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Turkish Journal of Ophthalmology
Avrupa Konutları Kale, Maltepe Mah. Yedikule Çırpıcı Yolu Sk. 9. Blok No: 2 Kat:1 Ofis:1 Zeytinburnu-İstanbul-Türkiye
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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

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/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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All visual materials together with their legends should be located on separate pages that follow the main text.

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All results of data and analysis should be presented in the Results section as tables, figures and graphics; biostatistical methods used and application details should be presented in the Materials and Methods section or under a separate title.

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Results: The detailed results of the study should be given and the statistical significance level should be indicated.

Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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EDITORIAL

2022 Issue 2 at a Glance:

Esteemed colleagues,

The Turkish Journal of Ophthalmology's second issue of 2022 features 7 original studies, a review, 3 case reports, and a letter to the editor with a reply from the authors.

A clinical study by Harbiyeli et al. titled "Clinical and Mycological Features of Fungal Keratitis: A Retrospective Single-Center Study (2012-2018)" included 38 eyes of 38 patients without polymicrobial etiology among 72 fungal keratitis cases (12.8%) diagnosed in 559 patients with microbial keratitis. The most common predisposing factor in patients under the age of 40 was trauma (63.6%), while pathologies that impaired ocular surface immunity were the leading factor (48.1%) in patients older than 40 years. In their detailed analysis, the authors recommended considering aggressive treatment options for patients presenting with large and central lesions and to follow these cases more closely.

In their study titled "Evaluation of the Clinical Findings of Patients with Penetrating Keratoplasty Followed by Telephone Due to the COVID-19 Pandemic", Yarımada et al. reported that in situations such as pandemics which can disrupt in-person office visits, patients can be safely followed up with telemedicine visits until the challenging circumstances resolve.

In their study titled "Impact of COVID-19-Related Lockdown on Glaucoma Patients", Barış et al. drew attention to the pandemic and the problem of following chronic disease that can sometimes require urgent care. They reported that the number of emergency glaucoma surgeries decreased by 71.7% while the lockdown was imposed, and that 5.5% of patients who were examined after lockdown was lifted had significant vision loss. Based on these findings, the authors concluded that some patients were unable to seek care at hospitals despite the need for urgent intervention.

In their article titled "How to Manage a Strabismus Clinic During the COVID-19 Pandemic; What Is Really Urgent, What Is Not?: A Single-Center Case Series from Turkey", Yabanoğlu et al. pointed out that acute-onset neurological conditions were more common during the COVID-19 pandemic.

A study by Vural et al. titled "A Comparative Evaluation of Globe Trauma Features in a Tertiary Care Hospital Before and During the COVID-19 Pandemic" shows that during lockdowns imposed due to the pandemic, there was an increase in injuries occuring in garden/farm settings and a decrease in occupational accidents.

In a joint study from Thailand and the Netherlands titled "Idiopathic Epiretinal Membranes: Visual Outcomes and Prognostic Factors", Kunavisarut et al. analyzed 130 eyes of 130 patients, 87 of whom underwent surgery and 43 of whom were followed without treatment, and reported that the baseline grade of disorganization of the retinal inner layers and the presence of ellipsoid zone disruption were the most informative prognostic factors in patients with idiopathic epiretinal membrane.

In their study titled "Heavy Silicone Oil as an Endotamponade in Recurrent or Complicated Retinal Detachment and Macular Hole", Kurt and Kapran reported that although the use of heavy silicone oil as an endotamponade has some limitations, such as increased intraocular pressure, emulsification, inflammation, and possible complications during removal, it is an effective and safe treatment option for indications such as proliferative vitreoretinopathy, recurrent macular holes, and other conditions that require inferior retinal support.

The review article in this issue was written by Gündüz and Mirzayev, who comprehensively address the subject of "Surgical Approach in Intraocular Tumors" with rich visual support.

In the case reports section, the first case is presented by Kaderli et al. under the title "Endogenous Fungal Endophthalmitis in a Patient Requiring Intensive Care Hospitalization and Systemic Steroids for the Treatment of COVID-19". The authors recommended keeping endogenous endophthalmitis in mind in patients with complaints of decreased visual acuity and a history of systemic steroid therapy and hospitalization due to COVID-19.

Özdemir et al. state in their case report titled "Half-fluence Photodynamic Treatment for Central Serous Chorioretinopathy in a Patient Receiving Corticosteroids for Behcet's Uveitis" that half-fluence photodynamic therapy (PDT) was a safe and effective method for uveitis patients who develop corticosteroid-induced central serous chorioretinopathy (CSCR) that persists after corticosteroid discontinuation.

TURKISH JOURNAL OF OPHTHALMOLOGY

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EDITORIAL

Yanık et al. also reported in their study titled "Atypical Chronic Central Serous Chorioretinopathy Mimicking Vogt-Koyanagi-Harada Disease: Full Therapeutic Response to Half-Fluens Photodynamic Therapy" that half-fluence PDT with oral eplerenone may be a successful treatment option for atypical CSCR by preventing subretinal fibrosis and scar formation.

In their letter to the editor, Ardakani et al. criticized a study by Taheri et al. titled "Dry Eye and Meibomian Glands in Vitiligo", which focused on meibomian gland function and lipid tear film in a series of 86 patients with vitiligo. They stated that to eliminate confounding factors, the researchers should have excluded smokers, contact lens users, and patients using topical cyclosporine A from the study group, and also recommended using a validated local language version of the Ocular Surface Disease Index instead of the original English version. In their reply, Taheri and Nikandish stated that they found the additional exclusion criteria recommendations appropriate, but that the patient distribution in their study group would not affect the results. In addition, they stated that they would consider the use of the local adaptation of the Ocular Surface Disease Index in future studies and attempted to bridge the gap verbally in the current study.

As the pandemic seems to be following a favorable course, the 13 papers in this issue included 4 original research articles and 1 case report related to the pandemic. In future issues, we hope that studies comparing the pre-pandemic and pandemic periods will be replaced by studies in which the effects of the pandemic on our clinical routines have been completely eliminated.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

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Turk J Ophthalmol 2022;52:75-85

Original Article

Clinical and Mycological Features of Fungal Keratitis: A Retrospective Single-Center Study (2012-2018)

İbrahim İnan Harbiyeli*, Elif Erdem*, Nuhkan Görkemli*, Astan İbayev*, Hazal Kandemir**, Arbil Açıkalın***, Macit İlkit**, Meltem Yağmur*

*Çukurova University Faculty of Medicine, Department of Ophthalmology, Adana, Turkey
**Çukurova University Faculty of Medicine, Department of Microbiology, Division of Mycology, Adana, Turkey
***Çukurova University Faculty of Medicine, Department of Patology, Adana, Turkey

Abstract

Objectives: To present the demographic, etiological, clinical, and mycological characteristics and treatment results of fungal keratitis patients admitted to our clinic.

Materials and Methods: The medical records of patients diagnosed with fungal keratitis between October 2012 and 2018 were reviewed. The diagnosis of fungal keratitis was confirmed mycologically and/or cytologically. Treatment response was defined as complete infiltrate resolution and re-epithelization with medical treatment and minor surgical interventions. Patients who underwent penetrating keratoplasty or evisceration due to clinical deterioration despite treatment were classified as treatment nonresponders and were compared with responders in terms of demographic, etiological, and clinical characteristics.

Results: Seventy-two (12.8%) of 559 patients diagnosed with microbial keratitis in the 6-year period were fungal keratitis. Of these, 38 cases (38 eyes) without polymicrobial etiology were included in the study. The patients' mean age was 44.9±19.0 years (range: 2-80) and males predominated (14 females [36.8%], 24 males [63.2%]). Trauma (63.6%) was the most common predisposing factor in patients younger than 40 years old, whereas pathologies impairing ocular surface immunity were the leading risk factor (48.1%) in patients older than 40 years. Filamentous fungi were detected in 34 (89.5%) cases, while yeasts were found in 4 (10.5%) cases. Among 26 cases with positive cultures, *Aspergillus* species were the most common pathogens (42.3%). Infiltrate size before treatment was larger in nonresponders (14/38, 36.8%) compared to treatment responders (19/38, 50%) (p=0.049). In addition, rates of treatment response were higher in cases in which the infiltrate was located paracentrally compared to other cases (p=0.036).

Conclusion: Fungal keratitis is an important public health problem in our region. Ocular trauma is a leading etiology in men under the age of 40 years. In the 6-year period, we observed that the main causes of fungal keratitis were filamentous fungi, and most commonly *Aspergillus* species. In cases presenting with large and central lesions, aggressive treatment options should be considered and these patients should be followed up more closely.

Keywords: *Aspergillus, Candida, Fusarium*, filamentous fungus, fungal keratitis, yeast fungus

Address for Correspondence: İbrahim İnan Harbiyeli, Çukurova University Faculty of Medicine, Department of Ophthalmology, Adana, Turkey
E-mail: iharbiyeli@cu.edu.tr **ORCID-ID:** orcid.org/0000-0003-2586-1096
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Introduction

Infectious keratitis is one of the leading causes of unilateral blindness worldwide.[1] Among infectious keratitis etiologies, fungal keratitis is less common than bacterial keratitis but poses a greater threat to vision. In fungal keratitis, the main diagnostic challenges are that clinical diagnosis requires experience, and cytological examination and fungal cultures involve a meticulous and relatively long process, while the major therapeutic challenges include the low corneal penetration and generally fungistatic nature of antifungal drugs, and variations in drug sensitivity among fungal pathogens.[1,2] These difficulties lead to a poorer prognosis and 5- to 6-fold higher prevalence of corneal perforation than in bacterial keratitis.[3,4] Therefore, early diagnosis and effective treatment of fungal keratitis are essential.[1]

The prevalence of fungal keratitis, the causative microorganisms, and associated risk factors vary by geographic region.[2] In tropical and subtropical regions, where the incidence is high and the etiology is often traumatic, molds are the leading pathogen, whereas in colder and drier climates, the etiology usually involves factors that impair ocular surface immunity and yeasts are the predominant pathogens.[2,5] Regional variations in the epidemiology of fungal keratitis and the difficulty of treating these infections increase the importance of results reported from referral centers in different geographical regions.

This study aimed to present the demographic, etiological, clinical, and mycological characteristics and treatment results of fungal keratitis patients admitted to a tertiary referral center in southern Turkey over a 6-year period.

Materials and Methods

The medical records of patients diagnosed with microbial keratitis in the cornea unit of the Çukurova University Faculty of Medicine, Department of Ophthalmology between October 2012 and October 2018 were retrospectively analyzed. Of the patients with a fungal pathogen demonstrated by culture and/or cytological examination, those with complete medical records were included in the study. The presence of endophthalmitis at admission was accepted as the exclusion criterion. The study was approved by the Çukurova University Faculty of Medicine Ethics Committee (date: 03.07.2020, meeting/decision no: 101/12) and the study was conducted in accordance with the principles of the Declaration of Helsinki. Demographic and etiological characteristics, symptom duration, risk factors, systemic comorbidities, causative microorganisms and diagnostic methods, pre-treatment best corrected visual acuity, infiltration characteristics and presence of hypopyon at presentation, treatments, and treatment results were recorded. Infiltrate location was recorded as central, paracentral, or peripheral.[6] Infiltrate depth was assessed biomicroscopically and classified as superficial (less than two-thirds of the corneal thickness) or deep (more than two-thirds of the corneal thickness).[6]

Cytological and Mycological Examination

Under topical anesthesia, scraping samples were obtained from the base and margins of all infiltrates. The clinical specimens were examined by direct microscopy in the pathology department of the Çukurova University Faculty of Medicine. The presence of epithelial cells and associated fungal hyphens in the samples was investigated using Papanicolaou and periodic acid-Schiff stains. Samples in liquid brain-heart infusion (bioMérieux, Marcy l'Etoile, France) transport medium were delivered to the Medical Mycology unit of the Çukurova University School of Medicine, Department of Microbiology and inoculated onto appropriate culture media (blood agar [bioMérieux], Sabouraud-glucose agar [Merck, Darmstadt, Germany], potato dextrose agar [Merck], and brain-heart infusion agar [bioMérieux]) using a "C" streak. The plates were incubated at 28 °C and 37 °C and examined for growth.

The molecular diagnosis of isolated fungi was made in the Westerdijk Fungal Biodiversity Institute in Utrecht, Netherlands. *Aspergillus* species were identified using primers targeting the rDNA internal transcribed spacer (ITS) and partial calmodulin gene regions, and *Fusarium* species were identified using primers targeting the partial elongation factor 1-alpha (tef1-alpha) gene region.[7,8] All isolates were stored under their Centraalbureau voor Schimmelcultures (CBS; Utrecht, Netherlands) or Macit İlkit Working Collection (MI; Adana, Turkey) registration numbers.

Treatment

In all cases of microbial keratitis, treatment was initiated empirically. Empirical topical treatment consisted of combination fortified vancomycin (50 mg/mL; Kocak, Istanbul, Turkey)/amikacin (50 mg/mL; Osel, Istanbul, Turkey) or moxifloxacin (0.5%; Vigamox, Alcon, Fort Worth, USA), depending on the severity of clinical findings. If fungal keratitis was strongly suspected based on medical history and clinical findings, topical fortified voriconazole (10 mg/mL; Vfend, Pfizer, New York, USA) was added to the empirical treatment without waiting for laboratory results. The subsequent treatment protocol was modified according to clinical response and the results of microbiological examination.

In patients whose cytological examination and/or culture yielded a fungal pathogen, a topical antifungal agent (fortified voriconazole or amphotericin B [when *Aspergillus* species or yeast infection is detected] 2.5 mg/mL; AmBisome, NeXstar Pharmaceuticals, San Dimas, USA) hourly was added to the treatment if it had not been initiated empirically. In patients with positive fungal culture, antifungal treatment was changed according to the species of microorganism detected. In *Fusarium* cases, if the patient did not respond to the antifungal treatment initiated, topical posaconazole (10 mg/0.1 mL; Noxafil, Schering Plough, New Jersey, USA) was added, and in the presence of yeast infection, caspofungin (10 mg/mL; Cancidas, Merck Sharp Dohme, New Jersey, USA) was added to treatment. Systemic administration of antifungal drugs selected according to the pathogen, intrastromal and/or intracameral voriconazole or amphotericin B injections, and corneal cross-linking (CXL) were performed as needed based on the severity of clinical findings and response to treatment. In all cases, the frequency and duration of treatment were determined according to the clinical response observed during follow-up. In cases where

medical treatment was inadequate, various surgical treatments (amniotic membrane transplantation [AMT], corneal patch graft, penetrating keratoplasty [PK], and evisceration) were performed.

Treatment response was defined as complete infiltrate resolution and re-epithelialization after medical treatment and minor surgical interventions (AMT, corneal patch graft). Patients who discontinued clinical follow-up after recovery (post-recovery follow-up period <2 weeks) or did not show complete resolution at their last examination were evaluated as having insufficient clinical follow-up. Patients in whom progression of the infection could not be halted despite all treatments and those who underwent PK or evisceration were classified as nonresponsive to treatment. Demographic, etiological, and clinical characteristics were compared between patients whose clinical follow-up period and post-treatment findings met the criteria for treatment response and those who were nonresponsive. In addition, an increase of 1 or more Snellen lines after treatment compared to initial visual acuity was considered visual improvement with treatment. Treatment responders with and without visual improvement with treatment were compared.

Statistical Analysis

SPSS version 25.0 software package (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Categorical values were summarized as frequency and percentage; continuous data were summarized as mean and standard deviation (or median, minimum, and maximum, as appropriate). Chi-square test or Fisher test statistic was used to compare categorical variables. For between-group comparisons of continuous measures, data distributions were tested and Student's t-test was used for normally distributed variables and Mann-Whitney U test was used for non-normally distributed variables. Independent risk factors associated with treatment outcome were identified using logistic regression analysis. The level of significance was accepted as 0.05 for all tests.

Results

Of 559 patients diagnosed with microbial keratitis within the 6-year study period, 72 (12.8%) had fungal keratitis. Seven patients whose medical records were not fully accessible were excluded. Of the remaining 65 patients, 27 (41.5%) had polymicrobial etiology and were reported in a previous study.[9] As a result, 38 cases of fungal keratitis not accompanied by another type of microbial agent were included in this study. The mean age of the patients was 44.9±19.0 years (range: 2-80). Male patients outnumbered females (14 females [36.8%], 24 males [63.2%]) and this male predominance was more pronounced among patients under 40 years of age (8/11, 72.7%). When examined in terms of age distribution, most patients were 40-60 years of age (n=20, 52.6%) (Figure 1). Case numbers were higher in 2012 and 2018 and evenly distributed among the other years (Figure 2). When the seasonal distribution of patient admissions was examined, we observed that most cases presented during the fall (n=16, 42.1%) (Figure 3).

The most common predisposing factor was trauma, present in 17 patients (44.7%) (Table 1). Ten (10/17; 58.8%) of these patients had plant- or animal-related trauma. Diabetes mellitus was the most common systemic risk factor (n=8, 18.2%), while no predisposing factor was identified in 9 patients (23.7%). Predisposing factors were evenly distributed according to season and year of presentation but differed by age group. The most common predisposing factors were trauma before the age of 40 years (7/11, 63.6%) and local and systemic pathologies impairing ocular surface immunity after the age of 40 years (13/27, 48.1%).

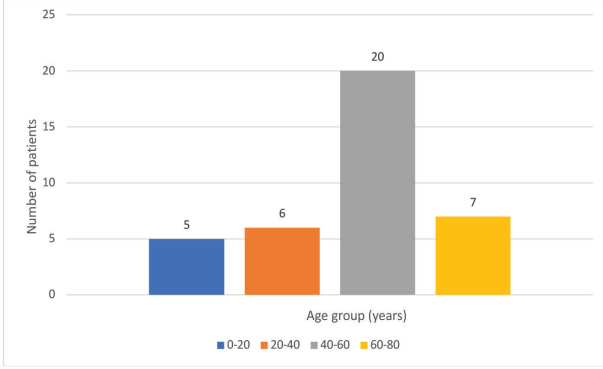

Figure 1. Age distribution of the patients

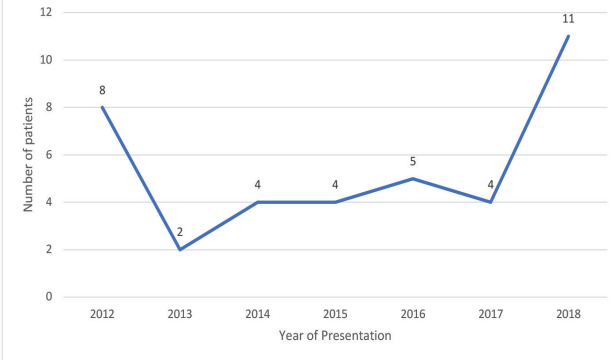

Figure 2. Distribution of cases by year of presentation

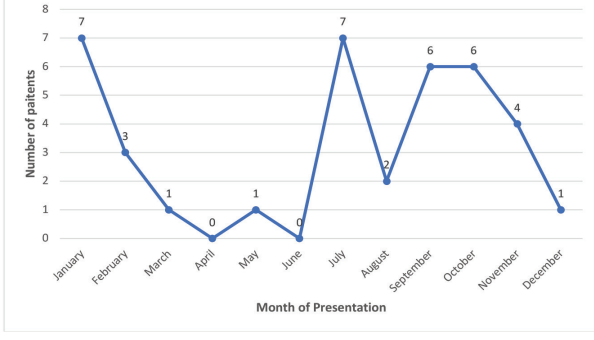

Figure 3. Distribution of cases by month of presentation

The causative microorganism was detected by fungal culture in 26 patients (68.4%) and both fungal culture and cytological examination in 15 patients (39.4%). In the 12 patients (31.6%) with negative fungal culture, the diagnosis was made by cytological examination. Molds were detected in 34 patients (89.5%) and yeasts were detected in 4 patients (10.5%) (Table 2). The epidemiological and clinical characteristics of the two fungal groups at presentation are shown in Table 3. The most common pathogens detected in the 26 patients with positive cultures were *Aspergillus* species (11/26, 42.3%). There was no significant difference between fungal isolates in terms of epidemiological and clinical characteristics at presentation ($p>0.05$ for all).

The median symptom duration before presentation was 15 days (range: 1-120). The mean infiltrate area at presentation was 38.2±30.2 mm^2 (range: 1.3-143.7; n=36, could not be measured in 2 patients). When the patients were examined in terms of lesion characteristics, 14 patients (36.8%) had satellite infiltrates, 5 (13.2%) had ring infiltrates, and 16 (42.1%) had hypopyon. Infiltrates were superficial in 11 patients (28.9%) and deep in 27 patients (71.1%). Infiltrate location was central in 22 patients (57.9%), paracentral in 14 patients (36.8%), and peripheral in 2 patients (5.3%). Ten patients (26.3%) received only topical antifungal therapy. In addition to topical treatment, 22 patients (57.8%) received systemic antifungal therapy, 20 (52.6%) received intrastromal antifungal (amphotericin or voriconazole) injections, and 5 patients (13%) underwent CXL. Antifungal therapy could not be administered to 1 patient who had corneal perforation and underwent evisceration before the results of corneal specimen examination were available. During follow-up, AMT was performed in 15 patients (39.5%) and corneal patch grafting was performed in 4 patients (10.5%). After these treatments, 19 patients (50%) with a mean follow-up time of 19.5 months (range: 1-65) demonstrated complete infiltrate resolution and re-epithelialization, with persistence of these findings for at least 2 weeks (treatment responders). In 14 patients (36.8%), progression of the infection could not be halted despite all treatments (non-responders). Eight (21%) of these patients underwent PK and 6 (15.8%) underwent evisceration. In 2 of the 6 patients who underwent evisceration, long symptom duration and late presentation to our clinic (26 and 30 days) contributed to the poor prognosis. In another patient who had corneal perforation at presentation and developed endophthalmitis within the first week of clinical follow-up, tectonic surgery was not possible and evisceration was performed. In the other patients, infections extending to the limbus and sclera or spreading to the posterior segment despite antifungal therapy precluded PK.

Comparison of treatment responders and nonresponders showed that initial infiltrate area was larger in nonresponders ($p=0.049$; Table 4). In addition, the response rate was higher among patients with paracentral infiltrates than in other patients ($p=0.036$). Because a larger infiltrate area increases the risk of the lesion involving the central cornea, these variables were evaluated in a logistic regression model to determine whether the relationship between infiltrate location and treatment response was affected by lesion size. This analysis revealed that lesion location was an independent parameter associated

Table 1. Predisposing factors identified in fungal keratitis cases

Predisposing factor	Number of patients	Percentage
Trauma	**17**	**38.6**
Plant injury (branch, thorn, grass)	8	18.2
Animal injury (horn, tail)	2	4.5
Other (metal, stone, dust)	7	15.9
Risk factors impairing ocular surface immunity	**25**	**56.8**
Local factors	15	34.1
Chronic ocular surface disease[†]	7	15.9
Topical steroid use	3	6.8
Previous ocular surface surgery[‡]	4	9.1
Long-term topical drug use (>6 months)[§]	1	2.3
Systemic diseases	10	22.7
DM	8	18.2
Other[¶]	2	4.5
Contact lens use	**2**	**4.6**
Total	44[&]	**100**

[†]Chronic blepharitis, dry eye, atopic keratoconjunctivitis, herpes simplex keratitis, lagophthalmic keratopathy
[‡]Penetrating keratoplasty, pterygium surgery, pars plana vitrectomy
[§]Topical antiglaucoma, topical antibiotic
[¶]Bullous pemphigoid, immunodeficiency secondary to genetic syndrome
[&]Seven patients had multiple factors that impaired ocular surface immunity.

Table 2. Data related to the fungal isolates		
Fungal isolates	**Isolate number (%)**	**CBS/MI no.**
Molds	**34 (89.5)**	
Cytologic diagnosis	12 (31.5)	
Culture diagnosis	22 (57.8)	
***Aspergillus* species**	**11 (28.9)**	
Aspergillus fumigatus	4 (10.5)	CBS 145410/CBS 145409/MI 198905
Aspergillus flavus	3 (7.8)	
Aspergillus terreus	1 (2.6)	CBS 135845
Aspergillus spp.	3 (7.8)	
***Fusarium* species**	**8 (21)**	
Fusarium solani	3 (7.8)	CBS 143255/CBS 138564/MI 198906
Fusarium falciforme	2 (5.2)	CBS 198901/CBS 143254
Fusarium spp.	3 (7.8)	CBS 145411
Unidentified black fungus	**1 (2.6)**	
Unidentified mold	**2 (5.2)**	
Yeasts	**4 (10.5)**	
Cytologic diagnosis	None	
Culture diagnosis	4 (10.5)	
***Candida* species**	**3 (7.8)**	
Candida tropicalis	1 (2.6)	
Candida spp.	2 (5.2)	
Unidentified yeast	1 (2.6)	
Total isolates	**38 (100)**	
CBS: Centraalbureau voor Schimmelcultures, MI: Macit Ilkit Working Collection		

with treatment response rate (odds ratio: 6.6, 95% confidence interval: 1.1-42; p=0.048). Five patients (13.2%) were evaluated as having insufficient clinical follow-up and their data were not included in the analysis of treatment outcome.

At initial presentation, vision level was between light perception and hand movements in 23 patients, counting fingers at 1-5 meters in 2 patients, and ≥0.1 (Snellen, decimal) in 10 patients. One patient had no light perception at presentation, while visual acuity could not be evaluated in 2 cases (1 child and 1 patient with cognitive disability). Among the treatment responders (n=19), 8 patients (42.1%) had a visual improvement of 1 Snellen line or more at final post-treatment examination compared to their visual acuity at initial presentation. Visual acuity after treatment was unchanged in 6 patients (31.5%) and declined in 3 patients (15.7%) compared to pre-treatment levels (visual acuity could not be measured in 1 pediatric patient; the patient with no light perception was not included in the evaluation). The 8 patients with visual improvement after treatment were compared with the other 9 patients in terms of data at initial presentation, but there was no statistically significant difference between the two groups in terms of demographic or clinical parameters (p>0.05 for all). Four (50%) of the patients that underwent PK showed visual improvement of 1 or more Snellen lines at last examination compared to presentation. Visual acuity remained unchanged after PK in 2 patients (25%) and declined in the other 2 patients (25%).

Discussion

Fungal keratitis is one of the leading causes of vision loss in developing countries.[1] Difficulties in both mycological and clinical diagnosis and the limited efficacy of antifungal drugs may result in reduced treatment success and unfavorable visual outcomes in these infections.[10] This study presents detailed data regarding the demographic characteristics, predisposing factors, causative microorganisms, and treatment results in fungal keratitis cases from a referral center with experience in fungal keratitis.

Table 3. Comparison of patient data at initial admission according to fungal species				
	Mold (n=34)		**Yeast (n=4)**	
	n	**%**	**n**	**%**
Sex				
F	12	35.3	2	50.0
M	22	64.7	2	50.0
Year of presentation				
2012-2015	18	52.9	0	0.0
2016-2018	16	47.1	4	100.0
Season of presentation				
Spring	2	5.9	0	0.0
Summer	9	26.5	0	0.0
Fall	15	44.1	1	25.0
Winter	8	23.5	3	75.0
Predisposing factor				
Trauma	12	35.3	1	25.0
Conditions impairing ocular surface immunity	8	23.5	3	75.0
Contact lens use	1	2.9	0	0.0
Multiple factors	5	14.7	0	0.0
None identified	8	23.5	0	0.0
Hypopyon	14	41.2	2	50.0
Central lesion	20	58.8	2	50.0
Deep lesion	25	73.5	2	50.0
Satellite lesion	13	38.2	1	25.0
Ring infiltrate	5	14.7	0	0.0
Baseline visual level†				
≤Hand motions	22	66.6	2	66.7
Counting fingers at 1-5 m	4	12.1	1	33.3
0.1-1 Snellen decimal	7	21.2	0	0.0
	Mean ± SD (min-max)		**Mean ± SD (min-max)**	
Age (years)	46±18.33 (7-80)		55±27.86 (2-62)	
Symptom duration	13±25.65 (1-120)		22±10.9 (13-35)	
Infiltrate area‡	30±34.68 (1.3-143.7)		20.2±19.12 (16.4-20.2)	

There were no statistically significant differences in the shown variables among the fungal species. Due to the small number of cases associated with yeasts, p values are not included in the table.
†Vision level could not be evaluated in 1 patient from each group.
‡Infiltrate area could not be measured in 2 patients.
SD: Standard deviation, min: Minimum, max: Maximum

The prevalence of fungal keratitis varies regionally according to socioeconomic profile, climate, and environmental conditions.[11] Fungal infections constitute a substantial proportion of microbial keratitis cases, especially in areas with large populations of agricultural workers and in hot, humid areas.[1] Different studies in India have reported that they account for 8% to 47% of all cases of infectious keratitis.[11,12] In a study examining microbial keratitis in a center in western Turkey, Yilmaz et al.[13] reported the prevalence of fungal keratitis to be 24.2%. Hilmioğlu-Polat et al.[14] estimated the annual incidence of fungal keratitis in Turkey as 33/100,000. The Çukurova region has a subtropical climate and extensive agricultural land use, resulting in a geographic predisposition to fungal infections. This study includes data from a tertiary hospital in this region and showed that the rate of fungal keratitis was 12.8% among 559 cases of microbial keratitis over a 6-year period.

Table 4. Comparison of patients grouped by treatment response					
	Treatment outcome¶				
	Treatment response (n=19)		**Treatment non-response (n=14)**		
	n	**%**	**n**	**%**	**p**
Sex					
F	7	36.8	5	35.7	1
M	12	63.2	9	64.3	
Year of presentation					
2012-2015	10	52.6	5	35.7	0.482
2016-2018	9	47.4	9	64.3	
Season of presentation					
Spring	1	5.3	1	7.1	0.755
Summer	4	21.1	4	28.6	
Fall	9	47.4	4	28.6	
Winter	5	26.3	5	35.7	
Predisposing factor					
Trauma	4	21.1	6	42.9	0.218
Conditions impairing ocular surface immunity	7	36.8	2	14.3	
Contact lens use	0	0.0	1	7.1	
Multiple factors	2	10.5	3	21.4	
None identified	6	31.6	2	14.3	
Fungal species					
Mold§	17	89.5	13	92.9	0.616 / 1
Fusarium	2	10.5	4	28.6	
Aspergillus	7	36.8	4	28.6	
Yeast	2	10.5	1	7.1	
Hypopyon	7	36.8	7	50.0	0.497
Central lesion	8	42.1	12	85.7	0.036
Deep lesion	12	63.2	10	71.4	0.719
Satellite lesion	6	31.6	5	35.7	1
Ring infiltrate	2	10.5	2	14.3	1
Baseline visual level†					
≤ Hand motions	10	55.6	12	92.3	0.086
Counting fingers at 1-5 m	4	22.2	1	7.7	
0.1-1 Snellen decimal	4	22.2	0	0.0	
	Mean ± SD (min-max)		**Mean ± SD (min-max)**		
Age (years)	47±20.41 (2-80)		47±16.08 (7-45)		0.747
Symptom duration	10±17 (1-60)		20±21.56 (4-90)		0.209
Infiltrate area‡	28.2±24.51 (1.3-110.0)		45.5±50.83 (2.0-143.7)		0.540

¶5 patients with insufficient clinical follow-up are not shown in the table.
§Patients with isolates identified at the species level
†Vision level could not be evaluated in 1 patient from each group.
‡Infiltrate area could not be measured in 2 patients.
SD: Standard deviation, min: Minimum, max: Maximum

The prevalence and predisposing factors of fungal keratitis vary with gender and age.[4,11,15,16] In studies conducted in different regions of India, the highest prevalence was found in men 50-60 years of age.[12,17,18] In developing countries, the prevalence was reported to be 2 to 5 times higher in men than in women,[11,12] whereas Tanure et al.[19] determined that the rates of men and women were similar among cases reported from North America.

In our study, male patients outnumbered females (36.8% females, 63.2% males) and the majority of cases (27/38, 71%) were over 40 years of age. Male predominance was more pronounced in patients under the age of 40 years (8/11; 72.7%), and consistent with this, trauma was the most common predisposing factor in this age group (7/11; 63.6%). In general, the 20-40 age range is most actively studied; therefore, the risk of trauma is highest among those working in agriculture and animal husbandry.[11] In this age group, men experience ocular trauma more frequently than women because they work more in jobs based on physical strength.[11] In our study, 13 (76.4%) of the 17 patients with a history of trauma were men.

In our patients over 40 years of age, the gender distribution was more balanced (40.7% females, 59.2% males) and the prevalence of trauma was lower (10/27; 37%). In this age group, local and systemic pathologies that impair ocular surface immunity were the leading predisposing factors (13/27; 48.1%). With older age, the body's immune resistance weakens, corneal epithelialization slows, and susceptibility to chronic ocular and systemic diseases increases.[20] All of these factors facilitate the development of fungal keratitis.

The species of fungus involved in fungal keratitis is closely associated with medical history and predisposing factors.[4] Yeasts largely cause infection in patients with underlying ocular or systemic disease, while molds are often associated with ocular trauma.[21,22] In this study, a history of trauma was present in 16 (47%) of 34 cases caused by molds but only 1 (25%) case caused by yeasts. All other cases involving yeasts were associated with chronic ocular surface disease, as well as a history of systemic disease in 2 patients (one with immunodeficiency secondary to a genetic syndrome and one with bullous pemphigoid).

Fungal keratitis pathogens may vary geographically depending on climate and environmental conditions.[23] Molds are the most common isolates in cases of microbial keratitis in studies conducted in many developing countries with tropical or subtropical climates.[24] Of these, *Aspergillus* species are more prevalent in subtropical regions, while *Fusarium* is more common in tropical regions.[12,25,26,27,28] Binnani et al.[15] reported that of 180 fungal isolates in their study, 63.3% were *Aspergillus* species and most of those (55%) were *Aspergillus fumigatus*. The authors stated that in regions where *Aspergillus* spores are concentrated in the air, contact with eyes that have an infectious disposition leads to infection.[15] In our study, molds were the causative agent in 34 patients (89.4%). *Aspergillus* species (11/26, 42.3%) were the most commonly identified agents in positive fungal cultures. *Aspergillus fumigatus* was the most frequently isolated species, detected in 4 patients. *Fusarium* species, detected in 8 patients (30.7%), were the second most frequently isolated agents in our study, similar to the results reported in many developing and hot climate countries.[29,30] Yeasts, which are the predominant cause of fungal keratitis in temperate climates and developed countries, were identified in 4 patients (10.6%) in our study. Considering the socioeconomic level of the patients in our study, the geographic conditions of our region, and the high prevalence of trauma in our cases, this numerical distribution of fungal isolates can be considered an expected result.

Fungal keratitis is therapeutically challenging, and many studies have reported limited treatment success.[17,18,31] In similar studies, nonresponse to medical treatment and the need for keratoplasty have been reported at rates of 40-47% in developing countries[18,32] and 21-25% in developed countries.[4,19,33,34] Nielsen et al.[3] reported in their study that only 36% of patients could be successfully treated with medical therapies and 52% underwent keratoplasty. Similar to the rates reported in the literature, anatomic success was achieved with medical treatment and minor surgical interventions (AMT and corneal patch graft) in 50% of the patients in our study (19/38; treatment responders).

Resistance to many antifungal drugs among *Fusarium* species limits treatment success in *Fusarium* keratitis, both in terms of preserving anatomical integrity and vision level.[35,36] Many studies have demonstrated the efficacy of topical natamycin and its superiority to voriconazole in *Fusarium* keratitis.[37,38] Pérez-Balbuena et al.[35] reported that 14 (23%) of 61 *Fusarium* keratitis cases underwent tectonic PK and 14 (23%) underwent evisceration. The authors stated that evisceration was not needed in any of the patients treated with natamycin, and that other antifungal drugs were used in many cases due to the lack of access to natamycin in Mexico for a large part of the study period.[35] Walther et al.[36] reported that 9 (60%) of 15 *Fusarium* keratitis patients underwent keratoplasty and 3 (20%) underwent evisceration. The authors attributed this unfavorable clinical outcome with the absence of a commercially available natamycin product in Germany.[36]

Although statistical significance could not be determined due to the small number of patients, the improvement rate was lower in *Fusarium* cases in our study compared to other fungal keratitis cases (Table 4). Only 2 (33.3%) of 6 *Fusarium* cases (2 patients were not included in the evaluation due to insufficient clinical follow-up) improved with medical treatment. This rate was 63.6% in *Aspergillus* cases and 66.6% in Candida cases (Table 4). Of the other *Fusarium* cases, 2 patients underwent PK and 2 underwent evisceration. In our study, clinical indicators of corneal infection severity at initial presentation did not differ according to the species of fungus involved. Therefore, the poor prognosis of *Fusarium* cases may be attributable to the multidrug resistance of this fungus against the antifungals

administered. The absence of natamycin as a commercial product in our country is an important barrier to the treatment of these challenging cases. On the other hand, systemic and topical posaconazole was shown to be effective in cases of *Fusarium* keratitis resistant to conventional antifungal therapies.[39,40] The high lipophilicity of this drug increases its penetration into the ocular tissues and thus its efficacy.[39] Of the 4 patients with *Fusarium* keratitis who did not respond to conventional antifungal therapy, 2 patients were no longer eligible for medical treatment by the time *Fusarium* was identified, and 1 patient could not be treated with posaconazole because the drug could not be obtained at that time. Consequently, 2 of these 3 patients underwent evisceration.

