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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/);

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EDITORIAL

2019 Issue 4 at a Glance:

In its fourth issue of 2019, the Turkish Journal of Ophthalmology is publishing six original studies, a review, and four case reports.

Kösekahya et al. evaluated corneal endothelial health in their controlled clinical study comparing 50 patients with gout and 50 healthy individuals. Because previous investigations of the cornea in gout have always focused on whether crystal deposition also occurs in the stroma, the significant changes in endothelial health reported in this study represent novel findings. The study demonstrated that corneal endothelial dysfunction tends to increase with disease duration and uncontrolled rise in uric acid levels in gout patients. This suggests that gout is not merely the accumulation of uric acid, but may also warrant consideration as a metabolic disease that accelerates ageing (see pages 178-182).

Soyugelen Demirok et al. report the 1-year follow-up results of glaucoma drainage implant in 6 patients with aniridia and medically refractory glaucoma. They recommended glaucoma drainage implantation as first-line surgical treatment in cases of aniridic glaucoma where intraocular pressure cannot be controlled with the maximum medical treatment. This concluding remark is a noteworthy recommendation, especially for younger patients (see pages 183-187).

Elangovan et al. report from India a series of 29 cases of ocular tuberculosis, which is extremely underreported due to deficiencies in diagnosis and treatment. The approximately 80% rate of favorable response of intraocular inflammation associated with ocular tuberculosis after 6 months of antituberculosis therapy suggests that better cooperation and interaction is needed between chest physicians and ophthalmologists (see pages 188-193).

In their study of eyes with cystoid diabetic macular edema, Yalçın and Özdek report that increased central foveal thickness and damage to the outer retinal layer increase the likelihood of macular ischemia. This is an interesting and exemplary study in that, as opposed to optical coherence tomography being only a tool for diagnosis and follow-up, it identifies parameters that can also be used as prognostic indicators (see pages 194-200).

Özdemir et al. performed pneumatic vitreolysis in 13 eyes of 12 patients with vitreomacular traction syndrome and achieved successful results in all cases. The authors recommend pneumatic vitreolysis as a primary approach because it is cost-effective, safer, and relatively easier compared to other surgical alternatives, and subsequent pars plana vitrectomy is always an option if the procedure is not successful (see pages 201-208).

Yaşar et al. determined that retinal tears and holes, which are believed to result from vitreoretinal traction, occur in patients with macular hole at a similar frequency as seen in the general population, and showed that the vitreous may have different pathologies in the anterior and posterior aspects of these diseases (see pages 209-212).

In this issue's review, Özmert and Arslan address one of the hottest topics in recent years-retinal prostheses and artificial vision-and share their experience with the Argus II implant. About 30% of the macular ganglion cell layer remains intact in retinal diseases that cause outer retinal degeneration, such as retinitis pigmentosa, choroideremia, and geographic atrophy. This enables the inner retinal cells to be stimulated with controlled electrical current by a microphotodiode array implanted subretinally or a microelectrode array tacked to the epiretinal region. However, the authors point out that in order for these stimuli to become visual information that will improve the patient's orientation, mobility, and quality of life, the patient must learn to interpret the phosphene sequences formed in the brain through special rehabilitation exercises. For diseases in which the ganglion cells and optic nerve are completely destroyed, implants that stimulate the lateral geniculate nucleus or occipital cortex offer hope for artificial vision (see pages 213-219).

Barut Selver et al. demonstrates the successful treatment of multiple drug-resistant P. aeruginosa-induced corneal abscess in a patient with Kaposi's sarcoma with the topical application of colistin, an antibiotic that ophthalmologists are not very familiar with. Colistin was abandoned many years ago due to its systemic side effects; however, this is not a problem with the use of ophthalmic topical preparations. Topical colistin appears to be both safe and effective in the treatment of resistant bacterial keratitis (see pages 220-223).

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EDITORIAL

Yazıcı et al. report that six cases of solitary neurofibroma without neurofibromatosis type 1 in the eyelid and conjunctiva have been described to date, with only one previously reported case of solitary neurofibroma originating from the eyelid tars. They present the second case in this issue (see pages 224-225).

Batıoğlu et al. publish the optical coherence tomography angiography findings of a 22-year-old patient with Best vitelliform macular dystrophy whose pregnancy was a contraindication for fluorescein angiography. Using optical coherence tomography angiography to visualize the neovascular network, the authors describe for the first time the coexistence of Best vitelliform macular dystrophy with pachychoroid neovasculopathy in this case report (see pages 226-229).

Hasanreisoğlu et al. present two cases of congenital toxoplasmosis with ocular involvement together with findings of retinopathy of prematurity accompanied by incomplete retinal vascularization, peripheral avascular regions, and retinal detachment. With these two cases, the authors draw attention to the possibility that retinopathy of prematurity and congenital toxoplasmosis can exist simultaneously with clinical presentations that mask one other, making it difficult to distinguish the cause of retinal detachment in such eyes (see pages 230-234).

We believe that our colleagues will benefit greatly from these studies and case reports that will raise substantial awareness in terms of rare and difficult-to-diagnose cases, predicting prognosis, and uncommon treatment options, as well as the review, which will serve as an important bedside reference on artificial vision.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

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Turk J Ophthalmol 2019;49:178-182

Original Article

Corneal Endothelial Morphology and Thickness Changes in Patients with Gout

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Abstract

Objectives: To investigate corneal endothelial cell density (ECD), morphology, and central corneal thickness (CCT) in patients with gout compared with healthy subjects.

Materials and Methods: Fifty eyes of 50 gout patients and 50 eyes of 50 healthy subjects without gout or any other systemic disease were included in this study. After detailed ophthalmologic examination, specular microscopy (Tomey EM-4000; Tomey Corp) measurement was performed for all participants. ECD, average cell area (ACA), coefficient of variation (CV), hexagonality ratio, and CCT values were recorded.

Results: Mean ECD and hexagonality ratio were lower (p=0.004 and p=0.002) and CV, ACA, and CCT values were higher (p=0.001, p=0.007, and p=0.001) in patients with gout when compared to healthy subjects. There were significant correlations between gout disease duration and CD and hexagonality ratio (p=0.019 and p=0.043) and also between uric acid value and hexagonality ratio and CCT (p=0.044 and p=0.003).

Conclusion: Altered corneal endothelial function was found in patients with gout when compared to healthy subjects and the alteration increased as gout duration and uric acid value increased.

Keywords: Gout, corneal endothelial cell density, corneal endothelial function, specular microscopy

Introduction

Gout is an inflammatory metabolic disorder characterized by the accumulation of monosodium urate (MSU) in the extracellular spaces, especially joints.[1] High uric acid levels (≥6.8 mg/dL) is the most important risk factor, and the condition is triggered by the precipitation of MSU crystals from oversaturated body fluid into the ligaments, soft tissues, and intraarticular space.[2] Its clinical characteristics include arthritis attacks, nephrolithiasis, nephropathy, and tophi.[3]

The global prevalence of gout has been reported as 1-4%.[4] In two prevalence studies conducted in Turkey, the prevalence of gout was found to be 0.02% in the Havsa region and 0.31% in the İzmir region.[5,6] Although the frequency of gout varies between societies due to genetic and cultural differences[7], its prevalence worldwide nearly doubled between 1990 and 2010.[8] This increase may be related to changes in eating habits and increasing obesity rates. There was a 3-fold increase in the number of academic studies on gout between 2005 and 2015.[9]

Ocular tophi have been demonstrated in the lateral canthus, upper eyelid, orbit, iris, anterior chamber, subconjunctival space, and cornea.[10] Uric acid deposition in the cornea was confirmed by polarized light microscopy in two case reports.[11,12]

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Good visual acuity requires a transparent cornea, and a transparent cornea requires healthy endothelial function and healthy stromal layer organization.[13] Measurement of corneal transparency can be done using corneal densitometry analysis. In one of our previous studies, we evaluated corneal densitometry in gout patients and found increased corneal densitometry values indicating reduced corneal transparency in gout patients compared to healthy individuals.[14] Tekin et al.[15] demonstrated a correlation between corneal densitometry analysis and corneal endothelial morphometry in healthy corneas and stated that corneal densitometry may be an indicator of endothelial health.

Reduced corneal transparency in gout patients may be a result of uric acid accumulation in the stroma or endothelial dysfunction. Therefore, in this study we aimed to investigate corneal endothelial cell density, morphology, and central corneal thickness in gout patients compared to healthy individuals.

Materials and Methods

This prospective study was conducted in accordance with the Declaration of Helsinki and legal regulations. All patients and healthy participants signed a written informed consent form approved by the local ethics committee (1151/2017).

Patients with gout were included in the study based on 2015 gout classification criteria from the American College of Rheumatology.[16] These criteria include clinical (joint/bursa involvement, characteristic symptomatic episodes), laboratory (serum uric acid levels, MSU crystals in the synovial fluid), and imaging findings.

Individuals with systemic diseases other than gout, such as diabetes mellitus, chronic kidney disease, heart disease, and cancer, and individuals using systemic drugs that may increase uric acid levels were excluded from the study. Individuals with history of intraocular surgery, trauma, uveitis, optic nerve disease, glaucoma, corneal scar and ectasia, contact lens use, or topical eye drop use were not included.

Fifty eyes of 50 patients followed for gout in the nephrology unit of the Dışkapı Training and Research Hospital and 50 eyes of 50 healthy individuals without gout or any other systemic diseases were included in the study. Disease duration and uric acid levels were recorded for the gout patients, all of whom were using low-dose colchicine (0.5-1.5 mg/day). Allopurinol was adjusted according to the patients' uric acid levels.

All patients and healthy individuals underwent best corrected visual acuity examination with Snellen chart, slit-lamp biomicroscopy examination, and fundus examination. Measurements of all patients were performed by the same technician using a noncontact specular microscope (Tomey EM-4000; Tomey Corp). All measurements were performed at least 3 times using the "center" method and at least 110 cells were included in each measurement. Endothelial cell density (ECD), average cell area (ACA), minimum cell area (CAmin), maximum cell area (CAmax), (SD) standard deviation of cell area, coefficient of variation in cell area (CV), hexagonal cell ratio (HEX), and central corneal thickness (CCT) were noted. Intraocular pressure (IOP) was measured using Goldmann applanation tonometry and corrected according to the Ehlers formula (corrected IOP = uncorrected IOP - [CCT - 520] x [5/70]).

Statistical Analysis

Although both eyes were examined, for statistical analysis one eye of each participant was selected by generating random numbers using Microsoft Excel software. Statistical analysis of the data was performed using SPSS 22.0 software (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics are expressed as mean ± SD. Categorical variables were compared using chi-square test. Independent-samples t-test was used to compare two groups. Correlations between gout duration and uric acid levels and endothelial morphometry were analyzed using Pearson correlation test. A p value <0.05 was considered statistically significant.

Results

Mean age was 59.12±7.50 years in the gout group and 59.92±7.45 years in the control group (p=0.59). There were 18 women and 32 men in the gout group and 27 women and 23 men in the control group (p=0.10).

The mean disease duration in the gout group was 79.05±62.39 (12–240) months. Mean uric acid level was 8.49±2.14 mg/dL in the gout group and 3.30±0.75 mg/dL in the control group (p<0.001).

Best corrected visual acuity values on Snellen chart were 0.89±0.11 in the gout group and 0.92±0.10 in the control group (p=0.15). Mean Goldmann IOP was 17.04±3.82 mmHg in the gout group and 15.05±3.33 mmHg in the control group (p=0.03), while mean corrected IOP values in the two groups were 14.44±2.57 mmHg and 14.26±2.60 mmHg, respectively (p=0.72).

The mean ECD and HEX values were lower in the gout group than in the control group (p=0.004 and p=0.002). CV, SD, ACA, CAmax, and CCT values were significantly higher in the gout group than in the control group (p=0.001, p<0.001, p=0.007, p=0.002 and p=0.001). CAmin was also higher in the gout group, but the difference was not statistically significant (p=0.176) (Table 1).

Gout duration was negatively correlated with ECD and HEX (r=-0.400, p=0.019 and r=-0.348, p=0.043, respectively). In addition, there was a significant negative correlation between uric acid level and HEX (r=-0.245, p=0.044), and a significant positive correlation between uric acid levels and CCT (r=0.355, p=0.003) (Table 2).

Table 1. Comparison of corneal endothelial and thickness values in gout patients and healthy controls			
	Gout group	**Control group**	**p value***
ECD (cell/mm^2)	2463.08±276.89	2638.41±200.52	**0.004**
SD	159.79±29.64	133.82±20.32	**<0.001**
CV	38.73±4.52	35.11±4.44	**0.001**
HEX (%)	45.00±5.73	49.26±5.35	**0.002**
CCT (µm)	540.79±39.50	512.15±29.28	**0.001**
ACA (µm^2)	412.26±58.86	381.14±29.02	**0.007**
CAmin (µm^2)	106.08±22.65	98.82±21.14	0.176
CAmax (µm^2)	1027.23±210.92	856.79±223.69	**0.002**

ECD: Endothelial cell density, SD: Standard deviation of cell area, CV: Coefficient of variation in cell area, HEX: Hexagonal cell ratio, CCT: Central corneal thickness, ACA: Average cell area, CAmin: Minimum cell area, CAmax: Maximum cell area, *Independent-samples t-test

Table 2. Analysis of correlations between corneal parameters and gout duration and uric acid levels		
	Gout duration	**Uric acid level**
ECD	**r=-0.400, p=0.019***	r=-0.201, p=0.100
CV	r=0.011, p=0.952	r=0.236, p=0.053
HEX	**r=-0.348, p=0.043***	**r=-0.245, p=0.044***
CCT	r=-0.313, p=0.072	**r=0.355, p=0.003***

ECD: Endothelial cell density, CV: Coefficient of variation in cell area, HEX: Hexagonal cell ratio, CCT: Central corneal thickness, *Pearson correlation analysis

Discussion

The corneal endothelium is a nonmitotic tissue that plays a crucial role in the maintenance of corneal transparency. Similar to vascular endothelial cells, the corneal endothelium acts as a barrier.[17] It maintains the equilibrium between aqueous humor flow into the stroma and pumping of aqueous humor from the stroma to the anterior chamber. The age-related decrease in endothelial cell number in a healthy cornea is compensated by increased Na,K-ATPase activity, which is the basis of endothelial pump function.[18] Increased endothelial permeability and inability of the metabolic pump to compensate for the influx leads to stromal thickening and initiates a process that later results in corneal edema.[19]

Specular microscopy is used for noninvasive imaging and morphological analysis of the corneal endothelium. ECD is the most commonly used parameter to determine endothelial function and is expressed as cell number per mm^2.[20] In addition to ECD, CV and HEX are often used to evaluate endothelial morphology and stability. CV is an indicator of variation in cell area and is an objective criterion of polymegathism. It is the ratio between the SD of ACA in the endothelial zone to ACA, and should ideally be below 30%. HEX is the ratio of hexagonal cells to those of other geometric shapes. Although the ideal ratio is 100%, it has been reported in the 60-70% range in studies of healthy patients.[21] CCT can be used as a marker that provides information about both the barrier and pump functions of the endothelium, and can be measured using specular microscopy.[20]

In a study including 380 gout patients, crystal deposits were detected in the corneas of 2 patients, located in the corneal epithelium in 1 case and the corneal stroma in the other.[22] In another study evaluating 69 gout patients, deposits were detected in the corneal stroma of 1 patient.[23] To the best of our knowledge, there are no studies in the literature that investigate the corneal epithelium in gout patients. In our study, gout patients had lower ACA and HEX values and higher CV and CCT values compared to healthy controls. These findings indicate that corneal endothelial functions are poorer in gout patients compared to age- and sex-matched healthy individuals.

In humans, the gene for urease, which is responsible for uric acid catabolism, is nonfunctional; as a result, overproduction or reduced excretion of uric acid leads to hyperuricemia.[24] The best known disease related to hyperuricemia is gout, although it has also been associated with systemic inflammation, cardiovascular diseases, hypertension, and endothelial dysfunction in the literature.[25,26,27] Hyperuricemia was shown to induce oxidative stress and inflammatory response, thus reducing nitric oxide release and causing endothelial dysfunction.[28] It was reported that ocular inflammation negatively affects corneal endothelial functions and increases corneal thickness, and in another study, corneal endothelial changes were even observed in Behçet's patients without ocular involvement.[29,30] Uric acid deposition

in the anterior chamber has been previously demonstrated in individuals with gout.[31] Uremic toxins can disrupt the balance between both proinflammatory and inflammatory factors and proapoptotic and apoptotic factors.[32] Disruption of the apoptotic equilibrium may accelerate apoptosis in endothelial cells that are in contact with uric acid in the anterior chamber,[33] and the higher apoptosis rate may explain the low ECD in gout patients.

While ECD and HEX decrease with longer duration of gout, HEX decreases and CCT increases with higher uric acid level. An in vitro study showed that Na,K-ATPase activity decreases in a dose-dependent manner in cells exposed to increasing doses of uric acid.[34] The longer a patient has been followed for gout and the higher their uric acid levels, the more corneal endothelial dysfunction they have. This shows the importance of close monitoring of uric acid levels in patients with gout.

Increased CCT is caused by corneal endothelial dysfunction and the subsequent increase in stromal hydration; increased stromal hydration is also important because it explains the decreased corneal transparency in gout patients shown in our previous study.[14] Another importance of CCT is that it impacts IOP values measured using Goldmann applanation tonometry, which is still the gold standard in IOP measurement.[35] IOP measurements obtained using this method may be incorrectly high in thick corneas and incorrectly low in thin corneas. In our study, Goldmann IOP was significantly higher in the gout group than the control group, whereas IOP values adjusted for CCT were similar in both groups. It might be useful to take the increase in CCT into consideration when interpreting IOP measurements in gout patients.

Colchicine is an alkaloid that exerts anti-inflammatory activity by disrupting intracellular microtubule and leukocyte function.[36] Colchicine has been detected in the tears of patients using systemic colchicine.[37] Because colchicine inhibits neutrophil migration and expression of adhesion molecules, it was claimed to delay the recovery of corneal epithelial damage.[38] While there are no studies on its direct effect on corneal epithelial cells, it is presumed to affect disease activity and the amount of inflammatory mediators and cytokines. These anti-inflammatory properties are expected to protect against uric acid damage rather than reducing corneal endothelial function, but in vitro studies are required to corroborate these hypotheses.

Study Limitations

A limitation of our study may be error caused by specular microscopic measurements. In order to minimize this error, all measurements were performed by the same technician and were repeated three times. Another limitation is the systemic drugs used by gout patients. All patients were using colchicine and allopurinol. There are no studies regarding whether these drugs affect the corneal endothelium. In vitro studies evaluating the effect of colchicine on the corneal endothelium may be beneficial. The effects of uric acid on the corneal epithelium should also be demonstrated with in vitro studies. Further research that includes laboratory analyses in larger patient series is needed.

Conclusion

Our study showed that in patients with gout, corneal endothelial dysfunction tends to increase with disease duration and uncontrolled uric acid levels. Uric acid deposition may disrupt endothelial stability and increase corneal thickness by reducing Na,K-ATPase pump activity. The effects of chronic hyperuricemia on the corneal endothelium should be taken into consideration when examining gout patients for potential complications and treating diseases that increase with age, such as cataract and glaucoma.

Ethics

Ethics Committee Approval: Ankara Numune Training and Research Hospital (approval no: 1151/2017).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Kemal Tekin, Kadir Gökhan Atılgan, Concept: Mustafa Koç, Cemile Üçgül Atılgan, Design: Pınar Kösekahya, Mustafa Koç, Data Collection or Processing: Kadir Gökhan Atılgan, Pınar Kösekahya, Analysis or Interpretation: Mehtap Çağlayan, Literature Search:Cemile Üçgül Atılgan, Yasin Şakir Göker, Writing: Pınar Kösekahya.

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Original Article

Short- and Long-term Results of Glaucoma Valve Implantation for Aniridia-related Glaucoma: A Case Series and Literature Review

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Abstract

Objectives: To report the results obtained from glaucoma drainage device (GDD) implantation in patients with aniridia-related glaucoma and to review the literature.

Materials and Methods: We retrospectively reviewed 6 patients who underwent GDD implantation for glaucoma secondary to congenital aniridia between April 2001 and February 2015. Data on age at surgery, gender, laterality, surgeries before GDD implantation, GDD model, concomitant ocular disorders, visual acuity, and intraocular pressure (IOP) values before and at 1 and 12 months after GDD implantation, medications, follow-up period, findings during last visit, complications, and course of disease were collected.

Results: Mean age at surgery was 16.00±12.31 years (range 5-37 years). Mean IOP was 33.00±12.11 (range 22-50) mmHg just before the GDD implantation with a mean of 3.5±1.2 medications. Mean IOP 1 month after implantation was 16.33±4.22 (range 12-24) mmHg with a mean of 1.5±0.8 medications; at 12 months, mean IOP was 19.50±4.76 (range 15-26) mmHg with 3.0±0.8 medications. At the last follow-up visit, IOP was 21.16±4.07 (range 16-26) mmHg with a mean of 3.33±0.51 medications. Mean follow-up was 19.16±8.8 (range 12-36) months. Surgical success rates were 83.3%, 66.6%, and 50.0% at 1 month, 12 months, and the last visit, respectively.

Conclusion: GDD implantation was effective in controlling aniridic glaucoma with a success rate of 83.3% at 1-month follow-up and 66.6% at 1-year follow-up. Therefore, it should be considered as an initial surgical treatment for aniridic glaucoma; the clinician should be alert for concomitant ocular disorders.

Keywords: Aniridia-related glaucoma, congenital aniridia, glaucoma, glaucoma drainage devices

Introduction

Congenital aniridia is a rare bilateral panocular disorder caused by a mutation in the *PAX6* gene, which is located on chromosome 11p.[1,2] The disease is characterized by partial or complete hypoplasia of the iris, corneal opacification, cataract, glaucoma, nystagmus, foveal, and optic disc hypoplasia.[3,4,5] The incidence of glaucoma associated with aniridia ranges from 6% to 75% and remains one of the most challenging features of aniridia.[6] Although several studies have attempted to clarify the mechanism underlying aniridic glaucoma, the currently accepted one is progressive anterior rotation of the rudimentary iris, leading to angle closure. On the other hand, maldeveloped anterior chamber angle and undeveloped Schlemm canal are other possible mechanisms.[7]

Aniridic glaucoma is frequently refractory to medical treatment, and patients eventually need surgery.[8] Surgical options include goniotomy, trabeculotomy, trabeculectomy, glaucoma drainage devices (GDD), and cyclodestructive procedures, but there is no consensus as to the best surgical treatment.[7,9,10,11]

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Visual prognosis is generally poor due to intractable glaucoma or concomitant ocular disorders.

In this study, we report the results obtained from GDD implantation in patients with congenital aniridia-related glaucoma, along with a literature review.

Materials and Methods

This retrospective, noncomparative study was approved by the Review Board of Ankara Training and Research Hospital and adhered to the provisions of the Declaration of Helsinki for research involving human subjects.

Patient Data

Medical records of patients who underwent GDD implantation for glaucoma secondary to congenital aniridia between April 2001 and February 2015 were analyzed. The following data were collected: age at time of surgery, gender, laterality, surgeries before GDD implantation, GDD model, concomitant ocular disorders, visual acuity, intraocular pressure (IOP) values before and at 1 and 12 months after GDD implantation, medications, follow-up period, findings in last visit, complications, and disease course. Surgical success for GDD implantation was defined as postoperative IOP between 5 and 22 mmHg with or without glaucoma medication. IOP was measured by Goldmann or Perkins applanation tonometry.

