lesional Th17 cells and Treg cells in bullous pemphigoid (BP). Correlations between these cells and disease severity of BP were also evaluated. Immunohistochemical studies showed that both IL-17+ and Foxp3+ cells were present in higher numbers in BP lesions, compared with control skin. IL-17/CD4 ratio in BP was significantly higher than that in PF. Foxp3/CD4 ratio in BP was significantly less than that in either PV or PF. There were no obvious correlations between these cells and disease severity of BP. This study suggests that, compared with pemphigus, BP shows more Th17 cell-related inflammation and less Treg-related regulation.

Key words: bullous pemphigoid – IL-17 – pemphigus foliaceus – pemphigus vulgaris – Th17 – Treg

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Background

Th17 cells, characterized by interleukin-17 (IL-17) production, play crucial roles in the pathogenesis of autoimmune diseases (1). We previously reported that Th17 cells are recruited to the lesional skin in pemphigus vulgaris (PV) and pemphigus foliaceus (PF) (2).

Questions addressed

The aim of the present study was to evaluate the status of lesional Th17 cells and regulatory T cells (Treg) in bullous pemphigoid (BP) by an immunohistochemical approach.

Experimental design

Twenty-five patients (15 men and 10 women, 32–92 years old, average 71.84 years) were allocated to this study. The data on PV and PF were retrieved from our previous study (2). All patients were diagnosed by histological subepidermal blister, linear IgG deposition at the basement membrane zone and detection of circulating autoantibodies to BP antigens by an enzyme-linked immunosorbent assay (ELISA). The severity indexes in the 24 BP cases (unknown in one case), ranged from 2 to 10 (average: 5.875); they were scored according to the diagnostic criteria of the Specified Disease Treatment Research Program by the Japanese Ministry of Health, Labour and Welfare.

The lesional skin biopsy specimens were obtained before treatment. The control skin was taken from three healthy people. One half of each specimen was used for histological analyses. The rest of the specimens were used for immunohistochemical studies; goat anti-human IL-17 antibody (R&D, Minneapolis, MN, USA), mouse anti-human Foxp3 (Abcam, Cambridge, UK) and mouse anti-human CD4 antibodies (Nichirei, Tokyo, Japan) were used as primary antibodies. The counts of IL-17+, possibly Th17 cells (IL-17); Foxp3+, possibly Treg cells (Foxp3) and CD4+ cells (CD4) in two sections were evaluated. The ratio of IL-17+ or Foxp3+ count to CD4+ count (IL17/CD4, Foxp3/CD4, respectively) was also evaluated. IL-17 levels in BP patient sera and control sera were evaluated by ELISA.

We analysed correlations between two groups of data as follows: (a) IL-17/CD4 vs CD4, (b) Foxp3/CD4 vs CD4, (c) IL-17/CD4 vs age at onset (d) Foxp3/CD4 vs age of onset, (e) IL-17/CD4 vs maximal dose of prednisolone (PSLmax: as the index for disease severity), (f) Foxp3/CD4 vs PSLmax, (g) IL-17/CD4 vs BP180 ELISA index (BP180), (h) Foxp3/CD4 vs BP180, (i) IL-17/CD4 vs severity index, (j) Foxp3/CD4 vs severity index, (k) number of eosinophils (Eos) vs IL-17/CD4, (l) Eos vs Foxp3/CD4 and (m) Eos vs severity index.

Results

Both IL-17+ and Foxp3+ cells were present in higher numbers in BP lesions (Fig. 1a–c), compared to control skin (Fig. 1d–f). The IL-17/CD4 ratio in BP was 16.28%, significantly higher than that in PF (1.8%) and not significantly but relatively higher than that in PV (5.2%) (Fig. 1g). The Foxp3/CD4 ratio was 5.52%, which was significantly lower than that in either PV or PF (more than 20%) (Fig. 1h). The Th17/Foxp3 ratio in BP was significantly higher (2.95%) than those in PV and PF (Fig. 1i). The serum IL-17, assessed by ELISA, was significantly higher (3.6-fold) in BP

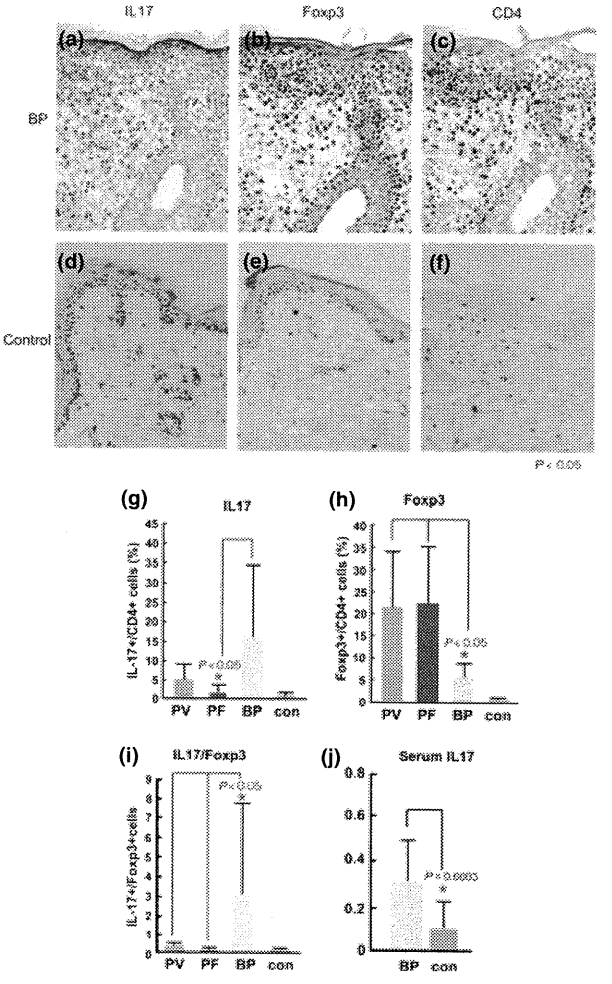

Figure 1. Immunohistochemical studies of lesional skin specimens (a–c) and control skin specimens (d–f). Positively stained lymphocytes were detected by antibodies to IL-17 (a, d), Foxp3 (b, e) and CD4 (c, f). Quantification of the number of IL-17-producing (g), Foxp3-expressing (h) and the ratios of IL-17-producing cells/Foxp3 expressing cells (i) in BP, PV, PF and normal control (con). The significance of the differences was assessed by an unpaired *t*-test. (j) Serum IL-17 levels in BP and normal control. BP, bullous pemphigoid; PV, pemphigus vulgaris; PF, pemphigus foliaceus.

serum than in control serum (Fig. 1j). Although not statistically significant as assessed by Spearman's rank correlation coefficient ($P > 0.05$), some pairs of parameters showed tendencies to correlate, i.e., negative correlations are seen in [IL-17/CD4 vs CD4] (Figure S1a), in [Foxp3/CD4 vs CD4] (Figure S1b) and in [Foxp3/CD4 vs BP180] (Figure S1h). Other pairs showed no correlation (Figure S1c–g, i–m).

Conclusions

This is the first study in which lesional IL-17+ cells and Foxp3+ cells have been quantitatively evaluated in BP. The numbers of Th17 cells were increased in BP and PV skin lesions, but not in PF lesions, while the number of Treg cells in BP lesional skin was significantly smaller than those in PV and PF lesional skin.

The first issue that should be considered is that the numbers of IL-17+ cells were increased in BP and PV, but not in PF. A potential role of Th17 cells in BP was recently suggested (1), because an increased recruitment of IL-17+ cells in the lesional tissue was observed in mucous membrane pemphigoid (MMP), another pemphigoid member (3). Although the role of Th17 cells in the pathogenesis of autoimmune diseases is unresolved, they may be the initiators of diseases (2). Alternatively, Th17 cells may possibly appear in a protective response to maintain epithelial homoeostasis (4). In fact, IL-17 production was induced by keratinocytes in an *in vitro* system (5). If the latter is the case, the more severe disruption in epithelial integrity in BP and PV, when compared with PF, may increase the number of regional Th17 cells.

The second intriguing issue is that the number of Foxp3+ cells in BP was significantly smaller than that in pemphigus groups. In fact, a decreased number or impaired functions of circulating Treg cells in several autoimmune diseases have been reported (6). Therefore, the decrease in Treg cells in BP is plausible. However, the different results between the BP and pemphigus groups cannot be explained. Treg cells were reported to be upregulated in pemphigus groups (2,7). One possibility is the difference in pathogenesis between pemphigus and BP; inflammation is more crucial for blister formation in BP than in pemphigus (8). Therefore, it is tempting to speculate that the involvement of an inflammatory milieu may decrease the number of Treg cells in BP skin lesions. In fact, it was reported that IL-6 secretion was upregulated, TGF-β secretion was downregulated, and the number of circulating $\gamma\delta$ T cells was reduced in BP (9–11). The other possibility is repression of the migration of Treg cells into the inflammatory region in BP, but it may not be the case, because Treg chemoattractants were observed in both the affected skin and the bullae in BP (12,13). Previously, another group suggested that Treg cells accumulated in BP or MMP tissue (14,15). The discrepancy between our results and theirs is unexplained, but the genetic or racial differences maybe involved.

Our studies showed clear differences in the status of lesional effector/regulatory T-cell subsets between BP and pemphigus, although this study was not conducted in a perfectly blinded fashion. The results in the present study provide clues to elucidation of the pathogenesis of BP.

