

Pemphigoid diseases

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Pemphigoid diseases are a group of well defined autoimmune disorders that are characterised by autoantibodies against structural proteins of the dermal–epidermal junction and, clinically, by tense blisters and erosions on skin or mucous membranes close to the skin surface. The most common of these diseases is bullous pemphigoid, which mainly affects older people and the reported incidence of which in Europe has more than doubled in the past decade. Prognosis and treatments vary substantially between the different disorders and, since clinical criteria are usually not sufficient, direct immunofluorescence microscopy of a perilesional biopsy specimen or serological tests are needed for exact diagnosis. In eight pemphigoid diseases the target antigens have been identified molecularly, which has allowed the development of standard diagnostic assays for detection of serum autoantibodies—some of which are commercially available. In this Seminar we discuss the clinical range, diagnostic criteria, diagnostic assay systems, and treatment options for this group of diseases.

Introduction

Pemphigoid diseases are characterised by the presence of autoantibodies against distinct structural components of the dermal–epidermal junction (figure 1). Junction proteins link the cytoskeleton of the basal keratinocytes to the extracellular matrix of the dermis. Binding of pemphigoid autoantibodies leads to the separation of the epidermis and dermis by a complex, yet fairly well understood process.

The pemphigoid diseases include eight disorders for which the molecular target antigens have been identified (table). In addition to the seven named diseases listed in the table, a few patients have a pemphigoid disease that is characterised by renal insufficiency and autoantibodies against the $\alpha 5$ chain of type IV collagen.¹ IgG and IgA autoantibodies that target several not-fully-characterised antigens (including 105 kDa, 125 kDa, and 168 kDa proteins) have also been detected in serum samples from patients with pemphigoid disorders.^{2,3} Dermatitis herpetiformis, another subepidermal immunobullous disease, is not regarded as a pemphigoid disorder since the autoantigen epidermal transglutaminase is not a structural component of the dermal–epidermal junction.

Pemphigoid diseases share some clinical characteristics, such as tense blisters and erosions and, by contrast with pemphigus, a negative Nikolsky sign—ie, friction of non-lesional skin does not lead to intraepidermal disruption and visible erosion. The disorders are, however, heterogeneous with respect to overall clinical presentation, target antigens, and autoantibody isotype. Importantly, prognosis and treatment can vary substantially, so exact diagnosis is

necessary. However, the different diseases cannot usually be distinguished on clinical grounds alone, so an assessment of skin-bound or mucous membrane-bound autoantibodies and serum autoantibodies is needed.

In 1953, Lever⁴ differentiated pemphigoid diseases from pemphigus clinically and histopathologically. He described intraepidermal split formation and loss of cell adherence between keratinocytes (acantholysis) as hallmarks of pemphigus, and coined the term pemphigoid for disorders characterised by subepidermal splitting. About 10 years later, Jordon and colleagues⁵ (including Lever) first described serum and skin-bound autoantibodies in bullous pemphigoid. Since then, detection of skin-bound or epithelium-bound and serum autoantibodies have become diagnostic cornerstones for pemphigoid diseases, alongside clinical characteristics (table).

Bullous pemphigoid Incidence

In a prospective study of bullous pemphigoid that encompassed the entire Swiss population, the investigators calculated an incidence of 12·1 new cases per 1 million people per year.⁶ In Germany, Scotland, and France, incidences of 13·4, 14, and 21·7 per 1 million people per year, respectively, have been reported.^{7–9} A 2008 report¹⁰ from the UK calculated a higher incidence of 66 new cases per 1 million people per year, on the basis of a data registry established in general practice. In the UK, Germany, and France, incidence has increased substantially (two to five times) in the past 10 years,^{7,9,10} a finding that might be related to the increasing age of the general population, the availability of more sensitive and specific diagnostic assay systems, or both.

Bullous pemphigoid mainly affects older people, with onset usually in the late 70s. Incidence rises substantially to 150–330 per 1 million people per year in people older than 80 years.^{6–11} With the changing age structure of the European population, the incidence is likely to rise. Bullous pemphigoid rarely occurs in individuals younger than 50 years (incidence <0·5 cases per 1 million people per year).^{6,7,10,11} Few cases in infants, children, and adolescents have been reported, and

Search strategy and selection criteria

We searched PubMed using the terms “pemphigoid”, “linear IgA”, “herpes gestationis”, and “epidermolysis bullosa acquisita”. Our search covered articles published in English between Jan 1, 2000, and May 31, 2012. We identified additional reports from the reference lists of selected articles. Some important older publications are cited either directly or indirectly through review articles.

treatment responses in these patient groups do not differ greatly from those in adults.¹²

Mortality, risk factors, and associated diseases

1-year mortality for patients with bullous pemphigoid ranges from 20% to 40%, which is about two to three times higher than that of age-matched and sex-matched controls.^{9,10,13} Old age, widespread disease, a low Karnofsky score, and, importantly, high doses of oral corticosteroids are key risk factors for death.^{14,15} Patients with bullous pemphigoid are also three times more likely to develop pneumonia and pulmonary embolism than are matched controls.¹⁰

In the past 5 years, researchers have learned of an association between bullous pemphigoid and neurological disorders. Between a third and half of all bullous pemphigoid patients have neurological diseases (odds ratios from 2.4 to 10.6).^{16–19} In particular, major cognitive impairment, Parkinson's disease, stroke, epilepsy, and multiple sclerosis have been associated with bullous pemphigoid in controlled studies.^{16–19} These findings are especially intriguing since both bullous pemphigoid target antigens, BP180 (also termed type XVII collagen, COL17, or bullous pemphigoid antigen 2, BPAG2) and BP230 (dystonin or BPAG1), are expressed in the central nervous system. BP180 expression has been reported in the cerebellum of rats and in autopsy samples of various neuroanatomical regions of human brain,^{20,21} and the antigen is predominantly seen in lipofuscin granules of ageing, post-mitotic neurons.²⁰ Mice with mutations in the dystonin gene that encodes for various isoforms of BPAG1, including the epithelial isoform BP230, develop severe dystonia and sensory nerve degeneration.²²

Investigators discovered an independent association of bullous pemphigoid with psoriasis in a population-based study based on data from the national health insurance database in Taiwan.¹⁷ Various autoimmune disorders and cancer have also been linked with the disease. However, investigators of a case-control study²³ did not report any increased risk for other autoimmune disorders and investigators of two case-control studies into bullous pemphigoid and cancer risk reported no association²⁴ or only a weak association with gastric cancer²⁵ in Swedish and Japanese cohorts, respectively, compared with age-matched controls.

