

Progression of disease in ocular cicatricial pemphigoid

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Abstract

Background—Ocular cicatricial pemphigoid (OCP) is a sight threatening autoimmune disease that can lead to severe conjunctival cicatrization and keratopathy. It has a variable course and little is known about the factors that determine disease progression. This study analysed the factors that have prognostic significance regarding disease outcome, progression, and keratopathy.

Methods—Sixty six patients with OCP were monitored prospectively at Moorfields Eye Hospital. The influence of ocular features, the systemic disease, and the management were analysed to identify factors that influence the outcomes and disease progression.

Results—The mean age at presentation was 67 years; 56% were men. The binocular visual acuities were 6/24 or worse in 25%. Extensive cicatrization at presentation was common but correlated only weakly with the visual prognosis. Systemic manifestations included lesions of the mouth in 44%, pharynx in 30%, oesophagus in 27%, nose/sinus in 18%, and skin in 17%. There was no association between the ocular and systemic manifestations. Persistent corneal epithelial defects and limbitis occurred in 18% and 32%, respectively, and both were associated with a worse visual prognosis. Systemic immunosuppression was ultimately prescribed in 74%, mainly in patients with advanced stages of conjunctival cicatrization. Of patients with more than 24 months follow up, progression of cicatrization occurred in 35% of eyes (16/46) all but one of which were associated with episodes of conjunctival inflammation.

Conclusions—Persistent epithelial defects, limbal inflammation, and ongoing conjunctival inflammation are important factors that lead to keratopathy and visual handicap. These require aggressive management, often with systemic immunosuppressive treatment. Close follow up is required in cases with extensive cicatrization.

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Ocular cicatricial pemphigoid (OCP) is an inflammatory and cicatrizing disease of the conjunctiva and mucous membranes that causes severe visual handicap in up to one third of patients.¹ The disease is characterised by the abnormal binding of immunoglobulins to the

basement membranes of the skin and mucous membranes.^{2–4} Acutely, this causes complement activation and infiltration of the conjunctiva by neutrophils, macrophages, and activated T cells.^{5–7} The scarring is a consequence of this. The key ocular features are the conjunctival fibrosis and the keratopathy. Once these have occurred, the prognosis for visual of rehabilitation is poor and, therefore, the prevention of disease progression is important.⁸ This study presents data from a prospective study of a large cohort of patients and analyses the factors that have prognostic significance regarding disease progression and the keratopathy. These data may improve management and allow more appropriate follow up.

Materials and methods

Patients attending the corneal and external disease clinics of Moorfields Eye Hospital were assessed prospectively and the data recorded. OCP was diagnosed on the characteristic clinical and laboratory features. Other causes of cicatrization, such as previous infection or drug associated cicatrization, were excluded. Conjunctival biopsy was performed on all but nine patients and was defined as positive if there was immunostaining showing linear basement membrane deposition of IgG, IgA, or complement as demonstrated by immunofluorescence on frozen sections.^{3,4} This technique reveals no staining of the basement membrane of conjunctiva and skin from patients without OCP.^{3,4}

Each eye was staged using both Mondino's^{3,9,10} and Foster's¹¹ classification systems. Mondino's classification quantifies inferior fornix depth loss; stage II is a reduction of 25–50%, stage III, 50–75%. Normal depth is approximately 11 mm.¹² Foster's staging uses specific clinical signs; stage II – any fornix shortening, stage III – symblepharon, stage IV – ankyloblepharon. Data in this study extend from October 1991 to October 1994 and include patient characteristics, visual acuities, specific ocular findings, systemic features, and patient management.

Progression of disease was defined as a shift from one stage to another and was assessed in a cohort of patients with 24 months or more of follow up. For all patients, the ocular and systemic features were correlated with the final outcomes of visual acuity and the amount of cicatrization. The visual acuity data were from the last clinic assessment in order to exclude the effects of acute disease. If there was an acute or subacute cause for reduced visual acuity, then the acuity was recorded from the

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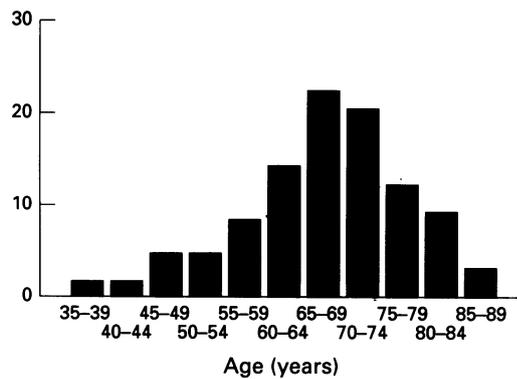


Figure 1 Age at initial presentation.

contiguous, preceding visit when the problem was not present. Visual acuity was classified into the WHO definitions of 'visual impairment' (>6/18-6/60), 'severe visual impairment' (>6/60), and 'blind' (>3/60). All χ^2 tests used Yates's correction.

