The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Bullous autoimmune skin diseases

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1 Introduction

Autoimmune blistering disorders are a heterogeneous group of chronic and severe skin diseases caused by circulating autoantibodies against various structural proteins of the epidermis, the basement membrane zone, or the dermis (Table 1, Fig. 1). The autoantigens play an important role in intraepithelial, epidermo-dermal, or dermal adhesion, and loss of adhesion subsequent to autoantibody-induced inflammation results in blister formation.

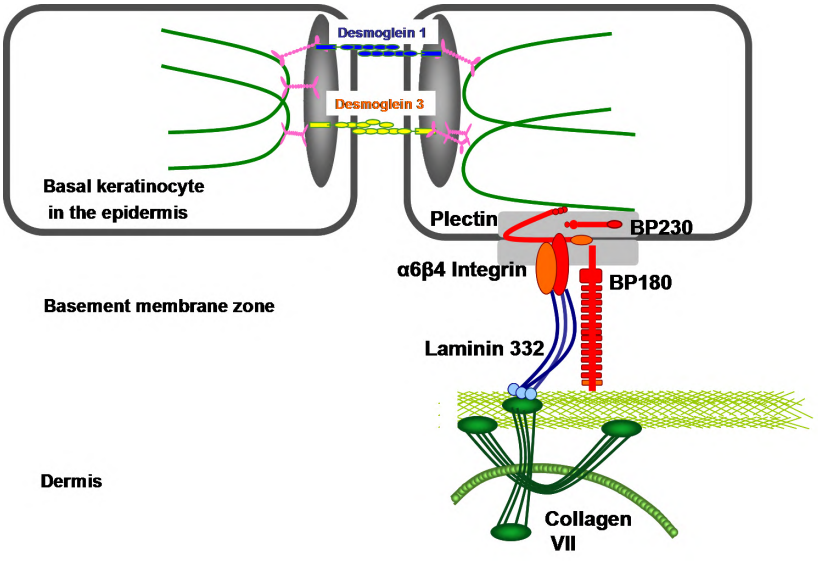

Figure 1. Schematic representation of the localisation of the relevant autoantigens for bullous autoimmune disorders. Desmosomes (depicted in dark grey) are adhesion complexes connecting two epidermal keratinocytes, while hemidesmosomes (light grey) are multiprotein adhesive complexes located at the dermo-epidermal junction.

Pemphigus vulgaris, pemphigus foliaceus and bullous pemphigoid represent the most frequent bullous autoimmune skin diseases. In addition, the group of autoimmune bullous disorders includes rare entities such as gestational pemphigoid, mucous membrane pemphigoid, linear IgA dermatosis, epidermolysis bullosa acquisita, or dermatitis herpetiformis.

Table 1. Autoantigens of bullous autoimmune disorders.

Disease	Autoantigen	Localisation in the skin
Pemphigus disorders:		
Pemphigus vulgaris	Desmoglein 3 Desmoglein 1	Desmosome (Epidermis)
Pemphigus foliaceus	Desmoglein 1	Desmosome (Epidermis)
Pemphigoid disorders:		
Bullous pemphigoid	BP230	Hemidesmosome (Basement membrane)
	BP180 (collagen XVII)	Hemidesmosome (Basement membrane)
Mucous membrane pemphigoid	BP180 (collagen XVII) α6β4-Integrin	Hemidesmosome (Basement membrane)
	Laminin 332	Anchoring filament (Basement membrane)
Gestational pemphigoid	BP180 (collagen XVII)	Hemidesmosome (Basement membrane)
Linear IgA-Dermatosis	Extracellular domain of BP180	Hemidesmosome (Basement membrane)
Other bullous autoimmune disorders:		
Epidermolysis bullosa acquisita	Collagen VII	Anchoring fibril (Dermis)
Dermatitis herpetiformis	Epidermal and tissue transglutaminase	Dermis

2 Diagnostic criteria

Pemphigus vulgaris and pemphigus foliaceus are intraepidermal bullous disorders, in contrast to bullous pemphigoid, which is associated with subepidermal blister formation. The site of blister formation (intraepidermal versus subepidermal) relates to the clinical presentation, which, in pemphigus, is characterised by superficial and therefore flaccid blisters (that due to their fragility often rapidly result in erosions) and in pemphigoid patients as tense blisters (increased stability due to an intact epidermis as blister roof) (Fig. 2). The clinical features, in combination with histology, direct and indirect immunofluorescence, and detection of autoantibodies to epidermal or dermal autoantigens allow an exact diagnosis to be made (compare Tables 2 and 3).

