

AUTOIMMUNE SUBEPITHELIAL BLISTERING DISEASES WITH OCULAR INVOLVEMENT

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Autoimmune bullous diseases are a group of blistering diseases characterized by *in vivo* bound and circulating autoantibodies directed against components of epithelia. They can be divided histologically into two main groups based on the location of the cleavage plane in the epithelia—intraepithelial for the pemphigus group and subepithelial for the group of subepithelial blistering diseases. These two groups of diseases can also be distinguished by the types of molecules that serve as target antigens. Autoantibodies associated with the pemphigus group react with protein constituents of the desmosome, a cell structure that functions in cell-cell adhesion, whereas the autoimmune response in the subepithelial group is directed against components of the basement membrane zone (BMZ). Both groups of bullous diseases are composed of multiple disease entities that are distinguishable at the clinical, histological, and immunological levels.

This article focuses on ocular manifestations of autoimmune subepithelial blistering diseases. The diseases that fall into this category are listed in Table 1. They include cicatricial pemphigoid (CP), the proto-

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TABLE 1. AUTOIMMUNE SUBEPITHELIAL BLISTERING DISEASES WITH OCULAR INVOLVEMENT

Disease	Clinical Features	Direct IF on Skin or Mucosae	Indirect IF on Salt-Split Skin	Ultrastructural Localization	Target Antigen(s)
Cicatricial pemphigoid	Mucosal blistering and erosions with scarring; minimal skin blistering	IgG, IgA, and C3; linear at BMZ	Roof, floor, or combined	Lower lamina lucida; lamina densa	BP180, BP230, laminin 5
Epidermolysis bullosa acquisita	Mucocutaneous blistering and erosions at sites of trauma with scarring	IgG and C3; linear at BMZ	Floor	Sublamina densa (anchoring fibrils)	Collagen VII
Linear IgA disease	Mucocutaneous tense blisters with occasional scarring of mucosae	IgA; linear at BMZ	Roof, floor, or combined	Lamina lucida, sublamina densa; combined	LAD-1, 255 kD protein

IF = immunofluorescence; BMZ = basement membrane zone.

typic disease with the most severe ocular involvement, epidermolysis bullosa acquisita (EBA), and linear IgA disease (LAD). This article describes the clinical, histological, and immunopathological findings, with an emphasis on ocular involvement. Pathogenesis and treatment are also discussed. Pemphigus vulgaris and paraneoplastic pemphigus, which are defined by an intraepithelial cleavage, and bullous pemphigoid (BP) and dermatitis herpetiformis, which are rarely associated with ocular lesions, are not covered.

CICATRICIAL PEMPHIGOID

CP is a chronic disease that predominantly involves mucous membranes and is characteristically associated with scarring.⁶⁴ Historically, cases that have been termed cicatricial pemphigoid, or benign mucosal pemphigoid, represent a heterogeneous group both clinically and immunologically. CP should be considered a protean systemic disease requiring a multidisciplinary approach that should include dermatologists, ophthalmologists, otolaryngologists, and clinical immunologists.

Clinical Presentation

Patients with CP typically present with tense blisters evolving into erosions in mucous membranes and, to a lesser extent, the skin. The mouth (80% to 90%) and the eyes (50% to 70%) are the most frequently affected mucosae. Erythema, oral erosions, and pseudomembrane-covered ulcerations of the mouth are typical clinical manifestations. CP can involve the gums, resulting in the typical “desquamative gingivitis”; however, the palate, buccal mucosa, and less frequently, labial mucosa, floor of mouth and tongue, may also be involved.⁸⁵ Residual scarring in the mouth is unusual. Ocular lesions usually begin with unilateral or bilateral nonspecific conjunctivitis followed by insidious scarring of conjunctivae (Fig. 1). Fibrous tracts fuse the bulbar and palpebral conjunctivae, resulting in symblepharon formation. Complete obliteration of the conjunctival sacs (ankyloblepharon) can also occur. Scarring can lead to the occlusion of lacrimal ducts, with decreased tear secretion, and a reduction in the number of goblet cells, with decreased mucus in tears, resulting in an unstable tear film. Entropion—inversion of the lid margin, and trichiasis—a condition in which eyelashes grow toward the eyeball, can also occur and may be responsible for superficial keratopathy and corneal ulceration. This combined pathology ultimately results in corneal opacity and blindness. Blindness, frequently bilateral, has been found in 27% of the patients in one study.⁶⁸

In certain cases other mucosae can become involved, including the genitals (15%), the nose (15%), the larynx (8%), the anus (4%), and the esophagus (4%). External genital lesions involve the glans penis in men, and scarring can result in urethral stenosis. The labia minora can be



Figure 1. Ocular involvement demonstrating erythema and shrinkage of the conjunctiva and symblepharon formation in a patient with cicatricial pemphigoid.

involved in women, with the possibility of fusion. Involvement of the nasal mucosa often leads to stenotic nasal obstruction and perforation of the nasal septum. Laryngeal manifestations are rare, but can be life-threatening (e.g., laryngeal stenosis may necessitate tracheostomy). Esophageal involvement can cause dysphagia due to stenosis, with the risk of aspiration leading to pneumonia. The skin is involved in about 25% of CP patients. The blisters are scattered over erythematous plaques of the head, the neck, or the trunk, and heal with atrophic scars and milia. There is no pruritus.

Several clinical variants of CP have been described. Certain cases of CP exhibit lesions restricted to a single mucous membrane, most common among these being oral CP followed by pure ocular CP. Patients with disease localized only to the oral mucosa tend to have a more benign course.⁸⁵ Pure ocular CP, in contrast, has the more typical chronic, relapsing course and may lead to blindness. Benign pemphigoid of Brunsting-Perry is characterized by the presence of localized and recurrent blisters on the head or neck, which evolve to scarring.¹⁶ It predominates in men and does not involve mucous membranes. The histologic, immunopathologic, and ultrastructural findings reported in this clinical variant are similar to CP; however, this clinical presentation is not specific for CP and has been reported in EBA and in BP.^{41, 87} A disseminated form of CP has also been reported.^{37, 49}

CP is a rare disease. The rate of incidence has been calculated by dermatologists as 1.16 and 0.87 new cases per 1 million people annually in France and Germany, respectively.^{11, 104} CP affects the elderly, with a mean age of onset of 65 years.^{3, 67} There is a female predominance, with a ratio of female-to-male patients of 2-to-1. There is no known racial or geographic predilection, but it has been reported that ocular CP is associated with HLA-DR4 and HLA-DQw7/DQB1*0301^{14, 20}; HLA-DQB1*0301 is a marker of oral CP.^{92, 100}

Laboratory Investigations

Histological examination of skin or oral mucosal lesions in CP shows subepithelial blistering associated with a dermal infiltrate of lymphocytes, mononuclear cells, neutrophils, and some eosinophils. In affected mucosal tissues, subepithelial clefts or erosions are present and are subtended by a mixed inflammatory infiltrate in a perivascular location. No vasculitis is found in early lesions. More advanced lesions typically show a chronic inflammatory infiltrate and fibrosis. Light microscopy of conjunctival epithelial layers demonstrates squamous metaplasia with parakeratosis, keratinization, and reduction or absence of goblet cells. The stroma shows an inflammatory infiltrate consisting of lymphocytes and plasma cells. There are occasional eosinophils and neutrophils that increase in number during an acute exacerbation of CP.