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Conflict of interest

There is no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Correlation of lesional lymphocytes or eosinophils with various parameters.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

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Brunsting–Perry type pemphigoid with IgG autoantibodies to laminin-332, BP230 and desmoplakins I/II

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MADAM, Brunsting–Perry type pemphigoid is characterized clinically by recurrent blisters and vesicles and histopathologically by subepidermal blisters. The blisters are limited to the head, face, neck and upper trunk and leave atrophic scars on healing.[1] It is a matter of debate whether Brunsting–Perry type pemphigoid is a variant of pemphigoid[1,2] or of epidermolysis bullosa acquisita.[3,4] In support of the former notion, some previous reports suggested that the target antigen in Brunsting–Perry type pemphigoid was BP180 and that the clefts of the bullae were located at the lamina lucida, based on an ultrastructural study.[1,2,5] In support of the latter notion, some patients with Brunsting–Perry type pemphigoid had autoantibodies against type VII collagen, and the clefts of the bullae were located at the sublamina densa area.[3,4] Moreover, there are also reports of autoantigen targets other than BP180 and type VII collagen in Brunsting–Perry type pemphigoid; for example, Honoki *et al.*[6] reported on a patient with autoantibodies against a 145-kDa antigen combined with type VII collagen. We report here the first case of Brunsting–Perry type pemphigoid with autoantibodies toward laminin-332, BP230 and desmoplakins.

An 86-year-old woman was referred to Tokyo Medical University Hospital because of a 6-month history of blistering lesions resistant to topical steroids. Clinical examination revealed erythema, erosions and small vesicles limited to the left preauricular region (Fig. 1a) and the left breast. Additionally, scarring was observed on epithelialized old lesions (Fig. 1b). No mucosal lesions were observed. Laboratory values were within normal range, except for a slightly elevated erythrocyte sedimentation rate (23 mm in the first hour) and high IgE level (1230 IU mL^{-1}). Systemic computed tomography did not show any internal malignancies. Histopathology of specimens from the left preauricular area and left breast revealed subepidermal bullae with massive lymphocyte and eosinophil infiltration (Fig. 2a). Direct immunofluorescence showed IgG deposition at the epidermal basement membrane zone (BMZ) (Fig. 2b) and C3 deposition at the hair follicle BMZ (Fig. 2c). Indirect immunofluorescence using healthy human skin sections as the substrate showed IgG anti-BMZ antibodies and IgG antikeratinocyte cell surface antibodies in the patient's serum (Fig. 2d). Indirect immunofluorescence using 1 mol L^{-1} NaCl-split skin sections revealed that the anti-BMZ antibodies bound to both the roof and floor of the split. Immunoblotting using normal human epidermal extract showed that the patient's IgG antibodies reacted with a doublet of 250-kDa and 210-kDa protein bands that comigrated with desmoplakin I and desmoplakin II (Fig. 2e). Immunoblotting on purified human laminin-332 revealed the presence of IgG antibodies reacting with the β3 and γ2 subunits of laminin-332 (Fig. 2e). No reactivity to recombinant proteins of NC16a and C-terminal domains of BP180 was detected. Immunoblotting using normal dermal extract showed negative results. The enzyme-linked immunosorbent assay (ELISA) index value for the BP180 NC16a domain recombinant protein was 11 (cut-off value: 15), but ELISA for the BP230 recombinant protein was positive at 76·9 (cut-off value: 9). From the clinical findings and histopathological and immunological studies, we diagnosed this patient as having Brunsting–Perry type pemphigoid. Topical steroids controlled the bullae and erosions.

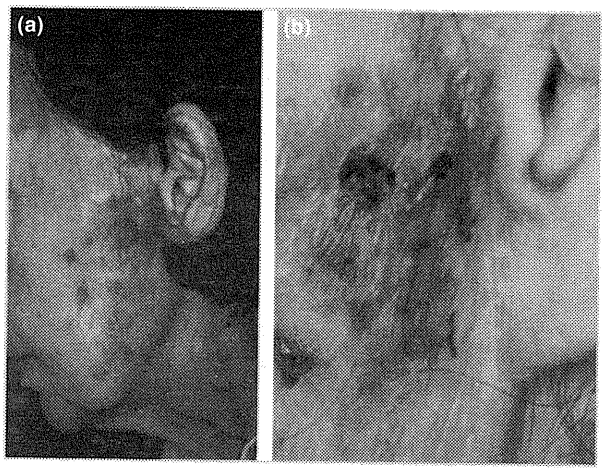

Fig 1. (a) Erythema, erosions and small vesicles limited to the left preauricular region. (b) Scar formation was also observed on the epithelialized old skin lesions.

The most intriguing finding in this study on a patient with Brunsting–Perry type pemphigoid is the autoantibody profile:

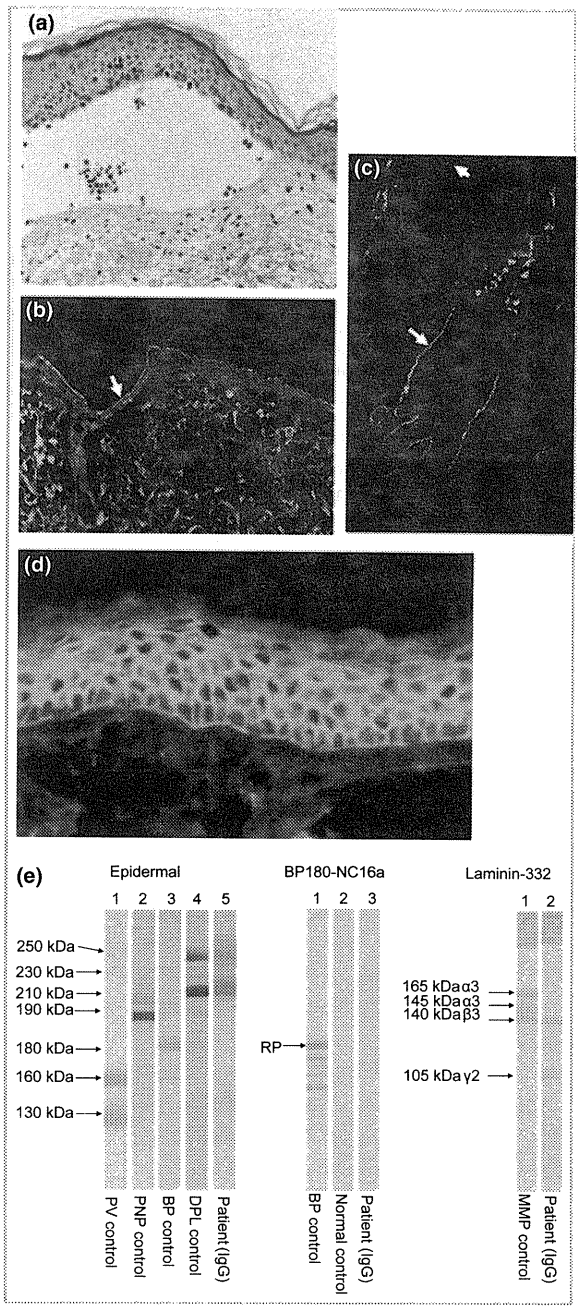

Fig 2. (a) Haematoxylin and eosin-stained section revealing subepidermal bulla. (b, c) Direct immunofluorescence showing IgG (b) and C3 (c) deposition to basement membrane zone (BMZ) (arrows). (d) Indirect immunofluorescence revealing IgG autoantibodies reactive with both keratinocyte cell surface and BMZ. Original magnification: (a, b) ×200; (c, d) ×400. (e) Immunoblotting using human epidermal extract, showing reactivity with the 210 and 250-kDa desmoplakins I and II, as well as the 230-kDa BP230. Immunoblotting using BP180 NC16a recombinant protein (RP) showing no reactivity. Immunoblotting using purified laminin-332 showing reactivity with the 140-kDa β3 and the 105-kDa γ2 subunits of laminin-332. PV, pemphigus vulgaris; PNP, paraneoplastic pemphigus; BP, bullous pemphigoid; DPL, desmoplakin; MMP, mucous membrane pemphigoid.

i.e. autoantibodies to BP230, laminin-332 and desmoplakins I/II. This is the first report on this combination of autoantibodies. BP230, a plakin family protein, and BP180 are major target antigens in bullous pemphigoid.[7] Laminin-332 is a target antigen in antilaminin-332 type mucous membrane pemphigoid.[8] Binding between laminin-332 and its receptor α6β4 integrin transduces signals for keratinocyte functions, such as cell motility, cell adhesion, cell growth and apoptosis.[7] Desmoplakin is a known target in paraneoplastic pemphigus and is a major intracytoplasmic component of the desmosome.[9] It is possible that an epitope-spreading mechanism is responsible for the formation of multiple autoantibodies.[10] As BP230 and desmoplakin are cytoplasmic proteins, the formation of autoantibodies towards the extracellular protein, laminin-332, may trigger the production of autoantibodies to BP230 and desmoplakin. As direct immunofluorescence revealed that the IgG deposit was present only at the BMZ, antidesmoplakin antibodies in this patient may be nonpathogenic.

At the present time, it is not known how the different autoantigens, i.e. BP180, type VII collagen, laminin-332, desmoplakin and BP230, are involved in characteristic clinical features of Brunsting–Perry type pemphigoid. Because the autoantigens in previous cases of Brunsting–Perry type pemphigoid have not been fully investigated, the antigenic profiles in this disease should be extensively examined by different methods, including immunoblot analyses and ELISA.

