Correlation of IgE Autoantibody to BP180 With a Severe Form of Bullous Pemphigoid

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**Objective:** To determine the prevalence, immunoglobulin subclass distribution, and clinical correlation of antibodies (Abs), especially of IgE Abs, to BP180 and BP230 in patients with bullous pemphigoid (BP).

**Design:** Retrospective case series analysis.

**Setting:** Department of Dermatology, Nagasaki University Graduate School of Biomedical Science.

**Patients:** Serum samples from 37 patients with BP, 6 with pemphigus vulgaris, 5 with pemphigus foliaceus, and 26 healthy controls (n=26) were examined by enzyme-linked immunosorbent assay.

**Main Outcome Measures:** Prevalence, immunoglobulin subclass distribution, and clinical correlation of Abs, especially of IgE Abs, to BP180 and BP230.

**Results:** IgG anti-BP180 and anti-BP230 Abs were detected in 35 (95%) and 26 (70%) of the 37 BP serum samples, respectively. IgG1 and IgG4 isotypes were positive in 32 (87%) and 25 (68%), respectively, of the BP serum samples for anti-BP180 Abs, while they were detected in 16 (44%) and 26 (70%), respectively, for anti-BP230 Abs. IgE anti-BP180 and anti-BP230 Abs were equally detected in 8 (22%) of the BP serum samples. Similar to IgG anti-BP180 Abs, the presence or levels of IgE anti-BP180 Abs was associated with broader skin lesions. Furthermore, patients with BP positive for IgE anti-BP180 Abs required longer duration for remission, higher dosage of prednisolone, and more intensive therapies for remission. By contrast, this was not true for those with IgE anti-BP230 Abs. Remarkably, when analyzed in patients with BP who had a high titer of IgG anti-BP180 Abs, the presence or levels of IgE anti-BP180 Abs, but not IgG anti-BP180 Abs, were associated with a more severe form.

**Conclusions:** The present study suggests that IgE anti-BP180 Abs are related to the disease severity and activity of BP. Moreover, it may be possible to identify treatment-refractory patients with BP more specifically by assessing the presence or levels of IgE anti-BP180 Abs in those with a high IgG anti-BP180 Ab titer.

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**Bullous Pemphigoid (BP) is the most common blistering autoimmune disease, in which patients have autoantibodies, mostly of the IgG class, to basement membrane zone (BMZ) components. The 230-kDa intracellular hemidesmosomal protein (BP230) and the 180-kDa transmembrane hemidesmosomal protein (BP180) have been identified as autoantigens in BP. It has been shown that the combination of enzyme-linked immunosorbent assay (ELISA) for BP180 and ELISA for BP230 is the highly sensitive method for the diagnosis of BP. Recently, specific ELISA kits have been made commercially available to accurately measure IgG anti-BP180 and BP230 antibody (Ab) levels in serum samples from patients with BP. In addition, it has been reported that IgG anti-BP180 Ab indexes determined by ELISA correlate with the disease activity. However, among patients with BP who had a high IgG anti-BP180 Ab ELISA titer, we sometimes encounter treatment-refractory patients who are resistant to moderate to high dosages of prednisolone, and consequently require other interventions, such as methylprednisolone pulse therapy, double-filtration plasmapheresis (DFPP), or other immunosuppressive agents. It would be difficult to identify these treatment-refractory patients at the early stage of disease, based only on IgG anti-BP180 Ab levels determined by ELISA.

The common features of BP are elevated serum total IgE levels and increased eosinophil counts that correlate with the disease severity. Moreover, the
presence of IgE anti-BMZ Abs in the lesional skin and serum has been reported. Therefore, it has been speculated that IgE-dependent mechanisms play some pathophysiologic roles in BP. A great deal of effort has been made on the relationship between clinical features of BP and subclass distribution of Abs, including IgE anti-BP180 and BP230 Abs. Delaporte et al reported that IgE anti-BP230 Abs were found in patients with a severe form of BP, but IgE anti-BP180 Abs were not detected. By contrast, Hofmann et al have reported that IgE reactivity to BP180 is clearly associated with a more severe phenotype of BP. In addition, Döpp et al have reported that IgG4 and IgE are major isotypes of autoantibodies to BP180 and that their serum levels reflect that disease activity.

