Summary

Background and objectives: The features of bullous pemphigoid (BP) patients presenting with mucosal lesions are not established. We aimed to elucidate the clinical and immunological features of BP patients with mucosal involvement, and to identify factors associated with mucosal lesions.

Patients and methods: A retrospective study encompassing all consecutive patients diagnosed with BP throughout the years 2009–2019 in a tertiary referral center.

Results: The study encompassed 273 patients with BP, of whom 31 (11.4%) presented with mucosal lesions. The oral mucosa was the most frequently affected mucosal surface (71.0%), followed by the genital (25.8%) and the nasal (22.6%) mucosae. Relative to other patients with BP, patients with mucosal involvement had a more prominent palmoplantar involvement (67.7% vs. 37.2%; P = 0.001); lower seropositivity rate (18.2% vs. 54.2%; P = 0.027) and lower levels (29.3 ± 64.5 vs. 129.5 ± 304.4 U/ml; P = 0.016) of anti-BP230 autoantibodies; and decreased peripheral eosinophil counts (760.0 ± 638.6 vs. 1296.3 ± 1013.7; P < 0.001). Absence of anti-BP230 autoantibodies (OR, 5.32; 95% CI, 1.07–26.32; P = 0.026) and lack of peripheral eosinophilia (OR, 4.31; 95% CI, 1.14–16.39; P = 0.021) were associated with the presence of mucosal involvement in BP.

Conclusions: Mucosal involvement is present in a notable subgroup of patients with BP and is associated with the absence of both anti-BP230 antibodies and peripheral eosinophilia.

Immunological features and factors associated with mucocutaneous bullous pemphigoid – a retrospective cohort study

Introduction

Bullous pemphigoid (BP) is the most widespread subepidermal autoimmune disease worldwide [1], imposing a substantial burden of morbidity and mortality [2–4]. Characteristically, BP is typified by an intensely pruritic bullous eruption, mainly affecting the flexural limbs and the abdomen, often in conjunction with urticarial plaques [5]. However, a sizable proportion of patients, estimated at 20% in recent studies, present neither with obvious blisters nor erosions at the onset of the diseases [6]. These patients may experience non-bullous manifestations of BP, including the urticaria-like, eczema-like, prurigo-like, and dyshidrosiform types [4, 7]. Furthermore, the involvement of the mucous membranes was considered as an unusual morphological feature that diminishes the likelihood of a clinical diagnosis of BP (when approaching patients with linear deposits of immunoreactants along the dermal-epidermal junction) [8]. If mucosal lesions predominate in a pemphigoid disease, the diagnosis is per definition mucous membrane pemphigoid [9].

Mucosal lesions in BP may occur in up to 20% of patients, where they are classically constrained to the oral mucosa and respond favorably to treatment [6, 9, 10, 11]. However, a notable heterogeneity interferes with drawing firm conclusions regarding the true prevalence of this significant morphological feature. The immunological characteristics of BP patients with mucosal involvement, as well as factors predisposing patients with BP to present with the mucocutaneous...
phenotype, were barely investigated and remain unclear. So far, one study from a French referral center, including a total of 95 patients with BP, indicated that a higher clinical disease severity and absence of anti-BP230 autoantibodies were associated with the presence of mucosal lesions [10].

The aim of the current study was to assess the prevalence of mucosal involvement in patients with BP. The secondary endpoints were to characterize the subgroup of patients with mucosal lesions and to identify factors associated with the mucocutaneous presentation in BP.

Methods

Study population and definition of cases

We performed a retrospective study, including all patients diagnosed with BP between January 1st 2009, and February 28th, 2020, at the Department of Dermatology, University of Lübeck, Lübeck, Germany. The current study was approved by the institutional ethical committee (20-110A).

The diagnosis of BP was established based on the following criteria: (1) suggestive clinical presentation; (2) linear deposits of IgG and/or C3 along the dermal-epidermal junction in direct immunofluorescence (IF) microscopy of a peri-lesional skin biopsy; (3) the detection of circulating auto-antibodies binding to the epidermal side of 1 ml NaCl-split normal human skin by indirect IF microscopy and/or the presence of circulating IgG autoantibodies against BP180 and/or BP230, as identified by BP180 NC16A and BP230 enzyme-linked immunosorbent assay (ELISA), respectively [12, 13]. Cases with predominant mucosal involvement were defined as mucous membrane pemphigoid (MMP) and excluded from the current study according to the international consensus on MMP [8]. This consensus statement postulates that the main clinical feature of MMP is being a mucous membrane-dominant disease, thus distinguishing it from all other immune-mediated blistering skin diseases that may have some component of mucous membrane involvement [8].