Particular regard was given to any associations with corneal disease. A quantitative assessment of the degree of chronic corneal involvement was made from the visual acuity after all cases with non-corneal causes of reduced visual acuity were excluded. Specific acute or subacute corneal problems were persistent epithelial defects (PED), limbitis, and acute microbial keratitis. PED was defined as an area of cornea that was not covered by epithelium for 1 month or more, despite treatment. This did not include punctate epithelial keratopathy. Limbitis was defined as a raised, inflamed region involving the limbal tissues extending for one quadrant or more. To assess whether limbitis was associated with any of the specific systemic manifestations of ocular cicatricial pemphigoid, the patients were divided into those that had bilateral limbitis and those that had never had limbitis in either eye.

Results

This study reports data from 132 eyes of 66 patients of whom the mean age (SD) was 67.1 (10.9) years and ranged from 37-88 years. The male:female ratio was 37:29 (1.3:1). The age at presentation, visual acuities, and stages of disease are detailed in Figures 1 and 2 and Table 1. Conjunctival biopsies were obtained from 57/66 patient and were positive in 54% (31/57). The bound products were IgA 74% (33/31), IgG 42% (13/31), complement C3 52% (16/31), fibrinogen 42% (13/31), and

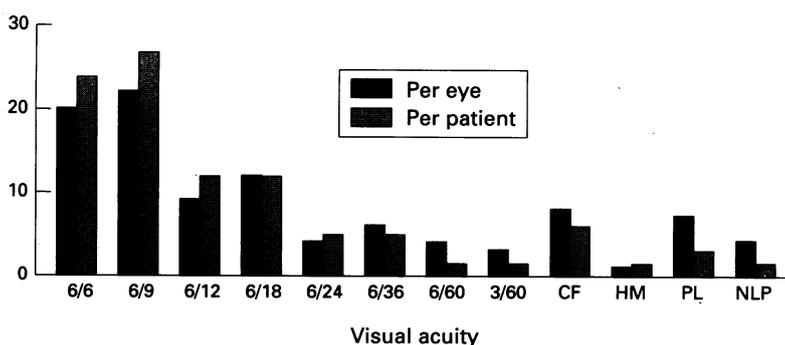


Figure 2 Visual acuity per eye and per patient at initial presentation.

IgM 13% (4/31). This compares with biopsies of non-lesional skin of 50%, 33%, 17%, 0%, 17% respectively from 12 of these patients. Thirteen patients had reduced visual acuity caused by pathology other than corneal disease; cataract (n=6), macular degeneration (n=4), glaucoma (n=2), and amblyopia (n=1). These patients were excluded in the assessment of associations with corneal disease.

For Foster's staging system, the proportion of eyes classified as stages I-IV were 2%, 33%, 61%, and 14% respectively (Table 1). Those eyes that were stage IV had a worse visual acuity than stage III for visual impairment and severe visual impairment (χ^2 , $p=0.003$ and $p=0.0001$, 95% confidence intervals (CI), 1.1-1.8 and 1.3-2.7). For Mondino's staging system, the proportion of eyes classified as stages I-IV were 4%, 20%, 34%, and 42% respectively (Table 1). There was no statistical association between any stage and the visual acuity. However, there was a trend between stage IV and blindness (χ^2 , $p=0.06$, 95% CI=0.96-3.7). For corneal disease solely, there were statistically significant differences between Foster's stage III and IV at both the level of visual impairment and severe visual impairment (χ^2 , $p=0.001$, $p=0.0001$, 95% CI 1.1-2.0 and 1.3-3.6). For Mondino's stage III and IV, there was a trend at the level of severe visual impairment (χ^2 , $p=0.052$, 95% CI 0.97-4.9).

