Practice and Educational Gaps in Blistering Disease

Nazanin Ehsani-Chimeh, MD[a], M. Peter Marinkovich, MD[a,b,*]

KEYWORDS

• Blistering • Bullous • Autoimmunity • Pemphigus • Pemphigoid

KEY POINTS

- Autoimmune bullous patients often remain either undiagnosed for prolonged periods of time or poorly diagnosed without immunologic confirmation, resulting in significant additional morbidity.
- The most important principle in management of autoimmune bullous disease is to halt blistering activity while minimizing side effects of medications especially corticosteroids.
- Judicious use of systemic steroids and steroid-sparing agents are essential tools in the management of autoimmune bullous disease patients.
- Rituximab and intravenous immunoglobulin are playing increasingly important and earlier roles in the management of many autoimmune bullous patients.
- Understanding of and surveillance for drug side effects are critical in the long-term management of the autoimmune bullous patient.

DIAGNOSTIC POINTS

Diagnosis is a critical first step in the care of autoimmune bullous disease patients. It is, unfortunately, all too common for a patient to go for many months, or even years, until the correct diagnosis is finally made.[1] Excess suffering due to the painful blisters and erosions of pemphigus, or the intractable itching of pemphigoid is only part of the costs paid to delayed diagnosis. During this undiagnosed period, the patients are usually empirically given high-dose systemic steroids. This incurs its share of the cumulative morbidity. Another factor to consider in late diagnosis is the degree of chronicity it evokes on the disease phenotype. Most dermatologists can appreciate that it is often the case that the more chronic a skin condition becomes, the longer and more difficult it is to eradicate. In the instance of poorly treated autoimmune bullous disease, this may translate into increased development of a B cell memory compartment promoting the chronic production of pathologic antibodies, which may become more difficult to eradicate with specific therapies such as rituximab[2] once the diagnosis is finally made.

In addition to delay of diagnosis, another common problem is the assumption of a diagnosis based on clinical and histologic examination only. Well-intentioned dermatopathologists, whose histologic observations "suggestive of" or "consistent with" some type of autoimmune bullous disease, are too often taken by clinicians as proof of a given diagnosis, without further testing. This can be a great disservice for patients.

Consider the case of a patient with a putative diagnosis of bullous pemphigoid, based on histology and clinical appearance alone, without immunologic confirmation. After high-dose corticosteroid therapy for many months or even years, this cushingoid patient presents to the clinician's office, who immediately performs a direct immunofluorescence

Disclosure Statement: The authors have nothing to disclose.
[a] Department of Dermatology, Stanford University School of Medicine, 269 Campus Drive, CCSR Building, Room 2145, Stanford, CA 94305-5168, USA; [b] Veterans Administration Medical Center, Palo Alto, CA, USA
* Corresponding author.
E-mail address: mpm@stanford.edu

Dermatol Clin 34 (2016) 251–256
http://dx.doi.org/10.1016/j.det.2016.02.001
0733-8635/16/$ – see front matter Published by Elsevier Inc.

(DIF) biopsy and demonstrates linear immunoglobulin (Ig)A disease, which can look clinically and histologically identical to bullous pemphigoid. After dapsone therapy is initiated and the patient completely weaned off prednisone with excellent disease control, the clinician realizes that if prompt immunologic testing had been performed, prolonged high-dose steroid use and all the concomitant morbidity could have been avoided. This example is just 1 of many demonstrating why an immunologic diagnosis is so essential for these patients.

The choices of immunologic tests available for correctly diagnosing immunobullous diseases are numerous. In addition to perilesional DIF microscopy biopsy (the most sensitive test), serum from patients with active disease can be analyzed by indirect immunofluorescence (IIF). More recently, enzyme-linked immunosorbent assay (ELISA) assays are also used. It is not just for desmogleins 1 and 3, but it is also now available for bullous pemphigoid and epidermolysis bullosa acquisita (EBA) antigens.

With a positive DIF or high enough titer IIF or ELISA, any of these are sufficient to make the correct diagnosis. One key point is that these tests should be performed while the patient is showing disease activity. It is suboptimal to perform these tests after the patient has been placed on high-dose immunosuppressive therapy. A diminution of the immune response from such high-dose therapy could lead to a false-negative result. For this reason, it is important to plan ahead and look to perform the immunologic diagnosis early before systemic therapy is implemented.

False-negative results can also be a result of lesional, as opposed to perilesional, DIF biopsies or because DIF biopsies are inadvertently placed in a medium other than Michel's or Zeus medium. Biopsies that sit around for too long while one is trying to obtain the proper medium, or sera that is not promptly sent out to the appropriate laboratory, are also very likely to result in false-negative results. It is, therefore, critical to plan ahead, obtain the proper holding medium in advance, and communicate with the testing laboratories as well as clinic staff to make sure transfer of specimens for immunologic testing is carried out correctly and expeditiously.

These examples illustrate that it is important to look at negative immunologic results in suspected autoimmune bullous patients with a skeptical eye. Were the biopsies correctly performed? Was the serum correctly analyzed? Was the patient tested at a time when the disease was active? These are the questions that should come to mind when analyzing negative immunologic test results. Based on experience with the above variables, it is clear that 1 negative immunologic result does not necessarily rule out the diagnosis. Therefore, if the patient continues to display characteristic features of autoimmune bullous diseases, it is important to consider repeat testing of previously negative results, especially during periods of high disease activity.

Another difficulty sometimes encountered in subepidermal autoimmune bullous diagnosis is in distinguishing among the individual subtypes. For example, EBA can sometimes histologically and clinically mimic either cicatricial or bullous pemphigoid. However, these diseases can differ in their prognosis and response to therapy. In addition, there is a subtype of cicatricial pemphigoid characterized by antibodies against laminin-332 (sometimes still referred to by its previous name epiligrin). This antilaminin-332 form of cicatricial pemphigoid has an increased association with (and can sometimes precede) the development of a variety of different types of cancers.[3] It is important, therefore, to correctly determine which of these subepidermal diseases the autoimmune patient has and this requires specialized evaluation of the dermal-epidermal basement membrane (BMZ).

Common belief is that periodic acid–Schiff–diastase stain permits visualization of the BMZ; however, what is in fact visualized is a precipitation of dye many times the thickness of the actual BMZ.[4] In fact, at approximately 0.2 μm in thickness, the dermal-epidermal BMZ is well below the resolution of light microscopy. However, a useful light microscopy–based tool has been developed to circumvent this limitation. Skin samples incubated in 1 M sodium chloride will eventually separate in the center of the BMZ, in a region known as the lamina lucida.[5,6] Above the lamina lucida in the epidermal roof of salt-split skin lies the bullous pemphigoid antigens, as well as other less commonly encountered antigens such as β4 integrin, targeted in some forms of cicatricial pemphigoid. Other antigens, such as type VII collagen (the EBA antigen) and laminin-332 localize to the dermal side of the salt-induced split.

Therefore salt-split skin analysis has the ability to distinguish bullous pemphigoid and many forms of cicatricial pemphigoid, in which immunoreactants would mainly localize to the epidermal roof of the split from EBA, and the laminin-332 subtype of cicatricial pemphigoid, in which immunoreactants would localize to the dermal floor of the split. This type of salt-split skin analysis can be performed on DIF as well as IIF samples, depending on the capabilities of the laboratory. Thus, when one suspects a subepidermal bullous skin