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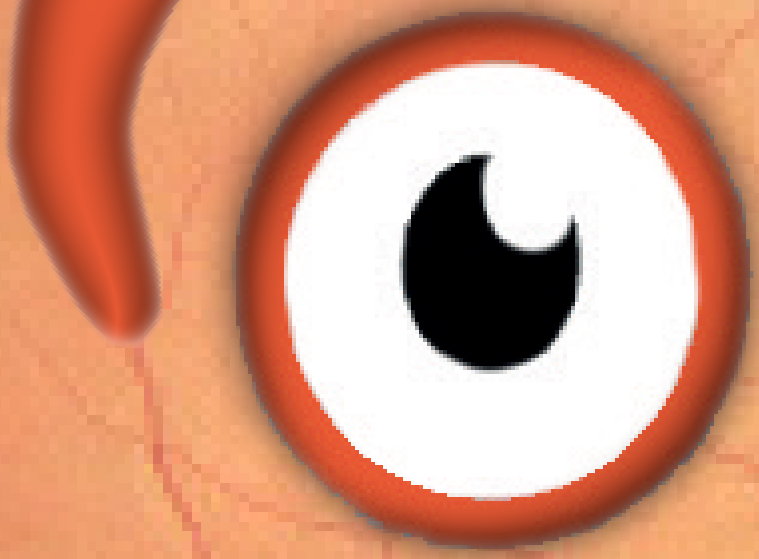

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Original Article

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Impact of phacoemulsification on choroidal and ganglion cell complex thickness assessed by spectral-domain optical coherence tomography

Kadriye Demir[1], Erkan Çelik[2]

[1]Department of Ophthalmology, Faculty of Medicine, Sakarya University, Sakarya, Turkiye
[2]Department of Ophthalmology, Sakarya Dünyagöz Hospital, Sakarya, Turkiye

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ABSTRACT

Aims: To investigate the effects of phacoemulsification on subfoveal choroidal thickness (SFCT) and ganglion cell complex thickness (GCCT), using spectral-domain optical coherence tomography (SD-OCT).

Methods: This retrospective study included 40 eyes of 40 patients who underwent phacoemulsification with intraocular lens implantation for senile cataract. Preoperative examinations included best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure, central corneal thickness, and axial length. Operative time and effective phaco time were recorded. SFCT, GCCT, central macular thickness (CMT), and peripapillary retinal nerve fiber layer thickness (pRNFLT) were measured preoperatively and at 1 month using SD-OCT.

Results: At one month postoperatively, all parameters showed statistically significant increases ($p<0.001$): SFCT (298.6±41.3 µm to 304.6±40.8 µm), GCCT (83.2±4.4 µm to 91.4±6.1 µm), CMT (244.6±16.6 µm to 248.3±17.4 µm), and pRNFLT (95.3±5.1 µm to 100.9±5.8 µm). No significant associations were found between changes in SFCT or GCCT and demographic or clinical factors.

Conclusion: Phacoemulsification may induce mild inflammatory changes that affect posterior segment structures, even in uneventful cases. SFCT, GCCT, CMT, and pRNFLT should therefore be re-evaluated postoperatively to establish new baselines for accurate monitoring. Larger, long-term studies are warranted to clarify the clinical relevance of these changes.

Keywords: Subfoveal choroidal thickness, ganglion cell complex thickness, phacoemulsification, cataract surgery

INTRODUCTION

The choroid, located between the sclera and the retinal pigment epithelium, contains a dense vascular network that supplies oxygen and nutrients to the outer third of the retina.[1] Due to its close anatomical relationship with the outer retina, it plays a central role in the pathogenesis of various ocular diseases, including choroidal neovascularization, central serous chorioretinopathy, and polypoidal choroidal vasculopathy.[2-4] Choroidal thickness is regarded as an indirect marker of choroidal vascular status and is influenced by multiple factors such as age, sex, axial length, refractive status, and circadian rhythm.[5,6] The development of the enhanced depth imaging (EDI) mode in spectral-domain optical coherence tomography (SD-OCT) has enabled non-invasive, high-resolution visualization of deep ocular structures, allowing for reliable and reproducible choroidal measurements.[7]

The ganglion cell complex (GCC)-comprising the inner plexiform layer, ganglion cell layer, and retinal nerve fiber layer, which correspond to the dendrites, cell bodies, and axons of retinal ganglion cells-has also been shown to undergo subtle but statistically significant transient thickness changes after uncomplicated phacoemulsification surgery. These changes, demonstrated in recent SD-OCT studies, are thought to reflect postoperative inflammatory responses or biomechanical alterations.[8,9] Beyond GCC changes, phacoemulsification has been associated with other retinal complications, such as progression of diabetic retinopathy and pseudophakic cystoid macular edema, although the mechanisms underlying its effects on the posterior segment remain incompletely understood.[10,11]

The present study aimed to evaluate changes in ganglion cell complex thickness (GCCT) and subfoveal choroidal thickness (SFCT) following cataract surgery. In addition, alterations in peripapillary retinal nerve fiber layer thickness (pRNFLT) and central macular thickness (CMT) were assessed. Although

Corresponding Author: Kadriye Demir, kadriye_dmr@hotmail.com

postoperative changes in choroidal thickness have been widely investigated, data regarding GCC alterations remain limited. Therefore, this study provides an insight into the early structural effects of uncomplicated phacoemulsification on the posterior segment.

METHODS

This retrospective study included 40 eyes of 40 patients who underwent uncomplicated phacoemulsification with intraocular lens implantation for grade 1-3 senile cataracts at Sakarya University Faculty of Medicine between 2018 and 2021. The study adhered to the tenets of the Declaration of Helsinki, and Ethical approval was obtained from the Sakarya University Ethics Committee (Date: 02.06.2022, Decision No: E-71522473-050.01.04-136949).

Preoperative assessments included best-corrected visual acuity (BCVA, LogMAR), intraocular pressure (IOP, Goldmann applanation tonometry), axial length (AL, optical biometry; Nidek Co., Japan), and intraocular lens (IOL) power. SFCT was measured using the Cirrus EDI-OCT system (Carl Zeiss Meditec AG, Germany), while GCCT was assessed with the macular cube 512×128 protocol. Only scans with a signal strength ≥6 were included.

SFCT was determined at the subfoveal point using the linear caliper tool, defined as the vertical distance from the outer border of the retinal pigment epithelium-Bruch's membrane complex to the inner scleral surface (Figure). Measurements were performed by two independent observers; if interobserver variability exceeded 10%, scans were repeated and averaged values were recorded. To minimize the effects of pharmacological mydriasis and diurnal variation, all OCT scans were acquired without dilation between 2:00 and 4:00 p.m. GCCT was automatically analyzed by the OCT software.

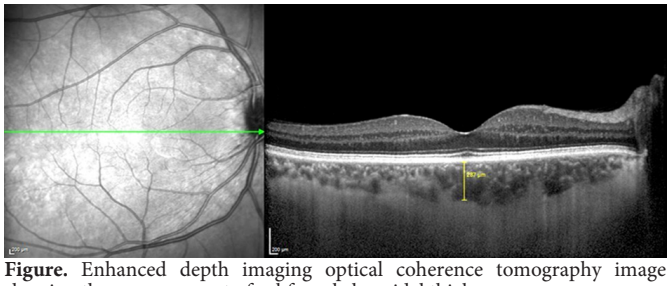

Figure. Enhanced depth imaging optical coherence tomography image showing the measurement of subfoveal choroidal thickness

Additional parameters, including CMT, pRNFLT, operative time (OT), and effective phaco time (EPT) were also recorded. All OCT acquisitions were performed by an experienced technician who was independent of the study team and masked to the study objectives.

Surgical Technique and Exclusion Criteria

All surgeries were performed by a single experienced surgeon using the INFINITI Vision System (Alcon Inc., Fort Worth, TX, USA). A foldable hydrophobic acrylic intraocular lens was implanted in the capsular bag in all eyes. No intraoperative or postoperative complications were observed. Postoperatively, patients received topical moxifloxacin 0.5% (eight times daily for 1 week) and prednisolone acetate 0.1% (eight times daily, tapered over 4 weeks). Follow-up visits were scheduled on postoperative day 1, week 1, and month 1. For this study, preoperative and 1-month postoperative data, including comprehensive ophthalmologic examinations and OCT measurements obtained after pharmacologic pupil dilation, were analyzed.

Exclusion criteria included a history of intraocular surgery or laser treatment; ocular pathologies such as retinal disorders, glaucoma, uveitis, diabetic retinopathy, age-related macular degeneration, or central serous chorioretinopathy; high refractive error (≥±6.00 D); poor fixation during imaging; severe cataracts precluding OCT acquisition (grade 4-5, Oxford Cataract Classification System); or systemic use of prostaglandin analogs, steroids, or diuretics that could affect retinal or choroidal thickness.

