Circulating bullous pemphigoid 180 autoantibody can be detected in a wide spectrum of patients with other dermatologic conditions: A cross-sectional study

To the Editor: Detection of serum bullous pemphigoid 180 (BP180) autoantibody by enzyme-linked immunosorbent assay (ELISA) has proven a practical and reliable diagnostic test for bullous pemphigoid (BP).[1] However, in multiple studies, elevated serum BP180 autoantibody has been reported in non-BP dermatologic conditions,[2-4] highlighting the necessity to reevaluate the presence of BP180 autoantibody in non-BP dermatologic conditions and establish an optimized cutoff value to better differentiate genuine BP from BP-like conditions.

To achieve these goals, we performed a cross-sectional study including all the in-patients who were tested for serum BP180 autoantibody during March 2016-October 2017 in a tertiary dermatologic center in Shanghai, China. The serum level of BP180 autoantibody was analyzed by using the commercially available BP180 NC16A ELISA (MBL, Nagoya, Japan), for which a result >9 U/mL was defined as abnormal. Receiver operating characteristic (ROC) curve analysis, a plot of the test sensitivity versus 1 −specificity (Fig 1), was used to generate paired sensitivity and specificity values on the basis of the input BP180 autoantibody titers through SPSS software (version 21.0, IBM, Armonk, NY). The optimum cutoff value to differentiate BP from non-BP patients was calculated on the basis of maximizing the Youden index (J = sensitivity + specificity − 1).

A total of 173 in-patients were included, consisting of 26 patients with BP and 147 patients with other dermatologic conditions for whom a BP diagnosis was suspected but later excluded. On the basis of a comprehensive assessment of clinical, histologic, and immunologic findings, we found 14.3% (21/147) of patients with non-BP dermatologic conditions showed abnormal BP180 autoantibodies (Table I). Serum BP180 autoantibodies were found in 7.69% (4/52) of eczema patients, 12% (3/25) of pemphigus patients, 4.34% (1/23) of erythema multiform patients, 7.14% (1/14) of prurigo patients, and 44.4% (4/9) of Stevens-Johnson syndrome. In these diseases, the primary inflammation around the basement membrane zone might lead to the exposure or release of BP180 antigen and subsequent hormonal immune responses, as hypothesized by former researchers.[2,4,5]

The titers of BP180 autoantibodies in non-BP patients were significantly lower than those of genuine BP patients, with a median titer of 17.1 U/mL (n = 21) versus 67.1 U/mL (n = 19, $P < .0001$, Mann-Whitney test). ROC analysis was then performed to optimize the cutoff value that could differentiate BP from non-BP patients more effectively. On the basis of maximizing the Youden index (J = sensitivity + specificity − 1), the optimum cutoff value was set at 27.2 U/mL, which has a sensitivity of 65.4% and a specificity of 98.0% (Youden index $J = 0.633$). By contrast, the standard cutoff value of 9 U/mL achieved a higher sensitivity of 73.1% but much lower specificity of 85.7% (Youden index $J = 0.588$). The relatively lower sensitivity of our study was probably due to the control group consisting of only patients with active BP-like dermatologic conditions and no healthy persons.

