Profils cliniques évolutifs de la pemphigoïde bulleuse : étude rétrospective monocentrique de 312 cas

Élise Dandache

UNIVERSITE DE MONTPELLIER
FACULTE DE MEDECINE MONTPELLIER-NIMES

THESE

Pour obtenir le titre de

DOCTEUR EN MEDECINE

Présentée et soutenue publiquement

Par

Elise DANDACHE

Le 23 novembre 2018

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LISTE DES ABREVIATIONS FRANCAISES

BPAG1 bullous pemphigoid antigen 1

BPAG2 bullous pemphigoid antigen 2

ELISA Enzyme-Linked ImmunoSorbent Assay

IFD immunofluorescence directe

Ig immunoglobuline

JDE jonction dermo-épidermique

kD kiloDalton

PB Pemphigoïde Bulleuse

PDM pemphigoïde des muqueuses

PNE polynucléaire éosinophile

CONTEXTE GENERAL

La pemphigoïde bulleuse (PB) est la maladie bulleuse auto-immune sous-épidermique la plus fréquente. La PB fait partie d'un groupe de 8 maladies bulleuses auto-immunes sous-épidermiques qui comprend également pemphigoïde gestationnelle, pemphigoïde des muqueuses (PDM), pemphigoïde des enfants, dermatite herpétiforme, dermatose à IgA linéaire, pemphigoide anti-p200/laminin g1 et épidermolyse bulleuse acquise (1).

Dans la PB, les autoanticorps déposés à la jonction dermo-épidermique sont dirigés contre les hémi-desmosomes et entraînent la formation d'une bulle sous-épidermique se développant au sein de la lamina lucida, dans la région supérieure de la membrane basale. Ces autoanticorps sont dirigés contre des protéines de structure des hémi-desmosomes, principalement BPAg1 (protéine de 230kD) et BPAg2 (ou collagène XVII, protéine de 180 kD). Le domaine NC16a de l'ectodomaine de la protéine BP180, épitope proche du pôle basal des kératinocytes, a été identifié comme domaine immunodominant dans la PB et est différent de l'épitope-cible des autoanticorps anti-180kd des PDM avec autoanticorps anti-BPAg2 (2,3).

L'incidence dans le monde est estimée à 4,5 à 14 nouveaux cas par million d'habitants (4–9) et par an et en France à 21,7 nouveau cas par million d'habitants et par an, soit 3 fois supérieure à l'incidence estimée il y a 15 ans (10). Il n'y a pas de prédominance de sexe, d'ethnie ou géographique. Le taux de survie cumulée à 1 an est de 62% (10). Le risque de décès est 3 à 6 fois plus important que dans la population générale du même âge et de même sexe, plus en lien avec l'âge, l'état général du patient, les comorbidités neurologiques et les traitements spécifiques de la pemphigoïde bulleuse tels que la prise prolongée de corticostéroïdes systémiques qu'avec la sévérité de la maladie elle-même (10).

La PB est significativement associée à des affections neurologiques, principalement neurodégénératives mais également vasculaires. L'affection neurologique précède la PB dans 50 à 72% des cas, en moyenne 5,5 ans avant le diagnostic de PB. Le

lien physiopathologique entre BP et maladie neurologique n'est pas bien établi, peut-être par autoimmunité croisée vis-à-vis de l'antigène BPAG1 également présents dans le système nerveux central et démasquée par la maladie neurologique (11−14).

Cliniquement la PB se manifeste par un prurit souvent isolé au départ puis associé à une éruption bulleuse généralisée ou localisée accompagnée de lésions inflammatoires pseudo-urticariennes ou eczématiformes. La lésion élémentaire est une bulle reposant classiquement sur des plaques inflammatoires pseudo-urticariennes. Il existe des formes non-bulleuses où les symptômes sont un prurit isolé, à type de prurigo nodulaire, des plaques pseudo-urticariennes ou eczématiformes sans bulle, voire une érythrodermie. Contrairement à d'autres maladies bulleuses auto-immunes sous-épidermiques, les lésions cicatricielles sont classiquement absentes et la PB épargne la tête et cou ainsi que les muqueuses.

Le diagnostic de PB repose sur l'aspect clinique décrit ci-dessus, la présence d'une bulle sous épidermique avec un infiltrat dermique à PNE en histologie, la présence de dépôts linéaires d'IgG et/ou C3 à la jonction dermo-épidermique en IFD et la mise en évidence fréquente d'anticorps circulants anti BPAG1 et surtout anti BPAG2 par ELISA et Western Blot.

En 1998 le Groupe Bulle (Centre de référence national sur les maladies bulleuses auto-immunes) a proposé et validé un ensemble de 4 critères cliniques fortement associés au diagnostic de PB : âge supérieur à 70 ans, absence de cicatrices atrophiques, absence d'atteinte muqueuse, absence d'atteinte prédominante de la tête et du cou. Si au moins 3 critères sur 4 étaient présents, le diagnostic de PB pouvait être affirmé avec une sensibilité de 90%, une spécificité de 83% et une valeur prédictive positive de 95%. En 2004, le Groupe Bulle a confirmé la validité de ces critères clinique pour le diagnostic de PB en utilisant l'analyse du sérum des patients en immunoblot comme critère diagnostique principal, avec une sensibilité de 86%, une spécificité de 90% et une excellente valeur prédictive positive supérieure à 95%, si au moins 3 des 4 critères étaient présents, confirmant ainsi l'intérêt de cet ensemble de caractéristiques cliniques pour le diagnostic rapide de PB.

