A challenging case of a chronic, relapsing bullous dermatosis with negative serologic tests treated successfully with dapsone

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MANY STRENGTHS. ONE MISSION.

A Seventh-day Adventist Organization

LOMA LINDA UNIVERSITY

School of Medicine

Case: 39-year-old F with long h/o relapsing tense vesicles and bullae on extremities

HPI:

- First started in pregnancy in her late teens resolving after delivery
- Recurred during 4 subsequent pregnancies, each resolving with delivery
- Recurrence 5 yrs after last pregnancy without associated pregnancy
- Failed tx with oral prednisone, methotrexate, doxycycline, mycophenolate mofetil, and topical steroids prior to presentation at clinic

PE:

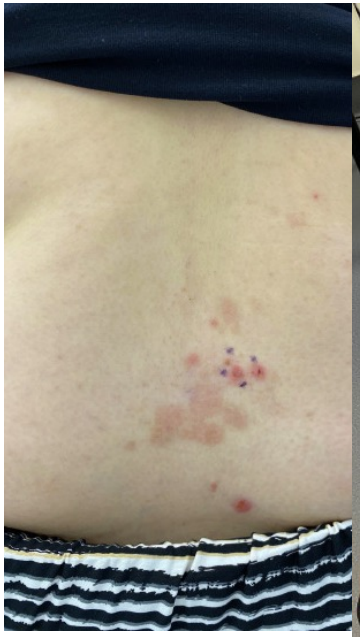
- Pruritic vesicles and bullae on her lower extremities (Figure 1)

- **Work-Up:**
- DIF negative on 3 separate occasions
- IIF, and ELISA BPAG 180, BPAG 230, desmoglein-1, and desmoglein-3 were all negative
- ANA screen, deamidated gliadin IgA, and tTg IgA and IgG: negative
- Serum IgA level: normal
- Biopsies were taken on 4 separate occasions over the course of 3 years (Figure 2).
  - ~ Presence of neutrophils prompted initiation of **dapsone**
- **Treatment and Response:**
- Dapsone gradually increased from 50 mg to 125 mg daily.
- Dapsone was immunosuppression-sparing, allowing her to first be tapered off mycophenolate mofetil and doxycycline, before tapering off systemic prednisone
- Complete resolution of her eruption

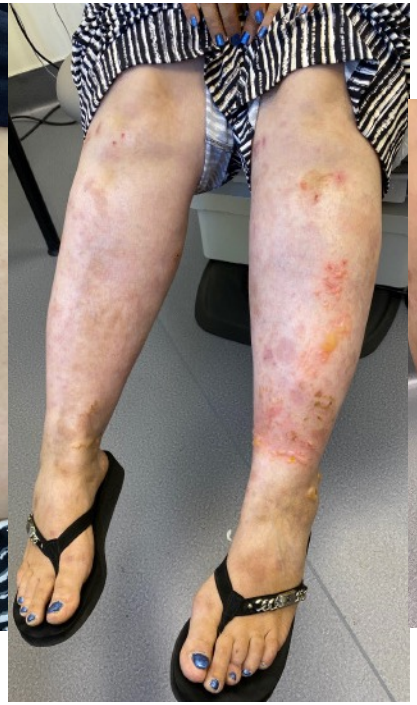
Limiting factors: insurance coverage of additional specialty tests and patient preference to defer further sampling

Acronyms: PE HPI history of present illness, PE physical exam, DIF direct immunofluorescence, IIF indirect immunofluorescence

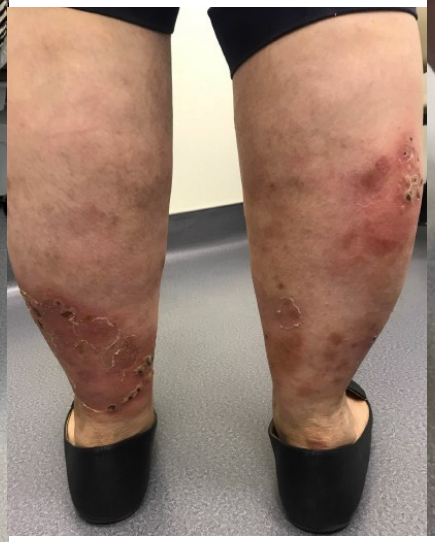
Figure 1. Clinical photos. A-B) June 2020, C-E) December 2020



