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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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EDITORIAL

2017 issue 3 at a glance:

For this issue we have selected from among the valuable research of our colleagues six original articles, one review, five case reports, and a letter to the editor that we believe will engage your interest and contribute to the literature.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by synovial joint involvement and various extra-articular signs, and is the most common autoimmune disease to affect the cornea. Anayol et al. evaluated anterior segment parameters and corneal densitometry in 23 consecutive RA patients and 22 healthy subjects using Scheimpflug corneal topography. They reported no difference between the two groups in anterior segment parameters; however, they found that the RA group had significantly higher corneal densitometry values compared to the healthy subjects, despite having clinically clear corneas. They emphasized that corneal densitometry may be important in the clinical evaluation of these patients (see pages 125-129).

Kaya describes the 'ophthoselfie' technique, in which a 90-diopter aspheric lens is attached to the rear camera of a smartphone to allow anyone, whether a medical professional or not, to obtain detailed images of the cornea and anterior segment. He states that the technique may facilitate patients' early recognition of certain conditions such as keratoconus, refraction errors, corneal rejection, and uveitis, and will allow patients to take ocular self-images and share them with a physician in urgent situations (see pages 130-132).

In a study comparing functional and anatomic outcomes of intravitreal aflibercept injection in patients with wet age-related macular degeneration resistant to treatment with intravitreal bevacizumab or ranibizumab, Topal et al. evaluated data from 22 eyes of 22 patients switched to intravitreal aflibercept after lack of treatment response to at least 6 intravitreal bevacizumab or ranibizumab injections and followed for at least 3 months. They report that intravitreal aflibercept resulted in a significant reduction in central retinal thickness, but no statistically significant changes in best corrected visual acuity or the height of serous and fibrovascular pigment epithelium detachments (see pages 133-137).

The internal limiting membrane (ILM) is the basal lamina of the inner retina, formed by Müller cells. ILM peeling has become a key component of the current vitrectomy technique because it significantly increases the closure rate of macular holes (MH). However, this technique can lead to changes such as thinning of the inner retinal layers and dissociated optic nerve fiber layer (DONFL) appearance. Demirel et al. used spectral domain optical coherence tomography (SD-OCT) to evaluate the effect of vitrectomy with ILM peeling on the ganglion cell-inner plexiform layer (GCIPL) in patients with idiopathic MH. Eighteen eyes of 18 patients with unilateral idiopathic MH were operated using the technique and were compared to the unoperated fellow eyes of the patients and 18 eyes of 18 age-matched healthy individuals. The authors concluded that there may be functional changes and/or structural changes apparent on OCT that may be associated with visual acuity and that significant GCIPL thinning and DONFL appearance may occur after ILM peeling (see pages 138-143).

Baz et al. report that 1.25 mg intravitreal bevacizumab therapy administered to 10 patients for subretinal neovascularization due to type 2 juxtafoveal telangiectasia preserved visual acuity and caused the regression of macular edema. The authors emphasize that intravitreal bevacizumab is an effective treatment option for these patients (see pages 144-148).

In their study investigating surgical outcomes and patient satisfaction after interventions for lid malpositions due to facial palsy, Uğurlu and Karakaş retrospectively analyzed the records of 14 female and 21 male patients with follow-up periods ranging from 2 to 60 months. They determined that the most common intervention was gold weight implantation, the postoperative success rate was 90% for upper lid procedures and 75% for lower lid procedures, and lubricant use, lagophthalmos, and keratopathy were significantly reduced postoperatively. They highlighted the importance of individualized therapy based on palsy severity and the accompanying malpositions, as well as long-term follow-up (see pages 149-155).

Nurözler Tabakcı and Ünlü review the efficacy, safety, and therapeutic potential of intravitreal corticosteroids for the treatment of diabetic macular edema, the most common cause of vision loss in diabetic patients, in light of recent literature. They present a detailed discussion of the mechanisms of action, advantages and disadvantages, and side effects of steroids, and address in which cases they should be used (see pages 156-160).

Bozkurt Oflaz et al. share the case of a patient who underwent keratoplasty 6 months earlier and later developed a large keratitis focus in the center of the corneal graft from which *Streptococcus pneumonia* was isolated in culture. After showing no response to medical therapy for 1 month, the patient was treated with corneal collagen crosslinking (CCC). After this treatment, the patient improved rapidly and showed a significant improvement in visual acuity. The authors state that CCC treatment can be utilized as an adjuvant therapy in cases of bacterial keratitis refractory to medical therapy because it has a bactericidal effect and reduces the risk of perforation (see pages 161-164).

Bingöl Kızıltunç et al. report a 20-year-old female patient presenting with bilateral diffuse lacrimal gland involvement as an initial sign of systemic sarcoidosis. Orbital magnetic resonance imaging revealed involvement of the upper lids and anterior orbit, and bilateral symmetric diffuse enlargement of the lacrimal glands. Definitive diagnosis was established upon lacrimal gland biopsy showing non-necrotizing granulomas and the patient was treated with oral steroids for 9 months. The authors point out that sarcoidosis should be considered in the differential diagnosis of patients with orbital masses, noting that all organs and systems must be screened and therapy should be tailored to the organs and systems involved (see pages 165-168).

Başarır et al. present the case of patient with history of travel to a tuberculosis-endemic area who presented with unilateral decreased vision. Vitritis, occlusive vasculitis, and granuloma were observed on fundus examination. The patient was diagnosed with tuberculous uveitis after systemic and ocular evaluations and was successfully treated with antituberculous therapy. With this report, the authors aimed to emphasize the importance of taking a detailed history in early diagnosis and treatment and avoiding ocular complications in uveitis patients (see pages 169-173).

Acute retinal necrosis (ARN) is a rapidly progressive condition with poor prognosis, and leads to vision loss in the majority of cases. Rapid diagnosis and early antiviral therapy significantly affect the long-term visual prognosis. Şimşek et al. report a patient presenting with reduced vision and ocular pain who was previously diagnosed with acute glaucoma at another center. They diagnosed the patient with ARN based on clinical findings and were able to completely control the disease by immediately initiating antiviral therapy. They discuss different approaches to the treatment of ARN (see pages 174-179).

Von Hippel-Lindau (VHL) disease a familial cancer syndrome characterized by benign or malignant tumors and cystic lesions affecting multiple systems. Retinal hemangioblastomas are usually the initial sign of VHL disease and can cause vision loss. In a case report from Şahin Atik et al., ophthalmologic examination of a patient presenting with vision loss revealed multiple retinal hemangioblastomas and genetic analysis confirmed a VHL diagnosis. They discuss their treatment and follow-up of the patient and his family, and stress that identifying retinal hemangioblastomas and determining whether they are related to VHL are crucial steps in the early diagnosis and treatment of life-threatening tumors and complications that may develop in these patients and their families (see pages 180-183).

Finally, we have included a letter to the editor written in response to a previously published article entitled "Spontaneous Resolution of Optic Disc Pit Maculopathy", as well as a response from the authors of that study (see pages 184-185).

Respectfully on behalf of the Editorial Board,
Özlem Yıldırım, MD

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Turk J Ophthalmol 2017;47:125-129

Original Article

Assessment of Corneal Densitometry in Rheumatoid Arthritis Patients

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Abstract

Objectives: To evaluate corneal densitometry and anterior segment parameters of rheumatoid arthritis (RA) patients and compare these results with those of age-matched healthy control subjects.

Materials and Methods: Anterior segment parameters and corneal densitometry of patients with RA and healthy control subjects were assessed by Scheimpflug corneal topography. For densitometry analysis, the 12-mm diameter area of the cornea was subdivided into four concentric radial zones and anterior, central, and posterior layers based on corneal depth. Right eyes of subjects were used for statistical analysis.

Results: Twenty-three consecutive patients with RA and 22 healthy control subjects were included in the study. There was no significant difference with regard to age (p=0.487) or gender (p=0.514). When anterior segment parameters of both groups were compared, no significant difference was found (p>0.05). Total corneal densitometry values were statistically higher in the RA group (p=0.030). In addition, when subdivisions of the cornea were evaluated, higher densitometry values were found in the RA group in 0-2 and 2-6 mm radial zones both in the anterior and total depth (p=0.001, p=0.003 for the 0-2 mm zone and p=0.002, p=0.009 for the 2-6 mm zone). Corneal densitometry measurement was not correlated with central corneal thickness or simulated keratometry value in RA patients or healthy control subjects.

Conclusion: The corneal densitometry values were higher in RA patients when compared to healthy control subjects, even if they had clinically clear corneas. Corneal densitometry as an objective measure of corneal clarity warrants further studies in order to ascertain its clinical relevance in RA patients.

Keywords: Corneal densitometry, rheumatoid arthritis, corneal topography

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder characterized by synovial joint involvement and extra-articular manifestations ranging from subcutaneous nodules to pulmonary, cardiovascular, cutaneous, and neurological involvement.[1,2] The ocular surface is frequently affected and dry eye syndrome is the most common ophthalmic manifestation, followed by scleritis, episcleritis, anterior uveitis, and retinal vasculitis.[3,4,5,6] Scleromalacia perforans and peripheral ulcerative keratopathy are other rare but frightening ocular complications. Rheumatoid arthritis is known to be the most common autoimmune disease to affect the cornea.[7,8,9,10,11]

Scheimpflug imaging is a useful tool for evaluating the cornea. The Pentacam® HR (Oculus, Inc., Wetzlar, Germany) enables investigators to image both anterior and posterior corneal surfaces, providing a full pachymetry map. In addition, it is also possible to measure the amount of backscatter light for evaluating densitometry of different regions of the cornea with the new add-on software program.

Because anatomical regularity of the collagen fibrils, integrity of connective tissue, and balanced keratocyte components play an

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important role in corneal clarity, it can be hypothesized that corneal densitometry may be altered in the presence of a systemic inflammatory disease, even in the absence of any corneal haze or scar.[12] The purpose of the present study was to evaluate anterior segment parameters and corneal densitometry in RA patients with clinically clear corneas and to compare these results with those of healthy control subjects.

Materials and Methods

This prospective controlled clinical trial was conducted at Ulucanlar Eye Training and Research Hospital. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee. The study included 23 consecutive RA patients and an age-matched control group of 22 healthy individuals. RA diagnosis and classification were based on previously published data and the patients with mild disease without any joint deformity were recruited for the study.[13] All patients underwent ophthalmic examination including assessment of best-corrected visual acuity, intraocular pressure, slit-lamp examination, and fundoscopy prior to Scheimpflug imaging. Patients with corneal opacity; severe dry eye; glaucoma; any inflammatory ocular disorder or infection including blepharitis, conjunctivitis, meibomitis and dacryocystitis; central or peripheral thinning evident in slit-lamp examination; history of ocular surgery, trauma, or contact lens use; and patients using any topical medication other than artificial tears were excluded from the study.

Corneal power, corneal thickness, and corneal volume measurements were performed by Pentacam® HR. Corneal densitometry analysis, provided as an add-on to the standard software of the Pentacam® HR, was used for densitometry assessment. Using the 25 scan settings, the rotating system allowed corneal scans from 0 to 180 degrees, each photograph displaying the cornea at a specific angle.

Measurements were performed in the same clinical assessment room, using the black shield supplied by the company. In order to minimize the effect of diurnal changes in corneal hydration, all measurements were performed within the same time interval of the day (between 10 and 12 AM). The automatic release mode was used to determine when correct focus and alignment with the corneal apex had been achieved in order to reduce operator-dependent variables which may be associated with manual scanning. The output was expressed in gray-scale units. A maximum light scatter of 100 was defined for minimum transparency (completely opaque cornea), and minimum light scatter of 0 as maximum transparency (no clouding).

For analysis, the 12-mm diameter of the cornea was subdivided into four radial zones, the central zone being the area centered on the apex with a diameter of 2 mm; the second zone was an annulus between the 2 mm and 6 mm diameters; the third zone was between the 6 mm and 10 mm diameters; and the fourth zone from the 10 mm to 12 mm diameters. In addition, the cornea was also subdivided into three parts based on depth. The anterior layer was the anteriormost 120 µm, the posterior layer was the posteriormost 60 µm, and the central layer was defined as the part between these two layers. Right eyes of the participants were used for the statistical analyses. Demographic data, mean corneal power, corneal volume, anterior chamber depth, central corneal thickness, and corneal density were compared between the groups.

Statistical Analysis

Statistical analyses were done using SPSS software (version 21.0, SPSS, Inc. Chicago, IL, USA). The results are presented as the mean ± standard error of mean (SEM). Normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. Independent-samples t-test and chi-square tests were used to compare measurements between the two groups. The Pearson correlation coefficient was used to assess the strength of the correlations between corneal densitometry and simulated keratometry (Sim K) and central corneal thickness. Statistical significance was defined as a p value less than 0.05. Post-hoc calculation of statistical power was performed using NCSS-PASS software (NCSS, Utah, USA).

Results

Twenty-three consecutive RA patients and 22 age-matched healthy individuals were included. The demographic findings of the groups are presented in Table 1. There was no statistically significant difference between the RA and control groups with respect to age or gender (p=0.487 and p=0.514, respectively).

Anterior segment parameters of the groups, measured by the Pentacam system, are presented in Table 2. There were no significant differences among the groups in terms of Sim K (p=0.381), posterior K (p=0.837), corneal volume (p=0.337), or anterior chamber depth (p=0.487). Central and thinnest corneal thickness measurements of the RA patients (544.43±6.79 µm, 535.13±7.22 µm) were lower than those of the control group (554.54±6.25 µm, 547.68±6.34 µm), though the difference was statistically insignificant.

When corneal densitometry findings were compared, it was seen that total corneal densitometry was higher in the RA group (p=0.030), although there was no evident opacity. In addition, when the corneal subdivisions were evaluated, a higher density was found in the RA group in the 2 mm and 2-6 mm radial zones of the anterior layer (p=0.001 and p=0.002, respectively) and 10-12 mm zone of both the central and posterior layers (p=0.035 and p=0.018, respectively). The corneal densitometry

Table 1. Demographic data of patients

Groups	n	Age (years)	Gender (Male/ Female)
Rheumatoid arthritis	23	53.96±2.73 (33-83)	5/18
Control	22	51.91±0.85 (47-61)	7/15
p	-	0.487*	0.514**

*Independent samples t-test, **chi-square test, p<0.05 statistically significant, results are denoted as mean ± standard error of mean (minimum-maximum)

measurements of RA patients and healthy control subjects are shown in detail in Table 3. Corneal densitometry was not significantly correlated with Sim K or central corneal thickness both in RA patients and healthy control subjects.

Discussion

Analysis of corneal densitometry has gained popularity after the introduction of the Pentacam densitometry program. The technique allows assessment of pathologies and changes in the cornea by means of a noninvasive examination that is repeatable and quick to perform. Since corneal transparency is the result of a complex organization including regular spacing of the collagen fibrils and extracellular matrix and balanced keratocyte components, high levels of corneal light backscatter may be observed even in the absence of haze or scar.[14,15] In the present study, we measured the corneal densitometry of RA patients with clinically clear corneas and compared their results with those of age-matched healthy control subjects.

Villani et al.[16] observed significantly higher numbers of hyperreflective stromal cells in the corneas of RA patients when compared to healthy individuals. They stated that those keratocytes were in a specific stage of metabolic activation induced by proinflammatory cytokines such as interleukin (IL)-1 and IL-6. They also demonstrated an increase in basal epithelial cells and anterior and posterior stromal cells. We hypothesized that corneal densitometry of RA patients may be altered in the absence of haze or scar due to changes in the cellular components of the cornea and subclinical inflammation.

Table 2. Comparison of anterior segment parameters

	Rheumatoid arthritis	Control	p*
Simulated keratometry			
Mean ± SEM (D)	43.97±0.33	43.62±0.20	0.381
Median (D)	43.90	43.65	
Range (D)	41.20 to 47.00	41.50 to 45.60	
Posterior keratometry			
Mean ± SEM (D)	-6.30±0.05	-6.31±0.03	0.837
Median (D)	-6.30	-6.35	
Range (D)	-6.80 to -5.80	-6.50 to -6.00	
Central corneal thickness			
Mean ± SEM (µm)	544.43±6.79	554.54±6.25	0.281
Median (µm)	548	557	
Range (µm)	472 to 602	502 to 600	
Thinnest corneal thickness			
Mean ± SEM (µm)	535.13±7.22	547.68±6.34	0.200
Median (µm)	548	551	
Range (µm)	464 to 599	495 to 596	
Corneal volume			
Mean ± SEM (mm^3)	59.95±0.86	60.97±0.56	0.337
Median (mm^3)	60.40	60.65	
Range (mm^3)	52.60 to 69.30	55.90 to 66.90	
Anterior chamber depth			
Mean ± SEM (mm)	2.66±0.10	2.56±0.08	0.487
Median (mm)	2.71	2.58	
Range (mm)	1.88 to 4.09	1.89 to 3.21	

SEM: Standard error of mean, D: Diopter, *Independent sample t-test, $p<0.05$ statistically significant

In our study, it was seen that total corneal densitometry was statistically higher in the RA group, although there was no evident opacity or infiltration. In addition, when subdivisions of the cornea were evaluated, a higher density was found in the RA group in the 0-2 and 2-6 mm radial zones in the anterior layer.

In the central and posterior layers, a higher densitometry was also observed in the peripheral 10-12 mm annulus. But peripheral regions must be interpreted with caution in this method, as the repeatability and reproducibility are low according to previous studies.[17,18]

Reduced superficial and stromal thickness has been reported even in the absence of secondary Sjögren's syndrome and was associated with increased proteolytic activity of the stroma and increased tangential forces on an abnormal, irregular epithelial surface.[16,19] Cingü et al.[20] noted lower central corneal thickness and corneal volume in RA patients, but statistically similar corneal power findings. In our study, corneal thickness in the RA group was also lower than in the control group, but the difference was statistically insignificant. This may be attributed to the low number of subjects. When other anterior segment parameters of RA patients were evaluated, it was seen that the groups were similar in terms of anterior chamber depth, corneal volume, and Sim K.

To our knowledge this is the first study to demonstrate abnormal densitometry findings in patients with RA. The reason RA patients had higher corneal densitometry values in our trial may be explained by formation of a hyperreflective stroma due to the increase in the number of activated keratocytes and subclinical inflammation in the clear cornea.

Study Limitations

One important limitation of this study is the lack of an a priori sample size calculation. In this study, post-hoc calculation of the statistical power rather than a calculation of the sample size was performed due to the paucity of published data. Although the relatively small sizes of the groups may be a limitation, the present study is unique in measuring corneal densitometry in RA patients. A further limitation of the study is the lack of repeated lens densitometry measurements. Nevertheless, the high interobserver and intraobserver repeatability of Scheimpflug images and densitometric analyses has been demonstrated previously in the literature.[21] Finally, dry eye may be a confounding factor for corneal densitometry. Since the major differences in corneal densitometry between the groups were observed in the anterior layer, it could also be attributed to dry eye.

Conclusion

RA patients have significantly higher corneal densitometry values when compared to healthy control subjects. However, our results should be confirmed with further prospective studies investigating corneal densitometry in RA and other inflammatory conditions which may affect the ocular surface.

Table 3. Comparison of corneal densitometry measurements

	0-2 mm	2-6 mm	6-10 mm	10-12 mm	Total
Anterior layer (120 µm) Rheumatoid arthritis Control p*	 25.52±0.99 (18.60-41.20) 21.60±0.47 (18.10-26.30) 0.001*	 24.47±1.18 (17.90-40.00) 20.20±0.52 (16.10-27.60) 0.002*	 29.45±2.27 (19.50-54.90) 26.00±1.44 (14.70-45.40) 0.212	 36.41±2.56 (20.50-64.70) 30.17±1.81 (12.60-47.20) 0.058	 28.19±1.43 (21.40-47.60) 24.19±0.80 (16.50-34.20) 0.021*
Central layer Rheumatoid arthritis Control p*	 15.15±0.34 (12.40-18.40) 14.47±0.41 (12.00-18.80) 0.210	 14.65±0.63 (11.90-26.50) 13.52±0.38 (11.40-18.90) 0.144	 19.66±1.50 (12.40-39.40) 17.82±0.90 (11.30-28.90) 0.306	 22.86±1.21 (15.50-38.80) 19.50±0.94 (10.60-28.00) 0.035*	 17.70±0.79 (13.70-26.90) 16.08±0.50 (12.00-21.00) 0.094
Posterior layer (60 µm) Rheumatoid arthritis Control p*	 12.26±0.29 (10.30-15.00) 11.52±0.25 (9.00-14.30) 0.066	 12.09±0.40 (9.40-17.80) 11.13±0.28 (9.30-15.40) 0.062	 16.30±0.79 (11.50-24.60) 15.20±0.64 (10.70-23.40) 0.292	 19.06±0.79 (13.90-27.30) 16.39±0.73 (10.20-25.50) 0.018*	 14.61±0.46 (11.60-18.80) 13.41±0.37 (10.40-18.40) 0.052
Total Rheumatoid arthritis Control p*	 17.63±0.42 (13.80-22.30) 15.85±0.36 (13.30-19.50) 0.003*	 17.07±0.66 (13.60-28.00) 14.95±0.39 (12.50-20.70) 0.009*	 21.81±1.49 (15.00-39.60) 19.67±0.96 (12.20-31.70) 0.240	 26.11±1.42 (17.60-43.60) 22.65±1.29 (11.10-39.70) 0.080	 20.16±0.84 (16.20-29.50) 17.90±0.53 (13.20-23.60) 0.030*

*Independent samples t-test, $p<0.05$ statistically significant, results are denoted as mean ± standard error of mean (minimum-maximum)

Corneal densitometry as an objective measure of corneal clarity warrants further longitudinal studies in order to ascertain its clinical relevance.

Ethics

Ethics Committee Approval: The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee, Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: Mustafa Alpaslan Anayol, Pelin Yılmazbaş, Design: Mehmet Ali Şekeroğlu, Data Collection or Processing: Mert Şimşek, Süleyman Günaydın, Analysis or Interpretation: Mustafa Alpaslan Anayol, Literature Search: Başak Bostancı, Writing: Başak Bostancı.

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

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References

1. Turesson C. Extra-articular rheumatoid arthritis. Curr Opin Rheumatol. 2013;25:360-366.
2. Prete M, Racanelli V, Digiglio L, Vacca A, Dammacco F, Perosa F. Extra-articular manifestations of rheumatoid arthritis: An update. Autoimmun Rev. 2011;11:123-131.
3. Vignesh AP, Srinivasan R. Ocular manifestations of rheumatoid arthritis and their correlation with anti-cyclic citrullinated peptide antibodies. Clin Ophthalmol. 2015;25:393-397.
4. Generali E, Cantarini L, Selmi C. Ocular Involvement in Systemic Autoimmune Diseases. Clin Rev Allergy Immunol. 2015;49:263-270.
5. Mohsenin A, Huang JJ. Ocular manifestations of systemic inflammatory diseases. Conn Med. 2012;76:533-544.
6. Tong L, Thumboo J, Tan YK, Wong TY, Albani S. The eye: a window of opportunity in rheumatoid arthritis? Nat Rev Rheumatol. 2014;10:552-560.
7. Choudhary MM, Hajj-Ali RA, Lowder CY. Gender and ocular manifestations of connective tissue diseases and systemic vasculitides. J Ophthalmol. 2014;2014:403042.
8. Can ME, Erten S, Can GD, Cakmak HB, Sarac O, Cagil N. Corneal Biomechanical Properties in Rheumatoid Arthritis. Eye Contact Lens. 2015;41:382-385.
9. Gunes A, Inal EE, Tok L, Tok O. Evaluation of central and peripheral corneal thicknesses in patients with rheumatoid arthritis. Arq Bras Oftalmol. 2015;78:236-240.
10. Schargus M, Wolf F, Tony HP, Meyer-Ter-Vehn T, Geerling G. Correlation between tear film osmolarity, dry eye disease, and rheumatoid arthritis. Cornea. 2014;33:1257-1261.
11. Artifoni M, Rothschild PR, Brézin A, Guillevin L, Puéchal X. Ocular inflammatory diseases associated with rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:108-116.
12. Meek KM, Knupp C. Corneal structure and transparency. Prog Retin Eye Res. 2015;49:1-16.
13. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW,

Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-2581.

14. Oliveira CM, Ribeiro C, Franco S. Corneal imaging with slit-scanning and Scheimpflug imaging techniques. Clin Exp Optom. 2011;94:33-42.
15. Quantock AJ, Winkler M, Parfitt GJ, Young RD, Brown DJ, Boote C, Jester JV. From nano to macro: studying the hierarchical structure of the corneal extracellular matrix. Exp Eye Res. 2015;133:81-99.
16. Villani E, Galimberti D, Viola F, Mapelli C, Del Papa N, Ratiglia R. Corneal involvement in rheumatoid arthritis: an in vivo confocal study. Invest Ophthalmol Vis Sci. 2008;49:560-564.
17. Ní Dhubhghaill S, Rozema JJ, Jongenelen S, Ruiz Hidalgo I, Zakaria N, Tassignon MJ. Normative values for corneal densitometry analysis by Scheimpflug optical assessment. Invest Ophthalmol Vis Sci. 2014;55:162-168.
18. Lopes B, Ramos I, Ambrósio R Jr. Corneal densitometry in keratoconus. Cornea. 2014;33:1282-1286.
19. Prata TS, Sousa AK, Garcia Filho CA, Doi LM, Paranhos A Jr. Assessment of corneal biomechanical properties and intraocular pressure in patients with rheumatoid arthritis. Can J Ophthalmol. 2009;44:602.
20. Cingü AK, Cınar Y, Türkcü FM, Sahin M, Kaya S, Bozkurt M, Sahin A, Yüksel H, Ari S, Caça I. Evaluation of corneal parameters with scheimpflug imaging in patients with rheumatoid arthritis. Ocul Immunol Inflamm. 2013;21:360-365.
21. Kirkwood BJ, Hendicott PL, Read SA, Pesudovs K. Repeatability and validity of lens densitometry measured with Scheimpflug imaging. J Cataract Refract Surg. 2009;35:1210-1215.

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Original Article

Ophthoselfie: Detailed Self-imaging of Cornea and Anterior Segment by Smartphone

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Abstract

Objectives: To describe the ophthoselfie, a method by which everyone can take detailed self-images of the cornea and anterior segment with a smartphone.

Materials and Methods: A 90-diopter non-contact double aspheric lens was attached to posterior camera of the smartphone by clear tape. Images of one eye on the screen of the smartphone could be seen with the other eye in the mirror and images were taken.

Results: Accurate and detailed images of the cornea and anterior segment of the eye could be taken.

Conclusion: The ophthoselfie allows everyone to take their own detailed anterior segment images by smartphone. To create a clear and detailed self-image of the cornea and anterior segment on the screen of a smartphone may lead to the development of new applications and facilitate patients' early recognition of certain conditions like keratoconus, refractive errors, corneal rejection, and uveitis. This method may also be useful in some urgent situations by allowing patients to take self-images of the eye and share them with a physician.

Keywords: Anterior segment, cell phone, imaging, selfie, ophthoselfie

Introduction

It would be amazing if everyone could take their own detailed anterior segment images of the eye with a smartphone and share them with ophthalmologists or friends. Now it is possible with the ophthoselfie. With technological advancement, smartphones and social media have become essential components of our daily life. Smartphones provide possibilities to access the internet, take photos and videos, and share documents immediately via social media. Technological advancements have always had a major impact on medicine.[1] Recording photos or videos of some pathologies is very important for medical education or follow-up survey of pathologies. Almost all physicians have a smartphone now. Thus, smartphones provide an opportunity to record certain pathologies immediately. Imaging is especially important in ophthalmology. A majority of diagnoses can be made by biomicroscopy. Camera systems can be attached to biomicroscopes in order to acquire images. However, it was not possible to have such technologies everywhere. Mohammadpour et al.[2] identified a method that enabled the acquisition of ocular images by smartphone, without the use of a slit-lamp. They used a 90 diopter lens and were able to take detailed images of the anterior segment. The authors discussed the potential usage of this method by patients. Here I describe a method that provides an opportunity to take detailed self-images of the ocular surface, cornea, anterior segment and eyelids.

A selfie is a self-portrait photograph typically taken by a cell-phone camera held in the hand. It has become very popular in recent years. The ophthoselfie may also be a new trend among friends to share photos of the inside of their eyes and among patients to show their eye pathologies to ophthalmologists from afar.

Materials and Methods

A smartphone with Android operating system (LG G2 mini, LG® Electronics, South Korea) was used for imaging. A 90 diopter Volk® (Volk Optical, Inc., Mentor, OH, USA) non-contact double aspheric lens was attached to the smartphone with clear tape (Figure 1). The focus setting was adjusted to

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manual, then the phone was passed in front of a mirror (Figure 2). As the camera was brought near one eye, the other eye could see the formation of the image in the mirror. The accuracy of the image could be arranged easily using the free eye.

Results

Detailed self-images of the cornea and anterior segment could be taken by this method. High-resolution video was captured and even the iris crypts could be seen by adjusting the focus of the smartphone camera (Figure 3). An accurate image could not be taken without a 90 diopter lens (Figure 4).

Discussion

Self-imaging the eye was performed successfully using a smartphone and 90 Diopter lens while facing a mirror. This method allows even non-ophthalmologists to take images of the eye easily. Patients will be able to take images in cases of anterior segment traumas, blepharitis, hordeolum, keratitis, conjunctivitis, and hyphema. Furthermore, patients will be able to send postoperative images to their doctors. This will be a convenience to both patient and doctor. The ophthoselfie is not only an opportunity for patients but also for healthy individuals. While everyone can see their own eyes in the mirror, it is not possible to take a detailed image of the iris. The opportunity to take self-images of the inside of the eye and share them with friends may prove popular.

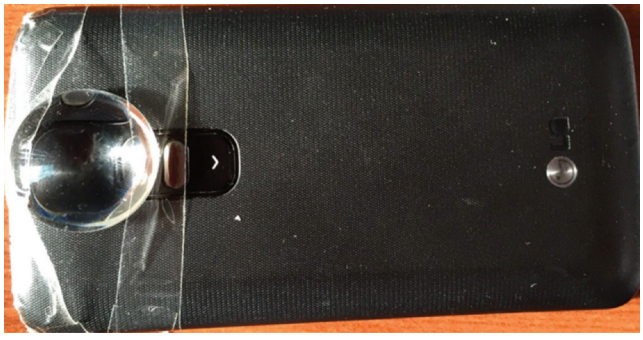

Figure 1. A 90 Diopter non-contact double aspheric lens was attached to the posterior camera of a smartphone using clear tape

Figure 2. Taking an ophthoselfie facing a mirror. The screen of the smartphone can be seen in the mirror with the left eye and the most appropriate images are taken. Detailed anterior segment images including the iris crypts are visible

This method may be useful in some urgent situations by allowing patients to take self-images of the eye and share them with a physician. For example, corneal traumas or eye diseases

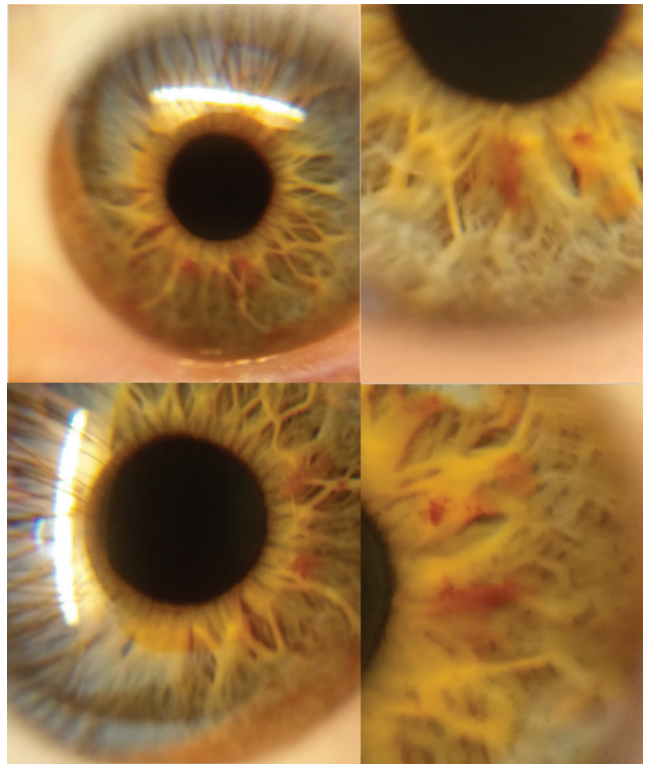

Figure 3. Ophthoselfies at different magnifications. Details of the cornea and anterior segment can be seen clearly. The images provide information similar to those taken with biomicroscopy

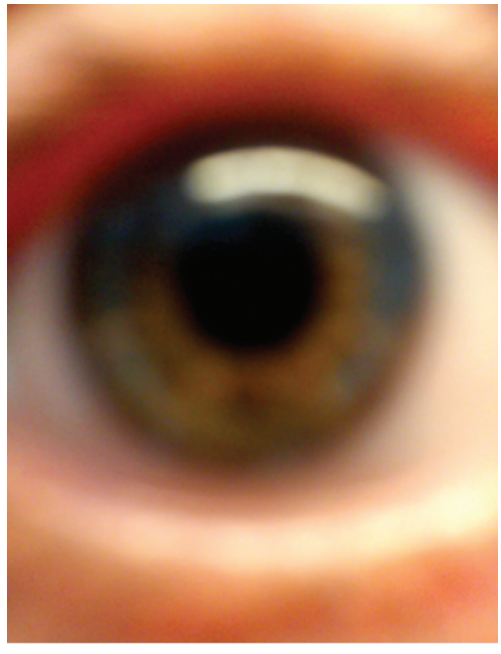

Figure 4. An image taken without using 90 diopter lens is not clear

like keratitis may happen to anyone while on vacation and an ophthalmologist is not readily accessible. Ophthoselfies may be life-saving in such a situation.

Although this method is user-friendly, it does have a limitation. The lens used in this study is a 90 diopter ophthalmic lens that is produced for ophthalmologists. These lenses are expensive and are not available everywhere. Special lenses that can be adapted to smartphones for this purpose may be developed.

Conclusion

In conclusion, the main purpose of this study was to demonstrate the possibility of taking selfies of the eye. The ophthoselfie may become a popular phenomenon in the future.

Ethics

Ethics Committee Approval: All products and photos are provided by author. Thus, ethic commity approval was not taken.

Peer-review: Externally peer-reviewed.

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References

1. Ozdalga E, Ozdalga A, Ahuja N. The smartphone in medicine: a review of current and potential use among physicians and students. J Med Internet Res. 2012;14:e128.
2. Mohammadpour M, Mohammadpour L, Hassanzad M. Smartphone Assisted Slit Lamp Free Anterior Segment Imaging: A novel technique in teleophthalmology. Cont Lens Anterior Eye. 2016;39:80-81.