Cependant, le spectre clinique de la PB se modifie avec le temps et récemment un certain nombre de caractéristiques cliniques inhabituelles semblent émerger chez certains patients atteints de PB, notamment des atteintes palmo-plantaires prédominantes, des érosions extensives et une plus grande fréquence de lésions intra-buccales et de la tête et du cou. Cette étude monocentrique rétrospective portant sur une cohorte de grande taille de PB bien documentées a été menée pour mettre en évidence un changement possible des caractéristiques cliniques au cours du temps avec 2 objectifs principaux complémentaires : (i) décrire la fréquence des caractéristiques cliniques atypiques, dichotomisées en topographies atypiques et lésions cutanées élémentaires atypiques, et leur possible émergence au cours des 2 dernières décennies (ii) vérifier la validité au cours du temps des 4 critères cliniques diagnostiques mentionnés ci-dessus étant donné la possible augmentation de fréquence de caractéristiques cliniques atypiques.

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TIME-RELATED EVOLVING CLINICAL PATTERN OF BULLOUS PEMPHIGOID: A MONOCENTER RETROSPECTIVE SURVEY OF 312 CASES

Elise Dandache[1], Aurélie Du Thanh[1], Bernard Guillot[1], Céline Girard[1], Didier Bessis[1], Olivier Dereure[1]

1: Department of Dermatology, University of Montpellier and INSERM U1058, Montpellier, France

Correspondence to:

Olivier Dereure
Department of Dermatology
Hôpital Saint-Eloi
University of Montpellier and INSERM U1058
80 avenue Augustin Fliche
Montpellier Cedex 5 France
Tel : (33) 467 33 69 06
Fax : (33) 467 33 69 58
Email: o-dereure@chu-montpellier.fr

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ABSTRACT

Background : The clinical spectrum of Bullous Pemphigoid (BP) may have changed over time as suggested by the recently growing occurrence of unusual clinical features reported in daily practice. Accordingly a retrospective, large-scale time-related analysis was conducted to reappraise BP clinical profile during the last 2 decades and to reassess the validity of a set of 4 previously established clinical criteria.

Patients and methods : All well-documented BP patients diagnosed between January 2001 and April 2017 in a tertiary referral center were included and the following data were collected : baseline characteristics of patients, extent of the disease, distribution and type of cutaneous lesions, presence of mucous lesions, presence of at least one atypical clinical (topographical or lesional) feature, presence or absence of at least 3 of previously validated diagnostic clinical criteria. In order to identify a possible time-related shift of clinical features, data from 4 chronological groups of 4 years were statistically compared.

Results : 312 patients were finally included and analyzed. At least 3 of the 4 classical criteria were present in 278 patients (89.1%), but with a trend toward a steady decrease of relevance over time (G1 93.0% vs G4 83.8%, p 0.067). The most frequent missing criteria were absence of mucosal involvement followed by absence of head and neck involvement. 206 patients (66.0%) displayed at least one atypical clinical feature and chronological analysis confirmed a significant time-related increase of atypical pattern frequency (G1 57.9%, G4 73.7%, p 0.041). Head and neck, palmoplantar, mucosae involvement were observed in 56 (17.9%), 151 (48.4%) and 58 (18.6%) patients respectively, with an upward, although non significant trend between G1 and G4 (p 0.071, p 0.088, p 0.094 for these 3 items respectively).

Discussion : Clinical presentation of BP seems to have evolved over time with a progressively higher proportion of atypical topographical and/or lesional characteristics, mainly regarding mucous membrane, head and neck and palmo-plantar involvement. This shift probably underlies the progressive reduction of the percentage of BP patients fulfilling at least 3 of the 4 BP previously validated diagnostic criteria even though these criteria remain robust in our study. Environnemental causes, mainly drugs might affect clinical presentation of BP since a higher frequency of mucosal lesions has been recently reported in dipeptidyl peptidase 4 inhibitors (DPP4is)-induced BP compared to other BP patients.

Conclusion : BP clinical spectrum seems to have changed with the emergence of more atypical forms, perhaps under the influence of etiological factors including drugs.

ABBREVIATIONS AND ACRONYMS LIST

BP: bullous pemphigoid

BPag1: Bullous Pemphigoid antigen 1

Bpag2: Bullous Pemphigoid antigen 2

DIBP : Drug-induced bullous pemphigoid

DIF: direct immunofluorescence

DPP4is: dipeptidyl peptidase 4 inhibitors

ELISA: Enzyme-Linked Immunosorbent Assay

G1-G4: group 1-group 4

IgG: immunoglobulin G

PD-1/PD-L1 inhibitors: programmed cell death 1/ programmed death ligand 1

PMSI: programme de médicalisation des systèmes d'information

INTRODUCTION

Bullous pemphigoid (BP) is the most frequent autoimmune bullous disease and mainly affects the elderly population. (2,3). Causative autoantibodies target structural proteins of hemidesmosomes, mainly 230 kD BPag1 and 180 kD BPag2 at the dermo-epidermal junction, resulting in subepidermal blistering within the upper part of lamina lucida. The annual world incidence has been estimated between 4.5 and 14 new cases per million per year (4–9) and may be higher in France with 21.7 new cases per million per year. This latter value is about 3 times higher than the estimated incidence 15 years ago, according to a recent survey (10). The overall 1-year survival rate is 62% (10) with a death hazard three to six times higher than in the age- and gender-matched general population, mainly related to general health status, comorbidities with a significant association with degenerative and vascular neurological disorders and to treatment complications especially of systemic steroids rather than to the severity of the blistering disease itself (10).

