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Review

Autoimmune blistering diseases of the skin

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ABSTRACT

Autoimmune skin diseases represent a heterogeneous group of disorders with grossly diverging clinical manifestations but partly shared underlying immunological mechanisms. They may affect the skin as an isolated organ or among systemic diseases. In addition unspecific cutaneous symptoms or drug-induced unwanted effects can be seen and have to be carefully dissected from an exacerbations of the underlying disease. Growing pathogenic knowledge has elucidated serological and clinical pictures heterogeneity and at the same time increased the therapeutic armentarium for these partly life-threatening diseases. In this review, the focus is on autoimmune bullous diseases with the skin as the major target which involve antigens of epidermis, basal membrane or dermis. Among these the pemphigoid and pemphigus group may be differentiated from dermatitis herpetiformis Duhring and epidermolysis bullosa acquisita. Interestingly, pathogenetically relevant antibody responses of IgA subtype can be found in any of the first three groups. Their clinical picture as well as therapeutic response are distinctly different from the other mainly IgG mediated subsets. Though systemic corticosteroids are still the mainstay of therapy, differential approaches using diverse adjuvant drugs are available. Immunoserological data may help characterize subsets and monitor clinical diseases as well as therapeutic response.

Contents

1. Introduction

Autoimmune skin diseases represent a heterogeneous group of disorders with grossly diverging clinical manifestations but partly shared underlying immunological mechanisms. Autoimmunity may affect (1) the skin organ as the one and only organ as in autoimmune bullous diseases, (2) the skin organ among other organs with characteristic symptoms and dermatologically well-described disorders like in connective tissue diseases, (3) with unspecific cutaneous symptoms in the context of systemic autoimmune disorders like exanthema, itching or scaling and (4) with unwanted cutaneous effects due to therapeutic drugs which may mimic or exacerbate the underlying disease and are often hard to separate diagnostically. In this review, the focus is on autoimmune diseases with the skin as the major target and will thus refer to autoimmune bullous diseases.

2. Autoimmune bullous diseases

Blisters are among the very basic skin reactions to diverse pathogens like bacterial or viral infections, accidental trauma or genetic disorders which cause either dissection of intraepidermal keratinocytes or

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dissection of the entire epidermis from the underlying dermis at various levels immediately above or below the basement membrane [1]. Within the group of blistering diseases, autoantibodies to major players of skin integrity, namely integrins and adhesion molecules will clinically result in partly devastating symptoms with high impact on morbidity and even mortality of affected patients. Interestingly, the major antigens tackled by autoantibodies in these acquired disorders are genetically affected in corresponding inherited bullous diseases where respective mutations result in missing or malfunctional proteins. Consequently, the resulting clinical pictures are quite similar in many cases (Table 1).

The group of autoimmune bullous diseases can be categorized by the skin level at which the blister occurs and by the structural proteins that are targeted by autoantibodies [1,2]. In a simplified view four groups of diseases can be distinguished: pemphigus, pemphigoid, epidermolysis bullosa acquisita and dermatitis herpetiformis Duhring (Table 2).

The extent and progress of skin lesions, the age of the patient and the impact of co-morbidities and co-medication will dictate the time-point as well as extent of local or systemic immunosuppressive or immunomodulatory therapy. Only few evidence-based studies are available on the optimal treatment of autoimmune bullous disorders.

3. Pemphigus group

This group of autoimmune blistering diseases is rare with an incidence of 0, 1–0, 5/100.000/a and a clinical manifestation in the fourth and fifth decade of life with a slight female preponderance (1.5:1). Intraepidermal acantholysis is induced by antibodies against structural and adhesion molecules of the keratinocyte desmosome resulting in flaccid blisters or erosions on the skin and mucous membranes. Oral or genital lesions may precede full-blown pemphigus by three and more months. Desmogleins (Dsg) 1 and 3 are regarded the most important target antigens. Increasing evidence for immunoserological heterogeneity of the disease with antibodies against other desmosomal proteins may characterize disease subsets of divergent clinical picture, course of the disease or therapeutic response [2]. Pemphigus vulgaris (PV) with characteristic anti-Dsg 3 (and 1) antibodies will present with skin *and* mucous membrane involvement, whereas pemphigus foliaceus (PF) with its two endemic (*fogo selvagem*) and non-endemic subsets is characterized by anti-Dsg 1 antibodies and blistering on the skin only. Different highly sensitive ELISA are commercially available using recombinant Dsg 1 and 3 for detecting and quantifying specific antibodies. Antibody concentration was found to correlate to the clinical course and therapeutic response as well as to predict a clinical relapse. The pathogenic as well as diagnostic relevance of IgA and IgE subtype autoantibodies still has to be elucidated [3]. IgG1 and 4 antibodies are indicative of active disease whereas IgG2 is found in remission. A characteristic and limited number of genes coding for variable regions of heavy chains in pathogenetically relevant autoantibodies indicate a genetically fixed immune response. However, apart from an immunogenetic background characterized by an association with HLA-DR antigens and suspected viral or drug triggers the induction of autoantibodies is hardly clarified. On the other side, a large body of literature can be found on the consequences of antibody binding. In this context the more mechanistic view of antibody binding with subsequent changes of protein conformation and adhesiveness may be opposed to an activation of intracytoplasmic signal transduction pathways with ensuing indirect cell damage, apoptosis and acantholysis [4–8] (Table 3). Proteinase C, c-myk, members of the Rho A family of GTPases and phospholipase have been studied recently. Both partly opposing ideas suggest different therapeutic strategies and therefore are clinically important but need to be further studied by evaluating the differential impact of the diverse pathogenetically relevant aspects of immunogenetics, antibody specificity and consequences of antibody binding. In addition to autoantibodies, a specific T cell response could be demonstrated with autoreactivity to restricted epitopes on Dsg 1 and 3 [9].

