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Research Articles

Review

Case Reports

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The Turkish Journal of Ophthalmology is currently published in Turkish and English languages. TJO is an independent international periodical journal based on single-blind peer-review principle. TJO is regularly published six times a year and special issues are occasionally released. The aim of TJO is to publish original research papers of the highest scientific and clinical value at an international level. Furthermore, review articles, case reports, editorial comments, letters to the editor, educational contributions and congress/meeting announcements are released.

The target audience includes specialists and physicians in training in ophthalmology in all relevant disciplines.

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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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To ensure controllability of the research findings, the study design, study sample, and the methodological approaches and applications should be explained and their sources should be presented.

The "P" value defined as the limit of significance along with appropriate indicators of measurement error and uncertainty (confidence interval, etc.) should be specified. Statistical terms, abbreviations and symbols used in the article should be described and the software used should be defined. Statistical terminology (random, significant, correlation, etc.) should not be used in non-statistical contexts.

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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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

2020 Issue 6 at a Glance;

Esteemed colleagues,

In the sixth and final issue of 2020, the Turkish Journal of Ophthalmology features six original studies, one review, four case reports, and two letters to the editor with a response from the authors.

In a comment on Keskinbora and Güven's review titled "Artificial Intelligence and Ophthalmology", Martins emphasized the privacy and security of personal data, the anonymization of data while using algorithms for common retinal diseases in different studies, and the difficulty of developing algorithms for rare retinal diseases. He also concluded his criticism by pointing out the common blind spot of all artificial intelligence applications: the contribution of the social and psychological aspects of human nature in diagnosis. In their response, Keskinbora and Güven state that sensitivity to data privacy and ethical issues continues, especially in advanced artificial intelligence applications, and this specific problem can be overcome by continuous monitoring and ethical evaluation of technological developments in the narrowest of the artificial intelligence categories. However, as both iris and retinal images are as unique as fingerprints, it is clear that anonymization efforts and the powers and access granted to artificial intelligence applications are issues that will continue this debate.

Cataract surgery and the continually developing modern optic designs of intraocular lenses have given rise to a patient group seeking excellent visual outcomes and comfort. Erdinest and London read with interest the article titled "Dry Eye Disease after Cataract Surgery: Study of its Determinants and Risk Factors" published in our journal by Garg et al. and offer their contribution to this topic. For this patient group, in addition to the use of topical lubricants, they recommend that patients with clinical signs of dry eye, even those who are asymptomatic, be treated with topical cyclosporine, which has been shown to improve visual acuity and contrast sensitivity after cataract surgery in patients who receive multifocal intraocular implants.

Gümüş et al. retrospectively analyzed the results of 59 patients titled "Prognostic Factors Affecting Graft Survival in Patients Undergoing Penetrating Keratoplasty for Infectious Keratitis". Penetrating keratoplasty is an effective treatment option in keratitis patients who are resistant to treatment or have impending perforation, and the authors' report that both performing re-keratoplasty and doing so early improved outcomes is encouraging for those undertaking surgery in these difficult cases.

Chitamparam et al. share the results of 27 eyes of 27 patients with culture-positive fungal keratitis in their study titled "Mycotic Keratitis in a Tertiary Hospital in Northeastern Malaysia". In their cohort, which may serve as a reference for the Pacific Asian region, *Fusarium* was the most common organism causing mycotic keratitis and ocular trauma was identified as the main predisposing factor. Additionally, as a prognostic finding, they noted that peripheral ulcers may resolve without antifungal therapy, while visual prognosis was worse with centrally located ulcers.

Akkaya Turhan et al. conducted a study titled "Use of a Mini-Scleral Lens in Patients with Keratoconus" and demonstrated an increase in both high- and low-contrast visual acuity with mini-scleral lenses in 29 eyes of 24 patients. The authors' emphasis that a successful mini-scleral lens fitting, which improves not only visual acuity but also contrast sensitivity, is facilitated by anterior segment optical coherence tomography (OCT) and the example images shown in the article also make this study interesting in terms of the use of current technology.

Cheong et al. studied vascular endothelial growth factor (VEGF) inhibitor therapy in 22 eyes with diabetic macular edema (DME) and determined that the effect of VEGF inhibitors in the treatment of DME was not related to increasing vascular density. They state that larger and longer term studies are needed to investigate the role of vascular density measurements in OCT angiography images as a biomarker of treatment response.

Aside from the complicated ocular evaluations such as zone, grade, and signs of threshold disease in retinopathy of prematurity, Şahinoğlu Keşkek et al. present a new and important awareness measure that requires a systemic investigation to assess retinopathy risk. In their retrospective study titled "Impact of Platelet Count in Retinopathy of Prematurity" based on the records of 137 newborns, they report that low platelet count in the first week after birth is an additional risk factor for retinopathy of prematurity in addition to the known risk factors of need for ventilation, low birth weight, and low gestational age.

Karaca et al. determined in their study titled "Evaluation of Periorbital Tissues in Obstructive Sleep Apnea Syndrome" (OSAS) that patients with OSAS had greater eyelid laxity and significantly more frequent and severe eyelash ptosis.

In this issue's review on conjunctival melanoma, Koç and Kıratlı present classical treatment approaches as well as new treatment options and up-to-date information about the molecular biology of the disease. Although treatment is the area of our colleagues specializing in ocular oncology, its diagnosis is based on biomicroscopic examination of the eye (i.e., a part of routine ophthalmological evaluation) and therefore, referring patients for treatment and providing the first information about treatment options is the responsibility of every ophthalmologist. With its current content encompassing chemotherapy to radiotherapy, surgery to molecular biological treatment options, this review is a complete bedside reference.

Kahar et al. report the first patient with neuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome with neuroretinitis caused by *Bartonella henselae*, the pathogen responsible for neuroretinitis in cat scratch disease. With

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EDITORIAL

this case report, they aimed to increase awareness regarding POEMS syndrome and possible initial ocular symptoms among ophthalmologists.

Kalogeropoulos et al. emphasize that patients with non-ocular malignancy may present with posterior scleritis as an ophthalmic manifestation of paraneoplastic syndrome months before the onset of systemic symptoms and diagnosis of the malignancy, and that the possibility of malignant neoplasia should not be ignored in patients with posterior scleritis, particularly older adults.

In their case report titled "Cryptic Myiasis by *Chrysomya bezziana*: A Case Report and Literature Review", Rana et al. present a destructive and rapidly progressive orbital myiasis that can also generally be seen in healthy tissues and requires early intervention to prevent mortality due to the possibility of intracranial invasion from the orbital apex, together with a comprehensive review of the literature.

Vision loss and blindness in children with Stickler syndrome have classically been associated with the presence of retinal detachment. In their case report, Navarrete et al. present a 9-year-old child with high myopia who presented with decreased visual acuity in both eyes and after 2 years of follow-up developed progressive unilateral vision loss accompanied by marked atrophy of the outer retinal layers and peripheral vascular leakage but without retinal detachment.

As our journal bids farewell to 2020, we have for you an issue more than half penned by international authors, as eight of the published articles, including two letters to the editor, are from ophthalmologists abroad. Thus, as our national ophthalmology journal exhibits its status as a reference in the global ophthalmology literature, we hope to reunite in 2021 for a joyful new year in which the global problems we have faced, especially the pandemic, are put behind us.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

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Original Article

Prognostic Factors Affecting Graft Survival in Patients Undergoing Penetrating Keratoplasty for Infectious Keratitis

Gülşah Gümüş, Ahmet Kırgız, Yusuf Yıldırım, Nilay Kandemir Beşek, Selim Genç, Burçin Kepez Yıldız, Muhittin Taşkapılı

University of Health Sciences Turkey İstanbul Beyoğlu Ophthalmology Training and Research Hospital, İstanbul, Turkey

Abstract

Objectives: To evaluate the prognostic factors affecting graft survival in patients undergoing penetrating keratoplasty (PKP) for infectious keratitis.

Materials and Methods: Patients who underwent PKP for keratitis in our hospital between 2013 and 2018 were retrospectively reviewed. Patients who underwent therapeutic PKP at the inflammatory stage and were followed for at least 12 months were included in the study. Age, gender, follow-up period, time between diagnosis and surgery, lens status, presence of limbal involvement, presence of corneal ulceration, perforation, or corneal abscess, type of microorganism detected in culture, number of fortified medications used before surgery and duration of use, preoperative and postoperative visual acuity, postoperative graft transparency, postoperative complications, recurrence of infection, rate of re-keratoplasty, and indication for and timing of re-keratoplasty were recorded. The relationship between these findings and anatomic, therapeutic, and functional success were evaluated.

Results: Fifty-nine patients were included in the study; 40 (67.8%) were male and 19 (32.2%) were female, and the mean age was 59.78±19.46 (6-91) years. Anatomic success was achieved in 58 patients (98.3%). Therapeutic success was achieved in 47 patients (79.7%) and there was a significant relationship between therapeutic success and re-keratoplasty and early re-keratoplasty ($p<0.001$ for both). Thirty-two patients (54.2%) had functional success and there was a significant relationship between the absence of postoperative complications and functional success ($p=0.014$).

Conclusion: PKP is an effective treatment option in treatment-resistant keratitis or keratitis with impending perforation. The absence of postoperative complications and performing early re-keratoplasty in patients with recurrence increase the success rate.

Keywords: Infectious keratitis, penetrating keratoplasty, graft survival

Introduction

Infective keratitis is a common sight-threatening condition worldwide.[1] Between 1.5 and 2 million new cases of blindness associated with keratitis are reported each year in developing countries.[2,3] Even with appropriate treatment, stromal abscess, severe corneal ulceration, descemetocele, and perforation can occur in some cases.[4] Depending on the clinical presentation, available treatment options for patients with perforation include amniotic membrane transplantation, conjunctival flap cover surgery, repair with tissue adhesive, and therapeutic lamellar or penetrating keratoplasty (PKP).[5,6,7,8]

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In infective keratitis, PKP can be performed for tectonic purposes to preserve globe integrity in patients with infectious perforation or suspected perforation, for therapeutic purposes to control infection in patients with uncontrolled infection, or for visual rehabilitation purposes in the late stage. PKP is known to yield more successful outcomes if performed at a later stage, after inflammation has regressed.[9] However, cases with uncontrolled infection, perforation, or high risk of perforation may require PKP without waiting for inflammation to regress. Previous studies have evaluated the effects of patient age, sex, contact lens use, presence of systemic disease, history of trauma, whether keratitis was in the inflammatory stage, degree of corneal vascularization, graft diameter, ulcer and perforation size, type of microorganism detected in culture, postoperative complications, pre- and postoperative visual acuity, time elapsed between diagnosis and surgery, intraocular pressure (IOP), and lens status on graft survival in patients undergoing therapeutic PKP for keratitis.[9,10,11,12] However, there has been no investigation into the impact of factors such as additional procedures performed concurrently with PKP, presence of corneal abscess, number of fortified drugs used preoperatively, whether re-keratoplasty was performed, and the indication and timing of re-keratoplasty.

The aim of this retrospective study was to evaluate the prognostic factors that affect graft survival in patients who underwent therapeutic PKP in our clinic due to infective keratitis.

Materials and Methods

Patients who underwent therapeutic PKP due to keratitis in our clinic between 2013 and 2018 were retrospectively reviewed. Cases who underwent therapeutic keratoplasty in the inflammatory stage and were followed for at least 12 months were included in the study. Patients who did not have active infection, underwent refractive PKP, had suspected endophthalmitis in addition to keratitis, or were followed for less than 12 months were excluded. The study adhered to the principles of the Helsinki Declaration of Human Rights and received ethics committee approval. Consent was obtained from all patients for the use of their medical records.

The patients' age, sex, duration of follow-up, time from diagnosis to surgery, history of contact lens use, presence of limbal involvement, corneal ulceration, perforation, or abscess, type of microorganism detected in culture, number of fortified drugs used preoperatively, PKP indication, additional procedures performed concurrently with PKP, graft diameter, pre- and postoperative visual acuity, postoperative graft transparency, postoperative complications, recurrence of infection, whether re-keratoplasty was performed, and the indication and timing of re-keratoplasty were recorded. Recurrence of infection was diagnosed upon repeated detection of infiltration by a microorganism previously detected on the graft at any time after PKP or based on the clinical presentation in cases with negative culture.

Pre- and postoperative visual acuity was measured as light perception, hand motions, counting fingers, or for longer distances, using Snellen chart and expressed in decimal. For microbiological diagnosis, corneal swab was collected from the site of infection. Samples were sent to the microbiology laboratory for direct examination, culture, and antimicrobial susceptibility testing. In case of suspected viral infection, corneal material was sent for polymerase chain reaction (PCR) analysis. Patients with suspected bacterial etiology were empirically treated with 50 mg/mL topical fortified vancomycin (Vancotek, Koçak, İstanbul, Turkey) and amikacin (Amikozit, Sanofi, Vilnius, Lithuania) or 50 mg/mL ceftazidime (İesetum, İbrahim Etem Ulagay, İstanbul, Turkey) drops (1 drop hourly) until a microbiological diagnosis was determined. Patients with suspected fungal keratitis were treated with 0.5 mg/mL fortified amphotericin B (Ambisome, Gilead Sciences, California, USA) or 10 mg/mL fortified voriconazole (Vfend, Pfizer, New York, USA) (one drop hourly) and 200 mg oral fluconazole (Fluzamed, World Medicine, İstanbul, Turkey) twice a day or 200 mg oral voriconazole (Vfend, Pfizer, New York, USA) twice a day. In addition, patients with suspected herpes simplex virus (HSV) infection were given 1.5 mg/g topical gancyclovir (Virgan, Thea, İstanbul, Turkey) 5 times a day and 800 mg oral acyclovir (Aklovir, Sandoz, Holzkirchen, Germany) 3 times a day. Empirical therapies were modified according to microbiologic and antimicrobial sensitivity results.

PKP outcome was evaluated separately as anatomic, therapeutic, and functional success. Anatomic success was defined as preservation of globe integrity and prevention of progression to phthisis bulbi. Therapeutic success was defined as the complete elimination of primary infection following PKP. Findings of corneal or scleral infiltrate, vitritis, or endophthalmitis were considered therapeutic failure. Functional success was defined as a postoperative gain in visual acuity compared to preoperative level.

Prognostic factors such as patient age, sex, time from diagnosis to surgery, lens status, presence of limbal involvement, corneal ulceration, perforation, or abscess, type of microorganism detected in culture, number of fortified drugs used preoperatively, PKP indication, additional procedures performed concurrently with PKP, graft diameter, preoperative visual acuity, postoperative complications, whether re-keratoplasty was performed, and the indication and timing of re-keratoplasty were evaluated in terms of their effects on anatomic, functional, and therapeutic success. Number of fortified drugs used before PKP was classified as ≤2 drugs or >2 drugs. Indication for PKP was categorized as treatment non-response or infective complications such as corneal ulcer, abscess, and perforation. Other procedures performed concurrently with PKP were grouped as lensectomy, vitrectomy, intraocular lens (IOL) extraction, intrastromal injection, subconjunctival injection, and intravitreal injection. Graft diameter was classified as <8.00 mm and ≥8.00 mm. Postoperative complications were noted as postoperative glaucoma, persistent epithelial defect, graft failure, cataract, endophthalmitis, phthisis bulbi, and retinal detachment. Indications for re-keratoplasty were grouped as graft rejection and recurrence of infection. The timing of re-keratoplasty was classified as <20 days or ≥20 days.

Surgical Technique

All operations were performed under general anesthesia, retrobulbar anesthesia, or sub-Tenon's anesthesia. Trephination extending 0.5 mm beyond the infected area was performed. After partial-thickness trephination of the recipient cornea, an anterior chamber incision was made with a 15-degree blade and the anterior chamber was filled with viscoelastic. The remaining corneal areas then were dissected using scissors. After removing the infected cornea, the anterior chamber was irrigated and any pupillary membrane, hypopyon, or fibrotic materials were cleared and anterior and posterior synechiae were released. The anterior chamber was washed with 1% vancomycin (Vancotek, Koçak, İstanbul, Turkey) and 2% ceftazidime (Iesetum, I.E. Ulagay, İstanbul, Turkey) in patients with anterior chamber bacterial keratitis and with 0.005% amphotericin B (Ambisome; Gilead Sciences, California, USA) or 1% voriconazole (Vfend, Pfizer, New York, USA) in patients with fungal keratitis until the corneal graft was placed. When required, the phakic lens or IOL was removed and anterior vitrectomy was performed. The donor cornea was cut from the endothelial side using a punch 0.25 mm larger than the trephine used. The donor cornea was sutured to the recipient bed using 10-0 nylon sutures. The operation was concluded with an intracameral injection of 2% ceftazidime (Iesetum, I.E. Ulagay, İstanbul, Turkey) or 1% voriconazole (Vfend, Pfizer, New York, USA) as an antifungal agent.

Postoperative Treatment

Topical antimicrobial therapy was continued for at least 4 weeks in cases of bacterial keratitis and at least 12 weeks in cases of fungal keratitis. For patients with bacterial keratitis, topical 0.1% dexamethasone (Dexa-Sine SE, Liba, İstanbul, Turkey) or 1% prednisolone (Pred Forte, Allergan, Dublin, Ireland) was initiated at 6 times a day and was tapered to discontinuation at 12 months. For patients with fungal keratitis, 0.5% topical cyclosporine (Restasis, Allergan, Dublin, Ireland) was initiated for the first 2 weeks and if no recurrence of keratitis was observed, 0.1% dexamethasone or 1% prednisolone twice a day was added to the treatment after 2 weeks and was tapered to discontinuation at 12 months. Patients with herpetic keratitis received oral acyclovir (Aklovir, Sandoz, Holzkirchen, Germany) 800 mg 3 times a day for the first 4 weeks postoperatively and continued at a dose of 800 mg for at least 1 year. Artificial tears were prescribed to all patients. Antiglaucoma therapy was initiated if needed. Loose sutures were removed immediately.

Statistical Analysis

Statistical analyses of the data were done using SPSS version 20.0 (IBM Corp., Armonk, NY) statistical package software. Statistical data were expressed as mean ± standard deviation. Descriptive statistics were expressed as frequency and percentage. Relationships between categorical variables and PKP success (anatomic, functional, therapeutic) were evaluated using chi-square test (Pearson or Fisher's exact). For all analyses, the statistical significance level was accepted as $p<0.05$.

Results

Of the 59 patients included in the study, 40 (67.8%) were male and 19 (32.2%) were female. The mean age was 59.78±19.46 (6-91) years. The mean follow-up time was 30.78±17.4 (12-72) months.

The patients' preoperative characteristics and surgical indications are summarized in Table 1. The mean time from symptom onset to surgery was 18.68±15.2 (3-66) days. Of the 28 patients who underwent surgery within 10 days of symptom onset, PKP indication was keratitis-related complications (corneal abscess, perforation, ulceration) in 18 patients (64.29%) and non-response to treatment in 10 patients (35.71%) ($p=0.01$). The number of fortified drugs used before PKP varied between 1 and 4 (mean: 1.93±0.72). In the same session as PKP, concurrent lensectomy was performed in 6 patients, anterior vitrectomy in 1 patient, intrastromal injection in 1 patient, IOL removal in 1 patient, subconjunctival antibiotic injection in 3 patients, and 2 patients with intense anterior chamber reaction and hypopyon that underwent lensectomy received prophylactic intravitreal 1 mg/0.1 mL vancomycin (Vancotek, Koçak) and 2 mg/0.1 mL ceftazidime (Iesetum, IE Ulagay) because the posterior capsule was opened during lensectomy. Graft diameter ranged from 7.25 to 8.50 (mean: 7.76±0.31) and was ≥8.00 mm in 24 patients (40.68%) and <8.00 in 35 patients (59.32%).

One patient with no light perception underwent keratoplasty due to perforation and their postoperative vision was still at the level of no light perception. Preoperative visual acuity in the other patients ranged from light perception to 0.1 and their postoperative best corrected visual acuity ranged from light perception to 0.7 (Table 2). Thirty-one patients (52.54%) had postoperative visual acuity of light perception or hand motions, which was significantly reduced from the preoperative number of 49 patients (83.05%) ($p=0.007$). Postoperative visual acuity was

Table 1. Preoperative data

	n (%)
Side	
Right eye	30 (50.8%)
Left eye	29 (49.2%)
Lens status	
Phakic	47 (79.7%)
Pseudophakic	8 (13.6%)
Aphakic	4 (6.8%)
Limbal involvement	
Yes	3 (5.1%)
No	56 (94.9%)
PKP indication	
Treatment non-response	24 (40.7%)
Corneal ulceration	23 (39.0%)
Corneal perforation	4 (6.8%)
Abscess	8 (13.6%)

Table 2. Pre- and postoperative visual acuity levels		
Visual acuity	**Preoperative**	**Postoperative**
No light perception	1	1
Light perception	14	10
Hand motions	34	20
Counting fingers	7	13
<0.2	3	9
≥0.2	0	6

0.05 or better in 15 patients (25.42%), which was a significant increase from the 3 patients (5.08%) with that level of vision preoperatively (p=0.004). Seven patients (11.86%) had visual acuity of 0.1 or better at final examination.

Five (8.47%) of the patients had a history of contact lens use, 17 (28.81%) had trauma history, and 9 (15.25%) had a recent surgical history, while no etiology could be determined for 28 patients (47.46%). Trauma etiology was organic in 12 (70.59%) of the patients with trauma history. In microbiological examinations, bacteria were detected in 20 patients (33.90%), fungi in 12 patients (20.34%), and viruses in 5 patients (8.47%) as keratitis agents. Bacteriologic cultures yielded *Staphylococcus aureus* in 6 patients, *Streptococcus pneumonia* in 5 patients, *Viridans streptococci* in 3 patients, and *Pseudomonas aeruginosa* in 3 patients. In 1 patient, gram-negative bacillus was detected on direct examination but culture was negative. Fungal culture yielded *Fusarium* in 5 patients, *Candida* in 3 patients, and *Aspergillus* in 3 patients. In 1 patient, fungal hyphae were observed on direct examination but fungal culture was negative. PCR analysis for patients with suspected viral keratitis revealed HSV in 5 patients.

One patient (1.7%) who developed postoperative endophthalmitis was successfully treated with intravitreal antibiotic therapy. Retinal detachment occurred in 1 patient (1.7%) and pars plana vitrectomy was performed. Nine patients (15.3%) who developed cataract underwent phacoemulsification and IOL implantation surgery after achieving infection control. Twelve patients (20.3%) with elevated IOP responded well to medical treatment and none required glaucoma surgery. In 3 patients (5.1%) with refractory persistent epithelial defects, amniotic membrane transplantation resulted in epithelial healing. One patient (1.7%) with no light perception before PKP developed phthisis bulbi postoperatively. Three patients (5.08%) with limbal involvement received subconjunctival injection of fortified antibiotic. Despite no signs of recurrence, graft failure occurred in these patients. A total of 4 patients (23.7%) had graft failure. No complications were observed in 18 patients (32.2%).

At final examination, a clear graft was observed in 31 patients (52.5%), while 28 patients (47.5%) showed varying degrees of loss of graft transparency. Thirteen patients (22.03%) underwent re-keratoplasty. Indication for re-keratoplasty was graft rejection in 3 patients (23.07%) and recurrent infection in 10 patients (76.92%). Except for the patient with phthisis bulbi, anatomic success was achieved in the other 58 patients (98.3%) patients.

Therapeutic success was achieved in 47 patients (79.7%). Recurrent infection was observed in 12 patients (20.33%). Of these patients, 10 (83.33%) underwent re-keratoplasty, while in the other 2 patients (16.66%) the recurrent infection was controlled with antibiotic therapy. The mean time to detection of reinfection was 179±267.87 (3-720) days. Infection recurrence occurred within the first month in 6 patients (10.17%), within 1-3 months in 4 patients (6.78%), and between 3 months and 2 years in 2 patients (3.39%). The mean time between diagnosis and re-keratoplasty was 12.6±8.47 (2-26) days. Re-keratoplasty was performed earlier than day 20 in 8 patients (80%) and at day 20 or later in 2 patients (20%) with recurrent infection. Undergoing re-keratoplasty and early re-keratoplasty were significantly associated with therapeutic success (p<0.001 for both). Therapeutic success was not associated with patient age, sex, time from diagnosis to surgery, lens status, presence of limbal involvement, corneal ulceration, perforation, or abscess, type of microorganism detected in culture, number of fortified drugs used preoperatively, PKP indication, procedures performed concurrently with PKP, graft diameter, preoperative visual acuity, postoperative complications, or re-keratoplasty indication (p>0.05 for all) (Table 3).

Functional success was achieved in 32 patients (54.2%). The absence of postoperative complications was significantly associated with functional success (p=0.014). Functional success was not associated with patient age, sex, time from diagnosis to surgery, lens status, presence of limbal involvement, corneal ulceration, perforation, or abscess, type of microorganism detected in culture, number of fortified drugs used preoperatively, PKP indication, concurrent procedures, graft diameter, preoperative visual acuity, undergoing re-keratoplasty, or re-keratoplasty indication and timing (p>0.05 for all) (Table 3).

Discussion

Patients with refractory keratitis are at risk of perforation, endophthalmitis, panophthalmitis, and even loss of the eye. Therapeutic PKP helps to eliminate the microorganism from the environment and to ensure tissue survival in cases of resistant keratitis. In these cases, successful PKP eradicates infection and ensures preservation of anatomic integrity and function of the eye.[13] In the literature, anatomic success rates of 85.96% and 89.7% were reported by Raj et al.[11] and Sharma et al.[10], therapeutic success rates of 89.47%, 89.7%, and 97.6% were reported by Raj et al.[11], Sharma et al.[10], and Doğan and Arslan[14], respectively, and Raj et al.[11] reported 70.17% functional success in patients who underwent PKP due to keratitis. In our series of patients who underwent therapeutic PKP due to infectious keratitis, we achieved 98.3% anatomic success, 79.7% therapeutic success, and 54.2% functional success.

In their study on keratitis patients requiring inpatient treatment, Akova Budak et al.[15] reported history of surgery in 10%, trauma in 10%, and contact lens use in 5% of patients and concluded that contact lens use and history of surgery and trauma were the most commonly identified etiologies in keratitis

Table 3. Relationships between prognostic factors and therapeutic and functional success						
Prognostic parameters	**Therapeutic success**			**Functional success**		
	Success	**Failure**	**p**	**Success**	**Failure**	**p**
Age (years)						
<40	10	2		7	5	0.185
40-60	14	4	0.175	10	8	
>60	23	6		15	14	
Sex						
Female	15	4	0.543	10	9	0.865
Male	32	8		22	18	
Time from diagnosis to surgery						
<10 days	22	6	0.734	15	13	0.222
≥10 days	25	6		17	14	
Lens status						
Phakic	38	9		26	21	0.070
Pseudophakic	6	2	0.450	4	4	
Aphakic	3	1		2	2	
Limbal involvement						
Yes	2	1	0.499	1	2	0.479
No	45	11		31	25	
Keratitis-related complications						
None	20	4		14	10	
Corneal ulcer	19	4	0.296	12	11	0.479
Abscess	5	3		4	4	
Perforation	3	1		2	2	
Microorganism detected in culture						
None	18	4		11	11	
Bacterium	16	4	0.699	11	9	0.320
Fungus	9	3		7	5	
Virus	4	1		3	2	
Number of fortified drugs used before surgery						
≤2 drugs	38	9	0.679	25	22	0.315
>2 drugs	9	3		7	5	
PKP indication						
Infective complications (corneal ulcer. abscess.	27	8	0.651	18	17	0.174
perforation)	20	4		14	10	
Treatment non-response						
Additional procedures performed with PKP						
None	36	9		23	22	
Lensectomy	4	2		3	3	
Vitrectomy	1	0		0	1	0.232
IOL removal	1	0	0.169	1	0	
Intrastromal injection	0	1		1	0	
Subconjunctival injection	3	0		2	1	
Intravitreal injection	2	0		2	0	
Graft diameter						
<8.00 mm	28	7	0.917	18	17	0.393
≥8.00 mm	19	5		14	10	
Preoperative BCVA						
No light perception	1	0		0	1	
Light perception	11	3		9	5	0.591
Hand motions	26	8	0.311	18	16	
Counting fingers	6	1		4	3	
Counting fingers-0.2	3	0		1	2	

Table 3. contiuned

Postoperative complications						
None	15	3		17	1	
Postoperative glaucoma	10	2		5	7	
Persistent epithelial defect	2	1		1	2	
Graft failure	11	3	0.881	5	9	**0.014**
Cataract	7	2		4	5	
Endophthalmitis	0	1		0	1	
Phthisis bulbi	1	0		0	1	
Retinal detachment	1	0		0	1	
Re-keratoplasty						
Yes	11	2	**<0.01**	8	5	0.363
No	36	10		24	22	
Re-keratoplasty indication						
Graft rejection	3	0	0.079	0	3	0.085
Re-infection	8	2		3	7	
Re-keratoplasty timing						
<20 days	8	0	<0.01	4	4	0.880
≥20 days	0	2		1	1	

Statistically significant parameters are shown in bold. P: Pearson chi-squared test, PKP: Penetrating keratoplasty, BCVA: Best corrected visual acuity

requiring inpatient treatment. Miedziak et al.[16] reported that 3.3% of keratoplasty cases requiring PKP had a history of trauma, 8% had a history of contact lens use, and 46.7% had a history of surgery. Sharma et al.[10] reported that although no etiology could be determined in 55.3% of cases, 33.2% of the patients had a history of trauma and that 54.7% of patients with trauma history had organic trauma. In our study, 8.47% of the patients had a history of contact lens use, 28.81% of patients had a history of trauma (70.59% of which were organic), and 15.25% of the patients had a history of recent surgery. The rate of organic trauma was higher in our study when compared with the literature.