Clinically, BP is mainly characterized by pruritus, often isolated at onset of the disease, associated with inflammatory, urticaria-like lesions and a widespread or more localized bullous eruption characteristically developing on inflammatory skin and predominant on some body areas. (15). Contrasting with other subepithelial auto-immune blistering diseases, scarring is theoretically absent and the disease usually spares head and neck regions and mucous membranes (1,16)(17). BP diagnosis is based on a combination of consistent clinical features, subepidermal cleavage with an with eosinophil-rich infiltrate on histopathological examination and IgG and/or C3 deposits at the dermoepidermal junction on direct immunofluorescence (IF) microscopy. Circulating anti-BPAg1 and mainly anti-BPAg2 autoantibodies are usually detected on immunoblot or by ELISA (1,18).

In 1998, The French Auto-immune Bullous Diseases taskforce proposed and validated a set of 4 clinical criteria highly consistent with BP diagnosis that consisted of age greater than 70 years, absence of atrophic scars, absence of mucosal involvement and absence of predominant bullous lesions on the neck and head. If 3 of these 4 characteristics were present, a clinical diagnosis of BP could be made with a sensitivity of 90%, a specificity of 83% and a positive predictive value of 95% (19). In 2004 the same taskforce reappraised the validity of these clinical criteria for BP diagnosis using immunoblot analysis of patients' sera as the main diagnostic criterion (18) which confirmed a sensitivity of 86%, a specificity of 90% and an excellent predictive diagnostic value of more than 95% if at least 3 of these 4 clinical criteria were present, therefore confirming the interest of this set of clinical features for the rapid

diagnosis of BP (18).

However, clinical spectrum of diseases may change over time and recently a number of unusual clinical features appear to have emerged in some BP patients including merely or predominant palmo-plantar blistering, extensive erosions and a higher than expected occurrence of intrabuccal and head and neck lesions. Accordingly a monocenter retrospective study based on a large cohort of well-documented BP was designed to document this possible shift of BP clinical pattern over time with two main complementary objectives: (i) to describe the possible occurrence of unusual/atypical clinical patterns of BP with respect to lesions' topography and/or clinical subtype and their possible time-related emergence over the last two decades (ii) to reassess the validity of the four aforementioned clinical diagnostic criteria over time in this setting of possibly increasing frequency of atypical features.

PATIENTS AND METHODS

Patients' selection procedure

All patients with a well-established diagnosis of BP and treated in the department of dermatology of the University of Montpellier, a tertiary reference center, from January 2001 to April 2017 were considered for inclusion. The identification of patients was based on a list of individuals obtained from the computerized epidemiological database in use in French healthcare establishments through a specific coding (PMSI) with bullous pemphigoid selected as principal, related or associated diagnosis. Data from selected patients were then retrospectively collected using electronic medical records from the local medical software and anonymized before analysis.

In a second step, BP diagnosis was verified in all patients selected through this procedure using consistent histological (subepidermal blister with eosinophil-rich dermal infiltrate) and direct immunofluorescence (IgG and/or C3 linear deposits at the dermoepidermal junction) data obtained on initial skin biopsies. BP180 ELISA was often performed on patients' sera, particularly in case of unclear diagnosis mainly owing to inconclusive and/or discrepant histological and DIF data. Patients with diagnostic or coding errors (most often other auto-immune bullous diseases or skin infections) or patients for whom clinical details were missing were excluded of final analysis.

Collected data

The following data were systematically collected from selected patients' files:

- Baseline characteristics of patients: age at diagnosis, gender, presence and type of associated neurological disorder.
- Initial extent of the disease: multibullous (at least 10 new blisters daily), paucibullous (less than 10 blisters daily) or nonbullous subset (solitary pruritus or associated with prurigo-like lesions or excoriations or merely inflammatory lesions); localized disease (one affected body area only).
- Initial distribution of cutaneous lesions: limbs, trunk, head and neck, palmo-plantar regions
- Type of non-bullous cutaneous lesions: urticaria-like or eczematous

plaques, atrophic scars, erythematosquamous lesions, extensive skin erosions.

- Presence, clinical pattern and topography of mucous membranes lesions.
- Histological, DIF and if applicable ELISA findings
- Presence or absence of at least 3 of the clinical criteria of BP validated in prior reports by the French taskforce (19).

