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CHAPTER 1
Introduction in pemphigoid diseases

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Pemphigoid diseases

Pemphigoid diseases are autoimmune skin diseases mediated by autoantibodies targeting structural proteins within, or closely related to the hemidesmosome (figure 1).[1,2] Hemidesmosomes are specialized protein-complexes which connect the keratin cytoskeleton of the keratinocytes to the extracellular matrix in the dermis, providing structure and integrity to the skin.[3]

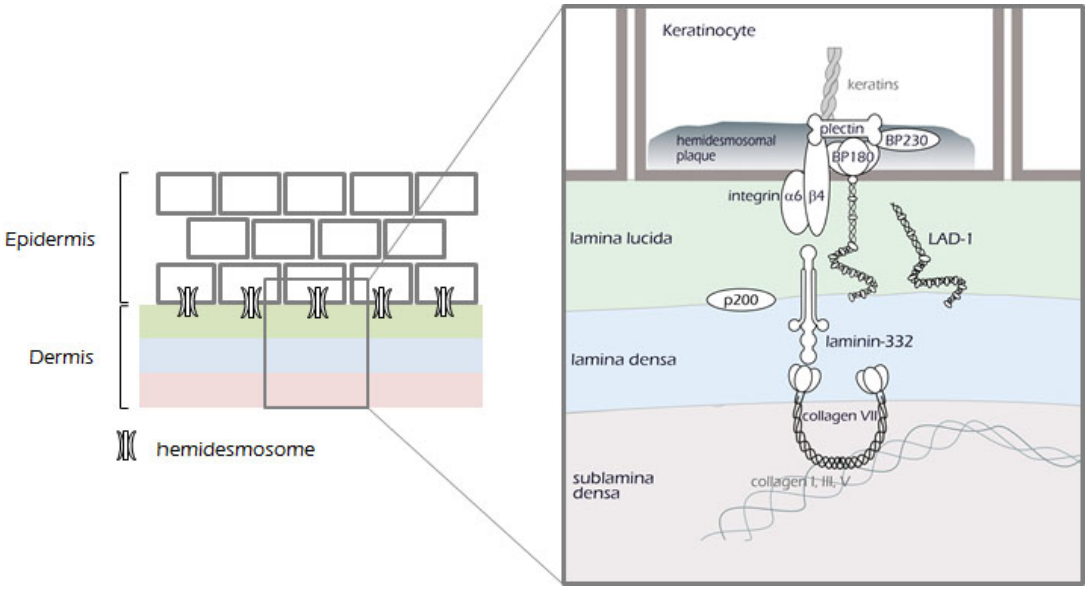

Figure 1. Schematic overview of the skin on the left. The epidermis is attached to the dermis by hemidesmosomes that connect the basal keratinocytes to the extracellular dermal matrix. On the right, an overview is given of proteins within, or closely related to the hemidesmosome. Proteins in white can be targeted by autoantibodies in pemphigoid diseases. Adapted from M.F. Jonkman.

Many subtypes of pemphigoid diseases exist, and they can be subdivided into pemphigoid diseases predominantly affecting the skin, or mucous membranes. Beside the clinical subdivision, pemphigoid diseases can also be characterized by the targeted antigen. While clinical disease features may overlap, management and prognosis often differs. It is therefore important to differentiate between the various pemphigoid subtypes.

Bullous pemphigoid

Bullous pemphigoid (BP) is the most common autoimmune blistering disease, and predominantly affects the skin.[1] The disease presents with severe pruritus and blisters, and typically has an onset at old age, with a reported median of 77 to 83 years.[4–8] The annual incidence of BP is estimated between 2.4 to 21.7 new cases per million inhabitants in the general population of countries worldwide, and exponentially increases to 190-312 cases per million in the elderly population aged above 80 years.[5–8] Interestingly, reported incidence numbers show an increasing trend over the last two decades, possibly related to more awareness for atypical BP variants, and the development of better diagnostic tests.[5,9] Moreover, several drugs that can trigger BP are more commonly used, such as gliptins, TNF-α inhibitors, and check point inhibitors.[10–12] Another possible explanation is the increasing incidence of neurodegenerative diseases, which are associated with BP.[5,13] The highest associations were found between the co-occurrence of BP and Alzheimer's disease, multiple sclerosis, and Parkinson's disease.[13–15] Neurological disorders precede BP in the majority of the cases.[15] Interestingly, BP antigens BP180 and BP230 are also expressed in a neuronal isoform in the central and peripheral nervous system, and theories on cross reactivity have been postulated, yet, no strong conclusions could be drawn.[14,16]