In microbiological analysis of corneal samples from the patients in our study, bacteria were detected in 20 patients (33.90%), fungi in 12 patients (20.34%), and viral agents in 5 patients (8.47%), while no microorganisms were detected in culture or direct examination in 22 cases (37.29%). Doğan and Arslan[14] determined the causative factor to be bacterial in 69.7%, viral in 14%, fungal in 11.6%, and *Acanthamoeba* in 4.6% of keratitis patients who underwent PKP. Yılmaz et al.[17] reported bacterial infection in 28.2% and fungal infection in 8.06% of keratitis cases followed in their clinic. Sharma et al.[10] detected bacteria in 31%, fungi in 20.9%, multiple pathogens in 6.9%, viruses in 5.3%, and *Acanthamoeba* in 1.6% of their patients. There may be several reasons for the inability to detect a microbiological agent in 37.29% of the patients in our study. First, most of the keratitis patients who presented to our clinic were referred from other centers after starting antimicrobial and steroid treatments, which may have prevented the detection of microbiological agent in some cases. Second, since our center is a branch hospital without facilities for microbiological analyses, the loss of time during sample transport to another center might have resulted in the inability to detect the microbiological agent.

The anatomic success rate was 98.3% in our study, consistent with previous studies.[10,18,19,20,21] Raj et al.[11] reported an anatomic success rate of 85.96% and cited preoperative visual acuity, PKP indication, postoperative complications, and graft transparency factors that significantly affected anatomic success. Sharma et al.[10] attained 89.7% anatomic success in their study, and although the rate of anatomic failure was high in PKP performed on perforated eyes, they stated that this was not statistically significant. In our study, anatomic failure was not observed except in a patient with no light perception preoperatively who underwent PKP due to the risk of perforation.

Previous studies reported rates of graft transparency between 23% and 84.6%.[22,23,24,25,26] Doğan and Arslan[14] reported graft transparency rates of 83.3% at 1-year follow-up and 71% at 2-year follow-up, and noted that graft transparency was lower with grafts that were larger than 8 mm and those that were close to the limbus. In our study, the graft transparency rate was 52.5% after a mean follow-up of 30 months, and our results were in concordance with the literature. We also observed that graft transparency decreased in cases with larger graft diameter, but the difference was not statistically significant (p=0.09).

Functional success was achieved in 54.2% of the patients and there was a significant association between the absence of postoperative complications and functional success. The most common postoperative complications in our patients was elevated IOP (20.3%) and graft failure (23.7%). Raj et al.[11] reported that postoperative complications significantly affected anatomic, functional, and therapeutic success. Although Sharma et al.[10] determined that postoperative visual acuity was better in patients with smaller grafts, we did not observe a significant relationship between graft diameter and functional success (p=0.393). In our study, 11.86% of the patients had a visual acuity of 0.1 or better at final examination, which is a low

rate compared to those in previous studies.[27] The high rate of organic trauma and contamination in our patients and delayed presentation to our center due to starting treatment at another center are possible explanations for the poor visual outcomes.

Our therapeutic success rate was 79.7%. Recurrent infection was observed in 20.33% of patients and occurred after a mean of 179 days. Recurrent infection was observed within the first month in 10.17%, within 1-3 months in 6.78%, and between 3 months and 2 years in 3.39% of the patients. In their study, Lomholt et al.[9] observed recurrent infection in 11% of patients within the first year, 16% within the first 2 years, and 24% within the first 5 years after therapeutic PKP. Bates et al.[28] reported recurrent infection within 1-10 months (mean 3 months) after PKP performed in patients with keratitis. The mean time from diagnosis to re-keratoplasty in our study was 12.6 days. We observed that performing re-keratoplasty and early re-keratoplasty were significantly associated with therapeutic success. This may be because the most common indication for re-keratoplasty in our study was recurrence of infection, and performing re-keratoplasty at an early stage facilitated the eradication of the recurrent infection. Koçluk and Sukgen[12] reported that early PKP yielded better anatomic and therapeutic outcomes. Sharma et al.[10] also stated that PKP performed at an early stage, before perforation and limbal involvement, provided better outcomes. The lower therapeutic success rate in our study may be attributed to the high prevalence of microbiologically detected fungus.

Sharma et al.[10] reported that small-diameter grafts (<9 mm) were associated with greater anatomic and functional success and that rates of recurrent infection and postoperative glaucoma increased with larger graft diameter. Raj et al.[11] determined that when grafts were classified as larger and smaller than 8 mm in diameter, graft size had no effect on anatomic, functional, or therapeutic success. We also observed no significant relationship between graft diameter and functional or therapeutic success in our study. The fact that we used grafts larger than 8.50 mm in diameter in our patients may have limited the impact of graft size. Similarly, we did not detect a significant association between functional or therapeutic success and additional procedures performed concurrently with PKP, presence of corneal abscess, or the number of fortified drugs used preoperatively.

Study Limitations

Limitations of our study include the limited number of patients, the retrospective study design, and that most of our patients were referred to our hospital from another center after the initiation of antibiotic treatment, which resulted in negative cultures.

Conclusion

In conclusion, due to its high anatomic, therapeutic, and functional success, PKP is an effective treatment option in keratitis patients with resistant infection or impending perforation. Knowledge of the factors associated with post-PKP success will guide treatment planning.

Ethics

Ethics Committee Approval: The study adhered to the principles of the Helsinki Declaration of Human Rights and received ethics committee approval.

Informed Consent: Consent was obtained from all patients for the use of their medical records.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., Concept: M.T., S.G., Design: Y.Y., S.G., M.T., Data Collection or Processing: G.G., N.K.B., Literature Search: N.K.B., B.K.Y., S.G., Writing: G.G.

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Original Article

Mycotic Keratitis in a Tertiary Hospital in Northeastern Malaysia

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Abstract

Objectives: To identify the clinical profile, etiology, and outcome of culture-positive mycotic keratitis in a tertiary referral centre in the Northeastern part of Malaysia.

Materials and Methods: A retrospective review of all patients with culture-positive mycotic keratitis in Hospital Universiti Sains Malaysia over a 3-year period, from January 2015 to December 2017.

Results: This study included 27 eyes of 27 patients treated for mycotic keratitis based on a positive fungal culture. The most common predisposing factor was ocular trauma, in 22 patients (81.5%). Eleven patients (40.7%) had a presenting visual acuity worse than 6/60, due to central ulcer involvement. Approximately half of these (6 patients) experienced visual improvement post-treatment. *Fusarium* sp. was the most common fungus isolated (37%), followed by non-sporulating fungi and *Curvularia* spp. Three patients (7.4%) had corneal microperforations, which healed after gluing and bandage contact lens application. One patient (3.7%) required tectonic penetrating keratoplasty and 1 patient (3.7%) underwent evisceration. The final visual acuity was 6/18 or better in approximately half (14 patients) of our cohort and worse than 3/60 in approximately 20% (5 patients).

Conclusion: Mycotic keratitis occurred mainly in males and secondary to ocular trauma. The most common organism isolated was *Fusarium*. Although treatment may improve vision, the visual outcome is guarded.

Keywords: Keratitis, fungi, *Fusarium*

Introduction

The cornea is the transparent, protective outer layer of the eye and the main structure responsible for focusing light rays onto the retina. Microbial keratitis refers to corneal inflammation secondary to infectious causes. The causative organisms of microbial keratitis include bacteria, viruses, and fungi. Fungal keratitis, also known as mycotic keratitis, is one of the leading causes of blindness, and remains the most challenging of all microbial keratitis.[1,2] The incidence of fungal keratitis is significantly higher in developing countries, likely due to its close association with vegetative trauma in agricultural societies.[2,3] Although reports on infectious keratitis are not uncommon, variations in causative organisms and their antimicrobial susceptibility among different study populations underscores the need for local data, which may provide individualized risk factor analysis and predict treatment outcomes.[1] The Asia Cornea Society Infectious Keratitis Study (ACSIKS) included eight Asian countries (India, China, Japan, South Korea, Taiwan, Thailand, Philippines, and Singapore) and analyzed the risk factors, microbiology, and outcomes of infectious keratitis in Asian countries. Unfortunately, Malaysia was not included in ACSIKS. Our study thus aimed to identify the clinical profile, etiology, and outcomes of culture-positive mycotic keratitis in a tertiary referral center in the northeastern part of Malaysia.

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Materials and Methods

This was a retrospective review of all culture-positive fungal keratitis in Hospital Universiti Sains Malaysia over a 36-month period, from January 2015 to December 2017. Exemption from ethical review was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia, as it was a fully anonymized study. The study adhered to the tenets of the Declaration of Helsinki.

All culture-positive fungal keratitis patients were identified from the database of corneal ulcers in the Department of Ophthalmology, Hospital Universiti Sains Malaysia. This database included both patients seen in the ophthalmology outpatient clinic and those who required inpatient care. All patients were examined under slit lamp and corneal scrapings were obtained under aseptic technique by using a sterile 21-gauge needle after the instillation of a local anesthetic (proparacaine hydrochloride 0.5%). The culture plates we used were blood agar, chocolate agar, MacConkey agar, and Sabouraud dextrose agar. The culture plates were then sent to our microbiological laboratory for incubation. Each patient's treatment regimen was individualized based on the clinical features and progression of the ulcer.

Data obtained from the hospital medical records included demographic features, clinical comorbidities, precipitating factors, location of ulcer, presenting and final visual acuity, organism cultured, and treatment. Presenting and final visual acuity was measured with a Snellen chart placed at 6 meters, with spectacle correction in the presence of refractive errors. Presenting visual acuity was defined as the documented visual acuity during first consultation, while final visual acuity was defined as the visual acuity at least 6 months after ulcer healing. Patients with incomplete data were excluded from the study.

Results

A total of 136 patients were diagnosed with infective keratitis during this period. Among these, 27 eyes of 27 patients were diagnosed as fungal keratitis based on a positive fungal culture. Their median age was 54 years (range: 21-77 years). Approximately 80% were male. The most common predisposing factor for developing fungal keratitis was trauma (81.5%). Other demographic features are shown in Table 1.

Table 2 shows the presenting visual acuity of our cohort. Ten patients (37.0%) had a presenting visual acuity of 6/18 or better, while 11 patients (40.7%) had a presenting visual acuity worse than 6/60. All patients in the latter group had centrally-located ulcers (Table 3). Among them, 6 (54.5%) experienced visual improvement after treatment; 1 (16.7%) achieved a final visual acuity of 6/18 or better, while 5 (45.5%) had a final visual acuity between 6/18 and 6/60.

Fusarium was the most commonly isolated genus (n=10, 37%), followed by non-sporulating fungi (n=5, 18.5%) and *Curvularia* (n=5, 18.5%). Most of our cohort were treated with dual topical antifungals (topical amphotericin B and topical fluconazole), as shown in Table 4. Choice of treatment was based on the clinical appearance and progression, as well as response to treatment. The ulcers in approximately one-fifth of cases healed with antibiotic and antiviral therapy only; antifungals were not started as the initial clinical appearance was not suggestive of fungal infection. In these patients, we noted that the ulcers were peripheral, and the presenting vision correspondingly good. One patient whose corneal scraping initially grew *Staphylococcus aureus* required evisceration; culture of the eviscerated tissue later revealed *Candida* sp.

Out of the 5 cases with perforation, three were caused by *Fusarium* spp. and 2 by *Candida*. However, both *Candida* cases resulted in a vision level of no light perception, while the one patient who needed evisceration was the patient with mixed infection with *S. aureus*.

Table 1. Demographics of the study sample

Variables	n (%)
Gender	
Male	22 (81.5%)
Female	5 (18.5%)
Affected eye	
Right	10 (37%)
Left	17 (63%)
Comorbidities	
Hypertension	8 (29.6%)
Smoking	8 (29.6%)
Diabetes	6 (22.2%)
Precipitating factors	
Trauma	22 (81.5%)
Ocular surface disorder	3 (11.1%)
Contact lens use	2 (7.4%)
Occupation	
Farmer	18 (66.7%)
Unemployed	6 (22.2%)
Office (others)	3 (11.1%)

Table 2. Presenting and final visual acuity of study subjects

VA range	Presenting VA, n=27 (%)	Final VA, n=27 (%)
6/6-6/18	10 (37.0)	14 (51.9)
Worse than 6/18-6/60	6 (22.2)	8 (29.6)
Worse than 6/60-3/60	0 (0)	0 (0)
Worse than 3/60-1/60 or CF	2 (7.4)	2 (7.4)
Worse than 1/60 or CF-LP	9 (33.3)	1 (3.7)
NLP	0	2 (7.4)

VA: Visual acuity, CF: Counting fingers, LP: Light perception, NLP: No light perception

Table 3. Presenting and final visual acuity based on ulcer location

VA range	Presenting VA			Final VA		
	Central, n=12 (%)	Paracentral, n=10 (%)	Peripheral, n=5 (%)	Central, n=12 (%)	Paracentral, n=10 (%)	Peripheral, n=5 (%)
6/6 - 6/18	0 (0)	5 (50)	5 (100)	2 (16.7)	7 (70)	5 (100)
Worse than 6/18-6/60	1 (8.3)	5 (50)	0 (0)	5 (41.7)	3 (30)	0 (0)
Worse than 6/60-3/60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Worse than 3/60-1/60 or CF	2 (16.7)	0 (0)	0 (0)	2 (16.7)	0 (0)	0 (0)
Worse than 1/60 or CF-LP	9 (75.0)	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)
NLP	0 (0)	0 (0)	0 (0)	2 (16.7)	0 (0)	0 (0)

VA: Visual acuity, CF: Counting finger, LP: Light perception, NLP: No light perception

Table 4. Organism, mode of therapy, and sequelae

Variables	N=27 (%)
Organism cultured	
Fusarium spp.	10 (37.0%)
Curvularia spp.	5 (18.5%)
Non-sporulating fungi	5 (18.5%)
Candida spp.	3 (11.1%)
Aspergillus spp.	3 (11.1%)
Phoma spp.	1 (3.7%)
Mode of therapy	
Antibiotic/antiviral therapy	5 (18.5%)
Monotherapy with a topical antifungal	5 (18.5%)
Dual topical antifungals	5 (18.5%)
Combined topical and oral antifungals	7 (25.9%)
Topical, oral and intrastromal antifungal	5 (18.5%)
Sequelae	
Scarring	22 (81.5%)
Perforation	5 (18.5%)
Bandage contact lens	3 (11.1%)
Tectonic penetrating keratoplasty	1 (3.7%)
Evisceration	1 (3.7%)

Duration of treatment was not analyzed, as we believed that confounding factors such as questionable compliance to treatment post-discharge rendered it irrelevant. However, we observed that most of the patients (n=16, 59.3%) required a long duration of hospitalization (more than 14 days) for the initial treatment (minimum 3 days, maximum 44 days, median 15 days).

Discussion

Fungal keratitis is a global public health problem which is especially challenging for ophthalmologists in developing counties.[1,2] It is a particular burden in tropical countries, where it may comprise up to 67% of infectious keratitis.[3] Obstacles to successful management include delayed diagnosis, longer healing times, a higher risk of corneal perforation, and overall worse visual outcome.[2,3] Our case series presents the clinical profile and etiology of mycotic keratitis in a tertiary referral center in northeastern Malaysia. We also evaluated the treatment regimens, sequelae, and visual outcomes of mycotic keratitis in this cohort.

The median age in our cohort was 54 years. This is similar to the age distribution reported in developed countries.[3,4] In developing countries, however, teenagers and young adults appear to be at greater risk, possibly due to occupational factors.[5] Males were predominant, which is in accordance with the literature.[6,7] Most of our patients were farmers; being a farmer, laborer, or unemployed has been shown to be associated with increased risk of fungal keratitis.[5] These findings may also explain why patients in rural areas are at higher risk of fungal keratitis than those in urban areas.[5]

Our study showed that trauma was the most common precipitating factor for mycotic keratitis. Immunocompromise and trauma, particularly vegetative, are the most common factors reported in association with fungal keratitis.[5,8,9] Presence of risk factors appears to be common with fungal keratitis, as in our series.[7] Diabetes mellitus has been shown not only to be a risk factor, but also to affect the severity of fungal keratitis.[10] Typical clinical signs of fungal ulcers such as feathery infiltrate (Figure 1), satellite lesions (Figure 2), endothelial plaque, and ring infiltrate are not present in all cases during the initial stages. Factors affecting the timing of onset of mycotic keratitis after trauma include the type of organism, the size of epithelial defect, and host immune system.[7] Dalmon et al.[11] reported that corneal specialists were able to correctly differentiate bacterial from fungal etiology by visual inspection in only 66% of cases. Thus, in the presence of risk factors, clinical suspicion is crucial for timely management of fungal keratitis.

The etiology of fungal keratitis shows geographical variations. We found *Fusarium* sp. to be the most common organism isolated, followed by *Curvularia* spp. and non-sporulating fungi (mycelia sterilia). The two most common fungi causing fungal keratitis worldwide appear to be *Aspergillus* spp. and *Fusarium* spp.[1,8,12,13,14,15], while *Curvularia* spp. have been cultured in Australia and the United States of America.[15,16]

Intrastromal amphotericin B was injected in a few of our patients with severe fungal keratitis. Hu et al.[17] observed that a combination of intrastromal and intracameral amphotericin

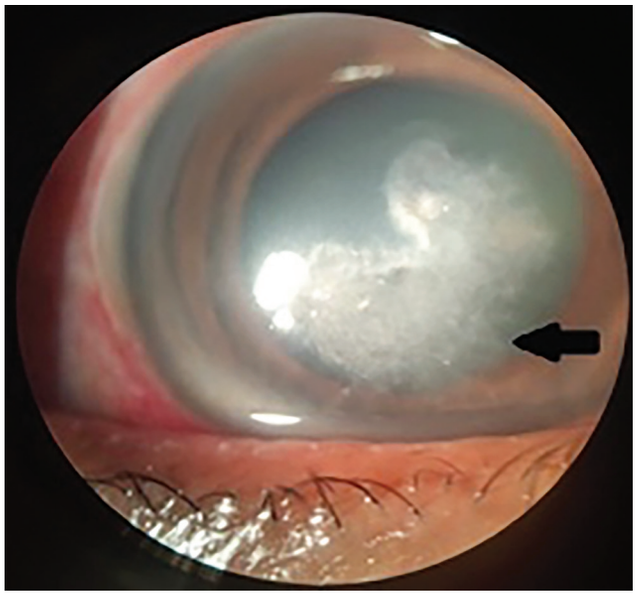

Figure 1. Anterior segment photo showing a typical fungal infiltrate with feathery edges (arrow)

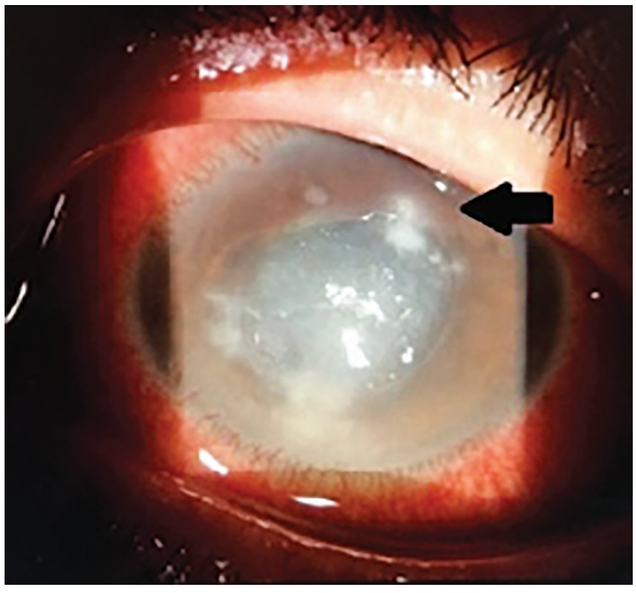

Figure 2. Anterior segment photo demonstrating satellite lesions (arrow)

B is safe and effective for refractory fungal keratitis. However, a randomized controlled trial of intracameral amphotericin B in fungal keratitis found no benefit of this regimen over topical therapy.[18] A Cochrane review on medical interventions for fungal keratitis evaluated various treatment regimens including voriconazole, itraconazole, and natamycin, concluding that natamycin is more effective than voriconazole in the treatment of fungal ulcers.[19] Unfortunately, natamycin is unavailable in Malaysia, while voriconazole is prohibitively expensive. This is the reason that most of our patients were on combined topical amphotericin B and topical fluconazole, with oral fluconazole added in severe cases. We do not use corticosteroids in the management of fungal keratitis, as we are of the opinion that corticosteroids increase fungal replication by lowering host resistance.[10] This prolongs the fungal clearance period, thus delaying the clinical response.[17]

We observed that approximately 60% (16 out of 27) of our cohort improved, with a third of our patients achieving a visual acuity of 6/12 or better. Those with better initial presenting vision had better final visual acuity, which is in keeping with the literature.[8] Prajna et al.[20] reported that large infiltrate size and severe fungal ulcers with presence of hypopyon were significantly associated with higher risk of corneal perforation. Other factors like visual acuity, epithelial defect size, baseline culture positivity, type of organism, and duration of symptoms are not strong predictors of corneal perforation.[20] In our one patient who required evisceration secondary to corneal perforation, the progression of her disease was attributed to a missed diagnosis of fungal keratitis, as her initial culture grew *S. aureus,* while the histopathology of the eviscerated specimen grew *Candida* sp. This is a reminder that one should consider mixed infection in cases of poor response to treatment despite a positive culture and sensitivity to prescribed antibiotics.

Our study provides a comprehensive overview of the clinical profile, etiology, and outcome of culture-positive mycotic keratitis in a tropical center. Strengths of our study over other published studies (Table 5) are its documentation of visual acuity and evaluation of the relationship between ulcer location and final visual acuity. Additionally, we show that small peripheral ulcers may recover without antifungal therapy, as occurred in 20% of our patients. Spontaneous resolution of small fungal keratitis has been attributed to host immune response and inhibition of fungal growth by use of topical fluoroquinolones.[21]

Study Limitations

There are several limitations of our study. First, as our sample was restricted to those with a positive fungal culture, our conclusions may not apply to fungal keratitis identified by other methods, such as *in vivo* corneal confocal microscopy. Secondly, due to its retrospective nature, there was lack of a standardized treatment protocol for mycotic keratitis; thus, we are unable to make any inferences regarding the comparative efficacy of different treatment approaches. Future research should involve a prospective, multicenter study to determine the optimal management of mycotic keratitis.

Conclusion

The most common organism causing mycotic keratitis in our cohort was *Fusarium*. Ocular trauma was the main predisposing factor. Peripheral ulcers may resolve without antifungal therapy, while central ulcer involvement has a worse visual prognosis. Dual topical antifungal agents were the main treatment initiated. The visual outcome generally improved post-treatment. A strong clinical suspicion of fungal or mixed infection is important in cases of poor treatment response, as a missed diagnosis of mycotic keratitis can have severe visual consequences.

Table 5. Comparison of clinical profiles, etiologies, and outcomes of mycotic keratitis in published studies

	Present study	**Khor et al.[1]**	**Ong et al.[3]**	**Iselin et al.[4]**
Country	Malaysia	India, China, Singapore, Philippines, Japan, Thailand, South Korea, Taiwan	United Kingdom	Switzerland
Year	2019	2018	2016	2017
Sample size of mycotic keratitis	27	2166	112	17
Mean age (years)	50.5	NA	NA	52
Median age (years)	54	NA	47.2	NA
Main risk factor, n (%)	Trauma, 22/27 (81.5%)	NA	Contact lens use, 64/112 (%57.1)	Contact lens use, 11/17 (65%)
Most common organism cultured	*Fusarium* spp. (37.0%) *Curvularia* spp. (18.5%) Non-sporulating fungi (18.5%)	*Fusarium* spp. (23.9%) *Aspergillus* flavus (10.9%) Non-sporulating moulds (8.8%)	*Fusarium* spp. (41.8%) *Candida* spp. (40.0%) *Aspergillus* spp. (11.4%)	*Fusarium* spp. (23.5%) *Candida albicans* (23.5%) *Fusarium oxysporum* (11.8%)
Baseline visual acuity	- 6/18 and better: 10/27 (37.0%) - Worse than 6/18, to 6/60: 6/27 (22.2%) - Worse than 6/60: 11/27 (40.7%)	NA	- 6/12 and better: 18/111 (16.2%) - 6/18 to 6/60: 39/111 (35.1%) - Worse than 6/60: 54/111 (48.7%)	NA
Final visual acuity	- 6/18 and better: 14/27 (51.9%) - Worse than 6/18, to 6/60: 8/27 (29.6%) - Worse than 6/60: 5/27 (18.5%)	NA	- 6/12 and better: 59/106 (55.7%) - 6/18 to 6/60: 26/106 (24.5%) - Worse than 6/60: 21/106 (19.8%)	NA
Most common antifungal therapy	Topical ampho Topical fluco Oral fluco	NA	Topical natamycin Topical ampho Topical vorico Oral vor	Topical natamycin Oral vor
Perforation / % requiring corneal graft	1/27 (3.7%)	NA	34/112 (30.4%)	4/17 (24%)

ampho: Amphotericin B, fluco: Fluconazole, vor: Voriconazole

	Kibret and Bitew[5]	**Zbiba et al.[8]**	**Farrell et al.[14]**	**Thew and Todd[15]**	**Ho et al.[16]**
	Ethiopia	Tunisia	Ireland	Australia	Southeastern USA
	2016	2016	2017	2008	2016
	69	30	42	16	63
	NA	48.9	47.4	40	56.1
	NA	NA	NA	NA	NA
	Trauma. 54/69 (78.3%)	Trauma. 13/30 (%43.3)	Preexisting ocular surface disease, 18/42 (42.9%)	Trauma. 7/16 (43.8%)	Contact lens use, 15/63 (24%) Prior PK, 15/63 (24%)
	Fusarium spp. (27.6%) *Aspergillus* spp. (25%) *Candida albicans* (15.8%)	*Fusarium* spp. (50.0%) *Aspergillus* spp. (33.3%) *Candida* spp. (11.1%)	*Aspergillus* spp. (38.1%) *Candida* spp. (31.0%) *Fusarium* spp. (21.4%)	*Fusarium* spp. (50%) *Aspergillus* spp. (12.5%) *Curvularia* spp. (12.5%) *Lasiodiplodia Theobromae* (12.5%)	*Curvularia* spp. (16%) *Fusarium* spp. (14%) *Aspergillus* spp. (14%)
	NA	Worse than 6/60: 24/30 (80.0%)	NA	- 6/12 and better: 6/16 (37.5%) - 6/18 to 6/60: 5/16 (31.3%) - Worse than 6/60: 5/16 (31.3%)	NA
	NA	Worse than 6/60: 16/30 (53.3%)	NA	- 6/12 and better: 10/16 (62.5%) - 6/18 to 6/60: 3/16 (18.8%) - Worse than 6/60: 3/16 (18.8%)	NA
	NA	Topikal amfo Oral vor	Topikal amfo Topikal vor Oral vor	Topical natamycin	NA
	NA	1/30 (3.3%)	11/42 (26.2%)	2/16 (12.5%)	23/63 (37%)

Ethics

Ethics Committee Approval: Exemption from ethical review was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia, as it was a fully anonymized study.

Informed Consent: Retrospective.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.I., Concept: S.C., E.T., Design: S.C., E.T., Data Collection or Processing: S.C., Analysis or Interpretation: T.H.L.., E.T., Literature Search: S.C., E.T., Writing: S.C., T.H.L., E.T.

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Original Article

Use of a Mini-Scleral Lens in Patients with Keratoconus

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Abstract

Objectives: To assess the visual performance of a mini-scleral lens in patients with keratoconus and to evaluate its fit by optical coherence tomography (OCT).

Materials and Methods: Twenty-nine eyes of 24 patients with keratoconus were fitted with a mini-scleral lens (Esclera; Mediphacos Inc., Belo Horizonte, Brazil). Diagnostic lenses were used in the initial fitting process. The lens fit was evaluated by the fluorescein pattern and also by anterior segment OCT (RTVue, Optovue Inc., Fremont, CA). Within 30-45 minutes after insertion, the lens fit parameters including central corneal and limbal clearance, and peripheral landing zone alignment were evaluated by OCT. High- and low-contrast visual acuity (VA), subjective performance for comfort and vision (5-point Likert scale), and overall satisfaction with the lens (100 mm visual analog scale [VAS]) were measured before and after lens wear.

Results: The mean decimal high-contrast VA (best spectacle-corrected VA: 0.40±0.14 vs VA with the scleral lens: 0.93±0.12, p<0.0001) and low-contrast VA (best spectacle-corrected VA: 0.60±0.24 vs VA with the scleral lens: 1.15±0.18, p<0.0001) significantly improved with lens wear. The mean central corneal clearance was 120.7±24.5 µm. There were no correlations between the keratometric values and the sagittal depth of the scleral lens. The mean number of trial lenses required for ideal fit was 2.2 lenses (range: 1-8). Patients reported high scores for comfort (mean score: 4.69; range: 4-5), vision (mean score: 4.62; range: 3-5) and overall satisfaction with the lens (mean VAS score: 88.1; range: 70-100).

Conclusion: The mini-scleral lens provided good high- and low-contrast visual acuity and high patient satisfaction in patients with keratoconus. Anterior segment OCT imaging facilitated the evaluation of the fit.

Keywords: Visual performance, keratoconus, mini-scleral lens

Introduction

Optical correction methods are used to improve the visual function of keratoconus patients. Progression of the disease leads to complex optical aberrations.[1,2] Rigid contact lenses can be used to reduce these aberrations.[3] However, despite the optical benefits provided by rigid contact lenses, they may not be a good fit for every patient. Lens decentration due to increased corneal irregularity, corneal scarring, and patient discomfort are important problems in more advanced cases.[4] Today, scleral lenses are a good option that can be used to prevent or delay surgery, especially when other lens options have been unsuccessful.[5] The tear reservoir between the scleral contact lens and cornea provides optical neutralization of irregular corneas, corneal hydration in ocular surface diseases, and high optical quality for vision and therapeutic applications.[6,7,8]

The key in scleral lens fitting is to position the lens parallel to the scleral contour, leaving a gap over the cornea and limbus but without creating pressure on the conjunctiva or edge lift. The fitting of scleral lenses differs from other lenses because it

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is based on sagittal height. An apical clearance between 100 and 400 µm is recommended depending on the material and design of the lens used.[9] Anterior segment optical coherence tomography (OCT) provides valuable information in the quantitative determination of clearance at each meridian from the central cornea to the limbus.[10] Evaluating the fit with OCT enables better lens fit and comfort to be achieved with the use of fewer trial lenses.[11] The aim of this study was to evaluate the visual performance and fit of a mini-scleral lens in keratoconus patients with OCT.