Several triggers have been implicated in disease onset in individual patients, including trauma, burns, radiotherapy, ultraviolet radiation, and vaccination—most frequently against influenza.^{26,27} Investigators of two studies reported weak but significant associations with chronic use of spironolactone and phenothiazines with aliphatic side chains,^{19,28} so use of these drugs should be carefully assessed by prescribing physicians.

Clinical presentation

Bullous pemphigoid typically presents with tense, mostly clear, blisters and erythema, frequently in conjunction

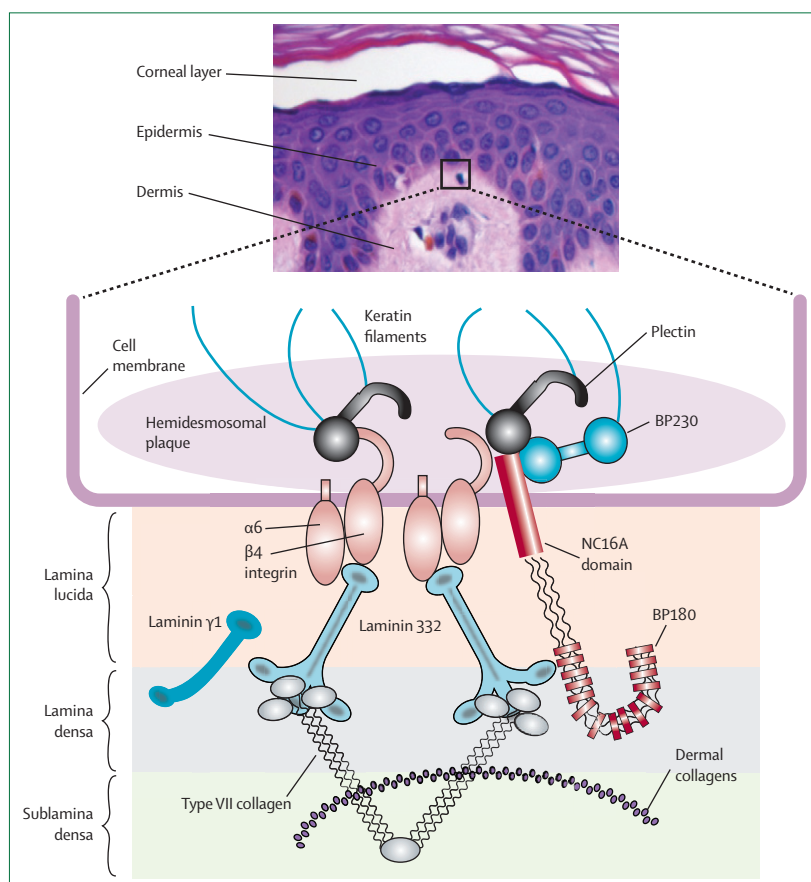


Figure 1: Schematic diagram of the dermal-epidermal junction

Only molecules that are targeted by autoantibodies in pemphigoid diseases are shown.

with urticarial plaques (figure 2). Blisters often arise on the flexural aspects of the limbs and on the abdomen and can persist for several days, leaving erosions and crusts. In almost all patients, severe pruritus is present. Mild oral lesions develop in 10–20% of patients, but other mucosal areas are rarely affected.²⁹ Before development of blisters, the disease is typically preceded for several weeks and even months by a prodromal phase in which pruritus alone or in association with excoriated, eczematous, and papular or urticarial lesions occur (figure 2). In some patients, these non-bullous skin symptoms persist and are defined as several clinical variants—eg, prurigo-like, erythroderma-like, ecthyma gangrenosum-like, intertrigo-like, and toxic epidermolysis-like bullous pemphigoid.²⁹ Localised forms of the disease frequently affect the pretibial area. In 2011, an international panel of experts defined outcome measures for clinical studies and developed a clinical scoring system, the BP Disease Area Index,³⁰ to allow comparisons of clinical trials. This index will need further validation.

Target antigens

Two hemidesmosomal proteins, BP180 and BP230, have been identified as target antigens in bullous

	Autoantibody specificities (main target antigens listed in the first line)	Clinical signs	First-line treatment
Bullous pemphigoid	BP180 NC16A domain* BP230*	Tense blisters and erosions without predominant mucosal involvement	Whole-body highly potent topical corticosteroids or oral prednisolone at 0.5 mg per kg per day (level A) Possible effects have been attributed to azathioprine, chlorambucil, dapsone, methotrexate, mycophenolic acid, and tetracyclines (all level B)
Mucous membrane pemphigoid	BP180, laminin 332 BP230,* α6β4 integrin, laminin 311,† type VII collagen	Predominant mucosal involvement	Low-risk:‡ potent topical corticosteroids plus a tetracycline or dapsone (level C) High-risk:‡ prednisolone 1.0–1.5 mg per kg per day (level B) plus cyclophosphamide, azathioprine, or mycophenolic acid (all level C) Ocular: prednisolone 1.0–1.5 mg per kg per day (level C) plus cyclophosphamide, dapsone, intravenous immunoglobulin, mycophenolic acid (all level B)
Pemphigoid gestationis	BP180 NC16A domain* BP230*	Pregnancy or post-partum period	Potent topical corticosteroids plus cetirizine (level C)§
Linear IgA disease	LAD-1, BP230 (IgA reactivity)	Tense blisters and erosions without predominant mucosal involvement	Dapsone or sulfapyridine (both level B) plus potent topical corticosteroids (level C)
Epidermolysis bullosa acquisita	Type VII collagen*	Mechanobullous and inflammatory variant	Oral corticosteroids (0.5–2.0 mg per kg per day, dependent on severity) plus colchicine or dapsone (level C)
Anti-laminin g1/anti-p200 pemphigoid	Laminin γ1 (p200 protein)	Tense blisters and erosions without predominant mucosal involvement	As for bullous pemphigoid (level C)
Lichen planus pemphigoides	BP180 NC16A domain* BP230*	Tense blisters that do not arise directly on lichen planus lesions	Therapy for lichen planus plus same treatment algorithm as for bullous pemphigoid (level C)

Treatment regimens are based on the scientific literature cited in the text and the authors' own experience. Doses are detailed in the text. Recommendations are based on different evidence levels: A= randomised controlled trials; B= poor-quality controlled trials and large case series; C= small case series, case reports, and expert opinion. Since no international guidelines are available, these regimens and doses should be adapted to individual patients by physicians with experience in the treatment of pemphigoid diseases. *Commercial detection systems are available for BP180 NC16A domain and BP230; a commercial detection system exists for type VII collagen, but has not been approved by the US Food and Drug administration. †Laminin 311 shares the α3 chain with laminin 332 so is cotargeted. ‡Low-risk= mucosal lesions are limited to the mouth; high-risk= any other mucosal site affected. §Not licensed during pregnancy and breastfeeding.

