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Clinical presentations and diagnostic delay in bullous pemphigoid: a prospective nationwide cohort

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Summary

Background: Prospective systematic analyses of the clinical presentation of bullous pemphigoid (BP) are lacking. Little is known about the time required for its diagnosis. Knowledge of the disease spectrum is important for diagnosis, management and inclusion of patients in therapeutic trials.

Objectives: The primary aims of the study were :1) to characterize the clinical features of BP at time of diagnosis; and2) to assess the diagnostic delay in BP and its impact on prognosis

Methods: All new cases of BP diagnosed in Switzerland between 1 January 2001 and 31 December 2002 were prospectively registered by means of a standardized data collection form.

Results: 117 patients with BP were included in the study. 97cases (82.9%) had typical features with vesicles, blisters and/or erosions at time of diagnosis, while in the remaining cases (17.1%) only excoriations, eczematous and/or urticarial infiltrated lesions were observed. 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. Diagnosis was made after a mean of 6.1 months after the first symptoms. In patients, in whom the diagnostic delay was 4 months or more (defined as late diagnosis group), lesions were more often limited to one body area. The type of lesions did not affect the diagnostic delay. Diagnosis was made more rapidly in patients with limb involvement compared to those without. The calculated mortality rate in the early and late diagnosis group was 18.9% and 17.9 %,respectively, without significant difference.

Conclusion: BP often presents with bullous lesions at time of diagnosis after a mean diagnostic delay of 6 months. Nevertheless, up to 20% of patients lack obvious blistering and postbullous erosions, mimicking thus a variety of inflammatory dermatoses. Localized disease is associated with an increased diagnostic delay, which has however no impact on prognosis.

Introduction

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering dermatosis of the skin.^{1,2} It is characterized by the presence of circulating IgG autoantibodies to BP180 (also called BPAG2 or type XVII collagen) and BP230 (BPAG1-e), two molecular components of the hemidesmosomes, junctional adhesion structures in stratified epithelia.^{1,3} These autoantibodies have been demonstrated to be directly pathogenic by triggering an inflammatory cascade that lead to tissue damage and, ultimately, to subepidermal blister formation.⁴⁻⁶

BP is characteristically a disease of the elderly and its diagnosis is usually made in patients aged after the age of 70 years.⁷⁻¹⁰ The annual incidence of BP has been estimated between 4.5 and 14 new cases per million. After the age of 80 years, the estimated incidence significantly increases, up to 150-180 new cases per 1 million per year.⁷⁻¹⁰ A retrospective study from the U.K as well as data from France described nevertheless a clear trend for an increase of the incidence of BP in the last two decades.^{11,12}

BP typically presents with a generalized blistering eruption associated with eczematous and/or urticarial infiltrated lesions, with frank vesicles and blisters. Lesions predominantly affect the inner parts of the limbs and the trunk, while mucous membranes, face and neck region are typically spared. Diagnosis is usually based on a combination of criteria, including typical clinical features and positive immunopathological findings.^{13,14} Nevertheless, a number of “atypical” variants with either localized bullous lesions or “non-bullous” presentations have been described under a variety of terms, such as vesicular, dyshidrotic, eczematous, pigmented, prurigo-like, nodular, ecthyma-like, or erythrodermic pemphigoid.¹³⁻¹⁷ These atypical variants often represent a diagnostic challenge.

Besides a significant impact on the quality of life related to severe and the cutaneous lesions, BP has a considerable mortality rate. The latter has been estimated, between 12% and 40% in the first year.¹⁸⁻²⁰

Despite the relative frequency of BP, there are only few and almost invariably retrospective studies which have assessed the spectrum of clinical presentations of BP in affected patients at time of diagnosis as well as the diagnostic delay. Prompt diagnosis of BP in an early stage of the disease may affect both the quality of life of affected patients as well as the prognosis. Finally, future therapeutic interventions should also consider the clinical heterogeneity of BP.

In this prospective nation-wide study encompassing all newly diagnosed cases of BP, we have systematically studied the clinical features of BP patients at time of diagnosis and further assessed the time required to diagnosis after onset of the first symptoms related to BP.

Finally, we have assessed whether diagnostic delay had an impact on mortality of affected patients.

Materials and methods

The primary aims of this prospective study were: 1) to characterize the clinical features of BP in affected patients at the time of diagnosis; and 2) to precisely assess the delay in diagnosis, that is, the interval between the development of the first symptoms and the time of definite diagnosis, and its impact on mortality.