Materials and Methods

This retrospective study included 29 eyes of 24 keratoconus patients fitted with mini-scleral lenses (Esclera; Mediphacos Ltd., Belo Horizonte, Brazil).

Trial lenses were used for initial fit assessment. Points to consider during scleral lens fitting include:[9]

1. The scleral lens should extend 2 mm beyond the limbus.
2. The minimum sagittal depth should ensure central clearance. If there is apical contact, sagittal depth should be increased to achieve central clearance of at least 100 µm (Figure 1).
3. The lens edges should be checked to ensure they are not too raised or tight on the sclera (Figure 2a,b).
4. Final refraction should be evaluated through the lens.

Lens fit was evaluated by fluorescein pattern and anterior segment OCT (RTVue, Optovue Inc., Fremont, CA) imaging. At 30-45 minutes after lens application, lens fit parameters including central clearance, limbal clearance, and peripheral fit (no conjunctival compression or blanching, no edge lift) were evaluated with OCT. An ideal peripheral fit is shown in Figure 3.

All patients underwent a complete ophthalmologic examination. High-contrast visual acuity (VA) was measured in decimal using a standard Snellen chart at a distance of 6 meters. Low-contrast VA was measured using the Pelli-Robson Test (Vision Chart v 1.3.0 CSO, Florence, Italy) from a distance of 3 meters.[12] The Pelli-Robson Test, which includes optotypes of varying sizes and contrasts, consists of 16 sets of 3 letters at the same contrast, which decreases by 0.15 logCS between each set. Topographic measurements were made using a Scheimpflug camera system (Pentacam; Oculus Optikgerä te GmbH, Wetzlar, Germany). The flat meridian (K1), steep meridian (K2), and maximum keratometric value (Kmax) were recorded in diopters (D). Keratoconus staging was performed using the Amsler-Krumeich classification system.[13] High- and low-contrast VA, subjective performance for comfort and vision (5-point Likert scale), and overall satisfaction on a 100-mm visual analog scale (VAS) were evaluated before and after lens wear.

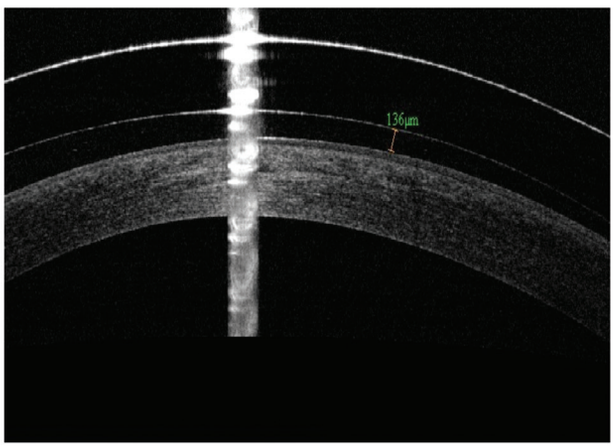

Figure 1. Measurement of apical clearance with optical coherence tomography

Statistics Analysis

The study data were evaluated using SPSS version 21.0 (IBM Corp., Armonk, NY) software. The Kolmogorov-Smirnov test was used to evaluate whether the data showed normal distribution. Parameters before and after scleral lens wear were compared using Wilcoxon test, with a p value <0.05 considered statistically significant. The relationship between keratometric values and sagittal depth was evaluated using Spearman correlation test.

Results

The study included 10 men and 14 women with a mean age of 25.2±5.9 (range: 17-36) years. Preoperative mean keratometry values were K1: 45.97±2.01 (range: 41.20-50.20) D, K2: 50.08±3.51 (range: 43.10-60.30) D, and Kmax: 57.51±5.18 (range: 48.60-69.80) D. Keratoconus was advanced in 72.4% of eyes (55.2% stage 3, 17.2% stage 4). High- and low-contrast

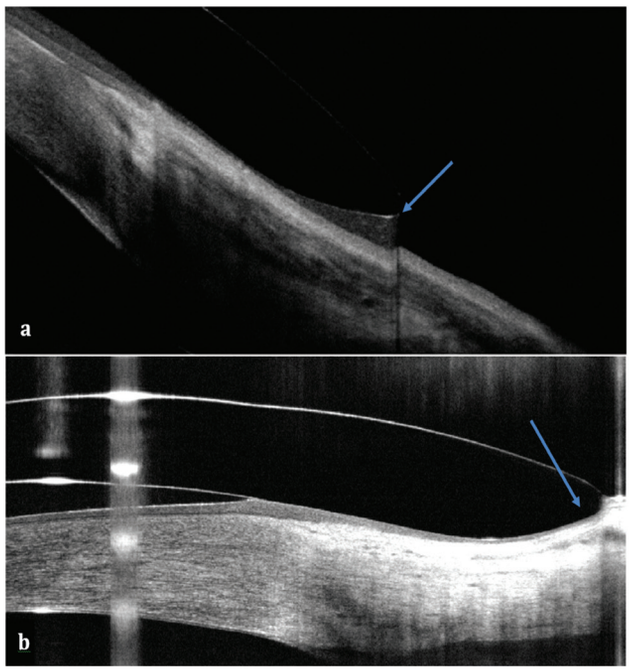

Figure 2. a) Edge lift: the lens edge is raised off the sclera (blue arrow). b) Conjunctival billowing: the lens compresses the conjunctival epithelium, causing it to thin and gather at the lens edge (blue arrow)

VA improved significantly with the scleral lens (p<0.0001) (Figure 4). Mean central corneal clearance measured by OCT was 120.7±24.5 µm. There was no correlation between keratometry values and the sagittal depth of the scleral lens (Table 1). The mean number of trial lenses required for a successful fit was 2.2 (range: 1-8) lenses. After scleral contact lens application, the patients reported high scores for comfort (mean score: 4.69; range: 4-5) and vision (mean score: 4.62; range, 3-5). The patients' mean VAS score for overall satisfaction was 88.1 (range, 70-100).

Discussion

Gas-permeable rigid contact lenses have been used for many years for visual rehabilitation in keratoconus. However, in patients with advanced keratoconus, anterior corneal irregularity leads to centration problems and application difficulties. For this reason, scleral lenses can be used successfully for the visual rehabilitation and management of a variety of corneal disorders in which adequate response is not achieved with other treatments. The main indication for scleral lenses is optical correction of an irregular corneal surface, especially due to keratoconus or corneal transplantation.[5,14] In previous studies, visual results of 20/40 or better were reported in 91% of keratoconus patients.[1,15,16] In our study, the patients' visual acuity was 0.9±0.1 with the scleral lens. Most (72.4%) of the patients were stage 3 or 4 keratoconus and there were no corneal scars. Therefore, high VA was obtained after scleral lens application.

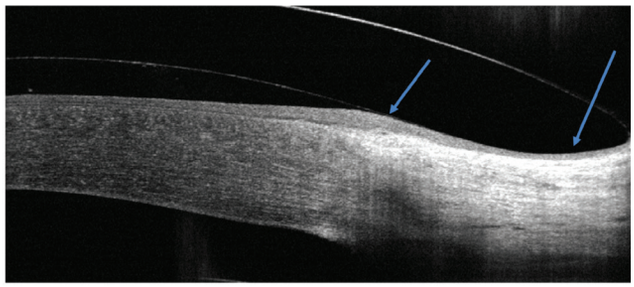

Figure 3. Peripheral edge fit: the lens edge should not have too much lift or be too tight on the sclera (ideal fit)

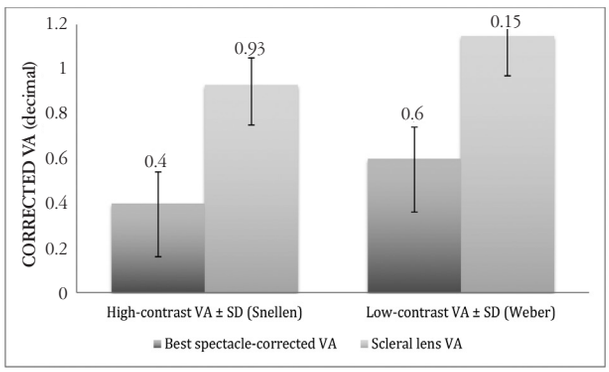

Figure 4. Evaluation of high- and low-contrast visual acuity after scleral lens application

VA: Visual acuity, SD: Standard deviation

Some fitting difficulties associated with scleral lenses may limit their use. Compared to other lenses, scleral lenses are larger in diameter, take longer to apply, and are costly. Our clinical experience showed that scleral lens fitting with the use of standard trial sets may be comparable or easier than fitting corneal or corneoscleral rigid lenses. We used an average of 2 trial lens to achieve a successful fit. Similar to our results, this number is between 2 and 3.2 in the literature.[1,17,18]

OCT imaging has improved modern scleral lens fitting by providing accurate measurements for trial lens selection and contact lens fit assessment and preventing ocular complications associated with lens application. High-resolution imaging of the anterior segment has also provided more information on corneal and scleral morphology and physiology. Measuring central corneal clearance with OCT has allowed us to objectively determine the amount of settling that occurs over time.[19] In addition, the use of OCT during fitting has enabled the evaluation of peripheral edge alignment and objective measurement of the central corneal opening.[10] In our study, anterior segment OCT was used both to measure central corneal clearance (120 µm) and to visualize edge alignment. Topography data obtained from keratoconus patients before contact lens fitting can guide lens selection. In our study, there was no correlation between measured topography values of the patients' eyes and the sagittal height of the lens. Therefore, scleral lenses can be fitted successfully even in the absence of topographic data.

Scleral lenses are expected to be more comfortable than gas-permeable rigid contact lenses because they rest on the sclera and do not touch the cornea. In a study by Yan et al.[18], 91% of patients reported comfortable 10-hour daytime lens wear. In another study evaluating patient satisfaction, 78.9% comfort, 78.2% visual quality, and 87.7% overall satisfaction were reported.[20] In our study, patients also reported high scores for comfort (93.8%), visual acuity (92.4%), and overall satisfaction (88.1%).

Table 1. Correlation between sagittal height and keratometry values

	Mean ± SD	Pearson correlation coefficient	p value
K1 (D)	45.9±2.01	0.06	0.7
K2 (D)	50.08±3.51	0.17	0.37
Kmax (D)	57.51±5.18	-0.08	0.67
Sagittal depth (mm)	4.63±0.25		

SD: Standard deviation, K1: Flat keratometry, K2: Steep keratometry, Kmax: Maximum keratometric value, D: Diopters

Conclusion

In conclusion, scleral lenses are an important option that offers optical rehabilitation and comfort for keratoconus patients. The use of OCT is a valuable adjunct to traditional contact lens fitting techniques. It is also an easy and fast way to evaluate lens fit with relation to the cornea, limbus, and sclera.

Ethics

Ethics Committee Approval: This study was performed after obtaining approval from the Marmara University Faculty of Medicine Ethics Committee (No: 09.2019.678).

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: S.A.T., E.T., Design: S.A.T., E.T., Data Collection or Processing: S.A.T., D.Ö.Ö., Analysis or Interpretation: S.A.T., Literature Search: S.A.T., Writing: S.A.T.

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

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Original Article

Vessel Density Changes on Optical Coherence Tomography Angiography after Vascular Endothelial Growth Factor Inhibitor Treatment for Diabetic Macular Edema

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Abstract

Objectives: To evaluate the changes in macular vessel density after treatment with vascular endothelial growth factor (VEGF) inhibitors in center-involving diabetic macular edema (DME) and to compare these changes between anatomical responders and non-responders.

Materials and Methods: This retrospective study included 22 eyes with center-involving DME. All eyes had 3 consecutive administrations of VEGF inhibitors. Optical coherence tomography (OCT) and OCT angiography (OCTA) of the macula with manual adjustment of segmentation lines were performed at baseline and after treatment. Vessel density in the central and parafoveal regions of the superficial and deep capillary plexus (SCP/DCP) were measured at baseline and after treatment. Vessel density and changes therein were compared between anatomical responders and non-responders as defined by changes in central subfield thickness (CST).

Results: Overall, there were no significant differences in vessel density in the central and parafoveal regions of the SCP and DCP after treatment compared to baseline. After categorization by anatomical response, 12 eyes were responders (CST decreased by 173.7±47.7 µm) and 10 eyes were non-responders (CST increased by 20.8±38.9 µm) ($p<0.0001$). There were no corresponding significant differences between responders and non-responders in SCP and DCP vessel density or changes therein after treatment.

Conclusion: There were no significant changes in macular vessel density after the early stages of VEGF inhibitor treatment for DME, and there was no relationship with the anatomical response. The effect of VEGF inhibitors in DME treatment may not be related to increasing vessel density.

Keywords: Optical coherence tomography angiography, vessel density, superficial capillary plexus, deep capillary plexus, vascular endothelial growth factor inhibitor, treatment response

Introduction

Diabetic macular edema (DME) is a major cause of visual impairment in patients with diabetes mellitus and it occurs as a result of the breakdown of the blood retinal barrier due to metabolic changes associated with hyperglycemia.[1] The current treatment for DME targets vascular endothelial growth factor (VEGF), which has been identified as the most important factor in the pathogenesis of DME.[2] However, while there is often a functional improvement after the resolution of DME with VEGF inhibition, ischemic changes may still result in irreversible vision loss in the absence of edema.

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Assessment of the perfusion status of the macula, which is an important prognostic factor in DME, requires fundus fluorescein angiography (FA).[3,4] FA requires the administration of fluorescein dye. FA is invasive and relatively more time consuming compared with optical coherence tomography angiography (OCTA).[3,4] OCTA is a relatively new, non-invasive and rapid method of producing high-resolution and depth-resolved images of the retinal vasculature without the intravenous administration of dye.[5,6,7,8,9,10] Layer-by-layer imaging can be performed on OCTA to assess the superficial and deep capillary plexuses (SCP/DCP) separately. En face images showing vascular changes on OCTA can be correlated with corresponding structural changes on OCT B-scans.[5,6,7,8,9,10] OCTA is also easier to perform on sequential visits compared with conventional FA.[5,6,7,8,9,10]

In the assessment of diabetic retinopathy (DR) and DME, OCTA attempts to provide various quantitative parameters including vessel density and foveal avascular zone (FAZ) area.[11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27] Of interest in this study is vessel density on OCTA, which is a quantification of the number of vessels in a region of interest.[23] Many studies have reported decreased vessel density in the SCP and DCP in eyes with DR and DME compared with normal controls.[11,12,13,14,16,17,19,21,22] This decrease is also more consistent in the DCP than the SCP.[13,16,20] Notably, the changes in these OCTA parameters have been reported in diabetic patients without clinical signs of DR, which suggests a potential role of OCTA parameters in demonstrating early microvascular alterations in the capillary plexuses.[28,29] In a recent prospective study, vessel density of the SCP and DCP were reported to predict the progression of DME and DR, respectively.[21]

However, the effect of VEGF inhibitor on macular vessel density in DME treatment remains controversial. While some studies reported an increase in vessel density after VEGF inhibitor treatment,[20,22] others reported no change in vessel density in both the DCP and SCP despite reductions in edema and retinal thickness after treatment.[17,18,19,25] It was also reported that certain eyes may not respond to VEGF inhibitors and demonstrate lower vessel density in the DCP but not the SCP.[16,20] Damage to the DCP could thus be a useful predictor of response to VEGF inhibitor treatment in DME.[16,20] Identification of factors associated with response and non-response to VEGF inhibitors is important because non-responders often require more treatments, which in turn increases cost and poses a significant burden on patients.[30] In addition, delayed resolution of macular edema may cause photoreceptor damage that is irreversible.[31]

The equivocal findings in prior studies have resulted in the lack of widespread clinical use of OCTA in assessing DME. These inconsistencies can be attributed to the inherent shortcomings of OCTA. These include inaccurate segmentation and difficulty in obtaining vascular quantification as a result of distorted anatomy in diseased states.[32] Furthermore, there is no consensus regarding the interpretation of DME features such as cysts and non-perfusion areas on OCTA.[26]

This study aimed to evaluate changes in macular vessel density in the central and parafoveal regions at the level of the SCP and DCP after 3 consecutive intravitreal VEGF inhibitor treatments in patients with treatment-naïve DME by comparing pre- and posttreatment OCTA images. Meticulous manual adjustment of the segmentation lines in each OCTA scan was performed when necessary to ensure accuracy and to allow quantification of the macular vessel density with the in-built software. Macular vessel density in the SCP and DCP and changes therein were subsequently compared between anatomical responders and non-responders.

Materials and Methods

We performed a retrospective comparative study. All subjects had treatment-naïve center-involving DME diagnosed by a trained retina specialist with fundus slit-lamp biomicroscopy and OCT. All eyes had 3 consecutive administrations of VEGF inhibitors at least 30 days apart. A trained retinal specialist reviewed all the participants.

The inclusion criteria were treatment-naïve center-involving DME eyes with a central subfield thickness (CST) of 250 µm or greater,[33] no previous documented DME, and adequate media clarity to obtain OCT and OCTA images. Exclusion criteria were significant ocular media opacity affecting the quality of the ophthalmic imaging, clinical evidence of retinal disease apart from DR, previous retinal surgery, and previous DME treatment.

Response was defined anatomically as a 10% decrease in CST from baseline.[33] The DRCR Network has established that a change in OCT thickness of 10% or more is indicative of a real change in thickness that can be considered in the decision to continue or initiate treatment.[34] Spectral-domain OCT and OCTA were performed at baseline and after the 3 VEGF inhibitor treatments. The study was conducted at the Singapore National Eye Centre, Singapore Health Services, Singapore. The study was approved by the Institutional Review Board and conformed to the tenets of the Declaration of Helsinki.

Optical Coherence Tomography Angiography

The Triton (Topcon DRI OCT Triton Swept Source OCT; Topcon, Tokyo, Japan) features a wavelength of 1050 nm, an A-scan rate of 100000 A-scans per second, and an axial and transversal resolution of 8 and 20 µm in tissue, respectively. The scanning area was captured in 3x3 mm sections centered on the fovea. An active eye tracker was employed to reduce motion and blinking artifacts during OCTA.

The OCTA images were obtained with a minimum signal strength index of 50 and above and a quality score of 40 and above. The OCTA images were also assessed to look for blurriness, localized weak signals or signal loss, irregular vessel patterns and disc boundaries due to motion artifacts, and off-centered scans. The OCTA images were processed by the OCT Angiography Ratio Analysis (OCTARA) detection software.

OCTA Segmentation

Automatic segmentation lines were used to divide the retinal capillary plexus into the SCP and DCP layers. The SCP was

defined as the region between the vitreoretinal interface and the outer border of the ganglion cell layer. It was segmented with one boundary at 2.6 μm below the internal limiting membrane and the other 15.6 μm below the inner plexiform layer (IPL). The DCP, defined as the region between the inner border of the IPL and the outer border of the outer plexiform layer, was automatically segmented with the boundaries set at 15.6 μm and 70.2 μm beneath the IPL, respectively.

The accuracy of the automatic segmentation lines was verified visually and independently by experienced graders (K.Y.C.T. and K.X.C.) by examining each B-scan image. Visual verification was necessary because large intraretinal cysts in DME often spanned multiple layers and this frequently caused segmentation errors, especially in the IPL, which is the layer that differentiates the SCP and DCP. Inaccurate segmentation was defined if the border between the SCP and DCP was not located within the range of the IPL. Segmentation errors were manually corrected by both graders using the built-in OCTARA software and vessel density was recalculated based on the new segmentation boundaries. Segmentation was deemed satisfactory when both graders agreed that the lines correlated to the correct anatomical layer.

The segmentation boundaries for all eyes in the SCP and DCP were assessed and manually corrected on two separate occasions by the same experienced grader (K.Y.C.T.). The resultant measurements were compared to calculate the intraclass correlation coefficient (ICC) as an assessment of the inter-session repeatability of the measurements for all sectors in the SCP and DCP.

Vessel Density Measurement

The vessel density values were obtained from a 3-mm circular Early Treatment DR Study (ETDRS) grid centered over the fovea. Vessel density was calculated as the proportion of the measured area occupied by blood vessels at the level of the SCP and DCP. The grid displayed the vessel density of each of the sectors. The central region was defined as the central 1-mm sector of the ETDRS grid. The parafoveal region was defined as the intervening region from the central 1-mm sector to the 3-mm boundary of the ETDRS grid. The vessel density of the central, parafoveal regions, and entire 3-mm region at the levels of SCP and DCP were obtained. Figure 1 is a schematic diagram that indicates the relative locations of the central and parafoveal regions.

Optical Coherence Tomography of the Macula

To assess CST, the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) was used. A 25-line horizontal raster scan (20°x20°, 6.0x6.0 mm) centered on the fovea was performed, with 9 frames averaged in each OCT B-scan. The CST was read off from the central 1-mm sector of the ETDRS grid centered over the fovea.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp, Armonk, New York). Continuous variables were expressed as the mean ± standard deviation. Comparisons between groups were evaluated using the paired samples t test, chi-square test, or Fisher exact test where appropriate. A p value <0.05 was considered statistically significant.

Results

A total of 22 eyes of 22 patients (10 males and 12 females) were studied. The average age was 53.6±8.0 years. At the point of diagnosis, all 22 eyes had center-involving DME with DR at different clinical stages (13 eyes had mild non-proliferative DR, 4 eyes had moderate non-proliferative DR, 5 eyes had severe non-proliferative DR). The mean follow-up time was 96.0±8.0 days. As treatment, 20 eyes received monthly intravitreal bevacizumab and 2 eyes received monthly intravitreal aflibercept.

Table 1 shows the CST and vessel density for the entire study population at baseline and after treatment. Overall, there were no significant differences in SCP or DCP vessel density in the central and parafoveal regions after treatment compared to baseline, while CST decreased from 416.5 μm to 331.2 μm (p=0.025).

The eyes were subsequently categorized according to anatomical response: 12 eyes were considered responders and 10 eyes were considered as non-responders. There were no significant differences in the age (54.2±7.6 vs 52.8±8.9 years, p=0.695), gender (7 vs 6 females, p=0.938), and follow-up time (97.6±7.8 vs 94.1±8.3 days, p=0.321) between the responders and non-responders. CST and vessel density of the SCP and DCP also did not differ significantly between the responders and non-responders at baseline (p>0.05).

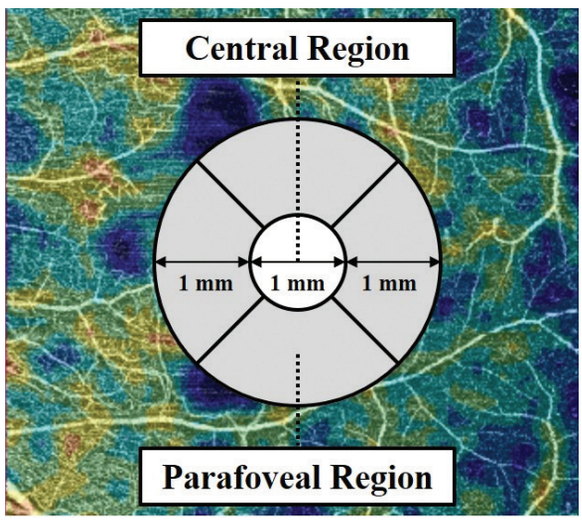

Figure 1. Schematic diagram of the 3 mm ETDRS grid centered over the fovea. The central 1-mm sector (shown in white) is the central region. The parafoveal region is the area (shown in gray) between the central 1-mm sector and the boundary of the 3-mm grid. The vessel density of the parafoveal region is the mean of the vessel density of the 4 sectors surrounding the central region. The average vessel density of the SCP and DCP were calculated as the mean of the vessel density of the area encompassed by the entire grid

ETDRS: Early treatment of diabetic retinopathy study, SCP: Superficial capillary plexus , DCP: Deep capillary plexus

After treatment, CST decreased by 173.7 µm in responders and increased by 20.8 µm in non-responders (p<0.0001). There were no corresponding significant differences in vessel density or changes therein between the responders and non-responders in the SCP and DCP after treatment. Table 2 shows the CST and vessel density of the responders and non-responders at baseline and after treatment.

Figure 2 shows serial multimodal images of a responder and non-responder. These images demonstrate the lack of corresponding change in vessel density in the SCP and DCP regardless of the anatomical response in the retina after VEGF inhibitor treatment.

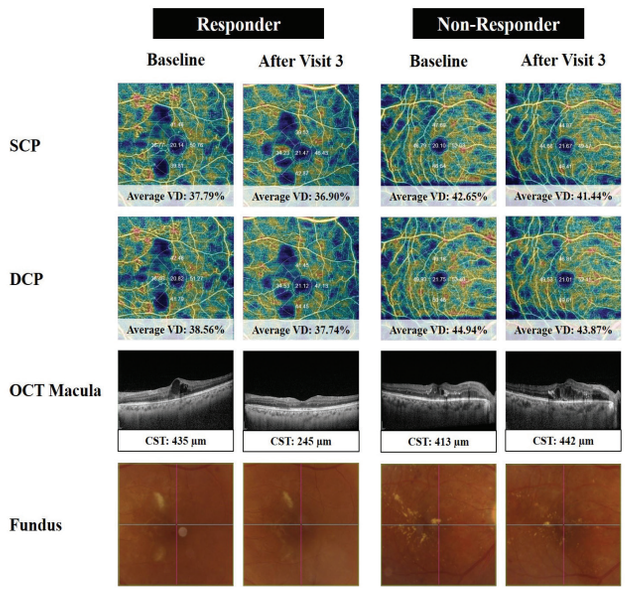

Figure 2. Serial multimodal images of a responder and non-responder. The vessel density (VD) of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), optical coherence tomography (OCT) images of the macula, and fundus photographs at baseline and after the third visit are shown. Responder: Though the responder demonstrated anatomical improvement with a decrease in central subfield thickness, intraretinal fluid, subretinal fluid, and cystic spaces, there was no significant corresponding change in the vessel density in the SCP and DCP. Non-responder: The non-responder demonstrated anatomical worsening. Similarly, there was also no significant corresponding change in the vessel density in the SCP and DCP

The automatic segmentation lines, particularly over the areas affected by DME, had to be readjusted for all eyes in this study. Inter-session repeatability of the measurements was good for all sectors in the SCP and DCP (ICC =0.96 and 0.85, respectively).

Discussion

In this pilot observational study which involved detailed manual segmentations of OCTA scans to evaluate macular vessel density in DME, the macular vessel density of the SCP and DCP were evaluated after 3 consecutive treatments of VEGF inhibitors. The vessel density and its changes were subsequently compared between anatomical responders and non-responders as defined by the CST change. We demonstrated that there were no significant changes in macular vessel density after VEGF inhibitor treatment and no relationship between macular vessel density and CST.