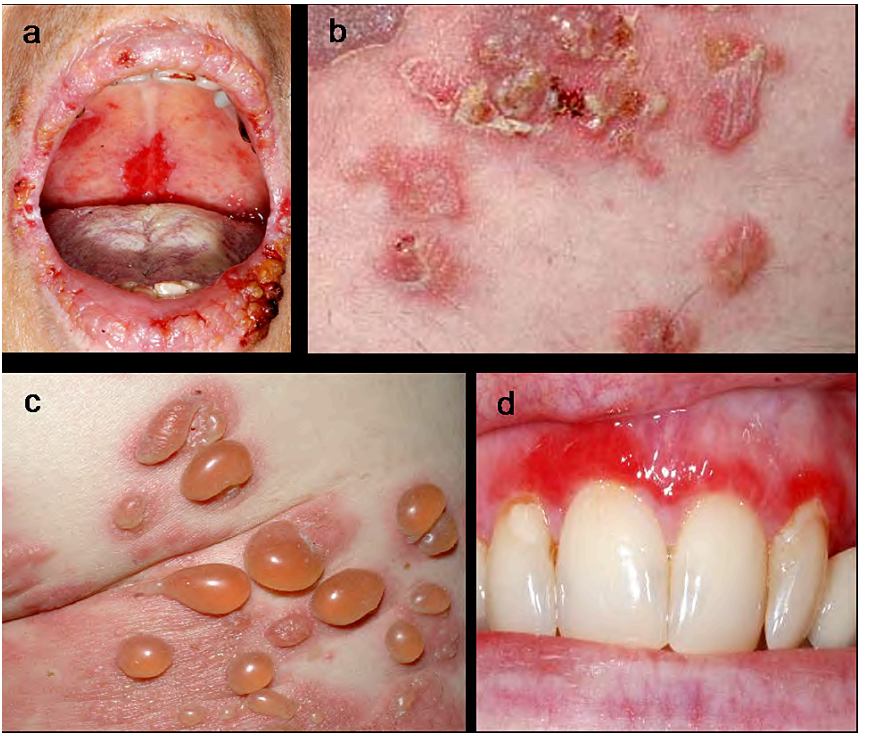

Figure 2. Clinical features of pemphigus and bullous pemphigoid. The initial manifestations in pemphigus vulgaris are often mucosal erosions (a). Both, pemphigus vulgaris and foliaceus, manifest with flaccid blisters and erosions of the skin (b), but mucosal involvement is lacking in pemphigus foliaceus. Tense blisters on erythematous skin are a hallmark of bullous pemphigoid (c), while mucosal lesions such as desquamative gingivitis (d) are rare in bullous pemphigoid, but occur in mucous membrane pemphigoid.

Table 2. Clinical presentation of pemphigus vulgaris, pemphigus foliaceus and bullous pemphigoid.

	Pemphigus vulgaris	Pemphigus foliaceus	Bullous pemphigoid
Symptoms	Painful mucosal erosions, weight loss	(Pruritus)	Pruritus often as initial symptom
Typical clinical presentation	Flaccid blisters and erosions	Flaccid blisters and erosions	Tense blisters, urticarial plaques
Mucosal involvement	Present in 100 % (oral and /or nasal, ocular, genital)	In 0 %	In 10–20 % (most frequently oral erosions, desquamative gingivitis)
Age prevalence	30–60 yrs.	30–60 yrs.	> 60 yrs.
Incidence	1–5/million/year	1–5/million/year	12/million/year

Table 3. Laboratory findings in pemphigus and pemphigoid.

	Pemphigus vulgaris	Pemphigus foliaceus	Bullous pemphigoid
Histology	Suprabasal acantholysis	Subcorneal acantholysis	Subepidermal blistering, eosinophilic infiltrate
Direct immuno-fluorescence	Intercellular IgG and C3 deposits in the epidermis	Intercellular IgG and C3 deposits in the upper epidermis	Linear IgG and C3 deposits at the basement membrane zone
Indirect immunofluorescence on monkey oesophagus	Intercellular IgG deposition within epidermis	Intercellular IgG deposition within epidermis	Linear IgG deposition at the basement membrane zone
Autoantibodies directed to	Desmoglein 3 in 100 %, Desmoglein 1 may be additionally positive (in 45 %)	Desmoglein 1 in 95 %	BP180 in 90 %, BP230 in 60 %