Pathogenesis - Several studies observed a genetic susceptibility to develop pemphigoid diseases in patients carrying the human leucocyte antigen (HLA) allele DQB1*03:01.[17–20] This HLA allele presumably contributes in the pathophysiology by presenting pemphigoid-specific antigens to autoreactive T cells.[17–20] T cell activation subsequently leads to B cell activation, and ultimately to the production of autoantibodies by plasma cells. In BP, these autoantibodies are directed against BP180 and BP230 (figure 1).[1,2] BP230, also termed BP antigen 1, is a member of the plakin family and is located intracellular.[2] BP180 is a transmembrane protein, and is also termed type XVII collagen, or BP antigen 2.[1,2] The extracellular noncollagenous 16A (NC16A) domain of BP180 is an important immunodominant region, and the pathogenicity of IgG autoantibodies to NC16A is proven in multiple studies, while studies on the relevance of BP230 reactivity showed conflicting results.[10,21–24] Circulating IgE autoantibodies against BP180 and BP230 were also detected in BP patients, and anti-NC16 IgE showed a correlation with disease activity as well. [21,25–31] In the skin, IgE was found in a linear pattern along the basement membrane zone

(BMZ)[32–35], whereas others reported IgE bound to mast cells and eosinophils in the upper dermis[31,36]. Yet, the exact role of IgE in the disease pathogenesis of BP is unknown.

The mechanism of blister formation in BP may follow complement dependent and independent pathways.[37,38] Complement activation, also termed complement fixation, can be induced through the classical pathway by autoantibody binding, or through the lectin or alternative pathway.[39] Upon activation, a cascade of cleavage of complement components is initiated, resulting in stimulation of chemotaxis and phagocytosis of immune cells, inflammation, and direct cell lysis by forming a membrane attack complex.[39] Evidence suggests that in BP the complement system is activated by binding of autoantibodies to BP180, which leads to migration of mast cells, eosinophils, and neutrophils towards the skin.[40,41] It is hypothesized that, upon activation, immune cells release cytotoxic substances and proteases that degrade extracellular matrix proteins, therefore causing a subepidermal split.[10] Other studies suggest complement independent blistering through autoantibody induced internalization of the complete BP180 protein.[37,38] Depletion of BP180 from the hemidesmosome weakens its adhesion strength, and may result in blister formation.

Clinical presentation - The clinical presentation of a typical BP patient includes symptoms of severe pruritus accompanied by tense blisters on erythematous plaques (figure 2).[42–44] In early stages of BP, a prodromal phase may occur in which pruritic symptoms are the sole manifestation, and patients are frequently misdiagnosed.[45,46] Lesions are predominantly located on the extremities and trunk, and limited mucosal involvement can be observed in 10-15%.[42–44] BP has a chronic disease course with a tendency to relapse, and symptoms negatively influence the patients' quality of life.[47,48] Mortality rates in BP are heightened 3.4- to 6.6-fold compared with the general population[49–51], with a pooled 1-year mortality rate in BP patients of 23.5% worldwide[49]. These findings emphasize the importance of early disease recognition, and timely adequate therapy in patients with BP.

Nonbullous pemphigoid

Several studies reported that approximately 20% of BP patients present with atypical clinical features in which blisters are absent (figure 3).[9,44,52,53] In these reports patients commonly present with severe itch and skin lesions, which were

