THE IMMUNOLOGICAL FEATURES AND PATHOPHYSIOLOGY OF OCULAR CICATRICIAL PEMPHIGOID

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SUMMARY

Ocular cicatricial pemphigoid is an uncommon but severe and potentially blinding systemic disease. It shares many pathophysiological features with the other bullous skin diseases such as dermatitis herpetiformis, bullous pemphigoid and pemphigus vulgaris. All of these diseases have circulating antibodies that bind to the basement membrane of mucous membranes. The individual diseases differ by each having a specific component of the basement membrane complex as its antigen. In acute ocular cicatricial pemphigoid, the conjunctiva is infiltrated with neutrophils, macrophages, Langerhans cells and CD8+ and CD4+ T-cells while in the chronic disease the conjunctiva is infiltrated mainly by CD8+ T-cells. There is evidence of activation of these T-cells as CD4+ cells as shown by expression of the interleukin-2 receptor and increased expression of major histocompatibility class II antigens within the tissue. The aetiology of the fibrosis is unknown but increased amounts of several fibrogenic growth factors are demonstrable by immunohistochemistry.

Clinically, cicatrising conjunctivitis may range from asymptomatic subtarsal or canthal fibrosis to a complete obliteration of the fornices with total keratinisation of the ocular surface.¹ The cicatrization may have a wide range of aetiologies including physical, chemical, pharmaceutical, infectious, inflammatory and immune stimuli.¹ This cicatrization may impair corneal function by a variety of mechanisms. These include a dysfunction in any of the three tear film layers, abnormal lid-globe contact or movement, trichiasis, exposure, and a predisposition to blepharitis and keratitis. This paper summarises current

knowledge about the immune basis and pathophysiology of ocular cicatricial pemphigoid.

BULLOUS SKIN DISEASES

All of the bullous skin diseases may be associated with cicatricial conjunctival changes but they are uncommon, mild and frequently asymptomatic. These diseases include dermatitis herpetiformis,^{1,2} epidermolysis bullosa,^{1,4-10} pemphigus vulgaris^{1,3,11-16} and bullous pemphigoid.¹⁷⁻²² As a family of diseases, they all have circulating antibodies to skin and mucous membrane basement membrane. Antibodies and complement are bound to the basement membrane of lesional and non-lesional skin. However, the diseases differ by each having a unique component of the basement membrane as its antigen (Table I). The exceptions to this are that dermatitis herpetiformis does not have a circulating antibody² and the antigen in pemphigus vulgaris is the intercellular cement substance.^{12,13,15} The disease with the most severe ocular consequences is ocular cicatricial pemphigoid.¹

CLINICAL FEATURES OF OCULAR CICATRICIAL PEMPHIGOID

Ocular cicatricial pemphigoid (OCP) affects elderly patients, with a mean age at presentation of 58–69 years.²³⁻²⁶ Ocular involvement occurs in 66–77% of cases.²³⁻²⁷ In an ophthalmic series, skin lesions were present in 9% of cases.²⁵ Other mucous membrane involvement included the mouth (15%), nose (12%) and oesophagus (9%).²⁵ There is an association with HLA-DQw7 (DQB1*0301)²⁸ and affected patients have a four-fold increase in the prevalence of other autoimmune diseases ($p < 0.01$) – mainly rheumatoid arthritis but also systemic lupus erythematosus and polyarteritis nodosa.²⁵

The disease may be acute and associated with inflammation, or chronic and not associated with inflammation.

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Table I. The immune-related cicatrising conjunctivitides

Disease	Antibody binding site
Ocular cicatricial pemphigoid	Lamina lucida of BMZ
Dermatitis herpetiformis	Sublamina densa region of BMZ
Epidermolysis bullosa	Type VII procollagen in BMZ
Pemphigus vulgaris	Intercellular cement substance
Bullous pemphigoid	220 kDa glycoprotein in BMZ
Stevens-Johnson syndrome	Blood vessel wall

BMZ, basement membrane zone.

