

Clinical Letter

Specific IgE to *Staphylococcus aureus* superantigens in patients affected by bullous pemphigoid

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Dear Editors,

Recently it has been proved that IgE against BP180 and BP230 are involved in bullous pemphigoid (BP) pathogenesis [1], with IgE anti-BP180 related to the disease severity and activity [2]. An elevated serum level of allergen-specific IgE antibodies is also a sign of an atopic disease (AD). Specific IgE against staphylococcal superantigens (SsAgs) are found in approximately 80 % of patients with severe AD [3]. SsAgs are exotoxins and comprise staphylococcal enterotoxin (SE) A, SEB, SEC, SED and toxic shock syndrome toxin-1 (TSST-1) [4]. We investigated whether BP patients produce IgE antibodies specific to antigens other than BP180 and BP230 and the possible effects on the clinical outcome of the disease.

A prospective observational study was conducted involving patients with BP and two groups of control: IgE-positive atopic and healthy patients. Demographic data and a blood sample were collected for each patient for the determination of total IgE, specific IgE against BP180, BP230, and the four staphylococcal toxins. IgE value was considered positive above 250 kU/l. Bullous Pemphigoid Disease Area Index (BPDAI) was used to evaluate the disease activity. A total of 120 patients (70 men, 50 women) were enrolled, with a mean age of 76 ± 11 years. Forty patients (23 men and 17 women, mean age 78 years) presented active BP, forty patients (28 men and 12 women, mean age 76 years) were a control group affected by IgE positive atopy, and forty patients (19 men and 21 women, mean age 75 years) constituted the healthy control group.

The mean total IgE value was 739.8 KU/l for the pemphigoid group, 1123.43 KU/l for the atopic group; 50.47 KU/l for the non-atopic group. The variability analysis performed with the Kruskal-Wallis test showed significant differences in total IgE values in the three groups and also in the comparison between the individual groups ($P < 0.008$).

IgE against toxic shock syndrome toxin-1 (TSST-1) were present in 32 atopic patients (80 %, mean value 2.59 kUA/l), in 3 non-atopic patients (7.5 %, mean value 0.18 kUA/l) and in 24 pemphigoid patients (60 %, mean value 1.49 kUA/l). IgE against Staphylococcal enterotoxin A (SEA) were present in 18 patients of the atopic group (45 %, mean value

0.72 kUA/l), in one patient of the non-atopic group (2.5 %, 0.08 kUA/l) and in twelve patients of the pemphigoid group (30 %, mean value 0.48 kUA/l). IgE against Staphylococcal enterotoxin B (SEB) were present in 25 patients of the atopic group (62.5 %, mean value 1.49 kUA/l), in two patients of the non-atopic group (5 %, mean value 0.19 kUA/l) and in 14 patients of the pemphigoid group (35 %, mean value 0.81 kUA/l). IgE against Staphylococcal enterotoxin C (SEC) were present in 24 patients of the atopic group (60 %, mean value 1.78 kUA/l), in one patient of the non-atopic group (2.5 %, 0.11 kUA/l) and in 15 patients of the pemphigoid group (37.5 %, mean value 0.67 kUA/l). Figure 1 provides an overview of the data.

Although the variability analysis using the Kruskal-Wallis test showed no statistically significant difference in levels of specific IgE among the atopic and pemphigoid group, patients affected by BP showed higher levels of specific IgE to SsAgs compared to healthy controls (except for SEC, which was different among the three groups with $P < 0.008$).

Table 1 shows the characteristics of pemphigoid patients divided according to whether total IgE was above the normal value or not. Patients with high total IgE show a tendency to a shorter disease duration, a more severe clinical and serological form and marked positivity for all four staphylococcal toxins. This finding might be in line with other studies correlating IgE levels with disease activity [5–7], to be included in a Th2-oriented inflammatory response, but the question is still debated [8, 9].

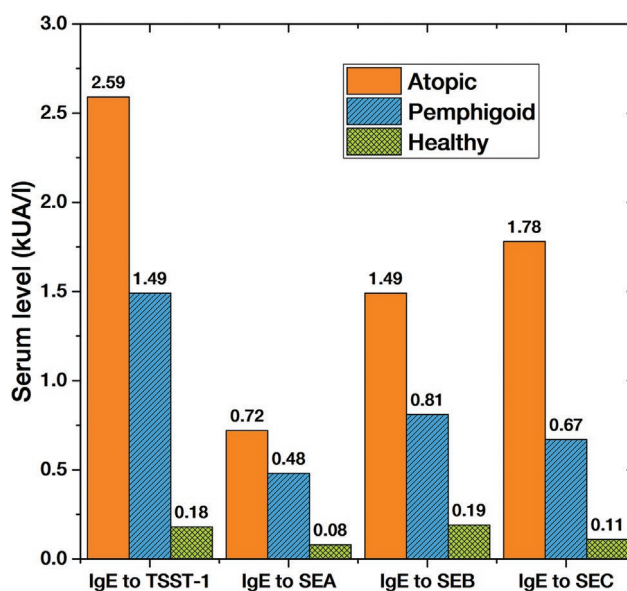


Figure 1 Specific IgE levels against the staphylococcal superantigens. *Abbr.*: TSST-1, toxic shock syndrome toxin-1; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; SEC, staphylococcal enterotoxin C.

Table 1 Characteristics of pemphigoid patients divided according to the total IgE level.