The previous studies describing longitudinal changes in vessel density after treatment reported conflicting results.[16,17,18,19,20,21,22] Three studies demonstrated no significant differences in vessel density measured on OCTA after intravitreal injections despite improvement in edema and CST.[17,19,25] These findings are similar to those of the current study. Several reasons have been postulated to explain this. Firstly, the retinal vessels which sustain ischemic damage in DME may not recover and perfuse after VEGF inhibition.[17] Secondly, the displacement of the vessel plexus secondary to cystoid spaces in DME may only displace the retinal vessels without causing additional loss, hence the unchanged vessel density after resolution of the fluid and cystic spaces following treatment.[15] The absence of significant change can also be attributed to the limitation and inaccuracy of automatic segmentation in OCTA as a result of anatomical distortion of the retinal layers in DME.[17,18,19]

Our findings were not confounded by segmentation inaccuracies because of our meticulous manual adjustment of the segmentation lines with the resultant good inter-session repeatability. The decrease in CST among responders supports previous findings that VEGF inhibitors reduce macular leakage by targeting VEGF and decreasing vessel hyperpermeability.[2] However, the lack of corresponding change in the vessel density in the SCP and DCP regardless of the anatomical response of the

Table 1. Central subfield thickness (CST) and vessel density in the study population at baseline and after treatment

	Baseline n=22	**After treatment n=22**	**p**
	Mean (SD)	Mean (SD)	
CST (µm)	416.5 (73.9)	331.2 (91.4)	0.025
SCP central vessel density (%)	19.9 (2.7)	20.4 (2.7)	0.670
SCP parafoveal vessel density (%)	45.8 (4.3)	45.8 (3.9)	0.999
SCP average vessel density (%)	40.6 (4.2)	40.7 (3.8)	0.954
DCP central vessel density (%)	20.9 (2.9)	21.4 (2.9)	0.692
DCP parafoveal vessel density (%)	45.9 (4.6)	45.8 (4.3)	0.959
DCP average vessel density (%)	40.9 (4.3)	41.0 (4.1)	0.956

n: number, SD: Standard deviation, SCP: Superficial capillary plexus, DCP: Deep capillary plexus

retina after VEGF inhibitor treatment indicates that the effect of VEGF inhibitors in DME treatment may not be related to increasing vessel density. Any improvement of macular ischemia, therefore, may be an indirect effect of improved tissue perfusion and nutrition and not necessarily due to significant changes in the retinal vasculature.[25]

In contrast, other studies have reported a relationship between macular vessel density and response to DME treatment. A study reported that vessel density in the DCP, but not the SCP, was significantly increased after 12 months subsequent to the initial resolution of DME.[20] There was also a study which reported that vessel density in the central region decreased by 8% after 3 aflibercept injections but remained unchanged in the parafoveal region.[24] It was also reported that certain eyes may not respond to VEGF inhibitors and demonstrate a lower vessel density in the DCP but not the SCP.[16,20] Another study reported that the vessel density of the SCP and DCP in the inner and outer parafovea increased significantly after 3 ranibizumab injections, but did not return to the normal levels.[22]

In comparison, we demonstrated that there were no significant changes in the macular vessel density of the SCP and DCP after the VEGF inhibitor treatment and there was no relationship between macular vessel density and CST. The inconsistency in findings among different studies can be attributed to differences in study populations, baseline characteristics, treatment, follow-up time, and imaging modalities used. See Table 3 for a comparison among studies. Of note, the criterion for response to VEGF inhibitor treatment used is also different. Two studies defined response by a reduction of more than 50 µm in CST after 3 consecutive anti-VEGF treatments.[16,20] Therefore, responders which were defined as such might have been a subgroup with a very robust response to VEGF inhibitor treatment.[25] In contrast, we defined response anatomically as a 10% decrease in CST from baseline.[33,34]

The mechanisms supporting an association between the improvement in the DCP and treatment response are also not clearly defined.[16,20] A suggestion is that retinal fluid production originates from the SCP and is absorbed through Müller cells and the DCP in normal eyes.[35] Hence, a recovery in the DCP could theoretically help resolve the edema in DME. Another possible explanation is that an improvement in the DCP will decrease the drive for VEGF production and aid the response to VEGF inhibitors.[16,20]

Separately, the observations in this study also agree with previous studies that demonstrated that VEGF inhibitors do not worsen retinal capillary nonperfusion.[36] The link between

Table 2. Central subfield thickness (CST) and vessel density at baseline and after treatment categorized by anatomical response

	Responder n=12	**Non-responder n=10**	**p**
	Mean (SD)	Mean (SD)	
Baseline			
CST (µm)	436.3 (78.9)	392.7 (63.2)	0.174
SCP central vessel density (%)	19.8 (2.5)	20.1 (3.1)	0.804
SCP parafoveal vessel density (%)	45.7 (4.6)	46.0 (4.1)	0.875
SCP average vessel density (%)	40.5 (4.5)	40.8 (4.1)	0.873
DCP central vessel density (%)	20.2 (3.0)	21.7 (2.7)	0.236
DCP parafoveal vessel density (%)	46.5 (4.5)	45.2 (4.8)	0.520
DCP average vessel density (%)	41.2 (4.3)	40.5 (4.6)	0.716
After treatment			
CST (µm)	262.6 (56.9)	413.5 (41.8)	**<0.0001**
SCP central vessel density (%)	20.5 (2.6)	20.2 (2.9)	0.801
SCP parafoveal vessel density (%)	45.3 (3.9)	46.5 (4.1)	0.491
SCP average vessel density (%)	40.3 (3.9)	41.2 (3.8)	0.592
DCP central vessel density (%)	21.1 (3.0)	21.8 (2.8)	0.581
DCP parafoveal vessel density (%)	46.6 (4.3)	44.9 (4.4)	0.372
DCP average vessel density (%)	41.5 (4.2)	40.3 (4.1)	0.508
Change			
Change in CST (µm)	-173.7 (47.7)	20.8 (38.9)	**<0.0001**
Change in SCP average vessel density (%)	-0.2 (2.7)	0.4 (2.5)	0.598
Change in DCP average vessel density (%)	0.3 (2.7)	-0.2 (2.8)	0.675

n: number, SD: Standard deviation, SCP: Superficial capillary plexus, DCP: Deep capillary plexus

Table 3. Comparison of studies

Study	Intravitreal treatment	Number of injections	OCTA device	Outcome
Ghasemi Falavarjani et al.[19]	Bevacizumab, ranibizumab, or aflibercept	1	Angiovue/RTVue XR Avanti OCT	No significant change in SCP or DCP vessel density
Toto et al.[17]	Dexamethasone implant	1	Angiovue/RTVue XR Avanti OCT	No significant change in SCP or DCP vessel density
Moon et al.[20]	Bevacizumab, ranibizumab, aflibercept, with/without dexamethasone implant	Variable, depending on response	Angiovue/RTVue XR Avanti OCT	Increase in vessel density in DCP but not in SCP
Hsieh et al.[22]	Ranibizumab	3	Angiovue/RTVue XR Avanti OCT	Increase in SCP and DCP vessel density, but not to normal levels
Dastiridou et al.[24]	Aflibercept	3	DRI OCT Triton Plus	Decrease in vessel density in the central region, but no significant change in the parafovea
Sorour et al.[25]	Bevacizumab, ranibizumab, or aflibercept	3	Angiovue/RTVue XR Avanti OCT	No significant change in SCP or DCP vessel density

OCTA: Optical coherence tomography angiography, SCP: Superficial capillary plexus, DCP: Deep capillary plexus

ischemia and the administration of VEGF inhibitors has been investigated with other imaging modalities.[27] Previous case series reported an increased risk of worsening of retinal nonperfusion in eyes with retinal vascular disease following the administration of VEGF inhibitors.[37] These studies attributed the worsening of retinal nonperfusion to the blockage of VEGF, which is a survival factor for vascular endothelial cells.

A strength of this study is the meticulous manual segmentation of the automatic segmentation lines that were erroneous due to the disruption of anatomy in DME. The majority of the automatic segmentation lines, particularly over areas affected by the DME, had to be readjusted for all eyes. This process was performed twice, and the inter-session repeatability of the measurements was good. Another strength is the longitudinal design with the same number of treatments. In addition, the use of the in-built vessel density measurement tool ensured that this technique could be applied in clinical practice without complex image analysis.

Study Limitations

There are several limitations in this study. It was retrospective with a small sample size, which may have made it difficult to detect small but significant changes in vessel density. The follow-up period was relatively short, and this may not have allowed for enough time to detect vessel density changes which may have manifested with long-term treatment. This study also included eyes with DR of different severities and treated with different VEGF inhibitors. The capillary response and vessel density changes with each VEGF inhibitor may differ. Averaging the vessel density in the central 3 mm of the ETDRS grid may have resulted in the loss of detection of focal areas of change in vessel density and FA was not performed to confirm the presence of ischemia. Although poor quality images were excluded and the segmentation lines were manually corrected, there is still a possibility of measurement error due to projection artifacts on OCTA that may also have confounded the results. This study was also dependent on manual segmentation of the layers on OCTA to overcome the issues of inaccurate segmentation and difficulty in obtaining vascular quantification as a result of distorted anatomy in diseased states. This was very labor-intensive. However, other methods currently involve custom image processing software that is usually unavailable in clinical settings.

Conclusion

There were no significant changes in macular vessel density after the early stages of VEGF inhibitor treatment for DME, and there was no relationship with anatomical response. The effect of VEGF inhibitors in DME treatment therefore may not be directly related to increasing vessel density. This is a small pilot study with manual segmentation of each OCTA scan to overcome the issues of inaccurate segmentation and difficulty in obtaining vascular quantification as a result of distorted anatomy in diseased states. Further studies with larger population size and longer duration are needed to exposure the role of OCTA vessel density measurements as a potential biomarker of response to VEGF inhibitor treatment for DME.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: K.X.C., S.Y.L., M.A., K.YC.T., Consept: K.X.C., S.Y.L., M.A., K.Y.C.T., Design: K.X.C., S.Y.L.,

M.A., K.Y.C.T., Data Collection or Processing: K.X. C., S.Y.L., M.A., K.Y.C.T., Analysis or Interpretation: K.X.C., S.Y.L., M.A., K.Y.C.T., Literature Search: K.X.C., S.Y.L., M.A., K.Y.C.T., Writing: K.X.C., S.Y.L., M.A., K.Y.C.T.

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Original Article

Impact of Platelet Count in Retinopathy of Prematurity

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Abstract

Objectives: The aim of the study was to investigate the risk factors for retinopathy of prematurity (ROP), including platelet count.
Materials and Methods: This retrospective study analyzed 137 infants in 3 subgroups: no ROP; mild ROP, and severe ROP requiring laser treatment (type 1 ROP). A retrospective review of records was performed and statistical analysis of possible risk factors for ROP including platelet count was evaluated by using logistic regression.
Results: Birth weight (BW), gestational age (GA), and low platelet count in the first week after birth were significant risk factors for developing ROP (p=0.038, 0.02, and 0.004, respectively). BW, GA, ventilation, and lower platelet count were associated with progression to type 1 ROP (p=0.004; 0.027, and 0.021, respectively).
Conclusion: Lower platelet count in the first week after birth is a risk factor for ROP development in addition to the previously established factors of ventilation need, low BW, and low GA.
Keywords: Birth weight, gestational age, retinopathy of prematurity, risk factors, platelet

Introduction

Retinopathy of prematurity (ROP) is a proliferating retinal vascular disorder that can result in poor vision in premature infants.[1] The frequency of ROP-associated blindness is low in developed countries. However, in developing countries, the incidence of ROP-associated blindness is higher due to the increased survival of premature infants, a lack of standardized neonatal intensive care unit (NICU) conditions, and limited fundoscopic follow-up evaluations.[2,3] The crucial risk factors for ROP development are low birth weight (BW) and low gestational age (GA).[4,5] The other risk factors are oxygen therapy needs, sex, sepsis, patent ductus arteriosus (PDA), intraventricular hemorrhage, neonatal infections, necrotizing enterocolitis (NEC), and blood transfusion needs.[4,6,7,8,9,10]

Several studies have focused on the role of platelets in angiogenesis and hypothesized that thrombocytopenia might be a possible factor for developing ROP.[11,12] Platelets accumulate, carry, and deliver distinct key regulators of angiogenesis such as vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and platelet-derived growth factor (PDGF).[13] Low platelet count may cause delay in normal retinal vascularization and lead to subsequent unregulated retinal neovascularization due to lack of VEGF, IGF-1, and PDGF.[11,12] Lundgren et al.[14] noted that aggressive posterior ROP is associated with multiple infectious episodes and thrombocytopenia.

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The purpose of this study was to investigate the impact of platelet count in ROP development beyond other known risk factors.

Materials and Methods

The study included 137 infants with a GA of up to 34 weeks who were screened for ROP in the NICU of Başkent University in Adana, Turkey between July 2014 and July 2017. All infants with a GA of up to 34 weeks that were followed up until at least 43 weeks postconception were enrolled in the study (n=137). All the babies included in the study were born at the study site. Exclusion criteria were GA of more than 34 weeks (n=20) and lack of regular follow-up examinations at our institution until 43 weeks postconception (n=18). The Institutional Review Board of Başkent University Faculty of Medicine approved the study (KA:17/308). Informed consent was obtained from the parents of all infants included in the study.

ROP screening was performed by an experienced ophthalmologist (N.S.) using an indirect ophthalmoscope at the postnatal age of 4 weeks or PMA of 31 weeks according to screening guidelines.[15] Follow-up examinations were conducted until retinal vascularization reached the ora serrata for 360°. Follow-up intervals were scheduled according to ROP severity. Infants with ROP were examined more often, according to the severity of the disorder. Phenylephrine 2.5% and tropicamide 0.5% were used for dilatation of the pupils. Fundus examination was conducted using an indirect ophthalmoscope and 28 D lens. Fundus findings were noted, and ROP was categorized according to the International Classification of Retinopathy of Prematurity.[15]

The infants were divided into 3 groups: Group A (no ROP) included babies without retinopathy, Group B (mild ROP) included babies diagnosed with stage 1 or stage 2 ROP but regressed, and Group C (severe ROP) included infants that progressed to Type 1 ROP and underwent laser treatment.[16] We noted no noticeable asymmetry in any patient, and no eye progressed to stage 4 or 5 ROP.

We retrospectively reviewed the patient medical records from birth to 43 weeks of age for data such as GA, BW, sex, neonatal morbidities, respiratory distress syndrome (RDS), NEC, intraventricular hemorrhage, PDA, sepsis, red blood cell (RBC) transfusion, apnea, multiple pregnancy of the mother, ventilation need, and surfactant use for RDS. All available laboratory measurements of platelet counts were recorded. The values in the first postnatal week and within 1 week of ROP diagnosis were noted.

Univariate analysis was performed to reveal the significant risk factors for ROP, and the risk factors were included in the logistic regression. Ten potential risk factors (BW, GA, multiple pregnancy, ventilation need, RDS, NEC, PDA, RBC transfusion, apnea, sepsis, surfactant use, and platelet count in the first postnatal week) were analyzed with logistic regression to determine relationships between the variables and identify independent risk factors for ROP. Our criteria for dropping variables during backward stepwise logistic regression was p=0.05.

Results

We evaluated 137 neonates in our NICU with GA ≤34 weeks during the study period. ROP was diagnosed in 47 cases (34.3%). Severe ROP was detected and treated in 15 cases (10.9%).

Univariate analysis showed that, in order of significance, BW, GA, PDA, RDS, RBC transfusion, apnea, low platelet count in the first postnatal week, ventilation need, surfactant, and sepsis were associated with ROP based on the p values. Risk factors are listed in Table 1.

With subsequent logistic regression analysis, BW, GA, and low platelet count in the first postnatal week were shown to be independent risk factors for ROP development. Also, logistic regression analysis demonstrated that GA, ventilation, and low platelet count in the first postnatal week were independently related to severe ROP. Low platelet count in the first postnatal week was shown to be an independent risk factor for both ROP development and progression.

The mean GA was 31.3±2.2 weeks for Group A, 28.5±1.8 weeks for Group B, and 27.4±1.5 weeks for Group C. The mean GA of Group A was significantly different from Group B and Group C ($p<0.05$ for each). Group B and C were not statistically significantly different (p=0.17).

Mean platelet count in the first postnatal week was 280±103x10^3/μL in Group A, 222±69x10^3/μL in Group B, and 214±62x10^3/μL in Group C. According to the post hoc analysis, Group A had a significantly higher mean platelet count than Groups B and C (p=0.002). Group B and C were not statistically significantly different.

The mean platelet count in the week of ROP diagnosis was 339±147x10^3/μL in Group B and 366±121x10^3/μL in Group C. Group B and C were not statistically significantly different (p=0.5).

Discussion

The incidence of ROP varies among countries due to different socioeconomic development and variability in study designs and survival rates. In the current study, the overall ROP incidence was 34.3%, while severe ROP was recorded in 10.9% of the infants. These results were similar to the rates of developing countries.[17,18,19]

In developing countries, infants with higher BW and GA are at risk for ROP development.[20,21] Therefore, the current study consisted of infants with a GA ≤34 weeks. In a recent ROP study, fundus examinations of infants with GA ≤34 weeks or BW <1,700 g was recommended for Turkey.[22]

In our study, low GA, low BW, and low platelet count in the first week after birth were independent risk factors for developing ROP. However, low GA, ventilation need, and low platelet count in the first week after birth arose as independent risk factors for ROP progression.

Table 1. Comparison of the demographic characteristics and morbidities of infants with and without retinopathy of prematurity (ROP)

	Group A	Group B	Group C	p
Number: 137	90	32	15	
Sex (male/female)	48/42	18/14	7/8	0.828
Gestational age (weeks)	31.3±2.2	28.5±1.8	27.4±1.5	<0.001
Birth weight (g)	1622±408	1166±254	1002±258	<0.001
Respiratory distress syndrome	21 (23.3%)	19 (59.4%)	12 (80.0%)	<0.001
Sepsis	15 (16.7%)	12 (37.5%)	12 (80.0%)	<0.001
Necrotizing enterocolitis	9 (10.0%)	7 (21.9%)	3 (20.0%)	0.190
Patent ductus arteriosus	5 (5.6%)	7 (21.9%)	5 (33.3%)	0.002
Intraventricular hemorrhage	3 (3.3%)	3 (9.4%)	2 (13.3%)	0.193
Apnea	26 (31.0%)	27 (84.4%)	13 (86.7%)	<0.001
Red blood cell transfusion	25 (27.8%)	23 (71.9%)	13 (86.7%)	<0.001
Multiple pregnancy	27(30.0%)	13 (40.6%)	2 (13.3%)	0.163
Mechanical ventilation	6 (6.7%)	7 (21.9%)	9 (60.0%)	<0.001
Cesarean section	83 (92.2%)	29 (90.6%)	13 (86.7%)	0.772
Surfactant	21 (23.3%)	18 (56.3%)	10 (66.7%)	<0.001
Platelet count (first postnatal week)	280±103	222±69	214±62	0.002
Platelet count (at ROP diagnosis)	--	339±147	366±121	0.551

Values are presented as number of neonates (with the percentage in brackets) or mean ± standard deviation. Group A: No retinopathy; Group B: Mild ROP; Group C: Prethreshold or threshold ROP, receiving laser treatment

Both low GA and low BW are associated with incomplete vascular and retinal neural development at birth, given the vulnerable structure of the retina.[4] In our study, according to the logistic regression, GA was an independent risk factor for developing mild and severe ROP. However, BW was not statistically significant as a risk factor of severe ROP. This result may indicate the importance of weight gain to prevent the progression of ROP.[23,24,25]

The association between ROP and blood transfusion is well documented.[26] The number of blood transfusions received by premature infants has been a major indicator of ROP in addition to GA and BW. Stutchfield et al.[26] hypothesized that changing fetal hemoglobin to adult hemoglobin during transfusion may lead to ROP development by rapidly increasing oxygen accessibility to the retina. In our NICU, RBC transfusion was performed rather than whole blood transfusion when necessary. Therefore, RBC transfusion and platelet count were considered independent risk factors in our study. RBC transfusion was not found to be an independent risk factor for ROP, but this result may be due to the existence of many other risk factors in these infants.

Several pro- and antiangiogenic regulators were shown to be accumulated and carried in platelets.[11,12] Platelet alpha granules have been shown to include IGF-1, IGF-binding protein 3 (the primary serum binding protein for IGF-1), VEGF, and platelet-derived growth factor. IGF-1 and VEGF levels are critical for ROP development.[27] Our first hypothesis about the mechanism linking low platelet count and ROP development implies the delivery of IGF-1 by platelets. While IGF-1 is needed for VEGF-induced vessel growth, low platelet count at an early gestational week slows down vasculogenesis and leads to development of subsequent type 1 ROP.

ROP is a disorder with pathological angiogenesis in the inner retina and preretinal space.[28] The newly formed blood vessels are not mature, which may lead to vascular leakage.[28] Pericytes have a crucial role in angiogenesis by contributing survival signals for endothelial cells.[29] PDGF is essential for pericyte viability.[30] Moreover, PDGF is fundamental for both proliferation and migration of endothelial cells.[30] A lack of pericytes is connected with endothelial hyperplasia, dilated capillaries, irregularly shaped endothelial cells, and increased transendothelial permeability.[30] Hammes et al.[31] indicated that PDGF-deficient mice had fewer pericytes compared to wild-type mice during the early postnatal phase of the growing retina. They studied a PDGF-receptor β-deficient mice model of oxygen-induced proliferative retinopathy (resembling ROP) to investigate the proliferative phase of diabetic retinopathy. PDGF-receptor β-deficient mice had significantly lower pericyte numbers and significantly higher numbers of acellular capillaries compared with wild-type. After exposure to a high-oxygen environment, the neovascular response to hypoxia nearly doubled in PDGF-receptor β-deficient mice. They also noted the degeneration of endothelial cells (indicated by narrow vessels) and obstructive occlusion in the absence of the PDGF-β

receptor.[31] Pericytes likely have a role in promoting endothelial cell survival and limiting endothelial hyperplasia. Our second hypothesis about the mechanism linking low platelet count and ROP development is the lack of PDGF. Our results and data from the literature demonstrate that at high VEGF levels (e.g., ROP), the deficiency of pericyte coverage due to low levels of circulating PDGF may lead to an increased neovascular response.

In ROP models, the introduction of hyperoxia to the retinas of newborn rats decreased VEGF levels and weakens retinal angiogenesis.[32,33] Relative hypoxia of room air during the second week led to increased VEGF synthesis and pathological angiogenesis.[34] During this proliferative phase of ROP, VEGF levels increase locally and systemically.[35]

VEGF induces endothelial cell migration and proliferation after hypoxia.[36] During that period, thrombocytopenia may deepen the PDGF deficiency which is necessary for pericyte viability. PDGF deficiency may result in pathological angiogenesis.

Vinekar et al.[12] presented a case of aggressive posterior ROP with severe thrombocytopenia regressing after serum platelet transfusions. Jensen et al.[11] showed a relation between thrombocytopenia and the existence of type 1 ROP in zone 1 cases. The results of these studies suggest thrombocytopenia is a risk factor for zone 1 ROP. Cakir et al.[37] showed that any episode of thrombocytopenia at ≥30 weeks postmenstrual age (PMA), was associated with severe ROP in a mouse model of ROP. The researchers evaluated mean weekly platelet count of mice and found a statistically significant difference between the severe ROP group and the no or less severe ROP group. On the contrary, Jensen et al.[38] demonstrated that thrombocytopenia from birth to 34 weeks of PMA was related to severe ROP. In the current study, we evaluated the platelet count of the infants on the week of delivery and found lower platet count as a risk factor for ROP development. Our result is compatible with study by Jensen et al.[38]

The study group of the current study included all ROP cases classified in zone 1 and zone 2. Although platelet counts did not reach the level of thrombocytopenia and none of the infants needed a platelet transfusion, there was a significant difference in platelet count between infants that developed ROP and those who did not. Platelets are major regulators of angiogenic regulatory proteins such as VEGF and PDGF, which are stored, transported, and delivered by platelets.[13] Our findings suggest that the growth factors in circulating platelets have a potential protective role against ROP and are necessary for retinal vascular maturation.

Conclusion

The infants with lower platelet counts may have a higher risk for developing ROP. Our findings further contribute to the body of work producing a predictive model to estimate the likelihood for an infant to develop ROP. Further large-scale studies are required to define the potential relation between thrombocytopenia and ROP.

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Ethics

Ethics Committee Approval: There was no funding for the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from the parents of all infants included in the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: N.Ş.K., H.G., G.Y., İ.A., Design: N.Ş.K., H.G., G.Y., İ.A., Data Collection or Processing: N.Ş.K., H.G., G.Y., İ.A., Analysis or Interpretation: N.Ş.K., H.G., G.Y., İ.A., Literature Search: N.Ş.K., H.G., G.Y., İ.A., Writing: N.Ş.K., H.G., G.Y., İ.A.

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Original Article

Evaluation of Periorbital Tissues in Obstructive Sleep Apnea Syndrome

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Abstract

Objectives: To evaluate periorbital tissue alterations including eyelid laxity and eyelash ptosis in patients with obstructive sleep apnea syndrome (OSAS).

Materials and Methods: Based on polysomnography, 96 eyes of 48 patients with moderate/severe OSAS (Group 1) and 44 eyes of 22 patients with simple snoring (Group 2) were enrolled. Comprehensive eye examination along with eyelid laxity measurements including vertical and anterior distraction, presence of dermatochalasis, interpalpebral distance, and levator function were assessed. The presence and severity of eyelash ptosis were also noted.

Results: The mean ages of Group 1 and Group 2 were 49.9±11.4 (range: 26-67) and 50.6±8.9 (range: 27-69) years, respectively (p=0.557). The mean vertical and anterior distraction distances in Group 1 (13.3±4.1 [range, 6-27] mm and 7.4±2.1 [range, 3-13.5] mm, respectively) were significantly higher than in Group 2 (p<0.05). Dermatochalasis and eyelash ptosis were found to be significantly more frequent in Group 1 (52.1% and 81.3%, respectively). The severity of eyelash ptosis was also higher in OSAS (p<0.05). No significant difference in interpalpebral distance or levator muscle function was detected.

Conclusion: In patients with severe OSAS, eyelid laxity was more prominent and eyelash ptosis was more frequent and severe.

Keywords: Obstructive sleep apnea syndrome, periorbital tissue, floppy eyelid, eyelid laxity, eyelash ptosis

Introduction

Obstructive sleep apnea syndrome (OSAS) is a sleep disorder characterized by recurring episodes of apnea-hypopnea (AH) lasting 10 seconds or longer and a decrease in oxygen saturation.[1] The prevalence of OSAS is 2-4% for symptomatic cases, although it has been estimated that a large proportion of the population may have undiagnosed OSAS.[2,3] The prevalence is up to 21-90% among patients referred to sleep outpatient clinics.[4] With the increase in obesity in recent years, the prevalence of OSAS is rising rapidly.[5] As awareness increases among society and healthcare workers, more people are presenting to sleep clinics with typical symptoms such as snoring, witnessed apnea, and excessive daytime sleepiness. However, the disease can still be easily overlooked.[6]

In terms of pathophysiological changes in OSAS, intermittent hypoxia, cyclic desaturations, and elevated catecholamine levels affect the sleep-wake cycle.[7] Resultant changes such as systemic hypertension, atherosclerosis, endothelial dysfunction, insulin resistance, and autonomic dysfunction may result in comorbidities such as coronary heart disease, stroke, congestive heart failure, and even death.[8,9] The possibility that OSAS may impact ocular vascular health via these mechanisms and cause or

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exacerbate ocular problems remains a concern and the subject of ongoing research.[10] In the literature, OSAS has been associated with floppy eyelid syndrome (FES)[11,12], glaucoma[13], ischemic optic neuropathy[14], papilledema[15], nocturnal lagophthalmus[16], central serous chorioretinopathy[17], and retinal vein occlusion.[18]

This study aimed to evaluate periorbital tissue alterations such as eyelid laxity and eyelash ptosis in patients with OSAS.

Materials and Methods

This single-center, prospective, cross-sectional study was performed between March 2016 and May 2017 in the ophthalmology department of Ege University Faculty of Medicine (EUFM). The study included a total of 70 patients with no previous OSAS diagnosis, among whom 48 and 22 patients were diagnosed as having OSAS and simple snoring, respectively, according to their AH index (AHI) score in polysomnography (PSG) evaluation in the sleep laboratory of the EUFM chest diseases department. Patients with AHI ≥15 were classified as moderate or severe OSAS (Group 1; 39 men and 9 women) and patients with AHI <5 were classified as simple snoring (Group 2; 12 men and 10 women).

Exclusion criteria were: 1) previous or current nasal continuous positive airway pressure therapy; 2) history of intraocular/extraocular surgery, ocular trauma or chemical injury; 3) presence or treatment history for any eye disease other than refractive error such as glaucoma, dry eye syndrome, thyroid ophthalmopathy; 4) history of contact lens use; 5) history of chronic steroid use; 6) smoking; and 7) diabetes mellitus or thyroid dysfunction detected in systemic evaluation.

Ethics approval was obtained from the Institutional Review Board of EUFM (16.02.2016, no: 16-1/6). The study was conducted in accordance with the principles of the Declaration of Helsinki and the patients were informed about the study scope and the evaluations involved.

Following PSG evaluation, all patients were referred for detailed ophthalmological examination including best corrected visual acuity, intraocular pressure measurement, anterior segment examination, funduscopy, and evaluation of cup/disc ratio, as well as evaluations of interpalpebral fissure height and levator function, eyelid laxity assessment with upper lid vertical distraction distance[19] and upper lid anterior distraction distance[20], presence and degree of eyelash ptosis[21], loss of eyelash alignment, presence of FES[11,12], and presence of dermatochalasis. The researcher who performed the ophthalmological examinations (I.K.) was blind to the patients' PSG results.

Interpalpebral distance was defined as the maximum distance between upper and lower lids with the eyes in primary gaze. Levator function was measured as the distance traveled by the edge of the upper lid between downward and upward gaze while applying pressure to the brow to block frontalis muscle action. Moreover, during ophthalmological examination, the upper eyelid was grasped from the pretarsal skin and pulled vertically by manual traction to evaluate whether the eyelid folded easily and upper lid vertical distraction distance was recorded for both eyes as the distance between the palpebral rim of the upper lid and the pupil center after applying manual vertical traction on the upper eyelid.[19] In both eyes, upper eyelid anterior distraction was determined, with the palpebral rim as a reference point (0 mm), as the distance between the horizontal projection of the upper eyelid margin and palpebral rim while the eye is held manually from the eyelashes and pulled forward horizontally when the eye is in primary gaze. The clinical presence of eyelash ptosis was graded between 0 and 3.[21] Dermatochalasis was defined as the presence of an excessive skin fold over the upper eyelid that may be accompanied by periorbital fat prolapse.

Statistical Analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL) software pack. Comparisons between groups were analyzed using Student's t-test for data with normal distribution and Mann-Whitney U test for data with non-normal distribution. Categorical variables were compared using chi-square test and Fisher's exact test. A p value <0.05 was considered statistically significant.

Results

The mean age of the patients was 49.9±11.4 (26-67) years in Group 1 and 50.6±8.9 (27-69) years in Group 2 (p=0.557). Group 1 showed statistically significant male predominance and significantly higher body mass index (BMI) when compared with Group 2 (Table 1).

The upper lid vertical and anterior distraction distances were 13.3±4.1 (6-27) mm and 7.4±2.1 (3-13.5) mm in Group 1, respectively, which were significantly greater than the distances in Group 2 (p<0.05). There were no significant differences in interpalpebral distance and levator function between the groups (p>0.05) (Table 2).

When the patients were compared in terms of periorbital alterations, dermatochalasis and eyelash ptosis were significantly more common in Group 1 (52.1% and 81.3% in Group 1, 27.3% and 22.7% in Group 2, respectively; p<0.05). It was

Table 1. Demographic characteristics of the patients

OSAS Severity	AHI	Number (n)	Age (years)	Sex (M/F)	BMI (kg/m^2)
Moderate/Severe OSAS (Group 1)	≥15	48	49.9±11.4 (26-67)	39/9	32.4±6.7 (19.6-60.2)
Simple snoring (Group 2)	<5	22	50.6±8.9 (27-69)	12/10	28.4±2.8 (18.7-31.2)
P value			*0.557**	*0.028***	*0.036**

OSAS: Obstructive sleep apnea syndrome, AHI: Apnea-hypopnea index, M: Male, F: Female, BMI: Body mass index
*Kruskal-Wallis test, **Chi-square test

observed that the degree of eyelash ptosis was also higher in patients with OSAS (p<0.05) (Table 3).

The prevalence of FES was calculated as 16.6% among all OSAS patients, and all patients with FES (n=8) were diagnosed as having severe OSAS. The comparison of demographic and clinical characteristics between patients with and without FES is shown in Table 4.