Thus, the presence or prevalence of IgE autoantibodies to BP180 or BP230 and their clinical correlation were still controversial. Furthermore, previous studies seemed to be lacking in detailed clinical information regarding the area of skin lesions, treatment methods, the duration necessary for remission, serum eosinophil counts, serum IgE levels, and other laboratory data. Therefore, it remained unknown whether these autoantibodies, especially IgE isotypes, were associated with the disease severity and activity of BP or whether IgE autoantibodies could be a useful serological marker to identify treatment-refractory patients with BP. To clarify these issues, the presence or levels of IgE anti-BP180 and BP230 Abs, IgG subclass distribution, and their clinical correlation were investigated in the present study.

METHODS

SERUM SAMPLES AND CLINICAL ASSESSMENT

Serum samples were obtained from 37 Japanese patients with BP (19 women and 18 men). All patients represent typical clinical, pathologial, and immunological features of BP. By direct immunofluorescence, all patients showed IgG or C3 deposition along the BMZ of peribullous skin. The mean (SD) age of patients was 75 (11) years. Twenty-six age- and sex-matched healthy Japanese individuals were used as normal controls. We also used serum samples from 6 patients with pemphigus vulgaris and 5 patients with pemphigus foliaceus as disease controls. Fresh venous blood samples were centrifuged shortly after clot formation. All samples were stored at −70°C prior to use. Physical examinations and laboratory tests with complete medical histories were conducted for all patients. The area of skin lesions including erythema, blisters, and erosions was measured as percentage of body surface area at the time of blood sampling. A clinical remission was defined as follows: skin lesions healed completely, and only a low dose (<5 mg/d) of oral prednisolone or no treatment was needed to maintain this condition. Serial serum samples during the disease course were taken from 2 treatment-refractory patients with BP (case 1, a 51-year-old woman; and case 2, a 74-year-old woman). Although both patients were resistant to the moderate to high dosage of prednisolone or methylprednisolone pulse therapy, they were successfully treated with DFPP. Treatments and clinical course of each patient are summarized in Figure 1. Disease activity in each patient was arbitrarily assessed on a scale of 1 (the remission stage) to 4 (the highest activity) as previously described. The protocol was approved by the Nagasaki University Graduate School of Biomedical Sciences and Nagasaki University Hospital, Nagasaki, Japan, and oral informed consent was obtained from all patients.

ELISA FOR AUTOANTIBODIES TO BP180 AND BP230

Enzyme-linked immunosorbent assay for IgG anti-BP180 and anti-BP230 Abs was performed using specific ELISA kits (MBL Co Ltd, Nagoya, Japan) according to the manufacturer’s protocol. Results were evaluated as an index value that was calculated according to the manufacturer’s instructions. The cutoff value was 9 in both ELISA kits.

ELISA FOR TOTAL SERUM IgE LEVEL

Total serum IgE levels were assayed using a specific ELISA kit (DRG International Inc, Mountainside, New Jersey), according to the manufacturer’s protocol. The total serum IgE level in a normal, allergy-free adult is less than 100 IU/mL.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Mann-Whitney test for determining the level of significance of differences between sample means, the Fisher exact probability test for comparison of frequencies, and the Bonferroni test for multiple comparisons. Spearman rank correlation coefficient was used to examine the relationship between 2 continuous variables. \( \mu < .05 \) was considered statistically significant.

RESULTS

IgE ANTI-BP180 AND ANTI-BP230 Abs BY ELISA

The level and presence of IgE anti-BP180 and anti-BP230 Abs in serum samples from patients with BP, normal controls, and disease controls were assessed by ELISA (Figure 2). Optical density values greater than the mean + 2 SD values (0.103 for IgE anti-BP180 Abs and 0.0892 for IgE anti-BP230 Abs) of the normal controls were subsequently determined. Optical density values greater than the mean + 2 SD values of the normal controls were considered positive in this study.
IgG ANTI-BP180 AND ANTI-BP230 ABS BY ELISA AND THEIR SUBCLASS DISTRIBUTION

