Prevalence and presumptive triggers of localized bullous pemphigoid

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Abstract

Bullous pemphigoid (BP) is an autoimmune skin disease, caused by autoantibodies to BP180 and/or BP230. While both these autoantigens are expressed in the entire skin, only some parts of the body become affected. Rare clinical observations indicate that BP may also manifest locally, usually following exposure to triggers. Here, we evaluated the occurrence and potential triggers of localized BP (LBP) in a cohort of 285 BP patients. Medical records of all BP patients hospitalized between 2009 and 2019 were reviewed. In 7/285 BP patients, a localized variant was identified. In 5/7 LBP patients, the disease remained local, while in 2/7 patients, an initial LBP subsequently spread. All cases were preceded by presumptive triggers, including previously described triggers and bacterial infections. Overall, LBP is rare. LBP, however, might be underdiagnosed and should thus be considered in the differential diagnosis, particularly when trigger factors preceded.

KEYWORDS
bullous pemphigoid, infection, localized bullous pemphigoid, prevalence, triggers in bullous pemphigoid

1 | INTRODUCTION

Pemphigoid diseases are a group of autoimmune bullous dermatoses (AIBD) caused by autoantibodies binding to distinct structural proteins of the dermal–epidermal junction.1 Within this group, bullous pemphigoid (BP) is the most frequent and characterized by autoantibodies targeting the hemidesmosomal proteins BP180 (type XVII collagen, COL17) and/or BP230.1 The vast majority of BP patients show a generalized disease. Less frequently, skin lesions may be restricted to one or a few sites, for which the term localized BP (LBP) was coined. Presumptive triggers that have been described to precede the onset of LBP include radiotherapy, thermal and chemical irritation, ultraviolet (UV) and photodynamic therapy, and local injury, such as pressure and surgical treatments.2–8 Despite these insights, scant data on the prevalence of LBP has been reported. To address this knowledge gap, we retrospectively evaluated the prevalence of LBP.

2 | METHODS AND RESULTS

This study was performed at the Department of Dermatology, University of Lübeck, Germany. Between January 2009 and April 2019, a total of 285 hospitalized patients with the confirmed diagnosis of BP were identified. For this purpose, the database of hospitalized patients was searched for the International Classification of Diseases, 10th Revision (ICD-10) code L12.0. Next, in all patients with the ICD-10 code L12.0, BP was validated based on: (i) a suggestive clinical presentation; (ii) tissue-bound immunoglobulin (Ig) G and/or C3 as detected by routine direct immunofluorescence (IF)
microscopy; and (iii) circulating autoantibodies binding to the epidermal side of 1 mmol/L NaCl-split normal human skin and/or monkey esophagus by indirect IF microscopy and/or presence of IgG reactivity to BP180 and/or BP230 as identified by enzyme-linked immunosorbent assay (ELISA; Euroimmun). Based on a review of the patients’ charts, we determined the prevalence of LBP and if LBP was preceded by any presumptive trigger. We defined LBP as the initial occurrence of BP at a restricted body site, that either remained localized or subsequently spread to other sites. In order to distinguish between LBP from initial lesions in BP, LBP was only considered if BP remained localized for at least 3 months. Charts were also reviewed for the development of typical generalized BP, especially during hospitalization and after the initial diagnosis of LBP, and for presence of presumptive trigger factors preceding the onset of LBP. This investigation was reviewed and approved by the ethics committee of the University of Lübeck (AZ 20-068). The patients in this manuscript gave written informed consent to publication of their case details.