This is the first report of a patient with Brunsting–Perry type pemphigoid with antilaminin-332 antibodies. However, this case cannot be diagnosed as antilaminin-332 type mucous membrane pemphigoid because the patient had no mucosal lesions. Our study further emphasizes the complex antigen profile in Brunsting–Perry type pemphigoid and suggests that this disease entity is quite heterogeneous.

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Leucoderma in chronic graft-versus-host disease: excellent repigmentation with noncultured cellular grafting

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MADAM, Noncultured cellular grafting techniques have been employed with good results in the treatment of stable leucoderma associated with vitiligo, piebaldism and halo naevi.[1] We report a case of stable leucoderma associated with chronic graft-versus-host-disease (cGVHD) that achieved excellent repigmentation following autologous noncultured cellular transplantation.

A 48-year-old Chinese woman was diagnosed with hypoplastic myelodysplastic syndrome in March 2003. She received an unmanipulated filgrastim-mobilized allogeneic peripheral blood stem cell transplantation (PBSCT) in April 2003 from her human leucocyte antigen-identical brother following a nonmyeloablative conditioning regimen. However, the disease relapsed with secondary acute myeloid leukaemia transformation 6 months post-transplant. Following salvage chemotherapy which achieved complete remission, she received a second allogeneic PBSCT from the same sibling donor using a myeloablative conditioning regimen consisting of cyclophosphamide (120 mg kg^{-1} over 2 days) and busulfan (16 mg kg^{-1} over 4 days) in April 2004. GVHD prophylaxis consisted of ciclosporin and a short course of intravenous methotrexate. The course of transplantation was complicated by steroid-refractory grade III acute GVHD of the liver at 6 months post-transplant, requiring intensive immunosuppressive therapy with prednisolone followed by subsequent addition of tacrolimus and mycophenolate mofetil (MMF). Her liver function improved gradually with these combined immunosuppressive agents. Severe cGVHD (National Institutes of Health grading) ensued over the following few months when her immunosuppressive agents were tapered.[2] This resulted in multiorgan manifestations which mimicked those of scleroderma, with ocular (dry eyes, reduced tear production in Schirmer's test), mouth (decreased range of movement due to sclerosis, xerostomia), musculoskeletal system (joint contractures with mild limitation of activities of daily life) and cutaneous (lichenoid inflammation, sclerosis and leucoderma over approximately 30% of the body surface area) involvement. She was treated with a variety of immunosuppressive agents over the following year, ranging from prednisolone, calcineurin inhibitors, MMF and thalidomide to sirolimus. Notably, none of these drugs was given for more than 1 month duration, as on most occasions, the treatment was prematurely discontinued either because of toxicity or poor compliance. However, despite suboptimal treatment, her clinical manifestations of cGVHD did not progress further over the following 4 years.

In 2009, 5 years after her second allograft, she was referred to our dermatological centre for management of her disfiguring leucoderma. She had been off systemic immunosuppression for 4 years at the time of consultation. On examination, she had large areas of depigmentation on her face, trunk and limbs, associated with sclerosis and microstomia (Fig. 1a). A biopsy of the depigmented skin on her face revealed normal epidermal thickness with compact hyperkeratosis, absent basal pigmentation and reduced melanocyte numbers, associated with dense dermal collagen bands orientated parallel to the skin surface. Dermal sclerosis and paucity of pilosebaceous units was also noted in adjacent pigmented skin (Fig. 2a, b).

She was treated with targeted phototherapy (Multiclear™; Curelight, New York, NY, U.S.A.) to the area of leucoderma

Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts

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Sydney, Australia; Rouen, Bobigny, and Reims, France; Bern, Switzerland; Tokyo, Kurume, and Sapporo, Japan; Zagreb, Croatia; Buffalo and New York, New York; Marburg, Luebeck, and Dresden, Germany; Rome and Modena, Italy; Iowa City, Iowa; Groningen, The Netherlands; Dallas, Texas; Chapel Hill and Durham, North Carolina; Los Angeles and Irvine, California; Philadelphia, Pennsylvania; Sao Paulo, Brazil; Barcelona, Spain; Salt Lake City, Utah; Manila, Philippines; Atlanta, Georgia; and Petah Tikva, Israel

Our scientific knowledge of bullous pemphigoid (BP) has dramatically progressed in recent years. However, despite the availability of various therapeutic options for the treatment of inflammatory diseases, only a few multicenter controlled trials have helped to define effective therapies in BP. A major obstacle in sharing multicenter-based evidences for therapeutic efforts is the lack of generally accepted definitions for the clinical evaluation of patients with BP. Common terms and end points of BP are needed so that experts in the field can accurately measure and assess disease extent, activity, severity, and therapeutic response, and thus facilitate

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and advance clinical trials. These recommendations from the International Pemphigoid Committee represent 2 years of collaborative efforts to attain mutually acceptable common definitions for BP and proposes a disease extent score, the BP Disease Area Index. These items should assist in the development of consistent reporting of outcomes in future BP reports and studies. (J Am Acad Dermatol 2012;66:479-85.)

Key words: bullous pemphigoid; consensus; definitions; outcome measures; severity score.

CAPSULE SUMMARY

- It is impossible to compare the therapeutic outcomes from the majority of bullous pemphigoid studies using meta-analysis, as they have varying definitions and outcome measures.
- These recommendations, developed over the last 3 years by experts, provide appropriate definitions for the various stages of disease activity and therapeutic end points in bullous pemphigoid.
- These definitions can be used in case series and clinical trials to compare the efficacy of treatments for bullous pemphigoid.

Bullous pemphigoid (BP) is a common autoimmune bullous disease typically affecting the elderly. There have been only a handful of well-designed randomized controlled trials assessing the effectiveness of therapies for BP.[1] In relatively rare diseases where it is difficult to include enough patients to have sufficient power to compare different treatments, meta-analysis is a powerful tool that is used to pool data across trials. However, it is impossible to compare the therapeutic outcomes from the majority of these BP studies using meta-analysis, as they have varying definitions and outcome measures.

PURPOSE

The purpose of this statement is to provide appropriate definitions for the various stages of disease activity, define therapeutic end points in BP, and to propose an objective disease extent measure that can be used in clinical trials. The use of the same definitions and outcome measures makes the results of trials more comparable. Since definitions and outcome measures for pemphigus[2-4] have been published, most trials in pemphigus and reports have begun adopting these systems or referring to them when their existing trials using other measures were unable to show a difference.[5]

METHODS

An international BP definitions committee was organized in 2008, at the point when the international pemphigus definitions committee completed its similar work on pemphigus.[2] The committee was an expansion of the first committee and convened 7 times over 2 years to discuss the appropriate definitions. These meetings were held at the American Academy of Dermatology (AAD) annual meeting in San Antonio, TX, in 2009 (D. F. M. and V. P. W.); European Society for Dermatologic Research in Budapest, Hungary, in 2009 (D. F. M. and P. J.); the European Academy of Dermatovenereology in Berlin, Germany, in 2009 (D. F. M. and L. B.); the AAD in Miami, FL, in 2010 (D.F.M. and V. P. W.); the Pemphigus 2010 Meeting in Bern, Switzerland (V. P. W. and D. F. M.); and the International Pemphigus and Pemphigoid Meeting at the National Institutes of Health in November 2010 (V. P. W. and D. F. M.), in Bethesda, MD. The final meeting was held at the AAD in 2011 in New Orleans, LA (D. F. M. and V. P. W.). Meetings were supported in part by local dermatology societies. The draft definitions and end points were electronically mailed to the larger group, allowing for comments between meetings.

THE RECOMMENDATIONS

Observation points

The end points are illustrated and summarized (Fig 1 and Table I).

Early end points

"Baseline" is the point at which a physician starts treatment for BP.

"Control of disease activity" (disease control; beginning of consolidation phase) is defined as the point at which new lesions or pruritic symptoms cease to form and established lesions begin to heal. The time to disease control is the time between baseline and this control point.

"End of the consolidation phase" is defined as the time at which no new lesions or pruritic symptoms have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions has healed. At this point tapering of corticosteroids often occurs. The length of the consolidation phase is the time between disease control and the end of consolidation phase.

Abbreviations used:

AAD:	American Academy of Dermatology
BP:	bullous pemphigoid
BPDAI:	Bullous Pemphigoid Disease Area Index
DAI:	Disease Area Index
PDAI:	Pemphigus Disease Area Index

"Transient lesions" are new lesions that heal within 1 week or pruritus lasting less than a week and clearing without treatment.

"Nontransient lesions" are new lesions that do not heal within 1 week or pruritus continuing more than a week with or without treatment.

Intermediate end points

During this period, the corticosteroids and other treatments are usually being tapered, but for some patients medication doses do not change because of flaring with attempts to taper treatment. "Complete remission during tapering" is the absence of nontransient lesions while the patient is receiving more than minimal therapy. There is no minimum time point here as the patient is under control but has not yet reached the desired outcome of disease remission on minimal or no therapy.

Late observation end points

Late observation end points of disease activity are identified as: (1) complete remission off therapy; and (2) complete remission on therapy, both of which only apply to patients who have had no new or established lesions for at least 2 months. "Complete remission off therapy" is defined as an absence of new or established lesions or pruritic symptoms while the patient is off all BP therapy for at least 2 months.

"Complete remission on therapy" is defined as the absence of new or established lesions or pruritus while the patient is receiving *minimal* therapy for at least 2 months. "Minimal therapy" is defined as less than or equal to 0.1 mg/kg/d of prednisone (or the equivalent) or 20 g/wk of clobetasol propionate and/or minimal adjuvant or maintenance therapy for at least 2 months, as shown in Fig 1 and discussed further below.

