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STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

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CONTENTS

Original Articles

Review

Case Reports

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EDITORIAL

2018 Issue 2 at a Glance:

The second issue of 2018 mainly features articles focusing on the retina and ocular surface.

In the first article of the issue, Doğan et al. show that reproducible measurements can be obtained with the Sirius corneal topographer in dry eye patients when the most severe cases (stage 4) are excluded (see pages 57-60).

With increasing awareness of conjunctivochalasis, the efficacy of medical treatment alone has come into question. In their prospective controlled study, Çağlayan et al. showed that electrocauterization led to significant increases in tear meniscus height, tear meniscus area, and tear film break-up time but significant decreases in conjunctivochalasis area and ocular surface disease index. In contrast, the medical treatment group (topical lubrication and nonsteroidal anti-inflammatory therapy) showed a significant change only in ocular surface disease index. Their findings that electrocauterization improves both signs and symptoms while topical drugs provide only symptomatic relief are of clinical significance for our colleagues (see pages 61-65).

Öztaş and Menteş used multimodal imaging to describe the diagnostic features and clinical course of precursor retinal angiomatous proliferation lesions in the asymptomatic eyes of patients diagnosed with age-related macular degeneration (AMD) and receiving anti-vascular endothelial growth factor (VEGF) therapy in the fellow eye. They emphasized the importance of spectral domain optical coherence tomography imaging in diagnosis and the necessity of utilizing eye-tracking mode during follow-up (see pages 66-69).

Seyhan Karatepe et al. determined that the most important factors affecting corrected visual acuity in idiopathic macular hole are the duration, stage, and base diameter of the macular hole, the presence of inner segment/outer segment junction defects, and the size of those defects. As the authors suggest, these parameters will be valuable indicators in prognosis and treatment decisions (see pages 70-74).

Akıncıoğlu et al. report that epiretinal membrane caused heterogeneous changes in macular anatomy in 45 eyes of 45 patients who underwent vitreoretinal surgery due to idiopathic epiretinal membrane within a two-year period and were followed-up for a mean of 7 months. They attributed their inability to detect a correlation between visual gain and central macular thickness to this heterogeneity, and therefore suggested that central macular volume may be a better parameter in the follow-up of these patients (see pages 75-80).

The review article in this issue was written by Kaynak et al. They discuss evidence that intravitreal anti-VEGF agents, which allow successful treatment of choroidal neovascularization secondary to AMD, potentially increases the development of geographic atrophy. They point out that a causal relationship between geographic atrophy and neovascular AMD has not been directly demonstrated, and extensively discuss the available evidence concerning the relationship between anti-VEGF therapy and geographic atrophy development (see pages 81-84).

When preparing Descemet membrane grafts for Descemet membrane endothelial keratoplasty (DMEK), large radial tears may make the trephination stage impossible due to insufficient graft diameter. Özmen et al. used these irregular-edged grafts for DMEK in two pseudophakic patients with bullous keratopathy and report reduction of corneal edema without need for air/gas injection to the anterior chamber. Knowing that irregular DMEK grafts do not need to be disposed of but can instead be implanted into the anterior chamber with favorable clinical outcomes should alleviate concerns about this situation, which could confront anyone who performs corneal transplants (see pages 85-88).

In the acute phase, penetrating ocular traumas pose difficulties in the detection of other posterior segment injuries such as retinal detachment and optic nerve avulsion due to eyelid ecchymosis and hematomas and accompanying vitreous hemorrhage. Değirmenci et al. demonstrate that the diligent use of imaging methods in these patients, who pose a major medicolegal risk, enabled the detection of retinal detachment and optic nerve avulsion despite the presence of vitreous hemorrhage after penetrating trauma. In their 11-year-old patient, they illustrate that penetrating ocular

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TJO

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trauma due to impact with a hard object can result in both penetrating and blunt force injury (see pages 89-91).

Olfactory neuroblastoma, which is a neuroectodermal tumor of the nasal cavity, is also capable of orbital invasion. Kartı et al. report the case of a 62-year-old woman with a history of proptosis and visual impairment in the left eye and demonstrate the importance of awareness of this malignancy, as some of these patients may present with ophthalmic findings such as external ophthalmoplegia, proptosis, or compressive optic neuropathy (see pages 92-94).

Although rare, Stickler's syndrome is the most common hereditary cause of rhegmatogenous retinal detachment. Öztürk et al. present a 17-year-old female patient with chronic severe retinal detachment due to Stickler's syndrome and report achieving effective and reliable results with scleral buckling in one eye and pars plana vitrectomy in the other eye during 3 years of follow-up (see pages 95-98).

Respectfully on behalf of the Editorial Board,
Sait Eğrilmez, MD

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Turk J Ophthalmol 2018;48:57-60

Original Article

Does Dry Eye Affect Repeatability of Corneal Topography Measurements?

Aysun Şanal Doğan, Canan Gürdal, Mehmet Talay Köylü
University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ophthalmology Clinic, Ankara, Turkey

Abstract

Objectives: The purpose of this study was to assess the repeatability of corneal topography measurements in dry eye patients and healthy controls.
Materials and Methods: Participants underwent consecutive corneal topography measurements (Sirius; Costruzione Strumenti Oftalmici, Florence, Italy). Two images with acquisition quality higher than 90% were accepted. The following parameters were evaluated: minimum and central corneal thickness, aqueous depth, apex curvature, anterior chamber volume, horizontal anterior chamber diameter, iridocorneal angle, cornea volume, and average simulated keratometry. Repeatability was assessed by calculating intra-class correlation coefficient.
Results: Thirty-three patients with dry eye syndrome and 40 healthy controls were enrolled to the study. The groups were similar in terms of age (39 [18-65] vs. 30.5 [18-65] years, p=0.198) and gender (M/F: 4/29 vs. 8/32, p=0.366). Intra-class correlation coefficients among all topography parameters within both groups showed excellent repeatability (>0.90).
Conclusion: The anterior segment measurements provided by the Sirius corneal topography system were highly repeatable for dry eye patients and are sufficiently reliable for clinical practice and research.
Keywords: Dry eye, corneal topography, repeatability

Introduction

The need for precise anterior segment measurements has driven the innovation of new, more reliable devices. An ophthalmic device must provide excellent correlation among repeated measurements in order to obtain consistent values. With the advent of new diagnostic and treatment modalities for many ocular conditions, precise analysis of the anterior segment is becoming increasingly important in various contexts including intraocular lens calculations, keratoconus, cataract and refractive surgery, corneal surgery, fitting of contact lenses, and glaucoma. Corneal topography enables fast and precise measurements of the anterior segment.[1] The Sirius topography device (Sirius; Costruzione Strumenti Oftalmici, Florence, Italy) is a dual combined Scheimpflug camera and Placido-disk topography device that provides rapid, precise measurements of a wide range of anterior segment parameters.[1] Recent studies have proved that Sirius and similar corneal topography systems are repeatable for healthy subjects.[1,2,3,4,5]

Dry eye is a multifactorial disease of the tears and ocular surface that is accompanied by increased osmolarity of the tear film and causes symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.[6] The tear film provides a smooth refracting surface for the cornea.[7] When the tear film is disrupted, the optical surface becomes irregular and may cause additional aberrations or unpredictable keratometry measurements.[8,9,10,11] Dry eye is one of the most common entities in ophthalmology practice; previous studies have reported its prevalence as ranging between 3.9% and 16.7%, with higher rates in the elderly and women.[12,13] As dry eye and other eye pathologies may coexist, it is essential to know the repeatability of topography measurements among dry eye patients.

The aim of this study was to assess the repeatability of measurements provided by the Sirius topography device in dry eye patients and to evaluate whether there was a difference in measurements between dry eye patients and healthy controls.

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Materials and Methods

This retrospective study was performed at a tertiary referral center was approved by the ethics committee (16.01.17 34/12), and followed the tenets of the Declaration of Helsinki.

All patients underwent ophthalmologic examination including Scheimpflug-based corneal topography (Sirius; Costruzione Strumenti Oftalmici, Florence, Italy) (Figure 1). Noninvasive break-up time (NIBUT) and meibography were also examined using the same device.

The dry eye group constituted patients who were diagnosed according to the 2007 Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop.[6] NIBUT values of 10 seconds or less were included in the dry eye group. The healthy control group included volunteers who had no known ophthalmic pathologies and had NIBUT longer than 10 seconds. Exclusion criteria were history of ocular disease, contact lens use, previous ocular surgery, and other anterior segment abnormalities. Patients with dry eye severity level 4 (severe and/or disabling constant discomfort and visual symptoms, marked conjunctival injection, filamentary keratitis, mucus clumping, tear debris, ulceration, trichiasis, keratinization, symblepharon) were also excluded.[6]

Corneal Topography

The Sirius system is a topography device that combines a monochromatic 360-degree rotating Scheimpflug camera and a Placido disk to analyze the anterior segment by dual acquisition of 25 radial sections of the cornea and anterior chamber in just a few seconds. In a single scan, it provides tangential and axial curvature data of the anterior and posterior corneal surfaces, the global refractive power of the cornea, a biometric estimation of various structures, complete corneal pachymetry, and wavefront analysis. A 475 nm blue LED light is used to measure 35,632 points for the anterior corneal surface and 30,000 for the posterior corneal surface. A pachymetric map is then reconstructed using the point-by-point anterior and posterior corneal surface data. In our study, minimum corneal thickness, central corneal thickness (CCT), aqueous depth (AD), apex curvature, anterior chamber volume, horizontal anterior chamber diameter, iridocorneal angle, cornea volume, and average simulated keratometry (SimKAvg; arithmetic average of the steep and flat axes) were used for analysis.

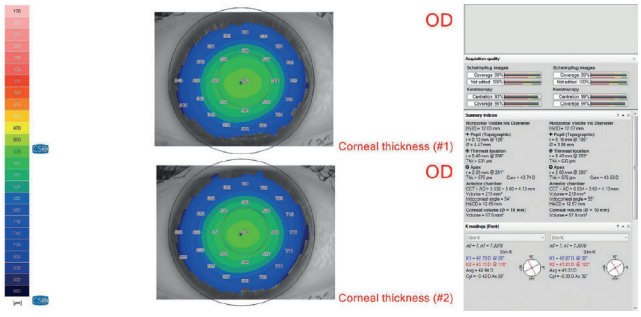

Figure 1. Two corneal topography images and parameters of the same eye
OD: Right eye

Topography was performed with at least >90% acquisition quality by the same experienced examiner (A.S.D.). For each eye, the corneal topography measurement was performed consecutively. All examinations were made in the same environment with stable humidity and temperature. Patients were instructed to completely refrain from using their artificial tear supplements from the previous evening until after examination. Subjects were positioned with a headrest and instructed to fixate on an internal fixation point. The patients were told to blink several times before corneal topographic images were captured. The corneal images were captured within 1-3 seconds immediately after blinking.

Statistical Analysis

Statistical tests were performed using the Statistical Package for Social Sciences, version 20.0 (SPSS Inc, Chicago, Illinois, USA). Only the right eyes' parameters were used for statistical assessment. In descriptive statistics, discontinuous data were shown as numbers and percentage (%); continuous data were shown as mean ± standard deviation and median (minimum-maximum). Chi-square test was used for categorical values. When comparing two groups, Student's t test was used for continuous variables that showed normal distribution; Mann-Whitney U test was used for continuous variables that did not show normal distribution. Reliability assessment between two measurements of the same participant (intra-class correlation, [ICC]) was assessed. The ICC is an ANOVA-based correlation that measures relative homogeneity within groups between the repeated measurements in proportion to the total variation. The ICC will approach 1.0 when there is no variance within repeated measurements, indicating that total variation in measurements is due solely to variability in the parameter being measured. ICC values are commonly classified as follows: ICC <0.75, poor agreement; 0.75≤ICC<0.90, moderate agreement; ICC ≥0.90, high agreement.[14] Parameters were also compared between the dry eye group and healthy control group. A p value less than 0.05 was considered statistically significant.

Results

The study included 33 eyes of 33 patients with dry eye and 40 eyes of 40 healthy controls. The groups were similar in age and gender distribution, while meibomian gland loss was higher and NIBUT was lower in the dry eye group compared to healthy controls (Table 1).

Repeated corneal topographic measurements of the same patients within both groups showed excellent agreement for minimum corneal thickness, CCT, AD, apex curvature, anterior chamber volume, horizontal anterior chamber diameter, iridocorneal angle, cornea volume, and SimKAvg. All ICCs were greater than 0.90 (Table 2).

Discussion

Our study showed that in both the dry eye group and healthy controls, repeated dual corneal topographic measurements

were in excellent agreement for minimum corneal thickness, CCT, AD, apex curvature, anterior chamber volume, horizontal anterior chamber diameter, iridocorneal angle, cornea volume, and SimKAvg. All ICCs were greater than 0.90. Especially parameters that were used in biometric measurements, CCT, SimKAvg and AD, had ICC values greater than 0.99 in dry eye except AD, which also showed a high level of agreement. One can expect that the unstable tear film may result in an irregular surface and may disrupt the topographic measurements. With tear-film instability, the quality of the refractive surface is unpredictable, often changing dramatically between blinks.[11] In our study, we think that the speed of the measurements, obtained within a few seconds after a blink and before the tear break-up time, increased ICC. In addition, the high quality images, careful and skillful data image acquisition by the same user, and constant room conditions might have role in high repeatability results. The meaning of relatively lower ICC may be as a result of different NIBUT patterns (e.g., central vs. peripheral dry spots); however, this study did not include dry spot patterns.

The quality of images is automatically determined by the corneal topographer. In our study, two images with high quality were included in order to avoid the risk of operator bias. Our results suggest that, particularly in dry eye patients, repeated numerous measurements may be more time consuming but are required to achieve images with the highest quality. This can be an objective for further investigation.

To the best of our knowledge, the effect of dry eye on the repeatability of anterior segment topography has not been reported to date except for CCT. Lee et al.[15] reported an ICC of 0.891 for CCT, which was lower than in our study, but the image quality of the accepted measurements was not mentioned. However, Epitropoulos et al.[11] showed that intraocular lens Master device resulted in intraocular lens power calculation difference of more than 0.5 D in 10% of hyperosmolar eyes. In their study, tear hyperosmolarity was found to be associated with lower repeatability of keratometry measurements.[11] Artificial eye drops therapy in dry eye patients has been shown to be effective in increasing corneal optical quality by improving the higher order aberrations[8] and topographic ectasia parameters[16] of the anterior corneal surface. Zemova et al.[17] showed that there was no association between dry eye and topographic changes in keratoconus patients by Pentacam topography device. Koh et al.[7] reported that ocular forward light scattering and corneal backward light scattering from the anterior cornea were greater in dry eyes than in normal eyes using the C-Quant straylight meter of Oculus Scheimpflug imaging system. Akyol Salman et al.[18] reported that there was no significant difference between dry eye patients and healthy controls in terms of ultrasonic pachymetry measurements. However, in the study of Dayanir et al.[19], preventing the patients from blinking during ultrasonic pachymetry measurement caused a significant decrease in corneal thickness during 1 minute of drying.

There are several reports regarding the repeatability of Sirius Scheimpflug-Placido topography devices in the current literature which are consistent with the results of our study. These studies were conducted in healthy eyes, in eyes after myopic refractive surgery, and in eyes with keratoconus.[1,3,4,20] To the best of our knowledge, there have been no repeatability studies in dry eye patients conducted with corneal topography devices. In our dry eye group, which excluded severe cases, the repeatability of corneal topography parameters was excellent.

Other anterior segment imaging systems have also been shown to have good repeatability. Güler et al.[21] assessed the repeatability

Table 1. The groups were similar in terms of age and gender (p>0.05). The dry eye group had significantly higher meibomian gland loss and lower noninvasive break-up time values

	Dry eye group (n=33)	Healthy control group (n=40)	p value
Age (median, range, years)	39 (18-65)	30.5 (18-65)	0.198[a]
Gender (male / female)	4/29	8/32	0.366[b]
MG loss (%) (median, range)	21.1 (8.7-42.4)	15.1 (6-30.7)	<0.001[a]
NIBUT (seconds) (median, range)	6.5 (2.5-9.8)	17 (10.1-17)	<0.001[a]

[a]: Mann-Whitney test, [b]: Chi-square test, MG: Meibomian gland, NIBUT: Noninvasive break-up time

Table 2. Intra-class correlations were excellent for comparison of two images in terms of all parameters within both the dry eye group and healthy controls

	Dry eye group (n=33)	p value	Healthy controls (n=40)	p value
	ICC		ICC	
MCT1 / MCT2	0.996	<0.001	0.992	<0.001
CCT1 / CCT2	0.996	<0.001	0.991	<0.001
AD1 / AD2	0.914	<0.001	0.992	<0.001
APCurv1 / APCurv2	0.951	<0.001	0.937	<0.001
ACVol1 / ACVol2	0.991	<0.001	0.999	<0.001
HACD1 / HACD2	0.964	<0.001	0.992	<0.001
ICAng1 / ICAng2	0.987	<0.001	0.992	<0.001
CorVol1/ CorVol2	0.991	<0.001	0.991	<0.001
SimKAvg1/SimKAvg2	0.994	<0.001	0.997	<0.001

MCT: Minimum corneal thickness, CCT: Central corneal thickness, AD: Aqueous depth, APCurv: Apex curvature, ACVol: Anterior chamber volume, HACD: Horizontal anterior chamber diameter, ICAng: Iridocorneal angle, CorVol: Cornea volume, SimKAvg: Average simulated keratometry

and reproducibility of the anterior segment measurements performed with a Galilei dual Scheimpflug analyzer in normal, keratoconic, and post-refractive surgery corneas and showed that the measurements showed good repeatability and reproducibility. Martin et al.[22] assessed the repeatability of corneal thickness in healthy eyes with the Pentacam instrument and showed good repeatability. Ortiz-Toquero et al.[23] compared the repeatability of Oculus Keratograph in a sample of healthy and keratoconus eyes and found repeatable measurements in both groups.

Study Limitations

The present study has several limitations. In our sample, severity level 4 cases were not included. Further studies in a larger group including severe cases with high tear film osmolarity may be required in order to validate the diagnostic ability of this device in all dry eye patients.

Conclusion

In conclusion, the Scheimpflug imaging-based Sirius corneal topography system provides repeatable examinations in both dry eyes and healthy eyes. Therefore, besides the healthy population, the device may be useful even in dry eye syndrome as a screening and diagnostic tool for anterior segment pathologies. Further studies are needed to compare the repeatability of measurements in very severe dry eye patients.

Ethics

Ethics Committee Approval: Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethical Committee for Clinical Investigations (decision no: 34/12).

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Aysun Şanal Doğan, Canan Gürdal, Design: Aysun Şanal Doğan, Canan Gürdal, Data Collection or Processing: Aysun Şanal Doğan, Canan Gürdal, Analysis or Interpretation: Aysun Şanal Doğan, Canan Gürdal, Literature Search: Aysun Şanal Doğan, Mehmet Talay Köylü, Writing: Aysun Şanal Doğan, Mehmet Talay Köylü.

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Original Article

Comparison of Electrocoagulation and Conventional Medical Drops for Treatment of Conjunctivochalasis: Short-Term Results

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Abstract

Objectives: To compare the effectiveness of electrocoagulation and conventional medical drops for treatment of conjunctivochalasis using anterior segment-optical coherence tomography (AS-OCT).

Materials and Methods: Forty eyes of 20 patients with bilateral conjunctivochalasis were included in this prospective study. Twenty eyes of 10 patients were assigned to Group 1 and underwent electrocoagulation. The other 20 eyes of 10 patients were assigned to Group 2 and received conventional medical treatment consisting of non-steroidal antiinflammatory drop (topical 0.5% ketorolac tromethamine) 4 times a day and artificial tears (0.15% sodium hyaluronate) 6 times a day for 4 weeks. Before and 4 weeks after treatment, all patients were evaluated by slit-lamp biomicroscopy, tear film break-up time (TBUT) test, and ocular surface disease index (OSDI) questionnaire. Tear meniscus height (TMH), tear meniscus area (TMA), and conjunctivochalasis area (CCA) were measured with AS-OCT.