Chronological group and time-related comparative analysis of data

In order to identify a possible time-related shift of clinical features, patients were chronologically divided in four groups of 4 years each:

- Group 1 (G1) diagnosed between January 2001 and December 2004
- Group 2 (G2) diagnosed between January 2005 and December 2008
- Group 3 (G3) diagnosed between January 2009 and December 2012
- Group 4 (G4) diagnosed between January 2013 and April 2017

The following data were described as figures and percentages, and Pearson's Chi-squared test or Fisher's exact test according to samples' size were used to compare these data between the 4 chronological groups (G1, G2, G3, G4) and more specifically between G1 and G4 to search for a possible time-related shift of clinical pattern:

- presence of at least one atypical clinical element, either topographic or lesional, formally defined as involvement of palmoplantar regions, head and neck or mucous membranes (topographic atypical features) and extensive erosions, erythematosquamous or eczematous lesions, atrophic scars (lesional atypical features)

- presence/absence of at least 3 of 4 of the above-mentioned validated clinical BP diagnostic criteria

RESULTS

Baseline characteristics of patients

360 files were initially selected through PMSI database survey but only 312 patients (86.67%) were retained for final analysis. 48 patients were excluded: 17 for diagnostic errors (3 prurigo or isolated pruritus, 1 eczema, 3 mucous membrane pemphigoid, 1 cutaneous adverse drug reaction, 1 bullous impetigo, 2 epidermolysis bullosa acquisita, 2 pemphigoid gestationis, 1 linear IgA disease, 2 pemphigus, 1 eosinophilic cellulitis) and 31 for missing clinical details. 146 (46.8%) were female and 166 (53,3%) male patients. Age ranged from 49 to 106 years (median 82.0 years, Q1 74.8 – Q3 88.0 years). 165/313 (52.9%) patients had a medical history of neurological disease (degenerative, vascular or neuropsychiatric) (Table A). Histological and DIF findings were consistent with BP in 285 (91.3%) and 263 (84.3%) patients respectively but all patients had at least one consistent criteria. BP180 ELISA was performed in 224 patients and was positive for 197 (87.9%) patients (Table B).

Overall descriptive analysis of initial clinical pattern (Table C).

Topographic distribution of lesions

Initially non bullous, paucibullous, multibullous, or localized BP was diagnosed in 12 (3.8%), 137 (43.9%), 158 (50.6%) and 5 (1.6%) patients respectively.

A typical topographic distribution of lesions (limbs and abdomen) was solely or mainly observed in a minority of patients (121; 38.8%) while head and neck, palmo-plantar regions and at least one mucosae were affected in 56 (17.9%), 151 (48.4%) and 58 (18.6%) patients respectively regardless of the relative importance of these latter lesions regarding overall location of skin and mucosae changes. Conversely, a predominant atypical distribution including head and neck, palmo-plantar and/or mucosal involvement was observed in 191 (61.2%) cases including 146 (46.8%) cases with exclusive atypical topography. As regards mucosal involvement, oral mucosae was mainly affected in 52 (16.67%) cases followed by genital mucosae in 14 (4.49%) cases including 6 cases with exclusive genital involvment; no ocular involvement was reported.

Clinical pattern of lesions

A typical clinical pattern of urticaria-like plaques and blisters was exclusively present in 234 (75%) cases. 50 (16.0%) patients presented with blisters with no urticaria-like plaques nor atypical clinical features. Conversely, at least one atypical/unusual clinical feature was observed in 28 (9.0%) patients overall including 9 (2.9%) patients where atypical features were solely present: atrophic scars in 3 (0.96%), eczematous lesions in 14 (4%), erythematosquamous lesions in 5 (2%) and extensive erosions in 7 (2%) patients respectively.

Overall, 206/312 (66.0%) patients displayed at least one atypical element, either lesional or topographic with a ratio atypical topography / atypical clinical features of 6.8 (191/28). 13 (4.2%) patients displayed a totally atypical form (both lesional and topographic) while 95 (30.4%) showed no atypical element whatsoever.

Presence/absence of formerly validated clinical criteria for BP diagnosis
(Table D)

Overall, the 4 criteria were present at diagnostic in 196 (62.82%) patients while 3, 2, 1 or 0 criteria were present in 82 (26.28%), 30 (9.61%), and 4 (1.28%) patients respectively. Accordingly, at least 3 of 4 criteria were present in 278 (89.10%) patients. By order of frequency, the missing criteria were the absence of mucosal involvement (58 patients, 18.59%), of predominant bullous lesions on the neck and head (56 patients, 17.95%), an age greater than 70 years (41 patients, 13.14%) and the absence of atrophic scars (3 patients, 0.96%).

Comparative data analysis in chronological groups (Table C and D)

Proportion of woman and median age were similar across the 4 groups (G1 63%, G2 48%, G3 51%, G4 53%, p = 0.165; G1 83.0 years, G2 81.5 years, G3 83.0 years, G4 81.0 years, p = 0.153 respectively) and between G1 and G4 (P = 0?242 and 0.294 respectively). The association with neurological comorbidities, irrespective of their subtype, increased over time, but with no significant difference between the 4 groups (G1 43.8%, G2 47.6%, G3 54.0%, G4 61.6%, p = 0.063) nor between G1 and G4 (p = 0.045). The proportion of multibullous BP was similar in the 4 groups (G1 47.4%, G2 45.1%, G3

52.7%, G4 55.6%, p= 0.508) and between G1 and G4 (p= 0.324).

