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Original Article

Mucosal involvement in bullous pemphigoid in Northeast Morocco

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ABSTRACT

Background: Bullous pemphigoid is a common autoimmune bullous disease that mainly affects the elderly. Mucosal involvement in bullous pemphigoid remains rare and is in the order of 10% to 30%. Our objective was to evaluate the prevalence of mucosal involvement in our patients with bullous pemphigoid and to study its epidemiological, clinical, and therapeutic particularities. **Material and Methods:** We conducted a prospective epidemiological study, collecting patients with bullous pemphigoid, over a period of eleven years. We divided our study population into two groups, with and without mucosal damage, and compared different parameters between these two groups. **Results:** We collected 85 patients diagnosed with bullous pemphigoid. The mean age at diagnosis was 70.54 years. A neurological history was reported in nine (10.7%) of our patients, Drug intake was noted in 14.3%. Associations with autoimmune diseases were found in 25 patients. The typical form of PB was found in 74% of our patients with extensive skin involvement of more than 30% of the body surface in 44.7% of the patients. Twenty-nine patients (34.1%) presented mucosal lesions. The oral mucosa was the most frequently affected surface. Among the patients with mucosal involvement, twenty-five (86.2%) had isolated mucosal surface involvement. In patients with oral involvement, the most frequent mucosal lesions were erosions of the soft palate and the inner face of the cheeks. The comparative analysis between the two groups revealed that patients with mucosal involvement were younger, with an average age of 69.5 years vs. 71.12 years, $p = 0.54$. We also noted that patients with mucosal involvement more frequently presented with heard skin disease ($p = 0.01$). Regarding therapeutic management, we noted a more frequent need for the addition of systemic treatment to topical corticosteroids as compared to other patients ($p = 0.01$). **Conclusion:** The involvement of the oral mucosa remains rare and is correlated with more severe and extensive involvement of the disease with the ineffectiveness of first-line treatment. Further studies are needed at the national level to better assess these characteristics in the Moroccan population.

Key words: Bullous pemphigoid; Mucosa; Severity

INTRODUCTION

Bullous pemphigoid is a common autoimmune bullous disease that mainly affects the elderly. It is characterized by the presence of autoantibodies directed against basement membrane proteins [1]. Clinically, the typical form associates naked pruritus with eczematous and urticarial lesions that precede the appearance of tense bullae, usually large, bilateral, and symmetrical. In more atypical forms, eczematous lesions, prurigo type lesions, vesicles, cocoon lesions, and scratching excoriations are found [2,3]. Mucosal involvement in bullous pemphigoid remains rare and is in the order of 10% to 30% in the form of bullae or erosions, it mainly affects the oral mucosa and generally is the involvement of a single mucosa [4]. The objective of our study was to evaluate the prevalence of mucosal involvement in our patients with bullous pemphigoid and to study their epidemiological, clinical, and therapeutic particularities.

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MATERIALS AND METHODS

Study Design

We conducted a prospective, epidemiological study, bringing together patients with bullous pemphigoid hospitalized or followed in consultation at the dermatology department of the Hassan II CHU in Fez, Morocco, over a period of eleven years.

The diagnosis of PB was retained by confrontation with clinical data: a bubble stretched on an erythematous or healthy skin, histological; a subepidermal bubble with eosinophilic infiltrate and immunohistochemistry; direct immunofluorescence IFD showing deposits of IGG and complement the slow of the dermo–hypodermic junction. Indirect immunofluorescence has been performed only in several patients, showing the presence of anti-PB180 and anti-PB230 antibodies.

Faced with an atypical presentation of bullous pemphigoid, NACL cleavage was performed. All patients with subepidermal labeling in favor of acquired epidermolysis bullosa in the cleavage were subsequently excluded.

All patients were interviewed and examined. Patient information and clinical, biological, and therapeutic data were entered into a computer system, allowing easy data collection. Photographs were taken during hospitalization or at the first consultation, then during follow-up after patient consent.

The severity of the disease was evaluated depending on the skin surface. The diagnosis of a severe form was retained if the skin surface involved was higher than 30%.

We divided our study population into two groups—with and without mucosal involvement—and compared different parameters between these two groups.

Statistical Analysis

Descriptive, univariate analysis with SPSS Statistics, version 21, was performed. In descriptive analysis, the quantitative variables were expressed by means ± standard deviations and the qualitative variables by percentages. The chi-squared test was employed to compare the percentages in order to determine the factors associated with mucosal involvement in patients with BP. A p value less than 0.05 was considered statistically significant.

