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Clinical Pearls

Clinical Pearls help prepare residents for the future by providing them with top tips from experts about what they should know about specific, key subject areas by the time they complete their residency.

Pearls for autoimmune bullous dermatoses

By Sylvia Hsu, MD

Pearl #1: I don't perform mouth biopsies for pemphigus vulgaris anymore, since ELISA is more reliable than histopathology and DIF for the diagnosis.

The most accurate diagnostic and disease activity-monitoring tool for pemphigus vulgaris (PV) and pemphigus foliaceus (PF), anti-Dsg3 ELISA has a sensitivity of 97% and specificity of 98% in PV. Anti-DSG1 ELISA had a sensitivity of 96% and specificity of 99% in PF. The location of the split on histopathologic examination classically distinguishes PV and PF; however, in practice there is variability and overlap in the level of clefting. In PV and PF, DIF reveals intercellular binding of IgG or C3 in the epidermis with 90 – 100% sensitivity. In PF, epifluorescence is stronger in the upper epidermis but stronger in the lower epidermis in PV; however, this differentiation based on the concentration of the target antigen is not always reliable.

References:

1. Ohata C, Ishii N, Furumura M. Locations of acantholysis in pemphigus vulgaris and pemphigus foliaceus. *J Cutan Pathol.* 2014; 41:880-889.
2. Schmidt E, Dähnrich C, Rosemann A, et al. Novel ELISA systems for antibodies to desmoglein 1 and 3: correlation of disease activity with serum autoantibody levels in individual pemphigus patients. *Exp Dermatol.* 2010; 19:458-463.
3. Tampona M, Giavarina D, Di Giorgio C, et al. Diagnostic accuracy of enzyme-linked immunosorbent assays (ELISA) to detect anti-skin autoantibodies in autoimmune blistering skin diseases: a systematic review and meta-analysis. *Autoimmun Rev.* 2012; 12:121-126.
4. Ishii K, Amagai M, Hall RP, et al. Characterization of autoantibodies in pemphigus using antigen-specific enzyme-linked immunosorbent assays with baculovirus-expressed recombinant desmogleins. *J Immunol.* 1997; 159:2010-2017.
5. Tjarks BJ, Billings SD, Ko JS. Efficacy of Triaging Direct Immunofluorescence in Intraepidermal Bullous Dermatoses. *Am J Dermatopathol.* 2018; 40:24-29.
6. Chowdhury J, Datta PK, Chowdhury SN, et al. A Clinicopathological Study of Pemphigus in Eastern India with Special Reference to Direct Immunofluorescence. *Indian J Dermatol.* 2016; 61:288-294.

Pearl #2: In practice, the DIF (and the histopathology) of dermatitis herpetiformis (DH) and linear IgA bullous dermatosis (LABD) may be indistinguishable from one another.

The DIF of DH classically shows granular IgA in the papillary dermis and the DIF of LABD classically shows linear IgA along the basement membrane zone. However, in practice, the distribution of the IgA is not always clear-cut. The histopathology of DH and LABD can be indistinguishable, since they both show a subepidermal split with neutrophils.

Pearl #3: The histopathology of DH and bullous lupus erythematosus are indistinguishable from one another.

Both show a subepidermal split with neutrophils.

Reference:

1. Elder DE, et al, ed. *Noninfectious Vesiculobullous and Vesiculopustular Diseases*, Lever's Histopathology of the Skin 11th ed. Lippincott Williams & Wilkins 2015, pp. 277-328.

Pearl #4: Low-level bullous pemphigoid 180 autoantibodies can be found in patients who do not have bullous pemphigoid.

The commercially available bullous pemphigoid 180 (BP180) NC16A enzyme-linked immunosorbent assay (ELISA) is a test that can be used to aid in the diagnosis of bullous pemphigoid (BP). A result of > 9 U/mL is defined as a positive test. However, a positive test does not necessarily mean the patient has BP. Circulating BP180 autoantibody can be detected in patients who do not have BP. In a study by Liu et al, the authors sought to determine an optimum cutoff value of BP180 ELISA to detect true BP. A total of 173 in-patients were included: 26 patients with BP and 147 patients in which BP was initially suspected, but later excluded. The titers of BP180 autoantibodies in non-BP patients were significantly lower than those of BP patients (median titer 17.1 U/mL versus 67.1 U/mL). Receiver operating characteristic curve [plot of sensitivity vs (1 – specificity)] analysis was used to generate paired sensitivity and specificity values based on BP180 autoantibody titers. The optimum cutoff value to determine true BP patients from non-BP patients was calculated on the basis of maximizing the Youden index (J = sensitivity + specificity – 1). This optimum cutoff was found to be 27.2 U/mL, which has a sensitivity of 65.4% and a specificity of 98.0%, in contrast to the standard cutoff of 9 U/mL, which has a sensitivity of 73.1% and much lower specificity of 85.7%. These results show that low-level BP180 autoantibodies can be found in patients who do not have BP and the results of BP180 ELISA should be interpreted in conjunction with clinical findings and immunopathologic test results.

Reference:

1. Liu Z, Chen L, Zhang C, Xiang LF. Circulating bullous pemphigoid 180 autoantibody can be detected in a wide spectrum of patients with other dermatologic conditions: A cross-sectional study. *J Am Acad Dermatol* 2019; 80(3): 774-5.

Pearl #5: A DIF for any autoimmune bullous dermatosis taken from the lower extremities may be false-negative.

Reference:

1. James WD, ed, et al. *Chronic Blistering Dermatoses in Andrews Diseases of the Skin 12th ed.*, Elsevier, Philadelphia 2015, pp. 451-570. **DR**



If you have suggestions for topics or content for Clinical Pearls, contact Dean Monti at dmonti@aad.org