Table: Autoantibody specificities, diagnostically relevant clinical signs, and first-line treatments of pemphigoid diseases

pemphigoid.^{31–33} BP180 is a 180 kDa transmembrane glycoprotein of about 1500 aminoacids that ultrastructurally spans the lamina lucida before kinking back from the lamina densa into the lamina lucida (figure 1). The extracellular portion of the 16th non-collagenous (NC16A) domain is the immunodominant region in bullous pemphigoid.³⁴ Most patients also raise IgG antibodies against epitopes outside the NC16A domain.^{35–37} IgG reactivity with C-terminal epitopes seems to be associated with mucosal involvement and severe skin disease, whereas the intracellular domain is preferentially targeted at an early clinical stage.^{36,38} In addition to IgG reactivity, IgA and IgE anti-BP180 antibodies are present in serum samples from most patients.^{39–42}

BP230 is a 230 kDa intracellular constituent of the hemidesmosomal plaque and belongs to the plakin family of proteins. As with BP180, B-cell epitopes are not equally distributed on the molecule but preferentially localise to the globular C-terminal domain.^{37,43} In addition to IgG reactivity, IgE antibodies against BP230 can be detected in the serum samples from most patients.⁴⁴

Pathophysiology

Ample evidence exists for the pathogenic importance of humoral and cellular autoimmunity against BP180.

Clinical evidence consists of the association of disease activity with serum concentrations of IgG antibodies against the NC16A domain and other epitopes on the BP180 ectodomain.^{36,37,45–47} Fc receptor-independent effects have been shown in cultured human keratinocytes in which incubation with BP180-specific antibodies resulted in reduced BP180 expression followed by cell detachment and signal transduction events leading to the release of interleukin 6 and interleukin 8 (figure 3).^{48–50} Fc receptor-mediated effects are pivotal in blister formation, as has been shown *in vitro*^{51,52} and in various animal models.⁵³ Most data were generated in neonatal mice in which the injection of rabbit antimurine BP180 antibodies duplicated major characteristics of the human disease.⁵⁴ This model has shown the importance of complement activation at the dermal–epidermal junction, neutrophils, macrophages, mast cells, and various proteases including neutrophil elastase, matrix metalloproteinase 9, plasmin, α1 proteinase inhibitor, and mast cell proteinase 4 for blister formation (figure 3).^{53,55}

The generation of transgenic mice that express human BP180 in murine skin has allowed replication of the essential features of human disease.^{56–58} Subsequently, two active mouse models have been developed that have elucidated the role of autoreactive T cells. These are

wild-type mice immunised with recombinant murine NC15A and *Rag2^{-/-}/COL17*-humanised mice that received splenocytes from wild-type mice that had been immunised by grafting of human *COL17*-transgenic mouse skin, both of which developed anti-BP180 antibodies and a blistering phenotype.^{59,60} Results of work with the *COL17*-humanised mouse model⁶¹ showed the importance of NC16A-reactive CD4 T cells and accorded with evidence from previous in-vitro studies^{62,63} with human cells that showed a restriction of NC16A-reactive CD4 T cells to the *HLA-DQB1*0301* allele, which has been identified as a susceptibility gene for bullous pemphigoid. Patients cells with this allele preferentially produce both Th1 and Th2 cytokines by contrast with Th1-restricted controls.^{62,63} Raised cytokines and chemokines such as interleukin 1 β , interleukin 5, interleukin 6, interleukin 8, interleukin 10, interleukin 15, tumour necrosis factor α , chemokine (c-c motif) ligand 2 (CCL2), CCL5, CCL11, CCL13, and CCL18 have been reported in serum samples and blister fluids of bullous pemphigoid patients, and some parallel disease activity.⁶⁴ Although we can speculate that these mediators orchestrate the inflammatory reaction in the skin, no data for their functional relevance are available.

Evidence for the pathogenic role of IgE autoantibodies comes from clinical findings and two mouse models.^{65,66} IgE BP180 NC16A-specific antibodies are associated with more severe forms of disease in people, and one corticosteroid-resistant patient responded very well to omalizumab, which is a humanised monoclonal antibody that inhibits IgE binding to its high-affinity receptor.^{40,41,67}

By contrast with BP180, the pathogenic relevance of autoantibodies against BP230 remains elusive: two animal models that were intended for investigation of the relevance of antibodies to BP230 have been reported, but blisters were not,⁶⁸ or not consistently,⁶⁹ seen. Results of studies into the relation between serum anti-BP230 autoantibodies and disease have been contradictory, with most reporting no association.^{37,45,70} However, since *Bp230^{-/-}* mice, in addition to mild skin fragility, developed neurological defects with sensory neuron degeneration²² and with the known association between the disease and neurological disorders,^{16–19} autoimmunity to BP230 might contribute to more than only the skin phenotype in patients with bullous pemphigoid.

Diagnosis

Diagnosis of bullous pemphigoid is based on a combination of clinical criteria, direct immunofluorescence microscopy of a perilesional specimen, and serology (table). Direct immunofluorescence microscopy reveals linear deposits of IgG or complement component 3 at the dermal–epidermal junction, sometimes combined with weaker linear IgA or IgE staining (figure 2). The most sensitive immunofluorescence microscopy substrate for the screening of serum autoantibodies in bullous pemphigoid is healthy human skin in which