Of 37 patients with BP, 35 (95%) and 26 (70%) had IgG anti-BP180 Ab and anti-BP230 Ab ELISA index values, respectively, that exceeded the cutoff value (≥H/11022). Of the 37 BP serum samples, 36 (97%) were positive for either IgG anti-BP180 Abs or anti-BP230 Abs. Then, to characterize the subclass distribution of IgG anti-BP180 and anti-BP230 Abs, 37 BP serum samples were analyzed by ELISA for the presence of IgG1-4 anti-BP180 and anti-BP230 Abs (Figure 3). Optical density values greater than the mean + 2 SD values (0.158, 0.260, 0.148, and 0.068 for IgG1, IgG2, IgG3, and IgG4 anti-BP180 Abs, respectively; 0.470, 0.325, 0.272, and 0.104 for IgG1, IgG2, IgG3, and IgG4 anti-BP230 Abs, respectively) of normal controls were considered positive in this study. Of the 37 BP serum samples, IgG1 anti-BP180 Abs were detected in 32 (87%), IgG2 anti-BP180 Abs were detected in 7 (19%), IgG3 anti-BP180 Abs were detected in 9 (24%), and IgG4 anti-BP180 Abs were detected in 25 (68%), and 16 (44%) were positive for IgG1 anti-BP230 Abs, 5 (14%) were positive for IgG2 anti-BP230 Abs, 5 (14%) were positive for IgG3 anti-BP230 Abs, and 4 (11%) were positive for IgG4 anti-BP230 Abs.

Figure 1. Clinical course of 2 treatment-refractory patients with bullous pemphigoid. A, case 1; B, case 2. Abs indicates antibodies; DDS, diaphenylsulfone; DFPP, double-filtration plasmapheresis; and OD, optical density.
26 (70%) were positive for IgG4 anti-BP230 Abs. Thus, IgG1 and IgG4 were the major isotypes of both anti-BP180 and anti-BP230 Abs.

ASSOCIATION OF IgG AND IgE ANTI-BP180 ABS WITH DISEASE SEVERITY AND ACTIVITY OF BP

Then, we assessed clinical correlation of IgE anti-BP180 and anti-BP230 Abs in patients with BP. The presence of IgE anti-BP180 Abs was associated with broader skin lesions ($P = .02$; Table). Patients with BP positive for IgE anti-BP180 Abs required a higher prednisolone dosage ($P = .01$), longer duration necessary for remission ($P = .04$), and more intensive therapies (such as methylprednisolone pulse therapy, DFPP, or other immunosuppressive agents) for remission compared with those who were negative ($P = .03$) (Table). IgE anti-BP180 Ab levels also correlated positively with area of skin lesions ($r = 0.52$; $P = .002$), prednisolone dosage ($r = 0.44$; $P = .009$), and duration for remission ($r = 0.41$; $P = .03$) (Figure 4A-C). In addition, IgE anti-BP180 Ab levels correlated positively with IgG2 anti-BP180 Ab levels ($r = 0.38$; $P = .02$) and IgG4 anti-BP180 Ab levels ($r = 0.32$; $P = .04$). However, there was no significant correlation between IgE anti-BP180 Ab levels and IgG BP180 Ab levels ($r = 0.23$; $P = .17$). In addition, the presence or levels of IgE anti-BP180 Abs did not correlate with any other laboratory data, including serum eosinophil counts, IgE levels, white blood cell counts, and C-reactive protein levels (data not shown).

On the other hand, the presence of IgE anti-BP230 Abs was associated with elevated serum IgE levels ($P < .001$), IgG anti-BP230 Abs ($P < .001$), IgG1 anti-BP230 Abs ($P = .001$), and IgG4 anti-BP230 Abs ($P < .001$) (Table). IgE BP230 Ab levels also correlated with serum total IgE levels ($r = 0.48$; $P = .003$), IgG BP230 Ab levels ($r = 0.68$; $P < .001$), IgG1 anti-BP230 Ab levels ($r = 0.55$; $P < .001$), and IgG4 anti-BP230 Ab levels ($r = 0.63$; $P < .001$). However, the presence or levels of IgE anti-BP230 Abs did not correlate with area of skin lesions ($r = 0.13$; $P = .46$) and other clinical parameters or laboratory data (data not shown).