Progression of the ocular cicatrization occurs in 75% of patients not receiving treatment.^{26,29} The cicatrization may occur as a gradual event not associated with inflammation or in a stepwise manner during periods of acute inflammation.^{24,30,31} Surgically induced inflammation can cause rapid progression, such as may occur with entropion correction or cryotherapy.^{26,30–33}

Clinically, the sequence of progression is usually that of progressive shrinkage of the conjunctiva with symblepharon, development of cicatricial entropion of both upper and lower lids, trichiasis, obliteration of the fornices, ocular surface keratinisation, diminution of the tear film and eventual keratopathy. At any point there may be an exacerbation of conjunctival inflammation.

**IMMUNE FEATURES IN OCULAR
CICATRICIAL PEMPHIGOID**

Circulating antibodies to conjunctival basement mem-

Fig. 1. Acute ocular cicatricial pemphigoid showing intense infiltration with neutrophils in the conjunctival stroma and epithelium. $\times 125$. (Courtesy of Dr W. Bernauer.)

brane are detected in about 50% of patients.^{30,32,34–38} This antibody is directed against basement membrane antigens of 230 kDa and/or 160–180 kDa. There is some cross-reactivity with bullous pemphigoid antigen.^{18,33,39} Immunoglobulins G and A and complement are bound to conjunctival basement membrane in up to 67% of cases.^{25,33,36,40} The binding is strictly linear and is along the superficial and deep aspects of the lamina lucida.¹⁸ Various components of complement are bound to the basement membrane including C1q, C3, C4 and properdin,^{30,31,39,40} and complement may be activated via both the classical and the alternative pathway.⁴¹ Lysis of the desmosomal attachments of the basal layer of the epithelium causes the subepithelial bullae, which may be clinically manifest, especially involving the skin or mouth.^{42,43}

Further evidence for an autoimmune basis of the disease comes from the development of an animal model in rabbits.⁴⁵ The injection of a monoclonal antibody into basement membrane of conjunctival epithelium (MAb63) causes conjunctival inflammation, neutrophil infiltration and basement membrane deposition of IgG in a pattern similar to that seen in acute OCP.

Immunohistochemical studies^{25,33,40,44} have shown that the acute, ulcerative phase affects both the conjunctival epithelium and the substantia propria. The stromal

Fig. 2. Subacute ocular cicatricial pemphigoid stromal conjunctiva showing T-cells staining positive for interleukin 2 receptor suggesting activation. $\times 500$. (Courtesy of Dr W. Bernauer.)

Fig. 3. Chronic ocular cicatricial pemphigoid stromal conjunctiva showing CD4+ T-cell infiltration. $\times 312$. (Courtesy of Dr W. Bernauer.)

changes in acute disease are characterised by a marked infiltration of neutrophils (Fig. 1), macrophages, Langerhans/dendritic cells and T lymphocytes compared with normal controls. In addition, there is significantly increased expression of the major histocompatibility class II antigen (HLA-DR), there are equal numbers of CD4+ and CD8+ T-cells and 4–10% of the T-cells stain positive for interleukin 2 receptor, suggesting that they are activated^{33,40,44} (Fig. 2). Staining for transforming growth factor-beta (TGF- β) is significantly increased.

The subacute phase of the disease is histologically similar to acute disease although the CD4+/CD8+ ratio drops to 0.4. The chronic phase is characterised by an infiltration with T lymphocytes (Fig. 3), HLA-DR expressing cells and macrophages which are mildly increased in number. The CD4+/CD8+ ratio is 0.5.³³ Mild to severe subepithelial fibrosis may be found in any of the three clinical phases.

For the conjunctival epithelium, the acute disease reveals marked infiltration with neutrophils and Langerhans cells. In chronic disease there is a similar cell profile to normal conjunctiva. T-cell infiltrate and upregulation of HLA-DR expression are not a feature of the epithelial disease. The epithelium may become thickened, metaplastic and may keratinise at any phase. Overall, the population of B-cells and plasma cells is no different to normal conjunctival epithelium or stroma at any stage of the disease.³³