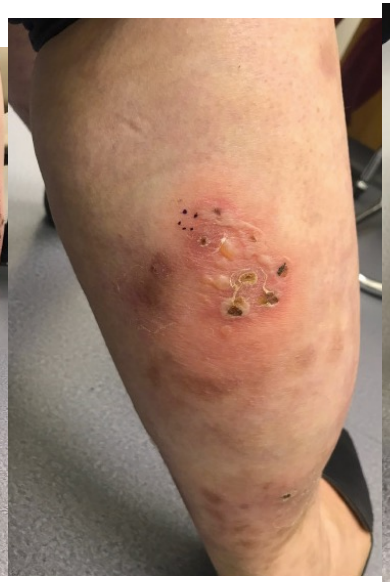
A) Lower back



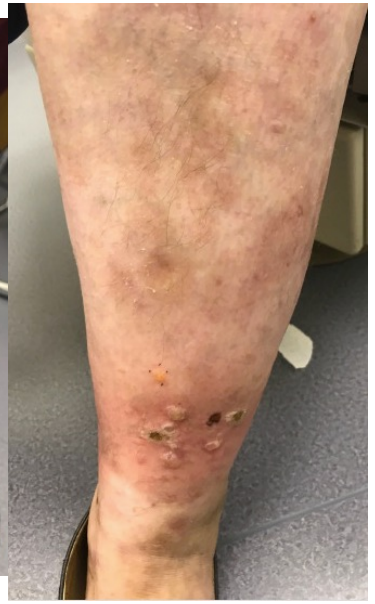
B) Lower legs



C) Posterior lower legs

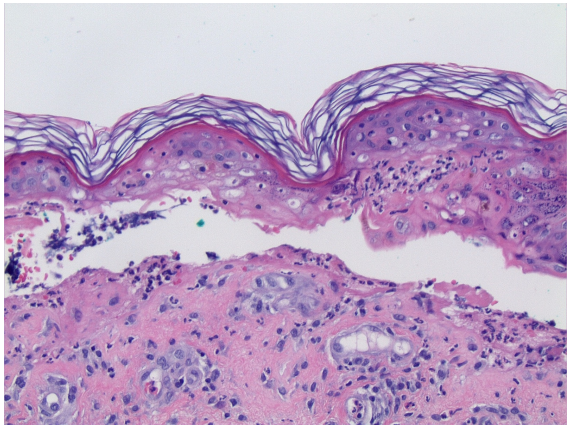


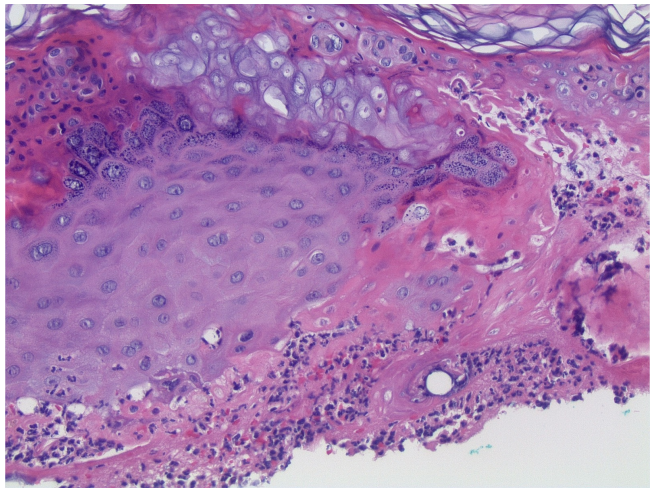
D) R posterior leg