The prevalence of polymicrobial infection in microbial keratitis has been reported in the range of 1.9-15.8%.[41,42] It is noteworthy that in fungal keratitis, the reported range is wider and includes higher rates (5-60%).[6,43,44] Fernandes et al.[43] reported the prevalence of polymicrobial infection as 36.1% in 94 fungal keratitis cases, while Ahn et al.[6] reported this rate as 39.7% in their 7-year case series. In our study, polymicrobial etiology was present in 27 (41.5%) of 65 fungal keratitis cases over a 6-year period, consistent with the literature. Antibiosis and the ability to produce biofilm are properties of both molds and yeasts which are prominent features related to the bacterial-fungal interaction, although their role in polymicrobial infections has not been fully elucidated.[45,46]

In our study, we found that central and large infiltrates were associated with treatment failure (p=0.036 and p=0.049, respectively). Different studies have shown that the presence of central infiltrate in infectious keratitis is associated with an increased need for PK.[47,48] Prajna et al.[49] showed that in fungal keratitis, many parameters related to lesion characteristics at presentation, including infiltrate size and presence of a central lesion, were associated with the development of perforation, epithelialization time, post-treatment vision level, and scar size. Keay et al.[4] reported that infiltrate size was associated with vision loss and the need for surgical intervention in cases of fungal keratitis in contact lens wearers. Lalitha et al.[50] stated that ulcers exceeding 14 mm^2 in size and the presence of hypopyon may be predictors of treatment failure. In infectious keratitis, a large infiltrate at presentation may be related to the patient presenting late, receiving inadequate treatment or not complying with treatment prescribed at another center, resistance of the pathogen to treatment, or the patient's immune status.[43] Although these factors often coexist and the main cause can be difficult to determine, understanding the relationship between infiltrate characteristics and treatment outcome can be important in terms of considering aggressive treatment options in cases presenting with large and central lesions and monitoring these patients more closely.

Study Limitations

Our study data were limited by the retrospective study design and the absence of information on epidemiological factors of fungal keratitis not included in the patients' medical records, such as socioeconomic status, occupation, and rural/urban residence.

Conclusion

Fungal keratitis is an important public health problem in our region, and ocular trauma is a major etiological factor in patients under 40 years of age. In our study, molds were the main pathogens of fungal keratitis in our region, with *Aspergillus* species being predominant. With intensive topical and systemic antifungal treatment and minor surgical interventions when necessary, this challenging infection can be treated without the need for emergency keratoplasty in the majority of cases. In cases presenting with large and central lesions, aggressive treatment options should be preferred and close follow-up is recommended.

Ethics

Ethics Committee Approval: Çukurova University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (date: 3 July 2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y., E.E., İ.İ.H., H.K., A.A., Concept: M.Y., M.İ., İ.İ.H., Design: M.Y., M.İ., İ.İ.H., Data Collection or Processing: N.G., A.İ., H.K., A.A., Analysis or Interpretation: İ.İ.H., E.E., M.Y., M.İ., Literature Search: İ.İ.H., M.İ., Writing: İ.İ.H., E.E., M.Y., M.İ., H.K.

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Original Article

Evaluation of the Clinical Findings of Patients with Penetrating Keratoplasty Followed by Telephone Due to the COVID-19 Pandemic

Semir Yarımada, Özlem Barut Selver, Melis Palamar

Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

Abstract

Objectives: To evaluate changes in the clinical findings of keratoplasty patients who could not be examined face-to-face and were followed up by telephone during the coronavirus disease 2019 (COVID-19) pandemic.

Materials and Methods: Patients with penetrating keratoplasty who presented to the cornea department between March 2020 and February 2021 were grouped according to whether they showed clinical deterioration (Group 1: no deterioration, Group 2: deterioration). The patients' last visit prior to the COVID-19 pandemic and their first visit after the pandemic-related lockdown ended were evaluated. The demographic data, follow-up period, and ophthalmological examination findings of all patients were recorded and the data were compared between the groups.

Results: Thirty-five eyes of 35 patients were included in the study. Signs of deterioration were detected in 8 (22.8%) of the patients (Group 1), while no deterioration was detected in 27 (77.2%) of the patients (Group 2). In the last follow-up visit prior to the COVID-19 pandemic, mean best corrected visual acuity (BCVA) was 1.26±0.43 LogMAR (range: 0.52-1.80) in Group 1 and 1.41±1.02 LogMAR (range: 0-3.1) in Group 2 (p=0.692). Mean BCVA in the first control during the pandemic was 2.07±0.86 LogMAR (range: 1.3-3.1) in Group 1 and 1.49±1.08 LogMAR (range: 0-3.1) in Group 2 (p=0.08). At the first visit during the COVID-19 pandemic, the mean intraocular pressure of Group 1 was 16.38±8.58 mmHg (range: 0-31), and Group 2 was 17.11±3.7 mmHg (range: 11-26) (p=0.984).

Conclusion: The continuation of treatment initiated prior to the pandemic was probably the most important reason why deterioration was not observed in keratoplasty patients. In situations such as pandemics where face-to-face visits with patients may be disrupted, it may be possible to follow the patients safely with telemedicine visits until the difficult circumstances resolve.

Keywords: COVID-19, penetrating keratoplasty, telemedicine

Address for Correspondence: Melis Palamar, Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
E-mail: melispalamar@gmail.com **ORCID-ID:** orcid.org/0000-0002-2494-0131

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by a member of the coronavirus family called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] SARS-CoV-2 first appeared in Wuhan, China in 2019 and spread from person to person.[1] COVID-19 was declared a pandemic by the World Health Organization on March 11, 2020.[2]

The COVID-19 pandemic brought about radical changes in many areas of life, including reshaping patient follow-up.[3] The Centers for Disease Control and Prevention recommended telemedicine instead of face-to-face clinic visits in order to maximize social distancing.[4] Virtual patient visits were reported to increase by 257% to 700% because of the pandemic.[5] In accordance with this recommendation, ophthalmology clinics also triaged patients and scheduled face-to-face examinations only for emergency cases. For patients classified as non-urgent, telemedicine followed up was initiated.[6]

Corneal blindness is the third most common cause of blindness in the world.[7] Corneal transplantation is essential in the treatment of end-stage corneal decompensation and is the most commonly performed tissue transplantation in the world.[8] Because of the avascular structure of the cornea, corneal transplantation has more successful outcomes compared to other organ transplants.[9] During the COVID-19 pandemic, the number of keratoplasty surgeries decreased while emergency surgeries such as tectonic keratoplasty continued to be performed.[10]

This study aimed to evaluate changes in the clinical findings of corneal transplant patients who were unable to have face-to-face visits during the COVID-19 pandemic and were followed up by telephone.

Materials and Methods

Thirty-five eyes of 35 patients who presented to our cornea unit and underwent corneal transplantation between March 2020 and February 2021 were included in the study. The patients' demographic data, follow-up period, and complete ophthalmologic examination findings including best corrected visual acuity (BCVA), intraocular pressure (IOP) measurements, and anterior and posterior segment examinations at their last visit prior to the COVID-19 pandemic and their first in-person visit during the COVID-19 pandemic were recorded. The medications used by the patients and any changes in these medications were noted. Patients were grouped as having clinical deterioration (Group 1) and not having deterioration (Group 2). Clinical deterioration was defined as signs of graft failure or graft rejection and recurrence of keratitis in patients with keratitis etiologies. The patients' treatment and complaints were managed by telephone visits during the interim period when they patients could not attend in-person follow-up visits because of the pandemic.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ege University Ethics Committee (decision number: 21-5T/4).

Statistical Analysis

Statistical analysis was performed using SPSS version 26 (IBM Corp, Armonk, NY, USA) software package. The Wilcoxon test was used to compare data from before and during the pandemic data. The Mann-Whitney U test was used to compare data between the groups with and without clinical deterioration. P values <0.05 were accepted as statistically significant.

Results

Thirty-five eyes of 35 patients, 14 (40%) women and 21 (60%) men, were included in the study. The patients' mean age was 63.40±13.43 years (range: 28-86) and the mean follow-up time was 45.22±51.23 months (range: 5-280). The mean time without follow-up was 5.03±2.20 months (range: 2-11) (Table 1). Twenty-seven (77.1%) of the patients had received their first corneal transplant, 7 (20%) had their second, and 1 (2.9%) had received a third corneal transplant.

The patients' mean BCVA was 1.38±0.92 LogMAR (range: 0-3.1) at last follow-up before the COVID-19 pandemic and 1.62±1.05 LogMAR (range: 0-3.1) at the first visit during the COVID-19 pandemic. There was a statistically significant decrease in BCVA (p=0.009, Wilcoxon test).

Mean IOP values at last follow-up visit before the COVID-19 pandemic and at the first visit during the pandemic were 16.14±3.30 mmHg (range: 8-22) and 16.94±5.07 mmHg (range: 0-31) (p=0.128, Wilcoxon test) (Table 2).

Table 1. Demographic data of the patients included in the study

Sex	**n (%)**
Female	14 (40)
Male	21 (60)
Total	35 (100)
	Mean ± SD (range)
Age (years)	63.40±13.43 (28-86)
Follow-up time (months)	45.22±51.23 (5-280)
Time without follow-up (months)	5.03±2.20 (2-11)

SD: Standard deviation

Table 2. Clinical findings of the patients before and during the pandemic

	Pre-pandemic Mean ± SD (range)	**First visit during pandemic Mean ± SD (range)**	**p value**
BCVA (LogMAR)	1.38±0.92 (0-3.1)	1.62±1.05 (0-3.1)	0.009
IOP (mmHg)	16.14±3.30 (8-22)	16.94±5.07 (0-31)	0.128

BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SD: Standard deviation

Eight (22.8%) of the patients included in the study showed signs of deterioration, while the other 27 (77.2%) were clinically stable. The mean age was 66.25±12.94 years (range: 47-86) in Group 1 and 62.56±13.7 years (range: 28-78) in Group 2. There was no significant age difference between the groups (p=0.798, Mann-Whitney U test). Patients in Group 1 went without follow-up for a mean of 5.76±2.3 months (range: 4-11), while those in Group 2 went without follow-up for 4.81±2.16 months (range: 2-11). The time without follow-up was similar in both groups (p=0.08, Mann-Whitney U test). The mean time since corneal transplantation was 49.75±36.77 months (range: 1-131) in Group 1 and 36.77±54.57 months (range: 0-274) in Group 2 (p=0.265, Mann-Whitney U test). BCVA at last follow-up before the COVID-19 pandemic was 1.26±0.43 LogMAR (range: 0.52-1.80) in Group 1 and 1.41±1.02 LogMAR (range: 0-3.1) in Group 2 (p=0.692, Mann-Whitney U test). BCVA at first follow-up during the COVID-19 pandemic was 2.07±0.86 LogMAR (range: 1.3-3.1) in Group 1 and 1.49±1.08 LogMAR (range: 0-3.1) in Group 2 (p=0.08, Mann-Whitney U test). The mean IOP before the COVID-19 pandemic was 17.13±1.55 mmHg (range: 14-19) Group 1 and 15.85±3.64 mmHg (range: 8-22) in Group 2 (p=0.312, Mann-Whitney U test). During the COVID-19 pandemic, the mean IOP values in Group 1 and Group 2 were 16.38±8.58 mmHg (range: 0-31) and 17.11±3.7 mmHg (range: 11-26), respectively (p=0.984, Mann-Whitney U test) (Table 3).

In Group 1, there was a significantly decrease in BCVA during the pandemic compared to pre-pandemic values (p=0.027, Wilcoxon test). BCVA in Group 2 did not show a significant decrease during the pandemic (p=0.309, Wilcoxon test).

No significant change in pre-pandemic IOP was observed during the pandemic in Group 1 (p=0.931, Wilcoxon test) or Group 2 (p=0.055, Wilcoxon test).

In Group 1, 5 patients had graft failure, 2 had loosening of sutures, and 1 had recurrence of herpes.

The most common causes of corneal transplantation in the patients included in the study were pseudophakic bullous keratopathy (n=13), herpetic keratitis (n=7), keratoconus (n=4), and perforated corneal ulcer (n=3). Indications for keratoplasty in Group 1 were herpetic keratitis (n=4), keratoconus (n=1), pseudophakic bullous keratopathy (n=1), perforated corneal ulcer (n=1), and gelatinous drop-like dystrophy (n=1).

Corneal sutures were still present in 54.3% (n=19) of the patients, while 45.7% (n=16) of the patients no longer had corneal sutures. There was no statistically significant relationship between suture presence and clinical deterioration (p=0.782, chi-square test).

At the last follow-up visit before the COVID-19 pandemic, all patients used artificial tears, 88.5% used topical cyclosporine, 34.2% (n=12) used topical dexamethasone, 34.2% (n=12) used topical fluorometholone, and 20% (n=7) used loteprednol. Of the patients who could not come for in-person follow-up due to the pandemic, 91.4% (n=32) continued the same treatment, 2 patients were switched from topical dexamethasone to topical fluorometholone at other centers, and 1 patient used dexamethasone instead of fluorometholone.

The most common ocular comorbidities were herpetic keratitis (50%, n=4) and glaucoma (37.5%, n=3) in Group 1 and glaucoma (55.5%, n=15) and herpetic keratitis (11.1%, n=3) in Group 2. None of the patients in Group 1 had systemic disease, while 3.7% (n=1) of the patients in Group 2 had hypertension and 3.7% (n=1) had diabetes mellitus.

Discussion

In this study we analyzed changes in the clinical findings of penetrating keratoplasty patients who had telephone follow-up

Table 3. Comparison of clinical findings in patients with clinical deterioration (Group 1) and without clinical deterioration (Group 2)

	Group 1 Mean ± SD (range)	Group 2 Mean ± SD (range)	p value
Age (years)	66.25±12.94 (47-86)	62.56±13.7 (28-78)	0.798
Time without follow-up (months)	5.76±2.3 (4-11)	4.81±2.16 (2-11)	0.08
Time since corneal transplantation (months)	49.75±36.77 (1-131)	36.77±54.57 (0-274)	0.265
BCVA before pandemic (LogMAR)	1.26±0.43 (0.52-1.80)	1.41±1.02 (0-3.1)	0.692
BCVA at first visit during pandemic (LogMAR)	2.07±0.86 (1.3-3.1)	1.49±1.08 (0-3.1)	0.080
IOP before pandemic (mmHg)	17.13±1.55 (14-19)	15.85±3.64 (8-22)	0.312
IOP at first visit during pandemic (mmHg)	16.38±8.58 (0-31)	17.11±3.7 (11-26)	0.984

BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SD: Standard deviation

instead of face-to-face visits because of the COVID-19 pandemic, and we found no clinical deterioration except for a statistically significant decrease in BCVA. When the patients were grouped according to whether or not they showed clinical deterioration, there were no significant differences in ophthalmological findings between the groups.

The indication for penetrating keratoplasty is an important factor affecting post-keratoplasty graft survival. Keratoconus and pseudophakic bullous keratopathy are the pathologies with the best prognosis for keratoplasty.[11,12,13] Approximately half (48.5%) of the cases in our study were keratoconus and pseudophakic bullous keratopathy, which we believe is one of the reasons the patients' prognosis was not markedly affected by pandemic-related disruptions in follow-up examinations.

Nearly all (91.4%) of the patients continued medical treatment as initiated before the pandemic. We consider this to be the main factor contributing to the low rate of clinical deterioration despite the interruption in face-to-face visits. In addition, the use of topical cyclosporine or steroids by most patients reduces the likelihood of graft rejection by reducing inflammation. This is supported by studies showing that inflammation is an important risk factor for graft rejection.[14,15]

Of the patients included in the study, 22.9% had a history of recurrent keratoplasty. In their study including 377 patients, Yu et al.[16] reported that repeated penetrating keratoplasty was an important risk factor for graft failure. Consistent with their findings, the low percentage of patients with recurrent keratoplasty in our study may also be a reason for the low rate of deterioration.

The long time since corneal transplantation in the groups with and without deterioration (mean, 49.75 and 36.77 months, respectively) and the fact that these patients were clinically stable during this period significantly reduced the likelihood that their condition would deteriorate. In addition, the short time without face-to-face follow-up (mean, 5.76 and 4.81 months for Groups 1 and 2, respectively) is likely responsible for the low rate of deterioration and comparable outcomes in the groups.

When all patients in the study were analyzed together, we observed a significant decrease in BCVA during the pandemic compared with pre-pandemic BCVA values. However, when the patients were grouped according to whether they showed deterioration, there was no significant difference between BCVA values before and during the pandemic. This may be a result of the decrease in BCVA in the group without deterioration, which could be related to ophthalmological problems unrelated to corneal transplantation, such as the development of cataract in phakic patients and posterior capsular opacification in pseudophakic patients.

The presence of corneal sutures triggers inflammation and is an important risk factor for neovascularization.[17] Although sutures were present in over half of our patients (54.3%), there was no relationship between the presence of sutures and clinical deterioration. This can be attributed to the regular continuation of anti-inflammatory therapy.

Conclusion

The implementation of movement restrictions and the potentially fatal prognosis of COVID-19 resulted in dramatic reductions in admissions to health institutions. This in turn led to disruptions in patient follow-up. As in many surgical interventions, postoperative follow-up after corneal transplantation is important. The main reason the patients in our study did not exhibit deterioration was that they continued their treatment after their last face-to-face examination. Emphasizing this during phone visits with patients also played an important role. In situations such as pandemics where face-to-face visits with patients may be disrupted, it may be possible to follow up patients safely with telemedicine visits until the unfavorable circumstances are resolved.

Ethics

Ethics Committee Approval: Ege University Medical Research Ethics Committee (decision no: 21-5T/4, date: 06.05.2021).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.P., Design: M.P., Data Collection or Processing: S.Y., Ö.B.S., Analysis or Interpretation: S.Y., Ö.B.S., M.P., Literature Search: S.Y., Writing: S.Y., Ö.B.S., M.P.

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Original Article

Impact of COVID-19-Related Lockdown on Glaucoma Patients

Mine Esen Barış, Mukaddes Damla Çiftçi, Suzan Güven Yılmaz, Halil Ateş

Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

Abstract

Objectives: To analyze emergency and outpatient admissions by glaucoma patients during complete lockdown due to coronavirus disease 2019 (COVID-19) to assess the effect of pandemic-related complete lockdown on glaucoma patients.

Materials and Methods: This retrospective chart review included all glaucoma patients who were either examined and/or underwent emergency surgery between March 11, 2020 and May 31, 2020, a period of complete COVID-19-related lockdown in Turkey. The data were compared with data from patients seen during the same time period in 2019. Visual acuity and intraocular pressure data from patients examined after the lifting of the lockdown were also evaluated.

Results: According to Turkish Ministry of Health guidelines, only emergency examinations and surgeries could be performed during the 82 days of the COVID-19 lockdown. During this period, a total of 11 eyes of 10 patients were operated and 123 patients were examined in the outpatient clinic. During the same period in 2019, 122 surgeries were performed, 39 of which were emergencies. In the first 4 weeks after the lockdown ended, 163 patients were examined at the outpatient clinic and marked visual loss was detected in 10 eyes of 9 (5.5%) patients who did not attend follow-up visits due to the pandemic.

Conclusion: During the lockdown, emergency surgeries related to glaucoma decreased by 71.7% and marked visual loss was detected in 5.5% of the patients examined after the lockdown. These findings suggest that some patients were unable to present to clinics despite needing emergency care.

Keywords: COVID-19, glaucoma, glaucoma treatment

Address for Correspondence: Mine Esen Barış, Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
E-mail: mine.baris@yahoo.com **ORCID-ID:** orcid.org/0000-0003-1341-6737
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Introduction

Lockdowns imposed because of the coronavirus disease 2019 (COVID-19) pandemic limited the care received by patients for many medical conditions. Governments, public health agencies, and health care professionals have evaluated methods to provide health care to all patients with non-COVID-19 diseases while simultaneously battling the pandemic itself. For glaucoma in particular, telemedicine practices were already in use prior to the outbreak because they offer patients easier access to glaucoma specialists. However, when the lockdown and movement restrictions started at the beginning of March 2020, both patients and glaucoma specialists, along with many other health care professionals, were caught unprepared for the drastic changes in circumstances.

To have a better understanding of the effect of the lockdown on glaucoma patients and thereby find feasible solutions for the problem, we reviewed the surgeries performed and outpatient visits in our glaucoma department during the 3-month COVID-19-related lockdown and compared the results with the same period in the previous year. We also analyzed data from patients who were examined in the first month after the end of the lockdown.

Materials and Methods

A retrospective chart review was performed in the glaucoma department of the Ege University Hospital Ophthalmology Clinic. All outpatient treatments and surgeries carried out between March 11 and May 31, 2020 were analyzed. These dates were chosen based on the days of movement restriction determined by the government and Ministry of Health of the Republic of Turkey. The number of surgeries performed, the mean age of surgical patients, the preoperative intraocular pressure (IOP) and best-corrected visual acuity (BCVA) of the operated eyes, and the number and mean age of outpatients during this period were compared with data from the corresponding period in 2019. Additionally, all outpatient treatments and surgeries carried out in the first month after the lockdown ended (June 1-30, 2020) were analyzed.

Primary outcome measures were the number of emergency operations in the lockdown period vs. the previous year and the number of outpatient examinations during lockdown. Secondary outcomes were the number of emergency surgeries and outpatient examinations in the first month after the lockdown and the number of eyes that had significant visual loss due to restrictions.

During the lockdown period, only emergency surgeries were performed and only patients with acute complaints were examined. The definition of emergency surgery was not changed compared to the pre-pandemic definition. Therefore, eyes in which target IOP could not be reached with medical or laser treatment and eyes with severe optic disc damage and high IOP at the first visit were considered eligible for emergency surgery. All appointments for non-emergency examinations were cancelled. At the glaucoma department where this study was carried out, patients with advanced glaucoma with poor/borderline control of IOP, monocularity with severe optic disc damage in the only seeing eye, and history of intraocular surgery in the past month were classified as emergent cases and their appointments were not cancelled.

On June 1, 2020, when the official lockdown period ended in Turkey and the restrictions were eased, a return to the pre-pandemic order with precautions against disease spread was suggested. In our glaucoma department, emergency surgeries resumed and outpatient appointments were scheduled with 30-minute intervals between patients. Due to such time limitations, a triage system was needed to prioritize patients with end-stage and advanced glaucoma, patients with vision in only one eye, and patients with the lowest BCVA. BCVA was evaluated with Snellen chart and converted to logMAR. IOP measurements were obtained by Goldmann applanation tonometry (GAT). For disinfection of the GAT tips, 70% isopropyl alcohol was preferred as a protective measure against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). All precautions were taken to protect both patients and staff from infection, as recommended.[1]

The study was approved by the Institutional Ethics Review Board of Ege University, Turkey, and conducted in agreement with the tenets of the Helsinki Declaration. Each participant signed a written informed consent form for the use of their medical data.

Statistical Analysis

SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Chi-square test and Mann-Whitney U test were used to compare variables between the groups, and $p \leq 0.05$ was considered to be statistically significant.

Results

During the lockdown period, 11 eyes of 10 patients (5 [50%] female, 5 [50%] male) met the criteria for emergency surgery and were operated. The clinical features of the eyes and the surgeries performed are presented in Table 1.

During the same period of 2019 (March 11-May 31), 122 eyes of 99 patients (37 [37.4%] female and 62 [62.6%] male) were operated. The mean age of the patients was 59.02±24.01 years (range: 15 days-90 years), mean BCVA was 0.66±0.96 logMAR (range: 0-3), mean preoperative IOP was 27.04±10.5 mmHg (range: 2-54), and mean cup-to-disc ratio was 0.64±2.3 (range: 0.2-1). Data from 2019 indicated that general anesthesia was used in 34 surgeries (27.9%) and local anesthesia was used in 88 surgeries (72.1%). Of the 122 eyes operated in the 2019 period, 39 eyes (31.9%) of 33 patients (12 [36.4%] female and 21 [63.6%] male) required urgent intervention. The mean age, mean IOP, mean BCVA, and type of anesthesia used in the emergency surgeries performed during the 2020 lockdown and the same period in 2019 are summarized in Table 2.

The number of emergency surgeries during the lockdown was decreased by 71.7% compared to the same time period in 2019. The ratio of patients operated under general anesthesia/

local anesthesia during lockdown was significantly higher than in the corresponding period of 2019 and after the lockdown was lifted in 2020 (p=0.05). The types of surgery performed and the number of eyes operated in each time period are summarized in Table 3.

A total of 123 patients were examined in the outpatient glaucoma clinic during the lockdown. All of them were examined either because of acute-onset symptoms or because their conditions were considered emergent and their appointments were not cancelled. In the first 4 weeks after the end of the

Table 1. Clinical features of operated eyes and types of surgeries performed during lockdown period

Eye no.	Age/gender	Diagnosis	Preop BCVA (logMAR)	Preop IOP (mmHg)	Indication for surgery	Anesthesia	Surgery
1	91/F	Phacolytic glaucoma	2.8	32	High IOP	Local	Phaco-IOL
2	81/M	Absolute glaucoma	3	50	Severe pain	General	Evisceration
3	50/M	Neovascular glaucoma	1.8	62	High IOP	Local	Cyclodestruction
4	10/M	Uveitic glaucoma with mature cataract	2.8	17	Very low BCVA in only seeing eye	General	Phaco-IOL
5	10/M	Uveitic glaucoma with bleb failure	2.3	27	High IOP	General	Bleb needling
6	54/M	Glaucoma after keratoplasty	1.3	29	High IOP	General	Cyclodestruction
7	53/F	Uveitic glaucoma with IOL dislocation	1.3	12	Endothelial decompensation	Local	IOL repositioning
8	90/F	Phacomorphic glaucoma	2.8	30	High IOP	General	Phaco-IOL
9	46/M	Glaucoma after keratoplasty	2.8	39	High IOP	Local	Cyclodestruction
10	44/F	Angle closure glaucoma with bleb failure	0	36	High IOP	Local	Bleb needling
11	46/F	Primary angle-closure glaucoma	0.1	28	Acute increase in IOP	Topical	Laser iridotomy

F: Female, M: Male, Preop: Preoperative, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, Phaco-IOL: Phacoemulsification and intraocular lens implantation, F: Female, M: Male

Table 2. Mean age, preoperative IOP, preoperative BCVA, and type of anesthesia used for emergency surgeries performed during the lockdown period in 2020 and the corresponding period in 2019

	During lockdown (11 March-31 May 2020)	Previous year (11 March-31 May 2019)	P value
Age, years; mean ± SD (range)	52.27±26.0 (10-91)	44.36±7 (0.04-84)	0.9*
Preoperative IOP, mmHg; mean ± SD (range)	32.9±13.3 (17-62)	29.24±10.49 (6-54)	0.5*
Preoperative BCVA, logMAR; mean ± SD (range)	1.42±1.05 (3-0)	1.14±1.08 (2.8-0)	0.09*
Preoperative c/d; mean ± SD (range)	0.89±0.16 (0.5-1)	0.83±0.20 (0.3-1)	0.47*
Anesthesia (n, %) General Local	 5 (45.4) 6 (54.6)	 14 (34.15) 27 (65.85)	0.05**

BCVA: Best corrected visual acuity; c/d: Cup-to-disc ratio, IOP: Intraocular pressure, SD: Standard deviation, *Mann-Whitney U test, **Chi-square test

Table 3. Types and numbers of emergency surgeries performed during the lockdown of 2020 and the corresponding period in 2019

Surgery type	During lockdown (11 March-31 May 2020)	Previous year (11 March-31 May 2019)
Phaco-IOL implantation	3	6
Trabeculectomy	0	9
Deep sclerectomy	0	0
Cyclodestruction	3	5
Bleb needling	2	3
Trabeculectomy + phaco-IOL	0	2
IOL repositioning	1	0
Drainage device revision	0	3
AC irrigation	0	2
Pupilloplasty	0	1
Laser iridotomy	1	8
Evisceration	1	0
Total	11	39

Phaco: Phacoemulsification, IOL: Intraocular lens, AC: Anterior chamber

lockdown, 163 outpatients were seen, of whom 12 patients (7.36%) required urgent surgery (14 eyes in total). The mean age of the operated patients was 52.8±15.7 years (range: 21-76), the mean preoperative IOP was 30.4±10.9 mmHg (range: 16-60), and the mean preoperative BCVA was 1.71±1.07 logMAR (range: 2.8-0.0). Three (21.4%) of these eyes were operated under general anesthesia, while local anesthesia was used in 11 eyes (78.6%).

During this period, we observed that 10 eyes of 9 patients (5.5%) with advanced glaucoma had a marked loss of vision (at least 2 logMAR lines decrease) since their last visit. All of these patients were diagnosed with open-angle glaucoma. The mean age of these patients was 56.1±22.8 years (range: 18-76). Their mean BCVA was significantly decreased from 0.78±0.34 logMAR at the pre-lockdown visit to 2.09±0.62 logMAR at the post-lockdown visit. Additionally, the mean IOP of the patients was markedly increased from 20.5±5.3 mmHg pre-lockdown to 28.1±7.2 mmHg post-lockdown. Seven eyes (70%) of 6 patients had progressed to absolute glaucoma (all had BCVA ≤2.1 logMAR). Of these patients, 4 had an appointment for examination and 2 were scheduled for surgery during the lockdown period. All 6 patients failed to attend their appointments, either because they were afraid to come to the hospital due to the risk of COVID-19 infection or were of advanced age (2 patients were over 70 years old). The older patients were living alone and needed assistance from their family to reach the hospital, but these family members had deemed it too risky to take the patients to the hospital. During the lockdown, one patient progressed to absolute glaucoma in both eyes and suffered from a delirium-like condition, while 3 patients suffered a loss of vision in their only seeing eye. The 3 patients whose appointments were rescheduled to after the lockdown experienced symptoms such as decreased vision and ocular pain during the lockdown but opted to wait for their appointments and not leave the house for a non-life-threatening condition. One of these patients lost most of her visual field in her only seeing eye, with only the central 5 degrees or less remaining, although the BCVA (0.7 logMAR) remained unchanged.

Discussion

The ongoing COVID-19 pandemic continues to severely limit the medical care that patients can receive for chronic diseases. Among ophthalmology patients, we observed that glaucoma patients required emergency care the most since the start of the pandemic. Du et al.[2] also reported in their letter that glaucoma surgeries were the most commonly performed ophthalmic surgeries during the outbreak in Wuhan city.

In the current study, we observed that the number of emergency glaucoma surgeries conducted during the COVID-19 lockdown was significantly lower than the number of emergency surgeries performed in the same time period in 2019, but was similar to the number of surgeries performed after the end of the lockdown. The reason for this is probably a reduction in routine examinations and the hesitation of the patients to travel to the hospital. Preoperative BCVA and preoperative IOP did not differ significantly between the lockdown in 2020 and the same period in 2019 or the first month after the lockdown was lifted. This was predictable because the criteria for emergency operations remained unchanged. The criteria for emergency surgeries were also consistent with the guidelines of the American Academy of Ophthalmology.[3]

Even though local anesthesia was used as often as possible since the start of the COVID-19 outbreak, the percentage of patients who were operated under general anesthesia during the lockdown was significantly higher than in the previous year or after the lockdown was lifted. A closer look at each patient who

was operated under general anesthesia during the lockdown showed that 2 eyes belonged to a pediatric patient, 1 patient underwent evisceration, 1 patient had dementia, and 1 patient had panic disorder. Although the exact reason for such a high number of uncooperative patients during lockdown remains unclear, the most likely explanation is that their compliance to medical treatment was poor, especially in terms of self-administrating eye drops. The IOP values in these eyes were thus worse and the need for surgery was urgent.

The fact that some patients had reduced visual acuity during the lockdown compared to pre-lockdown period was not surprising. However, the real surprise was the common features of the eyes that presented with a decrease in vision. Eyes with poorly monitored IOP and severe optic disc damage were expected to show decreased vision. Anticipating this, these patients were followed-up closely and were examined in regular visits with treatment updates when necessary. Patients who had red/painful eyes or a sudden decrease in vision also presented to the glaucoma clinic and received the necessary medical care. However, the eyes that had moderate to advanced glaucoma with well- to borderline-controlled IOP deteriorated the most during the lockdown period. These patients were not prioritized in our triage system, and the patients themselves were not that anxious to have their IOP monitored. Additionally, half of the patients who lost their vision during the lockdown period had open-angle (primary or exfoliation) glaucoma. Because of the insidious nature of open-angle glaucoma, the patients did not seek medical care until they suffered from acute symptoms. IOP started to increase in these eyes and the optic disc was already damaged by the time the patient felt the need to consult their ophthalmologist.

Ophthalmologists have always emphasized the importance of making regular visits to glaucoma specialists easier for glaucoma patients.[4] Telemedicine has long been a focus of these discussions. This pandemic brought attention to the need to improve every aspect of care for glaucoma patients.[5] The current study revealed the shortcomings of our triage system. Nonetheless, all glaucoma patients in our system were called and advised to seek medical care in the event of acute ocular symptoms or concerns regarding their treatment, even during the lockdown. The lower number of emergency surgeries since the start of the pandemic and the fact that some people suffered a loss of vision during the lockdown period suggest that some patients who required emergency intervention simply did not seek medical care. Regardless of whether this is due to a defect in our triage system or patients' anxiety about potential exposure to COVID-19, solving this problem should be a priority.

Conclusion

In our opinion, telemedicine in its current state is inadequate for emergent conditions during a pandemic. Routine examination by family practitioners or local ophthalmology clinics during the pandemic may still be deemed risky for vulnerable patients, and these doctors are already highly overworked because of the pandemic. A report by Husain et al.[6] described the presence of local investigation units in Singapore which are located within the community and are staffed by technicians. While this is an attractive option for some countries, most countries do not have enough staff to for such units. Patients may still hesitate to attend their appointments in these local clinics. Additionally, the results of our study indicate that the patients who are at the highest risk of loss of vision still need to consult a glaucoma specialist. A triage system that will cover every patient and not miss any potential vision loss is difficult to create and requires time and experience to ensure that mistakes are not made. Bommakanti et al.[7] suggested a triage system in which the patients' glaucoma severity-progression risk score and COVID-19 morbidity risk score are calculated. While this scaling system seems reasonable and feasible, additional research is needed to determine whether it will lead to better clinical outcomes and patient adherence. It seems like a combination of telemedicine, a strong triage system, and educating the patients about their disease might provide the best outcomes in terms of reduced progression of glaucoma, less spread of disease, and minimum loss of vision.

Ethics

Ethics Committee Approval: Ege University Medical Research Ethics Committee (decision no: 20-10.1T/25 date: 15.10.2020).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: S.G.Y., H.A., Concept: M.E.B., Design: M.E.B., Data Collection or Processing: M.D.Ç., Analysis or Interpretation: S.G.Y., M.E.B., Literature Search: M.D.Ç., M.E.B., Writing: M.E.B.

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Original Article

How to Manage a Strabismus Clinic During the COVID-19 Pandemic; What is Really Urgent, What is Not?: A Single-Center Case Series from Turkey

Demet Yabanoğlu, Hande Taylan Şekeroğlu

Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

Objectives: To evaluate the management of the pediatric ophthalmology and strabismus clinic when strict quarantine conditions were adopted during the coronavirus disease 2019 (COVID-19) pandemic in Turkey.

Materials and Methods: The study presents a review of the patients examined during the quarantine period. All patients were assessed with the highest possible level of personal protection.

Results: Ten patients (6 girls, 4 boys) with a mean age of 9 years (range: 2-16) were evaluated. The patients presented 3-20 days after symptom onset. Ocular misalignment and diplopia were the main symptoms. Four of the 10 patients were diagnosed with sixth cranial nerve palsy and three patients were diagnosed with acute-onset comitant esotropia. Six patients had significant cranial magnetic resonance imaging findings.