Statistical Analysis

All data analyses were conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as means±standard deviations. The normality of data distribution was assessed using the Shapiro-Wilk test. Pearson correlation analysis was employed to explore associations between continuous variables. One-way analysis of variance (ANOVA) regression was used to evaluate differences in pre- and postoperative measurements. p-value <0.001 was considered statistically significant in all analyses.

RESULTS

A total of 40 patients [21 males (52.5%) and 19 females (47.5%)] with a mean age of 63.4±4.7 years were included in the study (Table 1). The mean preoperative BCVA was 0.38±0.18 LogMAR, which significantly improved to 0.05±0.39 LogMAR at postoperative month 1 (p<0.001). AL and CCT were 22.6±0.5 mm (range, 21.5-24.1 mm) and 553.5±24.3 µm, respectively. The mean surgical duration was 8.9±2.3 minutes, and the mean EPT was 7.1±2.3 seconds (Table 2). At postoperative month 1, statistically significant increases were observed in all OCT parameters compared with baseline values. Mean SFCT increased from 298.6±41.3 µm (range, 201-356 µm) to 304.6±40.8 µm (range, 231-367 µm) (p<0.001). Mean GCCT increased from 85.0 ± 4.4 µm (range, 78-94 µm) to 89.2±5.3 µm (range, 81-99 µm) (p<0.001). Similarly, mean pRNFLT increased from 95.3±5.1 µm (range, 87-110 µm) to 100.9±5.8 µm (range, 91-113 µm), and mean CMT increased from 244.6±16.6 µm (range, 211-280 µm) to 248.3±17.4 µm (range, 213-278 µm), both with statistical significance (p<0.001 for all).

Table 1. Demographic characteristics of the patients

Parameter	Value
Age (years)	63.4±4.7
Sex (male/female)	21/19
Operated eye (right/left)	18/22

Table 2. Ocular and surgical parameters

Parameter	Value
Preoperative BCVA (LogMAR)	0.38±0.18
Postoperative BCVA (LogMAR)	0.05±0.39
Axial length (mm)	22.6±0.5
Central corneal thickness (µm)	553.5±24.3
Operation time (minutes)	8.9±2.3
Effective phaco time (seconds)	7.1±2.3

BCVA: Best-corrected visual acuity

No significant correlations were found between changes in SFCT, GCCT, pRNFLT, or CMT and demographic or surgical parameters, including age, sex, AL, CCT, OT, or EPT (Table 3).

Table 3. Preoperative and postoperative month 1 OCT parameters

OCT parameter (µm)	Preoperative (mean±SD)	Postoperative month 1 (mean±SD)	p-value
SFCT	298.6±41.3	304.6±40.8	<0.001
GCC	83.2±4.4	91.4±6.1	<0.001
CMT	244.6±16.6	248.3±17.4	<0.001
pRNFLT	95.3±5.1	100.9±5.8	<0.001

OCT: Optical coherence tomography, SFCT: Subfoveal choroidal thickness, GCC: Ganglion cell complex thickness, CMT: Central macular thickness, pRNFLT: Peripapillary retinal nerve fiber layer thickness, SD: Standard deviation

DISCUSSION

In our study, a statistically significant increase in SFCT and GCCT was observed in the early postoperative period following cataract surgery. Although fundus changes following uncomplicated phacoemulsification have not been fully elucidated, proposed mechanisms include vitreomacular traction, vascular instability, ocular hypotony, and intraoperative light exposure; postoperative inflammation has also been shown in recent studies to play a significant role in these structural alterations.[12,13] However, the precise mechanism underlying changes in choroidal thickness remains unclear. Current evidence suggests that choroidal thickness tends to increase by approximately 5-30 µm, typically beginning as early as the third postoperative day, with values often returning to baseline by the third month.[14] Historically, choroidal evaluation was limited to angiography and ultrasonography, both of which lacked the resolution to detect subtle morphological changes in choroidal thickness. With advances in OCT, non-invasive and reproducible imaging of the choroid has become feasible. In 2008, Spaide et al.[15] introduced the EDI technique using conventional OCT systems, enabling detailed visualization of the choroid. Our findings align with those of Falcão et al.,[16] who investigated the impact of uncomplicated phacoemulsification on retinal and choroidal structures using EDI-OCT. In their study, a statistically significant increase in retinal macular thickness was observed one month postoperatively, which was attributed to inflammatory responses following surgery. However, unlike our study, no significant alterations were detected in SFCT. When evaluating previous studies examining the relationship between choroidal thickness and cataract surgery, Aslan Bayhan et al.[17] and Pierru et al.[18] also reported an increase in SFCT at the first postoperative month. In Pierru's study, this thickening was observed to return to baseline levels by the third postoperative month. These studies suggest that inflammation in the anterior segment caused by cataract surgery may also affect the posterior segment. Surgical trauma and disruption of the blood-aqueous barrier are believed to initiate this inflammatory process.[19] An experimental animal study demonstrated that the inflammatory response is induced by surgical stress, and that proinflammatory cytokines increase within the choroid and inner retinal layers.[20] In another study evaluating SFCT, it was reported that SFCT peaked on postoperative day 7 and gradually decreased by the third month, returning close to baseline levels.[21] These findings are partially consistent with the current study, in which a significant increase in subfoveal choroidal thickness was observed at the first postoperative month. However, as measurements were limited to a single subfoveal point and follow-up did not extend beyond the first month, it remains uncertain whether this increase represents a transient inflammatory response or a more sustained structural change. In line with this, Yilmaz et al.[22] reported in a prospective study that although central macular thickness returned to baseline levels within 6 months after cataract surgery, subfoveal choroidal thickness remained slightly elevated even at 12 months. This suggests that postoperative choroidal alterations may persist beyond the early inflammatory phase, potentially indicating longer-term remodeling or subclinical vascular changes. Additionally, Icoz[23] demonstrated that subfoveal, nasal, and temporal choroidal thickness significantly increased at the first postoperative month and returned to baseline at the third month, while the Choroidal Vascular Index (CVI) remained elevated. These findings indicate that vascular changes may persist even after structural normalization, providing further insight into postoperative choroidal physiology.

Neurodegenerative eye diseases, particularly glaucoma, predominantly target the GCC. The GCC is anatomically composed of the RNFL, the ganglion cell layer, and the inner plexiform layer, which respectively contain the axons, cell bodies, and dendritic connections of retinal ganglion cells.[9,24] Because these layers directly reflect the structural integrity of ganglion cells, alterations in their thickness are considered reliable markers of neuroaxonal loss. Recent investigations have demonstrated that assessment of macular GCCT is at least as effective as peripapillary RNFLT in detecting glaucomatous damage.[25,26] Moreover, these studies have emphasized that GCC analysis may capture early neurodegenerative changes even when RNFL alterations are minimal, thereby offering an additional diagnostic advantage. In the present study, a significant increase in GCCT and pRNFLT was observed in the early postoperative period following cataract surgery. Previous research has indicated that cataract surgery may alter GCC and peripapillary RNFL thickness measurements, highlighting the importance of considering such changes during postoperative follow-up.[27-29] In one of these studies evaluating early postoperative changes, a decrease in pRNFLT and GCCT was observed on postoperative day 1; however, by the first week, values had exceeded baseline levels and peaked at one month.[29] Moreover, the increase in these layers began earlier than the increase in total retinal thickness. Another study comparing femtosecond laser-assisted cataract surgery (FLACS) with conventional phacoemulsification reported that, although no statistically significant differences were found between the two groups, both GCCT and pRNFLT showed a significant increase from baseline in each surgical group.[30] Based on these observations, the authors suggested the importance of establishing a new postoperative baseline for GCCT and pRNFLT to accurately monitor future structural changes. Similarly, the increase observed in our study, despite being statistically significant, may reflect transient postoperative alterations rather than true pathological progression. Thus, follow-up evaluations should consider the influence of recent cataract surgery when interpreting OCT-based measurements of inner retinal structures. Another secondary finding of our study was the increase in CMT observed at postoperative month 1. Numerous studies in literature have reported similar increases in CMT following uncomplicated cataract

surgery.[31-34] The authors observed a slight increase in foveal thickness following cataract surgery without affecting visual acuity and suggested that this change could be attributed to both subclinical alterations and the influence of improved media clarity on measurement accuracy. Surgical and biometric parameters such as EPT, and AL were not found to be associated with the degree of macular thickening, which is consistent with the findings of our study. In another study that examined all retinal layers, a decrease in retinal thickness was observed on the first postoperative day, followed by a significant increase at one month, and a subsequent reduction at three months after surgery. These findings support the hypothesis that the inflammatory response following uncomplicated cataract surgery, characterized by thickening of the retinal layers, peaks around the first postoperative month and gradually subsides thereafter. Based on these results, the authors suggested that additional treatment for cystoid macular edema may not be necessary as early as the first month in mild cases.[35]

Limitations

The primary limitations of this study include its relatively small sample size and the short duration of follow-up. Measurements were limited to a single time point at one month postoperatively, which prevents assessment of the long-term structural changes in choroidal and retinal layers. In addition, choroidal thickness was only measured at the subfoveal region; regional variations across the posterior pole were not evaluated. Furthermore, the retrospective design of the study limits the ability to control for potential confounding factors.