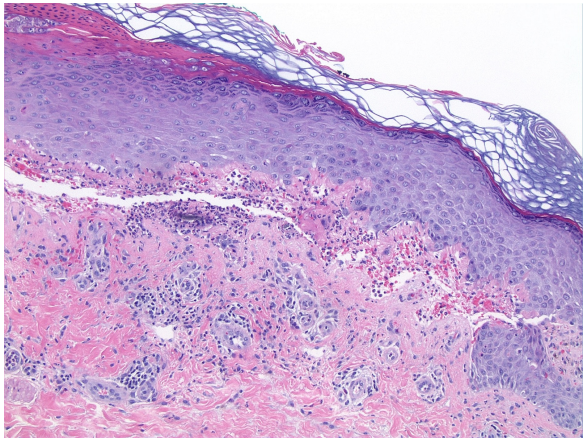


E) L lower shin

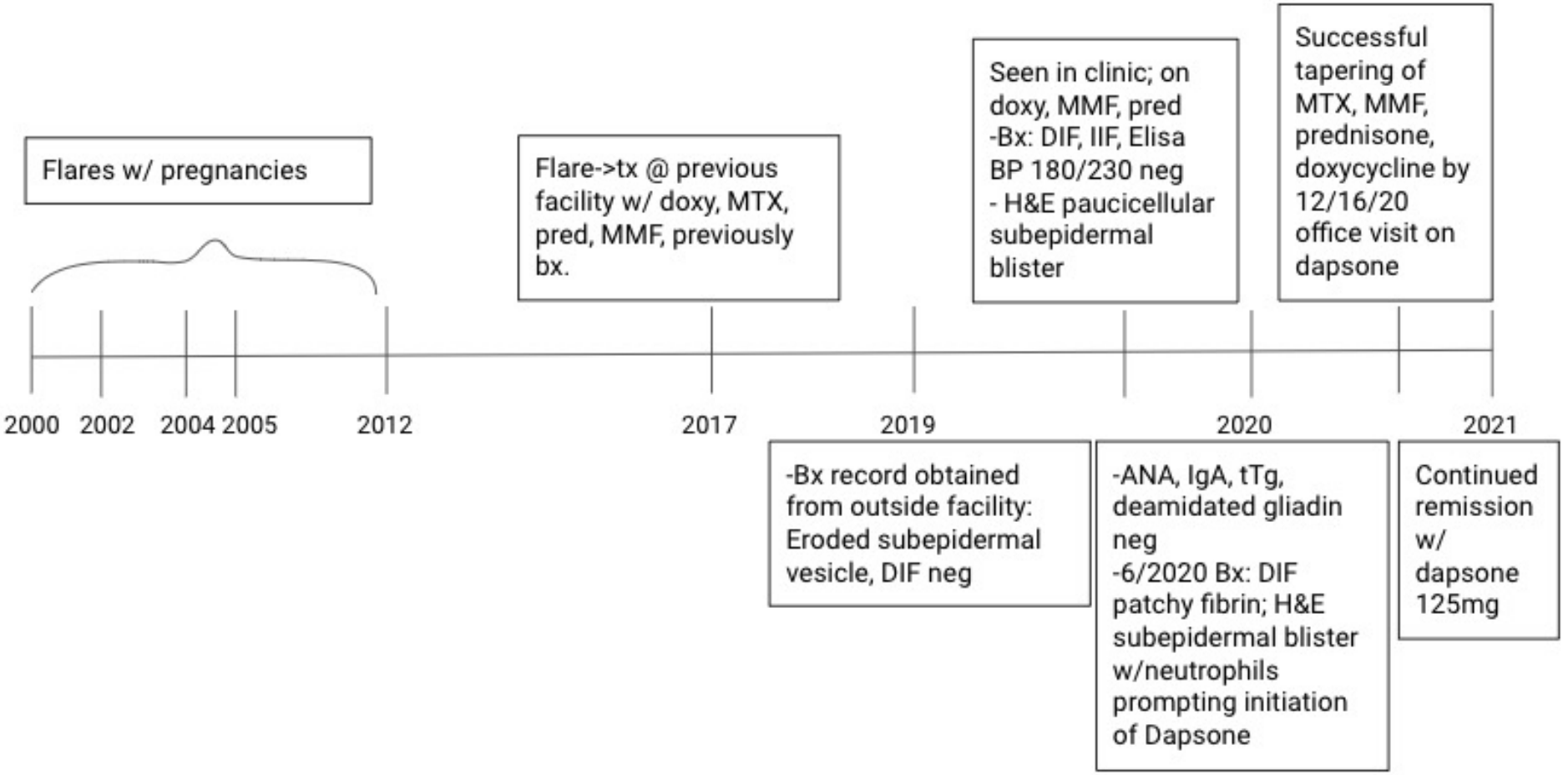
Figure 2. H&E images of one of her biopsies showing subepidermal neutrophilic vesicular bullous disorder with perivascular lymphocytic and neutrophilic inflammation.







