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LETTER TO THE EDITOR

Response to Letter to the editor of Borradori et al. How to diagnose bullous pemphigoid and its variants: the question is still open

Dear Editor

With interest, we read the recent letter by Borradori *et al.*,¹ giving their opinion on how to diagnose bullous pemphigoid and its variants. The discussion about diagnosis of pemphigoid diseases has been continuous and is needful since no evidence-based diagnostic criteria are established yet and more than 20% of patients with bullous pemphigoid do not present with initial skin blistering.^{2–4} In the non-bullous pemphigoid variant, clinical features are not as recognizable as in typical bullous pemphigoid and histopathology is often non-specific, opposing a real diagnostic challenge and potential diagnostic delay.⁵

In the letter, the authors state that dermatologists should not diagnose bullous or non-bullous pemphigoid based on indirect immunofluorescence microscopy (IIF) findings alone, because of borderline results of serological tests, the need of a thorough assessment of elderly with chronic itch and the consequence of overdiagnosing patients with pemphigoid leading to considerable morbidity and mortality. The authors address that direct immunofluorescence microscopy (DIF) is adopted as an essential criterion to diagnose BP by a European panel of experts.

Their opinion is directed against a recently published multi-variable diagnostic accuracy study by our group and suggested minimal diagnostic criteria for bullous and non-bullous pemphigoid.⁶

In this study, pairwise testing of DIF, IIF on human salt-split skin (IIF SSS), IIF on monkey oesophagus, BP180 and BP230 enzyme-linked immunosorbent assays (ELISA) and immunoblot for BP180 and BP230 were analysed in 1125 consecutive patients with suspected bullous or non-bullous pemphigoid. In absence of evidence-based diagnostic criteria, criteria for diagnosis of the 2015 German S2k Guideline were used as a composite reference standard.⁷ Although positive linear DIF is adopted as essential criterion for BP by experts, it does not provide an error-free classification of bullous pemphigoid.^{6–8} For example, biopsy site for DIF influences sensitivity, DIF sensitivity has not previously been studied sufficiently in non-bullous patients and a differential diagnosis of epidermolysis bullosa acquisita remains.⁶

Our study confirmed results of the study of Sárdy *et al.*⁸ in BP ($n = 313$) with similar sensitivity and specificity of DIF (90.8%; 98.0%) and IIF SSS (76.0%; 100%). When re-analysing our data of only BP in our study (and excluding all non-bullous patients), sensitivity of 76.2% and specificity of 100% was seen for IIF SSS. No statistical difference was found for DIF and IIF SSS between bullous and non-bullous patients.⁶ Both DIF and IIF SSS are excellent diagnostic tests to correctly identify patients with pemphigoid, comparing diagnostic tests with only DIF as reference will lead to biased accuracy estimates.

An important distinction should be made by the authors between the frequently published borderline results by ELISA, IIF on monkey oesophagus or immunoblot and the high specificity of IIF SSS. The mentioned retrospective case series by Wang *et al.*⁹ is a good example of borderline ELISA results and the need for diagnostic criteria. Wang *et al.* conclude low positive BP180 and BP230 autoantibody levels (by ELISA) should not be overinterpreted as evidence for BP in the setting of a negative DIF, a conclusion we support with our study. Unfortunately, no IIF SSS was performed by Wang *et al.* We found 11.3% single false-positive ELISA results among 782 controls with various dermatoses or only pruritus.⁶ Moreover, no additional diagnostic value of ELISA was seen compared to IIF SSS, and we recommended to only perform ELISA as add-on test after confirmed diagnosis to prevent these borderline results.⁶

We completely agree with the authors that elderly patients with chronic itch require a thorough assessment. As a matter of fact, we routinely perform both DIF and IIF SSS in the thorough assessment of patients with chronic itch or prurigo, to identify these patients with non-bullous pemphigoid included in our study.^{5,10}

Conflicts of interest

None declared.

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