CONCLUSION

Although the main limitations of our study are the small sample size and lack of long-term follow-up, we observed a significant increase in SFCT and GCCT one month after uncomplicated cataract surgery in a homogeneous patient group operated on by the same surgeon under similar ocular and surgical parameters. Increases in pRNFLT and CMT were also recorded. While these changes may be transient, clinicians should be aware that SFCT, GCCT, or pRNFLT measurements may vary during the early postoperative period. This should be considered when monitoring patients with chronic diseases affecting the choroid and retinal layers, and when adjusting treatment parameters in individuals who have recently undergone cataract surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Sakarya University Ethics Committee (Date: 02.06.2022, Decision No: E-71522473-050.01.04-136949).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Assessment of quality of life in patients with epiphora: a cross-sectional study using a structured clinical performa

Asra Warees[1], Mohd Faraz[2], Mudassir Alam[3], Sahab Kausar[4]

[1]Department of Ophthalmology, Jawaharlal Nehru Medical College, Paramedical College, Faculty of Medicine, Aligarh Muslim University, Uttar Pradesh, India

[2]Department of Radiodiagnosis, Jawaharlal Nehru Medical College, Paramedical College, Faculty of Medicine, Aligarh Muslim University, Uttar Pradesh, India

[3]Department of Biological Sciences, Indian Biological Sciences and Research Institute (IBRI), Noida, India

[4]Department of Statistics and Operations Research, Aligarh Muslim University, Uttar Pradesh, India

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ABSTRACT

Aims: This study aims to evaluate the impact of epiphora (watery eyes) on various daily life activities and to assess the overall quality of life in adult patients suffering from epiphora.

Methods: A cross-sectional study analysed the quality of life of 298 patients who visited the ophthalmic department of a tertiary-level hospital in North India. Patients presented with complaints of epiphora at the Eye OPD of Jawaharlal Nehru Medical College in Aligarh between January 2025 and May 2025. A self-designed structured performa was used to collect demographic details (age, gender), patient's history, and other clinical features of epiphora (continuous or occasional tearing). We used the Chi-square test for this analysis to check if there's a significant association between the variables being studied. The results show how they relate to each other. The analysis was performed using SPSS version 26.0 and Python.

Results: This study reveals that females are more prone to epiphora than males. Out of 298 patients, there were 206 (69.10%) women, while 92 (30.9%) were men. The Chi-square goodness-of-fit tests revealed statistically significant differences between the observed and expected distributions for all variables in the study. For onset, the result (χ^2=4.35, p=0.037) shows that the distribution between acute and chronic cases differs from what was expected. The side involved showed a highly significant difference (χ^2=290.54, p<0.0001), indicating unequal distribution between unilateral and bilateral cases. Wiping times also differed significantly (χ^2=77.07, p<0.0001), as did the diagnosis categories (χ^2=126.55, p<0.0001). These results confirm that the variations observed are statistically significant and not due to random chance. The majority of patients reported frequent eye wiping (5 to 10 times) (39.59%), blurred vision (65.4%), epiphora, and symptoms variations in the evening (46.66%), morning (37.24%), and during specific activities (49.32%). Difficulty in activities such as reading (9.39%), driving (22.48%), and using digital devices (9.73%) and other activities (58.72%) are commonly observed by this condition.

Conclusion: This study suggested that in many individuals, epiphora affects nearly every part of their daily activities. Constant wiping creates difficulties in performing various tasks, such as driving and, for females, completing household chores. It also leads to challenging social interactions, feelings of embarrassment, self-consciousness, and frustration.

Keywords: Blur vision, conjunctivitis, dry eye syndrome, epiphora, ocular surgery, tearing

INTRODUCTION

The eye, as a delicate and finely tuned organ, maintains its function and integrity through a precise balance of tear production and drainage. Disruption of this equilibrium often brings excessive tears, a medical condition called epiphora or watering of eye.[1] It is one of the most common complaints among patients in ophthalmology and oculoplastic clinics. During the process of tearing, the lacrimal gland produces tears, which are then spread over the ocular surface to maintain lubrication, protection, and support clear vision.[2] Periodic blinking helps in an even distribution of a thin layer of tear (tear film) across the surface of the eye, and some of the tears evaporate from the eye's surface, while the remaining tears drain through the nasolacrimal duct.[3] True epiphora refers to excessive tearing due to impaired tear drainage,

Corresponding Author: Mudassir Alam, syedalamalig@gmail.com

while pseudoepiphora is excessive tearing due to increased tear production (hyperlacrimation). It can be caused by reflex hypersecretion from ocular surface disease.[4] It is due to various factors, including environmental irritants, allergies, infections, or structural problems with the tear drainage pathways.[5] Exposure to smoke, bright light or chemical fumes can trigger the eyes to produce more tears as a protective mechanism.[6] Moreover, Allergic reactions to pollen, dust, or pet dander can cause severe inflammation and increased tear production. Infections such as conjunctivitis (pink eye) and keratitis can lead to excessive tearing along with other symptoms like redness and pain.[7,8] Similarly, dry eye syndrome can cause reflex tearing as the eyes try to compensate for the lack of lubrication. A retrospective studies of 180 patients at Kim's Eye Hospital, in Seoul of South Korea, identified that, In the 320 eyes of 180 patients, the most common etiology of epiphora was reflex tearing due to dry eye syndrome, which occurred in 167 eyes (52.19%). The other etiologies of epiphora included anatomical abnormality (68 eyes, 21.25%), multifactorial (60 eyes, 18.75%), functional epiphora (14 eyes, 4.38%), ocular surface disease (seven eyes, 2.19%), and eyelid abnormality (four eyes, 1.25%).[9] Furthermore, several other studies have discussed the causes and treatment outcomes of epiphora, and some have specifically reported its causes. In another study by Woog[10] reported that the typical annual rate of symptomatic acquired lacrimal outflow obstruction is 30.47 cases for every 100,000 individuals, and this rate is observed to increase as age advances. For some individual, epiphora may be merely a minor annoyance, while for others, it can have a considerable impact on patients' vision-related quality of life (QoL). This has been evident in outdoor activities, prolonged focus such as driving, using a computer, and other digital devices, and tasks that require looking down, like reading or going downstairs and cooking, may become frustrating and thus increase tearing. The physical discomfort and functional limitations associated with epiphora, along with the psychological distress of dealing with a visible symptom, can lead to increased stress levels and, in some cases, contribute to the development or worsening of depressive symptoms.[13,14] For example, a study by Guo et al.[15] investigated the prevalence and risk factors for depression and anxiety in 344 patients with nasolacrimal duct obstruction (NLDO). They identified high prevalence of depression and anxiety disorders among NLDO patients along with hypertension and dry eye disease (DED) as significant risk factors.[16] The results indicated that the tendency for anxiety and depression was closely associated with DED and sleep disorders.[17,18]

This study addresses underestimated symptoms of epiphora which is often neglected in many individuals. Unlike headaches, eyestrain, or other asthenopic symptoms, people are often unaware of epiphora, even though it can cause severe issues such as acquired NDLO in advanced stages. Many studies have focused solely on the etiology, management, and treatment of epiphora rather than on existing experiences. This study provides an overview of the impact of epiphora on patient's QoL and its overlooked effects on daily activities. Unlike other studies that utilize vision-related QoL questionnaires, this study is designed around a self-made performa, which has several advantages, including a direct focus on the individual's epiphora issues. It captures missed questions unlike typical questionnaires, it is more flexible, and easily adaptable for different patients. It improves relevancy by allowing for qualitative inputs and enables the collection of both qualitative and quantitative data. This study aims to evaluate the impact of epiphora on various daily life activities and to assess the overall quality of life in adult patients.

METHODS

This study was approved by the Jawaharlal Nehru Medical College Faculty of Medicine Aligarh Muslim University Ethics Committee (Date: 10.06.2025, Decision No: IECJNMC/1855, https://jnmc.edu/institutional-ethics committee/). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study involved a cross-sectional analysis of 298 patients visiting the ophthalmic department of a tertiary-level hospital in North India. Patients presented with complaints of epiphora at the Eye OPD of Jawaharlal Nehru Medical College in Aligarh, India between January 2025 and May 2025. Informed consent was obtained from all participants before enrolment (**Figure 1**).