Minimal adjuvant therapy in BP corresponds to the following doses or less: methotrexate 5 mg/wk; azathioprine 0.7 mg/kg/d (with normal thiopurine s-methyltransferase level); mycophenolate mofetil 500 mg/d; mycophenolic acid 360 mg/d; or dapsone 50 mg/d. There has only been one small randomized controlled trial on tetracycline and niacinamide,[6] which was underpowered because of low numbers and was unable to demonstrate a difference. Nevertheless, the committee's expert opinion is that full therapeutic doses of the tetracyclines may work in localized forms of BP. As the tetracycline class of drugs is relatively nontoxic, the full therapeutic dose was listed among minimal therapies for BP.

"Partial remission off therapy" is defined as the presence of transient new lesions that heal within 1 week without treatment and while the patient is off all BP therapy for at least 2 months.

"Partial remission on minimal therapy" is defined as the presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy.

A newer term, "mild new activity," refers to fewer than 3 lesions a month (blisters, eczematous lesions, or urticarial plaques) that do not heal within 1 week, or the extension of established lesions or pruritus once per week but less than

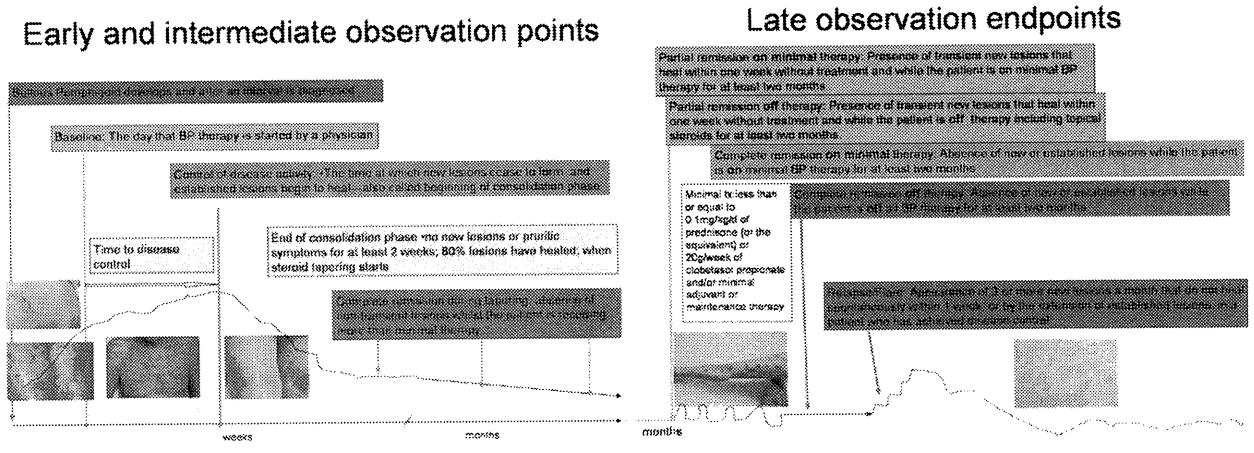

Fig 1. Pictorial depiction of end points in bullous pemphigoid.

Table I. Definitions for bullous pemphigoid

Early observation points	
Baseline	Day that BP therapy is started by physician
Control of disease activity	Time at which new lesions cease to form and established lesions begin to heal or pruritic symptoms start to abate
Time to control of disease activity (disease control; beginning of consolidation phase)	Time interval from baseline to control of disease activity
End of consolidation phase	Time at which no new lesions have developed for minimum of 2 wk and approximately 80% of lesions have healed and pruritic symptoms are minimal
Intermediate observation end points	
Transient lesions	New lesions that heal within 1 wk or pruritus lasting <1 wk and clearing without treatment
Nontransient lesions	New lesions that do not heal within 1 wk or pruritus continuing >1 wk with or without treatment
Complete remission during tapering	Absence of nontransient lesions while patient is receiving more than minimal therapy
Late observation end points	
Minimal therapy	≤0.1 mg/kg/d Of prednisone (or equivalent) or 20 g/wk of clobetasol propionate and/or minimal adjuvant or maintenance therapy
Minimal adjuvant therapy and/or maintenance therapy	Following doses or less: methotrexate 5 mg/wk; azathioprine 0.7 mg/kg/d (with normal thiopurine s-methyltransferase level); mycophenolate mofetil 500 mg/d; mycophenolic acid 360 mg/d; or dapsone 50 mg/d
Partial remission on minimal therapy	Presence of transient new lesions that heal within 1 wk while patient is receiving minimal therapy for at least 2 mo
Complete remission on minimal therapy	Absence of new or established lesions or pruritus while patient is receiving minimal therapy for at least 2 mo
Partial remission off therapy	Presence of transient new lesions that heal within 1 wk without treatment while patient is off all BP therapy for at least 2 mo
Complete remission off therapy	Absence of new or established lesions or pruritus while patient is off all BP therapy for at least 2 mo
Mild new activity	<3 Lesions/mo (blisters, eczematous lesions, or urticarial plaques) that do not heal within 1 wk, or extension of established lesions or pruritus once/wk but less than daily in patient who has achieved disease control; these lesions have to heal within 2 wk
Relapse/flare	Appearance of ≥3 new lesions/mo (blisters, eczematous lesions, or urticarial plaques) or at least one large (>10 cm diameter) eczematous lesion or urticarial plaques that do not heal within 1 wk, or extension of established lesions or daily pruritus in patient who has achieved disease control
Failure of therapy for initial control	Development of new nontransient lesions or continued extension of old lesions, or failure of established lesions to begin to heal or continued pruritus despite: Clobetasol propionate 40 g/d for 4 wk; or Prednisone 0.75 mg/kg/d equivalent for minimum of 3 wk with or without drugs used for maintenance therapy; or A tetracycline on full dosing for 4 wk; or Dapsone 1.5 mg/kg/d for 4 wk; or Methotrexate 15 mg/wk (if >60 kg and no major renal impairment) for 4 wk; or Azathioprine 2.5 mg/kg/d for 4 wk (if thiopurine s-methyltransferase level is normal); or Mycophenolate mofetil 40 mg/kg/d (if normal renal function, otherwise according to age/creatinine clearance) for 4 wk

BP, Bullous pemphigoid.

daily, in a patient who has achieved disease control. This term was not included in the pemphigus definitions but the committee thought that it might be important to capture this phase during studies to determine if some patients with BP and certain characteristics or treatments experienced new mild activity not significant enough to constitute a flare. In this way, it could be determined in the future if these patients with BP might benefit from a change of treatment plan or not.

Relapse/flare

The terms "relapse" and "flare" are used interchangeably and are defined as the appearance of 3 or more new lesions a month (blisters, eczematous lesions, or urticarial plaques) or at least one large (>10 cm diameter) eczematous lesion or urticarial plaque that does not heal within 1 week, or the extension of established lesions or daily pruritus in a patient who has achieved disease control.

Treatment failure

"Failure of therapy for initial control" is defined as the development of new nontransient lesions or continued extension of old lesions, or failure of established lesions to begin to heal or daily pruritus despite certain strengths of corticosteroids with or without higher doses of adjuvants. The dose of prednisone defined as treatment failure is 0.75 mg/kg/d equivalent for minimum of 3 weeks. This dose was selected because the Cochrane review of interventions for BP[1,7] determined that in acute BP there was no purpose in using prednisone at a higher dose than this. Topical clobetasol propionate at 40 g/d for 4 weeks was selected on the basis of the randomized controlled trials conducted by the French group.[8,9] Other therapies include tetracycline at full doses for 4 weeks; dapsone 1.5 mg/kg/d for 4 weeks; methotrexate 15 mg/wk (if >60 kg and no major renal impairment) for 4 weeks; azathioprine 2.5 mg/kg/d for 4 weeks (if thiopurine s-methyltransferase level is normal); or mycophenolate mofetil 40 mg/kg/d (if normal renal function, otherwise according to age/creatinine clearance) for 4 weeks. The definition does not imply these drugs and their respective doses are equivalent in therapeutic efficacy. Rather it provides a standardized agreement as to what can be defined as a failure of therapy.

BP disease activity index

Like the Pemphigus Disease Area Index (PDAI),[3] the BP Disease Area Index (BPDAI) measure has separate scores for skin and mucous membrane activity. Damage scores are separate as well and are included to remind physicians that not all visible lesions in BP represent active disease. Areas of the skin predominantly affected in BP[10] were taken into account when selecting the skin sites so that trials would better differentiate clinical response in BP. Hence, additional weighting was given to the arms and legs and less emphasis to the face and scalp, slightly different from the PDAI. The mucous membrane areas were retained from the PDAI even though it is relatively rare to see mucous membrane involvement in BP, so that the activity could be compared with extent of mucous membrane involvement in different autoimmune bullous diseases. There are separate columns for the extent of blistering and for the urticarial/eczematous lesions that may be more extensive in BP.

BPDAI PRURITUS COMPONENT - VAS

DATE: .....