The diagnosis of limbal stem cell deficiency (LSCD) was made largely on clinical grounds. Loss of limbal anatomy, corneal conjunctivalization, persistent epithelial defects, and irregular fluorescein staining were considered as LSCD.

After establishing the prediagnosis, renal ultrasound and genetic analysis were performed if necessary.

GDD Implantation Technique

Under peribulbar or general anesthesia, a 8-0 silk suture was inserted into the superior limbal cornea. Conjunctival dissection was performed posteriorly by blunt dissection in the superior-temporal quadrant and a fornix-based opening was created. The GDD implants (Ahmed Glaucoma Valve-AGV) (New World Medical, Inc., Rancho Cucamonga, CA) were irrigated with 2 mL of balanced saline solution (priming). The plate was secured to the superficial sclera 8 mm from the limbus using 2 interrupted 6-0 absorbable sutures after passing through the holes. The tube was cut to extend 1-3 mm beyond the posterior surgical limbus. The anterior chamber was entered 2.0 mm posterior to the limbus with a 22-gauge needle directed parallel to and just anterior to the iris plane, and viscoelastic was administered. The tube was inserted through the needle tract using a smooth forceps, making sure not to touch the iris or cornea. The tube was secured to the sclera using 10-0 nylon sutures, then covered with the donor graft. The conjunctiva was closed using a 10-0 nylon suture. A subconjunctival antibiotic and steroid injection was performed.

Results

Six eyes of 6 patients (5 males, 1 female) who underwent GDD implantation for glaucoma secondary to aniridia were included in the study. The patients' demographics and preoperative clinical findings are given in Table 1. The mean age at surgery was 16.00±12.31 (range 5-37) years. Preoperatively, the mean IOP was 33.00±12.11 (range 22–50) mmHg using a mean of 3.5±1.2 anti-glaucomatous medications. In 4 cases (66.6%), lens extraction was performed due to cataract before GDD implantation.

The patients' postoperative outcomes are shown in Table 2. At 1 month, the mean IOP was 16.33±4.22 (range 12-24) mmHg with a mean of 1.5±0.8 medications, and surgical success was 83.3%. At 12 months, surgical success was 66.6% and mean IOP was 19.50±4.76 (range 15-26) mmHg with a mean of 3.0±0.8 medications.

The average follow-up was 19.16±8.8 (range 12-36) months. Mean IOP was 21.16±4.07 (range 16-26) mmHg with a mean of 3.33±0.51 medications, and surgical success was 50.0% at the last visit.

In Patient 1, GDD implantation was complicated by tube exposure at postoperative 1 month and retinal detachment associated with vitreous hemorrhage. The exposed tube area was repaired with fascia lata, and detachment surgery was performed. No other complications associated with GDD were observed for 6 months, after which the patient continued follow-up in his area of residence.

The right eye of Patient 4 was complicated with vitreous hemorrhage and retinal detachment after trabeculectomy.

Table 1. Patients' demographics and preoperative clinical findings

Patient	Age (years)	Gender	Eye	Prior surgeries	VA (decimal)	IOP (mmHg)	Tx
1	8	M	Right	LE	LP	50	2
2	8	M	Right	LE, IOL im	0.1	22	5
3	14	M	Right	None	0.2	30	4
4	24	M	Left	LE	0.04	46	2
5	37	F	Right	LA, PK	0.1	28	4
6	5	M	Right	LE, AIOL im	HM	22	4

AIOL im: Aniridia intraocular lens implantation, M: Male, F: Female, HM: Hand motion, IOL im: Intraocular lens implantation, IOP: Intraocular pressure, LA: Limbal allograft, LE: Lens extraction, LP: Light perception, PK: Penetrating keratoplasty, VA: Visual acuity, Tx: number of topical treatment agents

Therefore, GDD implantation was considered as the first surgical treatment for the left eye.

Patient 5, who underwent penetrating keratoplasty and allogenic keratolimbal allograft from cadaver 3 years before GDD implantation, developed corneal graft rejection and total corneal leucoma. A second keratoplasty was not considered due to risk of graft rejection.

Patient 6 received an aniridia intraocular lens implantation after lens extraction (Figure 1). This was the only case associated with Wilms' tumor, bilateral sporadic aniridia, genitourinary abnormalities, and mental retardation syndrome.

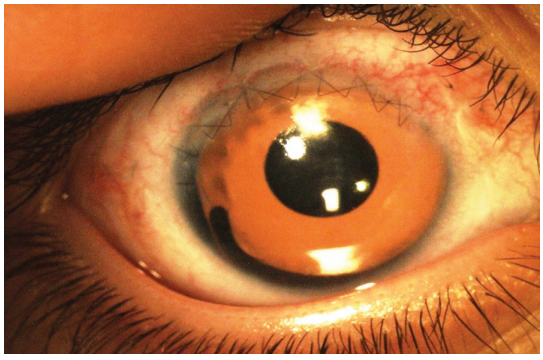

Figure 1. Aniridia intraocular lens (lens with artificial iris)

Discussion

Aniridia is a severe panophthalmic disorder characterized by the presence of only a rudimentary iris peripherally. It is often difficult to manage due to progressive features with many ocular complications such as cataract, glaucoma, and corneal opacity.[3] Fortunately, the incidence of disease is between 1:64,000 and 1:100,000.[12]

Aniridic glaucoma is thought to be due to developmental abnormalities in the drainage angle or progressive closure of the angle by the rudimentary iris. Treatment is very difficult, and a surgical approach is often required due to limited response to medical therapy. The rate of response to medical treatment, including miotic eye drops and oral carbonic anhydrase inhibitors, was reported as 38.7%.[13] In addition, successful results were not obtained with argon laser trabeculoplasty or diode laser photocoagulation in patient with aniridic glaucoma.[7,14] Prophylactic goniotomy to separate the abnormal extensions of the rudimentary iris to the angle was reported to be an effective method for preventing or delaying the onset of aniridic glaucoma.[10] However, glaucoma does not develop in a significant proportion of those with aniridia, so it should not be used routinely.

Ciliary body destruction was performed with cyclocryotherapy in patients with aniridic glaucoma by Wagle et al.[15] However, it was not presented as a first-line treatment because of serious

Table 2. Patients' surgical outcomes

	Type of valve	Postoperative 1 month			Postoperative 12 months			Follow-up (months)	Complications and course of disease
		VA (decimal)	IOP (mmHg)	Tx	VA (decimal)	IOP (mmHg)	Tx		
1	AGV S2	0.1	15	0	HM	25	4	15	Tube exposure, RD
2	Molteno	0.3	14	2	0.2	18	2	18	None
3	AGV S2	0.2	12	1	0.05	15	2	21	Decompression rp
4	AGV FP7	HM	18	2	HM	17	3	13	None
5	AGV S2	0.2	15	2	0.04	16	3	12	Leukoma
6	AGV FP8	HM	24	2	HM	26	4	36	WAGR, LSCD

AGV: Ahmed glaucoma valve, IOP: Intraocular pressure, LSCD: Limbal stem cell deficiency, RD: Retinal detachment, rp: Retinopathy, VA: Visual acuity; Tx: treatment; WAGR: Wilms tumor, Aniridia, Genitourinary anomalies, Retardation syndrome

Table 3. Previously published data on glaucoma drainage device in eyes with aniridic glaucoma

Author (year of publication)	Number of patients	GDD type	Follow-up period	Surgical success rate
Molteno et al.[19]	3	3 Molteno	Not indicated	100%
Billson et al.[20]	2	2 Molteno	3 years	100%
Wiggins and Tomey[7]	6	6 Molteno	Not indicated	83%
Adachi et al.[17]	3	3 Molteno	9 years	66%
Cunliffe and Molteno[21]	3	3 Molteno	8 years	83%
Arroyave et al.[11]	8	1 Molteno, 7 Baerveldt*	19 months	88% (at 12 months)
Almousa and Lake[18]	8	8 AGV	37.4 months	87% (at 12 months)

*One 250 mm^2, Six 350 mm^2 Baerveldt implant
AGV: Ahmed Glaucoma valve, GDD: Glaucoma drainage device

complications such as hypotony, phthisis bulbi, cataract, and vision loss. Considering that most cases occur in young patients and affect both eyes, these complications could be more destructive. Wiggins and Tomey[7] reported a success rate of only 25% after cyclocryotherapy in aniridic glaucoma. Conversely, Kirwan et al.[16] found cyclodestruction with cyclophotocoagulation diode laser as an effective treatment in refractory pediatric glaucoma patients, including 5 aniridic eyes.

Many studies have tried trabeculectomy in aniridic glaucoma. While Grant and Walton[13] reported failures in all eyes that underwent trabeculectomy, Nelson et al.[6] reported successful outcomes in 11 of 14 eyes even 1 year after trabeculectomy. Okada et al.[9] reported successful IOP control in their study, including 10 eyes of 6 patients with 14.6-month follow-up.[9] Adachi et al.[17] achieved IOP control for 1 year in only 1 of 5 patients who underwent trabeculectomy as an initial treatment. The fibrotic nature emerging from cell adhesion of aniridia may be the main reason for higher risk of treatment failure than that seen in patients with primary glaucoma who undergo the same treatment. This situation requires the use of antimetabolites (e.g., 5-fluorouracil, mitomycin C), which damage stem cells and accelerate the progression of corneal complications.

In the present study, GDD implantation was performed as an initial procedure for aniridic glaucoma in 6 eyes of 6 patients. While our success rate was 83.3% at 1 month, it fell to 66.6% at 12 months, and was 50.0% at the last follow-up visit. This decrease in success rate over time is consistent with the literature. Arroyave et al.[11] presented 8 eyes of 5 patients who underwent GDD placement as initial surgery (6 eyes) or after unsuccessful glaucoma surgeries (2 eyes). The rate of success, which was defined as postoperative IOP of 21 mmHg or less with or without glaucoma medications, was 100% at 6 months and 88% at 1 year. Hence, the success rate decreased over time similarly to our result. This may be attributed to the fibrotic process of this disease, which leads to reduced drainage over time. The latest study on GDD implantation for aniridia-related glaucoma was presented in 2014 by Almousa and Lake,[18] who reported successful IOP control in 87% of eyes (7 of 8 eyes). In addition, the success rate varied between 66% and 100% in another 5 studies in which Molteno GDD was used for aniridic glaucoma.[7,17,19,20,21] Previously published data are shown in Table 3. The success rate of GDD surgery in studies, including ours, seems good despite the poor prognosis of the disease.

As observed in a series which included the medical records of 128 eyes of 64 patients with aniridic glaucoma, one-fourth of patients had phthisis in at least 1 eye at the last postoperative follow-up.[22] Okamoto et al.[23] suggested that ciliary body hypoplasia could be responsible for the higher rates of phthisis compared to other pediatric glaucomas in these patients. However, there were no phthisis or hypotony in our series; this may be due to the small number of patients, or selecting the GDD implantation as an initial surgery for glaucoma.

Study Limitations

The small number of cases, the nonadherence to follow-up of some patients, and the retrospective, noncomparative design should be considered limitations of this study. Even so, this is the second largest case series in the literature.

Conclusion

In conclusion, GDD implantation for aniridia-related glaucoma achieved successful IOP control in most patients. Hence, GDD placement could be considered as an initial surgical treatment when IOP remains uncontrolled, despite maximal medical therapy in aniridic glaucoma. Randomized studies are needed to determine the best surgical method for aniridia-related glaucoma.

Ethics

Ethics Committee Approval: Review Board of Ankara Training and Research Hospital.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ümit Ekşioğlu, Mehmet Yakın, Gülizar Soyugelen Demirok, Concept: Gülizar Soyugelen Demirok, Design: Gülizar Soyugelen Demirok, Data Collection or Processing: Ahmet Kaderli, Analysis or Interpretation: Gülizar Soyugelen Demirok, Firdevs Örnek, Literature Search: Sema Tamer Kaderli, Writing: Gülizar Soyugelen Demirok.

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Original Article

Clinical Profile and Treatment Response of Patients with Ocular Inflammation due to Presumed Ocular Tuberculosis: A Retrospective Study

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Abstract

Objectives: Ocular tuberculosis is an extrapulmonary tuberculous infection and has varying manifestations which pose a huge challenge to diagnosis and treatment. The purpose of this study is to describe the various clinical manifestations of ocular inflammations due to tuberculosis and to assess the response to treatment following antituberculous therapy (ATT) and corticosteroids in these patients.

Materials and Methods: We performed a retrospective analysis of 29 patients with presumed ocular tuberculosis who were started on ATT and completed follow-up of at least 6 months after ATT was initiated. The data collected were: age at presentation, sex, laterality, presence or absence of pulmonary/extrapulmonary tuberculosis, history of exposure to tuberculosis, site of ocular involvement and duration of illness, visual acuity at presentation and at 6-month follow-up, and response to treatment.

Results: Most of the patients were of economically productive age, between 21-60 years. This most common presentation in our study population was unilateral nongranulomatous anterior uveitis. In spite of the delay between symptom onset and start of therapy, favorable response was noted in 79.3% of patients at completion of 6 months of ATT. The various reasons for the delay in start of therapy were also evaluated.

Conclusion: In this case series, we presented the various ocular manifestations and the difficulties faced in the diagnosis of presumed ocular tuberculosis. Outcomes of ATT were favorable in most of our patients. Thus, the clinician should exercise a very high degree of suspicion and should not withhold a trial of ATT.

Keywords: Presumed ocular tuberculosis, tuberculosis, ocular inflammation, extrapulmonary tuberculosis

Introduction

Tuberculosis is one of the leading infectious causes of morbidity and mortality worldwide, especially in the developing world. Data from the World Health Organization states that tuberculosis infects approximately one-third of the global population.[1,2] In 2016, there were an estimated 10.4 million new tuberculous cases worldwide. Sixty-four percent of the global burden was contributed by seven countries: India, Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa.[3] Under-reporting and under-diagnosis have been cited as the major challenges to the treatment of tuberculous infection.

Ocular inflammation due to tuberculosis occurs either because of direct invasion by the tuberculosis bacilli or as a result of immunogenic reaction due to the extraocular infective foci. The prevalence of presumed ocular TB has been reported to vary widely depending upon the population studied and the diagnostic methods used, ranging between 1.4 and 18% in various studies.[4,5,6,7,8,9,10,11]

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Patients can present with a wide variety of clinical manifestations in the external eye such as lid granulomas, conjunctival ulceration, hypertrophied excrescences, scleritis, keratitis, and phylectenulosis, to name a few. Intraocular signs of inflammation due to tuberculosis may also be varied, including uveitis, choroidal tubercles, choroiditis, retinal vasculitis, and optic nerve involvement.[12,13,14] Thus, a high degree of suspicion is needed to diagnose and treat ocular tuberculosis.[15]

A definitive diagnosis is possible only when the tubercle bacilli can be visualized in or cultured from or its DNA amplified from the involved tissue. Because this is difficult to achieve, tuberculosis is often presumed, as suggested by Gupta et al.[16] in 2007. In 2014, Gupta et al.[17] proposed a newer classification of ocular tuberculosis with confirmed, possible, and probable categories in an effort to include ambiguous cases.

Recognition of the clinical signs of tuberculosis is important, as most of these patients will be treated with corticosteroids, which may flare up latent infection if missed. It will also help us to tailor investigations and promote better decision-making for initiating treatment in such cases.

The treatment of ocular tuberculosis usually consists of the four-drug regimen isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for 2 months followed by isoniazid and rifampicin (HR) to be continued up to 6-12 months. Concomitant use of corticosteroids by all routes (oral/topical/periocular) is needed in all ocular tuberculosis patients depending upon the clinical presentation. In 2003, the Centers for Disease Control and Prevention recommended prolonged therapy in cases of tuberculous infection at sites which respond slowly to therapy. Hence, patients with confirmed or presumed intraocular TB may require prolonged therapy.[18] The recently updated guidelines published in 2016 recommend 6-9 months of therapy for extrapulmonary tuberculosis, though clear-cut recommendations for confirmed and presumed ocular tuberculosis have not been proposed.[19]

The purpose of this study was to describe the course and outcome of treatment and the various clinical manifestations of ocular inflammations observed in our center due to tuberculosis involving the anterior and posterior segments of the eye. Specifically, our objectives were to assess response to treatment following antituberculosis therapy (ATT) and corticosteroids in patients with ocular inflammation due to presumed ocular tuberculosis, and to analyze the various ocular manifestations and disease course in these patients.

Materials and Methods

We performed a retrospective evaluation of patient data from the departmental records after obtaining ethical clearance from our institutional ethical committee. These patients presented to our ophthalmology outpatient clinic between June 2014 and May 2016.

We included patients with ocular inflammation who received ATT for presumed ocular tuberculosis and completed follow-up of at least 6 months after treatment was initiated.

All patients with ocular inflammation due to other causes (infectious and noninfectious) and those who did not come for follow-up were excluded from the study.

The criteria used in our center for diagnosis of presumed ocular tuberculosis were the presence of suggestive ocular findings in combination with

- Positive tuberculin sensitivity test (greater than 10 mm induration)

and/or

- Positive chest x-ray or computed tomography (CT)

and/or

- evidence of confirmed extrapulmonary tuberculosis
- and exclusion of other possible entities.

Clinical signs of ocular inflammation which were considered suggestive of tuberculosis included granulomatous and nongranulomatous anterior uveitis, scleritis, keratoconjunctivitis, intermediate uveitis, retinal vasculitis, and optic neuritis. Since this was a retrospective study, no working protocol had been followed for all cases. Instead, individualized patient workup was done according to clinical findings.

From the records, the details of the complete ophthalmic examination with measurement of visual acuity, tonometry, slit-lamp examination, and dilated fundus exam were noted. Other modalities such as fundus fluorescein angiography, optical coherence tomography, perimetry, and B-scan ultrasound were used only as and when required. Blood analyses comprising complete blood count, erythrocyte sedimentation rate, blood glucose evaluation, and inflammatory workup including antinuclear antibody, C-reactive protein, HLA-B27, rheumatoid factor, TORCH (toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV), and serum angiotensin-converting-enzyme to rule out other possible etiologies were performed when needed before initiating ATT. Immunological workup for tuberculosis such as Quantiferon TB gold assay and Mantoux were also done. Radiological studies like chest x-ray were done in all patients and chest CT was performed as required by a pulmonologist. A chest physician/internist evaluated the patients for signs of extrapulmonary and pulmonary tuberculosis.

The parameters included in our study were: age at presentation, sex, laterality, presence or absence of pulmonary/extrapulmonary tuberculosis, history of exposure to tuberculosis, site of ocular involvement and duration of illness, visual acuity at presentation and at 6-month follow-up, and response to treatment.

Response to treatment was assessed based on visual improvement and clinical response, time of onset of clinical improvement, and development of other complications. We defined a favorable outcome as vision improvement of at least 2 lines on Snellen chart and/or a decrease in clinical signs of inflammation (difference of more than 2 grades of inflammation as per Standardization of Uveitis Nomenclature Working Group and National Institutes of Health guidelines).[20,21,22,23]

Results

We included 29 patients in our study, of which 69% were female (20 women, 9 men). The majority of patients belonged to the 41-60 year age group (62%, 18 patients) in comparison to 10 patients (34%) in the 21-40 year age group.

Eighty-three percent of the patients had unilateral involvement, of which right eye involvement was more common. The patients' demographic characteristics are presented in Table 1. Four of the 29 patients were diabetics on oral antidiabetic therapy.

Thirty-eight percent (n=11) of the patients were found to have evidence of tuberculosis other than the ocular involvement. Five patients had active pulmonary tuberculosis and four showed evidence of old pulmonary tuberculosis or hilar adenopathy. One patient had cervical adenopathy with histopathological evidence of tuberculosis and one patient was on treatment for genitourinary tuberculosis.

The various clinical presentations are shown in Table 2. The mean time from onset of clinical symptoms to the start of ATT was 47 days (ranged from 11 to 72 days) in 25 patients, as 4 patients developed ocular symptoms while on ATT.

Chest x-ray and Mantoux test were performed for all patients. Among the 29 patients of this study, 90% showed strongly positive Mantoux test (<15 mm) and 10% showed Mantoux response of 10-15 mm. None of the patients had a Mantoux response of less than 10 mm.

Table 1. Characteristics of patients with presumed ocular tuberculosis

Parameters (total no. of patients=29)	Frequency (n)	Percentage (%)
Sex distribution		
Males	9	31
Females	20	69
Age range: (overall 17-60 years)		
<20 years	1	3.4
21-40 years	10	34.5
41-60 years	18	62.1
Laterality		
Unilateral involvement	24	83
Bilateral involvement	5	17
History of exposure to TB		
Yes	6	20.7
No	23	79.3
Past/present tuberculous infection	11	37.9
Active pulmonary TB	5	17.2
Evidence of old pulmonary TB (x-ray/CT/history)	4	13.8
Extrapulmonary TB	2	6.9

TB: Tuberculosis, CT: Computed tomography

Quantiferon TB gold assay was performed for 21 patients out of the 29, all of whom were found to be positive. Quantiferon test was found to be positive for the 3 patients who had Mantoux test results between 10-15 mm.

The main cause for delayed initiation of ATT was the time taken for the extensive laboratory and clinical workup. The various reasons for the delay in start of therapy are presented in Table 3.

Twenty-eight patients had been treated with category I ATT consisting of a 4-drug regimen (HRZE) for 2 months followed by a 2-drug regimen (HR) for 4 months. One patient was given category II therapy as he was a defaulter with active pulmonary tuberculosis. Concomitant oral/topical/periocular corticosteroid and cycloplegic therapy was administered depending upon the clinical presentation and need.

Seventeen patients on Category I completed 6 months of ATT. Twelve patients were subjected to 9 months of therapy. Five of these 12 patients had good resolution of symptoms after ATT and were given another 3 months of therapy. Four had relapses of inflammation and hence were treated with 9 months of ATT. Three patients had ocular inflammation with active pulmonary TB and were given therapy for up to 9 months.

Favorable clinical response was noted in 22 patients (75.9%) at 4-week follow-up after starting ATT and steroids. Two patients did not attend the 4-week follow-up but showed a favorable

Table 2. Clinical presentations of presumed ocular tuberculosis in our study population

Site of involvement	Number of patients	Percentage %
Anterior uveitis, granulomatous	5	17.2
Anterior uveitis, nongranulomatous	7	24.1
Intermediate uveitis	3	10.3
Posterior uveitis/choroiditis	5	17.2
Scleritis	7	24.1
Eales/periphlebitis	1	3.4
Corneal	1	3.4

Table 3. Reasons for delay between symptom onset and start of antituberculous therapy among patients with presumed ocular tuberculosis

Reason	Number of patients (total=29)	Percentage (%)
Delay in seeking medical help	3	10.3
Anti-inflammatory treatment started elsewhere, delaying appropriate treatment	5	17.2
Physician hesitancy to start ATT without definitive evidence	6	20.7
Time taken for clinical workup	11	37.9
*Already on ATT	4	13.8

*4 patients were already on antituberculous treatment
ATT: Antituberculous therapy

response when they visited at 7 and 8 weeks, respectively. Five patients showed minimal or no resolution of inflammation at 4 weeks. Their outcomes were as follows in subsequent follow-ups:

- Patient 1: presented with scleral inflammation, had recurrent attacks of scleritis and developed progressive scleral thinning and panuveitis through the ATT period, and developed staphyloma. Patient was re-evaluated after 2 months of ATT, but no other cause for the inflammation was ascertained.
- Patient 2: Presented with retinal periphlebitis (Eales disease), developed recurrent inflammation, vitreous hemorrhage and tractional retinal detachment, and underwent retinal detachment surgery.
- Patient 3: Developed recurrent bilateral corneal inflammation and pannus with corneal opacification in both eyes
- Patient 4: Developed recurrent intermediate uveitis and cystoid macular edema while on ATT
- Patient 5: Presented with choroiditis and post-uveitis, initially showed favorable improvement but relapsed in month 5 of ATT and was restarted on steroid therapy, developed retinal detachment.