Discussion

OSAS is a sleep disorder characterized by recurring upper respiratory tract obstructions and reduced oxygen saturation.[1] The prevalence of moderate and severe OSAS is 2-6%, while this rate is about 14% for mild OSAS. The prevalence among patients referred to sleep clinics reaches 21-90%.[4] In addition to associated symptoms such as loud snoring, episodes of apnea, and excessive daytime sleepiness, OSAS is also clinically important because it increases the severity and risk of life-threatening diseases (such as coronary artery disease, cerebrovascular events, atrial fibrillation, hypertension, neurocognitive disorders, and endocrine and metabolic diseases) that cause serious morbidity and mortality.[9]

FES is the most widely known ocular comorbidity of OSAS, and OSAS is also reported as the most common systemic disease associated with FES.[16] The association between FES and OSAS was first identified by Woog[11] FES is characterized by lax, easily foldable eyelids and papillary conjunctivitis.[12] In previous studies, the prevalence of FES has varied between 2% and 32%.[22,26] This may be due to the lack of standardized diagnostic criteria for FES

Table 2. Comparison of best corrected visual acuity, lid function, and lid laxity of the patients

	Moderate/severe OSAS (Group 1)	Simple snoring (Group 2)	p (Mann-Whitney U test)
BCVA (Snellen)	0.92 (0.7-1.0)	0.99 (0.9-1.0)	0.352
Interpalpebral distance (mm)	9.7±1.5 (7-12)	10.3±0.9 (9-12)	0.433
Levator function (mm)	15.1±0.7 (15-18)	15.6±0.4 (15-17)	0.996
Anterior distraction distance (mm)	7.4±2.1 (3-13.5)	4.2±1.3 (3-8)	*<0.001*
Vertical distraction distance (mm)	13.3±4.1 (6-27)	9.8±2.4 (7-15)	*0.021*

OSAS: Obstructive sleep apnea syndrome, BCVA: Best corrected visual acuity

Table 3. Comparison of periorbital tissue changes observed in the patient groups

	Moderate/severe OSAS (Group 1)	Simple snoring (Group 2)	p (chi-square test)
Floppy eyelid syndrome (n; %)	8 (16.6%)	0 (0%)	*<0.001*
Dermatochalasis (n; %)	25 (52.1%)	6 (27.3%)	*0.032*
Eyelash ptosis (n; %) Grade 0 Grade 1 Grade 2 Grade 3	36 (81.3%) 13 (27.1%) 21 (43.7%) 12 (25%) 2 (4.2%)	5 (22.7%) 17 (77.3%) 5 (22.7%) 0 (0%) 0 (0%)	*<0.001*

OSAS: Obstructive sleep apnea syndrome

Table 4. Comparison of periorbital tissue changes in OSAS patients with and without floppy eyelid syndrome (FES)

	FES(+) (n=8)	FES(-) (n=40)	p value
Dermatochalasis (n; %)	8 (100%)	12 (42.9%)	*0.033**
Eyelash ptosis (n; %) Grade 0 Grade 1 Grade 2 Grade 3	8 (100%) 0 (0%) 3 (37.5%) 4 (50%) 1 (12.5%)	21 (52.5%) 19 (47.5%) 16 (39.3%) 5 (12.5%) 0 (0%)	*<0.001**
Loss of eyelash alignment (n; %)	8 (100%)	0 (0%)	*<0.001**
Anterior distraction distance (mm)	8.6±2.1 (5-12)	5.4±1.4 (3-9)	*<0.001***
Vertical distraction distance (mm)	14.6±3.8 (8-29)	12.3±3.4 (8-20)	*0.028***

OSAS: Obstructive sleep apnea syndrome, FES: Floppy eyelid syndrome, *Fisher's exact test, **Mann-Whitney U test

and the use of subjective diagnostic methods.[22,23,24,25,26] In studies reporting high FES rates, generally only upper eyelid laxity was considered, without evaluation of the presence of other findings associated with a diagnosis of FES.[19,23] On the other hand, as both FES and OSAS are independently associated with obesity and male sex, it is difficult to say that OSAS is directly associated with FES.[27] Beis et al.[28] demonstrated that FES was associated with OSAS but not with obesity. In a large cross-sectional study by Ezra et al.[29], FES was shown to be strongly correlated with OSAS and keratoconus. Wang et al.[30] proposed in their meta-analysis that the prevalence of FES was higher in OSAS and its incidence increased with OSAS severity. In our study, the prevalence of FES among all OSAS patients was 16.6%. The FES prevalence determined in the present study is in concordance with the literature and all patients with FES (n=8) had severe OSAS.

Various qualitative and quantitative methods for the evaluation of eyelid laxity have been described in the literature. Liu et al.[31] classified FES severity as grade 0 (no FES, no tarsal conjunctiva visible), grade 1 (less than one-third of the upper tarsal conjunctiva visible), grade 2 (one third to half of the upper tarsal conjunctiva visible), and grade 3 (more than half of the upper tarsal conjunctiva visible). McNab[22] measured the vertical manual displacement of the lax upper eyelid in patients with FES and termed this the "vertical eyelid pull." Robert et al.[19] measured the maximum distance between the palpebral rim and pupil after vertical manual lid traction and termed this "vertical hyperlaxity." Karger et al.[24] calculated the force required for vertical displacement of the upper eyelid with a strain gauge device they developed. Mojon et al.[23] evaluated eyelid displacement based on the lower lid laxity assessment described by Liu and Staisor in OSAS patients. Iyengar and Khan[20] measured the anterior displacement of both upper lids in patients with symptomatic FES in one eye and asymptomatic FES in the other eye who were followed up for more than 5 years. They obtained measurements by manually holding the eyelashes and pulling forward horizontally and measuring the distance between the distracted eyelid and the corneal apex. The mean anterior distraction distance was 17.09 (14-20) mm in the symptomatic lids and 11.72 (10-15) mm in the asymptomatic lids. The mean difference between the two lids was statistically significant at 5.6 mm ($p<0.02$, t test). Considering the possibility that globe size could lead to inaccuracies in the measurement technique used by Iyengar and Khan[20], in our study we calculated anterior distraction distance using the palpebral rim as a reference point (0 mm) and subtracting the distance between this point and the horizontal projection of the lid margin with the eye open in primary gaze from the distance measured when the eyelid was held manually from the eyelashes and pulled forward. Vertical distraction distance was determined based on the method described by Robert et al.[19] According to these measurements, both anterior and vertical lid distraction distances in patients with OSAS were significantly higher than in patients with simple snoring. When only OSAS patients were evaluated, those with FES had higher distraction distances than those without FES. While this supports the presence of a certain amount of lid laxity in OSAS, it also suggests that it is more severe in the presence of FES. Moreover, the lax eyelid was associated with a lower amount of elastin in the tarsal tissue, while pathologic examination of uvula tissue from OSAS patients who underwent uvulopharyngoplasty also revealed loss of elastic fibers and elastin disorganization.[32,33] Our findings are in parallel with this elastic tissue theory explaining the association between FES and OSAS. On the other hand, Fox et al.[34] quantitatively evaluated eyelid laxity in bedside ophthalmological examinations of patients evaluated with PSG and reported that these markers (upper lid vertical traction, horizontal eyelid distraction, eyelash ptosis) were not associated with the presence and severity of OSAS. However, statistical analyses in the study were performed based on mean values obtained after grading the data between 0 and 4, and although not significant, the laxity measurements tended to increase as OSAS severity increased.

Langford and Linberg[35] argued that eyelash ptosis and loss of eyelash alignment may be new signs of FES. Eyelash ptosis has been attributed to loss of tissue elasticity around the eyelashes. In our study, eyelash ptosis was more common among OSAS patients than patients with simple snoring. The mean eyelash ptosis grade was also significantly higher in the patients with OSAS. In addition, eyelash ptosis prevalence and severity were higher in OSAS patients with FES than in those without FES. Moreover, all FES patients showed substantial loss of eyelash alignment in addition to eyelash ptosis, whereas this was not seen in patients without FES. This can be interpreted as evidence that in addition to the presence of eyelash ptosis, the grade of eyelash ptosis and accompanying loss of eyelash alignment may be more specific for the diagnosis of FES. On the other hand, Malik et al.[21] reported that eyelash ptosis accompanied a considerable proportion of cases of congenital and acquired blepharoptosis. They reported that grade 2 eyelash ptosis was detected in 28.9% of patients with acquired blepharoptosis and 6.7% of the control group, whereas eyelash ptosis of grade 1 or higher was found in 83.5% of patients with acquired blepharoptosis and 33.3% of the control group. In the present study, eyelash ptosis of grade 2 or higher was observed in 29.2% of patients with OSAS but was not detected in any patient with simple snoring. Among the OSAS group, this rate was 62.5% among those with FES and 12.5% among those without FES. Among the OSAS patients without FES, grade 1 eyelash ptosis was detected in 39.3% in addition to the presence of dermatochalasis. Therefore, it can be thought that the low-grade eyelash ptosis observed in OSAS patients without FES is caused by connective tissue laxity/increased elasticity in periorbital tissues, which is also associated with the accompanying dermatochalasis.

Study Limitations

The strengths of the present study included that the patients were diagnosed with OSAS or simple snoring according to the results of PSG, the gold standard method, lid laxity was determined by quantitative measurements, and eyelash ptosis was objectively graded. The study limitations were that it was

cross-sectional and included a small number of patients. For the moderate/severe OSAS group, the exclusion of patients with systemic diseases such as diabetes mellitus prevented pathological processes that may be associated with other systemic diseases from affecting the results. However, because the OSAS patients included in the study were in the early stages in terms of their systemic status and may not yet have developed systemic effects, their findings may have been less severe than expected. In addition, the male dominance and significantly higher BMI values in the OSAS group may also have been a source of bias in the results. More accurate data may be obtained from future studies that use the same objective evaluations in larger patient series and use regression analysis to rule out factors that may have a role.

Conclusion

In conclusion, the present study determined that OSAS patients had greater eyelid laxity and significantly more frequent and severe eyelash ptosis. In ophthalmology practice, questioning patients with lax eyelids and especially eyelash ptosis about the typical symptoms for OSAS diagnosis and referring patients with those symptoms to sleep clinics seems potentially beneficial in terms of limiting the morbidity and mortality of the disease.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the Institutional Review Board of EUFM (16.02.2016, no: 16-1/6).

Informed Consent: The study was conducted in accordance with the principles of the Declaration of Helsinki and the patients were informed about the study scope and the evaluations involved.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: I.K., A.Y., M.P., Ö.K.B., M.S.T., Concept: A.Y., M.P., Ö.K.B., M.S.T., Design: A.Y., M.P., Ö.K.B., M.S.T., Data Collection or Processing: I.K., Analysis or Interpretation: I.K., A.Y., M.P., Ö.K.B., M.S.T., Literature Search: I.K., M.P., A.Y., Writing: I.K.

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Review

Current Management of Conjunctival Melanoma Part 2: Treatment and Future Directions

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Abstract

Conjunctival melanoma is a rare disease which requires tailored management in most cases. The mainstays of treatment can be classified as surgery, topical chemotherapy, radiotherapy, cryotherapy, and other emerging treatment modalities. Herein we review conventional approaches as well as more recently introduced treatment options, together with advances in molecular biology in this particular disease.
Keywords: Conjunctival melanoma, prognosis, management

Introduction

Conjunctival melanoma (CM) is a rare malignant tumor arising from atypical melanocytes in the basal layer of the conjunctival epithelium and due to its rarity, the treatment is based on evidence from limited series. There is a growing number of recognized clinical and surgical prognostic factors. The current gold-standard treatment of limited CM can be summarized as surgical excision with or without adjuvant therapy. Adjuvant therapy can be classified further under topical chemotherapy, radiotherapy, and cryotherapy. Incisional biopsy is not recommended to avoid tumor seeding and iatrogenic tumor recurrence.[1] Tailored management depends on the location and extent of disease. Several studies, however, have revealed that patients treated with excisional biopsy alone without adjuvant therapy had higher risk of local recurrence, distant metastasis, or poorer all-cause and disease-related survival rates.[2,3,4] Additionally, large, diffuse, or multifocal tumors are more challenging in terms of local control rates even when combined with cryotherapy or radiotherapy.[5]

Surgery

Primary excision of the CM is the mainstay of treatment when a limbal tumor covers ≤4 clock hours or for any tumor with ≤15 mm basal dimension, using a wide excision with 2- to 4-mm margins.[6] The main surgical principle is the "no-touch technique" with a dry ocular surface to avoid irritation, as described in the literature.[6] Frozen section biopsy may also be utilized.[7] In all cases of CM, care is taken to minimize direct contact between the surgical instruments and tumor and different instruments are used for excision and closure to further avoid surgical implantation. Because limbal CM has a potential to invade the cornea and anterior chamber into the sclera, an additional four-step procedure for limbal CM is described in detail. Step 1 includes localized alcohol corneal epitheliorhexis followed by epitheliectomy to remove any corneal component of the tumor and removal of devitalized cells within a 2-mm margin of the corneal lesion. Step 2 is wide resection including the lesion with 5-mm margins, the underlying Tenon's fascia, and a 0.2-mm deep partial lamellar sclerokeratoconjunctivectomy avoiding disruption of Bowman's membrane. Step 3 and step

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4 involve cryotherapy on the conjunctival edges followed by alcohol application to the scleral base and closure of the wound with partial or complete peritomy creating transpositional conjunctival flaps, respectively.[6] Some centers perform sclerectomy only when the tumor is found to be attached to the underlying sclera; for other cases, post-excisional radiotherapy is applied in the form of ruthenium plaque brachytherapy of 100 Gy to a depth of 1 mm to all excised CMs, due to formation of post-sclerectomy scars and an area of possible recurrence or intraocular infiltration with sclerectomy.[8] With this approach, for forniceal or caruncular tumors, adjuvant proton-beam therapy is employed.[8] Recently, Cohen and O'Day[9] clarified their surgical approach to circumscribed CM as adopting a "no-touch" technique and complete resection with 2-mm margins, followed by cryotherapy to conjunctival margins at all times. They also discussed reduction of surgical margins and expanding the use of postoperative strontium applicators for less ocular morbidity, mentioning that the strontium applicator is easily applied and removed without surgery, and strontium radiotherapy has fewer side effects than other radiotherapy methods. The reported recurrence rate with this approach was 10% after a median of 59 months. The authors also limited limbal cryotherapy to adherent disease and lamellar sclerectomy to lesions adherent to the sclera.[9] For corneally displaced CMs, penetrating keratoplasty could be performed at its own risk if there is a suspicion for a stromal invasion but no further.[10] Remaining large conjunctival defects after CM excision may require buccal mucosal/conjunctival grafts or amniotic membrane transplantation with fornix-deepening measures such as symblepharon rings.[11] Amniotic membrane grafts in these cases act as a scaffold for conjunctival epithelial migration and healing, reducing inflammation and fibrosis.[12] As for more extensive measures for more extensive cases of CM, enucleation for CM is rarely performed since this method leaves potentially diseased conjunctiva behind.[13] Orbital exenteration, which aims for complete conjunctivectomy, currently is reserved for extensive cases which are unmanageable with other surgical modalities, even though the impact of this procedure on overall survival once there is orbital invasion is considered negligible. For tumors thicker than 1 mm, melanoma-related mortality rate is between 33% and 50% despite orbital exenteration, which is thus reserved as a palliative measure.[14]

Topical Chemotherapy

The ocular surface is an advantageous location in that it is directly accessible to titratable, repeatable, and high concentrations of topical chemotherapy with minimal systemic exposure to the drugs. Topical chemotherapy in CM is especially beneficial when there is a need to treat the whole ocular surface such as in diffuse or multifocal lesions with ill-defined borders.[15] In addition, the clinically defined pigmented border of the lesion recognized as the tumor edge may not correlate with the pathological borders which cover the amelanotic edges. However, the use of topical chemotherapy as a primary treatment in CM in contrast to Primary acquired melanosis (PAM) has been limited to a subgroup involving superficial and intraepithelial melanoma, and has been shown to be of limited use when there is nodularity or subepithelial nests; therefore, topical chemotherapy for CM is usually reserved as pre- or post-surgical adjuvant treatment.[5,15] Topical mitomycin C does not readily cross the basement membrane, thus it is contraindicated as a primary treatment in invasive conjunctival lesions. A literature review of topical antiproliferative therapy for CM is summarized in Table 1.[5,16,17,18,19]

A recurrent CM cell line named CRMM-1 and CRMM-2 has been studied by Westekemper et al.[20] in terms of sensitivity to chemotherapeutic agents and combinations. Among the tested agents, only mitomycin C and cisplatin were found to have a growth inhibitory effect on tumor cells. The expanded results of the same study group revealed that, after 24-hour exposure of CRMM-1 and CRMM-2 cells to the same agents, the combination of mitomycin C and imatinib had an additive inhibitory effect on tumor growth, whereas combinations of imatinib with fotemustine or cisplatin resulted in antagonism.[20] All-trans retinoic acid had a synergistic effect with mitomycin or imatinib in CRMM-2 but showed antagonism in CRMM-1. Although 24-hour exposure is impractical in the clinical setting, the authors suggested that a combination of mitomycin with imatinib or all-trans retinoic acid could protect the conjunctiva from mitomycin-related side effects.[20] These recent results encourage the use of combination therapy or novel potential agents as a part of local treatment in CM.

Mitomycin C: Mitomycin C is an alkylating agent isolated from *Streptomyces caespitosus* that exerts an antiproliferative effect during all phases of the cell cycle, making it a powerful tool against both proliferating and non-proliferating cells. It primarily acts by forming a covalent bond with DNA, thereby interfering with DNA synthesis. Secondarily, with topical application under aerobic conditions, it generates free radicals and causes lipid peroxidation. In addition, at the immunohistochemical level, CMs and to a certain extent PAM, express NAD(P)H:quinone oxidoreductase, which promotes bioactivation of mitomycin C.[21] Table 1 lists the studies in which mitomycin C was used as primary or adjuvant treatment for CM.[5,16,17,18,19]

The reported transient or long-term side effects of topical mitomycin C for ocular surface malignancies include limbal stem cell deficiency, punctal stenosis, ocular irritation, conjunctival hyperemia, tearing, punctate keratopathy, blepharospasm, corneal haze, and ocular pain, with the first two being the most serious complications limiting the use of the drug.[16] Keratoconjunctivitis and punctate keratopathy are mostly expected to be transient, ceasing over several months and related to longer courses of treatment.[17] As a countermeasure for acute ocular surface toxicity, cycles are given with 1- to 2-week breaks and with artificial tears or mild topical corticosteroids during, between, or throughout cycles.[16,17] Care should be taken to avoid direct scleral exposure to avoid further complications. There is no clear dose-response curve to predict side effects; even a single drop of mitomycin C can result in chronic tissue alterations in the conjunctiva by an unknown mechanism. Postoperative use should only be initiated when the wound is properly healed and should be commenced only when surgical margins are proven negative for invasive melanoma.[5,15]

Table 1. Literature review on topical chemotherapy for conjunctival melanoma (CM). Case reports and studies with less than 5 CMs are excluded

Study group	Year	Drug	Dosage	Number of eyes with CM	Primary or adjuvant	Results	Adverse effects
Kurli and Finger[5]	2005	MMC	QID, 0.04% MMC for: • 28 days as primary treatment, 2 weeks on, 2 weeks off • 7 days as adjuvant treatment	8	2 Primary 6 Adjuvant	• No local control in primarily treated CM, 50% recurrence rate in adjuvant group • Follow-up: 13-144 months • Nodular and subepithelial nests of melanoma were resistant to topical MMC • Recurrence originated in the deeper layers of the substantia propria and orbital tissues	• Short term: transient keratoconjunctivitis (14 eyes), severe keratoconjunctivitis (1 eye), corneal scar (1 eye) • Long term: pannus (2 eyes), corneal haze (1 eye)
Russell et al.[16]	2010	MMC	QID, 0.04% MMC, 3 weeks on, 3 weeks off, 3 weeks on	22	1 Primary 3 Primary treatment for recurrence 18 Adjuvant	• 25% recurrence rate for CM • Mean follow-up: 36 months for all eyes	• 52% short-term complications including allergy and keratoconjunctivitis • 31% long-term complications including corneal erosions/limbal stem cell deficiency and punctal stenosis
Ditta et al.[17]	2011	MMC	QID, 0.04% MMC, 3 weeks on, 1 week off	15	Adjuvant	• Mean follow-up: 23.8 months • 33.3% eyes developed at least 1 recurrence	Injection (13 eyes), tearing (10 eyes), irritation (9 eyes), pain (9 eyes), limbal stem cell deficiency with keratopathy (4 eyes)
Finger et al.[18]	2008	IFN-α2b	1 million units/mL, QID for 3 months	5	2 Adjuvant 3 Primary treatment for recurrence	• Follow-up: 8-17 months • 4/5 showed complete regression	No systemic side effects 1 chemosis 1 irritation 1 corneal edema and superficial punctate keratopathy
Benage et al.[19]	2019	IFN-α2b	1 million units/mL, QID for 3-6 months	5	Adjuvant	• 2 cases with preceding PAM at surgical margin showed remission • 3 cases with preceding invasive melanoma at surgical margin showed recurrence • Follow-up: 12-54 months	Not reported

QID: 1 drop 4 times a day, MMC: Mitomycin C, IFN-α2b: Interferon-alpha-2B

Interferon-alpha-2B (IFN-α2b): Interferons are a group of glycoproteins whose antitumor activity is derived from increasing the length of cell cycle, depleting essential metabolites, direct cytotoxicity, modifying expression of cell surface antigens, and induction of antibodies against tumor cells. Data on the ocular use of IFN-α2b for ocular malignancies are mainly derived from studies of ocular surface squamous neoplasia with administration in the form of topical drops or subconjunctival/perilesional injections, and number of studies on its use and effectiveness in CM are limited. When used topically for ocular surface neoplasias, interferons are well tolerated with no or limited ocular surface side effects, such as mild conjunctival hyperemia or follicular keratoconjunctivitis. Perilesional injections might result in systemic side effects such as flu-like symptoms, overnight fevers, and myalgias that respond to acetaminophen. More recently, neoadjuvant intralesional IFN-α2b application has been suggested by Kim and Salvi[22] for immunoreduction of CM in the hope of better definition of surgical margins and lower local recurrence rates. A review of the literature involving topical IFN-α2b eye drops for CM is summarized in Table 1.[5,16,17,18,19]

Others: Peroperative use of sodium hypochlorite or alcohol during excision is practiced in some centers to reduce the risk of dissemination. Sodium hypochlorite in 0.5% concentration with dilutions up to 1/4 and exposure of at least 3 minutes was shown to be cytotoxic to CM cell line (CM2005.1) in vitro, with comparable cytotoxicity to 99% ethanol.[23] The side effects must be tested in humans.

In terms of adjuvant local intervention, in a recent report studying 2D and 3D cell cultures of CRMM1, CRMM2, and normal conjunctival epithelial cell lines, electrochemotherapy has been suggested as a treatment modality to enhance the antitumor activity of bleomycin, but not mitomycin C and 5-fluorouracil.[24]

Radiotherapy

The use of radiotherapy for CM can be grouped as internal and external, depending on the mode of application. Radiotherapy currently constitutes a complementary approach as adjuvant treatment to surgical excision of CM. It can be used as a palliative measure solely in the most advanced cases who cannot tolerate exenteration, have surgically unresectable lesions, or tumors irresponsive to other treatments.[25,26] In postoperative adjuvant settings, it should be used after the wound is completely healed.[27]

Internal radiotherapy (brachytherapy): Plaque brachytherapy for epibulbar tumors can be applied with I-125 and Ru-106 isotopes or with Sr-90.[27] For CM, most recent reports exist on brachytherapy with Sr-90 and I-125.[3,28,29,30,31] Additionally, Kenawy et al.[8] have reported their current use of adjuvant Ru-106 plaque for deep invasion with a dose of 100 Gy at 2 mm until 2006 and 100 Gy at 1 mm since 2006, instead of sclerectomy or cryotherapy, resulting in improved local recurrence rates. Plaque brachytherapy with I-125 also poses an adjuvant treatment option in CM when there is corneoscleral involvement. In a study including 5 CM cases with histopathological evidence of scleral and/or corneal stromal involvement that were treated with a 15-mm I-125 plaque for residual disease with 100 Gy at 1.5- to 2.5-mm depth, there were no new local recurrences after a mean 23.4-month follow-up with no intraocular complications. Additional reduced vascularity and inflammation at the brachytherapy site in all patients was noted as a secondary gain.[31]

In a series of 19 bulbar CMs with TNM stage pT1c or less, treatment was carried out as surgical excision avoiding sclerectomy, followed by adjuvant I-125 plaque brachytherapy at a dose of 100 Gy and depth of 1.5-3.0 mm. No local recurrences at the treatment site were observed after a mean 41.3-month follow-up with side effects limited to the perioperative period.[30]

For CM in more challenging anatomical locations such as palpebral conjunctiva or fornix, external beam radiotherapy, proton beam therapy, and even I-125 plaque application have been described.[27] With this method, a stainless steel shield positioned in the perilimbal position and a dose of 55-60 Gy over 5 days yielded effective local control in 13 of 14 patients over 11-227 months of follow-up (median: 13 months).[27]

Lommatzsch et al.[28] applied Sr-90/Y-90 brachytherapy in 10-Gy fractions until the applied total dose was 150-200 Gy, depending on the thickness of the lesion. The local recurrence rate was 19/81 in this cohort of CMs, where 46 had adjuvant or primary plaque brachytherapy and 3 had adjuvant external beam radiotherapy. Their series reported a total of 23.5% local recurrence rate after a mean of 66 months regardless of the mode of treatment.[28] In their nationwide study of 194 CMs, Missotten et al.[3] reported local recurrence rates of 67% with excision only and 26% when Sr-90/Y-90 brachytherapy was performed in combination with surgery, with median follow-up of 6.8 years. Twenty patients with bulbar CM undergoing Sr-90 beta irradiation with a handheld applicator with 5 fractionated doses of 50 Gy to the scleral surface as an adjuvant treatment also had successful results in terms of a local control rate of 90% after a median of 59 months with mild local complications and no cataracts.[29] The authors define the indication for this treatment as positive deep surgical margins.[29]

External radiotherapy: The use of external beam radiotherapy (EBRT) in CM has been reported in patients who cannot tolerate surgery due to old age and bad health, as an adjuvant therapy, and with lesions too large for resection.[26,27] Some studies justify the use of postoperative EBRT with a median of 60 Gy when there is aggressive histology, microscopic perineural invasion, advanced-stage disease, or positive margins in malignant lesions of the conjunctiva and eyelid.

Proton beam irradiation is another method of external irradiation which is more selective to the target tissue with less collateral damage than EBRT. Currently, some centers have expanded the use of proton beam radiotherapy in CM to include patients with tumors >1.5 mm in thickness, diffuse or multifocal disease, presence of PAM, forniceal or caruncular lesions, and positive histopathological margins, applied as 36 Gy in 6 fractions 2 weeks after excisional surgery. With this method, 5-year recurrence free survival was reported as 81%.[32]

Wuestemeyer et al.[25] studied proton beam therapy in 20 patients as an alternative to orbital exenteration. Most tumors were stage T3, and all had forniceal or caruncular location except 2 bulbar tumors. After excisional biopsy and conjunctival mapping, 31 Gy in 6 fractions and an additional 2 fractions up to 45 Gy were applied. The median follow-up was 34 months. The recurrence rate was reported as 30%. As a result, proton beam radiotherapy was proposed as an alternative to exenteration for T3 or diffuse T1 and T2 tumors. The most frequent notable complications were dry eye (95%), focal cataract (35%), and limbal stem cell deficiency (20%).[25]

In another study where proton beam radiotherapy was used more liberally in a larger cohort of 89 patients with CM from stage T1c/d to T3, the 5-year cumulative rate of eye preservation was 69% and the estimated overall 5-year survival was 71%, thus offering proton beam radiotherapy as an alternative to orbital exenteration in T2 and T3 tumors.[33] Thirty-six (41%) patients were previously treated, and 29 patients (33%) developed local recurrence.[33] The most common side effects were sicca syndrome in 27, secondary glaucoma in 10, and limbal stem cell deficiency in 7 patients.[33]

Cryotherapy

At present, adjuvant cryotherapy is described as one of the stages in excision of CM, as previously mentioned. The freezing process in cryotherapy ultrastructurally mimics the damage of a thermal burn, which causes shedding of the superficial epithelium from the substantia propria with the superficial

atypical melanocytes, in addition to direct damage to tumor cells due to ice crystals, which cause cell lysis. It is advised to target the very superficial melanocytes or the small number of melanocytes potentially left behind in the deeper layers of conjunctiva after excision, and not to treat the nodular portion with cryotherapy only.[34] The use of cryotherapy aids in reduced exenteration rates in unifocal CM, but multinodular CM has metastatic rates as high as 45% when surgery is combined with cryotherapy. It is also advisable not to perform cryotherapy on bare sclera but to prefer alcohol application to avoid potential scleral melt. To overcome inadvertent tissue damage and enhance the effectiveness of cryotherapy, Finger introduced "finger-tip" cryotherapy probes which formed more homogenous burns over larger areas and covered flat target areas more effectively with less chance of missing the tumor.[35]

Application of cryotherapy has been shown to effectively reduce local recurrence rates in a series by De Potter et al.[36] In their cohort of 68 histologically proven CMs, treatment modality was the only factor associated with local tumor recurrence, which was reported at a rate of 68% with surgical excision only and was reduced to 18% when surgery was combined with cryotherapy over a mean 7.5-year follow-up. Thus, it still remains one of the most effective adjuvant modalities in current practice.

Other

The molecular biology of CM and biological similarities to cutaneous melanoma has implications in its treatment. Vemurafenib is a V600E mutation-specific BRAF inhibitor that has been suggested as a treatment of metastatic disease.[37] *In vitro* studies of vemurafenib, dabrafenib, a MEK inhibitor (MEK162), and an AKT inhibitor (MK2206) showed that the combination of the latter two drugs had a synergistic effect in the inhibition of cell proliferation, but a *BRAF* wild-type and *NRAS* mutated cell line was irresponsive to *BRAF* inhibition.[38]

For cutaneous melanoma, *BRAF* mutation has been a point of interest for potential targeted therapy in metastatic melanoma; however, there are only a few publications consisting of single reports regarding BRAF with or without MEK inhibition in CM. Among these, one reported 12-month recurrence-free, stable, initially metastatic CM with dabrafenib (BRAF inhibitor) combined with trametinib (MEK 1 and 2 inhibitor) in a 70-year-old male[39], and 2 reports described complete regression of metastatic CM and non-metastatic CM with trametinib combined with vemurafenib or dabrafenib, respectively.[40,41] Kiyohara et al.[42] reported 2 cases of metastatic CM, one of which was initially managed with vemurafenib for metastasis, which was later switched to dabrafenib with trametinib due to keratoacanthoma-like eruptions thought to have been caused by vemurafenib, but the patient was lost after 24 months of follow up. The other patient had been followed successfully for 6 months with dabrafenib with trametinib without local recurrence. These data and the non-uniform results provide little on which to make generalized assumptions, but it is clear that BRAF inhibition in *BRAF*-mutated cases, particularly with MEK inhibitors, is one of the most promising targeted therapies for CM.