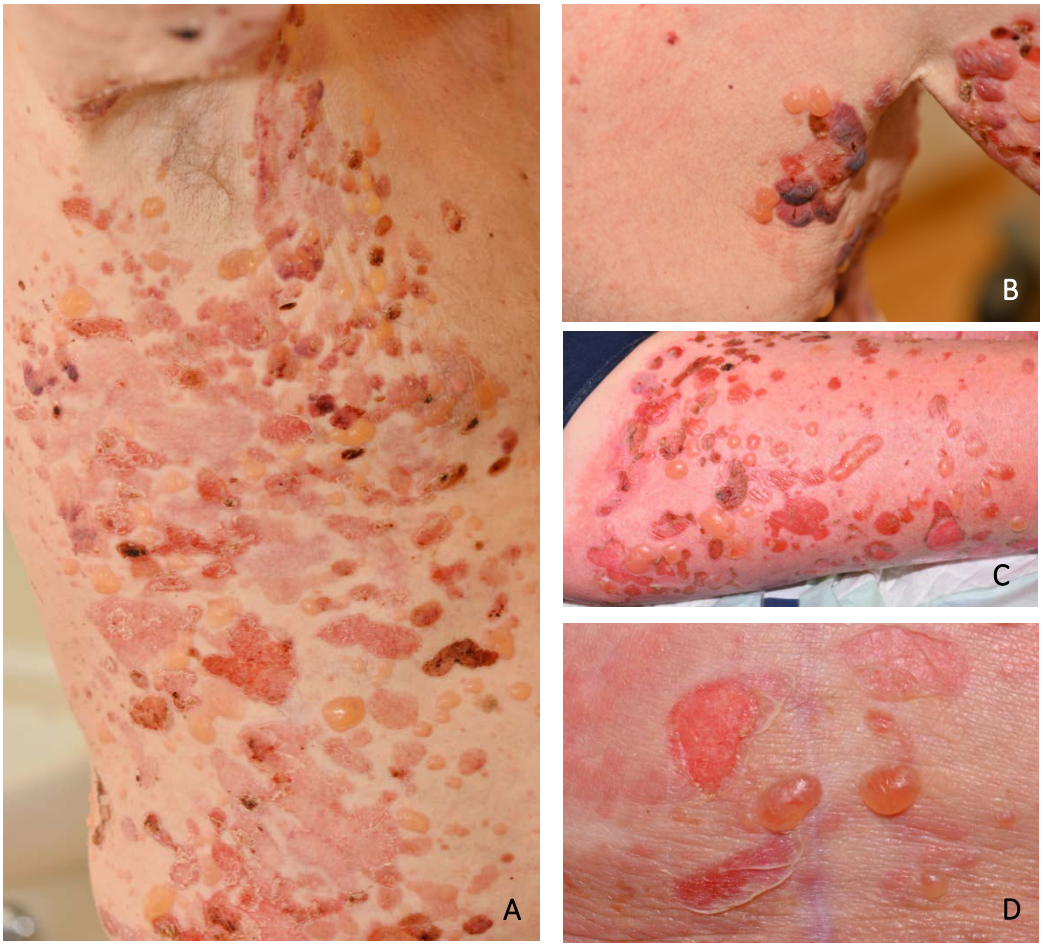

Figure 2. Bullous pemphigoid. A/B. Tense fluid-filled and hemorrhagic blisters, erosions, erythematous plaques and crusts on the right flank, the chest, and upper arm in a patient with severe bullous pemphigoid. C. Tense blisters, erosions and crusts on erythematous skin on the right upper leg. D. Detail of tense blisters and erosions with remnants of the blister roof.

eczematous-like, prurigo nodularis-like, or consisted of erythematous urticarial plaques. Also, few cases that displayed no primary skin lesions at all were described.[53] The diagnosis of pemphigoid was confirmed in all cases by the detection of pemphigoid-specific autoantibodies in serum and skin. Authors have given the nonbullous disease phenotype various descriptive names, such as *pruritic pemphigoid, pemphigoid incipiens*, *pemphigoid nodularis*, or *prodromal bullous pemphigoid*.[52,54–56] The shared clinical characteristic in the reported cases is the lack of a blistering phenotype, therefore, we favor the term *nonbullous pemphigoid*

(NBP). It is not clear whether NBP patients are diagnosed during an early (prodromal) phase of BP, or whether NBP should be seen as a different disease entity within the pemphigoid spectrum. Moreover, NBP is not well characterized and is understudied. It is unknown why blisters do not develop, while these patients have autoantibodies against antigens that are also targeted in BP patients (BP180 and BP230). Furthermore, important clinical practice data on the management and prognosis of NBP patients are lacking.

