Characteristics of patients with ocular cicatricial pemphigoid referred to major tertiary hospital

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ABSTRACT • RÉSUMÉ

Objective: To evaluate the demographic and clinical characteristics of patients referred to a tertiary care hospital cornea clinic for ocular cicatrical pemphigoid (OCP) assessment.

Methods: Database search of patients from 2003 to 2012 with a referral request or diagnosis of OCP was conducted at a tertiary care hospital cornea clinic. Charts of 33 patients (64 eyes) were reviewed. Outcome measures included patient demographics, methods of diagnosis, visual acuity, ocular features, and disease staging using Foster’s staging system, systemic modes of treatment, disease progression, and presence of systemic involvement.

Results: Mean patient age at presentation was 69.8 years (range 40–91), and 81% (27/33) were female. At presentation, disease staging consisted of stage I (subepithelial fibrosis) 7.8% (5/64), stage II (shortened fornices) 21.8% (14/64), stage III (symblepharon formation) 65.6% (42/64), and stage IV (keratinization with or without globe immobility) 4.6% (3/64). At the final follow-up visit, the proportions of the involved eyes for stages I to IV were 1.5% (1/64), 10.9% (7/64), 76.5% (49/64), and 10.9% (7/64), respectively. Conjunctival biopsies were obtained from 81% (27/33) of patients and reported as positive in 30% (8/27), negative in 63% (17/27), and inconclusive in 7% (2/27) of patients. Mean duration of follow-up was 6.8 ± 5.6 years (range 0.5–22), and 66.6% (22/33) of patients had progressive disease. Systemic mucocutaneous involvement was noted in 36.3% (12/33) of patients.

Conclusions: The high rate of disease progression suggests the need for improved therapeutic options. Additional modalities are needed in addition to conjunctival biopsy to confirm a diagnosis of OCP in patients with clinical signs of the disease.

Objet : Évaluer les caractéristiques démographiques et cliniques des patients dirigés vers la clinique de la cornée d’un hôpital de soins tertiaires pour l’évaluation d’une pemphigoïde oculaire cicatricielle (POC).

Nature : Étude de cas rétrospective, non randomisée et consécutive.

Méthodes : Nous avons cherché dans des bases de données des patients qui, entre 2003 et 2012, ont été dirigés vers une clinique de la cornée d’un hôpital tertiaire pour confirmer un diagnostic de POC. Les données concernant 33 patients (64 yeux) ont été analysées. L’analyse a porté sur les éléments suivants : renseignements sur le patient, méthode de diagnostic, acuité visuelle, caractéristiques oculaires et stade de la maladie selon la classification de Foster, modes systémiques de traitement, progression de la maladie, manifestation systémique.

Résultats : L’âge médian des patients à la consultation était de 69,8 ans (de 40 à 91 ans), et 81 % (27/33) étaient des femmes. À la consultation, la maladie était aux stades suivants : stade-I (fibrose sous-épithéliale) 7,8 % (5/64); stade-II (fornix raccourci) 21,8 % (14/64); stade-III (formation d’un symblépharon) 65,6 % (42/64); stade-IV (kératinisation +/- immobilité du globe oculaire) 4,6 % (3/64). À la dernière visite de suivi, la maladie était rendue aux stades suivants (de I à IV respectivement) : 1,5 % (1/64); 10,9 % (7/64); 76,5 % (49/64) et 10,9 % (7/64). Des biopsies conjonctivales ont été pratiquées chez 81 % (27/33) des patients ; les résultats étaient positifs dans 30 % (8/27) des cas, négatifs dans 63 % (17/27) des cas, et non concluants dans 7 % (2/27) des cas. La durée moyenne du suivi était de 6,8 ± 5,6 années (de 0,5 an à 22 ans), et la maladie était évolutive chez 66,6 % (22/33) des patients. Une manifestation cutanéo-muqueuse systémique a été signalée chez 36,3 % (12/33) des patients.