Immunohistochemical studies have revealed an abnormally high number of T lymphocytes in conjunctival biopsies obtained from patients with CP.^{13, 79} Of the T-cell subsets, there are usually more CD8⁺ than CD4⁺ cells, and some of the T cells are activated, as demonstrated by expression of the interleukin-2 receptor. The composition of the subepithelial cellular infiltrate is variable with disease activity, and acute disease is characterized by an abundance of macrophages and neutrophils and occasional observations of small numbers of eosinophils. A recent study has demonstrated that the granular toxic proteins of eosinophils (e.g., secreted eosinophil cationic protein) can be detected at the BMZ and perivascular region of conjunctival biopsies.⁸² In addition, the total number of mast cells is increased in conjunctival biopsies taken from patients with CP.³⁸ Fibroblasts from patients with untreated CP behave in a hyperproliferative manner in tissue culture, and staining for the fibrogenic cytokines has demonstrated increased levels of TGF- β in conjunctival biopsies of the acute stage of CP.¹³

Electron microscopic examination of conjunctival biopsies has shown alterations of the basal lamina, including discontinuity, duplication, and focal thickening. A higher number of desmosomes has also been observed, along with a disorganization of collagen fibrils in a thickened stroma and a mucin-like material covering the conjunctival surface. These alterations are reversible after successful treatment of the disease.

In 80% to 95% of biopsies, direct immunofluorescence (IF) analysis shows linear deposits of immunoglobulins and complement along the BMZ of skin, buccal mucosa, or conjunctiva.^{45, 54, 83} These deposited immunoreactants are more frequently detected in mucosae than in skin biopsies. IgG is the most frequently detected class of immunoglobulins bound to the BMZ, but IgA and IgM can also be present.⁸³ In ocular CP, IF analysis of conjunctival biopsies shows the same immune deposits at the BMZ.⁷⁰ Use of an immunoperoxidase-labeling protocol increases the sensitivity of detection of immune deposits.⁷⁰ Circulating anti-BMZ autoantibodies are found in about 20% of CP patients by indirect IF on human skin, and the titers are usually low.² The indirect IF reactivity is

largely accounted for by IgG class autoantibodies, with the predominant subclass being IgG4.⁸ IgA can also be detected by indirect IF, and can be the sole anti-BMZ immunoglobulin class detected.⁸⁰ The use of several substrates (e.g., human oral mucosa, human conjunctiva, rabbit esophagus) increases the sensitivity of the indirect IF analysis to approximately 80%. Performing indirect IF on 1 M NaCl-split skin also increases the sensitivity of detection of circulating antibodies. The IgG binding is frequently observed on the epidermal side of the split, but a dermal/epidermal-combined binding pattern, or binding on just the dermal side of the split, occurs in some cases (Fig. 2).

By direct immunoelectron microscopy (IEM) on skin and mucosae, immune deposits are localized to the lower part of the lamina lucida, sometimes overlapping with the lamina densa (Fig. 3).^{10, 27, 65} In contrast, three patients with pure ocular CP contained conjunctival immune deposits located only in the upper part of the lamina lucida.⁷² By indirect IEM, circulating CP autoantibodies produce a staining of the lamina densa and the lower part of the lamina lucida in regularly spaced clumps.⁷ Recently, Shimizu et al⁸⁴ demonstrated two different CP labeling patterns by indirect immunogold EM. CP sera that stained the epidermal side of NaCl-split skin by indirect IF were shown to label the junction between the hemidesmosome and the basal keratinocyte plasma membrane whereas CP sera that exhibited a dermal side staining of NaCl-split skin labeled the lamina lucida/lamina densa interface.⁸⁴

Several antigens from the BMZ have been identified as the target of

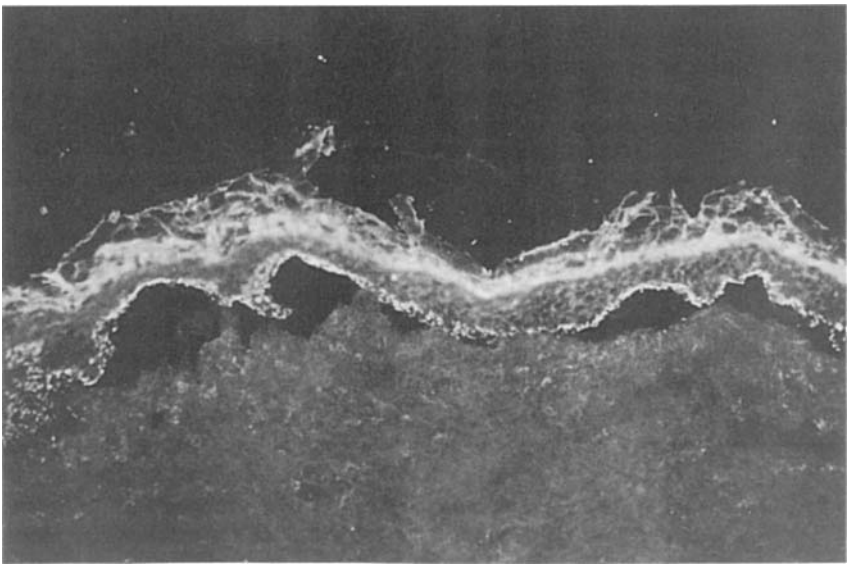


Figure 2. Indirect immunofluorescence analysis of a cicatricial pemphigoid serum using NaCl-split human skin, demonstrating linear IgG staining of the epidermal side of the cleavage.

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Figure 3. Direct immunoelectron microscopy performed on a perilesional skin biopsy specimen from a patient with cicatricial pemphigoid, showing immune deposits (*arrow*) on the lamina densa of the basement membrane. Ep = epidermis, De = dermis. (Courtesy of Dr. Catherine Prost, Paris, France.)

