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

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Conflicts of interest
None declared.

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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.

Objective The primary aims of the study were: (i) to characterize the clinical features of BP at time of diagnosis; and (ii) 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 One hundred-seventeen patients with BP were included in the study. 97 cases (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.

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering dermatosis of the skin.1,3 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 leads to tissue damage and, ultimately, to subepidermal blister formation.4–6

Bullous pemphigoid is characteristically a disease of the elderly and its diagnosis is usually made in patients aged > 70 years.7–10 The annual incidence of BP has been estimated to be between 4.5 and 14 new cases per million. After the age of 80 years, the estimated incidence significantly increases, with up to 150–180 new cases per 1 million per year.7–10 A retrospective study from the U.K. and data from France described a clear trend for an increase in the incidence of BP in the past two decades.11,12

Bullous pemphigoid 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, and face and neck regions are typically spared. Diagnosis is usually based on a combination of criteria, including typical clinical features and positive immunopathological findings. Nevertheless, a number of ‘atypical’ variants with either localized bullous lesions or ‘nonspecific’ presentations have been described under a variety of terms, such as vesicular, dyshidrotic, eczematous, pigmented, prurigo-like, nodular, ecthyma-like or erythrodermic pemphigoid. These atypical variants often represent a diagnostic challenge.

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

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

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

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

Materials and methods

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

From 1 January 2001 to 31 December 2002, all patients with a new diagnosis of BP were recruited and prospectively collected using a standardized, anonymized data collection form in all dermatology clinics, and from dermatologists and specialized laboratories routinely performing immunopathological studies for the diagnosis of autoimmune blistering disease in Switzerland. The study was approved by the local ethics 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 and positive immunopathological studies, including direct immunofluorescence (IF) microscopy, indirect IF microscopy and enzyme-linked immunosorbent assays (ELISA) for BP180 and BP230, as detailed elsewhere. In the 2-year time frame of the study, 140 new cases of BP were diagnosed nationwide. Detailed information about clinical features and their temporal evolution in affected patients was 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 whose clinical details were missing were excluded; these were almost invariably cases identified by private immunopathology laboratories. Clinical features, including type, localization and extent of lesions were noted. The clinical presentation was assessed based on the presence of vesicular, bullous or post-bullous erosive lesions and on ‘nonspecific’ lesions, including erythema, eczematous lesions, infiltrated papular and urticarial-like lesions, and 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 of BP in affected patients according to the diagnostic delay, we decided on a cut-off of 4 months to define an ‘early’ and a ‘late’ diagnosis group. 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 the diagnosis was made, such as in private practice, or 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 using χ² tests (or Fisher’s exact test when an expected count was < 5) except for the age, which was compared using a Mann–Whitney test. In each group (early and late diagnosis), the number of affected sites was compared by using McNemar’s test. The diagnostic delay was also analysed as a continuous variable. The median diagnostic delays were reported and the association with the affected body sites was tested by the Mann–Whitney test. The probability of death 1 year after the diagnosis was assessed by dividing the counts of patients who died in the first year by the number of patients not lost to follow-up at the end of the year. As the exact date of death and of the last follow-up were unknown, a Kaplan–Meier estimator could not be used. The relative risk (RR) 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 aged 8 years, while the oldest was aged 97 years. The mean age was 78.2 years, and the median
age was 80 years (interquartile interval 73–87, range 8–97). No data about socioeconomic status were available.

The clinical features in affected patients at the 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 the 117 cases, a diagnosis of BP was made without obvious blistering or postbullous erosions. In the latter group, patients presented with either eczematous lesions (n = 12, 60%) or erythematous papules and plaques (n = 11, 55%). In a few patients, lesions were further described as urticaria-like (n = 2, 10%) and erythema multiforme-like (n = 2, 10%). Finally, in some patients, milia (n = 1, 5%) and atrophic scarring (n = 3, 15%) 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 (76%) of the 117 cases, respectively. Twenty-three patients (19.6%) exhibited palmar/plantar involvement. In two of these cases, limbs were also affected, whereas in the other 21 cases lesions concomitantly affected limbs and trunk. Isolated palmar/plantar involvement was thus not present. In 23 (19.6%) patients, lesions were also found 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%) of 17 cases. In 3 (17.6%) 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 the time of diagnosis, respectively (Fig. 2). With regard to the time required for a 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 2 days to a maximum of 6 years (Fig. 3).