Immune checkpoint inhibitors are novel drugs for targeted therapy, also used in cutaneous or unresectable cutaneous melanoma, which act on receptors of activated T lymphocytes and facilitate recognition of tumor cells by the host immune system. A recent report of 5 patients with metastatic CM examined the results of immunotherapy with programmed cell death 1 (PD-1) inhibitors. Four patients had received nivolumab and one received pembrolizumab as PD-1 inhibitor. The patients treated with nivolumab were disease-free after 36 months. The patient treated with pembrolizumab showed progression after 11 months and was switched to another therapy.[43] Considering a recent analysis by Cao et al.[44] in which PD-ligand-1 was detected in 19% of primary CMs, immunotherapy is a potential treatment option for systemic disease. The study also suggested that this expression was correlated with distant metastases and a worse melanoma-related survival.[44] To predict the success of PD-1 inhibitors, the additional determination of HLA Class I antigen status is recommended, as its expression is found to be independent from PD-1/PD-L1 expression in CM.[45]

In a recent case series of 5 patients, 3 patients with locally advanced CM who refused orbital exenteration and 2 with metastatic disease received multiple cycles of an anti-PD1 agent together with ipilimumab or nivolumab.[46] All cases showed improvement in local and metastatic CM and complete response was seen in 2 patients, 1 of whom initially had systemic disease.[46]

Another newly proposed potential target is an epigenetic modifier, enhancer of zeste homolog 2 (EZH2), which is highly expressed in primary CM and lymph node metastases (50% and 88%, respectively) but absent in normal conjunctival tissue.[47] Pharmacological inhibition of EZH2 with GSK503 and genetic knock-down resulted in diminished cell growth in vitro and zebrafish xenografts.[47]

Tumor-associated lymphangiogenesis is another potential target for treatment in CM. A study of intratumoral lymphatic vessel density by staining lymphatic vascular endothelial hyaluronan receptor-1 and podoplanin as lymphatic endothelial markers showed that higher intratumoral lymphatic vessel density was correlated with higher tumor thickness and larger tumor diameter, as well as lower recurrence-free and higher melanoma-related death rates.[48] The same markers were used to compare intra- and peritumoral lymphatic vessel density in C-MIN with and without atypia and in CM. CM showed the highest intra- and peritumoral lymphatic vessel density while none of the C-MIN lesions without atypia showed positive staining for these markers intra- and peritumorally, which implies lymphangiogenesis as an early step in malignancy development, even before invasive stages.[48] Additionally, non-limbal tumors with tarsus or fornix involvement are shown to have a tendency for higher lymphatic vessel density than limbal tumors, which implies that non-limbal tumors would benefit more from a potential anti-lymphangiogenic treatment.[49] In terms of comparison of the lymph- and hemangiogenic profile of CM and uveal melanoma cell lines, vascular endothelial growth

factor (VEGF)-A, -C, and -D mRNA, and VEGF-A and -D protein expressions were all seen in CM and uveal melanoma cell lines, and they did not differ in lymph- and hemangiogenic potential. This suggests the existence of *in vivo* mechanisms that act on the tumor microenvironment and lead to a preference for lymphatic spread of CM and hematogenous spread of uveal melanoma.[50]

One final putative target for inhibition is the mTOR (mammalian target of rapamycin) pathway, since phosphorylated m-TOR effectors are highly expressed in CM, unlike uveal melanoma where PTEN was responsible for mTOR pathway downregulation.[51] mTOR pathway inhibition as a potential therapy has been a part of an *in vitro* study where 3 cell lines (CRMM1, CRMM2, T1527A), have been subjected to a BRAF inhibitor (vemurafenib), two MEK inhibitors (trametinib, selumetinib), a PI3K inhibitor (pictilisib), and a dual PI3K/mTOR pathway (dactolisib).[52] The cell lines differed in their mutational profile which included *BRAF* V600E mutation for CRMM1, *NRAS* Q61L mutation for CRMM2 and *BRAF* G466E mutation for T1527A. As a result, CRMM1 was found to be sensitive to inhibitors of both MAPK (trametinib and only marginally to vemurafenib), CRMM2 was found to be moderately sensitive to pictilisib, and T1527A was resistant to all tested agents; vemurafenib sensitivity was only displayed by CRMM1.[52] Thus, 2 of 3 cell lines, CRMM1 and CRMM2, which harbored the most commonly encountered mutations, showed significant growth inhibition with pictilisib (PI3K inhibitor). Interestingly, however, this effect was reduced when pictilisib was combined with the downstream mTOR inhibitor, dactolisib.[52]

Molecular Biology

The most commonly studied and reported mutations found in CM include *BRAF, NRAS,* and *KIT* mutations. Furthermore, the similarities in genetic alterations have suggested a biological kinship between CM and cutaneous melanoma in recent years, which raised interest for the development of potential new therapies.[53,54]

The *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) gene encodes a serine/threonine kinase involved in signal transduction in the mitogen-activated protein kinase (MAPK) pathway. Activating *BRAF* mutations can be found in up to 50% of CM, and among *BRAF* mutation-bearing samples, the ratio of *BRAF* V600E to *BRAF* V600K is nearly 4:1.[37,53,54] It is debatable whether *BRAF* mutations are of prognostic significance, but a population-based study in Denmark has correlated *BRAF* mutation status with male gender, younger age, sun-exposed tumors (which included bulbar conjunctiva or caruncle), mixed or non-pigmented color, absence of PAM, and CM of nevi origin.[2]

NRAS stands for neuroblastoma v-Ras oncogene homolog, and this gene encodes a GTPase promoting proliferative cycle of the cell. Activating *NRAS* mutations can be found at up to 18% frequency and are mutually exclusive with *BRAF* mutations.[38] Remarkably, *GNAQ* and *GNA11* mutations are virtually nonexistent in CM, which differs from uveal melanoma.[54] The *KIT* gene encodes a receptor tyrosine kinase which promotes cell survival and growth and is found to be mutated in nearly 2% of CM.[55] *KIT*-mutated melanomas are shown to be sensitive to imatinib, a tyrosine kinase inhibitor including c-kit. CD117 expression and c-kit immunostaining do not correlate with *KIT* mutation status or copy number; therefore, an analysis of mutational status is advised be performed before commencing to imatinib treatment.[56,57]

A more recent large cohort of 63 CMs demonstrated *NF1* mutations as the most frequent mutation in CM (33%), followed by activating mutations of *BRAF* and *RAS* genes, all of which induce activation of the MAPK pathway.[58] The authors proposed a genetic classification of CM similar to cutaneous melanoma, including *BRAF*-mutated, *RAS*-mutated, *NF1*-mutated and triple wild-type CMs, implying mutual exclusion of each entity.[58]

As for other mutations that were detected in CM, whole exome sequencing in excised material of 5 CM patients showed that in addition to *BRAF, NRAS,* and *NF1* mutations, CM harbors previously unreported mutations in *EGFR, APC, TERT*, and other cancer-associated genes and the C→T mutation signature consistent with UV-induced DNA damage. The most common chromosomal alteration was 6p gain.[59] Recent studies of molecular and genetic/epigenetic alterations seen in CM are summarized in Table 2.[37,44,54,60,61,62,63,64,65]

As a contribution to clinical interpretation of the copy number alterations in CM, single nucleotide polymorphism array has been conducted in a multi-center study in 59 CM to study the correlation between copy number alterations and clinical outcome.[66] Four tumor suppressor genes (*NEURL1, SUFU, PDCD4, C10orf90*) which were affected by deletions of chromosome 10q24.32-26.2 were found to be significantly related to CM metastasis. Deletions of 10q24.32-26.2 were also strongly associated with lymphatic invasion and increasing tumor thickness.[66]

Conclusion and Future Directions

Even though CM is a rare disease, the potential mortality makes accurate diagnosis and appropriate treatment imperative. The literature data consists mostly of a limited number of studies due to the rarity of the disease. Currently there is an almost uniform approach for initial treatment of limited, focal disease, consisting of excisional surgery and cryotherapy, although approaches to more advanced disease or adjuvant treatment differ between centers. Even with adjuvant treatment, mortality rates can only be reduced to a certain extent. Further classification of CM is still needed for individual prognostic and survival prediction. Genetic and molecular alterations common to CM and cutaneous melanoma make it amenable to studies on targeted molecular therapy. Multi-center and prospective trials would improve our understanding of the biological behavior of this potentially deadly tumor by providing more information about the molecular alterations implicated in the development of the disease and the corresponding targeted therapy.

Table 2. Studies on molecular pathology, genetics, and epigenetics of conjunctival melanoma (CM)

Cell/protein/molecule/ gene studied	Method	Results	Limitations
PD-L1 ligand[44]	Immunohistochemistry	Expression is lower than cutaneous melanoma	Small sample size, possible tumor heterogeneity
Tumor-infiltrating lymphocytes[44]	Immunohistochemistry	CM contains higher densities of CD4, CD4 helper, Foxp3 cells, and less densities of CD8, CD68 and CD68CD163 cells than uveal melanoma	Small sample size, possible tumor heterogeneity
S100A1, S100A6, S100B, Melan-A, CEA[60]	Immunohistochemistry	Melan A has variable expression. CEA is not expressed. S100A1 and S100B are highly expressed. UM has low S100B expression. S100A1 and S100B1 proposed as serum markers of metastatic CM	Small study size
Chromosomal analysis[54]	Comparative genomic hybridization	CM showed similar patterns to cutaneous melanoma: gains of 1q, 3p, 7, 17q; losses of 9p, 10, 11, 12q. Uveal melanoma expresses losses of 1p, 3, 6q; gains of 6p, 8q.	Larger cohorts with longer follow-up are needed for prognostication
HSP-90, PTEN, Bcl-2[61]	Immunohistochemistry	HSP-90 expression and loss of PTEN can serve as an adjunct to differentiate CM from nevi. Bcl-2 expression is also higher in CM	None stated
TERT[62]	SNaPshot analysis	TERT promoter mutations are frequent in CM (41%), PAM with atypia (8%); rare in uveal melanoma and absent in benign conjunctival melanocytic lesions	None stated
Gene copy number changes[37]	Multiplex Ligation-Dependent Probe Amplification	CDKN1A and RUNX2 amplification is present in most primary CMs. MLH1 and TIMP2 amplification and MGMT and ECHS1 deletion are frequently present in metastatic CMs	None stated
Circular RNA profile in CM[63]	RNA sequencing	CircMTUS1 is upregulated in CM and silencing circMTUS1 inhibits CM proliferation	Not stated
MicroRNA profiling of metastatic CM[64]	Microarray profiling analysis	Two groups of miRNA profile regarding metastatic potential were detected Hsa-miR-194 is downregulated in CM metastases	Poor correlation among microarray and qPCR, small sample size
ß-catenin expression and activation[65]	Immunohistochemistry, wound healing assays	Limited activation of ß-catenin in CM, unlike skin melanoma Motility or nuclear translocation of ß-catenin in CM is not associated with Wnt5a	Not stated

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Case Report

Bartonella henselae Neuroretinitis: A Rare Coinfection in POEMS Syndrome

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Abstract

Bartonella henselae is a recognized cause of neuroretinitis in cat scratch disease. Meanwhile, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome with Castleman disease (evidence of lymph node hyperplasia), is a chronic debilitating condition that predisposes to various superimposed infections. *B. henselae* neuroretinitis implicated in POEMS syndrome has not been reported previously. A 34-year-old asymptomatic man was referred for an eye assessment. Examination showed visual acuity of 6/18 in the right eye and 6/24 in the left eye. On fundus examination, both eyes exhibited typical features of neuroretinitis (optic disc swelling and incomplete macular star). There was otherwise no vitritis or chorioretinitis. Serology for *B. henselae* revealed high immunoglobulin M (IgM) titer (1:96) indicative of acute disease, and positive immunoglobulin G (IgG) (1:156). He was treated with oral azithromycin for 6 weeks and a short course of oral prednisolone. Subsequently, the visual acuity in both eyes improved with resolution of macular star. However, both optic discs remained swollen.

Keywords: *Bartonella henselae* neuroretinitis, POEMS syndrome, bilateral disc swelling

Introduction

Bartonella henselae is the most common causative agent in neuroretinitis and is transmissible to humans through scratches, bites, or licks from cats or kittens. However, the main vector of transmission between cats and humans is the cat flea (*Ctenocephalia felis)*. Cat fleas are found on up to 33% of healthy household pets and strays. However, prior contact with these vectors is not a prerequisite for diagnosis, as Tan et al. reported that only 25% of cases had specific history.[1]

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome is a rare cause of bilateral optic disc swelling. It was first described in 1938 by Scheinker and was previously known as Takatsuki or Crow-Fukuse syndrome. The prevalence of POEMS was estimated to be 0.3 cases per 100,000 population per year, initially reported in Japanese.[2] Although polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes constitute the acronym POEMS, other salient features were not included in the acronym. Despite an abundance of reports regarding POEMS syndrome in Asian countries, especially Japan, China, and India, it remains relatively rare in the South-east Asia region. In Malaysia, there have been only a few reported cases of POEMS syndrome.[3,4]

This is the first reported case of bilateral *B. hensalea* neuroretinitis in a patient with POEMS syndrome.

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Case Report

A 34-year-old man diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) 2 years earlier was referred for an eye assessment. However, he did not have any visual complaint. He presented initially with progressive bilateral upper and lower limb weakness. After several courses of intravenous immunoglobulin (IVIg), his condition showed minimal improvement.

On ocular examination, his best-corrected visual acuity (BCVA) was 6/18 in the right eye and 6/24 in the left eye with absence of relative afferent pupillary defect. Contrast/brightness sensitivity, color vision, and extraocular muscle movements were normal. Anterior segment examination was unremarkable in both eyes. Fundoscopy showed bilateral gross optic disc swelling with splinter hemorrhages. Both maculae were edematous with incomplete stellate macular star (Figure 1). Otherwise, vitritis, dilated tortuous vein, retinal hemorrhages, or chorioretinitis were not seen. Optical coherence tomography of the maculae showed bilateral subretinal fluid collection with exudates extending from the optic disc (Figure 2, 3). Visual field examination revealed a diffusely enlarged blind spot with no central scotoma (Figure 4).

On physical examination, the patient was of medium build with body mass index of 22. He was normotensive with regular heart rate. There was bilateral sensorimotor weakness in the upper limbs and lower limbs until below knee level. Upper limb strength was 3/5 and lower limb strength was 2/5 with reduced plantar reflexes. Other cranial nerve examinations and anal tone were normal.

Infective and immunology screening was performed. *B. henselae* serology showed abnormally high titer of IgM (1:96)

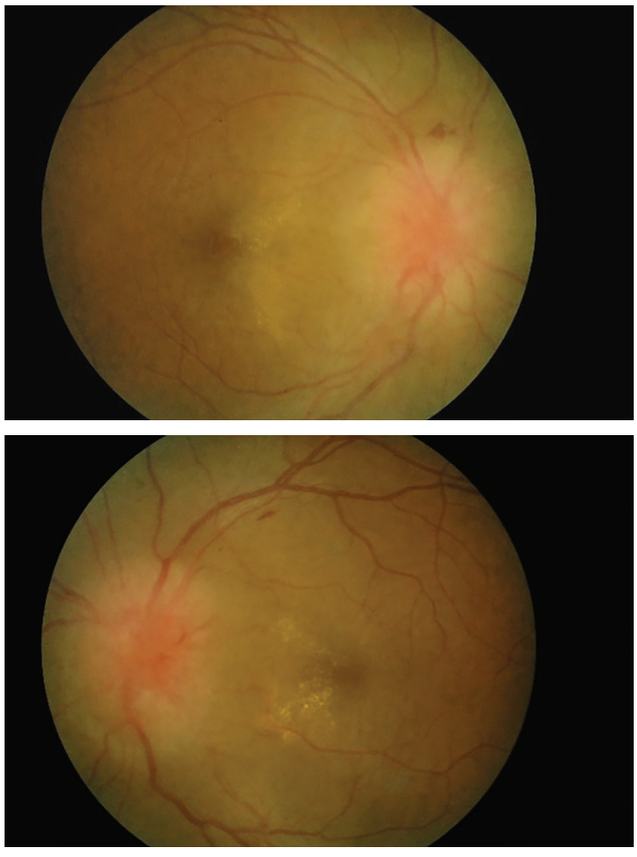


Figure 1. Fundus photography during initial assessment shows bilateral optic disc swelling with disc hemorrhages and incomplete macular star

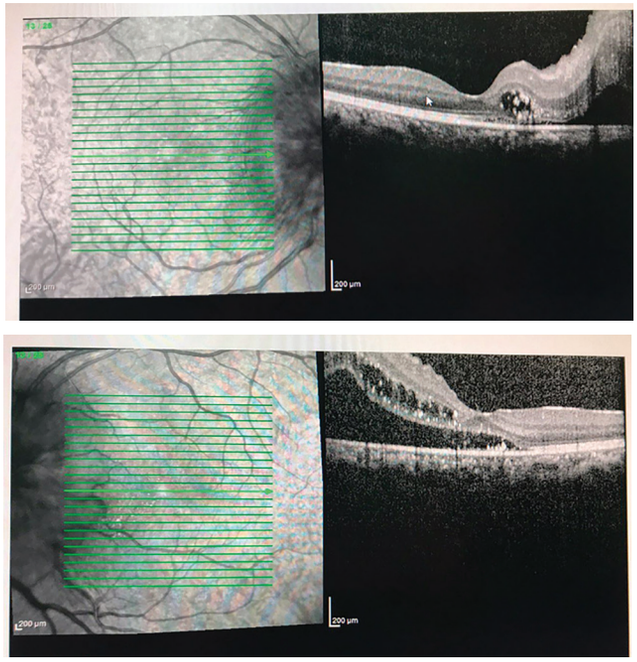


Figure 2. Macular optical coherence tomography shows presence of subretinal fluid, intraretinal edema, and exudates involving the fovea

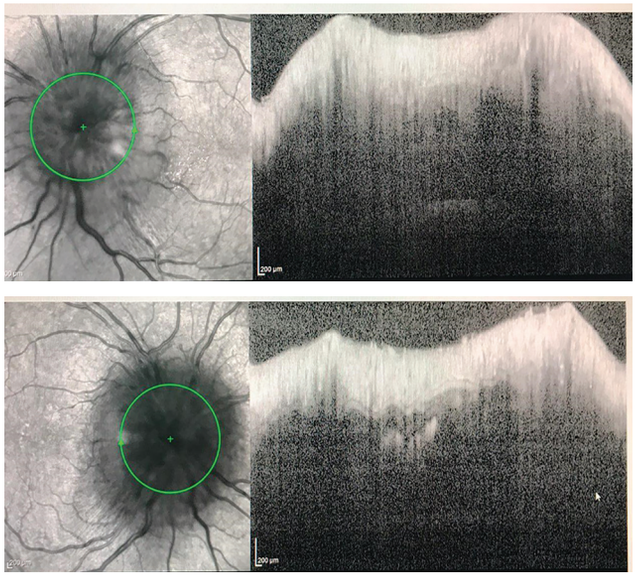


Figure 3. Optical coherence tomography of the bilateral optic nerve head shows diffuse optic nerve edema

and IgG (1:156), which supported the diagnosis of *B. henslelae neuroretinitis*. Other infective screening investigations such as syphilis, viral hepatitis, Mantoux test, and tuberculosis quantiferon tests were negative. Contrast-enhanced computer tomography (CT) scans of the optic nerve and brain to delineate the optic nerve course and evaluate gross structure of the brain were normal. However, the patient refused lumbar puncture.

Oral azithromycin 500 mg daily was given for 6 weeks. Oral prednisolone 60 mg daily (1 mg/kg) was added due to the macular edema. The BCVA in both eyes improved to 6/9 upon treatment completion and the macular edema resolved. However, both optic discs remained swollen (Figure 5).

The ocular findings of polyneuropathy prompted further investigations. Follow-up within the next 6 months revealed myriad symptoms that finally led to the diagnosis of POEMS syndrome. Further blood investigations showed microcytic hypochromic anemia with evidence of subclinical hypothyroidism. Systemic work-up revealed hepatomegaly and splenomegaly with recurrent ascites by CT of the hepatobiliary system. Abdominal X-ray showed multiple lytic lesions in the spine and iliac bone (Figure 6,7). Repeated nerve conduction study revealed segmented demyelination of sensory and motor polyneuropathy that was initially confused for CIDP instead of POEMS syndrome. Electrophoresis of serum protein showed presence of monoclonal IgG-lambda paraprotein. Biopsy of supraclavicular and inguinal lymph nodes swellings pointed to multicentric Castleman disease (MCD). Plasma vascular endothelial growth factor (VEGF) levels, however, was not sent as was not available in the country.

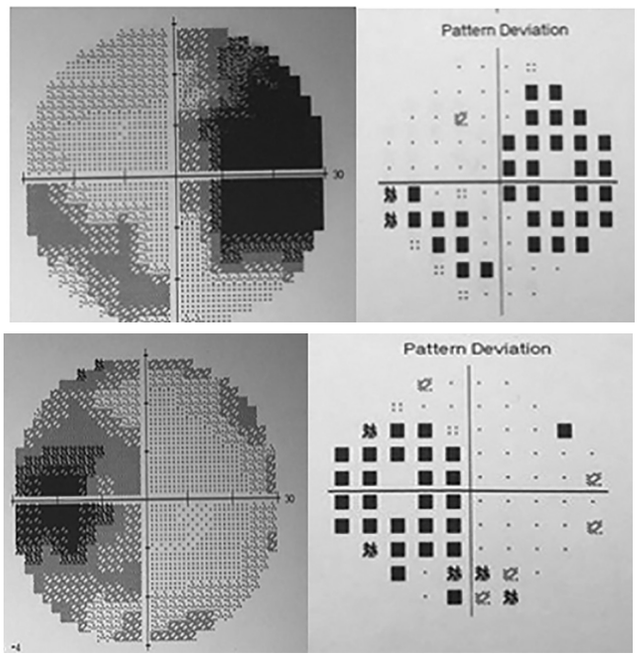


Figure 4. Humphrey visual field grayscale shows bilateral enlarged blind spot

Chemotherapy was subsequently started using vincristine, ifosfamide, carboplastin, dexamethasone; cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; and cyclophosphamide, doxorubicin, vincristine, prednisone regimens.

His vision further improved to 6/7.5 bilaterally. However, both optic discs remained persistently swollen. Repeated brain CT with contrast showed no sign of any intracranial lesions, infections, or neurodegenerative changes. Due to financial constraints, the patient refused further investigations including fundus fluorescence angiography or magnetic resonance imaging of the central nervous system.

He subsequently had multiple episodes of extravascular fluid overload and infections due to pneumonia that required multiple hospitalizations. His polyneuropathy worsened and rendered him bedridden. His general condition deteriorated relentlessly, and he finally succumbed to his condition 2 years after diagnosis.

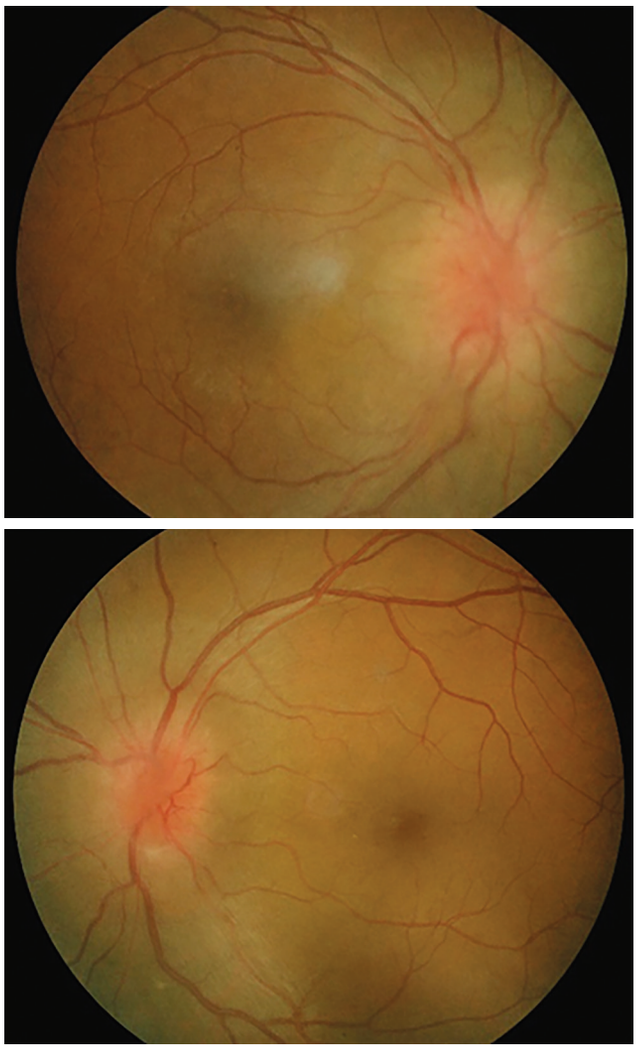


Figure 5. Fundus photography after completed antibiotic and corticosteroid treatment shows resolution of macular star and disc hemorrhages with persistent bilateral optic disc swelling

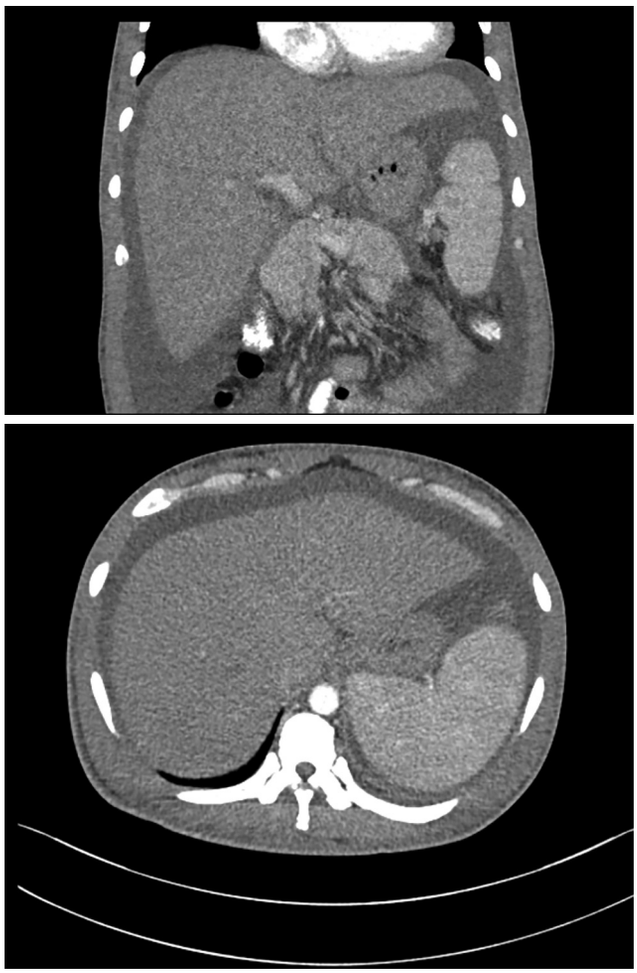
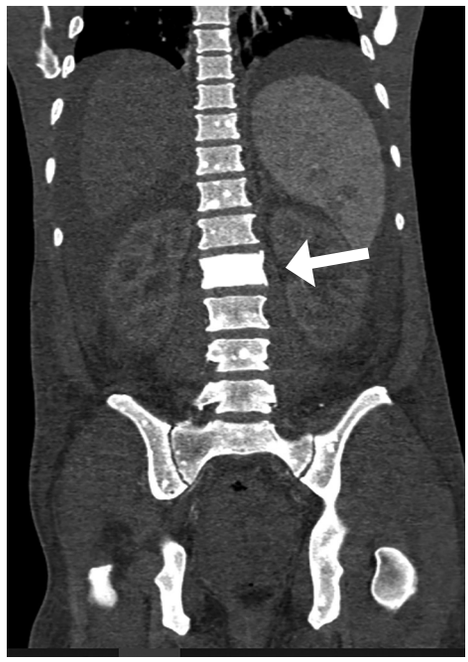


Figure 6. Computed tomography scans of the abdomen showing hepatosplenomegaly



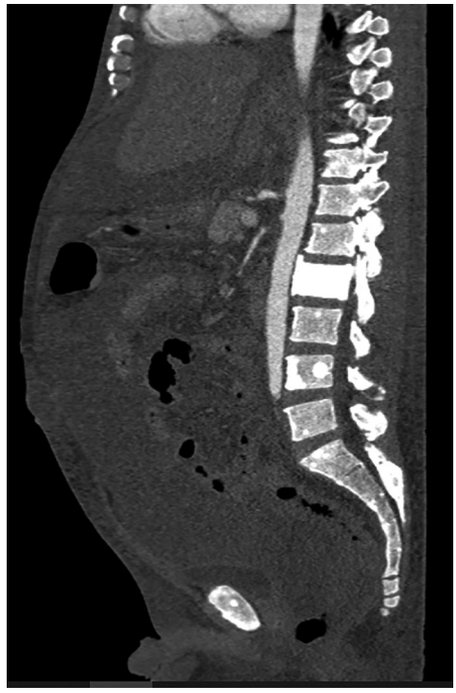


Figure 7. Computed tomography scan of the abdomen and pelvis showing multiple sclerotic bony lesions over the spine with ivory vertebral appearance of L1 (white arrow)

Discussion

POEMS syndrome is a collection of clinical manifestations resulting from nonmetastatic systemic plasma cell neoplasm. It is now recognized that not all symptoms need to be present to reach the diagnosis. A recent update by Dispenzieri et al.[5] described the requirement of 2 major mandatory criteria and highlighted the emergence of other important features including Castleman disease, sclerotic bone lesions, elevated VEGF levels, optic disc edema, extravascular volume overload, thrombosis, and abnormal pulmonary function tests (Table 1). Castleman disease is a lymphoproliferative disorder, and can be present concomitantly in 11-50% of patients diagnosed with POEMS syndrome.[6] This patient fulfilled the minimum of 2 mandatory major criteria with at least 1 major and 1 minor criteria for diagnosis of POEMS syndrome.