Results: In Group 1, posttreatment values of TMH, TMA, and TBUT were significantly higher ($p<0.001$, $p=0.006$, and $p<0.001$, respectively), while CCA and OSDI scores were significantly lower than pretreatment values ($p<0.001$ for both values). In Group 2, only OSDI decreased significantly between pretreatment and posttreatment values ($p<0.001$). The other parameters did not change significantly after treatment ($p>0.05$ for all values).

Conclusion: Electrocoagulation is an effective modality for treatment of conjunctivochalasis

Keywords: Conjunctiva, electrocoagulation, optical coherence tomography

Introduction

Conjunctivochalasis (CCh) was first described at 1942 by Hughes[1] as redundant, loose, nonedematous inferior bulbar conjunctiva interposed between the globe and the lower eyelid. Increased collagenolytic activity and conjunctival elastic fibril degeneration related to oxidative stress, and ocular surface inflammation are responsible for the etiopathogenesis of CCh, but neither is solely responsible for the disease.[1,2,3,4] CCh is a clinical diagnosis but is generally overlooked by clinicians. Patients with CCh can be asymptomatic or symptomatic. Symptoms can vary along a broad spectrum, ranging from tearing, itching, and eye burning to gritty feeling, localized pain, ulceration, and subconjunctival hemorrhage. Asymptomatic cases do not require treatment, while symptomatic cases usually require medical and/or surgical treatment. Artificial tears are commonly used in CCh treatment due to tear film instability and dry eye symptoms in eyes with CCh.[5] In addition, topical anti-inflammatory eye drops are often prescribed in clinical practice to reduce ocular surface inflammation.[5] The most preferred surgical technique is crescent-shaped conjunctival excision and primary suturation.[5] Other surgical procedures include amniotic membrane transplantation with fibrin glue and suturing the CCh tissue directly to sclera.[5,6,7] Electrocauterization of loose conjunctival tissue is another non-surgical modality for the treatment of CCh. It is applied 5 mm from the limbus and causes no damage to the fornices.[8,9,10]

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Anterior segment-optical coherence tomography (AS-OCT) has rapidly become a valuable tool in the field of ophthalmology. Dry eye evaluation by measuring the tear meniscus and tear film with AS-OCT has been well described previously.[11,12,13,14] AS-OCT has also been described as a useful and reproducible instrument to measure the cross-sectional area of conjunctiva prolapsing into the tear meniscus of eyes with CCh.[8]

In this study, we aimed to use AS-OCT to compare the effectiveness of electrocoagulation and conventional medical drops in the treatment of CCh.

Materials and Methods

This prospective study was conducted in compliance with the institutional and government review board regulations, informed consent regulations, and the Declaration of Helsinki. Written informed consent, which was approved by our institutional ethics committee (approvel number: 26379996/122), was obtained from all patients.

The study included 40 eyes of 20 consecutive patients with CCh suffering from dry eye symptoms. Twenty eyes of 10 patients were treated with electrocauterization (Group 1), and the other 20 eyes of 10 patients were treated with conventional medical drops including non-steroidal antiinflammatory agent (topical 0.5% ketorolac tromethamine) and artificial tears (0.15% sodium hyaluronate) (Group 2). Patients who wore contact lenses, had any ocular surface disease or eyelid disorder, history of previous eye surgery, or systemic and/or topical medication usage within the last year, as well as any patients who were pregnancy or breastfeeding were excluded from the study.

All patients were evaluated with the Ocular Surface Disease Index questionnaire (OSDI), tear film break-up time (TBUT) measurement, and a complete ophthalmologic examination including visual acuity measurement, slit-lamp biomicroscopic anterior and posterior segment examination, and intraocular pressure measurement. CCh was diagnosed biomicroscopically as redundant, loose conjunctival tissue between the inferior eyelid margin and globe. CCh was graded according to Lid Parallel Conjunctival Folds (LIPCOF) grading system, using the method described by Höh et al.[15] (Table 1).

Ocular symptoms were analyzed with the OSDI, a 12-item questionnaire consisting of 3 categories (ocular symptoms, environmental factors, and visual functions).[16] Each OSDI item is scored on a scale from 0 (never) to 4 (always). Total OSDI score was calculated with the following formula: Total OSDI score= (Sum of scores *25)/number of questions answered.[16] The overall OSDI scores range from 0 to 100.

Fourier-domain OCT (RTVue, software version 2.7; Optovue Inc., Fremont, California, USA) anterior segment module (Cam-L) was used for measuring tear meniscus parameters including tear meniscus area (TMA), tear meniscus height (TMH), and CCh area (CCA). All measurements were made by the same clinician (M.C.). The patient was seated in front of the OCT device, asked to look straight ahead after blinking and the inferior temporal region was scanned in the vertical plane in 2 seconds. Unlike previous studies, the CCA, TMH, and TMA values were measured manually from the inferotemporal wedge region between the bulbar conjunctiva and eyelid margin.

After AS-OCT measurement, TBUT was evaluated. Fluorescein 2% solution was instilled into the inferior fornix before asking the patient to blink three times and then look straight forward. The tear film was analyzed by slit-lamp biomicroscopy with cobalt blue filter. The elapsed time until initial break-up, rupture of the tear film, or formation of any tiny dry spots was recorded. TBUT was measured three times and the measurements were averaged.[17]

Electrocauterization was performed on the eyes in Group 1 according to the method described below. After the instillation of topical anesthetic, the patients were seated in front of the slit-lamp biomicroscope and instructed to look upward. In order not to cause any corneal injury, the excess conjunctiva was grasped 5 mm away from the limbus at the inferotemporal region and coagulated with low-voltage manual electrocautery. Coagulation was considered to be adequate when the conjunctiva turned white. Coagulation was performed at approximately 10 sites in an arc on the inferior temporal bulbar conjunctiva. Postoperatively, topical antibiotic drops (0.3% lomefloxacin) were prescribed 4 times daily and stopped 1 week later.

Conventional medical drops were prescribed to the eyes in Group 2. Non-steroidal antiinflammatory drops (topical 0.5% ketorolac tromethamine) 4 times a day and artificial tears (0.15% sodium hyaluronate) 6 times a day were administered for 1 month. The patients in the second group were monitored for treatment compliance and the patients who could not adhere to the treatment were excluded from the study. All medications were discontinued 3 days before the post-treatment examinations. All examinations were performed in both groups before and 4 weeks after treatment.

Statistical Analysis

Statistical analysis was performed with SPSS 17.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Normality of data was analyzed with a Shapiro-Wilk test. Descriptive statistics were performed as mean ± standard deviation. Statistical analyses were performed using independent samples t-test and paired samples t-test. Categorical variables between the groups were analyzed using chi-square (x^2) tests. A p value of less than 0.05 was considered statistically significant.

Results

The mean age was 57.6±9.9 years in Group 1 and 59.2±8.10

Table 1. LIPCOF grading[15]

Grade	Number of folds / relationship with tear meniscus height
0	No folds
1	One fold, below tear meniscus height
2	Several folds, up to tear meniscus height
3	Several folds, over tear meniscus height

years in Group 2 (p=0.29). There were 5 (50%) females and 5 (50%) males in Group 1 and 7 (70%) females and 3 (30%) males in Group 2 (p=0.36).

The LIPCOF grading (Table 1) distribution was similar between groups: 8 eyes were in grade 2 and 12 eyes were in grade 3 in Group 1, while 9 eyes were in grade 2 and 11 eyes were in grade 3 in Group 2 (p=0.74).

In Group 1, the mean TMA and TMH values significantly increased after treatment (p=0.006 and p<0.001 respectively). CCA decreased from 0.35±0.18 to 0.10±0.07 mm^2 after treatment (p<0.001) (Figure 1). Mean TBUT increased and OSDI score decreased after treatment (p<0.001 and p<0.001) (Table 2), indicating improvement of dry eye symptoms and tear functions after electrocauterization treatment.

In Group 2, the mean TMA and TMH values increased after treatment but the differences were not significant (p=0.05 and p=0.85). CCA was 0.34±0.08 mm^2 before treatment and 0.32±0.08 mm^2 after treatment (p=0.15). The mean OSDI score significantly decreased after treatment, while TBUT did not significantly change after treatment (p<0.001 and p=0.07).

Discussion

CCh is a senile, usually bilateral process related to conjunctival laxity in which the excess conjunctiva interposes between the globe and the lower eyelid margin.[3] CCh localization can be temporal, nasal, central or along the entire eyelid.[3] The presence of these folds in the conjunctiva causes a destabilization in the tear film and tear meniscus and an impairment in the tear drainage mechanism, resulting in foreign body sensation and tearing. As the vessels below the folds are fragile, minimal trauma may cause subconjunctival haemorrhage.[1,18,19]

Recent research on CCh has focused on grading, etiopathogenesis and new treatment modalities of this disorder. The most commonly used grading method in CCh is the LIPCOF grading scale.[15] Lid-parallel conjunctival folds are evaluated in the area perpendicular to the temporal and nasal limbus above the lower lid with a slit-lamp biomicroscope and classified using the optimized grading scale. Another grading method was described by Meller and Tseng[3] according to CCh localization, the relationship between conjunctival folds and tear meniscus, punctal occlusion, and changes with down-gaze and digital pressure.

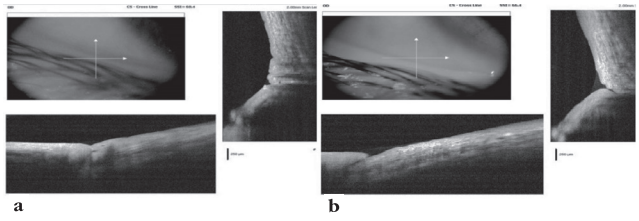

Figure 1. Optical coherence tomography view before (a) and after (b) electrocauterization

Although the exact etiopathogenetic mechanism of CCh remains unclear, the most likely local factors are repeated conjunctival trauma, exposure to ultraviolet radiation, aging, and tear stasis. CCh accompanied by Ehlers-Danlos syndrome in a 55-year-old man showed that systemic etiologies like collagen tissue diseases must also be kept in mind in the etiopathogenesis.[20] Current immunohistochemical studies revealed that inflammatory mediators like interleukin-1, matrix metalloproteinase (MMP)-3, MMP-9, and tumor necrosis factor-α are higher in CCh than in normal conjunctival tissue.[4,21,22] Therefore, ocular surface inflammation has an important role in the etiopathogenesis of CCh.[2,22] Topical anti-inflammatory therapies in clinical practice are frequently preferred in CCh treatment with artificial tears. However, patient cooperation generally decreases in long-term medical treatments, and symptoms may reappear when the topical treatment is stopped.

In the management of CCh, if medical treatment fails, surgical treatment is advised.[5] The most preferred surgical technique is crescent-shaped excision of the CCh tissue and primary suturation of the conjunctiva.[5] Despite its advantages, surgical treatment of CCh has some disadvantages. Conjunctival excision which is excessive and extending to inferior fornix can cause corneal problems and impaired ocular movements.[19] Suture material can cause foreign body sensation, giant papillary conjunctivitis, granuloma, or abscess formation.[9] These complications have led clinicians to invent new treatment modalities. In recent years electrocauterization has been preferable for clinicians as it can be applied easily and quickly in clinical practice. Local inflammation produced by the heat during cauterization promotes fixation of the loose conjunctiva to the underlying Tenon's capsule.[9] High-temperature electrocauteries can cause conjunctival epithelial injury, fibrosis, scar formation in Tenon's

Table 2. The data classified by groups

	Group 1			Group 2		
	Before treatment	**After treatment**	**p**	**Before treatment**	**After treatment**	**p**
TMA (mm^2)	0.03±0.02	0.06±0.03	0.006	0.03±0.02	0.04±0.04	0.05
TMH (μm)	204.5±84.4	280±94.2	<0.001	217.2±124.1	222.3±98.9	0.85
CCA (mm^2)	0.35±0.18	0.10±0.07	<0.001	0.34±0.08	0.32±0.08	0.15
TBUT (s)	5.4±1.9	9.3±2.8	<0.001	5.8±1.9	5.5±2.3	0.07
OSDI score	50.7±12.4	19.1±13.8	<0.001	50±12	37.7±12.3	<0.001

CCA: Conjunctivochalasis area, OSDI: Ocular surface disease index, TBUT: Tear film break-up time, TMA: Tear meniscus area, TMH: Tear meniscus height
p<0.05: statistically significant, *Paired samples t test

capsule, and fornix shortening.[10] Low-temperature cauteries may be preferable because they minimize heat spreading and cause less cell injury. Therefore, pain and scar formation are reduced while the speed of wound healing increases.[23,24,25]

In this study we compared the efficacy of electrocauterization and conventional medical drop treatment in CCh patients. We made TMA, TMH, and CCA measurements with AS-OCT using a standard measurement protocol that was developed previously for objective efficacy evaluation.[8] Four weeks after the electrocauterization, CCA decreased while TMA and TMH increased. In Group 2, TMA, TMH, and CCA did not significantly change 4 weeks after the conventional medical treatment. We also compared the effects of electrocauterization and conventional medical drops on dry eye symptoms and signs. We used the OSDI questionnaire to evaluate dry eye symptoms and TBUT test to evaluate tear functions. Ocular surface disease index score significantly decreased after treatment in both of the groups but this decrease was more evident in the electrocauterization group. TBUT increased in only the electrocauterization group after treatment. Therefore, tear functions improved after treatment in the electrocauterization group while there was no change in the medical drop group.

AS-OCT is a useful and reproducible instrument to provide cross-sectional images of the cornea, conjunctiva, tear meniscus, and anterior chamber angle.[26,27,28] The importance of AS-OCT in the diagnosis and follow-up of CCh was first described by Gumus et al.[8] They obtained AS-OCT measurements before and after electrocauterization in 12 eyes of 7 patients with CCh to evaluate the reproducibility and repeatability of AS-OCT in CCh, and concluded that CCA measurement was more reliable than TMA and TMH measurements when assessing CCh with AS-OCT.[8] The lower reliability of TMA and TMH may be due to destruction of the smooth tear meniscus in repeated measurements. The reproducibility and repeatability of AS-OCT were found to be high in measuring cross-sectional CCA, and AS-OCT was described as a useful clinical research tool for the objective study of CCh.[8]

The relationship between dry eye and CCh has been discussed many times in the literature, and CCh was found to be an important factor in dry eye etiopathogenesis.[3,29,30,31] Loose conjunctival tissue excision alleviates dry eye symptoms and signs. In one study, crescent-shaped excision of loose conjunctival tissue and subconjunctival cauterization reduced dry eye symptoms and signs assessed with OSDI questionnaire, Schirmer tear test, and TBUT test.[32] Another study comparing the results of electrocauterization and surgical excision in CCh treatment demonstrated significant improvement in dry eye symptoms (decrease in OSDI scores) in the electrocauterization group.[9]

In the literature, increased meibomian gland dysfunction has been reported in CCh. However, it is not known whether or how meibomian gland dysfunction is related to CCh. [3,29,30,31] Meibomian gland function can be evaluated using meibomian gland expression, lipid layer thickness, and, indirectly, TBUT test. In the present study, TBUT values increased after electrocoagulation. Conjunctival folds at the eyelid margin may obstruct meibomian gland orifices and block meibum delivery to the tear film. As meibum aids in reducing the evaporation of tears, this obstruction may lead to a dysfunctional tear film and subsequent evaporative dry eye. Decreasing or eliminating the conjunctival folds by electrocoagulation might reopen the meibomian gland orifices, resulting in improved TBUT results.

Study Limitations

There are some limitations in this study. The AS-OCT measurements were obtained manually from the inferotemporal wedge region between the bulbar conjunctiva and eyelid margin because we hypothesized that taking the measurements from the electrocauterized area would be more appropriate. Another limitation is that aqueous deficient dry eye was not investigated in our study.

To the best of our knowledge, there are no previous studies comparing the efficacy of electrocauterization and conventional medical drops in the treatment of CCh. Medical treatment is the most preferred treatment, although cauterization is gaining popularity in CCh treatment. Electrocauterization may be more successful than medical treatment in CCh treatment.

Conclusion

Conjunctival cauterization is an effective and safe treatment modality in CCh. It could be a first-line treatment for CCh, especially in patients who may not want to use or may not adhere to long-term topical treatment. Further studies with larger samples are needed to evaluate the long-term effects of electrocauterization in the treatment of CCh.

Ethics

Ethics Committee Approval: Yıldırım Beyazıt University Faculty of Medicine Ethics Committee (number: 26379996/122).

Informed Consent: It was taken.

Peer-Review: Externally peer-reviewed.

Author Contributions

Concept: Canan Gürdal, Design: Özge Saraç, Data Collection or Processing: Mehtap Çağlayan, Pınar Kösekahya, Analysis or Interpretation: Mehtap Çağlayan, Pınar Kösekahya, Literature Search: Mehtap Çağlayan, Writing: Mehtap Çağlayan.

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Original Article

Retinal Angiomatous Proliferation: Multimodal Imaging Characteristics and Follow-up with Eye-Tracked Spectral Domain Optical Coherence Tomography of Precursor Lesions

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Abstract

Objectives: To present the multimodal imaging characteristics of precursor retinal angiomatous proliferation (RAP) lesions and follow-up results with eye-tracked spectral-domain optical coherence tomography (SD-OCT).
Materials and Methods: Six eyes of 6 patients aged 77.5±5.9 years diagnosed with precursor RAP lesion were included in this prospective observational case series. Best corrected visual acuity (BCVA) measurement and complete ophthalmologic examination were performed for all subjects, as well as fundus photography (FP), fundus autofluorescence (FAF), SD-OCT, fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography angiography (OCTA), and their long-term follow-up results are presented.
Results: The mean BCVA was 0.8±0.16 (0.6-1) Snellen and the mean follow-up was 26.3±14.8 months. Images of the precursor RAP lesions demonstrated no specific findings on FP and FAF, showed focal hypofluorescent foci with no leakage on FA and IGA, and appeared as extrafoveal small, round, well-defined, hyperreflective foci typically located in the outer retinal layers on SD-OCT B-scans with high sampling density. OCTA demonstrated the precursor lesions as the deep capillary plexus abnormalities in 3 eyes. Two eyes progressed to stage 1 RAP during the follow-up period.
Conclusion: This study defined the diagnostic characteristics and clinical course of precursor RAP lesions. Our findings highlight the importance of B-scans with high sampling density for the diagnosis of precursor lesions and using eye-tracking mode SD-OCT during follow-up.
Keywords: Retinal angiomatous proliferation, spectral-domain optical coherence tomography, type 3 neovascularization

Introduction

The term retinal angiomatous proliferation (RAP), first used by Yannuzzi in 2001, describes a specific clinical form of age-related macular degeneration (AMD) characterized by neovascularization (nv) originating from the outer layers of the retina.[1] It is known that the initial stage (precursor lesion) of RAP, also called type 3 nv, involves the development of an angioma (neovascular complex) originating from the deep capillary network (DCN) of the retina. The disease progresses to advanced stages (stages 1, 2, and 3) as this highly vasogenetic angioma proliferates and progresses toward the pigment epithelium and choroidal layers, leading to vision loss.[1,2,3,4,5]

The rapid clinical course and typical lack of response to anti-VEGF (vascular endothelial growth factor) therapy in patients with advanced RAP make the early detection and monitoring of precursor lesions of great importance.[2,3,4,5]

In this article, we describe the multimodal imaging features of precursor RAP lesions, including optical coherence tomography angiography (OCTA), and present the results of long-term follow-up with B-scan spectral domain optical coherence tomography (SD-OCT) using high sampling density and eye-tracking mode.