Based on a cut-off value of 4 months, we next analysed whether the clinical presentation of patients in which the diagnosis was made within 4 months (< 4 months = early diagnosis) was different from that of the group in which the diagnosis was made after a diagnostic delay of more than 4 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 > 4 months) and was selected to identify more clearly the distinctive clinical features of patients with a delayed diagnosis and their prognosis.

In the early diagnosis group (n = 80, 68.4%), the clinical presentation in 68 (85%) cases was characterized by the presence of frank vesicles and blistering, while in 12 patients (15%) there were no specific features. In 46 patients (57%), two areas were affected, while 15 (19%) and 5 (6%) patients had three areas and more than three areas affected, respectively. In only 14 cases (17%), lesions were limited to one region. Specifically, in 76 (95%), 63 (79%), 13 (16%) and 11 cases (14%), lesions were present on the limbs, trunk, hands/feet and head, respectively. Finally, nine patients (11%) had mucosal involvement (Fig. 1). Lesions on the limbs were significantly more frequent than lesions on the trunk (P = 0.006). The frequency of lesions on the hands/feet, head and mucosa was not significantly different from each other (P = 0.81), but was significantly lower than that on the trunk (P < 0.01).

The late diagnosis group comprised 37 patients (31.6% of the total 117). In 29 cases (78%), typical bullous lesions were present, whereas in 8 (22%), ‘nonspecific’ lesions were noted. In 13 (35%) patients, the disease was restricted to one area, while 8 (22%), 10 (27%) and 6 (16%) had two, three or more than three involved areas, respectively. Twenty-seven (73%) patients had lesions on the limbs, 26 (70%) on the
trunk, 12 (32%) on the head, 10 (27%) on the palmoplantar region and, finally, 8 (22%) had mucosal involvement (Fig. 2). In this group, extremities and trunk were similarly affected ($P = 0.001$), while the trunk was again more frequently involved than the hands/feet ($P < 0.001$). There was no significant difference in the frequency of involvement of hands/feet vs. head ($P = 0.79$) or of head vs. mucosae ($P = 0.42$).

When characteristics of the early diagnosis group were compared with those of the late diagnosis group, there was a trend for an older age in the early diagnosis group (median age 82 years vs. 78 years; $P = 0.07$), while the trunk was again more frequently involved than the hands/feet ($P < 0.001$). There was no significant difference in the frequency of involvement of hands/feet vs. head ($P = 0.79$) or of head vs. mucosae ($P = 0.42$). Nevertheless, three significant differences were observed. In the early diagnosis group, limbs were more frequently affected (95% vs. 73%; $P = 0.001$), while head involvement was less frequently observed compared with the late diagnosis group (13.8% vs. 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% vs. 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 with those without (median 2.2 months vs. 5.9 months; $P = 0.008$). In contrast, diagnostic delay was longer in patients presenting with head involvement compared with those without (median 4 months vs. 2.1 month; $P = 0.02$) (Table 1).

We next analysed 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 groups, 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 a board-certified dermatologist either in an office practice ($n = 41, 35$%) or in a tertiary referral centre ($n = 66, 56.4$%). Finally, six 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 comprising 117 cases of BP indicates that > 80% of the affected patients present with vesicles and tense bullae at the time of diagnosis. Nonetheless, 17% of our...
patients showed 'nonspecific' 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, ectoparasitosis, fixed urticaria or chronic prurigo.