Definition of Covariates

The severity of disease was assessed based on the Bullous Pemphigoid Disease Area Index (BPDAI) [14]. This score had been documented including its following subcomponents (cutaneous erosion/blister activity, cutaneous urticaria/erythema activity, mucosal erosion/blister, damage, and pruritus). Since this scoring system was introduced only in 2012, BPDAI scores were available for 132 out of 273 (48.4 %) patients. In concurrence with the current literature [15], the non-inflammatory phenotype of BP was defined in patients whose BPDAI cutaneous urticaria/erythema score is zero.

The levels of circulating anti-BP180 NC16A and anti-BP230 antibodies were measured using the commercially available ELISA systems (Euroimmun, Lübeck, Germany). The cutoff values proposed by the manufacturer (that is, 20 U/ml) were adopted for the definition of seropositivity. Eosinophil counts were documented upon the admission of patients with new-onset BP (prior to the administration of any systemic therapy). Peripheral eosinophilia refers to an absolute count of ≥ 500 eosinophils/μl in peripheral blood [16, 17].

Statistical analysis

All continuous parameters were expressed as mean values (standard deviation [SD]). Percentages of different patient groups were compared by a chi-square test. Normally distributed data was analyzed using the student t-test. Data found to be non-normally distributed were analyzed using the Mann-Whitney U test for independent subgroups and the Wilcoxon test for dependent subgroups. To identify predicting factors of mucosal involvement in BP, a logistic regression model was used to calculate odds ratios (ORs) and 95 % confidence intervals (CIs). SPSS software, version 25 (SPSS, Armonk, NY: IBM Corp) was utilized to conduct all statistical analyses.

Results

Demographic characteristics of the study population

The study cohort encompassed 273 patients with BP, of whom 119 (43.6 %) were males and 154 (56.4 %) females. The mean age (SD) at diagnosis was 79.1 (9.9) years, and the median age was 80.4 (range, 49.6–98.2) years.

The prevalence of mucosal involvement

Thirty-one (11.4 %) patients with BP presented with mucosal lesions. The most frequently involved mucosal surface was the oral mucosa (n = 22; 71.0 %), followed by the genital (n = 8; 25.8 %), nasal (n = 7; 22.6 %), and anal (n = 4; 12.9 %) mucosae.

Of patients with mucosal involvement, 22 (71.0 %) had isolated involvement of only one mucosal surface, whilst eight (25.8 %) patients and one (3.2 %) patient, respectively, presented with concomitant involvement of two and three mucosal surfaces. In none of these patients was an concomitant involvement of more than three mucosal surfaces seen. Out of the eight patients with genital and seven with nasal involvement, three (37.5 %) and two (28.6 %) had isolated genital and isolated nasal involvement, respectively. The
average (SD) score of the mucosal component of the BPDAI score was calculated at 5.6 (5.2).

Characterization of BP patients with mucosal involvement relative to BP patients without mucosal involvement BP

We next addressed the morphological and immunological differences between BP patients with mucosal involvement (n = 31) in relation to BP patients without mucosal involvement (n = 242). No significant differences were noted between the subgroups regarding age and sex (Table 1). With regard to the anatomical location of cutaneous lesions, patients with mucosal involvement had more frequent palmoplantar involvement (67.7 % vs. 37.2 %, respectively; P = 0.001), whilst the involvement of other body sites was comparable between the two subgroups (Table 1). We then evaluated the number of patients in whom palmoplantar affection was the sole cutaneous manifestation of the disease in both subgroups. One (3.2 %) patient with mucosal involvement and 6 (2.5 %) patients without mucosal involvement presented with isolated cutaneous palmoplantar involvement (P = 0.817).