The percentage of patients displaying at least one atypical, either lesional or topographic clinical feature steadily increased over time in the 4 chronological groups: G1 57.9%, G2 59.8%, G3 68.9%, G4 73.7%, with no overall difference (p = 0.111) between the 4 groups but a significant difference (p = 0.041) was observed between G1 and G4. No difference was identified between the 4 groups regarding the proportion of exclusively atypical disease regarding both topographic and lesional pattern (G1 5.3%, G2 <0.1%, G3 <0.1%, G4 5.0%) (p 0.859) nor between G1 and G4 (p = 1.000). Regarding the proportion of exclusively typical diseases as to both topographic and lesional features, a steady but non significant decrease was identified over time when comparing the four chronological groups (G1 40.3%, G2 34.1%, G3 24.3%, G4 26.3%, p = 0.151) but a more marked trend (although still non significant) was observed when comparing G1 and G4 (p = 0.068).

The presence of a mere or predominant typical topographic pattern (mainly involving limbs and abdomen) was statistically different in the 4 groups (G1 to G4: 43.8%, 37.8%, 23.0%, 48.5% respectively; p= 0.006) but with no clear chronological shift toward progressive decrease over time as no significant difference between G1 and G4 (p= 0.577) was found. As to the initial presence of typical urticaria-like plaques, no significant difference was identified between the 4 groups (75.4%, 69.5%, 73.0%, 80.8% respectively; p= 0.372) nor between G1 and G4 (p 0.126).

Comparative analysis of data regarding patients with predominant atypical distribution of lesions revealed a trend to steady increase over time between the 4 groups (G1 50.9%, G2 54.9%, G3 66.2%, G4 68.7%) (p= 0.070) and a statistically significant difference between G1 and G4 (p= 0.027). Conversely, the specific analysis of patients with exclusive atypical topography failed to identify significant difference between the 4 groups (G1 42.1%, G2 42.7%, G3 58.1%, G4 44.4%) (p= 0.166) nor between G1 and G4 (p= 0.777).

The percentage of patients with at least one atypical lesional subtype was not different between the 4 groups (G1 10.5%, G2 0.1%, G3 5.4%, G4 11.1%) (p= 0.595) nor between G1 and G4 (p= 0.910). The restricted number of patients with exclusively

atypical lesions (9) precluded any significant statistical analysis between chronological groups.

The main atypical features identified from files' review among predefined atypical elements (involvement of palmoplantar regions, of head and neck or of mucous membranes, extensive erosions, erythematosquamous or eczematous lesions, atrophic scars) were individually submitted to a specific time-related analysis and in most cases no significant difference was identified between the 4 chronological groups nor between G1 and G4 more particularly. However, a trend toward a significant difference was observed between G1 and G4 for oral lesions (10.5% vs 22.2%; p= 0.075) and for head and neck lesions (12.3% vs 24.2%; p= 0.071) with a steady increase in frequency over time for both features, highly consistent with overall clinical feeling. Additionally, a significant difference between the 4 groups (p= 0.026) and a trend to significant difference between G1 and G4 (p= 0.060) were observed for extensive erosive lesions but the limited size of the sample must be pointed out (G1 7.0%, G2 0%, G3 1.4%, G4 1.0%).

Finally, the percentage of patients fulfilling at least 3 of 4 clinical criteria of BP diagnosis was no statistically significant difference between the 4 groups (93% G1, 91.5% G2, 90.5% G3, 83.8% G4; p= 0.227) despite a steady decrease over time but a trend toward significance was observed between G1 and G4 (p = 0.067). Conversely, a significant decrease of the percentage of patients fulfilling the 4 clinical criteria was observed over time (75.4% G1, 68.3% G2, 62.2% G3, 51.5% G4 : p=0.016) and between G1 and G4 (p=0.003).

DISCUSSION

This retrospective analysis based on a large cohort of 312 cases of BP initially diagnosed over a long period of time (approximatively 2 decades) is the first study ever specifically designed to evaluate a possible shift over time of BP clinical profile and of the relevance of the previously established set of 4 clinical criteria for BP diagnosis, with a specific emphasis on the frequency and spectrum of atypical clinical features related to either topographic or lesional features.

This large-scale descriptive, monocenter series mainly shows a significant increase over time of the proportion of patients displaying at least 1 atypical feature, either topographic or lesional or both, with head and neck, palmoplantar and mucous membranes involvement being by far the more frequently observed atypical features compared to atypical clinical subsets of lesions. In parallel, the proportion of patients with an exclusively typical pattern regarding both clinical subtype and topography of lesions tended to decrease over time even though only a trend was observed. Likewise, the proportion of patients fulfilling at least 3 of the 4 previously validated diagnostic criteria steadily decreased over the past two decades but with no significant difference, meaning that these criteria are probably still robust. Conversely, the proportion of patients fulfilling the 4 criteria significantly decreased during the period of the study.

BP severity regarding disease extension was similar across the 4 chronological groups and the rare localized form cases were all pretibial. Baseline characteristics of patients reflected previous data regarding age, sex ratio and association to neurological disorders (1,12,13,20-22).