	IgE value above the normal range	IgE value within the normal range
Number (men, women)	23 (16, 7)	17 (7, 10)
Mean age (years)	79.2	76.4
Mean disease duration (months)	13	18
Mean BPDAI	55.57	35.70
Urticarial lesions	17 (73.9 %)	11 (64.7 %)
Mean SEA value (number of positive patients, %)	0.78 (12, 52.2 %)	0.04 (0, 0 %)
Mean SEB value (number of positive patients, %)	1.36 (14, 60.9 %)	0.05 (0, 0 %)
Mean SEC value (number of positive patients, %)	1.12 (14, 60.9 %)	0.07 (1, 5.9 %)
Mean TSST-1 value (number of positive patients, %)	2.43 (19, 82.6 %)	0.21 (5, 29.4 %)
At least one specific IgE to SsAgs positivity	22 (95.7 %)	6 (35.3 %)
Mean BP180 value (number of positive patients, %)	67.97 (20, 87.0 %)	47.84 (12, 70.6 %)
Mean BP230 value (number of positive patients, %)	45.90 (17, 73.9 %)	13.92 (6, 35.3 %)

Abbr.: BPDAI, Bullous Pemphigoid Disease Area Index; TSST-1, toxic shock syndrome toxin-1; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; SEC, staphylococcal enterotoxin C; SsAgs, staphylococcal superantigens.

The presence of IgE directed towards exogenous antigens/allergens in the BP subjects has never before been taken into consideration. Although a pathogenetic role cannot be demonstrated, our data show that the presence of staphylococcal toxins may play an aggravating role in clinical presentation, as suggested by the higher mean BPDAI value in sensitized patients (49.82 vs. 40.83), despite lacking statistical significance. This would further justify the clinical efficacy of therapeutic protocols considering the initial use of systemic antibiotics with anti-inflammatory properties [10], such as doxycycline [11, 12]. Interestingly, IgE directed toward staphylococcal exotoxins were present even in patients with mainly urticarial manifestations and no statistically significant difference was present when comparing specific IgE values at baseline and after six months of treatment, indicating that the specific IgE level are not influenced by the disease activity [2, 13]. Nevertheless, it is still possible that specific IgE to SsAgs represents a skin barrier dysfunction and is not a specific finding for BP.

It has been reported that total IgE increases during aging, with a peak in the oldest subgroup (> 85 years), which is most at risk for developing BP [14]. The same study states that allergen-specific IgE levels significantly decreased with age, indirectly confirming that the findings of specific IgE to SsAgs in BP patients is not casual [14].

Conflict of interest

None.

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References

- 1 Freire PC, Muñoz CH, Stingl G. IgE autoreactivity in bullous pemphigoid: eosinophils and mast cells as major targets of pathogenic immune reactants. *Br J Dermatol* 2017; 177(6): 1644–53.
- 2 Döpp R, Schmidt E, Chimanovitch I et al. IgG4 and IgE are the major immunoglobulins targeting the NC16A domain of BP180 in bullous pemphigoid: Serum levels of these immunoglobulins reflect disease activity. *J Am Acad Dermatol* 2000; 42(4): 577–83.
- 3 Nomura I, Tanaka K, Tomita H et al. Evaluation of the staphylococcal exotoxins and their specific IgE in childhood atopic dermatitis. *J Allergy Clin Immunol* 1999; 104(2 Pt 1): 441–6.
- 4 Leung DYM, Hauk P, Strickland I et al. The role of superantigens in human diseases: Therapeutic implications for the treatment of skin diseases. *Br J Dermatol* 1998; 139(Suppl 53): 17–29.
- 5 Ghohestani RF, Cozzani E, Delaporte E et al. IgE antibodies in sera from patients with bullous pemphigoid are autoantibodies preferentially directed against the 230-kDa epidermal antigen (BP230). *J Clin Immunol* 1998; 18(3): 202–9.
- 6 Kelly LA, Holubkov R, Campbell MA et al. Serum IgE concentrations in bullous pemphigoid correlate with disease activity. *J Allergy Clin Immunol* 2007; 119(1): S204.
- 7 Kalowska M, Ciepiela O, Kowalewski C et al. Enzyme-linked immunoassay index for anti-NC16a IgG and IgE auto-antibodies correlates with severity and activity of bullous pemphigoid. *Acta Derm Venereol*. 2016; 96(2): 191–6.
- 8 Cozzani E, Parodi A, Rebora A et al.; Gruppo Ligure di Studi in Dermatologia (GLISID). Bullous pemphigoid in Liguria: a 2-year survey. *J Eur Acad Dermatol Venereol* 2001; 15(4): 317–9.
- 9 Delli FS, Sotiriou E, Lazaridou E et al. Total IgE, eosinophils, and interleukins 16, 17A, and 23 correlations in severe bullous pemphigoid and treatment implications. *Dermatol Ther* 2020; 33(6): e13958.
- 10 Henehan M, Montuno M, De Benedetto A. Doxycycline as an anti-inflammatory agent: updates in dermatology. *J Eur Acad Dermatol Venereol* 2017; 31(11): 1800–8.
- 11 Williams HC, Wojnarowska F, Kirtschig G et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. *Lancet* 2017; 389(10079): 1630–8.
- 12 Krakauer T, Buckley M. Doxycycline is anti-inflammatory and inhibits staphylococcal exotoxin-induced cytokines and chemokines. *Antimicrob Agents Chemother* 2003; 47(11): 3630–3.
- 13 Iwata Y, Komura K, Kidera M et al. Correlation of IgE autoantibody to BP180 with a severe form of bullous pemphigoid. *Arch Dermatol* 2008; 144(1): 41–8.
- 14 De Amici M, Ciprandi G. The age impact on serum total and allergen specific IgE. *Allergy Asthma Immunol Res* 2013; 5(3): 170–4.