RESULTS

Descriptive Study

Characteristics of the general population

Over this period, we collected 85 patients diagnosed with bullous pemphigoid, among which 37 (43.5%) were males and 48 (56.5%) were females. The mean age at diagnosis was 70.54 years, ranging from 24 to 113. Fifty-six patients (65.9%) reported the presence of a personal history, including diabetes (n = 17; 21.3%), dyslipidemia (n = 8; 10.0%), hypertension (n = 21; 25.9%), and heart disease (n = 4; 4.9%). Regarding neurological ATCDs, these were reported in nine (10.7%) of our patients. We noted a stroke in eight (9.9%) patients and Parkinson's disease in five (7.7%) patients. Drug intake was noted in twelve (14.3%) of our patients. Associations with autoimmune diseases were found in twenty-five patients (29.8%), including diabetes in seventeen patients, dyslipidemia in three patients, one case of vitiligo, Biermer's disease, psoriasis, and also lupus. Clinically, the typical form was found in 74% of our patients, with extensive skin involvement of more than 30% of the body surface in 38 patients (44.7%). Mucosal involvement was reported in 29 patients (34.1%); IC 95% (25.4%; 42.8%). Biologically, 62.4% of the patients had hypereosinophilia. All our patients were administered a protocol for PB: clobetasol propionate with a recourse to another systemic treatment (oral corticosteroid, DDS, cyclins, rituximab, etc.) in 38.8% of the cases.

Mucosal involvement

Twenty-nine patients (34.1%) presented mucosal lesions. Descriptive analysis of this group of patients (Table 1) showed that the oral mucosa was the most frequently affected surface (n = 27; 93.1%). Seven patients (24.1%) had genital involvement, two (6.9%) had nasal involvement, and one (3.4%) had anal and eye involvement. Among the patients with mucosal involvement, 25 (86.2%) had isolated mucosal surface involvement, while seven (24.2%) patients had two types of mucosal surface involvement concomitantly. In patients with oral involvement, the most frequent mucosal lesions were erosions of the soft palate (n = 17; 62.9%) (Fig. 1), followed by erosions of the inner faces of the cheeks (n = 16; 59.3) (Fig. 2), the tongue (n = 4; 14.8%), the gums (n = 2; 7.4%), and the labial mucosa (n = 2; 7,4%) (Fig. 3).

Genital involvement was observed in six patients, four of whom were females with erosions of the lips. Two

Table 1: Distribution of mucosal involvement in the study population.

Characteristic	Patients with Mucosal Involvement (*n*=29)	Patients without Mucosal Involvement (*n*=56)	*p* value
Mean age	69.5 yrs.	71.12 yrs.	0.54
Sex			
Male	13 (44.8%)	24 (42.8%)	0.34
Female	16 (55.2%)	32 (57.2%)	
Associations			
Neurological pathology	5 (17.2%)	4 (7.14%)	0.28
Autoimmune pathology	6 (20%)	19 (33.9%)	0.30
Medication intake	3 (10.3%)	9 (16.07%)	0.69
Distribution of bullous lesions			
Limbs	27 (93.1%)	40 (71.4%)	0.67
Trunk	27 (93.1%)	46 (82.1%)	0.29
Head and neck	14 (48.2%)	20 (35.7%)	0.37
Extent (> 30%)	18 (62.1%)	20 (35.7%)	0.01*
Peripheral eosinophilia	20 (68.9%)	33 (58.9%)	0.54
Need for systemic treatment	17 (58.6%)	16 (28.5%)	0.01*

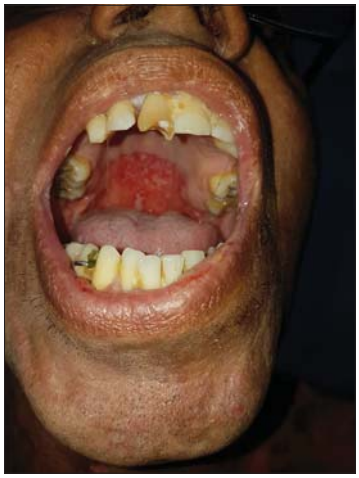

Figure 1: Erosions on the palate

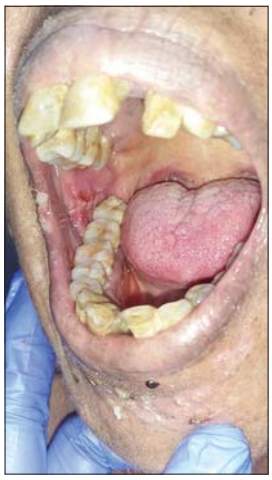

Figure 2: Multiple erosions on the inner side of the cheeks.

male patients presented with erosions on the glans penis. We noted nasal involvement in two patients with endonasal erosions and anal involvement in only one patient. Ocular involvement was detected in only one patient with conjunctival hyperemia without ophthalmic sequelae.

