



Research Article

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Outcomes of Entropion Repair in Ocular Cicatricial Pemphigoid Compared to Other Cicatricial Etiologies: A Retrospective Study

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Abstract

Background: Ocular cicatricial pemphigoid (OCP) can lead to severe conjunctival scarring and cicatricial entropion, which often necessitates repair. Surgical manipulation can increase the risk of inflammation, scarring, and disease progression. The objective of this study was to understand the characteristics of OCP patients who received entropion repairs and determine the difference in entropion recurrence or revision in patients with OCP or other cicatricial entropion repair.

Methods: A retrospective chart review was performed from January 2010 to June 2020. OCP patients from an autoimmune blistering disease clinic with entropion repair were compared to patients with repair of cicatricial entropion of other etiology. A generalized estimating equation assessed for evidence of recurrence of entropion or required revision.

Results: 19 OCP patients with cicatricial entropion and 60 patients with cicatricial entropion secondary to other etiologies received 38 and 75 entropion repairs, respectively. No difference in prevalence of revision or recurrence was found between groups.

Conclusion: This study provides evidence that in a population of OCP patients where the majority were systemically immunosuppressed, the likelihood of entropion recurrence or further repair was no different than that for repair of cicatricial entropion of other etiology.

Keywords

Ocular cicatricial pemphigoid, Cicatricial entropion, Mucous membrane pemphigoid

Introduction

Mucous membrane pemphigoid (MMP), a systemic autoimmune blistering disease, is characterized by recurrent blistering of the skin and mucous membranes [1]. When MMP affects the eye it is termed ocular cicatricial pemphigoid (OCP) [1]. OCP is a rare condition, with a reported incidence between 7 and 11 patients per 10,000 [2]. The ocular manifestations of OCP occur due to recurrent blister formation secondary to disruption of the adhesions between conjunctival epithelium and sub-epithelium, seen as linear deposits of immunoglobulins such as IgG, IgA, and IgM autoantibodies in the basement membrane zone on direct immunofluorescence [2,3]. The resultant inflammation of the conjunctiva typically presents as chronic inflammatory

conjunctivitis that progresses to fibrosis and can potentially lead to blindness [4,5].

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Multiple eyelid abnormalities including trichiasis, lagophthalmos, symblepharon, and entropion can form as a result of the cicatrization, or scarring. These, in turn, can often further the progression of OCP by causing increased local irritation and inflammation that usually necessitates surgical repair [1,3]. However, perioperative control of ocular inflammation is essential, as it is thought that surgical trauma can result in increased inflammation, scarring, and disease progression [1].

Cicatricial entropion can also result from insults such as trauma, burns, and infection [6]. With cicatricial entropion secondary to non-autoimmune inflammatory causes, surgical procedures may be more successful due to lack of active inflammation [1]. One study assessed entropion repairs outcomes among 11 operated eyes across seven patients with OCP and found 1 (14%) patient required a secondary repair on both eyes (2/11 (18%) of eyes operated on) [1]. However, the outcomes of surgical repair for OCP-related entropion repair compared to that for other cicatricial entropion has yet to be elucidated. This study aims to describe the characteristics of patients with OCP who received entropion repairs and determine the difference in entropion recurrence in patients with OCP versus patients with cicatricial entropion of other etiology.

Methods

After obtaining approval and a waiver of consent from the Institutional Review Board, a retrospective chart review was performed in the departments of ophthalmology and dermatology at the Emory University School of Medicine. OCP patients were identified as those with a diagnosis of OCP (including clinical and biopsy negative OCP) through the Autoimmune Blistering Disease Clinic in the dermatology department and cross-referenced with those that underwent an entropion repair at the Emory Eye Clinic between January 2010 and June 2020. OCP patients were excluded if they received a prior entropion repair at an outside hospital or if pertinent information was not available in their records. Patients that underwent repair with other causes of cicatricial entropion were identified by CPT code 67924 or 67825 between January 2010 and June 2020. Exclusion criteria for the non-OCP group included age less than 18-years-old at the time of repair, biopsy-negative OCP, including all patients receiving conjunctival or eyelid direct immunofluorescence (DIF), senile or suspected senile entropion repair, previous entropion repair at an outside hospital or at this institution prior to 2010, and if no postoperative follow-up occurred.

