## Reply to: "Pruritus with pemphigoid autoantibodies is the tip of an iceberg"

*To the Editor*: We appreciate the response of Dr Byth to our article,[1] and we agree that nonbullous pemphigoid (NBP) deserves more attention in the clinical practice guidelines for chronic pruritus because it is a rather unknown cause of chronic pruritus in elderly patients.[2,3] We politely disagree with Dr Byth that patients with NBP who have pruritus without rash should be referred to as having *pruritus with pemphigoid autoantibodies (PPA)*. First, we advocate for *NBP* as umbrella term for all pemphigoid variants without blisters and believe that introducing the term *PPA* is needless and confusing. Second, *PPA* does not accurately describe the intended population of patients with NBP without primary skin lesions because all patients with bullous pemphigoid (BP) and NBP experience pruritus and have pemphigoid autoantibodies.

Dr Byth questioned whether testing for pemphigoid autoantibodies in elderly patients with pruritus would be cost effective. In our opinion, the burden of disease in these patients with chronic pruritus is too high to deny them a possible diagnosis of NBP and adequate therapy. Therefore, we included pemphigoid in the standard diagnostic workup of elderly patients with chronic pruritus.

We would like to emphasize that caution is needed if only enzyme-linked immunosorbent assay (ELISA) is used as a screening method because this yields frequent false positive results. The recently published article by Wang et al.[4] reports positive BP180 and BP230 autoantibodies by ELISA in 208 patients with negative results from direct immunofluorescence (DIF) of skin biopsy samples. Various lesion morphologies were described in these patients, most commonly dermatitis but also essential pruritus. The researchers concluded that low positive levels of BP180 and BP230 autoantibodies by ELISA should not be overinterpreted as evidence for BP in the setting of a negative DIF result, and they still consider DIF positivity to be the criterion standard for diagnosis of NBP.

Recent work of our group assessed this clinical dilemma with a diagnostic accuracy study in 1125 patients suspected of having NBP or BP, providing minimal diagnostic criteria.[5] Indirect immunofluorescence (IIF) on salt-split skin (SSS) showed a positive predictive value for diagnosis of pemphigoid of 99.6%, and therefore it plays an essential role for the serologic diagnosis of pemphigoid. The BP180 NC16A ELISA showed frequent false positivity (11.3%) and is not recommended for initial diagnosis but only for monitoring in patients with confirmed disease. The established minimal diagnostic criteria consist of a 2-out-of-3 rule: (1) pruritus and/or predominant cutaneous blisters, (2) linear (n-serrated) IgG and/or C3c deposits by DIF on a skin biopsy specimen, and (3) positive epidermal side staining of IgG by IIF SSS on a serum sample. This extends the spectrum of pemphigoid to the unrecognized nonbullous variant and allows a diagnosis with a negative DIF result.

Our article complements the study of Wang et al[4] by showing the use of the minimal diagnostic criteria in the broad spectrum of NBP. In conclusion, not all patients with *pruritus with pemphigoid autoantibodies* with ELISA positivity have pemphigoid, and IIF SSS positivity is essential for diagnosis in cases with a negative DIF result.

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**REFERENCES**

1. Lamberts A, Meijer JM, Pas HH, Diercks GFH, Horvath B, Jonkman MF. Nonbullous pemphigoid: insights in clinical and diagnostic findings, treatment responses and prognosis. *J Am Acad Dermatol*. 2019;81(2):355-363.
2. Weisshaar E, Szepietowski JC, Dalgard FJ, et al. European S2k guideline on chronic pruritus. *Acta Derm Venereol*. 2019;99(5):469-506.
3. Millington GWM, Collins A, Lovell CR, et al. British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. *Br J Dermatol*. 2018;178(1):34-60.

4. Wang M, Lehman JS, Camilleri MJ, Drage LA, Wieland CN. Circulating bullous pemphigoid autoantibodies in the setting of negative direct immunofluorescence findings for bullous pemphigoid: a single-center retrospective review. *J Am Acad Dermatol*. 2019;81(2):472-479.

5. Meijer JM, Diercks GFH, de Lang EWG, Pas HH, Jonkman MF. Assessment of diagnostic strategy for early recognition of bullous and nonbullous variants of pemphigoid. *JAMA Dermatol*. 2019;155(2):158-165.

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