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The association between bullous pemphigoid and comorbidities: a case-control study in Moroccan patients

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Abstract

Introduction: Comorbidities of bullous pemphigoid (BP) have not been thoroughly described in Morocco. This study investigates clinical features, comorbidities, and medications in a cohort of Moroccan patients with confirmed BP to help decrease morbidity and mortality.
Material and methods: This cross-sectional study involved 81 cases of BP diagnosed in 2015–2018 and 162 age- and sex-matched controls with complete follow-up at the Department of Dermatology in a university hospital setting.
Results: Eighty-one individuals were included in the study; the mean age at diagnosis was 71.3 years, and 53% were men. The most common comorbidities were hypertension (58%), type 2 diabetes (43%), and dyslipidemia (31%). Almost a quarter of the cohort (28%) had been diagnosed with at least one neurological disease before the onset of BP. BP was significantly associated with the presence of malignancies (14%; $p = 0.017$) and stroke (16%; $p = 0.009$) compared to an age-matched control group. The most common standard medications were beta-blockers, diuretics, and statins. In total, 86% of the patients with type 2 diabetes were taking antidiabetic drugs, especially metformin (82%) and gliptins (51%).
Conclusions: This study showed that BP is associated with stroke and the presence of malignancy compared to the age-matched general population. This study also calls for investigation into the specific role of some drugs as inducing factors for BP.

Keywords: pemphigoid, comorbidity, neurological disease, stroke, malignancy

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Introduction

Bullous pemphigoid (BP) is the most prevalent autoimmune skin blistering disease commonly seen in the elderly (1, 2). It is caused by the deposition of auto antibodies along the dermal-epidermal border, followed by either complement activation and/or non-complemental blistering mechanisms (1). In recent years, the incidence of BP has increased worldwide due to increasing life expectancy (3, 4). BP is associated with increased morbidity and mortality (2). Current awareness of the signs and manifestations of BP is insufficient, and clinicians should recognize and manage the chronic comorbidity associated with BP to limit disease-related morbidity and mortality.

Several studies have indicated a significant correlation between BP and neurological diseases, such as dementia, stroke, multiple sclerosis, and Parkinson's disease (5, 6). The prevalence and significance of BP's correlations with other comorbidities, in particular diabetes mellitus, cancers, and specific types of neurological diseases, differ from one study to another (6, 7). However, those reports have been limited by a potential misclassification bias and/or were incapable of identifying the impact of BP treatment of associated chronic health conditions. In contrast to neurological disorders (8), pathophysiological mechanisms for the association between BP and systemic disorders, such as hypertension, coronary artery disease, diabetes mellitus, and malignancies, have not been clearly established.

Nevertheless, only a few reports regarding the comorbidity profiles of BP have been reported in North Africa. As such, this work investigates the major health comorbidities of participants with BP from data collected in a university hospital setting.

Methods

An observational document-based retrospective controlled study included all consecutive patients diagnosed with BP and followed in a Moroccan referral hospital between January 1st, 2015 and December 31st, 2018. The cases were matched by age (± 2 years) and sex, and two controls were ascertained for each case. These controls were selected from hospitalized cases that were referred to the inpatient dermatology service for a variety of skin disorders other than BP. The data were extracted by a single investigator from medical records for all cases and controls. Because this study was based on medical records only and no patient was directly contacted, no ethical committee statement was needed. In this work, the inclusion criteria were age ≥ 18 years, males and females that received care at the university hospital, and patients diagnosed with BP. Exclusion criteria were based on inadequate documentation to support a diagnosis of BP and incomplete follow-up. The diagnosis of BP included positive findings of direct immunofluorescence (DIF) of the skin biopsy, defined by linear deposits of IgG and/or C3 along the basement membrane zone. All data were retrieved, including sociodemographic characteristics (age at onset and sex), presence of any comorbidities, medication history, and clinical data (type and distribution of lesions, and time from symptoms to diagnosis).

Statistical analysis

All statistical analyses were conducted using SPSS (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, New York). Patients' baseline characteristics are described as means and

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standard deviations (*SD*) for continuous factors and as frequencies (%) and proportions for categorical factors. The association between BP and comorbid health conditions was analyzed using binomial logistic regression analysis. *P*-values < 0.05 were considered statistically significant.