We compared the patients' best corrected visual acuity (BCVA) at presentation and at completion of 6 months of ATT. Six patients (20.6%) had worsening of presenting BCVA (caused by optic atrophy in 1 patient, staphyloma and retinal detachment in 1, corneal opacity in 1, macular scar in 1, and retinal detachment in 2 patients). Twenty-three patients (79.3%) maintained presenting BCVA or had improvement in BCVA.

Twenty-five of the 29 patients were followed up for an additional 6 months after completion of ATT (1 year of follow-up in total). Four patients, 2 with favorable and 2 with unfavorable outcomes at 6 months, were lost to follow-up after 6 months. Twenty-one of the 25 followed patients maintained their visual improvement (including 2 patients who underwent cataract surgery during the period) and were symptom-free for a year after starting ATT. One patient developed secondary glaucoma during this period of extended follow-up.

In total, 4 patients underwent uneventful cataract surgery for complicated cataract, 2 during the course of ATT and 2 after completing ATT. Two patients underwent surgery for retinal detachment during the course of ATT.

Discussion

Extrapulmonary tuberculosis, especially ocular tuberculosis, poses many diagnostic and treatment dilemmas such as the lack of specific disease entities or clinical findings, protean manifestations, and multiple limitations to confirmatory diagnostic procedures. Therefore, most cases are diagnosed presumptively and not definitively after excluding other possible etiologies. Response to ATT may also provide indirect evidence for the correct diagnosis.

The patients who were analyzed were the economically productive strata between 21-60 years, with 62% belonging to age group of 41-60 years. Although tuberculosis is a systemic affliction, 83% of the study group showed unilateral involvement. The predominant clinical presentation in our group of patients was anterior uveitis (41% of patients) rather than posterior uveitis, which has been the commonest presentation in previous reports.[16,24] In addition, the anterior uveitis was nongranulomatous in the majority of patients rather than the granulomatous variety which is more suggestive of tuberculosis.[16,24]

Tuberculosis elsewhere in the body was present in 38% and history of exposure to tuberculosis was elicited in only 20.7% of our patients. This shows that we cannot rely on history of exposure or presence of tuberculous lesions elsewhere as reliable criteria for diagnosis of ocular TB.

Ocular diagnostic methods like PCR assays require invasive tissue/sample procurement, are expensive and not readily available, and cannot be performed in all patients. We still have to rely on non-ocular methods like Mantoux test and gamma interferon release assays like Quantiferon Gold TB assay. When used judiciously, they have been shown to provide reliable results.[25]

In this study group, 90% of patients showed a strongly positive reaction to Mantoux test. Only 3 out of 29 showed reactions of 10-15 mm but they tested positive on Quantiferon TB assay. This clearly demonstrates that the Mantoux test cannot be disregarded as a way of evaluating a presumed ocular TB patient. It is also among the easiest tests to perform and is still largely available in many centers across India. A study conducted in Iraq showed high sensitivity and specificity of tuberculin sensitivity test with more than 14 mm induration.[26] Many researchers recommend using combination of Mantoux test, interferon gamma release assays, and clinical signs to diagnose ocular tuberculosis.[27,28,29,30] Ang et al.[31] suggested that interferon assays should be preferred in areas where the prevalence of infection is low, and tuberculin skin test should be preferred where there is high prevalence of TB associated infection. Sudharshan et al.[32] in their study established the utility of the Quantiferon TB Gold test in suspected TB uveitis.

We observed a mean duration of 47 days between symptom onset and start of therapy. The main reasons for the delay were the time required for the extensive workup to rule out other causes and hesitancy on the part of the clinician to start ATT without definitive evidence of the disease.

Among our patients, favorable response to therapy was noted in 75.9% of patients after 1 month of ATT. At completion of 6 months of ATT, favorable response was noted in 79.3% of patients. Relapses were noted in 2 patients during ATT therapy, which were controlled by restarting steroids. Five patients (17%) worsened in spite of therapy. A study by Basu et al.[33] also observed progressive inflammation following ATT initiation for presumed ocular TB.

We followed up 25 patients (4 patients were lost to follow-up) for a further 6 months (1 year total). Of these, 21 maintained their visual outcome at end of 1 year (2 underwent cataract extraction) and had no relapses during the follow-up period.

Our data suggest that most patients benefitted from the therapy in the short term. A study in the UK showed that a

minimum of 6 months of therapy provided good visual outcomes in the majority of patients.[34] Sanghvi et al.[35] recommended a full 6-month course of ATT although it may not cure the uveitis. Recently, Damato et al.[36] also observed that most patients showed improvement even when start of treatment was delayed. In 2016, Lee et al.[37] reported a 60-70% resolution of uveitis after a full course of ATT.

Definitive diagnostic methods like PCR with ocular samples are invasive and expensive, and the facilities are not widely available. Hence, the utility of tuberculin skin sensitivity testing and interferon gamma release assays is to be considered. Though there are wide variations in recommendations, they must be interpreted with caution.[38,39,40]

Therefore, we feel there should be no hesitancy to consider TB etiology in ocular inflammation or to consider a clinical trial of therapy in suspicious cases. Bansal et al.[41] have suggested that treatment with ATT decreased the recurrence rate of uveitis by two-thirds when compared to treatment with anti-inflammatory drugs like steroids. Also, early administration of steroids without starting ATT has been shown to produce detrimental effects and may lead to poorer visual outcomes.[42] Ang et al.[43] in 2012 showed an 11-fold reduction in recurrence of uveitis when ATT was given for more than 9 months. In their case series published in 2016, Özdal et al.[44] showed that uveitis did not recur in the majority of patients on ATT.

Study Limitations

Our study has certain limitations. We included only patients with ocular inflammation with adequate follow-up while on ATT until completion of therapy. In addition, we did not investigate age-matched controls, which would have given more insight into the reliability of the immunological tests in this group of patients. Furthermore, since the number of patients in each clinical category was not large enough, we could not assess response to therapy in each clinical category.

Conclusion

In this case series, we present the various ocular manifestations and the difficulties faced in the diagnosis and treatment of presumed ocular tuberculosis. Outcomes of ATT were favorable for most of our patients, even in those with delay in initiation of therapy. Thus, the clinician should excise a very high degree of suspicion and should not withhold a trial of ATT.

Uncertainties in the management of ocular tuberculosis must be addressed by creating protocols to be followed by both ophthalmologists and pulmonologists and infectious disease specialists.

Because of such inadequacies in diagnosis and treatment, ocular TB is probably grossly under-reported. Diagnostic guidelines and a protocol for investigation should be formulated and followed to ensure uniformity in treatment.

As we battle presumptive ocular TB, we should address the need for a multicenter study with long-term follow-up, which will help us to formulate better diagnostic and treatment guidelines for managing this public health issue.

Ethics

Ethics Committee Approval: We performed a retrospective evaluation of patient data from the departmental records after obtaining ethical clearance from ESIC Medical College Ethical Committee (no.16-13/07/2016).

Informed Consent: Not obtained as it was retrospective study from departmental records

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Suma Elangovan, Senthamarai Govindarajan, Lakshmi Mayilvakanam, Nithya Gunasekaran, Concept: Suma Elangovan, Senthamarai Govindarajan, Design: Suma Elangovan, Senthamarai Govindarajan, Data Collection or Processing: Senthamarai Govindarajan, Lakshmi Mayilvakanam, Suma Elangovan, Nithya Gunasekaran, Analysis or Interpretation: Suma Elangovan, Senthamarai Govindarajan, Literature Search: Suma Elangovan, Lakshmi Mayilvakanam, Writing: Suma Elangovan.

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Original Article

The Relationship Between Macular Cyst Formation and Ischemia in Diabetic Macular Edema

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Abstract

Objectives: To evaluate the relationship between cyst characteristics and macular and peripheral ischemia in diabetic macular edema (DME).

Materials and Methods: We retrospectively reviewed eyes with DME and included those with clinically significant macular edema as defined by ETDRS (Early Treatment Diabetic Retinopathy Study) and cystoid spaces in optical coherence tomography scans in this study. Central subfield thickness (CSFT), horizontal and vertical diameters of the largest cyst, cyst area, and the remaining retinal thickness outside the cyst were determined. The presence and number of hyperreflective foci in the cyst wall and the internal reflectivity of the cyst were analyzed. Outer retinal damage was graded. Fluorescein angiography was used to determine the areas of macular and peripheral ischemia, which were graded as mild or severe. Correlations between macular and peripheral ischemia and cyst-related measurements and structural changes in the retina were evaluated.

Results: This retrospective study included 250 eyes of 186 patients with DME. Mean CSFT was significantly greater in eyes with macular ischemia (510.4±144.7 µm) compared to eyes without macular ischemia (452.1±114.6 µm) (p=0.001). Horizontal and vertical diameter of the largest cyst increased with the presence and severity of macular ischemia (p=0.045 and p=0.016, respectively). Remaining retinal thickness increased with the presence and severity of peripheral ischemia (p=0.009). There was a statistically significant relationship between the number of the hyperreflective foci in the cyst wall and internal reflectivity of the cyst (p=0.007). Patients with greater CSFT had a 1.04-times higher odds of having macular ischemia and 0.25-times higher odds of having outer retinal damage.

Conclusion: The likelihood of macular ischemia increases with larger cyst diameter, CSFT, and extent of outer retinal damage. Thickness of the noncystic area is increased in the presence of peripheral ischemia.

Keywords: Diabetic macular edema, diabetic macular ischemia, cystic changes, optical coherence tomography, peripheral ischemia

Introduction

The most common cause of visual loss in people with diabetes is diabetic macular edema (DME).[1] There are two different aspects of the diabetic retinopathy (DR) spectrum in terms of retinal vasculature: hyperpermeability (leakage and edema) and hypoperfusion (ischemia).[2] Ischemia can occur both in the macula and in the peripheral retina. The enlargement of the foveal avascular zone (FAZ) can be described as diabetic macular ischemia (DMI).[3,4] This definition includes occlusion of retinal capillaries in the macula and obliteration of precapillary arterioles.[4] DMI is associated with poor visual prognosis.[5,6]

A remarkable association was found between the extent of peripheral nonperfused areas and the degree of DME.[7] Vascular endothelial growth factor (VEGF), which is the most significant factor in the pathogenesis of DR, is released from ischemic areas.[8] Neovascularization and increased permeability of the vascular structures occur with the activation of VEGF, which was found in patients with DME.[8,9,10]

Cystoid macular edema (CME) is one of the morphological patterns of DME on optical coherence tomography (OCT).[11] In the process of cyst formation, fluid accumulates in the intercellular space in the acute phase. Later, in the chronic

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stage, fluid begins to form in the intracellular space. Thus, this accumulation leads to large cystoid cavities.[12] Cystoid spaces at the fovea and enlarged FAZ were found to be related to each other.[13] Besides the common pathogenesis of cyst and ischemia, cyst presence has been linked to decreased retinal sensitivity.[14] To date, there has been no description in the literature of quantitative and qualitative cyst features associated with retinal ischemia as a part of the degenerative process.

The aim of this study was to investigate the relationship between cyst formation and related OCT features and both macular and peripheral retinal ischemia.

Materials and Methods

In this retrospective cross-sectional study, medical records of patients who were followed up with the diagnosis of cystic DME at Gazi University Department of Ophthalmology between November 2011 and March 2015 were evaluated for inclusion. The study was approved by the local ethics committee of Gazi University.

Eyes with clinically significant macular edema as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), cystoid spaces in OCT scans, and high-quality fluorescein angiography (FA) and spectral domain images were included in the study. Eyes with macular edema due to other causes such as uveitis; retinal vein occlusion; concurrent macular degeneration; macular hole; visually significant cataract or any other pathology causing visual loss such as amblyopia, corneal opacity, significant vitreous hemorrhage, and optic atrophy were excluded from the study. Eyes that had undergone cataract surgery within the last 6 months were also excluded from the study to exclude Irvine-Gass syndrome.

The demographic features of the patients (age, sex, duration of diabetes) and stage and duration of DR were recorded. The records of patients were reviewed for best corrected visual acuity (BCVA), DR findings in fundus examination, OCT and FA evaluation. BCVA was converted to LogMAR for statistical analysis. All OCT scans and FA investigations were performed with Heidelberg Spectralis OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). All images were obtained by the same experienced technician. In OCT, 25-line raster scans were obtained for each eye after pupil dilation and the average thickness in the central 1000-µm diameter circle of the ETDRS grid was accepted as central subfield thickness (CSFT).

Cystic space was defined as round or oval-shaped low reflective intraretinal spaces separated by hyperreflective septa.[11] In the analyses of cysts in OCT, we used the largest cystoid space in the area within 1000 µm of the foveal center as representative of degenerative status. The horizontal and vertical diameters of the largest cyst, the area of the cyst (product of the diameters), and the remaining retinal thickness outside the cyst were determined in the quantitative analyses part of the study. Remaining retinal thickness outside the cyst was calculated by subtracting the vertical diameter of the cyst from the CSFT. All measurements were performed by the same investigator (N.G.Y.) with a manual caliper.

In the qualitative examination of the cyst, the presence and the number of hyperreflective foci in the cyst wall and the internal reflectivity of the cyst were analyzed. Hyperreflective foci were defined as the hyperreflective dots less than 30 µm in thickness and having the same reflectivity of clustered hard exudates, as described by Bolz et al.[15] The internal reflectivity of the cysts was classified as isoreflective when similar to the retinal layers, hyporeflective when similar to the vitreous, or heterogeneous (as described in an earlier study).[16] Accompanying outer retinal damage in the ellipsoid zone was also determined and any loss of continuity of either the external limiting membrane (ELM) or inner segment/outer segment (IS/OS) band in the central 0.1 mm of the fovea was noted as outer retinal damage.[17]

Macular and peripheral ischemia were assessed from FA images. Macular ischemia was defined as an enlarged FAZ (≥1000 µm) or presence of capillary nonperfusion within one disc diameter (DD) from the foveal center.[18] The severity of macular ischemia was graded according to disruption of the FAZ outline. If the ischemic area affected less than half of the FAZ outline, it was evaluated as mild; further disruption was graded as severe (Figure 1).[19] Peripheral ischemia was defined as hypofluorescent areas corresponding to retinal nonperfusion/capillary drop-out or intraretinal microvascular anomaly in at least a 1-DD area.[7] It was graded as mild when the peripheral ischemia covered less than a 5-DD area and as severe when it was more than a 5-DD area when evaluated on images taken in all gaze directions (Figure 2). This cut-off level was chosen because it was shown that the risk of neovascularization emerged over this value.[20]

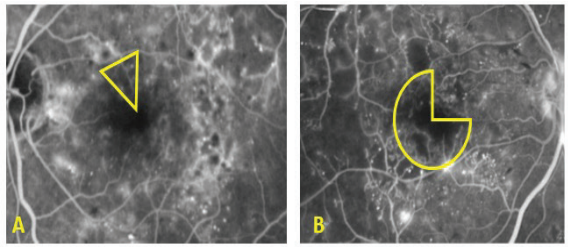

Figure 1. Macular ischemia: A) Mild ischemia, disruption of less than half of the foveal avascular zone (FAZ) outline, B) Severe ischemia, disruption of more than half of the FAZ outline

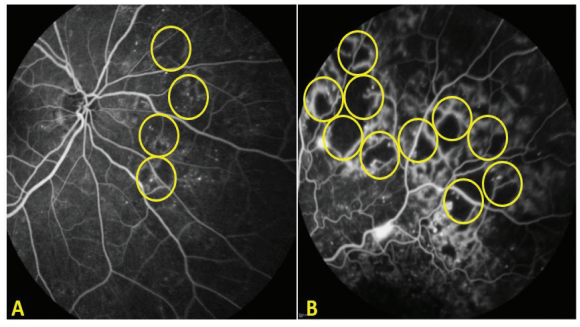

Figure 2. Peripheral ischemia: A) Mild ischemia, covers less than a 5-disc diameter area, B) Severe ischemia, covers more than a 5-disc diameter area

Statistical Analysis

Data obtained from the study were recorded using Excel for Windows (version 2010, Microsoft, Redmond, WA) and statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 15.0, SPSS, Chicago, IL). The statistical level of significance was set to p>0.05. Kolmogorov-Smirnov test, histograms, and P-P plots were used to test continuous variables for conformity to normal distribution. One-way ANOVA and LSD test for post-hoc analyses were used for the comparison of three or more groups if the variables were normally distributed. The Kruskal-Wallis test was used for the comparison of three or more groups if the variables were not normally distributed. Mann-Whitney U test with Bonferroni correction was used for post-hoc analysis if the result revealed a significant difference. Pearson chi-square or Yate's corrected chi-square tests were used for categorical variables. Binary logistic regression analyses were done.

Results

A total of 250 eyes of 186 patients met the inclusion criteria. There were 64 patients (34.4%) with bilateral involvement and 122 patients (65.6%) with unilateral DME. One hundred ninety-four eyes (77.6%) had received prior intravitreal injection and/or laser therapy. Other demographic features of the cases are shown in Table 1. The mean BCVA of the patients was 0.5±0.38 (0-1.6) LogMAR.

Macular ischemia was present in 110 eyes (44%). Seventy-two eyes (28.8%) had mild macular ischemia and 38 eyes (15.2%) had severe macular ischemia. The relationship between DR stage and ischemia is shown in Table 2. Mean BCVA was 0.36±0.28 LogMAR in eyes with normal macular perfusion and 0.68 ± 0.42 LogMAR in eyes with macular ischemia (p=0.001). The mean CSFT was 510.35±144.68 µm in the eyes with macular ischemia, which was significantly higher than that of the eyes with normal macular perfusion (452.11±114.61 µm) (p=0.001). Outer retinal damage was also more prevalent in eyes with macular ischemia and prevalence increased with ischemia severity (Table 3). Severity of macular ischemia and related OCT features are given in Table 3.

Table 1. The demographic and clinical features of the patients

	Mean ± SD	Number	%
Age (years)	60.26±8.3	-	-
Sex (F/M)	-	88/98	47.3/52.7
Duration of DM (year)	14.85±7.2*	-	-
Type of DM (Type 1/Type 2)	-	11/88*	11.1/88.9
Type of DR (NonPDR/PDR)	-	141/45	75.8/24.2

*This information was missing from some of the records. Only available data are included here
SD: Standard deviation, F: Female, M: Male, DM: Diabetes mellitus, DR: Diabetic retinopathy, PDR: Proliferative diabetic retinopathy

Table 2. Macular and peripheral ischemia according to the stages of diabetic retinopathy

The type of the ischemia	Stage (n, %)		p value*
	NonPDR	PDR	
Macular			
None	109, 58%	31, 50%	0.46
Mild	53, 28.2%	19, 30.6%	-
Severe	26, 13.8%	12, 19.4%	-
Peripheral			
None	56, 29.8%	2, 3.2%	0.001
Mild	84, 44.7%	12, 19.4%	-
Severe	48, 25.5%	48, 77.4%	-

*Pearson chi-square test
n: Number, NonPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

Table 3. Best corrected visual acuity and optical coherence tomography findings according to presence of macular ischemia

	Macular ischemia			p value
	None	Mild	Severe	
BCVA (LogMAR) Mean ± SD	0.36±0.28	0.58±0.37	0.85±0.46	0.0001*
CSFT (µm) Mean ± SD	452±114	503±122	523±181	0.004*
Horizontal diameter (µm) Median (min-max)	403 (126-1606)	445 (184-1966)	452 (189-2213)	0.045**
Vertical diameter (µm) Mean±SD	284±132	319±113	353±204	0.016*
Area of the cyst (mm^2) Median (min-max)	0.1 (0.01-0.77)	0.14 (0.03-0.98)	0.14 (0.02-2.34)	0.018**
RRT (µm) Mean ± SD	168±83	184±91	170±98	0.461*
Outer retinal damage (n,%)	24, 17.1%	26, 36.1%	27, 71.1%	0.001***

*One-Way ANOVA test, **Kruskal-Wallis test, ***Chi-square test
BCVA: Best corrected visual acuity, CSFT: Central subfield thickness, RRT: Remaining retinal tissue, SD: Standard deviation

Peripheral ischemia was present in 192 eyes (76.8%). Half of these eyes (96 eyes, 38.4%) had mild peripheral ischemia and the other half (96 eyes, 38.4%) had severe peripheral ischemia. The mean BCVA was 0.43±0.35 LogMAR in eyes without peripheral ischemia and 0.52±0.39 LogMAR in eyes with peripheral ischemia (p=0.076). The mean CSFT was 483.91±138.7 µm in eyes with peripheral ischemia and 457.31±103.5 µm in eyes without peripheral ischemia (p=0.36). Severity of peripheral ischemia and related OCT features are given in Table 4.

Hyperreflective foci in the cyst wall were detected in 170 eyes (68%). Most of these hyperreflective foci (155 eyes, 91%) were in the outer retinal layers. The median number of the foci was 1 (0-14) in the cyst wall and 1 (0-8) in outer retinal layers. The number of the hyperreflective foci did not change significantly with the severity of macular or peripheral ischemia (p>0.05).

Internal reflectivity of the cyst did not differ significantly between eyes with and without ischemia (p>0.05). Eighty-two eyes (33%) had hyporeflective cysts and 60 (24%) had isoreflective cysts. Heterogeneous internal reflectivity was observed in 108 eyes (43%). The number of hyperreflective foci in the cyst wall was significantly higher in the isoreflective internal reflectivity group than the others (p=0.007) (Table 5).

In binary logistic regression analyses, only CSFT and outer retinal damage status were statistically significant for macular ischemia. No significant risk factor for peripheral ischemia was identified in binary logistic regression analyses (Table 6).

Discussion

Pericyte loss and autoregulatory dysfunction play an important role in the pathophysiology of DR. Thus, weakening and destruction of retinal vessels occur.[6] Hyperpermeability and ischemia are different components of DME and also the main outcomes of the distorted vascular network. In an earlier study, the presence of a cyst was associated with decreased retinal sensitivity independent of IS/OS damage and increased retinal thickness.[14] In this study, we focused on the impact of diabetic cystic changes on the ischemic process.