Conclusion: Acute-onset neurological conditions are more common during the COVID-19 pandemic. These reports will contribute to global experience and understanding of COVID-19.

Keywords: COVID-19, acute-onset strabismus, neuro-ophthalmology

Address for Correspondence: Demet Yabanoğlu, Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: demet.aban@hacettepe.edu.tr **ORCID-ID:** orcid.org/0000-0003-4532-3543

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Introduction

No one predicted that the world would face an outbreak of such magnitude when the first cases of coronavirus disease 2019 (COVID-19) were reported in Wuhan, China.[1,2] The World Health Organization announced on 11 March 2020 that COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was a pandemic[3] and later identified several SARS-CoV-2 variants of concern (alpha, beta, gamma, delta, and omicron). Three criteria are required for a disease to be declared a pandemic. First, the disease must be caused by a factor that society has not previously been exposed to. Second, this factor should be easily transmitted to humans and easily spread from person to person. Third, it must cause serious illness.[4,5]

Beginning in China, the number of COVID-19 cases steadily increased and spread rapidly to other countries, causing infections all around the world, including in Turkey.[6,7,8,9,10,11] According to current statistics, there have been 9,300,000 confirmed cases and 81,000 deaths in Turkey.[6] As in other countries, sweeping measures were taken in Turkey to control the outbreak.[5] Triage practices were introduced in hospitals. Fever assessment and symptom questioning were conducted at hospital entrances and any background of suspicious and international contact investigated. These precautions taken in Turkey and the rest of the world aimed to prevent uncontrolled spread, reduce morbidity and mortality, and thus reduce overcrowding in hospitals. In the ophthalmology department, only emergency cases were assessed. The pediatric ophthalmology and strabismus clinic was one of the departments in which ophthalmological emergencies were most frequently assessed during this period. The purpose of the present study was to evaluate patient management during the COVID-19 pandemic in the pediatric ophthalmology and strabismus clinic, to present and discuss the cases evaluated, and to share our center's experience of the fight against the pandemic with ophthalmologists around the world who deal with strabismus.

Materials and Methods

The present study provides an analysis of patients examined in the Faculty of Medicine of Hacettepe University Pediatric Ophthalmology and Strabismus Unit early in the COVID-19 pandemic. This retrospective study was conducted according to the Declaration of Helsinki and was approved by Hacettepe University Faculty of Medicine Ethics Committee (decision number: 2020/14-36). Informed consent was obtained from the legal guardians of the patients. All patients who were admitted to the clinic underwent a complete ophthalmological and orthoptic evaluation, including dynamic and static retinoscopy, best corrected visual acuity, anterior and posterior segment examination, prism cover test, and ocular motility evaluation, performed with maximum personal protective measures.

Results

Ten patients (6 girls, 4 boys) with a mean age of 9 years (range: 2-16) presented between 13 March 2020 and 1 June 2020, when strict quarantine conditions were being applied in Turkey. They presented within 3-20 days of symptom onset. The leading symptoms were ocular misalignment and diplopia. The cases are summarized below and detailed clinical information is given in Table 1.

Case 1

A 4-year-old boy was admitted to the emergency department for inward deviation of the right eye. His medical history was significant in that he had undergone surgical excision, chemotherapy, and radiation therapy for an atypical teratoid rhabdoid tumor detected at the C5-7 level 3 years previously. The patient had 40 prism diopters (PD) of esotropia. Abduction of the right eye was -4 limited. The patient also had papilledema. Cranial and spinal magnetic resonance imaging (MRI) performed for right sixth nerve palsy revealed leptomeningeal metastases.

Case 2

A 16-year-old girl with complaints of dizziness and diplopia for 20 days was referred to the strabismus unit by the emergency department. The patient reported no systemic condition. She exhibited right head tilt and was diplopic on left gaze and down gaze. Best corrected visual acuity was 20/20 in both eyes. She had horizontal nystagmus that increased in amplitude on left gaze. She had 5 PD left hypertropia and 10 PD left esotropia. The anterior segment structures appeared normal on slit-lamp examination. The temporal quadrant of the left optic disc was pale. Active multiple demyelinating plaques were detected in the infra- and supratentorial regions by cranial MRI. The patient was diagnosed with left third and fourth nerve palsy. She was subsequently diagnosed with multiple sclerosis.

Case 3

A 12-year-old girl was referred to the strabismus unit because of diplopia lasting 20 days. Best corrected visual acuity was 20/20 in both eyes. She had 14 PD left esotropia. Abduction was limited bilaterally. Anterior and posterior segment structures were all normal. MRI revealed an increase in density in the calvarial bones suggesting leukemic infiltration. Fortunately, no pathology was found in the bone marrow biopsy. Bilateral herniation of the cerebellar tonsils and swelling of the upper pituitary surface were interpreted as intracranial hypotension. The patient was diagnosed with bilateral sixth cranial nerve palsy and was followed up frequently by the pediatric neurology department.

Case 4

A 3-year-old boy was referred to the strabismus clinic for diplopia and left eye crossing for 7 days. Visual acuity was 20/32 bilaterally. He had 25 PD left esotropia. Ocular motility was normal. Cranial MRI revealed a minimal increase in the perioptic cerebrospinal fluid distance in both eyes. However, fundus examination and neurological assessment were normal. The patient was diagnosed with acute-onset comitant esotropia and underwent full correction of the refractive error, despite having mild hyperopia.

Table 1. Clinical characteristics of the patients admitted/referred to the strabismus unit during COVID-19 pandemic

Patient no.	Age (years)	Gender	Initial complaint	Diagnosis	MRI	Etiology	Treatment
1	4	M	Ocular deviation	Right sixth CN palsy; papilledema	Leptomeningeal metastases	Atypical teratoid rhabdoid tumor	Chemo-radiation therapy
2	16	F	Double vision	Left fourth CN palsy	Supratentorial demyelinating plaques	Multiple sclerosis	Interferon beta 1a
3	12	F	Double vision	Bilateral sixth CN palsy	Herniation of the cerebellar tonsils, swelling of the upper pituitary surface	Intracranial hypotension	Follow-up
4	3	M	Ocular deviation	Acquired comitant esotropia	Increased perioptic cerebrospinal fluid distance	N/A	Follow-up
5	2	F	Ocular deviation	Acquired accommodative esotropia	Normal	Post-viral	Refraction
6	15	F	Double vision	Acquired comitant esotropia	Normal	N/A	Prism
7	3	M	Ocular deviation	Bilateral sixth CN palsy	Normal	Mycoplasma infection	Refraction
8	10	F	Ocular deviation and droopy eyelid	Left third CN palsy	Paramedian- mesencephalic infarction	Behçet's disease	Immunosuppressive therapy
9	10	F	Double vision	Bilateral sixth CN palsy; papilledema	Normal	Pseudotumor cerebri	Lumbar puncture, oral carbonic anhydrase inhibitors
10	15	M	Double vision	Right third and fourth CN palsy	Mesencephalic and pontine infarction	Neuro-Behçet's disease	Immunosuppressive therapy

M: Male, F: Female, CN: Cranial nerve, MRI: Magnetic resonance imaging, N/A: Not available

Case 5

A 2-year-old girl was assessed in the strabismus clinic due to ocular deviation lasting 3 days. She had a previous history of respiratory system infection 3 months before. Fixation preference was grade 4 and she had 30 PD right esotropia. Dynamic retinoscopy revealed no accommodative response in either eye. Ocular motility was normal bilaterally. The anterior and posterior segments were normal. Refraction errors in the right and left eyes were +4.75 and +5.00 diopters (D), respectively. Neurological examination and MRI were normal. The patient was diagnosed with acute-onset accommodative esotropia and underwent full refractive correction.

Case 6

A 15-year-old girl with double vision for 8 months was evaluated. Visual acuity was 20/20 with -1.00 D refractive correction. She had 10 PD left esotropia with a fixation preference of grade 1. Abduction was -0.5 limited in both eyes. Neurological evaluation and MRI were normal. The patient was diagnosed with acute comitant esotropia and prismatic glasses were prescribed.

Case 7

A 3-year-old boy complaining of double vision was diagnosed with bilateral sixth nerve palsy. He had 30 PD left esotropia with a fixation preference of grade 1 and -0.5 abduction limitation bilaterally. Neurological examination and imaging were completely normal. The only significant finding was positive immunoglobulin M for mycoplasma. The patient was followed up in the pediatric infection department.

Case 8

A 10-year-old girl with left eye ptosis, diplopia, and ataxic gait was transferred from the emergency department to the strabismus outpatient clinic. The patient had no documented systemic condition. She exhibited right head tilt. Margin reflex distance was 5 mm and 3 mm and best corrected visual acuity was 20/25 and 20/32 in the right and left eyes, respectively. She had 14 PD left hypotropia and 8 PD left exotropia. All ocular movements were -4 limited except abduction (Figure 1). Her pupils were anisocoric and the direct light reflex was weak in the left eye. Fundus examination was normal. The patient was diagnosed with left cranial third nerve palsy and MRI revealed an acute infarction in the left paramedian of the mesencephalon. Incomplete Behçet's disease was suspected.

Case 9

A 10-year-old girl with precocious puberty presented to the emergency department due to double vision lasting 10 days.

The patient exhibited a 20° face turn to the left and had 25 PD left esotropia. Ocular movements were -2 limited in abduction bilaterally. Dilated examination of the fundus revealed stage 3 papilledema. The patient had bilateral sixth cranial nerve palsy. She was diagnosed with pseudotumor cerebri following a detailed neurological examination.

Case 10

A 15-year-old previously healthy adolescent boy was referred from the emergency department to the outpatient strabismus clinic with a 10-day history of diplopia, loss of balance, nausea, and numbness in the mouth. Best corrected visual acuity was 20/20 in both eyes. He had 30 PD right exotropia and 20 PD hypertropia. With the exception of abduction and depression, all eye movements were -4 limited (Figure 2). He was diplopic in all quadrants except left and down gaze. No convergence was observed in the right eye. The pupils were anisocoric. Relative afferent pupillary defect was observed in the right eye. The structures of the anterior segment and the fundus were normal. The patient had right cranial third and fourth nerve palsy and MRI showed acute mesencephalon and pons infarction. Neuro-Behçet's disease was suspected in the etiology of the patient's central nervous system vasculitis.

Discussion

The major dilemma during the COVID-19 outbreak was whether going to the hospital or staying at home would be better for people's well-being. During the quarantine period, many people with pre-existing conditions requiring follow-up sought ways to manage their conditions without going to hospitals.[12] The most popular of these solutions was self-examination and communication via teleconference with the physician.[13] This approach was adopted in particular by the high-risk group older than 65 years of age and having multiple chronic diseases. However, there are problems that cannot be adequately addressed without going to the hospital. The sudden onset of heterotropia or diplopia is among these conditions. Sudden-onset heterotropia and diplopia is a serious condition that frightens patients and their relatives cosmetically and concerns ophthalmologists etiologically.

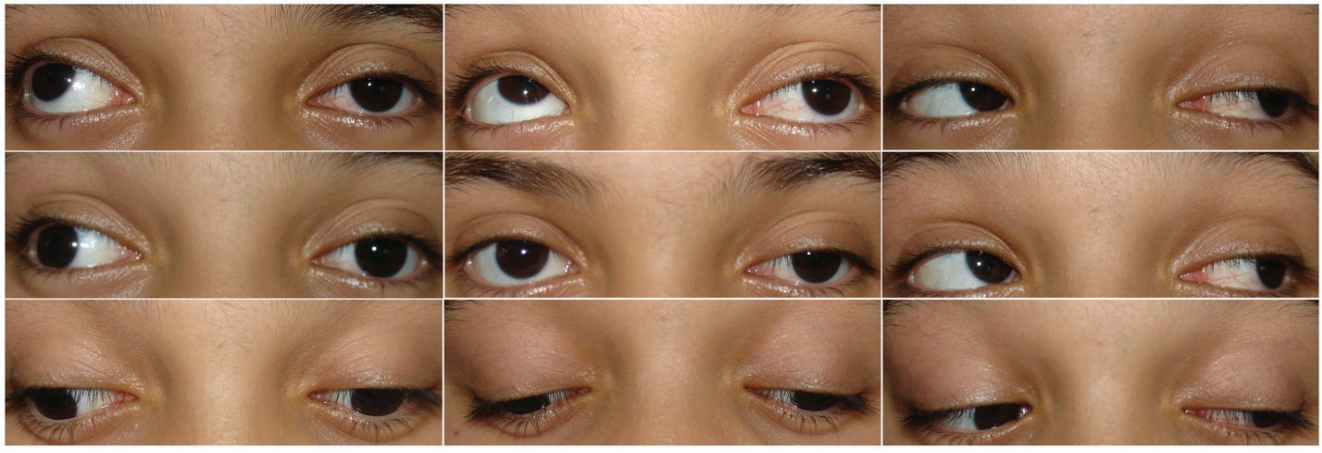

Figure 1. Nine diagnostic gaze positions of patient 8. Left hypotropia and exotropia in primary position. All ocular movements were -4 limited except abduction in the left eye

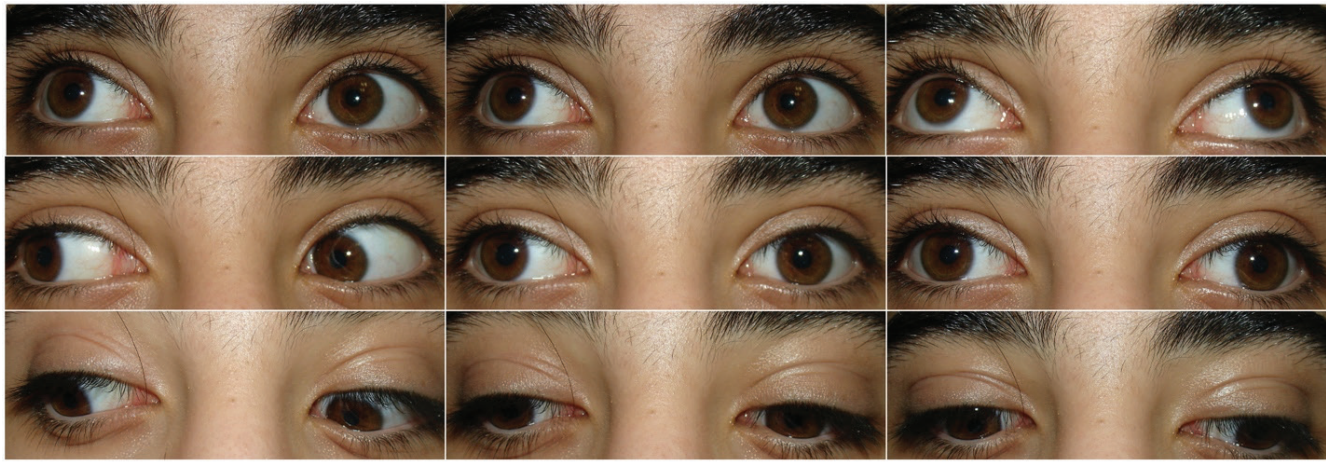

Figure 2. Nine diagnostic gaze positions of patient 10. Right exotropia and hypertropia in primary position. All ocular movements were -4 limited except abduction and infraduction in the right eye

While people who need glasses can wait a few weeks, those with diplopia prefer to go to the ophthalmologist immediately. However, during the COVID-19 pandemic, the patient or parent was so afraid of being infected with COVID-19 that despite this very disturbing symptom, they decided to delay seeking treatment. In the present study, patients waited 3-20 days before presenting to the hospital.

Due to COVID-19, examinations were postponed for many patients being followed up in the pediatric ophthalmology and strabismus unit. Operations for strabismus cases requiring surgery were also canceled after conducting a risk-benefit analysis.[14]

However, all patients in this report presented to our clinic with sudden-onset clinical pictures that warranted urgent examination, and all were referred to the neurology department. The most common causes of heterotropia or diplopia in this series were acute comitant esotropia and sixth nerve palsy. There are many different causes of abducens palsy. In the pediatric age group, the most common causes of sixth nerve palsy are intracranial tumors and head trauma.[15] Our series also included a case with intracranial etiology.

Acute comitant esotropia may result from acute disruption of fusion due to near work, patching, trauma, illness, or psychophysical stress.[16] The COVID-19 pandemic has created a great deal of tension, especially for children.[17] This stress may have impaired cranial compensation mechanisms and triggered acute comitant strabismus by disrupting motor fusion.[16] In addition, during the quarantine period there was increased exposure to digital screens among the pediatric age group, causing excessive accommodative convergence. This may explain the etiology of heterotropia detected in patients 4 and 6.

Almost all of our patients were diplopic. Diplopia is a very disturbing symptom. Monocular patching is generally advised until the etiology is determined and appropriate treatment can be initiated.[18] Patients are temporarily relieved when monocular patching eliminates one of the discordant images. However, to avoid cortical suppression in children, it is necessary to encourage binocular fusion.

One of the most important aspects of the present study is that numerous cases of acute diplopia or heterotropia were evaluated over a short period, namely 3 months. There may be several reasons for this. First and foremost, COVID-19, which is often asymptomatic in children, may cause an intracranial complication potentially resulting in acute diplopia or heterotropia.[19,20,21,22] Regrettably, the patients in this study were not tested for COVID-19 because diplopia was not included among the COVID-19 screening criteria early in the pandemic. Moreover, most hospitals affiliated with the Turkish Ministry of Health were designated as pandemic hospitals. Consequently, our hospital, which is a university hospital, experienced a sudden increase in admissions. As a result, we may have seen a false rise in the rate of acute diplopia and heterotropia.

It seems like the COVID-19 pandemic will persist for some time longer and nobody knows when it will end. Because of the shortcomings of long-term isolation and the economical and sociological realities of Turkey, normalization policies have been implemented promptly. The risk of SARS-CoV-2 infection is higher in the pediatric ophthalmology and strabismus unit than in other clinics. This is mainly because the pediatric age group is being examined. It is not always possible to evaluate children without their crying. Adapting the examination environment to the child's interests; wearing colorful scrubs; turning the examination into a game; using colorful stickers, hand-paintings, and exciting and colorful toys; singing; and talking about cartoon characters may prevent the child from crying. These ideas are currently used in pediatric ophthalmology. However, this approach has become even more value during this time. Children cannot adapt to wearing masks as well as adults, and their glasses fog up frequently due to mask use. In our clinic, we addressed the issue of fogging glasses by applying a bandage to the patient's mask. Performing orthoptic tests and retinoscopy are almost impossible at a distance of 6 feet. Therefore, the use of a mask is obligatory for the pediatric ophthalmologist, if not for the child. In our clinic, examinations are performed while wearing a surgical mask over an N95 mask, and the surgical mask is replaced after each patient.

During the COVID-19 pandemic, appointments in our outpatient clinic were scheduled at 30-minute intervals, taking dilation waiting times into account, to ensure that patients did not encounter each other. One day prior to the appointment, the infection status of all patients and their parents was checked in the National Health System of the Turkish Ministry of Health. Additionally, at the entrance of Hacettepe University Hospital, patients were asked for their HES code (a code implemented by the Ministry of Health to monitor SARS-CoV-2 exposure and contact with COVID-19 patients) and their body temperature was measured using thermal cameras. Priority was given to urgent and forensic cases. Parents were reminded that only one parent could accompany the child during the appointment, that mask use was obligatory, and that they should not arrive before the appointment time. On the appointment day, even if the patient's system check was clear, if they exhibited any symptoms consistent with upper respiratory tract infection, the appointment was postponed until the patient's situation was determined and they were directed to the appropriate unit for COVID-19 screening. Only one family was allowed in the waiting room at a time, the examination room was ventilated regularly, the number of people in the examination room was reduced as much as possible, and the patient was instructed to wait outside the hospital for pupil dilation to occur.

Study Limitations

Additionally, patients scheduled for occlusion therapy check-ups were interviewed via teleconference one day prior to the appointment date to ascertain their compliance with the occlusion treatment. If the patient was not implementing the recommended occlusion treatment, they were reminded to adhere to occlusion therapy and their appointment was rescheduled to a later date.

Conclusion

In conclusion, for physicians working in pediatric ophthalmology and strabismus, adaptation to personal protective equipment during the COVID-19 pandemic has been more challenging than in other ophthalmological units because of the close proximity between the ophthalmologist and the patient. Since the end of the pandemic cannot yet be determined, appropriate measures should be taken in terms of personal protective equipment during examinations. It should be borne in mind that acute-onset complaints and underlying neurological conditions seemed to be more frequent during the pandemic. However, different country-based reports and large-scale multicenter studies from all over the world will contribute to global knowledge and experience and help improve our understanding of the pathogenesis of COVID-19.

Ethics

Ethics Committee Approval: Hacettepe University Non-Interventional Clinical Research Ethics Committee (date: 01.09.2020/decision no: 2020/14-36).

Informed Consent: Informed consent was obtained from the patients' legal guardians.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Y., H.T.Ş., Concept: D.Y., H.T.Ş., Design: D.Y., H.T.Ş., Data Collection or Processing: D.Y., H.T.Ş., Analysis or Interpretation: D.Y., H.T.Ş., Literature Search: D.Y., H.T.Ş., Writing: D.Y.

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Original Article

A Comparative Evaluation of Globe Trauma Features in a Tertiary Care Hospital Before and During the COVID-19 Pandemic

Gözde Şahin Vural, Semih Yılmaz, Eyyüp Karahan, Cenap Güler

Balıkesir University Faculty of Medicine, Department of Ophthalmology, Balıkesir, Turkey

Abstract

Objectives: To compare the clinical features, preoperative evaluation, and surgical approaches of globe trauma patients presenting to the emergency department before and during the coronavirus disease 2019 (COVID-19) pandemic.

Materials and Methods: We retrospectively analyzed 54 eyes of 54 patients with traumatic globe perforation who underwent primary globe repair. The patients were divided into two groups according to the official start of the COVID-19 pandemic in Turkey: Group 1, 1 May 2019-11 March 2020 and Group 2, 11 March 2020-1 January 2021. The demographic features, trauma history, time from trauma to admission and from admission to surgery, COVID-19 serology (polymerase chain reaction [PCR]) result, ophthalmological examination findings at admission, surgical interventions, and postoperative clinical features were obtained from the patients' records.

Results: The mean ages of the patients in Group 1 (n=21) and Group 2 (n=33) were 42.76±20.72 and 37.78±23.47 years, respectively (p=0.431). During the pandemic, garden/farm injuries increased while workplace injuries decreased. In Groups 1 and 2 respectively, time from trauma to admission was 461.4±1228.6 and 935.4±2039.6 min (p=0.342), time from admission to surgery was 604.2±679.8 and 392.7±306.9 min (p=0.125), and length of hospital stay was 7.23±4.96, and 3.78±2.28 days (p<0.005). All patients had a COVID-19 PCR test and all resulted negative. There was no significant difference between the groups in terms of the clinical features of the ocular and adnexal injuries, surgical interventions, or postoperative complications (p>0.05). Preoperative visual acuity was found to be an important prognostic factor associated with postoperative visual acuity.

Conclusion: Globe injuries require urgent intervention in terms of visual morbidity. Patterns of injury differ during the pandemic due to both restrictions and lifestyle changes. During the pandemic, patients were discharged as soon as possible after emergency treatment to minimize the time spent in the hospital.

Keywords: COVID-19, globe trauma, pandemic

Address for Correspondence: Gözde Şahin Vural, Balıkesir University Faculty of Medicine, Department of Ophthalmology, Balıkesir, Turkey
E-mail: gozdejcgrl@hotmail.com **ORCID-ID:** orcid.org/0000-0002-6989-4378

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Introduction

The clinical entity characterized by severe lower respiratory tract infections of unknown cause that first appeared in the Wuhan province of the People's Republic of China in 2019 has affected the whole world. The World Health Organization named it coronavirus disease 2019 (COVID-19) and declared it a pandemic on 11 March 2020. Cases were also detected in Turkey and it spread rapidly through society. In response, the Turkish Ministry of Health decided in March 2020 to continue only emergency and oncological surgery and suspend all elective procedures.[1] During this period, the Turkish Ophthalmological Association published a list of which emergency surgeries and interventions can be performed, and globe injuries were the leading condition requiring urgent intervention according to this recommendation.[2] Globe traumas are common in developing countries and are important because they lead to vision loss and a subsequent decline in quality of life.[3,4] In contrast to vision-impairing pathologies that are more common in advanced age, such as cataract, glaucoma, and age-related macular degeneration, globe trauma affects the younger population and leads to greater labor loss.

As in many countries, in Turkey it was recommended to stay at home as much as possible and leave only for essential reasons due to the COVID-19 pandemic. This led to many changes in work and social routines across the entire population. During the pandemic, there have also been changes in patterns of ocular injury in connection with the changes in people's social life and in the organization of the health system. Differences have emerged in the types of globe injuries, length of hospital stay, surgical decisions, preoperative COVID-19 serological evaluation, preparation for surgery, and the precautions taken during and after surgery. In addition to being a tertiary health care hospital, our center is also a pandemic hospital, so attempts were made to treat emergency globe traumas while implementing the appropriate precautions and protective methods during this period. The aim of this study was to retrospectively examine parameters such as injury type, preoperative characteristics, anesthesia methods, and surgical techniques in cases of globe trauma treated in our tertiary care hospital by emergency surgery before and during the pandemic.

Materials and Methods

Patients who were referred to the Department of Ophthalmology in Balıkesir University Faculty of Medicine between May 2019 and January 2021 due to emergency eye trauma and underwent emergency primary globe repair were included in the study. Approval for the study was obtained from Balıkesir University Clinical Research Ethics Committee (decision number: 2021/122) and the Turkish Ministry of Health (registration number: T00-18-07). Patients without appropriate preoperative or postoperative follow-up were excluded. Study data were obtained retrospectively from patient records. The patients were divided into two groups, those who presented before the pandemic (Group 1) and during the pandemic (Group 2), based on the date of 11 March 2020, when pandemic restrictions began in Turkey. The patients' demographic characteristics (age, gender), initial ophthalmological examination findings, trauma history, time from trauma to hospital admission, and time from admission to surgical intervention were recorded. Visual acuity, intraocular pressure, side of trauma, ocular history, and Ocular Trauma Score (OTS) recorded during detailed eye examination were analyzed.[5] In addition, operation time, type of anesthesia (local or general anesthesia), serological tests (hepatitis B virus, hepatitis C virus, and human immunodeficiency virus), American Society of Anesthesiologists physical status classification, and COVID-19 real-time polymerase chain reaction (PCR) test result were recorded. The anatomic location of the trauma (skin, cornea, limbus, conjunctiva, sclera, lens), presence of tissue loss, orbital fracture (confirmed by computed tomography), intraocular or intraorbital foreign body, chemosis, proptosis, prolapse of ocular tissues (iris, choroid, vitreous, lens, intraocular lens), vitreous hemorrhage, and the type of trauma according to Birmingham Eye Trauma Terminology System (BETTS) were recorded.[6] Among the procedures performed during surgery, canthotomy, exploration with 360-degree limbal peritomy, surgical interventions to the periorbital muscles, anterior chamber lavage, conjunctival autografting to the corneal/limbal area, intracameral antibiotic administration at the end of surgery, and temporary tarsorrhaphy were examined. The patients' total length of hospital stay was recorded. Visual acuity at postoperative 1 week was accepted as postoperative vision. Lens extraction pars plana vitrectomy, penetrating keratoplasty, and evisceration performed in a different session in the late postoperative period were noted. The patients' total follow-up time was evaluated.

Statistical Analysis

The data were analyzed using SPSS version 23.0 software (IBM Corp, Armonk, NY, USA). Chi-square analysis was used for the age and gender distributions of the groups. Independent-samples t-test was used to compare quantitative values between the groups. Pearson's correlation analysis was used to evaluate correlations between the data. Results with p values less than 0.05 were considered statistically significant.

Results

Fifty-four eyes of 54 patients who met the inclusion criteria were evaluated in this study. There were 21 patients in the pre-pandemic group (Group 1) and 33 patients in the post-pandemic group (Group 2). Both periods covered approximately 10.5 months (Group 1: 1 May 2019-11 March 2020; Group 2: 11 March 2020-1 January 2021). The mean age was 42.76±20.72 years in Group 1 and 37.78±23.47 years in Group 2 (p=0.431). The female:male ratio was 0.16 (3:18) in Group 1 and 0.22 (6:27) in Group 2 (p=0.708). The right:left eye ratio was 2.00 (14:7) in Group 1 and 1.53 (20:13) in Group 2 (p=0.653).

Characteristics pertaining to the etiology of globe traumas are shown in Figure 1. In Group 1, home accidents occurred due to falls in 3 patients (14.2%) and sharp objects in 4 patients

(19.0%) (knives in 2 cases, scissors in 1 case, and a paper clip in 1 case). In Group 2, home accidents were related to sharp objects in 9 patients (27.2%) (scissors in 3 cases, exploded glass bottles in 3 cases, a knife in 1 case, a paper clip in 1 case, and broken spectacle glass in 1 patient) and falls in 3 patients (9.0%). According to BETTS, there were 18 open-globe injuries (85.7%), 2 ruptures (9.5%), and 1 penetrating injury (4.7%) in Group 1, while in Group 2 there were 27 open-globe injuries (81.8%), 1 rupture (3.0%), 2 penetrating injuries (6.0%), and 3 perforating injuries (9.0%). There was no significant difference between the groups in terms of injury types (p=0.400). All patients with globe injuries in the pre-pandemic period were operated under general anesthesia (100%), while 93.9% (n=31) of post-pandemic patients were operated under general anesthesia and 6.1% (n=2) were operated under local anesthesia (p=0.250). COVID-19 PCR test was performed on all 33 patients operated during the pandemic, with results obtained preoperatively in 21 of these patients (63.6%) and postoperatively in 12 patients (36.3%). None of the patients' COVID-19 PCR tests resulted positive. Two of the patients in Group 2 (6.06%) had a previous history of ocular surgery, while there was no history of ocular surgery in Group 1 (Table 1). In terms of preoperative and intraoperative clinical characteristics, there were no significant differences in findings or surgical interventions between globe injuries before and during the pandemic (Table 2). There was a significant correlation between preoperative visual acuity and postoperative visual acuity (p=0.04, R=0.733). The time from emergency admission to surgery was not associated with postoperative visual acuity (p=0.879).

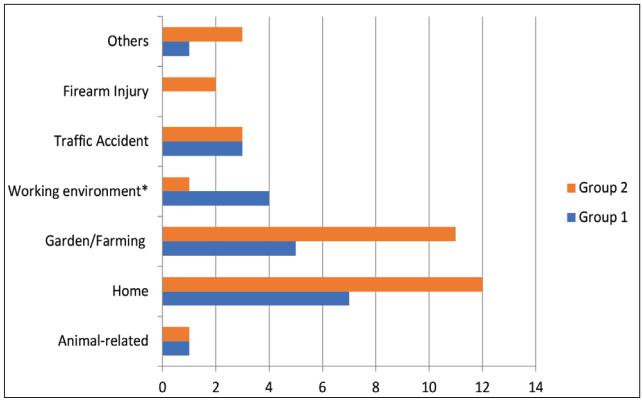

Figure 1. Etiological characteristics of globe traumas before and during the pandemic; *Statistically significant difference (p<0.048)

Discussion

The COVID-19 pandemic brought about dramatic changes in both social and working life all over the world. In Turkey, COVID-19 pandemic-related movement restrictions were implemented for all age groups over time, starting with citizens over 65 years of age on March 21, 2020. During this period, people started to spend most of their time at home, in garden areas, and in fields. Workplace restrictions resulted in people spending less time in their work environments. According to this study, there was a 1.5-fold increase in globe traumas, especially those occurring indoors, after the start of the pandemic. In contrast, Pellegrini et al.[7] suggested that there was

Table 1. Demographic characteristics and results of preoperative and postoperative evaluations of patients with globe injury before (Group 1) and during (Group 2) the pandemic

	Group 1 (n=21) Mean ± SD	Group 2 (n=21) Mean ± SD	p value
Age (years)	42.76±20.72	37.78±23.47	0.431
Gender, F/M (n)	3/18	6/27	0.708
Ocular surgery history (n)	0	1	0.421
Side, right/left (n)	2.00	1.53	0.653
Preoperative visual acuity (Snellen decimal)	0.06±0.19	0.19±0.38	0.159
Time from trauma to admission (min)	461.42±1228.69	935.45±2039.62	0.342
Time from admission to surgery (min)	604.28±679.83	392.72±306.98	0.125
Anesthesia method, general/local (n)	21/0	31/2	0.250
Preoperative COVID-19 PCR result (%)	-	63.6	
ASA score	1.28±0.46	1.24±0.43	0.729
OTS	41.04±25.04	50.00±26.14	0.218
Operative time (min)	43.28±22.78	40.12±14.16	0.531
Length of hospital stay (days)	7.23±4.96	3.78±2.28	0.001*
Postoperative visual acuity (Snellen decimal)	0.25±0.34	0.33±0.39	0.464
Follow-up time (months)	6.69±6.19	2.54±3.14	0.002*

F: Female, M: Male, PCR: Polymerase chain reaction, ASA: American Society of Anesthesiologists Physical Status Classification, OTS: Ocular Trauma Score, SD: Standard deviation, min: Minute, COVID-19: Coronavirus disease 2019

Table 2. Preoperative clinical findings, intraoperative surgical procedures, and later surgical interventions of patients with globe trauma before (Group 1) and during (Group 2) the pandemic

	Group 1 (n=21)	Group 2 (n=33)	p value
Preoperative evaluation			
Skin	2	4	0.767
Cornea	13	24	0.404
Limbus	7	12	0.820
Conjunctiva	11	19	0.854
Sclera	10	14	0.708
Lens	3	7	0.523
Type of globe trauma*			
Open-globe injury	18	27	
Rupture	2	1	
Penetrating injury	1	2	
Perforating injury	-	3	
Tissue loss	1	5	0.236
Orbital bone fracture	2	1	0.310
Foreign body (intraocular/intraorbital)	1	2	0.839
Intraocular	1	1	
Intraorbital	-	1	
Chemosis	2	3	0.957
Proptosis	1	0	0.206
Ocular tissue prolapse			
Iris	4	4	0.485
Choroid	0	1	0.421
Vitreous	5	2	0.058
Lens	0	1	0.421
Intraocular lens	0	1	0.421
Vitreous hemorrhage	9	7	0.089
Intraoperative procedures			
Canthotomy	1	0	0.206
Exploration with 360-degree limbal peritomy	9	14	0.975
Surgical intervention to the periorbital muscles	3	5	0.930
Anterior chamber lavage	14	17	0.272
Conjunctival autograft to the cornea/limbal area	2	6	0.383
Intracameral vancomycin	1	1	0.743
Temporary tarsorrhaphy	1	0	0.206
Later surgical interventions			
Lens extraction	9	9	0.236
Vitrectomy	7	5	0.117
Penetrating keratoplasty	1	1	0.743
Evisceration	0	1	0.421

*Classified according to Birmingham Eye Trauma Terminology system

a decrease in globe injuries and that this was associated with behavioral changes during the quarantine period (reduction of sports competitions and related injuries, reduction of childhood globe injuries because of school closures) and patients' reluctance to present to emergency departments due to the risk of COVID-19 transmission. We believe that the increase in the number of cases in the present study is a result of the implementation of flexible working systems in many secondary hospitals and the lack of surgical intervention for globe traumas outside tertiary hospitals. As globe injuries especially affect the young age group,[8,9] investigating their etiology and taking appropriate preventive measures is as important as appropriate treatment and follow-up. According to the results of this study, the frequency of globe injuries occurring in the home and garden/farm environments and those caused by firearms increased during the pandemic. Similarly, Hamroush et al.[10] found an increase in traumatic ocular injuries at home compared to the corresponding period of the previous year. They showed this was a result of increases in gardening, do-it-yourself activities in the home, and home exercise (jump rope, elastic band injuries). Wu et al.[11] also determined that 84% of severe ocular traumas during the pandemic occurred at home. Some studies have demonstrated that the increase in time spent at home during the pandemic were associated with increases in alcohol consumption and subsequent home accidents and firearm injuries.[12] In our study, traumas caused by animals and traffic accidents were found to be stable compared to the pre-pandemic period. Apart from this, there was a decrease in globe traumas occurring in the workplace and working environment, but it was not statistically significant. Globe injuries, especially those accompanied by foreign bodies, are more common among males.[13,14,15] Consistent with this, 83.3% of the patients in our study were male. The risk of globe injury was five times higher in males than females (odds ratio: 5.0). This result may be attributable to the fact that men more frequently work in jobs with potential exposure to high-energy trauma, participate in contact sports, and engage in activities involving physical contact, such as fighting.