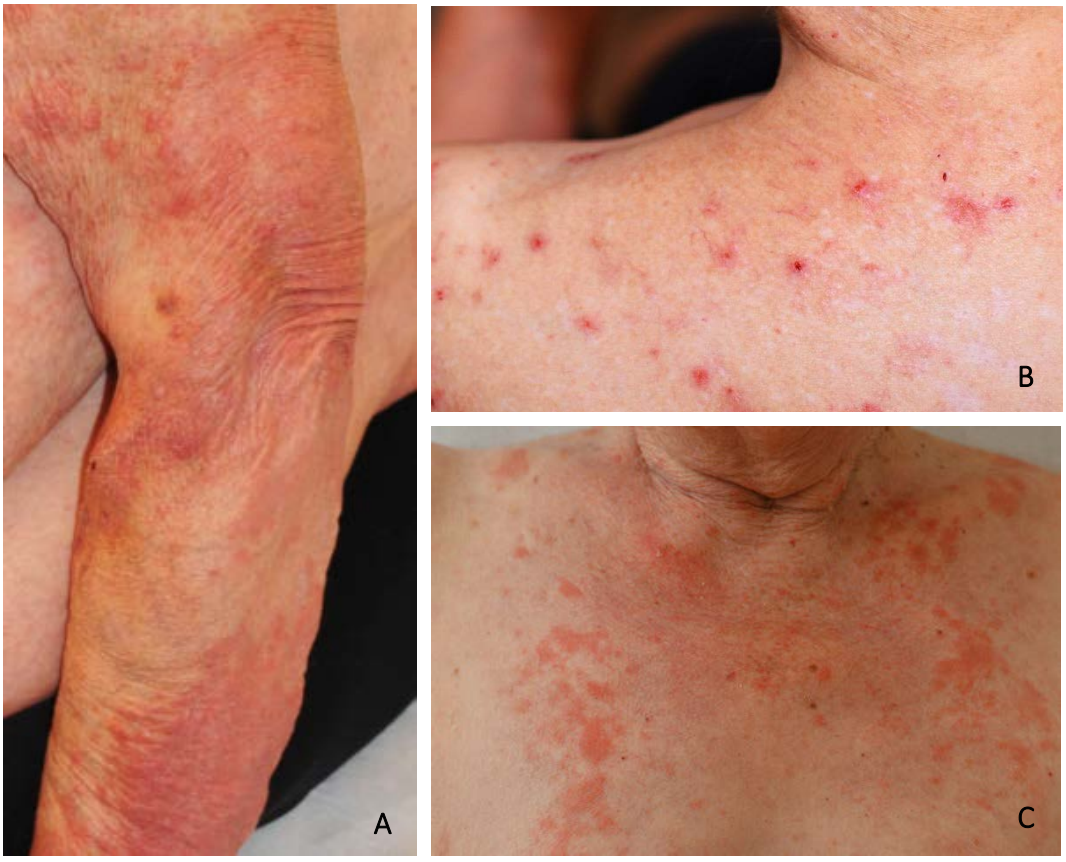

Figure 3. Nonbullous pemphigoid as cause of severe pruritus in elderly patients. A. Fixed erythematous urticarial plaques on the left arm. B. Secondary skin lesions by pruritus consisting of excoriations and hypopigmented maculae on the shoulders and back.
C. Erythematous papules and urticarial plaques on the chest.

Mucous membrane pemphigoid

Mucous membrane pemphigoid (MMP) is a group of pemphigoids that predominantly affect the mucous membranes.[1,57,58] The annual reported incidence is 1.3 to 2.0 newly diagnosed cases per million inhabitants of France and Germany, with an average age of disease onset of 60 years.[59–61] Patients present with blisters, erosions and inflammation of mucosal surfaces, and the oral (85%) and ocular (65%) mucosa are most frequently affected.[57,58,62] Other sites may include nasal (20-40%), anogenital (20%), pharyngeal (20%), laryngeal (20%), and esophageal mucosa (5-15%). One third of the MMP patients also display mild skin lesions. Most patients have autoantibodies against BP180, mainly targeting the C-terminal domain and/or the NC16A domain.[63–66] However, antibodies may also target BP230, type VII collagen, integrin α6β4, p200 or laminin 332 (figure 1). Anti-laminin 332 reactivity is associated with severe disease, scarring, and pharyngeal and laryngeal involvement, with risk of airway obstruction.[67–69] Several studies have reported an increased risk of malignancy in patients with anti-laminin 332 reactivity, whereas others did not find such association.[68–71]

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) comprises approximately 6% of all pemphigoid diseases.[72] The targeted antigen is type VII collagen, a major component of anchoring fibrils located below the lamina densa (figure 1).[73] EBA can roughly be divided into the mechanobullous subtype characterized by skin fragility, milia formation, nail dystrophy, and scarring, and the inflammatory subtype, clinically resembling other pemphigoid diseases.[72] Mortality data are lacking, however, clinical experience learns that mortality rates are lower compared to BP.[51] Nevertheless, EBA patients are often treatment resistant, and suffer from a chronic disease course.[74,75]

Linear IgA disease

Linear IgA disease (LAD) is a heterogeneous group of pemphigoids characterized by exclusive IgA class autoantibodies.[76] The disease can be drug induced, most commonly by vancomycin.[77] The annual incidence ranges between 0.2 and 1.0 cases per million estimated in different regions.[78] The majority of patients recognize the 120 kDa (LAD-1), or the 97 kDa (LABD97) antigen, both cleavage products of the extracellular domain of BP180 (figure 1).[79] A less common subtype

shows IgA reactivity to type VII collagen, and is named sublamina densa-type LAD, or IgA EBA. LAD has a biphasic distribution, affecting young children, and adults above 50 years.[76] Childhood LAD presents with blisters on urticarial plaques in a typical circinate or serpiginous configuration forming a 'crown of jewels' or a 'string of pearls'.[80] In adults LAD more often resembles BP. LAD is usually self-limiting in childhood within one to five years, whereas adults may have a chronic disease course with poor response to different therapies.[80]

Other pemphigoid diseases

Other rare pemphigoid variants, not further discussed in this thesis, include pemphigoid gestationis[81] with disease onset during pregnancy; Brunsting-Perry pemphigoid[82] with blisters localized on the scalp, face and neck, leaving atrophic scars; lichen planus pemphigoides[83] with clinical features of both BP and lichen planus; anti-p200 pemphigoid, with autoantibodies to a 200 kDa sized protein of yet unknown molecular identity.[84–86]

Diagnosis of pemphigoid diseases

The diagnosis of pemphigoid diseases is based on clinical features and autoantibody detection in skin and/or serum (figure 4).[1,87]

Histopathology

In general, histopathologic features of pemphigoid diseases include a subepithelial split, and a dermal infiltrate with eosinophilic or neutrophilic granulocytes and lymphocytes.[88] Histopathology alone is not sufficient to diagnose pemphigoid, but can support diseases in the differential diagnosis.