Several variants of pemphigus have been described including pemphigus herpetiformis, pemphigus erythematosus, IgA pemphigus and drug-induced pemphigus [2]. In addition to these, paraneoplastic pemphigus also referred to as paraneoplastic autoimmune multiorgan syndrome (PAMS) has recently been described [10]. It is characterized by periorificial and mucous membrane lesions and polymorphous skin lesions which may resemble erythema exsudativum multiforme (EEM). Apart from anti-Dsg 1 and 3 antibodies anti-envoplakin and periplakin as well as anti-BP 180 autoantibodies may be found. Recently the characteristic 170 kD antigen has been characterized as alpha-2-macroglobulin-like-1 protease inhibitor [11]. Typical malignancies involve the hematological system and solid organs as well as the rare Castleman-tumor, a semi-benign hypertrophy of lymph nodes with angiofollicular hyperplasia. Successful treatment of the underlying neoplasia will causally resolve this dramatic skin disease.

Pemphigus vulgaris is a potentially life-threatening disease and therefore requires an early and more intensive therapeutic regimen than other autoimmune blistering diseases [12–20]. The use of systemic corticosteroids well above 1 mg/kg body weight as pulse or continuous therapy is established and may be combined with adjuvant immunosuppressive/modulatory drugs like azathioprine, mycophenolatemofetil, methotrexate or cyclophosphamide in cases of severe disease [12]. Apart from intravenous immunoglobulins [18], immunoadsorption [19] in combination with the anti-CD20-antibody rituximab has been published recently in well above one hundred

Table 1
Comparison of hereditary bullous skin diseases and autoimmune bullous skin diseases with respect to their target proteins.

Hereditary bullous skin diseases	Adhesion molecule	Autoimmune bullous skin diseases
Epidermolysis bullosa hereditaria (EBH)	BP-AG 1, Plectin	Bullous pemphigoid
Generalized atrophizing EB (GABEB)	BP-AG 2	Bullous pemphigoid, Pemphigoid gestationis
EBH with pyloric atresia	α6ß4 integrin	Bullous pemphigoid
EBH junctionalis (Herlitz)	Laminin	Cicatricial pemphigoid
	Ladinin	Linear IgA dermatosis (LAD)
EBH dystrophica	Collagen VII	Epidermolysis bullosa acquisita (EBA), Bullous lupus erythematosus

Table 2
Autoimmune bullous skin diseases.

Pemphigus group	Pemphigus vulgaris (PV)
	Pemphigus foliaceus (PF)
	Paraneoplastic pemphigus (PNP)
	IgA Pemphigus
Pemphigoid-group	Bullous pemphigoid (BP)
	Pemphigoid gestationis (PG)
	Linear IgA-dermatosis (LAD)
	Cicatricial pemphigoid (CP)
Epidermolysis bullosa acquisita (EBA)	
Dermatitis herpetiformis Duhring (DH)	

Table 3
Differences among pemphigoid and pemphigus diseases.

Pemphigoid	Pemphigus
Anti-BP 180	Anti-Dsg1,3
Complement, PMN, innate immunity	Intracytoplasmic signal transduction
Necrosis	Apoptosis
B cells, (T-cells)	B cells, T cells

cases [14–17]. Apart from casuistical evidence most available clinical studies are either small or lacking a control arm and therefore the combination of corticosteroids and azathiorine still is the therapy of choice. The clinical effectiveness and feasibility of peptide therapy still has to evaluated, may however allow early targeting pathogenetically relevant disease mechanisms [20].