In our study, the time from trauma to hospital admission increased from 461 minutes in the pre-pandemic group to 935 minutes in the post-pandemic group. This may be due to both the delay in patients presenting to the hospital during the pandemic because of concern about infection and the movement restrictions enforced as part of lockdown measures during this period.

During the pandemic, practices such as preoperative COVID-19 PCR testing, minimizing length of hospital stay, and admission to an isolation ward until the results of pre-admission COVID-19 PCR tests are obtained were implemented in our hospital. In addition to the informed consent form for surgical interventions that patients previously signed before elective and emergency operations, consent was also obtained from patients or their relatives using the "Additional Information about the Risks Related to the COVID-19 (Coronavirus) Pandemic and Consent Form" issued by the Turkish Ophthalmological Association. Although samples for COVID-19 PCR tests were collected and sent for analysis for all patients who presented during the pandemic, surgery was performed after receiving the results in only 63.6% of cases. As trauma patients' PCR results were not known, each patient was considered COVID-19-positive and their operations were performed using all necessary precautions.

There are different opinions in the literature regarding whether to perform emergency or elective surgery on patients with globe trauma.[16,17,18,19] Endophthalmitis is one of the most important risk factors determining prognosis in globe traumas.[20] None of the patients in this study developed endophthalmitis. Essex et al.[21] showed that the risk of endophthalmitis increased by 1.01 fold with each hour after open-globe trauma. They argued that globe traumas should be treated as soon as possible, as the only modifiable factor in open-globe traumas is the time from trauma to surgery. In this study, there was no significant difference in the patients' time from emergency admission to surgery. The first goal in the treatment of globe injuries is to prevent tissue prolapse and ensure globe integrity by primary suturing, and to provide appropriate treatment for possible infections. Since late sequelae are also common in these patients, the change in visual acuity is evaluated secondarily. In our study, there was no difference between the two groups in terms of preoperative or postoperative visual acuity, but postoperative visual acuity was significantly increased in both groups.

Although elective ocular surgeries were restricted worldwide during the pandemic, it is not possible to prevent trauma cases. However, in some eye injuries (e.g., superficial injuries, corneal abrasions, lamellar conjunctival incisions, simple uncomplicated orbital fractures) it is recommended that surgery should not be performed or should be performed as an elective procedure.[22] Therefore, determining OTS during preoperative evaluation is crucial to estimate the urgency of surgery and postoperative visual expectation. In our study, we observed no difference in terms of OTS before and during the pandemic, and the mean operative time was similar. During the pandemic, local anesthesia methods (topical anesthesia) were preferred except for cases in which general anesthesia was absolutely necessary. All patients in the pre-pandemic group were operated under general anesthesia, whereas the ratio of general to local anesthesia was 31:2 in globe trauma cases during the pandemic (p=0.250).

There were no differences in the clinical characteristics and surgical interventions of globe injury cases before and during the pandemic (Table 2). In 2004, Kuhn et al.[6] developed an international identification system to create a standard definition for describing the features of mechanical globe traumas (BETTS). This classification system is important both in terms of creating a standardized language among ophthalmologists and providing a one-to-one relationship between definitions and clinical features. The aim of the system was to create a nomenclature that could be used in daily practice by classifying mechanical globe traumas in a simple and understandable way. We used the BETTS to classify the patients in this study and found that there were no significant differences between the groups in terms of clinical

characteristics. When we evaluated the cases according to trauma site, the groups showed no difference in traumatized tissues. The most commonly affected area in all patients was the cornea (68.5%). Intravitreous hemorrhage was detected in 29.6% of the patients. There is no definite information regarding the timing of vitrectomy in open-globe traumas. While some authors advocate early pars plana vitrectomy, others consider it more appropriate to wait 7-14 days after primary repair.[18] In our study, the average timing of pars plana vitrectomy was approximately 11.3 days after primary repair.

In this study, the length of hospital stay was significantly shorter for patients who presented during the pandemic. This difference can be attributed to the efforts made to move patients out of the emergency department and get them to a level where they can be treated in the outpatient or home setting as quickly as possible. In the literature, the recommendation for postoperative patient follow-up is to discharge the patient after the first postoperative day and schedule outpatient visits on postoperative day 3 and at 1 week.[23] As opposed to the face-to-face examinations we performed during follow-up, evidence indicates that telemedicine practices, which have not yet been widely implemented in Turkey, are beneficial in terms of reducing patients' hospital visits and minimizing the risk of transmission in situations such as the pandemic.[24] The significant difference in the mean follow-up times of the patients in our study is due to the fact that the operations of patients in the pre-pandemic group were performed chronologically earlier (Group 1: 6.6 months, Group 2: 2.5 months; $p<0.05$).

Conclusion

During the COVID-19 pandemic, emergency surgeries continue to be performed in other pandemic hospitals such as ours and throughout the country. As globe injuries occur mostly in the younger population and can cause permanent visual morbidity, they should be treated as soon as possible and with the most appropriate surgical approach. In this study, the postoperative improvement in vision was satisfactory in both groups. Therefore, if patients are treated with the appropriate precautions, visual gain is achieved. Considering that globe trauma is more common in the young population, it is very important to determine and apply appropriate treatment algorithms. All available protective measures should be taken to protect both patients and healthcare professionals during the pandemic. The data obtained in our study encompass a limited time period. Therefore, multicenter studies involving larger patient groups are needed.

Ethics

Ethics Committee Approval: Approval for the study was obtained from Balıkesir University Clinical Research Ethics Committee (decision number: 2021/122).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: G.S.V., E.K., Concept: G.S.V., Design: G.S.V., Data Collection or Processing: S.Y., G.S.V., Analysis or Interpretation: G.S.V., E.K., C.G., Literature Search: G.S.V., S.Y., Writing: G.S.V.

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

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Original Article

Idiopathic Epiretinal Membranes: Visual Outcomes and Prognostic Factors

Paradee Kunavisarut*, Montana Supawongwattana*, Direk Patikulsila*, Janejit Choovuthayakorn*, Nawat Watanachai*, Voraporn Chaikitmongkol*, Kessara Pathanapitoon*, Aniki Rothova**

*Chiang Mai University Faculty of Medicine, Department of Ophthalmology, Chiang Mai, Thailand
**Erasmus Medical Center, Department of Ophthalmology, Rotterdam, The Netherlands

Abstract

Objectives: To evaluate the associations between anatomical changes and visual outcomes in patients with idiopathic epiretinal membrane (ERM).

Materials and Methods: We performed a prospective study of 130 consecutive idiopathic ERM patients and report their visual outcomes and the factors associated with visual outcome and anatomical changes.

Results: Of 130 eyes of 130 patients, 87 eyes underwent surgery, while the remaining 43 eyes were observed. At 6-month follow-up, the best-corrected visual acuity (BCVA) increased in the whole population. Mean Early Treatment Diabetic Retinopathy Study letter score changed from 51 to 65 in the surgical group and from 67 to 68 in the non-surgical group. The surgical group had improvement in BCVA at all ERM stages and grades of disorganization of the retinal inner layers (DRIL) ($p<0.01$). In multivariable analysis of the surgical group, factors associated with BCVA of ETDRS 60 letters or more were no or mild DRIL and the absence of ellipsoid zone disruption at baseline ($p=0.002$ and $p=0.034$, respectively) and this statistically significant positive correlation was still maintained at 12-month follow-up

Conclusion: Baseline DRIL grade and presence of ellipsoid zone disruption were the most informative prognostic factors in patients with idiopathic ERMs. Patients with severe DRIL and/or advanced ERMs had improved vision after ERM removal.

Keywords: Idiopathic epiretinal membranes, disorganization of the retinal inner layers, visual outcome, prognostic factors

Address for Correspondence: Paradee Kunavisarut, Chiang Mai University Faculty of Medicine, Department of Ophthalmology, Chiang Mai, Thailand
E-mail: pkunavisarut@hotmail.com **ORCID-ID:** orcid.org/0000-0003-4997-6285
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Introduction

Epiretinal membranes (ERMs) are one of the common causes of visual impairment, with a reported prevalence of 6-7% of the population.[1,2] The prevalence of ERMs increases significantly by age group, especially in older adults (0.5% for 40 to 49 years, 2.6% for 50 to 59 years, 7.2-9.4% for 60 to 69 years, 11.6-15.1% for 70 to 79 years, and 9.3-11.3% for 80 years and older).[1,2] ERMs lead to deformation of the retinal architecture and may distort the distribution of photoreceptors, causing various visual complaints such as metamorphopsia and ultimately loss of visual acuity. ERMs can be associated with several vitreoretinal diseases such as retinal vasculitis, diabetic retinopathy, retinal venous occlusive disease, retinal detachment, retinal injury, previous retinal surgery. As a minority of idiopathic ERM cases become symptomatic, only a small proportion of affected patients require surgical removal.[1]

Multiple prognostic factors determining visual outcomes in ERM after pars plana vitrectomy (PPV) and ERM peeling have been evaluated, including preoperative visual acuity, symptom duration, patient age, central macular thickness, preoperative integrity of foveal photoreceptors, the status of the cone outer segment tips, and irregularity of the inferior border of the inner plexiform layer.[3,4,5,6,7,8,9,10,11,12] Spectral-domain optical coherence tomography (SD-OCT) has driven a transformative change in the study of ERMs to better identify anatomical characteristics, including central macular thickness (CMT), intraretinal cystic space, ellipsoid zone disruption, cotton ball sign, ectopic inner foveal layer, ERM stages, and recently, disorganization of the retinal inner layers (DRIL).[13,14]

The purpose of this study was to evaluate the associations between anatomical changes visualized by SD-OCT and visual outcomes in patients with idiopathic ERM.

Materials and Methods

A prospective study was conducted at Chiang Mai University Hospital, Thailand including all patients diagnosed with ERM and seen by retinal specialists at the Retinal Service Clinic between January 1, 2014 and December 31, 2018. The study was approved by the Ethics Committee of Chiangmai University Hospital and conformed to the Declaration of Helsinki.

Study Participants

The study inclusion criteria were: (1) age 18 years or older; (2) idiopathic ERMs; (3) no previous ocular surgery except uncomplicated cataract surgery more than 6 months ago; and (4) at least 6 months of follow-up after ERM diagnosis. In patients with bilateral idiopathic ERM, the more severely affected eye was included.

Exclusion criteria were: (1) Other concomitant ocular diseases that are usually associated with ERMs (i.e., diabetic retinopathy, age-related macular degeneration, retinal vascular disease, retinal inflammatory disease or infection); (2) secondary ERMs or ERMs associated with other vitreoretinal diseases; (3) macular hole; (4) vitreomacular traction; (5) any other ocular condition compromising visual acuity except the presence of cataract (i.e., amblyopia, glaucoma); and (6) need for intraocular surgery, especially cataract surgery, during study period.

After the patients were diagnosed, demographic data including their age, sex, laterality, underlying diseases, subjective visual symptoms, history of previous ocular surgery, and best-corrected visual acuity (BCVA) at baseline were recorded. Then the patients were divided into two groups by treatment option (surgery or observation), which was determined according to patient preference and the retinal specialist's recommendation based on factors such as visual acuity, complaints of distortion, and ERM grade. All patients signed an informed consent form prior to participation. Subsequent investigations and BCVA assessment were performed at 6-month and 12-month follow-up.

Surgical Procedure

The surgeries were performed by 5 surgeons (P.K., D.P., J.C., N.W., and V.C.) with more than 10 years of experience in vitreoretinal surgery. A 3-port 23-gauge transconjunctival sutureless vitrectomy was performed using the CONSTELLATION Vision System (Alcon Laboratories, Inc, Fort Worth, Texas, USA). In all eyes, a central vitrectomy was performed and the posterior vitreous humor was separated from the retina. After vitrectomy the ERM and internal limiting membrane were removed using end-gripping forceps (Alcon, Fort Worth, TX, USA) with the assistance of Brilliant Blue G dye (0.05% w/v, Aurolab, India) or triamcinolone (40 mg/mL, Triesence; Alcon, Fort Worth, Texas, USA). The ERM and internal limiting membrane were removed from the central macular area up to the arcades.

Optical Coherence Tomography Analysis

All subjects underwent SD-OCT scans centered on the fovea (Spectralis; Heidelberg Engineering, Heidelberg, Germany) with 25 section images and automatic real-time mean =9 at baseline, 6-month, and 12-month follow-up.

ERMs were defined as discrete, irregular, and hyperreflective lines above the inner retinal surface. Retinal thickness was analyzed and measured by the automated thickness map function. Continuous ectopic inner foveal layer was defined as the presence of a continuous hyporeflective or hyperreflective band that extends from the inner nuclear layer (INL) and inner plexiform layer (IPL) across the foveal region and is visible in all OCT scans.[15] Disruption of the ellipsoid zone was defined as a discontinuous ellipsoid band in the foveal region. The presence of a round or diffuse hyperreflective area between the ellipsoid zone and the cone outer segment tip line at the center of the fovea was defined as the "cotton ball sign" (Figure 1).[16]

The presence and severity of DRIL were assessed within the central 2,000 µm based on distinguishability (score 0 for distinguishable, 1 for indistinguishable) and boundary regularity (score 0 for regular, 1 for irregular) between the ganglion cell-inner plexiform layer complex (GC-IPL) and INL and between the INL and outer plexiform layer (OPL), resulting in a score

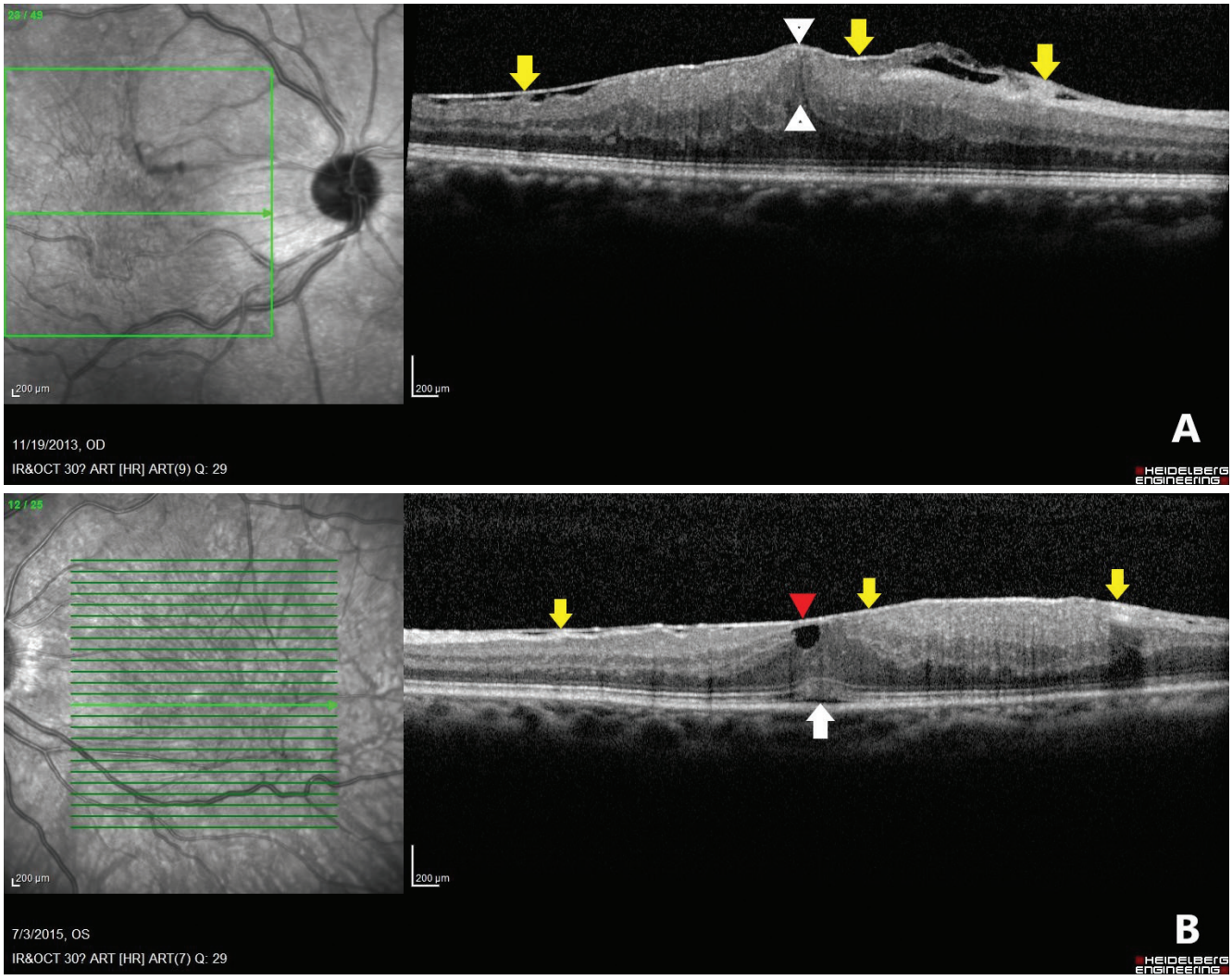

Figure 1. Morphologic characteristics of epiretinal membranes. Figure 1A shows stage 3 epiretinal membranes (yellow arrows) and continuous identified ectopic inner foveal layers (white arrow head), which appears as a continuous hyporeflective or hyperreflective band extending from the inner nuclear layer and inner plexiform layer across the foveal region. Figure 1B shows stage 3 epiretinal membranes (yellow arrows), cotton ball sign (diffuse hyperreflective area between the ellipsoid zone and the cone outer segment tip line at the center of the fovea; white arrow) and intraretinal cyst (hyporeflective intraretinal cystoid space; red arrow head)

ranging from 0-4 points. DRIL was classified into 3 grades: presence of no DRIL was considered grade 0 (0 points); presence of mild DRIL was considered grade 1 (1-3 points); presence of severe DRIL was considered grade 2 (4 points).[14]

ERM staging was also done in this study in order to describe disease severity. Stage 1 was defined as the presence of a mild ERM with negligible morphologic or anatomic disruption, with all retinal layers and foveal depression clearly identifiable; stage 2 was defined as the presence of ERM associated with progressive retinal distortion and loss of foveal depression, but all retinal layers were clearly identifiable; stage 3 was defined as the presence of ERMs with continuous ectopic inner foveal layers anomalously crossing the central foveal area, absence of foveal depression, but all retinal layers clearly identifiable; and stage 4 was defined as an ERM complicated by significant retinal thickening and marked anatomic disruption of the macula, with retinal layers that were significantly distorted, disorganized, and not clearly identifiable with OCT.[13]

Outcome Measures

The main outcome measure was visual outcome in the idiopathic ERM patients at 6 months. Secondary outcomes were associated factors and correlations between visual outcome and anatomical changes at 6 months. Visual acuity was tested using the Snellen acuity chart and converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores for all calculations and statistical analyses.

Statistical Analysis

All the analyses were carried out using the SPSS version 24.0 (IBM Corp, Armonk, NY). Descriptive statistics were

first calculated for all variables of interest. Mean and standard deviation values were calculated. Parametric and nonparametric tests (independent t-test, Mann-Whitney U test) were used to compare quantitative variables, and the chi-square test was used to test for correlation with confounders. Univariate and multivariate logistic regression was used to identify factors associated with BCVA. Differences were reported with 95% confidence intervals (CI). A p value <.05 was considered statistically significant.

Results

One hundred and ninety-one patients were diagnosed with idiopathic ERMs, of which 61 were excluded due to the presence of one or more exclusion criteria. The remaining 130 patients (130 eyes) were enrolled; 45 (35%) were men, 85 (65%) were women, and the mean age was 67 years. Demographic and baseline characteristics are shown in Table 1. Mean BCVA (approximate ETDRS letter score) was 56±17, 66±13, and 69±12 at baseline, 6-month, and 1-year follow-up, respectively, with a mean follow-up period of 9.8±5.5 months.

Anatomical Appearance and Changes in the Surgical and Non-Surgical Groups

Of the 130 eyes with ERMs, 87 eyes underwent surgery, while the remaining 43 eyes were observed as the control (non-surgical) group. Baseline anatomical apppearance in terms of ERM staging and DRIL grading was analyzed in both groups. We observed that patients with more severe ERM and DRIL more frequently underwent surgery (Table 2).

Comparisons of baseline characteristics between the surgical and non-surgical group in terms of mean baseline ETDRS letter scores and CMT revealed significant differences between the groups. The surgical group had lower mean baseline ETDRS letter score (51±14 vs. 67±17) and higher mean baseline CMT (503.3±92.6 µm vs. 400.6±103.9 µm) than the non-surgical group (p<0.01 for both). In addition, mean ERM stage and DRIL grade in the surgical group (2.9±0.8 and 1.4±0.5, respectively) were higher than those in the non-surgical group (2.2±1.0 and 0.7±0.7, respectively) (p<0.01).

At 6 months, the overall mean CMT decreased significantly from 469.31±107.6 µm to 408.7±81.5 µm (p<0.01). However, subgroup analysis showed that mean CMT only decreased in the surgical group, from 503.3±92.6 µm to 406.5±70.1 µm (p<0.01), while it increased slightly from baseline in the non-surgical group (from 400.6±103.9 µm to 412.4±99.2 µm, p=0.127). Evaluation of the anatomical changes according to ERM stages and DRIL grades at 6-month follow-up are shown in Table 3 and Figure 2.

Table 1. Demographic data and baseline characteristics of patients with idiopathic epiretinal membranes

Characteristics	Results
Age, years, mean ± SD (range)	67±23 (44-90)
Male:female, n (%)	45:85 (35:65%)
Laterality, OD, n (%)	72 (55.4)
Systemic co-morbidity, n (%) Hypertension Diabetes mellitus*	 55 (42.3) 19 (14.6)
Pseudophakia, n (%)	36 (27.7)
Metamorphopsia, n (%)	15 (11.5)
BCVA, approximate ETDRS, mean ± SD	56.22±16.56
Central macular thickness, µm, mean ± SD	469.31±107.61
Ellipsoid zone disruption, n (%)	8 (6.2)
Continuous ectopic inner foveal layers, n (%)	74 (56.9)
Cotton ball sign, n (%)	15 (11.5)
Intraretinal cystic space, n (%)	36 (27.7)
Epiretinal membrane (ERM) stage, n (%) 1 2 3 4	 17 (13.1) 33 (25.4) 52 (40.0) 28 (21.5)
Disorganization of retinal inner layers (DRIL) grade, n (%) 0 (none) 1 (mild) 2 (severe)	 20 (15.4) 63 (48.5) 47 (36.2)
Treatment, n (%) Monitoring/observation Surgery	 43 (33.1) 87 (66.9)

BCVA: Best-corrected visual acuity, ETDRS: Early treatment diabetic retinopathy study, *No patient had diabetic retinopathy, SD: Standart deviation

Table 2. Baseline anatomical appearance of patients with idiopathic epiretinal membrane

		Total (eyes)	Surgical group (eyes)	Non-surgical group (eyes)	P value
ERM stage	1	17	5 (29%)	**12 (71%)**	**0.02**
	2	33	18 (55%)	15 (45%)	0.46
	3	52	**42 (81%)**	10 (19%)	**<0.01**
	4	28	**22 (79%)**	6 (21%)	**<0.01**
DRIL grade	0 (none)	20	2 (10%)	**18 (90%)**	**<0.01**
	1 (mild)	63	**45 (71%)**	18 (29%)	**<0.01**
	2 (severe)	47	**40 (85%)**	7 (15%)	**<0.01**

ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layers

Visual Acuity Changes in the Surgical and Non-Surgical Groups

BCVA at 6-month follow-up increased in the whole ERM population, with no differences between the surgical and non-surgical groups (mean ETDRS letter score: 64.94 in the surgical group and 67.95 in the non-surgical group; p=0.234). However, a gain of 15 letters or more was seen in over half of patients in the surgical group (47/87 eyes, 54%) versus only 9% of patients in the non-surgical group (4/43 eyes) (p<0.01, odds ratio [OR]: 11.46, 95% CI: 3.77-34.83). This result increased over time to

Table 3. Anatomical changes at 6-month follow-up

Anatomical changes at 6-month follow-up		Surgical group (87 eyes)	Non-surgical group (43 eyes)
ERM stage	Improved	34 (39%)	0 (0%)
	Stable	51 (59%)	36 (84%)
	Worse	2 (2%)	7 (16%)
DRIL grade	Improved	39 (45%)	1 (2%)
	Stable	46 (53%)	36 (84%)
	Worse	2 (2%)	6 (14%)

ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layers

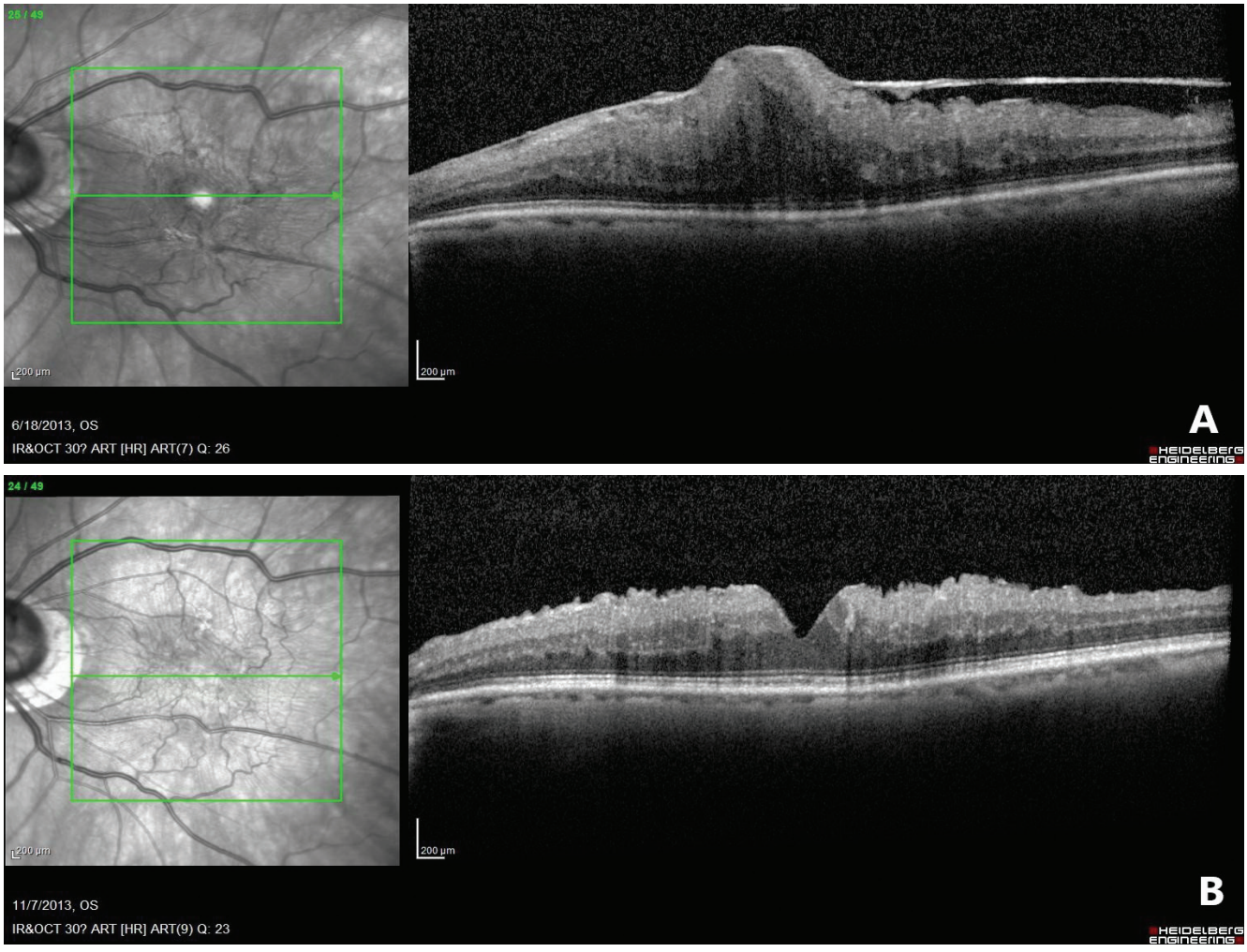

Figure 2. Anatomical changes evaluated by optical coherence tomography. Figure 2A shows stage 4 epiretinal membranes (ERMs), retinal thickening, and anatomic disruption of the macula with loss of foveal depression and significantly distorted and disorganized retinal layers. Disorganization of the retinal inner layers (DRIL) grade 2 was also considered in this morphologic characteristic. Figure 2B shows postoperative regression of ERM stage and DRIL grade at 6-month follow-up, with partial regression of the ectopic inner foveal layer and some remaining disorganization of the retinal layers

30/58 eyes (52%) in the surgical group and 4/34 eyes (12%) in the non-surgical group at the 12-month follow-up evaluation (p<0.01, OR: 8.04, 95% CI: 2.51-25.72).

ERM stage, DRIL grade, and their relationship with BCVA changes are shown in Table 4. The surgical group showed improvement in BCVA at all stages and grades (p<0.01), while there were no significant differences in BCVA in the non-surgical group. In a subgroup analysis of the surgical group, patients with good baseline visual acuity (20/60 or better; 22 patients) had a visual acuity improvement of 4.18 letters on average, while those with poor baseline visual acuity (20/200 or less; 15 patients) had a mean visual acuity improvement of 23.0 letters.

Factors Associated with Visual Outcome

The analysis of potential factors correlating with visual outcomes is shown in Table 5 and Table 6. In univariate analysis of the whole group (Table 5), we found several factors were positively associated with BCVA of ETDRS 60 letters or more at 6-month follow-up. However, in surgical subgroup univariate analysis (Table 6), we found only baseline visual acuity of ETDRS 55 letters or more, absence of ellipsoid zone disruption, and no or mild DRIL were positively associated with BCVA of ETDRS 60 letters or more at 6 months, whereas only no or mild DRIL was associated with gaining 15 letters or more. Furthermore, patients with severe DRIL experienced an improvement of 10 letters and a larger increase in CMT (>450 µm) was associated with a BCVA gain of 15 letters or more (p<0.01).

In multivariable analysis of the surgical group, the factors associated with a BCVA of ETDRS 60 letters or more at 6-month follow-up were no or mild DRIL and absence of ellipsoid zone disruption at baseline (p=0.002, OR: 5.676, 95% CI: 1.896-16.991 and p=0.034, OR: 11.745, 95% CI: 1.204-114.578, respectively). This statistically significant positive correlation was still maintained at 12-month follow-up (baseline no or mild DRIL; p<0.01, OR: 6.821, 95% CI: 2.190-21.244 and

Table 4. Correlation between visual acuity changes from baseline to 6-month follow-up and epiretinal membrane stage and disorganization of the retinal inner layers grade

Anatomical changes		Surgical group (n=87)	Non-surgical group (n=43)	P value
ERM stage	1-2 (n=50)	58.43 → 68.48 (p<0.01)	70.70 → 72.07 (p=0.519)	0.212
	3 (n=52)	52.02 → 67.52 (p<0.01)	65.30 → 65.70 (p=0.898)	0.527
	4 (n=28)	40.91 → 56.32 (p<0.01)	52.83 → 52.83 (p=1.00)	0.630
DRIL grade	0-1 (no/mild) (n=83)	55.94 → 69.55 (p<0.01)	68.89 → 70.69 (p=0.336)	0.594
	2 (severe) (n=47)	45.00 → 59.53 (p<0.01)	57.00 →53.57 (p=0.304)	0.311

ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layers

Table 5. Anatomical and clinical characteristics of epiretinal membranes and visual acuity at 6-month follow-up

Factors	ETDRS >60 letters (n=94)	ETDRS <60 letters (n=36)	P value (Odds ratio, 95% CI)
Mean baseline BCVA	60.8	44.25	<0.01
Baseline ETDRS >45 letters	84 (89%)	24 (67%)	<0.01 (4.20. 1.62-10.9)
Baseline ETDRS >55 letters	70 (74%)	10 (28%)	<0.01 (7.60. 3.20-18.0)
Ellipsoid zone disruption	1 (1%)	7 (19%)	<0.01 (22.45. 2.65-190.10)
Ectopic inner foveal layer	45 (48%)	29 (81%)	<0.01 (4.51. 1.80-11.31)
CMT <450 µm	48 (51%)	10 (28%)	0.019 (2.71. 1.18-9.22)
ERM stage 1-2 - Surgical group - Non-surgical group	42 (45%) 18 (19%) 24 (26%)	8 (22%) 5 (14%) 3 (8%)	0.019 (2.828. 1.167-6.848) 0.307 (0.45. 0.10-2.13)
ERM stage 3-4 - Surgical group - Non-surgical group	52 (55%) 43 (46%) 9 (9%)	28 (78%) 21 (58%) 7 (20%)	0.019 (2.828. 1.167-6.848) 0.559 (1.593. 0.52-4.87)
DRIL grade: none/mild - Surgical group - Non-surgical group	71 (76%) 41 (44%) 30 (32%)	12 (34%) 6 (17%) 6 (17%)	<0.01 (6.174.2.672-11.264) 0.617 (1.367. 0.40-4.66)
DRIL grade: severe - Surgical group - Non-surgical group	23 (24%) 20 (21%) 3 (3%)	24 (67%) 20 (56%) 4 (11%)	<0.01 (6.174.2.672-11.264) 0.727 (1.33. 0.26-6.74)

BCVA: Best-corrected visual acuity, ETDRS: Early Treatment Diabetic Retinopathy Study, CMT: Central macular thickness, ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layers, CI: Confidence interval

Table 6. Anatomical and clinical characteristics of epiretinal membrane patients in the surgical group and their association with ETDRS letter score of 60 and gain of 15 letters at 6-month follow-up

Factors	ETDRS letter score		P value (odds ratio, 95% CI)	Letter gain		P value (odds ratio, 95% CI)
	>60 (n=61)	<60 (n=26)		>15 (n=47)	<15 (n=40)	
Mean baseline BCVA	53.67	44.42	0.159	47.34	55.10	0,289
Baseline ETDRS >45 letters	51 (83.6%)	17 (65.4%)	0.088	34 (72.3%)	34 (85.0%)	0,154
Baseline ETDRS >55 letters	37 (60.7%)	7 (26.9%)	**<0.01 (4.185, 1.528-11.459)**	21 (44.7%)	23 (57.5%)	0.233
Ellipsoid zone disruption	1 (1.6%)	6 (23.1)	**<0.01 (18.00, 2.042-158.701)**	2 (4.3%)	5 (12.5%)	0.159
Ectopic inner foveal layer	39 (63.9%)	22 (84.6%)	0.054	31 (66.0%)	30 (75.0%)	0.358
CMT <450 µm	21 (34.4%)	6 (23.1%)	0.295	14 (29.8%)	13 (32.5%)	0.785
ERM stage 1-2	18 (29.5%)	5 (19.2%)	0.32	11 (23.4%)	12 (30.0%)	0.487
ERM stage 3-4	43 (70.5%)	21 (80.8%)		36 (76.6%)	28 (70.0%)	
DRIL grade: none/mild	41 (67.2%)	6 (23.1%)	**<0.01 (6.833, 2.374-19.672)**	30 (63.8%)	17 (42.5%)	**0.047 (2.388, 1.006-5.666)**
DRIL grade: severe	20 (32.8%)	20 (76.9%)		17 (36.2%)	23 (57.5%)	

BCVA: Best-corrected visual acuity, ETDRS: Early Treatment Diabetic Retinopathy Study, CMT: Central macular thickness, ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layers, CI: Confidence interval

no presence of ellipsoid zone disruption; p=0.023, OR: 12.925, 95% CI: 1.767-121.351).

No serious intraoperative or postoperative complications were registered over the follow-up period in the surgical group or the non-surgical group. However, 8 of 87 patients (9%) had decreased visual acuity after surgery. The factor associated with worsening visual acuity was stage 1 or 2 ERMs (p=0.028, OR: 5.648, 95% CI: 1.229-25.950). We found that 4 of these 8 patients had good baseline visual acuity (20/60 or better) and lost less than 5 letters in the follow-up period. The other 4 patients had a visual acuity loss of more than 10 letters (3 patients had severe DRIL at baseline and no regression after surgery, 1 patient had severe ellipsoid zone disruption).