From January 1st 2001 to December 31st 2002, all patients with a new diagnosis of BP were recruited and prospectively collected by using a standardized, anonymized data collection form by

all dermatology clinics, dermatologists and specialized laboratories routinely performing immunopathological studies for the diagnosis of autoimmune blistering disease in Switzerland. The study was approved by the local Ethic Committee of the steering team in Geneva (G.M., L.B.). Diagnosis of BP was based on clinical criteria (typical or consistent clinical features, itch), compatible histological findings as well as positive immunopathological studies, including direct IF microscopy, indirect IF microscopy as well as ELISA-BP180 and BP230, as detailed elsewhere.^{9,13,14} In the two-year time frame of the study, 140 new cases of BP were nationwide diagnosed. Detailed information about clinical features and their temporal evolution in affected patients were ultimately available for 117 cases (83%). In subjects presenting with dementia and cognitive problems, clinical history and symptoms were provided by the managing physicians. The patients, clinical details of which were missing, were excluded. The latter almost invariably encompassed cases identified by private immunopathology laboratories. Clinical features, including type, localisation and extension of lesions were noted. The clinical presentation was assessed based on the presence of vesicular, bullous or postbullous erosive lesions as well as “non-specific” lesions, including erythema, eczematous lesions, infiltrated papular and urticaria-like lesions, papulonodular and /or excoriated lesions. The clinical distribution of the lesions was evaluated according to the involvement of five different areas: head, trunk, (upper and lower) limbs, both hands and feet, and mucosae (oral, genital, nasal, ocular and or anal mucosa). Extent of the disease was thus evaluated based on the number of affected areas.

The diagnostic delay was defined as the time elapsed between the development of the first clinical manifestations (skin lesions and/or itch) and the date of definite diagnosis based on immunopathological studies. To identify potential differences of the clinical presentation and prognosis of BP in affected patients according to the diagnostic delay, we decided to put a cut-off of fourth months to define an “early” and a “late” diagnosis group. This cut-off represented *This* cut-off represented approximately the upper tertile of the diagnostic delay range in months and was selected to better identify distinctive clinical features of patients with a delayed diagnosis and their prognosis.

Finally, we noted the setting in which diagnosis was made, such as in private practice, regional or tertiary university hospitals.

The categorical variables were described by counts and percentage. The age was described by the median and the interquartile interval. Comparisons between early and late diagnosis groups were

performed by Chi-squared tests (or Fisher exact test when an expected count was lower than 5) except for the age, which was compared by using a Mann-Whitney test. In each group (early and late diagnosis), the number of affected sites was compared by using a McNemar test. The diagnostic delay was also analyzed as a continuous variable. The median diagnostic delays were reported and the association with the affected body sites was tested by Mann-Whitney test. The probability of death one year after the diagnosis was assessed by dividing the counts of patients dead in the first year by the number of patients not lost-of-follow up at the end of the year. Since the exact date of death and of the last follow up was unknown, the Kaplan-Meier estimator could not be used. The relative risk was assessed by the ratio of these probabilities.

Results

A total of 117 patients were included in the study. There were 70 (59.8%) female and 47 (40.2%) male patients. The youngest affected patient was 8-year-old, while the oldest 97-year-old. The mean age was 78.2 years, while the median age was 80 years (interval interquartile = [73;87], range [8;97]). No data about socioeconomic status were available.

The clinical features in affected patients at time of diagnosis were highly variable with regard to the morphology, distribution and extent of the lesions. In 97 (82.9%) of 117 patients there were frank vesicles, blistering and/or postbullous erosions. In contrast, in 20 (17.1%) of 117 cases diagnosis of BP was made without obvious blistering or postbullous erosions. In the latter group, patients presented with either eczematous lesions (n=12, 39%) or erythematous papules and plaques (n=11, 36%). In a few patients, lesions were further described as urticaria-like (n=2, 6%) and erythema multiforme-like (n=2, 6%). Finally, in some patients, milia (n=1, 3%) and atrophic scarring (n=3, 10%) were also noted.