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Original Article

Evaluation of Aflibercept Treatment Responses in Eyes with Bevacizumab/Ranibizumab-resistant Wet Age-related Macular Degeneration

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Abstract

Objectives: To evaluate anatomic and functional results after switching from intravitreal bevacizumab or ranibizumab treatment to aflibercept for wet (neovascular) age-related macular degeneration.

Materials and Methods: This retrospective study included 22 eyes of 22 patients resistant to treatment with at least 6 injections of bevacizumab or ranibizumab. The first three injections had been applied monthly, the others pro re nata (PRN). Outcome measures were follow-up period, injection number, best corrected visual acuity (BCVA), central retinal thickness (CRT) and pigment epithelial detachment (PED) height. Dosing regimen of aflibercept was determined PRN. The patients were examined monthly. In all visits, BCVA and optical coherence tomography results were assessed together and injections were applied according to these findings. Patients with at least three months of follow-up were included in the study.

Results: Twenty-two eyes of 22 patients treated with bevacizumab or ranibizumab were switched to aflibercept therapy. Seven patients had serous PED and 4 patients had fibrovascular PED. The mean follow-up periods for these groups were 20.59±6.76 months and 8.68±3.79 months, respectively. The mean injection numbers were 10.5±3.61 vs 4.54±1.56. Statistically significant reductions were noted in CRT (533.86±164.06 µm vs 412.04±143.86 µm, $p<0.05$). BCVA levels were almost equal before and after switching (0.18±0.17 vs 0.18±0.14). Serous and fibrovascular PED heights decreased suboptimally from 460±281.51 µm to 282.42±175.76 µm ($p>0.05$) for serous PEDs and 251.25±43.85 µm to 225.75±73.09 µm ($p>0.05$) for fibrovascular PEDs.

Conclusion: Switching to aflibercept resulted in significant improvement in CRT, but not in BCVA or PED heights.

Keywords: Aflibercept, central retinal thickness, visual acuity, pigment epithelial detachment

Introduction

Age-related macular degeneration (AMD) is the foremost cause of severe vision loss, particularly in populations over 55 years old in developed countries. The prevalence of AMD in individuals 40 years and older is estimated as 6.5%.[1] The condition is a chronic, degenerative process and is divided into the non-neovascular atrophic (dry) type and the neovascular (wet) type. Approximately 10-20% of all AMD patients exhibit the wet type, which is responsible for about 80% of vision loss due to its rapidly progressive and destructive course. The characteristic feature of wet AMD is neovascularization that originates from the choroidal vasculature and extends to the subretinal pigment epithelium or subretinal space. Though overexpression of the proangiogenic cytokine vascular endothelial growth factor (VEGF) has been shown to be the main cause, the pathogenesis of choroidal neovascularization (CNV) has not been fully elucidated. VEGF released by astrocytes and Müller cells due to ischemia and other secondary factors triggers the neovascular process by stimulating endothelial cell proliferation and migration. These neovascular structures cause hemorrhage, fluid accumulation, or fibrovascular tissue, which disrupt the retinal and subretinal anatomy, resulting in vision loss.

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Laser photocoagulation and photodynamic therapy (PDT) were used to treat wet AMD from the 1980s until the early 2000s. As the importance of VEGF's role in the pathogenesis of wet AMD became better understood, anti-VEGF agents were favored over these treatment modalities.

Bevacizumab and ranibizumab, the agents most commonly used in the management of wet AMD, inhibit all isoforms of VEGF-A. Aflibercept binds VEGF more strongly, for a longer time and with higher affinity than bevacizumab, ranibizumab or the body's VEGF receptors, and shows lower antigenicity.[2,3] Unlike the other two anti-VEGF agents, aflibercept also inhibits VEGF-B and platelet-derived growth factor (PDGF) and is able to penetrate through all the retinal layers and under the retinal pigment epithelium. The half-life of aflibercept (7.13 days) is shorter than that of bevacizumab (8.25 days) and longer than that of ranibizumab (4.75 days).

Wet AMD patients under long-term treatment with bevacizumab or ranibizumab may exhibit persistent subretinal fluid and exudative changes. For such patients who are resistant to these agents or show only partial or suboptimal response, it has been posited that changing their intravitreal treatment to aflibercept may be an effective approach.

The purpose of this study was to evaluate the functional and anatomic outcomes of intravitreal aflibercept injection in patients with wet AMD refractory to intravitreal bevacizumab or ranibizumab therapy.

Materials and Methods

This retrospective study included the medical records of wet AMD patients who had intraretinal and/or subretinal fluid resistant to at least 6 intravitreal bevacizumab or ranibizumab injections and were switched to aflibercept therapy between January 2014 and August 2015. The study was approved by the Ethics Committee Chair of the Haydarpaşa Numune Training and Research Hospital. Informed consent forms were obtained from all patients prior to injections. Optical coherence tomography (OCT) images were obtained using a spectral OCT-Scanning Laser Ophthalmoscope (Spectral OCT-SLO, Optos, Scotland).

Prior to changing therapeutic agents, the patients received one injection of a loading dose of bevacizumab or ranibizumab per month for the first three months; thereafter, injections were performed as deemed necessary based on a combination of OCT and best corrected visual acuity (BCVA) values obtained during monthly follow-up examinations. After the first three loading doses, repeat injections were applied if monthly follow-up revealed more than one line loss in BCVA or an increase of more than 100 µm in central retinal thickness (CRT). Patients with persistent intraretinal and/or subretinal fluid on OCT, no improvement in BCVA, or a CRT increase of more than 100 µm compared to baseline after at least 6 injections were considered resistant to bevacizumab/ranibizumab therapy and upon obtaining consent it was decided to change to intravitreal aflibercept therapy. Patients were examined for any possible complications of intravitreal injection on the first day after treatment and were followed monthly thereafter. The same criteria for repeated injections of the other agents were applied for aflibercept in patients' monthly follow-up examinations. The study included patients who were followed in this manner for at least three months. Changes in final BCVA, CRT and pigment epithelial detachment (PED) values on OCT from baseline were recorded and compared with pre-injection values.

Inclusion criteria of the study were: 1) age 50 years or older and wet AMD diagnosis; 2) treated with at least 6 intravitreal bevacizumab or ranibizumab injections; 3) followed in our outpatient clinic for at least 3 months after switching to aflibercept therapy; and 4) absence of any disease other than wet AMD that may cause macular edema or atrophy. Exclusion criteria were: 1) history of ocular procedures other than uncomplicated cataract surgery or Nd:YAG laser posterior capsulotomy; 2) any history of PDT; 3) any ocular or systemic conditions other than wet AMD which may cause macular edema or CNV.

All injections were performed in operating room conditions. Injections were performed with 30 gauge needles and doses of 1.25 mg bevacizumab, 0.5 mg ranibizumab or 2 mg aflibercept in a volume of 0.05 mL, injected intravitreally 3.5 mm from the limbus in pseudophakic eyes and 4 mm in phakic eyes.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 17.0 software was used for all statistical analyses. Descriptive statistics are expressed as minimum, maximum and mean ± standard deviation. The Wilcoxon test was used for paired samples. P values <0.05 were accepted as statistically significant.

Results

A total of 22 eyes of 22 patients with wet AMD received aflibercept injections. The patients' ages ranged from 50 to 90, with a mean of 74.9±9.92 years. Ten patients were male, 12 were female. Nine eyes were right, 11 were left. PED was present in 11 patients when therapy was switched to aflibercept, 7 with serous PED and 4 with fibrovascular PED. The mean number of intravitreal bevacizumab or ranibizumab injections was 10.5±3.61 (range, 6-21) and the mean number of aflibercept injections was 4.54±1.56 (range, 2-8). The mean follow-up time was 20.59±6.76 (range, 8-36) months before switching to aflibercept and 8.68±3.79 (range, 3-15) months after switching to aflibercept. CRT was 533.86±164.06 (range, 300-890 µm) at first aflibercept injection and 412.04±143.86 µm (range, 171-712 µm) at the end of follow-up; this difference was statistically significant (p=0.024). Serous PEDs had a mean height of 460±281.51 µm (range, 185-975 µm) at baseline and 282.42±175.76 µm (range, 59-519 µm) at final examination. Fibrovascular PEDs had a mean height of 251.25±43.85 µm (range, 159-318 µm) at baseline and 225.75±73.09 µm (range, 176-320 µm) at final examination. Neither PED type showed a statistically significant reduction in height after aflibercept injections (p=0.12 and p=0.71, respectively). Mean BCVA

values were 0.18±0.17 prior to first aflibercept injection and 0.18±0.14 at the end of follow-up (p=0.51). The findings of this study are summarized in Table 1.

No complications due to intravitreal injections were observed during follow-up.

Discussion

The majority of wet AMD patients require repeated intravitreal injections in the long term. The need for long-term monthly injections may be related to the pathologic activity becoming chronic, but may also arise due to drug tachyphylaxis, tolerance development, or an immune reaction to a component of the injected solution. In tachyphylaxis, there is no response to treatment, even at higher drug concentrations resulting from frequent repeated drug administration. However, efficacy may return if the medication is discontinued for a period of time. Tolerance is also a significant reduction in the extent and duration of a drug's efficacy as a result of long-term application. In such cases, efficacy can be increased by reducing the dosage or intervals between applications.[4] Unlike tachyphylaxis, discontinuing treatment after the development of drug tolerance does not restore efficacy. Gasperini et al.[5] reported that 81% of patients with bevacizumab or ranibizumab tachyphylaxis showed improved response after switching therapies. Local or systemic immune responses after intravitreal injections may arise due to the development of antibodies against one of the injected substances. Several authors have proposed that chronic VEGF blockage leads to overexpression of VEGF by macrophages in choroidal neovascular tissue.[6,7,8,9]

Table 1. Patients' demographic and clinical characteristics

Mean age (years)	**74.9±9.92**
Gender Male Female	 10 12
PED character Fibrovascular Serous	 4 7
Mean number of injections	10.5±3.61[a] 4.54±1.5[b]
Follow-up time (months)	20.59±6.76[c] 8.68±3.79[d]
CRT (µm) (p=0.024)	533.86±164.06[e] 412.04±143.86[f]
Serous PED (p=0.12)	460±281.51[g] 282.42±175.76[h]
Fibrovascular PED (p=0.71)	251.25±43.85[g] 225.75±73.09[h]
BCVA (p=0.51)	0.18±0.17[e] 0.18±0.14[f]

a: Intravitreal bevacizumab or ranibizumab injection number, b: Aflibercept injection number, c: Follow-up time before switching to aflibercept, d: Follow-up time after switching to aflibercept, e: Before aflibercept injection, f: After aflibercept injection, g: Height before aflibercept, h: Height after aflibercept

BCVA: Best corrected visual acuity, CRT: Central retinal thickness, PED: Pigment epithelial detachment

Aflibercept is now used for wet AMD patients resistant to the other anti-VEGF agents. The molecular structure of aflibercept results in a binding affinity 94 times greater than that of bevacizumab and 119 times that of ranibizumab. Aflibercept also inhibits other angiogenetic agents such as VEGF-B and PDGF.[10,11,12,13] The intraocular duration of effect of aflibercept is 48-80 days.[14]

There are studies documenting the efficacy of aflibercept in refractory wet AMD in terms of anatomic rather than functional success.[15,16,17,18] One such study by Yonekawa et al.[16] evaluated BCVA and CRT in 102 eyes of 96 patients who were switched to aflibercept after developing resistance to ranibizumab; their results showed that BCVA remained stable while CRT was significantly reduced. CRT decreased significantly in 91% of the patients and remained unchanged in 9%; no cases of increased CRT were observed. In contrast to this study, others have reported improved visual acuity after aflibercept therapy. Heussen et al.[17] evaluated 71 eyes of 65 patients with refractory wet AMD who were switched to aflibercept and reported a 33% increase in BCVA.

In the present study, we observed no significant increase or decrease in BCVA but found a significant reduction in CRT. According to OCT findings, intraretinal or subretinal fluid completely resolved in 6 of 22 eyes (Figure 1a, 1b),

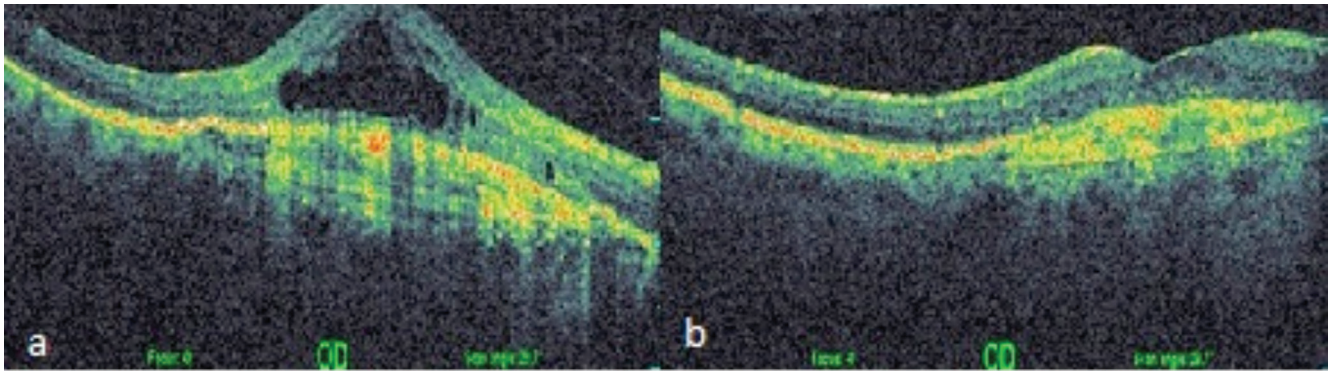

Figure 1. a) Before aflibercept therapy, central retinal thickness was 650 µm and intraretinal fluid and cysts were apparent, b) 15 months after 8 aflibercept injections, central retinal thickness was 347 µM, intraretinal cyst had resolved, and fluid was reduced. The patient's best corrected visual acuity increased from 0.12 to 0.3

partially resolved in 9 patients, remained nearly the same in 2 patients (Figure 2a, 2b), and increased in 5 patients following aflibercept injection. We believe long-term retinal damage due to persistent intraretinal and/or subretinal fluid prevented significant improvement in BCVA. The patients in our study had persistent intraretinal and/or subfoveal fluid despite an average of 10.5 intravitreal injections prior to switching to aflibercept. Though the inability of aflibercept to effect significant visual improvement may be attributable to advanced photoreceptor damage resulting from chronic fluid accumulation prior to treatment, it may also be related to not administering the loading dose of aflibercept.

Many studies have investigated the relationship between PED type and anti-VEGF treatment response. Hoerster et al.[18] reported that fibrovascular PED is resistant to ranibizumab therapy, while serous PED responds well. Inoue et al.[19] observed reduced height in 100% of serous and mixed-type PEDs versus 67% of fibrovascular PEDs. In the present study, both serous and fibrovascular PEDs decreased in height, but these reductions were not statistically significant (Figures 2a, 2b and 3a, 3b).

Various administration protocols for aflibercept have been documented in the literature. Horizon AMD, Secure and Seven-up studies reported that the best visual acuity and anatomic results are achieved with monthly regimens.[20] García-Layana et al.[21] reported comparable results from ranibizumab applied monthly and aflibercept applied once every two months. Batioglu et al.[22] administered 3 loading doses of aflibercept followed by repeated injections as needed based on examination and OCT findings, and reported no significant increase in BCVA but significant decrease in CRT in their patients. In the present study, we administered repeated aflibercept injections as needed based on BCVA and OCT findings after one initial injection and achieved only anatomic success.

Study Limitations

Limitations of our study are the retrospective method, the small patient number and administering aflibercept according to the pro re nata protocol, without giving the three-part loading dose.

Conclusion

To summarize, switching patients with refractory wet AMD to aflibercept therapy resulted in significant CRT reduction, but significant changes were not achieved in terms of BCVA improvement or decrease in PED height. The role of aflibercept in the management of wet AMD may be better clarified by future studies with larger patient numbers, longer follow-up times, and patients who were initially treated with aflibercept after being diagnosed with wet AMD.

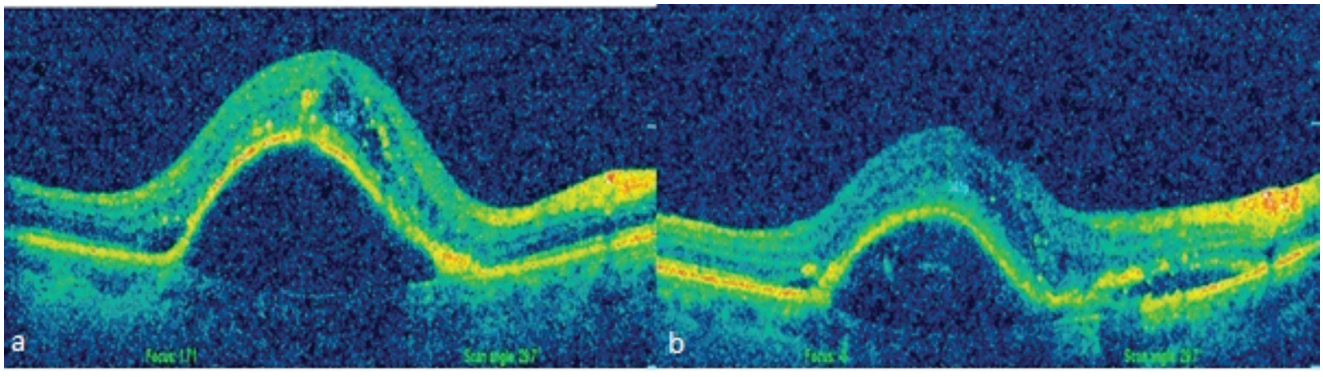

Figure 2. a) Before switching to aflibercept therapy, pigment epithelial detachment height was 975 µm, best corrected visual acuity was 0.4, b) 8 months after 5 injections, central retinal thickness was 345 µm, pigment epithelial detachment height was 519 µm, best corrected visual acuity was 0.3

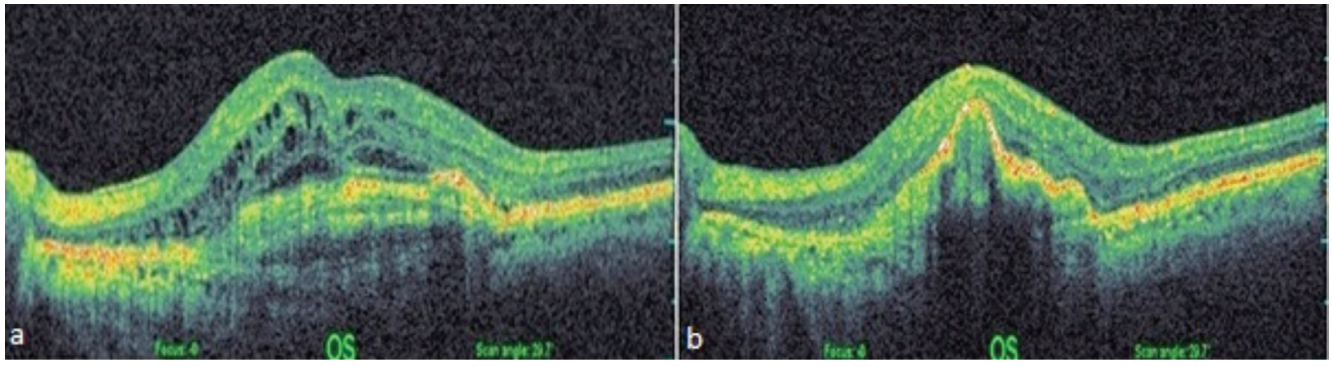

Figure 3. a) Before switching to aflibercept therapy, central retinal thickness was 695 µm and intraretinal cysts and fluid were observed. There was fibrovascular pigment epithelial detachment and best corrected visual acuity was 0.2, b) 8 months after 3 injections, central retinal thickness was 300 µm and the cysts and fluid were nearly completely resolved, but pigment epithelial detachment height increased and best corrected visual acuity was still 0.2

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee Chair of the Haydarpaşa Numune Training and Research Hospital. Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tuncay Topal, Sercan Koray Sağdıç, Cihan Büyükavşar, Abdullah Kaya, Ali Ayata, Murat Sönmez, Melih Hamdi Ünal, Concept: Tuncay Topal, Taner Kar, Yıldıray Yıldırım, Design: Tuncay Topal, Taner Kar, Data Collection or Processing: Tuncay Topal, Sercan Koray Sağdıç, Cihan Büyükavşar, Abdullah Kaya, Analysis or Interpretation: Taner Kar, Yıldıray Yıldırım, Ali Ayata, Murat Sönmez, Melih Hamdi Ünal, Literature Search: Tuncay Topal, Taner Kar, Writing: Tuncay Topal.

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

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References

1. Johnston SS, Wilson K, Huang A, Smith D, Varker H, Turpcu A. Retrospective analysis of first-line anti-vascular endothelial growth factor treatment patterns in wet age-related macular degeneration. Adv Ther. 2013;30:1111-1127.
2. Fassnacht-Riederle H, Becker M, Graf N, Michels S. Effect of aflibercept in insufficient responders to prior anti-VEGF therapy in neovascular AMD. Graefes Arch Clin Exp Ophthalmol. 2014;252:1705-1709.
3. Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R, Couvillion S, Nasir MA, Rabena MD, Le K, Maia M, Visich JE. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol. 2014;98:1636-1641.
4. Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? Br J Ophthalmol. 2012;96:1-2.
5. Gasperini JL, Fawzi AA, Khondkaryan A, Lam L, Chong LP, Eliott D, Walsh AC, Hwang J, Sadda SR. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol. 2012;96:14-20.
6. Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. Retina. 2009;29:723-731.
7. Grossniklaus HE, Ling JX, Wallace TM, Dithmar S, Lawson DH, Cohen C, Elner VM, Elner SG, Sternberg P. Macrophage and retinal pigment epithelium expression of angiogenic cytokines in choroidal neovascularization. Mol Vis. 2002;8:119-126.
8. Espinosa-Heidmann DG, Suner IJ, Hernandez EP, Monroy D, Csaky KG, Cousins SW. Macrophage depletion diminishes lesion size and severity in experimental choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003;44:3586-3592.
9. Sakurai E, Anand A, Ambati BK, van Rooijen N, Ambati J. Macrophage depletion inhibits experimental choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003;44:3578-3585.
10. Ho VY, Yeh S, Olsen TW, Bergstrom CS, Yan J, Cribbs BE, Hubbard GB. 3 Short-term outcomes of aflibercept for neovascular age-related macular degeneration in eyes previously treated with other vascular endothelial growth factor inhibitors. Am J Ophthalmol. 2013;156:23-28.e2.
11. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol. 2008;92:667-668.
12. Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). Retina. 2012;32:434-457.
13. Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, Pyles EA, Yancopoulos GD, Stahl N, Wiegand SJ. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012;15:171-185.
14. Browning DJ, Kaiser PK, Rosenfeld PJ, Stewart MW. Aflibercept for age-related macular degeneration: a game-changer or quiet addition? Am J Ophthalmol. 2012;154:222-226.
15. Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR, Mahajan VB. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. Am J Ophthalmol. 2013;156:15-22.e1.
16. Yonekawa Y, Andreoli C, Miller JB, Loewenstein JI, Sobrin L, Eliott D, Vavvas DG, Miller JW, Kim IK. Conversion to aflibercept for chronic refractory or recurrent neovascular age-related macular degeneration. Am J Ophthalmol. 2013;156:29-35.e2.
17. Heussen FM, Shao Q, Ouyang Y, Joussen AM, Müller B. Clinical outcomes after switching treatment from intravitreal ranibizumab to aflibercept in neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2014;252:909-915.
18. Hoerster R, Muether PS, Sitnilska V, Kirchhof B, Fauser S. Fibrovascular pigment epithelial detachment is a risk factor for long-term visual decay in neovascular age-related macular degeneretion. Retina. 2014;34:1767-1773.
19. Inoue M, Arakawa A, Yamane S, Kadonosono K. Variable response of vascularized pigment epithelial detachments to ranibizumab based on lesion subtypes, including polypoidal choroidal vasculopathy. Retina. 2013;33:990-997.
20. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). Ophthalmology. 2013;120:2292-2299.
21. García-Layana A, Figueroa MS, Araiz J, Ruiz-Moreno JM, Gómez-Ulla F, Arias-Barquet L, Reiter N. Treatment of Exudative Age-related Macular Degeneration: Focus on Aflibercept. 2015;32:797-807.
22. Batioglu F, Demirel S, Özmert E, Abdullayev A, Bilici S. Short-term outcomes of switching anti-VEGF agents in eyes with treatment-resistant wet AMD. BMC Ophthalmol. 2015;15:40.

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Turk J Ophthalmol 2017;47:138-143

Original Article

Evaluation of Ganglion Cell-Inner Plexiform Layer Thickness after Vitreoretinal Surgery with Internal Limiting Membrane Peeling in Cases with Idiopathic Macular Hole

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Abstract

Objectives: To evaluate macular retinal ganglion cell-inner plexiform layer (GCIPL) thickness after vitrectomy with internal limiting membrane (ILM) peeling for idiopathic macular holes using spectral domain optical coherence tomography (SD-OCT).

Materials and Methods: Eighteen eyes of 18 patients with unilateral idiopathic macular hole who underwent vitrectomy with ILM peeling were retrospectively analyzed. Healthy fellow eyes of the patients and 18 eyes of 18 age-matched healthy individuals constituted the control group. The patients were evaluated at 1 day, 1 week, 1 month, and 3 months after surgery. The best corrected visual acuity (BCVA) measurements, biomicroscopic examination findings and SD-OCT measurements were recorded. Ganglion cell-inner plexiform layer thickness was evaluated with ganglion cell analysis software of Cirrus HD-OCT before surgery and at 1 month and 3 months after surgery and compared with control groups. Presence of dissociated optic nerve fiber layer (DONFL) was evaluated with C-scan mode.

Results: Of the 18 patients, 9 were male and 9 were female with a mean age of 65.6±5.6 (55-77) years. Preoperative BCVA was 0.75±0.19 logMAR, while it was 0.44±0.17 logMAR and 0.36±0.15 logMAR at postoperative 1 and 3 months, respectively ($p<0.001$). Postoperative mean GCIPL thickness was 66.33±17.28 µm. There was a correlation between mean GCIPL thickness and BCVA at postoperative 3 months ($p<0.01$). When compared with the control group, GCIPL thickness was significantly thinner in all quadrants of all patients at postoperative 3 months. Dissociated optic nerve fiber layer appearance was observed on C-scan in 13 of 18 eyes postoperatively. There was no correlation between the presence of DONFL and BCVA ($p>0.05$).

Conclusion: Internal limiting membrane peeling during macular hole surgery may cause functional and/or structural changes that may be associated with visual acuity. Significant GCIPL thinning and DONLF appearance may occur postoperatively.

Keywords: Dissociated optic nerve fiber layer, ganglion cell-inner plexiform layer, macular hole

Introduction

The internal limiting membrane (ILM) is the basal lamina of the inner retina and is formed by Müller cells. This basal lamina constitutes the structural interface between the retina and the vitreous humor, and is composed of collagen, glycosaminoglycan, laminins, and fibronectin.[1] ILM peeling has become a key component of the current vitrectomy technique because it significantly increases the closure rate of macular holes (MH).[2] In the literature, ILM peeling has been shown to reduce perifoveal traction as well as induce gliosis through surgical trauma, increasing the rate of hole closure.[3] The rate of MH closure in surgeries performed with ILM peeling has been reported as 90-100%, compared to 60-90% in surgeries without ILM peeling.[1,4,5,6] In a retrospective study with 18-84 months (mean 44.5 months) of follow-up carried out by Brooks[4], functional and visual outcomes of patients with acute and chronic stage II, III, and IV MH were shown to be better among patients who underwent ILM peeling than among those who did not. The authors reported a 100% hole closure rate and a postoperative mean visual acuity of 20/40 in patients who underwent ILM peeling. Studies conducted in Turkey have reported anatomic success rates of 87.5% to 100% after ILM peeling in MH surgery.[7,8,9,10] However, Haritoglou et al.[11] showed in their study that more than half of the patients developed paracentral scotomas after ILM peeling. Most of these paracentral scotomas

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were subclinical, with no change in size, density, and shape reported over time.

In recent years, different spectral domain optical coherence tomography (SD-OCT) devices have been used in several studies to show the effect of ILM peeling on inner retinal layers such as the ganglion cell complex (GCC) after idiopathic MH surgery.[12,13,14] The GCC has been defined as a region encompassing the nerve fiber layer, the ganglion cell layer, and the inner plexiform layer, and is used to evaluate the morphology of the inner retinal layers.[15] Baba et al.[13] reported for the first time that there was thinning of the GCC and subsequent decrease in retinal sensitivity following ILM peeling. Kumagai et al.[16] demonstrated that there was significant decrease in the GCC in the temporal retina after ILM peeling and that this was associated with a decrease in retinal sensitivity. A new ganglion cell analysis software of the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA) allows measurement of ganglion cell-inner plexiform layer (GCIPL) thickness. This software enables mean and sectoral thickness measurements of the ganglion cell layer, containing ganglion cell bodies, and the inner plexiform layer, containing ganglion cell dendrites.

ILM peeling can cause changes in the inner retinal layers, such as dissociated optic nerve fiber layer (DONFL) appearance.[17,18] Although DONFL was not previously believed to affect retinal function,[17,19] another study conducted with microperimetry has shown that retinal sensitivity is reduced in areas with DONFL.[20]

Various dyes are used to make the ILM more visible during surgery.[21,22,23] Recently, a new dye solution called Membrane Blue-Dual (DORC International, Zuidland, The Netherlands) has come into use. This solution stains the ILM and the epiretinal membrane simultaneously by combining two separate dyes (0.025% Brilliant blue and 0.15% Trypan blue) in the same preparation, thus preventing the need for separate dyes.[24,25] In addition, the 4% polyethylene glycol component increases the viscosity and density of the dye solution, making the solution heavier and stickier. This eliminates the need for fluid-air exchange.[25]

The aim of the present study was to determine the effect of ILM peeling with the Membrane Blue-Dual dye on GCIPL thickness and the DONFL appearance using the Cirrus HD-OCT device and to investigate the relationship between these changes and visual acuity.

Materials and Methods

The medical records of patients who underwent pars plana vitrectomy with ILM peeling surgery due to idiopathic macular hole were reviewed retrospectively. Age, gender, medical and ocular history details, and presenting complaints were recorded.

Inclusion criteria were:

1. Presence of an idiopathic full-thickness macular hole on SD-OCT,

2. MH closure observed in postoperative OCT images,

3. The absence of a macular hole in the fellow eye, and

4. A follow-up duration of at least 3 months.

Eyes with any other ocular disease which may affect best corrected visual acuity (BCVA), such as glaucoma or uveitis, and eyes that underwent multiple vitrectomies and developed postoperative complications were excluded.

A detailed ophthalmologic examination including slit-lamp biomicroscopy, fundus examination, and intraocular pressure measurement was performed preoperatively on all patients. BCVA was measured using a Snellen chart. Macula images were recorded prior to surgery with fundus photographs, fundus autofluorescence (Heidelberg Retina Angiograph II [HRA2], Heidelberg Engineering, Heidelberg, Germany), and SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA). Patients were evaluated and all measurements were repeated at postoperative 1 day, 1 week, 1 month, and 3 months.

To compare GCIPL thickness at postoperative 3 months, the healthy fellow eyes of the patients and a randomly selected eye of 18 healthy age- and sex-matched individuals were used as a control group. A detailed ophthalmologic examination including slit-lamp biomicroscopy, fundus examination, and intraocular pressure measurement was performed on the healthy control group and the healthy eyes of the patients who had MH surgery. Macular images were recorded with fundus photographs, fundus autofluorescence, and SD-OCT.

OCT measurements were performed with the Cirrus HD-OCT (Carl Zeiss Meditec, Inc., software version 4.0) device after pupil dilation. The base diameter, height, and minimum diameter of the MH were measured manually with OCT. The integrity of the external limiting membrane and inner segment/outer segment (IS/OS) junctional layer was evaluated. The mean and sectoral (superior, inferior, superonasal, superotemporal, inferonasal, inferotemporal) GCIPL thicknesses were measured within the oval ring around the fovea using the macular cube 512x128 protocol with ganglion cell analysis software. Postoperative mean GCIPL thickness was compared with the healthy fellow eyes of the patient and the eyes of the 18 healthy age-matched individuals in the control group. In addition, DONFL presence was evaluated postoperatively in C-scan mode. Measurements were performed preoperatively and at postoperative 1 week, 1 month, and 3 months. To prevent segmentation errors, OCT measurements with a signal strength less than five were not included in the study.

Surgical Procedure

Sclerotomies were performed with a 23-gauge needle, followed by core vitrectomy. The vitreous humor was stained with intravitreal triamcinolone and the posterior hyaloid was separated. The ILM was stained with intravitreal Membrane Blue-Dual and was peeled using forceps. Fluid-air exchange was done and 20% SF6 was administered. The sclerotomies were not sutured. A sub-Tenon gentamicin-dexamethasone injection was administered. All operations were performed by the same surgeon using the same method.

Statistical Analysis

SPSS for Windows version 15 software package was used for all statistical analyses. Descriptive statistics were expressed as mean ± standard deviation for variables with normal distribution, as median (minimum-maximum) for variables without normal distribution, and as patient number and percentage for nominal variables.

The significance of intergroup differences in mean values was evaluated using a t-test and the significance of differences in median values was evaluated with the Mann-Whitney U test. The results were considered statistically significant at p values <0.05.

Results

Eighteen eyes of 18 patients were evaluated. Nine (50%) of the patients were male and 9 (50%) were female. Nine (50%) of the 18 eyes were right eyes and 9 (50%) were left eyes. The mean age of the patients was 65.6±5.6 (55-77) years. Randomly selected 18 eyes of 18 healthy individuals and the patients' healthy fellow eyes were included in the study as a control group. The demographic data of the patients are shown in Table 1.

Mean preoperative visual acuity was 0.75±0.19 logMAR; mean visual acuity at postoperative 1 and 3 months was 0.44±0.17 logMAR and 0.36±0.15 logMAR, respectively. The increase in vision at postoperative 1 and 3 months was statistically significant (p<0.001, p<0.001) (Figure 1).