Demographic data including sex and age was collected from electronic medical records. Race was not included due to high percentage of missing in the non-OCP patients (23%). OCP-related data included conjunctival biopsy immunofluorescence, indirect immunofluorescence, ELISA, other clinical sites of disease involvement, systemic immunosuppressive medication at time of surgery, ophthalmologic medications at time of surgery, and any history of rituximab. If multiple immunofluorescence results were reported, all relevant positives were reported. Ophthalmic medication history was recorded from the ophthalmology

visit immediately prior to surgery. Ophthalmic exam findings were collected from the oculoplastics pre-operative visit and at follow-up visits 2 and 3 post-surgery (usually reflecting 1- and 3-month follow-ups). The first follow-up exams at 1 week were excluded as these were cursory wound checks. Subsequent visits were analyzed for any evidence of entropion recurrence. Surgical repairs were classified into the following categories: a rotational procedure, a Wies procedure (a transverse blepharotomy with marginal rotation), a grafting procedure (i.e. mucous membrane, amniotic membrane, ear cartilage, etc.), or other. If a Wies procedure also included a graft, it was categorized as a Wies procedure.

Statistical analysis

Chi-square tests were run to assess demographic differences between groups. For tests with cell size < 5, Fisher's exact was used. Mean age was calculated and non-parametric Wilcoxon t-test estimation (two-sided) were run. Statistical analysis of differences in ophthalmologic findings between groups was not performed due to the sparsity of data.

A generalized estimating equation with binomial likelihood and logit link was used to analyze the association between a diagnosis of OCP and failure of the first entropion repair. Failure of first repair was measured as either recurrence or repair noted. Patient ID was included as the clustering variable with exchangeable correlation structure. We fit an unadjusted model with OCP diagnosis only and an adjusted model including age at first repair, sex, repair approach as described in surgical note, systemic steroid use, non-steroidal systemic immunosuppressants, ophthalmologic steroids, and non-steroidal ophthalmologic immunosuppressants. Collinearity between potential confounders was assessed by correlation > 0.7. Systemic steroids and systemic non-steroidal immunosuppressive agents were highly correlated with a diagnosis of OCP and were removed from the model. Statistical analysis was performed using SAS 9.4 (Cary, NC) and geepack in R 4.0.3 [7,8].

Results

19 patients with OCP and 60 patients without OCP met inclusion criteria and received a first-time entropion repair at this institution. Immune characteristics of OCP patients are displayed in Supplementary Table 1. Of the 15 who had an ocular direct immunofluorescence, 14 (93%) had evidence of immune deposition.

The 19 OCP patients underwent 38 separate eyelid repairs (Supplementary Table 2). Systemic immunosuppression (steroids, methotrexate (MTX), mycophenolate mofetil (MMF), cyclosporine, azathioprine (AZA), or cyclophosphamide) was documented prior to surgery in 35 (92%) of lid repairs (representing 17 (89%) of patients). The most commonly used non-steroidal immunosuppressant was MMF 29 (76%) of lid repairs, representing 13 (68%) of patients).

Patient populations did not differ by sex (Table 1). Age at first repair differed significantly by group while the eyelid repaired and procedure type did not differ by group. The

Table 1: Demographic comparison of OCP-related entropion versus other cicatricial entropion repair patients

	OCP	Cicatricial Entropion of Other Etiology	
Patient Demographics	N persons = 19	N persons = 60	P-value
Gender			
Male	8 (42.1%)	32 (53.3%)	0.39
Female	11 (57.9%)	28 (46.7%)	
Surgery Specific Characteristics	N eyelids = 38	N eyelids = 75	
Eyelid			
RUL	10 (26.3%)	14 (18.7%)	0.42
RLL	11 (29%)	16 (21.3%)	
LUL	7 (18.4%)	23 (30.7%)	
LLL	10 (26.3%)	22 (29.3%)	
Age at time of surgery (years) N (%)			
Mean (SD)	66.1 (9.2)	56.8 (19.3)	
< 55	4 (10.5%)	31 (41.3%)	0.001
55-64	16 (42.1%)	11 (14.7%)	
65-74	11 (29%)	23 (30.7%)	
≥ 75	7 (18.4%)	10 (13.3%)	
Procedure Type			
Wies*	23 (60.5%)	48 (64%)	0.07**
Graft (amniotic, mucous, ear cartilage, etc)	4 (10.5%)	17 (22.7%)	
Other	11 (29%)	10 (13.3%)	

*Wies is a transverse blepharotomy with marginal rotation. These include modified Wies with partial thickness blepharotomy and Wies with mucous membrane graft.

**Fisher's exact used if any cell size <5

Table 2: Ophthalmologic outcomes of OCP-related entropion versus other cicatricial entropion repair patients