Commonly, optic disc swelling with macular exudates arranged in partial or complete star configuration is a typical feature of neuroretinitis. In ocular infection with *B. henselae*, the diagnosis relies on the typical clinical signs, supported with positive serologic testing. We hence propose that due to his immunocompromised state, the patient had concurrent *B. henselae* neuroretinitis with POEMS syndrome. Although cat scratch disease (CSD) is generally a self-limiting disease, treatment of *B. henselae* neuroretinitis may hasten the resolution

Table 1. Revised diagnostic criteria for POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome from Dispenzieri et al.[5] (2007). Diagnosis of POEMS requires presence of both mandatory criteria, at least 1 of 3 other major criteria, and at least 1 of 6 minor criteria

Mandatory criteria • Polyneuropathy (typically demyelinating) • Monoclonal proliferative disease (frequently gamma-type)
At least 1 of the other major criteria • Multicentric Castleman disease • Sclerotic bone lesion • Elevated vascular endothelial growth factor level
At least 1 of the minor criteria • Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy) • Extravascular volume overload (including edema, pleural effusions or ascites) • Endocrinopathy (adrenal, gonadal, parathyroid, pancreatic or pituitary) • Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) • Papilledema • Hematological (polycythemia or thrombocytosis)

of macular edema and optic disc swelling, thus favoring good visual outcome. Efficacy in the eradication of *B. henselae* has been observed with doxycycline, rifampicin, gentamicin, cotrimoxazole, and ciprofloxacin. Although the benefit of corticosteroid is still controversial in CSD, a case series of 14 Japanese CSD patients with *B. henselae* neuroretinitis treated with combination antibiotic and corticosteroid therapy showed good visual outcome.[7]

Whilst the pathogenesis of CSD and POEMS syndrome may differ, use of corticosteroids may help control some degree of intraocular inflammation and optic neuropathy by inhibiting migration of inflammatory cells and mediators, especially prostaglandins, leukotrienes, and cytokines (importantly VEGF-A) in the retina, which further reduces vascular leakage and edema.[8]

Optic disc swelling in our patient may have also resulted primarily from POEMS syndrome, which was not diagnosed at primary ocular examination.

Bilateral optic disc swelling is the commonest ocular manifestation in POEMS syndrome. It was present in 30-70% of cases in a large retrospective series evaluating the frequency of POEMS syndrome manifestations.[9] Less frequently reported ocular signs are retinal hemorrhage, subretinal fluid, macular edema, cotton wool spot, choroidal neovascularization, central retinal artery occlusion, and serous retinal detachment.[10,11] The ocular findings of bilateral optic disc swelling with macula edema seen as a coinfection with *B. henselae* neuroretinitis as highlighted in our case has not been presented in any previous review.

The pathogenesis of optic disc swelling in POEMS syndrome, however, remains unclear. The possibility of increased intracranial pressure, overproduction of inflammatory mediators with microangiopathy, direct disc infiltrations, or elevated abnormal proteins has been proposed and debated over the years.[12,13] It has been postulated that as VEGF is a pro-inflammatory and potent angiogenic factor, its overproduction in POEMS syndrome leads to abnormal and leaky endothelial cell proliferation that subsequently leads to plasma leakage. This explains the manifestation of bilateral disc edema in POEMS syndrome despite the absence of increased intracranial pressure, direct compression, or optic nerve infiltrations. Other proinflammatory mediators including cytokines, interleukin-6, interleukin-1b, and tumor necrosis factor-alpha (TNF-α) released by abnormal plasma cells may have caused further vascular permeability, thus leading to worsening of disc edema and systemic fluid overload.[14]

The presence of overlapping features of *B. henselae* neuroretinitis and POEMS syndrome may have been misleading for the treating physician. Therefore, it is crucial that ophthalmologist is aware that chronic non-resolving bilateral disc edema with normal brain imaging and presence of polyneuropathy could point to other multisystemic disease.

Furthermore, it is not surprising that more symptoms that point to POEMS syndrome develop over time. The mean time of diagnosis from initial presentation was reported to be 15 months, ranging from 3 to 120 months according to Dispenzieri et al.[12]

Early diagnosis of POEMS syndrome is, however, crucial in reducing morbidity and also improves survival. Previous studies have reported median survival time after diagnosis of only 165 months and 30 months respectively for POEMS and MCD patients.[15] A recent study by Wang et al.[16] reported that most patients died due to cardiorespiratory failure, capillary leakage complications, and infection during the disease course. The total number of presenting features during the initial diagnosis of the disease was insignificant in predicting patient survival. However, finger clubbing and extravascular volume overload were reported as poor prognostic factors.[12,17] Our patient had these features and passed away 24 months after diagnosis due to severe respiratory tract infection.

In terms of management for POEMS syndrome, there is still no standard guideline established. Radiation is preferred if plasmacytoma is isolated, while chemotherapy is the best option for widespread disease. Successful treatment of POEMS syndrome with systemic anti-VEGF (bevacizumab) and blood stem cell transplantation has remained a controversy. Nakaseko et al.[18] has proposed the positive role of autologous peripheral blood stem cell transplant in terms of survival and quality of life. However, there is still no clinical trial data with which to conclude the best treatment guidelines for these conditions.

Conclusion

POEMS syndrome is difficult to diagnose due to its rarity and complexity with multiorgan involvement. Although ocular presentation is an essential part of POEMS syndrome, previous reports mainly highlighted the presence of optic disc edema and scarcely regarded other ocular findings, specifically neuroretinitis. Early diagnosis with meticulous systemic examinations and prompt initiation of treatment is crucial in achieving favorable

outcome in POEMS syndrome. Thus, this case report aims to increase awareness regarding POEMS syndrome and possible initial ocular associations, especially among ophthalmologists.

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Informed Consent: Consent was obtained from patient's guardian for images and other clinical information to be reported in the journal.

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Authorship Contributions

Surgical and Medical Practices: W.H.W.H., A.H., Concept: W.H.W.H., A.H., Design: M.E.P.I.A.K, J.M., W.H.W.H., Data Collection or Processing: M.E.P.I.A.K, J.M., Analysis or Interpretation: M.E.P.I.A.K, J.M., W.H.W.H., A.H., Literature Search: M.E.P.I.A.K, J.M., Writing: M.E.P.I.A.K, J.M., W.H.W.H., A.H.

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Case Report

Posterior Scleritis as a Paraneoplastic Syndrome in Colon Cancer: A Case Report

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Abstract

This study presents a rare case of unilateral posterior scleritis as an ophthalmic manifestation of a paraneoplastic syndrome. A 61-year-old man presented to our department complaining of gradual worsening of vision in his left eye. Visual acuity was 10/10 and 3/10 in his right and left eye, respectively. He also mentioned that he experienced posterior ocular pain while sleeping at night, but was otherwise asymptomatic. His past ophthalmic and medical history were clear. A thorough clinical, imaging (fundus photography, optical coherence tomography, fluorescein angiography, and B-scan), and laboratory investigation was carried out. A diagnosis of posterior scleritis was made, but no obvious cause or underlying disease was identified even after a thorough systematic assessment. Regular follow-up within the next few months did not reveal any further pathological findings. Finally, 6 months after the initial presentation, the patient was diagnosed with colon cancer. Posterior scleritis can present as an ophthalmic manifestation of a paraneoplastic syndrome in patients with an underlying malignancy, even months before the presentation of systemic symptoms and diagnosis of the underlying disease. In conclusion, in patients (especially older adults) with posterior scleritis, the possibility of a malignant neoplasia must not be ignored or underestimated (paraneoplastic syndrome).

Keywords: Scleritis, malignancy, colon cancer, paraneoplastic syndrome

Introduction

Scleritis is a painful, chronic, and potentially blinding inflammatory condition defined by edema and cellular infiltration of the entire thickness of the sclera. Non-infectious scleritis is the most common type and is frequently associated with an underlying systemic inflammatory condition of which it may be the first manifestation.[1] Scleritis may be clinically isolated to the eye, but is frequently associated with a systemic disorder. Anatomically, it can be categorized into anterior and posterior. Posterior scleritis often appears in patients younger than 40 years old, who are usually otherwise healthy, but about one third of individuals over the age of 55 have an underlying systemic disease. Approximately 50% of cases are associated with a systemic disease, especially collagen disorders such as rheumatoid arthritis, Wegener granulomatosis, relapsing polychondritis, and polyarteritis nodosa.[2,3] Some rare cases of malignant systemic disease have been described.[4,5] Scleritis may be the first or only presenting clinical manifestation of these severe and potentially lethal clinical entities. An early and accurate diagnosis of the associated systemic or infectious etiology in combination with appropriate treatment can stop the relentless progression of both ocular and systemic processes.[6] The diagnostic approach to scleritis can be challenging due to its perplexing and varied clinical signs and symptoms.[3] Herein,

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we report a case of posterior scleritis as the initial and only manifestation of paraneoplastic syndrome in a patient with colon cancer.

Case Report

A 61-year-old Caucasian man presented with a 2-month history of gradual decline in visual acuity (VA) and moderate pain in the left eye that radiated to the orbit and was awakening him at night. He reported no other ocular or systemic symptoms. His past ophthalmic history was clear and his blood pressure was well-controlled with antihypertensive medication. Otherwise, his past medical history was unremarkable, without any evidence of musculoskeletal diseases or systematic vasculitis.

On presentation, his Snellen VA was 10/10 (uncorrected) in the right eye (OD) and 3/10 (best corrected VA) in the left eye (OS). A thorough clinical, imaging, and laboratory investigation was carried out. Slit-lamp biomicroscopy of the anterior chamber revealed that there was no presence of flare and cells. Pupillary reflex and eye movements were normal in both eyes. Fundoscopy showed a retinal elevation at the posterior pole of OS along with a retinal pigment epithelium (RPE) rip (Figure 1a). The RPE rip probably occurred as a result of inflammation and exudation of fluid causing pressure on the RPE.[7] Optical coherence tomography scan (Figure 1b) confirmed the presence of sub-RPE fluid leading to a RPE detachment. Fluorescein angiography demonstrated subretinal pooling of fluorescence without leakage in the same area the retinal elevation was detected (Figure 2a). On the other hand, indocyanine green angiography showed a hypercyanescent area corresponding to the sub-RPE accumulation (Figure 2b). The sub-RPE fluid was also verified by B-mode ultrasound scan (Figure 3a, b). More specifically, ultrasound imaging highlighted retinal elevation (due to sub-RPE fluid accumulation) with thickened sclera and mild choroidal thickening with discrete fluid in sub-Tenon's space. Our diagnostic work-up aimed to exclude infectious or autoimmune causes of scleritis. Results of laboratory investigations, including full blood count and biochemistry assays, were unremarkable. Serum rheumatoid factor, angiotensin-converting enzyme, antinuclear antibodies, antineutrophilic cytoplasmic antibodies (p and c), enzyme-linked immunosorbent assay for human immunodeficiency virus (1 and 2), serology for syphilis (Treponema pallidum hemagglutinin antigen, Venereal Disease Research Laboratory) and viral hepatitis (B and C) were negative. Erythrocyte

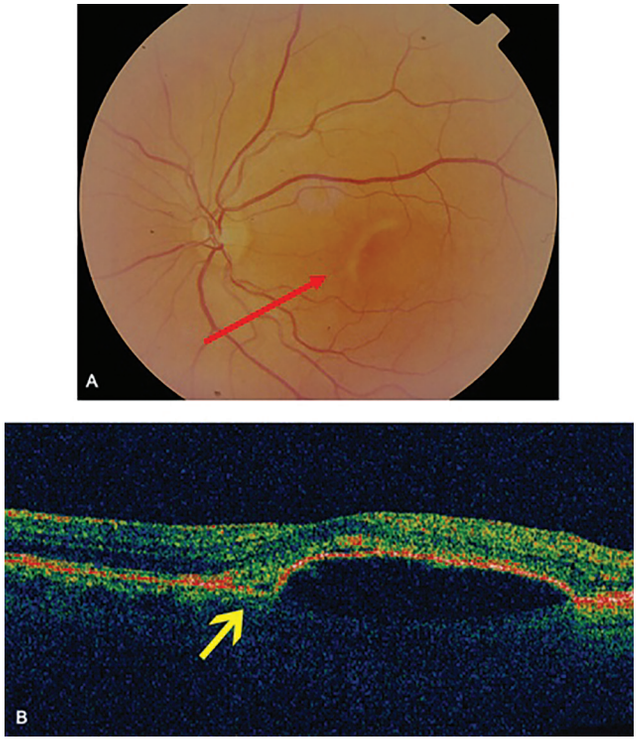

Figure 1. Posterior scleritis. A) Left eye posterior pole showing retinal elevation along with a retinal pigment epithelium (RPE) rip (red arrow). B) Optical coherence tomography of the left eye showing sub-RPE fluid leading to RPE detachment. The area corresponding to the RPE rip is indicated by the yellow arrow

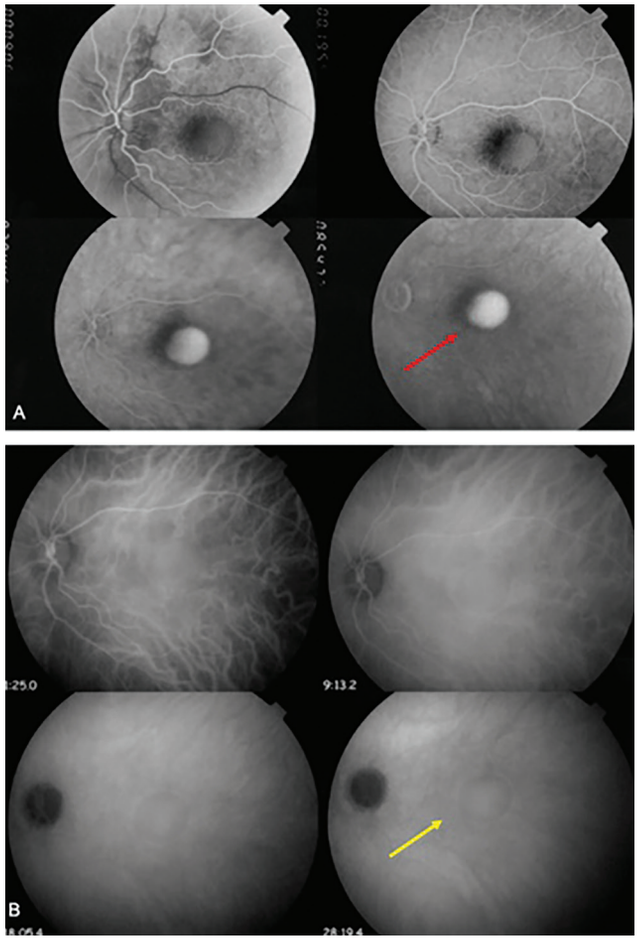

Figure 2. Posterior scleritis. A) Fluorescein angiography showing pooling of fluorescein without leakage (red arrow). The adjacent dark area corresponds to the RPE-rip. B) Indocyanine green angiography showing hypercyanescent area corresponding to the sub-RPE fluid accumulation (yellow arrow)

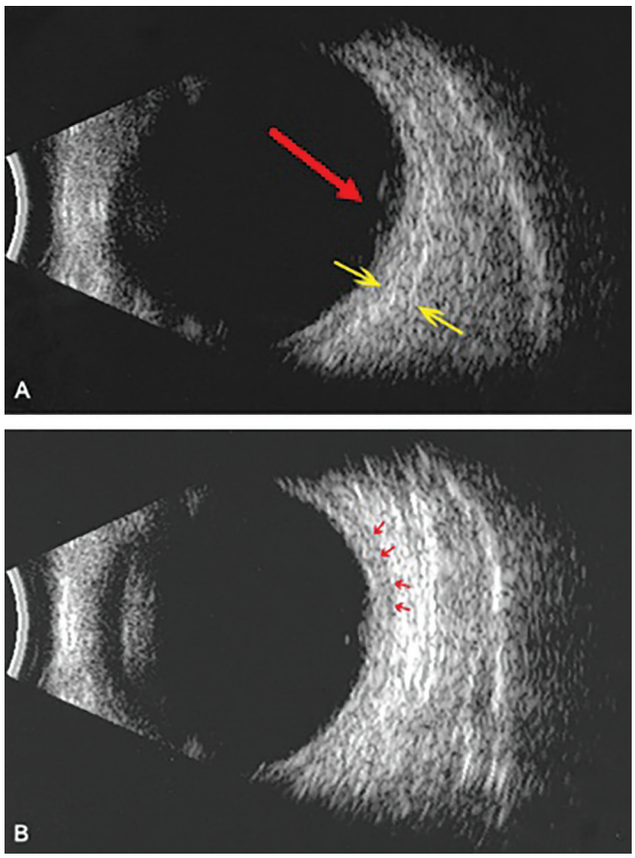

Figure 3. Posterior scleritis: B-Mode echography. A) Retinal elevation due to sub-RPE fluid accumulation (red arrow) with thickened sclera (yellow arrows). B) Mild choroidal thickening with discrete fluid in sub-Tenon's space (red arrows)

RPE: Retinal pigment epithelium

sedimentation rate and C-reactive protein were within normal limits. Furthermore, a routine systematic assessment did not raise any suspicion about the possibility of an underlying disease.

Taking into account the presenting symptoms together with the aforementioned findings, a diagnosis of posterior scleritis was made and oral nonsteroidal anti-inflammatory agents were administered for symptomatic relief. However, at that time it could not be associated with any obvious cause or known systemic disease. Regular follow-up over the next few months did not reveal any further pathological findings. Finally, 6 months after the initial presentation, the patient was diagnosed with colon cancer. The colon carcinoma was asymptomatic and diagnosed during a routine examination when a baseline colonoscopy was performed. At that time, all the required investigations were performed at the department of surgery in order to establish the diagnosis. A previous colonoscopy in his early 50s had not revealed any significant findings.

Discussion

Scleritis is an infrequent ocular inflammatory entity. The majority of ophthalmologists may not encounter more than 2 cases of scleritis per year.[8] It can lead to potentially severe ocular complications and approximately 50% of cases are associated with topical or systemic diseases, some of which may have lethal consequences.[3] Some of the most common and well-described systemic diseases associated with scleritis are systemic lupus erythematosus, inflammatory bowel disease, relapsing polychondritis, rheumatoid arthritis, polyarteritis nodosa and granulomatosis with polyangiitis (formerly called Wegener's).[3] Infectious agents such as herpes simplex viruses, tuberculosis, *Pseudomonas*, and *Aspergillus* may cause severe and difficult to treat scleritis.[8] Albeit rare, scleritis may be the initial or only feature of a masquerade[9,10] or paraneoplastic syndrome.[4] Therefore, malignancies must always be included in the differential diagnosis in cases of scleritis with no obvious cause.

Masquerade syndromes are typically described as pathologies that mimic inflammatory clinical entities but which are associated with a neoplastic process. Detailed medical history and thorough clinical assessment together with specific laboratory and histopathologic investigations can help establish an accurate diagnosis. A wide spectrum of conditions may lead to features imitating an inflammatory condition.[11] On the other hand, paraneoplastic syndromes involve complications of a systemic malignancy that present as various disorders of one or more systems, including dermatological, endocrine, hematological, neuromuscular, or even ocular abnormalities. Paraneoplastic syndromes are defined by a rapid development of atypical signs and symptoms without any obvious etiology or features of metastasis and may manifest up to 2 years before a diagnosis of cancer. Pathogenetic mechanisms encompass cell-mediated and humoral immune responses against antigens expressed by malignant cells, leading to inflammation and cellular destruction.[12] More specifically, following the activation of host immune mechanisms, antibodies are produced against the cancer antigen, resulting in autoimmunization and the production of autoantibodies against normal host tissue.[13,14] Any type of cancer may be associated with a paraneoplastic syndrome. Small cell lung cancer, non-small cell lung cancer, melanoma, and cancers of the breast, uterine, and thyroid are the most common cancers associated with paraneoplastic syndrome.[11] Cancer-associated retinopathy, optic neuropathy, bilateral diffuse uveal melanocytic proliferation, Lambert-Eaton myasthenic syndrome, and melanoma-associated retinopathy are some of the noted ophthalmic conditions that accompany paraneoplastic syndrome with ocular manifestations.[11] Early diagnosis of a paraneoplastic syndrome is vital for detecting the underlying disease and eventually facilitating the appropriate treatment and follow-up.[12]

Posterior scleritis is usually associated with a systemic disease (infectious or autoimmune). In approximately 2 out of 3 cases with posterior scleritis, an underlying disease is not revealed. According to the current literature, several masquerade symptoms, such as lymphomas, can manifest with scleritis.[10,15,16] For instance, Hoang-Xuan et al.[10] reported a new masquerade syndrome presenting with features of mucosal-associated lymphoid tissue lymphoma associated with choroidal white dots

and scleritis. Similarly, Mohsenin et al.[16] described the case of a 53-year-old man with coexisting necrobiotic xanthogranuloma and chronic lymphocytic leukemia presenting with scleritis and uveitis. In both of these cases, scleritis occurred as a masquerade syndrome. To our knowledge, although malignant neoplasias can masquerade as posterior scleritis,[17,18,19] there is only one recorded case of scleritis presenting in the context of a paraneoplastic syndrome.[4] Therefore, our case is unique because posterior scleritis as a paraneoplastic syndrome has not been described until now. In particular, there are no available reports of patients with colon cancer developing posterior scleritis.

Individuals with scleritis must be evaluated by means of a detailed medical history, ocular performance, and general physical examination, as well as appropriate laboratory and imaging investigations. A correct and rapid diagnosis of scleritis can halt the progression of topical and systemic disease, thus preventing destruction of the globe while prolonging survival and improving quality of life. In patients with posterior scleritis, especially older adults, the possibility of paraneoplastic syndrome due to a malignant neoplasia must not be ignored or underestimated.

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Informed Consent: This study does not involve interventions on humans or experimental studies on animals. Informed consent was obtained and is available upon request.

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Surgical and Medical Practices: C.K., M.M., Consept: C.K., Design: D.K., K.K., Data Collection or Processing: C.K., D.K., K.K., Analysis or Interpretation: C.K., M.M., Literature Search: D.K., K.K., Writing: D.K., K.K.

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Case Report

Cryptic Myiasis by *Chrysomya bezziana*: A Case Report and Literature Review

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Abstract

Myiasis is the invasion of living animal tissue by fly larvae. Orbital tissue infestation involvement occurs in 5% of all myiasis cases and is potentially destructive. Infection by *Chrysomya bezziana* is very rare in clinical practice. A 65-year-old woman with history of left eye evisceration presented to the emergency department due to a creeping sensation in the left eye socket and underwent medical and surgical treatment for *C. bezziana* ophthalmomyiasis. A systematic review was performed to identify ophthalmomyiasis cases caused by *C. bezziana* published in PubMed and Embase until December 2019. *C. bezziana* can cause major destruction to both vital and non-vital tissues. It should be treated promptly to prevent extensive damage and life-threatening conditions. This report provides an overview of the epidemiology, causes, risk factors, diagnosis, and treatment options that could assist clinicians in diagnosis and management of this condition.

Keywords: Anemia, *Chrysomya bezziana*, ophthalmomyiasis, orbital myiasis

Introduction

Myiasis is defined as the infestation of living tissues of humans and other animals by eggs or larvae of flies of the Orthopoda order Diptera. The parasites that most commonly affect the eye and orbit are the larva of *Hypoderma bovis* (hornet fly), *Oestrus ovis* (sheep botfly), and rarely, *Chrysomya bezziana,* which is an obligate parasite also known as the Old World screwworm.[1] Orbital involvement occurs in approximately 5% of all the cases of myiasis.[2] Human myiasis caused by *C. bezziana* was first reported in 1909 in India.[3] *C. bezziana* myiasis has been largely neglected and is a serious medical condition, though it has not been reported very frequently in humans.[4] *C. bezziana* infestation differs from typical maggot infestations as it can occur in the absence of existing necrotic tissue and cause extensive damage to living tissue, as in the case reported herein. The condition can even result in death if left undiagnosed.

Case Report

A 65-year-old housewife presented to the emergency department with complaints of fever along with pain, redness, watering, and swelling of the left upper eyelid for the past 2 days, followed by a crawling sensation with maggots coming out of the socket. Her history included evisceration of the left eye due to perforated corneal ulcer, but there was no history of recent trauma or lesions in the involved area, chronic systemic disease, prolonged use of medications, or progressive loss of weight or appetite.

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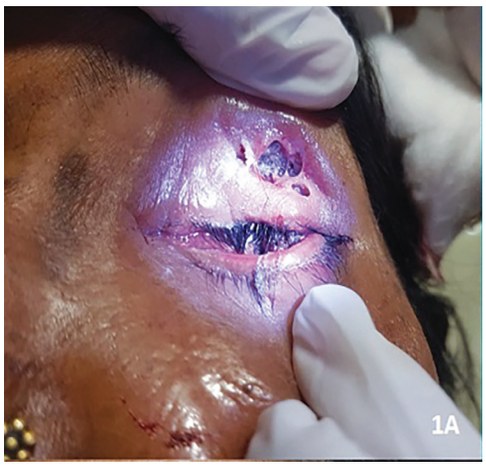
On examination, the best corrected visual acuity in her right eye was 20/60. It was pseudophakic with quiet anterior segment and unremarkable posterior segment. On the left side, severe periorbital edema and the eviscerated socket with severe conjunctival congestion and bloody discharge were observed. The upper and lower lids were inflamed and had defects filled with ulcerated necrotic tissue along with blood-stained discharge. Motile white maggots with black fronts were seen crawling in the defects (Figure 1A). They were photosensitive and tried to retract deeper inside in response to light.

On general examination, the patient was emaciated and malnourished (body mass index=18 kg/m^2). She was well oriented with normal vital signs. On further examination, stiffness of the interphalangeal joints of the hand and feet causing swan neck deformity of the fingers was observed (Figure 1B).

Computed tomography (CT) scan of the paranasal sinuses and orbit was unremarkable (Figure 2). An array of investigations was ordered. Her hemoglobin level was 7.653 g/dL with erythrocyte sedimentation rate of 35 mm/hour. Rheumatoid factor was positive, C-reactive protein (HS) level was 81 mg/dl, and intact parathyroid hormone level was 161 pg/ml. The peripheral blood smear showed normocytic normochromic to microcytic hypochromic with presence of tear drop cells. The rest of the blood reports were unremarkable.



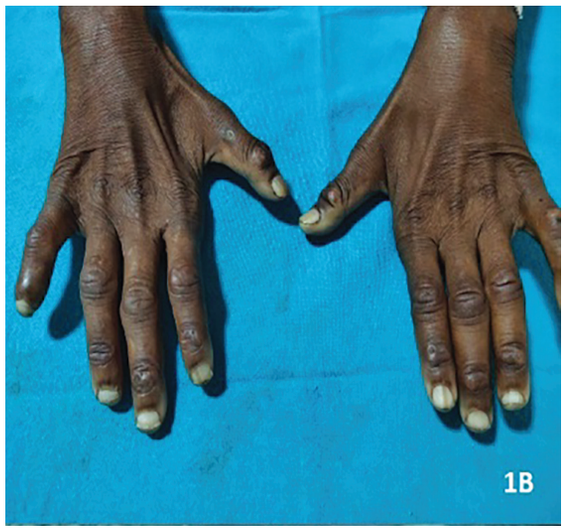


Figure 1. A) Initial presentation with myiasis, B) Swan neck deformity

The patient was diagnosed as having rheumatoid arthritis, microcytic hypochromic anemia with eosinophilia, hypothyroidism, and massive ophthalmomyiasis of the eviscerated socket. She was started on intravenous amoxicillin and clavulanic acid 1.2 g 3 times a day along with oral anti-inflammatory and antacid drugs. Oral albendazole 400 mg once daily was also given for 3 days, which was repeated after 1 week. Considering the wound and sparing of the sinuses and central nervous system on CT scan, topical proparacaine (anesthetic agent) was instilled into the left socket followed by turpentine oil packing, which immobilized the larvae. After 15 to 20 minutes, the larvae were gently removed with forceps (Figure 3A). This procedure was repeated once more. However, some larvae were deeply buried and not amenable to manual removal. Therefore, surgical exploration under local anesthesia was done. Topical moxifloxacin 0.5% drops and ointment were started in the left socket. Wound wash with diluted 3% hydrogen peroxide followed by dressing with 5% povidone-iodine was carried out twice daily under all aseptic precautions. More than 125 larvae were removed in total.

Based on her physical findings and laboratory reports, the patient was started on oral thyroxine sodium (0.25 mg) per day along with multivitamins, hematinic, and protein supplement. On follow-up at 6 weeks, a healed socket (Figure 3B) with improvement in general condition was noted and repeated blood investigations showed a better profile.

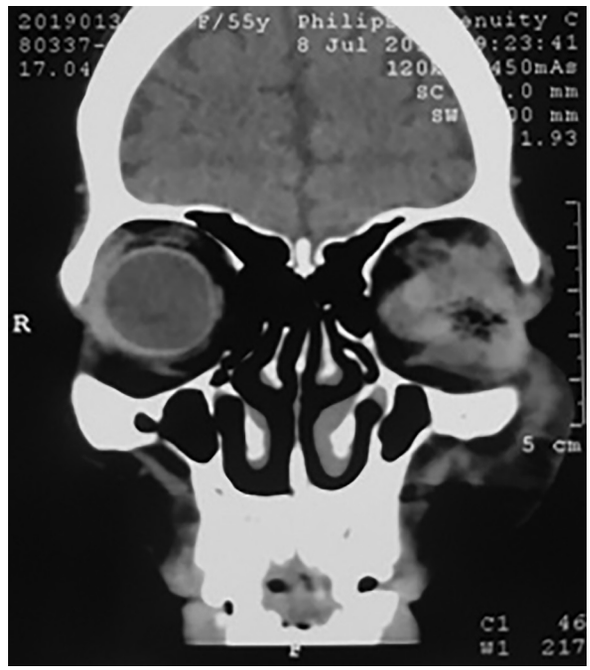


Figure 2. CT scan of the orbit and head

CT: Computed tomography

A specimen was preserved in 10% formalin and sent to the microbiology department. The larvae were creamy in color with cuticular spines (Figure 4a). They varied in size from 5 to 15 mm due to different stages of presentation. They had strong, robust mouth hooks (Figure 4b), with 4 to 6 papillae on the anterior spiracles. A pigmented dorsal tracheal trunk was noted in the terminal twelfth larval segment. Based on these findings they were confirmed to be larvae of *C. bezziana.*

Literature Review

A systematic literature review was performed through a search of the PubMed and EMBASE electronic databases to identify all articles related to human orbital myiasis published until December 2019. References from relevant articles were also included. The search strategy was based on an advanced search with the following terms: "*Chrysomya bezziana*" OR "ophthalmomyiasis", "*Chrysomya bezziana*" AND ophthalmomyiasis, "*C. bezziana*" AND "ophthalmomyiasis", "*Chrysomya bezziana*" AND orbital myiasis, "*C. bezziana*" AND "orbital myiasis". Only articles written in English were included. After screening the references, no articles needed to be added.