In total, 7/285 (2.5%) BP patients presented with LBP. The mean age (years ± SD) of the patients with LBP was 68.1 ± 8.2 years with a female : male ratio of 2:5:1. In 5/7 LBP patients, BP solely manifested locally and did not spread to any other skin sites during the follow-up period of 3–12 months (mean, 7 months; median, 5 months; patients 1–2 and 5–7; Table 1). In two patients (3 and 4), the initially localized disease subsequently spread to other anatomical regions. IgG and/or C3 deposits in perilesional skin biopsies were detected in all patients. In more detail, IgG deposits were detected in 5/7 patients, and in all seven patients, C3 deposition was noted. In indirect IF microscopy using human salt-split skin, circulating autoantibodies binding to the blister roof were detected in all patients, while binding to monkey esophagus was observed in 4/7 cases (Table 1). Regarding the specificity of circulating autoantibodies, 6/7 patients had anti-BP180 NC16A autoantibodies, and in 1/7 patients, autoantibodies targeting BP230 were detected. Of note, all cases of LBP were preceded by presumptive triggers, including mechanical irritation (i.e., surgery, presence of stoma or percutaneous endoscopic gastrostomy [PEG] tube), radiotherapy, lymphatic stasis, and/or bacterial infections.

Patient 1 with no previous history of BP was referred for the treatment of refractory blisters and erosions, located around a stoma at the upper abdomen. BP was among the differential diagnoses, and was subsequently confirmed (Table 1). The stoma surrounding was treated with clobetasol propionate solution and skin lesions improved. Patient 2 underwent radiation of the left axilla for treatment of a metastatic lung cancer. Several days after first radiotherapy with a total of 57 Gy applied, multiple tense blisters appeared which were strictly located at the radiation site. BP was diagnosed (Table 1, Figure 1). Topical treatment with clobetasol propionate improved the skin lesion within weeks. Patient 3 reported the development of a solitary tense blister at a scar 2 months after lipoma surgery. After 3 months, generalized erythema and pruritic blisters developed. After diagnosis of BP, based on positive direct and indirect IF microscopy as well as the detection of BP180 autoantibodies, topical clobetasol propionate and systemic dapsone treatment (50 mg/day) were initiated. Subsequently, skin lesions resolved during hospitalization. Patient 4 was diagnosed with oral carcinoma and underwent surgery and radiation. During this time period, a PEG tube was inserted. After completing radiotherapy of the right neck, she noticed blisters at the site of radiation. Approximately 1.5 years later, she developed persistent blisters at the surgical scar on the left arm after autologous graft removal for plastic reconstruction. Additionally, this patient developed blisters near the PEG tube and on both feet that subsequently spread to the proximal lower extremities. Diagnosis of BP was confirmed by positive direct and indirect IF microscopy, as well as detection of circulating BP180 autoantibodies. Collectively, in this patient, BP was potentially triggered by radiotherapy, scarring, as well as mechanical irritation (Figure 1). Patient 5 had a severe lymphatic edema of the left arm following total mastectomy due to breast cancer. She was referred because of refractory erythematous plaques and blisters on the left arm. BP was diagnosed (Table 1) and topical treatment with clobetasol propionate and lymphatic drainage was initiated. This led to an improvement of skin lesions within several weeks. Patient 6 acutely developed multiple blisters of the feet. Preceding antifungal and anti-inflammatory topical treatment had not influenced the blistering. Positive direct and indirect IF microscopy confirmed BP. Microbiologic samples displayed Gram-negative and -positive bacteria, and bacterial culture finally revealed a predominance of *Staphylococcus aureus*. Treatment with piperacillin plus tazobactam in combination with locally applied polyhexanide led to a clearance of skin lesions within 3 weeks. Patient 7 was referred for suspected relapse of bullous erysipelas of the left lower extremity. Erysipelas of the left leg had previously been successfully treated with systemic i.v. antibiotics. However, 5 days after clinically resolved skin inflammation, she developed blisters, erosions, and erythema of the left foot, and the left lower extremity relapsed. BP was confirmed by direct and indirect IF microscopy and ELISA. Topical clobetasol propionate led to an improvement of the skin lesions within 3 weeks.