Materials and Methods

This prospective, observational clinical series included a total of 6 eyes of 6 patients (4 females and 2 males; mean age

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77.5±5.9 [71-87] years) diagnosed with bilateral AMD. All of the patients were receiving anti-VEGF therapy for nvAMD in the other eye when precursor (early-stage) RAP lesions were incidentally detected on B-scan SD-OCT imaging. All patients underwent best corrected visual acuity (BCVA) measurement and full ophthalmologic examination, as well as fundus photography (FP), fundus autofluorescence (FAF), SD-OCT, fluorescein angiography (FA), indocyanine green angiography (ICGA), and OCTA examinations, and diagnostic features were determined. The patients' symptomatic eyes were already being followed, and their asymptomatic fellow eyes were also observationally examined in detail. Informed consent was obtained from all patients.

Precursor RAP lesions were diagnosed based on the appearance of hyperreflective lesions in the outer layers of the retina that originated from the DCN and were characteristically round and well-defined, and typically caused shadowing at the level of the retinal pigment epithelium (RPE) on B-scan SD-OCT. These lesions had not yet caused any intraretinal and/or subretinal fluid accumulation or increase in retinal thickness. Their course and progression over time were monitored at intervals of one or two months using B-scan OCT in eye-tracking mode with high sampling density.

BCVA measurements, anterior and posterior segment examinations, and SD-OCT scanning were repeated at each visit. In addition to FP, FAF, FA, ICGA, and high-density eye-tracked B-scan SD-OCT images acquired using a Heidelberg Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany), a Topcon OCT-2000 (Topcon, Tokyo, Japan) device was also used to record color photographs, en face (C scan), and three-dimensional (3D) images. OCTA images were acquired in a 3x3 mm area with 11-µm B-scan intervals using the Heidelberg Spectralis HRA + OCT OCT 2 module (Heidelberg Engineering, Heidelberg, Germany).

Results

All of the eyes were asymptomatic and had BCVA of 0.8±0.16 (0.6-1) Snellen at time of diagnosis. Mean follow-up time was 26.3±14.8 months. The lesions were accompanied by drusenoid pigment epithelial detachment (PED) in 4 eyes and by drusen in 2 eyes. Two of the eyes exhibited multiple hyperreflective lesions.

The precursor RAP lesions had no specific findings in clinical examination or color FP; however, they appeared as small, darkly colored areas on infrared FP and FAF, and as focal hypofluorescent foci with no leakage on FA and ICGA (Figure 1). On SD-OCT, they appeared as small, round, well-defined extrafoveal hyperreflective foci located in the outer layers of the retina (between the outer plexiform layer and outer nuclear layer) in both B-scan and in en-face and 3D images. All of the lesions were noted to cause typical back shadowing at the RPE level on B-scan OCT (Figure 1). Precursor RAP lesions could only be viewed with OCTA examination in 3 eyes (50%), and they were usually observed as a hyperreflective, small, round, well-defined microvascular tuft at the outer capillary plexus level (Figure 2).

During follow-up, the precursor RAP lesions remained stable in 4 eyes and became active in the other 2 eyes after an average of 21 months (at 12 and 30 months). The activated angiomas showed slight growth on OCT, enlarging and shifting slightly downward toward the RPE layer and/or the drusenoid PED (Figure 3). One to two months after these changes, these two patients exhibited a sudden, small decrease in BCVA (6-7/10 Snellen), together with OCT findings of increased retinal thickness and intraretinal cystoid fluid formation, indicating progression to stage 1 RAP.

Discussion

In this article, we present the multimodal imaging features of 6 eyes diagnosed with precursor RAP lesions as well as their high-density eye-tracked B-scan OCT findings from a mean follow-up period of 26.3±14.8 (6-42) months. RAP precursor lesions, or intraretinal neovascular complexes, are quite small, and our study emphasizes the importance of using high sample density B-scan SD-OCT imaging passing directly over the lesion

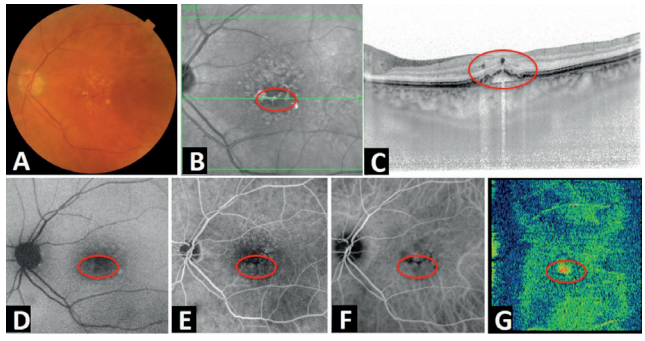

Figure 1. The multimodal imaging characteristics of a precursor retinal angiomatous proliferation lesion (in red circle) (patient 1). A) Drusen and pigment deposits on color fundus photography; B) small, dark areas on infrared fundus photography; C) precursor lesion and typical back shadowing are seen on B-scan spectral-domain optical coherence tomography; D) small hypoautofluorescent area on fundus autofluorescence; E) no leakage in fluorescein angiography; F) no leakage in indocyanine green angiography, G) extrafoveal small, round, well-defined, hyperreflective foci in the outer retinal layers on C-scan (en face) spectral-domain optical coherence tomography

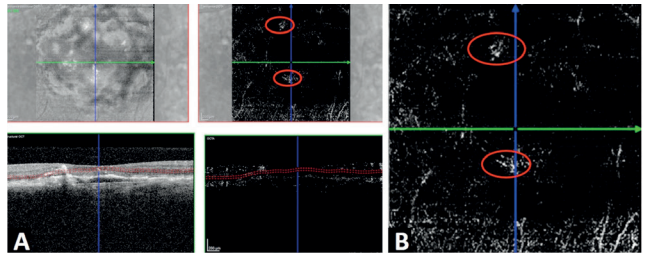

Figure 2. In optical coherence tomography angiography (OCTA) images of patient 1, the precursor retinal angiomatous proliferation lesion (in red circle) appeared as a hyperreflective, small, round, well-defined microvascular tuft at the outer capillary plexus level: A) OCTA image, B) magnified image of the OCTA section

as well as using eye-tracking mode, which yields reproducible images, in the diagnosis of precursor RAP lesions.

Precursor RAP lesions do not show leakage on FA or ICGA and have typical features on SD-OCT. Recognizing these lesions in the earliest asymptomatic stage, before the appearance of intraretinal cystoid fluid and serous PED, is important because advanced disease is very aggressive and often resistant to anti-VEGF therapy.

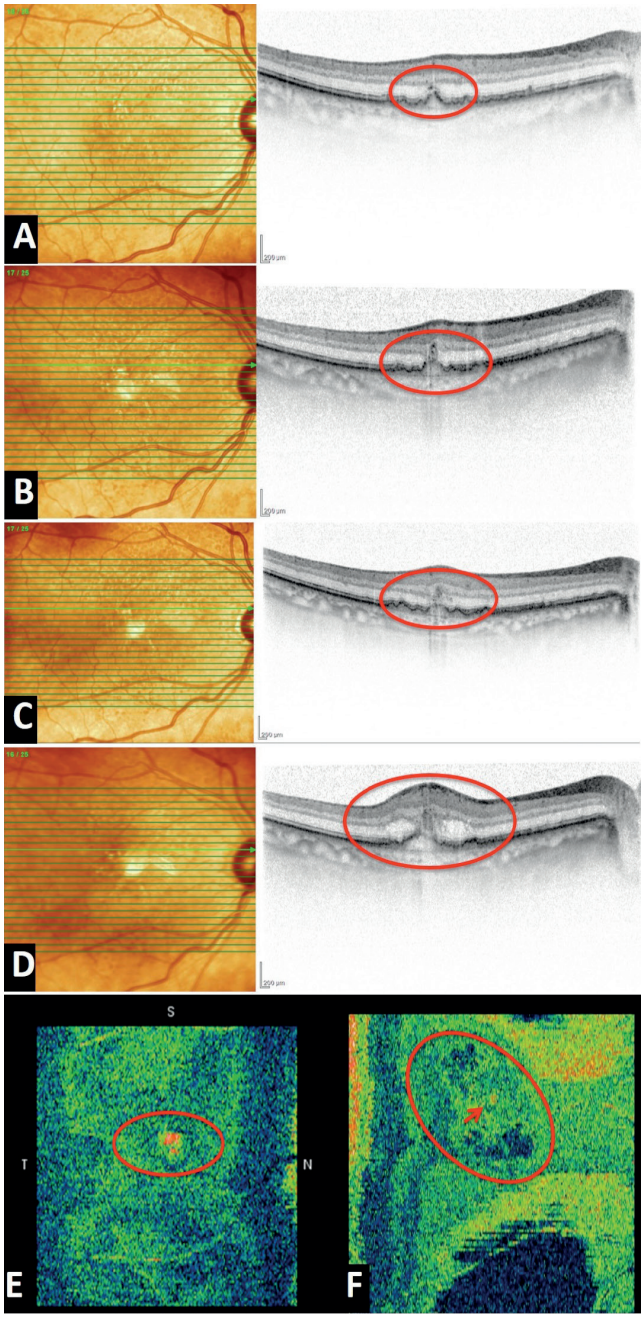

Figure 3. Progression of precursor lesion to stage 1 retinal angiomatous proliferation (RAP) in patient 2: A) The precursor RAP lesion (in red circle) with typical back shadowing in the right eye; B) the same section 6 months later shows the lesion changing form and approaching the retinal pigment epithelium; C) another image obtained 1 month later shows increased retinal thickness; D) intraretinal cystoid fluid accumulation is seen in the retina 2 months later. E) En face SD-OCT image of the precursor lesion; F) progression to stage 1 RAP and cystoid spaces formed around the precursor lesion (red arrow)

Su et al.[5] reclassified type 3 nv lesions according to SD-OCT findings. Although isolated punctate hyperreflective foci on the outer retinal layers were described as "precursor" lesions, the researchers acknowledged that hyperreflective foci may also appear in other macular diseases and that they alone do not constitute a specific sign of type 3 nv. They identified growth of precursor lesions, downward shift toward the retinal layers, and outer plexiform layer disruption as specific symptoms of activation, whereas they defined the presence of a larger precursor lesion accompanied by cystoid macular edema but without disruption of the outer retinal layers as stage 1 RAP. They reported that there may be a long period of time between the appearance of a precursor lesion and stage 1, with a mean interval of 3.6±3.3 months for the patients in their series.

The results of our study demonstrate that these very small hyperreflective lesions in the outer retinal layers, which we determined as being earliest stage RAP lesions and which were identified by Su et al.[5] as precursor lesions, can easily be identified with high-density SD-OCT. During follow-up in our patients, activation and progression to stage 1 were detected after an average of 21 months following initial diagnosis in 2 (33.2%) eyes. By diagnosing progression in the early stages, we were able to initiate treatment before permanent changes occured in the outer retinal layers.

Querques et al.[2] described the multimodal imaging features of their clinical series including type 3 nv patients with precursor lesions. All precursor lesions in their study were located over drusen or drusenoid PED, and they reported a 32% rate of progression from precursor lesion to stage 1 at a mean interval of 19.6±9.5 months after diagnosis. As we also observed in the patients in the present series, they noted that precursor lesions were hypofluorescent on FA and ICGA during their inactive period, but became hyperfluorescent or exhibited leakage after the appearance of signs of activation and after progression to stage 1.

Tan et al.[6] described the OCTA findings of active or inactive early type 3 nv patients. Their study did not include precursor lesions, and imaging rate was reported as 85%.

Conclusion

Our study using multimodal imaging to evaluate the diagnostic features and clinical course of precursor RAP lesions emphasizes the importance of high-density B-scan SD-OCT imaging for diagnosis and using eye-tracking mode to better detect possible activation during follow-up.

Ethics

Ethics Committee Approval: Not applicable for this prospective, observational, case series.

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zafer Öztaş, Jale Menteş, Concept: Zafer Öztaş, Jale Menteş, Design: Zafer Öztaş, Jale Menteş, Data Collection or Processing: Zafer Öztaş, Jale Menteş, Analysis or Interpretation: Zafer Öztaş, Jale Menteş, Literature Search: Zafer Öztaş, Jale Menteş, Writing: Zafer Öztaş, Jale Menteş.

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Original Article

Vitreoretinal Interface Characteristics in Eyes with Idiopathic Macular Holes: Qualitative and Quantitative Analysis

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Abstract

Objectives: To determine the qualitative and quantitative vitreoretinal interface characteristics with spectral domain optical coherence tomography (SD-OCT) in eyes with macular hole (MH) and investigate their relation with best corrected visual acuity (BCVA) and MH duration.

Materials and Methods: Sixty-one eyes of 46 consecutive patients diagnosed with idiopathic MH were included in the study. The mean age of the patients was 66.7±7.5 (51-79) years. Complete ophthalmologic examination and SD-OCT examination were performed in all eyes and MH stages were determined according to SD-OCT findings. Qualitative characteristics of the vitreoretinal interface were investigated, including vitreomacular traction, vitreopapillary traction, maculopapillary traction, vitreoschisis, intraretinal cyst, presence of epiretinal membrane, and the integrity of the photoreceptor inner segment-outer segment junction (IS/OS) and external limiting membrane (ELM). In addition, MH diameter, MH base diameter (MHBD), ELM defect diameter, IS/OS defect diameter, and MH height were quantitatively measured and the MH index was calculated.

Results: Out of 61 eyes, 9.8% were classified as stage 1a, 19.7% as stage 1b, 18% as stage 2, 23% as stage 3, and 29.5% as stage 4. Mean BCVA was 0.28±0.24 (1 mps-1.0) Snellen and MH duration was 10.08±18.6 (1-108) months. The most common interface characteristics associated with MH were determined as intraretinal cyst (91.8%), IS/OS defect (78.7%) and ELM defect (63.9%). Duration and stage of MH were inversely proportional to BCVA but directly proportional to the presence and diameter of IS/OS and ELM defects. BCVA was significantly lower in eyes with IS/OS and ELM defects ($p<0.0001$; $p<0.0001$ Mann-Whitney U test).

Conclusion: We determined that the most important factors affecting BCVA in cases with idiopathic MH were MH stage, MH duration, MHBD, and the presence and diameter of IS/OS and ELM defects, which suggests that these parameters should be considered while making decisions about prognosis and treatment.

Keywords: Idiopathic macular holes, vitreoretinal interface, optical coherence tomography

Introduction

Macular hole (MH) is defined as full-thickness tissue loss in the central macula, including the internal limiting membrane (ILM) and photoreceptor layer. Though 80% of cases are idiopathic, MH is known to be one of the anomalies that arises during the development of posterior vitreous detachment (PVD).[1,2,3] Mechanisms implicated in the pathogenesis of MH include abnormal interactions/adhesions between the posterior hyaloid membrane (i.e., the posterior cortical vitreous) and

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the macular surface (especially in the central fovea), as well as the forces exerted by anterior-posterior and tangential vitreous traction on the fovea.[4,5]

Spectral domain optical coherence tomography (SD-OCT) imaging of the retina, optic nerve head, and vitreomacular interface characteristics is currently regarded as an examination method that substantially facilitates our understanding of the course and pathogenesis of the disease.[6,7] In addition to the diagnosis and clinical staging of idiopathic MH, SD-OCT enables *in vivo* imaging of various anatomical parameters and changes occurring in both the vitreomacular interface and retina, thereby providing insight in terms of prognosis and treatment.[8,9]

In this prospective clinical study, we aimed to use SD-OCT to examine the qualitative and quantitative characteristics of the vitreoretinal interface and inner and outer retinal layers in eyes with idiopathic MH, and investigate the relationships between these characteristics and best corrected visual acuity (BCVA) and MH duration.

Materials and Methods

Sixty-one eyes of 46 consecutive patients diagnosed with idiopathic MH in the Retina Unit of the Ege University Medical Faculty Ophthalmology Department between January 2010 and January 2012 were included in the study. This prospective study was approved by the Ege University Ethics Committee (ETC-10-5.1/24) and written informed consent was obtained from all patients. Eyes with concomitant retinal conditions such as age-related macular degeneration, diabetic retinopathy, retinal detachment, or vascular diseases and eyes with uveitis, intraocular inflammation, or history of trauma or vitreoretinal surgery were excluded.

MH duration was accepted as time from the start of reduced vision (as reported by the patient) to the date of presentation. All patients underwent full ophthalmologic examination and vitreous/retinal examinations with non-contact and contact lenses. In addition, SD-OCT (Topcon 3D OCT-2000; Topcon Europe Medical BV, Rotterdam) images of a 6x6 mm macular area and 3x8 mm area including the macula and optic nerve head were acquired in vitreous mode. Presence and extent of PVD were evaluated by clinical examination, SD-OCT, and B-scan ultrasonography (USG).

MH stage classification was based on SD-OCT findings[8] as follows: stage 1a, presence of a cyst in the inner retinal layers at the central fovea due to vitreofoveal traction; stage 1b, extension of the cyst into the outer retinal layers, leading to a break in the outer retinal layers; stage 2, tractional break in the roof of the cyst, which forms a flap over a full-thickness hole; stage 3, full-thickness MH with free operculum and posterior vitreous attached to the optic disc; and stage 4 is characterized by a stage 3 MH with complete PVD.

Qualitative characteristics of the vitreoretinal interface assessed in this study included vitreomacular traction (VMT), vitreopapillary traction (VPT), maculopapillary traction (MPT), vitreoschisis, intraretinal cyst, presence of epiretinal membrane (ERM), integrity of the photoreceptor inner segment/outer segment (IS/OS) junction, and external limiting membrane (ELM). In addition, MH diameter (MHD), MH base diameter (MHBD), ELM defect diameter, IS/OS defect diameter, and MH height (MHH) were quantitatively measured, and the MH index (MHI) was also calculated using the formula MHI=MHH/MHBD (Figure 1).

Statistical Analysis

Correlations between BCVA and MH duration, MH stage, and quantitative and qualitative parameters of the vitreoretinal interface and inner/outer retinal layers were evaluated statistically. Kruskal-Wallis, Mann-Whitney U, chi-square, and Spearman tests were used for statistical analyses, and p value <0.05 was considered statistically significant.

Results

The patient group comprised 30 females (65.2%) and 16 males (34.8%) with a mean age of 66.7±7.5 (51-79) years. Seventeen patients (37%) had bilateral MH. Thirteen (21.3%) of the eyes were pseudophakic and 48 (78.7%) were phakic.

MH stage was 1a in 6 eyes (9.8%), stage 1b in 12 (19.7%), stage 2 in 11 (18%), stage 3 in 14 (23%), and stage 4 in 18 (29.5%) of the eyes. Mean BCVA was 0.28±0.24 (counting fingers at 1 m - 1.0) Snellen and the mean MH duration was 10.08±18.6 (1-108) months. BCVA and MH duration according to MH stage are shown in Table 1. There were significant negative correlations between BCVA and MH stage and duration (p<0.0001, p<0.0001; Kruskal-Wallis test).

The distribution of vitreomacular interface characteristics such as VMT, VPT, MPT, vitreoschisis, intraretinal cyst, presence of ERM and IS/OS defects, and ELM defects according to MH stage is shown in Table 2. The most common interface characteristics coexisting with MH were intraretinal cyst (91.8%), IS/OS defect (78.7%), and ELM defect (63.9%). BCVA was not significantly correlated with VMT, VPT, MPT, vitreoschisis, intraretinal cyst, or presence of ERM (p=0.643; p=0.896; p=0.643; p=0.9; p=0.291; p=0.628, respectively; Mann-Whitney U test). However, eyes with IS/OS defect or ELM defect had significantly lower BCVA (p<0.0001; p<0.0001 Mann-Whitney U test). The prevalence of IS/OS defect and ELM defect was 0% and 16.7% in stage 1a eyes; 50% and 50% in stage 1b; and 100% and 100% in stage 4 eyes, respectively (Table 3). The presence and frequency of outer retinal layer

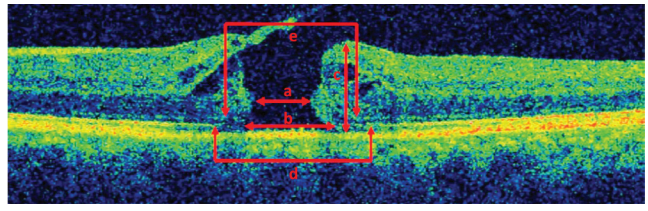

Figure 1. a) Macular hole (MH) diameter, b) MH base diameter, c) MH height, d) inner and outer segment defect diameter, e) external limiting membrane defect diameter

defects increased significantly with higher MH stage (p<0.0001, p<0.0001; chi-square test). However, there were no significant correlations between MH stage and vitreoschisis, intraretinal cyst, or ERM presence (p=0.893, p=0.097, p=0.222; chi-square test) (Table 3).