MH base diameter, minimum diameter, and height values were measured manually for all eyes from OCT images prior to surgery. Mean base diameter was 879.16±459.79 (327-1245) µm, minimum diameter was 437.11±238.86 (193-622) µm, and hole height was 454.88±177.45 (348-585) µm. There was no significant relationship between base diameter, hole height, and postoperative BCVA (p>0.05). There was a statistically significant relationship between the minimum MH diameter and BCVA at postoperative 1 month (p=0.026, r=0.522). DONFL was observed on C-scan in 13 of the 18 eyes in the postoperative period (Figure 2). There was no statistically significant relationship between the presence of DONFL and BCVA (p>0.05). A mean of 335.44±143.16 (118-500) µm of IS/OS damage was present in 9 of the 18 eyes. In 12 of the eyes, fundus autofluorescence imaging revealed a hyperfluorescent area with a mean diameter of 496.08±104.64 µm in the region of the hole, but there was no statistically significant relationship between this finding and postoperative BCVA (p=0.466).

We evaluated the GCIPL thickness of the healthy control subjects and MH patients at postoperative 3 months. GCIPL thickness values for all macular sectors (superior, inferior, superonasal, superotemporal, inferonasal, inferotemporal) are shown in Table 2. The mean postoperative 3 month GCIPL thickness of patients who had undergone MH surgery was

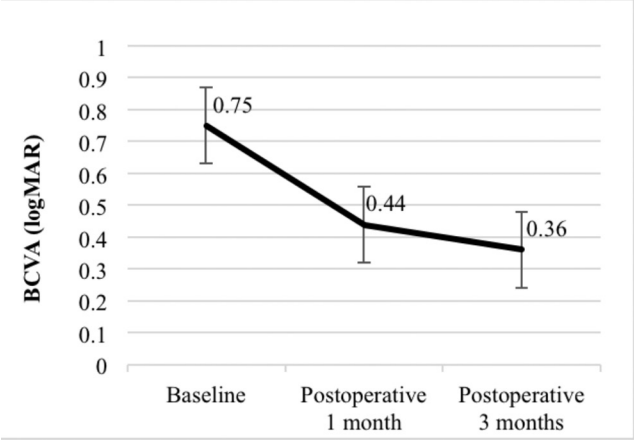

Figure 1. Changes in best corrected visual acuity (BCVA) after macular hole surgery. There is a significant increase in BCVA at postoperative 1 and 3 months (p<0.001, Friedman test)
BCVA: Best corrected visual acuity

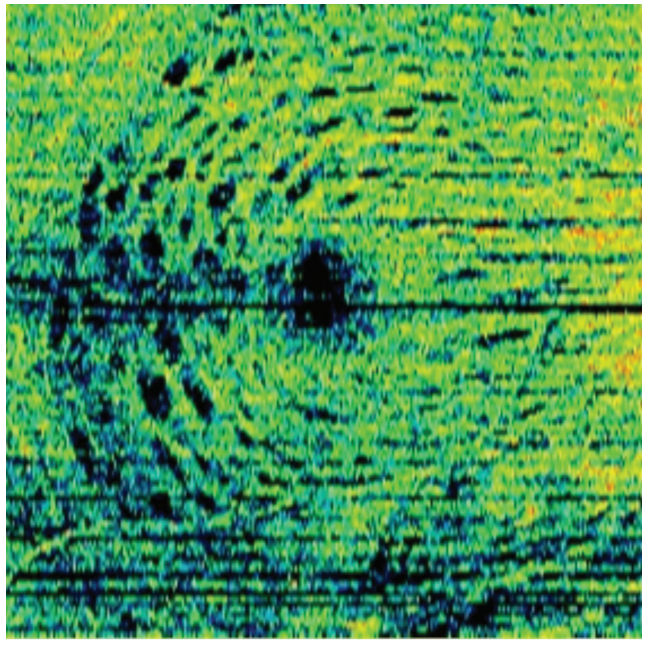

Figure 2. The right eye of a 68-year-old patient; dissociated optic nerve fiber layer appearance is evident in C-scan mode after macular hole surgery

Table 1. Demographic data of patients with macular hole

Parameter	Value	%
Gender		
Male	9	50
Female	9	50
Age (years)	65.6±5.6	
Laterality		
Right	9	50
Left	9	50
Visual acuity (logMAR)		
Preoperative	0.75±0.19	
Postoperative 1 month	0.44±0.17	
Postoperative 3 months	0.36±0.15	

52.61±13.97 µm. There was a statistically significant positive correlation between mean GCIPL thickness and postoperative 3 month BCVA (p=0.006, r=0.624). Mean postoperative 3 month GCIPL thickness was significantly thinner in all quadrants in eyes that had undergone MH surgery compared to the eyes of healthy subjects and the patients' healthy fellow eyes (p<0.001).

There were no intraoperative complications in any of the cases. Four of the 18 eyes underwent cataract surgery at various times after MH surgery.

Discussion

Studies have indicated that some preoperative parameters such as the duration and diameter of the MH may be associated with postoperative BCVA.[26,27] In persistent and large MHs, glial cell proliferation causes destruction of the central fovea. ILM peeling in MHs is a controversial topic. Tadayoni et al.[20] assert that ILM peeling may depend on the diameter of the MH. It has been noted that ILM peeling yields favorable results for MHs larger than 400 µm but does not give the same result for holes with smaller diameters. Ho et al.[28] reported that total ILM peeling for holes with small diameters may damage the fovea and is not beneficial in terms of visual outcome. In our study, we performed ILM peeling in all cases and found that base diameter did not affect final visual acuity.

The alteration that occurs in the inner retina after ILM peeling has been termed DONFL.[17,18,29,30] Tadayoni et al.[17] first reported that arcuate lines extending from the optic nerve to the macula appeared due to ILM peeling in the presence of DONFL. Studies conducted with time domain OCT have shown that DONFL is formed by multiple defects of the nerve fiber layer.[18,30] Ito et al.[30] reported that the DONFL appeared on OCT as a characteristic focal separation of the optic nerve fiber layer and that functional changes were not seen. The effect of ILM peeling on retinal function is debated in the literature. Two previous studies have shown that there is no significant difference in retinal sensitivity in areas with and without DONFL.[19,31] However, recent studies have shown that retinal sensitivity may be reduced after ILM peeling, which can be partially explained by SD-OCT images. In these images, it can be seen that the DONFL is not only confined to the nerve fiber layer but also extends to the ganglion cell layer and the inner plexiform layer, thus showing that ILM peeling can lead not only to morphological changes but also to functional changes.[29,32,33,11] In the present study, a DONFL was observed in the C-scan mode of SD-OCT in 13 of 18 eyes in the postoperative period. There was no relationship between DONFL associated with microtrauma and postoperative BCVA.

Today, agents such as indocyanine green, trypan blue, autologous serum, triamcinolone acetonide, and brilliant blue are used to make the ILM more visible during MH surgery. However, studies have shown that some of these agents may be toxic to retinal neurons and reduce GCC thickness. Among these dyes, brilliant blue seems more reliable because it is cytoprotective towards retinal neurons; however, Baba et al.[34] demonstrated a reduction in retinal sensitivity and GCC thickness, especially in the temporal quadrant, in MH patients who underwent ILM peeling using brilliant blue. On the other hand, Sevim and Sanisoglu[12] showed that the use of brilliant blue did not have an effect on the GCC. In another study involving 32 eyes in which GCIPL thickness was assessed after MH surgery, there was significant thinning in the temporal macular quadrant at postoperative 6 months after ILM peeling with brilliant blue G.[35] Hashimoto et al.[36] also reported thinning of the inner retina layers including the ganglion cell and inner plexiform layer, particularly in the parafoveal area, after ILM peeling with brilliant blue G. The authors observed no change in RNFL thickness. In another study including 42 eyes, significant decreases were observed in mean GCIPL thickness and superior sector GCIPL thickness at postoperative 3 and 6 months after ILM peeling with brilliant blue G compared to baseline values, and it was found that this thinning was also accompanied by RNFL thinning.[37]

More recently, the Membrane Blue-Dual dye has been commonly used in MH surgery. In a study of human retinal pigment epithelial cells, electrophysiological evaluations showed

Table 2. Comparison of average and sectoral ganglion cell inner plexiform layer (GCIPL) thickness (µm) at postoperative 3 months after macular hole surgery in operated eyes, healthy fellow eyes, and the eyes of healthy control subjects

	Operated eyes	Healthy fellow eyes	Control group	p
Mean GCIPL	52.61±13.97	82.06±5.35	80.83±5.81	0.000
Superior GCIPL	49.55±17.60	86.56±6.33	82.50±7.19	0.000
Inferior GCIPL	50.72±19.15	87.33±5.28	84.66±6.99	0.000
Superonasal GCIPL	52.50±14.68	86.72±5.48	83.33±7.30	0.000
Superotemporal GCIPL	55.77±20.64	83.44±6.84	82.83±7.37	0.000
Inferonasal GCIPL	51.38±21.42	87.00±4.88	81.44±10.67	0.000
Inferotemporal GCIPL	56.11±18.11	86.11±4.76	87.33±7.76	0.000

GCIPL: Ganglion cell inner plexiform layer

that dye applied for up to 5 minutes had no harmful effects on retinal ganglion cells.[38] In a retrospective comparative case series, successful surgical results were reported with Membrane Blue-Dual dye.[39] The clinical efficacy of Membrane Blue-Dual dye in macular surgery was compared with ILM blue dye in a prospective, multicenter cohort study including 63 eyes (35 males, 28 females) in the Membrane Blue dye group and 64 eyes (35 males, 29 females) in the ILM blue dye group. With both heavy dye solutions, 80-90% of cases showed postoperative BCVA improvement.[40]

In the present study, ILM peeling was facilitated by Membrane Blue-Dual dye in all patients. GCIPL thickness was found to be significantly thinner in all six sectors of the macular region in surgically treated eyes. In addition, when GCIPL thickness and BCVA at postoperative 1 and 3 months were compared, mean GCIPL thickness was significantly correlated with BCVA at postoperative 3 months. These findings demonstrate that ILM peeling in MH patients may cause both anatomic and functional changes.

The main limitations of the present study are the small number of patients and the short postoperative follow-up period. However, a long-term study showed that the reduction in inner retinal thickness continues until 24 months postoperatively.[16] Prospective studies with long follow-up periods will be more useful for understanding the morphological changes that occur after vitreoretinal surgery. Another limitation of this study is the absence of a control group comprising eyes treated with vitrectomy without ILM peeling. For this reason, we could not evaluate whether vitrectomy causes direct changes in the ganglion cell layer.

Conclusion

In conclusion, idiopathic MH is a macular pathology that can cause severe vision loss. ILM peeling during MH surgery can cause functional changes and/or structural changes that can be detected with OCT and may be related to visual acuity. Significant GCIPL thinning and DONFL appearance may occur after ILM peeling.

Ethics

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sibel Demirel, Figen Batıoğlu, Emin Özmert, Concept: Sibel Demirel, Ahmed Abdullayev, Özge Yanık, Figen Batıoğlu, Emin Özmert, Design: Sibel Demirel, Ahmed Abdullayev, Özge Yanık, Figen Batıoğlu, Emin Özmert, Data Collection or Processing: Sibel Demirel, Ahmed Abdullayev, Özge Yanık, Figen Batıoğlu, Emin Özmert, Analysis or Interpretation: Sibel Demirel, Ahmed Abdullayev, Özge Yanık, Figen Batıoğlu, Emin Özmert, Literature Search: Sibel Demirel, Ahmed Abdullayev, Özge Yanık, Figen Batıoğlu, Emin Özmert, Writing: Sibel Demirel, Ahmed Abdullayev, Özge Yanık, Figen Batıoğlu, Emin Özmert.

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References

1. Christensen UC. Value of internal limiting membrane peeling in surgery for idiopathic macular hole and the correlation between function and retinal morphology. Acta Ophthalmol. 2009;87:1-23.
2. Kadonosono K, Itoh N, Uchio E, Nakamura S, Ohno S. Staining of internal limiting membrane in macular hole surgery. Arch Ophthalmol. 2000;118:1116-1118.
3. Terasaki H, Miyake Y, Nomura R, Piao CH, Hori K, Niwa T, Kondo M. Focal macular ERGs in eyes after removal of macular ILM during macular hole surgery. Invest Ophthalmol Vis Sci. 2001;42:229-234.
4. Brooks HL. Macular hole surgery with and without internal limiting membrane peeling. Ophthalmology. 2000;107:1939-1948.
5. Mester V, Kuhn F. Internal limiting membrane removal in the management of full-thickness macular holes. Am J Ophthalmol. 2000;129:769-777.
6. Tognetto D, Grandin R, Sanguinetti G, Minutola D, Di Nicola M, Di Mascio R, Ravalico G; Macular Hole Surgery Study Group. Internal limiting membrane removal during macular hole surgery: results of a multicenter retrospective study. Ophthalmology. 2006;113:1401-1410.
7. Özkırış A. Makula Deliği Tedavisinde Brilliant Mavisi Yardımı ile İnternal Limitan Membran Soyulması. ACU Sağlık Bil Derg. 2010:140-144.
8. Ovalı T, Erkul Özdoğan S, Ovalı Ç, Bayançiçek Oygar D, Eroğlu F, Akarçay K, Yeniad B. İdiyopatik Makula Deliği Tedavisinde Pars Plana Vitrektomi, İnternal Limitan Membran Soyulması ve Bir Günlük Yatış Pozisyonunun Anatomik ve Fonksiyonel Sonuçları. Ret-Vit. 2009;17:238-244.
9. Şıngar E, Akkoyun İ, Yılmaz G. Maküler Hol Cerrahisi Sonrası Fotoreseptör Hücre Tabaka Bütünlüğünün Görsel Prognoz Üzerine Etkisi. Ret-Vit. 2013;21:23-27.
10. Yazgan S, Çakır M, Çekiç O, Kaldırım H. İdiyopatik Maküla Deliği Olgularının Tedavisinde 23 Gauge Transkonjonktival Pars Plana Vitrektomi Yönteminin Etkinliği ve Güvenirliği. Ret-Vit. 2013;21:99-104.
11. Haritoglou C, Gass CA, Schaumberger M, Gandorfer A, Ulbig MW, Kampik A. Long-term follow-up after macular hole surgery with internal limiting membrane peeling. Am J Ophthalmol. 2002;134:661-666.
12. Sevim MS, Sanisoglu H. Analysis of retinal ganglion cell complex thickness after Brilliant Blue-assisted vitrectomy for idiopathic macular holes. Curr Eye Res. 2013;38:180-184.
13. Baba T, Yamamoto S, Kimoto R, Oshitari T, Sato E. Reduction of thickness of ganglion cell complex after internal limiting membrane peeling during vitrectomy for idiopathic macular hole. Eye (Lond). 2012;26:1173-1180.
14. Baba T, Hagiwara A, Sato E, Arai M, Oshitari T, Yamamoto S. Comparison of vitrectomy with brilliant blue G or indocyanine green on retinal microstructure and function of eyes with macular hole. Ophthalmology. 2012;119:2609-2615.
15. Tan O, Chopra V, Lu AT, Schuman JS, Ishikawa H, Wollstein G, Varma R, Huang D. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology. 2009;116:2305-2314.e1-2.
16. Kumagai K, Hangai M, Larson E, Ogino N. Progressive changes of regional macular thickness after macular hole surgery with internal limiting membrane peeling. Invest Ophthalmol Vis Sci. 2013;54:4491-4497.
17. Tadayoni R, Paques M, Massin P, Mouki-Benani S, Mikol J, Gaudric A. Dissociated optic nerve fiber layer appearance of the fundus after idiopathic epiretinal membrane removal. Ophthalmology. 2001;108:2279-2283.
18. Mitamura Y, Suzuki T, Kinoshita T, Miyano N, Tashimo A, Ohtsuka K. Optical coherence tomographic findings of dissociated optic nerve fiber layer appearance. Am J Ophthalmol. 2004;137:1155-1156.

19. Imai H, Ohta K. Microperimetric determination of retinal sensitivity in areas of dissociated optic nerve fiber layer following internal limiting membrane peeling. Jpn J Ophthalmol. 2010;54:435-440.
20. Tadayoni R, Svorenova I, Erginay A, Gaudric A, Massin P. Decreased retinal sensitivity after internal limiting membrane peeling for macular hole surgery. Br J Ophthalmol. 2012;96:1513-1516.
21. Burk SE, Da Mata AP, Snyder ME, Rosa RH Jr, Foster RE. Indocyanine green-assisted peeling of the retinal internal limiting membrane. Ophthalmology. 2000;107:2010-2014.
22. Enaida H, Hisatomi T, Hata Y, Ueno A, Goto Y, Yamada T, Kubota T, Ishibashi T. Brilliant blue G selectively stains the internal limiting membrane/brilliant blue G-assisted membrane peeling. Retina. 2006;26:631-636.
23. Shah GK, Rosenblatt BJ, Blinder KJ, Grand MG, Smith M. Triamcinolone-assisted internal limiting membrane peeling. Retina. 2005;25:972-975.
24. A wad D, Schrader I, Bartok M, Mohr A, Gabel D. Comparative toxicology of trypan blue, brilliant blue G, and their combination together with polyethylene glycol on human pigment epithelial cells. Invest Ophthalmol Vis Sci. 2011;52:4085-4090.
25. Melles GRJ: The use of a vital dye for facilitating surgical procedures for vitreoretinal surgery. 2004. Patent WO 99/58159 and US 6,696,430.
26. Ip MS, Baker BJ, Duker JS, Reichel E, Baumal CR, Gangnon R, Puliafito CA. Anatomical outcomes of surgery for idiopathic macular hole as determined by optical coherence tomography. Arch Ophthalmol. 2002;120:29-35.
27. Ullrich S, Haritoglou C, Gass C, Schaumberger M, Ulbig MW, Kampik A. Macular hole size as a prognostic factor in macular hole surgery. Br J Ophthalmol. 2002;86:390-393.
28. Ho TC, Yang CM, Huang JS, Yang CH, Chen MS. Foveola nonpeeling internal limiting membrane surgery to prevent inner retinal damages in early stage 2 idiopathic macula hole. Graefes Arch Clin Exp Ophthalmol. 2014;252:1553-1560.
29. Miura M, Elsner AE, Osako M, Iwasaki T, Okano T, Usui M. Dissociated optic nerve fiber layer appearance after internal limiting membrane peeling for idiopathic macular hole. Retina. 2003;23:561-563.
30. Ito Y, Terasaki H, Takahashi A, Yamakoshi T, Kondo M, Nakamura M. Dissociated optic nerve fiber layer appearance after internal limiting membrane peeling for idiopathic macular holes. Ophthalmology. 2005;112:1415-1420.
31. Mitamura Y, Ohtsuka K. Relationship of dissociated optic nerve fiber layer appearance to internal limiting membrane peeling. Ophthalmology. 2005;112:1766-1770.
32. Spaide RF. "Dissociated optic nerve fiber layer appearance" after internal limiting membrane removal is inner retinal dimpling. Retina 2012;32:1719-1726.
33. Nukada K, Hangai M, Ooto S, Yoshikawa M, Yoshimura N. Tomographic features of macula after successful macular hole surgery. Invest Ophthalmol Vis Sci 2013;54:2417-2428.
34. Baba T, Sato E, Oshitari T, Yamamoto S. Regional reduction of ganglion cell complex after vitrectomy with internal limiting membrane peeling for idiopathic macular hole. J Ophthalmol. 2014;2014:372589.
35. Sabater AL, Velázquez-Villoria Á, Zapata MA, Figueroa MS, Suárez-Leoz M, Arrevola L, Teijeiro MÁ, García-Layana A. Evaluation of macular retinal ganglion cell-inner plexiform layer thickness after vitrectomy with internal limiting membrane peeling for idiopathic macular holes. Biomed Res Int. 2014;2014:458631.
36. Hashimoto Y, Saito W, Fujiya A, Yoshizawa C, Hirooka K, Mori S, Noda K, Ishida S. Changes in Inner and Outer Retinal Layer Thicknesses after Vitrectomy for Idiopathic Macular Hole: Implications for Visual Prognosis. PLoS One. 2015;10:e0135925.
37. Ambiya V, Goud A, Khodani M, Chhablani J. Inner retinal thinning after Brilliant Blue G-assisted internal limiting membrane peeling for vitreoretinal interface disorders. Int Ophthalmol. 2017;37:401-408.
38. Januschowski K, Mueller S, Spitzer MS, Hoffmann J, Schramm C, Schultheiss M, Bartz-Schmidt KU, Szurman P. Investigating the biocompatibility of two new heavy intraocular dyes for vitreoretinal surgery with an isolated perfused vertebrate retina organ culture model and a retinal ganglion cell line. Graefes Arch Clin Exp Ophthalmol. 2012;250:533-545.
39. Kovacević D, Mance TC, Markusić V. "Brilliant Blue G" and "Membrane Blue Dual" assisted vitrectomy for macular hole. Coll Antropol. 2011;35 (Suppl 2):191-193.
40. Veckeneer M, Mohr A, Alharthi E, Azad R, Bashshur ZF, Bertelli E, Bejjani RA, Bouassida B, Bourla D, Crespo IC, Fahed C, Fayyad F, Mura M, Nawrocki J, Rivett K, Scharioth GB, Shkvorchenko DO, Szurman P, Van Wijck H, Wong IY, Wong DS, Frank J, Oellerich S, Bruinsma M, Melles GR. Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment. Acta Ophthalmol. 2014;92:339-344.

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Original Article

Efficacy of Intravitreal Bevacizumab in Treatment of Proliferative Type 2 Idiopathic Juxtafoveal Telangiectasia

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Abstract

Objectives: To evaluate the effectiveness of intravitreal bevacizumab (IVB) in patients with subretinal neovascularization secondary to type 2 juxtafoveal telangiectasia.

Materials and Methods: Ten eyes of 10 patients were included in this retrospective study. All cases were treated with IVB (1.25 mg bevacizumab). Visual acuity and slit-lamp anterior and posterior segment examinations were performed at each visit. Central macular thickness (CMT) and intraretinal/subretinal fluid were evaluated via spectral domain optical coherence tomography (OCT). Loss of a line in visual acuity chart and presence of fluid on OCT were defined as criteria for repeated treatment.

Results: The mean age of patients was 66.0±7.0 years (56-75). The mean follow-up time was 54.7±16.0 month (24-72). The mean BCVA was 0.62±0.35 (0.00-1.00) logMAR at baseline and 0.54±0.35 (0.00-1.00) logMAR at final exam (p=0.03). The mean CMT was 251±25.4 µm at baseline and 239±39.3 µm at final exam (p=0.01). Patients received an average of 1.7±1.0 IVB injections during follow-up. At baseline, all cases had intraretinal/subretinal fluid. There was no fluid at final examination of all cases.

Conclusion: IVB treatment may be effective in the treatment of subretinal neovascularization secondary to type 2 juxtafoveal telangiectasia.

Keywords: Juxtafoveal telangiectasia, subretinal neovascularization, bevacizumab

Introduction

Retinal telangiectasia is generally idiopathic, but may also accompany various inflammatory and vascular pathologies.[1,2] It was first described in 1956 by Reese.[3] The current classification system for retinal telangiectasia was developed by Yannuzzi et al.[2] based on optical coherence tomography (OCT) findings. According to this system, juxtafoveal telangiectasia (JFT) is divided into two groups. Type 1 JFT features cystic macular edema, retinal thickening, and exudations, while type 2 JFT is characterized by perifoveal telangiectasia.[2]

Type 2 JFT is more common. The condition results in reduced visual acuity and metamorphopsia after an average age of 50. It nearly always manifests bilaterally (98%), and affects males and females equally.[1,2,4] The prevalence of type 2 JFT was reported as 0.1% in the Beaver Dam study.[5] According to the Yannuzzi classification, type 2 JFT consists of 5 stages. Findings associated with each stage are: occult telangiectatic vessels in stage 1; loss of retinal transparency in stage 2; dilated right-angle venules in stage 3; pigment hyperplasia into the retina in stage 4; and choroidal neovascularization in stage 5. The first 4 stages are referred to as the nonproliferative stage, and stage 5 as the proliferative stage.[2]

Laser photocoagulation, photodynamic therapy (PDT), intravitreal triamcinolone injection (IVTA), carbonic anhydrase inhibitors, and intravitreal anti-vascular endothelial growth factor (VEGF) injections are used in the treatment of nonproliferative type 2 JFT.[6] Treatment options for subretinal neovascularization (SRNV) associated with type 2 JFT include PDT, IVTA, and surgical interventions. The main disadvantage of PDT is subsequent retinal pigment epithelium atrophy. IVTA therapy poses a risk of cataract and glaucoma development and surgical removal of SRNV is difficult, leading to the search for new therapeutic options.[7,8] Although the pathogenesis of SRNV

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related to type 2 JFT is not completely understood, it is known that VEGF plays an important role. Anti-VEGF therapy has been shown to reduce retinal edema and fluid leakage.[9,10,11,12,13,14]

The purpose of this study was to investigate the long-term anatomic and functional outcomes of intravitreal bevacizumab (IVB) injection in the treatment of SRNV secondary to type 2 JFT.

Materials and Methods

Participants

We retrospectively analyzed the medical records of patients followed for type 2 JFT in our hospital from January 2009 to January 2014. Patients treated with IVB for SRVN secondary to proliferative type 2 JFT were included in the study. Patients with history of vitreoretinal surgery or other retinal disease were not included.

Ophthalmologic Examination

All subjects underwent a standard ophthalmologic examination prior to treatment. Visual acuity measurements were obtained in photopic conditions (85 candela/m^2) using the Bailey-Lovie chart at a distance of 4 meters. Anterior segment and fundus were evaluated by slit-lamp examination and intraocular pressure was measured by Goldmann applanation tonometry. Spectral domain OCT (SD-OCT) images were acquired at each visit using the Spectralis (Heidelberg Engineering, Heidelberg, Germany) instrument. The same instrument was used for fundus fluorescein angiography (FFA). FFA was conducted at time of diagnosis and at follow-up visits if patients exhibited vision loss and other examination methods were unable to reveal its cause. Follow-up examinations were done at 1, 3, 6, and 12 months, and at 6-month intervals thereafter.

Treatment Protocol

Patients were informed about the side effects and risks associated with IVB (Avastin; Genentech Inc, San Francisco, CA, USA) therapy and informed consent forms were obtained. All injections were done in sterile conditions. Before injection, the eyelids were cleaned with 10% povidone iodine (Betadine; Purdue Pharma, Stamford, CT, USA) and the conjunctival sac with 5% povidone iodine. After placing a sterile cover, IVB (1.25 mg/0.05 mL) was injected using a 30-gauge needle inserted 3.5 mm from the limbus in pseudophakic patients and 4 mm from the limbus in phakic patients. Patients used topical 0.5% moxifloxacin ophthalmic solution (Vigamox®, Alcon Laboratories Inc., Fort Worth, TX, USA) for 1 week after injection. Patients were examined monthly after the first injection and repeated injections were administered if necessary. Loss of a line or more in visual acuity and the presence of subretinal hemorrhage, intraretinal cyst, and/or subretinal fluid were defined as criteria for repeated treatment.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Monthly changes in visual acuity and central macular thickness (CMT) values were compared using a paired-samples t-test. P values ≤0.05 were considered statistically significant.

Results

Ten eyes of 10 patients (7 female, 3 male) were included in the study. Mean age of the patients was 66±70 (56-75) years. Mean follow-up time was 54.7±16 (24-72) months. Twenty percent of the patients had diabetes mellitus. Patient's fellow eyes had nonproliferative type 2 JFT. Intraretinal crystalline accumulation was observed in 3 patients (30%). Demographic characteristics of the patients are shown in Table 1.

Table 1. Patients' demographic and treatment characteristics

Patient	Age (years)	Gender	Initial BCVA (logMAR)	Final BCVA (logMAR)	Injection type	Injection number	Initial OCT (µm)	Final OCT (µm)	Follow-up time (months)
Case 1	65	F	0.7	0.5	IVB	4	283	260	24
Case 2	67	F	1.0	1.0	IVB	1	251	250	36
Case 3	61	M	0.7	0.5	IVB	1	237	214	36
Case 4	62	F	0.7	0.5	IVB	1	273	251	30
Case 5	75	F	1.0	1.0	IVB	1	197	160	60
Case 6	70	F	0.5	0.4	IVB	2	244	215	60
Case 7	66	M	0.1	0.1	IVB	1	230	225	60
Case 8	61	M	0.0	0.0	IVB	3	270	260	72
Case 9	56	F	1.0	1.0	IVB	2	270	310	60
Case 10	54	F	0.5	0.4	IVB	1	255	250	66

IVB: Intravitreal bevacizumab, F: Female, M: Male, BCVA: Best corrected visual acuity, OCT: Optic coherence tomography

Mean best corrected visual acuity (BCVA) before treatment was 0.62±0.35 (0.00-1.00) logMAR. Post-treatment mean BCVA values were 0.57±0.35 (0.00-1.00) logMAR at 3 months (p=0.10), 0.56±0.36 (0.00-1.00) logMAR at 12 months (p=0.06), and 0.54±0.35 (0.00-1.00) logMAR at final examination (p=0.03). Only the difference between baseline and final BCVA was statistically significant (Figure 1). BCVA improved by 1 line in 2 eyes and 2 lines in 3 eyes. Visual acuity remained at the same level in 5 eyes. Changes in BCVA are shown in Figure 1.

Mean CMT before treatment was 251±25.4 (197-283) µm. Post-treatment CMT values were 245±27 (186-280) at 3 months (p=0.02), 245±40 (168-222) µm at 12 months (p=0.30), and 239±39.3 (160-310) µm at final examination (p=0.01). Changes in CMT were statistically significant at 3 months and final examination. All patients had intraretinal and/or subretinal fluid prior to injection. In the final examinations, intra- and/or subretinal fluid was not detected in any of the patients on SD-OCT.

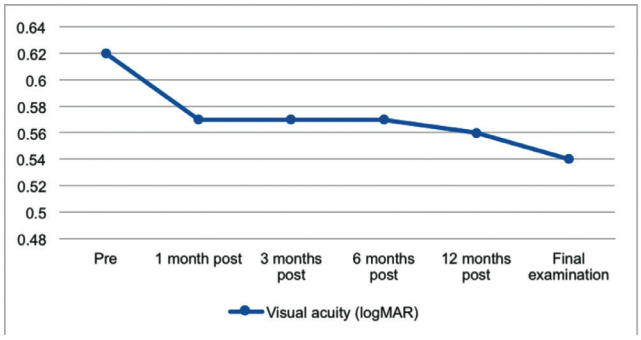

Figure 1. Visual acuity changes from before treatment (pre) to after treatment (post)

The patients received an average of 1.7±1.05 IVB injections. IVB injections were administered once to 6 eyes, twice to 2 eyes, 3 times to 1 eye, and 4 times to 1 eye. None of the patients experienced serious injection-related complications such as retinal detachment, endophthalmitis, or vitreous hemorrhage.

Discussion

The mechanism by which SRNV develops in type 2 JFT is not clear. SRNV usually begins intraretinally and progresses to the subretinal surface, but does not become widespread (Figures 2 and 3). However, if untreated the prognosis of SRVN is poor.[15] One study that followed 26 untreated eyes for an average of 107 months found that visual acuity was 20/200 or worse in 81% of the eyes.[16] Various studies have reported that bevacizumab is safe and effective in the treatment of SRNV secondary to myopia and age-related macular degeneration.[17,18]

In the present study, we observed no reduction in visual acuity in the 10 eyes with type 2 JFT treated with IVB injection. Visual acuity remained stable in 5 eyes (50%) and increased by 1 or more lines in 5 eyes (50%). None of the eyes had sub-/intraretinal fluid and there was a significant decrease in CMT in OCT examination done at the end of follow-up.

In a similar study, Mandal et al.[19] administered a single dose of IVB to 6 eyes with JFT-associated SRNV and reported

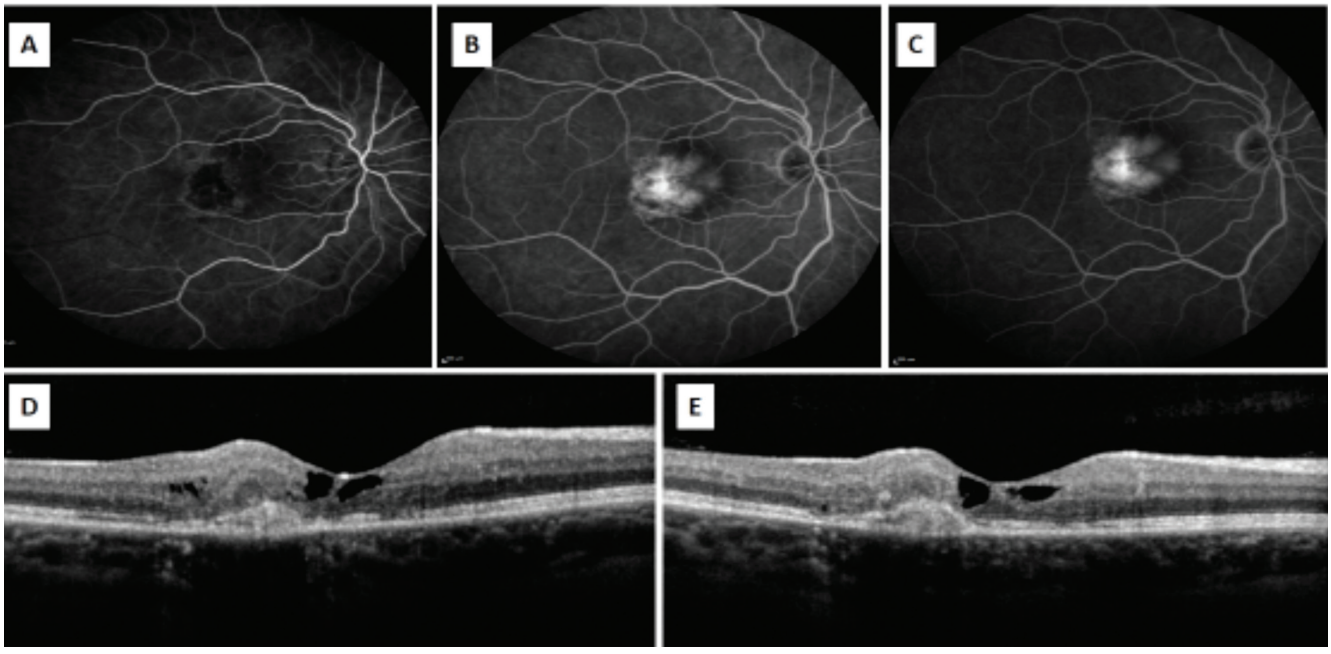

Figure 2. A-C) Fundus fluorescein angiography in a patient with type 2 juxtafoveal telangiectasia shows hyperfluorescence due to subretinal neovascularization (SRNV) beginning in the early phase and increasing in the later phases. D) Optical coherence tomography reveals the internal limiting membrane, foveal atrophy, and SRNV and intraretinal fluid temporal of the fovea. E) Regression of the intraretinal fluid is observed after intravitreal injection

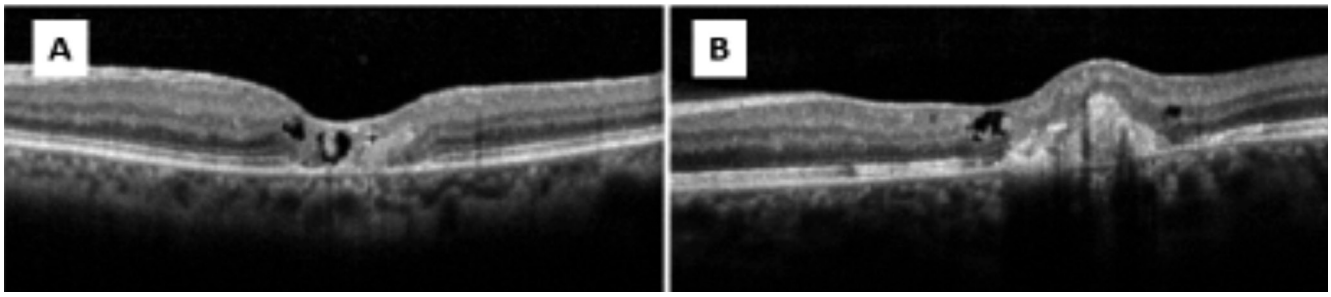

Figure 3. A) Optical coherence tomography (OCT) images of a patient with type 2 juxtafoveal telangiectasia reveals internal limiting membrane coverage and foveal atrophy. B) Subretinal neovascularization formation was noted on follow-up OCT images of the same patient taken three years later

visual acuity improvement of 2 or more lines in 5 eyes (83%) and no change in 1 eye at follow-up examination 4 months after injection. Narayanan et al.[20] administered IVB to 12 eyes and intravitreal ranibizumab injections to 4 eyes of 16 patients with JFT-associated SRNV and observed a significant increase in visual acuity after a follow-up period of 12 months. They reported the average number of annual injections as 1.9. In a study by Jorge et al.,[21] an eye with SRNV secondary to type 2 JFT was treated with IVB and at 24 weeks after treatment, visual acuity increased from 20/40 to 20/20 and the subretinal fluid resolved on OCT. Roller et al.[22] reported a 1.1 line increase in visual acuity at the end of 17 months of follow-up after IVB treatment of 9 type 2 JFT patients.