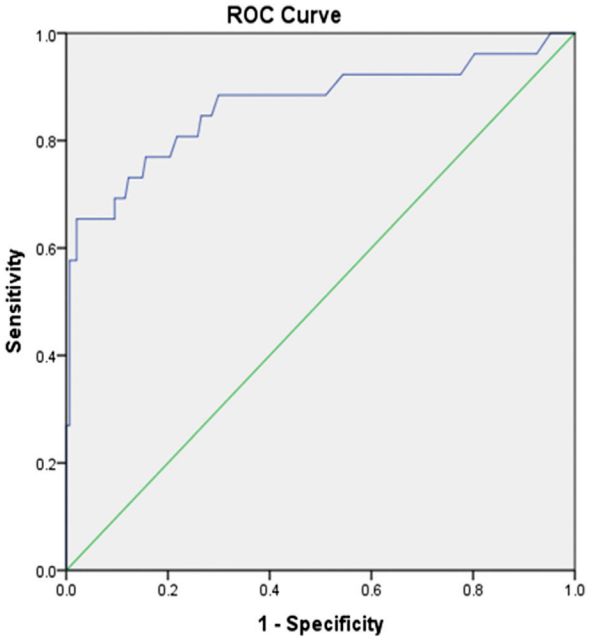

Fig 1. ROC curve for bullous pemphigoid 180 (BP180) autoantibody diagnostic test. Serum BP180 autoantibody was measured in 173 dermatologic in-patients seen during March 2016-October 2017 by using the BP180 NC16A ELISA (MBL, Nagoya, Japan). The performance of this test, measured by the area under the curve, was 0.866. When maximizing the Youden index (J = sensitivity + specificity − 1), the optimum cutoff value was set at 27.2. *ROC*, Receiver operative characteristic.

In brief, our results indicated that low-level serum BP180 autoantibodies could also be detected in patients with a wide range of non-BP skin diseases and, therefore, should be interpreted cautiously with clinical and immunopathologic findings. Besides, the prevalence we presented was in-line with the previously reported prevalence of abnormal serum

Table I. Summary of 21 non-BP inpatients with abnormal serum BP180 autoantibodies

Case no./sex/age, y	Diagnosis	BP180, U/mL	DIF	IIF pattern	IIF titer
1/M/33	Stevens-Johnson syndrome	23.1	Negative	Negative	<1:10
2/M/75	Stevens-Johnson syndrome	13.4	Negative	Negative	<1:10
3/F/28	Stevens-Johnson syndrome	12.4	Negative	Negative	<1:10
4/M/54	Stevens-Johnson syndrome	12.3	Negative	Negative	<1:10
5/M/24	Toxic epidermal necrolysis	17.1	Negative	Negative	<1:10
6/M/44	Lichen planus	24.5	Negative	Negative	<1:10
7/M/36	Atopic dermatitis	20.8	Negative	Negative	<1:10
8/M/49	Erythema annulare centrifugum	10.8	Negative	Negative	<1:10
9/M/67	Erythrodermic psoriasis	12.2	Negative	Negative	<1:10
10/M/60	Pemphigus erythematosus	15	IgG/C3 intercellular	Intercellular	1:40
11/F/45	Pemphigus vulgaris	11.5	IgG/IgM/C3 intercellular	Intercellular	1:10
12/M/17	Paraneoplastic pemphigus	11.3	IgG/C3 intercellular	Intercellular	1:40
13/M/49	Disseminated eczema	20.9	Negative	Negative	<1:10
14/F/64	Disseminated eczema	18.3	Negative	Negative	<1:10
15/M/57	Disseminated eczema	13.5	Negative	Negative	<1:10
16/F/71	Disseminated eczema	11.3	Negative	Negative	<1:10
17/F/57	Prurigo nodularis	19.8	Negative	Negative	<1:10
18/F/25	Erythema multiforme	35.5	Negative	Intercellular	1:10
19/F/56	Behcet disease	26.7	Negative	Negative	<1:10
20/M/39	Cutaneous T-cell lymphoma	30.3	Negative	Negative	<1:10
21/F/60	Pyodermatitis-pyostomatitis vegetans	80	Negative	Negative	<1:10

BP, Bullous pemphigoid; *BP180*, bullous pemphigoid 180; *C3*, complement 3; *DIF*, direct immunofluorescence; *IIF*, indirect immunofluorescence.

BP180 autoantibodies in patients with senile pruritus[3] (12%, N = 25), lichen planus[4] (17%, N = 47), and lichen sclerosus[5] (6%, N = 51).

In addition, we found that the cutoff value of 27.2 U/mL might achieve a satisfying specificity of 98.0%, which should be validated in further studies with larger sample sizes. Establishment of the proper cutoff value could better the diagnostic performance of the BP180 autoantibody ELISA test in future clinical practice.

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2-Methoxymethyl-*para*-phenylenediamine–containing hair dye as a less allergenic alternative for *para*-phenylenediamine–allergic individuals

To the Editor: Para-phenylenediamine (PPD) is the most common allergen specifically associated with allergic contact dermatitis to hair dyes.[1] The rate of positive PPD patch test results is approximately 6.2% in North America and 4% in both Europe and Asia.[1]