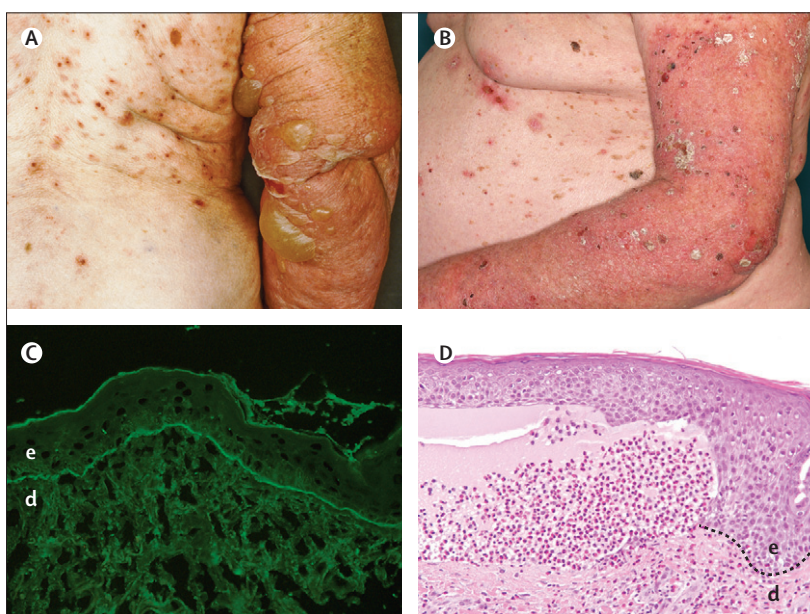


Figure 2: Clinical and immunopathological characteristics of bullous pemphigoid

Tense blisters and erosions on back and right arm (A) and eczematous lesions, erosions, and crusts on left arm and flank (B) of patients with bullous pemphigoid. Direct immunofluorescence microscopy of a perilesional specimen reveals linear deposits of IgG at the dermal–epidermal junction (C). Histopathology of a lesional skin specimen shows subepidermal splitting, a hallmark of all pemphigoid diseases, and a dense inflammatory infiltrate of eosinophils and neutrophils (D). The intact dermal–epidermal junction in D is indicated by a dotted line. e=epidermis. d=dermis.

dermal–epidermal splitting has been induced by 1 mol/L NaCl solution. This substrate also allows for differentiation between different autoantibody specificities: antibodies to BP180 and BP230 bind to the roof of the artificial split (figure 4).⁷¹ Circulating antibodies against BP180 NC16A and BP230 can be detected in serum samples with commercially available ELISA systems (Euroimmun, Lübeck, Germany; MBL, Nagoya, Japan) in 80–90% and 60–70% of cases, respectively.^{46,70,72,73} With the combined use of these two ELISA systems, diagnostic sensitivity is 90%.^{73–75} Use of various recombinant fragments of BP180 and BP230 can allow detection of autoantibodies in serum samples from all patients.³⁷

High serum concentrations of anti-BP180 NC16A antibodies at the time of discontinuation of corticosteroid treatment are associated with risk of relapse.⁷⁶ The BP180 NC16A ELISA, therefore, would seem to be useful for guiding treatment decisions during the course of the disease. Low serum concentrations of anti-BP180 or anti-BP230 antibodies can also be seen in about 4% of dermatological patients who do not have bullous pemphigoid, especially in those with pruritic dermatoses.^{77,78} In these patients, direct immunofluorescence microscopy is required to exclude bullous pemphigoid.

Histopathology of a lesional biopsy can vary with the clinical situation and typically shows subepidermal splitting and a moderate to dense inflammatory infiltrate composed of lymphocytes, neutrophils, and, characteristically, eosinophils. Histopathologically, bullous pemphigoid cannot be differentiated from other pemphigoid

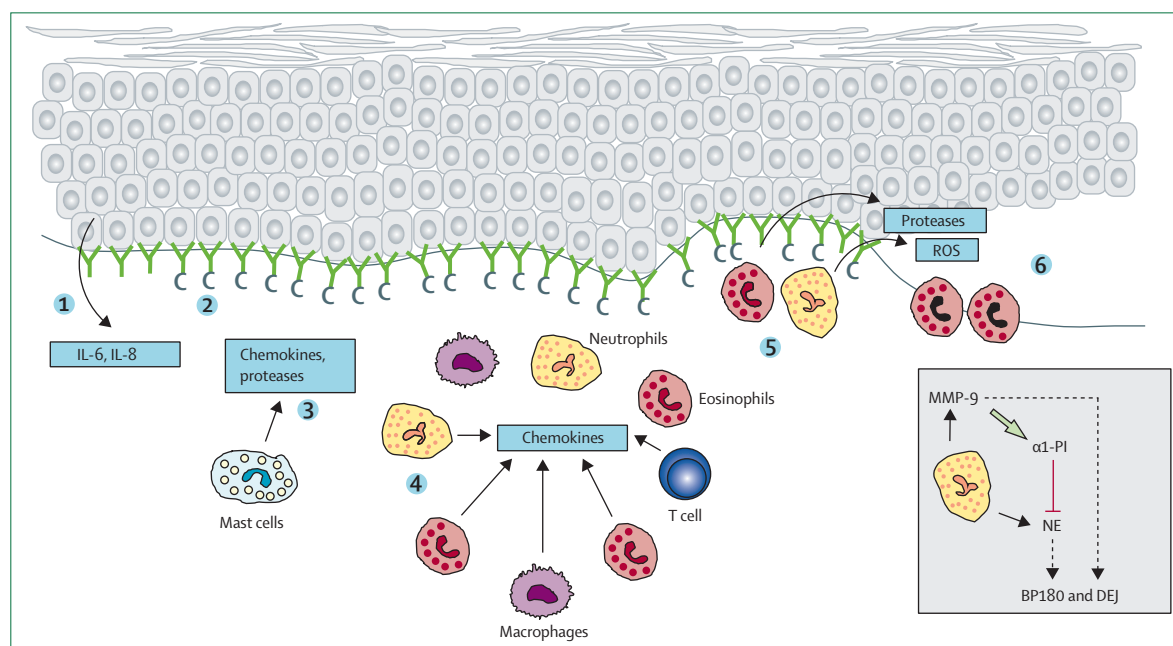


Figure 3: Hypothetical sequence of events leading to blister formation in bullous pemphigoid

Binding of autoantibodies to BP180 initiates Fc receptor-independent events leading to the release of interleukin 6 (IL-6) and IL-8 from basal keratinocytes (1). Complement is activated (2) at the dermal-epidermal junction (DEJ) and mast cells degranulate (3). Complement activation and chemokine gradients result in the infiltration of inflammatory cells into the upper dermis (4). Secretion of inflammatory mediators further increases the inflammatory reaction before granulocytes at the DEJ release proteases (insert) and reactive oxygen species (ROS) (5) that ultimately induce dermal-epidermal splitting (6). As shown in the neonatal mouse model of bullous pemphigoid, matrix metalloproteinase 9 (MMP-9) secreted from neutrophils cleaves (green arrow) α 1-proteinase inhibitor (α 1-PI) to remove neutrophil elastase (NE) inhibition (red bar). Both MMP-9 and NE also directly degrade proteins of the DEJ including BP180 (insert).