A total of 204 articles on ophthalmomyiasis in humans were found, in which only 16 cases were reported to be caused by *C. bezziana*. Two case reports had no abstract; information regarding one of these cases was obtained by contacting the author by email and was included in Table 1, and one case was a repetition. On thorough review of the literature, a total of 14 cases attributed to *C. bezziana* were identified (Table 1).[5,6,7,8,9,10,11,12,13,14,15,16,17,18,19]

Figure 3. A) Maggots emerging after application of turpentine oil, B) Healed socket after 6 weeks

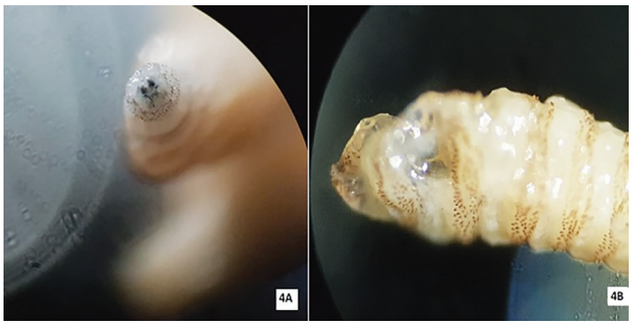


Figure 4. A) Cuticular spines of larva, B) Larva under microscope

Discussion

Epidemiology

Chrysomya bezziana is distributed in about 63 countries in the tropical and subtropical regions of South Asia, Africa, and the Middle East.[20,21] Cases of ophthalmomyiasis by *C. bezziana* have been observed mainly in India, China (Hong Kong), Iran, Saudi Arabia, Malaysia, and Indonesia, where the climatic conditions are hot and humid.[4]

C. bezziana belongs to the order Diptera, family Calliphyridae, and suborder Cyclorrhpha. There are 12 species in the genus *Chrysomya*. In the literature, most of the species cause myiasis in animals; only *C. bezziana* and *Cochliomyia hominivorax* have been implicated in ophthalmomyiasis in living humans. Humans act as an accidental host, but infections are rarely reported.[22]

Risk Factors

It is mainly seen with overcrowded conditions, poor sanitation, and poor personal hygiene and in immunocompromised individuals. Chronic debilitating conditions such as diabetes mellitus, fungating carcinomas, psychiatric illness, intellectual disability, hemiplegia, open wounds, use of immunosuppressive agents, poverty, rural background, and neglect may predispose individuals to myiasis.

Life Cycle

The adult *Chrysomya* fly is green or blue-green in color. Adult females lay approximately 150–200 eggs at a time on exposed wounds or the mucous membranes of the mouth, ears, and nose. After 24 hours, the eggs hatch and the larvae burrow deep into living tissue in a screw-like fashion, invading host tissues using their sharp mouth-hooks and anchoring with intersegmental spines. The larvae then undergo developmental changes (3 stages of instar) and complete development while feeding on host tissue for 5-7 days. Thereafter, they fall to the ground and pupate, which is temperature-dependent. Sexual maturation occurs in approximately 1-8 weeks. Thus, the life cycle is completed in about 12 weeks.[23,24]

Presentation

Common presenting features are swelling, itching, ulcer, blood-stained discharge, pain, crawling sensation, and sometimes maggots coming out of the wound. Overall, the presentation varies from minor itching to complete destruction of the globe with apparent myiasis. Early identification and management is very important, as the larvae cause local destruction and inflammation as well as spread deeper into the tissue, potentially extending into the nose, lacrimal gland, paranasal sinuses, and even the brain.

Diagnosis

Entomological evidence for the species is the gold standard for identification. The larvae are killed by immersion in near boiling water (90-100°C) for 30 seconds before being preserved in 70% to 95% ethanol.[25] The anatomical features of *C. bezziana* larvae can be used for initial identification: the body shape, body surface with prominent bands of thorn-like spines,

Table 1. Details of literature included in the review

Author	Date	Location	Age/ sex	Eye	Presentation	Risk factors
Present study	2020	India	65/F	OS	Ulcer, swelling, blood stained discharge, obvious maggots crawling out	Rural background, neglect, multiple ailments (anemia, rheumatoid arthritis, hypothyroidism)
Kersten et al.[5]	1986	Saudi Arab	65/M	OS	Orbital soft tissue swelling and proptosis with multiple cutaneous ulcerations	Rural background, trauma, hemiparesis and diminished mental status
Sachdev et al.[6]	1990	India	80/F	OD	Ulcer over lid with blood-stained discharge	Endophthalmitis after lens extraction
Verma et al.[7]	1990	India	61/M	OS	Secondary infection after herpes zoster ophthalmicus (HZO)	Rural background, farmer
David et al.[8] (details acquired through contact with author)	1995	India	47/F	OD	Swelling with pus on right eye medial canthus (lacrimal abscess), atrophic rhinitis	Non-Hodgkin's lymphoma
Radmanesh et al.[9]	2000	Iran	90/F	OD	Swelling, purulent and hemorrhagic discharge	Dementia, neglect, basal cell carcinoma
Alhady et al.[10]	2008	Malaysia	9/M	OD	Red eye	
Yaghoobi et al.[11]	2009	Iran	63/M	OS	Ulcer (left side of face involving left eye)	Lower socioeconomic level, neglect, squamous cell carcinoma
Yeung et al.[12] / Lui et al.[13]	2010/ 2005	Hong Kong	90/F	OD	Periorbital swelling, erythema and blood-stained discharge	Squamous cell carcinoma, bed-bound, COPD, old tuberculosis, aspergillosis, and dementia
Khataminia et al.[14]	2011	Iran	87/F	OS	Severe left ocular pain, swelling	Bedridden, previous eye lid surgery, apparently some type of skin cancer?
Nene et al.[15]	2015	India	42/F	OD	Swelling, itching, and blood-stained, foul-smelling discharge from the wound	Minor injury, neglect, poverty, a nd poor hygiene
Kalamkar et al.[16]	2016	India	65/F	OD		Rural background, history of skin cancer
Berenji et al.[17]	2017	Iran	55/F	OD	Presence of larvae for months and eye pain	Rural background, neglect, recurrent basal cell carcinoma
Lubis et al.[18]	2019	Indonesia	55/F	OS	Breathing difficulties and drooping of the left eyelid	Uncontrolled diabetes mellitus
Nabie et al.[19]	2019	Iran	75/M	OS	Tumor extension into orbit with intermittent pain	Poverty, neglect, squamous cell carcinoma

M= Male, F = Female, OD: Right eye, OS: Left eye, IV: Intravenous, COPD: Chronic obstructive pulmonary disease

papillae, spiracles (posterior and anterior), dorsal tracheal trunks, mouth hooks, and cephalopharyngeal skeleton.[23,24] Another method is by rearing the larvae to adults for the morphological identification using the adult taxonomic keys.[24]

Treatment

The larvae exhibit negative phototaxis due to photoreceptors on their anterior end, and they try to move away from light by burying deeper into the tissue. Forceful removal may result in incomplete removal and retention of larval tissue, leading to granulomatous inflammation and calcification.[26] Therefore, immobilization with ocular paralytics using topical anesthetic agents (cocaine 4-5% solution, lidocaine, pilocarpine 1-4%, proparacaine hydrochloride 0.5%) have been reported to be effective.[27,28] In spite of paralysis, larvae may adhere to the tissue with their hooks, so various suffocating agents (liquid paraffin, petroleum jelly, beeswax, adhesive tape, pork fat, glue, turpentine oil) and ophthalmic ointments (neomycin, bacitracin, and polymyxin B) are used for successful mechanical removal. Larvicidal agents such as hydrogen peroxide and isopropyl alcohol can also be used. Mechanical removal can be done with the help of jewelers or any other non-toothed forceps under aseptic conditions. Sometimes, the larvae are very deep or damage to the globe is so extensive that mechanical removal is not possible. In such cases, surgical intervention ranging from surgical debridement to complete exenteration of the globe is recommended.

Table 1 contiuned

Author	Number of larvae	Treatment given	Outcome	Comment
Present study	>125	Turpentine oil, proparacaine, manual removal, irrigated with hydrogen peroxide, surgical intervention, albendazole, IV antibiotics	Healed in 5-6 weeks	Eviscerated socket
Kersten et al.[5]	Numerous	IV antibiotics, exenteration	Healed	Secondary infection with *Pseudomonas aeruginosa*
Sachdev et al.[6]	~70	Turpentine, xylocaine, irrigated with hydrogen peroxide, manual removal, IV antibiotics	Healed	Immunocompetent host
Verma et al.[7]	Not known	Manual removal of maggots along with treatment of HZO	Healed	
David et al.[8] (details acquired through contact with author)	>50	Manual removal along with surgical removal by lateral rhinotomy	Postoperative sinocutaneous fistula on the rhinostomy wound. Patient died of septicemia and multiple organ failure	Histopathological examination of tissue specimen revealed Non-Hodgkin's lymphoma. Chemotherapy and radiotherapy were also given.
Radmanesh et al.[9]	Numerous	Orbital exenteration	Not mentioned	
Alhady et al.[10]	1	Manual removal	Healed	Simultaneous otomyiasis treated with surgical intervention
Yaghoobi et al.[11]	70	Antibiotics, manual removal		Known case of facial squamous cell carcinoma involving the medial canthus
Yeung et al.[12] / Lui et al.[13]	Numerous	Orbital exenteration	Postoperative exacerbation of COPD and fast atrial fibrillation. The patient died of acute infarct	
Khataminia et al.[14]	>150	Orbital exenteration	Healed	Tetanus toxoid was given
Nene et al.[15]	26	Mechanical debridement, medical management	Healed	Immunocompetent patient
Kalamkar et al.[16]	12	Turpentine oil, xylocaine, manual removal, IV antibiotics, ivermectin	Healed	Anophthalmic socket
Berenji et al.[17]	Numerous	Manual removal with surgical intervention (tissue removal), rest not mentioned	Healed	Secondary ophthalmomyiasis
Lubis et al.[18]	50	Manual removal, IV antibiotics, nasal endoscopy for nasal myiasis, insulin	Healed	Massive orbital myiasis arising from nasal myiasis
Nabie et al.[19]	Not known	Only irrigation of the site with normal saline	Lost to follow-up	

M= Male, F = Female, OD: Right eye, OS: Left eye, IV: Intravenous, COPD: Chronic obstructive pulmonary disease

Along with this, the use of systemic broad-spectrum antibiotics such as amoxicillin with clavulanic acid, metronidazole, and cefazolin is indicated to prevent secondary bacterial infections, and antihelminthic drugs such as ivermectin[16] and benzimidazoles like albendazole and mebendazole are recommended.

It is imperative to treat the underlying cause along with the primary treatment. Cases of orbital myiasis have been reported in immunocompetent patients,[6] and also in cutaneous malignancies like squamous cell carcinoma[12,13,19] and basal cell carcinoma.[9,17] The association with a malignant tumor can be due to the presence of ulcerated and necrotic lesions that are exposed to the environment. The eggs may also be transferred by the patient as a result of scratching.[29]

Myiasis by *C. bezziana* is overall a destructive and rapidly progressing infestation which can also be seen in healthy tissues. For massive ocular myiasis, as reported herein, early intervention is needed to prevent mortality, due to the proximity of the brain and the possibility of intracranial invasion from the orbital apex, which renders this a potentially life-threatening condition. Poor hygiene, rural background, and emaciated condition along with multiple underlying illnesses and neglect were the probable cause of the infection in our patient.

Public awareness of this infestation is needed to encourage personal hygiene and cleanliness. Wound exudates and their odor can attract gravid females to lay eggs on a host, so any open lesions should be kept clean and properly dressed, especially cancerous lesions. Also important is maintaining a clean environment and surroundings with proper disposal of garbage, which attracts flies. Better education and prompt medical services for the community along with improved living conditions are needed for its control.

Informed Consent: Informed consent was obtained from the patient for publication of this report and any presented images.

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Authorship Contributions

Surgical and Medical Practices: A.S., Concept: R.R., A.A., Design: R.R., Data Collection or Processing: R.R., A.S., S.P., H.U., Analysis or Interpretation: A.S., P.G., A.A., Literature Search: R.R, A.S., S.P., H.U., Writing: R.R, A.S., S.P., P.G., H.U., A.A.

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Case Report

Progressive Visual Loss Without Retinal Detachment in Stickler Syndrome: An Uncommon and Novel Presentation

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Abstract

Stickler syndrome is known to cause visual handicap due to the high incidence of retinal detachment. We aim to present an unusual case of a child with Stickler syndrome who had progressive visual loss secondary to atrophy of the outer retinal layers not associated with retinal detachment. This is a descriptive case report of a 9-year-old child with ocular history of high myopia who presented to our institution with suboptimal visual acuity in both eyes. After 2 years of follow up, he developed unilateral progressive visual loss with marked atrophy of the outer retinal layers and peripheral vascular leakage. Such a presentation has not been previously described in the literature to the best of our knowledge.

Keywords: Stickler syndrome, myopia, retinal atrophy

Introduction

Stickler syndrome is a hereditary connective tissue disorder associated with ocular, orofacial, musculoskeletal, and auditory manifestations. It is the most common inherited vitreoretinopathy, estimated to affect 1 in 7,500 to 9,000 newborns.[1]

Mutations in several genes cause the different types of Stickler Syndrome. The autosomal dominant types are Stickler type I, which is due to a mutation in *COL2A1* and accounts for 80-90% of cases; Type II, which is caused by mutation in *COL11A1* and accounts for 10-20% of cases; and Type III, which occurs due to a mutation in *COL11A2* and is characterized by non-ocular manifestations. The autosomal recessive types include Stickler type IV and V with mutations in the *COL9A1* and *COL9A2* genes, respectively.

The most common ocular manifestations are high myopia and vitreous syneresis (100% of patients). Stickler type I is characterized by membranous vitreous and type II by beaded, fibrillar vitreous.[2] Vitreous veils attached to the retina, radial perivascular atrophy, and retinal lattice degeneration are also common. Retinal detachments secondary to anterior giant retinal tears or posterior breaks are common, as well as pre-senile cataract.[3]

We present the case of a boy with high myopia and progressive visual loss not related to retinal detachment. After an exhaustive investigation including whole exome sequencing

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(WES), Stickler syndrome type I was diagnosed, with unusual ophthalmological findings not previously described in the literature.

Case Report

A 9-year-old patient was referred to our clinic due to suboptimal visual acuity. He had ocular history of high myopia, as did his father and grandfather.

At presentation, logMAR best corrected visual acuity (BCVA) was 0.48 in the right eye (RE) and 0.18 in the left eye (LE). The refraction was RE -7.50 -1.00 x180 and LE -7.50 -0.75 x180. On eye examination, the anterior segments were normal and the vitreous was quiet, with a vitreous strand overlying the superotemporal retina in the LE. The retina was flat with fine macular and perivascular pigmentary changes (RE more than LE).

Figure 1 summarizes additional test findings including spectral domain optical coherence tomography (SD-OCT) and fluorescein angiography (FA). Bilateral foveal hypoplasia was noted with attenuation of outer retinal bands in the RE and hyperfluorescence in the macular areas bilaterally. Electroretinogram (ERG) showed nonspecific decreased mixed cone-rod response.

Two years later, BCVA had decreased considerably to 1.0 logMAR in his RE and remained stable in his LE. During this examination there was evidence of bilateral marked vitreous syneresis with membranous formations. There were no vitreous cells and retinal findings remained unchanged. Repeated FA showed leakage from the peripheral vessels in the RE and focal areas of capillary nonperfusion. Fundus autofluorescence showed areas of hypoautofluorescence in the posterior pole. SD-OCT demonstrated total loss of the ellipsoid zone and marked atrophy of the outer retinal layers in the RE. The LE remained stable. Swept source OCT-angiography showed no abnormal vascularization (Figure 2). Repeated ERG examination evidenced worsening of cone-rod function.

The child was referred for genetic testing. WES revealed a frame-shift pathogenic variant (c.2807_2810dupGCCC; p.Gly939ProfsTer6) in exon 42 of the *COL2A1* gene, which suggested the diagnosis of Stickler syndrome type I. His parents were tested by Sanger sequencing for the genetic variant and were not found to carry the variant, indicating that it occurred as a de novo mutation in the child. WES was repeated by a laboratory specialized in inherited retinal diseases in order to rule out additional mutations that can explain a retinal dystrophy in this child, but no other mutations were identified.

The original anamnesis reported that the child was born with bifid uvula, and also described some mild orthopedic problems. Physical examination by a clinical geneticist following genetic tests results showed very subtle signs of malar hypoplasia with retromicrognatia and crowded teeth, bifid uvula and high arched

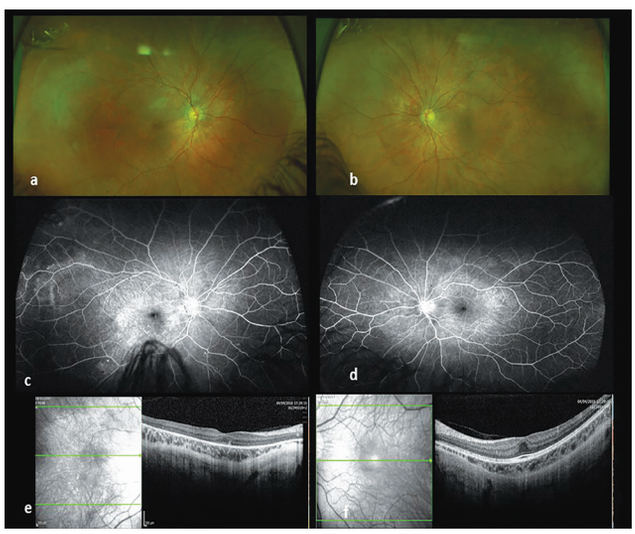

Figure 1. Auxiliary tests at presentation. a, b) Color fundus images (Optos 200 Tx, Optos PLC, Dunfermline, United Kingdom) of the right and the left eye respectively show prominence of the choroidal vessels around the optic discs and in the macular areas. c, d) Fluorescein angiography (Optos 200 Tx, Optos PLC, Dunfermline, United Kingdom) showed an area of hyperfluorescence around the optic discs and in the macular areas in both eyes and in the temporal peripheral retina of the right eye. e, f): Spectral domain optical coherence tomography (SD-OCT, Heidelberg Engineering, Heidelberg, Germany) showed an irregular area of the retinal pigmented epithelium in the right eye with attenuated outer retinal bands and decreased foveal pit bilaterally. Central macular thickness: 214 µm right eye; 295 µm left eye

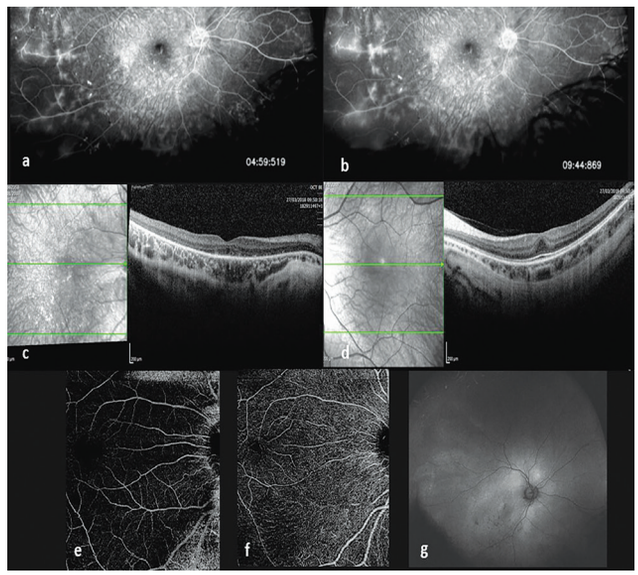

Figure 2. Auxiliary tests 3 years later. a, b) Fluorescein angiography of the right eye showing leakage of the temporal peripheral vessels and some mottling in the nasal peripheral retina. c, d) Spectral domain optical coherence tomography (SD-OCT) of the right and left eye respectively shows total disruption of outer retinal bands and atrophy of outer nuclear layer in the right eye. SD-OCT of the left eye shows foveal hypoplasia; no atrophy of the outer retinal bands was observed. Central macular thickness: 198 µm right eye; 292 µm left eye. e, f) OCT-angiography (AngioPlex Elite 9000, Carl Zeiss Meditec, Inc., Dublin, USA): superficial capillary plexus and deep capillary plexus were within normal limits. Choroidal thickness at the fovea in the right eye was 227 µm (1000 µm temporal: 182 µm, 1000 µm nasal: 221 µm, and maximal choroidal thickness was at 3000 µm temporal to the fovea, measuring 276 µm). In the left eye, choroidal thickness at the fovea was 175 µm (1000 µm temporal: 190 µm, 1000 µm nasal: 174 µm, maximal choroidal thickness was also at 1000 µm temporal to the fovea, 190 µm. g) Fundus autofluorescence of the right eye shows increased autofluorescence around the optic disc and tiny areas of hypoautofluorescence at the posterior pole

palate, and camptodactyly of the fifth finger. These findings supported the diagnosis of Stickler syndrome.

Discussion

Stickler Syndrome is a rare hereditary connective tissue disease. Clinical manifestations and targeted genetic testing are generally sufficient to reach a diagnosis. Most cases are inherited via autosomal dominant inheritance, while a minority of cases result from de novo mutations, as in our case.[4] Non-ocular findings can include incomplete palate, which ranges from open cleft, submucous cleft, to bifid uvula like in our case. Hearing loss, joint hypermobility, and other skeletal manifestations are also seen.[3,5]

When systemic signs are not evident, ophthalmologists play a major role in the diagnosis. This occurs especially in cases of mutations in exon 2 of the *COL2A1* gene that can produce a phenotype with predominantly ocular manifestations.[1,6] The majority of patients presenting to an ophthalmologist will have either type 1 or type 2 Stickler syndrome and are frequently high myopes.[7]

Our patient presented with progressive disruption of the outer retinal layers leading to visual loss in one eye. Peripheral vascular leakage (retinal capillaritis) and possible thick choroid were also detected. These changes have not been previously described in Stickler syndrome and may be the result of mild vascular changes. Retinal capillaritis has been previously described in the setting of CRB1-associated retinal dystrophy; the authors suggested that capillaritis may be due to the active phase of the disease in young patients, although the influence of modifier genes could not be excluded.[8]

Our patient also presented with radial perivascular pigmentary degeneration which is known to be a characteristic manifestation of Stickler that develops in childhood and progresses with time.[2,6] Abnormal ERG with progressive abnormalities of cone-rod function was seen in our patient and has already been described in Stickler Syndrome.[1]

Our patient also presented with bilateral foveal hypoplasia, with good vision in the LE. Recently, foveal hypoplasia has been associated with Stickler syndrome.[9,10] In 2018, Matsushita et al. studied the degree of foveal hypoplasia in patients diagnosed with Stickler syndrome type I and found that 82% of the subjects had mild foveal hypoplasia with persistence of the inner retinal layers in the fovea in OCT images.[9]

Foveal hypoplasia had not been commonly reported in patients with Stickler syndrome probably because these patients have fairly good visual acuity.[11] Recent advancements and accessibility of high-resolution OCT imaging have shown that a lack of foveal pit does not always indicate poor visual acuity.

Visual loss and blindness in children with Stickler syndrome has classically been related to the presence of retinal detachment.[2,11] In our case, there was progressive visual loss secondary to total loss of the ellipsoid zone and outer retinal layer atrophy without retinal detachment, not previously described in Stickler cases. Other possible additional diagnoses such as posterior uveitis, infection, and retinal dystrophy were ruled out, raising the suspicion that this retinal atrophy was not a coincidental finding but a potential Stickler-related ocular manifestation not previously reported.

WES is a useful tool that assists ophthalmologists in reaching the correct clinical diagnosis and ruling out additional genetic pathology in complex cases.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

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Letter to the Editor: "Dry Eye Disease after Cataract Surgery: Study of its Determinants and Risk Factors"

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Dear Editor,

This letter is regarding the article titled "Dry Eye Disease after Cataract Surgery: Study of its Determinants and Risk Factors".[1] We read this article with great interest and thank the authors for providing an excellent demonstration that phacoemulsification and small-incision cataract surgery can cause dry eye. The authors included in this study patients that pre-surgery were completely asymptomatic and without clinical dry eye signs and this study exhibits that the elements of the surgery itself indeed were the cause of dry eye development, which peaked one week post-surgery and subsided around one month post-surgery. It was apparent the authors appreciate the importance of eliminating the patients with dry eye from this study and their workup was thorough. We would like to stress the importance of treating those with clinical signs with or without symptoms prior to surgery, as an unstable tear film can profoundly undermine a successful outcome, for example, by affecting keratometry and topography readings and consequently the calculation of the intraocular lens.[2] One important element to add to the risk factors that was not mentioned, are the lid retractors that are utilized during surgery. Ptosis is a well-documented possible post-surgery complication caused by a number of factors including anesthesia myotoxicity and use of a lid speculum.[3] Studies have noted a lower lid laxity for up to three months after phacoemulsification,[4] particularly relevant over age 70 but important to mention considering the age group of this study as well. These retractors can slightly change the position of the lower lid, which potentially affects proper blink. The lower punctum's location moves slightly anteriorly, which potentially influences tear film and drainage. These temporary and sometimes permanent alterations can directly impact dry eye development. Considering the high presentation of dry eye postoperatively, we agree with the authors that the addition of topical lubrication would be helpful. Perhaps in cases with clinical signs, even if asymptomatic, an additional consideration would be to preemptively suggest treatment to improve the tear film prior to surgery with recognized therapies such as topical cyclosporine, which has been shown to improve visual acuity and contrast sensitivity in post cataract surgery patients with multifocal intraocular implants.[5]

Keywords: Dry eye disease, cataract surgery

Peer-review: Internally peer reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Letter to the Editor

Comment on: "Artificial Intelligence and Ophthalmology"

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To the Editor

In response to the article titled "Artificial Intelligence and Ophthalmology" published in your esteemed journal, which is a well thought of and written paper, I would like to raise a few points regarding this study. The article discusses developments and potential practices regarding the use of artificial intelligence in the field of ophthalmology, and the related topic of medical ethics.[1]

The development of artificial intelligence algorithms requires a large number of ophthalmic images to be developed. The effectiveness of the algorithm after being developed needs to be validated in clinical trials with a different database than the one used for training the algorithms, thereby evaluating the reliability and efficiency of the algorithm. Bearing in mind that the standard of effectiveness of the algorithms varies between studies, it is difficult to compare algorithms with each other.[2] Regarding ethical aspects, it is important that patient privacy rules are respected when sharing data between the research centers that develop the algorithms, which must generate the data anonymously.

Diseases such as diabetic retinopathy, macular degeneration, glaucoma, and retinopathy of prematurity are prevalent diseases that have a large amount of data stored in large study centers. However, rare eye diseases such as retinal dystrophies have greater difficulty in creating artificial intelligence algorithms, as they do not have much stored data.

The creation of algorithms can reduce diagnostic errors and facilitate the monitoring of ophthalmological diseases in regions that do not have an adequate number of ophthalmologists.[3]

Concerning ethical aspects, the bias in data collection can affect the generalization of the model trained for use in the population. Studies in different populations can minimize these problems.

In this way, algorithms have the potential to perform numerous tasks more quickly and efficiently than humans, such as data and information processing. However, they have limitations, such as the lack of perception of the social and psychological aspects of human nature that can eventually influence the diagnosis.

Keywords: Artificial intelligence, machine learning, deep learning, ophthalmology, medical ethics

Peer-review: Internally peer reviewed.

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

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Reply to Letter to the Editor

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Dear Editor,

First of all, we thank the author(s) for evaluating our article.[1] As the author(s) pointed out, we emphasized in our article that artificial intelligence will be of great usefulness for screening and rapid diagnosis in ophthalmology.

Artificial intelligence (AI) is divided into 3 groups based on capability: 1) Weak/Narrow/Simple AI (ANI), 2) Strong/General AI (AGI), and 3) Artificial Super Intelligence (ASI).[2] Here, possible ethical problems are solved by respecting the privacy of personal information and features that should be considered in the anonymization of information. Therefore, the serious ethical concerns regarding artificial intelligence are not related to the classification of massive photo data using simple/narrow artificial intelligence (ANI).

Medicine is a prominent field that has witnessed a nanotechnological revolution. However, due to the current views in philosophy and ethics, this emerging technology can be considered inconsistent or conflicting with what most ethicists in the area of medicine hold to be true. Nanotechnology and neuroscience are raising unavoidable questions concerning the ethical justification of human enhancement and intervention.[3]

The main ethical issues are related to the use of AI in general (AGI) and superintelligence (ASI) in particular. These two groups of AI need to be audited during their advancement, as they have the capacity to develop in a versatile and unpredictable direction. Providing safety measures to prevent any direct or indirect coercion can only be possible through continuous ethical evaluations and monitoring of technological development.[4]

Keywords: Artificial intelligence, machine learning, ophthalmology, medical ethics

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We would like to thank you for your contributions in "Turkısh Journal of Ophthalmology" by being as a reviewer and interest to our journal.

We wish you every success in your academic career.

Sincerely

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