4. Pemphigoid group

Bullous pemphigoid (BP) is both clinically and immunoserologically distinct form pemphigus and could only be characterized as an own entity fifty years ago. Apart from being much more frequent with an incidence of 10/100,000/a its peak manifestation is in the seventh decade of life with intense itiching and tense bullae on inflammatory skin [21,22]. Subepidermal blistering is induced by autoantibodies against hemidesmosomal structural proteins. Histologically, the blister develops in or just below the lamina lucida of the basement membrane with a linear antibody and complement deposition found at the dermoepidermal junction zone [23–25].

BP is most common within the pemphigoid group (Table 2) and mainly affects patients between 60 and 80 years of age with an equal incidence in men and women [21,22,24]. Blistering is sometimes preceded by urticarial or eczematous eruptions for months which have to be carefully examined for proper differential diagnosis. The lesions may be localized or generalized involving the mucosa in 60% of cases. On the other side, anti-BP 180 and 230 antibodies are found among healthy subjects above the age of 50 in 59% of cases [24]. If these patients are at risk of developing a BP or show immunoreactivity to pathogenetically irrelevant epitopes is still unclear. Anti-basal membrane antibodies may be induced by inflammatory processes in this region or by therapeutic measures as indicated by the casuistically well-described association of BP and psoriasis vulgaris in patients distinctly younger than the average manifestation age of BP [26].

Autoantibodies are specific for the hemidesmosomal antigen called BP 180. The serum levels of autoantibodies against its immunodominant NC16A-domain correlate with disease activity [23]. To establish the diagnosis of BP histological analysis as well as direct (band-like pattern of IgG and complement at the basement membrane zone of diseased skin) and indirect immunofluorescence (band-like pattern at the basement membrane zone of monkey esophagus) tests and ELISA have to be performed to detect tissue bound and circulating antibodies [25]. Increasing evidence shows immunoserological heterogeneity among the pemphigoid group which is reflected by diversity in clinical picture and therapeutic response. In contrast to pemphigus complement factors of both classical and alternative pathway and neutrophilic granulocytes are pathogenetically relevant [27] (Table 3). The relevance of IgA and IgE subtypes for pathogenesis and diagnosis remains to be elucidated [28,29]. Increasing awareness of specific IgE and mast cells within the pathogenesis of BP may reflect the clinical experience of elevated IgE levels and increased peripheral eosinophil counts in BP patients.

Autoantibodies against BP 180 can also be found in female patients with pemphigoid *gestationis (PG)*, a pregnancy-associated intensely pruritic skin disease presenting with eczematous or urticarial skin eruptions and frequently relapsing during further pregnancies. At an incidence of 1:50.000 pregnancies it is found in the second and third trimenon with lesions predominantly around the umbilicus. Though self-limiting after birth, PG may cause severe distress to the pregnant mother requiring treatment with topical corticosteroids and/or antihistamines. Due to incipient placental insufficiency, newborns may be small for date and delivered too early. Even in the absence of bullous lesions in the mother, skin eruptions are seen in 5–10% of newborns due to the diaplacentar transfer of IgG antibodies [1].

Mucous membrane or cicatricial pemphigoid (MMP) is primarily involving mucous membranes [30]. As lesions heal with deforming scars, blindness in conjunctival involvement or constrictions in the genital or respiratory tract as well as the esophagus are most devastating complications of MMP [30].

Another disease related to BP is *linear IgA dermatosis (LAD)* with two incidence peaks in childhood and early adolescence. This disease is the most common cause of autoimmune mediated blistering in childhood and therefore an important differential diagnosis. Blisters are found clustered in a chain like pattern at the edge of inflammatory erythema. The pathogenetically relevant IgA autoantibodies are directed against a 97 kD fragment of BP 180. Why IgA is involved to restricted epitopes on the otherwise shared antigenic structure still remains to be elucidated. The therapeutic response to systemic corticosteroids is poor, but patients usually respond well to diaminodiphenylsulfone (dapsone).

A heterogeneous panel of autoantibodies apart from anti-BP 180 is found in other subsets of BP such as anti-laminin-5 ($\alpha3\beta3\gamma2$, Laminin-332), anti-integrins or anti-anchoring filament proteins [23,25]. Both sensitive and specific assays become increasingly available to properly diagnose these subsets with their partly different therapeutic responses and clinical courses.

Although BP may spontaneously remit after an average course of 2.5 years, treatment has to be started in most cases and adapted to the severity and dynamics of skin involvement as well as the individual parameters like comorbidity and comedication [13]. The highest therapeutic evidence is available for potent topical corticosteroids (clobetasol diproprionate) with a clinical response within a few weeks [31] but prolonged application over several months. As the dosage of systemic corticosteroids was shown to correlate with mortality as well as severe unwanted effects, they should be restricted to more severe and rapidly progressing cases starting at 0.5 mg/kg body weight up to well below 1 mg/kg. For dose sparing reasons immunosuppressive agents like dapsone, azathioprine or mycophenolate mofetil may be added in an adjuvant setting [13,24]. As with pemphigus, anti-CD20 antibodies may alternatively be used in severe or recalcitrant cases [14,16,17]. Conversely, MMP has to be treated early and effectively by a combination of prednisolone and cyclophosphamide in severe cases [30]. An interesting therapeutic approach was published recently, albeit only studied in vitro and mice. Non-complement binding recombinant Fab fragments of pathogenic autoantibodies were able to inhibit binding of full antibody and subsequent complement activation [32].