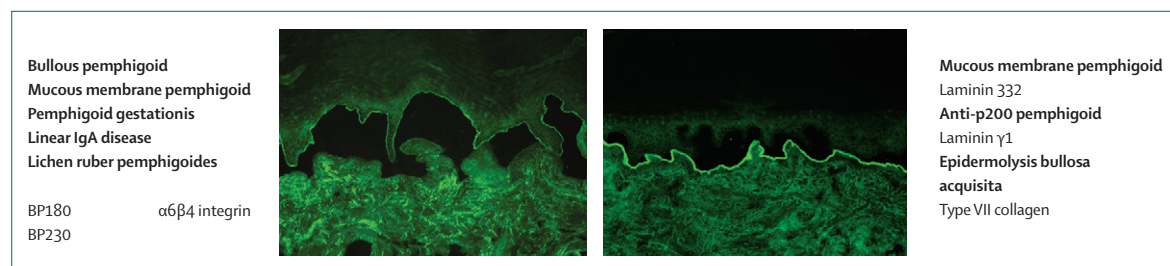


Figure 4: Indirect immunofluorescence microscopy of 1 mol/L NaCl-split human skin

Indirect immunofluorescence microscopy on salt-split skin is used as a practical test for serum autoantibodies in pemphigoid diseases. Antibodies against BP180, BP230, and α 6 β 4 integrin bind along the top of the artificial split (left), whereas antibodies to laminin 332, laminin γ 1/p200 antigen, and type VII collagen label the bottom (right). The specific disorders and the corresponding target antigens are shown.

diseases such as anti-laminin 332 mucous membrane pemphigoid and anti-p200/anti-laminin γ 1 pemphigoid.^{79,80} Knowledge of the histopathological range of bullous pemphigoid allows histopathologists to use direct immunofluorescence microscopy and appropriate serological analysis to obtain a definite diagnosis.

Treatment

Only ten controlled, prospective studies into treatment of bullous pemphigoid have been reported: several trials of oral corticosteroids, two studies of long-term whole-body use of potent topical corticosteroids, two studies of azathioprine, two studies of plasmapheresis, one of mycophenolate mofetil, and one of nicotinamide plus tetracycline.⁸¹

In a landmark study, Joly and colleagues¹⁴ showed in patients with moderate disease that clobetasol propionate 0.05% ointment (40 g per day, tapered over 12 months) was as effective and safe as oral prednisolone at 0.5 mg per day. In a subsequent study,⁸² lower dose clobetasol propionate (10–30 g, tapered over 4 months) did not differ in the time to achieve disease control compared with the more intensive topical regimen and was associated with fewer severe adverse events (including death), but more relapses, in patients with moderate disease. In patients with widespread disease (defined as >10 bullae per day), treatment with oral prednisolone at an initial dose of 1.0 mg per kg of per day resulted in substantially more frequent severe adverse events than were seen with high-dose topical corticosteroids.¹⁴

Prospective, controlled, multicentre trials with dapsone and doxycycline are currently being analysed and recruited for, respectively. Larger, uncontrolled studies of chlorambucil (prospective), dapsone, and methotrexate (both retrospective) have also been reported.^{83–86}

A 2010 Cochrane review⁸¹ summarised the available data for treatment of bullous pemphigoid: and concluded that very potent topical steroids are effective and safe, but their use in widespread disease might be limited by side-effects and practical issues; initial doses of prednisolone greater than 0.75 mg per kg per day do not give additional benefit, and doses lower than 0.75 mg can be adequate and reduce the incidence and severity of adverse reactions; and the effectiveness of adjuvant treatments to corticosteroids needs further validation.

Most clinicians treat localised and mild disease with topical corticosteroids alone (level C; evidence levels are defined in the table) and moderate and widespread disease with topical corticosteroids or oral prednisolone at 0.5 mg per kg per day (level A; table).¹⁴ Possible effects have also been attributed to azathioprine, chlorambucil, dapsone, methotrexate, mycophenolic acid, and tetracyclines (all level B). In refractory patients, plasmapheresis, high-dose intravenous immunoglobulin (both level B), immunoadsorption, or rituximab (both level C) can be added.

Mucous membrane pemphigoid

An international consensus conference⁸⁷ has defined mucous membrane pemphigoid as immunobullous disease with autoantibodies against components of the dermal–epidermal junction and predominant mucosal involvement. Previously, the term cicatricial pemphigoid was used synonymously for mucous membrane pemphigoid. Now, cicatricial pemphigoid refers only to the rare clinical variant in which mucous membranes are not predominantly affected and skin lesions heal with scarring.⁸⁷ Incidence of mucous membrane pemphigoid has been estimated at 1.3 and 2.0 per 1 million people per year in France and Germany, respectively.^{7,88} The disease arises earlier than does bullous pemphigoid, with a mean age of onset between 60 and 65 years.^{89,90} An association with *HLA-DQB1*0301* has been reported.⁹¹

Clinically, mucous membrane pemphigoid is a chronic and progressive disease that most frequently affects the oral cavity (85% of patients), followed by conjunctivae (65%), skin (25–30%), nasal cavity (20–40%), anogenital area (20%), pharynx (20%), larynx (5–10%), and oesophagus (5–15%) (table, figure 5).^{87,89,90} Clinical severity is highly variable and can range from subtle oral lesions and conjunctival injection to pervasive, very painful mucosal involvement and devastating oesophageal and conjunctival disease.^{87,89,90} At all affected body sites lesions tend to heal with scarring, though in oral lesions re-epithelialisation without scarring can occur. Ocular lesions usually start unilaterally with subtle symptoms such as burning, dryness, and a sensation of foreign body, and can proceed to scar formation causing

symblepharon, trichiasis, neovascularisation, and, finally, blindness (figure 5).⁹²

The disease is usually bilateral within 2 years of onset. When it is confined to the conjunctivae (about 20% of patients) the term ocular pemphigoid is used.^{87,89} All patients should be seen by an ophthalmologist, who can identify subtle changes by slit-lamp examination. In patients without initial ocular involvement, the annual risk for developing eye lesions is 5% over the first 5 years.⁸⁹ Notably, since a solid cancer is present in about 30% of patients with anti-laminin 332 mucous membrane pemphigoid, a thorough tumour search should be done in patients with this subset of the disease.⁹³

Six target antigens associated with the clinical phenotype of mucous membrane pemphigoid have been characterised molecularly: BP180 (in about 75% of patients),^{94,95} BP230 (25%; usually in conjunction with BP180 reactivity), laminin 332 (formerly called laminin 5 or epiligrin; 25%),⁹⁶ both subunits of $\alpha 6 \beta 4$ integrin, and type VII collagen (figure 1, table). By contrast with bullous pemphigoid, C-terminal epitopes on BP180 are predominantly recognised; the NC16A domain is targeted by about 50% of BP180-reactive serum samples.^{94,95,97} Laminin 332 is a heterotrimer consisting of $\alpha 3$, $\beta 3$, and $\gamma 2$ chains. In almost all patients with anti-laminin 332 reactivity, the $\alpha 3$ chain is targeted.⁹⁸ Autoantibodies to $\alpha 6$ integrin have been described in patients with oral lesions, and reactivity against $\beta 4$ integrin is associated with ocular involvement.^{94,99}