With regard to the distribution of the lesions, the two most frequently affected body areas were limbs and trunk in 103 (88%) and in 89 (75.2%) of the 117 cases, respectively. Twenty-three patients (19.6%) exhibited palmo-plantar involvement. In two of these cases, limbs were also affected, whereas in the other 21 cases lesions concomitantly affected also limbs and trunk. Isolated palmo-plantar involvement was thus not present. In 23 (19.6%) patients lesions were found also on the neck and/or head. In these cases, lesions were also often associated with both limbs and trunk (in 17 of 23 cases, 74%). In only two cases, head and neck regions alone were affected. Finally, in 17 (14.5%) cases, there was mucosal involvement. The latter was limited to

the oral cavity in 16 (94.1%) of 17 cases. In three (7.1%) of these 17 patients, genital mucosa was also involved. In one single case genital mucosa represented the only affected mucosal site (Fig. 1). In almost half of the patients (n=54; 46.2 %) two body regions were concomitantly affected. The remaining 27 (23.1%), 25 (21.4%) and 11 (9.4%) patients had one, three or more than three areas affected at time of diagnosis (Fig. 2). With regard to the time required for definite diagnosis, the latter was made after a mean of 6.1 months and a median of 2.3 months following the development of the first symptoms. The interval ranged from a minimum of two days to a maximum of 6 years (Fig. 3).

Based on a cut-off value of 4 months, we next analyzed whether the clinical presentation of patients in which the diagnosis was made within four months (< 4 months = *early diagnosis*) was different from that of the group in which diagnosis was made after a diagnostic delay of more than four months (≥ 4 months = *late diagnosis*). This cut-off represented approximately the upper tertile of the diagnostic delay range in months (31.6% of patients had a delay greater than 4 months) and was selected to better identify distinctive clinical features of patients with a delayed diagnosis and their prognosis.

In the *early diagnosis* group (n= 80; 68.4%), the clinical presentation was in 68 (85%) cases characterized by the presence of frank vesicles and blistering, while in 12 patients (15%) there were no specific features. In 46 patients (57.5%) two areas were affected, while 15 (18.8%) and 5 (6.3%) patients had 3 areas and more than three areas affected, respectively. In only 14 cases (17.5%) lesions were limited to one region. Specifically, in 76 (95%), in 63 (78.8%), 13 (16.3%) and in 11 case (13.8%) lesions were present on the limbs, trunk, hands /feet, and head, respectively. Finally, 9 patients (11.3%) had mucosal involvement (Fig. 1).

The lesions on the limbs were significantly more frequent than lesions on trunk ($p=0.006$). The frequency of lesions on hands /feet, head and of mucosae was not significantly different from each other ($p=0.81$), but was significantly lower than that on trunk ($p<0.01$).

The *late diagnosis* group encompassed 37 patients (31.6% of the total 117). In 29 cases (78.4%) typical bullous lesions were present, whereas in 8 (21.6%) “non-specific” lesions were noted. In 13 (35.1%) patients, the disease was restricted to one area, while 8 (21.6%), 10 (27%) and 6 (16.2%) had two, three or more than 3 involved areas. Twenty-seven (73%) patients had lesions on the limbs , 26 (70.3%) on the trunk, 12 (32.4%) on the head, 10 (27%) on the palmo-plantar region,

and, finally 8 (21.6%) had mucosal involvement (Fig. 2). In this group, extremities and trunk were similarly affected ($p=0.001$), while trunk was again more frequently involved than hands/feet ($p<0.001$). There was no significant difference in the frequency of involvement of hands/feet *versus* head ($p=0.79$) as well as of head *versus* mucosae ($p=0.42$).

When characteristics of the early diagnosis group were compared to those of the late diagnosis group, there was a trend for an older age in the early diagnosis group (median age 82 years *versus* 78 years; $p=0.07$), while the proportion of women was similar in both groups (58.8% and 62.2% in early and late diagnosis group, respectively, $p=0.88$). The type of cutaneous lesions, including presence of bullous lesions, did not differ between the two groups (85% *versus* 78.4% in the early and late diagnosis group, respectively; $p=0.43$). Nevertheless, three significant differences were observed. In the early diagnosis group, limbs were more frequently affected (95% *versus* 73%, $p=0.001$), while head involvement was less frequently observed compared to the late diagnosis group (13.8% *versus* 32.4%, $p=0.02$). Furthermore, disease limited to one single body site was more frequently observed in the late diagnosis group than in the early diagnosis group (35.1% *versus* 17.5%, $p=0.002$).