	Pre-Op		Post-Op 2		Post-Op 3	
	OCP	Other Cicatricial	OCP	Other Cicatricial	OCP	Other Cicatricial
Avg time pre/post surgery (weeks)	8.3 (5.2) N = 38	7.6 (4.4) N = 75	7.4 (7.5) N = 34	6.9 (3.2) N = 62	21.5 (12.6) N = 21	17.1 (11.5) N = 24
Ophthalmic Exam						
Visual Acuity Logmar (mean (SD))	0.35 (0.37) N = 34	0.29 (0.30) N = 44	0.34 (0.35) N = 29	0.40 (0.50) N = 33	0.22 (0.15) N = 16	0.21 (0.13) N = 12
Abnormal Motility Exam	1 out of 17	8 out of 32	0 out of 1	1 out of 7	0 out of 6	0 out of 5
External N (%)	N = 35	N = 73	N = 30	N = 53	N = 19	N = 18
Entropion	34 (97.14%)	(100.00%)	3 (10.00%)	2 (3.77%)	4 (21.05%)	2 (11.11%)
Fornix Shortening	5 (14.29%)	3 (4.11%)	1 (3.33%)	1 (1.89%)	0 (0%)	0 (0%)
Ptosis	5 (14.29%)	4 (5.48%)	0 (0%)	1 (1.89%)	0 (0%)	2 (11.11%)
Lid Margin N (%)	N = 27	N = 54	N = 25	N = 40	N = 20	N = 18
Trichiasis	11 (40.74%)	31 (57.41%)	2 (8.00%)	5 (12.50%)	6 (30.00%)	0 (0%)
Distichiasis	5 (18.52%)	2 (3.70%)	2 (8.00%)	0 (0%)	2 (10.00%)	1 (5.55%)
Conjunctiva Exam Findings	N = 29	N = 49	N = 22	N = 33	N = 19	N = 15
Injection	7 (24.14%)	13 (26.53%)	0 (0%)	5 (15.15%)	2 (10.53%)	2 (13.33%)

Symblepharon	13 (44.83%)	12 (24.49%)	7 (31.82%)	2 (6.06%)	5 (26.31%)	1 (6.67%)
Slit-lamp N (%)	N = 10	N = 28	N = 7	N = 18	N = 5	N = 5
Punctate Epithelial Erosions (PEE)	5 (50%)	14 (50.00%)	2 (28.57%)	3 (16.67%)	2 (40.00%)	4 (80.00%)
Punctate Epithelial Keratopathy (PEK)	3 (30%)	4 (14.29%)	1 (14.29%)	2 (11.11%)	0 (0%)	0 (0%)
Superficial Punctate Keratitis (SPK)	2 (20%)	1 (3.57%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neovascularization	1 (10%)	2 (7.14%)	1 (14.29%)	8 (44.44%)	1 (20.00%)	2 (40.00%)
Epithelial defect and/or ulcer	0 (0%)	1 (3.57%)	3 (42.86%)	1 (5.56%)	1 (20.00%)	0 (0%)

most commonly performed procedure among both groups was a Wies procedure.

Ophthalmic exam findings for the eyelid undergoing repair were collected from the oculoplastics clinic notes. However, documentation of examinations were inconsistent in their inclusion of ocular vitals, external exam findings, lid margin exam, exam of the conjunctiva, and slit-lamp findings (Table 2). At the pre-operative appointment, mean best-corrected visual acuity was 0.35 and 0.29 logMAR in the OCP cohort and other cicatricial entropion cohort, respectively. After lid surgery, the average best-corrected visual acuity in the operated eyes for both cohorts was 0.21 logMAR. A common pre-operative examination finding was punctate epithelial erosions (PEE), which was found in 50% of patients in both groups with a documented slit-lamp exam. Symblepharon was noted on pre-operative exam in 44.83% of the OCP group with a conjunctival exam documented, compared to just 24.49% of the eyelids with cicatricial entropion of a different etiology. Additionally, trichiasis was present on pre-operative examination in 40.74% of the OCP cohort and 57.41% of the comparison group with documented lid margin exams. Of note, trichiasis was noted post-operatively in 30% of OCP patients and 0% in the non-OCP group.

The unadjusted odds of recurrence or revision was higher in patients with OCP diagnosis than in those with no OCP diagnosis, but this result was not significant (unadjusted odds ratio (OR) 2.66, 95% confidence interval (CI) 0.92-7.69, $p = 0.07$). There was also no significant effect of OCP diagnosis when controlling for age, sex, ophthalmologic steroids, non-steroidal ophthalmic immunosuppression, and entropion repair approach (adjusted OR: 2.43, 95% CI: 0.75-7.87). Age at first repair was positively associated with revision or recurrence ($p = 0.026$). The use of ophthalmic steroids decreased the odds of recurrence or revision (OR: 0.27 95% CI: 0.07-0.96, $p = 0.045$). Mean follow-up time based on last oculoplastics notes was 83 weeks (SD = 67) and 50 weeks (SD = 70) for OCP and non-OCP patients, respectively.