Recurrence is rare after the first injection when treating SRNV secondary to type 2 JFT. Karagiannis et al.[23] administered 3 monthly doses of ranibizumab to a patient and reported an increase in visual acuity from 0.05 to 0.3 and no recurrence during 12 months of follow-up. We performed an average of 1.7 injections over the course of 5 years of follow-up in our patients, and 6 eyes were successfully treated with a single injection. Our injection number was similar to those reported in other studies. Over the course of long-term follow-up, fewer injections are required in the treatment of type 2 JFT-associated SRNV when compared to age-related macular degeneration. This result demonstrates that there is little need for anti-VEGF therapy when managing SRNV secondary to type 2 JFT.

A strength of our study compared to previous studies was our long follow-up time and relatively larger number of cases. Limitations of our study include its retrospective design and lack of a control group.

Conclusion

In summary, IVB is effective in stabilizing visual acuity and slowing the progression of SRNV in the treatment of SRNV secondary to type 2 JFT. Controlled, randomized studies with larger patient numbers are needed to evaluate the anatomic and functional outcomes of IVB therapy in type 2 JFT.

Ethics

Ethics Committee Approval: Since the study was designed retrospectively, ethics committee approval was not received, Informed Consent: Patient approval was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Cengiz Alagöz, Concept: Muhittin Taşkapılı, İrfan Perente, Design: İhsan Yılmaz, Data Collection or Processing: Ali Demircan, Analysis or Interpretation: Abdullah Özkaya, Literature Search: Ökkeş Baz, Writing: Ökkeş Baz.

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

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References

1. Nowilaty SR, Al-Shamsi HN, Al-Khars W. Idiopathic juxtafoveolar retinal telangiectasis: a current review. Middle East Afr J Ophthalmol. 2010;17:224-241.
2. Yannuzzi LA, Bardal AM, Freund KB, Chen KJ, Eandi CM, Blodi B. Idiopathic macular telangiectasia. Arch Ophthalmol. 2006;124:450-460.
3. Reese AB. Telangiectasis of the retina and Coats' disease. Am J Ophthalmol. 1956;42:1-8.
4. Özkaya A, Yazıcı AT, Demirok A. Jukstafoveal Telenjiektaziler. Ret-Vit. 2012;20:13-21.
5. Klein R, Blodi BA, Meuer SM, Myers CE, Chew EY, Klein BE. The prevalence of macular telangiectasia type 2 in the Beaver Dam eye study. Am J Ophthalmol. 2010;150:55-62.
6. Chen JJ, Sohn EH, Folk JC, Mahajan VB, Kay CN, Boldt HC, Russell SR. Decreased macular thickness in nonproliferative macular telangiectasia type 2 with oral carbonic anhydrase inhibitors. Retina. 2014;34:1400-1406.
7. Engelbrecht NE, Aaberg TM Jr, Sung J, Lewis ML. Neovascular membranes associated with idiopathic juxtafoveolar telangiectasis. Arch Ophthalmol. 2002;120:320-324.
8. Berger AS, McCuen BW, Brown GC, Brownlow RL Jr. Surgical removal of subfoveal neovascularization in idiopathic juxtafoveolar retinal telangiectasis. Retina. 1997;17:94-98.
9. Charbel Issa P, Finger RP, Holz FG, Scholl HP. Eighteen-month follow-up of intravitreal bevacizumab in type 2 idiopathic macular telangiectasia. Br J Ophthalmol. 2008;92:941-945.
10. Charbel Issa P, Finger RP, Kruse K, Baumüller S, Scholl HP, Holz FG. Monthly ranibizumab for nonproliferative macular telangiectasia type 2: a 12-month prospective study. Am J Ophthalmol. 2011;151:876-886.
11. Charbel Issa P, Holz FG, Scholl HP. Findings in fluorescein angiography and optical coherence tomography after intravitreal bevacizumab in type 2 idiopathic macular telangiectasia. Ophthalmology. 2007;114:1736-1742.
12. Kovach JL, Rosenfeld PJ. Bevacizumab (avastin) therapy for idiopathic macular telangiectasia type II. Retina. 2009;29:27-32.

13. Matsumoto Y, Yuzawa M. Intravitreal bevacizumab therapy for idiopathic macular telangiectasia. Jpn J Ophthalmol. 2010;54:320-324.
14. Takayama K, Ooto S, Tamura H, Yamashiro K, Otani A, Tsujikawa A, Yoshimura N. Intravitreal bevacizumab for type 1 idiopathic macular telangiectasia. Eye (Lond). 2010;24:1492-1497.
15. Narayanan R, Majji AB, Hussain N, Hussain A, Jalali S, Mathai A, Shah VA. Characterization of idiopathic macular telangiectasia type 2 by fundus fluorescein angiography in Indian population. Eur J Ophthalmol. 2008;18:587-590.
16. Engelbrecht NE, Aaberg TM Jr, Sung J, Lewis ML. Neovascular membranes associated with idiopathic juxtafoveolar telangiectasis. Arch Ophthalmol. 2002;120:320-324.
17. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology. 2006;113:363-372.
18. Yamamoto I, Rogers AH, Reichel E, Yates PA, Duker JS. Intravitreal bevacizumab (Avastin) as treatment for subfoveal choroidal neovascularisation secondary to pathological myopia. Br J Ophthalmol. 2007;91:157-160.
19. Mandal S, Venkatesh P, Abbas Z, Vohra R, Garg S. Intravitreal bevacizumab (Avastin) for subretinal neovascularization secondary to type 2A idiopathic juxtafoveal telangiectasia. Graefes Arch Clin Exp Ophthalmol. 2007;245:1825-1829.
20. Narayanan R, Chhablani J, Sinha M, Dave V, Tyagi M, Pappuru RR, Kuppermann BD. Efficacy of anti-vascular endothelial growth factor therapy in subretinal neovascularization secondary to macular telangiectasia type 2. Retina. 2012;32:2001-2005.
21. Jorge R, Costa RA, Calucci D, Scott IU. Intravitreal bevacizumab (Avastin) associated with the regression of subretinal neovascularization in idiopathic juxtafoveolar retinal telangiectasis. Graefes Arch Clin Exp Ophthalmol. 2007;245:1045-1048.
22. Roller AB, Folk JC, Patel NM, Boldt HC, Russell SR, Abramoff MD, Mahajan VB. Intravitreal bevacizumab for treatment of proliferative and nonproliferative type 2 idiopathic macular telangiectasia. Retina. 2011;31:1848-1855.
23. Karagiannis D, Georgalas I, Ladas I, Eustratios P, Mitropoulos P. A case of subretinal neovascularization treated with intravitreal ranibizumab in a patient with idiopathic juxtafoveal retinal telangiectasis. Clin Interv Aging. 2009;4:63-65.

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Original Article

Rehabilitation of Eyelid Malpositions Secondary to Facial Palsy

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Abstract

Objectives: To evaluate patient satisfaction and outcomes of surgical treatment of eyelid malpositions secondary to facial palsy.

Materials and Methods: Consecutive patients with facial palsy who underwent surgical treatment by the same surgeon at İzmir Katip Çelebi University Atatürk Training and Research Hospital between Jan 2007 and Dec 2012 were included in the study. Ophthalmic examination findings, surgical approaches, and their outcomes were evaluated. A successful result for upper eyelid position was defined as more than 50% reduction in lagophthalmos and induction of less than 2 mm of ptosis. A successful outcome for lower eyelid position was defined as the lower eyelid residing at or within 1 mm above or below the limbus. Linear visual analog scale 1 (VAS-1) (subjective complaints) and VAS-2 (cosmetic outcome), both ranging from 0 to 10, were used to compare preoperative findings with findings at last postoperative visit.

Results: The mean age of the 14 female and 21 male patients was 54.5±19.9 years. Gold weight implantation (n=31), lateral tarsal strip (n=22), tarsorrhaphy (n=15), suborbicularis oculi fat elevation (n=16), hard palate graft (n=14), and eyebrow ptosis repair (n=6) were performed. Average follow-up time was 17.9±16.9 months (range, 2-60). Surgical success rates were 90% for upper lids and 75% for lower lids. Mean lagophthalmos decreased from 7.1±2.7 mm to 1.6±1.6 mm postoperatively (p=0.000). The use of lubricating drops and gels was reduced from average preoperative daily values of 5.3±2.5 drops and 1.3±0.6 gel applications to 4.4±1.4 and 0.6±0.6, respectively (p=0.003, p=0.001).

Conclusion: An individualized surgical approach tailored according to each patient's severity of facial palsy and associated malpositions resulted in both functional and aesthetic improvements in our patients.

Keywords: Facial paralysis, eyelid malposition, lagophthalmos, gold weight, suborbicularis oculi fat pad

Introduction

In order to protect the functional and structural integrity of the eye following facial palsy, it is of utmost importance to accurately assess and plan appropriate therapeutic approaches to both ocular surface problems and eyelid malpositions. Inability of the eyelids to close completely can lead to a progressive continuum of problems ranging from diminished or absent blinking reflex and exposure keratopathy to corneal ulceration, perforation, and even blindness.[1] Epiphora, lid retraction, paralytic ectropion, and cosmetic issues may also occur.

The most common form of facial nerve palsy is idiopathic facial paralysis.[2] Infectious agents, trauma, neoplasmas, and autoimmune diseases are other disorders implicated in its etiology. While lagophthalmos secondary to idiopathic facial paralysis may be reversible, most other causes of facial nerve palsy result in irreversible lagophthalmos.

Various medical and surgical approaches are used to treat eyelid malpositions and ocular surface problems secondary to facial palsy. The primary goal of medical therapy is to ensure ocular surface integrity and patient comfort. Individual differences like disease severity and the patient's age and expectations play as much a role in the planning of surgical interventions for malpositions as eyelid anatomy and physiology.

In this study we aimed to evaluate the characteristics and surgical outcomes of patients treated for eyelid malposition

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secondary to facial palsy in the Clinic of Ophthalmology, İzmir Katip Çelebi University Atatürk Training and Research Hospital between January 2007 and December 2013.

Materials and Methods

After receiving approval from the İzmir Katip Çelebi University Atatürk Training and Research Hospital Ethics Committee, the medical records of patients who underwent surgical treatment by the same surgeon for eyelid malposition secondary to facial palsy in the oculoplastic surgery division between January 2007 and December 2013 were analyzed retrospectively. The patients' demographic characteristics, etiology of facial palsy, visual acuity, and anterior and posterior segment examination findings were recorded. Exposure keratopathy was graded in 5 levels based on the degree of corneal involvement (grade 0: none, grade 1: mild superficial punctate keratopathy, grade 2: punctate keratopathy on the inferior quarter of the cornea, grade 3: punctate keratopathy on the inferior third to half of the cornea, grade 4: punctate keratopathy on more than half of the cornea or any erosion or ulceration).[3] Patients were evaluated for the presence of Bell's phenomenon, any other pathologies limiting lower and upper lid movement, and degree of lagophthalmos.

Surgical methods utilized included gold weight implantation, lateral tarsal strip (LTS), suborbicularis oculi fat pad (SOOF) elevation with subperiosteal approach, hard palate graft, and tarsorrhaphy. A suitable combination of procedures was determined for each patient based on amount of lagophthalmos, position of the lower lid/cheek complex, and the patient's preference. In gold weight implantation procedures, the implant weight was determined using trial weight sets. The weight yielding the best lagophthalmos correction and minimal (approximately 1 mm) ptosis was selected.

To evaluate lid symmetry postoperatively, margin reflex distance-1 (MRD1) (distance from upper lid margin to light reflex) and MRD2 (distance from lower lid margin to light reflex) were recorded. Surgical success of upper eyelid procedures was defined as at least 50% reduction in lagophthalmos and induction of less than 2 mm of ptosis. For lower eyelids, surgical outcomes were defined as favorable when the lower lid rested at the limbus, acceptable when the lower lid margin rested within 1 mm above or below the lower limbus, and unsatisfactory when the lower lid rested more than 1 mm above or below the limbus. Patients with good or acceptable lower lid position were considered successful.

The visual analog scale (VAS) was used to compare preoperative findings with findings at the final postoperative follow-up examination. Two different scales evaluating subjective complaints (VAS-1) and cosmetic outcome (VAS-2) were applied. Patients were asked to select the most appropriate value that represented their outcome from a scale of 0 to 10. VAS-1 scoring assessed pre- to postoperative reduction in symptoms as 0: no reduction, 5: some reduction, 10: my symptoms are completely gone; the VAS-2 evaluated postoperative cosmetic appearance as 0: no change, 5: some improvement, I am satisfied, 10: big improvement, I am very satisfied.

In addition, the patients' artificial tear drops/gel application frequency was assessed pre- and postoperatively.

Results

Thirty-six eyes of 35 patients (21 male, 14 female) were included in the study. The patients' ages ranged from 11 to 93, with a mean of 54.5±19.9 years. Facial palsy affected the right side in 18 patients and the left side in 16 patients. One patient with bilateral facial palsy following trauma underwent procedures on both sides. Data from this patient were not included in analyses comparing the operated eyes and fellow eyes.

Intracranial tumor surgery was the most common cause of facial palsy; the other causes are listed by order of frequency in Table 1.

Time between onset of facial palsy and surgery ranged from 0 to 69 years, with a mean elapsed time of 14.2±20.6 years. Mean postoperative follow-up time was 17.9±16.9 (range, 2-60) months.

Mean visual acuity assessed by Snellen chart was 0.60±0.34 preoperatively and 0.64±0.32 postoperatively (p=0.078). The mean frequency of lubricant eye drop application pre- and postoperatively was 5.33±2.47 and 4.38±1.36 drops daily, respectively (p=0.03); for gel formulations, the mean frequency was 1.35±0.6 applications preoperatively and 0.56±0.71 postoperatively (p=0.001).

Pre- and postoperative mean keratopathy grades were 2.11±1.45 and 0.92±1.23, respectively (p=0.000).

Several procedures were utilized, the most common being gold weight implantation. The surgical procedures performed are presented in Table 2.

Thirty-one patients underwent gold weight implantation, and the average implant weight was 1.19±0.28 g. The implants ranged in weight from 0.6 to 1.6 g (Figure 1). The success rate among these patients was 90%. A total of 3 patients did not meet the criteria for successful outcome: less than 50% reduction in lagophthalmos was achieved in 1 patient and greater than 2 mm ptosis was induced in 2 patients.

Table 1. Distribution of patients by facial palsy etiology

Etiology	n	%
Intracranial tumor	11	30.6
Idiopathic	10	27.8
Trauma	8	22.2
Congenital	5	13.9
Radiotherapy	1	2.8
Parotid tumor	1	2.8

Mean amount of lagophthalmos decreased from 7.08±2.7 mm to 1.61±1.57 mm postoperatively (p=0.000; Table 3). Preoperative and postoperative amount of lagophthalmos was classified as 0-3 mm, 4-6 mm, or ≥7 mm; 22 patients (61.1%) had ≥7 mm lagophthalmos preoperatively. There were no patients with lagophthalmos ≥7 mm in the postoperative period (Table 4).

Postoperative MRD1 values were 2.06±1.12 mm on the operated side and 2.97±0.59 mm on the unoperated side. MRD1 differed significantly between operated and fellow eyes (p=0.003; Table 5). The distance from the lower lid to the limbus was 0.94±0.68 mm on the operated side and 0.47±0.62 mm on the unoperated side (p=0.067). Mean MRD2 values were 6.44±0.68 mm on the operated side and 5.97±0.62 mm on the unoperated side. The differences in lower lid-to-limbus distance and MRD2 values between operated and unoperated eyes were not significant (p=0.067; Table 5).

Table 2. Distribution of surgical procedures

Surgical procedure	n	%
Gold implant	31	86.1
LTS*	22	62.1
Tarsorrhaphy	15	41.7
SOOF elevation	15	41.7
Hard palate graft	14	38.9
Brow ptosis correction	6	16.7

LTS: Lateral tarsal strip, SOOF: Suborbicularis oculi fat pad

Table 3. Comparison of pre- and postoperative lagophthalmos amounts

	Mean	SD	Minimum	Maximum	p
Lagophthalmos (mm)					
Preoperative	7.08	2.7	2	12	0.000
Postoperative	1.61	1.57	0	5	

Figure 1. The gold weight implant was secured to the tarsal surface with 3 sutures

According to the criteria for lower lid success, of the 16 eyes of 15 patients who underwent SOOF elevation (LTS and/or hard palate graft), surgical success was achieved in 75% (6 successful, 6 partially successful) (Figures 2 and 3), while the other 25% (n=4) were not considered successful due to more than 1 mm of retraction.

After surgery, the patients' mean scores for subjective complaints (VAS-1) and cosmetic appearance (VAS-2) fell by 6.17±1.3 and 6.04±1.99, respectively.

Implant migration or expulsion was not observed in any of the patients in the early or late postoperative period. One patient with gold weight implant complained of increased heat and localized redness on the first postoperative day. The patient's findings resolved with oral antibiotic therapy. No other postoperative local or systemic complications were noted following the other surgical procedures.

Discussion

The etiology of facial palsy includes idiopathic, traumatic, infectious, and neoplastic causes. May and Klein[4] determined that idiopathic facial paralysis was the most common cause (49-51%). Studies conducted in Turkey have reported a comparable distribution.[5,6] In the present study, we found that facial paralysis resulting from surgical trauma and idiopathic paralysis were the first and second most common causes.

In facial palsy, visual acuity may decline due to exposure keratopathy and the toxic effects of applied medical therapies on the cornea. We did not observe a statistically significant change in visual acuity after surgery in the present study. Similarly, Berghaus et al.[7] noted no significant difference between pre- and postoperative visual acuity levels.

The reduced tear production, increased evaporation, and disruptions in tear film stability and the pump mechanism of the lacrimal drainage system that occur in facial palsy may give rise to ocular surface disorders.[1] Numerous studies have reported regression of ocular surface problems and keratopathy findings following both medical and surgical therapies.[7,8,9,10] Amer et al.[3] performed two forms of gold weight implantation and applied the same keratopathy classification system that we utilized in the present study; they reported that intervention reduced

Table 4. Pre- and postoperative classification of degree of lagophthalmos

		n	%
Preop lagophthalmos	0-3 mm	4	11.1
	4-6 mm	10	27.8
	≥7 mm	22	61.1
Postop lagophthalmos	0-3 mm	31	86.1
	4-6 mm	5	13.9
	≥7 mm	-	-

Table 5. Postoperative MRD1 and MRD2 values					
	Mean	**Standard deviation**	**Minimum**	**Maximum**	**p**
MRD1-FP (mm)	2.06	1.12	-1	4	0.003
MRD1-NFP (mm)	2.97	0.59	2	4	-
MRD2-FP (mm)	6.44	0.68	5.5	7.5	0.067
MRD2-NFP (mm)	5.97	0.62	5.5	7.5	-
FP: Facial palsy side, NFP: No facial palsy side (contralateral eye)					

keratopathy severity from a preoperative average of 1.2-1.4 to a postoperative average of 0.3-0.4. Similarly, the mean keratopathy severity in our study was 2.11±1.45 preoperatively and regressed to 0.92±1.23 postoperatively. These values also demonstrate that the patients in our study had more severe keratopathy initially and treatment provided significant improvement.

In facial palsy patients, surgical interventions to correct lid malpositions are performed to reduce exposure keratopathy. It can be expected that improvement in keratopathy will reduce the need for patients to use topical lubricants. We observed a significant pre- to postoperative reduction in the number of daily applications of both drop and gel forms of topical lubricants. Seiff et al.[11] also reported a reduction in topical lubricant use in their study including 12 patients. Golio et al.[8] determined in their study that all of the 44 patients who used a lubricant preoperatively reduced their usage postoperatively.

Many different methods may be utilized in the treatment of lid malpositions due to facial palsy. In the present study, the patients were not randomized; the surgical plan was determined based on patients' degree of paralysis and the position of the upper lid and lower lid/cheek complex. Tarsorrhaphy alone was preferred in a small minority of patients. This preference was based both on the fact that the procedure was not pleasing cosmetically and that none of the patients had accompanying fifth cranial nerve involvement. Methods like levator recession or müllerectomy were not preferred for upper lid retraction; instead, we opted for gold weight implantation, a procedure easy to perform and readily adjusted to meet each patient's needs. For lower lid malpositions, combined procedures yielded the best results. In patients with pronounced lower lid retraction, we used the LTS procedure to establish lateral canthal support in addition to SOOF elevation and hard palate graft to effectively lift atonic lids. Eyebrow surgeries were planned for patients with upper visual field loss or cosmetic concerns as the last step of rehabilitation, after surgeries that protect the cornea and correct eyelid malposition.

The preoperative amount of lagophthalmos caused by facial palsy varies, often ranging from 4 to 8 mm.[5,6,7] In our study, the mean preoperative amount of lagophthalmos was 7 mm; compared to other reports in the literature, our study group included patients with more severe lagophthalmos.

Gold weight implantation is often used in the treatment of lagophthalmos due to upper lid retraction because the implant is relatively inert, is well tolerated by patients, yields favorable cosmetic outcomes, and the procedure is reversible. We performed gold weight implantation in 31 patients with a mean implant weight of 1.19±0.28 g and encountered no serious complications. Comparable mean implant weight values have been reported in previous studies.[10,11,12]

Townsend[10] performed gold weight implantation in 23 patients and reduced the amount of lagophthalmos from a preoperative mean of 4 mm to a postoperative mean of 0.5 mm. Berghaus et al.[7] reported the mean lagophthalmos amount as 5 mm preoperatively and 0.3 mm postoperatively in 33 patients that underwent gold weight implantation. Akçay et al.[5] performed gold weight implantation in 18 patients and reported that the preoperative mean lagophthalmos amount of 4.96 mm decreased to 1.6 mm postoperatively. In our study, gold weight implantation performed alone (n=3) or in combination with other procedures (n=28) reduced the amount of lagophthalmos from 7.1 mm to 1.6 mm.

Aggarwal et al.[12] performed gold weight implantation in 29 patients and accepted outcomes with at least 50% reduction in lagophthalmos with induction of less than 2 mm ptosis as successful. The mean amount of lagophthalmos in their study fell from 7 mm to 2.3 mm, and their success rate was 68.9%. In the present study, we achieved a success rate of 90% among the 31 patients we treated with gold weight implantation. Three of our patients did not meet the criteria for successful outcome due to less than 50% reduction in lagophthalmos in 1 patient and induction of more than 2 mm ptosis in 2 patients.

SOOF elevation is an effective method for correcting lower lid/cheek problems due to seventh nerve palsy. It has been successfully used to correct eyelid asymmetry and achieve a better lower lid position.[13,14,15] SOOF elevation was shown to be particularly effective in congenital cases.[15] Ben Simon et al.[16] reported that successful results were achieved with subperiosteal midface lift performed in 34 patients with lower lid retraction (6 of whom had facial palsy) and that the patients whose procedure included a hard palate graft had greater improvement in MRD2.[16] In our study we performed SOOF elevation in 16 eyes of 15 patients. The procedure was combined with LTS and/or hard palate graft. Therefore, we are unable to comment on the effectiveness of SOOF elevation alone, but our study demonstrated that elevation of the lower lid/cheek complex as a whole provided significant improvement in patients with severe lower lid retraction.

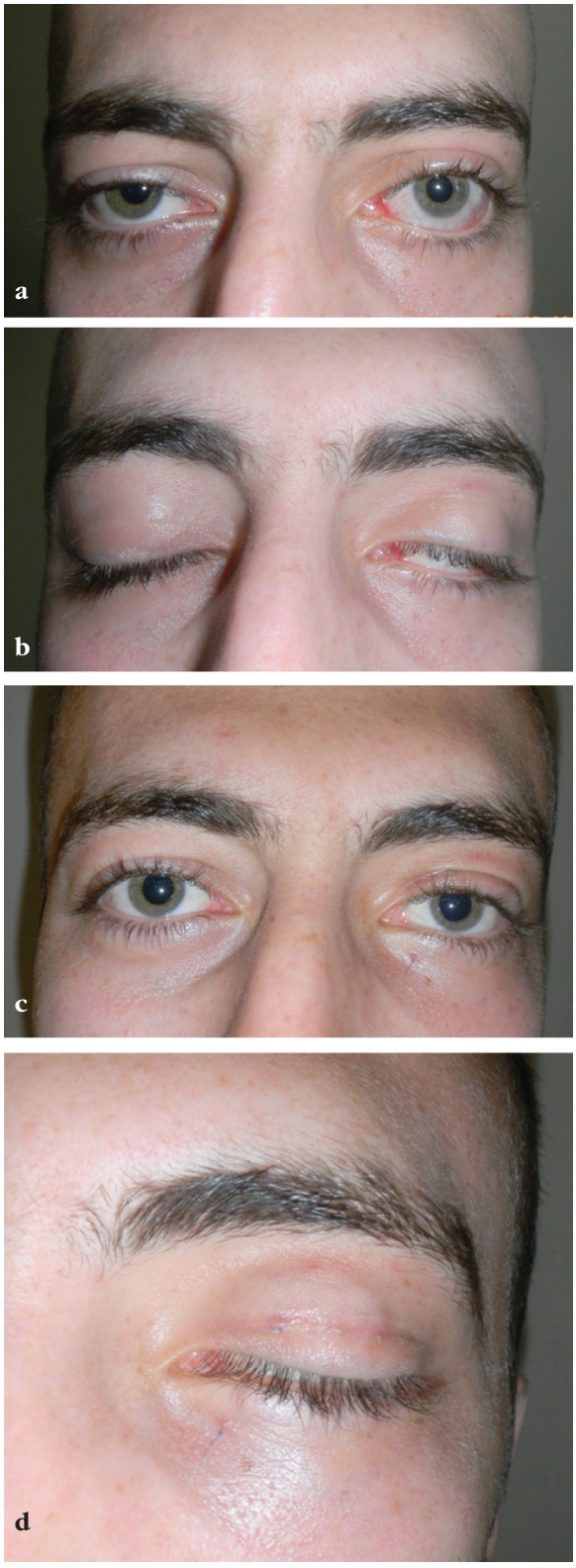

Figure 2. a, b) Upper-lower lid retraction and lagophthalmos due to left facial palsy. c, d) Improved upper and lower lid position and marked reduction in lagophthalmos were apparent after gold weight implantation, suborbicularis oculi fat elevation, hard palate graft, and lateral tarsal strip procedures

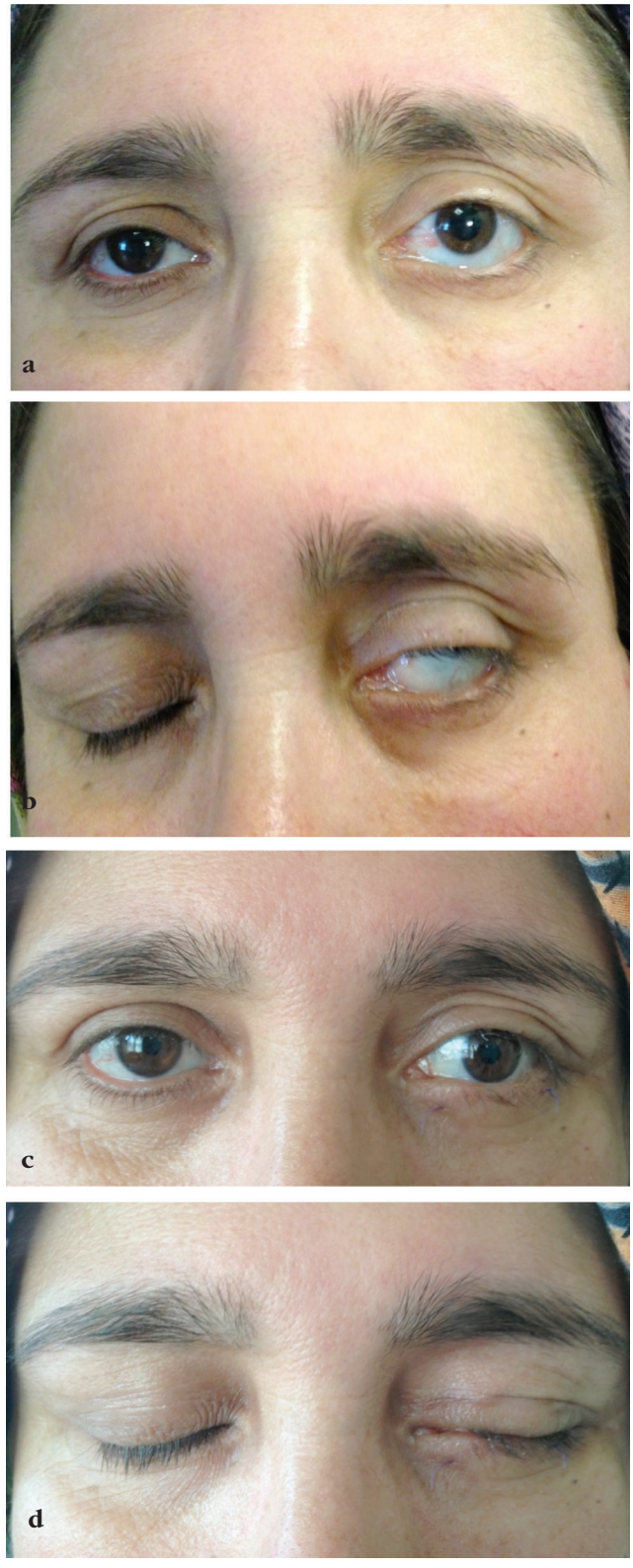

Figure 3. a, b) Mild upper lid retraction, pronounced lower lid retraction, and lagophthalmos due to left facial palsy. c, d) Lagophthalmos was alleviated and the lower lid rested at the limbus after gold weight implantation, suborbicularis oculi fat elevation, hard palate graft, and lateral tarsal strip procedures

Harvesting a hard palate graft causes temporary discomfort, and healing of the donation site usually takes time. However, previous studies have shown that procedures addressing multiple elements of lower lid retraction yield more favorable results.[17] Wearne et al.[18] reported good or acceptable outcomes in 85% and unsatisfactory outcomes in 15% of their study of 102 eyes of 68 patients with lower lid malpositions corrected using autogenic hard palate mucosa. Of the 16 eyes of 15 patients that underwent lower lid surgery in our study, we achieved good or acceptable results in 75% and unsatisfactory results in the remaining 25%. However, the patient group in Wearne et al.'s[18] study included only 3 patients with paralytic ectropion, and in most patients, hard palate graft was performed to correct lower lid retraction secondary to thyroid-associated orbitopathy. Furthermore, time elapsed since the procedure is also a determinant of lower lid position, as retraction may increase with longer follow-up. Wearne et al.[18] evaluated their patients at 3 months postoperatively, whereas we evaluated lid position based on findings at the patients' final examination after a mean postoperative follow-up period 17.9±16.9 months.

The LTS procedure preserves the natural anatomy while effectively correcting horizontal laxity. Chang and Olver[9] performed an augmented LTS procedure in 14 patients with paralytic lagophthalmos and determined their mean postoperative MRD2 to be 5 mm. The authors reported an average change in MRD2 of 3 mm. In a study by Loyo et al.,[19] 37% of 47 patients that had surgery for paralytic lower lid retraction benefited from standard LTS. We also employed the standard LTS procedure but based on lower lid/cheek position and patient preference, we preferred LTS for mild cases and SOOF + hard palate graft + LTS for more severe cases. Comparison with MRD2 values of patients' non-paralytic eyes showed that patients in both groups had good lower lid symmetry postoperatively.

Various scales are employed to evaluate patients' perceptions of their surgical outcomes after undergoing procedures for facial palsy. Sönmez et al.[20] used the visual analogue scale (VAS) to evaluate postoperative changes in ocular symptoms in 41 patients that underwent gold weight implantation. Patients showed the highest satisfaction in terms of eye closure ability, while visual acuity received the lowest score. We utilized the VAS-1 to assess postoperative changes in ocular complaints and the VAS-2 to assess postoperative cosmetic changes, and obtained results similar to those of Sönmez et al.[20] These results indicated that surgical therapy provided significant improvement in the ocular complaints of the patients, and in their subjective cosmetic perceptions.

Ensuring regular follow-up is important for patients undergoing surgical treatment for facial palsy. Over time, patients with gold weight implants may experience implant superficialization, ptosis, residual lagophthalmos, increased upper lid retraction, or implant expulsion, and may require additional surgery.[19,21] The same applies for procedures on the lower lid; recurrence of lower lid retraction in the long term may occur, resulting in reduced efficacy of the procedure and unfavorable cosmetic changes.[16] The mean postoperative follow-up time in our study was 17.9±16.9, ranging from 2-60 months. Other than signs of infection during early follow-up in one patient, we observed no other serious complications in our patients.