CP autoantibodies. By immunoblot and immunoprecipitation analyses, most CP sera react with a 180 kd epidermal protein, BP180, whereas a smaller subset of CP sera recognize a 230 kd epidermal antigen, BP230.^{6, 9, 10, 66} BP180 and BP230 were first identified as the major antigenic targets of BP sera.^{50, 88} Recently, a small subset of CP sera, which exhibit dermal side staining of salt-split skin, were shown to react with laminin-5 (formerly designated kalinin, nicein, or BM600), a component of anchoring filaments.^{24, 25, 36} Antibodies produced by these patients specifically bind the α subunit of this protein.⁴⁷ CP sera have also been reported to react with an unknown 120-kD epidermal protein, but the specificity of this reactivity has not been firmly established.^{21, 81} IgA antibodies in the sera of some ocular CP patients recognize a 45 kd epidermal protein.⁸⁶ Using extracts of tumor cell lines and a very sensitive immunoblotting method, autoantibodies against proteins of 230, 205, and 160 kd, two of which may correspond to BP230 and BP180, have been demonstrated in ocular CP.⁶²

Differential Diagnosis

The diagnosis of CP is suspected when a patient presents with blisters or erosions of mucous membranes. Direct IF, if positive, confirms the diagnosis of autoimmune bullous disease and excludes other causes

of cicatricial conjunctivitis, such as chronic atopic keratoconjunctivitis, rosacea, and drug-induced cicatricial conjunctivitis. The distinction between CP and other autoimmune bullous diseases, such as BP, EBA, and LAD, can be difficult and may necessitate IEM and western blotting studies.

The distinction between CP and BP is usually straightforward. In BP the cutaneous lesions are more profuse, with large, tense blisters and urticarial lesions on the flexural surfaces of the arms, legs, and trunk. Mucosal lesions are uncommon and limited to the oral cavity. Typically, there is no evolution to scar formation. By IEM, immune deposits are localized within the hemidesmosomal plaque and the subjacent lamina lucida. Circulating BP autoantibodies usually react with BP230 or BP180 by immunoblotting.

The differential diagnosis between CP and drug-induced cicatricial conjunctivitis can be more difficult. Drug-induced cicatricial conjunctivitis, also referred to as *pseudopemphigoid*, is a side effect of topically administered medications. A variety of antiglaucoma drugs (pilocarpine, echothiophate, demecarium bromide, epinephrine, timolol) and idoxuridine have been implicated. The clinical presentation of pseudopemphigoid is similar to, and in some cases indistinguishable from, CP. Typically, pseudopemphigoid initially involves the lower fornix and, in contrast to the early changes of ocular CP, is confined to the treated eye and has no extraocular manifestations.¹² The disease is usually not progressive if the offending drug is discontinued, but in some cases the disease does not resolve after withdrawal of the drug. In the majority of cases, direct IF is negative, but immune deposits have been reported in some patients.⁶⁹ Thus, the distinction between CP and pseudopemphigoid can be extremely difficult. All intraocular drugs should be discontinued in patients who develop conjunctivitis and forniceal shortening during the use of topical medications. If progression occurs despite discontinuation of the treatment with topical drugs, a diagnosis of ocular CP and systemic therapy should be considered.¹⁷

Pathogenesis

The pathogenesis of CP is still unclear. The autoimmune classification of this disease is based on in vivo deposition of immunoglobulins and complement at the BMZ of skin and mucous membranes and on the presence of circulating anti-BMZ antibodies. An important target antigen is probably the protein BP180, which is recognized by the majority of CP sera.^{6, 9} This molecule, which has been cloned from keratinocytes and characterized in the authors' laboratory, is a transmembrane protein with a long, extracellular domain with a predicted collagenous structure.^{32, 33} CP sera have recently been shown to react with at least two distinct epitopes on the extracellular domain of this protein.⁶ One is located within the noncollagenous NC16A domain and the other in the carboxy-terminal region of this protein.

Using a passive transfer mouse model system, the authors' research group recently showed that experimentally generated antibodies that react with the NC16A homologous region in murine BP180 are capable of inducing a subepidermal blistering condition that mimics many of the features of BP^{56, 57}; however, the pathogenicity of anti-BP180 autoantibodies produced by BP or CP patients has not been directly demonstrated. In ocular CP, local or systemic administration of an antibody directed against an unidentified component of the lamina densa can induce conjunctivitis and BMZ immune deposits in neonatal rabbits.⁷⁴ Using an *in vitro* model system, a monoclonal antibody directed against laminin 5 was shown to induce dermal-epidermal detachment in human skin.⁷⁶ In addition, it has more recently been demonstrated that passive transfer of rabbit antihuman laminin 5 antibodies can cause subepithelial blisters on the skin and mucous membranes of neonatal mice⁵³; however, there is no direct evidence indicating that antilaminin 5 autoantibodies are pathogenic in this subgroup of CP patients.

Course and Treatment

The course of CP is usually chronic. Some patients have limited disease with only mild scarring whereas others exhibit functional impairment of the mucous membrane. Recurrence of oral mucosal involvement can be responsible for reduction of feeding, and ocular scarring can result in blindness. Cutaneous lesions respond to therapy more readily than mucosal lesions, and oral lesions respond better than conjunctival lesions.

There currently exists no universal guidelines for CP therapy. Its treatment depends on location and severity of lesions. Mild oral lesions can often be effectively treated with a topical corticosteroid, such as triamcinolone acetonide, fluocinonide, or clobetasol propionate in Ora-base (Colgate-Hoyt, Canton, MA).⁸⁵ This treatment can be used alone or in combination with dapsone (diaminodiphenylsulfone). Reports indicate that dapsone is effective in many patients with CP.^{28, 75} Most patients tolerate a therapeutic dose of 100 mg/day unless they are deficient in glucose-6-phosphate dehydrogenase; however, other side effects, such as hepatotoxicity or bone marrow suppression, need to be carefully monitored. If dapsone is ineffective or in more severe cases with extensive involvement, systemic corticosteroids (1 mg/kg/d) can be administered alone or in combination with dapsone. Prolonged treatment with systemic corticosteroids is associated with numerous adverse effects, especially in the elderly, including gastric ulcer, hypertension, diabetes, myopathy, osteoporosis, and psychosis. Therefore, the dosage and the duration of corticosteroids must be carefully considered. When both dapsone and prednisone are ineffective or cannot be used, an immunosuppressive agent is indicated. Cyclophosphamide (1–2 mg/kg/d) should be tried first and then azathioprine (2 mg/kg/d), if necessary, in combination with systemic prednisone (1 mg/kg/d) for a brief period.^{26, 67}

Cyclophosphamide has been found to be effective in controlling the progression of ocular lesions.²⁹ It is the first line of therapy in patients with ocular CP with moderate inflammatory activity.⁹⁰ After full control of inflammation is achieved, therapy should be continued with the successful regimen for 1 year, and follow-up must be continued for life because of the risk of relapse.⁶⁷ In ocular CP, surgical correction may be necessary for trichiasis, sicca syndrome, lid margin keratinization, or corneal opacification or perforation. The surgical procedures should only be attempted after active inflammation is controlled by immunosuppressive therapy. For trichiasis, cryotherapy of eyelashes, which gives a permanent epilation, is preferred to mechanical epilation. For corneal opacification or perforation, mucous membrane grafting or penetrating keratoplasty can be performed, but these methods allow only poor prospects for restoration of sight.⁹¹ For scarring lesions, marginal rotation of the eyelid, fornix reconstruction, or tarsorrhaphy can be performed.