Regarding correlation of IgG and IgG1-4 anti-BP180 Ab or anti-BP230 Ab levels with clinical parameters, IgG anti-BP180 Ab levels correlated positively with area of skin lesions ($r = 0.69$; $P < .001$), prednisolone dosage ($r = 0.61$; $P < .001$), and duration for remission ($r = 0.54$; $P = .003$) (Figure 4D-F). IgG anti-BP180 Ab levels also correlated positively with IgG1 ($r = 0.72$; $P < .001$), IgG2 ($r = 0.72$; $P < .001$), IgG3 ($r = 0.43$; $P = .008$), and IgG4 anti-BP180 Ab levels ($r = 0.55$; $P < .001$). IgG1 anti-BP180 Ab levels correlated positively with area of skin lesions...
IgE Anti-BP180 Abs

<table>
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<tr>
<th>Characteristic</th>
<th>Positive, Mean (SD) (n=8)</th>
<th>Negative, Mean (SD) (n=29)</th>
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<td>Sex, No. (%)</td>
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<td>Male</td>
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<td>.55b</td>
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<td>Age, y</td>
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<td>Disease duration, mo</td>
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<td>Prednisolone dosage, mg/d</td>
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<td>Intensive therapies, No. (%)a</td>
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<td>3 (10)</td>
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<td></td>
<td>No</td>
<td>4 (50)</td>
<td>26 (90)</td>
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<td>Duration for remission, mo</td>
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<td>Area of skin lesions, %BSA</td>
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<td>14.8 (16.8)</td>
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<tr>
<td>IgG anti-BP180 Abs, index</td>
<td>129.3 (90.8)</td>
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<td>0.268 (0.582)</td>
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<td>Eosinophil count, cells/µL</td>
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<td>WBC count, cells/µL</td>
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<td>IgE, IU/L</td>
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<td>482 (310)</td>
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Abbreviations: BSA, body surface area; CRP, C-reactive protein; OD, optical density; WBC, white blood cell.

SI conversion factors: To convert CRP to nanomoles per liter, multiply by 9.524; to convert WBC and eosinophil counts to ×10⁹/L, multiply by 0.001.

a Intensive therapy includes methylprednisolone pulse therapy, double-filtration plasmapheresis, and immunosuppressive agents.

b Fisher exact test.

c Mann-Whitney test.

( r = 0.61; P < .001), prednisolone dosage ( r = 0.48; P = .004), duration for remission ( r = 0.38; P = .047), and serum C-reactive protein levels ( r = 0.39; P = .03). IgG2 anti-BP180 Ab levels correlated positively with area of skin lesions ( r = 0.71; P < .001), prednisolone dosage ( r = 0.45; P = .008), duration for remission ( r = 0.59; P < .001), and serum eosinophil counts ( r = 0.44; P = .01). In addition, IgG4 anti-BP180 Ab levels correlated positively with area of skin lesions ( r = 0.49; P = .004), prednisolone dosage ( r = 0.44; P = .009), and serum eosinophil counts ( r = 0.38; P = .03). However, IgG and IgG1-4 anti-BP180 Ab levels did not correlate with any other clinical parameters or laboratory data (data not shown). On the other hand, IgG1 anti-BP230 Ab levels correlated with serum IgE levels ( r = 0.48; P = .003), IgG1 anti-BP230 Ab levels ( r = 0.79; P < .001), and IgG4 anti-BP230 Ab levels ( r = 0.78; P < .001). In addition, both IgG1 and IgG4 anti-BP230 Ab levels correlated with serum IgE levels ( r = 0.43 [P = .008] and r = 0.61 [P < .001], respectively); however, they did not correlate with any other clinical parameters or laboratory data, including area of skin lesions (data not shown).

We compared the levels of IgE or IgG anti-BP180 Abs with the disease activity in 2 treatment-refractory patients with BP who were resistant to moderate to high dosages of prednisolone. Levels of IgG anti-BP180 and IgE anti-BP180 Abs correlated with the disease activity during the course of the disease (Figure 1). Thus, both IgG anti-BP180 and IgE anti-BP180 Abs were associated with the disease severity and activity of BP, whereas neither IgG anti-BP230 Abs nor IgE anti-BP230 Abs were associated with the disease severity as well as the disease activity of BP.