Discussion

Ocular cicatricial pemphigoid is a chronic autoimmune inflammatory condition causing recurrent blistering and inflammation with subsequent scarring of the ocular surface that can potentially lead to blindness [1]. Among the many ophthalmic manifestations found in OCP, cicatricial entropion can form as the posterior lamella of the eyelid scars and contracts causing the eyelid to turn inward [9]. The entropion ought to be repaired in order to prevent further corneal damage from the continuous ocular surface irritation, as well

as to improve patient comfort. It is generally accepted in OCP patients that surgery should ideally be attempted when the inflammation is controlled, in order to prevent potential disease exacerbation triggered by post-surgical inflammation [1,10,11]. However, to our knowledge the success rate of surgical repair of cicatricial entropion secondary to OCP, whether adequately controlled with systemic medication or not, has not been previously compared to the results of repair of cicatricial entropion secondary to other etiologies. Thus, this study aimed to examine the results of entropion repair in the two populations, and to determine whether patients with cicatricial entropion secondary to OCP had a recurrence or required a revision more frequently than those with cicatricial entropion secondary to another etiology.

The results show that the likelihood of recurrence or revision did not differ between the OCP-related entropion and entropion of other etiology. This was unexpected as the authors theorized that the underlying inflammatory response in OCP-related repair would increase the likelihood of required revision or recurrence. One explanation for this finding is that almost all patients in this study with OCP were on immunosuppressive medications, thus preventing an exaggerated immune response to the surgical repair. Due to the high collinearity between the use of systemic (both steroidal and non-steroidal) immunosuppression within the OCP patients, the separate effects of these medications cannot be statistically assessed. The use of ophthalmic steroids may be associated with lower likelihood of revision or recurrence.

These findings would suggest that in a population of OCP patients on immunosuppressive medications, entropion repair outcomes are similar to those receiving repair for other etiologies. This aligns with previous findings of Gibbons, et al. comparing entropion repairs among 11 operated eyes across seven patients with OCP, which found only one patient required repair during follow-up [1]. All seven patients were on either cyclophosphamide or mycophenolate mofetil (MMF), 4 with concomitant prednisone use. These findings support the previous recommendation that OCP patients should receive systemic immunosuppressive therapy when undergoing entropion repair [1]. Furthermore, it is worth noting that the majority of entropion repairs performed in both the OCP and comparison cohorts utilized a Wies procedure. This is significant because it has been previously suggested that entropion repairs in OCP patients should spare the conjunctiva in order to reduce the risk of inflammation and disease exacerbation [9]. Our results suggest that with adequate systemic disease control, the even a technique like

a Wies could be successful. However, interpretation is limited due to lack of comparison to OCP patients without systemic immunosuppression.

Our data also shows post-operative trichiasis in OCP patients more so than our comparison cohort. One possible explanation for this increased recurrence of trichiasis in the OCP population is disease continuance. Trichiasis is one of the most common eyelid abnormalities in OCP and may occur independently of entropion [1]. The non-OCP cohort typically had entropion due to trauma, previous surgeries, or other single inciting events like Stevens-Johnsons Syndrome rather than from an underlying chronic condition, it is reasonable that the trichiasis did not continue to be seen on follow-up examinations. Another possible explanation is that OCP patients have a higher incidence of distichiasis, a clinically distinct finding where lashes grow out from the meibomian gland. Unlike trichiasis, distichiasis is not corrected by rotational lid procedures. The Emory EMR does not distinguish between distichiasis and trichiasis unless distichiasis is manually entered and thus distichiasis may be misclassified as trichiasis.

Strengths of this study include the description of a large OCP population undergoing entropion repair, all of whom follow in an autoimmune blistering disease clinic and many of whom have long-term follow-up. Limitations of this study include that its retrospective nature and thus the reliance on prior documentation in patients' medical records. Specifically, which components of the ophthalmic exam were included in each clinic note was inconsistent both between patients and between clinic visits for each patient. This inconsistency resulted in the inability to assess ophthalmologic findings pre- and post-repair for patient. However, due to the rarity of the disease, a prospective study would be very difficult to perform. Another limitation of this study is that 35 of the 38 entropion repairs in OCP patients included in this study had documentation of systemic immunosuppressive therapy prior to surgery. Thus, comparison of surgical outcomes between OCP patients with and without a history of immunosuppressive therapy is limited. Future prospective studies should assess complete ophthalmologic findings pre- and post-surgical repair to assess for other potential negative outcomes secondary to surgical entropion repair.

OCP can result in severe and destructive ocular complications such as entropion. One of the biggest concerns with surgical repair is the risk of triggering an even more severe inflammation, scarring, disease progression. This study

provides evidence that entropion recurrence in a population of OCP patients where the majority were systemically immunosuppressed, the likelihood of recurrence or repair was no different than those due to other cicatrizing etiologies.

Potential Conflicts of Interest

Dr. Feldman has consulted for Astrazeneca and Alkahest and receives research support from Pfizer. Funders have no involvement in the study design; collection, analysis and interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication. Dr. Braun, Dr. Schaffer, Dr. Cole, Dr. Risk, and Dr. Kim have no conflicts of interest to disclose.

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