EPIDERMOLYSIS BULLOSA ACQUISITA

EBA is a blistering disease of the skin and mucous membranes affecting primarily the trauma-prone areas. It is characterized by *in vivo* bound and circulating IgG autoantibodies directed against the sublamina densa of the epithelial basement membranes.³⁰ The patients' autoantibodies recognize the amino-terminal, noncollagenous domain of type VII collagen, which is the major component of anchoring fibrils.⁵²

Clinical Presentation

Different phenotypes of this disease have been described, including the classic or mechanobullous form, the inflammatory form, and the cicatricial pemphigoid form, which is defined by predominant mucous membrane involvement.³⁰ The classic phenotype of EBA is a noninflammatory disease affecting the extensor surface areas, such as the dorsal surfaces of hands, elbows, knees, and ankles. Skin fragility and tense blisters appear on noninflammatory skin and heal with scar and milia formation. Such a clinical picture resembles dystrophic forms of epidermolysis bullosa in children and porphyria cutanea tarda in elderly patients. The inflammatory form is a generalized eruption with widespread tense blisters resembling BP. Generalized erythema, urticarial plaques, and pruritus can occur.

Despite frequent mucous membrane involvement in EBA, this involvement is usually mild and limited to the oral mucosa. A small subset of patients present with predominantly mucosal disease, which is termed the cicatricial pemphigoid form of EBA. Involvement of the oral, nasal, ocular, laryngeal, and esophageal mucosae in EBA has been reported.^{30, 89} Ocular lesions have been described in four cases of EBA in adults and included conjunctivitis, symblepharon formation, keratitis,

subepithelial vesiculation of the cornea, perforation, and opacification of the cornea.^{1, 51, 73, 102} In childhood EBA, the mucosal involvement frequently affects the mouth and the genitals, and ocular involvement with symblepharon formation has been reported in two cases.^{59, 77} In one case of EBA mediated by IgA, ocular involvement was severe, consisting of bilateral conjunctival ulcers and scarring, corneal neovascularization, symblepharon, and trichiasis, resulting in total blindness.¹⁰¹

EBA is a very rare disease. The incidence has been calculated as approximately 0.2 new cases per 1 million people annually in France and Germany.^{11, 104} The same incidence has been determined for vesiculobullous systemic lupus erythematosus. It has been reported that EBA is associated with HLA-DRB1*0101/02, *0301, and *0501.⁹³

EBA affects the elderly with a average age of onset of 53 years. There is no sex or racial predisposition.²¹

Laboratory Investigations

The histopathology of EBA shows subepidermal blisters with the epidermis remaining intact. In addition, there is a dermal infiltrate that is minimal in the classical form of EBA and more abundant in the inflammatory form, composed of mononuclear cells and neutrophils. Laboratory tests including urine porphyrin levels and antinuclear antibody are used to exclude porphyria cutanea tarda and to search for evidence of bullous systemic lupus erythematosus, which is also characterized by antibodies directed against type VII collagen.

By direct IF, immune deposits of IgG are consistently demonstrated in a linear pattern at the BMZ of the skin or mucosae. Complement, IgM, and IgA may also be detected. By indirect IF on human skin, circulating anti-BMZ autoantibodies can be detected, but only in a low percentage of patients' and with a low titer. If human salt-split skin is used as a substrate, autoantibodies bind exclusively to the dermal side. This pattern supports a diagnosis of EBA, but is not specific because a similar staining can be encountered in antilaminin 5 CP, in anti-p105 pemphigoid, and in a novel subepidermal blistering disease with autoantibodies recognizing a 200 kd dermal protein.^{19, 103}

IEM and immunoblotting using a dermal extract can establish a diagnosis of EBA. By direct or indirect IEM using an immunoperoxidase or immunogold method, immune deposits are ultrastructurally localized below the lamina densa on anchoring fibrils.³⁹ This localization is clearly distinct from that of immune deposits in the lamina lucida observed in BP, antilaminin 5 CP, anti-p105 pemphigoid, and the new disease described by Zillikens and colleagues that reacts with a 200 kd basement membrane protein.¹⁰³

By immunoblotting, circulating autoantibodies bind a dermal protein of 290 kd identified as collagen VII⁹⁹; however, the sensitivity of this assay is not particularly high, so a negative result in this test does not exclude the diagnosis of EBA. Detection of anticollagen VII antibodies by ELISA using fusion proteins corresponding to different portions

of the noncollagenous domain of collagen VII has been used by several research teams. The sensitivity of this assay is close to 90%.^{31, 42}

Pathogenesis

EBA is characterized by an autoimmune reaction directed against collagen VII. Using overlapping fusion protein covering around 80% of the primary sequence of collagen VII, Lapiere et al⁵² has demonstrated four major immunodominant epitopes localized within the amino-terminal, noncollagenous domain, NC1. For two epitopes located in the fibronectin type III homology repeats, octapeptide sequences targeted by autoantibodies have been identified.⁴² Although the precise role of autoantibodies against collagen VII is unknown, it has been hypothesized that they disrupt the assembly of collagen VII into anchoring fibrils or interfere with their interactions with other extracellular matrix molecules. The pathogenicity of such antibodies has not yet been demonstrated. Passive transfer of IgG from a patient with EBA into mice induces dermal edema and a granulocytic infiltrate in the superficial dermis, with immune deposits at the BMZ by direct IF localized by direct IEM to anchoring fibrils; however, no clinical disease was observed.¹⁵

Course and Treatment

EBA has a protracted course and is usually resistant to treatment. The drugs used are immunosuppressive or anti-inflammatory agents. Systemic immunosuppressive drugs, including prednisone, azathioprine, cyclophosphamide, methotrexate, and cyclosporine, are used in various dosages. In the group of anti-inflammatory drugs, dapsone, sulfapyridine and colchicine appear to be effective and may decrease the inflammation because of their antineutrophil effect. Bullous systemic lupus erythematosus usually responds rapidly and completely to dapsone. New therapies have recently been proposed, such as extracorporeal photochemotherapy, which was reported to be effective in one study, but which resulted in only partial improvement in two of three patients in another study.^{21, 61} Intravenous immunoglobulins have also been recently reported to be effective in two cases, but they were used in combination with several other immunomodulatory agents.^{60, 63} The determination of the efficacy of this new treatment requires further evaluation.

LINEAR IgA DISEASE

The diagnosis of LAD is based on the predominance of IgA deposits in a homogeneous linear pattern at the BMZ. It has been distinguished from dermatitis herpetiformis in 1979 by Chorzelski and colleagues,^{21a}

and is often referred to as *chronic bullous disease of childhood* in the pediatric age group. The clinical features of LAD are varied, although annular lesions resembling “cluster of jewels” are characteristic of this diagnosis. Several different target antigens are observed by immunoblotting and IEM. This diversity of target antigens suggests that LAD is a heterogeneous group of diseases, which may explain the variation of the clinical picture and therapeutic responses.