Patient Evaluation Performa for Epiphora

1. Demographic Information

Name: _____ **Age/Sex:** _____

Occupation: _____ **Address:** _____

Date of Examination: _____

2. Past History

History of eye trauma and surgery:	YES [ ]	NO [ ]
Diabetes:	YES [ ]	NO [ ]
Hypertension:	YES [ ]	NO [ ]
On Medication:	YES [ ]	NO [ ]
Any congenital anomalies:	YES [ ]	NO [ ]

3. Chief Complaint

Duration (months): _____

Onset of Epiphora: Acute / Chronic

Side Involved: Unilateral / Bilateral

Tearing: Continuous/Occasionally

4. Impact on daily life

Number of wiping times: _____

Blur vision: YES/NO

Worse during: Morning/Evening /Specific activities

Difficulty in: Driving [ ] Reading [ ] Mobile/Laptop [ ] Other activity [ ]

Emotional effect: Embarrassment [ ] Frustration [ ] Social Withdrawal [ ]

5. Consent: "I have been informed of the procedure in my language. I voluntarily consent to the epiphora examination study. The information provided is accurate, and I sign without duress. I'm willing to be enrolled in this study.

Signature: _____

Figure 1. This structured clinical performa is designed to systematically assess the quality of life (QoL), symptom severity, and daily functional impact in patients presenting with epiphora. It also records relevant demographic, medical, and emotional factors for comprehensive evaluation

Inclusion Criteria

The study included patients aged 20-70 years who had persistent epiphora for over one month and a history of exposure to dusty environments, particularly those residing near industrial areas or employed as factory workers and labours.

Exclusion Criteria

The exclusion criteria encompassed patients with other ocular diseases, a history of ocular surgery, congenital anomalies affecting the lacrimal system, or medications that influence tear secretion.

A self-designed patient evaluation performa was used to collect demographic details (age, gender, occupation, address) and to evaluate the impact of epiphora on patients' QoL and their daily life activities. Such self-designed performa have previously been utilized in gathering research data.[19,20]

This performa was designed after reviewing the literature and having informal discussions with other ophthalmologists to ensure it addressed the most common and relevant problems experienced by many individuals. It served as the primary data collection tool and consists of five sections. The first section includes demographic data such as the patient's name, age/sex, occupation, and address. It aims to identify trends associated with socio-demographic influences and relationships. In the second section, the patient's history was gathered to exclude specific conditions from the exclusion criteria. Similarly, third Section contains information about the patient's chief complaints. In this section, the duration (months) is acute and chronic epiphora with unilateral and bilateral involvement. The tearing pattern of epiphora is classified into continuous and occasional tearing to correlate with the patient's QoL for better consideration. The fourth section evaluates the impact on the patient's daily life, including psychosocial aspects. Several wiping times refer to the frequency of wiping tears each day. Patients were interrogated about how epiphora affects their daily tasks. Also asked about the watering of the eye is more in the morning, evening, or while doing any specific task, such as while driving, reading, using digital devices, or studying. Physical and emotional distresses were also recorded for every individual, including feelings of awkwardness and hindrance. The last section consists of the patient's consent and their signature.

RESULTS

All Chi-square tests require that no more than 20% of expected cell counts are below 5 and that all expected counts exceed 1. For onset and side involved, both expected counts were around 150, so all were greater than 5 and the assumptions were met. In the wiping times analysis, all categories ("<5," "5-10," ">10") had expected counts above 5, so the assumption was also satisfied. For diagnosis, some rare categories had expected counts below 5, so they were combined into an "other" group to ensure all expected counts were at least 5 before performing the Chi-square test (Figure 2).

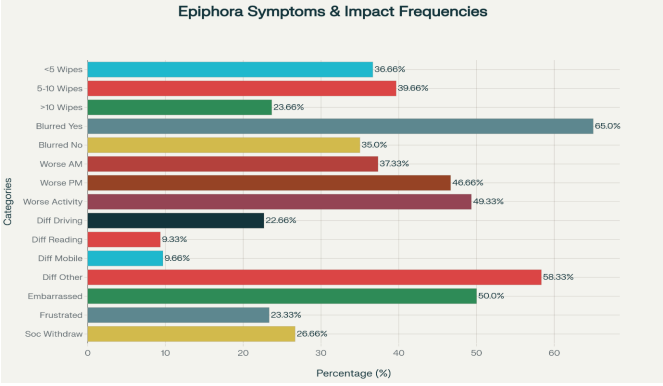

Figure 2. Bar chart illustrating the frequencies (percentages) of key symptoms and impacts reported by patients with epiphora

A p-value is the probability of observing data as extreme as the sample results if the null hypothesis is true, and we conclude by rejecting the null when the p-value is less than the chosen significance level (.05). If the p-value is low (typically ≤0.05), this suggests the results are statistically significant and unlikely to be due to random chance. We would reject the null hypothesis in favour of the alternative hypothesis. If the p-value is high (typically ≥0.05), this suggests the results are not statistically significant. The observed data could plausibly be due to chance, so you would fail to reject the null hypothesis. The p-value of this result is <0.05. The standard deviation and average age of an individual are 16.70 and 40.80, respectively. This study's results reveal the crucial findings associated with the patient's daily life activities, which are affected by epiphora. 298 patients were enrolled in this study, who visit the Eye OPD of Jawaharlal Nehru Medical Hospital in North India. Also, indicating that females are more prone to epiphora than males. Out of 298 patients, there were 206 (69.10%) women, while 92 (30.9%) were men. Epiphora duration was evaluated in months and was classified into subgroups in (Figure 3). Out of the 298 patients who experienced epiphora for 1 to 25 months were 238 (79.7%) were individuals, 26 to 50 months were experienced by 42 (14%) individuals, and for 51 to 75 months were experienced by 8 patients (2.67%). For 76 to 100 months, 3 (1%) individuals, for 101 to 125 months, 5 (1.67%) individuals, for 126 to 150 months, 1 (0.33%) individual, and for 176 to 200 months were experienced by 2 (0.66%) individuals. Out of 298 patients, 167 (56%) individuals have chronic epiphora, while 131 (44%) individuals have acute epiphora. Based on side involvement, 60 (20.1%) patients have unilateral epiphora, while 238 (79.9%) patients have bilateral epiphora. Continuous tearing was encountered by 225 (75.55%) patients, while occasional tearing was experienced by 73 (24.49%) individuals as mentioned in (Table 1, Figure 4).

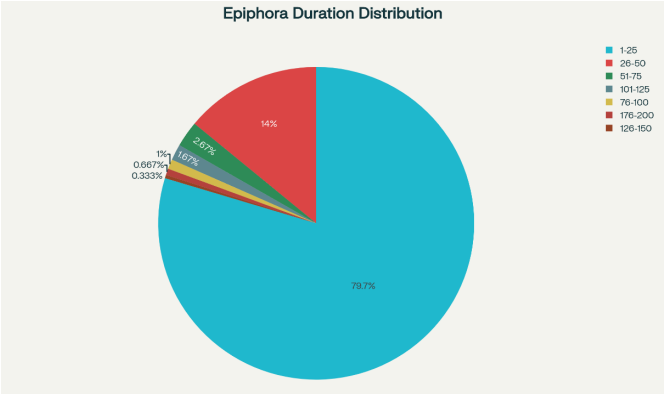

Figure 3. Duration of epiphora in months, representing 1 to 25 months, epiphora is more prevalent than the other. The Chi-square goodness-of-fit test shows a highly significant deviation from equal distribution across duration categories (χ^2=1076.39, p<0.0001), confirming that the 1-25-month category is disproportionately large

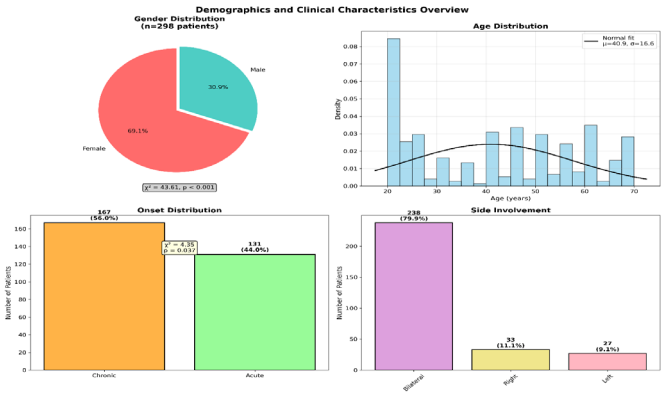

Figure 4. The onset of epiphora, acute is more than chronic. Laterality involved more cases of bilateral epiphora, while in the tearing pattern, continuous tearing is more than occasional tearing

Table 1. Demographic information of patients		
Age	20-70 years	
Average age	40.80	
Standard deviation of age	16.70	
Gender	**Total**	**Percentage**
Male	92	30.9%
Female	206	69.1%
Duration of epiphora (month)		
1 to 25	238	79.7%
26 to 50	42	14%
51 to 75	8	2.67%
76 to 100	3	1%
101 to 125	5	1.67%
126 to 150	1	0.33%
176 to 200	2	0.66%
Onset of epiphora		
Acute	131	44%
Chronic	167	56%
Laterality		
Bilateral	238	79.9%
Unilateral	60	20.1%
Tearing pattern		
Continuous	225	75.55%
Occasionally	73	24.49%

The Chi-square test for onset (χ^2=4.35, p=0.037) shows a significant difference from an equal distribution, meaning that acute and chronic cases are not evenly represented. The test for side involved (χ^2=290.54, p=8.11×10^{-64}) reveals a highly significant difference, with bilateral involvement being much more common than unilateral. These results suggest that both onset and side involvement are important factors with uneven distributions in the study population.