The ocular manifestations occurred in 100% of patients and systemic manifestations occurred in 50%. These included lesions of the mouth 44%, pharynx 30%, nose/sinus 18%, oesophagus 27%, anus 5%, vagina 5%, and skin 17%. There was no statistically significant association between the prevalence of systemic manifestations of OCP and the visual acuity of each patient (χ^2 , $p>0.05$), nor was there an association between the systemic manifestations and visual acuity reduced solely because of corneal disease (n=53, $p>0.05$).

Systemic immunosuppressive drugs were required in 74% of patients (49/66) at some stage of the disease. This was because of an inadequate response to topical immunosuppression and management of the ocular surface disease or because of moderate or severe inflammation.^{13 14} Agents used included prednisolone (30%, 20/66), cyclophosphamide (17%, 11/66), azathioprine (5%, 3/66), dapsone (15%, 19/66), sulphapyridine (33%, 22/66), and sulphamethoxypyridazine (12%, 8/66). Two additional patients were on steroids other than for OCP (Crohn's disease (one) and rheumatoid arthritis (one)). The group of patients who did not require systemic immunosuppression (26%, 17/66) had a mean age (SD) of 67.1 (13.6) years with a range 42-88 years. The comparison of the patients that did and those that did not require systemic immunosuppression is given in Tables 2 and 3. There was no statistically significant difference between the two groups regarding their ultimate visual acuity or the prevalence of the systemic manifestations of OCP. However, 62% of those who did not require systemic

Table 1 Ultimate visual acuity and the ocular staging (per eye)

Staging	Visual acuity				Total
	6/6*-6/18	6/24-6/60	>6/60-3/60	>3/60	
Foster's stages					
I	2 (67%)	-	-	1 (33%)	3
II	23 (77%)	5 (17%)	1 (3%)	1 (3%)	30
III	53 (66%)	13 (16%)	3 (4%)	11 (14%)	80
IV	5 (26%)	-	-	14 (74%)	19
Mondino's stages					
I	5 (100%)	-	-	-	5
II	20 (77%)	4 (15%)	1 (4%)	1 (4%)	26
III	27 (60%)	9 (20%)	2 (4%)	7 (16%)	45
IV	31 (55%)	5 (9%)	1 (2%)	19 (34%)	56
Total	83 (63%)	18 (14%)	4 (3%)	27 (20%)	132

*Best corrected visual acuity.

treatment were stage II or less compared with 10% of the treated group. Only 15% of the untreated group ended up as stage IV compared with 52% of the treated group. This is statistically significant ($p > 0.001$). Compared with patients who are stage III or IV, if a patient is stage I or II, then the relative risk of not requiring systemic immunosuppression at some stage in the disease is $4.4 \times$ (95% CI; 2.5-7.9) and $6.1 \times$ (95% CI; 3.2-11.5) for Foster's and Mondino's staging respectively.

Forty six eyes of 23 patients had follow up of 24 months or more (mean (SD), 27 (3.2) months, range 24-36 months). Follow up for less than 24 months was because of death ($n=5$), 'too frail to attend the hospital' ($n=4$), referral back to the original physician ($n=9$), and follow up for less than 24 months ($n=25$). Progression occurred in 35% of eyes (16/46) and in 43% of patients (10/23). Using Mondino's staging system, the number of these eyes that were stage I-IV were 1, 10, 18, and 17, respectively. Progression occurred in 7/10 stage II eyes and 9/18 stage III eyes. Using Foster's staging system, the number of eyes that were stage I-IV were 0, 3, 41, and 2, respectively. Progression occurred in 2/3 stage II eyes only. Fifteen of the 16 eyes progressed during episodes of conjunctival inflammation. This was related to corneal incision cataract surgery while not on systemic immunosuppression ($n=1$), treatment with topical steroids alone ($n=1$), recurrence after stopping dapsone ($n=1$), still being treated with dapsone ($n=9$), and still being treated with cyclophosphamide ($n=3$). Therefore, 12/16 eyes progressed while on oral immunosuppression.