Clinical Presentation

The cutaneous lesions are tense blisters occurring on normal or erythematous skin, often at the periphery of annular patches resembling a cluster of jewels or a “string of pearls.” They develop on the perineum, in the perioral region, and on the extremities, but can sometimes be generalized. Pruritus can be present. The clinical picture can resemble BP or dermatitis herpetiformis. In adults, mucous membranes are often involved, including the mouth (37%), the genitals (25%), and the conjunctivae (20%), and scarring can occur (Fig. 4). The ocular changes are indistinguishable from those of CP. Because they are frequent and can be asymptomatic, careful examination by an ophthalmologist is necessary for all patients with LAD.⁵ Ocular changes observed include loss of inner canthal architecture, loss of inferior forniceal depth, shrinkage of the conjunctival sac, fine conjunctival scarring, trichiasis, and symblepharon with secondary corneal opacification (Fig. 5, see Color Plate, Fig. 4).^{46, 54}

LAD is a rare disease. The incidence has been calculated as 0.52 and 0.22 new cases per 1 million people annually in France and Germany, respectively.^{11, 104} It has been reported that childhood LAD is associated with HLA-B8.

LAD has a bimodal age distribution, with one peak in childhood before 5 years and another in the fifth decade; there is no gender predisposition. Drug-induction of LAD has been observed, and the



Figure 4. Buccal erosion in patient with linear IgA disease



Figure 5. Loss of canthal architecture and symblepharon formation in linear IgA disease (same patient as in Figure 4, see also Color Plate, Fig. 4).

physician should search for exposure to medications in new cases of LAD. Suspect drugs include vancomycin, with eleven reported cases, captopril, diclophenac, cefamandol, and somatostatin.⁹⁴

Laboratory Investigations

Histopathological examination of a cutaneous blister in LAD shows subepidermal cleavage with inflammatory cells in the upper dermis. These cells may be eosinophils or neutrophils. In some cases, neutrophils may form microabscesses in the papillary ridges, similar to those observed in dermatitis herpetiformis.

By definition, direct IF of skin shows linear deposits of IgA along the BMZ. In some cases, however, deposits of IgG or C3 can be found. The tissue-bound IgA belongs to the A1 subclass.⁹⁶ Direct IF performed on conjunctiva or oral mucosa demonstrates similar deposits of IgA.^{5, 46} Circulating IgA autoantibodies against the BMZ can be demonstrated in some adult cases and most pediatric cases, but usually with low titers. Skin, oral mucosa, or conjunctiva can be used as substrates. When salt-split skin is used as the substrate, the sensitivity of the indirect IF assay increases.⁹⁷ The IgA reactivity can be observed on either the epidermal or dermal side of the split, or in a dermal/epidermal combined pattern.^{78, 95, 101, 106}

Direct IEM analysis of LAD biopsy samples using immunoperoxidase and immunogold methods revealed patient-to-patient variability in staining patterns. Some samples showed deposition of immunoglobulin in the lamina lucida, others showed staining in the sublamina densa region, and some samples showed a combined pattern, referred to as

the *mirror image pattern*.^{44, 71} By indirect IEM, autoantibodies were also shown to bind the lamina lucida or the sublamina densa.⁴⁸

Immunoblotting studies show variable reactivity profiles with LAD sera. A protein of 97 kd recognized by sera staining the epidermal side of 1 M NaCl-split skin has been reported.¹⁰⁶ This antigen has recently been characterized and named LAD-1. It is secreted by keratinocytes, detected in the BMZ of different tissues and localizes exclusively to anchoring filaments. The native protein has a molecular weight of 120-kd and is probably degraded to a protein of 97 kd during the extraction procedure.⁵⁸ Using patient autoantibodies that recognize the 97 kd antigen reported by Zone et al,¹⁰⁶ this antigen has been localized to the lamina lucida beneath the hemidesmosome and possibly to the hemidesmosomal plaque.^{34, 40}

A protein of 255 kd, recognized by sera staining the dermal side of 1 M NaCl split-skin and present in dermal extracts of human skin, has been described but not characterized.²³ Other target antigens have been identified as BP230, BP180, and collagen VII.^{35, 43, 78, 105} The difficulty in these cases is nosologic, and terminology has been proposed that favors the target antigen and not the immunoglobulin class in the classification of autoimmune bullous diseases. These cases can be classified as IgA-BP, IgA-CP, and IgA-EBA, as proposed by Woodley for the last disease.⁹⁸ In some cases, multiple antigens are recognized by the autoantibodies.^{22, 105}

Pathogenesis

The pathogenesis of LAD is unclear. For LAD with antibodies against LAD-1, it has been demonstrated that a monoclonal antibody recognizing this protein, mAb123, induced dermal-epidermal separation of human skin in vitro. This favors the hypothesis that autoantibodies in this form of LAD are directly pathogenic.⁵⁸ No animal model has been reported, and passive transfer of autoantibodies into mice is limited by the low circulating antibody titers encountered in this disease.

Course and Treatment

Treatment of LAD with dapsone (2 mg/kg/d in children, 100 to 300 mg/d in adults) or sulfapyridine usually results in good control of disease. The response is usually rapid, with improvement seen in 3 days to a few weeks. In patients who do not respond to this treatment, prednisone 20 to 30 mg/d may be added to dapsone. LAD may remit over a period of years, but mucosal lesions may be more resistant to therapy compared with cutaneous eruptions.

CONCLUSIONS

Autoimmune subepithelial blistering diseases with ocular involvement are a heterogeneous group including CP, EBA, and LAD. Management of these diseases requires collaborative efforts between the dermatologist, the ophthalmologist, and the clinical immunologist. Criteria for the positive diagnosis of a disease within this group should include the clinical presentation, histology, and immunofluorescence findings. Unfortunately, these data may be insufficient for a definitive diagnosis. For these difficult cases, further studies, including western blotting and mapping the deposition of immunoreactants by IEM, may be performed. These methods should allow for an accurate diagnosis and for a better understanding of these diseases.

