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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