The number of wiping times has this categorical description; patients who wipe less than 5 times per day number 109 (36.57%), those who wipe 5-10 times per day total 118 (39.59%), while patients who wipe more than 10 times per day count 71 (23.82%) (Figure 5). Blurred vision was reported by 195 out of 298 patients (65.4%). This symptom was more frequent among patients with chronic epiphora compared to those with acute symptoms. Epiphora is worse either in the morning among 111 patients (37.24%), in the evening among 139 patients (46.66%), or during specific tasks noted in 147 patients (49.32%). Many patients have difficulty driving, totaling 67 patients (22.48%). Reading difficulties were reported by 28 patients (9.39%), while 29 patients (9.73%) experienced trouble using mobile devices and laptops, and 174 patients (58.72%) faced challenges doing other activities. Many patients reported feelings of embarrassment (149 patients, 50%), frustration (70 patients, 23.48%), and social withdrawal (79 patients, 26.51%) in (Table 2, Figure 6).

The Chi-square test for wiping times (χ^2=312.15, p=1.66×10^{-57}) shows a strongly significant difference from equal frequencies, indicating that wiping times vary widely among participants and are not evenly distributed across categories.

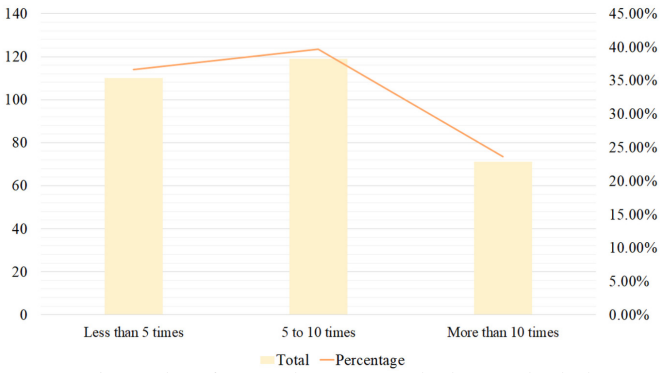

Figure 5. The number of wiping their tears per day by an individual. 5 to 10 wiping times are more prevalent

Table 2. Summary of patient-reported experiences and symptoms related to epiphora		
Number of wiping times per day	**Total**	**Percentage**
Less than 5 times	109	36.57%
5 to 10 times	118	39.59%
More than 10 times	71	23.82%
Blurred vision	195	65.4%
Epiphora symptoms are worse during		
Morning	111	37.24%
Evening	139	46.66%
Specific activity	147	49.32%
Difficulty in doing tasks		
Driving	67	22.48%
Reading	28	9.39%
Mobile/laptop	29	9.73%
Other activities	174	58.72%
Effect of epiphora on the well-being of patients		
Embarrassment	149	50%
Frustration	70	23.48%
Social withdrawal	79	26.51%

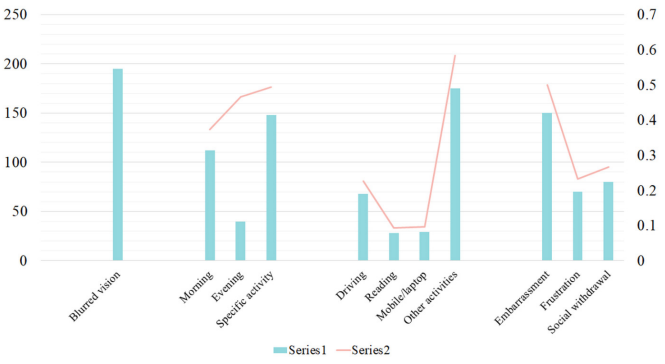

Figure 6. The bar graph (series 1) shows the frequency of symptoms and activity impairments, while the line graph (series 2) indicates the severity or impact level of each factor on daily life

Each variable shows a statistically significant deviation from an expected uniform distribution, indicating that the frequencies of categories differ strongly from equal proportions in the dataset. For example, "side involved" is dominated by 'bilateral' cases, and "onset" is more skewed towards chronic cases. Similarly, "wiping times" and "diagnosis" have uneven distributions across their categories (Table 3).

Table 3. Significance testing of study variables using Chi-square method

Variable	Chi- square statistic	p-value	Summary
Onset	4.35	0.037	The distribution of onset (acute vs chronic) significantly Differs from equal distribution
Side involved	290.54	8.11e-64	Highly significant difference in the distribution; bilateral involvement is far more common
Wiping times	312.15	1.66e-57	Strongly significant difference from equal frequencies; wiping times vary widely
Diagnosis	126.55	1.28e-25	Diagnosis categories show significant deviation from equal distribution

DISCUSSION

This study provides a comprehensive assessment of epiphora on QoL in a large sample of 298 patients, broad age range (20-70 years) and focus on the targeted population. Our findings demonstrate that epiphora significantly affect the QoL in daily routine activities include reading, driving, using digital devices and other aspects such as physical, social, and psychological well-being. Epiphora has been reported to cause blurred vision, scabbing around eyes, eyelid swelling, facial skin irritation, and laxity of the lower eyelids from constant wiping. There are very few studies that have extensively explored the impact of this eye disease on patients' lives.[21,22] These findings of this study suggest that load of watery eye includes psychological inferences, mental, and physical discomfort. Also, many individuals who are enrolled in this study acknowledged that epiphora affects some activities of their day-to-day life. A 55-year-old lady expressed that continuous watering from her eye affects her life. The findings of Bohman et al.,[23] suggest that patients with epiphora often complain about the watering of eye with itching and irritation. Outdoor activities were the most consistently emphasised area in our study, the similar result with the hospital-based survey of 342 Korean patients in which glare-related embarrassment and reflex wiping were the principal drivers of social withdrawal.[24] Additionally, neither bilaterality nor duration of symptoms predicted summary scores once nasolacrimal obstruction grade was entered into the multivariable model, suggesting that anatomical severity rather than laterality or chronicity is the determinant of patient-perceived disability. This finding aligns with the WEQOL validation study of Schulz et al.,[25] where irrigation pattern explained 28% of the variance in QoL, whereas symptom duration was non-contributory. The observation that one in four patients delayed surgical referral despite functionally significant epiphora underscores the "tolerability threshold" phenomenon described by Usmani and Selva.[26] Constant wiping can obstruct focus on specific tasks. Some patients feel embarrassed in public due to tearing, which diminishes their confidence and may lead to the avoidance of social situations.[27] Epiphora is not merely a minor issue; in severe cases, such as chronic epiphora, it can negatively influence both physical comfort and emotional well-being.

CONCLUSION

This study demonstrates that epiphora significantly compromise QoL by affecting functional vision, daily routine tasks, emotional well-being, and social participation. For students, epiphora may be distracting; it worsens whenever an individual focuses on a screen while reading or studying. The results of this study highlight the importance of early detection of nasolacrimal duct blockage, as chronic epiphora leads to severe watering, which can disrupt people's lives. Our findings highlight that the burden of epiphora extends beyond physical symptoms and should not be underestimated in clinical practice. Timely diagnosis and appropriate management can lead to substantial improvements in patient-reported outcomes. Although the investigation was conducted at a single centre and employed a locally developed data-collection proforma, these constraints highlight opportunities for future work rather than weaknesses. Multi-centre studies that deploy validated, standardized QoL instruments will deepen our understanding and guide nationwide strategies to mitigate epiphora's burden.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Jawaharlal Nehru Medical College Faculty of Medicine Aligarh Muslim University Ethics Committee (Date: 10.06.2025, Decision No: IECJNMC/1855).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Data Availability Statement

Research data can be provided on request through corresponding author.