Discussion

ERMs can cause decreased visual acuity as well as other visual disturbances such as micropsia and metamorphopsia that are often slowly progressive. The natural history of ERM from the Blue Mountain Study showed that without treatment, only 30% of patients had progressed at 5 years, while the others regressed or remained stable.[17] Therefore, the surgical management of ERMs is recommended for patients with severe complaints and those with poor visual acuity. PPV and membrane peeling are considered standard treatment for ERM patients with visual acuity of 20/50 or less, or for those with intolerable symptoms. In contrast, there is no consensus on the management of ERM patients with good visual acuity (better than 20/50 or 20/60) and those with severe ERMs (poor preoperative visual acuity, or severely disorganized retinal layers, or very thick macula). In ERM patients with BCVA better than 20/50, non-surgical follow-up is often recommended since the majority of the patients prefer to keep their satisfactory visual acuity and avoid unnecessary complications of PPV such as retinal detachment, endophthalmitis, and accelerated cataract formation.[18] Several studies have reported favorable success rates in visual improvement and low risk of complications from PPV and membrane peeling in patients with idiopathic ERMs.[4,10,19,20,21,22,23,24,25,26,27,28,29] It is possible that early PPV could result in the preservation of better visual acuity and less irreversible damage to the retina than the usual follow-up regimen, which basically results in performing PPV when visual impairment and/or more advanced anatomical changes have occurred.[30,31,32] In severe ERM patients, PPV is controversial because photoreceptor cells may be severely disrupted, resulting in permanent visual loss.

Our study demonstrates that PPV can improve anatomic appearance and vision significantly in all stages and all grades of ERM, though the greatest benefit was noted in more severe cases. We emphasize that all patients who are symptomatic, have loss of vision, and would like to improve their vision should undergo surgery earlier for better long-term visual preservation after a thorough discussion of the potential benefits and risks of surgery without unintentional bias (Table 4). Although several reports suggested that surgery can also cause retinal damage, including swelling of the arcuate nerve fiber layer[33], dissociated optic nerve fiber layer defect[34], secondary paracentral macular hole[35], and microcysts in the INL of the retina[36], none of these were observed in the present study. Another factor in support of early surgery is that it results in better postoperative visual acuity when there is good preoperative vision.[20,31,37,38]

Multiple studies have evaluated SD-OCT parameters as visual prognosticators in ERM surgery.[9,10,11,12,16,21,39,40,41,42,43,44,45,46,47] Various prognostic factors have been identified, including baseline visual acuity, degree of preoperative metamorphopsia, microstructural factors, CMT, ellipsoid zone disruption, and the inner-retinal layer irregularity index.[9,10,11,12,21,22,45,46,48,49,50,51,52,53,54] However, there is no consensus on the best marker. The present study showed that baseline visual acuity, presence of ellipsoid zone disruption, and DRIL grade were all relevant, but in the multivariate analysis, baseline DRIL grade and presence of ellipsoid zone disruption were identified as the most important markers.

Baseline visual acuity was strongly associated with visual prognosis, but this association was obviously predictable. Most patients in the non-surgical group with good visual acuity at baseline remained stable. Patients with good baseline visual acuity who underwent surgery also had good visual acuity at follow-up, whereas those with poor baseline visual acuity remained suboptimal but exhibited improvement. These findings are similar to previous studies.[20,24,29,45]

The OCT feature termed DRIL was firstly characterized by Sun et al.[55] as the horizontal extent in microns for which any boundaries between the GC-IPL, INL, and OPL could not be identified. Particularly, DRIL was found to be associated with visual acuity after the resolution of center-involving diabetic macular edema and improvement in DRIL was predictive of better visual outcomes.[56,57,58] Similarly, DRIL has been identified as an important biomarker for functional outcome in patients with ERMs. Recently, Zur et al.[14] reported that DRIL grading correlated with functional and anatomical measures and could play a role as a biomarker to predict the visual outcome after surgery in a patient with idiopathic ERMs. The authors reported that visual and anatomic outcomes of patients with severe DRIL were limited and that these patients were further prone to develop intraoperative and postoperative complications. However, this study did not include a control group and the prognosis of patients with severe DRIL without surgery was not reported. Our study reveals that visual outcomes in patients with severe DRIL after surgery were better (though limited) than in the observation group. All patients with severe DRIL and improvement of more than 15 letters were in the surgical group. There have been many mechanisms proposed to explain the association of DRIL with visual acuity, including the presence of disorganization or destruction of cells within inner retinal layers (bipolar, amacrine, or horizontal cells) causing a disruption of pathways that transmit visual information[55], or prolonged tractional forces leading to irregularity of the inner retinal layers that may progress and cause deformation or disconnection of synaptic junctions between photoreceptors and ganglion cells.[14] In addition, cellular damage to Müller cells and inner retinal cells is believed to influence the visual prognosis in eyes with ERM.

Cho et al.[12] reported that after ERM removal, tractional forces are reduced, but the recovery period for restoring natural retinal structure and function can be variable. We found that 6 months after surgery, the desired visual outcomes were not completely achieved even after apparently successful removal. The visual outcome in some patients was not associated with their ERM stage. To explain this phenomenon, future randomized controlled clinical trials are needed in order to investigate other factors affecting visual outcome apart from ERM morphology.

Study Limitations

This study had several limitations. Firstly, the surgical techniques varied, as some procedures were Brilliant Blue G-assisted and the internal limiting membrane peeling size depended on the surgeon's discretion. Secondly, the postoperative follow-up period of 6 months was relatively short. Moreover, visual outcomes after surgery might be underestimated since a majority of our patients remained phakic after PPV and their cataract progression might influence their vision. Nonetheless, we believe that at the first 6 months, the influence of cataract on visual outcome is minimal. Cataract surgery at the sole surgeon's discretion could also affect the results of this study because visual acuity may also improve from cataract surgery (not ERM removal). We attempted to minimize this effect by excluding all patients who developed visually significant cataracts and needed cataract surgery during the study period.

Conclusion

In conclusion, we identified baseline DRIL grade and the presence of ellipsoid zone disruption as the most informative prognostic factors in patients with idiopathic ERMs, independent from surgical intervention. Furthermore, we demonstrate that patients with severe DRIL and/or advanced ERMs could improve their vision after ERM removal.

Ethics

Ethics Committee Approval: Ethics Committee approval number OPT-2561-05442 Chiangmai University.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.K., D.P., J.C., N.W., V.C., Concept: P.K., M.S., D.P., J.C., N.W., V.C., Design: P.K., K.P., Data Collection or Processing: M.S., Analysis or Interpretation: M.S., J.C., Literature Search: P.K., M.S., K.P., A.R., Writing: P.K., M.S., K.P., A.R.

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Original Article

Heavy Silicone Oil as an Endotamponade in Recurrent or Complicated Retinal Detachment and Macular Hole

Rengin Aslıhan Kurt*, Ziya Kapran**

*Başkent University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
**Neoretina Eye Clinic, İstanbul, Turkey

Abstract

Objectives: To evaluate the efficacy and safety of heavy silicone oil as an endotamponade in patients with recurrent or complicated retinal detachment and macular hole.

Materials and Methods: Nineteen eyes of 19 patients who underwent heavy silicone oil endotamponade for different indications were included in the study and evaluated by retrospective chart review. At each visit, patients underwent detailed ophthalmological examination and anatomical and functional outcomes, silicone oil emulsification, intraocular inflammation, presence of proliferative vitreoretinopathy, preoperative and postoperative visual acuity, and postoperative complications were recorded.

Results: The study included 19 eyes of 19 consecutive patients: 13 women (68.4%) and 6 men (31.6%). The patients' median age was 60 years (interquartile range [IQR]: 44-70 years) and the median follow-up time was 19 months (IQR: 9-31 months). Indications for heavy silicone oil endotamponade were recurrent retinal detachment in 11 eyes (57.8%), inferior retinal detachment in 5 eyes (26.3%), inferior rhegmatogenous retinal detachment, recurrent macular hole in 2 patients (10.5%), and macular hole in 1 patient (5.2%). Median best corrected visual acuity was 2 logMAR (IQR: 1-2.6) preoperatively and 0.99 logMAR (IQR: 0.4-2) postoperatively ($p<0.001$). Postoperative anatomical success was achieved in all patients. Densiron 68 was used for endotamponade in 14 patients (73.7%), Densiron XTRA in 3 patients (15.8%), and AlaHeavy 1.07 in 2 patients. Heavy silicone oil emulsification was observed in only 3 patients (15.8%).

Conclusion: Although heavy silicone oil has limitations as an endotamponade, such as intraocular pressure increase, emulsification, intraocular inflammation, and the risk of complications during removal, it is a safe and effective alternative in eyes requiring inferior retinal tamponade for indications like proliferative vitreoretinopathy and recurrent macular holes.

Keywords: Heavy silicone oil, complicated retinal detachment, macular hole, proliferative vitreoretinopathy

Address for Correspondence: Rengin Aslıhan Kurt, Başkent University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
E-mail: renginakurt@yahoo.com **ORCID-ID:** orcid.org/0000-0002-9746-149X
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Introduction

Traditional endotamponades used during vitreoretinal surgery are air, sulfur hexafluoride (SF_6), octafluoropropane (C_3F_8), hexafluoroethane (C_2F_6), and silicone oils.[1] Silicone oil was first used as endotamponade in non-vitrectomized eyes in the 1960s, but the results were not very satisfying; in the 1980s, it was combined with pars plana vitrectomy and its clinical use increased.[2,3,4] Silicone consists of linear siloxane polymers, which are made of alternating silicon and oxygen molecules.[1] Due to its chemical structure, silicone can bind with organic and inorganic components and form polymers with different properties.[1,2] For example, silicone oils consist of polydimethylsiloxane (i.e., siloxane with two methyl side chains) and are divided into two groups, those lighter than water and those heavier than water.[1] There are two different types of light silicone oil, 1,000 centistokes and 5,000 centistokes. This group is lighter than water, with a specific gravity of 0.97. Therefore, when administered intraocularly, they are buoyant and provide more effective tamponade for the superior retina.[1] Because of this characteristic, they are not an ideal option in conditions such as proliferative vitreoretinopathy (PVR), inferior retinal tears, or macular surgery in which the patient cannot maintain a position. For these indications, heavy silicone oils may be more suitable endotamponade alternatives because they are heavier than water, with a specific gravity greater than 1.[1] Densiron 68 (Fluoron, Neu Ulm, Germany), Densiron XTRA (Fluoron, Neu Ulm, Germany), Oxane HD (Bausch & Lomb, Toulouse, France), and 11% silica solution are heavy silicone products used today.[5] AlaHeavy 1.07 (AlaMedics GmbH & Co. KG, Dornstadt, Germany), which was used in two of the eyes in our study, is no longer produced since the company's closure due to a problem with another product.[6,7] The chemical properties of these endotamponades are presented in Table 1. This study aimed to examine eyes that received heavy silicone oil in terms of anatomical and functional success, silicone emulsification, intraocular inflammation, presence of PVR, postoperative visual acuity, and postoperative complications and evaluate the safety of using heavy silicone oil.

Materials and Methods

This retrospective study was approved by the Başkent University Medical and Health Sciences Research Council (decision number: KA20/412) and was conducted in accordance with the principles of the Declaration of Helsinki. The study included 19 eyes of 19 patients who underwent pars plana vitrectomy due to recurrent retinal detachment, inferior rhegmatogenous retinal detachment, or macular hole between August 2015 and February 2020 and received heavy silicone as an endotamponade. At each visit, the patients underwent detailed ophthalmological examination and anatomical and functional success, silicone emulsification, intraocular inflammation, presence of PVR, preoperative and postoperative visual acuity, and postoperative complications were recorded.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 11.0, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR). Normal distribution was tested using skewness and kurtosis and histogram plots. Statistical comparisons between repeated measures of visual acuity were performed with the Wilcoxon signed-rank test and $p<0.05$ was considered significant for all analyses.

Results

Nineteen eyes of a total of 19 consecutive patients, 13 women (68.4%) and 6 men (31.6%), were included in the study. The patients' median age was 60 years (IQR: 44-70 years) and the median follow-up time was 19 months (IQR: 9-31 months). Indications for heavy silicone oil endotamponade were recurrent retinal detachment in 11 patients (57.8%), inferior rhegmatogenous retinal detachment in 5 patients (26.3%), recurrent macular hole in 2 patients (10.5%), and macular hole in 1 patient (5.2%). The median best corrected visual acuity (BCVA) was 2 logMAR (IQR: 1-2.6) preoperatively and 0.99 logMAR (IQR: 0.4-2) postoperatively ($p<0.001$). Postoperative anatomical success was achieved in all patients. The demographic characteristics of the patients are shown in Table 2.

Before heavy silicone oil endotamponade, standard silicone endotamponade was administered to 63.2% of the patients once, to 26.3% of the patients twice, and to 10.5% of the patients three times. Densiron 68 was used for endotamponade in 14 patients (73.7%), Densiron XTRA in 3 patients (15.8%), and AlaHeavy 1.07 in 2 patients (10.5%). Heavy silicone oil emulsification

Table 1. Heavy silicone oils and their properties

Heavy silicone oil	Viscosity (mPas)	Specific gravity (g/cm^3)	Composition
Densiron 68	1400	1.06	69.5% 5000 centistoke silicone oil + 30.5% F_6H_8
Densiron XTRA	1350	1.06	69.5% heavy silicone oil with 10% high molecular weight additive + 30.5% F_6H_8
Oxane HD	3300	1.02	80.1% silicone oil + 11.9% RMN3
AlaHeavy	1100	1.07	Homogenized fluorosilicone oil
Silica solution (aerosil)	2000	1.11	11% silica + 89% silicone oil

Table 2. Demographic and clinical characteristics of the patients

Patient no.	Diagnosis	Sex	Age (years)	Preop BCVA (logMAR)	Postop BCVA (logMAR)	No. of silicone injections	Silicone type	Silicone residence time (days)	Silicone emulsification	PVR	IOP increase	Hypotony	Follow-up time (months)
1	RRD	M	70	2.6	2.0	2	Densiron 68	120	-	+	-	-	6
2	RMH	M	87	1.0	2.3	1	Densiron 68	105	-	-	+	-	31
3	MH	F	65	1.33	0.2	1	Densiron 68	90	-	-	-	+	9
4	RRD	M	33	2.6	0.8	3	Densiron 68	120	-	-	+	-	34
5	RRD	F	63	2.6	0.3	1	Densiron 68	90	-	+	-	-	10
6	RRD	M	38	0.8	0.8	2	Densiron 68	900	-	-	+	+	25
7	RRD	M	58	2.6	0.8	1	Densiron 68	180	-	-	-	+	20
8	RRD	M	44	2.0	1.33	3	Densiron 68	30	-	-	-	-	15
9	RRD	M	60	1.33	0.8	2	Densiron 68	60	-	+	+	-	19
10	RD	M	54	0.8	0	1	Densiron 68	30	+	-	-	-	49
11	RD	F	39	2.6	2.0	2	Densiron 68	60	-	-	-	-	40
12	RRD	M	72	2.6	1.0	1	Densiron 68	180	-	+	-	-	21
13	RRD	F	41	2.0	0	1	Densiron 68	45	-	-	-	-	39
14	RRD	M	60	2.6	2.3	2	AlaHeavy 1.07	21	+	-	-	-	22
15	RRD	M	46	2.0	0.48	1	AlaHeavy 1.0	47	+	-	-	+	10
16	RMH	F	73	0.7	0.4	1	Densiron 68	30	-	-	+	-	4
17	RD	M	80	1.33	1.0	1	Densiron Xtra	80	-	-	+	-	3
18	RD	F	49	1.0	0.48	1	Densiron Xtra	10	-	-	-	-	12
19	RD	M	62	2.6	2.0	1	Densiron Xtra	300	-	+	-	-	1

No: Number, RRD: Recurrent retinal detachment, RD: Retinal detachment, RMH: Recurrent macular hole, MH: Macular hole, M: Male, F: Female, BCVA: Best corrected visual acuity, PVR: Proliferative vitreoretinopathy, IOP: Intraocular pressure

was observed in only 3 patients (15.8%). Two patients with emulsification received AlaHeavy 1.07 and the other patient received Densiron 68 for endotamponade. Emulsification was observed on postoperative day 21 and 47 in the 2 patients with AlaHeavy 1.07 and on day 30 in the patient with Densiron 68. The median intraocular residence time of the heavy silicone oil was 80 days (IQR: 30-120 days). The silicone endotamponade could not be removed in 2 patients (10.5%).

PVR was present at diagnosis in 5 of 19 patients (26.3%). In the postoperative period, 6 patients (31.6%) had increased intraocular pressure and 4 patients (21.1%) had hypotony. No intraoperative complications were observed during heavy silicone oil removal. Inflammation was not observed in any eye while the heavy silicone oil was present as an endotamponade.

Discussion

Vitreoretinal surgery outcomes are more satisfactory due to advances in instrumentation and intraocular tamponades over the last three decades. Despite these developments, cases with inferior retinal tears, PVR, recurrent retinal detachments, and macular holes are still difficult to treat.

As standard endotamponades could not meet the need for a more effective and long-lasting tamponade, especially for the inferior retina, the search began for heavier-than-water endotamponades in vitreoretinal surgery. Perfluorocarbon fluids, which were first used for this purpose by Chang et al.[8], facilitated intraoperative retinal manipulation due to their heavier-than-water formulations. Although their toxic structures do not allow them to remain in the eye for a long time, some authors have reported that liquid perfluorocarbon can be left in the eye for up to 2 weeks.[9,10] Fluorinated silicone oil, which is used for the same purpose, was also an effective endotamponade but is not widely used due to adverse effects such as early emulsification and intense intraocular inflammation.[11] These developments were followed by the use of semi-fluorinated alkanes as endotamponades. However, although they were shown to be well tolerated in animal studies, they were discontinued due to adverse effects in human eyes such as inflammation and retrolental and epiretinal membrane formation.[12] Therefore, as vitreous equivalents that are heavier than water but are well tolerated by the eye, heavy silicone oils have assumed an important place as endotamponades in certain cases.[1,5]

PVR is known to be mediated by growth factors and cytokines originating from inflammatory cells, retinal pigment epithelial cells, fibroblasts, glial cells, and the aqueous humor.[13,14] When lighter-than-water tamponades are used and the inferior retina is not adequately stabilized, the shift of aqueous humor to this region results in potential development of PVR. Although it is theorized that heavy silicone oil prevents PVR formation by exerting a barrier function between the aqueous humor and retinal PVR precursor cells, it has been shown that this is not the case in practice.[1] The Heavy Silicone Oil study, the first multicenter, randomized, controlled prospective study comparing PVR inhibition by heavy silicone oil and standard silicone oil demonstrated no difference between the two endotamponades. In our series, PVR was detected at diagnosis in 5 of 19 patients (26.3%), but no patient developed PVR under the heavy silicone endotamponade or after removal.[15,16]

Heavy silicone oils have been shown to be well tolerated in the eye for periods of 3-4 months, but the risk of causing intraocular inflammation increases when left for more than 6 months.[17,18] In their series of 75 patients, Dooley et al.[19] compared complications in 39 eyes with temporary heavy silicone oil endotamponade and 36 eyes with permanent heavy silicone oil endotamponade. Complications such as recurrent detachment, corneal pathology, secondary glaucoma, and emulsification were significantly more frequent in the 36 eyes from which endotamponade could not be removed for various reasons when compared with the 39 eyes with early tamponade removal. In our series, heavy silicone oil could not be removed in two cases due to hypotony, but no serious adverse effects were observed in these cases. One of these patients underwent pars plana vitrectomy with standard silicone oil tamponade twice due to giant tear retinal detachment secondary to degenerative myopia, and redetachment was observed after each silicone removal. As retinal reattachment could only be achieved with Densiron 68 and intraocular pressure is below 8 mmHg, this patient has been monitored for 30 months without removing the silicone (Figure 1). Similarly, in our other patient, Densiron 68 was not removed for 10 months due to hypotony.

Increased intraocular pressure after pars plana vitrectomy with silicone oil endotamponade may occur for different reasons, such as silicone oil emulsification and obstruction of the trabecular network, surgery-induced intraocular inflammation, or long-term corticosteroid use. The prevalence of intraocular pressure increase after heavy silicone oil endotamponade was 31.6% in our series, while this rate ranges from 0.3% to 33% in different series in the literature.[20,21,22,23] Wong et al.[24] compared the effects of light and heavy silicone oil on intraocular pressure and determined that patients who received heavy silicone oil had higher intraocular pressures in the first two weeks postoperatively, but there was no significant difference between the groups at 4 weeks. Ocular hypotony occurred in 4 (21.1%) of 19 patients in our series. In two studies using Densiron 68, Sandner and Engelmann[25] and Li et al.[26] reported hypotony at rates of 2% and 11%, respectively, while Wickham et al.[27] reported a rate of 17% in their study using Oxane HD. In our series, three patients who developed ocular hypotension showed spontaneous improvement, but one required viscoelastic injection into the anterior chamber.

Silicone oil emulsification was observed in 3 (15.8%) of 19 patients in our series, 2 of whom received AlaHeavy 1.07 for endotamponade and 1 of whom received Densiron 68. In the literature, emulsification rates between 1% and 24% have been reported in studies conducted with Densiron 68 and between 11% and 33% in studies conducted with Oxane HD.[18,28,29,30,31,32] Sandner and Engelmann[25] showed that heavy silicone oil is more

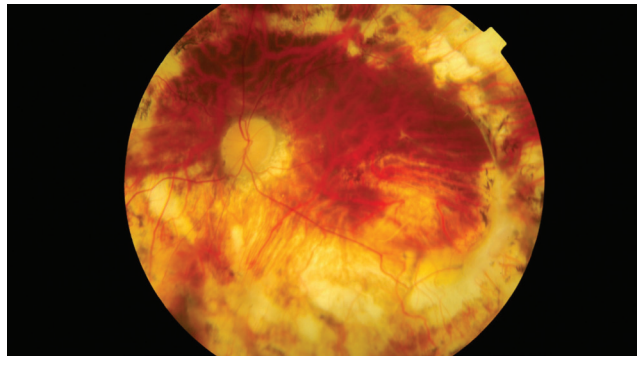

Figure 1. One patient underwent pars plana vitrectomy with standard silicone oil tamponade twice due to giant tear retinal detachment secondary to degenerative myopia, and redetachment was observed after each silicone removal. As retinal reattachment could only be achieved with Densiron 68 and intraocular pressure is below 8 mmHg, this patient has been monitored for 30 months without removing the silicone

prone to emulsification than standard silicone oil. Similarly, Caramoy et al.[33] found in their *in vitro* study that semi-fluorinated fluorocarbon made silicone more hydrophilic, and that Densiron is more prone to emulsification for this reason. Caramoy et al.[33] and Lu et al.[34] both determined that Densiron XTRA was more resistant to emulsification due to a 10% high molecular weight silicone additive to the chemical structure.

Kociok et al.[35] showed that emulsified silicone oil particles induce inflammatory cell chemotaxis and phagocytosis. Based on this finding, we believe that the absence of intraocular inflammation in any of the patients in our study during follow-up is related to the low prevalence of emulsification. Semeraro et al.[36] compared the intraocular inflammation inducing effects of heavy silicone oil and conventional silicone oil by measuring prostaglandin E2 and interleukin-1α levels in the aqueous humor and reported that heavy silicone oil had higher inflammatory potential than standard silicone oil.

In a prospective study by Avitabile et al.[20], the anatomical success rate in degenerative myopic eyes with posterior staphyloma was found to be higher in the group using heavy silicone oil than in the group using standard silicone oil. In our series, one patient received heavy silicone oil due to giant tear retinal detachment secondary to degenerative myopia, and the heavy silicone oil could not be removed in this case because the retina only remained attached with permanent silicone endotamponade (Figure 1).

Another advantage of heavy silicone oils is elimination of the need for postoperative positioning in patients with mental retardation, orthopedic problems, or comorbidities and in pediatric cases.[17] In our series, heavy silicone oil endotamponade was used in 3 patients with macular hole, two of which were recurrent, as the patients were unable to maintain positions due to preexisting orthopedic problems and low compliance.

In the literature, reports vary widely regarding anatomical success rates with pars plana vitrectomy and heavy silicone oil endotamponade. In our series, the anatomical success was 100%, with significant visual improvement from a median preoperative BCVA of 2 logMAR (IQR: 1-2.6) to a median postoperative BCVA of 0.99 logMAR (IQR: 0.4-2) ($p<0.001$). In a study by Ozdek et al.[37] using Oxane or Densiron in 41 patients, the anatomical success rate was 88%. In another study of 49 eyes, Caporossi et al.[38] used Densiron and reported a success rate of 61.2% after the first surgery and 81.6% after the second surgery, with redetachment occurring under intraocular heavy silicone in 19 eyes. Berker et al.[39] reported anatomical success in 85.7% and visual improvement in 71.4% at a mean follow-up of 5 months in a series of 21 patients that received Oxane HD. In another study from Turkey using Densiron, Aslankurt et al.[40] reported an anatomical success rate of 88%. Considering all of these different rates, it should be kept in mind when interpreting the success of heavy silicone endotamponade that most patients are complicated cases that have undergone one or more vitreoretinal surgeries. In addition, the most important disadvantage of heavy silicone oil, especially for developing economies, is its high price.

Study Limitations

The small number of patients, retrospective study design, and absence of a standard silicone oil control group are limitations of our study.

Conclusion

Heavy silicone oil is an effective and reliable endotamponade in patients with recurrent retinal detachment and macular hole, in the presence of PVR, and in patients who require inferior retinal support.

Ethics

Ethics Committee Approval: Başkent University Medical and Health Sciences Research Council (decision number: KA20/412).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.K., Concept: Z.K., Design: Z.K., R.A.K., Data Collection or Processing: R.A.K., Analysis or Interpretation: Z.K., R.A.K., Literature Search: Z.K., R.A.K., Writing: R.A.K.

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Review

Surgical Approach in Intraocular Tumors

Ahmet Kaan Gündüz, Ibadulla Mirzayev

Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

Surgery in intraocular tumors is done for excision/biopsy and the management of complications secondary to the treatment of these tumors. Excision/biopsy of intraocular tumors can be done via fine-needle aspiration biopsy (FNAB), transretinal biopsy (TRB), partial lamellar sclerouvectomy (PLSU), and endoresection. FNAB, TRB, and PLSU can be used in tumors that cannot be diagnosed by clinical examination and other ancillary testing methods. PLSU is employed in tumors involving the iridociliary region and choroid anterior to the equator. Excisional PLSU is performed for iridociliary and ciliary body tumors with less than 3 clock hours of iris and ciliary body involvement and choroidal tumors with a base diameter less than 15 mm. However, for biopsy, PLSU can be employed with any size tumor. Endoresection is a procedure whereby the intraocular tumor is excised using vitrectomy techniques. The rationale for performing endoresection is based on the fact that irradiated uveal melanomas may cause complications such as exudation, neovascular glaucoma, and intraocular pigment and tumor dissemination (toxic tumor syndrome), and removing the dead tumor tissue may contribute to better visual outcome. Endoresection is recommended 1-2 weeks after external radiotherapy. Pars plana vitrectomy is also used in the management of complications including vitreous hemorrhage, retinal detachment, and epiretinal membrane that can occur after treatment of posterior segment tumors using radiotherapy and transpupillary thermotherapy. It is important to make sure the intraocular tumor has been eradicated before embarking on such treatment.

Keywords: Intraocular tumors, ciliary body tumor, choroidal tumor, fine needle aspiration biopsy, partial lamellar sclerouvectomy, endoresection, pars plana vitrectomy, radiotherapy

Address for Correspondence: Ahmet Kaan Gündüz, Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: drkaangunduz@gmail.com **ORCID-ID:** orcid.org/0000-0001-5945-5657
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Introduction

Surgical approaches related to intraocular tumors can be summarized under two main headings: procedures performed for tumor excision/biopsy and procedures to manage complications secondary to treatment of the tumor.

The first intraocular biopsy was performed by Hirschberg in 1868.[1] Intraocular biopsy techniques have evolved over the years and are used in the diagnosis of malignant tumors before treatment. The intraocular biopsy technique used may vary depending on tumor location, size, and tumor-associated findings.[2] Intraocular tumor biopsy is performed by fine-needle aspiration biopsy (FNAB), pars plana vitrectomy (PPV) with transretinal biopsy (TRB), and partial lamellar sclerouvectomy (PLSU).

The first experiences with intraocular tumor excision date back approximately 100 years. The first excision of malignant tumors in the iris and ciliary body region was performed by Zirm in 1911.[3] In 1961, Stallard[4] introduced a new approach to intraocular tumor surgery. After forming a scleral flap, he excised the choroidal tumor by performing diathermy to the underlying sclera, choroid, and retina.[4] Foulds[5] also described a similar surgical technique. In the opposing school, Meyer-schwickerath[6] and Peyman et al.[7] excised tumors by performing a full-thickness eye wall (including sclera) excision including the tumor tissue. Of these two techniques, the method based on excising the underlying tumor after forming a scleral flap (i.e., the technique pioneered by Stallard and Foulds) was more widely adopted.[3] This surgical technique has been given various names, such as iridocyclectomy, PLSU, transscleral local resection, and exoresection. Regarding PLSU surgery, reports with large case numbers from Shields and Shields,[8] Shields et al.,[9] Damato,[10] made especially enlightening contributions to the ocular oncology literature.

Today, PLSU surgery is mainly performed for uveal melanomas. It can also be utilized for various tumors that are confused for melanoma or are known to be benign but still require excision, such as melanocytoma, medulloepithelioma, pigmented ciliary body adenoma, non-pigmented ciliary body adenoma (Fuchs' adenoma), schwannoma, and leiomyoma. External resection is widely used for iris and ciliary body tumors. This type of surgical resection can also be performed with peripheral choroidal and ciliochoroidal tumors. However, most surgeons avoid external tumor resection for choroidal tumors close to the optic disc and fovea.

Endoresection surgery refers to intraocular tumor excision using vitreoretinal surgery methods. This procedure was first described in 1988 by Peyman and Charles,[12] who used the term "internal eyewall resection" for this surgery. Damato et al.[13,14] further developed this surgical technique in the following years and named it endoresection.

Surgical procedures related to tumor excision/biopsy are grouped under the headings of FNAB, TRB, PLSU, and endoresection. In our review, these procedures will be discussed in turn. Surgical procedures for treatment complications will also be reviewed.

Fine-needle Aspiration Biopsy

FNAB, which is the most commonly used biopsy method for the diagnosis of intraocular tumors, can be performed via a transvitreal or transscleral approach. Transvitreal FNAB is performed for tumors posterior of the equator and transscleral FNAB is performed for tumors anterior of the equator. For tumors posterior to the equator, FNAB is performed by inserting a 22-27 gauge (G) needle into the eye at a distance of 3.5-4.0 mm from the limbus and advancing it into the tumor under indirect ophthalmoscopy.[15] Biopsy material is aspirated by pulling back the injector connected to the needle with a tubing line. At the end of the procedure, balanced salt solution is drawn into the syringe to collect fragments remaining in the needle and connector tubing.

The main limitations of the FNAB technique are the difficulty of navigating the needle into the tumor under indirect ophthalmoscopy and the possibility of obtaining insufficient material for pathological examination. Rates of obtaining adequate cytological material from FNAB have been reported as between 64.7% and 88.1%.[16,17,18] Complications such as vitreous hemorrhage, subretinal hemorrhage, and extraocular spread of tumor cells may occur after FNAB.[19,20,21] Considering these complications, it is essential that the material obtained by FNAB is evaluated by an experienced cytologist.

Transretinal Biopsy with Pars Plana Vitrectomy

In ciliary body and choroidal tumors, biopsy can be performed via the scleral route (i.e., using the PLSU approach described previously) or via PPV (Figure 1a-f and Figure 2a, b). TRB via PPV was originally performed with 20G vitrectomy, whereas 23G, 25G, and 27G vitrectomy systems are used today. A 3-port vitrectomy is performed. The vitrector is advanced into the tumor via the transretinal route and tumor tissue is aspirated using an injector connected to the vitrector to obtain material for cyto/histopathology. During this surgery, some clinicians perform additional procedures such as posterior hyaloid removal, total vitrectomy endolaser application to the biopsy area, laser photocoagulation endocerclage, fluid-air exchange, and gas-air exchange. Iatrogenic retinal tears can be treated effectively with this approach. However, performing minimal surgery is the more common approach in TRB. In minimal surgery, TRB is also performed via a three-port vitrectomy approach.[22] However, only ocutome-assisted retinal/choroidal tumor biopsy is performed, while other surgical procedures such as vitrectomy and intraocular gas injection are not employed. Performing all vitreoretinal surgical procedures is more appropriate in patients with significant exudative retinal detachment overlying and surrounding the tumor. In contrast, TRB alone can be performed if there is no or minimal fluid over the tumor. Applying endolaser around the biopsy entry site during TRB is also useful to create chorioretinal adhesions.

In cases of suspected primary vitreoretinal lymphoma in which vitreous aspiration does not provide sufficient yield, a retinal and choroidal biopsy should be performed because lymphoma infiltration is present under the retinal pigment epithelium. In

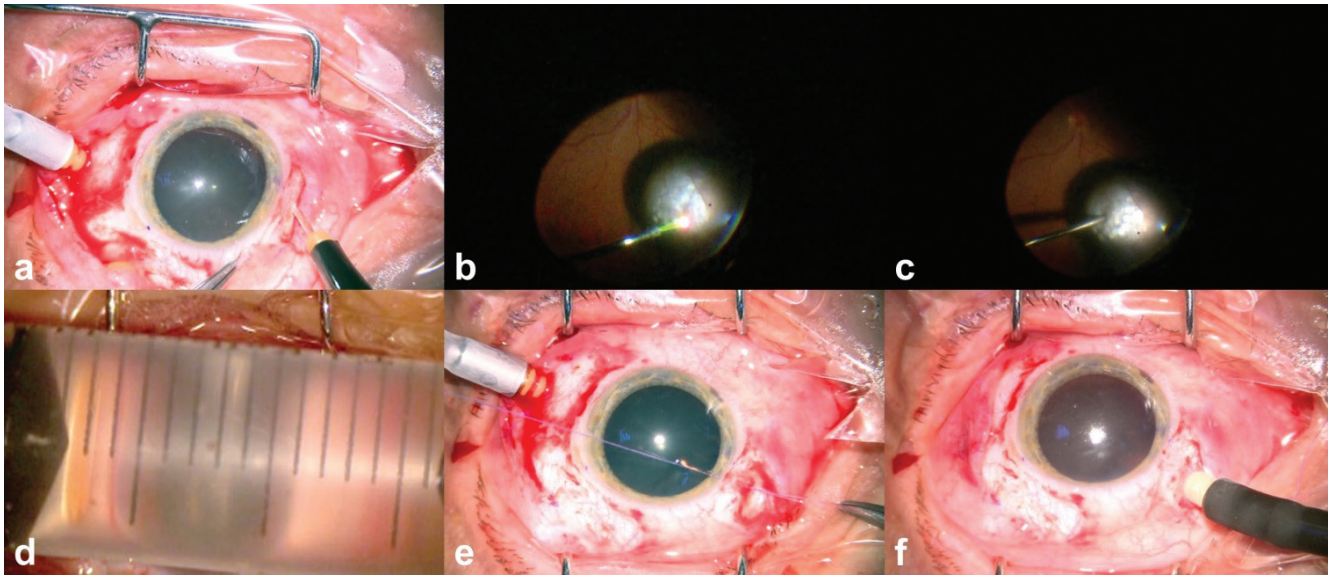

Figure 1. Intraoperative images from transretinal biopsy surgery. a) The trocar is advanced into the eye. b) Endolaser photocoagulation spots are seen on the tumor surface. c) The vitrector is inserted into the tumor during biopsy. d) After transretinal biopsy, the injector is checked for sufficient biopsy material. e) The sclerotomy is sutured. f) At the end of the procedure, triple freeze-thaw cryotherapy is performed after suturing

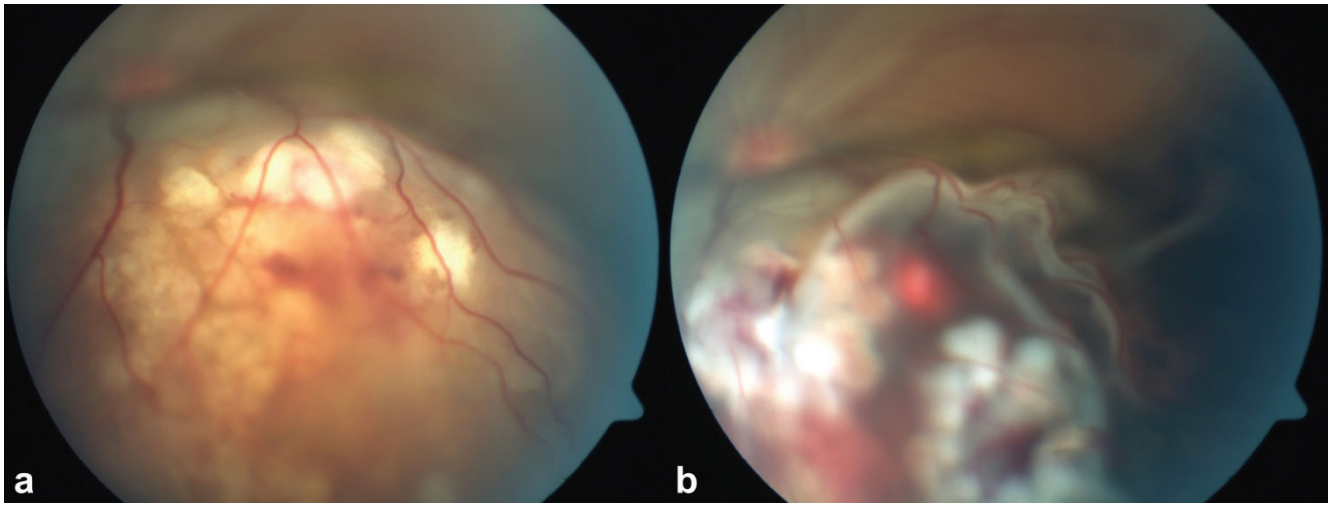

Figure 2. Preoperative and postoperative fundus photographs of a 56-year-old woman with metastatic choroidal tumor who underwent transretinal biopsy. a) An amelanotic tumor that could represent choroidal metastasis is observed on the inferotemporal aspect of the optic disc. However, since the possibility of melanoma could not be completely ruled out, it was decided to perform a transretinal biopsy of the tumor. b) At 1 week after pars plana vitrectomy and transretinal biopsy, endolaser spots and subretinal hemorrhage are observed around the tumor entry site

these cases, the minimal surgery approach discussed above may be insufficient, and all necessary vitreoretinal surgical procedures need to be performed.