Table 4. Best corrected visual acuity and optical coherence tomography findings according to presence of peripheral ischemia

	Peripheral ischemia			p value
	None	Mild	Severe	
BCVA (LogMAR) Mean ± SD	0.43±0.35	0.52±0.41	0.53±0.37	0.226*
CSFT (µm) Mean ± SD	457±104	471±117	497±157	0.15*
Horizontal diameter (µm) Median (min-max)	435 (137-1606)	452 (126-1966)	416 (175-2213)	0.855**
Vertical diameter (µm) Mean ± SD	305±132	307±126	304±164	0.99*
Area of the cyst (mm^2) Median (min-max)	0.13(0.01-0.72)	0.13(0.01-0.98)	0.12 (0.02-2.34)	0.712**
RRT (µm) Mean ± SD	153±81	164±90	194±86	0.009*
Outer retinal damage (n, %)	15, (25.9%)	33, (34.4%)	29, (30.2%)	0.534***

*One-Way ANOVA test, **Kruskal-Wallis test, ***Chi-square test
BCVA: Best corrected visual acuity, CSFT: Central subfield thickness, RRT: Remaining retinal tissue, SD: Standard deviation

Table 5. The relationship between the internal reflectivity of the cyst and the number of the hyperreflective foci in the cyst wall

The internal reflectivity of the cyst (n,%)	The number of the hyperreflective foci in the cyst wall (mean ± SD)	p value
Isoreflective (60, 24%)	2.51±3.14	0.007*
Heterogeneous (108, 43%)	1.71±1.98	-
Hyporeflective (82, 34%)	1.15±1.46	-

*Kruskal-Wallis test
SD: Standard deviation

Table 6. The odds of macular and peripheral ischemia in patients with diabetic cystic changes				
	Macular ischemia		Peripheral ischemia	
	OR (95% CI)	p value	OR (95% CI)	p value
CSFT	1.04 (1.01 to 1.08)	**0.024**	1.01 (0.97 to 1.05)	0.616
Horizontal diameter	1.01 (0.99 to 1.03)	0.424	1 (0.98 to 1.02)	0.994
Vertical diameter	0.98 (0.94 to 1.02)	0.353	1 (0.98 to 1.02)	0.974
Area of the cyst	1 (1 to 1)	0.726	1 (1 to 1)	0.98
RRT	1.01 (0.99 to 1.04)	0.334	1.04 (0.99 to 1.08)	0.14
Outer retinal damage	0.25 (0.14 to 0.47)	**0.001**	0.72 (0.36 to 1.47)	0.369
Hyperreflective foci in the cyst wall	0.9 (0.47 to 1.74)	0.755	0.86 (0.39 to 1.86)	0.695
OR: Odds ratio, CI: Confidence interval, CSFT: Central subfield thickness, RRT: Remaining retinal tissue				

Enlargement of the FAZ and perifoveal intercapillary area and disruption of macular circulation have already been demonstrated in conjunction with the progression of DR and visual disturbance.[5,13,21,22,23] In the present study, severe peripheral retinal ischemia was more prevalent in eyes with proliferative DR, as expected. However, no statistically significant difference was observed in the prevalence of macular ischemia between the groups according to the severity of DR or peripheral retinal ischemia.

Macular ischemia was found to be more prevalent in eyes with larger macular cysts and CSFT. Larger FAZ areas have been observed in the superficial, deep, and summated capillary plexus in diabetic patients in several studies using OCT angiography (OCTA), which is one of the current retinal imaging methods and allows construction of microvascular flow maps.[24,25,26,27] Also, similar to our study, disorganization and loss of retinal capillaries was observed more precisely in the deep plexus with more severe DME in OCTA images.[28] Although enlargement of the cyst in both planes seems to be associated with macular ischemia, vertical enlargement and retinal thickness had a greater impact on the ischemic process. However, we believe that the horizontal enlargement of the cyst is associated with degeneration of Muller cells. In contrast to this hypothesis, a study that classified diabetic CME based on the ratio of vertical size of the largest cyst to the maximum macular thickness showed that disruption of the cystic septa occurred in the most advanced stage.[29] In a previously published study, vascular hyperpermeability and ischemia were shown to cause necrosis and apoptosis in the neuroglia cells, resulting in large cystoid cavities. A vicious circle ensues, with the enlargement of the cystoid spaces causing enlarged FAZ and increased foveal ischemia.[13] In the same study, sponge-like retinal thickening and larger FAZ were more common in CME cases than in serous foveal detachment.

We hypothesized that the disruption of retinal structures and the ischemic process as a part of the degeneration occur together in the chronic stage of DME. The damaging effect of cyst formation on ganglion and bipolar cells has been suggested in previously published studies.[12,30,31] The presence of macular cystoid spaces was found to be predictive of visual deterioration, with larger cystoid spaces being more disruptive than small ones.[32] In light of this information and the findings in this study, larger cysts may have a damaging effect that triggers or exacerbates the ischemic state. Regression analyses more clearly demonstrated the association between CSFT and outer retinal disruption and macular ischemia. Patients with more severe DME had a 1.04-fold greater chance of having macular ischemia, and those with outer retinal damage had a 0.25-fold greater chance of having macular ischemia. Furthermore, outer retinal damage was observed more frequently in severe macular ischemia.

We have shown that as a result of the degenerative process, BCVA decreased gradually with increasing severity of ischemia. Similarly, Koleva-Georgieva and Sivkova[33] demonstrated a negative correlation between BCVA and cystoid DME groups (classified according to the horizontal diameter of cystoid spaces as mild <300 µm, intermediate 300-600 µm; and severe >600 µm). Both macular ischemia and cyst size affect visual acuity.

In our study, qualitative parameters such as the presence and number of hyperreflective foci in the cyst wall and internal reflectivity of the cyst were not associated with macular or peripheral ischemia.

Hyperreflective foci defined by Bolz et al.[15] were suggested to be subclinical characteristics of lipoprotein extravasation and an early manifestation of DME. Hyperreflective foci that can be found scattered throughout all retinal layers have also been detected in the cystoid space. They were correlated with modest fluorescein pooling and heterogeneous reflectivity.[34] In the current study, we studied hyperreflective foci in the cyst wall and hypothesized that they may be associated with the early period of degenerative process and ischemia. Although not associated with ischemia, we found a significant relationship between the number of hyperreflective foci in the cyst wall and the internal reflectivity of the cyst. It was hypothesized that internal reflectivity of cysts was related with degeneration; in the early period, the cyst is usually isoreflective, then becomes heterogeneous due to the debris accumulation resulting from degeneration, and finally,

the degenerated cyst becomes hyporeflective in the chronic stage. Our findings supported this hypothesis in that there were more hyperreflective foci in the isoreflective cysts.

The relationship between macular edema and peripheral ischemia was inconclusive. We failed to show any relationship between the presence and severity of the peripheral ischemia and CSFT. Similarly, the severity of DME was not found to be correlated with the global nonperfusion area in the DAVE study.[35] In contrast to these findings, Wessel et al.[7] claimed that the risk of having DME increases 3.75 times in the presence of ischemia. However, in the same study there was no relationship between degree of ischemia and DME. Similar to this study, peripheral ischemia was shown to be associated with greater degree of DME in a study using ultra-wide-field angiography (UWFA).[36] In the current study, there was a statistically significant relationship between the noncystoid retinal tissue and peripheral ischemia. Noncystoid retinal thickness increased with the presence and severity of ischemia in the peripheral retina. This may be explained by a diffuse thickening of the macula outside the cyst due to increased VEGF load in the presence of peripheral ischemia.

Study Limitation

The retrospective design is the main limitation of our study. Other limitations include unavailability of current retinal imaging methods that can be used for ischemia such as OCTA and UWFA in our clinic and the lack of image analysis software for the measurement of nonperfusion areas and calculation of ischemic index.

Conclusion

In conclusion, the possibility of macular ischemia increases when the diameter of the cyst increases. The main factors increasing the probability of ischemia were increased CSFT and the presence of outer retinal damage. In cystoid DME, greater CSFT is associated with larger cyst, more outer retinal damage, and higher likelihood of macular ischemia findings in FA. In addition, the presence of peripheral ischemia seems to increase retinal thickening in the noncystic retinal area.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Gazi University with the ethics committee decision numbered 37 and dated 26 January 2015.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Şengül Özdek, Design: Şengül Özdek, Data Collection or Processing: Nuriye Gökçen Yalçın, Analysis or Interpretation: Nuriye Gökçen Yalçın, Şengül Özdek, Literature Search: Nuriye Gökçen Yalçın, Writing: Nuriye Gökçen Yalçın.

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Original Article

Pneumatic Vitreolysis for the Treatment of Vitreomacular Traction Syndrome

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Abstract

Objectives: To evaluate the posterior vitreous release rates after a single injection of expansile gas in patients with vitreomacular traction (VMT) syndrome with or without associated full-thickness macular hole (FTMH).

Materials and Methods: Thirteen eyes of 12 consecutive patients with VMT (11 eyes) or VMT+FTMH (2 eyes) were reviewed retrospectively. Intravitreal injection of 0.3 mL of pure sulfur hexafluoride (SF6) (9 eyes) or perfluoropropane (C3F8) (4 eyes) was performed. Bobbing the head forward and backward similar to 'drinking bird' head movements was instructed until VMT release. Full ophthalmic examination and optical coherence tomography was performed at each visit.

Results: VMT was released in all patients (100%) and mean release time was 5.2 days (1-19 days). Macular hole closure was not achieved in either of the two eyes with FTMH. Mean central subfield thickness decreased significantly from 361 µm to 263 µm (p=0.007). The mean pretreatment visual acuity was 0.44 LogMAR, which significantly improved to 0.25 LogMAR at the last visit (p=0.003). One of 13 eyes had retinal tear after the procedure which was successfully treated with laser retinopexy. Gas migration to the anterior chamber occurred in one patient. No other complications were observed.

Conclusion: Pneumatic vitreolysis with C3F8 and SF6 gases is a relatively safe, low-cost, and minimally invasive treatment modality for VMT. However, FTMH closure could not be achieved with pneumatic vitreolysis.

Keywords: Vitreomacular traction, macular hole, pneumatic vitreolysis, SF6, C3F8

Introduction

The natural course of posterior vitreous detachment (PVD) begins at the perifoveal retina and extends, in order, to the superior, temporal mid-periphery, fovea, inferior mid-periphery, and finally the optic disc margin, resulting in complete PVD.[1] Abnormal vitreomacular adhesions cause incomplete PVD, which may in turn induce vitreomacular traction (VMT).[2] Patients with VMT experience visual disturbances such as loss of vision, metamorphopsia, and central scotoma with distortion of the fovea.[3] VMT is classified according to the size of vitreomacular adhesion (VMA) (focal ≤1500 µm and broad >1500 µm) and the presence of concurrent retinal pathology (isolated or not).[4] VMT is thought to provoke cystoid macular edema, macular hole, epiretinal membrane (ERM), diabetic macular edema, and neovascular age-related macular degeneration.[5,6,7,8,9]

The initial approach to VMT is a period of observation in most patients.[10] Wu et al.[11] reported that VMT released spontaneously only in 21.4% of eyes, with increase in BCVA from 0.4 to 0.2 logMAR. The Pan-American Collaborative Retina Study Group indicated that observation can be recommended to selected patients. Although pars plana vitrectomy (PPV) is one of the best options for symptomatic VMT, it involves risks such as cataract formation, retinal tears, and endophthalmitis.[12,13] Ocriplasmin (Jetrea; Thrombogenics, Inc, Iselin, NJ) was approved in 2012 by the Food and Drug Administration and came into the market for pharmacological vitreolysis, which is a less invasive

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intervention than PPV.[14,15] However, VMT release rates were only about 40%. Moreover, since it is relatively expensive and may cause side effects like transient visual loss, lens subluxation, electroretinogram changes, ellipsoid zone changes, retinal breaks, and dyschromatopsias, it is far from being an ideal solution for VMT.[16,17]

Previous studies of the efficacy of intravitreal gas bubble for stage 1 and 2 macular holes yielded promising results.[18,19] Chan et al.[18] were the first to describe the technique of pneumatic vitreolysis (PV) in 1995. They used 0.3 mL of perfluoropropane (C3F8) and asked patients to stay in face-down position for at least 8 to 10 hours in a 24-hour period. They reported induction of PVD in 18 of 19 patients and closure of full-thickness macular hole (FTMH; Gass stage 2) in 3 of 6 patients. Ochoa-Contreras et al.[20] demonstrated induction of PVD using intravitreal injection of sulfur hexafluoride (SF6) gas in nonproliferative diabetic retinopathy cases. Rodrigues et al.[21] reported their PV results in VMT patients using spectral-domain optical coherence tomography (SD-OCT) and found that VMT was released in 40% and 60% of the eyes with C3F8 at 1 month and 6 months, respectively. Steinle et al.[22] suggested the "drinking bird" maneuver to increase VMT release rates and reported successful release of VMT in 25 of 30 patients (83%).

In the present study, we aimed to evaluate the efficacy of intravitreal pure SF6 and C3F8 gas injections followed by "drinking bird" head movements for the treatment of symptomatic VMT syndrome and FTMH.

Materials and Methods

This retrospective, single-center study includes a case series of 13 eyes of 12 patients who underwent PV to release VMT between January 2016 and May 2018. The study was approved by the Ethics Committee of Ankara Numune Training and Research Hospital (no: E-18-2266). Treatments were done by two surgeons (S.O., M.H.). All patients underwent standard ophthalmologic examination including Snellen visual acuity, anterior and posterior segment biomicroscopy, tonometry and spectral-domain optical coherence tomography (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany). Informed consent was obtained from all patients before the procedure. This study was performed in compliance with the Declaration of Helsinki.

All patients were symptomatic either with impaired vision or metamorphopsia and had been observed for spontaneous release for at least 3 months before the intervention. VMT with or without macular hole was defined by OCT criteria published previously by the International Vitreomacular Traction Study Group.[1] OCT scans were obtained by the same experienced technician. Central subfield thickness (CST) was measured using the built-in retinal mapping software and corrected manually if measurement errors were detected. Horizontal vitreomacular adherence (HVMA) and macular hole size were measured manually with built-in calipers.

The procedure was performed under topical anesthesia (Proparacaine, Alcaine, Alcon, Fort Worth, TX). Povidone-iodine, eyelid speculum, and 30-gauge needle with a 1 mL syringe were used for injection. Intravitreal injection of 0.3-0.4 mL of pure SF6 or C3F8 was performed through the pars plana following a prophylactic limbal paracentesis to soften the eye. Intraocular pressure, vision, and central retinal artery perfusion were evaluated after the procedure. Patients were instructed to perform "drinking bird" head movements by bobbing their head from an upright to a face-down position 10 to 20 times every 30 minutes until VMT release for the first week after gas injection. Patients were seen daily in the first postoperative week, then weekly until VMT release in the first month, and at 3-month intervals thereafter, which could be modified according to the surgeon's preferences and patient's availability. OCT was performed in all visits. Additional examinations were done as needed. After VMT release was detected, FTMH patients were instructed to stay in face-down position for a week, while phakic patients were instructed to avoid supine position until resorption of the gas to prevent cataract formation.

Primary outcome measures were time to VMT release, changes in CST in OCT, and visual acuity. Secondary outcome measure was macular hole closure for patients with associated FTMH.

Statistical Analysis

Statistical analyses were performed with SPSS 22.0 (IBM, Armonk, NY, USA). Snellen visual acuity was converted to logMAR. Wilcoxon signed-rank test was used to compare results.

Results

Patient demographics, additional ocular pathologies, and baseline and post-treatment ophthalmological findings are presented in Table 1. There were 4 male and 8 female patients in the study. The mean age was 67.0 years (range: 51-87 years). The mean time between appearance of symptoms and PV was 3.85 months (range: 3-6 months). The mean follow-up time was 11.2 months (range: 2-25 months). Two eyes of 2 patients had small FTMH with VMT, 11 eyes of 10 patients had only VMT. Three of 13 eyes were pseudophakic (23.1%). The mean CST was 361 µm (range: 253-550 µm) and the mean HVMA was 369 µm (range: 64-630 µm). The diameter of macular hole was 160 µm in the first patient and 240 µm in the second patient. Pretreatment visual acuities ranged between 20/200 and 20/32 in eyes with VMT.

VMT was released in all eyes, with a mean release time of 5.2 days (range: 1-19 days) (Figure 1). VMT was released in both of the eyes with FTMH but the holes did not close (Figure 2). Both of those eyes underwent pars plana vitrectomy which resulted in closure of the hole. The mean CST was 361 µm preoperatively, which decreased to 260 µm (range: 160-524 µm) and the difference was statistically significant (Wilcoxon signed-rank test, p=0.007). The mean LogMAR visual acuity was 0.44 at baseline and improved significantly to 0.25 (Wilcoxon signed-rank test, p=0.003).

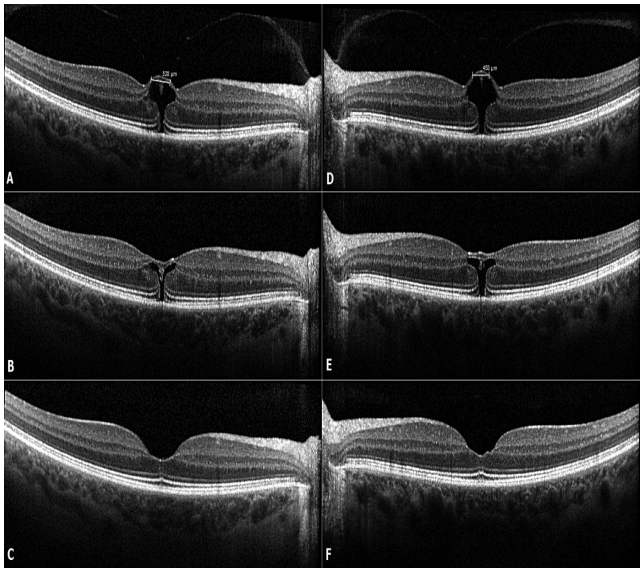

Figure 1. A 51-year-old woman (patient 6) presented with a complaint of blurred vision in both eyes. Snellen visual acuity was 0.63 and vitreomacular traction (VMT) was detected on spectral domain optical coherence tomography in the right (A) and left (D) eyes. Pneumatic vitreolysis was performed on the right eye first and VMT release was observed on day 3 (B). The same procedure was performed on the left eye and resulted in VMT release within 2 days (E). Snellen visual acuity increased to 0.9 in the right (C) and left (F) eyes within a month

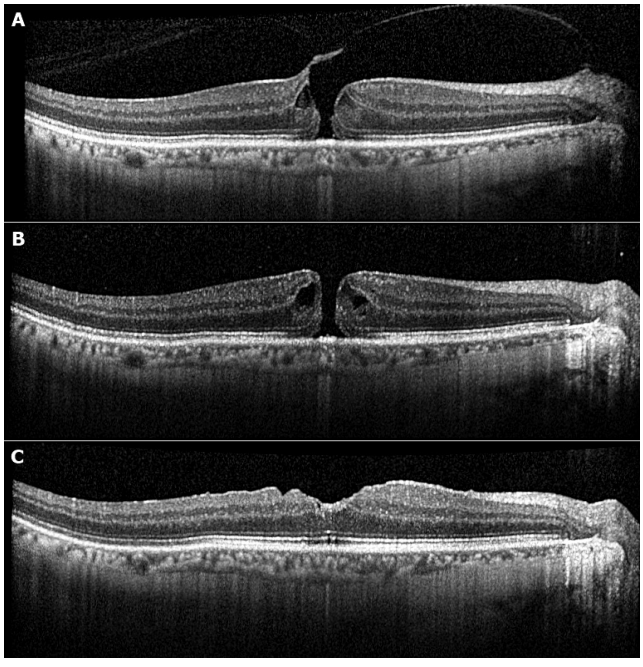

Figure 2. A 58-year-old man (patient 1) presented with complaint of metamorphosia involving his right eye. Snellen visual acuity was 0.5 with -6.75 D spectacle correction and there was small full-thickness macular hole (160 µm) with vitreomacular traction (VMT) on spectral domain optical coherence tomography (A). Pneumatic vitreolysis with pure C3F8 resulted in VMT release on postoperative day 4. However, a horseshoe tear was detected in the inferior equatorial retina and a laser retinopexy was performed. The patient was instructed to stay in face-down position for a week and followed-up for 45 days but the macular hole persisted (B). Macular hole closure could only be achieved after pars plana vitrectomy and final Snellen visual acuity was 0.6 (C)

Examination of fellow eyes revealed vitreomacular interface (VMI) disorders in 8 of 12 patients (Table 1). Five patients had VMT in the fellow eye, and VMT had resolved spontaneously in 2 eyes of 2 of those patients. Both eyes of patient 6 had VMT and were included in our study for PV treatment. PPV had been performed previously for the treatment of VMT causing total macular detachment in one patient and another one is still being followed up (Figure 3). One patient previously underwent PPV surgery for FTMH in the fellow eye. One patient had epiretinal membrane in the fellow eye.

A horseshoe retinal tear was detected at the 5 o'clock position in the equatorial area 5 days after pneumatic vitreolysis and was treated with laser photocoagulation in Patient 1. Intravitreal gas (C3F8) migrated into the anterior chamber during the procedure in another patient, who was phakic. The gas could be partially removed by anterior chamber paracentesis and caused no further complications. No other complication such as endophthalmitis or cataract progression was seen. Cataract progression can be reduced by avoiding supine position in order to prevent contact between gas and lens.

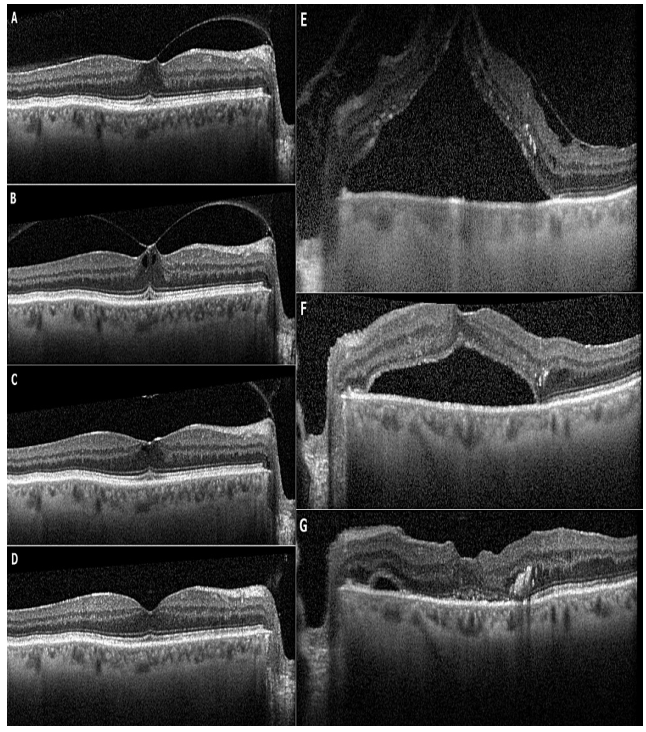

Figure 3. A 72-year-old patient (patient 5) who had glaucoma and nonproliferative diabetic retinopathy presented with complaint of blurred vision in both eyes. Snellen visual acuity was 0.6 and vitreomacular traction (VMT) was detected on spectral domain optical coherence tomography in the right eye (A). There was highly elevated serous macular detachment and epiretinal membrane in association with VMT with a visual acuity of 0.05 in the left eye (E). Pars plana vitrectomy was performed on the left eye. The macula gradually reattached after surgery and final visual acuity was 0.2 in the left eye (F, G). During follow-up, the right eye was observed for the first 3 months and traction was seen to progress with an associated visual acuity decrease to 0.4 (B). Pneumatic vitreolysis with pure SF6 resulted in VMT release the next day (C). Visual acuity increased to 0.7 at final visit 24 months after treatment (D)

Table 1. Patient demographics and characteristics before and after treatment

Patient no	Sex	Age (years)	Eye	Lens status	Additional diagnosis	Diagnosis	Fellow eye	Pre-treatment VA (LogMAR)	Pre-treatment CST	Pre-treatment HVMA	Gas used	VMT release	Release time (days)	Follow-up time (months)	Post-treatment VA (LogMAR)	Post-treatment CST	Adverse effect
1	M	58	OD	Phakic	High myopia	Small FTMH with VMT	Spontaneously separated VMT	0.3	330	172	C3F8	Yes	4	2	0.3	431	Retinal Tear
2	F	57	OS	Phakic	None	Small FTMH with VMT	VMT+	0.4	550	300	C3F8	Yes	5	3	0.3	524	None
3	F	70	OS	Phakic	None	VMT	PPV for MH	0.7	305	275	SF6	Yes	1	13	0.2	160	None
4	M	78	OD	Phakic	Glaucoma	VMT	Spontaneously separated VMT	0.4	420	64	SF6	Yes	17	27	0.2	328	None
5	F	72	OD	Phakic	Glaucoma, nonPDR	VMT	PPV for VMT	0.4	367	237	SF6	Yes	1	23	0.2	219	None
6	F	51	OD	Phakic	None	VMT	VMT+	0.2	360	528	SF6	Yes	3	11	0.1	182	None
6	F	51	OS	Phakic	None	VMT	VMT+	0.2	405	453	SF6	Yes	2	11	0.1	219	None
7	F	67	OD	Pseudophakic	Macular Telangiectasia	VMT	None	0.4	253	532	SF6	Yes	19	11	0.3	168	None
8	M	72	OD	Pseudophakic	AMD	VMT	None	0.3	343	430	SF6	Yes	3	25	0.1	259	None
9	F	78	OS	Phakic	None	VMT	None	0.5	420	239	SF6	Yes	6	17	0.4	200	None
10	F	66	OS	Phakic	None	VMT	PVD grade 3	1.0	278	354	C3F8	Yes	2	2	0.2	229	Gas migration to AC
11	F	64	OD	Phakic	None	VMT	None	0.2	299	589	C3F8	Yes	2	2	0.1	163	None
12	M	87	OS	Pseudophakic	None	VMT	ERM	0.8	374	630	SF6	Yes	3	2	0.8	301	None