Quantitative measurements of MHD, MHBD, MHH, MHI, ELM, IS/OS defect diameters, their distributions based on MH stage, and correlations with BCVA are shown in Table 4. There was no significant relationship between MHD and MH stage (p=0.192); however, MH stage was positively correlated with MHBD and MHH and negatively correlated with MHI (p=0.001, p <0.0001, p=0.011, Kruskal-Wallis test). Although BCVA and MHD were not statistically associated (p=0.974), BCVA levels were negatively correlated MHBD and MHH and positively correlated with MHI (p=0.002, r=-0.701; p=0.013, r=-0.589; p=0.018; r=0.566; Spearman test).

Mean IS/OS defect and ELM defect diameters were 1327.7±822.5 µ and 1180.4±745.4 µ, respectively, and MH stage was positively correlated with defect diameter (p<0.0001, p=0.001; Kruskal-Wallis test). There were negative correlations between BCVA and IS/OS and ELM defect diameters (p=0.011, p=0.001, Spearman test).

The SD-OCT and B-scan USG data in our study were not correlated in terms of presence of complete PVD (Kappa=-0.19); a total of 22 eyes (36%) were diagnosed with PVD according to USG and 26 (42.6%) with SD-OCT (Table 5).

Table 1. Best corrected visual acuity and macular hole duration of the eyes based on macular hole stage

Stages	Eyes (n)	Mean BCVA (Snellen)	Mean duration of MH (months)
Stage 1a	6 (9.8%)	0.85±0.25	2±3
Stage 1b	12 (19.7%)	0.49±0.23	2.2±3.2
Stage 2	11 (18.0%)	0.22±0.13	5±5.6
Stage 3	14 (23%)	0.17±0.12	5.4±4.8
Stage 4	18 (29.5%)	0.14±0.13	23.6±29.3
p value		p<0.0001 (Kruskal-Wallis test)	p<0.0001 (Kruskal-Wallis test)

BCVA: Best corrected visual acuity, MH: Macular hole

Discussion

In the present study, we utilized SD-OCT to investigate the qualitative and quantitative characteristics of both the vitreoretinal interface and inner/outer retinal layers in a total of 61 eyes from 46 patients with idiopathic MH, and we evaluated correlations between morphological findings and functional status.

Our results revealed statistically significant negative correlations between BCVA and MH stage and duration. Similarly, in a large-scale study conducted by Ho et al.[5], visual acuity decreased as the MH stage and duration increased.

Furthermore, we identified intraretinal cyst, IS/OS defect, and ELM defect as the most common concomitant interface characteristics in our MH patients. Huang et al.[8] reported intraretinal cysts in 93% of their idiopathic MH cases. Scholda et al.[9] examined the presence of IS/OS defect and intraretinal cyst in eyes with MH using ultrahigh resolution OCT. They reported that eyes with more intraretinal cysts had larger IS/OS defects and attributed this to the intraretinal cysts blocking reflectance in that region. Although we did not observe any significant relationships between BCVA and VMT, VPT, MPT, vitreoschisis, intraretinal cyst, or ERM in our MH cases, BCVA was significantly lower in patients with IS/OS and ELM defects. In addition, we detected IS/OS and ELM defects even in eyes with stage 1a MH; the frequency of these defects was 38.8% and 33.3% respectively in stage 1 eyes and 100% in stage 4 eyes. We observed a significant positive correlation between MH stage and the presence and frequency of these defects.

Although MHD was not significantly associated with BCVA or MH stage, we noted that MHBD and MHH were significantly greater and MHI lower at higher MH stages. Similarly, higher MHBD and MHH and lower MHI correlated with lower BCVA. In a study including stage 2, 3, and 4 MH cases, Wang et al.[10] reported a positive association between MHD and stage. The diameter referred to in that study was MHBD and the data were consistent with those of our study. Chew et al.[11] also reported

Table 2. Qualitative vitreoretinal surface characteristics according to macular hole stage

Interface characteristics	Stage 1a n=6	Stage 1b n=12	Stage 2 n=11	Stage 3 n=14	Stage 4 n=18
VMT	4 (66.7%)	4 (33.3%)	11 (100%)	3 (21%)	1 (5.6%)
VPT	6 (100%)	6 (50%)	11 (100%)	13 (92.8%)	2 (11.1%)
MPT	4 (66.7%)	4 (33.3%)	11 (100%)	3 (21%)	1 (5.6%)
Vitreoschisis	1 (16.7%)	2 (16.7%)	4 (36%)	2 (14.3%)	2 (11.1%)
Intraretinal cyst	5 (83.3%)	9 (75%)	9 (81.8%)	14 (100%)	18 (100%)
ERM	1 (16.7%)	4 (33.3%)	2 (18.2%)	3 (21%)	10 (55.6%)
IS/OS defect	1 (16.7%)	6 (50%)	11 (100%)	14 (100%)	18 (100%)
ELM defect	0	6 (50%)	11 (100%)	14 (100%)	15 (100%)

VMT: Vitreomacular traction, VPT: Vitreopapillary traction, MPT: Maculopapillary traction, ERM: Epiretinal membrane, IS/OS: Photoreceptor inner and outer segment junction, ELM: External limiting membrane

Table 3. Inner and outer segment and external limiting membrane defect presence and size according to macular hole stages						
	Stage 1a n=6	**Stage 1b n=12**	**Stage 2 n=11**	**Stage 3 n=14**	**Stage 4 n=18**	**p value (Kruskal-Wallis test)**
IS/OS defect (Eyes=n)	1 (16.7%)	6 (50%)	11 (100%)	14 (100%)	18 (100%)	
Mean IS/OS defect diameter (µ)	33	241.7±445.7	1284.3±737.6	1839.6±743.35	1963.4±335.2	<0.0001
ELM defect (Eyes=n)	0 (0%)	6 (50%)	11 (100%)	14 (100%)	18 (100%)	
Mean ELM defect diameter (µ)	0	214.8±354.7	1132.5±699.9	1598.4±591.72	1773.8±1773.8	<0.0001
IS/OS: Photoreceptor inner and outer segment junction, ELM: External limiting membrane						

Table 4. Quantitative macular hole characteristics and best corrected visual acuity according to macular hole stage						
Stage	**Stage 1a n=6**	**Stage 1b n=12**	**Stage 2 n=11**	**Stage 3 n=14**	**Stage 4 n=18**	**p value (Kruskal-Wallis test)**
Mean BCVA (Snellen)	0.85±0.25	0.49±0.23	0.22±0.13	0.17±0.12	0.14±0.13	p<0.0001
MHD (µ)	0	0	490.45±183.32	555.4±164.6	584.4±245.2	p=0.192
MHBD (µ)	0	0	804.36±449.05	1104.9±380.3	1212.2±403.3	p=0.001
MHH (µ)	0	0	346.18±131.94	422.5±66.8	405.8±50.8	p<0.0001
MHI	0	0	1±1	0.4±0.1	0.3±0.1	p=0.011
MH: Macular hole, MHD: Macular hole diameter, MHBD: Macular hole base diameter, MHH: Macular hole height, MHI: Macular hole index						

Table 5. Presence of posterior vitreous detachment according to spectral domain optical coherence tomography and ultrasonography data		
PVD	**USG n (%)**	**SD-OCT n (%)**
Present (+)	22 (36%)	26 (42.6%)
Partial (±)	2 (3.3%)	8 (13.1%)
Absent (-)	37 (60.7%)	27 (44.3%)
PVD: Posterior vitreous detachment, SD-OCT: Spectral domain optical coherence tomography, USG: Ultrasonography		

larger MHBD and lower BCVA levels with longer MH duration. They also noted a quantitative increase in IS/OS and ELM defect diameters and decreased BCVA levels with higher MH stage. Consistent with our study, Chang et al.[12] reported MHD and IS/OS defect diameter as the main parameters affecting BCVA levels in 24 eyes with MH and 17 eyes with closed MH, with larger diameters associated with lower BCVA levels.

We observed that B-scan USG and SD-OCT findings were not strongly correlated for diagnosis of complete PVD in patients with MH. Kicova et al.[13] used preoperative slit-lamp biomicroscopy, B-scan USG, and OCT to evaluate the presence of PVD in 30 eyes scheduled for vitrectomy due to MH or macular pucker. They reported that slit-lamp biomicroscopy and USG provided more accurate diagnostic results based on intraoperative findings.

Conclusion

In summary, we determined that in idiopathic MH, key factors in visual acuity are the base diameter and height of the MH and the presence and diameter of IS/OS and ELM defects. These parameters were positively associated with MH stage and duration, and we recommend that these parameters be taken into consideration when determining prognosis and making surgical decisions.

Ethics

Ethics Committee Approval: This prospective study was approved by the Ege University Ethics Committee (ETC-10-5.1/24) and supported by Ege University Medical Faculty (BAP-2010-Tıp-046).

Informed Consent: written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Arzu Seyhan Karatepe, Jale Menteş, E. Tansu Erakgün, Filiz Afrashi, Serhad Nalçacı, Cezmi Akkın, Yeşim Ateş, Concept: Jale Menteş, Design: Jale Menteş, Data Collection or Processing: Arzu Seyhan Karatepe, Analysis or Interpretation: Jale Menteş, Arzu Seyhan Karatepe, Literature Search: Arzu Seyhan Karatepe, Writing: Jale Menteş, Arzu Seyhan Karatepe.

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Original Article

Surgical Outcomes of Idiopathic Epiretinal Membrane: The Gülhane Experience

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Abstract

Objectives: We aimed to report our experiences and outcomes of vitreoretinal surgery in idiopathic epiretinal membrane.

Materials and Methods: We retrospectively reviewed patients who underwent vitreoretinal surgery for idiopathic epiretinal membrane between January 2012 and 2014. The patients' pre- and postoperative visual acuity, slit-lamp examination findings, and optical coherence tomography (OCT) images were evaluated.

Results: Forty-five eyes of 45 patients (36% male, 64% female) were included (mean age, 69±8.2 years). Mean postoperative follow-up time was 7±4 (1-12) months. The mean preoperative logMAR best corrected visual acuity was 0.58±0.32 and postoperatively 0.40±0.31, 0.33±0.33, 0.28±0.34 respectively at 3, 6, and 12 months. All OCT parameters showed statistically significant anatomical improvement at 1, 3, 6, and 12 months. Correlation analysis showed that central macular thickness ($r=0.69$, $p<0.05$) and central macular volume ($r=0.69$, $p<0.05$) were the only parameters that had strong positive correlations with visual improvement.

Conclusion: Epiretinal membrane causes heterogeneous anatomical changes in the macula for every patient. Therefore, a correlation between visual gain and changes in central macular thickness could not yet be demonstrated. We believe that central macular volume may be a better parameter for following these patients.

Keywords: Epiretinal, volume, internal limiting membrane, correlation

Introduction

Epiretinal membrane (ERM) is a fibrocellular membrane that forms on the vitreoretinal interface due to accumulation of cells and extracellular matrix, and is often idiopathic.[1] Besides primary idiopathic cases, ERM may also occur secondary to ocular inflammatory diseases, retinal vascular diseases, and pathologies such as retinal detachment. Unilateral ERM is more common in both primary and secondary cases, though 20-35% of patients have bilateral ERM.[2] The literature consensus is that primary idiopathic ERM occurs more frequently in the older population; however, there is significant variation between studies in terms of prevalance.[2,3,4,5] Prevalence rates in these studies were determined based on the presence of ERM in non-mydriatic fundus photograph. In contrast, the Beaver Dam Eye research group documented ERM by spectral domain optic coherence tomography (OCT) and reported a prevalence of 34.1% at the end of 20-year follow-up of a population with an average age of 74 years.[6] The wide variability in reported prevalence rates may be attributable to differences in ethnicity of the study populations or medical technology utilized in the studies. Advanced age has been reported as a commonly recognized risk factor in different study groups.[7] Despite speculation of the presence of ocular and systemic risk factors associated with ethnicity (myopia,[7] hypermetropia[7], smoking[5], high education level,[7] hypercholesterolemia,[7] diabetes mellitus[7]), these have yet to be proven.

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ERM is a vitreoretinal interface pathology, and abnormal posterior vitreous detachment plays a key role in its development. It may develop as the result of the migration of retinal glial cells through small holes in the internal limiting membrane (ILM) formed during separation by the posterior hyaloid, and/or due to retention and transformation of some hyaloid cellular components on the retina surface during separation.[8,9] The hypothesis that microperforations in the ILM may be responsible for the physiopathology is supported by findings of retinal pigment epithelium (RPE) cells and retinal glial cells in postoperative histopathologic ERM examination in patients with no history of trauma, laser photocoagulation, or crypexy and no previous clinical findings of retinal pathology such as tear or hole.[10] In another study, histopathologic examination of ERM revealed the presence of vitreous hyalocytes, which supports the hypothesis that cells remaining on the retina surface following posterior vitreous detachment form a scaffold for ERM physiopathology.[9] It is known that hyalocytes are not specific to the vitreous, but originate from bone marrow and have gone through regeneration.[11] Therefore, although there is no scientific study proving that the hyalocytes composing the ERM structure originate from the vitreous, it is believed that ERM physiopathology involves the transformation and extracellular matrix formation of cells originating from these two mechanisms.[7]

Because idiopathic primary ERM is often a thin and transparent membrane resembling cellophane, it is also referred to as cellophane maculopathy. Cellophane maculopathy causes no traction and therefore no distortion in the neurosensorial retina or vascular structures, and is generally asymptomatic. Membrane thickening and contraction due to cellular transformation leads to distortion in the external and internal layers of retina, resulting in anatomical changes ranging from altered foveal contour to full-thickness macular hole.[12] Patients with macular distortion generally present with complaints such as metamorphopsia, diplopia, and reduced vision. Depending on their visual complaints, the patients are either scheduled for follow-up or elective surgery. The aim of this study was to present our experiences and visual outcomes achieved with patients who underwent surgery for visual complaints and idiopathic ERM.

Materials and Methods

The records of patients who underwent vitreoretinal surgery in our clinic due to idiopathic ERM between January 2012 and June 2014 were examined retrospectively. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. Pre- and postoperatively all patients underwent a detailed ophthalmologic examination including best corrected visual acuity (BCVA), anterior and posterior segment examination, and OCT. Standard triple sclerotomy followed by standard phacoemulsification surgery, intraocular lens implantation, and vitrectomy were performed for patients with nuclear sclerosis; standard triple sclerotomy and pars plana vitrectomy (PPV) was performed in patients without cataract. All surgeries were done using a 23-gauge Constellation® vision system (Alcon; Fort Worth, Texas). In the PPV, cut and flow rates were adjusted according to the patient's condition during core vitrectomy and removal of the vitreous base and hyaloid. A standard cut rate was not used in the surgeries, but a lower rate was preferred for vitrectomy and a higher rate was preferred for shaving. Following core vitrectomy, posterior hyaloid removal assisted by 0.1 mL (4 mg) triamcinolone acetonide (Kenacort-A; 40 mg/

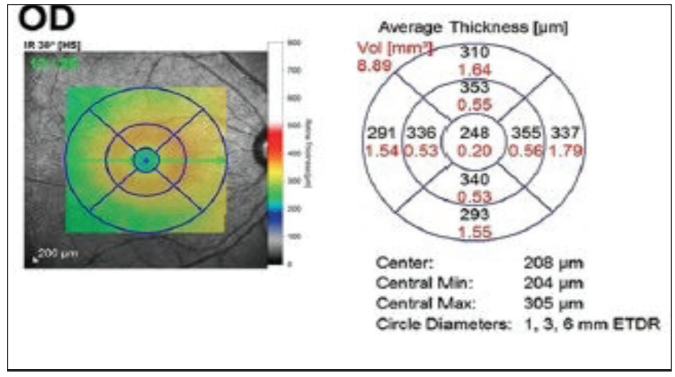

Figure 1. The thickness and volume values for the zones shown in the circle diagram were used as optical coherence tomography parameters
ETDR: Early Treatment Diabetic Retinopathy Study, OD: Right eye

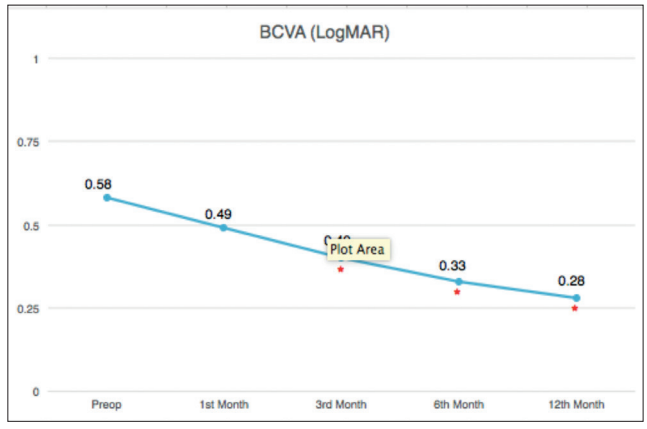

Figure 2. Best corrected visual acuity was significantly increased at postoperative 3, 6, and 12 months compared to preoperative levels

Table 1. Preoperative and postoperative best corrected visual acuity values (logMAR)

	Mean ± standard deviation	p value
Preop	0.58±0.32	
1st month	0.49±0.32	0.1
3rd month	0.40±0.31	<0.005
6th month	0.33±0.33	<0.005
12th month	0.28±0.34	<0.005

mL; Bristol-Myers Squibb, Princeton, NJ, USA), and vitreous base removal, the ILM was stained with brilliant blue or a dual dye and peeled from the area between the major vascular arcades. Examination and OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) findings at postoperative 1, 3, 6, and 12 months were evaluated. All imaging in the study was done by the same experienced technician using the same equipment, which is important in terms of data standardization for retrospective research. When evaluating the macula in patients with heterogeneous ERM-related macular changes, in our clinic we prefer raster scanning using a macular cube scanning protocol consisting of 6x6 mm square fovea-centered sections. Images obtained from the patients included in the study were used to prepare a macular map using a 1-, 3-, and 6-mm Early Treatment Diabetic Retinopathy Study grid (Figure 1).

Functional success was evaluated based on BCVA increase (logMAR). Evaluation of anatomic success was based on pre- and postoperative OCT measurements of central macular thickness (CMT) and the maximum, average, and minimum thicknesses in the central 1-mm zone and thickness/volume in the central 3-mm and 6-mm areas.