In another set of analyses, we compared whether the involvement of a distinct site affected the diagnostic delay. The results show that diagnosis of BP was made more rapidly in patients with limb involvement compared to those without [median 2.2 months *versus* 5.9 months, $p=0.008$]. In contrast, diagnostic delay was longer in patients presenting with head involvement compared to those without [median 4 months *versus* 2.1 month, $p=0.002$] (Table 1).

We next analyzed the impact of the diagnostic delay on the first year mortality after diagnosis in the two groups. Follow up and outcome measures were missing in 33.8% and in 24.3 % of the cases of the early and late diagnosis group, respectively. The calculated mortality rate was 18.9% and 17.9 %, respectively ($RR=0.95$ [0.59;1.53]), without significant difference.

Finally, we assessed in which setting diagnosis of BP was made. In > 90% of the cases ($n=107$; 91.5%) diagnosis was made by either a board-certified dermatologist in either an office practice ($n=41$; 35%) or in a tertiary referral centre ($n=66$; 56.4%). Finally, 6 cases (5.1%) were diagnosed by a general physician, while 4 (3.4%) patients were assessed in a regional hospital centre without dermatologists.

Discussion

Our prospective cohort encompassing 117 cases of BP indicates that more than 80% of the affected patients present with vesicles and tense bullae at time of diagnosis. Nonetheless, 17% of our patients show “non-specific” features, such as excoriations, infiltrated urticarial or eczematous lesions without obvious blistering or postbullous erosions. Hence, in these cases, the presentation closely mimics a variety of other inflammatory dermatoses, such as contact dermatitis, toxic drug reaction, ectoparasitoses, fixed urticaria or chronic prurigo.

Our study further shows that in BP lesions predominate on the limbs and trunk in more than 75% of cases. Involvement of a third area, such as head/neck and the palmo-plantar region is also noted in almost 20% of cases. Mucosae, most invariably the oral mucosa, are affected in up to 15% of patients.

Previous seminal studies underscored that *patients with bona fide* (in the absence of immunopathological studies) *or confirmed* BP commonly start BP with non-specific urticarial or eczematous lesions, which may last for months before development of blisters.²¹⁻²⁶ In the largest retrospective study available encompassing 53 patients, urticaria-like plaques, eczema-like and or dermatitis herpetiformis-like lesions were present during the prodromal phase of BP.²⁵

In this non-bullous phase diagnosis of BP critically relies on positive direct IF microscopy studies. In fact, the demonstration of circulating autoantibodies against BP180 and/or BP230 should be not regarded as diagnostic for BP in the absence of positive direct IF studies.^{13,14,26-29}

Diagnosis of BP can be made with high specificity and sensitivity in patients with linear IgG and/or C3 deposits along the dermo-epidermal junction when three of 4 clinical criteria are present: age greater than 70 years, absence of atrophic scars, absence of mucosal involvement and absence of predominant bullous lesions on the neck and head.^{30,31} In contrast to these latter reports, we have here noted that almost 20% and 15% of the BP patients have neck/head involvement and mucosal lesions, respectively. Future studies are needed to confirm whether presence of neck and head involvement really represents a criterion useful to dismiss the diagnosis of BP.

Our findings show that diagnosis of BP is made after a mean of 6.1 months and a median of 2.3 months after the development of the first symptoms. Specifically, up to 70% (n= 80) of the case were diagnosed early within four months after the first symptoms, while in the remaining cases it

was delayed up to several months. To gain better insight into these differences, we compared the clinical features in an early diagnosis group with those of a late diagnosis group with a cut-off of fourth months. This cut-off, representing the upper quartile of the diagnostic delay range, was chosen to better identify distinctive clinical features of patients with a delayed diagnosis and their prognosis. Three significant differences were observed. First, involvement of the limbs was more frequently observed in the early than in the late diagnosis group. Diagnosis of BP was made more rapidly in patients with limb involvement compared to those without limbs involvement (Table 1). Furthermore, in the late diagnosis group, lesions were more often limited to one body area compared to the early diagnosis group, in which two or more sites were more frequently affected (Fig. 2). Diagnostic delay was longer in patients presenting with head involvement compared to those without (Table 1). In contrast, typical features of BP with vesicles and blisters were present in both groups at comparable frequency (85% in early diagnosis group *versus* 78.4% in late diagnosis group, $p=0.43$). These observations suggest that the more localized the disease at first presentation is, the more difficult the diagnosis of BP is. Concomitant involvement of limbs seems to contribute to early diagnosis.