Fibrosis results from the stimulation of fibroblasts, often by fibrogenic growth factors. When quiescent fibroblasts are stimulated to proliferate by these modulators, there is transient expression of proto-oncogenes, including *c-fos*, *c-myc* and *c-myb*. These are a series of genes that are transducers of external growth factors and probably trigger the activation of genes that are required for proliferation.⁴⁶ Experimentally, *c-fos* and *c-myc* are expressed after application of TGF- β , platelet-derived growth factor (PDGF), tumour necrosis factor (TNF) and interleukin 1 (IL-1).^{46,47,54} Conjunctival fibroblasts from patients with active cicatricial pemphigoid express *c-myc* *in vitro*.⁴⁸ This suggests that these fibroblasts have been stimulated

with a growth factor similar to the effect produced by TGF- β , PDGF, TNF or IL-1. This is consistent with immunohistochemical findings of raised levels of TGF- β in acute disease and of TGF- β , PDGF and fibroblast growth factor in subacute OCP.³³ The origin of these fibrogenic cytokines is unknown, but it is probable that they are produced by both acute and chronic inflammatory cell types.

CLINICAL RESPONSE TO SYSTEMIC DRUGS

Further insight into the mechanisms involved in fibrosis can be gleaned from the response to various drug treatments in OCP. Both dapsone^{25,37,49,50} and cyclophosphamide^{25,29,50} have been shown to reduce inflammation and impair or halt the progression of the fibrosis compared with untreated controls.

Dapsone is a sulphone and both inhibits the myeloperoxidase in polymorphonuclear leucocytes and stabilises lysosomal membranes. This reduces the release of lysosomal enzymes.⁵¹ It also suppresses migration of neutrophils to extravascular sites through inhibition of the adhesion required for neutrophil recruitment.⁵² Therefore, a response to dapsone is mainly due to inhibition of neutrophil recruitment and function.

Moderate doses of cyclophosphamide suppress both B-cell and CD4+ and CD8+ T-cells. This leads to a suppression of both T-cell-mediated and humoral responses.⁵³ Therefore fibrosis may be inhibited by suppressing any or all of these cell lines. This points to a complex set of mechanisms that are involved in the aetiology of the fibrosis in OCP. This is further complicated by the number of growth factors demonstrated by immunohistochemistry.³³ Further research is necessary to dissect in detail the mechanisms of cicatrization in these inflammatory processes. This would be expected to lead to much more effective therapeutic regimes that may have fewer systemic side effects.

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Key words: T-cells, Cicatricial pemphigoid, Conjunctiva, Fibrogenic cytokines, HLA-DR.

REFERENCES

1. Wright P. Cicatrizing conjunctivitis. *Trans Ophthalmol Soc UK* 1986;105:1–17.
2. Hall RP. The pathogenesis of dermatitis herpetiformis: recent advances. *J Am Acad Dermatol* 1987;16:1129–44.
3. Moschella SL, Pillsbury DM, Hurley HJ. *Dermatology*. Vol. 1. Philadelphia: WB Saunders, 1975:460–76.
4. Gruis NA, Bavinck JN, Steijlen PM, Schroeff JG van der, Haeringen A van, Happle R *et al*. Genetic linkage between the collagen VII (COL7A1) gene and the autosomal dominant form of dystrophic epidermolysis bullosa in two Dutch kindreds. *J Invest Dermatol* 1992;99:528–30.
5. Mooney E, Falk RJ, Gammon WR. Studies on complement deposits in epidermolysis bullosa acquisita and bullous pemphigoid. *Arch Dermatol* 1992;128:58–60.
6. McDonnell PJ, Schofield OM, Spalton DJ, Eady RA. Eye involvement in junctional epidermolysis bullosa. *Arch Ophthalmol* 1989;107:1635–7.
7. Richter HH, McNutt S. The spectrum of epidermolysis bullosa acquisita. *Arch Dermatol* 1979;115:1325–8.