Conclusion

This retrospective study evaluating the treatment outcomes of eyelid malpositions secondary to facial palsy cannot compare and determine the superiority of the different surgical procedures over one another. Prospective studies utilizing classification systems focused on ocular findings may be more informative in this respect. On the other hand, our study demonstrates that satisfying outcomes can be achieved using an individualized approach in which treatment options are determined based on the patient's clinical presentation. This approach provides a high rate of improvement in both ocular and cosmetic complaints. Even with successful surgical outcomes, long-term follow-up is necessary for patients with facial palsy in order to detect and manage lid position changes that may occur over time and to enable timely intervention for the subsequent ocular surface problems that may arise.

Ethics

Ethics Committee Approval: İzmir Katip Çelebi University Atatürk Training and Research Hospital, Approved number: 80, Date: 08.04.2013, Informed Consent: Available for all procedures. Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şeyda Karadeniz Uğurlu, Concept: Şeyda Karadeniz Uğurlu, Design: Şeyda Karadeniz Uğurlu, Data Collection or Processing: Mustafa Karakaş, Analysis or Interpretation: Şeyda Karadeniz Uğurlu, Mustafa Karakaş, Literature Search: Mustafa Karakaş, Writing: Şeyda Karadeniz Uğurlu, Mustafa Karakaş.

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References

1. Rahman I, Sadiq SA. Ophthalmic management of facial nerve palsy: a review. Surv Ophthalmol. 2007;52:121-144.
2. Bergeron CM, Moe KS. The evaluation and treatment of upper eyelid paralysis. Facial Plast Surg. 2008;24:220-230.
3. Amer TA, El-Minawi HM, El-Shazly MI. Low-level versus high-level placement of gold plates in the upper eyelid in patients with facial palsy. Clin Ophthalmol. 2011;5:891-895.
4. May M, Klein SR. Differential diagnosis of facial nerve palsy. Otolaryngol Clin North Am. 1991;24:613-645.
5. Akçay L, Kartal B, Özgür Rodop Ö, Doğan ÖK. Fasiyal Paraliziye Bağlı Lagoftalmi Varlığında Üst Kapağa Altın Ağırlık Uygulaması ve Göz İçi Basıncına Etkisi. Turk J Ophthalmol. 2008;38:417-426.

6. Yalaz M, Özcan AA, Demircan N , Yağmur M. Fasiyal paralizili olgularda lagoftalminin düzeltilmesi. Turk J Ophthalmol. 2001;31:534-540.
7. Berghaus A, Neumann K, Schrom T. The platinum chain: a new upper-lid implant for facial palsy. Arch Facial Plast Surg. 2003;5:166-170.
8. Golio D, De Martelaere S, Anderson J, Esmaeli B. Outcomes of periocular reconstruction for facial nerve paralysis in cancer patients. Plast Reconstr Surg. 2007;119:1233-1237.
9. Chang L, Olver J. A useful augmented lateral tarsal strip tarsorrhaphy for paralytic ectropion. Ophthalmology. 2006;113:84-91.
10. Townsend DJ. Eyelid reanimation for the treatment of paralytic lagophthalmos: historical perspectives and current applications of the gold weight implant. Ophthal Plast Reconstr Surg. 1992;8:196-201.
11. Seiff SR, Boerner M, Carter SR. Treatment of facial palsies with external eyelid weights. Am J Ophthalmol. 1995;120:652-657.
12. Aggarwal E, Naik MN, Honavar SG. Effectiveness of the gold weight trial procedure in predicting the ideal weight for lid loading in facial palsy: a prospective study. Am J Ophthalmol. 2007;143:1009-1012.
13. Chung JE, Yen MT. Midface lifting as an adjunct procedure in ectropion repair. Ann Plast Surg. 2007;59:635-640.
14. Graziani C, Panico C, Botti G, Collin RJ. Subperiosteal midface lift: its role in static lower eyelid reconstruction after chronic facial nerve palsy. Orbit. 2011;30:140-144.
15. Olver JM. Raising the suborbicularis oculi fat (SOOF): its role in chronic facial palsy. Br J Ophthalmol. 2000;84:1401-1406.
16. Ben Simon GJ, Lee S, Schwarcz RM, McCann JD, Goldberg RA. Subperiosteal midface lift with or without a hard palate mucosal graft for correction of lower eyelid retraction. Ophthalmology. 2006;113:1869-1873.
17. Tan J, Olver J, Wright M, Maini R, Neoh C, Dickinson AJ. The use of porous polyethylene (Medpor) lower eyelid spacers in lid heightening and stabilisation. Br J Ophthalmol. 2004;88:1197-1200.
18. Wearne MJ, Sandy C, Rose GE, Pitts J, Collin JR. Autogenous hard palate mucosa: the ideal lower eyelid spacer? Br J Ophthalmol. 2001;85:1183-1187.
19. Loyo M, Jones D, Lee LN, Collar RM, Molendijk J, Boahene KD, Ishii LE, Byrne PJ. Treatment of the periocular complex in paralytic lagophthalmos. Ann Otol Rhinol Laryngol. 2015;124:273-279.
20. Sönmez A, Oztürk N, Durmuş N, Bayramiçli M, Numanoğlu A. Patients' perspectives on the ocular symptoms of facial paralysis after gold weight implantation. J Plast Reconstr Aesthet Surg. 2008;61:1065-1068.
21. Bladen JC, Norris JH, Malhotra R. Indications and outcomes for revision of gold weight implants in upper eyelid loading. Br J Ophthalmol. 2012;96:485-489.

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Review

Corticosteroid Treatment in Diabetic Macular Edema

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Abstract
Diabetic macular edema is the most common cause of visual impairment in patients with diabetes mellitus. The pathogenesis of macular edema is complex and multifactorial. For many years, laser photocoagulation has been considered the standard therapy for the treatment of diabetic macular edema; however, few patients achieve significant improvements in visual acuity. Today the intravitreal administration of anti-inflammatory or anti-angiogenic agents together with the use of laser photocoagulation represents the standard of care for the treatment of this complication. The intravitreal route of administration minimizes the systemic side effects of corticosteroids. Steroid-related ocular side effects are elevated intraocular pressure and cataract, while injection-related complications include endophthalmitis, vitreous hemorrhage, and retinal detachment. In order to reduce the risks and complications, intravitreal implants have been developed recently to provide sustained release of corticosteroids and reduce repeated injections for the management of diabetic macular edema. In this review, the efficacy, safety, and therapeutic potential of intravitreal corticosteroids in diabetic macular edema are discussed with a review of recent literature.
Keywords: Diabetic macular edema, intravitreal corticosteroid, triamcinolone acetonide, dexamethasone, fluocinolone acetonide

Introduction

Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetic retinopathy (DR). In the WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy), the 10-year incidence of DME was 20.1% among patients with type 1 diabetes, 13.9% among type 2 diabetics using insulin, and 25.4% among type 2 diabetes patients not using insulin.[1] Without timely and appropriate treatment, DME leads to permanent vision loss. Although the rate of serious vision loss due to DME is believed to have fallen in recent years, an additional 12,000-24,000 new cases are reported each year.[2]

Grid and focal laser photocoagulation have long been accepted as the standard treatment for vision loss associated with DME. It has been shown that laser photocoagulation reduces the risk of moderate vision loss in DME; however, many patients are unable to regain lost vision and the procedure is not effective in all DME patients.[3]

With the development of intravitreal agents such as anti-vascular endothelial growth factor (anti-VEGF) and steroids, new strategies are now recommended for the management of this complex disease. While intravitreal implantation offers potential visual gains compared to laser interventions, repeated application confers risks in terms of both drug- and surgery-related side effects.[3] With the longer duration of effect provided by intravitreal implants, the aim is to provide better visual recovery and fewer side effects. This review discusses the pathogenesis of DME, the rationale behind the use of corticosteroids, and current approaches to steroid use in the management of DME.

Pathogenesis of Diabetic Macular Edema

The pathogenesis of DME is complex and multifactorial. DME forms as a result of fluid accumulation in the retinal layers due to disruption of the blood-retina barrier (BRB). Hyperglycemia is the main risk factor for DR. Hyperglycemia causes high intracellular glucose levels, free radical production

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due to oxidative stress, and activation of protein kinase C. Chronic hyperglycemia leads to the formation of advanced glycation end products. Advanced glycation end products in the vitreous and vitreoretinal interface are responsible for the neurovascular damage seen in DR.[4]

The nervous and vascular systems are parallel systems in embryonic development. The two systems support each other during the formation of the vascular and nerve structures. Microvascular leakage and neuronal apoptosis occur in a mutual interaction. In the retinal neurovascular unit, Müller cells act as a bridge between the retinal nerves and the microcirculation. Müller cells are also an important component in the BRB. Cytoplasmic swelling in Müller cells is an early sign of macular edema, resulting in the accumulation of extracellular fluid within the cells.[5]

Other causes such as hypoxia, impaired blood flow, retinal ischemia, and inflammation are also associated with the progression of DME. Elevated VEGF levels, endothelial dysfunction, leukocyte adhesion, reduced levels of pigment epithelium-derived factor, and increased protein kinase C production lead to BRB destruction and increased vascular permability.[4]

VEGF is a homodimeric glycoprotein which stimulates vascular endothelial cell proliferation and increases vascular permeability. VEGF-A stimulates microvascular leakage and neuronal apoptosis, and is critical in the neurovascular unit.[5] Many studies have shown that VEGF plays an important role in the development of DME.[6,7] The main anti-VEGF agents used in the treatment of DME are ranibizumab, bevacizumab, pegaptanib sodium, and aflibercept.[3]

Although the contribution of VEGF to the development of DME is indisputable, the role of other non-VEGF pathways has also been emphasized. There are many studies demonstrating the role of inflammation in the development of DR. Research on steroids in the treatment of DME has been ongoing for many years due to their powerful antiinflammatory and antiedematous effects. Corticosteroids block the arachidonic acid pathway via phospholipase A2 inhibition. This inhibits the synthesis of thromboxanes, leukotrienes, and prostaglandins, and prevents vasodilation and increased capillary permeability. Corticosteroids also stabilize lysozymes, reduce synthesis of inflammatory mediators and VEGF, inhibit cell proliferation, stabilize the BRB, enhance the density and activity of tight junctions in the retinal capillary endothelium, and improve retinal oxygenation.[8]

Significant decreases in retinal thickness have been observed within 1 hour of intravitreal triamcinolone acetonide (IVTA) injection, though no change was seen with bevacizumab after 24 hours.[9] Steroids are fast-acting due to non-genomic interactions with the plasma membranes, independent of gene transcription. The inhibition of osmotic swelling in Müller cells due to endogenic adenosine release also contributes to the rapid improvement in retinal thickness after IVTA injection. Endogenic adenosine release activates A1 receptors and opens glial potassium and chloride channels. The outflow of ions stabilizes the osmotic gradient and prevents cellular swelling. IVTA also stabilizes Starling forces by reducing vasoconstriction and hydrostatic pressure.[8]

Anti-VEGF agents are the first choice in pharmacologic treatment of DME. However, 61% of the patients in the RISE-RIDE study did not show visual gains of 15 letters or more, and 43% did not achieve visual acuities of 20/40 or better. The limited visual gains in those patients was believed to be related to neural damage, retinal pigment epithelium changes, and subretinal fibrosis resulting from chronic macular edema (mean duration, 4.5 years) prior to treatment, as well as structural damage from repeated macular laser therapy, and the natural course of DR.[10]

Nonresponse to anti-VEGF therapy can be defined as a lack of anatomic improvement or the recurrence of retinal exudation when the interval between injections is extended. Steroid therapy should be considered in such cases.

Intravitreal steroid injections reduce DME and stabilize vision, but side effects are common. The most common side effects are elevated intraocular pressure (IOP) and cataract formation. Therefore, steroids are preferable in pseudophakic eyes that have persistent or recurrent disease. Steroid therapy for DME is administered as peribulbar injection, intravitreal injection, or intravitreal implant. There are currently three different intravitreal steroids utilized: triamcinolone acetonide, fluocinolone acetonide, and dexamethasone.

Triamcinolone Acetonide

TA is a synthetic steroid with five times the anti-inflammatory strength of hydrocortisone. TA has a long-acting profile due to its low water solubility. The therapeutic effect of intravitreal 4 mg TA persists for up to 3 months.

IVTA in suspension form is currently available as the following commercial preparations: Trivaris (Allergan, Irvine, CA, USA), Kenacort (Bristol-Myers-Squibb, Melbourne, Australia) and Kenalog (Bristol-Myers-Squibb, Princeton, NY, USA).[3] IVTA was first utilized in the treatment of age-related macular degeneration, and within a few years began to be used in the treatment of DME as well.[11,12] The sub-Tenon route was initially preferred for steroid injections to treat DME, but it was later established that intravitreal injection was more effective in treating refractory DME.

A prospective study conducted by Diabetic Retinopathy Clinical Research Network (DRCR.net) compared the safety and efficacy in the 3-year results of preservative-free 1 mg and 4 mg IVTA versus focal/grid laser therapy. Patients were randomly assigned to one of 3 groups receiving either focal/grid laser treatment, 1 mg IVTA, or 4 mg IVTA. After 4 months of treatment, the group receiving 4 mg IVTA showed the largest gains in best corrected visual acuity (BCVA), but there was no significant difference in BCVA between the groups at 1 year. At 2 years, mean BCVA was highest in the laser group, which

was confirmed by central retinal thickness (CRT) measurements taken with optical coherence tomography. At 3 years, the laser group showed a BCVA increase of 5 letters, while neither IVTA group showed a change in BCVA from baseline. In terms of side effects observed in the laser, 1 mg IVTA, and 4 mg IVTA groups, IOP elevation over 10 mmHg occured in 4%, 18%, and 33%, and the probability of cataract surgery increased by 31%, 46%, and 83%, respectively. Therefore, it was concluded that IVTA did not provide long-term benefits in the treatment of DME compared to laser photocoagulation.[13,14]

Following the publication of the DRCR.net study demonstrating that laser therapy was superior to IVTA, a phase 2b clinical trial of a triamcinolone sustained delivery intravitreal implant (I-vation, Surmodics, Inc., MN, USA) was terminated.

DRCR.net later initiated a large randomized clinical study comparing laser photocoagulation with two different intravitreal agents in the treatment of central DME. Patients were randomly divided into 4 groups: sham injection + prompt laser, 0.5 mg intravitreal ranibizumab (IVR) + prompt laser, 0.5 mg IVR + deferred laser, and 4 mg IVTA + prompt laser. At 1 year, improvements in BCVA were significantly greater in the IVR + prompt laser and IVR + deferred laser groups when compared with the IVTA and laser-only groups. Compared to the laser-only group, all 3 of the groups that received intravitreal injections showed significant and comparable decreases in CRT.[15] The results of extended follow-up at 2 years were consistent with those published at 1 year.[16] Mean changes in BCVA compared to the laser-only group were +3.7 letters in the IVR + prompt laser group, +5.8 letters in the IVR + deferred laser group, and -1.5 letters in the IVTA + prompt laser group. Visual improvement in phakic eyes receiving IVTA was limited by the incidence of cataract. Cataract surgery was necessary in 55% of patients receiving IVTA, compared to 12% in the IVR group. Among the pseudophakic eyes in that study, BCVA outcomes were better in the IVTA + prompt laser group compared to the laser-only group, and were comparable to those in the IVR groups. However, the risk of IOP elevation was higher in the IVTA group (38%) than in the IVR + prompt laser group (5%). It was concluded that IVR injection is effective in DME, and that IVTA is an alternative option for pseudophakic eyes.

Currently, the intravitreal application of triamcinolone acetonide to treat DME is an off-label use. For this reason, IVTA is recommended either alone or in combination with laser therapy in selected patients with persistent and refractory DME and vision loss, particularly pseudophakic patients.[3]

Dexamethasone

The intravitreal dexamethasone implant (DEX implant; Ozurdex, Allergan) contains 0.7 mg preservative-free dexamethasone, can be stored at room temperature, and is applied using a pre-loaded 22-gauge intravitreal injector system. It is a biodegradable, sustained-release implant which remains effective for up to 6 months.

The MEAD study was a 3-year, randomized, sham-controlled study evaluating the safety and efficacy of the 0.35 mg and 0.7 mg intravitreal DEX implants in DME. The mean number of injections over 3 years was 4.1, 4.4, and 3.3 in the 0.7 mg DEX implant, 0.35 mg DEX implant, and sham injection groups, respectively. At the end of follow-up, a visual gain of ≥15 letters was achieved in 22.2% of the patients that received 0.7 mg DEX implant, 18.4% with 0.35 mg DEX implant, and 12% in the sham injection group. The largest reduction in mean central macular thickness was observed in the 0.7 mg DEX implant group (-111.6 µm), followed by the 0.35 mg DEX implant group (107.9 µm) and the sham group (-41.9 µm). In terms of adverse effects, the rate of cataract development among phakic patients was 67.9%, 64.2%, and 20.4% and IOP increases >10 mmHg occured in 27.7%, 24.8%, and 9.1% in the 0.7 mg DEX implant, 0.35 mg DEX implant, and sham injection groups, respectively. IOP elevation was controlled in most cases with or without medication, but trabeculectomy was necessary for 2 patients (0.6%) in the 0.7 mg DEX implant group and 1 patient (0.3%) in the 0.35 mg DEX implant group.[17]

In the PLACID study, patients with diffuse DME randomly received either 0.7 mg DEX implant or sham injection, both followed by laser photocoagulation after 1 month. When necessary, a second DEX implant or sham injection was given 6 months after the initial injection, and in both groups up to 3 supplemental laser applications were done at 3-month intervals. The DEX implant and laser group showed a greater decrease in vascular leakage and retinal edema on angiography compared to the group treated with laser only. There was no significant differences between the groups in BCVA at 12 months. However, BCVA was significantly increased in the DEX implant group at 1 and 9 months. IOP elevation over 10 mmHg occured in 15.2% of patients in the DEX implant group, but was controlled without the need for glaucoma surgery. At 12 months, 3.2% of the patients had undergone cataract surgery.[18]

The BEVORDEX study was a randomized clinical study comparing bevacizumab and 0.7 mg DEX implant in patients with DME. The study included 88 eyes of 61 patients with central DME. Forty-two eyes received pro re nata intravitreal bevacizumab every 4 weeks, and 46 eyes received a pro re nata DEX implant injection every 16 weeks. BCVA increases of 10 letters or more were observed in 40% of eyes treated with bevacizumab and 41% of eyes treated with DEX implant. None of the eyes that received bevacizumab showed BCVA decreases of 10 letters or more, while 11% of the eyes that received DEX implant had vision loss, mostly due to cataract. Central macular thickness decreased by a mean of 122 µm in the bevacizumab group and 187 µm in the DEX implant group. Mean number of injections over 12 months was 8.6 among eyes treated with bevacizumab and 2.7 among eyes that received DEX implant.[19]

The CHAMPLAIN study reported the 26-week outcomes of 55 vitrectomized patients with refractory DME lasting for a mean of 43 months who were treated with 0.7 mg DEX

implant. Mean change in CRT from baseline (403 µm) was -156 µm at 8 weeks and -39 µm at 26 weeks. Mean increase in BCVA was 6.0 letters at 8 weeks and 3.0 letters and 26 weeks; at 8 weeks, 30.4% of patients had increases of 10 letters or more and 42.9% of patients had increases of 5 letters or more. The study demonstrated that in vitrectomized eyes with refractory DME, the DEX implant had an acceptable safety profile and provided statistically and clinically significant visual gains as well as reduced vascular leakage.[20]

Overall, the risk/benefit ratio of the DEX implant is favorable in pseudophakic patients or a limited patient group who do not respond to nonsteroid therapies or for whom these therapies are not suitable.

Fluocinolone Acetonide

Intravitreal fluocinolone acetonide (IVFA) is commercially available in two different extended-release drug delivery systems, Retisert (Bausch&Lomb, Rochester, NY, USA) and Iluvien (Alimera Sciences, Atlanta, GA, USA).

Retisert is a nonbiodegradable implant containing 0.59 mg fluocinolone acetonide. It is implanted through a pars plana incision and sutured to the sclera and continuously releases the drug for up to 30 months. After surgical implantation, it initially releases the steroid at 0.6 µg/day, which gradually decreases over the first month and stabilizes at approximately 0.3-0.4 µg/day.[21] Retisert has been approved for the treatment of noninfectious posterior uveitis.

In a multicenter study investigating the safety and efficacy of Retisert in the treatment of persistent and recurrent DME, patients were randomly assigned to receive either 0.59 mg IVFA or observation/additional laser photocoagulation (standard of care). BCVA increased by 3 or more lines in 16.8% of the IVFA-implanted eyes at 6 months, 16.4% at 1 year, 31.8% at 2 years, and 31.1% at 3 years, compared to 1.4%, 8.1%, 9.35%, and 20% at the same time points in the eyes that received standard care. Throughout the study, implanted eyes showed greater reductions in CRT when compared to the standard care group. By the end of a 4-year follow-up period, 91% of the phakic eyes treated with IVFA required cataract surgery. IOP elevation ≥30 mmHg was observed in 61.4% of IVFA-implanted eyes, and 33.8% underwent a surgical procedure to control IOP.[22]

Iluvien is a nonbiodegradable implant containing 250 µg fluocinolone acetonide. It is injected into the vitreous using a 25 G injector and releases 0.5 or 0.2 µg/day of active agent. Three-year follow-up outcomes have been published for the multicenter, double-blind FAME study about the efficacy of Iluvien implant in patients with DME refractory to laser therapy. Patients with DME who had received laser therapy at least once were randomly assigned to 3 groups: 0.2 µg/day IVFA (low dose), 0.5 µg/day IVFA (high dose), or sham injection. Visual gains of 15 letters or more were reported in 28.7%, 27.8%, and 18.9%, respectively, at 3 years. Treatment was repeated at 12 months in 25% of the patients. Patients were able to receive laser treatment 6 months after initial treatment, and 40% of the patients underwent additional laser therapy. In addition, subgroup analysis was conducted to investigate the effect of DME duration on treatment. Among chronic patients with DME duration of 3 years or more, BCVA gains of ≥15 letters were observed in 34% (low dose), 28.8% (high dose), and 13.4% (sham); the improvements in the steroid implant groups were significantly greater. However, this difference was not significant among patients with DME for less than 3 years. Although all of the patients treated with IVFA developed cataract, their visual gains after cataract surgery were comparable to those of pseudophakic patients. After 3 years, incisional glaucoma surgery was required in 4.8% of the patients in the low dose group and 8.1% in the high dose group.[23]

Intravitreal administration of corticosteroids reduces their systemic side effects and confers several advantages in the treatment of DME. Because anti-VEGF agents are administered at frequent intervals, treatment costs are high. Sustained-release steroid implants reduce the number of intravitreal injections and greatly lower the risk of endophthalmitis and traumatic cataract. However, the risk of developing corticosteroid-induced cataract is extremely high.

Although there is better patient compliance with the IVFA implant because its duration of effect is longer than the DEX implant, but it has also been associated with higher risk of ocular hypertension and cataract. However, no clinical studies directly comparing the two treatment methods have been conducted to date. There is insufficient evidence that repeated administration of a DEX implant does not carry the same risks as sustained-release IVFA.

In brief, anti-VEGF agents are recommended as initial treatment for DME involving the central macula. Laser photocoagulation is preferable in patients with noncentral DME due to the low risk, low cost, and patient compliance in this group. There are no studies comparing anti-VEGF agents and sustained-release corticosteroid therapy in the initial treatment of central DME.

Steroid therapy allows suppression of both the inflammation and the VEGF pathway in DME. The duration of effect is longer, and the injection number and follow-up frequency are lower than with anti-VEGF treatment. Therefore, particularly in chronic diffuse macular edema, steroid therapy is preferable for patients who do not respond to anti-VEGF therapy, or who have conditions contraindicated for anti-VEGF therapy such as recent cerebrovascular event or myocardial infarction. Due to the short half-life and probable low efficacy of anti-VEGF agents, steroid implants may be appropriate as initial treatment in vitrectomized patients with central DME. Corticosteroid implants are suitable alternatives to anti-VEGF therapy for pseudophakic patients with persistent central DME who do not have significant risk of glaucoma.[24]

In addition to monotherapies, the long duration of effect of corticosteroid implants may enable combination therapies. However, clinical studies are still needed to evaluate the synergistic effects of these implants used in combination with laser and anti-VEGF agents.

Ethics

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Concept: Burcu Nurözler Tabakcı, Design: Nurten Ünlü, Analysis or Interpretation: Burcu Nurözler Tabakcı, Literature Search: Nurten Ünlü, Burcu Nurözler Tabakcı, Writing: Burcu Nurözler Tabakcı.

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References

1. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. Ophthalmology. 1995;102:7-16.
2. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology. 2009;116:497-503.
3. Bandello F, Preziosa C, Querques G, Lattanzio R. Update of intravitreal steroids for the treatment of diabetic macular edema. Ophthalmic Res. 2014;52:89-96.
4. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol. 2009;54:1-32.
5. Zhang X, Zeng H, Bao S, Wang N, Gillies MC. Diabetic macular edema: new concepts in patho-physiology and treatment. Cell Biosci. 2014;4:27.
6. Funatsu H, Yamashita H, Noma H, Mimura T, Yamashita T, Hori S. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. Am J Ophthalmol. 2002;133:70-77.
7. Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology. 2003;110:1690-1696.
8. Stewart MW Corticosteroid use for diabetic macular edema: old fad or new trend? Curr Diab Rep. 2012;12:364-375.
9. Sonoda Y, Arimura N, Shimura M, Sakamoto T. Early change of central macular thickness after intravitreous triamcinolone or bevacizumab in diabetic macular edema or retinal vein occlusion. Retina. 2011;31:290-297.
10. Brown DM1, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS, Hopkins JJ; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. 2013;120:2013-2022.
11. Penfold PL, Gyory JF, Hunyor AB, Billson FA. Exudative macular degeneration and intravitreal triamcinolone. A pilot study. Aust N Z J Ophthalmol. 1995;23:293-298.
12. Jonas JB, Söfker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. Am J Ophthalmol. 2001;132:425-427.
13. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, Aiello LP, Bressler NM, Ferris F, Glassman AR, Hartnett E, Ip MS, Kim JE, Kollman C. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol. 2009;127:245-251.
14. Bressler NM, Edwards AR, Beck RW, Flaxel CJ, Glassman AR, Ip MS, Kollman C, Kuppermann BD, Stone TW; Diabetic Retinopathy Clinical Research Network. Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. Arch Ophthalmol. 2009;127:1566-1571.
15. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, Ferris FL 3rd, Friedman SM, Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117:1064-1077.
16. Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, Glassman AR, Scott IU, Stockdale CR, Sun JK; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011;118:609-614.
17. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121:1904-1914.
18. Callanan DG, Gupta S, Boyer DS, Ciulla TA, Singer MA, Kuppermann BD, Liu CC, Li XY, Hollander DA, Schiffman RM, Whitcup SM; Ozurdex PLACID Study Group. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. Ophthalmology. 2013;120:1843-1851.
19. Gillies MC, Lim LL, Campain A, Quin GJ, Salem W, Li J, Goodwin S, Aroney C, McAllister IL, Fraser-Bell S. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. Ophthalmology. 2014;121:2473-2481.
20. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, Liu CC, Lou J, Whitcup SM; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina. 2011;31:915-923.
21. Driot JY, Novack GD, Rittenhouse KD, Milazzo C, Pearson PA. Ocular pharmacokinetics of fluocinolone acetonide after Retisert intravitreal implantation in rabbits over a 1-year period. J Ocul Pharmacol Ther. 2004;20:269-275.
22. Pearson PA, Comstock TL, Ip M, Callanan D, Morse LS, Ashton P, Levy B, Mann ES, Eliott D. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. Ophthalmology. 2011;118:1580-1587.
23. Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, Garretson B, Gupta A, Hariprasad SM, Bailey C, Reichel E, Soubrane G, Kapik B, Billman K, Kane FE, Green K; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology. 2012;119:2125-2132.
24. Ciulla TA, Harris A, McIntyre N, Jonescu-Cuypers C. Treatment of diabetic macular edema with sustained-release glucocorticoids: intravitreal triamcinolone acetonide, dexamethasone implant, and fluocinolone acetonide implant. Expert Opin Pharmacother. 2014;15:953-959.

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Case Report

Corneal Collagen Crosslinking Treatment in a Case with Pneumococcal Keratitis

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Abstract

Bacterial keratitis is a serious ocular infectious disease that can threaten vision. The disease generally progresses rapidly and can lead to corneal scar, stromal abscess formation, perforation, and dissemination to adjacent tissues if not treated properly. Recent studies showed that corneal collagen crosslinking (CCC) using ultraviolet-A/riboflavin is effective in the treatment of bacterial keratitis refractory to topical antibiotic treatment. In addition to being bactericidal, CCC also decreases risk of perforation by strengthening the corneal collagen structure. Herein, we report a male patient with *Streptococcus pneumonia* keratitis 6 months after a keratoplasty procedure, which did not respond to fortified topical antibiotic therapy and was treated successfully with riboflavin/ultraviolet-A CCC. His pain decreased remarkably in a few days. The corneal epithelial defect healed and infiltration regressed within 2 weeks after CCC. His vision improved significantly from hand movement to 20/400. CCC might be used as adjuvant treatment in bacterial keratitis refractory to medical treatment.

Keywords: Bacterial keratitis, corneal collagen crosslinking, ultraviolet-A/riboflavin

Introduction

Bacterial keratitis is the leading sight-threatening ocular infection. The disease generally progresses rapidly, and may lead to corneal scar, stromal abscess, perforation, and dissemination to adjacent tissues if not treated properly.[1] Bacterial keratitis usually occurs in the presence of risk factors leading to disruption of the ocular surface immune mechanisms. Contact lens use; dry eye disease; eyelid disorders such as entropion, ectropion, and lagophthalmos; ocular surgery; and long-term corticosteroid use are among the risk factors.[2,3] Topical application of broad-spectrum, bactericidal antibiotic agents is used to treat bacterial keratitis.[4]

Corneal collagen crosslinking (CXL) is an extremely effective therapy shown to arrest the progression of keratoconus, pellucid marginal degeneration, and post-LASIK corneal ectasia, and has become widely used worldwide over the last decade.[5,6,7] In the procedure, ultraviolet-A (UV-A) irradiation causes riboflavin to form triplets and release reactive oxygen species such as singlet oxygen and superoxide, which form new covalent bonds between the amino acids of adjacent collagen fibrils (photopolymerization). This polymerization increases the rigidity of corneal collagen and improves resistance to keratectasia. Furthermore, the application of UV-A and riboflavin has been shown to inactivate certain viruses, bacteria, fungi, and parasites in several in vitro studies.[8,9,10] Clinical studies have also demonstrated that CXL is safe and effective in the management of corneal infections refractory to medical treatment.[11,12,13,14,15] CXL also reduces the risk of perforation by strengthening the cornea. Despite the widespread use of CXL in the treatment of keratoconus in Turkey, were unable to find any Turkish publications regarding its use in cases of infectious keratitis. In this report, we present the case of a keratoplasty patient with *Streptococcus pneumonia* keratitis refractory to topical antibiotic therapy who showed rapid clinical improvement after CXL, and discuss the case in the context of the literature.

Case Report

A 32-year-old male patient presented in October 2014 with complaints of pain, blurred vision, and photophobia in the right

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eye for approximately 1 week. In his medical history, he reported being followed at another center for keratoconus and undergoing keratoplasty 7 years earlier in his left eye and 6 months earlier in his right eye. He had been using moxifloxacin (Vigamox®, Alcon) every 3 hours for about 1 week. At presentation, his visual acuity was hand motions in the right eye, and his best corrected visual acuity in the left eye was 8/20. Slit-lamp examination of the right eye revealed conjunctival hyperemia, purulent secretions and a keratitis focus about 5x4 mm in size located centrally over the corneal graft, epithelial defect, and keratoplasty sutures (Figure 1). The patient was recommended for admission with a prediagnosis of infectious keratitis; swabs from over the infiltration and its margins were sent to microbiology for Gram staining and culture. There were no filamentous extensions, satellite lesions, or ring ulcers suggestive of fungal keratitis. We also detected no hyphae-like structures suggesting fungal infection on confocal microscopy. Moxifloxacin was discontinued and treatment was initiated with topical fortified vancomycin 50 mg/mL (Vancotek®, Koçak Pharmaceuticals) and ceftazidime 100 mg/0.5 mL (Zıdım®, Tum Ekip), alternating between them hourly and replacing the drops every 2 days. Gram staining revealed no bacteria in the swab specimens, but *Streptococcus pneumoniae* grew in culture toward the end of the second week. Antibiogram showed the isolate was sensitive to vancomycin and ceftazidime, so the same treatment regimen was continued. Considering the lack of substantial improvement in the patient's symptoms and the possibility of Candida superinfection due to long-term topical steroid use after keratoplasty, treatment was supplemented with topical amphotericin B 0.5 mg/mL (Fungizone®, Bristol-Meyers Squibb) every 2 hours and topical vancomycin/ceftazidime was reduced to every 3 hours. After 1 month of medical therapy, we observed that the corneal infiltration had deepened and the epithelial defect had not closed (Figure 2). Therefore, we decided to perform CXL with UV-A and riboflavin. The patient was fully informed about the procedure and provided informed consent before the procedure.

In operating room conditions under topical anesthesia, the eye and surrounding area were cleaned with 5% povidone iodine and a sterile covering was placed. The damaged epithelial tissue over the infiltration was debrided using a blunt spatula and sent to microbiology. A riboflavin solution (1% isotonic M) was applied to the cornea at 3-minute intervals for a total of 30 minutes. An area of the cornea about 7 mm in diameter was exposed to 365-370 nm UV-A from a distance of 4-5 cm for 30 minutes at 3 mW/cm^2. During this time, riboflavin solution and a lubricating agent (Tears Naturale Free®, Alcon) were applied every 4 minutes.

There was a substantial reduction in the patient's photophobia and pain the day after CXL treatment. In subsequent examinations, the corneal infiltration became smaller and split into two foci, the surrounding corneal tissue regained transparency, and the epithelial defect also became smaller (Figure 3). The dosage of topical antibiotics was reduced. On examination 1 month after the CXL procedure, we observed slackening of the keratoplasty sutures and corneal vascularization (Figure 4). The keratoplasty sutures were removed and subconjunctival anti-vascular endothelial growth factor (anti-VEGF) (bevacizumab, Avastin®, Genentech) was administered. Preservative-free artificial tears (Tears Naturale Free®, Alcon) 5 times daily and fluorometholone (Flarex®, Alcon) 3 times daily were initiated. At 6 weeks after the CXL procedure, the peripheral corneal neovascularization had regressed, corneal opacity was reduced, and visual acuity was 20/400 (Figure 5).