In the series reported in the literature, TRB provided sufficient material for pathological examination in 88.9% to 100% of cases.[22,23,24,25,26,27,28,29] Choroidal melanoma was detected in 50-100% of cases in cyto/histopathological examination of TRB material.[22,23,24,25,26,27,28,30,31,32] Therefore, TRB is mostly performed for the diagnosis of uveal melanoma. Other diagnoses include metastasis, lymphoma, retinal vasoproliferative tumor (RVT), choroidal hemangioma, choroidal plasmacytoma, choroidal neovascularization, and subretinal hemorrhage. The results of cyto/histopathology examination of TRB materials reported in the literature are presented in Table 1.

TRB-related complications reported in 354 cases included vitreous hemorrhage (n=151, 42.7%), retinal detachment (n=11, 3.1%), transient intraocular pressure increase (n=6, 1.7%), glaucoma (n=1, 0.3%), hyphema (n=1, 0.3%), macular hole (n=1, 0.3%), choroidal neovascularization (n=1, 0.3%), and phthisis bulbi (n=1, 0.3%).[22,24,26,27,28,30,31,32,33] Complications reported in previous studies on TRB are summarized in Table 2.

Table 1. Pathological examination results after transretinal biopsy via pars plana vitrectomy reported in the literature

Pathological examination method	Number of eyes	CM n (%)	Met n (%)	Lym n (%)	RVT n (%)	CH n (%)	RPE Ad n (%)	RAH n (%)	Deg n (%)	CP n (%)	CNV n (%)	SH n (%)	Mm n (%)	Gliosis n (%)	Sclerit n (%)	IS n (%)	Unspecified n (%)
Cyto[26,27,31]	75	58 (77.3)	5 (6.7)	2 (2.7)		1 (1.3)	1 (1.3)	1 (1.3)	4 (5.3)					1 (1.3)		2 (2.7)	
Histo[22,24,25,28,29]	222	164 (73.9)	14 (6.3)	10 (4.5)	2 (0.9)					1 (0.5)	1 (0.5)	3 (1.4)	2 (0.9)	1 (0.5)	2 (0.9)	6 (2.7)	16 (7.2)
Cyto/ Histo[32*]	9	9 (100)															

Cyto: Cytopathology, Histo: Histopathology, CM: Choroidal melanoma, Met: Metastasis, Lym: Lymphoma, RVT: Retinal vasoproliferative tumor, CH: Choroidal hemangioma, RPE Ad: Retinal pigment epithelium adenoma, RAH: Retinal astrocytic hamartoma, Deg: Degeneration, CP: Choroidal plasmacytoma, CNV: Choroidal neovascularization, SH: Subretinal hemorrhage, Mm: Melanomacrophages, IS: Inadequate sample, *Diagnosis was confirmed by cytopathological examination in 7 cases and histopathological examination in 2 cases

Partial Lamellar Sclerouvectomy (PLSU, Exoresection)

PLSU can be performed for excision or biopsy of tumors involving the ciliary body and/or choroid. Although there are limitations with respect to tumor size for tumor excision, biopsy can be performed for any size tumor. The surgical methods used for ciliary/choroidal tumors with and without iris involvement are based on the same basic principle but differ in some respects. Therefore, these two procedure types will be discussed separately.

Iridocyclectomy and Iridociliochoroidectomy

Anesthesia

The procedure is performed under hypotensive anesthesia, with systolic blood pressure maintained at approximately 50-70 mmHg. If it is not possible for the patient to receive hypotensive anesthesia, systolic blood pressure should be kept as low as possible.

Surgical Indication and Technique

PLSU is recommended for ciliary body tumors involving at most 3 clock hours. The pupil should not be dilated in excisions of tumors involving the iris. Pupil dilation can be done in masses involving the ciliary body and/or choroid. PLSU is a difficult surgical technique with a pronounced learning curve (Figure 3a-e and Figure 4a-f). Following approximately 240-degree conjunctival peritomy, traction sutures are placed under 2-3 rectus muscles adjacent to the tumor using 3-0 or 4-0 silk sutures. Tumor location is determined by transillumination. If the tumor is under the muscle or at the insertion site, muscle disinsertion with 6-0 vicryl is necessary.

A limbus-based scleral flap is prepared. The flap should be 2-3 mm larger than the tumor on each side. An 80% to 90% thickness scleral flap is dissected up to the limbus. Then, 0.5 to 1 cc of core vitreous is aspirated. A vitrectomy ocutome should be used for this purpose. Following a pars plana sclerotomy 3.5-4 mm from the limbus, the ocutome probe is advanced up to 1 cm into the eye, core vitrectomy is performed, and the vitreous is aspirated with an injector connected to the ocutome. Wide-angle imaging systems are not used at this stage because the pupil is not dilated and no port is made for the endoilluminator. After vitrectomy is completed, the sclerotomy is sutured with 7-0 vicryl. In the past, vitreous aspiration was performed with a 20-22G needle advanced through the pars plana into the eye instead of an ocutome.[8,9,34] However, vitreous aspiration with a needle increases the risk of retinal traction.

After vitreous aspiration via vitrectomy, the eye pressure becomes hypotonus. The deep scleral fibers are excised to expose the intact ciliary body around the tumor. Bipolar cautery is applied to the healthy ciliary body surrounding the tumor. Then, a limbal incision is made to access the anterior chamber. The corneoscleral incision is enlarged with Westcott scissors. The tumor surrounded by cauterized ciliary body is excised using Vannas scissors starting at the ciliary body and continuing with the iris. Attempts are made to spare the pupil. The tumor is then excised by scraping off the unpigmented ciliary epithelium with a Weck-Cel sponge. Attention is paid not to rupture the

unpigmented ciliary epithelium, as this will result in vitreous loss. If vitreous loss occurs, vitrectomy should be performed at the wound edges with an ocutome. The scleral flap is then sutured in place using 8-0 or 9-0 nylon.[3,8,9,11] After closure, vitrectomy is repeated at the wound margins to ensure removal of remaining vitreous fibers.

The results of histopathological examination after exoresection reported in the literature are shown in Table 3. Iridocyclectomy is performed in tumors involving less than one-third of the ciliary body and angle region.[9,35,36] There is a risk of hypotony in tumors with greater involvement. In such tumors, treatment with plaque radiotherapy or proton beam radiotherapy instead of surgical excision may be more appropriate.[37,38]

Complications

The most important intraoperative problem in PLSU surgery is the risk of vitreous hemorrhage.[8,9,11,34,39]

Table 2. Summary of complications after transretinal biopsy via pars plana vitrectomy reported in the literature

Study, date of publication	Number of eyes	VH n (%)	New RD n (%)	Increase in existing RD n (%)	MH n (%)	Hyphema n (%)	IOP increase n (%)	Phthisis n (%)	CNV
Kvanta et al., 2005[28]	10	1 (10)	1 (10)	1 (10)				1 (10)	
Angi et al., 2008[33]	1*								1
Abi-Ayad et al., 2013[32]	9	8 (88.9)							
Seregard et al., 2013[24]	43			5 (11.6)			6 (14.0)		
Bagger et al., 2013[22]	85	82 (96.5)†	5 (5.9)						
Nagiel et al., 2017[27]	17	14 (82.4)†							
Grewal et al., 2017[26]	18	13 (72.2)	2 (11.1)	2 (11.1)					
Angi et al., 2017[30]	131	17 (13.0)	2 (1.5)						
Gündüz et al., 2020[31]	40	16 (40.0)	1(2.5)		1 (2.5)	1 (2.5)	1 (2.5)		

VH: Vitreous hemorrhage, RD: Retinal detachment, MH: Macular hole, IOP: Intraocular pressure, CNV: Choroidal neovascularization.
*Case report
†VH spontaneously regressed in 71 of 82 cases.
‡Of 14 cases, 13 had focal and 1 had diffuse VH

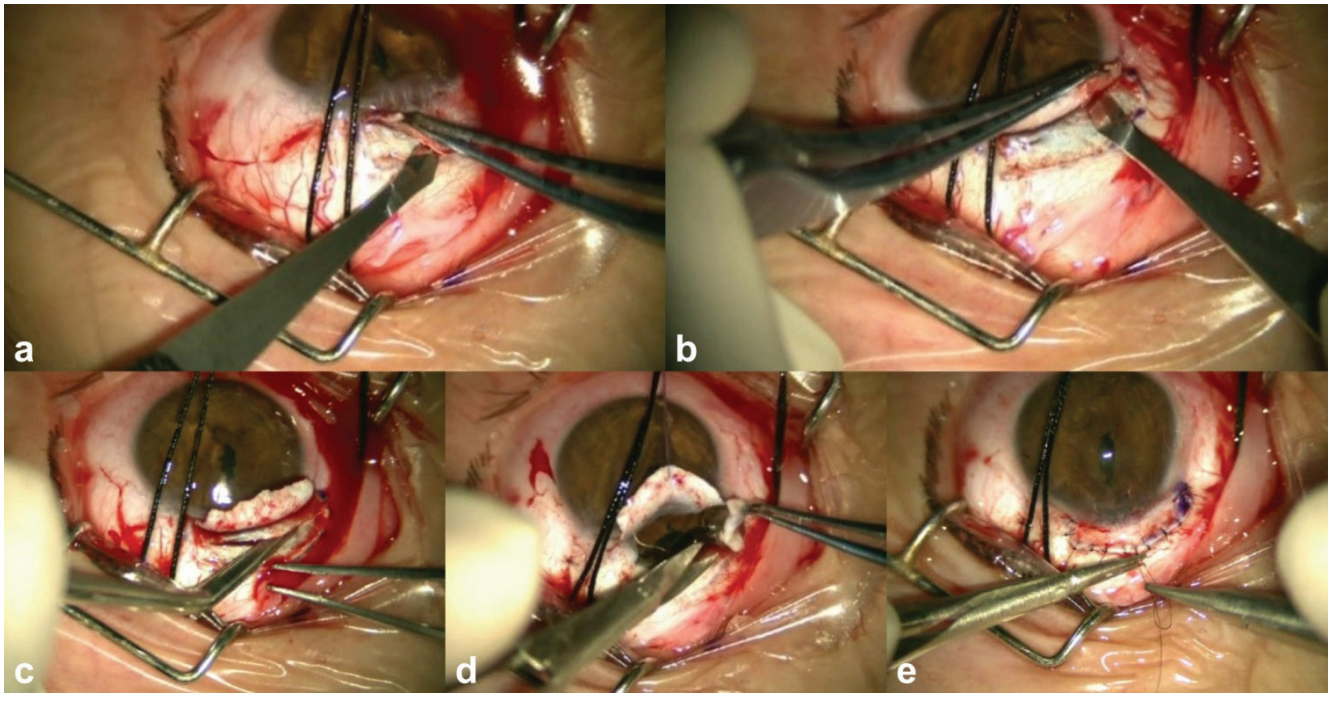

Figure 3. Intraoperative images from a partial lamellar sclerouvectomy surgery. a) A scleral flap of approximately 80-90% thickness is prepared with a #57 beaver knife. b) The flap is dissected up to the corneoscleral limbus. c) A full-thickness incision is made to expose the underlying uveal tissue. d) Tumor excision is performed using Vannas scissors. e) The scleral flap is sutured in place

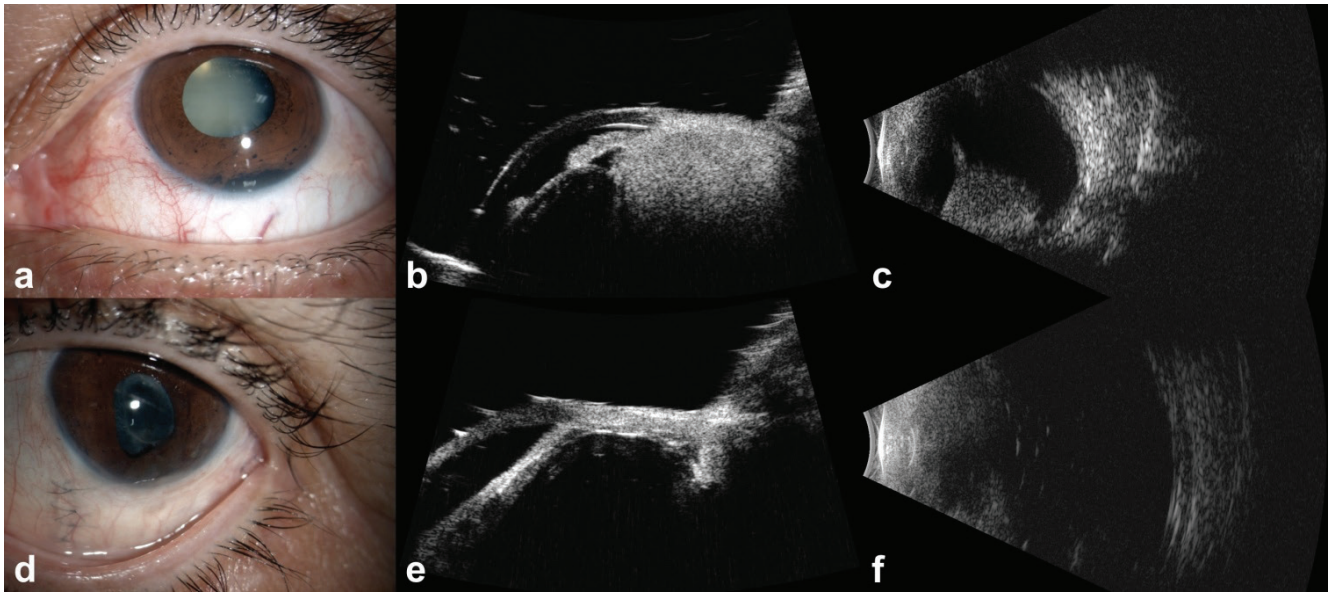

Figure 4. Photographs of a patient with melanoma with iridociliochoroidal involvement who underwent partial lamellar sclerouvectomy. a) Anterior segment image shows iridociliochoroidal melanoma in the left eye. The patient has mature cataract. b) Ultrasonic biomicroscopy shows a 4.1-mm thick acoustically hollow melanoma in the ciliary body region. c) B-mode ultrasonogram shows the choroidal component of the tumor. Choroidal tumor thickness is measured as 6.2 mm. d) In the postoperative anterior segment image, the inferior iridectomy after partial lamellar sclerouvectomy is not visible due to anterior synechia. Nylon sutures are seen in the sclera. e) No ciliary mass is observed in ultrasonic biomicroscopy at postoperative 6 months. f) No residual choroidal tumor or retinal detachment is observed in the silicone-filled eye on B-mode ultrasonogram at postoperative 6 months

Mild vitreous hemorrhage may occur while excising the tumor, but this hemorrhage resorbs spontaneously and is rarely a permanent problem. If vitreous loss occurs during tumor excision, vitrectomy should be performed with an ocutome to clear the wound margins from the vitreous.

Anteriorally located melanomas involving the iris and ciliary body compress the lens, causing notching and cataract. Cataract may also increase due to surgical trauma.[40,41] Postoperative hypotension may occur if the scleral flap is superficial or is of normal thickness but not well sutured. Excising more than one-third of the ciliary body carries the risk of hypotony. If the scleral flap is thinner than expected, anterior staphyloma may develop.[8,9,11,34,39]

Retinal detachment is not observed as long as the tumor is located anterior to the muscle insertions. The risk of retinal detachment is greater in choroidectomy procedures. Apart from these, hyphema, ptosis, corneal edema, and increased intraocular pressure may be seen in the early postoperative period.[8,9,11,34,39] The complications reported in previous publications related to exoresection are summarized in Table 4.

Cyclochoroidectomy or Choroidectomy

Surgical Indication and Technique

In tumors with posterior uveal involvement, the surgical technique differs slightly compared to iridociliary tumors. The hinge of the sclera flap is usually arranged to open posteriorly, toward the optic nerve. As there is no anterior chamber access or iris resection, the pupil can be dilated in this surgery and the ocutome probe's position in the vitreous cavity can be observed through the pupil during vitreous aspiration. The steps of the surgery are the same as those described for iridocyclectomy. The only difference here is that there is no entry into the anterior chamber. Firstly, the sclera flap is raised and vitrectomy is performed to make the eye pressure hypotonus. The deep scleral fibers are excised and bipolar cautery is applied to the ciliary body/choroid, followed by ciliary body/choroid excision and tumor removal by scraping from the underlying retina with a sponge. Retinal invasion may be present in mushroom-shaped tumors that rupture Bruch's membrane, and care must be taken to avoid retinal perforation. After the tumor is removed, the sclera flap is sutured in place with 8/0 or 9/0 nylon suture. In case of a retinal tear, PPV must be performed at the end of the procedure.

Peripheral choroidal, ciliary body, and ciliochoroidal tumors with a base diameter of <15 mm can be excised by this method. The risk of developing postoperative hypotony is high for iris and ciliary body tumors with more than 3 clock hours of involvement.[9,37,42] Although there is no clear consensus on the tumor thickness that can be removed with PLSU surgery, the accepted upper limit is 10 mm.[9,37,42] Enucleation is recommended for thicker tumors. In addition, it is preferable that the tumor does not extend more than 7 mm beyond the equatorial region of the eye. Scleral dissection and tumor excision become more difficult closer to the optic nerve.

Complications

Operative complications include retinal detachment and vitreous hemorrhage.[35,43] The risk of developing retinal detachment after excision is high, especially with tumors that

Table 3. Summary of histopathological examination results reported in previous studies on exoresection

Study, date of publication	Number of eyes	MM n (%)	Mel n (%)	Fuchs' Ad n (%)	CPE Ad n (%)	Leiomyoma, n (%)	Med n (%)	Granuloma n (%)	Nevus n (%)	Met n (%)	SCC n (%)	FB n (%)	Cyst n (%)	LGC n (%)	Gliosis n (%)	Hemorrhage n (%)	Sch n (%)
Shields et al., 1991[9]	95	81 (85.3)	4 (4.2)	4 (4.2)	2 (2.1)	2 (2.1)	1 (1.0)	1 (1.0)									
Char et al., 2001[35]	145	125 (86.2)	5 (3.4)		1 (0.7)	2 (1.4)			7 (4.8)	2 (1.4)	2 (1.4)	1 (0.7)					
Kurt and Gündüz, 2010[39]	22	16 (72.7)	2 (9.1)						4 (18.2)								
Ramasubramanian et al., 2012[36]	37	19 (51.4)	3 (8.1)			1 (2.7)	4 (10.8)		1 (2.7)				5 (13.5)	2 (5.4)	1 (2.7)	1 (2.7)	
Lee et al., 2013[3]	27	19 (70.0)	2 (7.0)	2 (7.0)	1 (4.0)	1 (4.0)	1 (4.0)										1 (4.0)
Mirzayev et al., 2021[47]	56	30 (53.6)	4 (7.1)	2 (3.6)					13 (23.2)	1 (1.8)			6 (10.7)				

MM: Malignant melanoma, Mel: Melanocytoma, Ad: Adenoma, CPE Ad: Adenoma of the ciliary pigment epithelium, Med: Medulloepithelioma, Met: Metastatic tumor, SCC: Squamous cell carcinoma, FB: Foreign body, LGC: Lacrimal gland choristoma, Sch: Schwannoma

infiltrate the retina. In the event of problems such as retinal detachment and vitreous hemorrhage, early vitreoretinal surgery is recommended. The success rate of vitreoretinal surgery decreases after the development of proliferative vitreoretinopathy. In this respect, vitreoretinal surgery for the treatment of complications should be performed at the end of the surgery or in the first postoperative days.[43] Other complications such as subretinal fibrosis, posterior synechia, glaucoma, cataract, and expulsive hemorrhage may also occur.[3,9,34,39]

Tumor Recurrence, Visual Prognosis, and Life Expectancy After PLSU

According to the results of the Collaborative Ocular Melanoma Study (COMS), intrascleral tumor cells are present in 57% of enucleated choroidal melanomas.[44] In addition, there is the possibility of microscopic tumor cells remaining in the surrounding choroid after surgery. For this reason, some authors recommend administering Ruthenium-106 plaque radiotherapy to deliver a dose of 100 Gy radiotherapy to a depth of 1 mm, either at the end of the procedure or within the first postoperative month.[45,46,47] Postoperative plaque radiotherapy reduces the likelihood of recurrence due to intrascleral melanoma cells.

In their PLSU series including 112 cases, Damato[48] reported that the rate of eye preservation was 88% and the proportion of patients with vision of 0.1 or better was 58%. Tumor recurrence occurred in 11 eyes, 8 of which did not receive plaque radiotherapy after PLSU. Retinal detachment developed in 9 eyes with a mean tumor diameter of 15 mm and thickness of 9 mm. As these eyes would normally be treated by enucleation, the authors considered this complication rate acceptable.[48]

Bechrakis et al.[49] reported that larger tumor base diameter, older patient age, lack of adjuvant plaque radiotherapy, and preoperative retinal detachment were risk factors for tumor recurrence after PLSU. The visual prognosis after PLSU depends on tumor location. Visual prognosis is better with nasal tumors and tumors located more than 1 disc diameter from the optic disc and fovea.[50]

Bechrakis et al.[49] and Augsburger et al.[51] evaluated the effect of PLSU surgery on survival prognosis and found that life expectancy after PLSU was equivalent to that obtained by plaque radiotherapy. In other words, PLSU surgery is not disadvantageous in terms of life expectancy. The prevalence of metastasis was reported to be 7% (5 of 95 patients) in a series by Shields et al.[9] and 15% (52 of 332 patients) in a series by Damato et al.[52]

Endoresection Surgery

Endoresection techniques have recently been adopted in the treatment of choroidal melanomas (Figures 5a-f and 6a, b). Residual tumor after radiation causes toxic tumor syndrome through the release of various cytokines and neuromediators, resulting in complications such as neovascular glaucoma, retinopathy, exudation, and retinal detachment.[53] In addition, tumor necrosis leads to the dispersion of pigment and necrotic tumor fragments into the eye, which makes it difficult to observe the tumor by indirect ophthalmoscopy. Endoresection prevents these complications by removing the tumor debris.[12,13,54]

Table 4. Summary of complications after exoresection surgery reported in the literature

Study, date of publication	Number of eyes	VH n (%)	Hyp n (%)	Hem n (%)	RD n (%)	CD n (%)	Pto n (%)	Cat n (%)	CC n (%)	Sy n (%)	CME n (%)	IOP ↑ n (%)	Fib n (%)	ST n (%)	ERM n (%)	VRT n (%)	Hypo n (%)	İN n (%)	ID n (%)	SO n (%)	ON n (%)
Shields et al., 1991[9]	95	79 (83.1)	32 (33.7)	33 (34.7)	26 (27.4)	23 (24.2)	12 (12.6)	32 (33.7)	8 (8.4)	20 (21.1)	13 (13.7)	8 (8.4)	25 (26.3)					2 (2.1)			
Damato, 1997[45]	163				49 (30.0)			25 (15.3)													
Char et al., 2001[35]	145				19 (13.1)							2 (1.4)									
Damato ve ark, 2002[43]	156				28 (17.9)																
Bechrakis et al., 2002[49]	36	*			*			14 (44.4)				2 (5.6)						2 (5.6)			
Kivelä et al., 2003[40]	49	**			14 (28.6)			**			1 (2.0)				4 (8.2)						
Puusaari et al., 2007[41]	33				14 (42.4)			30 (90.9)			3 (9.1)		7 (21.2)								3 (9,1)
Kurt et al., 2010[39]	22	2 (9.1)	2 (9.1)					11 (50.0)	1 (4.5)	1 (4.5)		2 (9.1)		4 (18.2)					1 (4.5)		
Ramasubramanian et al., 2012[36]	37	11 (29.7)	9 (24.3)		3 (8.1)			12 (32.4)	12 (32.4)			6 (16.2)				5 (13.5)	9 (24.3)				
Lee et al., 2013[3]	27	12 (44.4)	8 (29.6)	3 (11.1)	14 (51.9)	2 (7.4)		4 (14.8)	1 (3.7)			1 (3.7)			5 (18.5)					1 (3.7)	
Mirzayev et al., 2021[47]	56	15 (26.8)	6 (10.7)		1 (1.8)		2 (3.6)	21 (37.5)		6 (10.7)		6 (10.7)		10 (17.9)					1 (1.8)		

VH: Vitreous hemorrhage, Hyp: Hyphema, Hem: Intra/subretinal hemorrhage, RD: Retinal detachment, CD: Choroidal detachment, Pto: Ptosis, Cat: Cataract, CC: Corneal complications, Syn: Anterior or posterior synechia, CME: Cystoid macular edema, IOP: Intraocular pressure, Fib: Pre/subretinal fibrosis, ST: Scleral thinning, ERM: Epiretinal membrane, VRT: Vitreoretinal traction, Hypo: Hypotony, IN: Iris neovascularization, ID: Iridodialysis, SO: Sympathetic ophthalmia, ON: Optic neuropathy

* Rates of VH and RD were not reported, but vitreoretinal surgery was performed due to complications in 12 of 36 eyes (33.3%) that underwent exoresection.

**Cataract and VH was reported to develop in some patients after exoresection, but the exact rates were not been specified

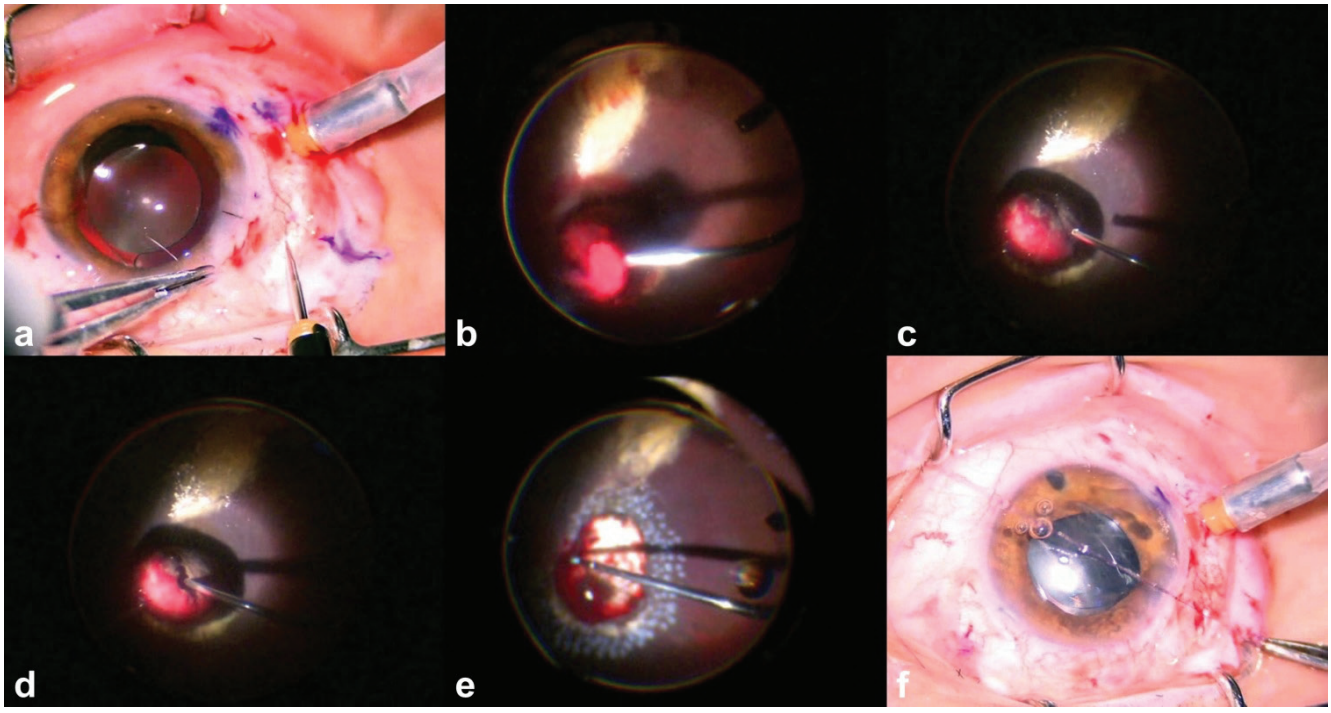

Figure 5. Intraoperative images from endoresection surgery. a) The trocar is advanced into the eye. b) The vitreous hemorrhage around the tumor is cleared using an ocutome. c) Fundus photograph of the choroidal melanoma before endoresection. d) The vitrector is inserted into the tumor during endoresection. e) After endoresection, the choroidal tumor has been resected to the bare sclera. Laser photocoagulation spots are seen around the resection area. f) The sclerotomy is sutured at the end of the procedure

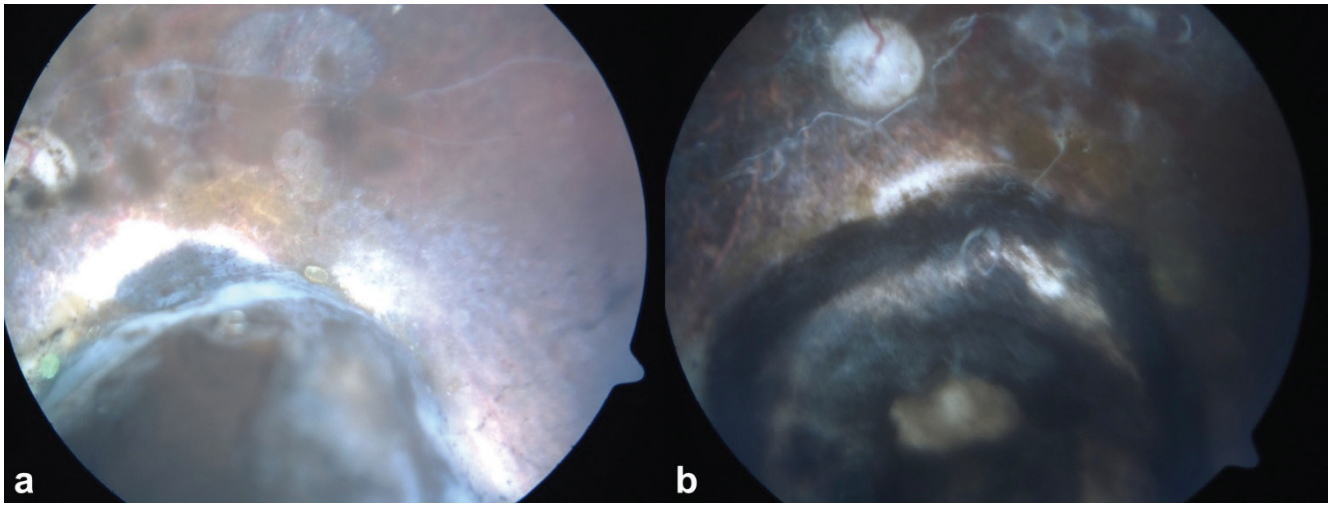

Figure 6. Preoperative and postoperative fundus photographs of a 44-year-old woman with choroidal melanoma who underwent secondary endoresection. a) After plaque radiotherapy and four sessions of transpupillary thermotherapy, the patient had diffuse radiation retinopathy, obliterated vessels, radiation maculopathy, optic atrophy, and vitreous spread from the necrotic tumor. Pigment granules are seen on the optic disc. b) After endoresection, no pigment granules are seen in the vitreous and the tumor is excised down to the bare sclera. The sclera shows areas of residual pigment

Performing endoresection after radiotherapy is recommended because of the risk of live tumor cells leaking out of the eye during the procedure. As radiotherapy kills the live tumor cells, this risk is eliminated.[13,54] However, Konstantinidis et al.[14] stated that preoperative radiotherapy was not necessary, reporting that there was no increased risk of metastasis after endoresection without radiotherapy in their series encompassing 71 cases. According to Konstantinidis et al.[14] and Damato et al.,[55] another advantage of endoresection, especially for tumors close to the optic disc, is the prevention of radiation papillopathy and radiation retinopathy because radiation is not applied. Although endoresection is usually performed for choroidal melanomas, it

can also be used to treat retinal hemangioblastoma, RVT, and (albeit controversial) retinoblastoma.[56,57,58,59,60,61,62,63,64,65,66]

According to generally accepted indications, endoresection should be used for tumors with a base diameter less than 15 mm and less than 3 clock hours contact with the optic disc.[13,54] The anterior border of the tumor is preferably at or posterior to the equator (towards the optic disc). Endoresection cannot be performed for tumors with ciliary body involvement because it is generally not possible to visualize the tumor in its entirety to ensure complete excision.

Endoresection surgery in a patient with cataract starts with phacoemulsification and in-the-bag intraocular lens implantation, followed by vitrectomy. Posterior hyaloid detachment, vitreous base removal, and clearing the vitreous over the tumor must be performed using wide-angle imaging systems. The ocutome is then introduced transretinally into the mass and the tumor is excised to the sclera. The retina is stabilized with perfluorocarbon, endolaser photocoagulation is applied to the excision margins, and intraocular silicone is administered. The intraocular silicone should be removed 3 months postoperatively. In some cases it may be necessary to leave the silicone in the eye for longer periods of time.

The main complications of endoresection surgery are retinal detachment and tumor recurrence.[55,67] Retinal detachment may occur for reasons such as proliferative vitreoretinopathy or retinal detachment at the edges of the retinotomy. Complications such as fibrosis in the scar base and macular ectopy may be observed. Tumor recurrence usually occurs at the margin of the coloboma resulting from tumor excision but may also arise in different, nonadjacent areas of the retina.[67]

Damato et al.[13] detected signs of subconjunctival, intraocular, and extraocular spread in less than 5% of the cases after endoresection surgery without radiotherapy. The authors noted that this was an acceptable risk in exchange for protection from other major complications associated with radiotherapy.