5. Epidermolysis bullosa acquisita (EBA)

The autoantibody response in this subepidermal blistering disease is directed against collagen VII, the main constituent of anchoring fibrils which are located in the upper dermis just below the basement membrane zone [1]. Immunodominant epitopes are found on the non-collagenous region (NC1). Similar to pemphigoid diseases, both complement and neutrophilic granulocytes are involved in addition to a specific T-cell activity. Antibody production and blistering can be induced by transfer of sensitized T-cells from mice immunized with type VII collagen [33]. In contrast to BP, blisters and erosions will result in superficial scars and miliae. Blisters are found primarily in acral location at mechanically irritated areas. Experimental animal models are available to study the differential impact of autoantibodies and complement in the pathogenesis. As with LAD, patients will respond best to dapsone, but only poorly to either topical or systemic corticosteroids. Associations of EBA with other diseases have been described like psoriasis and neuroendocrine pancreas tumor, however, the pathogenic link is unclear.

6. Dermatitis herpetiformis Duhring (DH)

DH is a distinctly itching skin disease with characteristic predilection sites [34]. Immunohistochemically, IgA and C3 deposits are found clustered within dermal papillae. DH is closely related to celiac disease

Table 4
Differences among gluten-sensitive enteropathy and dermatitis herpetiformis Duhring.

Gluten sensitive enteropathy (GSE)	Dermatitis herpetiformis Duhring (DH)
Frequent	Rare
Female preponderance	Male preponderance
First manifestation in childhood	First manifestation in adulthood
Gluten-free diet	Dapsone treatment

(CD) though their direct pathogenic link could not be characterized yet [35,36] (Table 4). Both diseases are characterized by antibodies against tissue transglutaminase (transglutaminase 2, TG2), DH additionally and more specifically by antibodies against epidermal TG3 [37]. The initial trigger of CD is a T-cell mediated intestinal immune reaction to alimentary gliadin. Transglutaminases (TG) seem to be of prime importance by deamidating and crosslinking gluten peptides which will eventually result in the gluten-dependent production of transglutaminase-specific autoantibodies. Overt DH is found in only 5–10% of CD patients, conversely CD in only rare incidences of DH. However, minimal duodenal involvement with lymphocyte infiltration of gut submucosa can regularly be found on endoscopic biopsy [38]. These tight, yet not strict relations are further substantiated by different therapeutic procedures [38]. The first line treatment of DH is dapsone which will result in rapid improvement of itching and inflammatory skin symptoms. In contrast, CD does not respond to dapsone at all. Whereas in CD strict alimentary gliadin avoidance is mandatory and will result in rapid improvement of gut symptoms, the beneficial effects of gluten restriction in DH will take months to a year to appear. Though recent epidemiological studies have challenged the relation of DH and lymphoproliferative diseases, gluten restriction is recommended for both diseases as the incidence of intestinal lymphoma can be distinctly decreased [38,39].

Disclosure statement

M.S. is speaker and advisory board member for Abbott, Pfizer, GSK and Leo. C.E.-B. has no conflict of interest to declare.

Take-home messages

- Autoimmune skin diseases are heterogeneous and may affect the skin as single organ or within the context of systemic diseases.
- Classical autoimmune diseases represent with blistering of skin and mucous membranes or as defined subsets of inflammatory connective tissue diseases.
- Drug-induced unwanted effects are at times difficult to dissect from the underlying disease.
- For most autoimmune blistering skin diseases both sensitive and specific serological tests are available.
- Based on clinical activity, comedication and comorbidity differential therapy is available to modulate clinical symptoms. However, pathogenetically orientated and curative approaches are not available yet.
- Early diagnosis and treatment are mandatory to halt either fatal or disabling or mutilating course of disease.

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Pulmonary infarction and lupus

Pulmonary thromboembolism is a manifestation seen in lupus patients, mainly if it is associated with antiphospholipid syndrome. In a large cohort, Weng et al. (**Lupus 2011;20:876-85**) evaluated 773 hospitalized patients and found 12 out of them with pulmonray infarction. Six of these 12 patients had antiphospholipid syndrome and all of them had simultaneous venous thromboembolism. All patients were treated with heparin and therapy was successful. In sumary, this study demostrated na incidence of lung infarction of 0.8% in lupus patients and this vascular abnormality was linked to antiphospholipid syndrome.
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