Only few past studies aimed to record atypical clinical features in BP, although based on a lower number of patients compared to our series and none of them were specifically designed to appraise a possible shift of clinical profile over time. Della Torre carried out a prospective nationwide cohort in Switzerland between 1 January 2001 and 31 December 2002 including 117 patients: 17.1% patients had only excoriations, eczematous and⁄or urticarial infiltrated lesions, head⁄neck as well as palmo-plantar involvement were found in up to 20% of patients, while mucosal lesions were present in 14.5% of the cases (16). Esmaili carried out a descriptive study in 2012 in Iran on 122

patients with documented bullous pemphigoid and found oral lesions in 27% cases, non-specific rash in 19.7%, eczema in 7.4%, genital lesions in 4.1%, face in 25.4%, scalp in 17.2%, palm and sole in 8.2% (20). Chang reported in 1996 in 86 cases of Taiwan 3 cases of dishydrosiform BP and mucous involvement in 12.8% cases (21). Di Zenzo reported 10 to 20% involvement of oral mucosae in a prospective study of 49 cases in 2008 (3). Eventually, Kridin included 82 patients with BP and diabetes in 2018 and revealed that mucosal involvement was present in 22.2% patients taking dipeptidyl peptidase 4 inhibitor (DPP4is) vs 6.5% in other patients (22).

Proportion of head and neck involvement was the same in our series as previous study. A bigger proportion of mucosal and palmoplantar involvement was observed in our series compared to previous study. However, the proportion of patients displaying an atypical pattern was smaller than in some previous other studies but such features are poorly described in literature. Literature data regarding the presence of clinical atypical features and our main results are summarized and compared in Table E.

In 1998, the the French Taskforce for Bullous disorders established a set of 4 clinical BP diagnosis criteria (age greater than 70 years, absence of atrophic scars, absence of mucosal involvement and absence of predominant bullous lesions on the neck and head) ; if 3 of these 4 characteristics were present, a diagnosis of BP could be made with a sensitivity of 90%, a specificity of 83% and a positive predictive value of 95% (19). Some years later, the validity of these clinical criteria were reassessed using immunoblot analysis of patient sera as the main diagnostic element, confirming a high degree of sensitivity (86%) and of specificity (90%) and an excellent prognostic positive value over 95% among patients with various subepidermal auto-immune bullous disorders if 3 of these 4 clinical criteria were fulfilled (18). If these results confirmed the interest of this set of clinical criteria for BP rapid diagnosis, no further study reappraised the validity of these criteria nor specifically investigated a possible shift of their relevance over time. In our study the overall percentage of patients fulfilling at least 3 criteria was still high (89.1%) favouring a persistent robustness of this set of criteria but a trend toward a steady decrease of this percentage over time must be pointed out especially when taking in account the two extreme chronological groups (93.0% vs 83.8% respectively; $p = 0.067$). The most frequent missing criteria were the absence of

mucosal involvement (missing in 18.6% of patients) and of predominant bullous lesions on the head and neck (missing in 17.9% of patients), results that match quite well the data regarding the steady increase over time of the frequency of these atypical features.

A number of hypothesis underlying this possible shift to a higher percentage of atypical features in BP over time may be raised. First, it cannot be ruled out that higher attention was recently paid to atypical features in PB with a more frequent recording of such unusual elements in clinical files as a consequence; in this setting, the observed time-related increase of atypical features might be at least partially artifactual. A second hypothesis could be related to etiological factors and more particularly to recently-introduced drugs that can act as antigenic haptens binding to and/or modifying basement membrane proteins (23–25). More specifically, dipeptidyl peptidase 4 inhibitors (DPP4is) currently largely used in diabetic patients has been recently repeatedly involved in BP occurrence and associated with a threefold increased risk for BP. Patients with DPP4is-induced BP display a higher mucosal involvement compared to non DPP4is-related BP wi (22,26–28). However, our study was not designed to evaluate the impact of medication on clinical presentation of BP. Further study are needed to more adequately investigate a possible relationship between medication uptake and the occurrence of atypical forms of BP.

CONCLUSION

A shift in the clinical spectrum of BP seems to have occurred during the past two decades with the emergence of more atypical forms mainly regarding the distribution of lesions. These changes in clinical pattern might at least partially be related to environmental causes, such as newly introduced drugs but further, large-scale prospective investigations are warranted to support this hypothesis.

Table A. Baseline characteristics of patients

	G1	G2	G3	G4	Total	P-value	
						4 groups	G1 vs G4
Number of patients	57 (18.3%)	82 (26.3%)	74 (23.7%)	99 (31.7%)	312 (100%)		
Sex : Female/Male	F 36 (63.2%) / M 21 (36.8%)	F 39 (47.6%) / M 43 (52.4%)	F 38 (51.3%) / M 36 (48.6%)	F 53 (53.5%) / M 46 (46.4%)	F 146 (46.8) / M 166 (53.3%)	0.165	0.242
Median age at diagnosis (Q1-Q3)	83.0 years (Q1 76.0- Q3 88.0)	81.5 years (Q1 75.0- Q3 87.0)	83.0 years (Q1 77.3- Q3 88.0)	81.0 years (Q1 73.0- Q3 89.0)	82.0 years (Q1 74.8- Q3 88.0)	0.153	0.294
Neurological disorders	25 (43.9%)	39 (47.6%)	40 (54.0%)	61 (61.6%)	165 (52.9%)	0.063	0.045

SD, standard deviation ; G1 to G4, chronological groups ; Q1, first quartile ; Q3, third quartile