Discussion

Riboflavin is able to pass through the lipid cellular membrane and be incorporated into nucleic acid chains. When activated by UV-A light, riboflavin releases reactive oxygen species that oxidize nucleic acids, thereby damaging the DNA and RNA

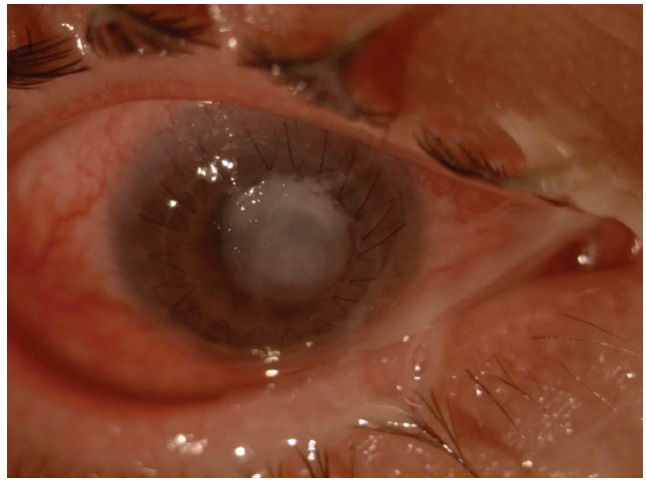

Figure 1. Infiltration in the center of the corneal graft, conjunctival hyperemia, and purulent secretion

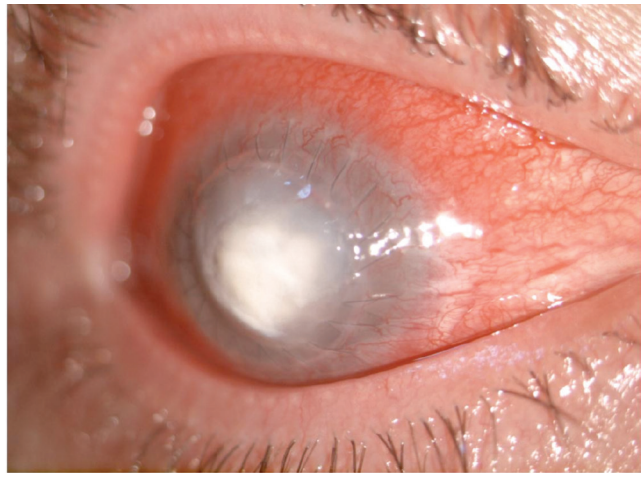

Figure 2. Corneal infiltration progressed and a large epithelial defect and peripheral corneal neovascularization developed despite topical fortified antibiotic therapy

of pathogens.[9,10] Pathogenic microorganisms produce certain enzymes that can destroy collagen and lead to corneal erosion and perforation. By eliminating pathogenic microorganisms and strengthening the collagen structure, CXL is able to halt the enzymatic destruction of the corneal stroma and reduce the risk of perforation. Previous studies have demonstrated the antibacterial effect of the combination of riboflavin and UV-A against multidrug-resistant *Pseudomonas aeruginosa, Staphylococcus aureus, S. epidermidis*, methicillin-resistant *S. aureus, S. pneumoniae*, and *Escherichia coli*.[9,12,13]

Iseli et al.[11] reported regression in the infectious keratitis foci of 5 patients being treated with topical and systemic antibiotic therapy after CXL treatment. In all patients, corneal ectasia was arrested and emergent corneal transplantation was not required. Makdoumi et al.[14] showed that CXL with riboflavin and UV-A could be used in combination with antibiotic therapy in a study of 7 eyes with severe keratitis. In another study, Makdoumi et al.[15] performed CXL as primary therapy in 16 cases of microbial keratitis. Other than 2 cases that required antibiotic therapy, all eyes showed epithelial healing and reduced inflammation. Price et al.[16] reported that CXL performed in addition to medical therapy successfully controlled infection in 34 of 40 eyes with keratitis (24 bacterial keratitis, 7 fungal keratitis, 2 protozoal keratitis, 1 viral keratitis, 6 unknown; 18% of eyes had keratoplasty). Treatment with CXL is especially effective with bacterial keratitis and with less deep infections.

Our patient developed severe *S. pneumoniae* keratitis in the eye that underwent keratoplasty 6 months earlier, and did not respond well to treatment despite antibiogram which indicated sensitivity to moxifloxacin, vancomycin, and ceftazidime. Because he was treated on an inpatient basis and his antibiotics were replaced every 2 days, we do not believe there were any

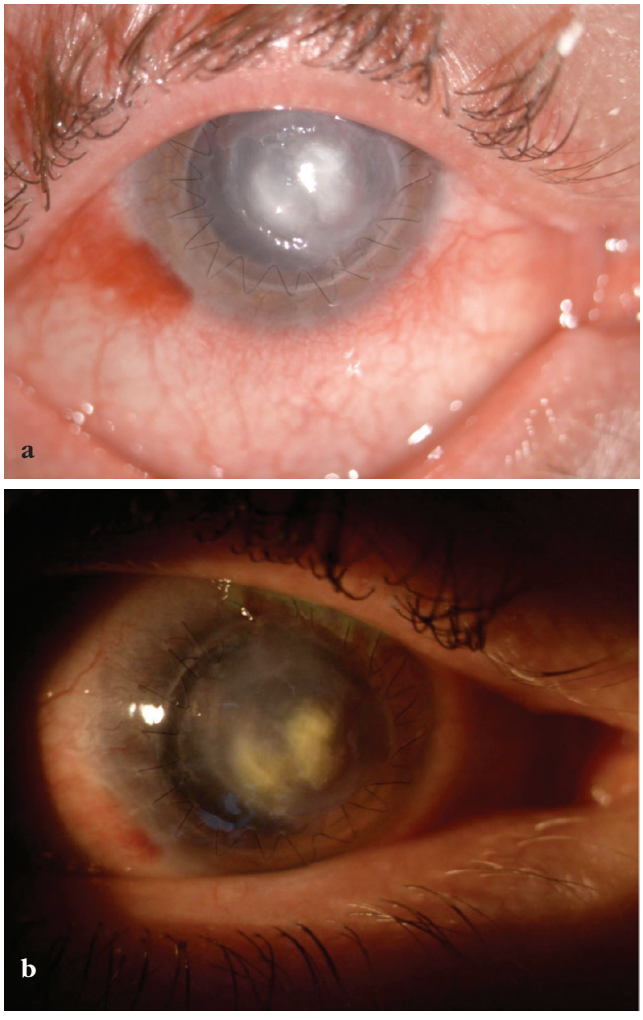

Figure 3. Examination at 1 day (a) and 1 week (b) after corneal collagen crosslinking revealed that the corneal infiltration diminished in size and split into two foci, the surrounding corneal tissue regained transparency, and the epithelial defect became smaller

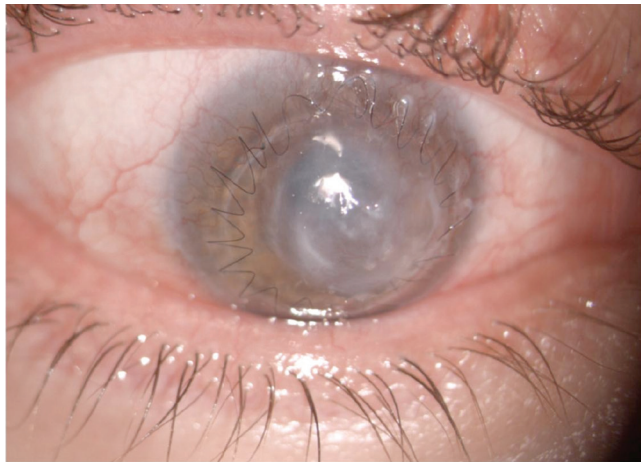

Figure 4. At 1 month after the corneal collagen crosslinking procedure, the corneal infiltrate and epithelial defect had resolved and there was slack in the corneal sutures

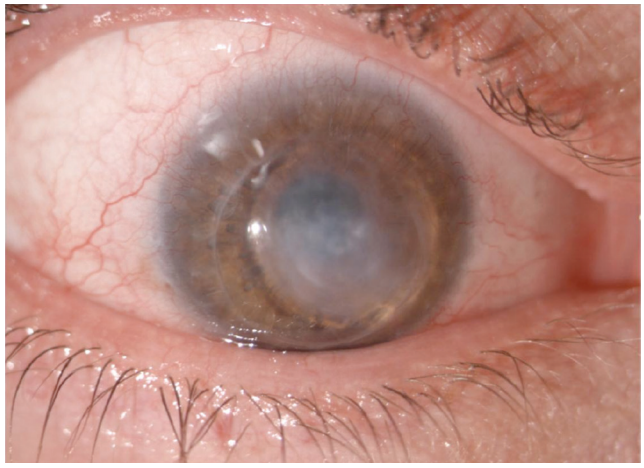

Figure 5. At 6 weeks after the corneal collagen crosslinking procedure, the corneal sutures were removed, peripheral corneal neovascularization had regressed, and corneal opacity was reduced

issues concerning treatment compliance or drug stability. The lack of treatment response may be attributable to microbial in vivo drug resistance, inadequate penetration of the drug into the cornea, toxicity and impaired healing due to long-term drug use, or the persistence of inflammation and tissue damage despite controlled infection. We performed CXL after 1 month of treatment in order to eliminate resistant microorganisms and reduce the risk of perforation by strengthening the cornea. Immediately following the procedure, the patient reported a significant reduction in pain; within a few days, the epithelial defect began to heal rapidly and the corneal infiltration became smaller and more superficial, healing with mild scarring.

Although there are studies in the literature supporting the use of CXL therapy, other reports argue that the procedure should not be routinely used in the management of infectious keratitis and emphasize that it may have a toxic effect in the diseased cornea, particularly on the endothelium. Kashiwabuchi et al.[17] found CXL ineffective both in vitro and in vivo against *Acanthamoeba* trophozoites. Galperin et al.[18] showed that riboflavin-CXL reduced the intensity and severity of infection but did not provide adequate healing in a experimental rabbit model of *Fusarium* keratitis. In addition, as UV-A can induce viral replication, it should not be used in cases of herpes simplex keratitis.[19,20] Demirci and Ozdamar[21] found that CXL was effective in patients with *Acanthamoeba* keratitis refractory to medical therapy.

In summary, CXL with UV-A and riboflavin may be effective in cases of bacterial keratitis refractory to medical therapy. Additional studies are necessary to determine the efficacy and reliability of CXL in infections caused by various microorganisms.

Ethics

Informed Consent: Retrospective study.

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Banu Bozkurt, Concept: Banu Bozkurt, Ümit Kamış, Design: Banu Bozkurt, Ümit Kamış, Data Collection or Processing: Banu Bozkurt, Ayşe Bozkurt Oflaz, Bengü Ekinci Köktekir, Analysis or Interpretation: Banu Bozkurt, Ümit Kamış, Literature Search: Banu Bozkurt, Ayşe Bozkurt Oflaz, Writing: Ayşe Bozkurt Oflaz, Banu Bozkurt.

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References

1. O'Brien TP. Management of bacterial keratitis: beyond exorcism towards consideration of organism and host factors. Eye (Lond). 2003;17:957-974.
2. Thomas PA, Geraldine P. Infectious keratitis. Curr Opin Infect Dis. 2007;20:129-141.
3. Parmar P, Salman A, Kalavathy CM, Kaliamurthy J, Thomas PA, Jesudasan CA. Microbial keratitis at extremes of age. Cornea. 2006;25:153-158.
4. Jones DB. Initial therapy of suspected microbial corneal ulsers II. Spesific antibiotic therapy based on corneal smears. Surv Ophthalmol. 1979;97:105-116.
5. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003;135:620-627.
6. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. J Cataract Refract Surg. 2007;33:2035-2040.
7. Spadea L. Corneal collagen cross-linking with riboflavin and UVA irradiation in pellucid marginal degeneration. J Refract Surg. 2010;26:375-377.
8. Tsugita A, Okada Y, Uehara K. Photosensitized inactivation of ribonucleic acids in the presence of riboflavin. Biochim Biophys Acta. 1965;103:360-363.
9. Martins SA, Combs JC, Noguera G, Camacho W, Wittmann P, Walther R, Cano M, Dick J, Behrens A. Antimicrobial efficacy of riboflavin/UVA combination (365 nm) in vitro for bacterial and fungal isolates: a potential new treatment for infectious keratitis. Invest Ophthalmol Vis Sci. 2008;49:3402-3408.
10. Tayapad JB, Viguilla AQ, Reyes JM. Collagen cross-linking and corneal infections. Curr Opin Ophthalmol. 2013;24:288-290.
11. Iseli HP, Thiel MA, Hafezi F, Kampmeier J, Seiler T. Ultraviolet A/riboflavin corneal cross-linking for infectious keratitis associated with corneal melts. Cornea. 2008;27:590-594.
12. Micelli Ferrari T, Leozappa M, Lorusso M, Epifani E, Micelli Ferrari L. Escherichia coli keratitis treated with ultraviolet A/riboflavin corneal cross-linking: a case report. Eur J Ophthalmol. 2009;19:295-297.
13. Morén H, Malmsjö M, Mortensen J, Ohrström A. Riboflavin and ultraviolet a collagen crosslinking of the cornea for the treatment of keratitis. Cornea. 2010;29:102-104.
14. Makdoumi K, Mortensen J, Crafoord S. Infectious keratitis treated with corneal crosslinking. Cornea. 2010;29:1353-1358.
15. Makdoumi K, Mortensen J, Sorkhabi O, Malmvall BE, Crafoord S. UVA-riboflavin photochemical therapy of bacterial keratitis: a pilot study. Graefes Arch Clin Exp Ophthalmol. 2012;250:95-102.
16. Price MO, Tenkman LR, Schrier A, Fairchild KM, Trokel SL, Price FW Jr. Photoactivated riboflavin treatment of infectious keratitis using collagen cross-linking technology. J Refract Surg. 2012;28:706-713.
17. Kashiwabuchi RT, Carvalho FR, Khan YA, de Freitas D, Foronda AS, Hirai FE, Campos MS, McDonnell PJ. Assessing efficacy of combined riboflavin and UV-A light (365 nm) treatment of Acanthamoeba trophozoites. Invest Ophthalmol Vis Sci. 2011;52:9333-9338.
18. Galperin G, Berra M, Tau J, Boscaro G, Zarate J, Berra A. Treatment of fungal keratitis from Fusarium infection by corneal cross-linking. Cornea. 2012;31:176-180.
19. Kymionis GD, Portaliou DM. Corneal collagen crosslinking and herpetic keratitis. J Cataract Refract Surg. 2013;39:1281.
20. Ferrari G, Iuliano L, Viganò M, Rama P. Impending corneal perforation after collagen cross-linking for herpetic keratitis. J Cataract Refract Surg. 2013;39:638-641.
21. Demirci G, Ozdamar A. A case of medication-resistant acanthamoeba keratitis treated by corneal crosslinking in Turkey. Case Rep Ophthalmol Med. 2013;2013:608253.

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Case Report

Bilaterally Diffuse Lacrimal Gland Involvement: Initial Presentation of Systemic Sarcoidosis

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Abstract
Orbital involvement in systemic sarcoidosis is a rare condition. We report a case of orbital sarcoidosis with bilaterally huge lacrimal gland involvement as the initial manifestation of systemic sarcoidosis. A 20-year-old woman admitted the ophthalmology department with progressive bilateral upper eyelid swelling for 6 months. The only pathologic finding was the presence of bilateral, symmetrical, solid, lobular masses at the lateral upper eyelids at the location of lacrimal glands. On systemic examination, bilateral parotid and submandibular glands appeared swollen. Magnetic resonance imaging of the orbit revealed bilateral symmetrical diffuse enlargement of the lacrimal glands with maximum and minimum thickness of 11 mm and 7 mm, respectively. The biopsy findings were compatible with sarcoidosis. Although lacrimal gland involvement has been reported in different studies, we for the first time report an unusual case with bilateral diffuse huge lacrimal gland involvement. Normal lacrimal gland thickness is approximately 4-5 mm in magnetic resonance imaging, while our case had bilateral diffuse enlargement of lacrimal glands, which showed maximum and minimum thickness of 11 mm and 7 mm, respectively. Although orbital involvement is uncommon in sarcoidosis, it should be remembered in the differential diagnosis of orbital masses.
Keywords: Lacrimal gland, orbit, sarcoidosis

Introduction

Sarcoidosis is an idiopathic, multisystem disorder that can affect any organ system and is mainly characterised by pulmonary, dermatologic, and ocular involvement. Its pathological hallmark is non-caseating granulomatous inflammation. Ocular involvement has been reported by different studies at a rate of 25-60%.[1,2] Although anterior uveitis is the most common manifestation of ocular sarcoidosis, any orbital structure can be involved. Lacrimal gland involvement is the most common form of orbital sarcoidosis.[1,3] We present a case of orbital sarcoidosis with bilateral enlargement of the lacrimal glands with eyelid and anterior orbital involvement as the initial manifestation of systemic sarcoidosis.

Case Report

A 20-year-old woman was admitted to the ophthalmology department with progressive bilateral upper eyelid swelling for 6 months. She had no other symptoms related to her eyes. A physical examination revealed dry mouth and nasal congestion. She had a history of triamcinolone (Nasacort) nasal spray usage for nasal congestion for nine months. Her family history was unremarkable. Her best corrected visual acuity was 10/10 in both eyes. The only pathologic finding identified through slit-lamp biomicroscopy was the presence of bilateral, symmetrical, solid, lobular masses in the lateral upper eyelids at the location of the lacrimal glands (Figure 1a). There was no proptosis. The patient's dilated fundus examination was unremarkable. Intraocular pressure was measured as 16 mmHg in both eyes.

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Pupillary response to light and eye movements was normal. The result of a Schirmer test without anaesthesia was 1 mm/5 minutes in both eyes.

Skin examination revealed subcutaneous nodules in the scalp. Upon systemic examination, the bilateral parotid and submandibular glands appeared swollen (Figure 1b). Magnetic resonance imaging (MRI) of the orbit revealed involvement of the superior eyelids and the anterior orbit and bilateral symmetrical diffuse enlargement of the lacrimal glands with an isointense signal intensity relative to muscle on T1-weighted images and a hypointense signal intensity on T2-weighted images (Figure 2). On MRI, the maximum and minimum thicknesses of the lacrimal glands were 11 mm and 7 mm, respectively. Parotid and submandibular glands were evaluated with ultrasound and MRI. Neck ultrasonography showed heterogeneous and hypoechoic areas in the parotid and submandibular glands bilaterally. MRI of the neck showed bilateral cervical lymph nodes of pathological size and bilateral enlargement of the parotid and submandibular glands with a heterogeneous appearance. For definitive diagnosis, a lacrimal gland biopsy was taken from the orbital lobe using an upper lid crease incision. Microscopic examination showed discrete non-necrotising granulomas (Figure 3). Acid fast bacilli were not identified by Ehrlich-Ziehl-Neelsen staining. Lymphoma was not considered in the differential diagnosis because of the absence of numerous atypical lymphocytes. The biopsy findings were consistent with sarcoidosis.

The patient was referred to the chest disease department for pulmonary involvement. Laboratory examination showed an elevated angiotensin converting enzyme level of 63 U/L. Blood and urine calcium levels were within normal limits. The tuberculin skin test result was anergic. A chest x-ray demonstrated bilateral hilar enlargement. A thoracic computer tomography revealed bilateral hilar, subcarinal, and aortopulmonary lymphadenopathies as well as perilymphatic and peribronchovascular nodules in both lungs. Pulmonary function test results (maximal expiratory flows with spirometry and diffusion capacity test) were normal. No treatment was recommended for the pulmonary involvement.

Due to the enlarged lacrimal glands and the eyelid and anterior orbital involvement affecting the patient's visual

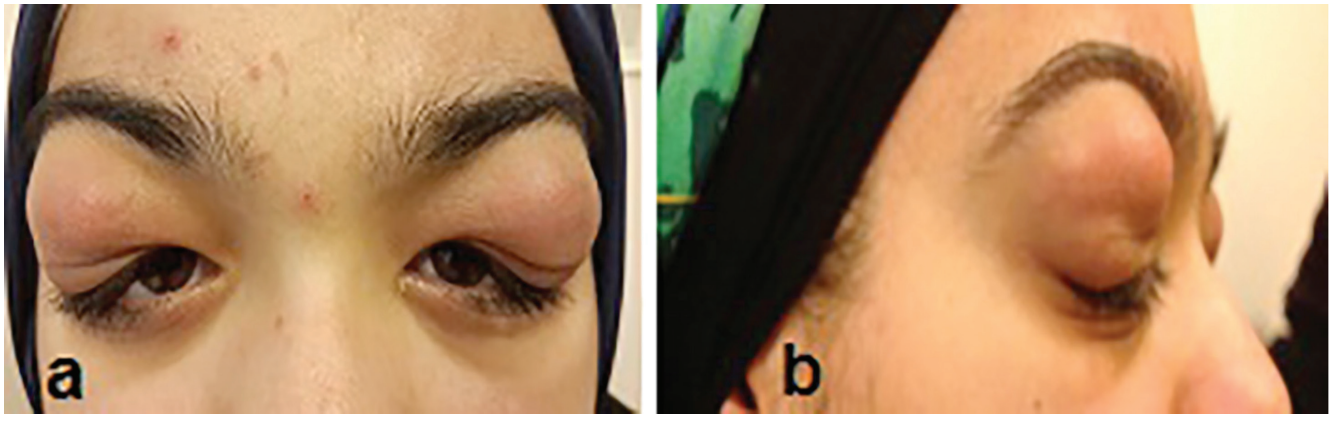

Figure 1. a, b) Anterior and lateral views showing solid, indurated, lobulated masses at the lateral parts of both upper eyelids corresponding to the location of the lacrimal glands

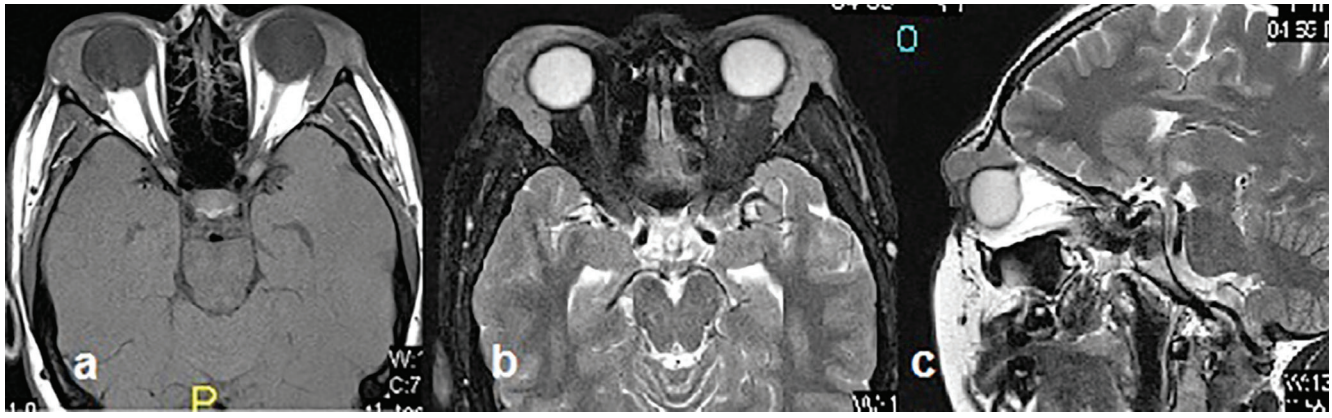

Figure 2. Magnetic resonance imaging showed bilateral symmetrical diffuse enlargement of the lacrimal glands and involvement of the superior eyelids and anterior orbit: isointense signal intensity relative to muscle on T1-weighted axial image (a); hypointense signal intensity on T2-weighted axial image (b); hypointense signal intensity on T2-weighted sagittal image (c)

capacity, oral methylprednisolone 0.5 mg/kg/day was prescribed. Symptomatic improvement soon became evident, and at the 21st day of treatment the steroid dose was reduced to 4 mg/2 weeks. The patient was treated with tapered dose steroids for nine months, and no relapse was observed at the first year follow-up (Figure 4). After the treatment, the Schirmer test result without anaesthesia was 4 mm/5 minutes in both eyes.

Discussion

Ocular adnexal sarcoidosis usually presents as a local mass. We present an unusual bilateral enlargement of the lacrimal glands and involvement of the anterior orbit and eyelids due to orbital sarcoidosis as the initial manifestation of systemic sarcoidosis.

Lacrimal glands are the most commonly involved structures of the orbit in orbital sarcoidosis.[3,4,5] The prevalence of lacrimal gland involvement varies across studies due to varying diagnostic criteria. Two large studies reported lacrimal gland involvement at rates of 7% and 15.8%.[2,6] These studies based the diagnosis of orbital sarcoidosis on lacrimal gland enlargement and the presence of dry eye symptoms. However, sarcoidosis is a pathologic diagnosis, so a biopsy is recommended for a definitive diagnosis.

Because of the inflammatory nature of sarcoidosis, orbital symptoms usually mimic other inflammatory diseases that involve orbital structures. Sjögren's syndrome, tuberculosis, lymphoma and immunoglobulin G4 (IgG4)-related Mikulicz's disease are the main pathologies that should be considered in the differential diagnosis of sarcoidosis. Although these diseases can be seen at any age, Sjögren's syndrome and tuberculosis are the primary diseases for the differential diagnosis of sarcoidosis in younger patients. These diseases can cause bilateral involvement and are usually characterised by painless enlargement of lacrimal glands for more than one month. Although clinical findings and imaging tests can help guide clinicians, a biopsy is required for all patients with orbital masses of unknown origin.

The characteristic histological feature of sarcoidosis is non-caseating granulomas consisting of epithelioid histiocytes and lymphocytes. Multinucleated giant cells are frequently seen. Although tuberculosis is also characterised by chronic granulomatous inflammation, in tuberculosis the granulomas tend to be coalescent with necrosis. The presence of atypical lymphocytes in lymphoma, IgG4-positive plasma cells in IgG4-related Mikulicz's disease, periductal and perivascular inflammation of lymphocytes and intralobular fibrosis in

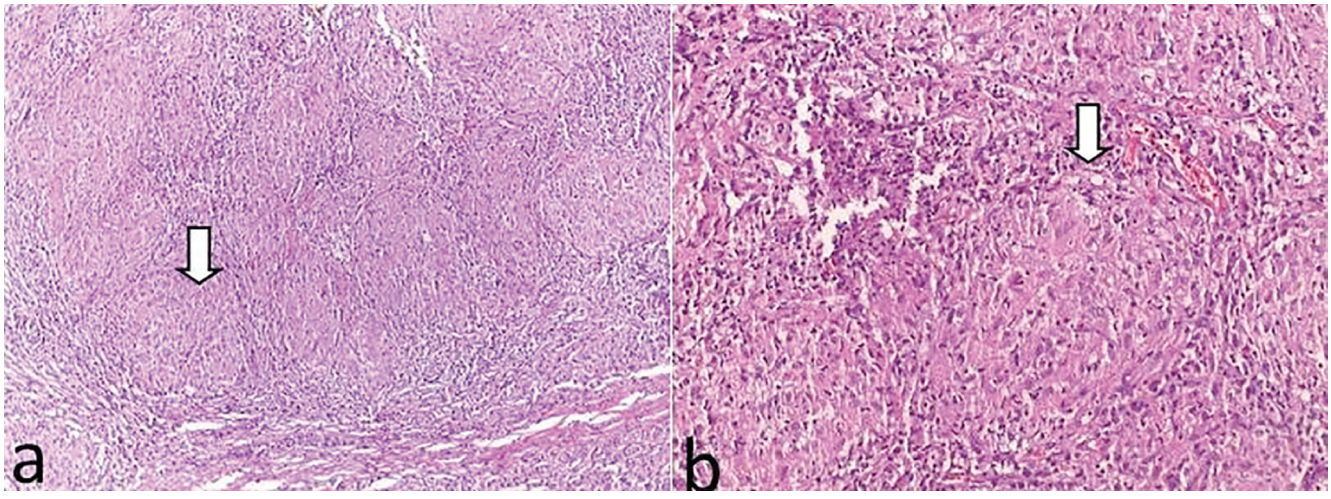

Figure 3. a, b) Left lacrimal gland biopsy showed discrete granulomas (arrow) (hematoxylin-eosin, x100, x200)

Figure 4. a, b) Marked regression in the ocular lesions is evident in anterior (a) and lateral (b) views after 1 year of treatment

Sjögren's syndrome are the main factors that aid in the differential diagnosis of sarcoidosis.[7]

This case is important because the first symptom of systemic sarcoidosis in this case was diffuse enlargement of the lacrimal glands with eyelid and anterior orbital involvement. MRI reveals normal lacrimal gland thickness to be approximately 4-5 mm,[8] whereas our case had bilateral diffuse enlargement of the lacrimal glands, which possessed maximum and minimum thicknesses of 11 mm and 7 mm, respectively.

Although orbital involvement is uncommon in sarcoidosis, it should be considered in the differential diagnosis of orbital masses. This case is striking compared to the previous case reports in the literature with respect to bilateral and substantially larger lacrimal gland involvement. The diagnosis of sarcoidosis should be made by clinical, laboratory, and radiological findings and confirmed by histopathological examination. It is necessary to screen all systems, and treatment decisions should be based on the presence of the organ and system involvement.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Concept: Banu Hoşal, Design: Banu Hoşal, Data Collection or Processing: Banu Hoşal, Pınar Bingöl Kızıltunç, Gülşah Kaygusuz, Fatma Çiftçi, Analysis or Interpretation: Banu Hoşal, Pınar Bingöl Kızıltunç, Gülşah Kaygusuz, Fatma Çiftçi, Literature Search: Banu Hoşal, Pınar Bingöl Kızıltunç, Gülşah Kaygusuz, Fatma Çiftçi, Writing: Banu Hoşal, Pınar Bingöl Kızıltunç.

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References

1. Prabhakaran VC, Saeed P, Esmaeli B, Sullivan TJ, McNab A, Davis G, Valenzuela A, Leibovitch I, Kesler A, Sivak-Callcott J, Hoyama E, Selva D. Orbital and adnexal sarcoidosis. Arch Ophthalmol. 2007;125:1657-1662.
2. Jabs DA, Johns CJ. Ocular involvement in chronic sarcoidosis. Am J Ophthalmol. 1986;102:297-301.
3. Mavrikakis I, Rootman J. Diverse clinical presentations of orbital sarcoid. Am J Ophthalmol. 2007;144:769-775.
4. Demirci H, Christianson MD. Orbital and adnexal involvement in sarcoidosis: analysis of clinical features and systemic disease in 30 cases. Am J Ophthalmol. 2011;151:1074-1080.
5. Collison JM, Miller NR, Green WR. Involvement of orbital tissues by sarcoid. Am J Ophthalmol. 1986;102:302-307.
6. Obenauf CD, Shaw HE, Sydnor CF, Klintworth GK. Sarcoidosis and its ophthalmic manifestations. Am J Ophthalmol. 1978;86:648-655.
7. Williamson J, Gibson AA, Wilson T, Forrester JV, Whaley K, Dick WC. Histology of the lacrimal gland in keratoconjunctivitis sicca. Br J Ophthalmol. 1973;57:852-858.
8. Izumi M, Eguchi K, Uetani M, Nakamura H, Takagi Y, Hayashi K, Nakamura T. MR features of the lacrimal gland in Sjögren's syndrome. AJR Am J Roentgenol. 1998;170:1661-1666.

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Case Report

A Case of Presumed Tuberculosis Uveitis with Occlusive Vasculitis from an Endemic Region

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Abstract

In this report, we present a case with presumed unilateral tuberculosis uveitis from an endemic region. A 23-year-old male presented with decreased vision in his left eye for 15 days. Visual acuities were 1.0 in his right eye and 0.3 in his left eye. Ophthalmologic examination was normal for the right eye. Slit-lamp examination revealed 2+ cells in the vitreous without anterior chamber reaction in his left eye. Fundus examination revealed occlusive vasculitis and granuloma. His history revealed that he had a respiratory infection with fever 3 months ago while visiting his native country, Rwanda, and was treated with non-specific antibiotic therapy. His visual symptom started 2 weeks after his systemic symptoms resolved. Laboratory findings included 15 mm induration in purified protein derivative tuberculin skin test, HIV negativity, and parenchymal lesions in chest X-ray. Bronchoalveolar lavage was negative for acid-fast bacillus. A pulmonary disease consultant reported presumed tuberculosis because of the patient's history. Anti-tuberculosis treatment was initiated. The patient's visual acuity improved rapidly and his signs regressed. A careful history should be taken from patients with uveitis. Travel to tuberculosis-endemic areas may be important for diagnosis and should be asked about directly.

Keywords: Tuberculosis, uveitis, endemic area

Introduction

Tuberculosis (TB) is a chronic granulomatous disease caused by the *Mycobacterium* family, which are aerobic, intracellular/acid-fast staining, non-spore-forming, nonmotile bacilli. In humans, the agents responsible for TB are *M. tuberculosis*, transmitted via aerosol droplets, and *M. bovis*, transmitted through unpasteurized milk. Other atypical mycobacteria, such as *M. avium* complex, may also cause disease in immunodeficient individuals.[1]

Approximately one-third of the global population is infected with TB bacilli. Although 33% of these cases are in southeast Asia, the highest mortality rates occur in Africa due to the high prevalence of HIV.[2] TB primarily affects the lungs due to the inhalation of infectious droplets (primary TB), and in 80% of cases, the disease is limited in the lungs by cellular immunity and is asymptomatic (latent TB). Conditions which affect cellular immunity may lead to infection through the activation of latent bacteria (post-primary TB). The bacteria may also spread through lymphatic and hematogenic pathways to involve extrapulmonary tissues such as the gastrointestinal system, genitourinary system, cardiovascular system, skin, central nervous system, and eye. These tissues may be affected in isolation or simultaneously with the pulmonary system.[3]

It is estimated that 1.4% of patients with pulmonary TB develop ocular signs.[4] Conversely, pulmonary TB is not seen in the majority of patients with ocular TB.[5,6] The ocular system is affected in nearly 20% of extrapulmonary TB patients.[2] In addition to involvement of the eyelids, conjunctiva, cornea, sclera, extraocular muscles, optic nerve, and orbit, there may also be intraocular involvement.

Intraocular TB can manifest as a wide clinical spectrum including granulomatous anterior uveitis, chronic anterior uveitis, intermediate uveitis, retinal vasculitis, serpiginous-like choroiditis, choroidal granuloma, neuroretinitis, and panuveitis.[7,8]

In this report, we present a case from an endemic region diagnosed as presumed TB whose uveitis completely resolved with antituberculous therapy.

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Case Report

A 23-year-old male patient presented to our clinic with complaints of decreased vision in his left eye for 15 days. We learned from his history that he was a native of Rwanda and while visiting there about 3 months earlier, he had a respiratory infection with fever and rash and had been treated for 1.5 months with empiric antibiotic therapy (doxycycline + cephalosporin), during which his respiratory infection had resolved.