The prevalence of the non-inflammatory subtype of BP (9.7 % vs. 5.8 %, respectively; P = 0.399) and dipeptidyl peptidase-4 inhibitor (DPP4i)-associated BP (9.7 % vs. 8.7 %, respectively; P = 0.854) was comparable between the investigated subgroups. When the two subgroups were compared with respect to the BPDAI score, no significant differences were noted between them, neither in the severity of the classical

| Table 1 | Demographic and clinical characteristics of BP patients with mucosal involvement as compared to the remaining patients with BP. |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
| **Age at diagnosis; years** | **BP with mucosal involvement** *(n = 31)* | **BP without mucosal involvement** *(n = 242)* | **P value** |
| – Mean (SD) | 79.5 (7.8) | 79.0 (10.1) | 0.747 |
| – Median (range) | 78.4 (65.5–97.8) | 80.7 (49.6–98.2) | |
| **Sex, n (%)** | | | |
| – Male | 11/31 (35.5 %) | 108/242 (44.6 %) | 0.337 |
| – Female | 20/31 (64.5 %) | 134/242 (55.4 %) | |
| **Distribution of bullous lesions; n (%)** | | | |
| – Limbs | 25/31 (80.6 %) | 206/242 (85.1 %) | 0.514 |
| – Trunk | 24/31 (77.4 %) | 182/242 (75.2 %) | 0.789 |
| – Hands/feet | 21/31 (67.7 %) | 90/242 (37.2 %) | 0.001 |
| – Isolated palmoplantar involvement | 1/31 (3.2 %) | 6/242 (2.5 %) | 0.817 |
| – Head and neck | 10/31(32.3 %) | 65/242 (26.9 %) | 0.527 |
| **Non-inflammatory phenotype, n (%)** | | | 0.318 |
| – Erosion/blister cutaneous activity | 3/14 (21.4 %) | 14/118 (11.9 %) | |
| – Urticaria/Erythema activity | 3/14 (21.4 %) | 14/118 (11.9 %) | |
| – Damage score | 3.0 (3.5) | 2.0 (3.1) | 0.138 |
| – Pruritus score | 19.6 (8.8) | 19.2 (9.1) | 0.814 |

Abbr.: BP, bullous pemphigoid; n, number; SD, standard deviation; DPP4i, dipeptidyl peptidase-4 inhibitors.

*Was defined as urticaria/erythema BPDAI score of zero.

BPDAI score was calculated for 14/31 of patients with mucosal involvement and 118/242 of patients without mucosal involvement. The chi-square test was utilized to compare between categorical variables and the t-test between continuous variables; **bold**: significant values.
Table 2 Immunological characteristics and laboratory findings of BP patients with mucosal involvement as compared to BP patients without mucosal involvement.

|                                | BP with mucosal involvement (n = 31) | BP without mucosal involvement (n = 242) | P value |
|--------------------------------|-------------------------------------|----------------------------------------|---------|
| Anti-BP180 NC16A ELISA*        |                                     |                                        |         |
| – Seropositivity, n (%)        | 28/30 (93.3 %)                      | 192/236 (81.4 %)                       | 0.105   |
| – ELISA index value, mean (SD); U/ml | 529.4 (1496.0)                     | 549.9 (1271.6)                        | 0.945   |
| Anti-BP230 ELISA**            |                                     |                                        |         |
| – Seropositivity, n (%)        | 2/11 (18.2 %)                       | 39/72 (54.2 %)                        | 0.027   |
| – ELISA index value, mean (SD); U/ml | 29.3 (64.5)                        | 129.5 (304.4)                         | 0.016   |
| Eosinophil count, mean (SD); cells/μl*** | 760.0 (638.6)               | 1296.3 (1013.7)                      | < 0.001 |
| C-Reactive protein, mean (SD); mg/L**** | 28.0 (30.5)                        | 29.8 (28.2)                           | 0.757   |

Abbr.: BP, bullous pemphigoid; n, number; SD, standard deviation; ELISA, enzyme-linked immunosorbent assay.
*Was performed in 30 patients with mucosal involvement and in 236 patients without mucosal involvement.
**Was performed in 11 patients with mucosal involvement and in 72 patients without mucosal involvement.
***Was available for 12 patients with mucosal involvement and in 124 patients without mucosal involvement.
****Was available for available for 14 patients with mucosal involvement and in 90 patients without mucosal involvement.

Anti-BP180 NC16A and anti-BP230 antibodies levels were measured via enzyme-linked immunosorbent assay; cut-off: 20.0 U/ml; The chi-square test was utilized to compare between categorical variables and the t-test between continuous variables; bold: significant values.

phenotype (as estimated by erosion/blister BPDAI) nor the erythematous phenotype (as estimated by urticaria/erythema BPDAI) [18] (Table 1).

