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HEALING INDICATORS AFTER PTERYGIUM EXCISION BY OPTICAL COHERENCE TOMOGRAPHY

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ABSTRACT

Purpose: To establish the sequence of tomographic changes in tissue recovery process after pterygium excision and propose healing indicators.

Methods: Optical coherence tomography (OCT) images were taken at 1 week, 1, 3 and 6 months after lesion excision in 73 eyes of 73 patients (33 male, 40 female; mean age 50 (S.D. 5.0), range 40-70 years) with primary nasal pterygium. Biomicroscopy was performed, in each visit and at 12 months, to diagnose clinical healing or lesion recurrence.

Presence of well demarcated corneal epithelium, conjunctival epithelium, limbal demarcation area, and graft thickening were analyzed. Comparison between tomographic data of both clinical situations was made in each time point using contingency tables.

Results: Eleven eyes displayed lesion recurrence (R group) and 62 eyes showed no recurrence (NR group). Normal anatomical structures, corneal and conjunctival epithelium and limbal demarcation area, were identified by OCT images in a higher percentage of NR cases over time, compared to the R group where most of the cases held without these markers of tissue recovery. In contrast, the variable graft thickening, which analyzed a pathological event, revealed similar results in both groups ($p>0.05$; Fisher's exact statistic), with a clear decrease of cases which showed GT over time.

Differences between groups started at 1 month, when no eye had yet presented clinical recurrence, with more identifications of corneal epithelium in NR group ($p=0.04$; Fisher's exact statistic). At 3 months, corneal and conjunctival

epithelium identification tended to be more frequent in NR than in R group (in both cases, $p=0.0001$; Fisher's exact statistic). Finally, at 6 months these different patterns consolidated adding a significantly higher number of limbal demarcation area identifications in NR group ($p=0.001$; Fisher's exact statistic). In fact, this landmark of a normally structured limbus was never found in R group.

Conclusions: Sequence of tissue restoration, by OCT images, seems to start in cornea and end in the limbal area, describing reverse process of pterygium injury. Although the visualization of corneal epithelium could be the earlier indicator of successful surgery, limbal demarcation area identification, as a normal limbal pattern in OCT images, seems to have a better positive predictive value to diagnose healing.

INTRODUCTION

Pterygium is a common ocular surface disease, characterized by the encroachment of a fleshy fibro-vascular formation from the bulbar conjunctiva across the limbus, invading the cornea. It is thought to be caused by increased ultraviolet light exposure and aggravated by micro-trauma from environmental factors.^{1,2,3} This wing-shaped lesion is often associated with chronic inflammation, increased corneal astigmatism, obstructed vision, and unfavourable cosmetic effect.⁴

As with other ultraviolet light related conditions, preventive measures remain the key to disease control⁵ and lesion excision is the main treatment. Several approaches have been attempted. The recurrence rate varies greatly, not only among different surgical procedures, but also between different studies using the same procedure.⁶⁻⁹ Despite the considerable reduction with the latest surgical techniques, recurrences have not been eliminated and regrowth process presents many unknowns.

Optical coherence tomography (OCT) is a well-established method that has supplied a valuable tool to ophthalmologists and optometrists¹⁰ for in vivo cross-sectional evaluation of ocular tissues. High-definition OCT has been recently introduced and it provides images with much greater detail. Using spectral-domain, this technique significantly increases the amount of data acquired in each session, resulting in an important reduction of motion artefacts compared with time-domain OCT.¹¹ Clinical benefits of high-definition OCT have been widely reported for differential diagnosis in optic disc¹², retina¹³ and anterior ocular diseases, such as pterygium.¹⁴⁻¹⁷ These reports showed strong

concordance between OCT images and histopathological results. Another application of OCT is to describe, over time, impairment of degenerative diseases¹³ or the recovery process after ocular surgery¹⁸. In addition, the predictive value of OCT images in several ophthalmic treatments has also been reported.^{19,20}

Despite the undeniable value of this technique describing tissue changes, only some OCT changes after pterygium^{14,15} have been reported until now. Hence, tissue progression after surgery remains unknown, except for graft thickness measurements^{21,22} and just clinical criteria are currently employed to distinguish between regrowth and healing of the lesion.

It is feasible that OCT postoperative monitoring may be a useful tool to complement clinical assessment after pterygium excision, helping clinicians in doubtful cases, and contributing to predict surgery final outcome. In any case, a better understanding of the mechanism that leads to tissue recovery or recurrence may provide new insights in the clinical management of this common pathology.