On ophthalmologic examination, his visual acuity was 1.0 (Snellen chart) in the right eye and 0.3 in the left. Slit-lamp examination of the right eye was normal, intraocular pressure was 9 mmHg, the vitreous was clear and the fundus appeared normal. In the left eye, slit-lamp examination revealed pigmented granulomatous keratic precipitates in the corneal endothelium and iris pigments on the lens. Intraocular pressure was 6 mmHg, and 2+ vitreous cells were observed; fundus examination revealed widespread occlusive vasculitis foci, retinal hemorrhages in the inferior and temporal quadrants, snowball opacities in the inferior, and a focus of choroiditis at 2 o'clock (Figure 1). Fundus fluorescein angiography (FA) was normal in the right eye. In the left eye, FA revealed dye leakage at the optic nerve head and superotemporal branch vein, a choroiditis focus in the inferotemporal vascular arcade showing early hypofluorescence and late hyperfluorescence with leakage, and hypofluorescence due to ischemia and vascular leakage in the temporal periphery (Figures 2 and 3).

Evaluated with clinical examination findings, the lesions in the left eye were considered to be papillitis, occlusive vasculitis, and choroiditis. In laboratory tests, widespread stromal infiltration was observed in the right lung and the left lung was normal on posterior-anterior chest X-ray; purified protein derivative (PPD) tuberculin skin test resulted in a 15 mm induration (the patient had no TB vaccination scar); whole blood and biochemical values were normal; hepatitis serology was negative; HIV ELISA test was negative, serum angiotensin converting enzyme level was 73 U/L, serum calcium level was normal, *Brucella* agglutination test was negative, and syphilis serology was negative. In light of these clinical and laboratory findings, the patient was diagnosed as suspected TB uveitis and a consultation with the department of pulmonary diseases was requested.

Bronchial fluid was negative in acid-fast bacillus staining. Bronchoscopy revealed mucosal swelling in the bronchial mucosa of the right upper lobe and the left main bronchus near its bifurcation. Biopsy results from these areas of swelling indicated granulomatous inflammatory tissue. After consultation with a pulmonologist, a 4-drug anti-TB regimen (isoniazid, rifampicin, pyrazinamide, ethambutol) was initiated. After 1 month of treatment, the patient's visual acuity had improved to 0.8 and the vasculitis and choroiditis foci had regressed. Additionally, argon laser scatter photocoagulation was applied to the ischemic area in the left eye. In consultation with the department of

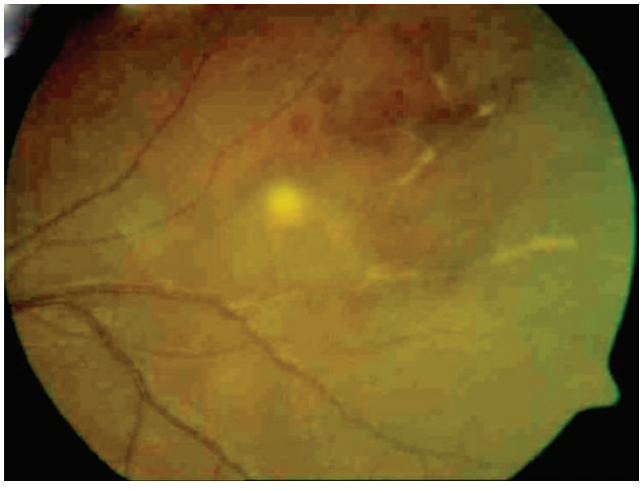

Figure 1. Occlusive vasculitis and choroiditis focus in the left eye

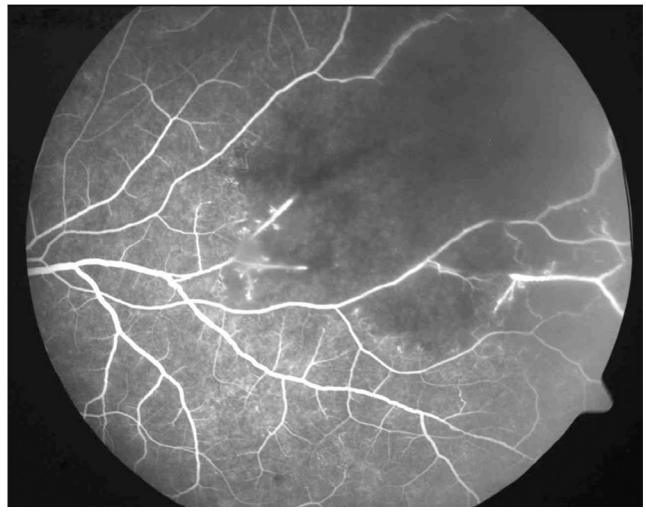

Figure 2. Left eye fluorescein angiography showing superotemporal areas of ischemia due to occlusive vasculitis

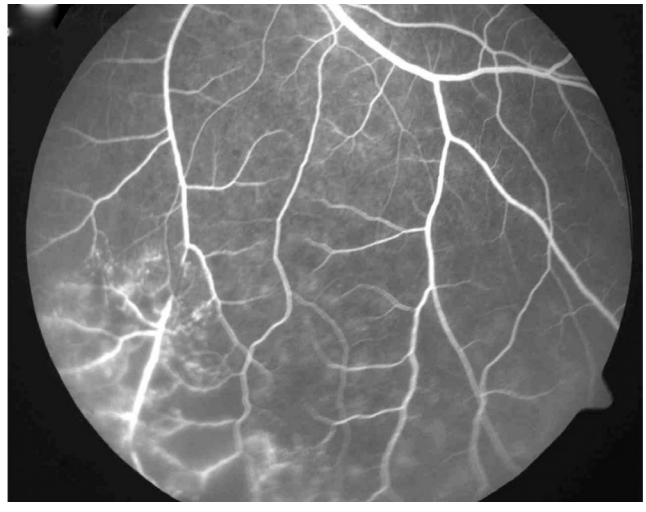

Figure 3. Left eye fluorescein angiography showing inferior areas of ischemia

pulmonary diseases, regression of the pulmonary lesions was observed and treatment was changed to a 2-drug anti-TB regimen (isoniazid and rifampicin).

In month 9 of anti-TB therapy, visual acuity was 1.0 in the right eye, intraocular pressure was 10 mmHg, and slit-lamp and fundus examinations were normal. In the left eye, visual acuity was 1.0, intraocular pressure was 9 mmHg, iris pigments on the lens were observed on slit-lamp examination, and argon laser photocoagulation scars were apparent in the temporal and inferior periphery on fundus examination. On FA, photocoagulation scars corresponding to the ischemic areas were visible and the optic nerve leakage had resolved (Figures 4 and 5). Treatment was discontinued after completing a total of 9 months of anti-TB therapy. No recurrence was observed during 2 years of follow-up.

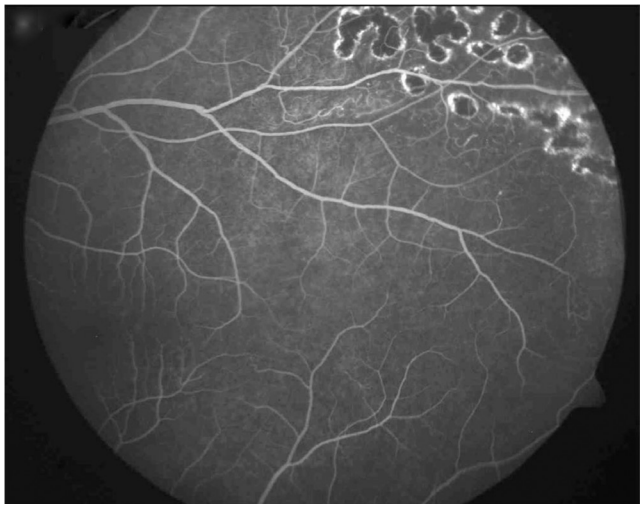

Figure 4. Left eye fluorescein angiography showing scars from laser photocoagulation applied to the areas of ischemia

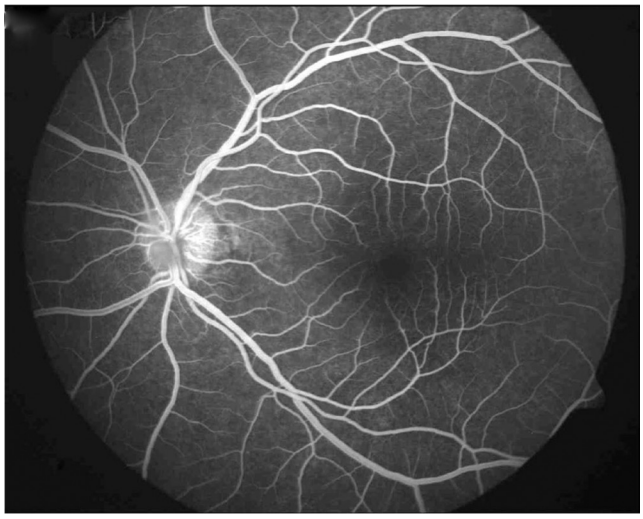

Figure 5. The posterior pole of the left eye appears normal on fluorescein angiography performed after 9 months of treatment

Discussion

Eighty percent of the total global TB is found in 22 countries: India, China, Indonesia, Bangladesh, Pakistan, Nigeria, the Philippines, South Africa, the Russian Federation, Ethiopia, Vietnam, the Democratic Republic of the Congo, Brazil, Tanzania, Kenya, Thailand, Myanmar, Afghanistan, Uganda, Peru, Zimbabwe, and Cambodia.[9] Drug and alcohol use, low sociocultural status, general ethnic differences in health status, and differences in access to health care are accepted as factors that may explain the unequal global distribution of the disease.[10] In developing countries, TB is the most common opportunistic infection in HIV-infected individuals due to poor hygiene, lack of sanitation, poverty, and drug resistance.[9] An epidemiologic study conducted in tertiary health centers in our country Turkey determined TB as the etiologic agent in 0.3% of uveitis patients.[11]

In the absence of histopathologic or microbiologic findings, there is no gold standard diagnostic method for TB uveitis.[6] Ocular TB is a wide-spectrum clinical entity that is difficult to diagnose and requires the expertise of both pulmonologists and ophthalmologists for treatment and follow-up.[6,8] It typically manifests with granulomatous anterior uveitis (nongranulomatous inflammation is rare) with or without iris nodules; intermediate uveitis; ciliary body tuberculoma; posterior uveitis, often in the form of choroidal tubercle or tuberculoma; retinal vasculitis (particularly venous); vitritis; retinal hemorrhages; neovascularization; serpiginous-like choroiditis; and rarely, neuroretinitis, endophthalmitis, or panophthalmitis.[5,8,9] In a study investigating ocular signs predictive of TB uveitis, Gupta et al.[8] found that the presence of broad-based posterior synechia, retinal vasculitis with or without choroiditis, and serpiginous-like choroiditis were strong indicators of TB uveitis in TB-endemic areas. Choroidal lesions have also been reported as the most common sign in patients with confirmed ocular TB diagnosis.[12] Our patient exhibited vitritis, choroiditis, and occlusive vasculitis. Although the patient's lesions regressed with anti-TB therapy, we also performed argon laser photocoagulation on the ischemic areas of the retina because the patient came from abroad and may not have been able to attend follow-up. Because our case was from a TB-endemic area and had a history of pulmonary infection, ocular TB was suspected and treatment was initiated accordingly, despite not being able to confirm the diagnosis with bronchoalveolar lavage culture or histopathologic analysis.

Our patient's native country Rwanda is endemic for both TB and acquired AIDS. HIV has increased the incidence of TB in Africa (sub-Saharan), which has the highest TB-related mortality rate worldwide.[2] Therefore, HIV testing was performed immediately in our patient and was negative. However, it should be kept in mind that HIV positivity may cause anergy to the PPD test and make TB diagnosis difficult.

FA is the most commonly ocular imaging method used in the diagnosis of intraocular TB. Tubercles show hypofluorescence in the early phase and hyperfluorescence in the late phase. Retinal vasculitis appears as fluorescein leakage, particularly from the retinal veins. Imaging of the peripheral retina is important for photocoagulation of peripheral capillary nonperfusion and accompanying neovascularization. Indocyanine green angiography is another imaging modality that is useful for measuring and evaluating choroidal involvement and monitoring treatment response in tuberculous posterior uveitis.[13] Optical coherence tomography (OCT) complements fundus photography and FA in uveitis patients. OCT facilitates the visualization of cystic macular edema and subretinal membranes. It is effective in determining visual prognosis and can also be used to evaluate treatment response. Spectral domain OCT allows choroidal imaging in patients with intraocular inflammation.[14] Recently, measuring the thickness of the choroid and its individual layers has become possible with enhanced depth imaging (EDI)-OCT technology. Mehta et al.[15] reported increased choroidal thickness in TB-related active granulomatous uveitis and stated that EDI-OCT may be useful in the diagnosis and follow-up of the disease. Ultrasonography may facilitate the differentiation of tuberculomas from malignant masses. Ultrasound biomicroscopy can assist the visualization of pars plana granulomas in eyes with seclusio pupillae or cataract.[16]

Proof positive tests for intraocular TB include demonstrating the presence of TB bacilli in secretion, fluid, or affected tissue specimens by acid-fast staining, culture, or amplification of bacterial nucleic acids. PCR is a highly sensitive and specific diagnostic test that replicates mycobacterial DNA. This method is especially advantageous when analyzing intraocular fluid because it requires a very small sample volume.[9] The PPD tuberculin skin test and interferon gamma release assay (QuantiFERON-TB Gold test, T SPOT TB test) assist diagnosis of latent TB. Pulmonary radiographic and tomographic imaging are other auxiliary modalities in intraocular TB.

Diagnostic criteria for intraocular TB have been developed based on laboratory results, clinical parameters, follow-up examinations, and response to anti-TB therapy.[16] According to these criteria, the presence of clinical signs together microscopic evidence of acid-fast bacilli or positive *M. tuberculosis* culture from ocular fluid is accepted as confirmed intraocular TB. Clinical signs together with positive PPD test, the presence of previous or active TB lesions on pulmonary X-ray, confirmed extrapulmonary TB (by microscopy or *M. tuberculosis* culture of the affected area), or the exclusion of other causes of uveitis, and positive response to a 4-drug anti-TB regimen within a period of 4-6 weeks is considered presumed intraocular TB. It is recommended that anti-TB therapy be initiated and monitored by a physician with expertise in TB. Ocular response to anti-TB therapy should be evaluated by an ophthalmologist.[16]

The treatment recommended for ocular TB is the same as that recommended for pulmonary involvement, and should be adjusted according to the patient's immune status. The main drugs utilized in therapy are isoniazid, rifampicin, ethambutol, and pyrazinamide. For patients with compromised immunity or disseminated TB, extending the 2-drug regimen to 7 months (total 9 months) is recommended.[17] When treating ocular TB, corticosteroids should be initiated with anti-TB therapy to reduce the tissue damage that may result from delayed hypersensitivity reaction and control inflammation. Corticosteroid dosage should be reduced gradually based on clinical response and discontinued after 4-6 weeks. However, the use of steroids alone, without anti-TB therapy, should be strictly avoided.[16] We were able to control uveitis in our patient with anti-TB therapy alone, and did not add steroid therapy.

This case report highlights the importance of early diagnosis and treatment to avoid ocular complications in TB uveitis. We excluded other uveitis etiologies in our patient and initiated anti-TB therapy with a diagnosis of presumed TB uveitis, and treatment was successful. The fact that the patient came from a TB-endemic area immediately suggested a diagnosis of TB.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Berna Başarır, Concept: Banu Şatana, Design: Çiğdem Altan, Analysis or Interpretation: Aslı İnal, Literature Search: Bulut Ocak, Writing: Yalçın Karaküçük.

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

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References

1. Brooks GF, Carrol KC, Butel JS, Morse SA, Mietzner TA, Jawetz Melnick & Adelberg's Medical Microbiology, 26th Edition, USA, Mc Graw Hill LANGE, 2013:313-326.
2. Gupta A, Gupta V, Bansal R, Arora S, Pradeep B. Ocular Tuberculosis, In; Gupta A, Gupta V, Herbort CP, Khairallah M eds. Uveitis Text and Imaging (First edition). Jaypee Brothers Medical Publishers. 2009:563-589.
3. Glassroth J, Robins AG, Snider DE Jr. Tuberculosis in the 1980s. N Engl J Med. 1980;302:1441-1450.
4. Donahue HC. Ophthalmologic experience in a tuberculosis sanatorium. Am J Ophthalmol. 1967;64:742-748.
5. Önal S, Tuğal-Tutkun İ. Ocular Tuberculosis I: Epidemiology, Pathogenesis and Clinical Features. Turk J Ophthalmol. 2011;41:171-181.
6. Gupta A, Gupta V. Tubercular posterior uveitis. Int Ophthalmol Clin. 2005;45:71-88.
7. Akduman L, Aydın O'dwyer P. Oküler Tüberküloz, Bölüm 4, Kısım 4, Üveit el kitabı, Tunç M. Güneş Tıp Kitabevleri. 2008:202-207.
8. Gupta A, Bansal R, Gupta V, Sharma A, Bambery P. Ocular signs predictive of tubercular uveitis. Am J Ophthalmol. 2010;149:562-570.
9. Gupta V, Gupta A, Rao NA. Intraocular tuberculosis-an update. Surv Ophthalmol. 2007;52:561-587.
10. Centers for Disease Control and Prevention (CDC). Racial disparities in Tuberculosis-selected southeastern states, 1991-2002. MMWR Morb Mortal Wkly Rep. 2004;53:556-559.

11. Kazokoglu H, Onal S, Tugal-Tutkun I, Mirza E, Akova Y, Ozyazgan Y, Soylu M, Batioglu F, Apaydin C. Demographic and clinical features of uveitis in tertiary centers in Turkey. Ophthalmic Epidemiol. 2008;15:285-293.
12. Sheu SJ, Shyu JS, Chen LM, Chen YY, Chirn SC, Wang JS. Ocular manifestations of tuberculosis. Ophthalmology. 2001;108:1580-1585.
13. Wolfensberger TJ, Piguet B, Herbort CP. Indocyanine green angiographic features in tuberculous chorioretinitis. Am J Ophthalmol. 1999;127:350-353.
14. Fung AT, Kaliki S, Shields CL, Mashayekhi A, Shields JA. Solitary idiopathic choroiditis: findings on enhanced depth imaging optical coherence tomography in 10 cases. Ophthalmology. 2013;120:852-858.
15. Mehta H, Sim DA, Keane PA, Zarranz-Ventura J, Gallagher K, Egan CA, Westcott M, Lee RW, Tufail A, Pavesio CE. Structural changes of the choroid in sarcoid- and tuberculosis-related granulomatous uveitis. Eye (Lond). 2015:1060-1068.
16. Önal S, Tuğal-Tutkun İ. Ocular Tuberculosis II: Diagnosis and treatment. Turk J Ophthalmol. 2011; 41:182-190.
17. Centers for Disease Control and Prevention (CDC); American Thoracic Society. Update: adverse event data and revised American Thoracic Society/ CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection-United States, 2003. MMWR Morb Mortal Wkly Rep. 2003;52:735-739.

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Case Report

Efficacy of Oral Valacyclovir Treatment in a Case with Acute Retinal Necrosis

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Abstract

Acute retinal necrosis (ARN) is a rapidly progressive disease with poor prognosis, leading to visual loss in most cases. Rapid diagnosis and early anti-viral treatment significantly affect the course and prognosis of the disease. In this case report, we present a 34-year-old female patient referred to our clinic with symptoms of blurred vision and ocular pain diagnosed as acute glaucoma elsewhere. A clinical diagnosis of ARN was made and anti-viral treatment was started immediately. We herein describe our treatment approach to this particular case and discuss previously reported treatment modalities.

Keywords: Acute retinal necrosis, treatment, valacyclovir, prognosis

Introduction

Acute retinal necrosis (ARN), first described in 1971, is a clinical condition characterized by areas of retinal necrosis, occlusive vasculopathy, vitritis, anterior chamber reaction, and optic neuritis.[1,2,3,4] Herpes virus family members herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus, and cytomegalovirus play a role in its etiology.[2,3,4,5,6] The most common agent is reported as VZV in some studies and HSV-1 in others.[5] Ganatra et al.[6] reported that VSV and HSV-1 were more common in patients over 25 years old, while HSV-2 was more common in those under 25 years old.

Prompt intervention is very important after ARN is detected. Patients with delayed treatment suffer rapidly progressive retinal necrosis; exudative, rhegmatogenous, or tractional detachment may occur, with possible outcomes as severe as phthisis bulbi. Treatment delay of more than 14 days after symptom onset has been reported as one of the factors associated with poor prognosis.[5] There is no standard treatment approach due to the rare occurrence of ARN and the fact that the data available in the literature consists of small case series. There are studies reporting favorable outcomes with early systemic antiviral therapy, intravitreal injections, and early vitrectomy.[7,8]

The most commonly used and current gold standard initial treatment for ARN is acyclovir; other antiviral options including valacyclovir, famciclovir, ganciclovir, valganciclovir, and foscarnet are also used.

Acyclovir is an antiviral guanosine analogue with proven efficacy against various viral agents, primarily HSV infections. It prevents viral replication by inhibiting viral DNA polymerase and may be administered via oral and intravenous systemic routes.[9]

Valacyclovir is another antiviral drug with proven efficacy against HSVs. Valacyclovir is a prodrug which is converted in vivo via hepatic first-pass metabolism to acyclovir, which is then modified by viral thymidine kinase and prevents viral proliferation.[9] In recent years, it has been reported that oral valacyclovir and intravenous acyclovir yield comparable results.[10]

In this report, we share a case of acute retinal necrosis that was completely controlled with oral valacyclovir therapy and discuss ARN treatment.

Case Report

A 24-year-old female patient presented to our clinic with complaints of blurred vision and pain in her left eye for 4 days. She reported that at another medical center, her intraocular pressure

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had been measured as 38 mmHg and she had been treated with intravenous mannitol, oral acetazolamide, and topical antiglaucomatous therapy for glaucoma. On ophthalmologic examination, her BCVA was 10/10 in the right eye and 5/10 in the left eye. Intraocular pressure was 12 mmHg in the right eye and 14 mmHg in the left eye. Examination findings were normal in the right eye. In the left eye, diffuse, medium-sized brownish-gray keratic precipitates (KP) were observed in the corneal endothelium (Figure 1) and 2+ cells were noted in the anterior chamber. Dilated fundus examination of the left eye revealed a small amount of vitreous cells and 1+ haze. There was pronounced hyperemia and swelling of the optic disc (Figure 2). There was peripheral vascular sheathing associated with vasculitis and a focus of hemorrhagic necrotizing retinitis in the superotemporal periphery (Figure 3), with multiple smaller foci located more peripherally (Figure 4). The patient reported no systemic symptoms or history of systemic disease.

The patient was diagnosed with ARN based on clinical findings and treatment with prednisolone acetate drops hourly, cyclopentolate hydrochloride drops 3 times daily, and intravenous acyclovir 750 mg, 3 times daily was initiated for anterior segment inflammation. Fundus fluorescein angiography (FFA) examination was recommended to confirm clinical findings, but the patient did not consent to the procedure. On day 3 of treatment, the patient decided she did not want to remain hospitalized and undergo the 14-day intravenous acyclovir treatment plan, and her therapy was changed to oral acyclovir 2 g, 3 times daily. On examination performed that day, the patient's corrected visual acuity was 5/10 in the left eye and fundus examination revealed no further progression of the retinal lesions. On day 4 of treatment, oral methylprednisolone 64 mg was added for optic neuropathy and severe vasculitis. The patient was followed closely at intervals of 2 days.

On day 7 of treatment, the patient's corrected visual acuity was 8/10. The KP and vitreous haze persisted, but fundus examination revealed no progression of the retinal lesions, reduced optic disc edema, and more distinct optic disc margins.

On day 9, the patient's corrected visual acuity was 10/10. On fundus examination, +1 vitreous haze and regression of optic disc edema were observed. The KP were still evident. Treatment was adjusted to prednisolone acetate drops every 2 hours and cyclopentolate hydrochloride twice daily; oral valacyclovir 2 g, 3 times daily was continued. Methylprednisolone was reduced to 54 mg.

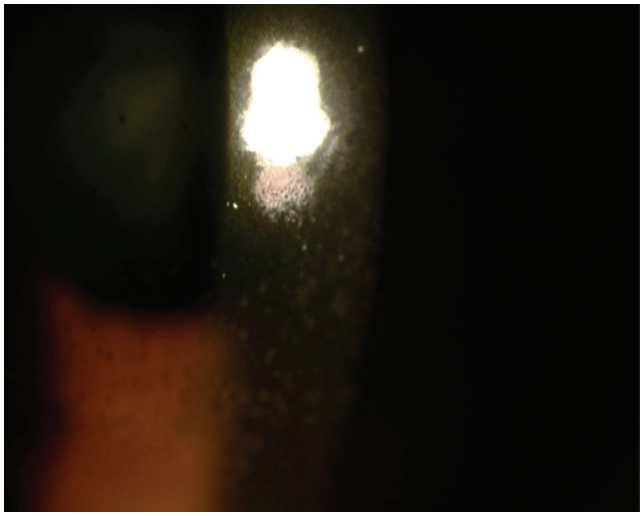

Figure 1. Diffuse brownish-gray, medium-sized keratic precipitates in the corneal endothelium

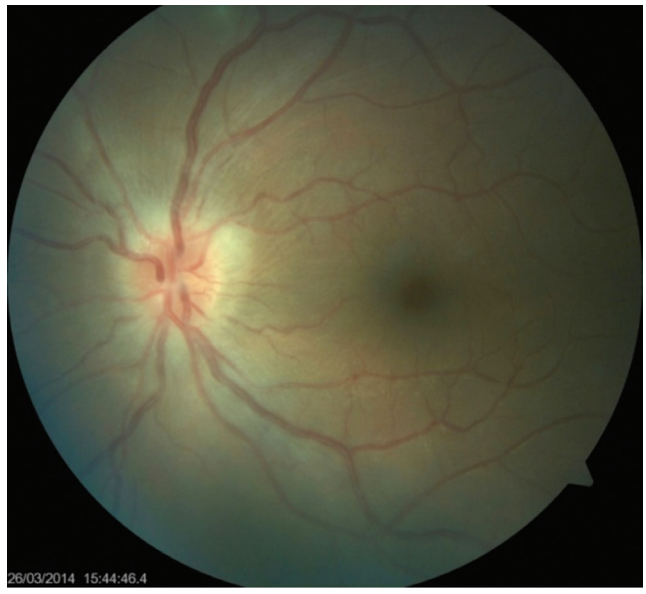

Figure 2. Blurred margins, hyperemia, and swelling of the optic disc

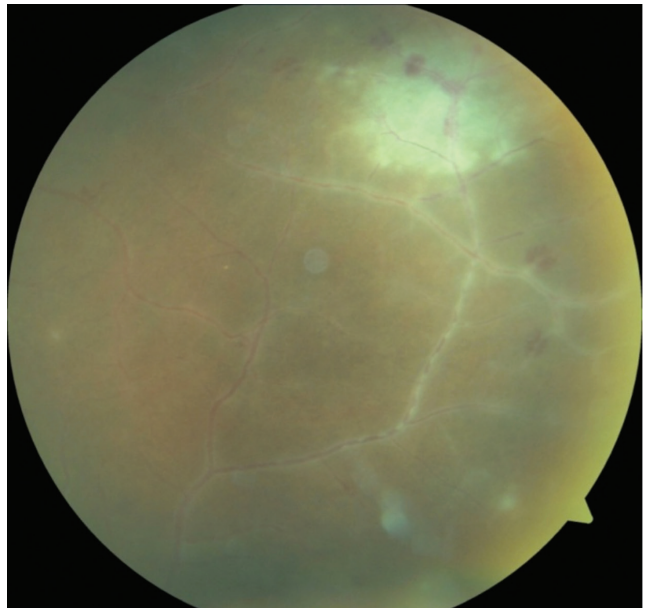

Figure 3. Peripheral vascular sheathing associated with vasculitis and a focus of hemorrhagic necrotizing retinitis in the superotemporal peripheral retina

On day 14 of treatment, visual acuity was 10/10, KP had resolved, complete resolution of the vitreous haze and optic disc signs was observed on fundus examination, and the necrotizing retinitis focus had regressed (Figures 5 and 6). Prednisolone acetate was reduced to 5 times daily, cyclopentolate hydrochloride to once daily. Valacyclovir dose was adjusted to 1 g, 4 times daily and methylprednisolone to 48 mg, planning to reduce the dose by 8 mg every 3 days.

On day 22 of treatment, the lesioned area of the retina appeared extremely atrophic and 3 rows of prophylactic laser photocoagulation was applied to this area only.

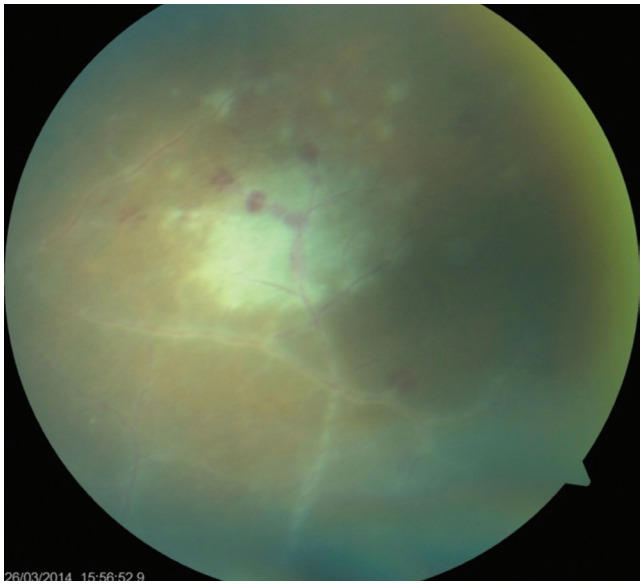

Figure 4. Numerous new infiltrates at the periphery of the necrotizing retinitis focus. Untreated, they progress by enlarging and merging

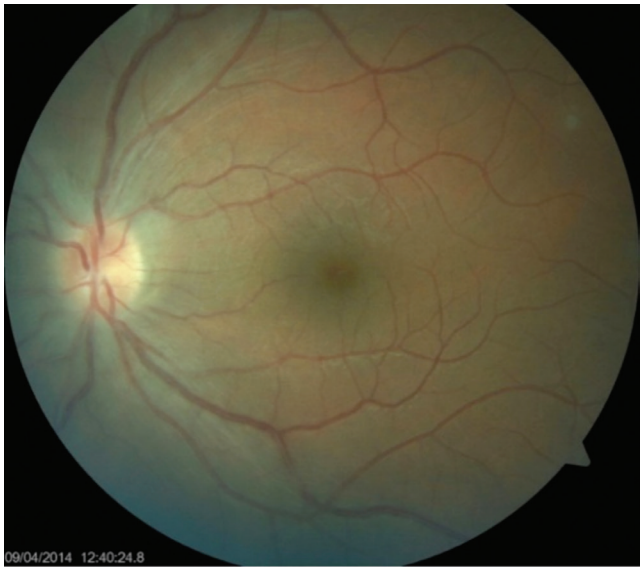

Figure 5. Retinal appearance on day 14 of treatment; optic disc findings have improved

On day 35 of treatment, fundus examination revealed empty vessels in the peripheral retina and the lesion had completely resolved. Valacyclovir therapy was maintained at 1 g, 3 times daily, while the local treatment and methylprednisolone were discontinued.

At 2 months after the initiation of treatment, the dose of oral valacyclovir was adjusted to 1 g twice daily, with a plan to reduce it by 500 mg with monthly follow-up examinations.

The patient regularly attended monthly follow-up, and was maintained on oral valacyclovir 500 mg daily from 6 months to 1 year.

At 1 year of treatment, corrected visual acuity was 10/10, KP had disappeared, the optic disc appeared normal on fundus examination, and pigmented laser scars were evident over the empty vessels in the peripheral retina and the inactive superotemporal necrotic retinal focus (Figure 7).

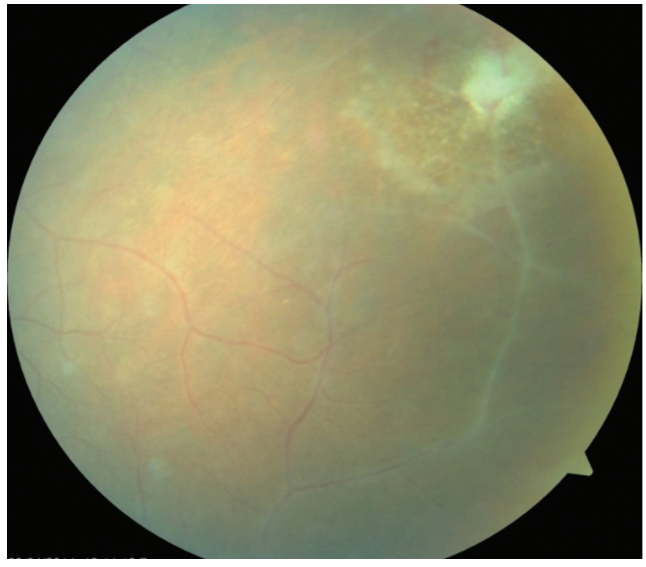

Figure 6. The focus of necrotizing retinitis reduced in size and regressed; empty vessels are apparent

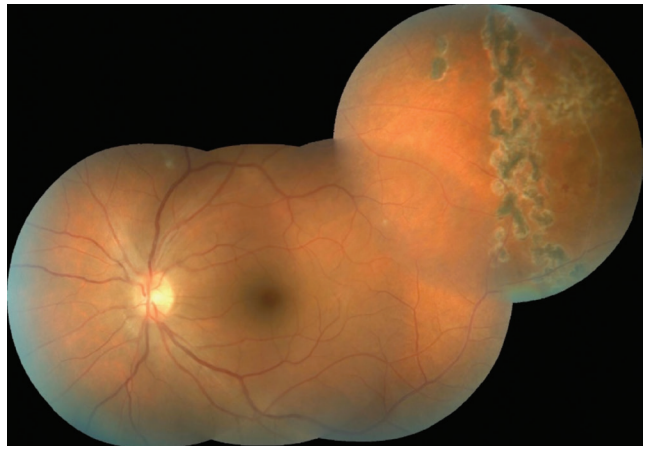

Figure 7. Retinal appearance after 1 year; laser scars are evident over the inactive necrotic retinal focus

Discussion

ARN is a syndrome caused by herpes viruses and does not show age or sex differences. In 1994, the American Uveitis Committee defined the criteria for this syndrome as follows:

- One or more areas of retinal necrosis in the peripheral fundus,
- Rapid progression in the absence of antiviral therapy,
- Circumferential spread,
- Occlusive vasculopathy with arterial involvement,
- Inflammatory reaction in the anterior chamber and vitreous.