Results

Population characteristics

A total of 81 patients with BP and 162 age- and sex-matched patients without BP were recruited into the study. Of the 81 patients, 43 (53%) were male and 38 (47%) were female. The mean age of the patients at the time of BP diagnosis was 71.3 ± 11.5 years (median 72 years, range 64–80 years). All BP participants were clinically diagnosed with BP and had a skin histopathology consistent with BP and a DIF. Positive indirect immunofluorescence or high titers of BP180 antibodies had only a supplementary role in the diagnosis of BP (35% of the BP patients). More than two-thirds of the patients (69%) had typical generalized BP with manifestations on two or more anatomical areas. The distribution of the BP manifestations at the onset of diagnosis was as follows: mucosal manifestations occurred in eight (10%) patients, and generalized manifestations occurred in 56 (69%) patients (Table 1).

Table 1 | **Demographic data and clinical characteristics of patients with bullous pemphigoid (*n* = 81).**

Characteristic	Value
Age at diagnosis, years (mean ± *SD*)	71.3 ± 11.5
Age group at diagnosis, years (%)	
‹ 60	7 (9)
60–69	26 (32)
70–79	20 (25)
≥ 80	28 (35)
Sex	
Male	43 (53)
Female	38 (47)
Time from symptoms to diagnosis (median)	85 (30–150)
Clinical features at the onset, % (*n*)	
Blisters	57 (70)
Generalized lesions	56 (69)
Pruritus	43 (53)
Eczema-like manifestations	9 (11)
Mucosal involvement	8 (10)
Urticaria-like features	31 (38)

SD = standard deviation.

Comorbidities associated with bullous pemphigoid

The most prevalent preexisting systemic diseases in the BP group included hypertension (*n* = 47, 58%), diabetes mellitus (*n* = 35, 43%), and dyslipidemia (*n* = 25, 31%) (Table 2). Only three patients were free of any of chronic health conditions. In the study group, nearly a quarter of the patients (28%) had at least one type of preexisting neurological disease at the onset of initial BP manifestations. Stroke was the most frequent neurological disease (*n* = 13, 16%), followed by dementia (*n* = 5, 6%) and Alzheimer's disease (*n* = 4, 5%). Psoriasis was recorded in only four (5%) patients in the study group. Of all the BP patients, 11 (14%) had at least one type of malignancy (excluding skin cancers) diagnosed either before BP diagnosis or during initial exams immediately after BP diagnosis. Of these, nine had a solid malignancy and two had a hematological malignancy (a case of Hodgkin's lymphoma and a case of nonfollicular lymphoma). The most common solid malignancies were prostate cancer (three cases), followed by breast cancer and lung carcinoma (two cases each). In the study group, the mean age of participants with malignancies was higher than the age of BP participants with no malignancies (79.1 ± 7.9 years versus 72.1 ± 11.9 years, respectively). However, this was not a statistically significant difference.

Correlates of comorbidity

BP was significantly associated with two of the 20 commodities explored, including the presence of malignancies (14%; $p = 0.017$) and stroke (16%; $p = 0.009$), compared to an age-matched control group. There was no statistically significant difference in the prevalence of other chronic health conditions compared (Table 2).

Table 2 | **Comorbid health disorders in the cohort of 81 patients with bullous pemphigoid compared to the control group.**