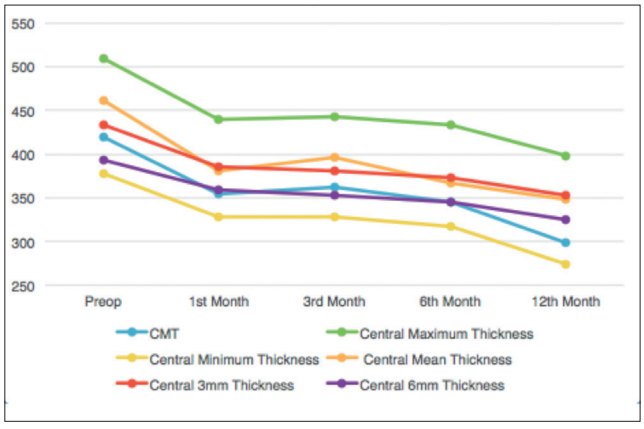

Figure 3. Postoperative change in optical coherence tomography parameters related to macular thickness

Statistical Analyses

Descriptive and statistical analyses of the data were done using SPSS version 21.0 software. Changes in visual acuity and OCT measurements were evaluated using paired-samples t-test. Correlation between these changes was assessed using Spearman's correlation coefficient for the non-normally distributed variables central maximum thickness, central 3-mm thickness, central 3-mm volume, and central 6-mm volume. Pearson's correlation coefficient was used for the other normally distributed variables.

Results

Of the 45 patients included in the study, 16 (36%) were males and 29 (64%) were females, and the mean age was 69±8.2 years. The mean postoperative follow-up period was 7±4 (1-12) months. BCVA was worse than 0.70 logMAR in 48.9% of the patients preoperatively but only 6.6% of the patients postoperatively. Mean BCVA of all patients was 0.58±0.32 preoperatively, 0.40±0.31 at postoperative 3 months, 0.33±0.33 at 6 months, and 0.28±0.34 at 12 months. The increase in BCVA was significant at 3, 6, and 12 months (Figure 2; Table 1). Postoperatively, 39 patients (86.8%) had a gain in visual acuity of at least two lines, while 4 patients (8.8%) showed no change. The lack of change was attributed to cataract in two of those patients and cystoid macular edema in the other two. Visual acuity declined in 2 (4.4%) cases, one due to retinal detachment in the third month and the other due to intense cataract development.

Comparison of pre- and postoperative OCT measurements of CMT, central maximum, central minimum, central average, and central 3-mm, and central 6mm thickness and volume values demonstrated significant anatomic recovery at 1, 3, 6, and 12 months (Figure 3 and 4; Tables 2 and 3).

Correlation analysis of increased BCVA and changes in OCT values revealed statistically significant, strong positive correlations between visual gain and central average thickness ($r=0.69$, $p<0.05$) and central volume change ($r=0.69$, $p<0.05$) (Table 4). CMT, central minimum thickness, and central 3-mm

Table 2. Comparison of preoperative and postoperative thickness parameters on optical coherence tomography

	CMT		Central maximum		Central minimum		Central average		Central 3 mm		Central 6 mm	
	Mean ± standard deviation	p value	Mean ± standard deviation	p value	Mean ± standard deviation	p value	Mean ± standard deviation	p value	Mean ± standard deviation	p value	Mean ± standard deviation	p value
Preop	419.40±125.35		509.77±103.03		377.47±127.56		444.19±117.18		432.58±52,55		392.92±40.83	
1st month	354.48±96.26	<0.05	439.59±53.06	<0.05	327.25±84.12	<0.05	380.60±98.65	<0.05	384.81±36,93	<0.0001	358.57±30.23	<0.0001
3rd month	362.39±129.61	<0.05	443.17±89.55	<0.05	328.60±108.43	<0.05	396.69±94.43	<0.05	380.60±48,61	<0.0001	352.89±37.71	<0.0001
6th month	344.85±120.90	<0.05	433.14±87.11	<0.05	316.71±96.02	<0.05	365.96±118.54	<0.05	372.22±56,41	<0.0001	345.32±43.38	<0.0001
12th month	298.50±86.58	<0.05	398.30±47.34	<0.05	274.10±78.79	<0.05	347.90±56.14	<0.05	352.26±32,60	<0.005	324.87±36.79	<0.005

CMT: Central macular thickness

volume values were negatively correlated with visual gain, but the relationships were not statistically significant. The other parameters had weak but nonsignificant positive correlation.

Discussion

In the Blue Mountains Eye study, of 245 eyes with baseline ERM, progression was observed in 29%, regression in 26%, and no change in 39% of the eyes at 5-year follow-up.[12] Only 20% of the cases classified as cellophane maculopathy in that study showed progression. In our clinic, we also inform patients diagnosed with cellophane maculopathy about the symptomatology and invite them for regular follow-up. Findings of irreversible photoreceptor damage in OCT are associated with poor postoperative visual prognosis, and thus early surgeries afford better visual prognosis.[13] Therefore, we recommend early surgical treatment before photoreceptor damage is detected in OCT. Cataract progression accelerates in phakic eyes following ERM surgery.[14] Rahman and Stephenson[15] also reported that patients who had early surgery, especially combined procedures including cataract removal, experienced faster postoperative visual rehabilitation with better visual gains. Among our patients, 14 (31%) underwent combined procedures, and there were no differences between the pseudophakic and combined surgery groups in terms of postoperative visual acuity or amount of visual improvement. In a 10-year retrospective analysis, Dawson et al.[16] observed no significant differences between the combined surgery and pseudophakic groups in terms of final visual acuity levels or pre- and postoperative complications. However, they reported that the patients with higher preoperative visual acuity had higher final visual acuity and those with lower preoperative visual acuity had more significant increases in visual acuity. The most common early complication after combined surgery is increased intraocular pressure.[17] The most common late complication is posterior capsule opacification.[18] We did not encounter elevated intraocular pressure or posterior capsule opacification severe enough to cause visual symptoms in any of our patients postoperatively. One of the shortcomings of this retrospective study is that we have no data regarding progression of posterior capsule opacification. In their prospective study, Ahfat et al.[18] reported a high rate of posterior capsule opacification (42.1%). ILM peeling in the same session is recommended because cells remaining after ERM removal can form a new scaffold on the ILM and lead to recurrent ERM.[19] None of the patients in our study who underwent routine ILM peeling assisted by dual dye experienced recurrence.

Surgical decisions for ERM patients should be based primarily on their OCT changes and symptoms such as metamorphopsia or micropsia instead of preoperative visual acuity because there is a known association between reduced visual acuity and

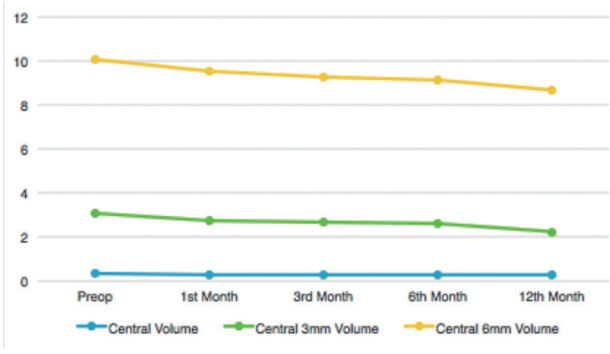

Figure 4. Postoperative change in the optical coherence tomography parameters related to macular volume

Table 3. Comparison of preoperative and postoperative volume parameters on optical coherence tomography

	Central volume		Central 3 mm volume		Central 6 mm volume	
	Mean ± standard deviation	p value	Mean ± standard deviation	p value	Mean ± standard deviation	p value
Preop	0.35±0.06	p<0.05	3.04±0,35	p<0.05	10.09±1.29	p<0.0001
1st month	0.30±0.04	p<0.05	2.71±0.24	p<0.05	9.50±1.09	p<0.0001
3rd month	0.31±0.07	p<0.05	2.68±0.30	p<0.05	9.24±1.11	p<0.0001
6th month	0.29±0.06	p<0.05	2.61±0.37	p<0.05	9.15±1.31	p<0.0001
12th month	0.27±0.04	p=0.275	2.24±0.68	p=0.057	8.67±1.36	p<0.05

Table 4. Correlation between postoperative optical coherence tomography parameters and best corrected visual acuity levels

	CMT	Central maximum	Central minimum	Central average	Central volume	Central 3 mm thickness	Central 3 mm volume	Central 6 mm thickness	Central 6 mm volume
BCVA	-0.339	0.46**	-0.432	0.694*	0.692*	0.468**	(-0.17**)	0.407	0.043**

Spearman correlation analysis, *Statistically significant
BCVA: Best corrected visual acuity, CMT: Central macular thickness

photoreceptor damage; therefore, these patients have poor visual prognosis.[13] Functional gains are evaluated based on visual acuity and improvement of patients' preoperative subjective complaints. Anatomic gains are followed with CMT and foveal contour on OCT imaging. In a study by Güngel et al.[20], no correlation was found between postoperative visual gains and reduced macular thickness. Other studies investigating this relationship also revealed no correlation between macular thickness and visual gains.[21,22] The present study was planned with the belief that the lack of correlation between reduced macular thickness and functional gains is due to the heterogeneous macular distortion caused by the ERM and that there may be a correlation with changes in central macular volume as opposed to thickness, and we found that the postoperative reduction in macular volume in the central 1-mm area was correlated with functional visual gains.

Conclusion

Although ERM formation may occur on different parts of the retina due to different etiologies, visual complaints are generally caused by ERM that develops over the macula. Macular ERMs can cause symptoms proportionate to the degree of distortion and subsequent photoreceptor damage that they cause. CMT is not a reliable source of information about heterogeneous tissue distortion; therefore, monitoring changes in central volume over follow-up can give more accurate results. Furthermore, in prospective studies, patients with different central volumes may be grouped preoperatively for a comparison of postoperative gains. This may allow the planning of surgical treatment for patients who have reached a predetermined central volume value before photoreceptor damage and the onset of visual complaints, thus enabling better outcomes.

Ethics

Ethics Committee Approval: Gülhane Training and Research Hospital Ethics Committee (decision no: 09.02.2016 2/82).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Küçükevcilioğlu, Ali Hakan Durukan, Concept: Dorukcan Akıncıoğlu, Gökhan Özge, Design: Dorukcan Akıncıoğlu, Fazıl Cüneyt Erdurman, Data Collection or Processing: Dorukcan Akıncıoğlu, Gökhan Özge, Analysis or Interpretation: Dorukcan Akıncıoğlu, Gökhan Özge, Literature Search: Dorukcan Akıncıoğlu, Writing: Dorukcan Akıncıoğlu.

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Review

Is There a Relationship Between Use of Anti-Vascular Endothelial Growth Factor Agents and Atrophic Changes in Age-Related Macular Degeneration Patients?

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Abstract
Choroidal neovascularization due to age-related macular degeneration (AMD) is currently treated successfully with anti-vascular endothelial growth factor (VEGF) intravitreal agents. Emerging evidence suggests that anti-VEGF treatment may potentially increase development of geographic atrophy. However, there is not yet direct proof of a causal relationship between geographic atrophy and use of anti-VEGF agents in nAMD. The aim of this review is to discuss the evidence concerning the association between anti-VEGF therapy and progression of geographic atrophy.
Keywords: Anti-VEGF agents, geographic atrophy, age-related macular degeneration

Introduction

Intravitreal anti-vascular endothelial growth factor (VEGF) application has been the most effective treatment method in recent years for neovascular age-related macular degeneration (AMD).[1,2,3] The common feature of the multicenter studies conducted in this area with different agents and for different purposes is that they first determined the efficacy and safety of these agents. In the MARINA and ANCHOR trials, monthly ranibizumab injections preserved visual acuity and maintained vision level, and this finding has been clearly demonstrated in evidence-based, controlled comparative studies.[1,2] Two main points have recently been raised regarding the safety of anti-VEGFs. The first concern is local side effects such as endophthalmitis, vitreal hemorrhage, or retinal detachment, and the second is systemic side effects, especially cerebrovascular events. However, studies of these extremely rare adverse events showed that the use of these agents was not significantly associated with the likelihood of developing such complications.[1,2,3,4,5]

Retrospective analyses of multicenter studies have provided new and interesting findings. One example is evidence from the CATT[3] trial which suggests a relationship between long-term anti-VEGF therapy and the development of geographic atrophy. The IVAN[4] and HARBOR[6] trials were also retrospectively analyzed in terms of this possible relationship and reported suspicious findings similar to those found in the CATT trial.[3,4,5,6,7,8]

Therefore, one of the most important questions of recent times is whether late geographic atrophy is really more prevalent in patients with long-term anti-VEGF use, and if so, what role the anti-VEGF agents play in the development of geographic atrophy.

Geographic Atrophy: Natural Course

Geographic atrophy is an age-associated pathology whose etiopathogenesis involves complex processes.[7,8,9] The main factor is an atrophic process that begins in the retinal pigment epithelium (RPE) and choriocapillaris.[9] Genetics and aging

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are the main risk factors.[10] Parallel to senescence of retinal pigment epithelial cells, lipofuscin begins to accumulate in the cytoplasm due to slowing lysosomal activities, resulting in a vicious cycle. Metabolism slows with aging, especially lysosomal metabolism, and phagocytosed lipid-rich material does not dissolve, accumulating as a result. These deposits, particularly of lipofuscin, increase oxidative stress and accelerate aging. This vicious cycle leads to faster atrophy and RPE cell loss. Lipofuscin increases oxidative stress and RPE cell apoptosis.[11] In geographic atrophy, autofluorescence imaging in particular shows RPE cells that are still viable but lipofuscin-laden concentrated along the margin of the advancing atrophic zone. After cell loss, this autofluorescence disappears and the area darkens, demonstrating RPE cell death. This phenomenon demonstrated by fundus autofluorescence can be assessed as the front of geographic atrophy expansion.[12]

In fact, geographic atrophy is atrophy of the RPE and choriocapillaris, and is consistent with the natural course of aging. In some patients, however, cells with an oncogenic phenotype undergo an exceptional change, with some regaining the ability to divide and starting to divide aggressively. In some patients who convert from geographic atrophic to wet AMD, the RPE cells exhibit high sensitivity to VEGFs, resulting in neovascularization. These appear as cases of wet AMD.[13] In wet AMD patients, the neovascular process continues on one hand, while geographic atrophy continues as part of the natural disease course on the other hand. Therefore, while the underlying process of geographic atrophy continues in these wet AMD patients, they are also receiving intravitreal anti-VEGF therapy. In fact, geographic atrophy may be related to the ongoing natural course.[14]

The Risk of Developing Geographic Atrophy due to Anti-VEGF Use: Results of Multicenter Studies

Significant visual gains can be achieved in AMD patients with choroidal neovascularization (CNV) with long-term intraocular injection of numerous anti-VEGF agents.[1,2,3,4,6] However, there is debate in the literature regarding whether the geographic atrophy seen during long-term follow-up in these patients, who had received many anti-VEGF injections at high frequency, was a result of the natural course of the disease or was associated with the anti-VEGF molecules used. Our current understanding of the relationship between geographic atrophy and anti-VEGF use is summarized in Table 1.

It was noted with the CATT[15] study that geographic atrophy may be associated with anti-VEGF agents. A retrospective evaluation of the CATT[15] study revealed that geographic atrophy had developed in 18.3% of the patients (187 of 1024 patients) at the end of 2 years. It was also observed in the retrospective analysis that there was a difference between the monthly application and pro re nata (PRN) groups in terms of geographic atrophy. Of the patients who were administered monthly ranibizumab, 4.7% exhibited foveal atrophy and 21.1% extrafoveal atrophy at the end of year 2. These rates were 3.7% and 11.5%, respectively, in the patients who received ranibizumab PRN. Although the monthly and PRN ranibizumab groups did not differ significantly in terms of foveal atrophy development, the difference in extrafoveal atrophy rate was statistically significant. It was determined in the CATT[15] study that the important common risk factors among patients who developed geographic atrophy were vision level of 0.1 or lower, retinal angiomatous proliferation, geographic atrophy in the fellow eye, and baseline intraretinal fluid. Conversely, factors associated with lower risk included blocked fluorescein, subretinal fluid thickness of 25 µm or more, subretinal tissue complex thickness of 275 µm or greater, and the presence of vitreoretinal adhesions. The CATT[15] study compared the 1- and 2-year results of treatment with ranibizumab and bevacizumab. Although the patients in the ranibizumab group showed a higher risk of developing geographic atrophy, there was no difference in incidence between the groups at the end of the treatment regimen. Geographic atrophy was extrafoveal in the majority of patients.

In contrast to the CATT, the 2-year results of the IVAN[4] trial did not reveal a significant difference in geographic atrophy rates between patients treated with ranibizumab and those treated with bevacizumab (28% with ranibizumab, 31.2% with bevacizumab, p=0.46). When the results of the CATT[15] and IVAN[4] trial were interpreted together, the relationship between

Table 1. Evaluation of the relationship between geographic atrophy and anti-vascular endothelial growth factor use according to the literature

Patients with wet AMD who receive intravitreal anti-VEGF injections develop geographic atrophy in later stages. This process also occurs in the natural course of the disease. However, there is some debate regarding the extent to which this atrophy is related to the use of the agent
No difference was observed between the agents used (bevacizumab and ranibizumab) in terms of geographic atrophy development. It can be said that the agents are not a risk factor. There is no data on aflibercept in this respect
Ranibizumab dosage (0.5 or 2 mg) was not associated with incidence of geographic atrophy development. In other words, ranibizumab dose was not considered a risk factor
Patients with atrophy in the fellow eye have been shown to have a slightly higher risk of atrophy in the presence of intraretinal fluid in the treated eye. In patients with baseline geographic atrophy, the geographic atrophy tends to expand more rapidly in cases with geographic atrophy in the fellow eye, wet AMD, or scar
The results of HARBOR indicated that risk of developing geographical atrophy was lower in the presence of subretinal fluid, suggesting that extreme efforts to eliminate fluid could be abandoned
In the HARBOR trial, when patients treated according to a PRN regimen were analyzed separately based on number of injections, a greater number of injections was associated with lesser extent of atrophic change. This result contradicts other findings that indicate monthly injection is disadvantageous compared to PRN. For example, patients receiving 7-12 injections over 2 years of PRN treatment had a 29% incidence of atrophy, while the incidence was 18% and 19% respectively for patients who received 13-18 injections and >18 injections (nearly equivalent to monthly)
In subanalysis of the CATT and IVAN trials, comparison of patients treated with monthly and PRN administration showed that the average rate of atrophy development was lower in the PRN group
AMD: Age-related macular degeneration, VEGF: Vascular endothelial growth factor, PRN: Pro re nata

intravitreal agents and the development of geographic atrophy could not be proven definitively. However, the IVAN[4] trial revealed a correlation between the development of geographical atrophy and the frequency of intravitreal anti-VEGF applications. At 2-year follow-up, the risk of developing geographic atrophy was reported as 34% with monthly intravitreal administration and 26% with PRN administration. The methods used to evaluate geographic atrophy in the CATT[15] and IVAN[4] studies were different. There was no agreement or consistency between the studies regarding the methodology of atrophy assessment. In the CATT[15] trial, fundus fluorescein angiography (FFA) and color fundus imaging were used to detect atrophic areas. In the IVAN[4] study, atrophic areas were visualized with FFA, color fundus, and optical coherence tomography (OCT) at baseline and during follow-up. Different techniques were also utilized to determine geographic area in the trials. However, there is still a lack of clarity concerning the questions of how geographic atrophy should be identified and which techniques (FFA, fundus autofluorescence, color fundus photography, OCT) should be used. The presence of active choroidal neovascular lesions presents the greatest challenge to the precise determination of the area of geographic atrophy. Atrophy is ideally detected by evaluating an atrophic area distant to the CNV lesion to demonstrate the effect of anti-VEGF therapy. The geographic atrophy surrounding areas of CNV may grow over time and merge with distant atrophic regions in the long term. Areas of geographic atrophy in CNV areas can actually be visualized with FFA and even with OCT, and their boundaries can be determined.