Previous reports described diagnostic delays varying between few weeks to more than one decade in BP, but no systematic prospective analyses are available.^{23,24,27,30,32} One early report described that while in presence of blisters diagnosis is made after about 6 weeks, diagnosis may take up to 6 years when only non-specific lesions are observed.^{24,27} In the present study, definite diagnosis following the development of the first symptoms was made after a mean of 6.1 months and a median of 2.3 months. Diagnostic delay appeared to be more dependent on the extent of the disease (as inferred from the number of affected sites) rather than on the presence of frank blistering, although we cannot exclude the possibility that some patients without blisters have not been diagnosed at all. A recent retrospective study assessing the diagnostic delay in two different groups of encompassing 341 and 322 cases reported a mean diagnostic delay 61 and 91 days, respectively, with two third of patients being diagnosed within two months.³² In our multicentre European study about the immunological profile of 43 BP patients the mean disease duration prior diagnosis was three months, an interval very close to that observed in the present study.³³

Since pruritus and skin lesions of BP have a significant impact on the quality of life of affected patients and should be promptly managed, it is unclear whether the diagnostic delay has an impact on mortality and prognosis. A retrospective analysis of 237 BP patients suggested that generalized cutaneous manifestations constituted a bad prognostic factor with an increased death

rate within 6 months after diagnosis of BP.¹⁸ In contrast, in recent studies, disease extent and severity were not found to constitute a negative prognostic factor, not even as risk factor for a relapse after cessation of therapy.^{19,34}

We have here assessed the first-year mortality rate of BP patients in two distinct group divided based on the diagnostic delay, that is within four months and more than four months (≥ 4 months), respectively. There were no obvious differences in the survival rate at one year between these two groups. Since outcome measures with the follow up were missing in up to one third of the cases within the early diagnosis group, we cannot exclude that in this group some dropouts were related to a fatal outcome (resulting in a first-year mortality higher than that calculated). However, it seems unlikely that an increased diagnostic delay would result in a better outcome. Previous studies have shown that the age- and sex-adjusted mortality was higher in BP than the general population with SMR of two to 15 greater than that expected.²⁰ Specifically, advanced age at diagnosis was a significant factor in the prediction of overall survival. Increased mortality rate was further associated with a poor general condition and presence of neurological diseases.³⁵

Finally, the diagnosis of BP in Switzerland made in more than 90% of cases by either dermatologists working in a private practice or by hospital-based dermatologists. It is well conceivable that the relatively rapid diagnosis of BP within 4 months in up to 70% of patients also reflect the health system in Switzerland, in which the population has enjoyed so far of an outstanding level of medical care and an unconstrained choice of provider including access to dermatologists. Future studies should assess whether limitation to the access to dermatologists has an impact on the diagnostic delays of BP and validate our overall findings in a larger cohort of patients from different geographical areas.

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Figure legends

Fig. 1. Bullous pemphigoid. Body sites involvement with further analysis of the distribution of the lesions

Fig. 2. Bullous pemphigoid. Number of affected body sites in the entire studied population as well as in the early and late diagnosis group.

Fig. 3. Time delay of diagnosis of bullous pemphigoid. Absolute number of diagnosed cases according to the months required to make the diagnosis of bullous pemphigoid after development of the first symptoms are indicated.

Table 1. Assessment whether involvement of a specific body site affects the diagnostic delay in patients with bullous pemphigoid. Limbs and head involvement in affected patients are associated with a shorter and a longer diagnostic delay, respectively (Mann-Whitney test).

		Diagnostic delay (months)			
		No.	Median	Range	p-values
<i>Limbs</i>	No	14	5.9	[0.0;46.5]	0.008
	Yes	103	2.2	[0.0;73.2]	
<i>Trunk</i>	No	28	3.2	[0.0;46.5]	0.23
	Yes	89	2.2	[0.0;73.2]	
<i>Hands/feets</i>	No	94	2.3	[0.0;73.2]	0.72
	Yes	23	2.3	[0.1;40.4]	
<i>Head</i>	No	94	2.1	[0.0;46.5]	0.02
	Yes	23	4	[0.1;73.2]	
<i>Mucosal involvment</i>	No	100	2.2	[0.0;73.2]	0.25
	Yes	17	3.5	[0.0;46.5]	