In the present study, tomographic pattern after pterygium excision was monitored. Differences between eyes that progressed to healing or lesion regrowth allowed establishing the sequence of changes that take place in tissue recovery process and propose some healing indicators.

METHODS

Patients

This observational prospective study initially enrolled 85 eyes of 85 patients with primary pterygium and was conducted at Consorci Sanitari de Terrassa-Hospital de Terrassa in Spain.

The study was approved by the Ethics Committee at Consorci Sanitari de Terrassa and informed consent was obtained from each patient. Patients with a history of contact lens wear, or ocular disease, except for pterygium, were excluded. The methods adhered to the tenets of the Declaration of Helsinki. In order to avoid unnecessary withdrawals all the patients were widely informed about recurrence possibility at the first visit.

Procedures

All surgeries were performed by the same surgeon (P.P.) using the same technique, excision of the pterygia with application of regular-tip microsponges soaked with 0.025% mitomycin C solution for 3 minutes (Mitomycin-C™ Inibsa-Hospital <http://www.inibsa.com>), followed by a free limbal-conjunctival autograft. After surgery, all patients received an identical regimen of topical chloramphenicol and dexamethasone eye drops (Colircusi de Icol®, Alcon <http://www.alcon.es>) which were tapered off in 1 month. Nylon sutures were removed at week 1.

The clinical aspect of the operated area was evaluated by biomicroscopy and, according to Prabhasawat criteria,⁶ recurrence was considered when the fibrovascular tissue invaded the cornea. This clinical assessment was carried

out at 1 week, 1, 3, and 6 months after the surgery and when changes in the tissue recovery were observed. If recurrence did not appear, a final revision at 12 months was made to definitively confirm lesion healing. Finally, cases that displayed lesion regrowth, at any time of the follow-up period, were included in the recurrence group (R group) and the rest of the cases in the no recurrence group (NR group).

Additionally, images of the affected tissues were performed, using a Cirrus HD-OCT 4000 (Carl Zeiss Meditec Inc., Dublin, CA; version 5.0.0; www.meditec.zeiss.com), at 1 week, 1, 3, and 6 months after the surgery. This system is a spectral domain OCT platform that takes 27000 axial scans per second and has a 5 µm axial resolution. The images were acquired using the Anterior Segment additional software on the device (updated for the model HD-OCT 5000), specifically centring its 5 Line Raster scan on the limbus, using as a reference the graft edges, and also including a part of the adjacent cornea and conjunctiva. The subjects viewed a peripheral fixation target, and the position was judged by the operator by changing the fixation point and scan line.

Four tomographic characteristics were analyzed. Three features were related to anatomical structures and 1 to a pathological event, all of them described previously in OCT images (**Figure 1**). Presence of a well demarcated corneal epithelium was assessed as a hyporeflective and uninterrupted band with underlying Bowman's layer in the cornea adjacent to the graft. Similarly, presence of a well-demarcated conjunctival epithelium was identified as a relatively hyporeflective and uninterrupted band in the graft that frequently showed a wavy lower limit. As landmark of a normally structured limbus²³,

identification of limbal demarcation area was made, if beneath conjunctival epithelium appeared a hyperelective triangular shape mass delimited by the anterior conjunctival stroma and episclera, with the apex in the end of Bowman's layer. Presence of graft thickening was also qualitatively assessed by comparing graft thickness with the curvature of the external surface of the globe. All the data were dichotomous. The researchers that analyzed the images were masked to any clinical recurrence at all visits.

Figure 1. Optical coherence tomography image of the limbal area in a control patient. and its anatomical interpretation, CE: corneal epithelium; BL: Bowman's layer; CS: corneal stroma; CJE: conjunctival epithelium; CjS: conjunctival stroma; ES: episclera and Tenon's capsule; S: limbal or corneo-scleral stroma. SC: Schlemm's canal. CjS and ES form the named limbal demarcation area (LDA in the text).