Conclusion : Le taux élevé de cas de progression de la maladie porte à croire qu’il est nécessaire d’améliorer les options thérapeutiques. Des modalités supplémentaires sont nécessaires, outre la biopsie conjonctivale, pour confirmer un diagnostic de POC chez des patients présentant des signes cliniques de la maladie.
keratinization. Early recognition, diagnosis, and treatment aiming to prevent further disease progression are crucial. The comprehensive ophthalmologist is frequently the first to assess these patients. Knowledge of the clinical presentation and timely referral to tertiary cornea clinics can assist in the prompt and proper management of these difficult eyes. The aim of this study was to describe the geographic distribution, clinical status, diagnostic modalities, treatment strategies, and outcomes of patients with OCP who presented to a large tertiary care hospital cornea clinic in Canada.

**METHODS**

This retrospective, observational case series received Research Ethics Board approval by the University Health Network, Toronto Western Hospital, Toronto, Ontario, Institutional Review Board (IRB 13-6208-BE). This study was conducted in compliance with the tenets of the Declaration of Helsinki.

Database search of patients from 2003 to 2012 with a referral request or diagnosis of OCP was conducted at a tertiary care hospital cornea clinic (Toronto Western Hospital). Charts of 33 patients (64 eyes) were retrospectively reviewed. Outcome measures included patient demographics, methods of diagnosis, visual acuity, ocular features and disease stage, topical and systemic modes of treatment, disease progression, and presence of systemic involvement. The parameters from the patients’ first and last clinic visits were compared.

For the purposes of disease staging, Foster’s classification system was used (stage I: subconjunctival scarring and fibrosis; stage II: fornix shortening; stage III: symblepharon; stage IV: ankyloblepharon). Disease progression was defined as an increase in clinical staging. Diagnosis of OCP was based on the characteristic clinical findings with confirmation by conjunctival biopsy for direct immunofluorescence testing. Positive biopsy results included linear deposition of immunoglobulins A, G, or M, or of complement C3 along the basement membrane. In patients with characteristic clinical findings but negative biopsy results, the diagnosis of OCP was presumed based on the presence of clinical features, active conjunctival inflammation, and documented disease progression.

**RESULTS**

Data were collected from 64 eyes of 33 patients (27 females, 6 males). The mean age at presentation was 69.8 (SD 11.9, range 40–91) years. Figure 1 shows the distribution of patient ages at time of presentation. On average, it took 4.2 (range 0–21) years from the onset of patient symptoms to referral. Mean follow-up time was 6.8 ± 5.6 (range 0.5–22) years. The mean age at presentation for those who progressed with the disease was older than those who remained stable (71 vs 63, p = 0.048).

Figure 2 presents the geographical distribution of patients referred. The majority of patients came from the Greater Toronto area, although the farthest referral presented from Cobalt, Ontario, situated 490 km from our hospital.

All but 2 patients had bilateral involvement at the time of initial presentation. Visual acuities in the involved eye during the first and last visits are presented in Figure 3. Four of 64 eyes (6.2%) lost light perception during the follow-up period. Conjunctival inflammation was noted in 55% (18/33) of patients at presentation and in 52% (17/33) of patients at the final visit. Trichiasis was noted in 43.9% (29/64) of eyes from 17 patients (12 patients presented with bilateral trichiasis and 5 with unilateral).

Systemic mucocutaneous involvement was noted in 35.2% (12/33) of patients. A total of 26.4% (9/33) of patients had oral involvement and 11.7% (4/33) had skin involvement. One patient had both oral and skin areas involved.

Conjunctival biopsies were obtained from 81% (27/33) of patients and reported as positive in 30% (8/27), as
negative in 63% (17/27), or as inconclusive in 7% (2/27) of patients.

At the time of referral, systemic immunomodulatory treatment was used in 27% (9/33) of patients. During the follow-up period, a total of 75.7% (25/33) of patients were treated using immunomodulatory agents (see Table 1). These drugs were used either consecutively or concomitantly at some stage of the follow-up period. One patient suffered from seronegative rheumatoid arthritis as well and was treated by systemic immunosuppressive drugs for that reason. During the follow-up period, 30.3% (10/33) of patients underwent a trial of topical steroids, and 15.1% (5/33) underwent a trial of topical cyclosporine 0.5% drops.