Baseline	Beginning Consolidation
Consolidation phase	End of Consolidation
Tapering phase	Partial remission on minimal therapy
Complete remission on minimal therapy	Partial remission off therapy
Complete remission off therapy	Flare

A. How severe has your itching been over the last 24 hours?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

B. How severe has your itching been the past week?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

C. How severe has your itching been in the past month?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

Average INTENSITY SCORE FOR PAST MONTH = (A+B+C) = /30

OR

For BP patients with impaired mental functioning:

	No evidence of itch (no excoriations)	0
	Mild itch (isolated excoriations up to two body sites)	10
	Moderate itch (excoriations on ≥ 3 body sites, impairment of daily activity	20
	Severe itch (generalized excoriation, sleep impairment)	30
	TOTAL SCORE	/30

Fig 2. Subjective Bullous Pemphigoid (*BP*) Disease Area Index (*BPDAI*) pruritus score. *VAS*, Visual analog scale.

As a major symptom that may herald the onset and recurrence of BP is pruritus, a separate subjective component of the BPDAI is proposed to measure the severity of this (Fig 2). Naturally, other causes of pruritus in the elderly must be excluded, such as xerosis, dermatitis, renal impairment, liver impairment, and scabies. Providing that only pruritus related to BP is considered in the definitions and scored, this system can be used to subjectively grade the intensity of pruritus using a visual analog scale to answer the question, "How severe is your itching today?" and the patient marks an "x" on the 0- to 10-cm line where 0 is no itch and 10 is maximal itching. The degree of itching is measured as the distance in centimeters from 0, out of 10. This is repeated for the severity overall of itching in the past week and month. A total score is calculated from this out of 30. If the patient with BP is incapable of completing a reliable visual analog scale rating, for example, as a result of dementia, then the degree of pruritus is inferred, based on the extent of excoriations alone, also scored

BPDAI					
SKIN	ACTIVITY		ACTIVITY		DAMAGE
Anatomical location	Erosions/Blisters	Number of Lesions if <3	Urticaria/ Erythema / Other	Number of Lesions if <3	Pigmentation / Other
	0 absent		0 absent		Absent 0, present 1
	1 1-3 lesions, none > 1 cm diameter		1 1-3 lesions, none >6 cm diameter		
	2 1-3 lesions, at least one > 1 cm diameter		2 1-3 lesions, at least one lesion > 6 cm diameter		
	3 >3 lesions, none > 2 cm diameter		3 >3 lesions, or at least one lesion > 10 cm		
	5 >3 lesions, and at least one >2 cm		5 >3 lesions and at least one lesion > 25 cm		
	10 >3 lesions, and at least one lesion >5 cm diameter or entire area		10 >3 lesions and at least one lesion > 50 cm diameter or entire area		
Head					
Neck					
Chest					
Left arm					
Right arm					
Hands					
Abdomen					
Genitals					
Back/Buttocks					
Left leg					
Right leg					
Feet					
Total skin	/120		/120		
MUCOSA	Erosions/Blisters				
	1 1 lesion				
	2 2-3 lesions				
	5 >3 lesions, or 2 lesions >2cm				
	10 entire area				
Eyes					
Nose					
Buccal mucosa					
Hard palate					
Soft palate					
Upper gingiva					
Lower gingiva					
Tongue					
Floor of Mouth					
Labial Mucosa					
Posterior Pharynx					
Anogenital					
Total Mucosa	/120				

Fig 3. Objective bullous pemphigoid disease area index

out of 30 (Fig 2). This subjective itch score will not be combined with the objective part of the BPDAI (Fig 3). Eventually, a quality-of-life tool for BP will be necessary as well. The BPDAI will be undergoing validation studies, similar to the partial validation done thus far with the PDAI.[3]

DISCUSSION AND CONCLUSION

Despite many trials evaluating therapeutic options for BP, it has been difficult to compare the results from these trials because of the large number of end points and definitions of disease. The formation of an international committee of bullous

disease experts able to meet face to face on a regular basis has provided a mechanism for developing agreement on these issues for BP. This statement with agreed-upon common definitions,. and the ongoing discussion and refinement of proposed common measurements for patients with BP, are the initial and necessary steps toward progress in the clinical evaluation and therapy of BP. Further progress and advancement will require a continued unified effort.

The following individuals who were unable to attend the meetings contributed by e-mail to the discussions: Cheyda Chams-Davatchi, Karen Harman, Pilar Iranzo, and Gudula Kirtschig. Molly Stuart and Will Zmchik at the International Pemphigus and Pemphigoid Foundation assisted with meeting setup.

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A Case of Epidermolysis Bullosa Acquisita Associated with Laryngeal Stenosis

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Epidermolysis bullosa acquisita (EBA) is an acquired inflammatory subepidermal blistering disease characterized by immunoglobulin G (IgG) auto-antibodies to type VII collagen in the dermal–epidermal junction of the skin (1). Patients usually present with skin fragility and tense bullae over areas of trauma. Occasionally, the clinical features of EBA are indistinguishable from those of mucous membrane pemphigoid (MMP) (formerly, cicatricial pemphigoid), when the main symptoms are seen on mucosae. However, cases with laryngeal lesions are uncommon. We report here a case of EBA with laryngeal stenosis occurring in a 73-year-old woman.

CASE REPORT

A 73-year-old Japanese woman noticed aphtha and dry mouth in May 2009. The primary physician suspected herpes simplex. Several months later, she noticed tense blisters on her waist. Skin biopsy showed subepidermal bullae with inflammatory cell infiltration including eosinophils in the upper dermis. Direct immunofluorescence analysis demonstrated deposition of C3 on the epidermal basement membrane. Serum anti-bullous pemphigoid antigen 180 (BP180) antibody was positive. A diagnosis of bullous pemphigoid was made. From February 2010, she was treated with oral prednisolone, 30 mg/day, which improved the blisters with erosions on her waist, but not the oral mucosal erosions.

She was referred to our hospital. Physical examination showed multiple erosions on the tongue, palate and buccal mucosa, together with an erosion 8 cm in diameter on the left waist (Fig. 1a, b). Blood examination demonstrated hypoproteinaemia (5.8 g/dl; normal 6.8–8.3 g/dl), hypokalaemia (3.2 mEq/l; normal 3.4–4.5 mEq/l), and anaemia (red blood cell count 3.72×10^6/ml; normal $3.73–4.95 \times 10^6$/ml, haemoglobin 10.3 g/dl; normal 10.7–15.3 g/dl). Enzyme-linked immunosorbent assay (ELISA) revealed increased levels of antibodies to BP180 (51; normal <9.0), but not desmoglein 1 or desmoglein 3. Although she did not have difficulty swallowing, upper gastrointestinal endoscopy demonstrated scarring in the oesophagus. A biopsy specimen obtained from a bullous lesion on her waist revealed subepidermal cleft without acantholysis. Indirect immunofluorescence analysis of 1 mol/l sodium chloride-split human skin revealed dermal side staining up to a titre of 1:10 (Fig. 1c). Immunoblotting analysis using an ethylenediaminetetraacetic acid (EDTA)-separated human dermal extract was performed as described previously (2) and revealed the presence of autoantibodies reactive with the 290-kDa type VII collagen (Fig. 2). The patient's serum did not recognize epidermal extracts, recombinant BP180 NC16a, recombinant C-terminus of BP180, purified laminin-332, or concentrated supernatant of HaCaT cells. A diagnosis of EBA was made based on the clinical, histological and immunopathological findings. An increase in oral prednisolone to 50 mg daily failed to resolve the mucosal manifestations. Dyspnoea occurred together with hoarseness. Laryngeal endoscopy showed supraglottic stenosis due to swollen bilateral aryepiglottis associated with severe oedema, erosion and erythema (Fig. 1d), which required tracheotomy. Furthermore, she was treated with 1 g methylprednisolone for 3 days twice, followed by prednisolone 50 mg daily. These therapies improved erosion in the oral cavity and swelling in the aryepiglottis, leading to removal of the tracheotomy tube. As small blisters relapsed in the oral mucosa during gradual tapering of the prednisolone dose, colchicine was added at a

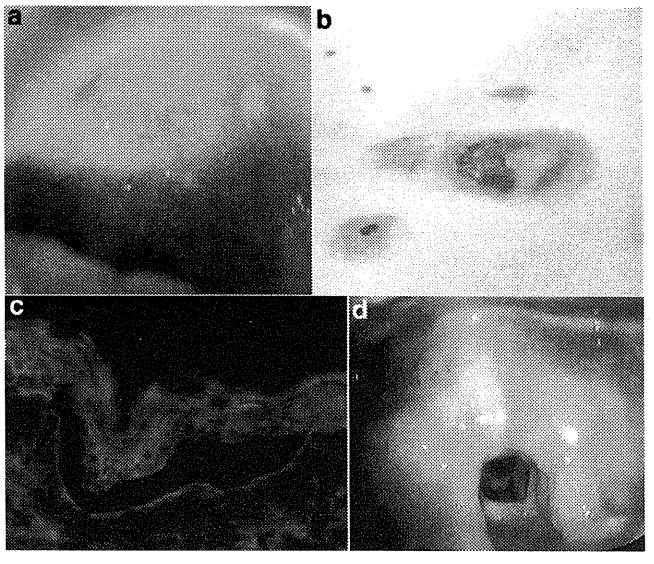

Fig. 1. (a) Multiple erosions in the oral mucosa. (b) Erosions on the waist. (c) Indirect immunofluorescence of patient serum on split human skin demonstrating binding of immunoglobulin G (IgG) to the dermal aspects of the blister. (d) Bilateral aryepiglottis with severe swelling.