Table 2 presents the immunological and laboratory characteristics of BP patients with mucosal involvement as compared to BP patients without mucosal involvement. Overall, 266 (97.4 %) patients were tested for the presence of circulating anti-BP180 NC16A antibodies. Neither the detection rate nor the average levels of these antibodies were significantly different between the two subgroups (Figure 1a). Moreover, 83 (30.4 %) patients were tested for circulating anti-BP230 antibodies. The seropositivity rate (18.2 % vs. 54.2 %, respectively; P = 0.027) and the mean (SD) levels (29.3 [64.5] vs. 129.5 [304.4] U/ml, respectively; P = 0.016) (Figure 1b) of anti-BP230 antibodies were significantly lower among patients with mucosal involvement.

In addition, BP patients with mucosal involvement had a significantly lower mean (SD) circulating eosinophil count (760.0 [638.6] vs. 1296.3 [1013.7] /μl; P < 0.001). C-reactive protein levels, as a marker of systemic inflammation, did not differ significantly between the two subgroups (Table 2).

Factors associated with mucosal involvement

We then performed a logistic regression analysis aiming to identify predictors of mucosal involvement. Anti-BP230 circulating antibodies below the diagnostic cut-off (OR, 5.32; 95 % CI, 1.07–26.32; P = 0.026) and normal eosinophil count (OR, 4.31; 95 % CI, 1.14–16.39; P = 0.021) were significantly associated with involvement of the mucosal surfaces. Other variables such as sex, age, BPDAI score, and seropositivity of anti-BP180 NC16A antibodies were not significantly associated with the development of mucosal involvement in BP.

Figure 1 Levels of anti-BP180 NC16A (a) and anti-BP230 (b) autoantibodies among BP patients with and without mucosal involvement. A t-test was used to compare between the two subgroups.
Discussion

The current retrospective study demonstrates that the prevalence of mucosal involvement among or cohort of German patients with BP is estimated at 11.4 %, with the oral mucosa being the most frequently involved mucosal surface. Compared to patients with an isolated cutaneous phenotype, those with mucosal involvement had higher palmoplantar involvement, lower circulating eosinophil counts, as well as lower detection rates and lower levels of circulating anti-P230 autoantibodies. Absence of anti-BP230 autoantibodies and a normal circulating eosinophil count were found to be associated with mucosal involvement in BP.

The prevalence of mucosal involvement in BP varied substantially in different study populations. The current study revealed an intermediate prevalence rate (11.4 %; 31/273), which compares with the corresponding figure observed in a multicenter European study (10.2 %; 5/49) [19]. Lower rates were reported in Singapore (5.3 %; 19/359) [20] and in three French regions (7.7 %; 42/502) [5], whereas higher rates emerged in studies originating from Switzerland (14.5 %; 17/117) [9], Israel (17.1 %; 56/328) [11], Northern France (18.9 %; 18/95) [10], and Central Germany (26.5 %; 31/117) [21].

It is held belief that mucosal involvement in BP takes an indolent and less aggressive course relative to pemphigus vulgaris and mucous membrane pemphigoid. Unlike the latter, mucosal lesions in BP are often restricted to the oral cavity and rarely involve other mucosal surfaces [6, 22, 23]. In their multicenter study, Joly et al. [5] revealed that oral lesions occurred in all of their 42 BP patients exhibiting mucosal lesions. The corresponding figures for oral involvement were 94.4 % (17/18) [10], 94.1 % (16/17) [9], 80.4 % (45/56) [11], and 80 % (45/5) [19] in other study populations. The relative frequency of oral involvement (71.0 %; 22/31) in the current study is the lowest reported so far. Of note is the considerable relative prevalence of genital involvement (25.8 %; 8/31) in this study, which outnumbers the corresponding figures in studies from France (5.6 %; 1/18) [10], Switzerland (17.6 %; 3/17) [9], Israel (17.8 %; 10/56) [11], and a Pan-European study (20 %; 1/5) [19]. This observation may stem from increased referral of patients with blistering diseases affecting the genital mucosa to our institution given that it possess a specialized outpatient clinic for vulvar diseases [24].

Compared to patients with typical cutaneous BP, those with mucocutaneous BP had a more frequent palmoplantar involvement. However, no significant differences were revealed between the two subgroups with respect to severity, neither in the blistering nor the urticarial phenotypes (as postulated by comparable figures in all the subcomponents of BPDAI score). Our findings are reasonable in light of the similar levels of autoantibodies directed against BP180 NC16A, which had been found to correlate with the disease severity and the major subcomponents of BPDAI score [18, 25, 26, 27]. This indicates that mucous membrane involvement in patients with BP is not merely a reflection of the disease severity and extensiveness. Consequently, we may postulate that specific immunological mechanisms render these patients more susceptible to develop mucosal lesions. Our findings, however, are discordant with the observations of two recent studies from Israel and France. Kridin and Bergman [11] had shown a higher prevalence of extensive disease (based on the descriptions of physical examination) among BP patients with mucosal involvement. Moreover, Clapé et al. [10] revealed that BP patients with mucosal lesions demonstrated higher erosion/blister BPDAI scores and a tendency to increased activity (as assessed by the number of daily new blisters). The latter failed to depict significant differences in anti-BP180 NC16A levels between BP patients with and without mucosal involvement [10].