VMT: Vitreomacular traction, FTMH: Full-thickness macular hole, VA: Visual acuity, CST: Central subfield thickness, HMVA: Horizontal vitreomacular adherence, M: Male, F: Female, OD: Right eye, OS: Left eye, nonPDR: Nonproliferative diabetic retinopathy, AMD: Age-related macular degeneration, MH: Macular hole, PPV: Pars plana vitrectomy, PVD: Posterior vitreous detachment, ERM: Epiretinal membrane, AC: Anterior chamber

Table 2. Comparison of the literature with our study

Author	Year	Number of eyes	Number of VMT	Number of MH	Gas Used	Posturing	Mean Follow-up (months)	Mean VMT release success	Mean VMT release Time	Mean initial VA (LogMAR)	Mean Final VA (LogMAR)
Mori et al.[26]	2007	20	0	20	0.5 mL SF6	Face-down (3-5 days)	19.5	19 of 20 eyes (95%)	2 weeks	0.38	0.19
Rodrigues et al.[21]	2013	15	15	0	0.3 mL C3F8	None	11.5	9 of 15 eyes (60%)	Not given (6 eyes in 1 month, 3 eyes in 6 months)	0.52	0.49
Day et al.[27]	2016	9	7	2	0.3 mL SF6	None	1	5 of 9 eyes (55.5%)	Not given	0.392	0.300
Yu et al.[24]	2016	8	7	1	0.3 mL C3F8	Face-down (2 days)	1	7 of 8 eyes (87.5%)	Not given	0.82	0.72
Steinle et al.[22]	2017	30	30	0	0.3 mL C3F8	Drinking bird	5	25 of 30 eyes (83%)	13 days	0.40	0.30
Claus et al.[23]	2017	20	20	0	0.2 mL C2F6 or SF6	Face-down	Not given	17 of 20 eyes (85%)	31 days	0.18	0.20
Chan et al.[25,28]	2017	50	35	15	0.3 mL C3F8	Avoid supine position	11.1	43 of 50 eyes (86%)	3 weeks	0.40	0.27
Present study	2018	13	11	2	0.3 mL C3F8 or SF6	Drinking bird	11.5	13 of 13 eyes (100%)	5.2 days	0.44	0.26

VMT: Vitreomacular traction, MH: Macular hole, VA: Visual acuity

Discussion

There is a consensus about observing patients with VMT for a few months before initiating any treatment, because spontaneous VMT release is not uncommon. Nevertheless, longstanding cases may lead to the formation of ERM; therefore, the timing of treatment is still questionable.[23]

This study presents our results of PV with C3F8 and SF6 gases with "drinking bird" head movements for the treatment of VMT syndrome with 100% release rate within a mean duration of 5.2 days.

PV was first described by Chan et al.[18] in 1995 (pre-OCT era) with complete PVD in 18 of 19 eyes (94.7%). Total PVD was achieved with 0.3-0.5 mL intravitreal C3F8 injection in 2-9 weeks (average 4 weeks) and B-scan ultrasonography was used for the PVD evaluation. Jorge et al.[19] reported similar results of PVD induction with C3F8. Rodrigues et al.[21] Yu et al.[24] and Steinle et al.[22] reported VMT release rates of 40%, 87.5% and 73% at 1 month with C3F8, respectively. Chan et al.[25] recently reported the largest series on PV with C3F8 and achieved successful PVD in 86% of 50 eyes at a median of 3 weeks. Although numerous studies have demonstrated the efficacy of C3F8 in PV, there are fewer studies in the literature regarding SF6, which has also been used for PV, with lower and delayed release rates.[26] Mori et al.[26] reported that 19 of 20 patients had total PVD following PV with SF6, confirming our results. They instructed patients to keep their head in prone position during the first 3-5 days after PV and achieved PVD induction in 2 weeks. Day et al.[27] recently reported 55.6% VMT release using PV with SF6. The procedure did not include positioning in their study, which may explain their lower release rates compared to other studies.

In our study, C3F8 was used in the 2 eyes with FTMH and 2 of the eyes with VMT, while the other 9 eyes with VMT received SF6. We used both gases to understand whether there was a difference in VMT release pattern and time. We observed 100% VMT release rate with both gases and there was no difference between them in terms of time to VMT release after the procedure. A shorter duration gas may be preferable for PV to eliminate the possible disadvantages of a longer acting gas like C3F8, such as increased rate of possible complications and restriction of patient's daily activities, head positions, and mobility. Therefore, SF6 may be the first option for PV, as it has the same efficacy and the advantage of shorter duration. C3F8 may be chosen for patients with additional VMI disorders such as ERM or FTMH.

Most studies present their release rates at 1 month, but it may still be prolonged until 9 weeks; therefore, waiting for 2 months before switching to an alternative treatment has been suggested.[25,28,29] Our average time of VMT release was 5.2 days. Initial release time was shorter in our study compared to the literature data. In most studies, face-down positioning or other maneuvers to facilitate the VMT release was not frequently applied after intravitreal gas injection. Only Steinle et al.[22] reported high (84%) VMT release success rates with drinking bird head movements and stated that it might accelerate vitreous

liquefaction and separation. On the other hand, Chan et al.[25] reported the largest series to date with successful release of VMT in 43 of 50 eyes (86%). They instructed patients to avoid supine position and lie on one side or the stomach during sleeping hours and observed results similar to those achieved with the drinking bird maneuver. Other studies which had >80% VMT release rates used face-down posturing.[23,24] All of our patients were instructed to bob their head forward and backward 10-20 times every 30 minutes until VMT release was detected. The possible mechanical separation effect provided by these movements may promote VMT release and shorten release time. We believe that the main reason for the complete and rapid success observed in our patient group was the addition of drinking bird head movements (Table 2). The increase in rates of VMT release over 80% with head positioning (face-down or drinking bird) suggests that posturing is crucial after PV. We believe face-down (or avoiding supine position) and drinking bird positioning have similar release rates, but that VMT release time may be shortened with drinking bird head movements 10-20 times every 30 minutes. The time to VMT release was 13 days in Steinle's study[22] and 5.2 days in our study. Mean VMT release time was longer in the other studies which did not use posturing or used only face-down positioning (Table 2).

All of our patients (13 of 13 eyes) had focal adhesion (≤1500 µm). The mean of HVMA in VMT patients was 369 µm (range: 64-630 µm). Our study results together with the current evidence in the literature suggest that having a focal VMA size close or under 500 µm seems to be essential to obtain good results in VMT syndrome.[21,22,25,27] Rodrigues et al.[21] previously defined three criteria that predicted treatment failure with 100% certainty: 1) HVMA ≥750 µm; 2) central foveal thickness ≥ 500 µm; and 3) moderate or high posterior hyaloid reflectivity. Foveal thickness and HVMA measurements were below these criteria in all of our VMT patients, but unfortunately we did not analyze vitreous face reflectivity.

OCT has increased our knowledge about VMA and the detection of VMI disorders.[30,31] OCT measurements can be used as a predictor of successful treatment and possible visual acuity increase.[21,32,33] Rodrigues et al.[21] reported that VMT release with PV increased in patients with low posterior hyaloid reflectivity on OCT. Sun et al.[32] determined that resolution of cone outer segment tips line and inner segment/outer segment line defects observed on SD-OCT was positively correlated with visual acuity improvement after VMT treatment with PV. SD-OCT based studies also showed that fellow eyes of patients with VMT or FTMH are at increased risk of developing VMI disorders.[34,35,36,37] It is important to examine the fellow eye and follow up with OCT. In our study, 8 of 12 patients had VMI disorders such as VMT, FTMH, and ERM. Five patients had VMT in their fellow eye, which was also a candidate for PV. One of our patients had bilateral VMT which was treated with PV 4 days apart (Figure 1).

The PV technique is also used for the treatment of stage 2 macular holes. Chan et al.[18] reported a 50% closure rate of FTMH with intravitreal injection of C3F8 in 1995. Jorge et al.[19] observed successful FTMH closure in 5 of 6 eyes with 0.4 mL intravitreal C3F8. Mori et al.[26] reported that 19 of 20 patients had total PVD and 50% of patients with FTMH had anatomical closure of the hole with SF6 injection alone. Chan et al.[25] recently reported a 100% VMT release rate in eyes with FTMH but the hole closure rate was only 53% with one injection of C3F8. We observed rapid VMT release in 2 patients with small FTMH with VMT, but hole closure could not be achieved in either of them. Previous studies have indicated that PV may be beneficial for small FTMH with VMT.[25,26] PPV should be the first option for the treatment of larger holes. Chan et al.[25] suggested additional gas injections to increase the closure rate of FTMH from 53% to 67%. We did not perform any additional injection for FTMH in the present study, however. Only C3F8, which has longer duration, was used in eyes with FTMH, and patients were instructed to stay in face-down position after VMT release for a week, which was still not sufficient to close the hole in our cases (Figure 2).

Pharmacologic vitreolysis with ocriplasmin was introduced to the market with promising results compared to placebo groups.[14,15] The MIVI-TRUST trial reported a 26.5% VMT release rate, while the OASIS study achieved 41.7% success.[14,38] PV has higher VMT release rate (56-95%) in the literature with lower cost. Yu et al.[24] compared PVD induction rates of ocriplasmin and PV and showed that PV had a higher VMT release rate than ocriplasmin (87.5% vs. 42.9%). Moreover, complications including transient vision loss, temporary ellipsoid zone attenuation, vitreous floaters, retinal breaks, lens subluxation, and retinal detachment have also been reported following ocriplasmin injection.[17,39,40,41]

Symptomatic VMT can be treated with PPV with a very high success rate. However, with this surgery, high cost and possible complications such as cataract, retinal tear, or endophthalmitis should always be considered.[6,12] The PV technique has many advantages over PPV, including shorter operative time, lower cost, and eliminating the need for any kind of local or systemic anesthesia. In addition, PV complications are now well defined because of the experience with pneumatic retinopexy. Low complication rates were observed in the literature, including retinal tears, progression of VMT to FTMH, and rhegmatogenous retinal detachments.[28] In the current study, one patient developed a peripheral retinal tear which was effectively treated with laser retinopexy. He was phakic and had high myopia. Patients that were complicated with retinal tear in the literature were also myopic and phakic patients.[28] Attention should be paid to high myopic and phakic patients for this complication. Neither endophthalmitis nor cataract progression has been reported in the literature following PV.

Conclusion

PV is a safe, low-cost, and relatively easier procedure than other surgical options. Consequently, for all patients with symptomatic focal VMT, in particular for older age groups with associated comorbidities, PV can be considered as first-line treatment following a certain duration of observation. Failed PV

can always be followed by PPV. Limitations of this study are the limited number of patients and its retrospective nature. Further studies with more patients are needed.

Ethics

Ethics Committee Approval: Ankara Numune Training and Research Hospital Clinical Research Ethics Committee E-18-2266.

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şengül Özdek, Murat Hasanreisoğlu, Concept: Hüseyin Baran Özdemir, Şengül Özdek, Design: Hüseyin Baran Özdemir, Şengül Özdek, Data Collection or Processing: Hüseyin Baran Özdemir, Analysis or Interpretation: Hüseyin Baran Özdemir, Şengül Özdek, Murat Hasanreisoğlu, Literature Search: Hüseyin Baran Özdemir, Writing: Hüseyin Baran Özdemir, Şengül Özdek, Murat Hasanreisoğlu.

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Original Article

Coexistence of Peripheral Retinal Diseases with Macular Hole

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Abstract

Objectives: To investigate the frequency of retinal tear, retinal hole, and lattice degeneration in peripheral retinal examination of patients with macular hole.

Materials and Methods: The files of patients who underwent pars plana vitrectomy surgery with a diagnosis of macular hole at Eskişehir Osmangazi University Department of Ophthalmology between 2008 and 2018 were retrospectively analyzed. A total of 106 patients with primary macular hole who underwent peripheral retinal examination were included in the study. The frequency of retinal tears, holes, and lattice degeneration associated with macular hole was investigated.

Results: Peripheral retinal examination of 106 patients who underwent macular hole surgery revealed retinal tear in 3 patients (2.8%), retinal hole in 4 patients (3.8%), and lattice degeneration in 10 patients (9.4%). Retinal hole and lattice degeneration were observed concomitantly in 1 patient.

Conclusion: This study showed that patients with macular hole have concomitant retinal tears and holes, which are also thought to arise due to vitreoretinal traction, at a frequency similar to that in the general population. This result suggests that both the anterior and posterior vitreous may have different pathologies at the same time related to these diseases.

Keywords: Macular hole, retinal tear, retinal hole, lattice degeneration

Introduction

Macular hole (MH) is a defect of the foveal neurosensory retina that is usually round in shape and includes all of the vertical retinal layers.[1] Although numerous factors have been implicated in its etiology, perifoveal posterior vitreous detachment (PVD) is considered the most important, as it leads to vitreomacular traction (VMT) by exerting a dynamic force in the anteroposterior direction.[2,3] Intraretinal pseudocysts develop following VMT, and these cysts merge and expand, transforming into a full-thickness hole.[3] The prevalence of MH in individuals over 40 years of age is 0.1-0.8%, with women comprising two-thirds of patients.[4,5] MH is associated with reduced visual acuity, metamorphopsia, micropsia, and rarely, photopsia.[6] Optical coherence tomography (OCT) is the gold standard in diagnosis and follow-up.[7,8] In surgery, tangential and anteroposterior vitreous traction on the macula is released and the detached retina adjacent to the hole is reattached. With posterior hyaloid and internal limiting membrane peeling and intravitreal gas tamponade, the success rate is 85-100%.[9,10]

Similar to MH, the prevalence of retinal tear associated with traction that occurs during PVD was found to be 1-3.3%, including the studies on postmortem eyes,[11,12,13,14] while the prevalence of retinal hole was found to be 2.4-4.4%.[15,16] In another study, the prevalence of retinal holes and tears was reported to be 2%, which was relatively less than in other

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studies.[17] The prevalence of lattice degeneration was found to be 6-10.7%.[18,19,20] Studies on the association of MH and peripheral retinal disorders are limited, but one study determined the total prevalence of retinal tear + retinal hole + lattice degeneration in patients with MH to be 33.8%.[21]

As these retinal defects are believed to be caused by vitreoretinal traction, similar to the etiopathogenesis of MH, the aim of our study was to determine the prevalence of retinal hole, retinal detachment, and peripheral retinal degenerations in MH patients in order to contribute to the literature regarding the need for peripheral retinal examination in this patient group.

Materials and Methods

The study was conducted according to the principles of the Declaration of Helsinki, and ethics committee approval was obtained from Eskişehir Osmangazi University Ethics Committee. We retrospectively analyzed surgical notes from the files of patients who underwent pars plana vitrectomy surgery for a diagnosis of MH between 2008 and 2018 at Eskişehir Osmangazi University, Faculty of Medicine, Department of Ophthalmology. A total of 103 eyes of 103 patients who were diagnosed with primary MH and underwent peripheral retinal examination were included in the study. Those with a history of trauma, vitrectomy, panretinal laser therapy, degenerative myopia, any retinal disorder that may affect the peripheral retina, and those without a surgical note regarding the peripheral retinal screening during MH surgery were excluded. MH staging was based on fundus examination and optical coherence tomography results.[22] According to the classification used, vitreopapillary traction was recorded as stage 1; MH ≤250 µm in diameter as stage 2; 250-400 µm MH as stage 3; and MH ≥400 µm as stage 4. In terms of PVD, those with stage 2 and 3 MH were considered incomplete PVD, and those with stage 4 MH were considered complete PVD. Retinal hole, retinal tear, and peripheral retinal degenerations detected via peripheral retinal examination with scleral indentation were recorded.

Statistical Analysis

IBM SPSS for Windows version 22.0 software was used for statistical analyses. Using descriptive statistical analysis, numerical variables were presented as mean ± standard deviation. Binominal logistic regression analysis was used to assess correlations between variables. A p value <0.05 was considered statistically significant.

Results

A total of 106 eyes of 106 patients were included in the study. The patients were between 41 and 87 years of age, with a mean age of 68.4±9.6 years. Sixty-six (62.2%) of the patients were female and 40 (37.8%) were male.

MH surgery was performed on the right eyes of 54 (50.9%) patients and on the left eyes of 52 (49.1%) patients. The surgery was done using 25-gauge vitrectomy in 49 (46.2%) patients, 23-gauge vitrectomy in 46 (43.4%) patients, and 20-gauge vitrectomy in 11 (10.4%) patients. We found that 10 of the 106 patients underwent simultaneous cataract and MH surgery.

Table 1. Peripheral retinal diseases associated with macular hole

	Number (n)	Percentage (%)
Tear	3	2.8
Hole	3	2.8
Hole + lattice	1	0.9
Lattice	9	8.4
Normal	90	84.9
Total	106	100

Preoperative MH staging of the operated patients was recorded as stage 2 in 12 patients (11.3%), stage 3 in 77 patients (72.6%), and stage 4 in 17 patients (16.1%). In addition, 89 patients (84%) had incomplete PVD while 17 patients (16%) had complete PVD.

The findings of peripheral retinal examinations performed at the end of MH surgery are summarized in Table 1.

According to these results, 16 (15.1%) of the 106 patients had peripheral retinal disorders, while 90 patients (84.9%) did not.

Binominal logistic regression analysis revealed no correlation between higher MH stage and retinal tear, retinal hole, or retinal degeneration (p>0.05). Of the 90 patients who had no accompanying peripheral retinal disorder, 55 (61.1%) were given SF6 gas and 35 (38.9%) were given C3F8 gas as intravitreal tamponade during MH surgery.

The other patients received intravitreal gas injection as well as 2-3 rows of endolaser around 9 lattice degenerations, 3 retinal holes, 1 lattice degeneration + retinal hole, and 3 retinal tears detected in the peripheral retina at the end of surgery.

Discussion

Although numerous factors have been implicated in the pathophysiology of age-related primary idiopathic MH, VMT is considered the main etiology.[2,3] Studies on MH have shown that its prevalence is higher among individuals 60-70 years of age and 2-3 times higher in women.[23,24] In our study, the mean age of 106 patients who underwent MH surgery was 68.4±9.6 years, and the prevalence was higher in females (62.2%).

In our study, peripheral retinal screening at the end of vitrectomy in 106 patients who underwent MH surgery showed that 3 patients (2.8%) had retinal tear, 4 patients (3.8%) had retinal hole, and 10 patients (9.4%) had lattice degeneration. One of these patients had both lattice degeneration and retinal hole.

Previous studies, including those in postmortem eyes, have determined the prevalence of retinal tear to be 1-3.3%.[11,12,13,14]

Consistent with these studies, retinal tear was detected in 2.8% of patients who underwent MH surgery in our study.

Studies including postmortem eyes showed the prevalence of retinal hole was 2.4-4.4%.[15,16] Similarly, in our study the prevalence of retinal hole was 3.8% among patients who underwent MH surgery.

The prevalence of the most common peripheral retinal degeneration, lattice degeneration, has been reported as 6-10.7%.[18,19,20] In the present study, we also found the prevalence of lattice degeneration to be 9.4%.

In a study similar to ours that included 167 patients, the total prevalence of peripheral retinal tear + retinal hole + lattice degeneration accompanying MH was 33.8%, which was higher than the population average.[21] In our study, the total prevalence of peripheral retinal tear + retinal hole + lattice degeneration was found to be 15.1%, which was similar to the population average.

In our study, the prevalence of retinal tear and hole in patients with MH, conditions believed to share the common etiology of VMT, was comparable to that in the general population, not higher. This will contribute to the literature, as it indicates that the vitreous does not have a uniform character, but may have different relationships with the macula and retina, and can develop different pathologies in these diseases.

As to why the detected retinal tears did not cause detachment, it may be due to the effect of other mechanisms that maintain adhesion between the retinal pigment epithelium and sensory retina, or there may not be sufficient vitreoretinal tractional force to cause detachment in every tear. Moreover, although the prevalence of retinal tear including in postmortem eyes was found to be 1-3.3%,[11,12,13,14] considering that the prevalence of retinal detachment is 5-10.39 per 100,000,[25,26,27] every tear may not lead to detachment.

Study Limitations

Limitations of our study are the relatively small number of patients and the retrospective design.

Conclusion

In summary, the prevalence of retinal tear and retinal hole in patients with macular hole, which are regarded as having similar etiologies, were similar to the population, suggesting that the pathologies involving the anterior and posterior vitreous may be different.

Ethics

Ethics Committee Approval: Eskişehir Osmangazi University Faculty of Medicine (2018/199).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Erdoğan Yaşar, Design: Nazmiye Erol, Data Collection or Processing: Mustafa Değer Bilgeç, Analysis or Interpretation: Erdoğan Yaşar, Literature Search: Ayşe İdil Çakmak, Writing: Erdoğan Yaşar.

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Review

Retinal Prostheses and Artificial Vision

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Abstract

In outer retinal degenerative diseases such as retinitis pigmentosa, choroideremia, and geographic atrophy, 30% of the ganglion cell layer in the macula remains intact. With subretinal and epiretinal prostheses, these inner retinal cells are stimulated with controlled electrical current by either a microphotodiode placed in the subretinal area or a microelectrode array tacked to the epiretinal region. As the patient learns to interpret the resulting phosphene patterns created in the brain through special rehabilitation exercises, their orientation, mobility, and quality of life increase. Implants that stimulate the lateral geniculate nucleus or visual cortex are currently being studied for diseases in which the ganglion cells and optic nerve are completely destroyed.