The pathogenic relevance of autoantibodies in mucous membrane pemphigoid has been shown both in vitro and in vivo. Antibodies against laminin 332 induced non-inflammatory subepidermal blisters when injected into mice or human skin grafted onto immunocompromised mice.^{100,101} By contrast with bullous pemphigoid, antigen-binding fragments of anti-laminin 332 antibodies are also pathogenic, and complement activation and mast cells are not necessary for blister formation in mice.¹⁰² Antibodies to $\alpha 6 \beta 4$ integrin induce separation along the dermal–epidermal junction in organ cultures.^{103,104} Since scarring is the major pathogenic process in conjunctival disease, fibrosis has been intensively studied in biopsy specimens and cultured conjunctival fibroblasts. Various profibrotic factors have been identified, including serpin h1 (heat shock protein 47), connective tissue growth factor, transforming growth factor β , interleukin 4, interleukin 5, and interleukin 13.^{105,106}

Diagnosis of mucous membrane pemphigoid is based on predominant mucosal lesions and direct immunofluorescence microscopy of a perilesional specimen that, indistinguishable from bullous pemphigoid, shows deposition of IgG, complement component 3, and, in some patients, IgA along the dermal–epidermal junction. In ocular disease, detection of autoantibodies in this way can be unsuccessful in up to 20% of cases.⁸⁹ By indirect immunofluorescence microscopy on salt-split skin, epidermal or dermal staining of the artificial split can be seen

dependent on the target antigen (figure 4). By contrast with bullous pemphigoid, serum samples from patients with mucous membrane pemphigoid contain anti-dermal-epidermal junction reactivity at low titres (usually 1:10–1:40) and in a low percentage of patients (50–80%).^{95,107}

IgA autoantibodies can be detected in about 60% of serum samples,^{42,94,95,107} and a combined IgA and IgG reactivity is associated with more severe disease than with IgG autoantibodies alone.^{94,107} Various recombinant fragments and the cell-derived soluble ectodomain of BP180 (linear IgA dermatosis antigen, LAD-1) have been used to detect anti-BP180 autoantibodies.^{42,94,95} Immunoblotting with bovine gingivae lysate allows detection of $\alpha 6\beta 4$ integrin-specific antibodies.⁹⁹ Serum samples that are unreactive with indirect immunofluorescence microscopy on salt-split skin or that show dermal binding should be tested for laminin-332 reactivity, since reactivity with laminin 332 is associated with malignant disease. On the basis of comparison of six different methods for the

detection of serum antilaminin 332 IgG, immunoprecipitation with radiolabelled human keratinocytes is the most sensitive method, whereas immunoblotting with extracellular matrix of cultured human keratinocytes seems to be the most practical alternative.¹⁰⁸ In suspected ocular mucous membrane pemphigoid with negative direct immunofluorescence microscopy of a conjunctival specimen, we recommend additional oral biopsy and serological analysis.

Treatment of mucous membrane pemphigoid is challenging for three reasons: only two small, controlled therapeutic trials have been done in patients with ocular disease; clinical response to immunosuppression in patients with severe disease, particularly those with ocular lesions, is poor; and conjunctival fibrosis is irreversible and, unlike other pemphigoid diseases, causes permanent damage when treatment is delayed or ineffective.^{87,109,110} In low-risk patients (lesions are limited to the mouth, with or without skin involvement), potent topical corticosteroids in combination with a tetracycline or dapsone might suffice (level C; table). In unresponsive patients, oral prednisolone (0.5 mg per kg per day) can be added, then azathioprine or mycophenolic acid (level C).⁸⁷ For high-risk patients (any other mucosal site affected) with severe disease or rapid progression, prednisolone (1.0–1.5 mg per kg per day) plus cyclophosphamide (1–2 mg per kg per day orally or 500–1000 mg intravenously every 3–4 weeks) is recommended (level C; table).⁸⁷ Alternatively, prednisolone can be combined with mycophenolic acid or, in mild disease, with dapsone (both level C).^{87,110,111}

In patients with ocular disease, cyclophosphamide (2 mg per kg per day), dapsone (in mild disease), mycophenolic acid, and intravenous immunoglobulin have had favourable results in combination with prednisolone at 1.0–1.5 mg per kg per day (level B; table).^{87,109–112} In oesophageal and severe or rapidly progressive conjunctival disease, the risk of use of fairly high doses of prednisolone (1.0–1.5 mg per kg per day), which frequently causes severe adverse events, should be weighed against the high risk of scarring, since fibrosis continues for some time even when the inflammatory reaction has been stopped. In refractory patients with mucous membrane pemphigoid, intravenous immunoglobulin and the anti-CD20 antibody rituximab have both been used successfully (both level B).^{112,113} For the assessment and treatment of ocular disease, ophthalmological consultations are necessary. Ophthalmological care, including topical and surgical treatment, has been reviewed by Saw and Dart⁹² and by Foster and Sainz De La Maza.¹⁰⁵

Pemphigoid gestationis

Pemphigoid gestationis, previously known as herpes gestationis, is a pregnancy-associated immunobullous disease with autoantibodies against BP180 NC16A. An annual incidence of between 0.5 and 2.0 cases per 1 million people has been reported in France, Germany, and Kuwait.^{7,88,114} A much higher incidence than in these