Timeline



Acronyms: Tx treatment, doxy doxycycline, MTX methotrexate, pred prednisone, MMF mycophenolate mofetil, Bx biopsy, neg negative

Objective

Refractory bullous dermatoses with negative serologic and immunofluorescence studies present a diagnostic and therapeutic challenge to dermatologists. We conducted a brief review of recent literature regarding sensitivity of common serologic tests used to diagnose bullous dermatoses in clinical practice.

Methods

We examined literature published in the last 5 years. Search terms used include linear IgA bullous dermatoses, epidermolysis bullosa acquisita, bullous pemphigoid, pemphigus vulgaris, dermatitis herpetiformis, ELISA, indirect immunofluorescence, direct immunofluorescence, sensitivity, and accuracy in varying combinations. Authors reviewed titles and abstracts for relevance. Published sensitivities were reported in a table, and combined sensitivities were calculated.

Results

	DIF	IIF	ELISA DSG1	ELISA DSG3	ELISA tTg	ELISA Type VII Collagen	ELISA BPAG 180	ELISA BPAG 230
BP	85.9% (63.0%-100%)[1,2,3,4,5]	68.8% (57.1%-100%)[1,2,6,7]	--	--	--	--	76.1% (70.0%-85%)[2,7,8]	48.1 (43.1%-55.5%)[2,7,8]
PV	97.7% (97.7%)[9]	73.9% (30%-87.4%)[9,10,11,12,13]	72.4% (12.5%-82%)[10,14]	77.9% (50%-100%)[10,14,15]	--	--	--	--
EBA	100% (100%)[3, 4]	85.7% (74.7%-96.0%)[16,17]	--	--	--	88.8% (80.2%-97.9%)[16,17]	--	--
LABD	100% (100%)[4]	44.1% (14.8%-63.0%)[18,19]	--	--	--	--	5.6% (5.6%)[18]	9.3% (9.3%)[18]
DH	94.9% (94.7%-100%)[4,20]	--	--	--	87.8% (53.8%-91.8%)[20,21]	--	--	--

Table 1. Combined sensitivities of diagnostic tests for bullous pemphigoid (BP), pemphigus vulgaris (PV), epidermolysis bullous acquisita (EBA), linear IgA bullous dermatosis (LABD), and dermatitis herpetiformis (DH). Range of reported sensitivities are in parentheses.

Discussion

Refractory bullous dermatoses with negative serologic testing present a diagnostic and therapeutic challenge to dermatologist. There is a wide range of sensitivities among standard diagnostic tests to diagnose bullous dermatoses like bullous pemphigoid, pemphigus vulgaris, and epidermolysis bullosa acquisita. A false negative result may lead to delay in diagnosis and appropriate treatment. In this case, our patient's initiation of immunosuppressive therapy could have caused her to have multiple false negative biopsy results, though there are no recent studies addressing the role of prior immunosuppression on diagnostic sensitivity. Sensitivity of DIF for bullous pemphigoid may be affected by poor tissue sample (such as biopsy of lesional skin) or subthreshold level of immune complexes.[22] Perilesional biopsies are the standard technique, but can often result in a negative DIF.[23]

Negative DIF in the presence of bullous pemphigoid autoantibodies may represent only a small subset of false negative bullous pemphigoid patients.[24] One should exercise caution on over-interpreting a negative DIF with low autoantibody titers in this setting. Detection by ELISA for autoantibodies to alternative antigens and special immunohistochemistry techniques provide further workup for patients when there is high clinical suspicion for an immunobullous disorder but negative results via standard tests.[25-17] Recent studies report that the BIOCHIP assay may be comparable with IIF sensitivity for bullous pemphigoid and become a first-line screening tool in the future.[7,28] When there is high clinical suspicion in the setting of negative serologic tests or histopathology, providers must use all clinical and histopathologic clues to optimize management decisions in these difficult cases.

Conclusion

Recently reported sensitivities for histopathologic and serologic studies vary for bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa acquisita, linear IgA bullous dermatosis, and dermatitis herpetiformis. The initiation of immunosuppressive therapy prior to biopsy may potentially affect the sensitivity of serologic tests, though there are no current studies to support this hypothesis. We reviewed the sensitivities of common tests used in clinical practice to evaluate suspected immunobullous disease. This case highlighted the challenge dermatologists face in light of imperfect diagnostic tests when treating patients with suspected bullous dermatoses.

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