Factor	Patients with BP, *n* = 81 (%)	Age-matched control sample, *n* = 162 (%)	*p*-value
Neurological disease	23 (28)	19 (12)	0.001
Stroke	13 (16)	9 (6)	0.009
Dementia	5 (6)	3 (2)	0.121
Parkinson's disease	4 (5)	5 (3)	0.486
Alzheimer	4 (5)	4 (2)	0.446
Transient ischemic attack	3 (4)	–	–
Cardiovascular			
Hypertension	47 (58)	91 (56)	0.891
Dyslipidemia	25 (31)	–	–
Ischemic heart disease	9 (11)	14 (9)	0.643
Atrial fibrillation	5 (6)	–	–
Endocrinopathies			
Diabetes mellitus	35 (43)	49 (30)	0.062
Hypothyroidism	7 (9)	–	–
Psychiatric diagnoses	16 (20)	15 (9)	0.092
Depression	7 (9)	7 (4)	0.101
Anxiety disorder	6 (7)	7 (4)	0.366
Schizophrenia	3 (4)	1 (1)	0.216
Pulmonary diseases			
Asthma	7 (9)	6 (4)	0.167
COPD	5 (6)	4 (2)	0.081
Malignancies	11 (14)	7 (4)	0.017
Psoriasis	4 (5)	5 (3)	0.251
Osteoporosis	6 (7)	–	–
Renal failure	5 (6)	–	–

BP = bullous pemphigoid, COPD = chronic obstructive pulmonary disease.

Preceding pharmacological treatments among BP patients

The most frequent medication classes used by the BP patients were those to treat cardiovascular and metabolic diseases. The following drugs were used by BP patients: beta blockers (60%), diuretics (47%), statins (38%), antidiabetics (36%), angiotensin-converting-enzyme inhibitors (34%), and acetylsalicylic acid (32%). In the study group, most diabetic patients (86%) had a classic oral hypoglycemic agent mainly with metformin (82%) and/or gliptins (51%). Gliptins were often prescribed in association with metformin or sulfonylureas (79%) and were only rarely prescribed alone. Overall, other oral hypoglycemic agents (sulfonylureas and incretin mimetics) were less frequent (Table 3).

Table 3 | Medication profile at the time of bullous pemphigoid diagnosis (n = 81).

Drugs	Frequency (%)
Beta blockers	49 (60)
Diuretics	38 (47)
Statins	31(38)
Antidiabetics	29 (36)
ACE inhibitors	28 (34)
Acetylsalicylic acid	26 (32)
Calcium blockers	18 (22)
Sartans	12 (15)
Benzodiazepines	9 (11)
Antidepressants	10 (12)
Neuroleptics	8 (10)
No medication	2 (2)

ACE = angiotensin converting enzyme.

Discussion

This study documents the profile of comorbidities in our cohort of 81 patients with BP in comparison to an age-matched sample of the general population. The findings are comparable to previous results showing a higher prevalence of neurological disorders and malignancies in other BP cohorts than in age-matched controls (9, 10). To the best of our knowledge, this is the first report to evaluate comorbidities in a cohort of Moroccan patients with confirmed BP managed in a university hospital setting.

In our study, the sex distribution was in line with other epidemiological studies, showing BP to be more prevalent among male participants (9, 11). The mean age of the participants in our study was 71.3 (SD ± 11.5) years, which is almost 5 years younger than that of previous reports in Europe (12–14). However, the mean age of BP in our cohort was higher than in other reports (10, 15). In our study, the mean age of BP participants with preexisting neurological comorbidities was significantly older than those with non-neurological comorbidities (76 vs. 70; p = 0.002). The result of this comparison is in line with other epidemiological studies (10, 16).

Over a quarter (28%) of the study population with BP had a preexisting neurological comorbidity. This is less than what has been mentioned in European countries; in particular, 32% in Finland (9), 35% in Denmark (17), 36% in France (16), 56% in Portugal (6), and 43% in the Czech Republic (18). In comparison, the prevalence of neurological comorbidity in our study was higher than that reported among BP patients from the following countries: 19% in Turkey (10), 19% in Iran (15), and 21% in the United States (19). Indeed, the increasing age of BP patients can partly explain this high frequency of comorbidity and concurrent drugs. However, the fact that some patients with memory loss lack a diagnosis for dementia will result in lower estimates of the prevalence of neurological comorbidity.