In brief, despite different assessment techniques, both the 2-year results of CATT[15] and the late subanalyses performed after conclusion of the IVAN[4] trial showed that treatment was associated with higher incidence of geographic atrophy, but it was usually extrafoveal and did not affect vision significantly. They also indicated that the agents used were not influential in this phenomenon but that administration regimen may have an effect, with a PRN regimen being more favorable than monthly injections. Subanalysis of the HARBOR[6] trial was similar to the CATT[15] and IVAN[4] trials. HARBOR[6] is a Phase 3 trial in which the 2-year efficacy results of two different doses of ranibizumab (0.5 mg and 2 mg) with two different administration regimens (monthly/PRN) were evaluated in treatment-naive wet AMD patients with active subfoveal CNV (n=1097). Geographic atrophy was assesessed using FFA and color fundus images at 3, 12, and 24 months. Similar to the IVAN[4] trial, baseline areas of atrophy were also taken into account in the HARBOR[6] trial. Included in the areas of geographic atrophy were depigmented areas with prominent borders and increased visibility of choroidal vessels, areas with diameters greater than ≥250 µm, and attached, flat areas with prominent borders on FFA. However, atrophic areas with RPE tears were excluded. In the HARBOR[6] trial, areas of atrophy adjacent to and nonadjacent to CNV were separately identified and evaluated. Lesions adjacent to CNV were especially included to achieve comparable results to the CATT[15] and IVAN[4] trials. In the HARBOR[6] study, the incidence of atrophy in the eyes with no detectable atrophy at baseline was 29% according to results at 24 months. Based on this finding, there were no significant differences in atrophy incidence when compared with the CATT[15] (20%) and IVAN[4] (28%) trials. In the CATT[15] trial, patients with baseline atrophy in the initial examination were not included in the evaluation. For this reason, the incidence of atrophy was found to be lower compared to the IVAN[4] and HARBOR[6] trials, which included patients with baseline atrophy. IVAN[4] and HARBOR[6] are more comparable in terms of patient groups, and the total incidence of atrophy, including existing (baseline) and newly developed atrophy, was equivalent at 28% and 29% respectively. In a subgroup analysis of the 5-year results of the CATT[16] trial, the incidence of geographic atrophy was found to be 38%. The development of geographic atrophy was common and risk factors present at 2 years persisted at 5 years. The most important risk factors at start of treatment for the development of geographic atrophy were advanced age, poor visual acuity, widespread CNV, retinal angiomatous proliferation, geographic atrophy in the fellow eye, and intraretinal fluid. Thick subretinal tissue complex and presence of subretinal fluid were less associated with development of geographic atrophy. Incidence rates of geographic atrophy in post hoc analyses of the IVAN, CATT, and HARBOR trials are summarized in Table 2.

These findings point to two major conclusions from the HARBOR[6] trial. One of these is that the agent used was not

Table 2. Comparison of the results of multicenter, randomized clinical trials showing the incidence of geographic atrophy related to anti- vascular endothelial growth factor use in wet age-related macular degeneration

	Patient number (n)	Anti-VEGF agent	Treatment regimen	Professional experience	Method	GA development
Chakravarthy et al.[4] (IVAN study)	525	Bevacizumab Ranibizumab	1.25 mg 0.5 mg	24 months	FFA, OCT, Color fundus photograph	Bevacizumab 31% Ranibizumab 28%
Grunwald et al.[15] (CATT study 2-year results)	1024	Bevacizumab Ranibizumab	1.25 mg 0.5 mg/PRN	2 years	FFA, Color fundus photograph	18%
Sarraf et al.[6] (HARBOR study)	1097	Ranibizumab	0.5 mg/PRN 2 mg/PRN	24 months	FFA, Color fundus photograph	PED (-) 29% PED (+) 32%
Grunwald et al.[16] (CATT study 5-year results)	517	Bevacizumab Ranibizumab	1.25 mg 0.5 mg/PRN	5 years	FFA, Color fundus photograph	38%

GA: Geographic atrophy, FFA: Fundus fluorescein angiography, OCT: Optical coherence tomography, PED: Pigment epithelial detachment, PRN: Pro re nata, VEGF: Vascular endothelial growth factor

influential on the development of atrophy, as in the CATT[15] and IVAN[4] trials. In the HARBOR[6] trial, it was observed that the dose (0.5 mg vs. 2 mg) and number (monthly vs. PRN) of ranibizumab injections administered were not associated with rates of atrophy development.

Another important issue that must be considered in relation to geographic atrophy development is the effects of atrophic changes on visual acuity. Especially in the CATT[15] trial, it may have been difficult to notice these extrafoveal atrophic areas if the retrospective analysis had not been performed, and since most of them had no effect on visual acuity, it is understandable that they could be overlooked by a researcher. In subanalysis of the study, no statistically significant difference was detected in the comparison of visual changes in patients with and without atrophy.

Conclusion

In conclusion, retrospective analyses of the CATT[15,16], IVAN[4], and HARBOR[6] trials suggest that long-term intravitreal anti-VEGF therapies increase geographic atrophy in wet AMD patients. Even if this is the case, however, considering that 80% of these atrophic changes are extrafoveal and do not directly affect visual acuity, wet AMD patients should nevertheless be treated with adequate duration and frequency despite this possibility. As observed in the MARINA[1] and ANCHOR[2] trials, treatment yields visual gains of over 20 letters, compared to the loss of 14 letters in the sham group, which reflects the natural disease course. Even if atrophy does develop, the difference in letters gained between the patients with and without atrophy is 2.4 letters at 24 months. In light of these findings, it remains to be clarified whether the areas of geographic atrophy seen after anti-VEGF therapy in wet AMD are associated with the natural course of the disease or emerge as a result of the anti-VEGF molecules used in treatment. Regardless, considering the approximately 20-letter gain achieved over a 2-year period in these patients compared to the natural course, we believe these therapies are still indispensable for the treatment of wet AMD.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Süleyman Kaynak, Concept: Süleyman Kaynak, Design: Süleyman Kaynak, Mahmut Kaya, Data Collection or Processing: Süleyman Kaynak, Mahmut Kaya, Derya Kaya, Analysis or Interpretation: Süleyman Kaynak, Mahmut Kaya, Literature Search: Mahmut Kaya, Derya Kaya, Writing: Süleyman Kaynak, Mahmut Kaya, Derya Kaya.

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Case Report

Descemet Membrane Endothelial Keratoplasty with Irregular-Edged Graft: A Salvage Method for Large Radial Graft Tears

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Abstract

Large radial tears of donor Descemet membrane (DM) during the preparation of Descemet membrane endothelial keratoplasty (DMEK) grafts can make the trephination stage impossible because of small graft diameter. This results in irregular-edged grafts. In this study, we report two pseudophakic bullous keratopathy patients who underwent DMEK surgery with irregular-edged Descemet membrane (DM) grafts. Main outcome measures were preoperative and postoperative 1-, 3-, and 6-month best corrected visual acuity (BCVA), endothelial cell density (ECD) and central corneal thickness (CCT). Intraoperative and early postoperative complications were also evaluated. Both irregular-edged grafts were successfully implanted into the anterior chamber, unfolded, and attached to the posterior corneal stroma. Patients' BCVA at 6 months was 1.0 (Snellen equivalent: 20/20) and 0.6 (Snellen equivalent: 20/32) respectively. Decrease in ECD at the last visit was 27% and 25%. CCT decreased from 723 µm and 850 µm to 530 µm and 523 µm, respectively. No intraoperative complications occurred except for the large radial Descemet membrane graft tears that developed during donor DM stripping. None of the cases needed a rebubbling procedure postoperatively. We have demonstrated that irregular-edged DM grafts can be successfully implanted for DMEK surgery with good clinical outcomes.

Keywords: Descemet membrane endothelial keratoplasty, large radial tears, irregular-edged Descemet membrane graft

Introduction

Descemet membrane endothelial keratoplasty (DMEK) is the latest refinement of endothelial keratoplasty procedures. Providing an exact anatomical replacement of only what is removed, it gives the possibility of excellent visual acuity with shorter healing time as well as minimal risk of immunological rejection.[1,2] However, preparing the 15-µm-thick Descemet membrane (DM) graft is still a challenging issue and is sometimes complicated by surgeon- or donor-related DM graft tears and graft failure. Standardized techniques for graft preparation, surgical instruments designed for endothelial keratoplasty, and accumulating experience over time have led to a significant reduction of tissue loss. However, as the donor-related risk factors for failure in donor tissue preparation have not been clearly determined, the potential risk for radial DM tearing still exists. By pulling the torn flaps peripherally and skipping the trephination stage of the graft preparation technique described by Melles et al.,[3,4] these irregular-edged grafts can still be successfully implanted. In this study, we describe the clinical results of two eyes with pseudophakic bullous keratopathy treated with DMEK with irregular-edged DM graft.

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Case Report

Patients

Case 1 was a 72-year-old female patient with a 1-year history of pseudophakic bullous keratopathy in the right eye. Intraocular lens was in the bag and posterior capsule was intact. Best corrected visual acuity (BCVA) was counting fingers from 1 meter (20/2000) with a central corneal thickness (CCT) of 723 µm. Case 2 was a 48-year-old female patient who underwent primary suturation after a penetrating corneal injury to her left eye 2 years earlier. She had scleral fixation of an IOL and trabeculectomy for glaucoma 1.5 years earlier. She had endothelial decompensation in the left eye with a BCVA of hand motions (20/20000). Her CCT was 850 µm with a central corneal scar. Both cases were contact lens-dependent and were using 5% hypertonic ophthalmic solutions.

Donors and Graft Preparation

Donor cornea-scleral buttons were obtained less than 24 h postmortem (donor ages 50 and 67 years, endothelial cell density (ECD) 2450 and 2530 cells/mm^2, respectively) and stored in corneal storage medium (Optisol-GS, Bausch & Lomb, Irvine, CA, USA) at 4 °C. Graft preparation was done preoperatively in the operating room by applying the technique described in detail by Melles et al.[3,4] Cornea-scleral buttons were mounted endothelial side up on a holder. Descemet membrane–endothelial complex (DEC) was dissected gradually from the periphery to the center starting with a hockey stick knife. In both cases, large radial tears formed during stripping because of focal adhesions between DM and stroma. Radial tears were manipulated by pulling the flap peripherally, forming an irregular edge with no radial tears. This technique allowed preparation of irregular-edged, non-uniform grafts. In our standard technique, stripped DEC surrounded by a 360-degree trabecular meshwork ring is transferred on a soft contact lens and trephined to obtain a 9-9.5-mm regular-edged circular graft. However, since both grafts were smaller than 9 mm in the largest dimension, trephination was not possible. For both cases, the irregular-edged grafts were formed into a DEC roll with the endothelium on the outside and stored in saline until the recipient's cornea was prepared.

Surgical Technique

Both surgeries were performed under general anesthesia using the "no-touch" technique described previously with slight modifications.[1,5] After making three 23-gauge and one 3.2-mm keratotomies, the DM was scored at a radius of 9.5 mm with a reverse Sinskey hook (DORC international BV, Holland) and removed from the anterior chamber under complete air fill. Then 0.1 mL of acetylcholine chloride (Miochol-e, 20 mg/mL, Novartis) was used to induce myosis in case 2 to reduce the risk of posterior dislocation of DEC roll. The DEC roll was injected into the recipient's anterior chamber using a glass injector (DORC international BV, Holland) and oriented endothelial side down by indirect manipulations with air and balanced salt solution. The graft was then uncurled and centered with a combination of corneal dome compression and sweeping of the corneal surface with cannulas. We ensured the graft covered the visual axis. Once the graft was centered, an air bubble was injected underneath the graft and left for 30 minutes under complete air fill. At the end of the procedure, 75% air fill was left (Figure 1). Incisions were not sutured.

Case 1 underwent a surgical peripheral iridotomy intraoperatively, while Case 2 had a preexisting peripheral iridectomy due to previous trabeculectomy surgery. The patients were requested to lie in supine position for 12 hours after surgery. We recommended 1% prednisolone acetate drops 5 times daily for 8 weeks (then tapered gradually), and 0.5% moxifloxacin drops 5 times daily for 2 weeks.

Postoperative Evaluations

The postoperative period was uneventful for both patients, with no DEC detachments requiring rebubbling. Both eyes had improved corneal clarity (Figure 2) and increased BCVA at 6 months. BCVA at 1 month and 6 months was 0.5 and 1.0 (with a -3.0 D cylinder) for case 1, and 0.2 and 0.6 (with a -2.0 D cylinder) for case 2, respectively. Intraocular pressures of cases 1 and 2 at 6 months were 18 mmHg and 20 mmHg, respectively.

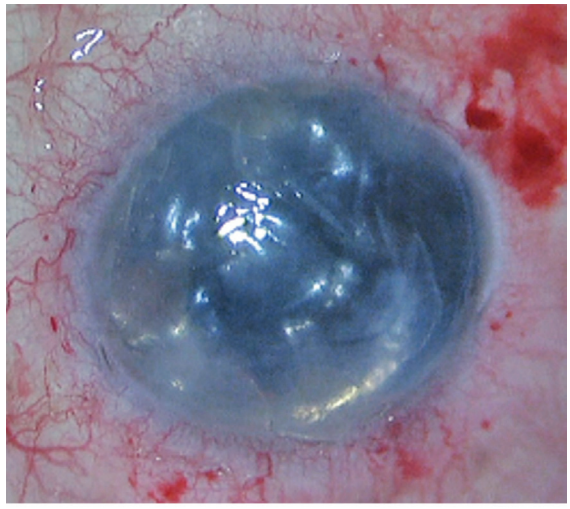

Figure 1. Graft position of case 1 at the end of surgery

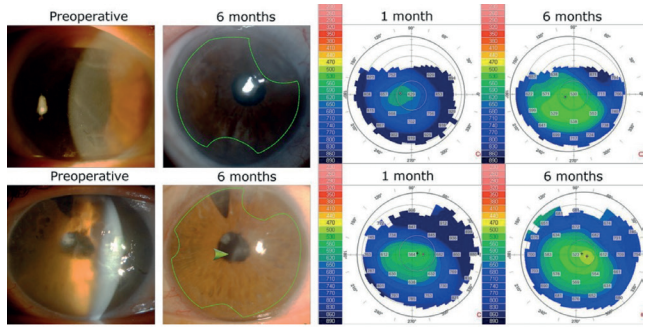

Figure 2. Preoperative and postoperative 6-month photos and corneal thickness maps of patients. Green lines outline the approximate position of irregular-edged Descemet membrane endothelial keratoplasty graft. Green arrowhead shows corneal scar in case 2 (First row represents case 1 and second row represents case 2)

Decrease in endothelial cell density at 6 months was 27% and 25% respectively. Central corneal thickness decreased from 723 µm and 850 µm before surgery to 530 µm and 523 µm respectively at postoperative 6 months (Figure 2). Preoperative and postoperative BCVA, ECD, and CCT values are summarized in Table 1.

In the immediate postoperative period, both cases had focal corneal edema limited to the areas of bare corneal stroma. These edematous areas corresponded with the denuded recipient stroma with no DEC because of the irregular graft shape. Edema resolved by the postoperative 6-month visit.

Table 1. Outcomes following Descemet membrane endothelial keratoplasty with irregular edged grafts

		Postoperative month		
Patient no (age)	**Preoperative**	**1 month**	**3 months**	**6 months**
1 (72)				
BCVA (Snellen equivalent)	CF (20/2000)	0.5 (20/40)	0.8 (20/25)	1.0 (20/20)
ECD, cells/mm^2 (%decrease)	2450	2000 (18)	1880 (23)	1800 (27)
CCT, µm Remarks	723 No	629	570	530
2 (48)				
BCVA (Snellen equivalent)	HM (20/20000)	0.2 (20/100)	0.4 (20/50)	0.6 (20/32)
ECD, cells/mm^2 (%decrease)	2530	2050 (19)	2000 (21)	1900 (25)
CCT, µm	850	564	550	523
Remarks	Central corneal scar and trabeculectomy			

BCVA: Best corrected visual acuity, ECD: Endothelial cell density of Descemet membrane graft, CCT: Central corneal thickness, CF: Counting fingers from 1 meter, HM: Hand motion

Discussion

DM graft preparation for DMEK surgery has been standardized previously with very low rates of tissue damage due to preparation.[6,7] However it can be complicated with large radial tears, making the trephination and usage of DEC graft impossible. Especially if the graft is prepared by the surgeon prior to surgery in the operating room, radial tear risk increases due to time limitations and surgical stress. To reduce the surgical stress, the surgeon can use eye bank-prepared donor tissue or prepare the tissue days before the surgery. It has been shown that eye bank-prepared grafts and surgeon-prepared grafts do not differ in terms of graft survival outcomes. Both preparation methods have a 5% graft preparation failure rate due to strong adhesions between DEC and stroma.[8] Although grafts prepared by the eye bank might have an advantage in decreasing the surgical stress, eye bank-preparation is more expensive compared to preoperative preparation. Even when the surgeon is preparing the graft days before surgery, the use of an extra corneal storage solution increases the total cost of the procedure. Radial tears in DEC grafts that are formed during preparation might increase in size during implantation and unfolding of the graft, resulting in dehiscence of the graft postoperatively.

This complication can be managed with a modification of standardized donor tissue preparation technique: rescuing the radial tears by pulling the flap peripherally, skipping the trephination phase, and implanting the irregular-edged graft. Recently, two studies have shown that partial DEC grafts can be implanted and may yield good clinical outcomes.[9,10] Since the risk of losing tissue is still the biggest concern of DMEK graft preparation, the modification we propose can be a salvage method for using grafts with large radial tears.

With irregular-edged grafts, large areas of denuded stroma with edema can be seen in the first postoperative months. Spontaneous resolution of focal edematous areas without DEC may be attributed to the migration of donor and/or recipient endothelial cells onto the denuded stroma.[9,10,11]

Although two cases may not be enough to evaluate the potential clinical outcomes of irregular-edged grafts, our results seem promising to salvage grafts with large radial tears. These irregular-edged, non-uniform DM grafts might be successfully implanted for DMEK surgery with the potential for favorable clinical outcomes.

Ethics

Informed Consent: Informed consent was obtained from both patients preoperatively.

Peer Review: Externally peer-reviewed.

Authorship Contributions

Concept: Mehmet Cüneyt Özmen, Design: Mehmet Cüneyt Özmen, Data Collection or Processing: Mehmet Cüneyt Özmen, Nilay Dilekmen, Erdem Yüksel, Bahri Aydın, Analysis or Interpretation: Mehmet Cüneyt Özmen, Erdem Yüksel, Bahri Aydın, Fikret Akata, Literature Search: Mehmet Cüneyt Özmen, Nilay Dilekmen, Writing: Mehmet Cüneyt Özmen.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Optic Nerve Avulsion and Retinal Detachment After Penetrating Ocular Trauma: Case Report

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Abstract

Optic nerve avulsion is a rare pathology with poor prognosis usually seen after blunt trauma. The optic nerve is separated from the sclera by indirect forces due to the relatively weak structure of the lamina cribrosa area. Here we describe an 11-year-old boy who experienced optic nerve avulsion and retinal detachment after penetrating ocular trauma.

Keywords: Ocular trauma, optic nerve, avulsion, retinal detachment

Introduction

Ocular trauma is among the leading causes of vision loss in children. In a population-based study conducted in the United States of America, the annual incidence of ocular trauma in children was found to be 15.2/100,000.[1] Studies conducted in other developed countries have yielded similar results, but the incidence is somewhat higher in developing countries. Traumatic optic neuropathy is seen in 0.5-5% of all head traumas.[2]

Avulsion of the optic nerve is a rare complication after ocular trauma but carries a poor prognosis. Traumatic optic nerve damage can occur via direct and indirect mechanisms in different parts of the optic nerve. These mechanisms can include anterior displacement of the globe, retraction of the nerve, sudden rotational movement of the globe, or sudden rise in intraocular pressure.[3] Due to the absence of connective tissue between the optic nerve fibers in the lamina cribrosa region and the absence of myelin sheathing around the nerve fibers, the optic nerve head is a relatively weak structure.