CORNEAL COMPLICATIONS OF OCP

Persistent epithelial defects (PED) occurred in 12/66 patients (18%) and in 17/132 eyes

(13%) at some stage during the disease. Using Mondino's staging, four eyes were stage II, three eyes were stage III, and 10 eyes were stage IV; hence 10/17 eyes with PED had less than 3 mm of inferior fornix. The PED occurred in 8/12 patients and 11/17 eyes while they were on systemic immunosuppression. This included regimens such as 5-30 mg of prednisolone, dapsone, sulphapyridine, azathioprine, cyclophosphamide, and combinations of the above. One eye had a PED associated with rapidly recurrent trichiasis and 6/17 eyes had a previous episode of limbitis. There were no other predisposing factors. Only 3/17 eyes were on topical steroids at the time. The final visual outcomes of these eyes were assessed 6 months after epithelial healing ($n=17$). This time was sufficient to allow visual rehabilitation but insufficient to allow disease progression to further impair the visual acuity. Only 4/17 eyes had an acuity of 6/60 or better (6/36, 6/9, 6/6, 6/6). One patient, with long standing glaucomatous optic atrophy had no perception of light after acute penetrating keratoplasty. Bacterial keratitis occurred in three eyes of three patients, with one patient having another episode in the same eye 6 months later. One eye perforated and required acute keratoplasty while all the others responded to intensive topical antibiotics.

Bilateral limbitis occurred in 16/66 (24%) patients and unilateral limbitis occurred in 5/66 (8%). This represented 37/132 (28%) of eyes. The results of the ultimate visual acuity and the occurrence of an episode of limbitis are detailed in Table 4. There is a statistically significant association between having an episode of limbitis and having a poorer final visual outcome in that eye (χ^2 , $p > 0.001$). There was no statistically significant difference between the prevalence of the systemic manifestations of OCP among those patients who developed bilateral limbitis and those who did not (χ^2 , $p = 0.05$).

Discussion

This study demonstrates the spectrum of disease in a population of patients with OCP and examines the natural history in a subgroup of patients with 2 or more years of follow up. The current staging systems correlate poorly with corneal disease that leads to visual loss. Table 1 shows that Mondino's system has a more uniform distribution of patients per stage. This would be expected as it is based on the inferior fornix depth which is a continuous variable whereas Foster's system is based on

Table 2 Ultimate visual acuity for those who did and did not receive systemic immunosuppression

Visual acuity	No systemic treatment (per eye)	Systemic treatment (per eye)	Total	No systemic treatment (per patient)	Systemic treatment (per patient)	Total
6/6*-6/18	26	57	83	16	34	50
>6/18-6/60	4	14	18	-	7	7
>6/60-3/60	-	4	4	-	1	1
>3/60	4	23	27	1	7	8
Total	34	98	132	17	49	66

*Best corrected visual acuity.

CF=counting fingers; HM=hand movements; PL=perception of light; NPL=no perception of light; WHO definitions; visual impairment >6/18-6/60, severe visual impairment >6/60-3/60, blind >3/60.

Table 3 Ultimate amount of cicatrization for those who required systemic immunosuppression compared with those that did not

Stage	Foster's staging			Mondino's staging		
	No systemic treatment	Systemic treatment	Total	No systemic treatment	Systemic treatment	Total
I	2 (6%)	1 (1%)	3 (2%)	4 (12%)	1 (1%)	5 (4%)
II	18 (53%)	12 (12%)	30 (23%)	17 (50%)	9 (9%)	26 (20%)
III	11 (32%)	69 (70%)	80 (61%)	8 (23%)	37 (38%)	45 (34%)
IV	3 (9%)	16 (17%)	19 (14%)	5 (15%)	51 (52%)	56 (42%)
Total	34 (100%)	98 (100%)	132 (100%)	34 (100%)	98 (100%)	132 (100%)

signs such as symblepharon (stage III) and ankyloblepharon (stage IV). Ankyloblepharon is clearly uncommon compared with symblepharon (14% versus 61%). Of Foster's stages I-IV, the percentage of eyes with severe visual impairment or blindness per stage was 33%, 6%, 18%, and 74% and, therefore, ankyloblepharon is associated with a poorer visual acuity whereas symblepharon is not. For Mondino's stages I-IV severe visual impairment or blindness occurred in 0%, 8%, 20%, and 36% of eyes, respectively. For example, an eye with a fornix less than 3 mm deep has an acuity of 6/18 or better in 55%. Therefore, there is a weak trend between a shallower inferior fornix and an impaired visual acuity although this was not statistically significant. This illustrates that the visual acuity may be maintained despite marked conjunctival shrinkage.