The most prevalent type of preexisting neurological disease in this study was stroke. As in previous cross-sectional reports, it was also documented to be statistically associated with BP patients (6, 10, 20). The mechanisms underlying the association between neurological conditions and BP are unclear. However, immune cross-reactions between BP autoantibodies and human brain tissue have been suggested as a potential initiating factor (21). Among other neurological comorbidities that were present at the onset of BP, dementia was occasionally reported as a frequent BP-associated neurological disease (9). This is in contrast to our study, which found a low prevalence of dementia in BP patients. As in previous studies, there was no association between the controls and BP patients (9, 10). Relatively lower median age and underestimation may be factors that contribute to the discord in results between studies. Similarly, our results showed that the prevalence of Alzheimer's disease and Parkinson's disease was not statistically different between the participants and controls in this study. In contrast to these results, previous studies showed that BP participants had a higher risk of having various neuropsychiatric disorders such as dementia and Parkinson's disease (18, 22).

Associations between malignancies and BP are controversial, and several pathogenic mechanisms for this association have been suggested (23, 24). However, BP is not considered a paraneoplastic syndrome. This study showed a higher prevalence of concomitant or previous malignancy in BP participants than in controls (14% vs. 4%), and this prevalence was significantly higher in men (9%) in the BP group. The same trend was found in a recent meta-analysis, which showed an incidence rate of 11% for cancers in BP participants, with a male predominance (13% vs. 9%) (25). In cohorts of patients with BP, older adults had a higher probability of malignancy compared to younger adults (23, 26). Some authors have therefore recommended a thorough examination for potential malignancies in patients presenting with BP in midlife or at a younger age. Our findings strongly suggest a link between BP and malignancies, which demands further prospective research.

This study found a low prevalence of psychiatric events (depression, anxiety disorder, and schizophrenia). At present, only a few reports have evaluated psychiatric disorders in BP patients, and significantly increased odds ratios (ORs) have been mentioned for schizophrenia, depressive disorder, and bipolar disorder (27–29). In addition, drugs prescribed to treat BP, principally corticosteroids, have been significantly associated with the beginning of psychiatric events (30, 31), and some antipsychotic, anxiolytic, and antidepressant drugs can amplify the risk of BP independent of the underlying disease (29, 32, 33). Several prospective case-control studies found that participants with BP were much more likely than the control group to be exposed to neuroleptic medications (29, 34). Although an association is present for many drugs within the neuroleptic category, no specific medications have been singled out (16, 34).

At present, over 90 medications have been associated with inducing BP (35). However, the levels of evidence for most such drugs were low because studies lacked control groups (36, 37). In addition, in these studies, a causal relation based on clinical judgement often remains elusive. These clinical judgements are subjective to several potentially confounding factors. In most of the cases reported, the patients have been exposed to multiple medications, making identification of the culprit drug more difficult. Another factor is that elderly patients may have memory disorders (38). In order to gain more definitive evidence of the

causal relationship, a drug challenge test may be proposed, although ethical concerns arise. However, some cases of BP can become autonomous despite drug withdrawal (39).

A meta-analysis including 13 case-control studies showed a significant association of BP with previous use of aldosterone antagonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, anticholinergics, and dopaminergic drugs (40). However, withdrawal of a culprit drug may be problematic if the drug is vital for the patient's health. Generally, neuroleptic and antidiabetic medications are more likely to be withdrawn than diuretics and cardiac medications. In this study, 51% of the participants with antidiabetic drugs had gliptins, either mainly in association with metformin (79%) or alone (21%). A retrospective study analyzed the use of DPP-4 inhibitors and the prevalence of BP among patients with diabetes, demonstrating that vildagliptin—and, to a lesser extent, linagliptin—were associated with an elevated risk of BP (41). This correlation with gliptins was shown to be independent of metformin exposure.

There are some limitations to our work that need to be considered. First, the retrospective character of the study with a small cohort of 81 participants does not permit an analysis of some comorbid health conditions. Certain morbidities are likely underdiagnosed and underreported, resulting in an underestimation of multimorbidity's impact in this population. Second, some drugs without a prescription or short-term drugs used prior to the onset of BP may have been missed in the medical records. In addition, to investigate the links between BP and medications, prospective analysis is required.

Conclusions

Based on this study, BP is associated with a number of comorbidities, in particular stroke and presence of malignancy. Our findings highlight the need to increase surveillance for and identify complex patients, and to provide them with coordinated care. More research is needed to determine the specific role of some medications as an inducing factor for BP.

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