Direct immunofluorescence microscopy

Direct immunofluorescence (DIF) microscopy has a highly important role in the diagnosis of pemphigoid diseases. Autoantibodies and complement bound in the skin are visualized by incubation of a fluorescent labeled antibody against human IgG, IgA or complement on a frozen skin section.[89] Additional serration pattern analysis differentiates pemphigoid variants with an n-serrated pattern (figure 5A) from EBA with a u-serrated pattern (figure 5B).[90]

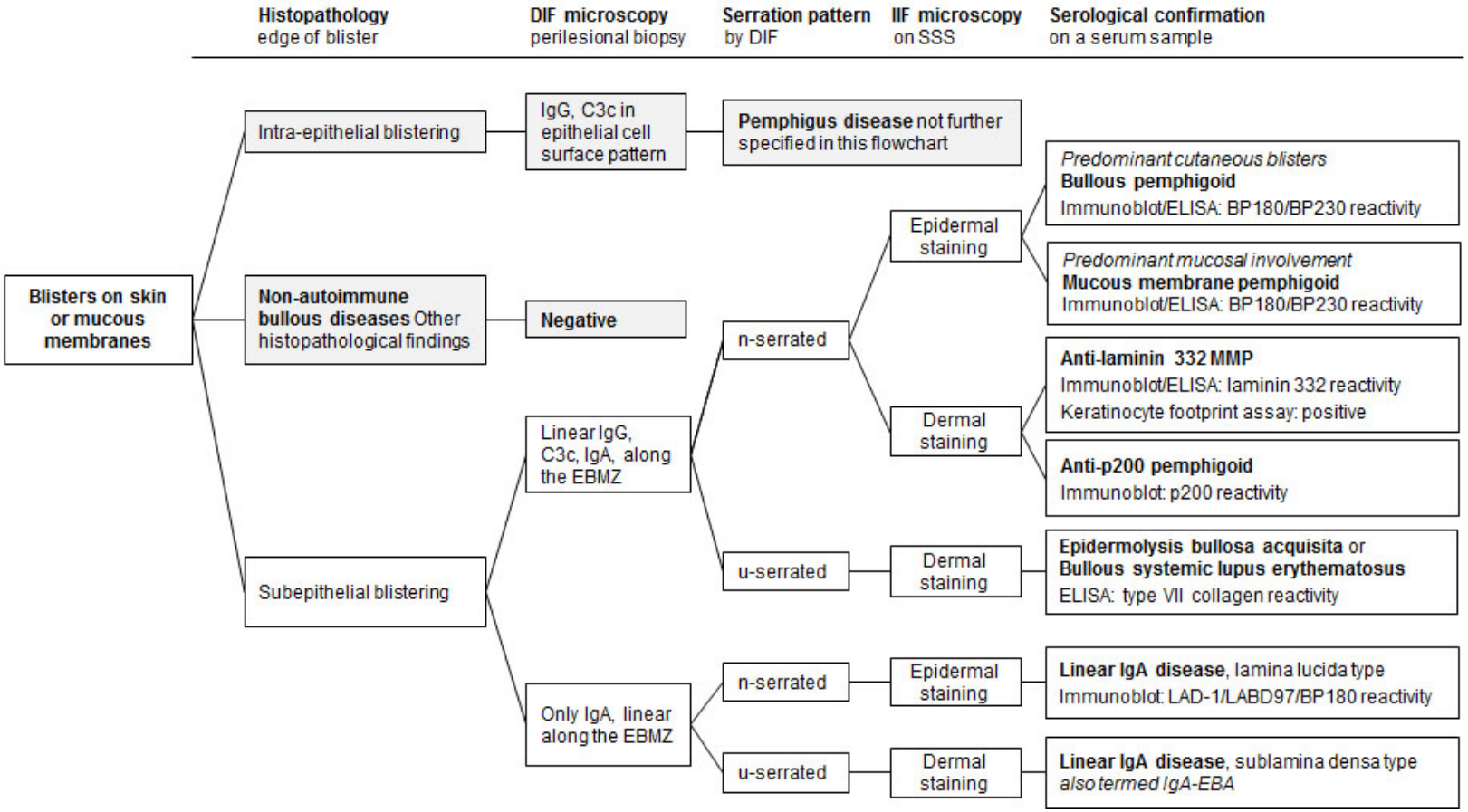

Figure 4. Flowchart of the diagnostic pathway in patients presenting with blisters on the skin or mucous membranes. DIF, direct immunofluorescence; EBMZ, epidermal basement membrane zone; IIF, indirect immunofluorescence microscopy; SSS, salt-split skin; ELISA, enzyme-linked immunosorbent assay; EBA, epidermolysis bullosa acquisita.