References

1. Aclimandos WA: Corneal perforation as a complication of epidermolysis bullosa acquisita. *Eye* 9:633-636, 1995
2. Ahmed RA, Hombal SM: Cicatricial pemphigoid. *Int J Dermatol* 25:90-96, 1986
3. Ahmed RA, Kurgis BS, Rogers RS III: Cicatricial pemphigoid. *J Am Acad Dermatol* 24:987-1000, 1991
4. Ahmed RA, Foster S, Zaltas M, et al: Association of DQw7 (DQB1*0301) with ocular cicatricial pemphigoid. *Proc Natl Acad Sci USA* 88:11579-11582, 1991
5. Aultbrinker EA, Starr MB, Donnenfeld ED: Linear IgA disease: The ocular manifestations. *Ophthalmology* 95:340-343, 1988
6. Balding SD, Prost C, Diaz LA, et al: Cicatricial pemphigoid autoantibodies react with multiple sites on the BP180 extracellular domain. *J Invest Dermatol* 106:141-146, 1996
7. Bedane C, Prost C, Bernard P, et al: Cicatricial pemphigoid antigen differs from bullous pemphigoid antigen by its exclusive extracellular localization: A study by indirect immunoelectron microscopy. *J Invest Dermatol* 97:3-9, 1991
8. Bernard P, Prost C, Aucouturier P, et al: The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. *J Invest Dermatol* 97:259-263, 1991
9. Bernard P, Prost C, Durepaire N, et al: The major cicatricial pemphigoid antigen is a 180-kD protein that shows immunologic cross-reactivities with the bullous pemphigoid antigen. *J Invest Dermatol* 99:174-179, 1992
10. Bernard P, Prost C, Lecerf V, et al: Studies of cicatricial pemphigoid autoantibodies using direct immunoelectron microscopy and immunoblot analysis. *J Invest Dermatol* 94:630-635, 1990
11. Bernard P, Vaillant L, Labeille B, et al: Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. *Arch Dermatol* 131:48-52, 1995
12. Bernauer W, Broadway DC, Wright P: Chronic progressive conjunctival cicatrization. *Eye* 7:371-378, 1993
13. Bernauer W, Wright P, Dart JK, et al: The conjunctiva in acute and chronic mucous membrane pemphigoid: An immunohistochemical analysis. *Ophthalmology* 100:339-346, 1993
14. Bhol K, Udell I, Haider N, et al: Ocular cicatricial pemphigoid: A case report of monozygotic twins discordant for the disease. *Arch Ophthalmol* 113:202-207, 1995
15. Borradori L, Caldwell JB, Briggaman RA, et al: Passive transfer of autoantibodies from a patient with mutilating epidermolysis bullosa acquisita induces specific alterations in the skin of neonatal mice. *Arch Dermatol* 131:590-595, 1995
16. Brunsting LA, Perry HO: Benign pemphigoid?: A report of seven cases with chronic,

- scarring, herpetiform plaques about the head and neck. *Arch Dermatol* 75:489-501, 1957
17. Camisa C, Meisler DM: Immunobullous diseases with ocular involvement. *Dermatol Clin* 10:555-570, 1992
18. Chan LS, Chen M, Woodley DT: Epidermolysis bullosa acquisita in the elderly: Clinical manifestations, diagnosis, and therapy. *J Geriatr Dermatol* 4:47-52, 1996
19. Chan LS, Fine JD, Briggaman RA, et al: Identification and partial characterization of a novel 105-kDalton lower lamina lucida autoantigen associated with a novel immune-mediated subepidermal blistering disease. *J Invest Dermatol* 101:262-267, 1993
20. Chan LS, Wang T, Wang XS, et al: High frequency of HLA-DQB1*0301 allele in patients with pure ocular cicatricial pemphigoid. *Dermatology* 189:99-101, 1994
21. Chan LS, Yancey KB, Hammerberg C, et al: Immune-mediated subepithelial blistering diseases of mucous membranes. *Arch Dermatol* 129:448-455, 1993
- 21a. Chorzelski TP, Jablonska S: IgA linear dermatosis of childhood (chronic bullous disease of childhood). *Br J Dermatol* 101:535-542, 1979
22. Darling TN, Cardenas AA, Beard JS, et al: A child with antibodies targeting both linear IgA bullous dermatosis and bullous pemphigoid antigens. *Arch Dermatol* 131:1438-1442, 1995
23. Dmochowski M, Hashimoto T, Bhogal BS, et al: Immunoblotting studies of linear IgA disease. *J Dermatol Sci* 6:194-200, 1993
24. Domloge-Hultsch N, Anhalt G, Gammon WR, et al: Antiepiligrin cicatricial pemphigoid: A subepithelial bullous disorder. *Arch Dermatol* 130:1521-1529, 1994
25. Domloge-Hultsch N, Gammon W, Briggaman R, et al: Epiligrin, the major human keratinocyte integrin ligand, is a target in both an acquired autoimmune and an inherited subepidermal blistering skin disease. *J Clin Invest* 90:1628-1633, 1992
26. Elder MJ, Lightman S, Dart JKG: Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 79:264-266, 1995
27. Fine JD, Neises GR, Katz SI: Immunofluorescence and immunoelectron microscopic studies in cicatricial pemphigoid. *J Invest Dermatol* 82:39-45, 1984
28. Fern AL, Jay JL, Young H, et al: Dapsone therapy for the acute inflammatory phase of ocular pemphigoid. *Br J Ophthalmol* 76:332-335, 1992
29. Foster CS, Wilson LA, Ekins MB: Immunosuppressive therapy for progressive ocular cicatricial pemphigoid. *Ophthalmology* 89:340-353, 1982
30. Gammon WR, Briggaman RA: Epidermolysis bullosa acquisita and bullous systemic lupus erythematosus: Diseases of autoimmunity to type VII collagen. *Dermatol Clin* 11:535-547, 1993
31. Gammon WR, Murrell DF, Jenison MW, et al: Autoantibodies to type VII collagen recognize epitopes in a fibronectin-like region of the noncollagenous (NC1) domain. *J Invest Dermatol* 100:618-422, 1993
32. Giudice GJ, Emery DE, Diaz LA: Cloning and primary structural analysis of the bullous pemphigoid autoantigen BP180. *J Invest Dermatol* 99:243-250, 1992
33. Giudice GJ, Squiquera HL, Elias PM, et al: Identification of two collagen domains within the bullous pemphigoid autoantigen, BP180. *J Clin Invest* 87:734-738, 1991
34. Haftek M, Zone JJ, Taylor TB, et al: Immunogold localization of the 97-kDa antigen of linear IgA bullous dermatosis (LABD) detected with patients' sera. *J Invest Dermatol* 103:656-659, 1994
35. Hashimoto T, Ishiko A, Shimizu H, et al: A case of linear IgA bullous dermatosis with IgA anti-type VII collagen autoantibodies. *Br J Dermatol* 134:336-339, 1996
36. Hashimoto T, Murakami H, Senboshi Y, et al: Antiepiligrin cicatricial pemphigoid: The first case report from Japan. *J Am Acad Dermatol* 34:940-942, 1996
37. Hausser I, Fartasch M, Schleiermacher E, et al: Disseminated cicatricial pemphigoid in a child and an adult: Ultrastructural diagnostic criteria and differential diagnosis with special reference to acquired epidermolysis bullosa. *Arch Dermatol Res* 279:357-365, 1987
38. Hoang-Xuan T, Foster CS, Raizman MB, et al: Mast cells in conjunctiva affected by cicatricial pemphigoid. *Ophthalmology* 96:1110-1114, 1989
39. Ishiko A, Hashimoto T, Shimizu H, et al: Epidermolysis bullosa acquisita: Report of a case with comparison of immunogold electron microscopy using pre- and postembedding labelling. *Br J Dermatol* 134:147-151, 1996