Table B. Histological, direct immunofluorescence and ELISA findings

	G1	G2	G3	G4	Total
Compatible histology	54/57 (94.7%)	73/82 (89.0%)	68/74 (91.9%)	90/99 (90.9%)	285/312 (91,3%)
DIF : linear IgG and/or C3 deposits at the DEJ	45/57 (78.9%)	72/82 (87.8%)	60/74 (81.1%)	86/99 (86.9%)	263/312 (84,3%)
ELISA if performed : detection of anti-BPAg2 antibodies	3/5 (60.0%)	51/54 (94.4%)	61/69 (88.4%)	82/96 (85.4%)	197/224 (87,9%)

DEJ, dermoepidermal junction; DIF, direct immunofluorescence; ELISA, Enzyme-Linked ImmunoSorbent Assay; G1 to G4, chronological groups

Table C. Clinical patterns of bullous pemphigoid

	G1	G2	G3	G4	Total	P-value Comparison 4 groups	P-value Comparison G1 vs G4
Topography							
- Typical	**25 (43.9%)**	**31 (37.8%)**	**17 (23.0%)**	**48 (48.5%)**	**121 (38.8%)**	**0.006**	**0.580**
*** Including exclusive typical topography**	**20 (35.1%)**	**21 (25.6%)**	**11 (14.9%)**	**24 (24.2%)**	**76 (24.4%)**	**0.064**	**0.147**
Trunk and flexural involvement	25 (43.9%)	31 (37.8%)	17 (23.0%)	48 (48.5%)	121 (38.8%)	0.006	0.577
- Atypical	**29 (50.9%)**	**45 (54.9%)**	**49 (66.2%)**	**68 (68.7%)**	**191 (61.2%)**	**0.070**	**0.027**
*** Including exclusive atypical topography**	**24 (42.1%)**	**35 (42.7%)**	**43 (58.1%)**	**44 (44.4%)**	**146 (46.8%)**	**0.166**	**0.777**
Head and neck involvement	7 (12.3%)	11 (13.4%)	14 (18.9%)	24 (24.2%)	56 (17.9%)	0.165	0.071
Palmo-plantar involvement	23 (40.3%)	35 (42.7%)	39 (52.7%)	54 (54.5%)	151 (48.4%)	0.248	0.088
Involvement of ≥ 1 mucosae	7 (12.3%)	15 (18.3%)	13 (17.6%)	23 (23.2%)	58 (18.6%)	0.435	0.094
* oral mucosae	6 (10.5%)	12 (14.6%)	12 (16.2%)	22 (22.2%)	52 (16.7%)	0.293	0.075
* genital mucosae	0 (0.0%)	6 (7.3%)	3 (4.0%)	5 (5.0%)	14 (4.5%)	0.202	0.159
* ocular mucosae	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000
Clinical features							
- Typical	**51 (89.4%)**	**75 (91.4%)**	**70 (94.6%)**	**88 (88.9%)**	**284 (91.0%)**	**0.595**	**0.910**
*** Including exclusive typical clinical features**	**41 (71.9%)**	**50 (61.0%)**	**51 (68.9%)**	**73 (73.7%)**	**215 (68.9%)**	**0.292**	**0.806**
Urticaria-like plaques	43 (75.4%)	57 (69.5%)	54 (73.0%)	80 (80.8%)	234 (75.0%)	0.372	0.429
Blisters solely	8 (14.0%)	18 (21.9%)	16 (21.6%)	8 (8.1%)	50 (16.0%)	0.034	0.238
- Atypical	**6 (10.5%)**	**7 (0.1%)**	**4 (5.4%)**	**11 (11.1%)**	**28 (9.0%)**	**0.595**	**0.910**
*** Including exclusive atypical clinical features**	**4 (7.0%)**	**0 (0%)**	**1 (0.01%)**	**4 (4.0%)**	**9 (2.9%)**	**0.057**	**0.465**
Presence of atrophic scars	0 (0.0%)	1 (1.2%)	1 (1.4%)	1 (1.0%)	3 (1.0%)	1.000	1.000
Eczematous lesions	3 (5.3%)	5 (6.1%)	1 (1.4%)	5 (5.0%)	14 (4.5%)	0.481	1.000
Erythematosquamous lesions	3 (5.3%)	0 (0.0%)	1 (1.4%)	1 (1.0%)	5 (5.0%)	0.078	0.139
Extensive erosive lesions	4 (7.0%)	0 (0.0%)	1 (1.4%)	1 (1.0%)	7 (2.2%)	0.026	0.060
All atypical patterns (topography or clinical features)	**33 (57.9%)**	**49 (59.8%)**	**51 (68.9%)**	**73 (73.7%)**	**206 (66.0%)**	**0.111**	**0.041**
* Ratio atypical topography/atypical features	4.8 (29/6)	6.4 (45/7)	12.2 (49/4)	6.2 (68/11)	6.8 (191/28)	0.570	0.656
* Including exclusive atypical patterns	3 (5.3%)	3 (< 0.1%)	2 (< 0.1%)	5 (5.0%)	13 (4.2%)	0.859	1.000
All typical patterns (topography or clinical features)	**49 (86.0%)**	**65 (79.3%)**	**58 (78.4%)**	**86 (86.9%)**	**258 (82.7%)**	**0.682**	**0.267**
* Including exclusive typical patterns	23 (40.3%)	28 (34.1%)	18 (24.3%)	26 (26.3%)	95 (30.4%)	0.151	0.068
Extent of the disease							
Localized	2 (3.5%)	3 (3.7%)	0 (0.0%)	0 (0.0%)	5 (1.6%)		
Paucibullous	24 (42.1%)	41 (50.0%)	32 (43.2%)	40 (40.4%)	137 (43.9%)		
Multibullous	27 (47.4%)	37 (45.1%)	39 (52.7%)	55 (55.6%)	158 (50.6%)	0.251	0.205
Nonbullous	4 (7.0%)	1 (1.2%)	3 (4.1%)	4 (4.0%)	12 (3.8%)		