Keywords: Artificial vision, bionic eye, visual prosthesis, Argus II, retinal prosthesis, outer retinal degeneration, retinitis pigmentosa, phosphene

Introduction

Nearly half of visual impairment worldwide is caused by retinal diseases. Degenerative retinal diseases such as retinitis pigmentosa (RP), choroideremia, and age-related macular degeneration (AMD) begin in the outer retinal layers and progress gradually, with the inner retinal layers remaining largely unaffected until advanced stages of disease. Histopathological studies have shown that 70% of photoreceptors are lost in AMD, while 93% of the retinal ganglion cells (RGCs) survive. RP mainly affects the photoreceptor layer; in the macular region, 78-88% of the inner nuclear layer (INL) and approximately 30% of the ganglion cell layer (GCL) remains intact. RP leads to cell loss in all retinal layers in the extramacular region; the INL and GCL are relatively less preserved than the macular region. There is no difference between the different genetic types of RP in terms of macular cell loss. In the extramacular region, more cells are preserved in autosomal-dominant RP.[1,2,3]

Neovascular AMD is treated at significant rates using intravitreal anti-VEGF drug injections, but there is not yet a proven effective treatment for geographic atrophy (GA), an advanced stage of dry AMD. RPE65 gene therapy and slow-release ciliary neurotrophic factor implants are being used in the treatment of RP, and stem cell research is ongoing. However, there is no proven, definite treatment approach. Retinal prostheses developed in recent years are promising for eyes with severe visual impairment due to outer retinal degeneration.[2,4]

Electrical Stimulation of the Retina

The neural network in the inner retina, which is relatively unaffected by the degenerative process, is electrically stimulated in a controlled manner with microelectrode arrays placed under the retina or on the macula. Spatial visual perception can be generated with simultaneous pattern stimulation of multiple retinal locations. Action potentials generated in the retinal ganglion cells are relayed to the brain through the intact optic

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nerve and optic tracts and perceived as phosphenes; these can be localized based on the stimulated retinal field. Phosphenes are generally seen as white, round or oval spots of light that are of varying size and cause no discomfort.[2,5]

Current research and development on visual prostheses and artificial vision is mainly focused on retinal implants (epiretinal, subretinal, suprachoroidal) and cortical implants. Retinal implants are being investigated for diseases such as RP, choroideremia, and GA, which cause degeneration of the outer retinal layers. Cortical implants placed in the primary visual cortex are being investigated as an option for patients who have completely lost their vision for various reasons.[6]

Microelectrode arrays placed in the subretinal space act as a phototransducer and are in a more natural position, like an artificial photoreceptor layer; however, the surgical and technical problems associated with them have not been totally solved.[7] Prostheses placed in the suprachoroidal space through a scleral incision stimulate the bipolar cells in the outer retinal layer indirectly via the choroidal layer, without touching the degenerated retinal tissue.[2]

A. Subretinal Implant

This retinal prosthesis is comprised of light-sensitive microphotodiode arrays. The array is placed under the retina, and is therefore in a more physiological position between the retinal pigment epithelium and degenerated photoreceptor layer. Placement of the implant in the subretinal space is done either externally via a scleral incision or internally via vitrectomy and retinotomy. The microphotodiode array consists of thousands of small, light-sensitive units, each comprising a diode, amplifier, and microelectrode components, which are embedded in a silicone matrix. Microelectrodes made of titanium nitrite and gold are in contact with the relatively intact retinal neural network. This array receives light, processes and amplifies the signal, and stimulates the nerve cells. The photovoltage process that occurs when crystal is exposed to natural light entering the eye generates an electric current that directly and precisely stimulates the degenerate photoreceptors and bipolar cells it contacts. These processes are carried out by the intact residual inner retinal layers; therefore, a small threshold is enough to generate a visual response. However, natural light cannot provide enough energy to the light-sensitive microphotodiode array, so power must be supplied by external electronics. Therefore, an induction coil is embedded subcutaneously in the retro-auricular region and power is supplied to the microphotodiode array through a cable. This implant has certain advantages: It provides a more physiological form of stimulation and implantation of the array into the submacular region is easy. Subretinal implants use the patient's own optic system; therefore, an external camera or external image processing unit is not required to capture images. Existing eye movements and gaze are sufficient for object localization, and scanning head movements are not necessary like with epiretinal implants. The Alpha-IMS is a 1500-pixel subretinal implant that obtained CE mark approval in Europe in 2013.[2,7]

B. Epiretinal Implant

Epiretinal implants do not have microphotodiode units that generate electric current via natural light, like those in subretinal implants. Visual information collected by a microcamera mounted on removable glasses is processed by a video processor and encoded as spatial electrical potential patterns that directly stimulate the ganglion cells and nerve fibers. Because the stimulated area is large, it generates indistinct malformed phosphenes whose shapes are corrected through electronic processing. As this system bypasses the residual inner retinal layers and directly stimulates ganglion cells, it requires complex image processing techniques with electronic circuitry instead of neural network processing.[2,8]

Epiretinal prostheses are not useful for vision losses associated with glaucoma and optic nerve pathologies in which retinal ganglion cells and axons are damaged. The optic nerve, lateral geniculate nucleus, and visual cortex can also be used as targets of stimulation in complete vision loss due to any cause. Human trials of visual cortical stimulators were initiated in 2017 (ORION project, Second Sight, Sylmar).[2,6,9]

There are ongoing studies of different epiretinal implant designs in various centers. However, the first and currently only product to receive both Food and Drug Administration (2013) and CE mark (2011) commercial approval is the Argus® II epiretinal prosthesis system (Second Sight Medical Products Inc., Sylmar, CA, USA).[3]

Argus II Epiretinal Prosthesis

Initial research into this prosthesis began in 1990. Following feasibility studies of the 16-electrode Argus I initiated in 2002, prospective multicenter studies with the 60-electrode Argus II were initiated in 2007. Biocompatibility, reliability, and benefit to the patient has been demonstrated, and it is now the most implanted visual prosthesis in many countries, including Turkey.[3]

The Argus II system uses an epiretinal approach, with the microelectrode array implanted into the inner macular surface, very close to the nerve fiber layer. Thus, direct and controlled electrical stimulation is applied to the partially functional inner retinal neural network, RGCs, and/or bipolar cells. The action potential formed by these inner retinal cells travels to the visual cortex via the optic nerve and optic tracts to generate a basic visual perception called a phosphene.[10]

1. System Components

A. Removable external component: Consists of two parts:

- Glasses the patient can wear and remove: A video microcamera is mounted in the bridge and an external connection coil is attached to the sidearm. The transmitter coil sends external power and incoming information from the video processing unit (VPU) to the implanted coil wirelessly via radiofrequency.

- The VPU is a portable computer the patient can mount on their belt or carry in their pocket.

When the patient puts on the glasses and switches on the system, the video microcamera receives images as the patient makes scanning head movements, and it sends these to the VPU via cable. The image processor reduces the images' resolution and converts them into electrical signals in real time to produce digital stimuli. A series of stimulation commands are generated. The VPU is custom programmed and cannot be used by other patients. Ultimately, visual images are converted into a template of electrical stimulations, which are sent to the external transmitter coil via the same cable. These signals are then transmitted wirelessly to the receiver coil sutured to the sclera via radiofrequency connection (Figure 1).

B. The permanent ocular implant component: The implanted part of the Argus II comprises the following interrelated electronic components that are mounted on a material similar to the silicone scleral band used in retinal detachment operations:

- Receiver coil: Following dissection of the conjunctiva and Tenon's capsule, the receiver coil is positioned under the lateral rectus muscle and then sutured to the sclera. It wirelessly receives electric power and visual signal information from the external transmitter coil at the sidearm of the glasses. The electrical power supplies the microelectrodes and electronic circuits that deliver controlled stimulation to the retina to produce a visual image.

- Electronics case: This component is sutured to the sclera and connected via electronic cable to the microelectrode array that will be tacked to the macular surface. Using its decoding circuitry, it decodes commands encoded in the radiofrequency signals. According to these commands, the necessary pixelated stimulation output is generated and sent to the intraocular microelectrode array.

- Microelectrode array: Located at the end of the electronic cable, it is inserted into the vitrectomized vitreous cavity through a 5.2-mm pars plana incision. This array comprises 60 independently active platinum microelectrodes organized in 6x10 grid embedded in waterproof silicone matrix. The dimensions of the array are 4.7x7.1 mm (Figure 2). The relatively intact neural network in the inner macular surface is stimulated by the spatial and temporal stimulation patterns transmitted to the array (Figures 3 and 4). The resulting action potentials are relayed to the brain via the optic nerve tract formed by RGC axons, generating visual perception in the form of an array of light spots (phosphenes).[3,7,11]

The electronic components constituting the Argus II system are compatible with magnetic resonance imaging (MRI) up to a field strength of 3 Tesla (glasses and VPU must be removed during imaging). However, the implanted components generate a 50x50 mm image artifact in MRI images, making it difficult to examine orbital structures.[3]

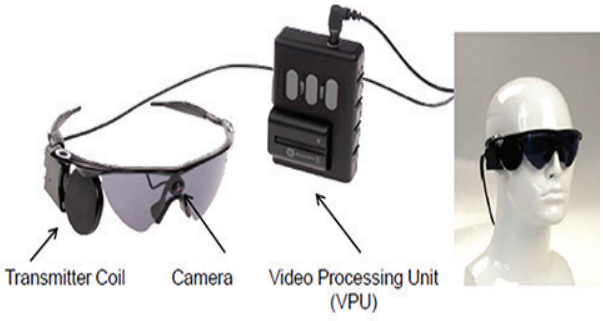

Figure 1. The removable external part of the Argus II epiretinal prosthesis system[13]

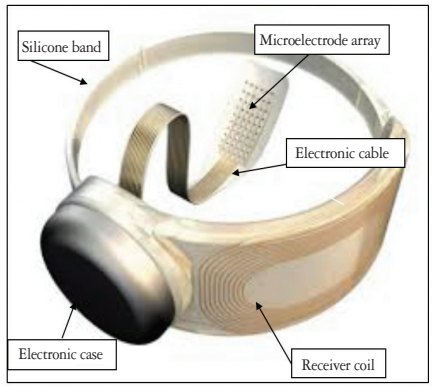

Figure 2. The permanent ocular implant part of the Argus II epiretinal prosthesis: electronics case and receiving coil on a silicone band, electronic cable, and microelectrode array[13]

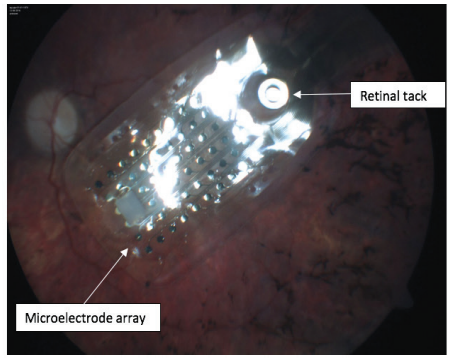

Figure 3. Argus II epiretinal prosthesis with a 60-electrode array positioned on the macula and attached to the sclera with the retinal tack piercing the choroid (surgery performed by E.Ö.)

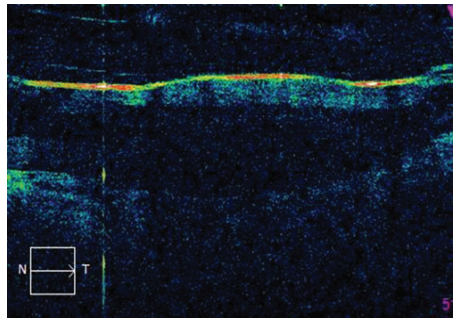

Figure 4. Cross-sectional spectral-domain optical coherence tomography image of the microelectrode array placed on the inner surface of the macula (surgery performed by E.Ö.)

2. Stimulation Strategies

The diameter of each electrode in the array is 200 µm, while the RGC bodies are 15 µm in diameter. Therefore, every electrode stimulates many RGCs together with their axons in the neural network it contacts. Thus, the generated phosphenes are not punctate but linear in shape, a factor that compromises the clarity of the image. Various stimulation strategies have been developed to prevent the formation of linear phosphenes:

- Varied current-controlled stimulation pulses are used for electrical stimulation. Of these, the use of a charge-balanced, biphasic, cathodal first pulse with zero net charge injection enables the stimulation of more ganglion cell bodies without retinal damage. When the cells bodies are stimulated, the threshold for phosphene generation is lowered, and a greater number of small, punctate phosphenes are generated.

- With the bipolar stimulation technique, in which one of the epimacular array electrodes is used as a return electrode, the stimulated retinal field is smaller and therefore the probability of generating small punctate phosphenes increases.

- Acceptable patient mobility can be achieved with about 600 electrodes; however, this requires a reduction in electrode diameter. As the electrode's surface area is reduced, current density and charge density increase rapidly, and the electrochemical reactions that occur lead to retinal tissue damage. In order to increase the number of pixels without changing the existing hardware in Argus II, stimulation strategy software such as "current focusing" and "current steering/virtual electrode" is being developed. With these virtual applications it is now possible to make 209 tiny electrical stimulations, which increases the likelihood of being able to stimulate fewer RGCs and to stimulate their bodies in particular. The ability to generate a greater number of smaller punctate phosphenes will enhance the clarity of the image.[2,12]

3. Stages of Argus II Implantation- Selecting suitable candidates

Patients should be in fair medical and psychological condition and be motivated. The patient's expectations from the surgery should be determined, and they should fully understand the benefits and limitations of implantation. Both the patient and their family members should be ready and capable of carrying out the long and challenging process ahead;

- Special preoperative training of the surgeon, medical personnel, and technical staff about the implantation;

- Introducing the patients to the system components and instructing them on their use;

- Procuring and preparing specialized surgical materials and making checklists;

- Performing the implantation procedure with special technical support;

- Closely following the patient postoperatively for conjunctival erosion/dehiscence, endophthalmia, severe hypotonia, choroidal/retinal detachment, and array position;

- Performing the calibration (fitting) procedure 15 days after implantation: The electrodes are activated and the minimum and maximum threshold values that generate phosphene perception without causing retinal damage are determined for each electrode. Individualized stimulation programs are created and uploaded to the VPU. The glasses-mounted video microcamera is adjusted and positioned. Because the patient's visual field is limited to 20° after implantation, they are taught how to recognize the position and shape of objects using head scanning movements;

- Rehabilitation process: One month after calibration, a long and difficult rehabilitation process using special methods under the supervision of specialists is required to teach artificial vision. This must be thoroughly explained to the patient and their family before implantation. At the end of the rehabilitation process, patients can distinguish the direction of movements; their orientation, mobility, and capacity for independent movement are improved; they can distinguish light and dark colors as shades of gray, see capital letters, and read short words; and their overall quality of life improves.[2,3,13]

4. Optimal candidates for Argus II retinal prosthesis:

This epiretinal prosthesis is appropriate for patients with severe outer retinal degeneration but relatively spared inner retina. There must be a significant amount of viable RGCs in the inner retina to send electrical stimulation to the visual cortex and create the perception of phosphene.[14] Therefore, this implantation is applicable in retinal degeneration patients with advanced RP, choroideremia, and advanced dry AMD. A preclinical study is also being conducted to test the feasibility and potential benefit of the system in GA.[15]

The patient's and their family's expectations from the implantation must be thoroughly understood and the potential benefits and limitations of the device must be accepted. Moreover, it is essential that the patient and their family be able and willing to follow through with the fitting and rehabilitation processes. Ophthalmologic examination findings in the patient must be within the appropriate range for implantation, which are:[13]

- The patient's level of vision must be light perception, with positive camera flash test. If light perception is suspect, visual evoked response test must be normal,

- The patient should have the experience of seeing shapes prior to visual impairment,

- Because the implant currently in production is uniform with standard dimensions, in order for the array to be placed in the appropriate position on the macula, the patient must be at least 25 years of age and the anteroposterior length of the globe must be 20.5-26 mm.

- There must be no advanced strabismus or nystagmus that would disrupt the wireless communication between external coil and implanted coil.

- There must be no conjunctival and scleral disorders or macular staphyloma that would prevent the appropriate and secure implantation of system components.

- There must be no conditions that preclude the use of general anesthesia or the related medications.

5. Surgical Method

The eye is prepared as for pars plana vitrectomy with scleral buckling. After the silicone band including the receiver coil and electronics case is passed under the four rectus muscles, the ends of the band are connected with a Watzke sleeve at the superonasal quadrant. The electronics case is sutured to the superotemporal quadrant and the receiver coil is sutured to the inferotemporal quadrant under the lateral rectus according to the predetermined limbus distances. Following pars plana vitrectomy, total posterior hyaloid peeling and excision, and vitreous base removal, the electronic cable and epiretinal electrode array are inserted into the vitreous space through a 5.2-mm pars plana incision made about 3.5 mm from the limbus, and the array is positioned on the macula. After leak-proof suturing of the scleral incision, the array is placed on the macular region and is secured to the sclera using a tack that passes through a hole in the silicone matrix (Figures 3 and 4). At various stages of the surgery, impedance measurements are done using special computer systems in order to test whether any of the electronic components have been damaged. After the pars plana sclerotomies are closed, the electronics case and receiver coil are covered with pericardium, allograft sclera, or autologous aponeurosis to reduce conjunctival irritation and risk of erosion. Tenon's capsule and the conjunctiva are sutured, and the procedure is concluded with intravitreal prophylactic antibiotic injection.[12,14,16,17]

6. Clinical Studies of Argus II

Phase 2 clinical studies on the feasibility and safety of this product were performed between 2007 and 2009. The poorer-seeing eyes of 30 patients aged 18-25 years who had previous history of useful form vision underwent implantation and the reliability of the implant was evaluated at 1 and 3 years.[14] In 2014, analysis of 30 patients with a mean follow-up time of 6.2±0.9 years revealed that the implant had to be removed from 3 patients and was still functional in 24 of the remaining 27 patients.[2]

Adverse effects, complications: The Argus II epiretinal prosthesis system demonstrated an acceptable long-term safety profile and benefit 3 years after implantation. A total of 23 severe adverse effects occurred in 37% of the cases. Of these, 61% occurred within the first 6 months and 22% occurred more than 12 months after implantation. The commonest severe adverse effects were hypotonia, conjunctival erosion or dehiscence, and endophthalmia. All of these adverse effects could be treated with standard ophthalmic approaches. Using prophylactic intravitreal antibiotics at the end of the surgery and modifying the surgical technique and device designs significantly reduced the incidence of severe adverse effects.[13,14,18]

Anatomical variations in the ora serrata and pars plana are found in 47% of normal eyes. Therefore, severe complications such as choroidal/retinal detachment may occur during insertion of the array and electronic cable through the 5.2-mm scleral incision. These complications can be reduced with ophthalmic microendoscopic evaluation of the pars plana and ora serrata prior to scleral incision (Figure 5).[19]

Visual function tests: The level of vision produced with prostheses is not high enough for evaluation using standard visual function tests. Patients are objectively evaluated using specially designed computer-based low vision tests such as target localization (high-contrast square localization), direction of motion, grating visual acuity, letter recognition, orientation, and mobility tests. The performance rates detectable with these tests are generally higher when the Argus II epiretinal prosthesis system is in operation.[14] Mean grating visual acuity test values at 1 and 3 years were 2.5 LogMAR and the best visual acuity was 1.8 LogMAR (20/1262 Snellen). Twenty-one patients performed the letter recognition test at a mean of 19.9 months after implantation. Letter groups organized according to certain properties were read correctly by 51.7-72.3% of the patients when the system was switched on and by 11.8-17.7% of the patients when the system was switched off. Six patients were able to read the smallest letter size of 0.9 cm from a distance of 30 cm.[2] Orientation and mobility tests evaluate the patient's performance in real-world conditions and includes indoor orientation tests, namely "door-finding" and "line-tracking". With the system switched on, success rates in these tests were 54.2% and 67.9%, respectively, compared to 19% and 14.3% with the system switched off.[14]

FLORA test (Functional Low-vision Observer-rated Assessment): This test evaluates the effects of the Argus II retinal prosthesis in the patient's everyday life. A visual rehabilitation specialist evaluated patients' functional capabilities such as orientation, mobility, and social interaction during everyday life in the home environment at 1 month after implantation. The effect of the system on quality of life was rated as positive or moderately-positive in 80% of the patients at 1 year and 65.2% of the patients at 3 years (Figure 6).[2,3]

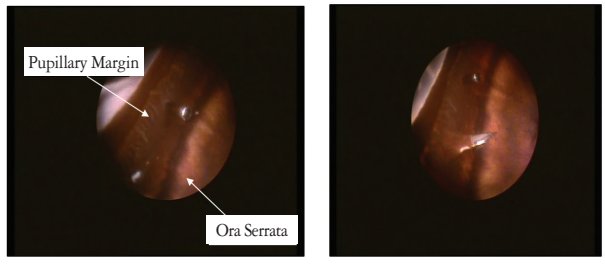

Figure 5. Endoscopic viewing of the retroiridal region during the implantation surgery to confirm the scleral incision site[19]

7. Problems with the Argus II System

No suitable and objective tests have been developed to determine the ideal candidate for implantation or to characterize the functional capacity of the residual retina. The effects of age, duration of low vision, and RP genotype on the outcomes of implantation are not fully known. However, the use of adaptive optics OCT in the near future should shed light on these problems.[2]

Figure 6. An end-stage retinitis pigmentosa patient able to perceive a basketball hoop 6 months after Argus II retinal prosthesis implantation; the black box at his waist is the Video Processing Unit (performed by surgeon E.Ö.)

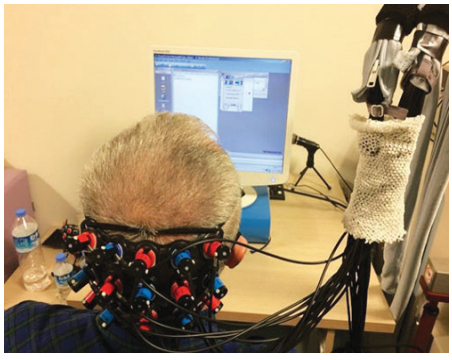

Figure 7. Functional near-infrared spectroscopy: a noninvasive optical method that provides information about cortical activity by measuring relative changes in oxy- and deoxyhemoglobin in the brain cortex upon stimulation of the visual cortex[20]

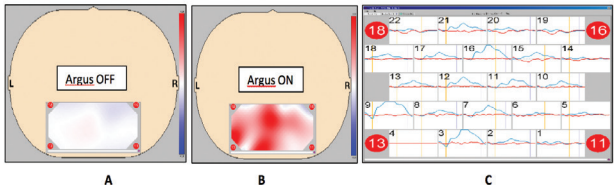

Figure 8. (A) There is ambiguous activity detected by functional near-infrared spectroscopy (fNIRS) in the occipital cortex when the Argus II system is nonoperational (Argus OFF). (B) Significant activity is detected by fNIRS in the occipital cortex when the Argus II system is operational (Argus ON). (C) Wave patterns recorded from the occipital cortex; blue wave: Argus ON, red wave: Argus OFF[20]

The long-term durability of the system's electronic components and their long-term effects on the retina are also not fully known. As the microelectrode array and its connector cable remain in the intravitreal chemical environment for an extended period of time, there may be changes in their performance. In order to prevent damage to the degenerated retina during electrical stimulation, minimizing and appropriately dissipating the heat generated by the array is an important issue.

Patients must learn to use the phosphenes generated by electrical stimulation as visual information. The patient can localize objects within a 20° area using the camera mounted to the glasses. To do this, the patient must scan the environment with head movements instead of eye movements. This is a difficult process that must be learned.

With functional MRI, it is possible to visualize the cortical areas that are activated and utilized during virtual vision tasks. However, the use of this method in patients with a metallic implant in their body involves various difficulties and disadvantages. These disadvantages can be eliminated by the development and use of functional near-infrared spectroscopy (fNIRS), which is easy to use, does not require a closed environment, and does not interact with metal implants. This would allow better postoperative functional assessment and more refined visual rehabilitation opportunities (Figures 7 and 8).[20,21]

8. Potential Developments Regarding the Argus-II

Considering the fact that there are millions of photoreceptors in a normal eye, the number of electrodes in the currently available arrays is very small. For this reason, patients do not yet have a general sense of their surroundings. Therefore, the current performance of the Argus II system must be increased.

- Developments in the glasses, VPU, battery, and digital camera design and the addition of eye-tracking, thermal perception, and depth information would improve the current system.

- Advances in the software and the image and signal processing algorithms can further enhance visual perception, orientation, and mobility without changing the existing hardware.[22] It is also possible to improve visual perception and widen the visual field through advances in the hardware.[23]

- Magnification and minimization of the acquired image may further enhance visual acuity. The image can be adjusted between 0.4x and 16x with a hand-held controller. A vision level equivalent to 20/200 was obtained in grating visual acuity test at 16x magnification and letters 2.3 cm in size were read from 30 cm distance with 4x magnification.[24]

- The addition of a face recognition algorithm to the system may enable face localization from a distance of 2-3 m.[25]

- With the introduction of three-dimensional needle electrodes, it will be possible to stimulate the retinal neural network while also evaluating the electrochemical events occurring within the retina in real time.