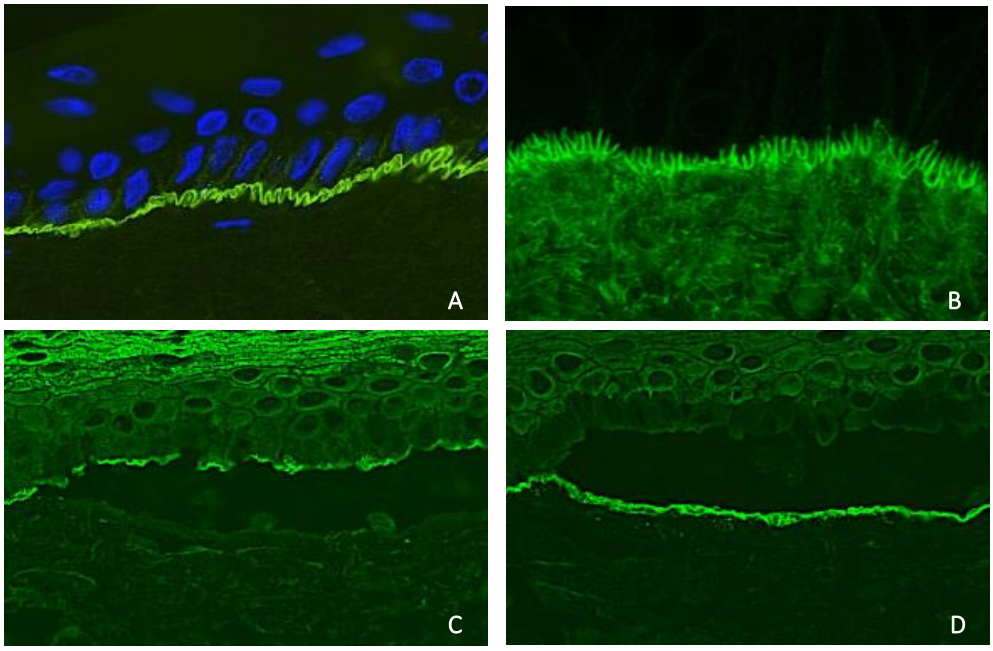

Figure 5. Immunofluorescence results compatible with the diagnosis of pemphigoid diseases. A. Direct immunofluorescence (DIF) microscopy shows linear IgG along the basement membrane zone (BMZ) in an n-serrated pattern. B. DIF microscopy shows linear IgG along the BMZ in a u-serrated pattern, compatible with epidermolysis bullosa acquisita. C. Indirect immunofluorescence microscopy on salt-split skin (IIF SSS) shows IgG bound to the epidermal side of the artificial split, compatible with pemphigoid diseases targeting BP180, BP230, LAD-1, LABD97, or integrin α6β4. D. IIF SSS shows IgG bound to the dermal side of the artificial split, compatible with pemphigoid diseases targeting p200, laminin 332, or type VII collagen.

Serologic tests

The detection of circulating autoantibodies against pemphigoid-specific antigens can be valuable to diagnose pemphigoid diseases.

Indirect immunofluorescence microscopy - Indirect immunofluorescence (IIF) microscopy is frequently performed using a monkey esophagus or salt-split skin (SSS) substrate. Monkey esophagus is commercially available, while SSS is obtained by incubation of human skin in 1M sodium chloride for 24 hours, resulting in a reproducible artificial split in the lamina lucida. Antigens are located either at the

epidermal or dermal side of the split. IIF SSS discriminates between pemphigoid diseases targeting BP180 and BP230 located in the lamina lucida (epidermal staining; figure 5C) and those targeting laminin 332, type VII collagen, or p200, all located beneath the lamina lucida (dermal staining; figure 5D).

ELISA and immunoblot – Enzyme-linked immunosorbent assay (ELISA) and immunoblot are the most commonly used techniques to specify the targeted antigen. ELISA kits are commercially available to detect and quantify antibodies to specific pemphigoid antigens (BP180 and BP230). By measuring the intensity of an enzyme induced color reaction, an antibody titer can be calculated. The immunoblot technique first sorts denatured skin proteins by molecular size through gel electrophoresis.[91,92] The sorted proteins are then transferred onto a membrane. Autoantibodies directed against skin proteins bind the membrane, and are visualized by staining the bound IgG. The molecular size of the stained protein identifies which pemphigoid antigen is targeted.