G1 to G4, chronological group61.2

Table D. Presence of clinical criteria of Vaillant and al. (absence of atrophic scars, absence of head and neck involvement, absence of mucosal involvement, and age greater than 70 years)

	G 1		G 2		G 3		G 4		Total	
≤ 1 criteria	1	(1.75%)	1	(1.22%)	1	(1.35%)	1	(1.01%)	4	(1.28%)
2 criteria	3	(5.26%)	6	(7.32%)	6	(8.11%)	15	(15.15%)	30	(9.62%)
3 criteria	10	(17.54%)	19	(23.17%)	21	(28.38%)	32	(32.32%)	82	(26.28%)
4 criteria	43	(75.44%)	56	(68.29%)	46	(62.16%)	51	(51.52%)	196	(62.82%)
≥ 3/4 criteria	53	(93.0%)	75	(91.5%)	67	(90.5%)	83	(83.8%)	278	(89.1%)

P-value ≥ 3/4 criteria : comparison /4 groups : p 0.227 ; comparison/G1 vs G4 : p 0.067
P-value 4/4 criteria : comparison/4 groups : p 0.016 ; comparison/G1 vs G4 : p 0.003

Table E. Atypical clinical features in BP patients as reported in the literature

Study	Number of patients	Atypical topography	Atypical lesional features
Chang 1996 (28)	86	12.8% mucosae	3.5% eczematous lesions
Di Zenzo 2008 (3)	49	10 to 20% oral mucosae	
Della Torre 2012 (16)	117	20% head and neck 14.5% mucosae	17.1% exclusive atypical lesions (excoriations, eczematous lesions)
Esmaili 2012 (28)	122	17.2% scalp 25.4% face 8.2% palm ans sole 27% oral mucosae 4.1% genital mucosae	7.4% eczematous lesions 19.7% non specific rash
Kridin 2018 (22)	82	22.2% mucosae with DPP4is, 6.5% mucosae without DPP4is	
This study, 2018	312	**61.2% atypical topography** 17.9% head and neck 48.4% palm and sole 18.6% mucosae	**9.0% atypical lesions** 1.0% atrophic scars 4.5% eczematous lesions 5.0% erythematosquamous lesions 2.2% extensive erosive lesions 3 .7% non bullous form

DPP4is, dipeptidyl peptidase 4 inhibitors

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SERMENT

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*

- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*

- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

ABSTRACT

ABSTRACT

Background : Bullous pemphigoid (BP) is the most frequent autoimmune bullous disease and a set of 4 clinical criteria highly consistent with BP diagnosis has been previously validated. However, clinical spectrum of diseases may change over time and recently a number of unusual clinical features seem to have emerged in some BP patients. Accordingly a retrospective study was designed to reappraise the validity of the aforementioned criteria over time in a large cohort of well-documented BP in this setting of a possibly increasing frequency of atypical features and to describe possible new clinical patterns of BP and their potential time-related occurrence over the last two decades.

Patients and methods : Well-documented BP patients diagnosed between January 2001 and April 2017 were included in this retrospective analysis. The following data were collected : baseline characteristics of patients, extent of the disease, distribution and type of cutaneous lesions, presence of mucous lesions, presence of at least one atypical clinical (topographical or lesional) feature, presence or absence of at least 3 of the prior validated diagnostic clinical criteria. In order to identify a possible time-related shift of clinical features, data from 4 chronological groups of 4 years (G1 to G4) were statistically compared.

Results : 312 patients were included and analyzed. At least 3 of the 4 classical criteria were present in 278 patients (89.1%), but with a trend toward a steady decrease of relevance over time (G1 93.0% vs G4 83.8%, p 0.067). The most frequent missing criteria were absence of mucosal involvement followed by absence of head and neck involvement. 206 patients (66.0%) displayed at least one atypical clinical feature and chronological analysis confirmed a significant time-related increase of atypical pattern frequency (G1 57.9%, G4 73.7%, p 0.041). Head and neck, palmoplantar, mucosae involvement were observed in 56 (17.9%), 151 (48.4%) and 58 (18.6%) patients respectively, with an upward, although non significant trend between G1 and G4 (p 0.071, p 0.088, p 0.094 for these 3 items respectively).

Discussion : Clinical presentation of BP seems to have evolved over time with a progressively higher proportion of atypical topographical and/or lesional characteristics, mainly regarding mucous membrane, head and neck and palmo-plantar involvement. This shift probably underlies the progressive reduction of the percentage of BP patients fulfilling at least 3 of the 4 BP previously validated diagnostic criteria even though these criteria remain robust in our study. Environnemental causes, mainly drugs might affect clinical presentation of BP since a higher frequency of mucosal lesions has been recently reported in dipeptidyl peptidase 4 inhibitors (DPP4is)-induced BP compared to other BP patients.

Key words: bullous pemphigoid, atypical presentation, clinical patterns