigus vulgaris has corticosteroid-sparing and immunomodulatory effects. Australas J Dermatol 2016; 57: 141–144.

33. Thomas RM, Colon A, Motaparthi K. Rituximab in autoimmune pemphigoid diseases: indications, optimized regiment, and practice gaps. Clin Dermatol 2020; 38: 384–396.

34. Moro F, Fania L, Sinagra JLM et al. Bullous pemphigoid: trigger and predisposing factors. Biomolecules 2020; 10: 1432.

35. García-Díez I, Ivars-Lleó M, López-Aventín D et al. Bullous pemphigoid induced by diptidase-4 inhibitors. Eight cases with clinical and immunological characterization. Int J Dermatol 2018; 87: 810–816.

36. Lambadiari V, Kountouri A, Kousathana F et al. The association of bullous pemphigoid with dipeptidyl peptidase 4 inhibitors: a ten-year prospective study. BMC Endocr Disord 2021; 21: 23.

37. Siegel J, Totonchy M, Damsky W et al. Bullous disorders associated with anti-PD-1 and anti-PD-L1 therapy: a retrospective analysis evaluating the clinical and histopathological features, frequency, and impact on cancer therapy. J Am Acad Dermatol 2018; 79: 1081–1088.

38. Lopez T A, Khanna T, Antonov N et al. A review of bullous pemphigoid associated with PD-1 and PD-L1 inhibitors. Int J Dermatol 2018; 57: 664–669.

39. Afacan E, Edek YC, Ilter N et al. Can Covid-19 vaccines cause or exacerbate bullous pemphigoid? A report of seven cases from one center. Int J Dermatol 2022; 61: 626–627.

40. Bardazzi F, Carpanese MA, Abbenante D et al. New-onset bullous pemphigoid and flare of preexisting bullous pemphigoid after the third dose of the COVID-19 vaccine. Dermatol Ther 2022; 35: e15555.

41. Dell´Antonia M, Anedda S, Usual F et al. Bullous pemphigoid triggered by COVID -19 vaccine: rapid resolution with corticosteroid therapy. Dermatol Ther 2022; 35: e15208.

42. Maronese CA, Caproni M, Moltrasio C et al. Bullous pemphigoid associated with COVID-19 vaccines: an Italian multicentre study. Front Med (Lausanne) 2022; 9: 841506.

43. Furer V, Eviatar T, Zisman D et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult cases with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021; 10: 1330–1338.

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