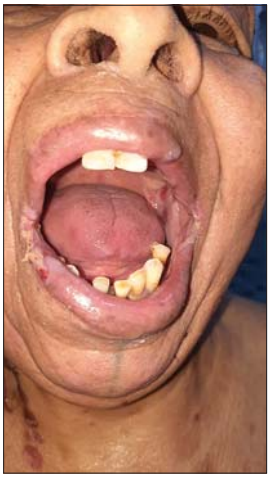

Figure 3: Bulla and erosions on the labial mucosa.

Analytical Study

We studied the epidemiological, clinical, biological, and therapeutic differences between patients with BP with mucosal involvement (n = 29) as compared to other patients with BP without mucous damage (n = 56) (Table 2). Patients with mucosal involvement were younger, presenting with an average age of 69.5 years vs. 71.12 years, without a statistically significant association ($p = 0.54$). We noted no significant difference regarding sex. Regarding the association of neurological pathologies and autoimmune disease, respectively, they were reported in 4 (7.14%) and 19 (33.9%) in the group without mucosal involvement, in 5 (17.2%) and 6 (20%) in the group with mucosal involvement without a statistically significant association ($p = 0.28$) and ($p = 0.30$). Concerning the anatomical distribution

Table 2: Demographics, clinical characteristics, and treatment of patients with bullous pemphigoid with mucosal involvement vs. other patients without mucosal involvement.

Mucosal Involvement	*n* (%)
Mucosal lesions	
yes	29 (34.1%)
no	56 (65.9%)
Distribution	
Oral mucosa	27 (93.1%)
soft palate	17 (62.9%)
inner face of the cheeks	16 (59.3%)
tongue	4 (14.8%)
gum	2 (7.4%)
labial mucosa	2 (7.4%)
Genital mucosa	7 (24.1%)
Nasal mucosa	2 (6.9%)
Ocular mucosa	1 (3.4%)
Anal mucosa	1 (3.4%)

of the bullous lesions, we observed no statistically significant difference between the two groups in relation to the involvement of the trunk, limbs, face, and folds. On the other hand, we noted that patients with mucosal involvement presented more frequently with heard skin disease (SC > 30%): n = 18 (62.1%) vs. n = 20 (35.7%), respectively ($p = 0.01$). We also noted peripheral eosinophilia in 20 (68.9%) patients with mucosal involvement vs. in 33 (58.9%) in the group without mucosal damage without a statistically significant relationship ($p = 0.54$). Regarding therapeutic management, we noted a more frequent need for the addition of systemic treatment to topical corticosteroids when compared to other patients (n = 17, 58,6%, vs. n = 16, 28,5%) ($p = 0.01$). The main associated systemic treatments were oral and bolus corticosteroid therapy, cyclins, Disulone, and rituximab with good evolution.

DISCUSSION

Mucosal involvement during bullous pemphigoid is generally rare. Its absence is one of the clinical criteria for the positive diagnosis of bullous pemphigoid. Several studies have been interested in estimating the prevalence of mucosal involvement in patients with PB as well as studying the characteristics of these patients. The prevalence of mucosal involvement in PB varies between 10% to 30% depending on the series [4,5]. Higher prevalence rates of 18.6% and 14.5% were observed in northern France [6] and Switzerland [7], respectively. A low prevalence of 5.7% was reported in Singapore [8]. In our study, we noted mucosal damage in 28 out of the 85 patients (34.1%).