Case Report

An 11-year-old boy was brought to the pediatric emergency department due to a right eyelid injury sustained after falling from a tree. Systemic evaluation was normal and he was referred to the ophthalmology department. The patient reported having fallen onto a branch fragment from the tree approximately one hour earlier. Edema and ecchymosis of the right upper and lower lids, and a cutaneous wound in the nasal aspect of the right upper lid were observed on examination. Visual acuity was suspected light perception in the right eye and 10/10 in the left eye. Color vision and eye movements were normal in the patient's left eye but could not be evaluated in his right. The right pupil was middilated with intact consensual but no direct light response. The left eye exhibited normal direct but absent consensual pupillary light reflexes. Anterior segment examination of the right eye revealed hyperemic conjunctiva, clear cornea, and +1 cells in the anterior chamber. The fundus could not be evaluated due to vitreous hemorrhage. Anterior and posterior examinations in the left eye were normal. The patient was admitted to our unit for wound exploration, repair of the lid wound, and fundus examination under general anesthesia (Figure 1). With a prediagnosis of traumatic optic neuropathy, treatment was initiated with systemic steroids, and topical steroids for the anterior chamber reaction, and bed rest in an upright position was recommended.

The following day, the patient underwent wound site exploration and primary incision repair under general anesthesia, followed by fundus examination. The vitreous hemorrhage in the right eye had partially regressed. The retina was attached but had a diffuse pale appearance due to retinal arterial occlusion, and

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Received: 16.04.2017 **Accepted:** 29.11.2017

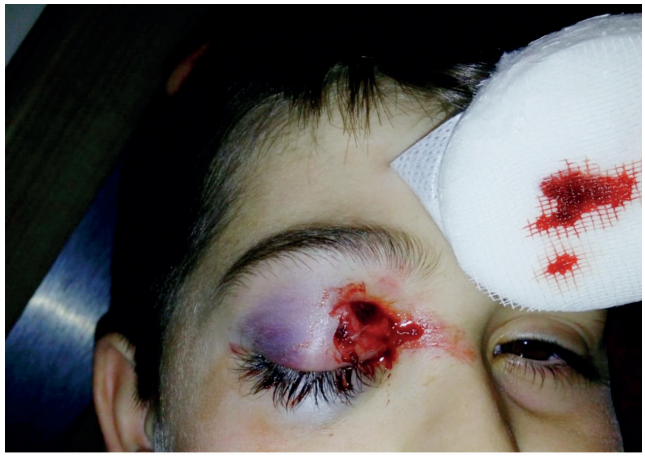

Figure 1. Ecchymosis of the upper and lower lids and laceration of the upper lid at presentation

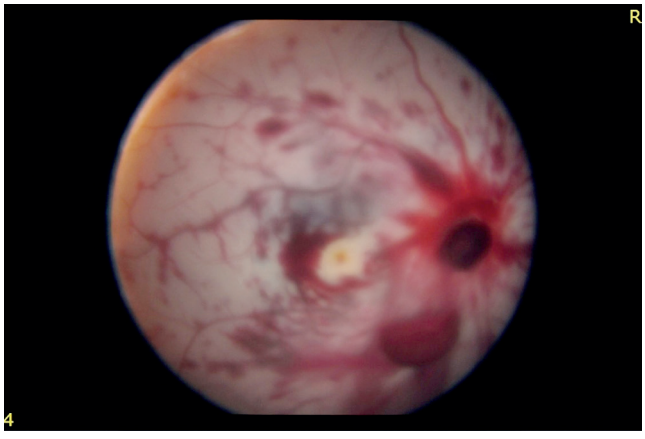

Figure 2. Fundus photograph in the right eye taken one day after the trauma

there were widespread intraretinal hemorrhages. The optic nerve head was apparently absent (Figure 2).

Brain tomography conducted in the emergency department and orbital magnetic resonance imaging (MRI) examination requested by ophthalmology showed no pathology other than sporadic hemorrhages in the vitreous and irregularity at the lamina cribrosa level consistent with right optic nerve avulsion. Based on the results of ophthalmologic examination and imaging, the patient was diagnosed with optic nerve avulsion (Figure 3). Systemic steroid therapy was not expected to be of benefit to the patient and was discontinued.

Examination one week later revealed total retinal detachment in the right eye, which was attributed the trauma. No interventions were considered due to the lack of light perception in the right eye and the patient was scheduled for follow-up, but he did not return.

Discussion

Avulsion of the optic nerve is a rare traumatic optic neuropathy which is currently untreatable, has poor visual

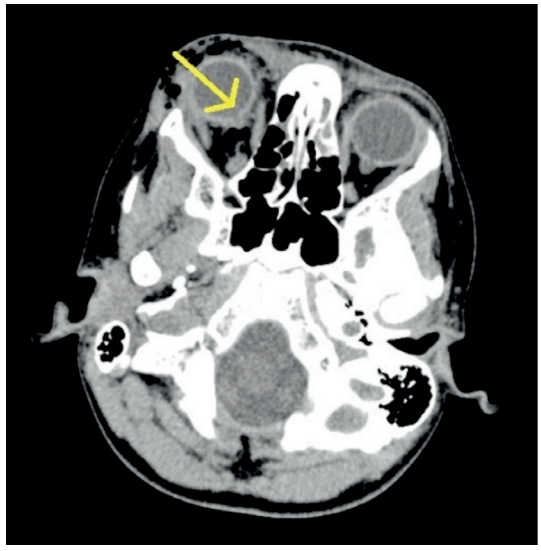

Figure 3. Computed tomography image taken one day after the trauma showing discontinuity of the right optic nerve in the sclera at the point of entry to the globe

prognosis, and occurs via indirect mechanisms and therefore, differentiating it from other traumatic optic neuropathies is important in terms of preventing unnecessary treatments and informing the patient.

Optic nerve avulsion can develop following blunt or penetrating ocular trauma through various indirect mechanisms. The optic nerve may become detached at the lamina cribrosa, which is the weakest point, due to trauma-related sudden increase in intraocular pressure, sudden posterior displacement of the optic nerve, and strong rotation or anterior displacement of the globe.[3] While it often occurs as a result of blunt trauma to the eye or impact to the face,[4] it occured after a penetrating orbital trauma in the present case. The only similar cases in the literature were described by Chaudhry et al.[5] in a retrospectively analysis of 14 children with severe vision loss due to door-handle injuries. They noted that in all cases the pointed door handle had penetrated the orbit medial to the globe and suggested that this caused optic nerve avulsion by creating a wedge effect which pushed the globe against the lateral orbital wall and displaced it anteriorly. Similar mechanisms occur in both blunt and penetrating orbital traumas. The wedge effect causes sudden anterior movement of the globe and the optic nerve can separate from the lamina cribrosa.

Because optic nerve avulsion is usually accompanied by vitreous hemorrhage, diagnosis by ophthalmoscopic examination is not always possible in the acute phase. Especially in cases of partial avulsion, imaging methods may not show definitive signs and the diagnosis may be overlooked.[6] Ocular ultrasound cannot be used in early evaluation of many patients due to the recent severe penetrating or blunt trauma.[7] However, radiologic imaging methods should be utilized without delay if ophthalmoscopic examination is inadequate to establish a diagnosis in suspected cases of optic nerve avulsion.

Based on previous reports in the literature, retinal detachment is uncommon after optic nerve avulsion. Only a few case reports have described late fibrosis and subsequent tractional retinal detachment in some patients with long-term follow-up.[3,8] In a case report by Mackiewicz et al.[9] a patient who was treated with high-dose systemic steroids for a week underwent ultrasonography due to lack of visual improvement (no light perception) and persistent vitreous hemorrhage, and retinal detachment was observed. Vitrectomy was performed at two months, after which cystic gliosis and optic nerve avulsion were detected. There was no change in visual acuity after six months of follow-up. Likewise, retinal arterial occlusion is rarely associated with optic nerve avulsion.[10] Our patient was distinct from other cases of optic nerve avulsion in that he exhibited both central retinal artery occlusion and early retinal detachment. The patient presented with a laceration in the superonasal region of the eyelid and was found to have complete avulsion of the optic nerve.

Although optic nerve avulsion can be diagnosed easily by ophthalmoscopic examination, accompanying vitreous hemorrhage can lead to delayed diagnosis and unnecessary high-dose systemic steroid treatment. Though rare, optic nerve avulsion should be considered in cases of severe post-traumatic vision loss when definite diagnosis cannot be established by ophthalmoscopic examination. Imaging with methods such as MRI and CT should be done promptly to diagnose pathologies of the globe and other intraorbital structures, including optic nerve avulsion.

Ethics

Informed Consent: Received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Fatih Kağan Değirmenci, Nilüfer Yalçındağ, Hüban Atilla, Concept: Mehmet Fatih Kağan Değirmenci, Nilüfer Yalçındağ, Hüban Atilla, Design: Mehmet Fatih Kağan Değirmenci, Nilüfer Yalçındağ, Hüban Atilla, Data Collection or Processing: Mehmet Fatih Kağan Değirmenci, Analysis or Interpretation: Mehmet Fatih Kağan Değirmenci, Nilüfer Yalçındağ, Hüban Atilla, Literature Search: Mehmet Fatih Kağan Değirmenci, Writing: Mehmet Fatih Kağan Değirmenci.

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Case Report

Olfactory Neuroblastoma: A Rare Cause of External Ophthalmoplegia, Proptosis and Compressive Optic Neuropathy

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Abstract

Olfactory neuroblastoma (ONB), which is a neuroectodermal tumor of the nasal cavity, is a rare and locally aggressive malignancy that may invade the orbit via local destruction. In this study, we report a patient with proptosis, external ophthalmoplegia, and compressive optic neuropathy caused by ONB. A detailed clinical examination including ocular imaging and histopathological studies were performed. The 62-year-old female patient presented to our clinic with complaints of proptosis and visual deterioration in the left eye. Her complaints started 2 months prior to admission. Visual acuity in the left eye was counting fingers from 2 meters. There was relative afferent pupillary defect. She had 6 mm of proptosis and limitation of motility. Fundus examination was normal in the right eye, but there was a hyperemic disc, and increased vascular tortuosity and dilation of the retinal veins in the left eye. Computerized tomography and magnetic resonance imaging of the brain and orbits demonstrated a large heterogeneous mass in the left superior nasal cavity with extensions into the ethmoidal sinuses as well as into the left orbit, compressing the medial rectus muscle and optic nerve. Endoscopic biopsy of the lesion was consistent with an ONB (Hyams' grade III). Orbital invasion may occur in patients with ONB. Therefore, it is important to be aware of this malignancy because some patients present with ophthalmic signs such as external ophthalmoplegia, proptosis, or compressive optic neuropathy.

Keywords: Compressive optic neuropathy, external ophthalmoplegia, olfactory neuroblastoma, proptosis

Introduction

Olfactory neuroblastoma (ONB), also referred to as esthesioneuroblastoma, was first described by Berger in 1924. It is a rare neuroectodermal malignant tumor of the nasal cavity originating from the olfactory neuroepithelium.[1] ONB constitutes 2-6% of all malignancies of the nasal cavity and paranasal sinuses. The incidence is highest in the second and sixth decades of life.[2,3,4] This fast-growing tumor can be asymptomatic until it fills the nasal cavity and causes obstruction and/or epistaxis. It may spread into the cranium, orbit, and paranasal sinuses. Orbital invasion can lead to vision loss, ophthalmoplegia, and proptosis. In this study, we present the clinical features of a 62-year-old female patient with olfactory neuroblastoma showing orbital invasion.

Case Report

A 62-year-old female patient presented to our unit with complaints of double vision. She stated that her double vision had started approximately one month earlier. Neuroophthalmologic examination revealed bilateral light responses with no afferent pupil defect. Color vision test with Ishihara (14 card print) was 14/14 in both eyes. The patient exhibited abnormal head posture (face turn to right) and hypertropia of the left eye (10 prism diopters). Slight restriction of left eye movement was noted in

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down/right gaze. There were no obvious limitations in the other positions of gaze. In the Bielschowsky head tilt test, hypertropia increased when the head was tilted to the left. Best corrected visual acuity on Snellen chart was 10/10 in both eyes. Anterior segment and fundus examinations were normal in both eyes. The patient was diagnosed with left fourth cranial nerve palsy and cranial imaging was requested to establish etiology; however, the patient did not return for follow-up. Approximately 2 months later, our unit was consulted again regarding the patient due to complaints of reduced vision and pain in the left eye. She also had complaints of progressive swelling in the left half of her face and enlargement of her left eye for about one month. On neuroophthalmologic examination, light response was normal in the right eye and weak in the left eye. Relative afferent pupil defect was noted in the left eye. Right eye movements were unrestricted in all directions, while left eye movements were restricted in all directions with minimal upward gaze (Figure 1). Proptosis was noted in the left eye, and Hertel exophthalmometer measurements were 18 mm for the right eye and 24 mm for the left eye. Best corrected visual acuity on Snellen chart was 9/10 in the right eye and counting fingers from 2 m in the left eye. Color vision score was 14/14 in the right and 0/14 in the left eye. Chemosis and upper lid edema were observed in the left eye on slit-lamp examination. The anterior segment appeared normal. Intraocular pressure measured by Goldmann applanation tonometry was 15 mmHg in both eyes. Fundus examination was normal in the right eye, while optic disc hyperemia and increased tortuosity and caliber of the retinal vessels were observed in the left eye (Figure 2). Reliable results could not be obtained in visual field and visual evoked potential tests. Computed tomography scans revealed a mass filling the left nasal cavity and anterior/posterior ethmoid sinuses, extending beyond the medial rectus muscle into the cone and compressing the optic nerve. Orbital magnetic resonance imaging revealed a soft tissue mass with homogeneous enhancement, hypointense in T1-weighted sequences and hyperintense in T2-weighted sequences, which appeared to be displacing the optic nerve inferiorly (Figure 3). Based on the results of histopathological examination of a punch biopsy obtained from the nasal passage, the patient was diagnosed with olfactory neuroblastoma (Hyams grade III). Immunohistochemical staining for differential diagnosis of the round cell tumor was negative for CD2, CD3, CD20, CD38, cytokeratin, CD99, HMB45 and GFAP. A small number of cells were positive for CD56, chromogranin, and synaptophysin, while very few cells were positive for BCL2, NF, and S100. Ki-67 labeling index was 25% (Figure 4).

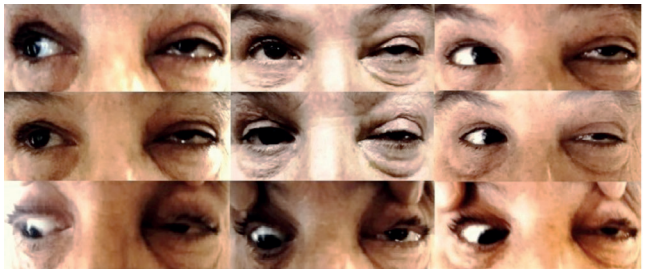

Figure 1. The nine cardinal positions of gaze. Periorbital edema and proptosis are seen in the left eye and movements are restricted in all directions except upgaze

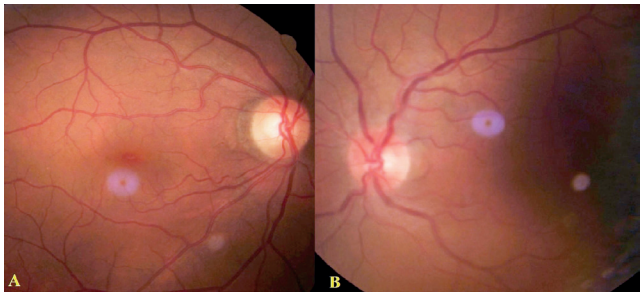

Figure 2. Color fundus photograph: the right eye appears normal (A), while the left eye shows hyperemic optic disc and increased vascular tortuosity and caliber of the retinal veins (B)

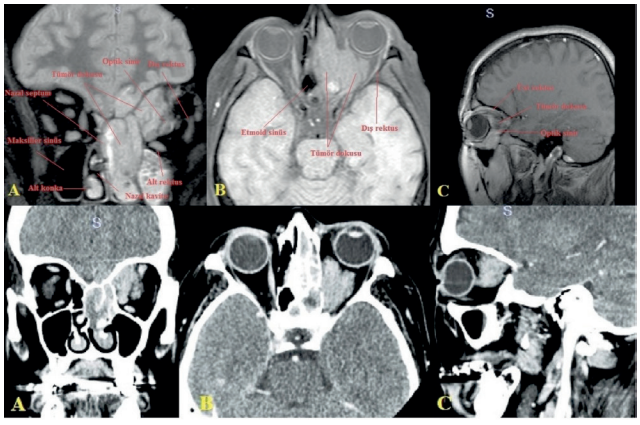

Figure 3. Magnetic resonance and computed tomography images: A mass is seen completely filling the left nasal cavity and anterior/posterior ethmoid sinuses, extending beyond the medial rectus muscle into the cone and displacing the optic nerve inferiorly in coronal (A), transverse (B), and sagittal (C) images

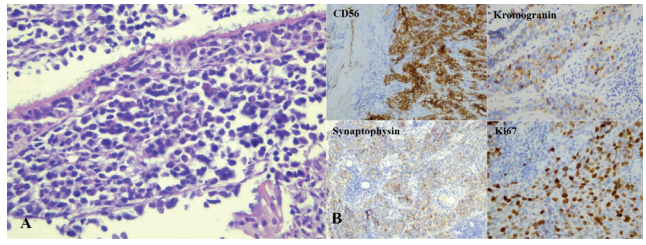

Figure 4. (A) Relatively uniform, noncohesive tumor cells with inconspicuous nucleoli, indistinct nuclear membranes, and low cytoplasmic ratio (hematoxylin and eosin; x400). (B) Immunohistochemical analysis of the tumor cells shows CD56, chromogranin, and synaptophysin positivity and Ki-67 labeling index indicated high proliferation

Discussion

The most common symptom of ONB was reported by Dulguerov and Calcaterra[5] as unilateral nasal obstruction,

which they observed in 71% of 26 patients. Other common symptoms are anosmia, headache, lacrimation, proptosis, and reduced vision. In rare cases, ONB secretes antidiuretic hormone (ADH) and causes syndrome of inappropriate ADH secretion, or produces ectopic adrenocorticotropic hormone and leads to Cushing's syndrome.[6] In a large series including 38 cases of ONB, Rakes et al.[7] reported that 53% of patients had orbital or ocular symptoms and that the most common symptoms were periorbital pain and lacrimation. In addition, they determined that diplopia was the initial ocular symptoms in 8% of the patients.[7] Most patients develop diplopia secondary to tumor invasion of the orbit. On the other hand, ONB can cause cranial nerve palsy without orbital invasion. Rakes et al.[7] reported cranial nerve palsy in a patient without orbital involvement in their series. Lee and Tang[8] also reported third cranial nerve palsy with pupil involvement due to mass extension to the cavernous sinus, without orbital involvement. Fourth cranial nerve palsy was the first clinical finding in our case; however, as the patient did not attend follow-up, the diagnosis was established after she presented a second time with ophthalmoplegia and proptosis, likely due to expansion of the tumor tissue within the orbit. ONB-associated optic neuropathy may develop due to compressive and/or infiltrative causes.[9] In our case, we observed that the tumor inferiorly displaced the optic nerve in orbital imaging and thus believed neuropathy was a result of compression. However, it should be noted that tumor infiltration cannot be excluded without histopathological evaluation.

Hyams et al.[10] divided ONB into four histological grades. The grading system is based on evaluations of mitotic index, necrosis, rosette formation, calcification, pleomorphism, lobular structure, and the neurofibrillary matrix. Grade III and IV have been associated with poor prognosis.[10] Currently, standard treatment of ONB consists of total surgical excision (open or endoscopic craniofacial resection) and adjuvant radiotherapy.[11,12] The most common site of metastasis in ONB patients is the cervical lymph nodes, seen in 20-25% of patients. Neck metastases are detected in 5-8% of patients at time of diagnosis.

In brief, ONB is a rare endonasal tumor. It may manifest with initial findings of cranial nerve palsy, proptosis, and/or compressive optic neuropathy. Therefore, this rare etiology must be considered in the differential diagnosis of cranial nerve palsy, external ophthalmoplegia, and proptosis.