Conclusion

Studies on the Argus II epiretinal prosthesis performed to date have demonstrated the long-term safety and potential benefits of controlled chronic electrical stimulation in patients with advanced visual impairment due to outer retinal degeneration associated with conditions such as RP, choroideremia, and GA. Some of the missing pieces in information obtained through artificial vision are filled in by the brain based on previous experiences. The limited number of clinical studies performed with various other retinal prostheses other than the Argus II system have also yielded promising results. However, each type of prosthesis has its own advantages and disadvantages. Cortical implants, which are currently in the preclinical study phase, may provide artificial vision to patients with complete retina and optic nerve destruction.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Emin Özmert, Umut Arslan, Concept: Emin Özmert, Design: Emin Özmert, Umut Arslan, Data Collection or Processing: Emin Özmert, Umut Arslan, Analysis or Interpretation: Emin Özmert, Literature Search: Emin Özmert, Umut Arslan, Writing: Emin Özmert.

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

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Case Report

The Utility of Colistin in Multiple Drug-Resistant *Pseudomonas aeruginosa* Bacterial Keratitis in a Kaposi's Sarcoma Patient

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Abstract

A 71-year-old male patient presented with decreased visual acuity, redness, and discharge in his right eye for 5 days. He had undergone evisceration of his left eye several years earlier. Before presentation, he had received chemotherapeutic agents for Kaposi's sarcoma of the scalp. Slit-lamp examination revealed severe hypopyon and an extensive corneal ulcer with surrounding infiltrate, which extended to the deep stroma. Microbiological evaluation identified the causative agent to be multiple drug-resistant *Pseudomonas aeruginosa.* Based on culture and susceptibility results, the patient was started on topical colistin 0.19% instilled hourly. Complete resolution of keratitis with residual corneal scarring was observed. In recent years, there has been an increase in drug resistance in *P. aeruginosa* keratitis. The lack of new antimicrobial agents against these resistant strains has led clinicians to reconsider colistin, which is an old drug. In this report, we aimed to stress the utility of colistin in multiple drug-resistant *P. aeruginosa* bacterial keratitis in a Kaposi's sarcoma patient.
Keywords: Colistin, multiple drug-resistant *Pseudomonas aeruginosa*, keratitis

Introduction

Microbial keratitis is one of the most important causes of corneal blindness.[1] *Pseudomonas aeruginosa* as a bacterial etiological agent for microbial keratitis can cause severe clinical presentation.[2] Drug resistance in ocular infections caused by *P. aeruginosa* was not common previously, but an increase in drug resistance in *P. aeruginosa* keratitis has been reported in recent years.[3,4,5,6]

Colistin (polymyxin E) is an old polypeptide antibiotic that mainly acts on the bacterial cell membrane and has outstanding in vitro activity against gram-negative bacilli. It currently has very limited systemic usage because of its potential nephrotoxicity and neurotoxicity.[7] Topical usage that avoids the systemic side effects of colistin was reported in only a few articles.[8,9,10]

In this case report, we describe the therapeutic outcome of colistin, which is an old drug, for multiple drug-resistant (MDR) *P. aeruginosa* bacterial keratitis in a monocular Kaposi's sarcoma patient. Our aim was to emphasize the risk factors for drug resistance for *Pseudomonas* keratitis, such as compromised immune system, and the importance of using targeted medication to control the disease.

Case Report

A 71-year-old man presented with decreased visual acuity, redness, and discharge in his right eye for the last 5 days. He had undergone evisceration of his left eye (unknown etiology) several years earlier. Before presentation, he had received chemotherapeutic agents for Kaposi's sarcoma of the scalp. Visual acuity in his right eye was light perception. Slit-

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lamp examination revealed severe hypopyon and an extensive corneal ulcer with surrounding infiltrate which extended to the deep stroma (Figure 1).

Fundus visualization was not possible, but B-scan ultrasound revealed a normal posterior segment. After epithelial scraping was taken and sent to the laboratory for culture, empirical antibiotherapy (fortified topical antibiotics: vancomycin 50 mg/mL, ceftazidime 50 mg/mL hourly) was started. Microbiological evaluation identified the causative agent to be MDR *P. aeruginosa*. Based on culture and susceptibility reports (resistant to tobramycin, netilmicin, piperacillin/tazobactam, cefepime, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, and ceftazidime; sensitive to colistin), previous empirical treatment was stopped and the patient was started on hourly instillation of topical colistin 0.19% with no systemic antibiotic until clinical regression was achieved. Three days after initiating hourly topical colistin, dosing was tapered first to every 2 hours, then to every 3 hours at 1 week, and to every 6 hours after 10 days. Topical colistin was continued every 6 hours for 1 month after the first diagnosis. Complete resolution of keratitis with residual scarring was noticed at 3 weeks (Figure 2). Renal function was assessed with blood urea nitrogen and serum creatine before topical colistin and weekly after treatment to monitor for nephrotoxicity. For ocular tolerance and toxicity, the gradual decreases in symptoms such as burning and stinging and signs such as conjunctival hyperemia, which existed before topical colistin treatment, were accepted as safety indicators and were examined repeatedly during treatment, first daily and later weekly.

During the hospitalization period, the oncology and plastic surgery departments were consulted and no additional chemotherapeutic or immunomodulatory agents were applied in accordance with these consultations.

Penetrating keratoplasty was performed 5 months after presentation. In follow-up examination on postoperative day 3, resolution of the corneal edema was observed (Figure 3) and best-corrected visual acuity (BCVA) was 20/400. BCVA remained stable during follow-up (6 months) with no recurrence of infection.

Discussion

Antimicrobial classes with activity against *P. aeruginosa* are the aminoglycosides, anti-pseudomonal/carbepenems/cephalosporins/fluoroquinolones/penicillins + β lactamase inhibitors, monobactams, phosphonic acids, and polymyxins. MDR *P. aeruginosa* is defined as lack of sensitivity to one or more agents in at least three antimicrobial categories.[11]

Recently, there has been an increase in drug resistance in *P. aeruginosa* keratitis.[12] Drug-resistant *P. aeruginosa* keratitis is a therapeutic challenge because of the lack of medications. This has led clinicians to the reconsideration of colistin, which is an old drug.[13]

Colistin was discovered in 1949[14] and its parenteral form was used extensively in the 1960s. The drug was then gradually abandoned in the early 1980s because it induced nephrotoxicity.[15,16,17,18] Given its excellent activity against a variety of gram-negative bacilli, colistin was later reconsidered for the treatment of systemic infections due to the rising number

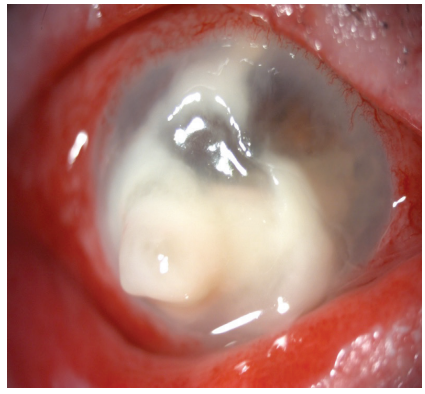

Figure 1. An extended corneal ulcer with surrounding infiltrate, which was extended to the deep stroma with severe hypopyon

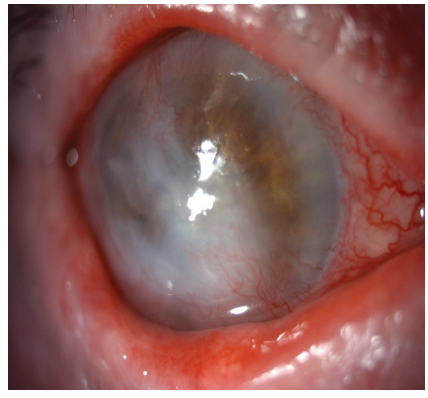

Figure 2. Complete resolution of keratitis with residual corneal scarring

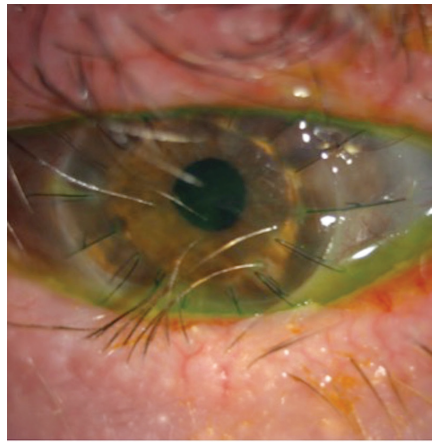

Figure 3. Clear corneal graft

of infections caused by MDR gram-negative bacteria in recent years.[19,20]

According to our literature search, there are only a few published articles reporting the topical use of colistin.[8,9,10]

In our case, antibiogram results indicated that the isolate was resistant to all antibiotics except colistin. Therefore, we opted to administer colistin as a topical treatment. Based on the antibiotic susceptibility tests, this *P. aeruginosa* strain was considered MDR because of the lack of sensitivity to at least one agent in at least three antimicrobial categories, as described above. A drug concentration of 0.19% was chosen for topical usage, in accordance with the literature.[8,21]

Moreover, most patients had either ocular (contact lens use, topical corticosteroids, ocular surface disorder) and/or systemic risk factors (leukemia, Stevens Johnson syndrome, diabetes mellitus) predisposing to microbial keratitis.[22,23,24] In the present case, the patient's history of Kaposi's sarcoma was considered a major risk factor, as a systemic immunocompromising condition that facilitates microbial keratitis. To the best of our knowledge, this is the first case report of *P. aeruginosa* keratitis in a patient with Kaposi's sarcoma who was treated with topical colistin.

In summary, we conclude from this case that the usage of topical 0.19% colistin for the treatment of MDR *P. aeruginosa* keratitis was an effective alternative that did not cause nephrotoxicity or ocular side effects. Because topical drug administration is the first and best method of keratitis treatment, the old and forgotten but still significantly effective agent colistin is a safe alternative that can be considered for MDR gram-negative bacterial keratitis. Further studies with larger sample sizes and control groups are needed to validate the efficacy of topical colistin.

Ethics

Informed Consent: Received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sait Eğrilmez, Özlem Barut Selver, Medine Yılmaz Dağ, Samir Hasanov, Alper Tunger, Concept: Sait Eğrilmez, Özlem Barut Selver, Design: Sait Eğrilmez, Özlem Barut Selver, Data Collection or Processing: Sait Eğrilmez, Özlem Barut Selver, Medine Yılmaz Dağ, Samir Hasanov, Alper Tunger, Analysis or Interpretation: Sait Eğrilmez, Özlem Barut Selver, Alper Tunger, Literature Search: : Sait Eğrilmez, Özlem Barut Selver, Medine Yılmaz Dağ, Samir Hasanov, Alper Tunger, Writing: Sait Eğrilmez, Özlem Barut Selver, Alper Tunger.

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

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Case Report

Palpebral Tarsal Solitary Neurofibroma

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Abstract

Solitary neurofibroma is a rare, benign tumor of the peripheral nerve sheath, and is often associated with neurofibromatosis type 1. Herein, a case of palpebral tarsal solitary neurofibroma in a patient without neurofibromatosis is presented, with a review of the literature. A 68-year-old man presented with a subcutaneous mass in the right upper eyelid of 6 months' duration. Eversion of the eyelid revealed a round, reddish mass on the lateral part of the tarsal plate which measured 12x8 mm in size. The lesion was excised with its tarsal base, diagnosed histologically, and did not recur during a follow-up of 34 months. Isolated, solitary neurofibroma of the eyelid has been reported in a total of 7 cases, including the case presented herein. The tumors arose from the eyelid margin in 4 cases, from the tarsal plate in 2 cases, and from the supratarsal conjunctiva in 1 case. The tumor did not recur after surgical excision in 5 cases for which follow-up data were available.

Keywords: Eyelid, neurofibroma, tarsus, tumor

Introduction

Neurofibromas are benign peripheral nerve sheath tumors and are usually associated with neurofibromatosis type 1 (NF1). Morphologically, there are plexiform, solitary (local or isolated), and diffuse subtypes. The most common subtype in the periocular area is NF1-associated plexiform neurofibroma.[1] Solitary neurofibroma (SN) not associated with NF1 is rare in the eyelid and conjunctiva. There is only one previously reported case of SN in the eyelid tarsal plates.[2]

Case Report

A 68-year-old man presented with a 6-month history of painless subcutaneous mass in his right upper eyelid (Figure 1A). Eversion of the eyelid revealed a round, reddish mass attached to the lateral tarsus by a short peduncle (Figure 1B). The ocular examination was otherwise unremarkable. The patient had no symptoms or history of NF1.

The lesion was excised together with its tarsal base under local anesthesia. The tarsal defect was left to heal by secondary intention. The tumor was 12x8 mm in size and hard in consistency (Figure 1C). Histologically, the tumor consisted of spindle-shaped peripheral nerve sheath cells and a collagenous stroma (Figure 1D). Masson's trichrome staining showed dense collagen fibers around the neoplastic cells (Figure 1E). Immunohistochemically, the tumor cells were positive for S100 and negative for smooth muscle actin protein and desmin (Figure 1F). These findings were consistent with SN. No postoperative complications were observed; there was no recurrence of the tumor during the 34-month follow-up period.

Discussion

Solitary, benign peripheral nerve tumors not associated with NF1 can be classified as traumatic neuroma, SN, and schwannoma. Solitary neurofibromas occur most frequently in adults, preferentially affecting males and presenting as

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subcutaneous masses on the extremities and trunk.[3] In the periocular region, SNs mostly originate from intraorbital nerves and particularly in the superior-posterior orbit.[4]

We found 6 cases of isolated eyelid SN in the literature.[2,5,6,7,8,9] Including the present case, 2 of the total 7 patients were male. One patient was 14 years old,[7] and the ages of the other patients varied between 39 and 81 years. The tumor was located in the upper eyelid in 5 patients: in the tarsus in 2 patients (including the present case), the eyelid margin in 2 patients, and at supratarsal conjunctiva in 1 patient.[2,6,8,9] In 2 patients, the lesions were in the lower eyelid and near the lacrimal punctum and lateral canthus.[5,7] The time from noticing the lesion to surgical excision ranged between 6 months and 5 years, and was not specified in one case.[6] In 3 cases, the lesion was mistaken for chalazion.

Our case was macroscopically similar to the tarsal SN described by Shibata et al.[2] In both cases, the lesion was round, hard, and located at the lateral aspect of the upper tarsus. The center of the lesion was more vascularized and slightly depressed. As in the earlier cases of eyelid SN, we were unable to identify the specific nerve that gave rise to our patient's tumor.

Concurrent systemic diseases in different patients included lymphoma[2], lung adenocarcinoma,[6] and Sjögren's syndrome.[7] In one patient, the tumor was associated with basal cell carcinoma of the eyelid.[6] Including the case presented here, tumor recurrence was not observed in a total of 5 patients during follow-up of 2-36 months after surgical excision.[2,5,8] There were no follow-up data for 2 patients.[6,9]

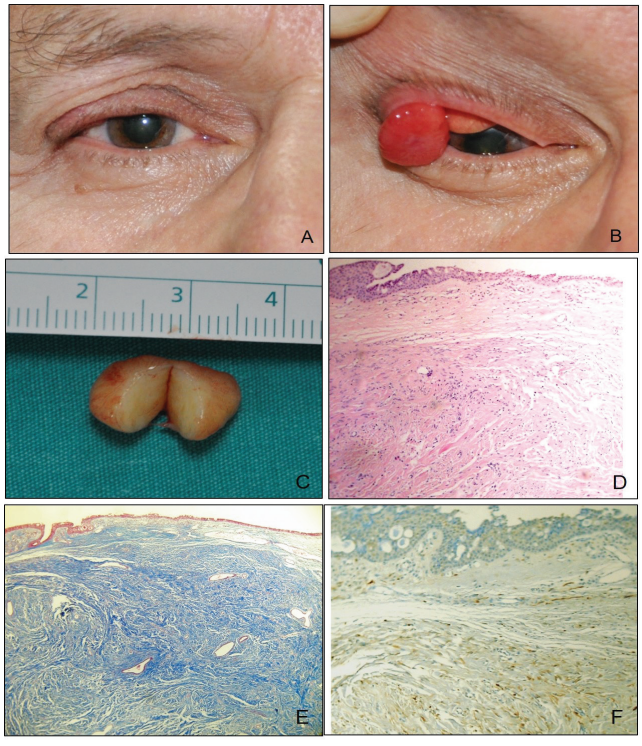

Figure 1. A) The patient presented with a painless subcutaneous mass located on the lateral side of the right upper eyelid; B) A solitary neurofibroma originates from the tarsal plate of the upper eyelid; C) Appearance of the tumor after bisection; D) Tumor tissue consisted of spindle-shaped, well-demarcated cells in the conjunctiva, with comma- or fusiform-shaped nuclei (Hematoxylin-eosin, x100); E) Masson's trichrome stain revealed intense collagenization in the tumor stroma (blue, x100); F) Immunohistochemical staining in tumor cells showing S100 positivity and indicating neural origin (x100)

Preoperative diagnosis of such a rare condition is challenging. However, the macroscopic features of the tarsal SNs in 2 patients were quite different from those of common tarsal masses such as chalazion and meibomian gland carcinoma. Schwannoma, leiomyoma, and malignant peripheral nerve sheath tumors must be included in the histological differential diagnosis of SN. Tumors of muscular origin are positive for desmin and smooth muscle actin proteins, while tumors of neural origin are positive for S100. Like neurofibromas, schwannomas are also positive for S100. However, they stain more intensely because neurofibromas have a more complex structure that includes Schwann cells, perineural cells, and fibroblasts. More cases are needed to better characterize tarsal SNs.

Ethics

Informed Consent: Received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Bülent Yazıcı, Şaduman Balaban Adım, Concept: Bülent Yazıcı, Design: Bülent Yazıcı, Sertaç Argun Kıvanç, Data Collection or Processing: Bülent Yazıcı, Sertaç Argun Kıvanç, Uğur Yayla, Şaduman Balaban Adım, Analysis or Interpretation: Bülent Yazıcı, Sertaç Argun Kıvanç, Uğur Yayla, Şaduman Balaban Adım, Literature Search: Bülent Yazıcı, Sertaç Argun Kıvanç, Uğur Yayla, Writing: Bülent Yazıcı.

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Case Report

A Case of Best Disease Accompanied by Pachychoroid Neovasculopathy

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Abstract

The aim of this case presentation is to describe ocular findings of a 22-year-old patient with Best vitelliform macular dystrophy accompanied by pachychoroid neovasculopathy. Color fundus photography, fundus autofluorescence (FAF), optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) images were reviewed. Funduscopic examination showed bilateral yellowish vitelliform-like submacular deposits. FAF revealed these deposits as hyperautofluorescent spots. OCT showed flat irregular pigment epithelial detachments corresponding to these submacular deposits. OCT showed choroidal thickening and dilatation of the large outer oval choroidal vessels. Fundus fluorescein angiography could not be performed because the patient was pregnant. En face OCTA images of the choriocapillaris illustrated the choroidal neovascular network. In this case report, we describe for the first time the coexistence of Best vitelliform macular dystrophy and pachychoroid neovasculopathy with OCTA images enabling visualization of the neovascular network in a patient with contraindication for fluorescein angiography.

Keywords: Best disease, optical coherence tomography angiography, pachychoroid neovasculopathy

Introduction

Best vitelliform macular dystrophy (Best disease) is characterized by the presence of a vitelliform macular lesion leading to the classic egg-yolk appearance in genetically predisposed individuals.[1] The *BEST1* gene (formerly known as *VMD2*), which encodes the protein bestrophin-1 and is located on the 11q12-q13, is responsible for this disease.[2] Bestrophin is a transmembrane protein found on the basolateral side of retinal pigment epithelium (RPE) cells[3] and is responsible for calcium-dependent chloride transport.[4]

A severe complication of a Best vitelliform lesion is the development of secondary choroidal neovascularization (CNV), the exact mechanism of which is unknown. Especially when there is a sudden decrease in visual acuity, the development of neovascular tissue should be suspected. Conventional dye angiography should be performed to visualize the CNV. However, dye injection may cause anaphylactic and urticarial reactions in patients both with and without a history of allergy, and hepatic diseases, hemodialysis, and pregnancy are strong relative contraindications for dye injection.[5] In the presence of such a contraindication, the best alternative is optical coherence tomography angiography (OCTA), which enables noninvasive visualization of the chorioretinal microvasculature layer by layer.

There are few studies in the literature reporting the microvasculature details of a Best lesion with OCTA.[6,7] To the best of our knowledge, this is the first report describing the coexistence of a Best lesion with bilateral pachychoroid neovasculopathy.

Case Report

A 22-year-old female was referred to our retina clinic due to the detection of submacular yellowish deposits during routine

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ophthalmological examination. Other than being 14 weeks pregnant, she had no systemic medical conditions or history of ocular disease. She complained that her vision had worsened in the last few months. Best corrected visual acuity was 20/63 in the right eye and 20/25 in the left eye. Anterior segment examination was unremarkable. Posterior segment examination showed bilateral yellowish vitelliform-like submacular deposits and tiny yellowish spots throughout the fundus (Figure 1). Fundus autofluorescence (FAF) imaging (Heidelberg Retina Angiograph 2®; Heidelberg Engineering Inc., Heidelberg, Germany) revealed these deposits as hyperautofluorescent foci. Optical coherence tomography (OCT) revealed flat irregular pigment epithelial detachments (PED). Choroidal thickening and dilation of the large outer oval choroidal vessels were also detected.

Fluorescein and indocyanine green angiography could not been performed because the patient was pregnant. Therefore, the retinal and choroidal vasculature was evaluated with OCTA using the RTVue-XR Avanti OCTA System (Optovue Inc, Fremont, CA). Choriocapillaris en face OCTA images illustrated a dense, highly branching choroidal neovascular network with polypoidal dilations in both eyes (Figure 2). Upon family examination, RPE changes, vitelliform deposits, and tiny peripheral yellowish flecks were detected on the retina of her brother. No treatment could be applied due to her pregnancy, so the patient was scheduled for follow-up visits. However, she did not attend follow-up visits.

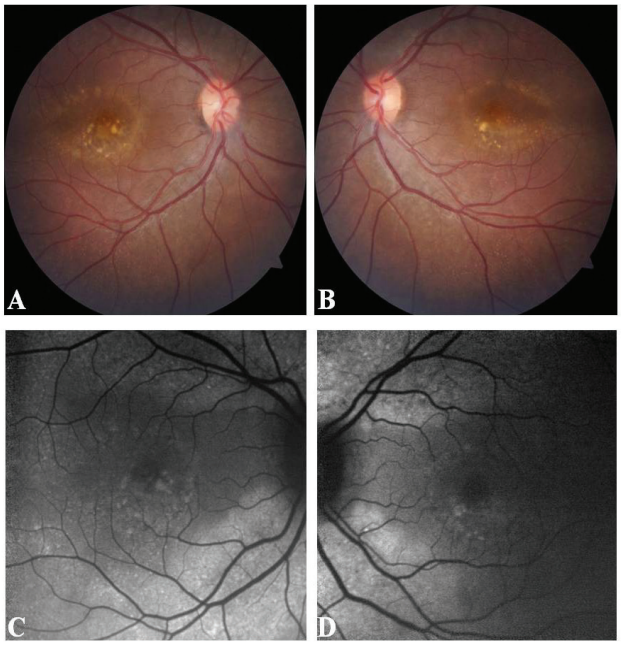

Figure 1. Multimodal imaging findings of the patient: (A, B) Color fundus photographs showing bilateral yellowish submacular vitelliform deposits and tiny yellowish spots located all around the fundus. (C, D) Fundus autofluorescence imaging revealed hyperautofluorescent spots corresponding to the yellowish material in the color photographs

Discussion

Best vitelliform macular dystrophy typically presents in the first two decades of life. However, atypical presentations of Best disease with late development of vitelliform lesions have also been reported.[8,9] Hormonal, hemodynamic, vascular, and immunological changes occur during pregnancy that can be associated with ocular changes or worsening of preexisting conditions.[10] Our patient experienced her first visual complaints in the first trimester of pregnancy. She did not report having any visual symptoms during adolescence.