Complications such as increased intraocular pressure, vitreous hemorrhage, epiretinal membrane, phthisis bulbi, hypotonia, macular hole, choroidal neovascularization, proliferative vitreoretinopathy, and endophthalmitis may also occur after endoresection.[13,14,64,65,68,69,70,71,72,73,74,75] A summary of

Table 5. Summary of complications after endoresection reported in the literature

Study, date of publication	Number of eyes	RD n (%)	Cataract n (%)	OH n (%)	Phthisis n (%)	ERM n (%)	VH n (%)	Endo n (%)	CNV n (%)	MH n (%)	CC n (%)	Hypo n (%)	PVR n (%)
Damato et al., 1998[13]	52	17 (32.7)	28 (53.8)	14 (26.9)	1 (1.9)	1 (1.9)	2 (3.8)	1 (1.9)	1 (1.9)				
Bechrakis et al., 2006[70]	58	16 (27.6)	21 (36.2)	1 (1.7)	1 (1.7)	1 (1.7)				2 (3.4)			
Karkhaneh et al., 2007[75]	20	3 (15)	5 (25)				16* (80)				2** (10)		
Caminal et al., 2013[68]	27				1 (3.7)								
Konstantinidis et al., 2013[14]	71	16 (22.5)	60 (94***)	8 (11.3)		9 (12.7)	2 (2.8)						
McCannel, 2013[74]	5			1 (20)									
Garcia-Arumi et al., 2015[73]	41	11 (26.8)	39 (95.1)	14 (34.1)	5 (12.2)	5 (12.2)	1 (2.4)		2 (4.9)			3 (7.3)	
Sinyavskiy et al., 2016[71]	21	3 (14.3)		4 (19.0)									
Süsskind et al., 2016[72]	35	4 (11.4)		2 (5.7)		2 (5.7)				1 (2.9)	3‡ (8.6)	2 (5.7)	
Vidoris et al., 2017[69]	14	2 (14.2)		1 (7.1)									
Avci et al., 2017[64]	12									1 (8.3)		1 (8.3)	1 (8.3)
Karacorlu et al., 2018[65]	13		7 (53.8)	4 (30.8)									1 (7.7)

RD: Retinal detachment, OH: Ocular hypertension or glaucoma, ERM: Epiretinal membrane, VH: Vitreous hemorrhage, Endo: Endophthalmitis, CNV: Choroidal neovascularization, MH: Macular hole, CC: Corneal complications, PVR: Proliferative vitreoretinopathy

*Mild vitreous hemorrhage in 9 eyes, moderate in 2 eyes, and severe in 5 eyes.

**Silicone oil keratopathy (1 eye) and bullous keratopathy (1 eye).

***Percentage calculated from 64 phakic eyes.

‡Persistent corneal erosion (1 eye) and band keratopathy (2 eyes)

the complications reported in previous publications related to endoresection is shown in Table 5. Metastasis rates of 0-20% and mortality rates of 0-18.2% have been reported after endoresection of choroidal melanomas.[13,14,68,69,70,71,72,73,74,75,76,77,78]

Surgeries for Complications Secondary to Tumor Treatment

The main posterior segment complications resulting from the treatment of posterior segment tumors with radiotherapy and transpupillary thermotherapy (TTT) are vitreous hemorrhage, retinal detachment, and epiretinal membrane formation (Figure 7a,b). In uveal melanoma, vitreous hemorrhage is the most important posterior segment problem that develops after radiotherapy and requires surgical intervention. Vitreous hemorrhage occurs in 8-15% of cases following plaque radiotherapy at 5 years.[79] Vitreous hemorrhage develops as a result of posterior vitreous detachment and tumor necrosis in the early period, whereas after the first year it usually occurs due to proliferative radiation retinopathy.[79] In patients with vitreous hemorrhage and an attached retina on ultrasonography, a period of 3 months should be allowed for spontaneous resolution. Clearance of the vitreous hemorrhage is observed in approximately 48% of eyes after this period. PPV and other necessary vitreoretinal surgical interventions should be performed for vitreous hemorrhages that have not cleared by this time.[79] At this point, tumor endoresection can also be added to the treatment.

Bansal et al.[80] evaluated the outcomes of PPV surgery performed due to vitreous hemorrhage in 47 eyes with uveal melanoma and found that there was no intraocular or extraocular melanoma cell spread. The authors also reviewed literature reports of PPV performed due to uveal melanoma and concluded that PPV surgery can be used in the treatment of various complications such as retinal detachment and vitreous hemorrhage in patients with radiotherapy-treated uveal melanoma and does not increase the risk of tumor spread. The only exception to this may be cases undergoing PPV for vitreous hemorrhage where recurrent necrotic melanoma could not be detected preoperatively.[79]

PPV is applied for retinal detachment secondary to radiotherapy and TTT for the treatment of posterior segment tumors, the persistence of exudative retinal detachment present before treatment, the formation of iatrogenic retinal tears (especially with TTT), and the development of fibrovascular proliferation and tractional retinal detachment. Another common problem, especially in patients who undergo TTT, is the development of epiretinal membranes. Epiretinal membrane formation, especially in tumors close to the macula, is a serious problem in terms of vision prognosis. Epiretinal membrane peeling surgery should be performed after the tumor regresses if there is any hope of visual improvement. In case of macular ischemia, macular tumor involvement, and atrophy/massive cystoid edema due to treatment, there is no point in performing such procedures.

In addition to the posterior segment complications that develop after intraocular tumor surgery, tumor containing eyes may require cataract surgery for complicated cataract; trabeculectomy, diode laser cyclophotocoagulation or cyclocryotherapy for secondary glaucoma. Enucleation should be considered as a last option for a painful blind eye.

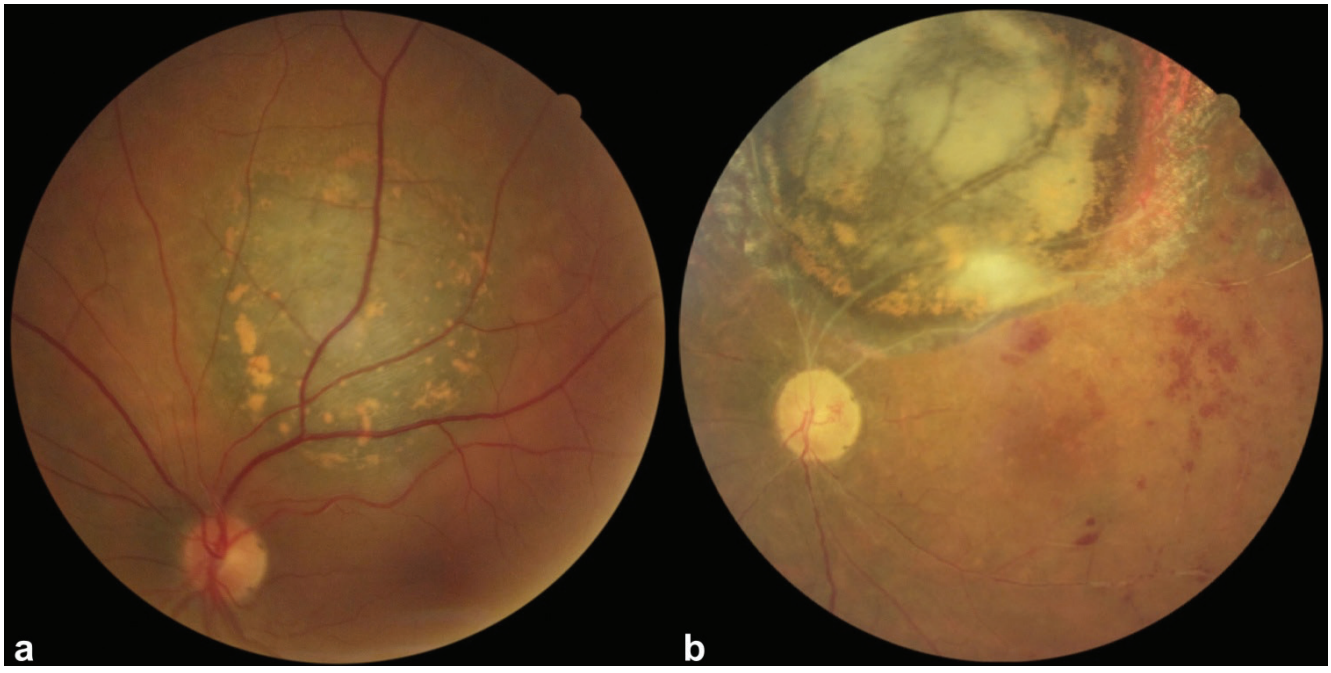

Figure 7. Fundus photographs of a 55-year-old woman who underwent pars plana vitrectomy for complications after plaque radiotherapy and transpupillary thermotherapy for choroidal melanoma. a) An 8 x 6 x 3.5 mm choroidal melanoma is seen in superotemporal of the optic disc. Vision was measured as 20/20. b) The patient underwent pars plana vitrectomy due to proliferative radiation retinopathy and vitreous hemorrhage after receiving plaque radiotherapy and three sessions of transpupillary thermotherapy. Postoperatively, vision was hand movements and optic atrophy, obliterated vessels, diffuse retinal hemorrhages, and macular edema are seen

Conclusions

In patients with intraocular tumors, surgery is performed for excision/biopsy and for the management of complications resulting from tumor treatment. FNAB and TRB are commonly used biopsy methods. Excision/biopsy by PLSU is performed for peripheral choroid and ciliary body/iris tumors. The procedure must be performed by experienced surgeons to ensure complete tumor excision and reduce or prevent complications. Endoresection surgery is a promising method for selected indications. Removing residual tumor after radiotherapy and thermotherapy is beneficial in preventing complications such as neovascular glaucoma, retinal exudation, retinal detachment, and subsequent vision loss. PPV surgery is performed for the management of complications such as vitreous hemorrhage, retinal detachment, and epiretinal membrane resulting from the treatment of posterior segment tumors. Before embarking on vitrectomy surgery for related complications, it should be made certain that there are no active tumor cells remaining in the eye.

In addition to posterior segment complications, the necessary surgical treatments should be performed in case of cataract and glaucoma development. Enucleation is necessary for painful blind eyes.

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Case Report

Endogenous Fungal Endophthalmitis in a Patient Admitted to Intensive Care and Treated with Systemic Steroid for COVID-19

Sema Tamer Kaderli*, Aylin Karalezli*, Burak Ekrem Çitil**, Ali Osman Saatci***

*Muğla Sıtkı Koçman University Faculty of Medicine, Department of Ophthalmology, Muğla, Turkey
**Muğla Sıtkı Koçman University Faculty of Medicine, Department of Microbiology, Muğla, Turkey
***Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

Abstract

A 61-year-old woman presented to our clinic with complaints of decreased visual acuity, pain, and redness in her left eye. Best corrected visual acuity (BCVA) was 20/20 in the right eye and counting fingers at 3 meters in the left eye. On slit-lamp examination, 1+ cells were detected in the anterior chamber. Fundus examination revealed 1+ haze in the vitreous and multiple creamy-whitish lesions in the retina and vitreous. Her history included a diagnosis of coronavirus disease 2019 (COVID-19) one month earlier, for which she was hospitalized in the intensive care unit for 20 days and received systemic corticosteroid treatment. Vitreous culture yielded *Candida albicans.* The patient's nasopharyngeal swab sample was positive for COVID-19 by reverse transcription polymerase chain reaction test. BCVA was improved to 20/40 after amphotericin therapy (via intravitreal injection and intravenous routes), and the vitritis and chorioretinitis lesion regressed after 2 weeks of treatment. Two weeks later, intravenous amphotericin was discontinued and oral fluconazole treatment was started at a dose of 400 mg/day. At 3-month follow-up, her BCVA was 20/25 and no inflammatory reaction was observed in the anterior chamber and vitreous.

Keywords: Endogenous endophthalmitis, posterior uveitis, endogenous fungal endophthalmitis, coronavirus disease 2019

Address for Correspondence: Sema Tamer Kaderli, Muğla Sıtkı Koçman University Faculty of Medicine, Department of Ophthalmology, Muğla, Turkey
E-mail: sematamerkaderli@hotmail.com **ORCID-ID:** orcid.org/0000-0003-4851-6527
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Introduction

Endogenous fungal endophthalmitis is a severe ocular inflammation that causes decreased visual acuity.[1] *Candida albicans* is the most common cause of endogenous fungal endophthalmitis, which is associated with predisposing risk factors such as an indwelling catheter, intravenous drug use, immunodeficiency, recent hospitalization, and use of corticosteroids or noncorticosteroid immunosuppressive agents.[2]

Coronavirus disease 2019 (COVID-19) is a global epidemic caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]).[3] Herein, we aim to report a case of *Candida albicans* endogenous endophthalmitis in a patient who required intensive care admission and systemic steroid therapy due to COVID-19 infection. To the best of our knowledge, this is the first description of a case of endogenous fungal endophthalmitis that may be relevant to the current treatment of COVID-19 infection.

Case Presentation

A 61-year-old woman presented to our clinic with a 15-day history of progressively decreased vision, pain, and redness in her left eye. A month earlier, she had been hospitalized in intensive care for 20 days and received systemic steroid for the treatment of COVID-19. Her COVID-19 diagnosis was confirmed by reverse transcription-polymerase chain reaction test of a nasopharyngeal swab sample. The patient had no history of recent ocular trauma, intraocular surgery, or additional systemic disease (diabetes mellitus, malignancy). Systemic dexamethasone and favipiravir had been administered while she was in the intensive care unit.

At presentation, her best corrected visual acuity was 20/20 in the right eye and counting fingers at 3 meters in the left eye. Intraocular pressure was 15 mmHg measured by Goldmann applanation tonometry. On slit-lamp examination, 1+ cells were detected in the anterior chamber. Fundus examination revealed multiple creamy-white intravitreal lesions in the vitreous and retina (Figure 1). Examination of the right eye was normal.

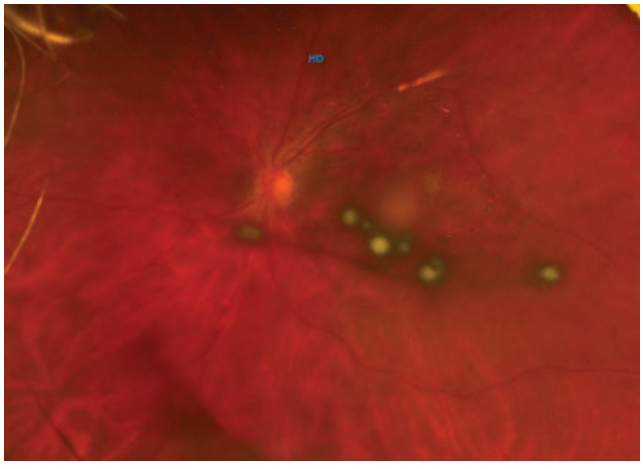

Figure 1. Widefield fundus image showing multiple creamy-white intravitreal lesions in the vitreous and retina

A comprehensive uveitis screening was performed, including chest X-ray, hemogram, biochemical investigations (plasma creatinine, potassium, sodium, C-reactive protein, erythrocyte sedimentation rate, urinary albumin to creatinine ratio, aspartate aminotransferase and alanine aminotransferase, alkaline phosphatase, and γ-glutamyl transferase), serology for *Toxoplasma,* venereal disease research laboratory pathogens, human immunodeficiency virus, hepatitis C and B virus, Epstein-Barr virus, cytomegalovirus, and varicella zoster virus. The results of all tests were normal or negative. In light of her medical history and clinical findings, we suspected endogenous endophthalmitis, and performed a vitreous tap of her left eye with intravitreal injection of empirical amphotericin (0.005 mg/0.1 mL), vancomycin (1 mg/0.1 mL), and ceftazidime (2.25 mg/0.1 mL). The vitreous specimen was plated directly onto chocolate agar, 5% sheep blood agar, and Sabouraud agar. Sabouraud agar was incubated at 35 °C for 72 hours and then at 25 °C for up to 2 weeks. The plate was examined daily for the detection of fungal growth. Colonies suggestive of fungal growth were evaluated by Giemsa and calcofluor white stains and with slice culture to detect microscopic morphologic features and characteristic conditions. The vitreous culture result was positive for *Candida albicans* (Figure 2). PCR test of the vitreous sample was negative for SARS-CoV-2. After culture positivity, a second dose of intravitreal amphotericin was administered and an intravenous form of the drug was added to treatment at 3 mg/kg/day. She also received routine topical uveitis treatment (prednisolone acetate 0.1% and cyclopentolate hydrochloride 1.0%) for her left eye. Visual acuity improved to 20/40, and after 2 weeks of treatment there were no signs of vitreous infiltrates and the chorioretinitis lesion has regressed (Figure 3). Intravenous amphotericin was stopped 2 weeks after admission and treatment was continued with oral fluconazole 400 mg/day. Best corrected visual acuity was 20/25 at 3-month follow-up and no inflammatory reaction was observed in the anterior chamber or vitreous.

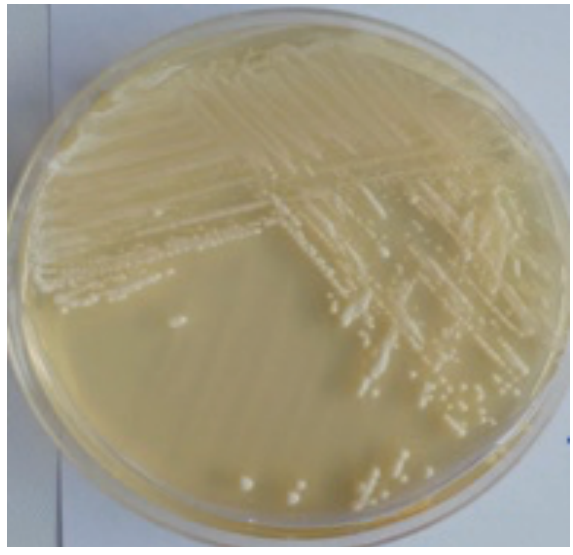

Figure 2. *Candida albicans* isolated by vitreous culture on Sabouraud agar

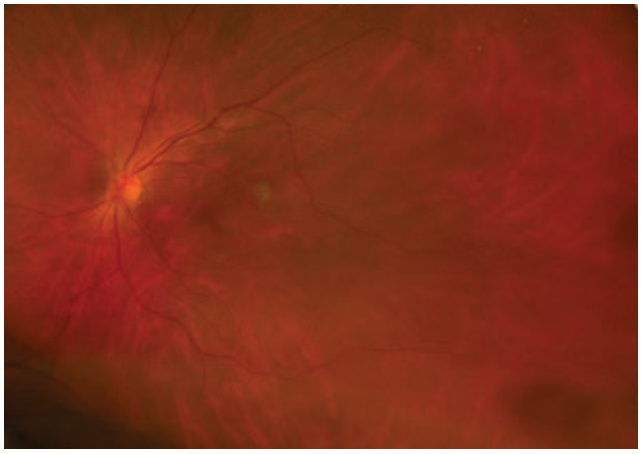

Figure 3. Widefield fundus image 2 weeks after intravenous amphotericin treatment

Discussion

Endogenous fungal endophthalmitis would be expected in an immunosuppressed patient with risk factors such as chronic immune-compromising disease, intravenous catheters, use of broad-spectrum antibiotics, immunosuppressive agents, or steroids, and diabetes mellitus.[1,4] As COVID-19 is a new disease, there is still limited evidence about it and the outcomes of treatment.[5] Hospitalization and systemic steroid use may be required during the treatment and management of COVID-19.[6] Presented here is a case of endogenous fungal endophthalmitis in a patient who required intensive care admission and systemic steroid use for the treatment of COVID-19.

Endogenous fungal endophthalmitis generally begins with choroidal spread and eventually invades the vitreous. In candidemia, the incidence of chorioretinitis is 11%, while that of endophthalmitis is only 1.6%.[7] It progresses slowly, some cases are clinically silent at the early stage, and symptoms usually increase after notable vitritis. Some patients develop subretinal abscess, which generally has a poor visual prognosis. Subretinal abscess is often associated with mold rather than yeast endophthalmitis.[8]

There is still controversy regarding the ophthalmological effects of SARS-CoV-2 and whether transmission can occur via ocular tissues (tears). In the studies and case reports in the literature, SARS-CoV-2 was detected in ocular samples in a very small proportion of patients who were positive for COVID-19.[9] It was also reported that SARS-CoV-2 has a lesser tropism for ocular tissue than the respiratory tract.[10] Gupta et al.[11] reported a case of atypical acute retinal necrosis in a COVID-19-positive immunosuppressed patient, but PCR test of a vitreous specimen was negative for SARS-CoV-2. Furthermore, in-vivo animal experiments on this subject have shown that coronaviruses can increase blood-retinal barrier destruction.[5,12] Perhaps the fact that the patient was positive for COVID-19 in our case caused a breakdown of the blood-retinal barrier, facilitating the development of endogenous fungal endophthalmitis.

The pandemic has spread rapidly, and it is important to report cases associated with COVID-19. Further studies may show how the SARS-CoV-2 virus and treatment of COVID-19 interact with ocular tissue. The treatment of COVID-19 may lead to other opportunistic infections for reasons such as hospitalization, intravenous drug administration, and broad-spectrum antibiotic and systemic steroid use. We recommend that endogenous endophthalmitis be kept in mind in patients who present with complaints of decreased visual acuity and have a history of systemic steroid therapy and hospitalization for COVID-19.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T.K., A.K., B.E.Ç., Concept: S.T.K., A.O.S., Design: S.T.K., A.K., B.E.Ç., A.O.S., Data Collection or Processing: S.T.K., A.K., B.E.Ç., Analysis or Interpretation: S.T.K., A.K., A.O.S., Literature Search: S.T.K., A.K., Writing: S.T.K., A.K.,

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Case Report

Half-fluence Photodynamic Therapy for Central Serous Chorioretinopathy in a Patient Receiving Corticosteroids for Behçet's Uveitis

Hüseyin Baran Özdemir*, Nazgül Zhoroeva*, Pınar Çakar Özdal**, Şengül Özdek*

*Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**University of Health Sciences Turkey, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Turkey

Abstract

Corticosteroid-induced central serous chorioretinopathy (CSCR) has been reported to develop in many intraocular inflammatory diseases and usually resolves spontaneously after discontinuation of corticosteroids. Patients without any improvement may require alternative therapies. In this case report, we present the case of a 35-year-old man with Behçet's disease who had complaints of decreased vision due to CSCR in his left eye while using systemic corticosteroids along with cyclosporine and azathioprine. Half-fluence photodynamic therapy (PDT) was performed because the CSCR did not regress despite discontinuation of systemic corticosteroids. After treatment, his visual acuity increased with complete resolution of the subfoveal fluid. Half-fluence PDT seems to be an effective and safe treatment for patients who develop acute CSCR while under systemic or local corticosteroid therapy for intraocular inflammatory diseases such as Behçet's uveitis and do not improve despite steroid discontinuation.

Keywords: Behçet's disease, uveitis, central serous chorioretinopathy, steroid, photodynamic therapy

Address for Correspondence: Hüseyin Baran Özdemir, Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: huseyinbaranozdemir@gazi.edu.tr **ORCID-ID:** orcid.org/0000-0002-5585-253X
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Introduction

Central serous chorioretinopathy (CSCR) causes an idiopathic serous detachment of the neurosensory retina due to leakage at the level of the retinal pigment epithelium (RPE) secondary to hyperpermeability of the choriocapillaris.[1] Although the exact mechanisms causing CSCR have not been elucidated, many associations have been suggested. Steroids, both endogenous and exogenous, have the strongest known association with CSCR.[2]

CSCR is not uncommon in patients receiving systemic or local corticosteroids for any type of uveitis. Corticosteroid-induced CSCR has been reported to develop in many intraocular inflammatory diseases such as Behçet's disease, Vogt-Koyanagi-Harada (VKH) disease, HLA-B27-associated uveitis, and birdshot chorioretinopathy. The occurrence of CSCR in such diseases can be misdiagnosed as uveitis activation.[3,4,5,6] This misjudgment may cause worsening of CSCR-related choroidal hyperpermeability and serous detachment due to increased corticosteroid dose. Most cases of CSCR develop while under treatment for uveitis and regress after cessation of corticosteroid therapy, with an increase in visual acuity.[7]

Here, we present a patient who developed acute CSCR during systemic steroid therapy for Behçet's uveitis.

Case Report

A 35-year-old man diagnosed with Behçet's uveitis for 2 years presented to our clinic with decreased visual acuity in his left eye. At the time of presentation, the patient was using oral methylprednisolone 16 mg/day, oral cyclosporine 100 mg/day, and oral azathioprine 50 mg/day for 3 years. Visual acuity was 1.0 in the right eye and 0.5 in the left eye on Snellen chart (decimal units). Bilateral anterior segment examination was unremarkable. No cells or haze were detected in the vitreous of either eye (Figure 1A), while peripheral retinal vascular sheathing and RPE changes at the fovea were observed in the left eye (Figure 1B). Fundus autofluorescence was normal in the right eye (Figure 1C) and showed speckled hyperfluorescence in the macula extending inferiorly in the left eye (Figure 1D). Optical coherence tomography (OCT) was normal in the right eye (Figure 1E) and revealed serous macular detachment, increased choroidal thickness, and focal pigment epithelial changes consistent with CSCR in the left eye (Figure 1F). Fluorescein angiography (FA) showed bilateral optic nerve head hyperfluorescence (Figure 2A, 2D, 2F) and diffuse "fern-like" vascular leakage and peripheral ischemia in the left eye (Figure 2A, 2F). There was pinpoint focal hyperfluorescence resembling CSCR leakage in the early-mid and late phases in the left eye (Figure 2A, 2F). Indocyanine green angiography (ICGA) revealed dilated choroidal vessels in both eyes (Figure 2B, 2C) and late focal hypercyanescence in the macula indicating choroidal hyperpermeability in the left eye (Figure 2G). Late-phase ICGA findings were unremarkable in the right eye (Figure 2E). OCT angiography (OCTA) was performed to investigate the presence of macular neovascularization (MNV) but did not reveal this complication (Figure 3).

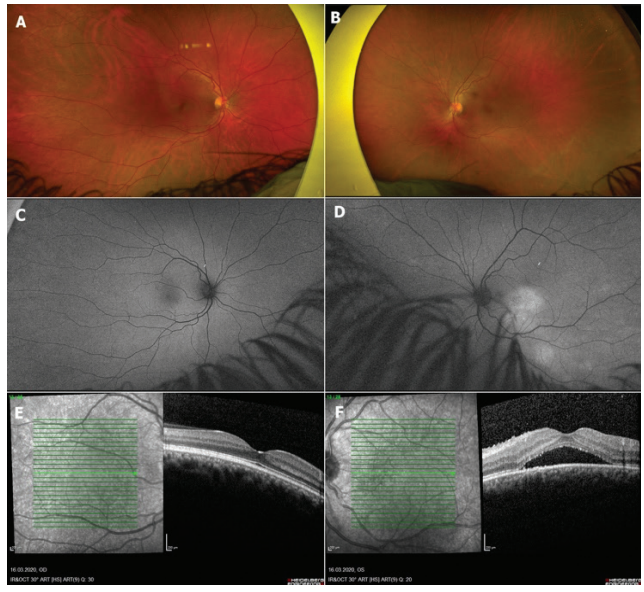

Figure 1. Multimodal imaging of the patient at presentation. Widefield fundus photography was unremarkable in the right eye (RE) (A) and retina pigment epithelium changes and peripheral vascular sheathing were observed in the left eye (LE) (B). Fundus autofluorescence showed normal autofluorescence in the RE (C) and speckled hyperautofluorescence in the macula extending inferiorly in the LE (D). There was no pathology in OCT of the RE (E) but serous macular detachment was present in the LE (F)
OCT: Optical coherence tomography

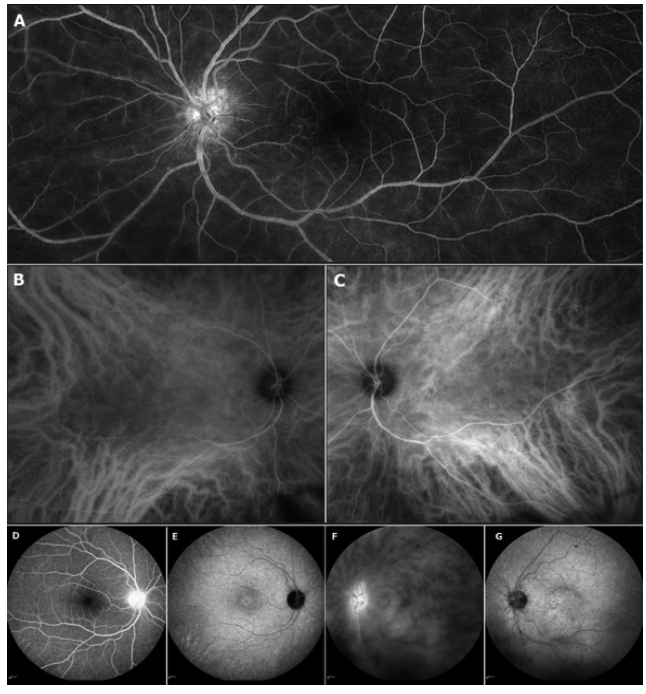

Figure 2. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed at presentation. FA of the left eye (LE) revealed optic nerve head hyperfluorescence, perivascular leakage, and multifocal leakage points which enlarged in the late phase (A). ICGA revealed bilateral dilated choroidal vessels in the early phase (B, C). Late-phase FA revealed bilateral optic nerve hyperfluorescence (D, F) and diffuse perivascular leakage in the LE (F). Late-phase ICGA was normal in the right eye (E) but a focal hyperpermeability area was observed in the macula of the LE (G)

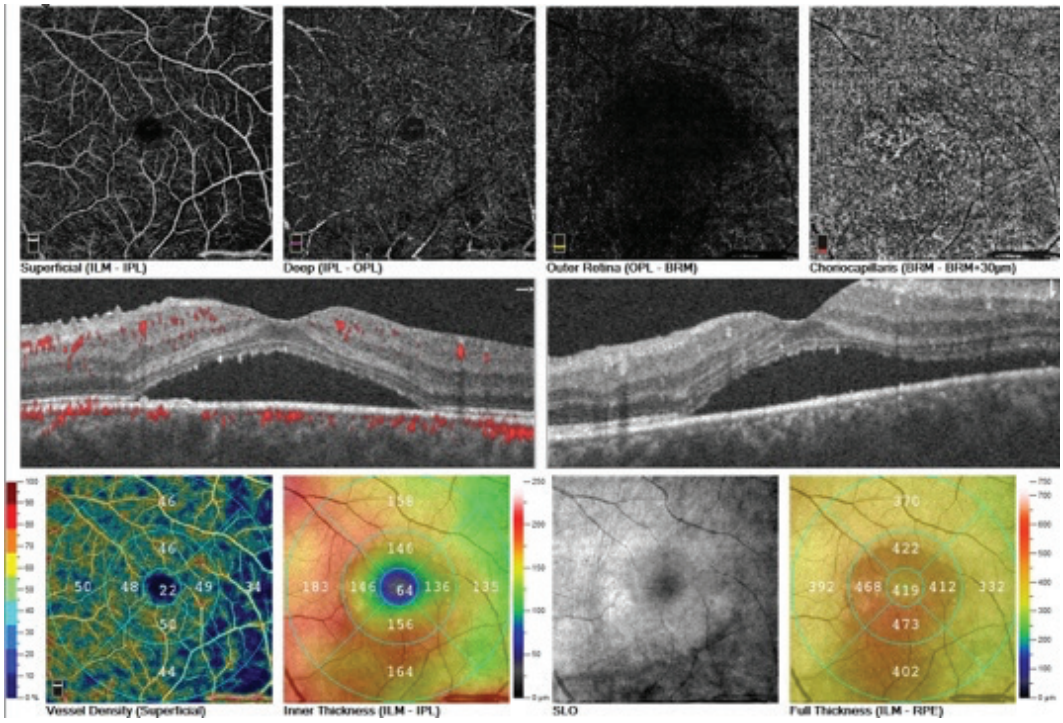

Figure 3. There was no macular neovascularization in optical coherence tomography angiography of the left eye

The patient was referred to the rheumatology department for cessation of steroid and administration of a biological agent. After systemic re-assessment, oral methylprednisolone was tapered and stopped, cyclosporine and azathioprine were discontinued, and intravenous infliximab (IFX) 400 mg/month was initiated after the loading dose. The patient was observed for 3 months after corticosteroid cessation, which resulted in only a slight decrease in the amount of subretinal fluid (Figure 4A-B). Therefore, we decided to perform half-fluence (25 J/cm^2) photodynamic therapy (PDT) with 6 mg/m^2 verteporfin (Visudyne, Novartis Ophthalmics AG, USA). The subretinal fluid completely resolved and BCVA increased to 0.7 at 1 month after PDT (Figure 4C). No recurrence of CSCR or exacerbation of uveitis has been observed during 6 months of follow-up. The patient was instructed not to use any kind of steroids via any route of administration.

Discussion

To the best of our knowledge, this is the first report of a case of CSCR that occurred in a patient with Behçet's uveitis under corticosteroid treatment and resolved with PDT.

Corticosteroid-related CSCR may develop in patients with posterior uveitis with or without an associated systemic condition, such as in Behçet's disease, VKH disease, birdshot chorioretinopathy, systemic lupus erythematosus, and sarcoidosis. Khairallah et al.[2] published a large series including 20 eyes of 14 patients with uveitis who developed corticosteroid-induced CSCR and reported that 14 eyes of 9 patients had Behçet's uveitis. Multimodal imaging including OCT, FA, and ICGA may help to distinguish CSCR from other uveitis entities.[8,9] OCT may reveal dome-shaped serous macular detachment and pigment epithelial detachment that might suggest CSCR. Increased choroidal thickness in CSCR can be assessed with EDI-OCT. FA findings may be masked by perivascular leakage or macular edema caused by uveitis. ICGA may reveal multiple areas of choroidal hyperpermeability in the mid-to-late phases in CSCR. In the present case, dome-shaped serous macular detachment on OCT, increased choroidal thickness on EDI-OCT, multifocal pinpoint leakage on FA, and late hypercyanescence indicating choroidal hyperpermeability at the macula in ICGA led us to diagnose corticosteroid-related CSCR concomitant with Behçet's uveitis.

As acute CSCR usually resolves spontaneously within 2 to 3 months, observation after discontinuing corticosteroids is the first step in treatment.[2] However, if patients must remain on corticosteroids, reductions in steroid dose have been shown to increase the speed of CSCR resolution.[2] Sharma et al.[10] reported that corticosteroid cessation alone resulted in retinal reattachment in 87.5% of eyes in a median of 49 days and an increase in visual acuity of ≥2 Snellen lines in 62% of eyes. Conventional immunosuppressives or biological agents should be given for sustained control of inflammation plus corticosteroid-sparing effect.[11] In our case, we switched the treatment to IFX to suppress retinal vasculitis and reduce the need for corticosteroids.

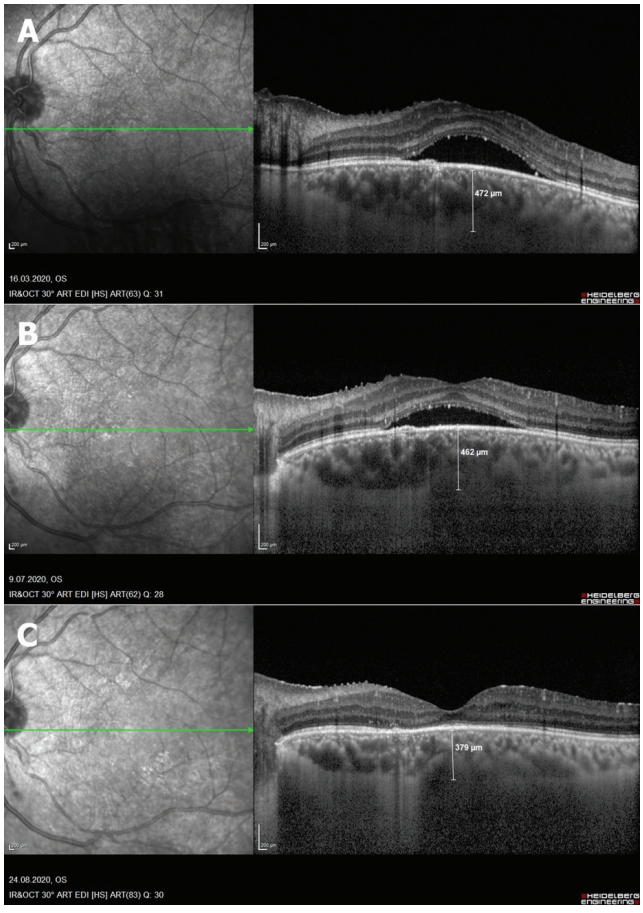

Figure 4. Enhanced depth imaging optical coherence tomography (EDI-OCT) images demonstrated serous macular detachment, minimal double-layer sign on the nasal edge of the detachment, and thickened choroid at presentation (A), slightly regressed subfoveal fluid 3 months after corticosteroid cessation (B), and completely resolved subfoveal fluid and thinned choroid 1 month after photodynamic therapy (C)

Patients who do not show any improvement on CSCR after a few months of observation may require alternative therapies such as laser photocoagulation, intravitreal anti-VEGF injections, or PDT. PDT with verteporfin, a photosensitizer that accumulates in vessels and helps target therapy, causes endothelial damage and vascular hypoperfusion to inhibit the choroidal hyperpermeability seen in CSCR.[12] PDT was first described for the treatment of CSCR using standard dosing protocols (6.0 mg/m^2, 50 J/cm^2). This standard PDT protocol is effective, but has been linked to some complications such as photosensitivity, transient visual loss, RPE atrophy, choriocapillaris ischemia, and secondary choroidal neovascularization.[13] To improve the safety of PDT, modified treatment parameters such as using half-fluence light energy or half-dose verteporfin have been considered.[14] Many retrospective studies in the literature have reported that the efficacy of half-dose and half-fluence PDT is similar,[14,15,16] except a multicenter retrospective study conducted by Nicolo et al.[17] They reported faster reabsorption and less recurrence with half-dose PDT, but both treatment modalities had equal visual improvement and safety in 12-month follow-up. On the other hand, Cheng et al.[18] reported in their prospective, randomized, observer-masked comparison study that the two methods were similarly effective and even caused comparable choroidal hypoperfusion. Therefore, strategy selection may be appropriate according to the characteristics of the patients. Half-dose can be chosen for patients with light sensitivity, and half-fluence for patients with difficulty in cooperation.[18] We chose half-fluence PDT treatment, considering that it would be difficult for our patient to cooperate. After the treatment with half-fluence PDT (25 J/cm^2), the patient's BCVA improved from 0.5 to 0.7, and OCT showed a complete reduction in subfoveal fluid in the left eye at 1 month. We did not observe any complication or exacerbation of uveitis related to PDT or recurrence of CSCR during 6 months of follow-up.