Figure 4 presents stages of disease at presentation and on the last visit. At presentation the proportions of patients at each disease stage were: stage I, 7.8%; stage II, 21.8%; stage III, 65.6%; and stage IV, 4.6%. At the final visit, the proportions of the involved eyes for stages I to IV were 1.5%, 10.9%, 76.5%, and 10.9%, respectively. Overall, 66.6% (22/33) of patients progressed to a more advanced stage. Fifty-nine percent (13/22) of patients who demonstrated disease progression had conjunctival inflammation. Of these patients, whereas 4 had clinical improvement in conjunctival inflammation, 2 showed clinical stability and 2 others had disease progression. Two additional patients had an increase in conjunctival inflammation noted during follow-up and progressed clinically. Table 2 summarizes the distribution of visual acuities at different Foster’s stages at presentation and at the final visit.

**DISCUSSION**

This study has described the general characteristic features of patients with OCP presenting to a tertiary care hospital cornea clinic.
hospital cornea clinic. Patient age at presentation was from 40 to 90 years, with an average of 70 years, similar to previously described studies. A strong female preponderance was noted in agreement with previously reported observations.

Visual acuity did not show a direct correlation with disease staging and progression. We noted more patients with severe visual impairment at the ankyloblepharon stage 4. However, some patients retained good visual acuity even with progressive conjunctival scarring. Visual impairment directly caused by OCP usually results from corneal damage. The combination of chronic inflammation and conjunctival fibrosis leading to severe meibomian gland dysfunction and tear abnormalities with mechanical trauma from keratinization of eyelid margins and eyelash disorganization all lead to corneal mutilation. The significance of ample lubrication and trichiasis care with aberrant eyelash removal, although only providing temporary relief and not being curative, should be emphasized. Visual outcomes also do not correlate directly with severity of OCP because of the concurrent comorbidities that exist in this patient population of eyes. This predominantly elderly population often has other ocular conditions, such as glaucoma, cataract, and age-related macular degeneration, which further jeopardize visual acuity.

The rate of positive conjunctival biopsies in our study was relatively low, being 30% of the examined patients. The rate of positive biopsies varies in different studies from 20% to 87%. Performing both conjunctival and buccal mucosal biopsies has been reported to help increase the yield for a positive result, which could be a consideration going forward.

Direct immunofluorescence technique was used at our centre, and when the biopsy was negative, the diagnosis was based on the classical clinical picture in the affected eyes. Although the recommended gold standard for OCP diagnosis is a combination of clinical and immunopathologic studies, some reports described ocular patients who have ocular features consistent with OCP but without a positive biopsy finding. We did not use immunoperoxidase staining with supplemental avidin-biotin complex methodology, which has been shown to be a more sensitive diagnostic method.

Adding immunoperoxidase testing for our diagnostic

Table 2—Visual acuity of eyes with ocular cicatricial pemphigoid according to Foster’s Staging System at presentation to a tertiary care hospital cornea clinic compared to at the final documented follow-up visit

<table>
<thead>
<tr>
<th>Staging</th>
<th>20/20 to &gt;20/60</th>
<th>20/60 to &gt;20/200</th>
<th>20/200 to 20/400</th>
<th>CF</th>
<th>HM</th>
<th>LP</th>
<th>NLP</th>
<th>Total</th>
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<td>II</td>
<td>6 (43%)</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
<td>3 (21%)</td>
<td>1 (7%)</td>
<td>2 (14%)</td>
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<td>14</td>
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<tr>
<td>III</td>
<td>16 (38%)</td>
<td>14 (33%)</td>
<td>8 (19%)</td>
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<td>IV</td>
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<td>6 (12%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
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<td>2 (28%)</td>
<td>7</td>
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CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception.
work-up is one of the steps we could consider in the future to allow for higher yield results from conjunctival biopsies.