Other serological tests – Additional serological tests can differentiate between anti-p200 pemphigoid, anti-laminin 332 pemphigoid and EBA. The IIF knockout analysis is a technique using skin sections of patients with hereditary epidermolysis bullosa, in which laminin 332, or type VII collagen is absent ('knocked-out').[86] IIF microscopy is negative if patient serum contains autoantibodies to the knocked-out protein. In anti-p200 pemphigoid IIF remains positive in both laminin 332 and type VII collagen knock-out skin. Another technique to confirm or rule out the presence of anti-laminin 332 autoantibodies is the novel keratinocyte footprint assay.[93] This fast and specific assay uses the unique laminin 332 footprints that cultured keratinocytes leave on the bottom of the culture dish when moving. Anti-laminin-332 autoantibodies in the serum of a patient will bind to the footprints, and can be stained by immunofluorescence.

Management of pemphigoid diseases

The treatment of pemphigoid diseases mainly relies on immunosuppressive or immunomodulating drugs. In general, there is a lack of randomized placebo controlled trials with a sufficient sample size. Reasons for this are the low incidence

of most pemphigoid variants, and, especially in BP, the fragile elderly population with multiple comorbidities in which the diseases mainly occurs.

Bullous pemphigoid

The consensus guideline for the management of BP provides treatment recommendations for mild limited BP, and extensive generalized BP.[87] The first treatment choice for both mild and generalized disease is super potent topical corticosteroids applied on the whole body, except the face.[94,95] Secondly, systemic corticosteroids are recommended if topical steroids are insufficient, in a dosage of 0.5-0.75 mg/kg/day.[94] Adjuvant therapies that may be considered are tetracyclines, azathioprine, mycophenolate mofetil, methotrexate, dapsone, chlorambucil, and cyclosporine.[87] For therapy resistant BP that does not respond to the therapies mentioned above, the guideline advises to consider intravenous immunoglobulins, rituximab (RTX), anti-IgE monoclonal antibodies and plasma exchange.[87]

Mucous membrane pemphigoid

The first international guideline for the treatment of MMP was developed in 2002 by Chan and colleagues, using a consensus based methodology.[96] Management recommendations were separated for 'high risk' and 'low risk' patients. 'High risk' patients were defined as those who have disease occurring in ocular, genital, nasopharyngeal, esophageal, and laryngeal mucosa, as they have high likelihood of therapy resistance and scarring, which in case of airway obstruction can be life threatening. First line therapy in 'high risk' MMP is prednisone (1-1.5 mg/kg/day), and cyclophosphamide (1-2 mg/kg/day).[97,98] Alternative therapeutic options are azathioprine, and dapsone.[97,99] 'Low risk' patients were defined as those who have disease occurring only in oral mucosa, or in both oral mucosa and skin. Recommendations for initial therapy in low risk patients include topical corticosteroids, or tetracycline hydrochloride with nicotinamide.[100,101] Alternatively, dapsone, low doses of prednisolone, or azathioprine are advised.[96,97]

Epidermolysis bullosa acquisita

The management of EBA is challenging, and systemic corticosteroids are widely used as first treatment choice, with dosages ranging from 0.5 to 2.0 mg/kg/day.[102] In mild cases the use of colchicine 1 to 2 mg/day is preferred, as it only gives minor side effects compared to other treatment options.[103] Other therapies that may be

prescribed as monotherapy, or may be combined with systemic corticosteroids, are dapsone, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, and cyclophosphamide.[102] For treatment resistant EBA cases it can be considered to treat with high-dose intravenous immunoglobulin, RTX, plasmapheresis, immunoadsorption, or extracorporeal photochemotherapy.[102]

Linear IgA disease

Dapsone is the first treatment choice in LAD, and on average a dose of 100mg/day is sufficient to induce disease control.[104,105] Dapsone is prescribed in a number of diseases that involve the accumulation of neutrophils, and inhibits the adherence of neutrophils to anti-BMZ autoantibodies.[106] In some LAD patients dapsone can be ineffective, and systemic corticosteroids, with or without adjuvant immunosuppressants, such as azathioprine, mycophenolate mofetil, cyclosporine or cyclophosphamide may be needed.[105] No additional treatment recommendations exist for the sublamina densa type LAD, also called IgA-EBA. In drug induced LAD, first the suspected drug needs to be stopped, which usually resolves the symptoms within four weeks after withdrawal.[77,107]

Novel and emerging therapies

The management of pemphigoid diseases can be challenging, partly due to the frailty of the patients. For many years high doses of systemic corticosteroids have been used to treat pemphigoid diseases, however, they have been associated with high mortality rates.[50,108] Conventional immunosuppressive drugs may give insufficient disease control or severe side effects. Therefore, the search for better therapies with more effectiveness and less side effects is ongoing. Several novel and emerging therapies are discussed below.