Our study signifies that anti-BP230 autoantibodies were less frequently detected and exhibited lower levels in patients with mucosal lesions. Furthermore, the seronegativity of anti-BP230 autoantibodies was a predictive factor of mucocutaneous BP in a logistic regression model. This intriguing finding aligns with the study of Clapé et al. [10], in which the absence of anti-BP230 antibodies emerged as an independent predictor of mucosal involvement (OR, 7.8; 95 % CI, 3.1–19.6; P < 0.001). The explanation of this phenomenon is unknown, but one may hypothesize that the immune response in these patients may be shifted towards other epitopes. Notwithstanding, two earlier studies by Mariotti et al. [28] and Di Zenzo et al. [29] revealed that mucocutaneous BP was associated with autoantibody reactivity against three extracellular epitopes of BP180 (NC16A, AA 1,080–1,107 and AA 1,331–1,404). The current study, as well as that of Clapé et al. [10], found both similar levels and seropositivity rates of antibodies targeting BP180 NC16A in BP with and without mucosal involvement. Further investigations will be of help to address the pathophysiological particularities of BP patients with involvement of mucous membranes. Additionally, caution should be exerted in interpretation of our results since anti-BP230 autoantibodies were screened in only 11/31 (35.5 %) patients with mucosal involvement.

Patients with mucosal lesions demonstrated lower counts of circulating eosinophils. Moreover, normal eosinophil count was associated with the presence of mucosal lesions in patients with BP. These findings accord with a recent study demonstrating decreased average eosinophil counts and a lower prevalence of peripheral eosinophilia among BP patients with mucosal involvement [11]. Congruently, a recent case-control study disclosed a higher frequency of mucosal lesions in BP patients with normal eosinophil counts as compared to those with peripheral eosinophilia [30]. Further
Mucosal involvement was overrepresented among patients with dipeptidyl peptidase-4 inhibitor (DPP4i)-associated BP in two recent studies [31, 32]. Nonetheless, other work refuted the presence of this morphological feature in other study populations of DPP4i-associated BP [15, 33–35]. Our research has shown that exposure to these agents was not significantly different between BP patients with and without mucosal involvement. It remains to be clarified how these agents are pathophysiologically associated with the clinical features of BP, including mucosal involvement.

The main limitation of the current study stems from its single center design and the retrospective collection of clinical and immunological data, which was originally retrieved for fulfilling diagnostic criteria rather than for research purposes. However, the routine workup in our department is extensive, thus enabling us to extendly profile the investigated patients. Selection bias could not be excluded owing to the tertiary-care referral center setting the study was performed in. This setting may overlook mild cases of BP managed by outpatient dermatologists. Although patients were invariably tested for anti-BP180 NC16A antibodies, only a third of patients were tested for anti-BP230. However, the study is statistically powered to reveal robust and significant differences in the levels and detection rate of these antibodies. The mucosal component of BPDAI was not available for all patients with mucosal involvement, rendering the study underpowered to reveal associations between this clinical variable and other immunological variables.

In conclusion, in our large cohort of German BP patients, 11.4 % presented with mucosal lesions. In the vast majority of cases (71.0 %), mucosal lesions were constrained to an isolated mucosal surface, and the oral mucosa was the most frequently encountered mucosal surface (71.0 %). Relative to BP patients with an isolated cutaneous phenotype, those with the mucocutaneous phenotype had greater palmo-plantar involvement, lower peripheral eosinophil counts, as well as lower levels and lower detection rates of anti-BP230 autoantibodies. Seronegativity of anti-BP230 and the absence of peripheral eosinophilia predicted mucosal involvement in patients with BP. Physicians managing patients with BP should be aware of the considerable prevalence of mucous membranes involvement.

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Correspondence to

Khalaf Kridin MD, PhD
Lübeck Institute of Experimental Dermatology
University of Lübeck
Ratzeburger Allee 160
23562 Lübeck, Germany
E-mail: dr_kridin@hotmail.com

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