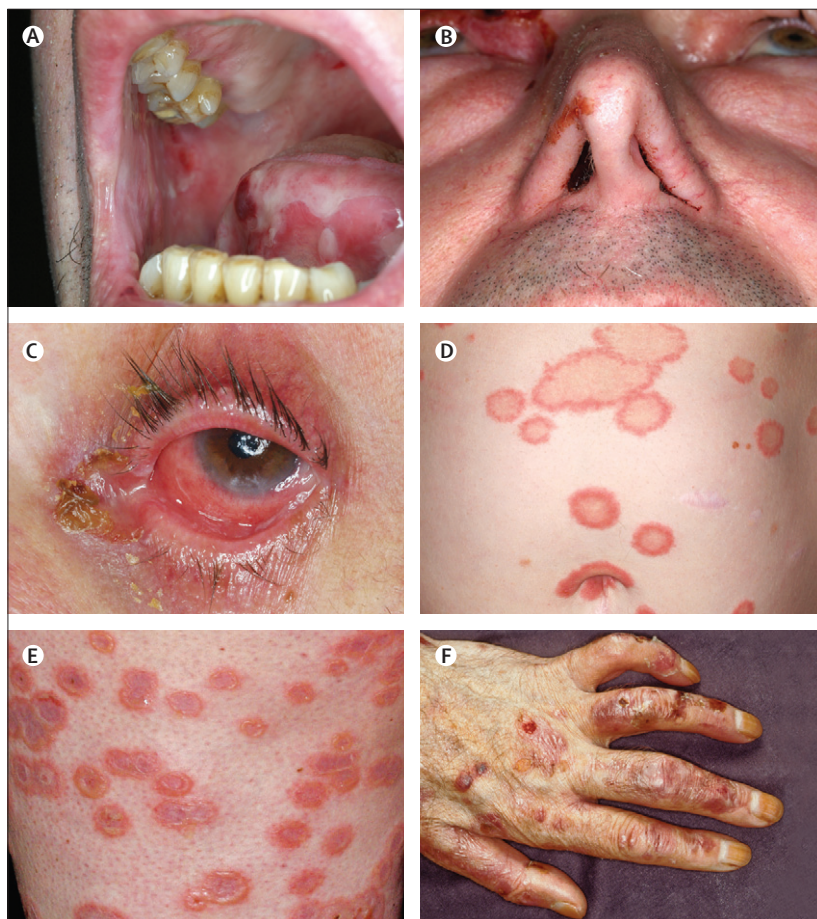


Figure 5: Clinical characteristics of other pemphigoid diseases

Erosions and fibrinous plaques in the oral cavity (A), haemorrhagic crusts on and scar-related miniaturisation of nasal orifices (B), and conjunctival injection, symblepharon, erosions, and yellow crusts (C) in a patient with mucous membrane pemphigoid. Wheel-like plaques on the abdomen (D) of a patient with pemphigoid gestationis. Annular erythematous plaques (E) with blistering along the edges (the so-called string-of-pearls sign) in a patient with linear IgA disease. Vesicles, erosions, atrophic erythematous plaques, and milia on the extensor surfaces of the left hand (F) of a patient with epidermolysis bullosa acquisita.

countries was noted in two English tertiary referral centres, with the disease reportedly occurring in 4·2% of pregnancies.¹¹⁵ Pemphigoid gestationis usually occurs in the second or third trimester, and in about 10% of patients within 4 weeks after birth.^{115,116} Typically, pruritic erythematous papules and plaques, erythema multiforme-like changes, eczematous lesions, or papulovesicles arise around the umbilicus and then spread over the abdomen and thighs (figure 5); frank blistering is not always present.

The clinical course is fairly benign, with an average duration of 4–6 months. In less than 5% of patients, the disease persists and converts to bullous pemphigoid.^{116,117} Pemphigoid gestationis recurs in more than 90% of cases when there is an additional pregnancy.¹¹⁶ A slightly increased risk for prematurity and small-for-gestational-age babies has been reported and transient skin lesions in newborn babies have been seen in individual cases.¹¹⁷ The disease is strongly associated with maternal HLA-DR3 and HLA-DR4.¹¹⁷

The major target antigen is BP180,^{34,118} which is expressed in the amniotic membrane and its shed ectodomain is a physiological constituent of the amniotic fluid. Diagnosis is made by direct immunofluorescence microscopy of a perilesional biopsy, with deposits of complement component 3, and, to a lesser extent, IgG seen along the dermal–epidermal junction. Circulating complement-fixing antibodies are an immunopathological hallmark of pemphigoid gestationis and are seen along the dermal–epidermal junction by indirect immunofluorescence microscopy on human skin after preincubation with a complement source. This finding is attributable to the strong complement-fixing properties of the predominant IgG1 and IgG3 anti-BP180 NC16A antibodies.¹¹⁹ The BP180 NC16A ELISA detects serum autoantibodies in more than 90% of patients.¹²⁰ As in bullous pemphigoid, the NC16A domain contains the major pathogenic sites—preadsorption of serum samples with peptides covering the N-terminal portion of this domain abolished their split-inducing potential *in vitro*.¹²¹

Most patients will be adequately controlled with potent or highly potent topical corticosteroids in combination with H1-receptor antagonists such as cetirizine (table). If not sufficient, oral prednisolone can be added at an initial dose of 0·25–0·5 mg per kg per day (level C). In a study in 61 patients, use of oral prednisolone had no effect on adverse pregnancy outcomes.¹²²

Linear IgA disease

Linear IgA disease is named for its main immunopathological feature, which is the linear binding of IgA at the dermal–epidermal junction. Some overlap is seen with bullous pemphigoid (patients with dual IgG and IgA deposition along the junction), with mucous membrane pemphigoid (patients with predominant mucosal involvement), and IgA epidermolysis bullosa acquisita. Incidences between 0·25 and 1·0 per 1 million people per year have been reported in central Europe, Singapore,

and Kuwait.^{7,88,114,123} Higher incidences than in these countries have been noted in some African countries (Mali, South Africa, Uganda) and in Malaysia.³ Linear IgA disease is the most common pemphigoid disorder in children and has two peaks of onset—before the age of 5 years and after the age of 60 years.¹²⁴ The disease is associated with HLA-B8, HLA-CW7, and HLA-DR3.³

Individual lesions are similar in children and adults, and include urticarial plaques, erosions, and blisters, frequently in an ring-shaped pattern with blistering along the edge of lesions, forming the so-called string-of-pearls sign (figure 5). Mucosal involvement is common (about 70% of patients), generally with oral erosions and ulcers; nasal crusting and genital lesions can also occur.¹²⁴ In children, the face and perineal area are more often affected and lesions arise more abruptly than in adults, in whom trunk and limbs are predominantly affected.³ Linear IgA disease can be triggered by various drugs, most frequently vancomycin, followed by non-steroidal anti-inflammatory drugs.³ The disease has a fairly benign course, with less severe relapses compared with the original presentation within 5 years.

The major target antigen is BP180. Serum samples from most patients react with a 97 kDa extracellular fragment of BP180 in skin extract and with LAD-1, the 120 kDa shed ectodomain of BP180 from cultured keratinocytes.^{125,126} The 97 kDa protein is an N-terminal portion of LAD-1. The BP180 NC16A domain is the target in only 20% of patients.¹²⁷ Since most serum samples from linear IgA disease patients, in addition to IgA anti-BP180 antibodies, contain IgG antibodies against BP180, and IgA anti-BP180 antibodies can be detected in serum samples of most bullous pemphigoid patients, the two diseases could be regarded as different ends of a continuous range.³⁹ Researchers have investigated the pathogenic role of autoantibodies in linear IgA disease by injecting monoclonal IgA antibodies against the BP180 ectodomain in human skin grafted onto SCID mice.¹²⁸ Subepidermal splitting was seen in some mice by histopathology, but none showed clinical disease.