Our study further shows that, in BP, lesions predominate on the limbs and trunk in > 75% of cases. Involvement of a third area, such as the head/neck and palmoplantar regions is also noted in almost 20% of cases. Mucosae, almost 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 nonspecific urticarial or eczematous lesions, which may last for months before development of blisters.21–26 In the largest retrospective study available on 53 patients, urticaria-like plaques, eczema-like and/or dermatitis herpetiformis-like lesions were present during the prodromal phase of BP.25

In this nonbullenous 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 dermoepidermal junction when three of four clinical criteria are present: age > 70 years, absence of atrophic scars, absence of mucosal involvement and absence of predominant bullous lesions on the neck and head.26–31 In contrast to these latter reports, we have here noted that almost 20% and 15% of the patients have neck/head involvement and mucosal lesions, respectively. Future studies are needed to confirm whether the presence of neck and head involvement really represents a criterion useful for dismissing 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 4 months of 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 4 months. This cut-off, representing the upper quartile of the diagnostic delay range, was chosen to identify more clearly the distinctive clinical features of patients with a delayed diagnosis and their prognosis. Three significant differences were observed. Firstly, involvement of the limbs was more frequently observed in the early than in the late diagnosis group. A diagnosis of BP was made more rapidly in patients with limb involvement compared with those without limb involvement (Table 1). Secondly, in the late diagnosis group, lesions were more often limited to one body area compared with the early diagnosis group, in which two or more sites were more frequently affected (Fig. 2). Thirdly, diagnostic delay was longer in patients presenting with head involvement compared with 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 vs. 78.4% in late diagnosis group, P = 0.43). These observations suggest that the more localized the disease is at first presentation, the more difficult is the diagnosis of BP. Concomitant involvement of limbs seems to contribute to early diagnosis.

Previous reports described diagnostic delays varying between a 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 the presence of blisters, diagnosis is made after about 6 weeks, diagnosis may take up to 6 years when only nonspecific 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) 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 341 and 322 cases reported a mean diagnostic delay 61 and 91 days, respectively, with two-thirds of patients being diagnosed within 2 months.32 In our multicentre European study on the immunological profile of 43 patients with BP the mean disease duration prior to diagnosis was 3 months, an interval very close to that observed in the present study.33

As 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 patients with BP suggested that generalized cutaneous manifestations constituted a bad prognostic factor with an increased death rate within 6 months of 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 factors for a relapse after cessation of therapy.19,34

We have here assessed the first-year mortality rate of patients with BP in two distinct groups divided according to the diagnostic delay, i.e. within 4 months and 4 months, respectively. There were no obvious differences in the survival rates at 1 year between these two groups. As 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 is higher in patients with BP than in the general population, with a mortality rate 2–15 times greater than that expected.20 Specifically, advanced age at diagnosis is 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.\textsuperscript{35}

Finally, the diagnosis of BP in Switzerland is made in > 90% of cases by dermatologists working in private practice or by hospital-based dermatologists. It is conceivable that the relatively rapid diagnosis of BP within 4 months in up to 70% of patients also reflects the health system in Switzerland, in which the population has enjoyed so far 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 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.

**What's already known about this topic?**

- Although bullous pemphigoid is characteristically associated with an intensely pruritic eruption with widespread blister formation, the presenting features in the early stages or in atypical variants of the disease may be polymorphous and misleading.
- To date, no study exists which has systematically assessed the clinical presentation of bullous pemphigoid at the time of diagnosis and whether distinct features affect the diagnostic delay and the overall prognosis.

**What does this study add?**

- We prospectively assessed in a cohort of patients the features of bullous pemphigoid at the time of diagnosis.
- The majority of patients show typical features. However, up to 20% of patients present only with excoriated, eczematous or urticarial lesions and lack obvious blistering and postbullous erosions at the time of diagnosis.
- Localized disease is associated with an increased diagnostic delay. The latter has no impact on the first-year mortality.

**References**