Ethics

Informed Consent: Patient's written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Taşkın Tokat, Concept: Ömer Kartı, Mehmet Özgür Zengin, Design: Ömer Kartı, Mehmet Özgür Zengin, Data Collection or Processing: Ozan Çelik, Ömer Kartı, Analysis or Interpretation: Tuncay Küsbeci, Ömer Kartı, Mehmet Özgür Zengin, Literature Search: Tuncay Küsbeci, Ömer Kartı, Mehmet Özgür Zengin, Taşkın Tokat, Ozan Çelik, Writing: Ömer Kartı.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report

Bilateral Asymmetric Rhegmatogenous Retinal Detachment in a Patient with Stickler Syndrome

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Abstract
Here we present the long-term anatomical and visual outcomes of bilateral asymmetric rhegmatogenous retinal detachment repair in a patient with Stickler syndrome. A 17-year-old girl presented with decreased visual acuity in both eyes for more than one year. Her best-corrected visual acuity (BCVA) was 0.1 in the right eye and 0.05 in the left eye. Slit-lamp anterior segment examination revealed subcapsular cataract in both eyes. Fundus examination showed bilateral rhegmatogenous retinal detachment, chronic retinal detachment accompanied by multiple retinal holes, tears and membranous fibrillary vitreous in the peripheral retina. Grade C2 proliferative vitreoretinopathy was observed in the left eye. Scleral buckling surgery was performed initially for both eyes. After the primary surgical procedure, retinal reattachment was achieved in the right eye and the left eye underwent phacoemulsification, intraocular lens implantation, pars plana vitrectomy (PPV), and silicone oil injection. After these surgical procedures retinal reattachment was achieved in the left eye. Silicone oil removal was performed six months after PPV surgery. After surgical treatment, BCVA was 0.6 in the right eye at the end of the 3.5-year follow-up period. After silicone oil removal, BCVA reached 0.2 in the left eye after 36 months of follow-up and retinal reattachment was achieved in both eyes. Scleral buckling surgery and PPV are effective and confidential methods for the treatment of chronic retinal detachment cases in Stickler syndrome.
Keywords: Stickler syndrome, rhegmatogenous retinal detachment, scleral buckling, vitrectomy

Introduction

Stickler syndrome is an autosomal-dominant hereditary clinical condition caused by structural abnormalities in collagen types 2, 9, and 11. It can manifest with widely varying clinical signs affecting the ocular, orofacial, musculoskeletal, and/or auditory systems.[1,2,3,4] Ophthalmologic complications of the syndrome are progressive and can lead to blindness.[5] In this report, we present a case of bilateral asymmetric rhegmatogenous retinal detachment associated with Stickler syndrome and the outcomes of treatment.

Case Report

A 17-year-old female patient presented to our clinic with complaints of low vision in both eyes for approximately 1 year. On ophthalmologic examination, her best corrected visual acuity (BCVA) was 0.1 in the right eye and 0.05 in the left eye. Bilateral subcapsular cataract was detected in anterior segment examination. Fundus examination revealed bilateral rhegmatogenous retinal detachment (Figures 1 and 2), membranous vitreous in the periphery, and chronic detachment with multiple holes and tears. There was proliferative vitreoretinopathy (PVR) grade C2 in the left eye. The patient exhibited the craniofacial structural features of Stickler syndrome (she did not consent to en face photography). Scleral buckling was performed in both eyes as an initial intervention and resulted in postoperative retinal attachment in the right eye (Figures 3, 4, 5). However, the procedure was insufficient for the left eye having PVR C2 (Figure 6). Phacoemulsification, intraocular lens implantation, and pars plana vitrectomy with silicone injection were performed in the left eye. Postoperatively the retina was reattached (Figure 7). Silicone extraction was done 6 months

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Received: 19.09.2017 **Accepted:** 29.11.2017

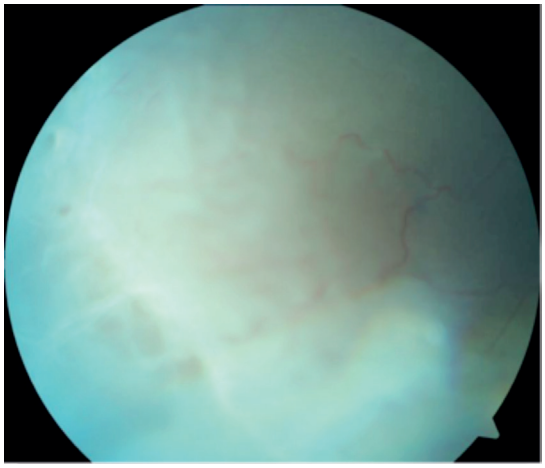

Figure 1. Preoperative appearance of the right retina in fundus photograph

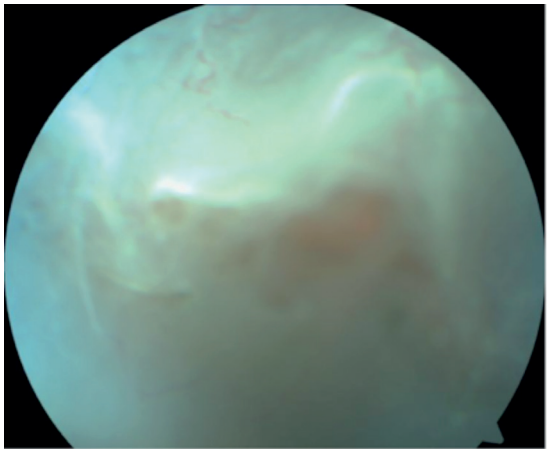

Figure 2. Preoperative appearance of the left retina in fundus photograph

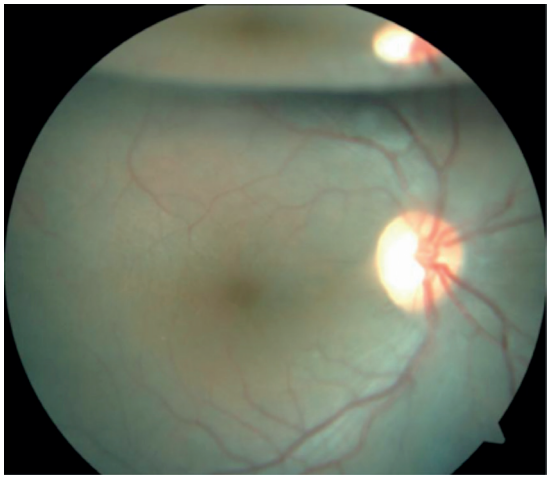

Figure 3. Right retinal appearance after scleral buckling in fundus photograph

after pars plana vitrectomy. All procedures were performed by the same surgeon (I.A.).

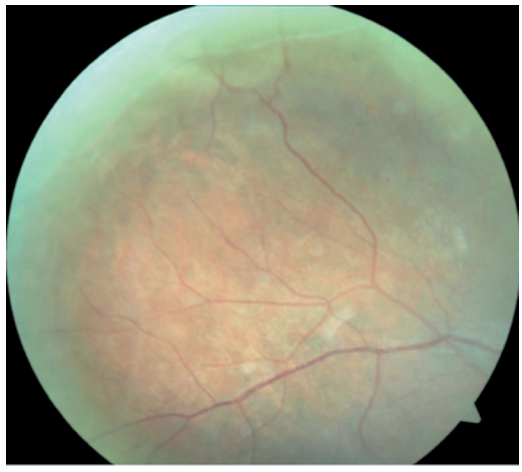

Figure 4. Right peripheral retinal appearance after scleral buckling in fundus photograph

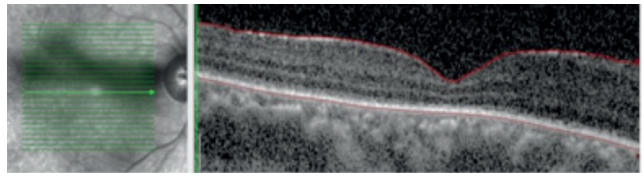

Figure 5. Optical cohorence tomography image of right eye after scleral buckling

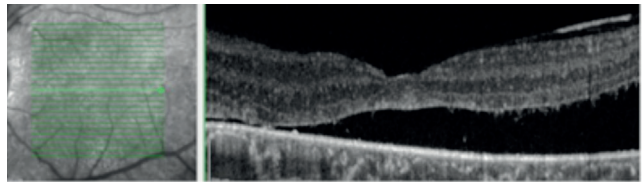

Figure 6. Optical cohorence tomography image of left eye after scleral buckling

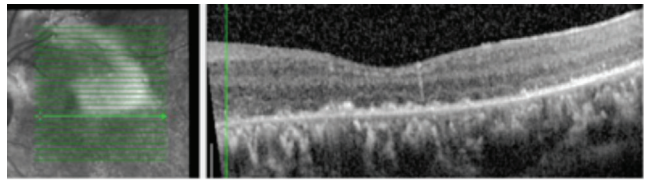

Figure 7. Optical cohorence tomography image of left eye after scleral buckling, pars plana vitrectomy, and silicone injection

In postoperative follow-up at about 3.5 years, the right eye had a BCVA of 0.6 and the retina was further attached (Figures 8, 9). In the left eye, the retina was attached and BCVA was 0.2 at 36-month follow-up after silicone extraction (Figures 10, 11, 12).

Discussion

Stickler syndrome is a disease spectrum that has been investigated since Stickler et al.[6] first described it in 1965. Though rare, it can involve serious complications. Ophthalmologic

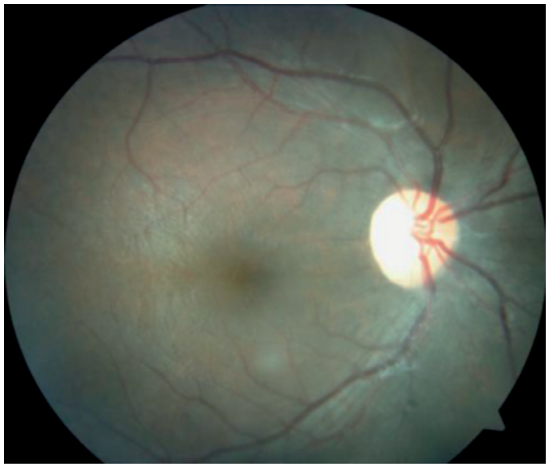

Figure 8. Fundus photograph showing right retinal appearance 3.5 years after scleral buckling

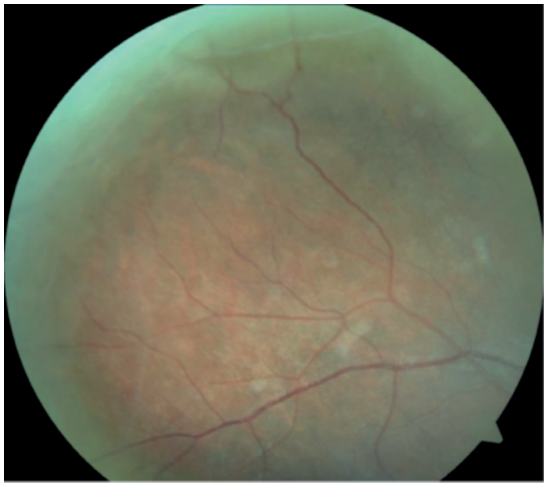

Figure 9. Fundus photograph showing appearance of the peripheral retinal of the right eye 3.5 years after scleral buckling

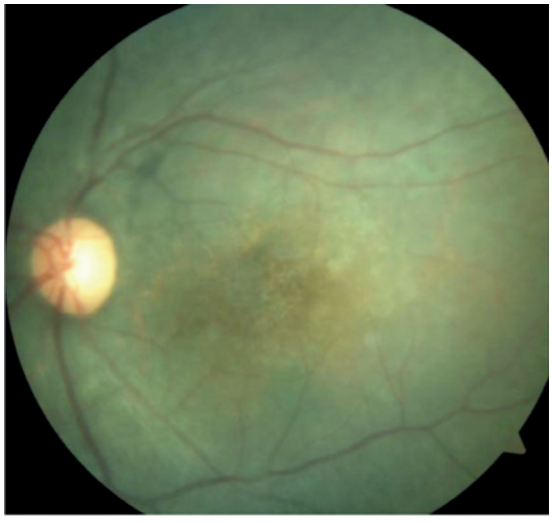

Figure 10. Fundus photograph showing left retinal appearance at 36 months after silicone extraction

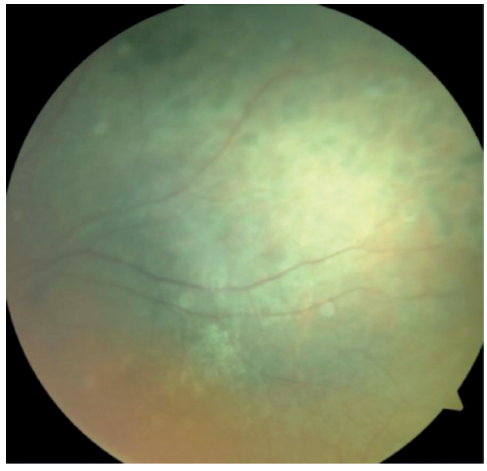

Figure 11. Fundus photograph showing appearance of peripheral retina of the left eye at 36 months after silicone extraction

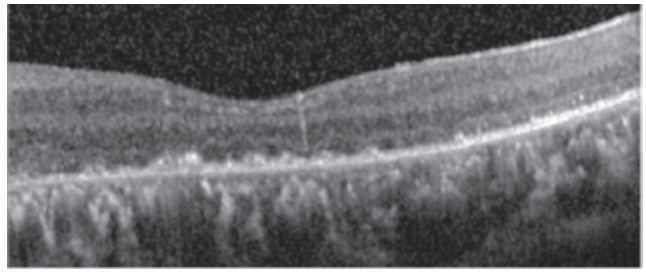

Figure 12. Optical cohorence tomography image of left eye 36 months after silicone extraction

complications of the disease include high myopia, open-angle glaucoma due to dysgenesis at the drainage angle of the anterior chamber, cortical and subcapsular cataract, perivascular retinal lattice degeneration, and adhesive vitreous bands. These vitreoretinal changes cause giant retinal tears and subsequent rhegmatogenous retinal detachment.[7,8] Although it is a rare condition, Stickler syndrome is the most common hereditary cause of rhegmatogenous retinal detachment.[9] In a study from Turkey by Yararcan et al.[10] including 6 individuals with Stickler syndrome in a single family, all of the patients had myopia of 10 diopters or greater, early onset cataract, chorioretinal atrophy, and vitreous liquefaction. Three of the 6 patients in that study had total retinal detachment, one had glaucoma, and one had phthisis bulbi.[10] Abeysiri et al.[11] presented the 17-year follow-up results of 30 eyes of 23 patients. In their study, the overall re-attachment rate was 78.4%, with rates of 67% for scleral buckling and 82.4% for pars plana vitrectomy. BCVA improved by 0.33 logarithm of minimum angle of resolution (logMAR) in patients that underwent scleral buckling and 0.32 logMAR in those that underwent vitrectomy.[11] In a study by Reddy et al.[12] including 16 eyes of 13 patients, the average age of patients with retinal detachment was 10.4 years and patients were followed for 94 months. Scleral buckling was performed in 5 patients (31%), pars plana vitrectomy in 7 patients (44%) and combined surgery in 4 patients (25%). The patients underwent a mean of

3.1 surgical interventions. In long-term follow-up, the retinal re-attachment rate was 100%, but 12 eyes (75%) developed PPV. The patient discussed in the present case had bilateral subcapsular cataract. Her fundus findings were consistent with those described in Stickler syndrome: fibrillary vitreous, lattice degenerations and adhesive vitreous bands, multiple retinal tears and holes, and PPV. The long-term outcomes of treatment were retinal re-attachment with BCVA of 0.6 in the right eye and 0.2 in the left eye. Scleral buckling and pars plana vitrectomy may be an effective and reliable treatment option for severe chronic retinal detachment due to Stickler syndrome.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İmren Akkoyun, Concept: İmren Akkoyun, Design: İmren Akkoyun, Data Collection or Processing: Caner Öztürk, Almila Sarıgül Sezenöz, Gürsel Yılmaz, İmren Akkoyun, Analysis or Interpretation: Caner Öztürk, Almila Sarıgül Sezenöz, Gürsel Yılmaz, İmren Akkoyun, Literature Search: Caner Öztürk, Almila Sarıgül Sezenöz, Gürsel Yılmaz, İmren Akkoyun, Writing: Caner Öztürk, Almila Sarıgül Sezenöz, İmren Akkoyun.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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TOA 15th March Symposium: Basic Imaging Methods in Ophthalmology
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Distance Visual Acuity Measurements Equivalency Table

						Spatial Frequency
ETDRS Standard Line Number	**Qualitative Measurements**	**Decimal**	**Snellen**	**LogMAR**	**Angle of Resolution**	**Cycle per Degree**
-3		2.00	20/10	-0.30	0.5	60.00
-2		1.60	20/12.5	-0.20	0.625	48.00
-1		1.25	20/16	-0.10	0.8	37.50
0		1.00	20/20	0.00	1	30.00
		0.90		0.05		27.00
1		0.80	20/25	0.10	1.25	24.00
		0.70		0.15		21.00
2		0.63	20/32	0.20	1.6	18.75
		0.60		0.22		18.00
3		0.50	20/40	0.30	2	15.00
4		0.40	20/50	0.40	2.5	12.00
		0.30		0.52		9.00
5		0.32	20/63	0.50	3.15	9.52
6		0.25	20/80	0.60	4	7.50
7		0.20	20/100	0.70	5	6.00
8		0.16	20/125	0.80	6.25	4.80
9		0.13	20/160	0.90	8	3.75
10	CF from 6 m	0.10	20/200	1.00	10	3.00
11	CF from 5 m	0.08	20/250	1.10	12.5	2.40
12	CF from 4 m	0.06	20/320	1.20	16	1.88
13	CF from 3 m	0.05	20/400	1.30	20	1.50
14		0.04	20/500	1.40	25	1.20
15	CF from 2 m	0.03	20/640	1.51	32	0.94
16		0.025	20/800	1.60	40	0.75
17		0.020	20/1000	1.70	50	0.60
18	CF from 1 m	0.016	20/1250	1.80	62.5	0.48
21	CF from 50 cm	0.008	20/2500	2.10	125	0.24
31	HM from 50 cm	0.0008	20/25000	3.10	1250	0.02

Abbreviations:
CF: Counting fingers, HM: Perception of hand motions, m= meter, cm= centimeter

Equations of conversions for Microsoft Excel:
- Log10 (Decimal Acuity)= LogMAR Equivalent
Power (10; -Logmar Equivalent)= Decimal Acuity (for English version of Microsoft Excel)
Kuvvet (10; -Logmar Equivalent)= Decimal Acutiy (for Turkish version of Microsoft Excel)

Reference
Eğrilmez S, Akkın C, Erakgün T, Yağcı A. Standardization in evaluation of visual acuity and a comprehensive table of equivalent. Turk J Ophthalmol. 2002;32:132-136.

Near Visual Acuity Measurements Related Equivalency Table*														
Snellen	**20/400**	**20/320**	**20/250**	**20/200**	**20/160**	**20/125**	**20/100**	**20/80**	**20/63**	**20/50**	**20/40**	**20/32**	**20/25**	**20/20**
Decimal	0.05	0.063	0.08	0.10	0.125	0.16	0.20	0.25	0.32	0.40	0.50	0.63	0.80	1.00
Jaeger	J19	J18	J17	J16	J15	J14	J13	J11	J9	J7	J5	J3	J2	J1
Times New Roman Point	60	48	36	30	24	18	14	12	10	8	6	5	4	3
LogMAR	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.0

*Adapted from Rabbets RB: Visual acuity and contrast sensitivity. In: Rabbets RB, editor. Clinical visual optics. Edinburgh: Butterworth-Heinemann, 1998:19-61.