40. Ishiko A, Shimizu H, Masunaga T, et al: 97-kDa linear IgA bullous dermatosis (LAD) antigen localizes to the lamina lucida of the epidermal basement membrane. *J Invest Dermatol* 106:739-743, 1996
41. Joly P, Ruto F, Thomine E, et al: Brunstig-Perry cicatricial pemphigoid: A clinical variant of localized acquired epidermolysis bullosa? *J Am Acad Dermatol* 28:89-92, 1993
42. Jones DA, Hunt SW III, Prisayanh PS, et al: Immunodominant autoepitopes of type VII collagen are short, paired peptide sequences within the fibronectin type III homology region of the noncollagenous (NC1) domain. *J Invest Dermatol* 104:231-235, 1995
43. Karitakis J, Mauduit G, Cozzani E, et al: Linear IgA bullous dermatosis of childhood with autoantibodies to a 230 kilodaltons epidermal antigen. *Pediatr Dermatol* 11:139-144, 1994
44. Karpati S, Stolz W, Meurer M, et al: Ultrastructural immunogold studies in two cases of linear IgA dermatosis: Are there two distinct types of this disease? *Br J Dermatol* 127:112-118, 1992
45. Kelly S, Wojnarowska F: The use of chemically split tissue in the detection of circulating anti-basement membrane zone antibodies in bullous pemphigoid and cicatricial pemphigoid. *Br J Dermatol* 118:31-40, 1988
46. Kelly SE, Frith PA, Millard PR, et al: A clinicopathological study of mucosal involvement in linear IgA disease. *Br J Dermatol* 119:161-170, 1988
47. Kirtschig G, Marinkovich P, Burgeson RE, et al: Anti-basement membrane autoantibodies in patients with anti-epiligrin cicatricial pemphigoid bind the α subunit of laminin 5. *J Invest Dermatol* 105:543-548, 1995
48. Kowalewski C, Haftek M, Jablonska S, et al: Ultrastructural localization of binding sites of sera from patients with linear IgA bullous dermatosis. *J Invest Dermatol* 287:633-640, 1995
49. Kurzhals G, Stolz W, Maciejewski W, et al: Localized cicatricial pemphigoid of the Brunstig-Perry type with transition into disseminated cicatricial pemphigoid. *Arch Dermatol* 131:580-585, 1995
50. Labib RS, Anhalt GJ, Patel HP, et al: Molecular heterogeneity of bullous pemphigoid antigens as detected by immunoblotting. *J Immunol* 136:1231-1235, 1986
51. Lang PG, Tapert MJ: Severe ocular involvement in a patient with epidermolysis bullosa acquisita. *J Am Acad Dermatol* 16:439-443, 1987
52. Lapiere JC, Woodley DT, Parente MG, et al: Epitope mapping of type VII collagen: Identification of discrete peptide sequences recognized by sera from patients with acquired epidermolysis bullosa. *J Clin Invest* 92:1831-1839, 1993
53. Lazarova Z, Yee C, Darling T, et al: Passive transfert of anti-laminin 5 antibodies to neonatal mice induces subepidermal blisters [abstract]. *J Invest Dermatol* 104:582A, 1995
54. Leonard JN, Hobday CM, Haffenden GP, et al: Immunofluorescent studies in ocular cicatricial pemphigoid. *Br J Dermatol* 118:209-217, 1988
55. Leonard JN, Wright P, Williams DM, et al: The relationship between linear IgA disease and benign mucous membrane pemphigoid. *Br J Dermatol* 110:307-314, 1984
56. Liu Z, Diaz LA, Swartz SJ, et al: Molecular mapping of a pathogenically relevant BP180 epitope associated with experimentally induced murine bullous pemphigoid. *J Immunol* 155:5449-5454, 1995
57. Liu Z, Diaz LA, Troy JL, et al: A passive transfer model of the organ-specific autoimmune disease, bullous pemphigoid, using antibodies generated against the hemidesmosomal antigen, BP180. *J Clin Invest* 92:2480-2488, 1993
58. Marinkovich MP, Taylor TB, Keene DR, et al: LAD-1, the linear IgA bullous dermatosis autoantigen, is a novel 120-kDa anchoring filament protein synthesized by epidermal cells. *J Invest Dermatol* 106:734-738, 1996
59. McCuaig CC, Chan LS, Woodley DT, et al: Epidermolysis bullosa acquisita in childhood. *Arch Dermatol* 125:944-949, 1989
60. Meier F, Sönnichsen K, Schaumburg-Lever G, et al: Epidermolysis bullosa acquisita: Efficacy of high-dose intravenous immunoglobulins. *J Am Acad Dermatol* 29:334-337, 1993
61. Miller JL, Stricklin GP, Fine JD, et al: Remission of severe epidermolysis bullosa

- acquisita induced by extracorporeal photochemotherapy. *Br J Dermatol* 133:467-471, 1995
62. Mohimen A, Neumann R, Foster SC, et al: Detection and characterization of ocular pemphigoid antigens on COLO and ScaBER tumor cell lines. *Curr Eye Res* 12:741-752, 1993
63. Mohr C, Sunderkötter C, Hildebrand A, et al: Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. *Br J Dermatol* 132:824-826, 1995
64. Mutasim DF, Pelc NJ, Anhalt GJ: Cicatricial pemphigoid. *Dermatol Clin* 11:499-510, 1993
65. Nieboer C, Boorsma DM, Woederman MJ: Immunoelectron microscopic findings in cicatricial pemphigoid: Their significance in relation to epidermolysis bullosa acquisita. *Br J Dermatol* 106:419-422, 1982
66. Niimi Y, Zhu XJ, Bystryń JC: Identification of cicatricial pemphigoid antigens. *Arch Dermatol* 128:54-57, 1992
67. Neumann R, Tauber J, Foster S: Remission and recurrence after withdrawal of therapy for ocular cicatricial pemphigoid. *Ophthalmology* 98:858-862, 1991
68. Person JR, Rogers RS: Bullous and cicatricial pemphigoid: Clinical, histopathologic, and immunopathologic correlation. *Mayo Clin Proc* 52:54-66, 1977
69. Poulquien Y, Patey A, Foster S, et al: Drug-induced cicatricial pemphigoid affecting the conjunctiva: Light and electron microscopic features. *Ophthalmology* 93:775-783, 1986
70. Power WJ, Neves RA, Rodriguez A, et al: Increasing the diagnostic yield of conjunctival biopsy in patients with suspected ocular cicatricial pemphigoid. *Ophthalmology* 102:1158-1163, 1995
71. Prost C, Colonna De Leca A, Combemale P, et al: Diagnosis of adult linear IgA dermatosis by immunoelectronmicroscopy in 16 patients with linear IgA deposits. *J Invest Dermatol* 92:39-45, 1989
72. Prost C, Robin H, Caux F, et al: Direct immunoelectron microscopy on the conjunctiva in ocular cicatricial pemphigoid versus subepidermal autoimmune bullous dermatoses with ocular involvement: Report of 10 cases [abstract]. *J Invest Dermatol* 106:852, 1996
73. Richter BJ, McNutt NS: The spectrum of epidermolysis bullosa acquisita. *Arch Dermatol* 115:1325-1328, 1979
74. Roat MI, Alstadt SP, Carpenter AB, et al: Antibasement membrane antibody-mediated experimental conjunctivitis. *Invest Ophthalmol Vis Sci* 31:168-175, 1990
75. Rogers RS III, Seehafer JR, Perry HO: Treatment of cicatricial (benign mucous membrane) pemphigoid with dapsone. *J Am Acad Dermatol* 6:215-223, 1982
76. Rousselle P, Lunstrum GP, Keene DR, et al: Kalinin: An epithelium-specific basement membrane adhesion molecule that is a component of anchoring filaments. *J Cell Biol* 114:567-576, 1991
77. Rubinstein R, Esterly NB, Fine JD: Childhood epidermolysis bullosa acquisita. *Arch Dermatol* 123:772-776, 1987
78. Rusenko KW, Gammon WR, Briggaman RA: Type VII collagen is the antigen recognized by IgA anti-sub lamina densa autoantibodies [abstract]. *J Invest Dermatol* 92:510, 1989
79. Sacks EH, Jakobiec FA, Wieczorek R, et al: Immunophenotypic analysis of the inflammatory infiltrate in ocular cicatricial pemphigoid: Further evidence for a T cell-mediated disease. *Ophthalmology* 96:236-243, 1989
80. Sarret Y, Hall R, Cobo LM, et al: Salt-split human skin substrate for the immunofluorescent screening of serum from patients with cicatricial pemphigoid and a new method of immunoprecipitation with IgA antibodies. *J Am Acad Dermatol* 24:952-958, 1991
81. Sarret Y, Reano A, Nicholas JF, et al: Bullous pemphigoid and cicatricial pemphigoid: Immunoblotting detection of involved autoantigens. *Autoimmunity* 2:145-153, 1989
82. Schaller J, Hellingsenhaus A, Engelbrecht S, et al: Detection of eosinophil cationic protein in active ocular cicatricial pemphigoid [abstract]. *J Invest Dermatol* 105:482, 1995