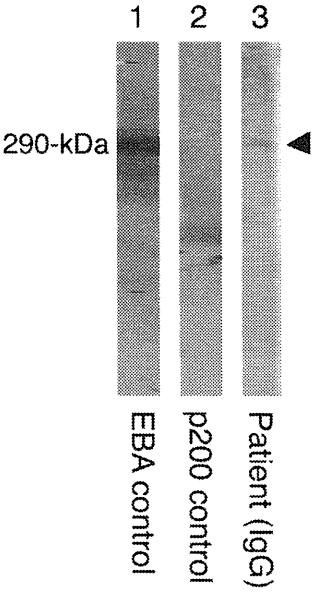

Fig. 2. Results of immunoblot analysis. Sera were reacted with human dermal extracts. Patient serum (*lane 3*) recognized 290-kDa type VII collagen, which was also detected by control epidermolysis bullosa acquisita (EBA) serum (*lane 1*). Lanes 1–2 show the reactivity of the control sera. Anti-p200 pemphigoid serum reacted with 200-kDa Laminin γ1 (*lane 2*).

dose of 1 mg daily. Thereafter, relapse has not been observed and no laryngeal stenosis has developed.

DISCUSSION

We diagnosed this case as EBA, because of the dermal binding on salt-split indirect immunofluorescence, and the detection of type VII collagen on immunoblotting using dermal extract. However, the most intriguing issue in this case was a role of anti-BP180 antibodies detected by ELISA, which made it necessary to differentiate from anti-BP180 type MMP. However, there was no reactivity to the epidermal side of salt-split skin. Moreover, this patient serum did not show IgG or IgA antibodies to the recombinant protein of BP180 C-terminal domain, which is responsible for mucosal lesions. The negative IgG reactivity to BP180 NC16a domain on immunoblotting also suggested that the positive result on ELISA might be non-specific. Therefore, we excluded the diagnosis of MMP.

The cutaneous lesions of EBA are varied and can mimic other types of acquired autoimmune bullous disease. The classical presentation is a mechanobullous disease marked by skin fragility, and the lesions are chiefly distributed in acral regions. Similar to our patient, some cases of EBA show predominant mucosal involvement with cicatricial pemphigoid-like clinical appearance. Our case was unique in the wide involvement of mucosal sites, such as the oral cavity, larynx and oesophagus. The mechanism of mucosal predominance remains to be determined. Three epitopes within the N-terminal non-collagenous (NC)-1 domain, the NC-2 domain and the triple-helical collagenous domain recognized by sera have been reported. Previous reports suggested that reactivity to different epitopes might be associated with variation of clinical phenotypes (2–4).

In EBA erosions and scars develop on the mucosal surfaces of the mouth, upper oesophagus, conjunctiva or anus with or without vesiculobullous lesions on the skin. However, laryngeal involvement is not a well-known complication of EBA, in contrast to that in cicatricial pemphigoid (5, 6). Luke et al. (6) reported four cases of EBA with manifestations in the pharynx and larynx. One of these patients had severe symptoms developing to airway deformity. Laryngeal damage occasionally caused hoarseness, impaired phonation and loss of voice, and led to irreversible respiratory distress. Although the symptoms are sometimes minimal and subclinical, disease activity may be extended to this area and be life-threatening. Accordingly, a laryngeal evaluation should be performed in cases of EBA with mucosal symptoms.

EBA usually responds poorly to treatment, and is often refractory to high doses of systemic corticosteroids. Cyclosporin A has been shown to be beneficial, but side-effects on renal function may limit its use (7). Intravenous immunoglobulin (IVIG) and rituximab have been successfully used for treatment of EBA (8, 9). Colchicine has also been recommended as a treatment option for EBA, although some patients did not respond to this agent (1, 10). In the present case, colchicine was useful for tapering of prednisolone.

At the time of writing, the patient has been in remission on 1 mg/day colchicine and prednisolone for 10 months.

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IgA-Pemphigus vom Typ der subkornealen pustulösen Dermatose

Erfolgreiche Kombinationstherapie mit Dapson und Acitretin

Unter der Diagnose „IgA-Pemphigus" werden 2 sehr seltene vesikulopustulöse Autoimmundermatosen zusammengefasst, die durch IgA-Autoantikörper (IgA-Aak) gegen Membranproteine von Keratinozyten definiert sind. Die 2 Varianten, der subkorneale pustulöse Dermatose (SPD)-Typ und der intraepidermale neutrophile IgA-Dermatose (IEN)-Typ, werden histologisch und v. a. immunologisch voneinander abgegrenzt [8]. Im Gegensatz zu anderen Erkrankungen aus dem Pemphigusformenkreis ist beim IgA-Pemphigus die Therapie der Wahl Dapson [12, 13]. Erstmals im deutschen Schrifttum präsentieren wir den Fall eines therapierefraktären IgA-Pemphigus vom SPD-Typ, der nur mit einer Kombination von Dapson und einem Retinoid (Acitretin) beherrscht werden konnte.

Anamnese

Der 74-jährige Patient entwickelte etwa 4 Wochen vor Zuweisung ausgedehnte, mäßig juckende Erytheme am Rumpf und in den großen Beugen. In den Erythemen traten multiple bis zu erbsengroße Bläschen auf, die rasch eintrübten und erodierten.

Aufgrund des Verdachts einer Impetigo contagiosa war er mit Cefalexin 3-mal 1000 mg/Tag für 14 Tage behandelt worden, als aber das Krankheitsbild an Schwere zunahm, erfolgte die Vorstellung an unserer Ambulanz. Der Patient war bisher im Wesentlichen gesund gewesen; es bestanden ein chronisches Vorhofflimmern und eine arterielle Hypertonie, die seit Jahren medikamentös gut eingestellt waren. Die Familienanamnese war unauffällig.

Klinischer Befund

Am gesamten Integument mit Betonung von Achseln, Leisten und Analfalte fanden sich multiple, unscharf begrenzte, polyzyklische bzw. landkartenartige Erytheme, die von einzeln stehenden, leicht zerreißlichen Bläschen und Pusteln – oft mit auffallender Hypopyonbildung – übersät waren. Diese erodierten rasch und heilten mit postinflammatorischer Hyperpigmentierung ab (◘ **Abb. 1a,b**). Direktes und indirektes Nikolski-Zeichen waren negativ, Schleimhäute und Hautanhangsgebilde waren frei.

Diagnostik

Labor. Blutbild, Nieren- und Leberfunktionsparameter, CRP, Eiweißelektrophorese und Immunfixation, Blutfette, Harnchemie (inklusive Bence-Jones-Proteine) waren normal.

Bildgebung. Thoraxröntgen und Oberbauchsonographie waren unauffällig.

Mikrobiologie. Abstriche aus Läsionen zeigten neben der residenten Hautflora auch MRSA 10^6. Nach einer topischen (Mupirocin – Bactroban® und 4% Undecylenamidopropyltrimonium Methosulfat mit 2% Phenoxyethanol – Stellicept®) und systemischen (Trimethoprim/Sulfametrol 160/800 mg 2-mal/Tag für 10 Tage) Eradikationstherapie waren die Kontrollabstriche negativ.

Histopathologie einer Pustel. Subkorneale Spaltbildung mit akantholytischen Keratinozyten sowie Neutrophilen und einzelnen Eosinophilen im Blaseninhalt. Reichlich Neutrophile, Eosinophile und Lymphozyten bilden ein dichtes perivaskuläres und diffuses entzündliches Infiltrat in der ödematösen papillären Dermis (◘ **Abb. 2**).

Immunfluoreszenz (IF)

Direkte Immunfluoreszenz (DIF). In vivo gebundenes IgA in interzellulärem Verteilungsmuster, streng beschränkt auf die obere Epidermishälfte (◘ **Abb. 3**); eine Bindung von anderen Immunglobulinen oder Komplement konnte nicht nachgewiesen werden.

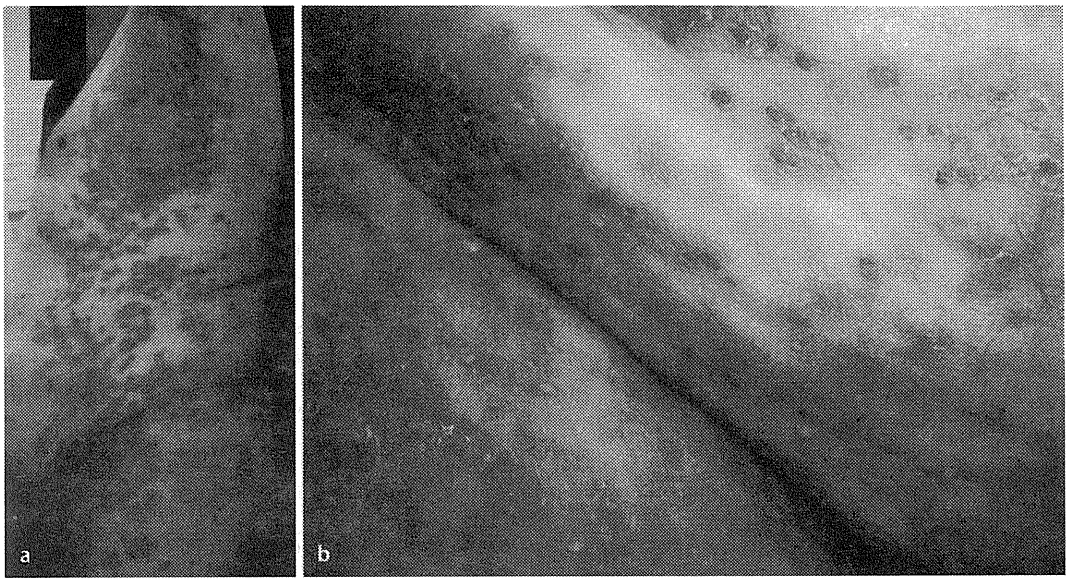

Abb. 1 ◀ **a** Ausgedehnte, polyzyklisch konfigurierte, konfluierende Erytheme lokalisieren sich typischerweise in die Körperfalten. **b** In den Erythemen finden sich zahlreiche, leicht zerreißliche Vesikel, die rasch zu Pusteln eintrüben; oft auffallende Hypopyonbildung; daneben Erosionen und postinflammatorische Hyperpigmentierungen