Rituximab

RTX is an anti-CD20 monoclonal antibody that has been used for many years in the fields of rheumatology and oncology.[109] In 2017 groundbreaking results of a multicenter open label randomized trial illustrated a beneficial effect of RTX 1000mg on day 1 and 15 combined with short term oral corticosteroids, over monotherapy with oral corticosteroids in pemphigus vulgaris.[110] Based on these outcomes, RTX was recently registered as therapy for pemphigus vulgaris. Limited data are available on RTX in pemphigoid diseases, however, it is suggested that RTX

could be a relatively safe and valuable therapeutic option.[111–113] Currently, most clinical guidelines recommend the use of RTX as a 3rd line therapy in pemphigoid diseases.

IgE targeting therapy

Based on potential pathogenic role of IgE in pemphigoid, targeting IgE can be a novel and interesting approach in the treatment portfolio. Omalizumab is a monoclonal antibody targeting unbound human IgE, and therefore prevents its binding to the high affinity IgE receptor.[114] The drug is registered for chronic urticaria. Fairley *et al*. were the first to publish a BP case successfully treated with omalizumab in 2009, and in the last ten years over 22 more cases were treated.[115,116] Meta-analysis of these cases showed a surprisingly high success rate, with complete remission in up to 80% of the cases, however recurrence was seen in 80% after an average duration of 3.8 months, or when the therapy was stopped.[116]

Anti-complement therapy

A novel innovative therapeutic target in inflammatory diseases is the complement system.[117] Most experience with anti-complement therapies was gained in renal disease, particularly in anti-neutrophilic cytoplasmic antibody associated vasculitis.[118] Several animal studies reported evidence that complement may play an important role in the pathogenesis of pemphigoid diseases, providing a rational for anti-complement therapy in BP.[40,41,119] Recently, complement component 1s (C1s) was blocked by BIVV009 (previously termed TNT009) in ten BP patients, intervening in the classical complement activation pathway.[120] The drug appeared relatively safe, however, no disease activity measurements were performed. BP180 and BP230 autoantibody levels remained stable throughout the treatment period, while C3 depositions in the skin disappeared in 80%. Studies reporting on effectiveness of anti-complement therapy are expected soon.

Outline and aim of this thesis

PART 1 Nonbullous pemphigoid: Disease characteristics and immunological aspects

NBP is an understudied disease, and only few case reports have provided limited information on its disease features. Therefore, NBP is easily overlooked as a cause of pruritus in elderly individuals. In part 1 of this thesis, we aim to provide clinicians with more insights in the clinical features of NBP to improve disease recognition, and to gain information on the prognosis and disease management of NBP. Moreover, we intended to learn more about the immunological aspects of NBP, to answer the question 'why do NBP patients lack blisters'.

Interpretation of serological pemphigoid test results can be challenging. Therefore, we investigated the presence of serum autoantibodies in a population of dermatology patients with nonbullous skin disorders in chapter 2. To give an overview of the available literature on NBP, we systematically reviewed the literature on NBP in chapter 3, and summarized the disease characteristics of all published cases. Chapter 4 describes patient characteristics of our cohort of NBP patients, and provides daily practice data on the treatment and prognosis. In chapter 5 we performed a cross-sectional study to determine the prevalence of pemphigoid as an unrecognized cause of pruritus in the potential high-risk population of nursing home residents. In chapter 6 we attempted to find an answer on the question 'why do NBP patients lack blisters?' by assessing the presence of IgE in the serum and skin of BP and NBP patients. A second effort to find the answer was made in chapter 7, where we analyzed and compared the gene expression profile of lesional skin in NBP and BP.

PART 2 Management of pemphigoid diseases

In part 2 of this thesis we focus on the management of pemphigoid diseases. In chapter 8 we performed an international survey study, in which we explored the unmet needs in pemphigoid diseases from the perspective of patients, researchers and clinicians. The disease management of pemphigoid diseases can be challenging, and off-label drugs may be necessary in treatment resistant

pemphigoid cases. The recent success of the CD20 targeting drug RTX for the autoimmune blistering disease pemphigus vulgaris caught our attention and made us question whether it may also be effective in pemphigoid diseases. Therefore, we retrospectively assessed the effectiveness and safety of RTX in recalcitrant pemphigoid diseases in chapter 9. In chapter 10 we assessed the prevalence of pneumocystis pneumonia in patients with autoimmune blistering diseases to answer whether or not routine prophylaxis is advised.

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PART 1

Nonbullous pemphigoid: Disease characteristics and immunological aspects