83. Setterfield J, Bhogal B, Morgan P, et al: Clinical and immunopathological correlation in cicatricial pemphigoid: A study of 36 cases [abstract]. *Br J Dermatol* 132:647, 1995
84. Shimizu H, Masunaga T, Ishiko A, et al: Autoantibodies from patients with cicatricial pemphigoid target different sites in epidermal basement membrane. *J Invest Dermatol* 104:370-373, 1995
85. Silverman S Jr, Gorsky M, Lozada-Nur F, et al: Oral mucous membrane pemphigoid: A study of sixty-five patients. *Oral Surg Oral Med Oral Pathol* 61:233-237, 1986
86. Smith EP, Taylor TB, Meyer LJ, et al: Identification of a basement membrane zone antigen reactive with circulating IgA antibody in ocular cicatricial pemphigoid. *J Invest Dermatol* 101:619-623, 1993
87. Soh H, Hosokawa H, Miyauchi H, et al: Localized pemphigoid shares the same target antigen as bullous pemphigoid. *Br J Dermatol* 125:73-75, 1991
88. Stanley JR, Hawley-Nelson P, Yuspa SH, et al: Characterization of bullous pemphigoid antigen: A unique basement membrane protein of stratified squamous epithelia. *Cell* 24:897-903, 1981
89. Stewart MI, Woodley DT, Briggaman RA: Epidermolysis bullosa acquisita and associated symptomatic esophageal webs. *Arch Dermatol* 127:373-377, 1991
90. Tauber J, Sainz de la Maza, Foster CS: Systemic chemotherapy for ocular cicatricial pemphigoid. *Cornea* 10:185-195, 1991
91. Tugal-Tutkun I, Akova YA, Foster CS: Penetrating keratoplasty in cicatrizing conjunctival diseases. *Ophthalmology* 102:576-585, 1995
92. Wakelin SH, Mallon E, Wojnarowska F, et al: Increased frequency of HLA DQ7 in female patients with cicatricial pemphigoid [abstract]. *Br J Dermatol* 132:651, 1995
93. Welsh EA, Prost C, Lepage V: A multinational study of HLA associations in autoimmunity to type VII collagen in patients with epidermolysis bullosa acquisita [abstract]. *J Invest Dermatol* 103:854, 1994
94. Whitworth JM, Thomas I, Peltz SA, et al: Vancomycin-induced linear IgA bullous dermatosis (LABD). *J Am Acad Dermatol* 34:890-891, 1996
95. Willsteed E, Bhogal BS, Black MM: Use of 1M NaCl split skin in the indirect immunofluorescence of the linear IgA bullous dermatoses. *J Cutan Pathol* 17:144-148, 1990
96. Wojnarowska F, Bhogal BS, Black MM: Chronic bullous disease of childhood and linear IgA disease of adults are IgA1-mediated diseases. *Br J Dermatol* 131:201-204, 1994
97. Wojnarowska F, Collier PM, Allen J, et al: The localization of the target antigens and antibodies in linear IgA disease is heterogeneous, and dependant on the methods used. *Br J Dermatol* 132:750-757, 1995
98. Woodley DT: Immunofluorescence on salt-split skin for the diagnosis of epidermolysis bullosa acquisita. *Arch Dermatol* 126:229-301, 1990
99. Woodley DT, Briggaman RA, O'Keefe EJ, et al: Identification of the skin basement membrane antigen in epidermolysis bullosa acquisita. *N Engl J Med* 310:1007-1013, 1984
100. Yunis JJ, Mobini N, Yunis EJ, et al: Common major histocompatibility complex class II markers in clinical variants of cicatricial pemphigoid. *Proc Natl Acad Sci USA* 91:7747-7751, 1994
101. Zambruno G, Manca V, Kanitakis J, et al: Linear IgA bullous dermatosis with autoantibodies to a 290 kd antigen of anchoring fibrils. *J Am Acad Dermatol* 31:884-888, 1994
102. Zierhut M, Thiel H-J, Weidle EG, et al: Ocular involvement in epidermolysis bullosa acquisita. *Arch Ophthalmol* 107:398-401, 1989
103. Zillikens D, Kawahara Y, Ishiko A, et al: A novel subepidermal blistering disease with autoantibodies to a 200-kD antigen of the basement membrane zone. *J Invest Dermatol* 106:1333-1338, 1996
104. Zillikens D, Wever S, Roth A, et al: Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 131:957-958, 1995
105. Zone JJ, Pazderka Smith E, Powell D, et al: Antigenic specificity of antibodies from patients with linear basement membrane deposition of IgA. *Dermatology* 189(suppl 1):64-66, 1994

106. Zone JJ, Taylor TB, Kadunce DP, et al: Identification of the cutaneous basement membrane zone antigen and isolation of antibody in linear immunoglobulin A bullous dermatosis. *J Clin Invest* 85:812-820, 1990

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