ASSOCIATION OF IgE ANTI-BP180 AB WITH A MORE SEVERE FORM OF BP

We analyzed patients with BP who had high index values (>150) of IgG BP180 Abs (n = 11 [4 patients with BP were positive for IgE anti-BP180 Abs and 7 were negative]). Despite no significant difference in IgG1 anti-BP180 Ab levels between patients with BP positive for IgE anti-BP180 Abs and those who were negative (Figure 5A), patients with BP positive for IgE BP180 Abs showed significantly broader skin lesions (P = .01) and required a higher prednisolone dosage (P = .006) and longer duration of remission (P = .01) (Figure 5B-D) compared with those who were negative. Furthermore, IgE anti-BP180 Ab levels showed strong correlation with area of skin lesions (r = 0.84; P = .002), prednisolone dosage

(r = 0.61; P < .001), prednisolone dosage (r = 0.48; P = .004), duration for remission (r = 0.38; P = .047), and serum C-reactive protein levels (r = 0.39; P = .03). IgG2 anti-BP180 Ab levels correlated positively with area of skin lesions (r = 0.71; P < .001), prednisolone dosage (r = 0.45; P = .008), duration for remission (r = 0.59; P < .001), and serum eosinophil counts (r = 0.44; P = .01). In addition, IgG4 anti-BP180 Ab levels correlated positively with area of skin lesions (r = 0.49; P = .004), prednisolone dosage (r = 0.44; P = .009), and serum eosinophil counts (r = 0.38; P = .03). However, IgG and IgG1-4 anti-BP180 Ab levels did not correlate with any other clinical parameters or laboratory data (data not shown). On the other hand, IgG1 anti-BP230 Ab levels correlated with serum IgE levels (r = 0.48; P = .003), IgG1 anti-BP230 Ab levels (r = 0.79; P < .001), and IgG4 anti-BP230 Ab levels (r = 0.78; P < .001). In addition, both IgG1 and IgG4 anti-BP230 Ab levels correlated with serum IgE levels (r = 0.43 [P = .008] and r = 0.61 [P < .001], respectively); however, they did not correlate with any other clinical parameters or laboratory data, including area of skin lesions (data not shown).

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By contrast, IgG BP180 Ab levels did not correlate with any of these clinical parameters (data not shown). Thus, IgE anti-BP180 Abs were associated with a more severe form of BP among patients with BP who had a high titer of IgG BP180 Abs.

COMMENT

In the present study, IgE anti-BP180 and IgE anti-BP230 Abs were equally detected in 8 of 37 patients with BP (22%). Interestingly, IgE anti-BP180 Ab levels correlated with area of skin lesions. Furthermore, patients with BP positive for this Ab required a higher prednisolone dosage, longer duration necessary for remission, and more intensive therapies for remission. In 2 treatment-refractory patients with BP, IgE anti-BP180 Ab levels also paralleled the disease activity. By contrast, neither the presence nor levels of IgE anti-BP230 Abs correlated with any of these clinical parameters, except for serum total IgE levels and IgG BP230 Ab levels. Thus, the results of the present study indicate that an elevated IgE anti-BP180 Ab level is associated with the disease severity and activity of BP, whereas the presence or levels of IgE anti-BP230 Abs are not.

Delaporte et al reported that IgE anti-BP230 Abs were found in patients with severe BP and that none of patients’ serum samples contained IgE autoantibodies to BP180. The factors causing this discrepancy seem to be the difference of assay system (ie, solid-phase radioimmuno-
munoassay or ELISA), or more importantly, selected populations of patients with BP. In their study, all BP serum samples were positive for anti-BP230 Abs by indirect immunofluorescence; however, only 37% were positive for anti-BP180 Abs. By contrast, in the present study, the prevalence of IgG anti-BP180 Abs (95%) was higher than that of IgG anti-BP230 Abs (74%). Therefore, this difference in the prevalence of IgG anti-BP180 and BP230 Abs may also be reflected as the difference in the prevalence of IgE autoantibodies.

Consistent with previous reports, in the present study, IgG anti-BP180 Ab ELISA titer correlated with the disease severity and activity of BP. Thus, both IgG and IgE anti-BP180 Ab levels were associated with the disease activity and severity of BP. To investigate which isotype of Ab would be more specific for a more severe form of BP, we analyzed clinical correlation of IgE or IgG anti-BP180 Abs in patients with BP who had a high (>150) IgG BP180 Ab titer. Remarkably, the prevalence of IgE anti-BP180 Abs was associated with broader skin lesions, and higher prednisolone dosage and longer duration required for remission. By contrast, IgG anti-BP180 Ab levels did not correlate with any of these parameters. Collectively, these results suggest that the presence of IgE anti-BP180 Abs in patients with BP who had a high IgG BP180 Ab ELISA titer could identify a more severe form of BP and that this IgE autoantibody is more useful than IgG anti-BP180 Ab to distinguish more patients with severe BP.

