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Pemphigoid diseases: Insights in the nonbullous variant and disease management

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4A

CHAPTER 4A

Reply to: “Pruritus with pemphigoid autoantibodies is the tip of an iceberg”

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To the editor: We appreciate the response of dr. Byth to our article¹, and agree that nonbullous pemphigoid (NBP) deserves more attention in the clinical practice guidelines for chronic pruritus, as a rather unknown cause of chronic pruritus in elderly patients.^{2,3} We politely disagree with dr. Byth that NBP patients with pruritus without rash should be referred to as '*pruritus with pemphigoid autoantibodies (PPA)*'. Firstly, we advocate for NBP as umbrella term for all pemphigoid variants without blisters, and believe that introducing the term PPA is needless and confusing. Secondly, PPA does not accurately describe the intended population of NBP patients without primary skin lesions, since 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 like to emphasize that caution is needed if only ELISA is used as screening method, as these have frequent false positive results. The recently published article of Wang *et al.*⁴ reports positive BP180 and BP230 autoantibodies by ELISA in 208 patients with a negative skin biopsy for direct immunofluorescence (DIF). Various lesion morphologies were described in these patients, most commonly dermatitis, but also essential pruritus. The authors conclude that low positive levels of BP180 and BP230 autoantibodies should not be overinterpreted as evidence for BP in the setting of a negative DIF, and still consider DIF positivity to be the golden standard for diagnosis of NBP.

Recent work of our group assessed this clinical dilemma with a diagnostic accuracy study in 1125 patients suspected of NBP or BP, providing minimal diagnostic criteria.⁵ IIF on salt-split skin (SSS) showed a positive predictive value for diagnosis of pemphigoid of 99.6%, and therefore plays an essential role for the serological diagnosis of pemphigoid. The BP180 NC16A ELISA showed frequent false-positivity (11,3%) and is not recommended for initial diagnosis, but only for disease monitoring in confirmed patients. The established minimal diagnostic criteria consists 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. Thereby, extending the spectrum of pemphigoid with the unrecognized nonbullous variant, and allowing a diagnosis with negative DIF.

Our article complements the study of Wang *et al.*, demonstrating 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 DIF negative cases.

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