Regarding the mucosal locations most affected in bullous pemphigoid, some studies as well as ours report that the involvement of the oral mucosa is the most frequent. In an Israeli study, the involvement of the oral mucosa was present in 45 out of 56 patients (80.4%). This mucosal involvement was mainly limited to non-keratinized mucous surfaces. The involvement of the oral mucosa and soft palate was observed in 25 (55.6%) and 24 (53.3%) patients with oral involvement, respectively, while the involvement of keratinized mucous structures, such as the gums and the back of the tongue, was less common. They also observed a prevalence of laryngeal involvement estimated at 4.8% following the performance of systematic laryngoscopy in all patients with mucosal involvement, even in the absence of laryngeal symptoms [5]. This was a new finding, only reported in anecdotal case reports and not found in other studies [9]. In our study, the oral mucosa was the most frequently affected surface (n = 27; 93.61%) with more frequent involvement of the palate and the inner face of the cheeks and less frequent in the tongue, gums, and lips. The other mucous membranes in bullous pemphigoid, including genital, ocular, and nasal, are less common [10].

Regarding the age of patients and its relationship with the presence of mucosal involvement, the results of studies are contradictory. Some studies have shown a significant relationship between a younger age and mucosal involvement. Others have not. In a 2019 Israeli study, patients with mucosal involvement were significantly younger at presentation (71.8 (14.4) years vs. 79.3 (8.10) years, respectively; $p < 0.001$) [5]. As in a study by Clapé et al. as in ours, we did not report this finding. This may be explained by a small sample size [6]. We found no significant association between sex and mucosal damage, and this was the case in most studies [11]. Clinically, we found that the presence of mucosal involvement was correlated with more extensive involvement, more than 30% of the skin surface, 62.1% versus 35.7%, $p = 0.01$. This is consistent with a recent French study, showing that patients with mucosal involvement had both more active and more extensive disease [6]. We found no relationship between the presence of mucosal involvement and the location of bullous lesions in the skin, unlike Kridin et al., who found that patients with mucosal involvement more frequently had skin lesions in the head and neck ($n = 29$; 51.8%). Biologically, we found no significant associations between peripheral eosinophilia and mucosal involvement, and this agrees with the conclusion of a recent study, which found no significant correlation between the severity

of mucosal damage and peripheral eosinophilia [12]. On the other hand, another study revealed a higher prevalence of mucosal damage in patients with BP with normal eosinophils when compared to those with peripheral eosinophilia ($p = 0.002$), which led them to question a likely protective role of peripheral eosinophilia in bullous pemphigoid with mucosal involvement [13]. In the present study, we found no correlation between mucosal involvement and the presence of neurological, autoimmune, or drug-induced disease. Recently, Chijiwa et al. reported more severe mucosal involvement in patients with BP when taking dipeptidyl peptidase-4 [14]. In addition, 36 patients with BP associated with dipeptidyl peptidase-4 were recently found to have mucosal lesions more frequently [15]. Regarding autoantibodies to bullous pemphigoid, the presence of mucosal involvement was correlated with the presence of IgG against the NH2- and COOH-terminals of BP180, the absence of anti-BP230 antibodies, and high deposits of IgA and C3 at the dermal–epidermal junction [16]. This was also reported in a study by Clapé et al., who objected that the absence of anti-BP230 autoantibodies was the only factor independently associated with mucosal involvement. In our study, we did not analyze this parameter.

Finally, in our study, we used systemic treatment in addition to topical treatment in patients with mucosal involvement (58.6% vs. 28.5%; $p = 0.01$). This result is similar to an Israeli study in which patients with mucosal involvement were treated with higher doses of systemic corticosteroids and adjuvants as compared to other patients with BP [5]. Another study showed that mucosal lesions respond more slowly to conventional treatment, thus prolonging the duration of treatment [17].

Through our study and the literature, we were able to focus on several characteristics of patients with bullous pemphigoid with mucosal involvement. In particular, patients with mucosal involvement tend to be younger with statistically varying degrees of significance depending on the study. Mucosal involvement is correlated with more extensive and severe disease with more probable involvement of the face and neck, the absence of anti-BP230 antibodies, and the presence of IGG against the NH2- and COOH-terminals of BP180. A low level of peripheral eosinophilia may also be correlated with the presence of mucosal involvement. Generally, in these patients, drug intake is, in particular, the oral antidiabetic, and these will resort to a systemic treatment for the control of the disease. This could lead us to think about attempting a systemic treatment in the case of PB with mucosal involvement for an earlier control of the disease. Further studies are needed at the national level to increase the study sample size and better assess these characteristics in the Moroccan population.

CONCLUSION

The involvement of the oral mucosa in patients with PB is frequent, with a prevalence ranging from 10% to 30% according to various studies. In our study, the prevalence was estimated at 34.1%. It is associated with more severe and extensive involvement of the disease, with the ineffectiveness of first-line treatment.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

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