Although the responsible gene and protein have been identified, the exact mechanism underlying Best disease is unknown. The responsible protein, bestrophin-1, is believed to serve as a calcium-dependent chloride channel, bicarbonate transporter, and volume regulator in the plasma membrane, and as a chloride channel or calcium sensor in the endoplasmic reticulum.[11,12,13,14] A molecular study reported disrupted fluid

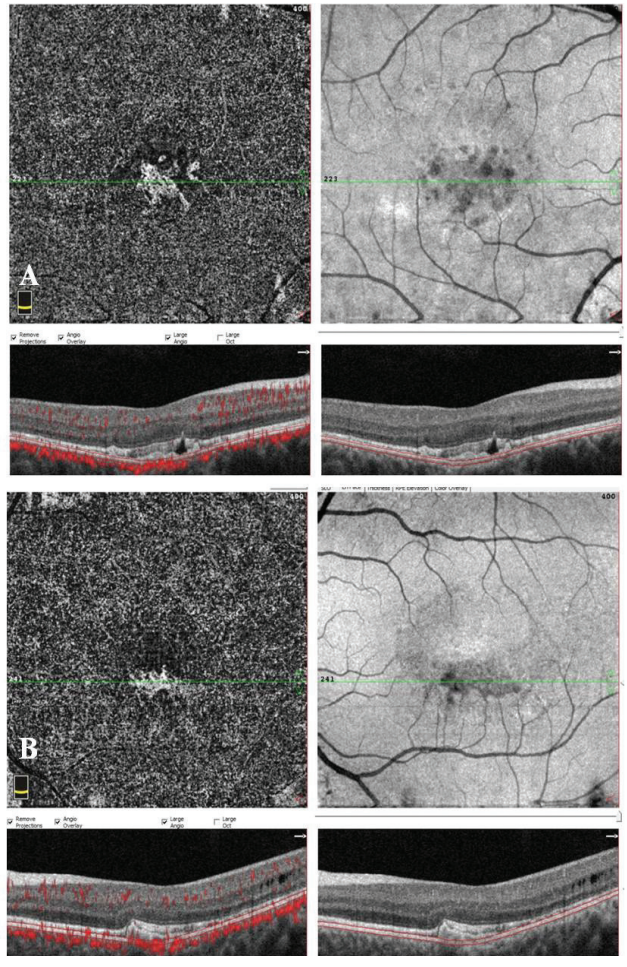

Figure 2. Optical coherence tomography angiography images showing the choriocapillary layer and corresponding B-scans with red flow overlay and segmentation boundary lines. Optical coherence tomography angiography images successfully illustrated the choroidal neovascular network in both the (A) right and (B) left eye. Optical coherence tomography revealed flat, irregular pigment epithelial detachments

flux and increased accrual of autofluorescent material after long-term photoreceptor outer segment feeding, delayed rhodopsin degradation, and altered calcium responses in Best disease.[15] The authors indicated that calcium signaling and oxidative stress are critical contributors to the clinical manifestation of Best disease. RPE dysfunction leads to impaired turnover of the shed photoreceptor outer segments, leading to an accumulation of this material in the subretinal space. FAF hyperautofluorecense corresponding to the yellowish material seen in fundus examination and flat irregular PEDs on OCT supported the association of this material with the photoreceptor outer segments. Due to accumulated material and subretinal fluid formation, the loss of the direct apposition between the RPE and photoreceptor outer segments may result in further accumulation of subretinal vitelliform material.

The superiority of the OCTA to fluorescein angiography in the visualization of the CNV in Best disease was reported previously.[6] It was also indicated that fluorescein angiography might grossly underestimate the actual neovascular area present.[6] The masking effect of the vitelliform lesion may limit the visualization of the underlying neovascular tissue. In our case, CNV is seen clearly within the vitelliform material in OCTA scans. Another advantage of OCTA is that it does not require dye injection, which eliminates all nephrotoxicity, anaphylaxis reactions, and contraindication due to pregnancy, as in our case. However, its inability to detect leakage limits its use in determining the activity of CNV lesions. Recent studies have tried to determine OCTA pattern characteristics in order to differentiate active versus quiescent CNV.[16,17]

Best disease was previously associated with choroidal thinning.[18,19] However, our patient had pachychoroid spectrum disease characteristics with increased choroidal thickness.[20] Flat irregular PEDs were present on OCT images. The high incidence (74%) of type 1 CNV in pachychoroid spectrum diseases with flat irregular PEDs was reported in another of our studies previously.[21] Consistent with these data, OCTA showed a dense, highly branching choroidal neovascular network in both eyes of the patient. To the best of our knowledge, this is the first report describing the association of Best disease with pachychoroid neovasculopathy. Further studies are needed in order to determine whether the coexistence of these two diseases is a coincidence or a consequence of a common mechanism in their pathophysiology.

Ethics

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Authorship Contributions

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Case Report

Effects of Congenital Ocular Toxoplasmosis on Peripheral Retinal Vascular Development in Premature Infants at Low Risk for Retinopathy of Prematurity

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Abstract

Congenital toxoplasmosis and retinopathy of prematurity (ROP) are two devastating clinical entities of the newborn. There is little information in the literature about the interaction between congenital infections and retinal vascular development at the fetal stage, and none regarding the relationship between ROP and congenital toxoplasmosis. In this report, we present two premature newborns diagnosed with congenital toxoplasmosis with ocular involvement, accompanied by ROP with interrupted retinal vascularization, peripheral avascular regions, and retinal detachment. The aim of this paper is to emphasize the possibility of ROP and congenital toxoplasmosis coexistence wherein one condition may mask the other and make it difficult to distinguish the cause of retinal detachment. Timely management with medical and surgical treatment of congenital toxoplasmosis and ROP could save eyes and vision in those cases.
Keywords: Retinopathy of prematurity, ocular toxoplasmosis, congenital toxoplasmosis, pars plana vitrectomy, toxoplasma gondii

Introduction

Toxoplasma gondii is an opportunistic parasite that can cause acquired or congenital infections.[1] Congenital infection occurs via vertical transmission from the mother and may result in fetal death, severe congenital malformation, fetal developmental retardation, and the infection of neural tissues. The best described clinical presentation of ocular toxoplasmosis is focal necrotizing chorioretinitis, ultimately resulting in characteristic atrophic scars.[1,2] Retinopathy of prematurity (ROP) is a vasoproliferative, multifactorial disorder of the retina that occurs principally in newborn preterm infants and is strongly related to low gestational age (GA), low birth weight (BW), and supplemental oxygen therapy.[3,4]

It is well known that serious congenital infections such as chorioamnionitis, placental infections, and sepsis increase the risk for ROP in susceptible premature infants.[4] When the constitutional features and risk factors are taken into consideration, ROP could accompany congenital toxoplasmosis as well, which is the focus of this paper. Here, we present two newborns who were diagnosed and referred to our ophthalmology clinic with congenital toxoplasmosis with ocular involvement, but also had accompanying ROP with interrupted retinal vascularization, peripheral avascular regions, and tractional retinal detachment.

Case Report

A premature newborn baby girl (Case 1) and baby boy (Case 2) were referred to our ophthalmology/uveitis clinic from the neonatology units for the confirmation of congenital ocular toxoplasmosis. Prenatally, hydrocephaly had been

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detected in both newborns via ultrasonography. *Toxoplasma* IgG and IgM antibodies were also detected in both mothers during pregnancy. Postnatally, the newborns were evaluated for congenital toxoplasmosis. Infectious markers in blood samples confirmed the diagnosis of congenital toxoplasmosis. Both infants were monitored in neonatal intensive care units, and systemic antiparasitic (pyrimethamine 2 mg/kg, sulfadiazine 100 mg/kg, and leucovorin 10 mg) and anti-inflammatory (prednisone 2 mg/kg) therapy was initiated. Systemic features are given in detail in Table 1. Detailed ophthalmic features of the two cases are given in Table 2.

Case 1: She was born at a GA of 34 weeks at a BW of 2230 g, and was post-gestational 40 weeks of age at the time of ophthalmologic consultation. Ophthalmological examination revealed a normal anterior segment in the right eye, with adequate pupil dilation. The left eye was microphthalmic in appearance. Dilated fundus examination of the right eye revealed a circular focus of active retinitis in the macular area with a fibrotic membrane starting from the retinitis area extending temporally to the peripheral retina, resulting in retinal traction and straightening of the vascular arcuates, causing a comet-like appearance of the optic disc. The view was hazy because of +2/+3 vitritis (Figure 1a). Examination of the left fundus revealed a similar lesion temporal to the optic disc accompanied by a foveal fold and traction in the arcuates towards the temporal lesion (Figure 1b). The left eye also had +2 vitritis. Peripheral vascular details were indistinct due to the intense inflammation and retinitis. At this stage, close observation with systemic medical treatment of CT was recommended. The vitritis had subsided by 1-month follow-up, enabling the detection of significant peripheral avascular regions in the temporal retina of the right eye and the fibrovascular membranes overlying these areas. Retinal traction towards the temporal periphery was also noted. The left eye already had seclusio pupilla and lens opacification at this stage. With these findings, the diagnosis

Table 1. Clinical features and treatment of two patients with retinopathy of prematurity and congenital toxoplasmosis

	Case 1	Case 2
Gestational age at birth (weeks)	34	32
Birth weight (g)	2230	1590
Hydrocephalus	Yes	Yes
Intracranial calcifications	No	No
Toxoplasmosis serology	Positive	Positive
Medical treatment (pyrimethamine 2 mg/kg, sulfadiazine 100 mg/kg, leucovorin 10 mg)	Yes	Yes

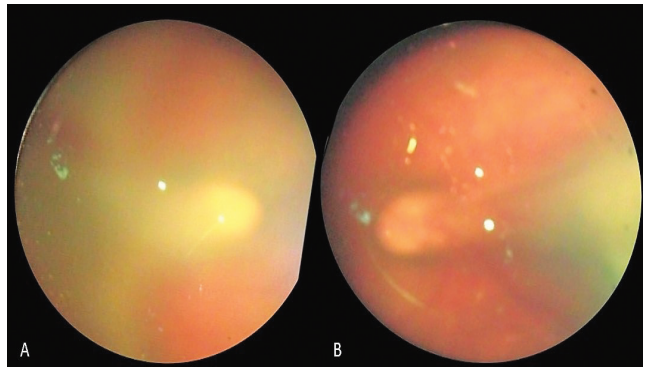

Figure 1. Case 1, fundus appearance at initial visit in the A) right eye and B) left eye; focus of active retinitis at posterior pole inside the vascular arcades starting from optic disc extending temporally, resulting in traction and straightening of the vascular arcades and causing a comet-like appearance of the posterior pole. The view was hazy due to vitritis

Table 2. Main ocular features, treatments, and outcomes in the two cases

EUA Ophthalmic findings	Case 1		Case 2	
	OD	OS	OD	OS
Microphthalmia	(-)	(+)	(-)	(+)
Posterior synechiae	(-)	(+)	(+)	(+)
Cataracts	(-)	(+)	(+)	(+)
Chorioretinitis	(+)	(+)	(+)	(+)
Avascular zones	(+)	(+)	(+)	(+)
Retinal detachment	Tractional	Tractional	Tractional	Combined tractional & Rhegmatogenous
Foveal fold / traction	(+)	(+)	(+)	(+)
ROP stage	Zone 1, Stage 2	n/a	n/a	Zone 1, Stage 2
Treatment	PPV+MP+EL	-	-	PPV+MP+EL
Retina attached	(+)			(+)

EUA: Examination under anesthesia, OD: Right eye, OS: Left eye, ROP: Retinopathy of prematurity, PPV: Pars plana vitrectomy, MP: Membrane peeling, EL: Endolaser, n/a: not available

was revised as ROP in addition to toxoplasma chorioretinitis. Since the left eye was pre-phthisic, a lens-sparing vitrectomy was planned for the right eye only. Intraoperatively, tractions were released by peeling the fibrotic membranes extending from the macular chorioretinitis scar to the temporal periphery. Laser photocoagulation was applied to the peripheral avascular areas extending to zone 1 in the temporal quadrant (Figure 2a-c) and fluid/air exchange was done at the end of surgery. ROP was graded as stage 2 at the ridge and the tractional membranes were considered to be of inflammatory origin. Postoperatively, the retina was attached, without any macular tractions, with a pigmented scar corresponding to the old chorioretinitis lesion. During the follow-up of 18 months, fundus findings were stable with attached retina. Intraocular pressure was 17 mmHg. She was able to fixate and follow objects with that eye. However, the fellow eye became totally phthisic.

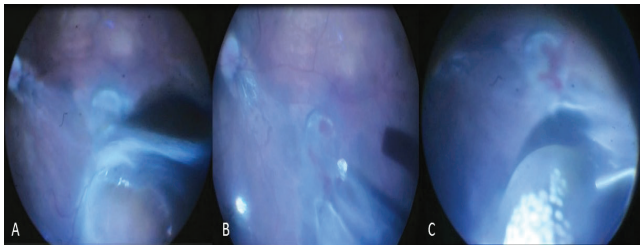

Figure 2. Case 1, intraoperative fundus images of the right eye: A) Peripheral retinal avascular regions and the thick fibrotic membrane at the temporal retina and chorioretinitis lesion causing tractional retinal detachment and narrowing of the angle between arcuate vessels; B) Intraoperative fundus view after peeling off all the fibrotic membranes; C) Endolaser application for peripheral avascular retina

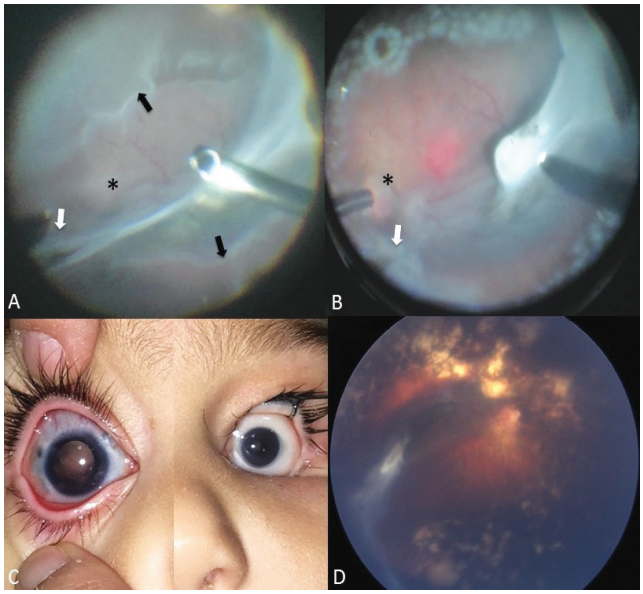

Figure 3. Case 2: A) Combined rhegmatogenous and tractional retinal detachment in the right eye. Note the fibrotic membrane extending from nasal to temporal periphery leading to a large triangular retinal break (white arrow) superior to the optic nerve head (black star), which is barely visible due to the nasal retina pulled over it, and avascular retina in zone 1 with stage 2 retinopathy of prematurity (black arrow); B) Peroperative fundus image after peeling the fibrotic membranes around the large, triangular retinal break (white arrow) and application of endolaser photocoagulation to avascular retina and around the breaks; C) Postoperative image showing the buphthalmic appearance of the right eye and microphthalmic appearance of the left eye; D) Postoperative fundus image of the right eye with attached retina and fibrotic membrane remnants in the temporal area and laser scars visible throughout the periphery

Case 2: He was born at a GA of 32 weeks and BW of 1590 g. He was post-gestational 37 weeks old at time of ophthalmologic consultation. Ophthalmological examination revealed bilateral cataracts and seclusio pupilla. We could detect buphthalmos with Haab's striae in the right eye (corneal diameters: 12x12 mm, axial length: 25 mm) and microphthalmus (corneal diameters: 7x8 mm, axial length: 13 mm) in the left eye. Right eye fundus examination was unable to provide clues regarding retinal detachment due to cataract and posterior synechia. Ultrasound examination revealed preretinal membranes and freely mobile retinal detachment resembling rhegmatogenous retinal detachment. Lensectomy and vitrectomy were performed on the right eye. During surgery, complete bullous retinal detachment was observed, as well as a thick, tight fibrotic membrane extending from the nasal to temporal retina passing superior to optic nerve head (ONH) and over the macular pigmented chorioretinitis scar, ending in a very thick and strong fibrotic adhesion in the temporal equator. The nasal retina was pulled towards the temporal scar tissue over the ONH. There was a large, triangular retinal break at the nasal end of the membrane superior to the ONH, and the peripheral retina was avascular in zone 1 with a stage 2 ridge at the junction (Figure 3a). The fibrotic tractional membranes were removed meticulously around the break to eliminate all tractions. The posterior hyaloid could be detached from the posterior pole to the ridge area but a small iatrogenic retinal hole formed in the inferior ridge region. Endolaser photocoagulation was applied to the retinal tears and avascular retina (Figure 3b), and 16% C3F8 gas was chosen as a tamponade. At 1-year follow-up, mild buphthalmic appearance with minimal corneal edema persisted, with the addition of minimal scleral staphylomas at the previous sclerotomy sites (Figure 3c). Glaucoma could not be controlled with medical treatment and an Ahmed Glaucoma Valve implantation was performed to prevent further glaucomatous damage. The retina remained attached throughout follow-up (Figure 3d). Vision could not be assessed well because of the mental-motor retardation, but the patient was able to follow light and large objects.

Discussion

CT is recognized as a major cause of child morbidity and mortality which occurs via vertical transmission from the mother primarily infected during pregnancy. CT may result in fetal developmental retardation and death. A history of hydrocephalus, retinochoroiditis, and calcifications in the central nervous system in the neonatal period should immediately alert a care provider to the possibility of toxoplasmosis.[1,2] In contrast, ROP is a

retinal neovascular disease of premature infants. Despite major advances in management, it continues to be a leading cause of childhood blindness throughout the world. ROP develops when the immature retinal vasculature exhibits a vasoconstrictive response to hyperoxia followed by a vasoproliferative phase that is driven by the surge in endothelial growth factors on the return to normal oxygenation.[3]

Prematurity and CT have different systemic manifestations, yet their ophthalmic manifestations may theoretically overlap. It is also well known that serious congenital infections such as chorioamnionitis, placental infections, and sepsis increase the risk for ROP.[4] Although not mentioned commonly in the literature, prematurity is a plausible consequence of CT since we know that fetal developmental retardation is a possible effect.[3,4] Incomplete retinal vascularization in ROP may either be a possible consequence of impaired fetal development resulting in prematurity, or an unexplained clinical presentation of the congenital ocular infection. No matter which etiopathogenetic mechanism is responsible, retinopathy associated with prematurity seems to be a possible comorbidity for these infants. Despite those facts, to the best of our knowledge, our paper is the first to emphasize the possible coexistence of congenital ocular toxoplasmosis (COT) and ROP.

In the modern era of medicine, when a baby is born premature and has obvious risk factors for ROP such as low BW, the diagnosis is straightforward after a good fundus examination.[3] However, as in the present cases, when the risk factors for ROP are indistinct and the newborn is already diagnosed with other devastating conditions such as COT, it may be challenging to recognize retinal features of ROP among widespread inflammation. In the current report, both babies were not referred for ophthalmological examination for ROP screening, but only for the possibility of COT. This is probably because the babies' GA and BW were slightly higher than the lower limits for screening. Another important and unique feature of this report is the presentation of the ROP clinical appearance under the inflammatory cover of the COT in these premature babies who had a low risk of ROP. The membranes causing traction in both babies were felt to be primarily inflammatory rather than ROP-related in origin since they were almost avascular, not originating from the ridge areas, and more prominent around the chorioretinitis scar. On the other hand, there were significant avascular zones which could not be simply explained by the child's BW or GA. That is why the stage of ROP was evaluated as not more than stage 2 in both eyes. It seemed that the inflammation caused by COT promoted progression of ROP in bigger, low-risk babies in whom ROP is not expected and screened routinely.

The classic medical treatment for COT includes a combination of pyrimethamine and sulphonamides.[5] It is especially important to halt parasite replication in the eye to prevent irreversible damage to the retina and optic nerve that can lead to permanent blindness.[5] However, for cases with widespread infection in the eye, intercepting the replication cycle may not be sufficient to save the eye and vision due to the severe inflammatory response, even if systemic steroid therapy is also administered. In the presence or absence of advanced ROP, the presence of tractional membranes and retinal detachments should be regarded as surgical indications in the management of COT. In the present report, both cases received systemic antibiotic and steroid treatment, but surgical treatment was also needed to prevent further loss of vision and possible loss of the globe. ROP and CT may mask each other and it may be difficult to distinguish the cause of retinal detachment in such eyes. It is well known that tractional retinal detachment may be caused by advanced ROP (stage 4/5) and this may be confused with the tractional retinal detachment caused by COT.[6] Fibrotic membrane formation and tractional retinal detachments during the acute stage of COT are rarely mentioned in the literature. This is consistent with the fact that there is hardly any suggested surgical treatment option for COT during infancy in the literature. The current report is not only unique in demonstrating vitrectomy as an effective treatment modality in COT in the presence of inflammatory fibrotic membranes leading to retinal detachment, but also in enabling the endolaser photocoagulation to treat avascular zones that were attributed to ROP.

In summary, these two cases emphasize the fact that two different retinal diseases, COT and ROP, may be intertwined in preterm infants and present with atypical manifestations. Therefore, in addition to history and routine fundus examination, peripheral retinal vascularization should also be carefully evaluated in bigger babies with COT.

Ethics

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şengül Özdek, Murat Hasanreisoğlu, Concept: Şengül Özdek, Murat Hasanreisoğlu, Tuba Atalay, Design: Murat Hasanreisoğlu, Data Collection or Processing: Gökçen Deniz Gülpınar İkiz, Analysis or Interpretation: Şengül Özdek, Murat Hasanreisoğlu, Zeynep Aktaş, Literature Search: Gökçen Deniz Gülpınar İkiz, Writing: Murat Hasanreisoğlu, Gökçen Deniz Gülpınar İkiz.

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2019 INTERNATIONAL CONGRESSES

EURETINA 2019
September 5 – 8, 2019
Paris, France
www.euroretina.org

ESCRS 2019
September 21 – 25, 2019
Stockholm, Swedish
www.escrs.org

AAO 2019
October 12 – 15, 2019
San Francisco, United States
www.aao.org

2020 INTERNATIONAL CONGRESSES

6th COPHy AA 2020
February 14 – 15, 2020
Bangkok, Thailand
http://cophyaa.comtecmed.com/

11th COPHy EU 2020
March 26 – 28, 2020
Lisbon, Portugal
http://cophy.comtecmed.com/

2019 NATIONAL CONGRESSES

21st Esat Işık Course
September 7 – 8, 2019
Sivas, Turkey

32nd Summer Symposium: Systemic Diseases with the Eye of Ophthalmologist: From Review to Diagnosis
September 27 – 29, 2019
İzmir, Turkey

TOA 53rd National Congress
November 6 – 10, 2019
Antalya, Turkey