In the present study, we found that IgG1 and IgG4 were major IgG subclasses in patients with BP. In a mouse model, IgG anti-BP180 Abs with activated complement are pathogenic for blister formation. Because IgG1 and IgG3 are the major IgG subclasses with the strongest complement-fixing properties, these Abs are considered of pathogenic relevance for blister formation in BP. In addition to the effect of activated complement by these IgG autoantibodies, cellular mechanisms including mast cells, T-helper \( (T_h) \) cells, monocytes/macrophages, neutrophils, eosinophils, and their mediators have been suggested to be involved in blister formation in BP. Human B cells can be induced to proliferate and to switch with high frequencies to IgG4 and IgE production by \( T_s/2 \) cytokines, such as interleukin \( (IL)-4 \) and IL-13 that are elevated in the BP blister fluid. The correlation of IgE anti-BP180 Ab levels with disease severity, together with the findings that IgG4 was a major IgG subclass and that both IgG anti-BP180 Ab and anti-BP230 Ab levels correlated with IgG4 anti-BP180 and anti-BP230 Ab levels suggest the possible relevance of \( T_s/2 \) cells in the development of BP. Furthermore, it has been reported that there are IgE-bearing mast cells and eosinophils in the dermis of patients with BP, and that basophils from untreated patients with BP release histamine in response to exposure to recombinant NC16A. In a mouse model, Fc receptor-deficient mice are resistant to experimental BP. Therefore, it has been speculated that IgE anti-BP180 Abs are bound to eosinophils and mast cells through a high-affinity receptor for IgE in the lesion tissue of BP and that exposure of NC16A to these cells causes the degranulation and release of chemical mediators, such as histamine and tryptase, setting off an inflammatory cascade. Our finding that IgE anti-BP180 Abs were associated with a more severe form of BP may support this possibility. Moreover, it has been reported that glucocorticoids up-regulate CD40 ligand expression on lymphocytes. As CD40 ligand synergizes with IL-4 in activating deletional switch recombination to IgE, its up-regulation induces the synthesis of IgE by IL-4-stimulated human B cells. This may be one of the reasons why patients with BP positive for IgE anti-BP180 Abs required a higher prednisolone dosage to control the disease.

Although systemic corticosteroids are considered the standard treatment, BP is most common in elderly patients who poorly tolerate systemic corticosteroids. It has been shown that a high dose of systemic corticosteroids is more hazardous because of incidence and severity of adverse reactions. Therefore, steroid-sparing therapies are important. As patients with BP positive for IgE anti-BP180 Abs had a severe form of disease and required a higher prednisolone dosage, it would be preferable not to increase prednisolone dosage but to add other steroid-sparing therapies at the early stage of disease. In 2 patients with severe BP, prednisolone dosage could be successfully decreased by adding DFPP without severe adverse effects. Several studies have suggested that plasmapheresis is effective as a steroid-sparing agent in the treatment of BP. Furthermore, DFPP has a safety advantage because it removes only high-molecular-weight proteins including immunoglobulins, but not low-molecular-weight proteins such as albumin. Therefore, although the effectiveness of the plasmapheresis has not been established so far, it is a possible steroid-sparing therapy for a severe form of BP.

In conclusion, the present study suggests that IgE anti-BP180 Abs are related to the severity and activity of BP. In addition, it may be possible to identify treatment-refractory patients with BP more specifically by evaluating the presence or levels of IgE anti-BP180 Abs in those with a high IgG anti-BP180 Ab titer determined by ELISA.

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Author Contributions: Dr Sato had full access to the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Iwata, Komura, Kodera, and Sato. Acquisition of data: Iwata, Komura, Kodera, Usuda, Yokoyama, Haru, Muroi, Ogawa, Takenaka, and Sato. Analysis and interpretation of data: Iwata, Komura, Kodera, and Sato. Drafting of the manuscript: Iwata. Critical revision of the manuscript for important intellectual content: Iwata, Komura, Kodera, Usuda, Yokohama, Haru, Muroi, Ogawa, Takenaka, and Sato. Study supervision: Komura and Sato.

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