Statistical analysis

Contingency tables were performed with data from each time point (1 week, 1, 3, and 6 months after surgery). OCT patterns of both, R and NR groups were compared, variable by variable, using Fisher's exact test. A p value of <0.05

was considered statistically significant. Statistical analysis was performed using SPSS V19 (SPSS Inc, Chicago, Illinois; www.01.ibm.com/software/analytics/spss)

RESULTS

Seventy-three eyes of 73 patients (33 male, 40 female) completed the study (data of three or more time points and 12 months revision). The mean patient age was 50 (S.D. 5.0) (range 40-70 years). The surgery was uneventful in all cases and no remarkable clinical complications were found during the follow-up period, except for pyogenic granuloma, out of the area of study, in 3 patients (4%) that were resolved with sub-conjunctival injection of triamcinolone at 2 weeks after surgery. The patients completed the follow up period and were included in NR group.

Eleven eyes displayed lesion recurrence and were included in R group. The mean time of clinical recurrence was at 4.8 (S.D. 1.7 months), range 2-8 months. Sixty-two eyes did not showed recurrence 12 months after surgery and were grouped in NR group. **Table 1** presents the data distribution of the 4 OCT studied characteristic in the two groups at the different time points. Significant differences between groups at each time were also showed.

Table 1. Presence of the studied optical coherence tomography characteristics in both groups over time

Presence of	No recurrence	Recurrence	p value*
One week after surgery (0% of the recurrence cases clinically identified)			
	n=61	n=11	
CE	29 (48%)	2 (18%)	-----

CjE	23 (38%)	2 (18%)	-----
GT	34 (56%)	7 (64%)	-----
LDA	7 (12%)	0 (0%)	-----
One month after surgery (0% of the recurrence cases clinically identified)			
	n= 62	n=11	
CE	46 (74%)	3 (27%)	0.04
CjE	44 (71%)	5 (46%)	-----
GT	10 (16%)	2 (18%)	-----
LDA	16 (26%)	0 (0%)	-----
Three months after surgery (18.20% of the recurrence cases clinically identified)			
	n= 54	n=11	
CE	45 (83%)	2 (18%)	0.0001
CjE	46 (85%)	3 (27%)	0.0001
GT	2 (4%)	1(9%)	-----
LDA	17 (32%)	0 (0%)	-----
Six months after surgery (81.82% of the recurrence cases clinically identified)			
	n=62	n=11	
CE	58 (94%)	2 (18%)	0.0001
CjE	57 (92%)	2 (18%)	0.0001
GT	4 (7%)	1 (9%)	-----
LDA	32 (52%)	0 (0%)	0.001

CE: corneal epithelium; CjE: conjunctival epithelium; GT: graft thickening; LDA: Limbal demarcation area. *Fisher's exact statistic; ----- = $p > 0.05$.

Normal anatomical structures, corneal and conjunctival epithelium and limbal demarcation area, were identified by OCT images in a higher percentage of NR cases over time, compared to the R group where most of the cases held without these markers of tissue recovery. In contrast, the variable graft thickening, which analyzed a pathological characteristic, revealed similar results in both groups, for all the time points, and the percentage of cases with alteration decreased over time (**figure 2**).

As it was expected, one week after surgery, no significant differences between groups were found. Corneal epithelium was the only variable that disclosed significant differences at 1 month after surgery, when no eye had yet presented clinical recurrence. Nevertheless, OCT patterns were clearly different three

months after surgery. In NR group corneal and conjunctival epithelium tended to be well delimited while in R group this delimitation was more infrequent due to an abnormal hyperreflectivity that masked these structures. Finally, at 6 months the different patterns consolidated and a significantly higher number of limbal demarcation area identifications were found in NR group. In fact, this landmark of a normally structured limbus was never found in the R group.

Figure 2. Typical Optical coherence tomography progression in the studied groups. No recurrence (NR) typical progression: from no identification of anatomical structures to the identification of all the features. Recurrence (R) typical progression: no identification of the anatomical variables remains unchanged in all the time point and images show an increasingly well defined pattern of lesion regrowth. One week after surgery, graft thickening is the only identifiable variable in both groups.

DISCUSSION

In this study, spectral domain OCT allowed to report the general sequence of progressive tissue changes after pterygium removal and the possible differences that would be related to the graft's success or lesion recurrence.

Differentiation in OCT pattern between NR and R group started with changes in corneal epithelium 1 month after surgery, when recurrences are still clinically unidentified. At three months, not only corneal but also conjunctival epithelium was more frequently delimited in NR group. This normal pattern consolidated at 6 months adding a new differentiate feature, that is, a clear tendency for identification of structured limbus. The presence of what has been called limbal demarcation area seems to have, among the studied characteristics, the better positive predictive value for successful surgery, since no cases of structured limbus were found in R group.