8. Woodley DT, Briggaman RA, O'Keefe EJ, Inman AO, Queen LL, Gammon WR. Identification of the skin basement-membrane autoantigen in epidermolysis acquisita. *N Engl J Med* 1984;310:1007-13.
9. Yancey KB, Lawley TJ. The immunology of the skin. In: Middleton E, Reed CE, Ellis EF, editors. *Allergy: principles and practice*. St Louis: Mosby, 1988:206-23.
10. Zierhut M, Theil HJ, Weidle EG, Steudhl KP, Sonnichsen K, Schaumburg-Lever G. Ocular involvement in epidermolysis bullosa acquisita. *Arch Ophthalmol* 1989;107:398-401.
11. Bean SF, Halubar K, Gillett RB. Pemphigus involving the eyes. *Arch Dermatol* 1975;111:1484-6.
12. Grando SA, Terman AK, Stupina AS, Glukhenky BT, Romanenko AB. Ultrastructural study of clinically uninvolved skin of patients with pemphigus vulgaris. *Clin Exp Dermatol* 1991;16:359-63.
13. Judd K, Lever W. Correlation of antibodies in skin and serum with disease severity in pemphigus. *Arch Dermatol* 1979;115:428-32.
14. Kaplan R, Callen J. Pemphigus associated diseases and induced pemphigus. *Clin Dermatol* 1983;1:42-71.
15. Korman N. Pemphigus. *J Am Acad Dermatol* 1988;18:1219-38.
16. Moy R, Jordan R. Immunopathology in pemphigus. *Clin Dermatol* 1983;1:72-83.
17. Venning V, Frith P, Bron A, Millard P, Wojnarowska F. Mucosal involvement in bullous and cicatricial pemphigoid: a clinical and immunopathological study. *Br J Dermatol* 1988;118:7-15.
18. Fine JD, Neises GR, Katz SI. Immunofluorescence and immunoelectron microscope studies in cicatricial pemphigoid. *J Invest Dermatol* 1984;82:39-43.
19. Zillikens D, Ambach A, Schuessler M, Dummer R, Hartmann AA, Burg G. The interleukin-2 receptor in lesions and serum of bullous pemphigoid. *Arch Dermatol Res* 1992;284:141-5.
20. Stanley JR. Bullous pemphigoid. In: Jegasothy BV, Lazarus GS, editors. *Symposium on blistering disease. Dermatologic clinics*. Philadelphia: WB Saunders, 1983:205-16.
21. Stanley JR, Woodley D, Katz S. Identification and partial characterisation of pemphigoid antigen extracted from normal human skin. *J Invest Dermatol* 1984;82:108-11.
22. Regnier M, Vaigot P, Michel S, Prunieras M. Location of bullous pemphigoid antigen in isolated human keratinocytes. *J Invest Dermatol* 1985;85:187-90.
23. Hardy KM, Perry HO, Pingree GC. Benign mucous membrane pemphigoid. *Arch Dermatol* 1971;104:467-75.
24. Foster CS, Wilson LA, Ekins MB. Immunosuppressive therapy for progressive ocular cicatricial pemphigoid. *Ophthalmology* 1982;89:340-53.
25. Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol soc* 1986;84:527-663.
26. Mondino BJ, Brown SI. Ocular cicatricial pemphigoid. *Ophthalmology* 1981;88:95-100.
27. Lever WF. Pemphigus and pemphigoid: a review of the advances made since 1964. *J Am Acad Dermatol* 1979;1:2-31.
28. Ahmed AR, Foster S, Zaltas M, Notani G, Awdeh Z, Alper CA, Yunis EJ. Association of DQw7 (DQB1*0301) with ocular cicatricial pemphigoid. *Proc Natl Acad Sci USA* 1991;88:11579-82.
29. Mondino BJ. Cicatricial pemphigoid and erythema multiforme. *Ophthalmology* 1990;97:939-52.
30. Mondino BJ, Brown SI, Rabin BS. Autoimmune phenomenon of the external eye. *Trans Am Acad Ophthalmol* 1978;85:801.
31. Mondino BJ, Brown SI, Lempert S, Jenkins MS. The acute manifestations of ocular cicatricial pemphigoid: diagnosis and treatment. *Ophthalmology* 1979;86:543-52.
32. Mondino BJ, Ross AN, Rabin BS, Brown SI. Autoimmune phenomena in ocular cicatricial pemphigoid. *Am J Ophthalmol* 1977;83:443-50.