3 Diagnostic measurements for experts

Pemphigus vulgaris is caused by autoantibodies against proteins of the desmosomes, the intraepithelial intercellular adhesion complexes. The pemphigus vulgaris antigen, desmoglein 3, and the pemphigus foliaceus antigen, desmoglein 1, belong to the cadherin supergene family and compensate for each other functionally. In epithelia of mucous membranes, desmoglein 1 is only expressed at very low levels. Therefore anti-desmoglein 3 antibodies in pemphigus vulgaris lead predom-

inantly to erosions in mucous membranes. Autoantibodies against desmoglein 1 and 3 result in a mucocutaneous type of pemphigus vulgaris with blisters on mucosae and the integument. Patients with pemphigus foliaceus develop antibodies against desmoglein 1 only. This antigen is predominantly expressed in the superficial layers of the epidermis where no compensatory desmoglein 3 is present. This explains why anti-desmoglein 1 antibodies induce loss of cell-cell adhesion in the upper epidermis, but not in mucosal epithelia.

Autoantibodies in bullous pemphigoid target two components of hemidesmosomes (adhesion complexes of the dermo-epidermal basement membrane zone): the transmembrane protein BP180 (bullous pemphigoid antigen with a molecular weight of 180 kDa; syn. collagen XVII) and the intracellular BP230.

Since the 1960s, direct immunofluorescence on perilesional skin biopsies has been the gold standard in the diagnosis of autoimmune blistering disorders. Pemphigus disorders demonstrate intercellular intraepidermal, bullous pemphigoid dermo-epidermal deposition of immunoglobulins and complement. Circulating autoantibodies can be detected by indirect immunofluorescence or western blot using recombinant antigens or keratinocyte extracts. Commercially available test systems using recombinant desmoglein 1, desmoglein 3, BP180 and BP230 allow the detection of specific circulating autoantibodies that are used to confirm the diagnosis and to monitor disease activity. The British Association of Dermatologists has developed guidelines for management of pemphigus and pemphigoid [1, 2].

4 Requirements for family practitioners

Pemphigus vulgaris and pemphigus foliaceus are potentially severe, autoimmune blistering skin diseases caused by autoantibodies against adhesion proteins of epidermal keratinocytes (desmogleins 1 and 3). These autoantibodies lead to intraepidermal blisters, which, in pemphigus vulgaris, manifest clinically with painful erosions of the oral mucosa, reduced food intake and weight loss. In addition, fragile skin blisters which may result in widespread, often haemorrhagic erosions on trunk and extremities may be present. The hallmark of pemphigus foliaceus are superficial skin blisters which heal without scarring and an absence of mucosal lesions.

Bullous pemphigoid is the most common autoimmune blistering disease and its incidence rises with increasing age. It is associated with autoantibodies against distinct basement membrane proteins (BP180 and BP230) leading to subepidermal blisters. Clinically, bullous pemphigoid presents as a pruritic eruption with large, tense blisters on normal or inflamed skin and rare involvement of mucous membranes. Of note, itch is often the first symptom and urticarial plaques may precede the blister formation.

When the diagnosis of an autoimmune bullous disorder is suspected, the patient should be referred to a dermatologist. A skin biopsy and serological tests

are essential to confirm the diagnosis of pemphigus or pemphigoid. Histology shows suprabasal acantholysis and direct immunofluorescence shows intercellular IgG and C3 deposits in the epidermis in pemphigus disorders. Serological studies demonstrate circulating autoantibodies that bind to the intercellular substance of the epithelium on monkey oesophagus (indirect immunofluorescence) and the molecular specificity of the antibodies is determined by commercially available test systems (e.g. Elisa) with recombinant desmogleins. Bullous pemphigoid is characterized by subepidermal blister formation in histology and linear C3 and/or IgG deposits at the dermoepidermal junction in direct and indirect immunofluorescence. Circulating autoantibodies against BP180 and BP230 are detectable by commercially available test systems (e.g. Elisa).

5 Follow up

Clinical observations

Usually, immunosuppressive treatment rapidly prevents new blister formation and pruritus and induces healing of skin and mucosal lesions within weeks or (in severe cases) months. Clinical scores such as the ABSIS (Autoimmune Bullous Skin Disease Intensity Score) or PDAI (Pemphigus Disease Area Index) can help to monitor the clinical improvement during treatment.

Expectations

Blistering autoimmune disorders are chronic diseases. Most patients require immunosuppression for years or sometimes life-long to remain in clinical remission.

Blood tests

Regular assessment of liver and kidney function, full blood counts, and glucose levels is required to recognise potential side-effects of corticosteroids and immunosuppressants. Determination of autoantibody levels to desmoglein 1 and 3 or BP180 is useful for monitoring disease activity. A rise in autoantibody titres can precede clinical relapse of the disease [3, 4].