These findings revealed a coherent description of healing process in two ways. First, the healing pattern described by OCT presented a progressive recovery of normal structures with decreasing pathological events, consistent with previous reports^{15,21}. Second, tissue restoration started in the cornea and ended in the limbus area, describing the reverse process that pterygium injury, hypothetically, had generated. Although exact pathogenesis of pterygium remains incompletely understood, experts agree that altered basal limbal epithelial cells play a key role in pterygium formation.^{4,24} Limbus seems to have also the key to complete healing process. In this sense, patterns of directionality in tissues impairment and restoration has also been described, using OCT images, in case of retinal disorders.¹³

Clear differences between recurrent and no recurrent cases seem to appear relatively early. It is worth mentioning, that these differences may appear earlier than we described, because in the OCT images it is impossible to discriminate transient inflammation (expected in the first time points after surgery) from tissue alteration that leads to recurrence. Both processes generate hyporeflectivity, an unspecific change in OCT normal pattern. In any case, NR group exhibited an earlier capacity of reducing inflammation, thus delimiting corneal and conjunctival epithelium in OCT images in a short period of time. Patients with a well delimited corneal epithelium at 1 month, by OCT images, could have a good prognostic for healing. Nevertheless, this OCT feature was also present in some eyes included in R group, which would detract predictive value from the indicator. Further assessments with a higher sample size of recurrences are necessary to elucidate this question and if recovery process may stop and lead to lesion regrowth.

Our results are consistent with pterygium recurrence time, first described by Hirst and coworkers.²⁵ Pterygia tend to recur relatively quickly after excision with a 50% chance within 4 months and a 97% within 12 months, suggesting an extended follow-up period of a year as adequate. Accordingly, the majority of clinical recurrences presented in this study appeared between 3 and 6 months, when healing process could have recently started, however some lesion regrowths were observed late, when the healing process could be still uncompleted due to the absence of limbus restoration, the hallmark that seems to culminate the process.

Evidence supporting this hypothesis is the extended period of limbal restoration, since 6 months after pterygium excision some eyes included in NR group did not show limbal demarcation area by OCT images while others presented it even at 1 month. In our opinion, this would be one of the reasons for the high variability in pterygium recurrence time. Further studies are required to elucidate the factors that cause a slow limbal recovery, including samples with a higher number of unsuccessful surgeries.

A high proportion of graft's thickening was found, in both groups (R and NR), at 1 week after the surgery and clearly decreased over time. Transient graft edema has been widely described as a common clinical feature after pterygium surgery. Previous quantitative studies, using OCT images,^{21,22} reported significant thickening of the conjunctival graft at 1 week after primary or secondary pterygium surgery, which continued to decrease up to 3 months. According to our results, it seems that the presence of this common event could be related with postoperative inflammation, caused by surgical trauma, rather than final outcome.

This sample size allowed us to find clear and coherent differences between groups, providing a general description of the healing process. It is plausible to think that the sequence of changes may be quite similar by both conjunctival and limbal-conjunctival autograft, the most currently used techniques. Conjunctival and corneal recovery may be much slower after bare sclera excision, thus overlapping stages. This last technique is becoming less used because its significantly higher recurrence rates.⁸

The relatively reduced number of recurrence cases and their variable recurrence time make difficult the description of pterygium regrowth process. This fact would explain why some cases in R group showed normal pattern at 1 month after the surgery and it disappeared at 3 months, while others held an altered pattern all over the follow-up period. An extended or reduced latency period in lesion regrowth could add more variability to OCT patterns of R group, above all in the first time points. In addition, the lack of secondary pterygia could have limited tissue reactions. In fact, it has been reported that with each subsequent recurrence, the time between excision and recurrence decreased.²⁵ Further studies with a higher number of recurrence cases, primary and secondary lesions and different surgical techniques are needed to better describe recurrence process.

In summary, changes towards an OCT normal pattern after pterygium excision were progressive and described the reverse process that the pathology, hypothetically, generated. Tissue recovery process seems to start in the cornea and end in the limbus. Normal pattern of corneal epithelium in OCT images could be the earlier indicator of healing, but a structured limbal pattern seems to have a better positive predictive value to diagnose healing. New studies are necessary to confirm the predictive value of these healing indicators and comprehensively know the process that leads to pterygium surgery failure.

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