3 | DISCUSSION

We here report a relatively low prevalence (2.5%) of LBP in a cohort of 285 BP patients seen at a single academic center. LBP was defined as the occurrence of site-restricted clinical BP lesions in patients with no history of BP. Interestingly, in all cases of LBP, a presumptive trigger preceded the onset. This is in line with previous reports that had described radiotherapy as the most common presumed trigger factor of localized BP, followed by thermal or chemical burns, surgical procedures, UV exposure, colostomy, and urostomy. So far, to the best of our knowledge, bacterial infections (as observed in patients 6 and 7) have not been noted to be a potential trigger for LBP. Interestingly, these observations in patients are in line with current findings in mouse models of experimental pemphigoid diseases. More specifically, in experimental bullous pemphigoid-like inflammatory epidermolysis bullosa acquisita, caused by autoantibodies targeting type VII collagen (COL7), skin sites exposed to slight
| BP patient | Age (years) | Sex | Local trigger | Localization | Subsequent transition into generalized BP | Time from LBP to generalized BP | BP180-NC16A antibodies (U/mL) | BP230 antibodies (U/mL) | Direct IF | Indirect IF: salt-split skin | Indirect IF: monkey esophagus |
|------------|-------------|-----|---------------|--------------|------------------------------------------|-------------------------------|--------------------------------|--------------------------|-------------|--------------------------------|---------------------------------|
| BP1        | 84          | M   | Stoma         | Upper abdomen | No                                       | N/A                           | 44                             | 79                       | Positive (IgG, C3)         | Positive, roof                | Positive, basal membrane zone |
| BP2        | 68          | M   | Axillary radiotherapy | Axilla       | No                                       | N/A                           | Negative                       | Negative                 | Positive (IgG, C3)         | Positive, roof                | Negative                        |
| BP3        | 72          | F   | Surgery       | Upper limb    | Yes                                      | 3 months                      | 300                            | Negative                 | positive (IgG, C3)         | Positive, roof                | Positive, basal membrane zone |
| BP4        | 61          | F   | Radiotherapy surgery, PEG | Neck, upper limb, abdomen | Yes                                      | 1.5 years                    | 135                            | Negative                 | Positive (C3)                | Positive, roof                | Positive, basal membrane zone |
| BP5        | 62          | F   | Lymphedema, surgery | Upper limb    | No                                       | N/A                           | 109                            | Negative                 | Positive (IgG, C3)         | Positive, roof                | Negative                        |
| BP6        | 69          | F   | Bacterial infection | Lower limb    | No                                       | N/A                           | 1172                           | Negative                 | Positive (IgG, C3)         | Positive, roof                | Negative                        |
| BP7        | 61          | F   | Erysipelas    | Lower limb    | No                                       | N/A                           | 660                            | Negative                 | Positive (C3)                | Positive, roof                | Positive, basal membrane zone |

Abbreviations: BP, bullous pemphigoid; IF, immunofluorescence; IgG, immunoglobulin G; LBP, localized bullous pemphigoid; N/A, not applicable; PEG, percutaneous endoscopic gastrostomy.
mechanical irritation experienced a more rapid autoantibody deposition in the skin and a more severe clinical disease manifestation in contrast to sites which were not mechanically irritated.11

Two previous studies addressed the topic of LBP: Chang et al. found 19 patients with localized BP in a cohort of 86 patients, which amounts to a 10-fold higher prevalence as reported herein.12 The reason for this difference is currently unknown; different races in the two studies may partially explain this discrepancy. In another study, an increased reactivity in LBP to BP230 was observed.13 Yet, due to a different focus, LBP was less well defined in this report. In line with this notion, the term LBP is not well defined, which also may explain differences between reports. Thus, we here propose to use the term LBP in BP patients where BP is located at a restricted body site for a minimal duration of 3 months.