The overall rate of systemic manifestations in our group was 35%, a lower rate than the 50% rate reported by others.\(^7,11\) Presumably, this difference originates in the retrospective character of our study and underreporting of the systemic complaints to the managing ophthalmologist. Twice as many patients suffered from oral involvement than from skin involvement, which is similar to previously described rates.\(^7,11\)

A third of the patients in this study were on systemic immunosuppressive therapy at the time of referral, similar to previously reported studies.\(^7\) During the follow-up period, the majority of patients had a change in their treatment based on recommendations from the co-managing dermatologist. Concomitant use of several immunomodulatory agents and escalating use of stronger immunosuppressive drugs was noted. No therapeutic modality was found to reverse the conjunctival scarring. The goal of immunosuppression was to reduce ocular surface inflammation, to halt or delay disease progression, and to preserve vision. Systemic steroids were most commonly used before the patients’ referral to our centre. Once seen at our cornea clinic by ophthalmologists and by the co-managing dermatologists, steroid-sparing agents were favoured. A role for tetracyclines in controlling OCP was previously described.\(^12\) In our patients, minocycline as a weak anti-inflammatory agent was used more than others. Dapsone was commonly used before the patient was seen and also during the follow-up period in cases where other weaker agents were found to be ineffective. Despite the fact that more than 75% of patients had been treated by systemic immunosuppression during the follow-up period, 65% of patients continued to progress to a more advanced disease stage. This fact might indicate not just the failure of systemic immunosuppression to halt OCP progression, but the difficulty in tailoring and maintaining an appropriate treatment plan.

Disease activity is not always accurately measurable in OCP because no quantitative index exists.\(^13\) Patients may require multiple trials of different drugs to achieve an initial effect and to decrease ocular surface inflammation. The majority of drugs require long-term treatment to reach therapeutic effect. Drugs may be discontinued because of intolerance and side effects and not because of poor efficacy. If a desirable effect is achieved, it may be from the prolonged result of previously used drugs or from multipharmacopeia, making it even more difficult to evaluate the treatment effect of a specific agent. Moreover, even if a desired response in inflammation is achieved, this cannot guarantee stability of OCP, because about 40% of our cohort showed progression of disease stage despite the absence of conjunctival inflammation. This makes building an immunosuppression treatment plan even more difficult for systemically ill or elderly patients in whom it would be important to avoid possible side effects. Overall, 26.5% of our patients were not treated with systemic immunosuppression, which is a rate similar to that previously described by Elder et al.\(^11\)

Another distinctive difficulty for the patients in this study was their geographic distance from the tertiary hospital. Patients from remote places who were required to travel long distances may lack appropriate local care that could have delayed the initiation of appropriate immunosuppression therapy or the timely recognition of disease exacerbation.

Weaknesses of this study include its retrospective nature. In the analysis, it was difficult to determine at what precise time point there was disease progression because of the indolent nature of this disease. The Foster staging system was used and in patients with rare follow-up visits, subtle changes may have gone unnoticed. Horizontal fibrosis and severity of obliteration of the fornices, and involvement of upper fornices may have been underreported. Based on the subjective nature of the assessment, no precise measures of amount of fornix shortening were performed. These difficulties in the precise documentation of OCP progression were previously reported by others.\(^7\) Nevertheless, this is the largest series of patients with OCP reported from Canada.

In summary, this study has presented the characteristics of patients with OCP who presented to a large tertiary care cornea clinic. Unfortunately, even though these patients were being followed and treated, the majority showed progression of their ocular disease. More liberal use of novel, less toxic therapeutic modalities at earlier disease stages should be considered to prevent progression to fibrosis and scarring. Comprehensive ophthalmologists who may be the first to see these patients should be aware of the clinical findings of OCP to initiate prompt referral to their cornea colleagues.

**Disclosures:** C.C.C. has received prior honoraria from Allergan, Bausch & Lomb, and Alcon Laboratories. D.S.R. has received prior honoraria from Abbott Medical Optics Inc.

**References**