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Review

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Gene therapy applications in ophthalmology

Leyla Eryiğit Eroğul[1], Kamuran Avcı[2], Özgür Eroğul[3]

[1]Department of Opthalmology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkiye
[2]Department of Medical Genetic, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkiye
[3]Department of Opthalmology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkiye

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ABSTRACT

Gene therapy has gained significant progress in recent years. The success of these therapies is based on efficient gene transfer and stable transgene expression. With the US Food and Drug Administration's (FDA) approval of gene therapy for Leber congenital amaurosis, the use of gene therapies has increased. Studies have provided new information about the benefits and limitations of using gene transfer routes to different regions of the eye. However, there are many old and new difficulties in the long-term effects, immunogenicity, targeting, and production of treatments. The eye's susceptibility to inflammation and immune and inflammatory reactions encountered in gene therapy can render the treatment ineffective or harmful. Although many strategies have some requirements in common, it is not possible for a single gene therapy system to be used for all applications. Moreover, genome-engineering tools based on new delivery methods facilitate more effective and targeted applications to eye compartments. This review presents data on various approaches to gene therapy, their applications to various eye diseases from the anterior segment to the posterior segment, clinical limitations of current systems, future prospects, research aimed at alternative solutions, and advantages and disadvantages of gene transfer routes.

Keywords: Ocular diseases, drug development, ocular gene therapy, gene editing, gene therapy vectors

INTRODUCTION

Ocular diseases comprise a variety of conditions that affect vision and quality of life. Traditional treatments aim to relieve symptoms or delay the progression of disease. Surgery is necessary in only special cases. These approaches are not always curative, and many patients may experience vision loss.[1] Gene therapy aims to cure diseases by transferring genetic material. Although currently offered in limited options, it is promising in ocular treatment.[2] Applications consist of strategies such as changing the gene structure and stopping, increasing, and regulating gene expression.[3] Treatments are administered through subretinal, intravitreal, and suprachoroidal injections.[4] Among the studies on this topic, adeno-associated virus (AAV) vectors for gene transfer and clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) systems for gene editing stand out.[5]

The eye is a special organ that is suitable for gene therapy applications due to its immune privilege, small size, and segmented structure. The risk of systemic exposure is quite low when therapeutic agents are applied.[6] In addition, therapy studies can be easily evaluated using noninvasive imaging techniques such as optical coherence tomography, fundoscopy, angiography, and new-generation two-photon microscopy. Thus, the real-time monitoring of therapeutic results and safety becomes easier.[7] Clinical research on gene therapy is currently being applied to various ocular diseases.[8] The efficacy of ocular gene therapy has been continuously improved in animal experiments and clinical studies. In the transition to clinical studies, gene transfer methods, uncertainty of disease molecular mechanisms, therapeutic delivery efficiency at the target site, and differences in disease models pose problems.[9] In this review, we present data on various gene therapy approaches, gene transfer methods to ocular tissues, their applications to various eye diseases from the anterior segment to the posterior segment, clinical limitations of current systems, future prospects, research aimed at alternative solutions, and advantages and disadvantages of gene transfer routes.

OPHTHALMOLOGIC GENE THERAPIES

Inherited retinal diseases (IRDs) are an important focus in ophthalmologic gene therapy research.[10] Currently, more than 300 genes have been associated with IRD.[6] The vast majority of variants lead to the dysfunction and degeneration of photoreceptors and/or retinal pigment epithelium (RPE). Autosomal dominant (AD), autosomal recessive (AR), X-linked

Corresponding Author: Kamuran Avcı, kamuran.avci@afsu.edu.tr

(XL), polygenic, and mitochondrial inheritances have been reported.[11] IRDs show a high rate of clinical heterogeneity. For example, diseases such as LCA can be seen congenitally or at an early stage, whereas diseases such as Retinitis pigmentosa (RP) and cone-rod dystrophy can be seen in adulthood.[12,13] Gene therapy applications aim to reduce the negative effects of these diseases and improve quality of life. Approaches to gene therapy vary according to genetic variants and heredity characteristics. These can be grouped as alteration, silencing, regulation, and modification of the target gene.[14]

APPLICATION METHODS OF GENE THERAPIES

Viral Vectors

Commercial Luxturna®, Glybera®, Zolgensma®, and Hemgenix® products exert AAVs as a gene therapy system.[14] Recent strategies utilize binary/multivectors to address genetic data transfer size limits in AAVs, employing extein residual and intein analogs to convert peptides into large functional proteins in target cells.[15,16]

The efficacy of Luxturna® has been demonstrated in clinical trials, showing improvements in light sensitivity and peripheral vision.[17] However, the link between these objective enhancements and patients' daily experiences remains unclear. AEs include eye inflammation, redness, and pain from injections, alongside ongoing long-term safety studies.[18] Reichel et al.[19] evaluated retinal atrophy in eight patients 6 to 24 months after Luxturna® treatment. The study indicated that subretinal Luxturna® may induce RPE atrophy and photoreceptor loss, despite maintaining treatment benefits. Lorenz et al.[20] assessed the impact of baseline data on psychophysical and morphological outcomes from subretinal Luxturna® in 19 patients over a median 15-month follow-up. The therapy showed consistent primary outcomes, but 50% of treated eyes exhibited new chorioretinal atrophy. Effects were notably stronger in the pediatric subgroup. Daruich et al.[21] studied Luxturna® outcomes in 12 eyes from six pediatric patients over 12 months, noting no intraoperative issues. While macular and outer nuclear layer thickness remained stable, a parafoveal hole emerged at three months, with atrophy at the injection site. One patient faced elevated intraocular pressure. Most showed significant visual function improvements at 12 months with no complications affecting these gains. Fischer et al.[22] conducted a study with 103 patients, the largest assessment of Luxturna®'s long-term safety and effectiveness within the PERCEIVE framework. AEs occurred in 35 patients, or 34% of the group, mainly linked to chorioretinal atrophy. Changes in visual acuity from baseline were not significant, matching the pivotal trials' results. Yang et al.[23] conducted a phase 1/2 study on subretinal AAV5 gene therapy in 15 patients with biallelic guanylate cyclase 2D variants. Over 2.5 years, most AEs were surgical, with no serious incidents. Mild ocular inflammation was noted, treatable with steroids. High-dose patients showed significant retinal sensitivity improvements from day 28, lasting over 12 months. Audo et al.[24] assessed the efficacy and safety of subretinal Luxturna® in six pediatric and six adult patients. All participants had at least one ocular AE. A child experienced retinal detachment, and chorioretinal atrophy was observed in four adults and one child. Improvements in low-light functional vision were noted, with safety results consistent with prior data.

Nonviral Vectors

Physical and chemical methods have been developed for the transfer of genetic material. However, because of the inability of nonviral systems to achieve continuity of gene expression, high transduction efficiency, and proper therapeutic levels, they are less preferred.[16] Plasmid DNA, siRNA, mRNA, or micro-RNA administered to the cell for gene therapy purposes are degraded in a short time.[25]

Among the commercial products, Macugen® has been approved for phase III clinical studies. Macugen® is an antagonistic RNA aptamer for VEGF that competitively binds to VEGF receptors on endothelial cells and prevents receptor activation.[26] It has been broadly studied as an intravitreal therapy to suppress angiogenesis, vascular permeability, and inflammation in AMD. Avacincaptad pegol, which has a stronger affinity for VEGF, was also developed by a similar mechanism and approved for phase II clinical studies.[27]

Antisense Oligonucleotides

ASOs target the gene expression according to the region in the RNA strand to which they bind. There are three methods of ASO application.[28] The first ASO system aims to prevent the interaction of splicing factors in deep intronic variants (DIVs) which create a new donor or acceptor site in the intron, producing splicing defects. Thus, during the splicing process, a portion of the intron is incorporated into the mature mRNA, forming a pseudoexon.[29] An example of this situation is the CEP290-related IRDs. The CEP290 pseudoexon leads to nonsense-mediated mRNA decay, resulting in the synthesis of abnormal protein or no protein at all. ASOs manage the splicing process by binding to the variant region, preventing the formation of the pseudoexon, and protecting protein synthesis.[30] The second ASO system prevents splicing factors from interacting with splice sites or regulatory elements containing variants, avoiding their inclusion in mature mRNA.[31] This applies to usherin2A (USH2A) variants, a major cause of AR RP, particularly in exon 13. QR-421a is a modified ASO that binds to USH2A pre-mRNA, inducing exon skipping and producing a truncated functional protein.[32] The third ASO system targets mRNA to reduce mutant protein synthesis, particularly in AD RP, where variant alleles cause the disease despite normal alleles, known as the dominant-negative effect.[31] ASOs identify these alleles at the pre-mRNA stage, removing pathogenic exons through splicing. They ensure allele-specific degradation of variant mRNA by activating the RNase H enzyme, leading to the production of normal allelic protein.[30,33]

The first commercial ASO product approved in ophthalmology is Fomivirsen, which targets viral genetic sequences to treat cytomegalovirus retinitis.[34] Reports highlight the ease of intravitreal transfer, increasing its clinical value, especially for gene therapy needing frequent dosing over decades.[35] Gérard et al.[36] showed that intravitreal splice-switching oligonucleotides effectively modified CEP290 splicing in retinal cells related to LCA. No significant AEs were reported from the injections, which allowed detection of CEP290-skipped mRNA for over a month. These injections bypassed protein truncation, offering a viable solution for large mRNA sizes beyond AAV vector limits, thus improving gene therapy effectiveness. Cideciyan et al.[37] studied intravitreal ASO to restore splicing in LCA patients with the c.2991+1655A>G allele in CEP290. No severe AEs occurred, and mild treatment-emergent AEs were

noted. After three months, retinal changes were absent, but significant effects were observed, with baseline improvements maintained at six months. Slijkerman et al.[38] studied ASOs for exon 13 skipping in USH2A, discovering that QR-421a effectively induced this in photoreceptor precursors from a USH2A variant patient. Intravitreal injections in non-human primates demonstrated that QR-421a penetrates the retina, achieving exon 13 skipping for at least three months, indicating its promise as an RP therapy for USH2A variants.