Our study is not without limitations. Specifically, the retrospective design might have led to a substantial amount of data loss. Possibly, there are more localized BP cases that may have not been documented due to a lack of awareness. Second, the analysis of outpatients would better account for the transferability of our observations, since often patients with solitary skin lesions and localized BP are not admitted to an academic hospital. Thus, we assume that localized BP is more frequent than the here reported prevalence of 2.5%. Third, in some cases where the diagnosis of BP and presumptive trigger factor were made within a short time frame, like in patients 6 and 7, the “chicken and egg” question may be difficult to address.

Despite these limitations, our study shows a rather higher than expected prevalence of localized BP. This should increase awareness for this condition, and LBP (especially if arising after a trauma) should be considered as a differential diagnosis. Furthermore, unnecessary trauma should be avoided in patients already diagnosed with (generalized) BP to avoid (localized) relapses, since BP poses a significant burden on affected patients and the health-care system.14

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CONFLICT OF INTEREST

Over the past 3 years, R.J.L. has received honoraria and/or research grants from the following companies: Adimirx, Almirall, Amryth, ArgenX, Biotest, Biogen, Euroimmun, Incyte, Immugenetics, Lilly, Novartis, UCB Pharma, Topadur, True North Therapeutics,
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REFERENCES
1. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013;381:320–32.
2. Mai Y, Nishie W, Sato K, Hotta M, Izumi K, Ito K, et al. Bullous pemphigoid triggered by thermal burn under medication with a dipeptidyl peptidase-IV inhibitor: a case report and review of the literature. Front Immunol. 2018;9:542.
3. Duschet P, Schwarz T, Gschnant F. Bullous pemphigoid after radiation therapy. J Am Acad Dermatol. 1988;18:441–4.
4. Dănescu S, Chiorean R, Macovei V, Sitaru C, Baican A. Role of physical factors in the pathogenesis of bullous pemphigoid: case report series and a comprehensive review of the published work. J Dermatol. 2016;43:134–40.
5. Sen BB, Ekiz Ö, Rifaioglu EN, Sen T, Atik E, Dogramaci A, et al. Localized bullous pemphigoid occurring on surgical scars. Indian J Dermatol Venereol Leprol. 2013;79:554.
6. Washio H, Hara H, Suzuki H, Yoshida M, Hashimoto T. Bullous pemphigoid on psoriasis lesions after UVA radiation. Acta Derm Venereol. 2005;85:561–3.
7. Vande Maele DM, Reilly JC. Bullous pemphigoid at colostomy site: report of a case. Dis Colon Rectum. 1997;40:370–1.
8. Batalla A, Peón G, De la Torre C. Localized bullous pemphigoid at urostomy site. Indian J Dermatol Venereol Leprol. 2011;77:625.
9. Saschenbrecker S, Karl I, Komorowski L, Probst C, Dähnrich C, Fechner K, et al. Serological diagnosis of autoimmune bullous skin diseases. Front Immunol. 2019;10:1974.
10. Koga H, Prost-Squarcioni C, Iwata H, Jonkman MF, Ludwig RJ, Bieber K, et al. Epidermolysis Bullosa Acquisita: the 2019 update. Front Med. 2018;5:362.
11. Hundt JE, Iwata H, Pieper M, Pfändl R, Bieber K, Zillikens D, et al. Visualization of autoantibodies and neutrophils in vivo identifies novel checkpoints in autoantibody-induced tissue injury. Sci Rep. 2020;10:4509.
12. Chang YT, Liu HN, Wong CK. Bullous pemphigoid–a report of 86 cases from Taiwan. Clin Exp Dermatol. 1996;21:20–2.
13. Thoma-Uszynski S, Uter W, Schwietzke S, Hofmann SC, Hunziker T, Bernard P, et al. BP230- and BP180-specific auto-antibodies in bullous pemphigoid. J Invest Dermatol. 2004;122:1413–22.
14. Ständer S, et al. Assessment of the healthcare costs for pemphigus and bullous pemphigoid patients in an academic center in Germany. Br J Dermatol. 2019;182(5):1296–7.

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