33. Bernauer W, Wright P, Dart JKG, Leonard JN, Lightman S. The conjunctiva in acute and chronic mucous membrane pemphigoid: an immunohistochemical analysis. *Ophthalmology* 1993;100:339-46.
34. Dabelsteen E, Ullman S, Thomsen K. Demonstration of basement membrane autoantibodies in patients with benign mucous membrane pemphigoid. *Acta Derm Venereol* 1974;54:189-92.
35. Franklin RM, Fitzmorris CT. Antibodies against conjunctival basement membrane zone. *Arch Ophthalmol* 1983;101:1611-13.
36. Leonard JN, Hobday CM, Haffenden GP. Immunofluorescent studies in ocular cicatricial pemphigoid. *Br J Dermatol* 1988;118:209-17.
37. Person JR, Rogers RS III. Bullous and cicatricial pemphigoid: clinical, histopathologic, and immunopathologic correlations. *Mayo Clin Proc* 1977;52:54-66.
38. Waltman SR, Yarian D. Circulating autoantibodies in ocular pemphigoid. *Am J Ophthalmol* 1974;77:891-94.
39. Niimi Y, Zhu XJ, Bystryjn JC. Identification of cicatricial pemphigoid antigens. *Arch Dermatol* 1992;128:54-7.
40. Rice BA, Foster CS. Immunopathology of cicatricial pemphigoid affecting the conjunctiva. *Ophthalmology* 1990;97:1476-83.
41. Jordan RE, Schroeter AL, Good RA. The complement system in bullous pemphigoid. II. Immunofluorescent evidence for both classical and alternate-pathway activation. *Clin Immunol Immunopathol* 1975;3:307-14.
42. Holubar K, Wolff K, Konrad K. Ultrastructural localization of immunoglobulins in bullous pemphigoid skin. *J Invest Dermatol* 1975;64:220-27.
43. Diaz LA, Calvanico NJ, Tomasi TB. Bullous pemphigoid antigen: isolation from normal human skin. *J Immunol* 1977;118:605-8.
44. Sacks EH, Wiecek R, Jakobiec FA, Knowles DM. Lymphocytic subpopulations in the normal human conjunctiva: a monoclonal antibody study. *Ophthalmology* 1986;93:1276-83.
45. Roat MI, Sossi G, Thoft RA. Hyperproliferation of conjunctival fibroblasts from patients with cicatricial pemphigoid. *Arch Ophthalmol* 1989;107:1064-7.
46. Liboiron E, Pelosi E, Di Francesco P, Gallanari P, Petrini M, Sposi NM. The EL2 rat fibroblast line: differential effects of growth factors (EGF, PDGF, FGF, TPA and TGF- β) on cell proliferation and *c-fos* expression. *Ann NY Acad Sci* 1987;511:318-28.
47. Muller R, Bravo R, Burckhardt J, Curran T. Induction of *c-fos* gene and protein by growth factors precedes activation of *c-myc*. *Nature* 1984;312:716-20.
48. Hunt LE, Vergnes JP, Roat MI. Altered proto-oncogene expression by conjunctival fibroblasts in cicatricial pemphigoid. *Invest Ophthalmol Vis Sci* 1991;32(Suppl):938.
49. Rogers RS III, Seehafer JR, Perry HO. Treatment of cicatricial (benign mucous membrane) pemphigoid with dapsone. *J Am Acad Dermatol* 1982;6:215-23.
50. Tauber J, Jabbur N, Foster CS. Improved detection of disease progression in ocular cicatricial pemphigoid. *Cornea* 1992;11:446-51.
51. Lang PG. Sulfones and sulfonamides in dermatology today. *J Am Acad Dermatol* 1979;1:479-92.
52. Booth SA, Moody CE, Dahl MV, Herron MJ, Nelson RD. Dapsone suppresses integrin-mediated neutrophil adherence function. *J Invest Dermatol* 1992;98:135-40.
53. Gilman AG, Goodman LS, Rall TW, Murad F. The pharmacological basis of therapeutics. New York: Macmillan, 1985.
54. Lin JX, Vilcek J. Tumour necrosis factor and interleukin-1 cause a rapid and transient stimulation of *c-fos* and *c-myc* mRNA levels in human fibroblasts. *J Biol Chem* 1987;262:11908-11.