6 Therapeutic management

Pemphigus disorders are treated with topical and oral corticosteroids, usually in combination with adjuvant immunosuppressive drugs [2]. Prednisolone is administered in an initial dose of 1–1.5 mg/kg/day and gradually reduced when no new lesions develop. Adjuvant immunosuppressive drugs (azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, methotrexate or dapsone) are prescribed because of their potential steroid-sparing effect. Such a combined

treatment is able to induce remission in the majority of patients. In recalcitrant cases, intravenous immunoglobulins, rituximab (a chimeric anti-CD20 antibody directed against B-cells), or immunoadsorption are often successful.

In localized forms of pemphigus foliaceus, superpotent topical steroids or topical calcineurin inhibitors may be sufficient to obtain clinical remission. Similarly, there is good evidence that bullous pemphigoid responds to superpotent topical corticosteroids (clobetasol propionate 10–30 g/day). Severe cases require systemic therapy with oral prednisolone (initially 0.5 mg/kg is usually sufficient) alone or combined with immunosuppressive agents such as azathioprine, dapsone or mycophenolate mofetil [1]. In the future, targeted therapies for blistering autoimmune dermatoses will hopefully improve efficiency of treatment and reduce side effects [5].

7 Diagnostic tests

Tissue-bound autoantibodies (IgG, to a lesser extent IgA) against desmosomes or basement membrane proteins are detected by direct immunofluorescence analysis on perilesional skin biopsies in practically all patients (Fig. 3 a, b). However, this initial test does not allow discrimination between e. g. bullous pemphigoid and other, more rare, subepidermal blistering disorders such as epidermolysis bullosa acquisita. This problem can be overcome by using salt-split-skin as a substrate for indirect immunofluorescence to assess circulating autoantibodies from patients' sera. By incubation of normal human skin in 1M NaCl, the proteins of the basement membrane zone are separated, and bullous pemphigoid-autoantibodies bind to the epidermal side (Fig. 3c), while autoantibodies against the antigen of epidermolysis bullosa acquisita, collagen VII, bind to the dermal side of the blister. The optimal substrate for indirect immunofluorescence diagnosis of pemphigus disorders is monkey oesophagus.

Using recombinant forms of the autoantigens, the specificity of circulating autoantibodies can be determined by commercially available test systems (e. g. Elisa). The recombinant protein is attached to a solid surface, and incubated with patient's serum. Antibodies against the respective antigen bind to it, and are subsequently detected by an enzyme-linked anti-human immunoglobulin antibody. Currently assay systems for the detection of antibodies directed against the following autoantigens are on the market: desmoglein 1, desmoglein 3, BP180, BP230, collagen VII, tissue and epidermal transglutaminase (see Table 1 for the different autoantigens and associated disorders).

8 Testing methods, limitations and benefits

The available assay systems are accurate, sensitive and specific (see Table 3). Many samples can be simultaneously assessed, and the autoantibody titres measured

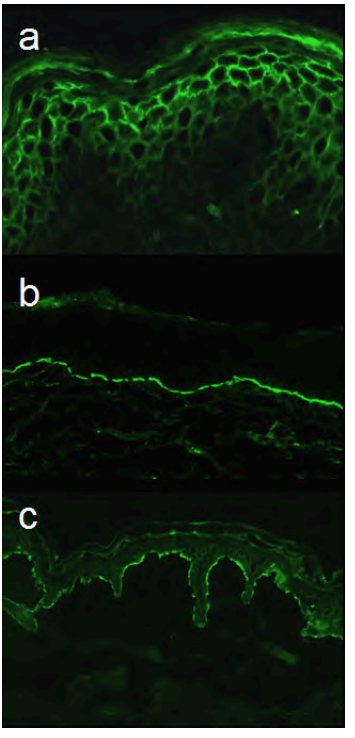

Figure 3. Direct immunofluorescence analysis showing intercellular IgG deposits in the epidermis in pemphigus vulgaris (a), and linear IgG deposits at the basement membrane zone in bullous pemphigoid (b). Circulating autoantibodies against the pemphigoid autoantigens BP180 or BP230 bind to the epidermal side of a 1M NaCl-induced artificial split by indirect immunofluorescence (c).

often correlate with the clinical disease activity. For some rare autoantigens (e. g. laminin 332) commercial assays are not yet available. These antibodies can be detected in selected research laboratories by western blot analysis using either keratinocyte extracts or recombinant laminin 332.

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