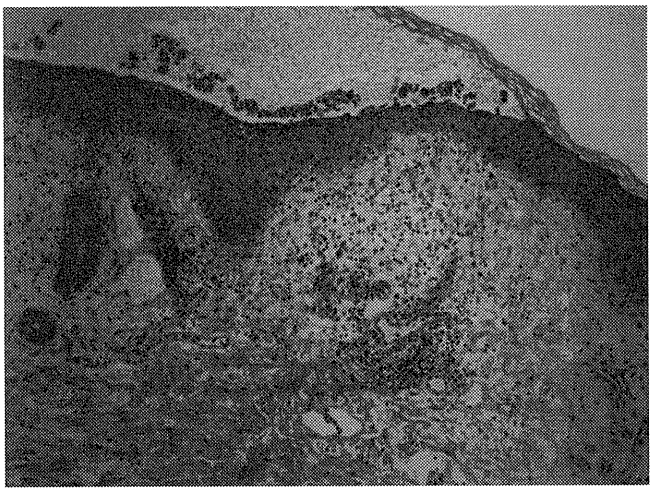

Abb. 2 ◀ Subkorneale Pustel mit charakteristischen akantholytischen Keratinozyten, neutrophilen sowie eosinophilen Granulozyten. In der ödematösen Dermis ein perivaskuläres und diffuses Entzündungsinfiltrat v. a. aus Granulozyten (HE, Vergr. 100:1)

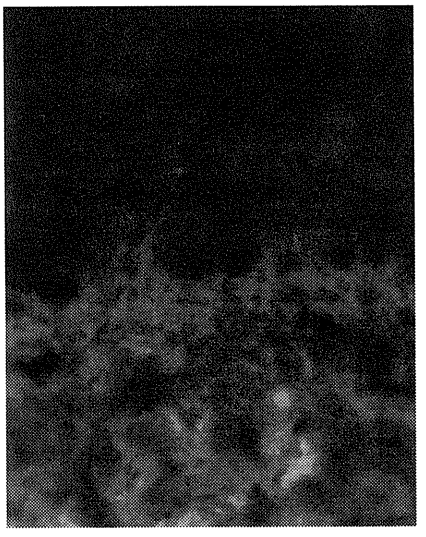

Abb. 3 ▲ Die direkte Immunfluoreszenz zeigt in vivo gebundenes IgA, in interzellulärem Muster, typischerweise in der oberen Hälfte der Epidermis (Vergr. 400:1)

Indirekte Immunfluoreszenz (IIF) an gesunder menschlicher Haut. Identes Färbemuster, keine Anfärbung am Affenösophagus.

ELISA und Immunoblot. ELISAs für IgG-Aak gegen Desmogleine (Dsg) 1 und 3 und gegen BP180/230 (MBL Nagoya/Japan) wie der Immunoblot am Extrakt normaler humaner Keratinozyten waren negativ.

Indirekte Immunfluoreszenz auf Dsc-1-, -2- und -3-transfizierten COS7-Zellen [5]. Nachweis von IgA-Aak gegen Desmocollin (Dsc) 1, nicht jedoch gegen Dsc 2 und Dsc 3 (■ **Abb. 4a–c**).

Diagnose

IgA-Pemphigus vom Typ der subkornealen pustulösen Dermatose.

Therapie und Verlauf

Eine Initialtherapie mit Methylprednisolon 1 mg/kg/Tag und Diaminodiphenylsulfon (DADPS, Dapson) 2-mal 50 mg/Tag führte zur raschen Rückbildung der Hautläsionen, allerdings rezidivierten die Blasen, sobald das Steroid auf 20 mg/Tag reduziert wurde. Wir verabreichten daher zusätzlich Acitretin 20 mg/Tag und erhöhten diese Dosis langsam auf 35 mg/Tag (0,5 mg/kg/Tag). Damit gelang es, das Steroid innerhalb von 3 Monaten auszuschleichen. Auslassversuche sowohl von Dapson als auch Acitretin führten prompt zum Rezidiv. Der Patient ist nun 24 Monate unter dieser Kombinationstherapie (Dapson 100 mg/Tag und Acitretin 35 mg/Tag) so gut wie erscheinungsfrei. Seltene milde Schübe lokalisierter Pustelbildung können mit Clobetasol-17-propionat-Creme völlig beherrscht werden.

Diskussion

Die klinisch morphologische Diagnose „subkorneale Pustulose" umfasst ein breites Spektrum unterschiedlicher Krankheiten, das in den letzten Jahren immer besser definiert wurden. Im Jahr

1979 konnten Varigos et al. [11] erstmals IgA-Aak in der Epidermis bei einer subkornealen pustulösen Dermatose nachweisen. Seither wurden über 70 solcher Fälle unter verschiedenen Bezeichnungen wie „intraepidermale IgA-Pustulose", „interzelluläre IgA vesikulopustulöse Dermatose" oder „IgA Pemphigus foliaceus" publiziert [8]. Erst seit einigen Jahren hat sich der Begriff „IgA-Pemphigus" in der internationalen Literatur durchgesetzt.

Der IgA-Pemphigus tritt in 2 Varianten, dem SPD-Typ und dem IEN-Typ, auf. In beiden Fällen ist die Klinik von rezidivierenden Erythemen mit kleinen, leicht zerreißlichen Vesikeln und Pusteln v. a. in den großen Körperfalten geprägt. Den Läsionen des IEN-Typs wird dabei eine sonnenblumenähnliche („sunflower like") Konfiguration zugeschrieben, die Schleimhäute sind bei beiden Varianten in der Regel frei [8].

Die klinischen Differenzialdiagnosen des IgA-Pemphigus umfassen:

- bullöse Impetigo contagiosa,
- Candidamykose,
- Psoriasis pustulosa,
- Pemphigus vulgaris oder foliaceus bzw. Pemphigus herpetiformis,
- Pustulosis subcornealis Sneddon-Wilkinson.

Ursprünglich war in unserem Fall eine ausgedehnte Impetigo wegen der hohen Keimzahl durchaus vorstellbar. Das Ausbleiben einer Besserung auf die MRSA-Eradikationstherapie schloss aber eine bakterielle Ursache praktisch aus. Der negative Pilznachweis und die Histologie waren schwer mit einer Candidiasis oder pustulösen Psoriasis vereinbar, sodass wir letzten Endes nach Ausschluss einer subkornealen Pustulose Sneddon-Wilkinson mittels positiver DIF einen IgA-Pemphigus diagnostizieren konnten.

Histopathologisch unterscheiden sich die beiden Varianten des IgA-Pemphigus beträchtlich. Während der SPD-Typ durch subkorneale Akantholysen mit konsekutiver Spalt- und Blasenbildung gekennzeichnet ist, zeigt der IEN-Typ lichtmikroskopisch einen Adhärenzverlust auf der gesamten Breite der Epidermis. In beiden Fällen prägen dichte Infiltrate neutrophiler Granulozyten das Bild [8]. Die zentrale Rolle in der Diagnose spielt jedoch die Immunfluoreszenz (IF): Typischerweise finden sich beim SPD-Typ – der Expression seines Autoantigens Dsc 1 entsprechend – in vivo gebundene IgA-Aak nur an Keratinozyten der oberen Epidermishälfte, während diese Aak beim IEN-Typ über die gesamte Epithelbreite verteilt sind [8]. Durch dieses spezifische immunmorphologische Färbemuster war in unserem Fall die Diagnose eines IgA-Pemphigus vom Typ der subkornealen pustulösen Dermatose nahezu eindeutig.

Auffallend ist, dass mittels der Standard IIF bei beiden Varianten nur in etwa 50% der Patienten zirkulierende IgA-Aak detektiert werden können [12]. Noch schlechter funktionieren biochemische Standarduntersuchungen wie Immunoblot und Immunpräzipitation. Der Grund könnte sein, dass manche Autoantigenbindungsstellen konformationsabhängige Epitope darstellen, die bei diesen Techniken denaturiert und von den Aak in vitro nicht mehr erkannt werden. Des Weiteren ist die Immunpräzipitation mit IgA methodisch nach wie vor nicht für Routineuntersuchungen geeignet [4]. Die definitive Diagnose eines IgA-Pemphigus

Zusammenfassung · Abstract

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IgA-Pemphigus vom Typ der subkornealen pustulösen Dermatose. Erfolgreiche Kombinationstherapie mit Dapson und Acitretin

Zusammenfassung

Der IgA-Pemphigus vom Typ der subkornealen pustulösen Dermatose ist eine seltene bullöse Autoimmundermatose aus der Pemphigusfamilie. Klinisch treten bevorzugt in den intertriginösen Arealen ausgedehnte Erytheme auf, die von zerreißlichen Vesikeln und Pusteln, gelegentlich mit Hypopyonbildung übersät sind. Histopathologisch imponieren subkorneale Akantholysen und Spaltbildung mit zahlreichen Neutrophilen im Spalt wie auch in der ödematösen papillären Dermis. In vivo binden die IgA-Autoantikörpern an Keratinozyten der oberen Hälfte der Epidermis. Als Autoantigen wurde Desmocollin 1, ein desmosomales Cadherin, identifiziert, das differenzierungsspezifisch an reifen Keratinozyten exprimiert wird. Der schwierige In-vitro-Nachweis des Autoantigens ist durch eine indirekte Immunfluoreszenzuntersuchung an Desmocollin-1-transfizierten COS7-Zellen möglich. Wir präsentieren hier einen Patienten mit einem therapierefraktären Verlauf, der nur durch den kombinierten Einsatz von Dapson und Acitretin beherrscht werden konnte.