In addition there is no correlation between systemic manifestations of pemphigoid and visual loss. The reason for this is unclear and invites speculation. OCP is a basement membrane disease affecting both mucous membrane and skin. However, the corneal disease is unrelated to the various non-ocular manifestations and only weakly related to conjunctival cicatrization. This may be due to antigenic differences between the tissues, or the corneal pathophysiology may be relatively independent of the immune driven basement membrane disease.

The development of limbitis is a poor prognostic sign of visual loss secondary to corneal disease. This has not been previously reported and can lead to visual loss secondary to corneal epithelial dysplasia. Therefore, limbitis demands aggressive therapy and this typically requires cyclophosphamide and high doses of prednisolone rather than sulphapyridine or dapson. ¹³ Limbitis was not associated with any of the systemic manifestations of OCP. This is consistent with the lack of correlation between the systemic manifestations of OCP and the visual acuity and it would appear that limbitis is an isolated ocular phenomenon.

Persistent epithelial defects were common (13%) and were a major risk factor for poor visual acuity and ocular morbidity. It was particularly associated with very shallow fornices –

59% had less than 3 mm of inferior fornix. Seventy six per cent of eyes ultimately had a visual acuity of less than 6/60 and 12% perforated acutely, despite most of these patients being on systemic immunosuppressive drugs. Microbial keratitis occurred in 3% of eyes with perforation occurring in 0.8%. In another series, Ormerod *et al*¹⁵ reported a 10% prevalence of keratitis for which the risk factors were trichiasis (52%), topical steroid use (27%), therapeutic contact lenses (18%), 'inadvertent surgical management' (18%), and lagophthalmos (12%); the major complications included perforation (4/33, 12%), endophthalmitis (2/33, 6%), and reinfection (5/33, 15%). The incidence of keratitis is significantly higher in this series ($p=0.03$, χ^2 with Yates's correction) although the patient profile and severity of disease is similar. There is no adequate explanation for these differences.

Overall, 26% of patients with OCP did not require systemic immunosuppression. This subgroup was similar to the treated group with respect to age, duration of follow up, ultimate visual acuities, and the systemic manifestations of OCP. Therefore, these criteria cannot be used to predict whether a patient may require immunosuppression at some stage of the disease. However, there were large differences in the amount of cicatrization between the groups. For example, 62% of the group who never required immunosuppression were Mondino's stage I or II compared with only 10% of the treated group (Table 3). Similarly, for Foster's staging, 87% of the treated group had symblepharon (stage III) compared with 41% of the untreated subgroup. These data are clinically useful. Patients who present with symblepharon are ultimately more likely to need systemic immunosuppression (87% versus 41%, 2.1 \times), as are patients who present with lower fornices less than 5.5 mm deep (90% versus 38%, 2.3 \times). These groups probably have more rapidly progressive disease and a worse prognosis which accounts for their relatively advanced conjunctival shrinkage at presentation. Patients without symblepharon may have such slowly progressive disease that there will be no significant morbidity in their lifetime and, therefore, no justifying risks associated with current immunosuppressive regimens, both topical and systemic.

Using Mondino's staging system, 70% of stage II eyes and 50% of stage III eyes progressed ($n=7$ and 9). Foster's staging system was not helpful in detecting progression; only 2/46 eyes changed stages. For untreated patients, Mondino has reported similar progression in stage I 40–50%, stage II 62–75%,

Table 4 Limbitis and the resulting visual acuity (per eye)

Visual acuity	Bilateral limbitis	No limbitis
Better than 6/18	15/37 (41%)	71/95 (74%)
>6/18–6/60	6/37 (16%)	12/95 (13%)
Worse than 6/60	16/37 (43%)*	12/95 (13%)
Total	37/37 (100%)	95/95 (100%)

*Statistically significant, $p<0.001$.

and stage III 73–78%^{9 16} whereas for patients treated with oral cyclophosphamide this was 25%, 10%, and 75%, respectively.¹⁶ Although patients with advanced disease require immunosuppression for inflammation more commonly than early disease, patients presenting with early disease have been shown to progress in this study and in others.^{9 16} It is probable that some patients with early disease, but without overt signs of inflammation, may progress and may benefit from immunosuppression as prophylaxis. This would require specific methods of monitoring disease activity.

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