Patients with ARN frequently present with unilateral pain, photophobia, redness, blurred vision, and floaters. On examination, one or more of the following findings may be observed in the anterior segment: episcleritis, scleritis, keratitis, anterior chamber cells, keratic precipitation (granulomatous/non-granulomatous). In the posterior segment, signs of vitreous inflammation (haze, cells, etc.), foci of retinal necrosis, vascular sheathing, areas of hemorrhage consistent with the vessel walls, and optic neuropathy characterized by optic disc edema and margin obscuration may be observed.[2,3]

Although ARN is usually a clinical diagnosis, analysis of anterior chamber and vitreous specimens may facilitate definitive diagnosis in uncertain cases.[2]

Due to its rare occurrence and lack of large case series, there is no established standard treatment scheme for ARN. Therefore, treatment may vary between medical centers. Intravenous acyclovir is the most commonly used therapy because of its high bioavailability. There are also different approaches regarding treatment duration. The most commonly recommended regimen is 10-21 days intravenous acyclovir therapy followed by at least 6 weeks of oral acyclovir.[11,12] However, some authors assert that longer maintenance therapy is necessary.

In addition, there are also studies recommending oral valacyclovir and famciclovir, or intravenous foscarnet and gancyclovir as alternatives.[11,12]

Valacyclovir is a L-valine esterified prodrug of acyclovir. After passing through the intestine, it is converted to an active form via hepatic first-pass metabolism.[9] Previous studies have shown that valacyclovir has better bioavailability than acyclovir and results in higher serum levels compared to acyclovir administration.[13,14]

Taylor et al.[10] reported first treatment response after an average of 7 days and complete resolution of retinitis after an average of 21 days of treatment in 10 ARN eyes treated with oral valcyclovir 2 g, 3 times daily. They emphasized that outcomes with oral valacyclovir were comparable to those achieved with intravenous acyclovir, with no recurrence or fellow eye involvement. Among our patients, first treatment response was noted after 9 days of treatment and complete resolution after 14 days.

ARN is usually seen in immunocompetent individuals, first appearing in one eye and later affecting the fellow eye in approximately one-third of cases. Fellow eye involvement usually appears within the first 6 weeks, although it has also been reported to develop months or even years later.[15,16] We did not observe fellow eye involvement in our patient during the 16-month follow-up period. The long-term maintenance and gradual tapering of valacyclovir therapy has an important role in this process. In a retrospective analysis of ARN cases, Palay et al.[17] reported that the group maintained on prophylactic antiviral therapy for 12 months had significantly better protection of the fellow eye compared to the group whose antiviral therapy was discontinued. In our case, oral valacyclovir therapy was initiated at 2 g, 3 times daily. The dose was reduced gradually according to disease course with regular follow-up examinations. We tapered the oral valacyclovir therapy to 500 mg after 6 months of treatment and maintained this dose for an additional 6 months to prevent fellow eye involvement.

Chen et al.[18] reported that oral valacyclovir therapy was effective in a case with multiviral infection, but the patient's final visual acuity was low due to macular detachment after therapy was discontinued. The multiviral infection in the etiology of that case suggests that the patient may have been immunosuppressed, and that valacyclovir therapy may be less effective in such cases than in immunocompetent patients.[19]

It is recommended to add systemic corticosteroids to treatment in addition to antiviral therapy in patients with ARN, especially in cases with optic neuropathy and to suppress inflammation.[2,11,20] It is critical to initiate systemic steroid therapy after antiviral therapy, and to discontinue it before antiviral therapy is discontinued. Otherwise, it is known to lead to viral replication.[20] A very recent study has demonstrated that ARN patients previously treated with systemic corticosteroids alone for various diagnoses had a longer healing time (mean: 53.8 days) compared to those who were not treated with corticosteroids (mean: 32.5 days).[5] We believe that the corticosteroids we administered within the antiviral therapy regimen was instrumental in the regression of inflammatory signs such as optic neuropathy, vascular sheathing, and vitreous haze in our patient.

There is debate in the literature regarding the place of prophylactic photocoagulation therapy in ARN. Lau et al.[2] showed that photocoagulation performed in the first 2 weeks of ARN reduced the risk of detachment. However, Tibbetts et al.[11] found that laser therapy conferred no additional advantage and even reported increased detachment rates in patients that underwent laser therapy.

Despite good treatment response in our patient, we decided to perform prophylactic laser photocoagulation on the area of necrosis and atrophic retinal focus in the superotemporal quadrant in order to reduce the likelihood of rhegmatogenous detachment.

The place of early vitrectomy in ARN treatment is also controversial. Hillenkamp et al.[19] reported that early vitrectomy had no effect on functional outcomes, but lowered the risk of secondary detachment. Regardless, vitrectomy is unavoidable in cases that develop complications like vitreous hemorrhage or retinal detachment.

In clinical practice, prompt hospitalization with rapid initiation of antiviral therapy in patients diagnosed with this syndrome is the main factor determining future visual prognosis.[8] Factors strongly affecting prognosis are time from symptom onset to diagnosis (better prognosis if less than 2 weeks), extent of retinal lesions, and presence of macular involvement.[2,6] Considering those factors, in addition to early diagnosis and treatment, close monitoring of treatment response and disease progression also substantially contributed to the complete recovery of our patient's visual acuity. Examinations were performed daily for the first 3 days of treatment, then every other day until a full response was observed at 2 weeks.

Many retinal syndromes and diseases may manifest with similar fundus appearance. The exclusion of other conditions is essential for reaching a definitive diagnosis and initiating appropriate treatment rapidly and effectively.

Although diagnosis of ARN is based on clinical observations and lesion progression according to the criteria defined by the American Uveitis Committee, additional diagnostic methods are required to exclude similar clinical presentations and confirm the diagnosis. The most important of these is viral DNA detection from anterior chamber fluid or vitreous samples via polymerase chain reaction analysis.[2,21] Although not directly diagnostic, FFA may be beneficial to support clinical findings in early cases without severe vitreous haze. In our case, we did not take an anterior chamber fluid sample to confirm our clinical diagnosis, and we could not perform FFA because the patient did not consent to the procedure.

In summary, patients with ARN should be diagnosed carefully, treated promptly, and followed closely. ARN should come to mind for patients presenting with a clinical constellation of unilateral, brownish-gray KP, acute intraocular pressure elevation, and optic neuritis, and a detailed peripheral retinal examination should be performed in such cases. The possibility of fellow eye involvement must be remembered during follow-up, and antiviral therapy should be maintained over the long term. High-dose oral valacyclovir therapy should be considered as an alternative to intravenous acyclovir therapy.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Pınar Çakar Özdal, Concept: Pınar Çakar Özdal, Mert Şimşek, Design: Mert Şimşek, Pınar Çakar Özdal, Data Collection or Processing: Mert Şimşek, Analysis or Interpretation: Mert Şimşek, Pınar Çakar Özdal, Literature Search: Mert Şimşek, Kemal Tekin, Writing: Mert Şimşek, Pınar Çakar Özdal.

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

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References

1. Urayama A, Yamada M, Susaki T. Unilateral acute uveitis with periarteritis and detachment [in Japanese]. Rinsho Ganka. 1971;25:607-619.
2. Lau CH, Missotten T, Salzmann J, Lightman SL. Acute retinal necrosis features, management, and outcomes. Ophthalmology. 2007;114:756-762.
3. Culbertson WW, Clarkson JG, Blumenkranz M, Lewis ML. Acute retinal necrosis. Am J Ophthalmol. 1983;96:683-685.
4. Holland GN. Standard diagnostic criteria for the acute retinal necrosis syndrome. Executive Committee of the American Uveitis Society. Am J Ophthalmol. 1994;117:663-667.
5. Khochtali S, Abroug N, Kahloun R, Ksiaa I, Nahdi I, Zaouali S, Ben Yahia S, Khairallah M. Pattern of Acute Retinal Necrosis in a Referral Center in Tunisia, North Africa. Ocul Immunol Inflamm. 2014;19:1-7.
6. Ganatra JB, Chandler D, Santos C, Kuppermann B, Margolis TP. Viral causes of the acute retinal necrosis syndrome. Am J Ophthalmol. 2000;129:166-172.
7. Gartry DS, Spalton DJ, Tilzey A, Hykin PG. Acute retinal necrosis syndrome. Br J Ophthalmol. 1991;75:292-297.
8. Duker JS, Blumenkranz MS. Diagnosis and management of the acute retinal necrosis (ARN) syndrome. Surv Ophthalmol. 1991;35:327-343.
9. Smiley ML, Murray A, de Miranda P. Valacyclovir HCl (Valtrex): an acyclovir prodrug with improved pharmacokinetics and better efficacy for treatment of zoster. Adv Exp Med Biol. 1996;394:33-39.
10. Taylor SR, Hamilton R, Hooper CY, Joshi L, Morarji J, Gupta N, Lightman SL. Valacyclovir in the treatment of acute retinal necrosis. BMC Ophthalmol. 2012;12:48.
11. Tibbetts MD, Shah CP, Young LH, Duker JS, Maguire JI, Morley MG. Treatment of acute retinal necrosis. Ophthalmology. 2010;117:818-824.
12. Tam PM, Hooper CY, Lightman S. Antiviral selection in the management of acute retinal necrosis. Clin Ophthalmol. 2010;4:11-20.
13. Lycke J, Malmeström C. Stahle L. Acyclovir levels in serum and cerebrospinal fluid after oral administration of valacyclovir. Antimicrob Agents Chemother. 2003;47:2438-2441.
14. Beutner KR. Valacyclovir: a review of its antiviral activity, pharmacokinetic properties, and clinical efficacy. Antiviral Res. 1995;28:281-290.
15. Martinez J, Lambert HM, Capone A, Sternberg P Jr, Aaberg TM, Lopez PF, Davidson C. Delayed bilateral involvement in the acute retinal necrosis syndrome. Am J Ophthalmol. 1992;113:103-104.
16. Okunuki Y, Usui Y, Kezuka T, Takeuchi M, Goto H. Four cases of bilateral acute retinal necrosis with a long interval after the initial onset. Br J Ophthalmol. 2011;95:1251-1254.
17. Palay DA, Sternberg P Jr, Davis J, Lewis H, Holland GN, Mieler WF, Jabs DA, Drews C. Decrease in the risk of bilateral acute retinal necrosis by acyclovir therapy. Am J Ophthalmol. 1991;112:250-255.

18. Chen S, Malik KJ, Shen D, Chan CC. Acute Retinal Necrosis with Multiple Viral Infections: A Case Report. Int J Ophthalmic Pathol. 2014;3.
19. Hillenkamp J, Nölle B, Bruns C, Rautenberg P, Fickenscher H, Roider J. Acute retinal necrosis: clinical features, early vitrectomy, and outcomes. Ophthalmology. 2009;116:1971-1975.
20. C Stephen Foster, Albert T Vitale. Diagnosis & Treatment of Uveitis, Second Edition, Highlights Medical Publishers. 2013;437-460.
21. Cottet L, Kaiser L, Hirsch HH, Baglivo E. HSV2 acute retinal necrosis: diagnosis and monitoring with quantitative polymerase chain reaction. Int Ophthalmol. 2009;29:199-201.

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Turk J Ophthalmol 2017;47:180-183

Case Report

Von Hippel-Lindau Disease: The Importance of Retinal Hemangioblastomas in Diagnosis

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Abstract

Von Hippel-Lindau (VHL) disease is a familial cancer syndrome characterized by benign or malignant tumors which may involve more than one system. Retinal hemangioblastomas are usually the initial manifestation of VHL disease and can cause vision loss. A 32-year-old man presented to our clinic with vision loss in the left eye for 2 months. He had a history of cerebral hemangioblastoma operation. Family history showed that his mother had unilateral vision loss and died because of renal cell carcinoma. Ophthalmologic examination revealed multiple retinal hemangioblastomas in both eyes. *VHL* gene sequencing was performed and heterozygous p.R161X mutation was detected. His sister and daughter were also found to have the same variant. A treatment and follow-up plan was initiated for the patient and affected family members. Considering VHL disease in the differential diagnosis of retinal hemangioblastomas has a very important role in the early detection of life-threatening tumors in these patients.

Keywords: Renal cell carcinoma, retinal hemangioblastoma, Von Hippel-Lindau syndrome

Introduction

Von Hippel-Lindau (VHL) disease a familial cancer syndrome characterized by benign or malignant tumors and cystic lesions affecting multiple systems. It may present with hemangioblastomas in the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma; pancreatic cysts and neuroendocrine tumors; endolymphatic sac tumors; and epididymal and ligamentum latum cysts. Retinal hemangioblastomas are usually the initial sign of VHL disease and can cause vision loss. Up to 70% of affected individuals are diagnosed at an average age of 25 years old by detection of retinal hemangioblastomas.[1,2,3] Renal cell carcinoma is seen in about 70% of VHL patients and constitutes the greatest cause of mortality.[4] Identifying patients with retinal hemangioblastoma and evaluating them for VHL is of vital importance to both the patients and their relatives. Herein, we present a case diagnosed with VHL based on retinal hemangioblastomas after presenting to our clinic with reduced vision, and the treatment and follow-up of the patient and his relatives.

Case Report

A 32-year-old male patient presented to our outpatient clinic with vision loss in his left eye that started 2 months earlier. Ophthalmologic examination revealed no refractive error; visual acuity was 1.0 in the right eye and 0.2 in the left eye. Intraocular pressure was 14 mmHg in both eyes. Slit-lamp examination was normal. Bilateral increases in arterial and venous diameters and increased tortuosity were observed on fundus examination. Retinal hemangioblastomas were observed in the superotemporal (size, 3.63x4.67 mm) and inferotemporal (size, 2.95x3.41 mm) retina of the left eye and in the temporal (size, 2.49x2.54 mm) retina of the right eye (Figure 1a-c). The

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hemangioblastomas showed early hyperfluorescence on fundus fluorescein angiography (FFA). The feeding arteries and draining veins were clearly visible. Fluorescein leakage was observed around the temporal hemangioblastomas and macular region in the left eye (Figure 2). Optic coherence tomography (OCT) in the left eye revealed intraretinal cystic fluid accumulation in the perifoveal region (Figure 1d).

In his medical history, the patient reported undergoing surgery approximately 8 years earlier due to a cranial mass. He also reported that his mother had suffered from advanced unilateral vision loss and died of renal cancer. In the pathology report from the patient's brain surgery, the tissue was identified as hemangioblastoma. VHL was suspected based on the presence of multiple, bilateral retinal hemangioblastomas and history of cerebral hemangioblastoma. *VHL* gene sequence analysis revealed a heterozygous p.R161X mutation.

The patient was diagnosed with VHL and underwent examination and imaging of the other systems. A cortical cyst 13 mm in diameter was detected in the left kidney on renal ultrasonography (USG) and the patient was followed in the department of nephrology with USG examinations at 6-month intervals. Due to the patient's vision loss and intraretinal cystic fluid collection in the left eye, cryotherapy with three freeze/thaw cycles was applied only to the superotemporal hemangioblastoma. The other lesions were monitored with examination and imaging. A reduction in the perifoveal intraretinal fluid was observed after cryotherapy. On examination 4 months after cryotherapy, visual acuity in the left eye was 0.4 and no perifoveal intraretinal fluid was visible on OCT (Figure 3). The patient's family members were also invited to the clinic to be evaluated for VHL. Ophthalmologic examination of the patient's sister revealed visual acuity of 0.2 in the left eye and an optic nerve head hemangioblastoma causing macular traction and edema (Figure 4). Another hemangioblastoma (size, 2.90x2.35 mm) was detected in the peripheral temporal retina of the same eye. She had full vision and fundus examination was normal in the right eye. Examination and imaging of her other systems was performed. Abdominal USG revealed cystic lesions in the pancreas and kidney; advanced study with contrast magnetic resonance imaging was recommended. No pathology was detected in ophthalmologic examination of the patient's 12-year-old daughter.

Based on these findings, *VHL* gene analysis was planned for the patient's sister and daughter. Both were found to be heterozygous for the p.R161X mutation. Intravitreal anti-vascular endothelial growth factor inhibitor therapy was planned for the patient's sister due to the hemangioblastoma on her optic nerve head. However, it was then determined that she was 6 weeks pregnant. As this agent is category C for use during pregnancy and its absolute benefit is still debated, it was decided to monitor the patient without treatment. She was referred to genetic counseling, and pregnancy follow-up and prenatal diagnosis were planned. All patients were followed for possible complications by the relevant departments.

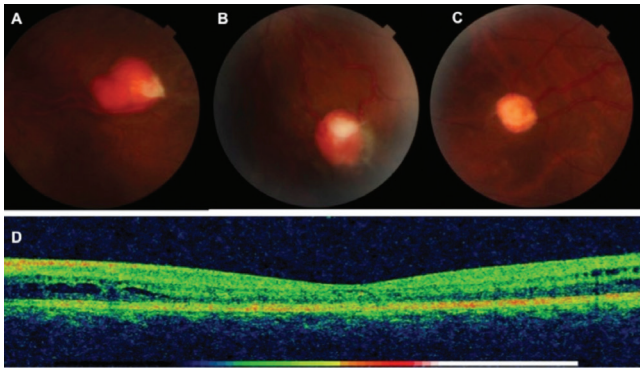

Figure 1. Retinal hemangioblastomas located in the (A) superotemporal left eye, (B) inferotemporal left eye, and (C) peripheral right eye, (D) Ocular computed tomography image showing perifoveal intraretinal cystic fluid accumulation

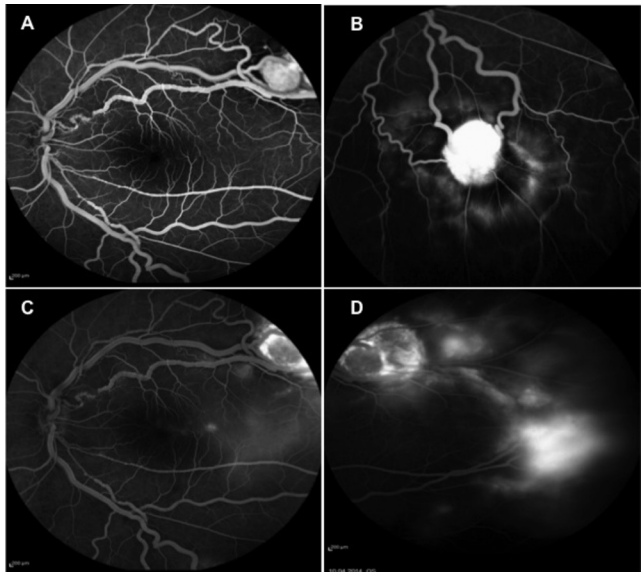

Figure 2. Left eye fundus fluorescein angiography images showing (A) increased arterial and venous diameter and hyperfluorescent appearance of the superotemporal hemangioblastoma, (B) inferotemporal hemangioblastoma, (C) edema in the temporal macula, and (D) increased late fluorescein leakage around the superotemporal hemangioblastoma

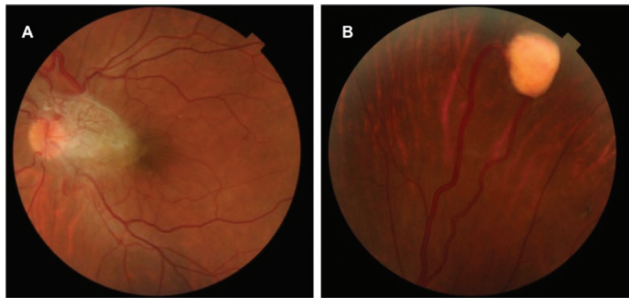

Figure 3. Images from the patient's sister's left eye showing (A) a hemangioblastoma on the optic nerve head and (B) a hemangioblastoma in the peripheral temporal retina

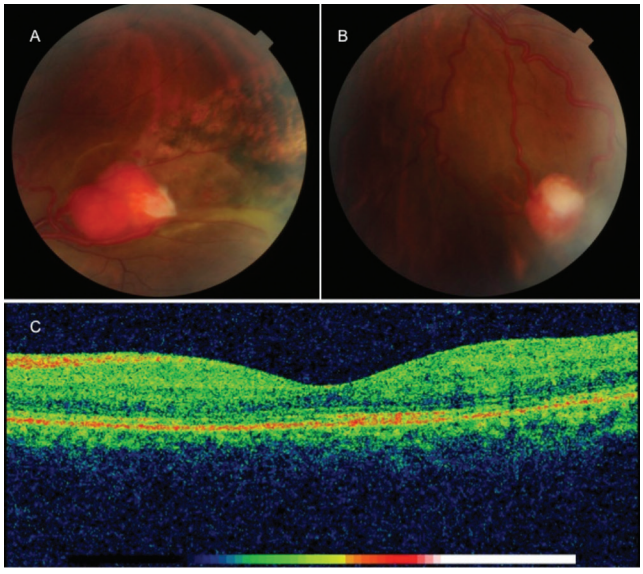

Figure 4. Images of the (A) superotemporal and (B) inferotemporal hemangioblastomas in the left eye after cryotherapy. (C) Ocular computed tomography image showing regression of the perifoveal intraretinal cystic fluid

Discussion

VHL disease is a rare, autosomal dominant, monogenic disease arising from heterozygous mutations of the *VHL* gene, located on chromosome 3p25.3. The incidence of VHL has been determined as approximately 1 in 36,000 live births.[5] Seventy-two percent of patients can be diagnosed with *VHL* gene sequence analysis; large exonic or whole gene deletions or duplications are responsible for the remaining 28%.[6] The p.R161X mutation identified in the family in the present study is a nonsense mutation described previously in the literature.[7] According to the phenotypic characteristics, VHL disease can be divided into 4 phenotypic groups based on the presence of pheochromocytoma or renal cell carcinoma (type 1, type 2A, type 2B, and type 2C). Pheochromocytoma is not present in type 1, but occurs with all other types. Considering his clinical findings and family/medical history, our patient was consistent with type 1. Although further evidence is needed in the literature to establish the genotype/phenotype relationship, it has been reported that missense and nonsense mutations lead to the type 1 VHL phenotype.[8]

Retinal hemangioblastomas are generally located in the peripheral temporal retina, but may rarely occur in the posterior pole and on the optic disc. Lesions are usually bilateral and multiple.[9] The differential diagnosis should include Coat's disease, retinal cavernous hemangioma, retinal macroaneurysm, and vasoproliferative tumor.[10]

In the retina, hemangioblastomas are slow-growing, benign tumors. Without treatment, however, they can cause complications such as macular edema, exudative and tractional retinal detachment, intravitreal hemorrhage, and neovascular glaucoma.[11] There is no standard treatment approach to retinal hemangioblastomas. The treatment method varies depending on the hemangioblastoma's location, size, and related complications. Treatment options include laser photocoagulation, cryotherapy, photodynamic therapy, transpupillary thermotherapy, plaque radiotherapy, external beam radiotherapy, and vitreoretinal surgical ablation.[12,13,14] Intravitreal anti-vascular endothelial growth factor inhibitors have recently come into use for reducing exudation resulting from hemangioblastoma.[15] Active surveillance is recommended for juxtapapillary hemangioblastomas and peripheral hemangioblastomas smaller than 500 microns that do not cause exudation or subretinal fluid. Laser photocoagulation is more common to treat small tumors, while cryotherapy is more often preferred for very peripheral tumors larger than 3 mm.[12] We chose cryotherapy for our patient because the hemangioblastoma causing perifoveal intraretinal cystic fluid collection in the left eye was larger than 4.5 mm in size and was situated peripherally. Cryotherapy resulted in regression of the perifoveal intraretinal cystic fluid and improved visual acuity. Early diagnosis and appropriate treatment reduces the risk of vision loss, especially with tumors located in the periphery. The likelihood of favorable outcome is lower with tumors located on or around the optic disc.[9]

In this case, VHL disease was suspected based on findings of multiple retinal hemangioblastomas and was confirmed with genetic testing. Although the patient had previously undergone surgery for cerebral hemangioblastoma, it was apparent that the possible role of VHL in its etiology had not been investigated through a comprehensive differential diagnosis. We also informed the patient's relatives about this genetic condition and performed the necessary examination and tests. Because hemorrhages associated with renal cancer and cerebral hemangioblastomas are the leading causes of mortality in these patients at young ages, systemic evaluation and monitoring is crucial. Our patient and his sister were diagnosed with renal cysts and routine follow-up was scheduled. The patients were advised to avoid tobacco products, as well as chemical and industrial toxins. They were also recommended to avoid contact sports due to their renal and pancreatic lesions.

As an ophthalmologist, identifying retinal hemangioblastomas and determining whether they are related to VHL is extremely important for the early diagnosis and treatment of life-threatening tumors and complications that may develop in these patients and their families.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sevinç Şahin Atik, Filiz Afrashi, Aslı Ece Solmaz, Zafer Öztaş, Tahir Atik, Concept: Sevinç Şahin Atik, Design: Sevinç Şahin Atik, Data Collection or Processing: Sevinç Şahin Atik, Emine Deniz Eğrilmez, Zafer Öztaş, Analysis or Interpretation: Sevinç Şahin Atik, Şeyda Uğurlu, Filiz Afrashi, Tahir Atik, Literature Search: Sevinç Şahin Atik, Writing: Sevinç Şahin Atik.

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

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References

1. Webster AR, Maher ER, Moore AT. Clinical characteristics of ocular angiomatosis in von Hippel-Lindau disease and correlation with germline mutation. Arch Ophthalmol. 1999;117:371-378.
2. Kreusel KM. Ophthalmological manifestations in VHL and NF 1: pathological and diagnostic implications. Fam Cancer. 2005;4:43-47.
3. Dollfus H, Massin P, Taupin P, Nemeth C, Amara S, Giraud S, Béroud C, Dureau P, Gaudric A, Landais P, Richard S. Retinal hemangioblastoma in von Hippel-Lindau disease: a clinical and molecular study. Invest Ophthalmol Vis Sci. 2002;43:3067-3074.
4. Kwon T, Jeong IG, Pak S, You D, Song C, Hong JH, Ahn H, Kim CS. Renal tumor size is an independent prognostic factor for overall survival in von Hippel-Lindau disease. J Cancer Res Clin Oncol. 2014;140:1171-1177.
5. Maher ER, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, Sampson J, Williams A, Ferguson-Smith MA, Morton N. Von Hippel-Lindau disease: a genetic study. J Med Genet. 1991;28:443-447.
6. Stolle C, Glenn G, Zbar B, Humphrey JS, Choyke P, Walther M, Pack S, Hurley K, Andrey C, Klausner R, Linehan WM. Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. Hum Mutat. 1998;12:417-423.
7. Crossey PA, Foster K, Richards FM, Phipps ME, Latif F, Tory K, Jones MH, Bentley E, Kumar R, Lerman MI. Molecular genetic investigations of the mechanism of tumourigenesis in von Hippel-Lindau disease: analysis of allele loss in VHL tumours. Hum Genet. 1994;93:53-58.
8. Stebbins CE, Kaelin WG Jr, Pavletich NP. Structure of the VHL-ElonginC-ElonginB complex: implications for VHL tumor suppressor function. Science. 1999;284:455-461.
9. Wang Y, Abu-Asab MS, Shen D, Zhuang Z, Chew EY, Chan CC. Upregulation of hypoxia-inducible factors and autophagy in von Hippel-Lindau-associated retinal hemangioblastoma. Graefes Arch Clin Exp Ophthalmol. 2014;252:1319-1327.
10. Shanmugam PM, Ramanjulu R. Vascular tumors of the choroid and retina. Indian J Ophthalmol. 2015;63:133-140.
11. Heimann H, Jmor F, Damato B. Imaging of retinal and choroidal vascular tumours. Eye (Lond). 2013;27:208-216.
12. Kim H, Yi JH, Kwon HJ, Lee CS, Lee SC. Therapeutic outcomes of retinal hemangioblastomas. Retina. 2014;34:2479-2486.
13. Teke MY., Cakar-Ozdal P, Sen E, Ozturk F. Von Hippel Lindau Hastaliğına bağlı retınal hemanjıoblastom: 14 yıllık izlem. Ret-Vit. 2011;19:64-67. http://retinavitreus.com//uploads/pdf/index.php?url=PDF_1173.pdf
14. Hondur A, Aydın B, Girelik G, Özdek Ş, Hasanreisoğlu B. Transpupillary Thermotherapy for Retinal Capillary Hemangiomas in Von Hippel-Lindau Disease. Ret-Vit. 2011;19:61-63.
15. Slim E, Antoun J, Kourie HR, Schakkal A, Cherfan G. Intravitreal bevacizumab for retinal capillary hemangioblastoma: A case series and literature review. Can J Ophthalmol 2014;49:450-457.

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Letter to the Editor

Spontaneous Resolution of Optic Disc Pit Maculopathy

Koushik Tripathy
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Dear Editor,

I read with interest the article reporting spontaneous resolution of optic disc pit maculopathy in a boy.[1] Though the presence of an optic disc pit and associated macular involvement is undoubted in the presented case, the provided optical coherence tomography (OCT) does not clearly show typical intraretinal schisis (Figure 1B)[1] at multiple retinal levels which may communicate with the pit. Instead, it shows a sub-internal limiting membrane (sub-ILM) cavity. Such cavities are known to occur following the resolution of sub-ILM bleed due to various cause including Valsalva retinopathy,[2] Terson syndrome, and also in some retinitis[3] cases.[4] In fact, some of these cavities may simulate a neurosensory retinal detachment or central serous chorioretinopathy on cursory clinical examination.[5] To confirm that the features of the current patient[1] are indeed related to the optic disc pit, it is necessary for the authors to provide an OCT scan which shows a connection of the presented cavity with the optic disc pit. Also, clear OCT scans of the fovea, both at presentation and at final follow-up would help our understanding of the visual recovery of the patient. The interval between the presenting (28 June 2012) OCT and final OCT (30 Nov 2012) is 5 months and not 6 months as described in the manuscript. For an effective comparison, both the presenting and final OCT scans should have been taken using either horizontal or vertical orientation over the macula. Though the spontaneous resolution of optic disc pit maculopathy is possible, visual recovery in usually unlikely and in such cases an alternate diagnosis needs to be excluded.

Keywords: Valsalva retinopathy, Terson syndrome, sub-internal limiting membrane cavity, central serous chorioretinopathy, retinitis

Ethic

Peer-review: Internally peer-reviewed.

References

1. Akça Bayar S, Sarıgül Sezenöz A, Yaman Pınarcı E, Yılmaz G. Spontaneous Regression of Optic Disc Pit Maculopathy in a Six-Year-Old Child. Turk J Ophthalmol. 2017;47:56-58.
2. Tripathy K, Chawla R. Valsalva retinopathy. Natl Med J India. 2015;28:310.
3. Chawla R, Tripathy K, Gogia V, Venkatesh P. Progressive outer retinal necrosis-like retinitis in immunocompetent hosts. BMJ Case Rep. 2016;2016.
4. Chawla R, Tripathy K, Temkar S, Kumar V. Internal limiting membrane: The innermost retinal barrier. Med Hypotheses. 2017;98:60-62.
5. Tripathy K, Chawla R, Vekaria L, Sharma YR. Sub-internal limiting membrane cavity following Valsalva retinopathy simulating central serous chorioretinopathy. J Ophthalmic Vis Res. 2017.

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Response from the Authors

Dear Editor,

We would like to thank Dr. Koushik Tripathy for his interest and constructive comments regarding our case report entitled "Spontaneous Regression of Optic Disc Pit Maculopathy in a Six-Year-Old Child" published in Turk J Ophthalmol. 2017 Jan;47(1):56-58.[1] We shall try to summarize our answer for his specific questions.

Dr. Tripathy has stated that the optical coherence tomography (OCT) image in Figure 1B[1] does not clearly show typical intraretinal schisis, it shows a sub-internal limiting membrane (sub-ILM) cavity. In our description of the case and in the discussion (Figure 1B)[1], we reported that OCT imaging revealed a schisis cavity and cystoid changes due to fluid collection under the ILM, not at multiple retinal layers. The term schisis cavity and cystoid changes has been used for fluid accumulation under ILM.

The author has declared that the interval between the presenting and final OCT 5 months not 6 months. Our patient's follow up was 6 months but better OCT scan was taken at 5 months and 2 days. Seventeen months after follow-up (December 19, 2013), foveal OCT showed a total regression of optic pit-induced maculopathy, and visual acuity was 20/20 in the right eye.

Finally, the author mentioned that the increase in visual acuity is usually unlikely and that alternative diagnosis should be considered. The patient's visual acuity at presentation was 20/32 and at final improved to 20/20. The increase in visual acuity was thought to be due to rapid absorption of the fluid and no structural change in the retina. We had already excluded such cavities which are known to occur following the resolution of sub-ILM hemorrhage due to various causes including Valsalva retinopathy,[2,3] Terson syndrome, or retinitis[4] as the author mentioned.

Again, we appreciate Dr. Tripathy's interest and constructive comments concerning our study.

Best Regards

Sezin Akça Bayar, Almila Sezenöz, Eylem Yaman Pınarcı, Gürsel Yılmaz

References

1. Akça Bayar S, Sarıgül Sezenöz A, Yaman Pınarcı E, Yılmaz G. Spontaneous Regression of Optic Disc Pit Maculopathy in a Six-Year-Old Child. Turk J Ophthalmol. 2017;47:56-58.
2. Tripathy K, Chawla R. Valsalva retinopathy. Natl Med J India. 2015;28:310.
3. Tripathy K, Chawla R, Vekaria L, Sharma YR. Sub-internal limiting membrane cavity following Valsalva retinopathy simulating central serous chorioretinopathy. J Ophthalmic Vis Res. 2017.
4. Chawla R, Tripathy K, Gogia V, Venkatesh P. Progressive outer retinal necrosis-like retinitis in immunocompetent hosts. BMJ Case Rep. 2016;2016.

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5-9 May 2017, Los Angeles, CA, USA
http://www.ascrs.org/

ARVO
7-11 May 2017, Baltimore, MD, USA
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Euretina 2017
7-10 September 2017, Barcelona, Spain

2017 ESA/AAPOS Joint Meeting
13-16 September 2017, Porto, Portugal
http://esa2017.com

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27-30 September 2017, Nice, France

ESCRS
7-11 October 2017, Lisbon, Portugal
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An International Perspective of Pediatric Ophthalmology and Strabismus AAPOS/CAPOS Joint Meeting
12-15 October 2017, Shanghai, China

AAO
11-14 November 2017, New Orleans, LA, USA
http://www.aao.org/annual-meeting

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16-18 June 2017, İstanbul, Turkey

TOA Summer Symposium
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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, editör. Clinical visual optics. Edinburgh: Butterworth-Heinemann, 1998:19-61.