Schlüsselwörter

IgA-Pemphigus · Subkorneale pustulöse Dermatose · Desmocollin · Dapson · Acitretin

IgA pemphigus of the subcorneal pustular dermatosis type. Successful therapy with a combination of dapsone and acitretin

Abstract

IgA pemphigus of the subcorneal pustular dermatosis type is a rare autoimmune blistering disease in the pemphigus spectrum. Patients are clinically characterized by extensive erythemas that primarily affect intertriginous areas. The erythematous macules are covered with numerous vesicles and pustules with occasional hypopyon formation. Histopathology shows subcorneal acantholysis with clefting and numerous neutrophils within the blister as well as in the edematous papillary dermis. IgA autoantibodies bind in vivo to keratinocytes within the upper half of the epidermis. Desmocollin 1, the autoantigen of this disease, is a member of desmosomal cadherins and is only expressed on more differentiated keratinocytes. The demonstration of circulating autoantibodies against desmocollin 1 in routine diagnosis is challenging and requires indirect immunofluorescence staining of desmocollin 1 transfected COS7 cells. We report a patient with a severe course of the disease who only responded to combined therapy with dapsone and acitretin.

Keywords

IgA pemphigus · Subcorneal pustular dermatosis · Desmocollin · Dapsone · Acitretin

Abb. 4 ▲ **a** Die indirekte Immunfluoreszenz von Patientenserum auf Dsc-1-transfizierten COS7-Zellen als Substrat zeigt eine deutliche Reaktivität. Diese Bindung von zirkulierendem IgA ist ein weiterer Hinweis darauf, dass Dsc 1 das Autoantigen dieser Erkrankung ist. **b, c** Die Färbungen auf Dsc 2 oder Dsc 3 exprimierenden COS7-Zellen sind negativ (Vergr. 300:1)

vom SPD-Typ kann derzeit am besten an Desmocollin-transfizierten COS7-Zellen gestellt werden [5]. Durch diese IIF-Färbungen identifizierten wir Dsc 1 als Autoantigen.

Desmocolline sind wie Desmogleine transmembrane Ca^{2+} abhängige Glykoproteine aus der Familie der desmosomalen Cadherine. Mit ihren extrazellulären Amino-terminalen Enden bilden sie mit den entsprechenden Proteinen der Nachbarzelle meist homo-, aber auch heterotypische Bindungen aus. Sie tragen so zur interzellulären Adhäsion bei und vermitteln damit Stabilität und Integrität der Epidermis. Die Expression der einzelnen Dsc-Isoformen in der Epidermis ist an den Differenzierungsgrad der Keratinozyten gebunden: Während Dsc 2 und Dsc 3 v. a. vom Stratum basale bis zum Stratum spinosum exprimiert werden, ist Dsc 1 auf das obere Stratum spinosum und v. a. das Stratum granulosum beschränkt [2].

Die pathogenetische Bedeutung der IgA-Aak gegen Dsc 1 ist bis heute weder in der Zellkultur noch in einem Tiermodell bewiesen. Spekuliert wird, dass beim IgA-Pemphigus vom SPD-Typ die Bindung der Aak die adhäsive Funktion von Dsc 1 beeinträchtigt, Folgen sind Akantholyse, Spalt- und schließlich Bläschenbildung. Letztere trüben durch den Einstrom zahlreicher Neutrophiler rasch ein. Diese wiederum tragen durch die Freisetzung ihrer proteolytischen Enzyme möglicherweise zur weiteren Degradation der Desmosomen bei [10].

Die Standardtherapie des IgA-Pemphigus erfolgt mit 4,4 Diaminodiphenylsulfon (DADPS, Dapson) 1–2 mg/kg/Tag [12, 13]. DADPS wird bei verschiedenen „neutrophilen Dermatosen" eingesetzt, da es

- die Extravasation neutrophiler Granulozyten verringert,
- die TNF-α-Synthese unterdrückt,
- die Neutrophilen-Myeloperoxidase blockiert und
- als Radikalfänger wirkt [7].

Alternativen dazu sind topische, v. a. aber systemische Steroide, Retinoide, PUVA, Colchizin sowie verschiedene Kombinationen selbiger [12, 13]. Anekdotisch wird in therapierefraktären Fällen über den erfolgreichen Einsatz von Immunsuppressiva wie Mycophenolat-mofetil – auch in Kombination mit Adalimumab – sowie Methotrexat und Cyclophosphamid berichtet [1, 3, 6, 13].

Primär konnten wir mit einer Kombinationstherapie aus Methylprednisolon 80 mg/Tag und DADPS 100 mg/Tag eine rasche Erscheinungsfreiheit erzielen, allerdings rezidivierten die Blasenschübe bei einer Steroiddosis von 20 mg/Tag. Da Retinoide die Differenzierung von Keratinozyten beeinflussen und v. a. die Migration von Neutrophilen und Monozyten hemmen [9], verabreichten wir zusätzlich Acitretin 35 mg/Tag. Daraufhin konnte das Steroid innerhalb von 3 Monaten ausgeschlichen werden. Auslassversuche von jeweils Dapson oder Acitretin führten prompt zu Rezidiven. Unter der Kombinationstherapie von Acitretin 35 mg/Tag und Dapson 100 mg/Tag konnte schlussendlich eine dauerhafte Remission erzielt werden.

Fazit für die Praxis

Der IgA-Pemphigus ist eine seltene, chronische, aber meist wenig aggressiv verlaufende bullöse Autoimmundermatose, welche die hautnahen Schleimhäute ausspart. Da die Autoantikörpertkonzentrationen oft niedrig sind, müssen immunpathologische Befunde bei klinischem und histologischem Verdacht sorgfältig erhoben und evtl. wiederholt werden. Hierbei kommt der Standard DIF und IIF sowie der IIF an transfizierten COS7-Zellen die zentrale diagnostische Bedeutung zu. Darüber hinaus machen therapierefraktäre Verläufe eine umfassende Risikoabwägung vor dem Einsatz nebenwirkungsreicher Therapeutika erforderlich. Die Kombination von Dapson und Acitretin ist dabei eine effiziente und zugleich schonende Alternative.

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Five Japanese cases of antidesmoglein 1 antibody-positive and antidesmoglein 3 antibody-negative pemphigus with oral lesions

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Summary

Background Oral mucosal lesions develop in pemphigus vulgaris, but not in pemphigus foliaceus. This clinical phenomenon is explained by the 'desmoglein (Dsg) compensation theory'. Dsg3 and Dsg1 are major autoantigens for pemphigus vulgaris and pemphigus foliaceus, respectively. Dsg3 is overexpressed and Dsg1 is weakly expressed on the oral mucosa. Thus, on the oral mucosa, suppression of Dsg3 function by anti-Dsg3 autoantibodies is not compensated by weakly expressed Dsg1 in pemphigus vulgaris, while suppression of Dsg1 function by anti-Dsg1 autoantibodies is perfectly compensated by richly expressed Dsg3 in pemphigus foliaceus.

Objectives We present five Japanese patients with pemphigus who deviate from this theory, i.e. all patients showed oral lesions (three also had cutaneous lesions) and reacted only with Dsg1, but not with Dsg3, by enzyme-linked immunosorbent assay.

Methods To confirm whether the unique clinical phenotypes in our patients were due to a different immunological profile from that in classical pemphigus, we examined the reactivity of the patient sera by immunoprecipitation-immunoblotting analysis using five Dsg1/Dsg2 domain-swapped molecules.

Results The sera of two patients who had only oral lesions tended to react with the extracellular (EC) 5 domain of Dsg1, the domain that is considered nonpathogenic in classical pemphigus foliaceus. Sera of three patients with mucocutaneous lesions reacted with EC1 domain or with both EC1 and EC2 domains of Dsg1, like classical pemphigus foliaceus.

Conclusions These results indicate that antigenic diversity of anti-Dsg1 antibodies in these patients may cause the unique oral mucosal and cutaneous lesions, although further studies are required to elucidate the pathomechanisms.

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Conflicts of interest
None declared.

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Pemphigus foliaceus (PF) is an autoimmune bullous disease, which clinically shows superficial blisters on the skin, but no oral mucosal lesions. PF is characterized immunologically by the presence of IgG autoantibodies reacting with desmoglein (Dsg) 1, a cell adhesion molecule of keratinocytes. In contrast, oral lesions occur frequently in patients with pemphigus vulgaris (PV) who have anti-Dsg3 antibodies. The difference in clinical phenotype between PF and PV is often explained using the 'Dsg compensation theory'.[1–3] According to this theory, anti-Dsg3 antibodies, but not anti-Dsg1 antibodies, cause oral mucosal lesions, as Dsg1 is only weakly expressed and Dsg3 is overexpressed on the oral mucosa.