Although patients' age and clinical presentation is generally suggestive of linear IgA disease, diagnosis is made on the basis of a combination of clinical appearance, linear deposition of IgA at the dermal–epidermal junction by direct immunofluorescence microscopy of a perilesional skin or mucous membrane biopsy, detection of IgA serum antibodies by indirect immunofluorescence microscopy on human salt-split skin (figure 4), and IgA reactivity against BP180 (table). No prospective controlled clinical trials or larger case series have been reported for treatment. Patients usually respond well to therapy. First-line treatment is dapsone (level B), which can be used in combination with topical glucocorticosteroids (table).¹²⁹ Sulfapyridine (also level B) is an alternative to dapsone. Some patients might need concomitant low-dose prednisolone (0·25–0·5 mg per kg per day) to suppress blister formation, and erythromycin, colchicine, flucloxacillin,

intravenous immunoglobulin, azathioprine, mycophenolic acid, and immunoadsorption have been used in unresponsive patients (all level C).¹²⁹

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita is a clinically heterogeneous disease characterised by autoantibodies against type VII collagen. Incidence reportedly ranges between 0·2 and 0·5 new cases per 1 million people per year.^{7,88,123} The disease is associated with HLA-DR2—notably the *DRB1*15:03* allele—and African descent.¹³⁰ Clinically, epidermolysis bullosa acquisita can either be the classic form or an inflammatory variant.^{131,132} The classic mechanobullous form presents with tense blisters and skin fragility preferentially localised to the extensor skin surfaces at trauma-prone areas. Lesions usually heal with scarring and milia formation (figure 5); hyperpigmentation and hypopigmentation are common. Nail loss and oesophageal stenosis can also occur.¹³¹ The inflammatory subtype can resemble bullous pemphigoid or mucous membrane pemphigoid.¹²⁸ In both subtypes, mucous membranes are affected in about half of patients.¹³³

The mucous membrane pemphigoid variant of epidermolysis bullosa acquisita can also be classified as mucous membrane pemphigoid.⁸⁷ In about 20% of patients with epidermolysis bullosa acquisita, concomitant inflammatory bowel disease has been reported.¹³⁴ The autoantigen is homotrimeric type VII collagen, a constituent of the anchoring fibrils (figure 1).^{135,136} The N-terminal 145 kDa NC1 domain is the immunodominant region and is recognised in almost all serum samples.¹³⁷

Anti-type VII collagen antibodies injected into mice elicit skin lesions resembling those in patients.^{138,139} The disease can also be induced in mice by immunisation with a portion of the murine NC1 domain.¹⁴⁰ In these models, neutrophils were identified as major effector cells that are recruited and activated via the FcγIV receptor after interaction with skin-bound autoantibodies.¹⁴¹ The glycolisation of type VII collagen-specific antibodies is essential for this interaction.¹⁴² The manipulation of neutrophil activation and autoantibody glycolisation might open novel therapeutic avenues.

Diagnosis is based on linear deposits of IgG, IgA, and complement component 3 at the dermal–epidermal junction by direct immunofluorescence microscopy of a perilesional skin or mucous membrane biopsy. By contrast with all other pemphigoid diseases, Ig labels the dermal–epidermal junction in a u-serrated pattern—ie, in upstanding arms of the sublamina densa zone between the rootlets of the basal keratinocytes.¹⁴³ In all other pemphigoid disorders, an n-serrated pattern is seen. Serration pattern analysis is of particular importance in epidermolysis bullosa acquisita, since only 40–60% of serum samples react by indirect immunofluorescence microscopy on salt-split skin, labelling the dermal side of the artificial split (figure 4).^{132,133} Serologically, epidermolysis bullosa acquisita is diagnosed by detection of anti-type VII

collagen antibodies—different tissue extracts or the recombinant NC1 domain can be applied by immunoblotting or ELISA.^{132,137} Two highly sensitive and specific assays have been commercialised, using the recombinant NC1 and NC2 domains by ELISA and NC1 domain-expressing cells by indirect immunofluorescence microscopy.^{144,145} In a subgroup of less than 10% of patients, autoantibodies are restricted to the IgA isotype—these patients tend to display the inflammatory phenotype.¹³³

Treatment of epidermolysis bullosa acquisita is challenging. No controlled prospective trials have been reported and disease activity is difficult to suppress.¹¹⁰ The mainstay is systemic corticosteroids (0·5–2·0 mg per kg per day, dependent on disease severity) in combination with colchicine or dapsone (level C; table). For refractory patients or severe cases, cyclosporine, azathioprine, mycophenolate mofetil, plasmapheresis, immunoadsorption, intravenous immunoglobulin, and rituximab can be added (all level C).

Anti-p200/anti-laminin γ1 pemphigoid and lichen planus pemphigoides

Both anti-p200 pemphigoid and lichen planus pemphigoides are rare, with fewer than 100 reported cases of each worldwide. Anti-p200 pemphigoid clinically mimics bullous pemphigoid, although patients tend to be younger and concurrent psoriasis is seen in about a third of cases.^{146,147} Serum samples from 90% of patients react with laminin γ1.¹⁴⁸ Diagnosis is made by detection of autoantibodies against the 200 kDa protein of the dermal–epidermal junction by immunoblotting with extract of dermis or against the C-terminus of laminin γ1 by immunoblotting or ELISA.^{147,149} Anti-p200/anti-laminin γ1 pemphigoid is very probably underdiagnosed because of low availability of the diagnostic assays. It is often classified as bullous pemphigoid, although patients tend to be younger and usually respond more rapidly to treatment;¹⁴⁶ treatment is the same as for bullous pemphigoid (level C; table).

Lichen planus pemphigoides always arises in conjunction with lichen planus. The main target antigen is BP180. By contrast with bullous pemphigoid, the disease affects fairly young patients (mean age of onset 40–50 years), mainly arises on the limbs, and preferentially targets C-terminal epitopes in the immunodominant NC16A domain. The disease tends to be less severe than bullous pemphigoid.¹⁵⁰ Diagnosis is made on the basis of the presence of tense blisters outside lichen planus lesions, detection of linear deposits of IgG or complement component 3 at the dermal–epidermal junction by direct immunofluorescence microscopy of a perilesional biopsy, and detection of circulating IgG antibodies against BP180 NC16A (table). Therapy for lichen planus is necessary to avoid further stimulation of the anti-dermal–epidermal junction autoimmune process. Simultaneous treatment for pemphigoid lesions should follow the same algorithm as for bullous pemphigoid (level C; table).

Contributors

Both authors reviewed the scientific literature, interpreted the data, and wrote the report. ES prepared the figures.

Conflicts of interest

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