GENE THERAPY STUDIES IN OPHTHALMOLOGIC DISEASES

Leber Congenital Amaurosis (LCA)

LCA is a severe retinal dystrophy causing progressive vision loss from birth or early infancy. Over 20 associated genes have been identified. The Luxturna® has been approved by FDA for RPE65 gene related LCA.[10] Genome editing technologies present potential therapies for LCA subtypes linked to CEP290 and RPE65.[17] CEP290 is vital for ciliary structure and photoreceptor trafficking, with its variants associated with LCA type 10.[39] Maeder et al.[13] designed the genome-editing therapeutic EDIT-101, which aims to eliminate a deep-intronic variant responsible for a pseudo-exon in the CEP290, thereby restoring normal CEP290 expression through accurate splicing. Subretinal delivery in animal models proved effective for CEP290 editing. A vector tested in nonhuman primates confirmed the CRISPR/Cas9 system's capacity for in vivo editing, advancing EDIT-101 and similar therapies for LCA10 and other inherited retinal diseases. RPE65 catalyzes compounds for visual chromophore regeneration in the retina. Variants are linked to LCA type 2. Jo et al.[40] used a CRISPR/Cas9 approach in an animal model for an RPE65 variant producing dysfunctional proteins. Their findings showed successful RPE65 correction without histological deterioration or tumors over 7 months. Russell et al.[41] conducted a phase III trial of AAV2 therapy, Luxturna®, in 29 pediatric LCA type 2 patients aged 3 years and older with 20/60 vision or less, showing functional improvement and no serious side effects.

RP

RP is a group of inherited retinal disorders marked by the degeneration of rod and cone photoreceptors. Pathogenic variants in over 80 genes have been linked to RP subtypes.[42] Approximately 70% of cases arise from variants in RP GTPase regulator (RPGR), 25% from RHO, and 20% from USH2A.[12] Current gene therapies have shown poor efficacy and safety issues.[43] Optogenetic therapy is a new method for RP, transferring genes for light-sensitive proteins to nonphotoreceptor retinal neurons like ganglion cells. This could enhance visual perception in RP and other inherited retinal diseases.[44]

The nonhomologous end joining (NHEJ) strategy has been applied in the treatment of AD RP for RHO gene. The S334 variant encodes a premature stop codon, whereas the P23H variant encodes a protein that misfolds and forms aggregates.[45] Bakondi et al.[46] examined the selective knockout of the S334ter variant by subretinal injection with electroporation using the CRISPR/Cas9 system in an animal model. Similarly, Giannelli et al.[47] examined the selective knockout of the P23H variant by intravitreal injection in an animal model and then in a human with the AAV vector using the CRISPR/Cas9 system. In these studies, allele-specific targeting of the variants via NHEJ prevented toxicity and retinal degeneration and improved visual function.

The homology-directed repair (HDR) strategy has been applied for the treatment of AR RP. The CRISPR/Cas9 therapeutic approach was conducted on the phosphodiesterase 6b (PDE6B). The enzyme PDE6B is involved in the visual signal transduction pathway in photoreceptor cells. The method targets specific editing of variants that disrupt enzymatic activity using a donor template. Cai et al.[48] investigated the correction of the Y347X variant using the AAV-based CRISPR/Cas9 system in an animal model. They reported that therapy promoted the survival of rod and cone photoreceptors, PDE6B expression was maintained, and visual function was improved. Similarly, Qin et al.[49] investigated the correction of the R560C variant with the AAV-based CRISPR/Cas9 system in an animal model. They reported significant improvement in optomotor responses driven by visual stimuli and electroretinogram after gene therapy.

The NHEJ strategy has been also applied in the treatment of XL RP. The CRISPR/Cas9 therapeutic approach was applied in the RPGR, which regulates the transfer of various proteins and vesicles required for photoreceptor survival and function. RPGR variants affect the functionality of proteins, disrupt cell homeostasis, and lead to photoreceptor death. Gumerson et al.[50] used an animal model to investigate the correction of the frameshift variant in the OFR15 region with the CRISPR/Cas9-mediated AAV vector. They found that early disease phenotypes such as incorrect localization of cone opsins were not observed in mutant mice due to the intervention. In addition, these authors stated that subretinal injection restored the reading frame and the variant was successfully corrected in adult mice.

Stargardt Disease (STGD1)

STGD1 is a common inherited retinal disorder leading to juvenile progressive central vision loss, caused by AR variants of ATP Binding Cassette Subfamily A Member 4 (ABCA4). Stargardt-like symptoms may arise from rare AD variants in ELOVL fatty acid elongase 4 or prominin 1, which are not suitable for gene therapy.[51]

ABCA4 is a crucial retinal protein for retinoid transport, found in the outer segment discs of rods and cones. Variants hinder the clearance of N-retinylidene-phosphatidylethanolamine, leading to toxic phosphatidylpyridinium cisretinoic levels and RPE lipofuscin buildup, resulting in degeneration of RPE and photoreceptors. STGD1 poses challenges for gene therapy due to the large size of the ABCA4 gene and the lack of approved treatments.[52] Various DIVs in the ABCA4 cause abnormal splicing outside exons, activating critical splice regions and affecting regulatory units.[53] Gene therapy studies have targeted these DIVs. DeAngeli et al.[54] assessed gene correction therapy for the c.5197-557G>T, causing premature termination, by adding a 188-bp intronic sequence to the ABCA4 mRNA using CRISPR-Cas9 in photoreceptor precursor cells. They achieved an 83% correction in splicing and a 1.8-fold increase in correctly spliced transcripts with *S. pyogenes* Cas9, highlighting the potential of CRISPR/Cas9 in correcting ABCA4 splicing defects. Approximately 25% of STGD1-associated ABCA4 variants disrupt pre-mRNA

splicing, emerging as the main pathological RNA processing events. This has led to interest in ASOs for modulating splicing, as an alternative to traditional gene knock-out methods.[55] Kaltak et al.[56] investigated ASOs designed to skip exon 17 in the ABCA4 gene, achieving 59% exon 17 skipping in retinal organoids. Exon 17 deletion does not fully eliminate protein activity or cause severe STGD1 phenotypes. The authors suggest ASOs could mitigate severe variant effects, restoring partial ABCA4 activity in STGD1 patients. Kaltak et al.[57] used ASOs to restore RNA splicing of the ABCA4 variant linked to severe disease. They tested ASO effectiveness in an ABCA4 midigene model, using 3D human retinal organoids. QR-1011 significantly increased correctly spliced transcripts, confirming ABCA4 protein restoration and marking it as a promising splice-correcting ASO. Kaltak et al.[58] investigated QR-1011 ASO and three other ASOs to address splicing errors in non-canonical splice site variants near exon 39 of the ABCA4 gene. QR-1011 showed the greatest effect, enhancing full-length ABCA4 transcript production for the c.5461-8T>G and c.5584+6T>C variants, indicating a potential treatment for STGD1 patients with various severe ABCA4 variants. There is an alternative approach to the large size of the ABCA4. Li et al.[59] devised dual split intein ABCA4 vectors to improve dual AAV gene therapy efficacy. They engineered a dual AAV8-ABCA4 vector, achieving considerable full-length ABCA4 expression. This reduced bisretinoid build-up and restored vision in ABCA4-knockout mice, highlighting the treatment potential for STGD1. Recently, Yang et al.[60] initiated the SB-007 study for STGD1, utilizing a dual AAV vector to replace ABCA4 and restore the full-length protein. It has orphan drug status in E.U. and the U.S., with dosing for the first trial patient now ongoing.