In conclusion, half-fluence PDT is a safe and effective technique for uveitis patients who develop corticosteroid-induced CSCR that persists after corticosteroid discontinuation.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.B.Ö., P.Ç.Ö., Concept: H.B.Ö., N.Z., P.Ö.Ç., Ş.Ö., Design: H.B.Ö., N.Z., P.Ö.Ç., Ş.Ö., Data Collection or Processing: H.B.Ö., N.Z., Analysis or Interpretation: H.B.Ö., N.Z., P.Ö.Ç., Ş.Ö., Literature Search: H.B.Ö., N.Z., Writing: H.B.Ö., N.Z.

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Case Report

Atypical Chronic Central Serous Chorioretinopathy Mimicking Vogt-Koyanagi-Harada Disease: Full Therapeutic Response to Half-Fluence Photodynamic Therapy

Özge Yanık, Figen Batıoğlu, Nilüfer Yalçındağ, Sibel Demirel, Emin Özmert

Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

The aim of this case report is to describe a case of atypical central serous chorioretinopathy (CSCR) definitively diagnosed after 8 years. A 44-year-old woman presented with reduced visual acuity in her left eye. Her visual acuity was light perception with projection in the right eye and 0.15 in the left. She described a similar decline in vision in her right eye 8 years ago. At that time, she had exudative retinal detachment and was treated with systemic immunosuppressive therapy for a presumed diagnosis of Vogt-Koyanagi-Harada disease. Despite resolution of the exudative retinal detachment, macular scarring developed. Eight years later, she developed inferior exudative retinal detachment in the left eye. A diagnosis of atypical CSCR was made with the help of multimodal imaging and her left eye was successfully treated with eplerenone and half-fluence photodynamic therapy (hf-PDT). In conclusion, early diagnosis and treatment of atypical CSCR may prevent subretinal fibrosis formation and permanent vision loss. Hf-PDT and eplerenone are successful treatment options for atypical CSCR.

Keywords: Atypical central serous chorioretinopathy, indocyanine green angiography, photodynamic therapy, eplerenone

Address for Correspondence: Özge Yanık, Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: oyanik05@hotmail.com **ORCID-ID:** orcid.org/0000-0002-1822-8703

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Introduction

Central serous chorioretinopathy (CSCR) is characterized by neurosensory macular detachment. However, in rare instances, the neurosensory detachment may be very extensive, causing bullous exudative retinal detachment. This rare variant of the disease is defined as atypical (bullous) CSCR. Characteristic fundoscopic features are multifocal exudative lesions in the posterior pole and inferior retinal detachment with shifting subretinal fluid.[1]

Due to the unusual presentation, this form may be incorrectly diagnosed as rhegmatogenous retinal detachment, Harada disease, uveal effusion, multifocal choroiditis, metastatic carcinoma, or lymphoma.[2] Inappropriate use of systemic corticosteroids and other immunosuppressive agents may cause exacerbation of the symptoms and lead to development of subretinal fibrosis and scarring.

Case Report

A 44-year-old woman presented in 2019 because of a gradual decrease in vision in her left eye. Best corrected visual acuity (BCVA) was light perception with projection in the right eye and 0.15 Snellen line in the left eye.

Her previous medical records revealed a similar progressive reduction of vision in her right eye 8 years ago. At that time, in 2011, visual acuity in her right eye decreased to 0.15 Snellen line within a month, while BCVA in the left eye was 1.0 Snellen line. Anterior segment biomicroscopy was unremarkable. Fundoscopy showed trace vitreous cells and inferior exudative retinal detachment involving the macula of the right eye (Figure 1a). Optical coherence tomography (OCT) showed subretinal fibrotic material (Figure 1b). Fluorescein angiography showed central irregular hyperfluorescence in the macula surrounded by a hypofluorescent area caused by the blockage of subretinal fibrotic material and window defects from the areas of diffuse retinal pigment epithelium (RPE) alterations (Figure 1c). A full diagnostic work-up was planned. Infectious markers were negative. Consultations with the departments of pulmonary diseases and neurology were requested to exclude tuberculosis, sarcoidosis, and neurological signs of Vogt-Koyanagi-Harada (VKH) syndrome. With a preliminary diagnosis of VKH disease, intravenous pulse corticosteroid therapy (250 mg methylprednisolone sodium succinate infusion 4 times a day) was given for 3 days, followed by oral prednisolone 60 mg/day tapered by 10 mg per week. Oral cyclosporine A at a dose of 200 mg/day was also prescribed. At 2 months, her BCVA decreased to counting fingers at 20 cm and exudative detachment progressed (Figure 1d). In addition, BCVA in her left eye decreased to 0.4 Snellen line due to acute-onset inferior retinal detachment. At this point, sight-threatening corticosteroid-resistant VKH disease was suspected and treatment with infliximab infusion at a dose of 5 mg/kg was initiated and applied every 4 weeks thereafter. After 6 monthly infliximab infusions, her BCVA was counting fingers at 20 cm in her right eye and 0.9 Snellen line in her left eye. Exudative retinal detachment completely

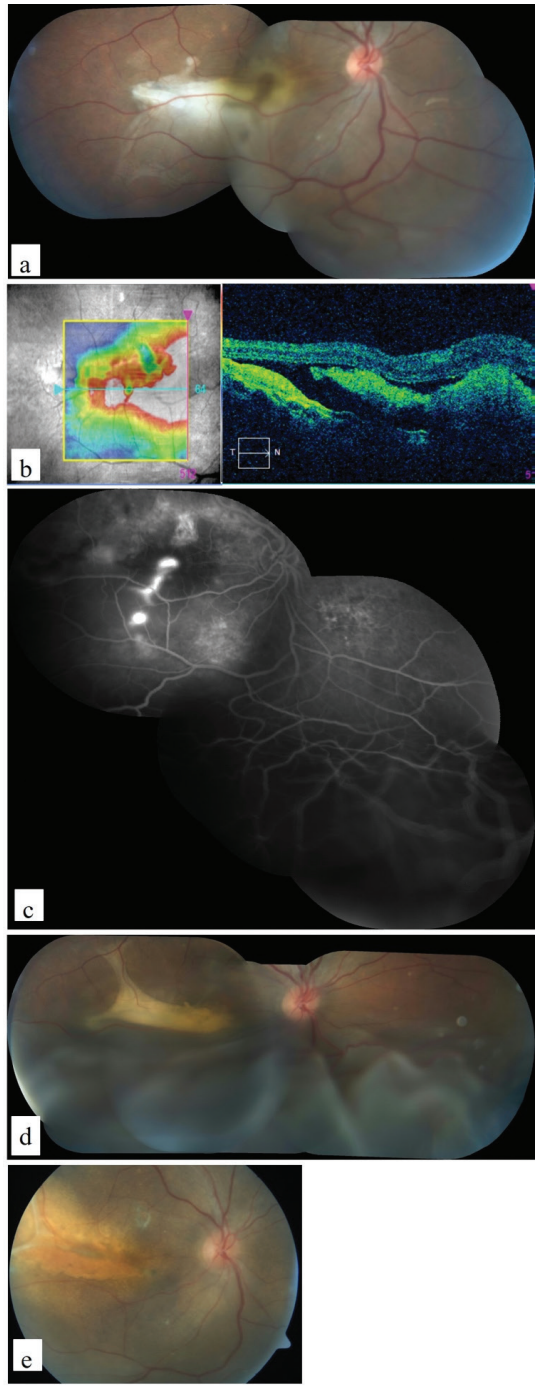

Figure 1. Multimodal retinal images obtained during initial involvement of the right eye: a) Color fundus photography revealed exudative retinal detachment involving the posterior pole and yellowish subretinal fibrin located at the macula. b) Optical coherence tomography showed the presence of subretinal fibrin along with subretinal fluid. c) Fluorescein angiography showed central irregular hyperfluorescence in the macula surrounded by a hypofluorescent area caused by the blockage of subretinal fibrotic material and window defects from the areas of diffuse retinal pigment epithelium alterations. d) Color fundus photography revealed the progression of exudative retinal detachment and yellowish fibrinous material in the macula of the right eye. e) Color fundus photography demonstrated complete regression of the exudative retinal detachment with atrophy and scarring in the macula after 8 months

regressed in both eyes. However, a centrally located macular scar and subretinal fibrotic bands remained as a sequel of the previous detachment in her right eye (Figure 1e). Infliximab therapy was discontinued and follow-up visits were scheduled every 3 months. Forty-four months after cessation of treatment, OCT revealed multiple serous pigment epithelial detachments without subretinal fluid in her left eye (Figure 2). At that time, her BCVA was light perception with projection in the right eye and 1.0 Snellen line in the left eye. Follow-up visits were extended to every 6 months.

In 2019, 98 months after initial presentation, she presented with decreased vision in her left eye. Her visual acuity was 0.8 Snellen line in her left eye and there was acute-onset inferior exudative retinal detachment. Infliximab infusions (5 mg/kg) were planned for week 0, 2, 6, and every 8 weeks thereafter. Oral azathioprine (125 mg/day) was also prescribed. After 2 doses of infliximab, her BCVA decreased to 0.15 Snellen line, and the detachment fluid in the posterior pole increased. Fluorescein angiography (FA) showed multiple leakage points and retinal pigment epithelial alterations, while indocyanine green angiography revealed areas of choroidal hyperpermeability (Figure 3). Based on these imaging findings, the patient was diagnosed with atypical CSCR. All treatments were ceased, and an oral mineralocorticoid receptor antagonist, eplerenone (Inspra®, Pfizer Pharmaceuticals LLC, Vega Baja, Puerto Rico), was initiated at a dose of 25 mg twice daily. A half-fluence photodynamic therapy (hf-PDT) protocol (25 J/cm^2, 300 mW/cm^2) using 6 mg/m^2 intravenous verteporfin (Visudyne®, Novartis, JHP Pharmaceuticals LLC, MI, USA) was applied to the areas of leakage and hyperpermeability in the inferior papillomacular region seen in combined FA and ICGA images. At 1 month after hf-PDT, subretinal fluid was markedly decreased, serous pigment epithelial detachment had regressed, and choroidal thickness was reduced (Figure 4). Visual acuity in her left eye was 0.16 ETDRS line. After 6 months, the inferior exudative retinal detachment had fully regressed and her visual acuity increased to 0.5 ETDRS line. Eplerenone therapy was discontinued. At 1 year after hf-PDT, her BCVA was light perception in the right eye and 0.63 ETDRS line in the left eye, with no recurrence of exudative retinal detachment and a completely dry macula (Figure 5).

Discussion

The pathogenesis of CSCR is not well documented. A breakdown in the permeability of the choriocapillaris has been implicated as the possible pathogenetic mechanism, leading to a focal loss of RPE-Bruch's membrane attachment and allowing passage of the choroidal fluid into the subretinal space.[3] Bullous retinal detachment is an extremely rare atypical variant of chronic CSCR which has been reported in a limited number of case presentations and case series.[1,4]

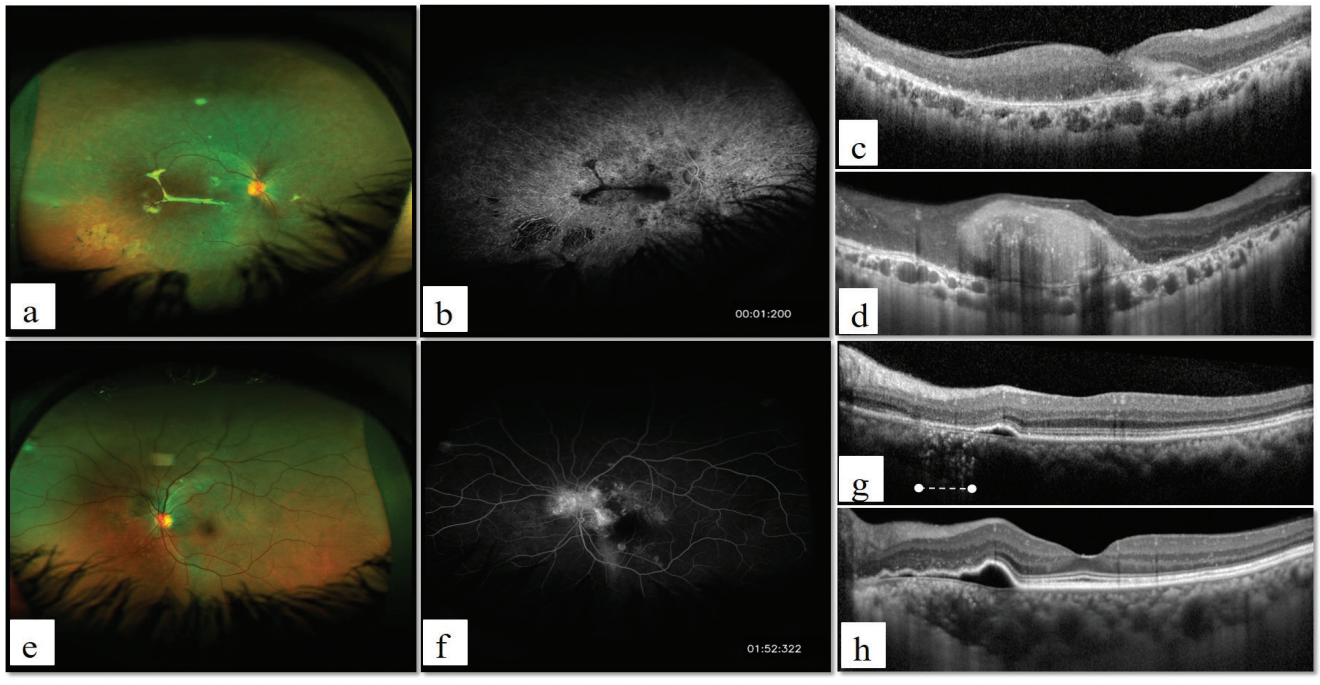

Figure 2. Multimodal fundus images of both eyes at 52 months after first presentation. Right eye: a) Ultra-widefield color fundus photography showed fibrinous scar at the posterior pole and inferotemporally located areas of atrophy. b) Early-phase fluorescein angiography (FA) revealed window defects due to diffuse retinal pigment epithelium (RPE) alterations, blockage by the fibrinous scar, and increased visibility of the choroidal vessels in the atrophic areas. c) Optical coherence tomography (OCT) showed complete retinal pigment epithelium and outer retinal atrophy (RORA). d) Enhanced depth imaging mode OCT (EDI-OCT) showed dense fibrinous scar in the macula, diffuse RPE loss, and dilated Haller layer vessels with prominent attenuation of the choriocapillaris layer. Left eye: e) Ultra-widefield color fundus photography showed grayish area located at the superior peripapillary region. f) Early-phase FA revealed peripapillary window defects due to RPE alterations and hyperfluorescent gravitational tract. g) OCT showed barcode sign (dashed line) due to incomplete RORA. h) EDI-OCT showed serous pigment epithelial detachment and increased choroidal thickness

Corticosteroid therapy is one of the many systemic factors implicated in the pathogenesis of the bullous variant of CSCR.[4] In our case, due to the presence of trace amount of vitreous cells, the patient was initially misdiagnosed with VKH disease and received intravenous high-dose corticosteroids. The use of steroids may aggravate the clinical findings of CSCR. Then, because the patient's findings did not improve and her vision worsened, steroid-resistant VKH was suspected and her treatment was changed to other immunosuppressive and biologic agents.[5]

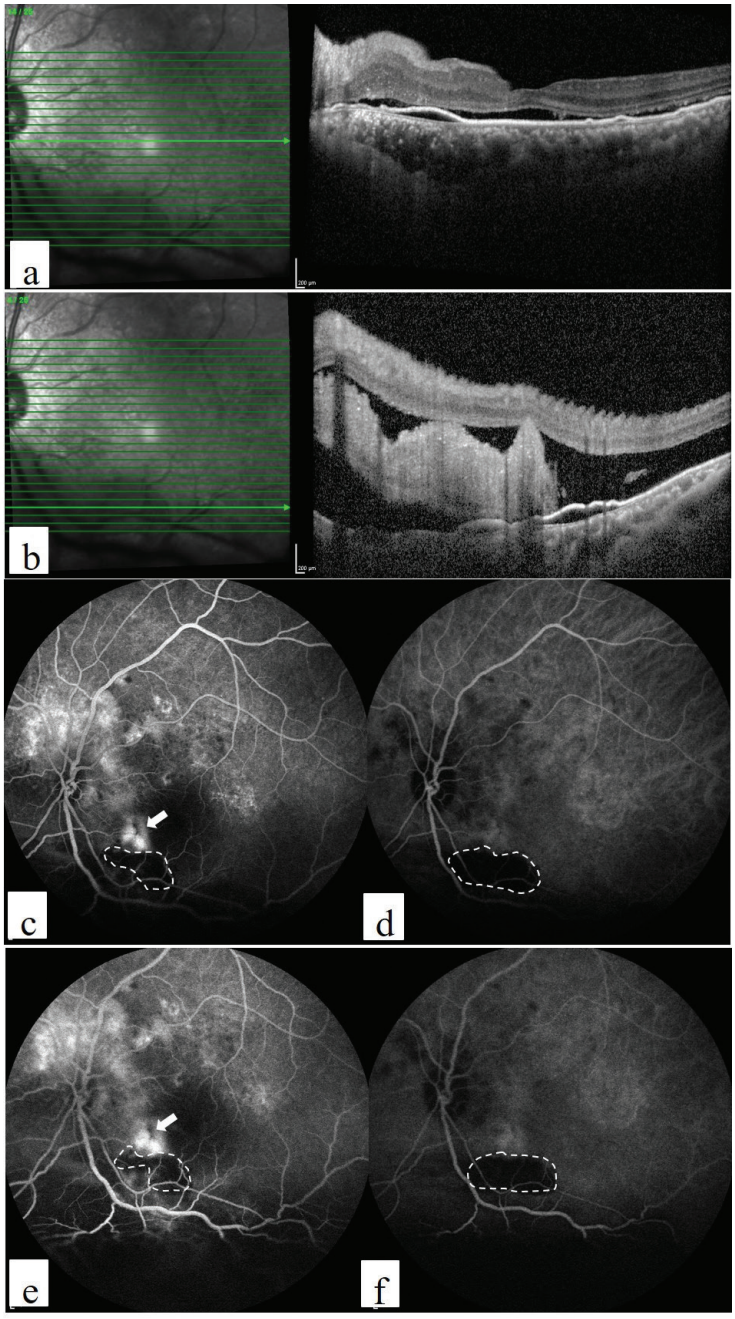

Figure 3. Multimodal retinal images obtained during latest activation in the left eye. a) Optical coherence tomography (OCT) showed subretinal fluid, serous pigment epithelial detachment, and increased choroidal thickness. b) Inferior section of OCT showed dense hyperreflective fibrotic material in the subretinal area and increased amount of subretinal fluid. Combined dye angiography images of the left eye: c) Early-phase fluorescein angiography (FA) revealed peripapillary window defects, a hypofluorescent area due to the blockage by the subretinal fibrotic material (dashed circle), and an active leakage point (arrow). d) Early-phase indocyanine green angiography (ICGA) showed dilated choroidal vessels, areas of choroidal hyperpermeability, and a hypocyanescent area due to blockage by the subretinal fibrotic material (dashed circle). e) Late-phase FA revealed increased hyperfluorescence at the side of active leakage (arrow) and hypofluorescence due to blockage by the subretinal fibrotic material (dashed circle). f) Late-phase ICGA showed hypercyanescent areas of choroidal hyperpermeability and an area of hypocyanescence due to blockage by the subretinal fibrotic material (dashed circle)

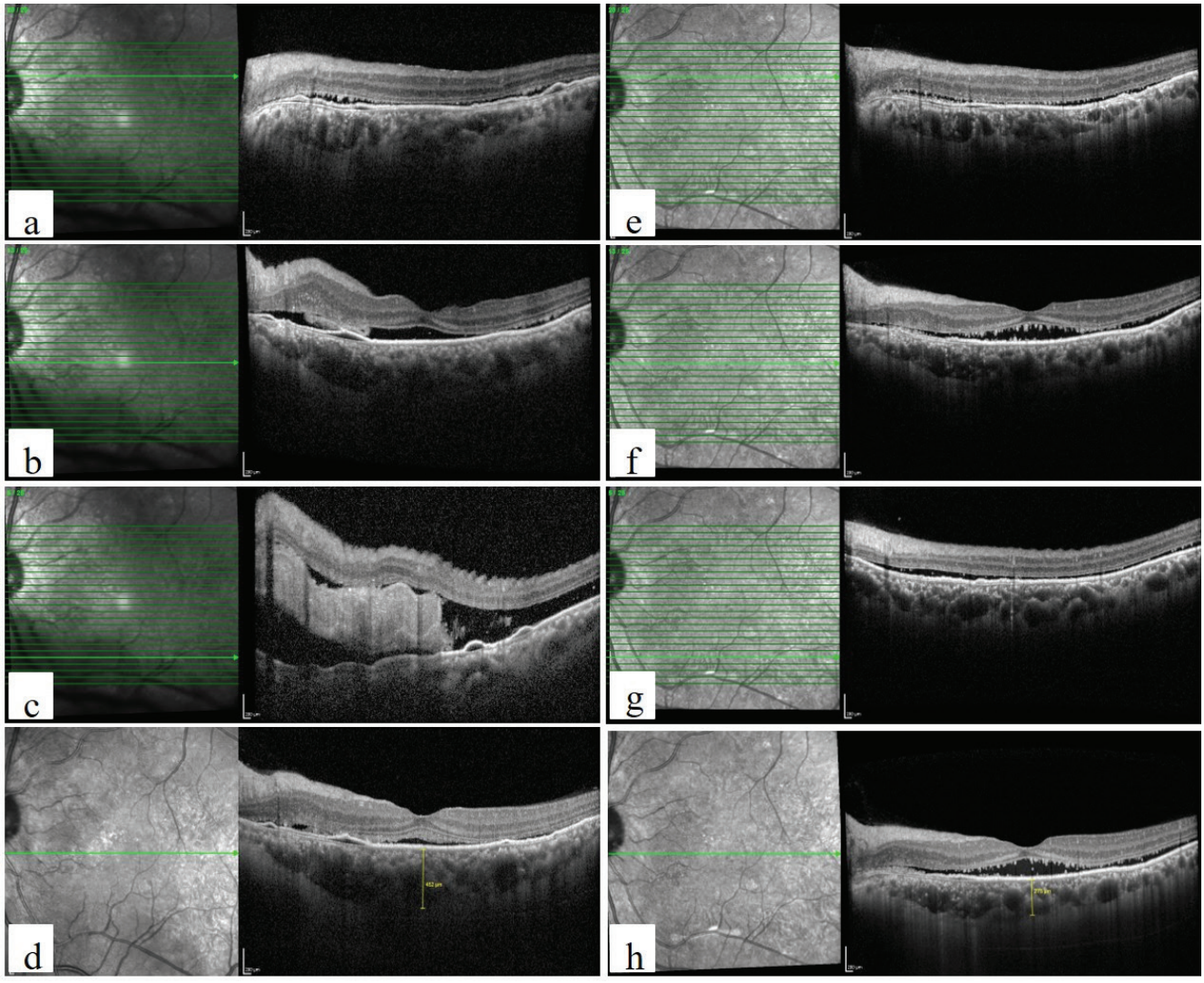

Figure 4. B-scan and enhanced depth imaging mode optical coherence tomography images passing through the same horizontal cross-sections before (a-d) and after (e-h) half-fluence photodynamic therapy. a-c) Increasing amount of subretinal fluid towards the inferior sections. c) Dense hyperreflective fibrinous material. d) Thick choroid, 452 µm. e-g) Regressed subretinal fluid. g) Loss of hyperreflective fibrinous material. h) Decreased choroidal thickness, 275 µm

In atypical CSCR cases, providing an earlier definitive diagnosis may be a clinical challenge. Atypical bullous CSCR is most commonly misdiagnosed as the acute phase of VKH due to the exudative retinal detachment.[6] Subretinal fibrin reaction and presence of generalized RPE irregularities in the absence of vitreous cells and lack of optic disc hyperemia and edema are signs in favor of CSCR. An absence of optic disc staining on FA and ICGA is a finding that further facilitates the diagnosis of CSCR. On OCT, RPE bulge may be seen in CSCR, whereas RPE folds, fluctuations of the internal limiting membrane, and subretinal septa are seen only VKH.[7] Subretinal fibrin reaction is frequently encountered in eyes with bullous CSCR.[8]

Therapeutic options for atypical CSCR include laser photocoagulation, PDT, and oral mineralocorticoid receptor antagonists.[9] The main mechanism of action of PDT is angio-occlusion leading to constriction of choroidal vessels and choroidal vascular remodelling.[10] Therefore, it may be the most appropriate treatment approach, being effective on the direct pathogenesis. In our case, we used a combination of half-fluence PDT and eplerenone therapy, which provided very rapid and complete resolution of subretinal fluid without complications.

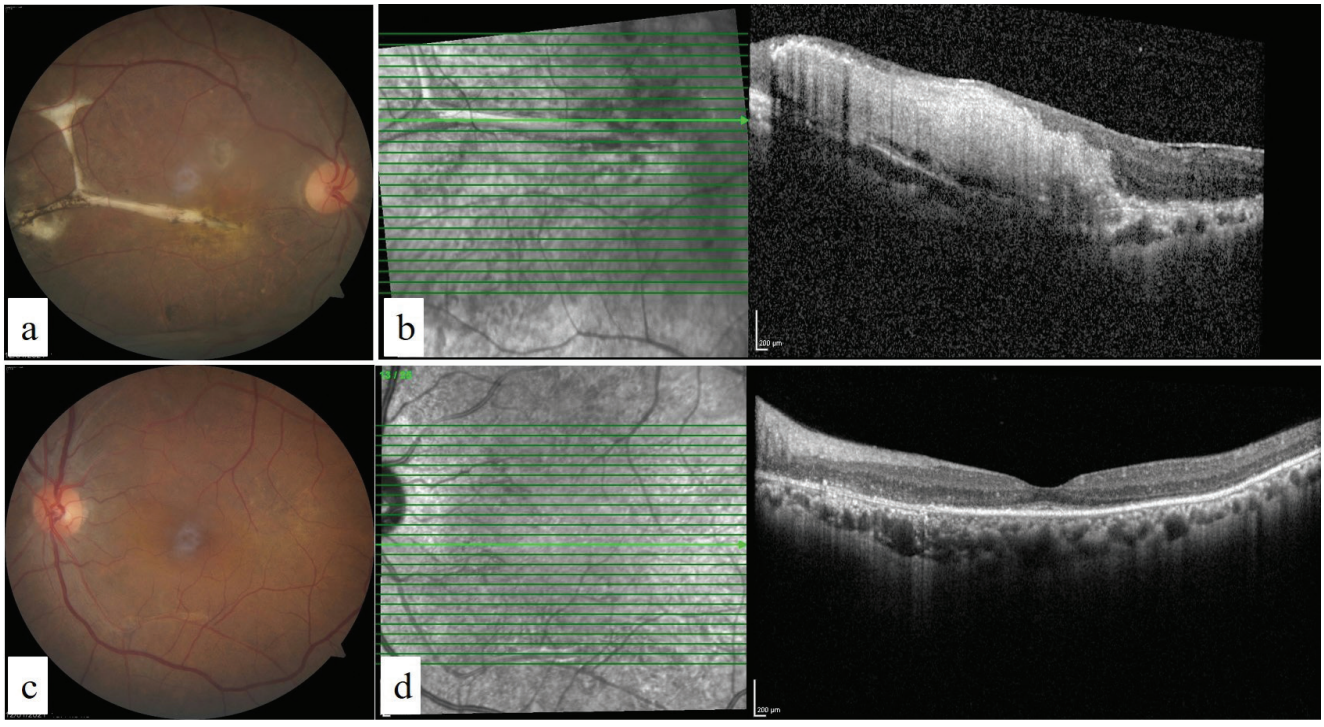

Figure 5. Color fundus photography and optical coherence tomography (OCT) images at the last visit: a) Color fundus photography of the right eye showed Y-shaped fibrinous scar with localized hyperpigmentation areas within it. b) OCT image of the right eye revealed dense fibrinous scar and epiretinal membrane formation. c) Color fundus photography of the left eye showed complete recovery. d) Optical coherence tomography of the left eye revealed loss of the external limiting membrane, ellipsoid and interdigitation zones, and disruption of the retinal pigment epithelium in the field of previous serous pigment epithelial detachment.

In conclusion, the use of multimodal imaging may enable early definitive differential diagnosis of atypical CSCR from other chorioretinal diseases. Otherwise, inappropriate use of corticosteroids and other immunosuppressive agents may worsen the clinical findings and lead to poor visual prognosis. Hf-PDT in combination with oral eplerenone may be a successful treatment option for atypical CSCR that prevents subretinal fibrosis and scar formation.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: F.B., N.Y., Concept: Ö.Y., F.B., N.Y., S.D., E.Ö., Design: Ö.Y., F.B., N.Y., S.D., E.Ö., Data Collection or Processing: Ö.Y., Analysis or Interpretation: Ö.Y., F.B., N.Y., S.D., E.Ö., Literature Search: Ö.Y., F.B., N.Y., Writing: Ö.Y., F.B., N.Y., S.D., E.Ö.

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Letter to the Editor re: Dry Eye and Meibomian Glands in Vitiligo

Hamidreza Jahanbani-Ardakani*, Afshin Moliani**, Sadaf Khorrami***, Mohammad Reza Khalili****, Seyed Hossein Abtahi*****

*Shiraz University of Medical Sciences, Department of Ophthalmology, Shiraz, Iran
**Isfahan University of Medical Sciences, Student Research Committee, School of Medicine, Isfahan, Iran
***Tehran University of Medical Sciences School of Medicine, Isfahan, Iran
****Shiraz University of Medical Sciences, Poostchi Ophthalmology Research Center, Department of Ophthalmology, Shiraz, Iran
*****Shahid Beheshti University of Medical Sciences, Ophthalmic Research Center, Research Institute for Ophthalmology and Vision Science, Tehran, Iran

Keywords: Vitiligo, dry eye, Ocular Surface Disease Index, meibomian gland

Dear Editor,

Recently, we read an interesting study by Taheri et al.[1] entitled "Dry Eye and Meibomian Glands in Vitiligo", focusing on meibomian gland (MG) function and the lipid tear film in vitiligo patients. They included 86 patients and controls, evaluated them with comprehensive ophthalmic physical examination to clarify the status of dry eye as well as MG structure and function. In this letter, we would like to address methodological comments regarding their paper.

In this study, the authors mentioned that patients with any systemic or ophthalmic diseases, patients using contact lenses, and patients taking drugs which may affect the lacrimal gland were excluded. Also, participants were not allowed to use artificial tears 2 hours before ophthalmic examinations. We commend their efforts in choosing appropriate subjects to remove any confounding factors; however, they did not consider cigarette smoking status. As we know, smoking is a possible cause of dry eye disease (DED) due to its influence on the quantity and quality of the tear film, as well as its reduction of corneal and conjunctiva sensitivity, which leads to chronic inflammation.[2]

In addition, vitiligo patients using topical medications, especially immunosuppressant agents such as cyclosporine A for the periocular area should be excluded, as cyclosporine A has beneficial effects on the status of DED.[3] It has been reported that cyclosporine A is helpful in halting the autoimmune-associated cascade and improving melanocyte pigments in vitiligo disease.[4] Therefore, including vitiligo patients with periocular involvement taking topical cyclosporine A could affect the dry eye parameters, as cyclosporine A may improve the DED.

Furthermore, it has been shown that MG dysfunction and lid wiper epitheliopathy with lid-parallel conjunctival folds are involved in pathophysiology of contact lens-associated dry eye.[5] Therefore, excluding not only current contact lens users but also recent contact lens users is necessary as it takes time (i.e., a couple of months) to recover to normal.

Address for Correspondence: Hamidreza Jahanbani-Ardakani, Shiraz University of Medical Sciences, Department of Ophthalmology, Shiraz, Iran
E-mail: hamidreza_jahanbaniardakani@yahoo.com **ORCID-ID:** orcid.org/0000-0002-3541-2828
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Finally, in their article, the authors recruited participants from Birjand city and they used the English version of the Ocular Surface Disease Index (OSDI) questionnaire, whereas the subjects were native Persian speakers. As we know, every questionnaire should be used in scientific studies after cultural and language adjustment for the target population because literally translated texts may have some conceptual flaws. As a Persian version of the OSDI has been validated by Pakdel et al.[6], it may be feasible to use the validated questionnaire instead of an English version or a mere translation.

Overall, we think that the results of the paper would be more valid if the authors had considered the above-mentioned points.

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Reply to Letter to the Editor re: Dry Eye and Meibomian Glands in Vitiligo

Ahmad Reza Taheri*, Malihe Nikandish**

*Mashhad University of Medical Sciences, Department of Dermatology, Mashhad, Iran
**Birjand University of Medical Sciences, Department of Ophthalmology, Birjand, Iran

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Dear Editor,

We would like to thank you for the opportunity to respond to the issues raised in the letter to the editor that was recently directed to us, and to clarify aspects of our methodology in relation to these concerns. We would also like to thank the authors of the letter for their interest in our article studying dry eye and meibomian glands in vitiligo, and for taking their valuable time to express their concerns.

In their letter, the authors recommended cigarette smoking as an exclusion criterion, as there may be a relationship between smoking and dry eye disease (DED) due to its influence on tear film quantity and quality. This association has been described previously in the scientific literature. However, the findings in this case are contradictory, and further investigations and meta-analysis are needed to validate the role of smoking in the incidence of dry eye.[1] Moreover, there are similar studies that have not excluded the smokers.[2,3]

They rightly recommended the exclusion of vitiligo patients using topical medications, especially immunosuppressant agents (i.e., cyclosporine A), in the pre-ocular area because of the beneficial effects of cyclosporine A on DED. In agreement with them, we mentioned "recent use of drugs affecting the lacrimal unit" as an exclusion criterion. It is necessary to explain that topical cyclosporine A is not a conventional medicine in vitiligo treatment[4], and none of our patients received this drug.

They also recommended excluding not only current contact lens users but also recent contact lens users. We agree that contact lenses affect the ocular surface and it takes time to recover to normal. None of our patients have ever used contact lenses. Based upon our practice, it is interesting to note that contact lens use is not common in our geographic region due to dusty air.

The authors properly suggested validated Persian questionnaire of Ocular Surface Disease Index (OSDI) instead of an English version. While appreciating the study of Pakdel et al.,[5] unfortunately, we did not have access to the Persian version of the OSDI at the time of our study. However, in order to reduce any error, each item of the questionnaire was explained in a language understandable to the patient and then filled in by the researcher (B.H.R) himself. Of note, there are many studies in non-English speaking countries that utilize the original version of the OSDI.[6,7] We hope to access and use the Persian version of this questionnaire in future studies on dry eye.

Address for Correspondence: Malihe Nikandish, Birjand University of Medical Sciences, Department of Ophthalmology, Birjand, Iran
E-mail: malihenikandish@yahoo.com **ORCID-ID:** orcid.org/0000-0002-6180-637X
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