Cataract

Cataract is lens opacity due to high-molecular-weight protein aggregates in lens cells or deterioration of lens microarchitecture, leading to light scattering. Its development rate is linked to protein accumulation and specific pathogenic gene variants.[61] Patients were evaluated in two groups by age of onset; age-related and congenital cataract. Age-related cataracts are influenced by genetic, environmental, and stochastic factors, leading to variability in onset age. In contrast, congenital cataracts are primarily driven by genetic factors, resulting in consistent onset age. Over 50 loci linked to congenital cataract have been reported, yet many cataract genetics remain unclear.[62] Genetic analyses have identified variants linked to crystalline, connexins, membrane proteins, and intermediate filament proteins that are vital for lens homeostasis. AD inheritance appeared in 44% of bilateral cataract families. Congenital cataracts were isolated hereditary cases in 70% and in association with other ocular abnormalities or syndromes in 15% of instances.[61]

Designing vectors is crucial to limit lens-specific target areas and minimize tissue interaction.[63] Lin et al.[64] developed a surgical technique for lens intervention in gene therapy, removing the cataractous lens while preserving the capsule and epithelial cells. This method aims to maintain endogenous epithelial stem/progenitor cells and their environment for functional lens regeneration, showcasing an effective strategy for tissue regeneration. However, CRISPR/Cas9 models may enable gene therapy combined with lens regeneration surgery. Wu et al.[65] studied gene correction for the dominant crystallin gamma C (CRYGC) variant causing nuclear cataract at the zygote stage. They found repair in mutant embryos via the HDR pathway, with healthy alleles passed to offspring. Wu et al.[66] studied correcting the CRYGC in spermatogonial stem cells and its effects on spermatogenesis and offspring after oocyte injection. They found the CRYGC variant could be repaired by NHEJ or HDR efficiently, preventing cataract phenotypes in offspring with 100% success. Yuan et al.[67] developed a cataract animal model by disrupting gap junction protein alpha 8 function, crucial for lens opacity. The system effectively generated a hereditary cataract model with 98.7% and 100% gene variant efficiency in embryos and offspring, respectively. Similarly, the researchers aimed to create a new animal model targeting αA-crystallin at the zygote stage for studying congenital cataracts. Findings revealed all F0 generation offspring had indel-mediated variants in αA-crystallin without off-target effects.[68] Recently, Zhao and colleagues developed an F0 animal model to identify genes linked to cataract formation and refine treatments, detailing design, microinjection, efficacy, evaluation, dose optimization, and CRISPR-Cas9 methods.[69]

CHALLENGES OF GENE THERAPY

The unique sensitivity of the eye necessitates specialized interventions. Challenges include identifying disease genes, ensuring precise delivery, application methods, clinical implementation, and immune responses.[70] Many products and trials aim to effectively target ocular tissues.[71] Ocular methods targeting eye tissues directly reduce immunogenicity but need expertise for implementation.[72] Invasive methods enhance bioavailability and delivery precision but risk complications like infection, retinal detachment, and hemorrhage.[73] Thus, selecting the right method for efficient transduction and minimal immune response is crucial.

CONCLUSION

The eye is a prime target for gene therapy due to its size and accessibility. Genome engineering can effectively treat ocular disorders by precisely targeting genes, facilitating therapy development. Future research will emphasize on new vectors, molecular targets, and standardized manufacturing to enhance safety and efficacy. Merging non-viral methods with viral efficiency is crucial. Next-generation therapies will address diseases lacking genetic diagnosis, targeting multiple variants simultaneously to lower costs and improve access, enabling objective assessment of transgene expression and clinical responses.

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Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Insights into a rare congenital abnormality: clinical and imaging features of two hiperpigmented torpedo maculopathy cases

Berk Kadir Kaynar, Ayna Sariyeva Ismayilov, Mahmut Oğuz Ulusoy
Department of Ophthalmology, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkiye

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ABSTRACT

Torpedo maculopathy (TM) is a rare congenital, nonprogressive macular anomaly of the retina pigment epithelium (RPE) or choroid. A characteristic feature is its presentation as an isolated, asymptomatic, hypopigmented nevus in the temporal macula, often described as torpedo-shaped. Contrary to what is known, two cases of TM, both hyperpigmented, one located in the fovea, the other located in the temporal macula, and the first case accompanied by a previously unreported posterior subcapsular cataract at a young age, are presented here. These cases, along with others documented in the literature, suggest that TM can present with atypical characteristics and locations. Recognition of these lesions is important in distinguishing them from more malignant diseases such as malignant melanoma, choroidal nevus, congenital hypertrophy of RPE, and congenital toxoplasmosis.

Keywords: Congenital abnormality, maculopathy, multimodal imaging, torpedo maculopathy

INTRODUCTION

Torpedo maculopathy (TM) is a rare congenital, nonprogressive macular anomaly of the retina pigment epithelium (RPE) or choroid.[1] A characteristic feature is its presentation as an isolated, asymptomatic, hypopigmented nevus, horizontally located, in the temporal macula, often described as torpedo-shaped. TM has recently expanded with the addition of atypically located and shaped torpedo lesions to the literature and has been named "torpedo retinopathy" or even "expanded spectrum torpedo retinopathy".[2,3] With the increasing use of multimodal imaging techniques-particularly spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) diagnosis and monitoring of torpedo maculopathy have become more precise. Typical TM is hypopigmented, and a few hyperpigmented TMs have been reported in the literature.[4,5] In this study, using multimodal imaging methods, two hyperpigmented cases and one of them with cataract at an early age, which has not been reported before, will be presented.

CASE PRESENTATION

Case 1

A 26-year-old female patient presented with bilateral complaints of decreased vision over the past few years. She reported no trauma, drug use, or gastrointestinal disease. Best corrected visual acuity (BCVA) was 5/20 (-0.50, -0.25 axis 160) in the right eye, 5/20 (-0.25, -0.50 axis 170) in the left eye. IOP was normal. Anterior segment examination revealed bilateral (more in the right eye) posterior subcapsular cataracts (PSC), with clear corneas and normal anterior chambers. Fundus examination was slightly blurred, but a solitary, oval-shaped, well-defined, partially hyperpigmented tail, torpedo-shaped lesion pointed towards the fovea in the inferotemporal macula of the right eye. FAF showed a hypoautofluorescent lesion, surrounded by a hyperautofluorescent border. SD-OCT of the right eye showed a hyporeflective subretinal cleft and defect in the RPE and ellipsoid zone corresponding to the lesion area (Figure 1). The left eye appeared normal. The patient was diagnosed with TM and was followed up for both cataract and TM.

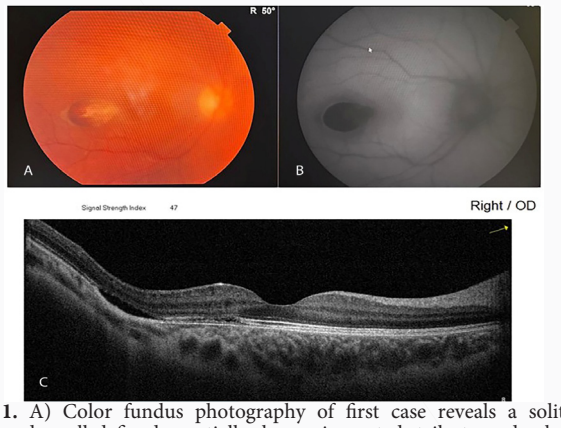

Figure 1. A) Color fundus photography of first case reveals a solitary, oval-shaped, well-defined, partially hyperpigmented tail, torpedo-shaped lesion pointing towards the fovea in the inferotemporal macula of the right eye. B) FAF demonstrates a hypoautofluorescent lesion, surrounded by a hyperautofluorescent border. C) SD-OCT of the right eye showed a hyporeflective subretinal cleft and defect in the RPE and ellipsoid zone corresponding to the lesion area

Corresponding Author: Ayna Sariyeva Ismayilov, sariyevaayna@hotmail.com

Case 2

A 32-year-old male patient presented with a complaint of preexisting vision loss in his left eye. He had no history of trauma or systemic disease. BCVA was 20/20 (+0.25, -0.25 axis 165) in the right eye and 10/20 (-0.50 axis 160) in the left. Intraocular pressure (IOP) was normal, and anterior segment examination was unremarkable in both eyes. Fundoscopic examination revealed a torpedo-shaped lesion at the center of the fovea in the left eye, characterized by a hypopigmented peripheral zone and a hyperpigmented center. FAF demonstrated a hypoautofluorescent lesion, surrounded by a hyperautofluorescent ring. SD-OCT of the left eye demonstrated thickening of the ellipsoid zone and the presence of a cleft between the ellipsoid zone and the thinned RPE and inner choroidal excavation (**Figure 2**). Fluorescein angiography (FA) shows hyperfluorescence nasal to the lesion due to a window defect. The patient was diagnosed with torpedo maculopathy and scheduled for follow-up. We obtained an informed consent form from two patients for the procedure.

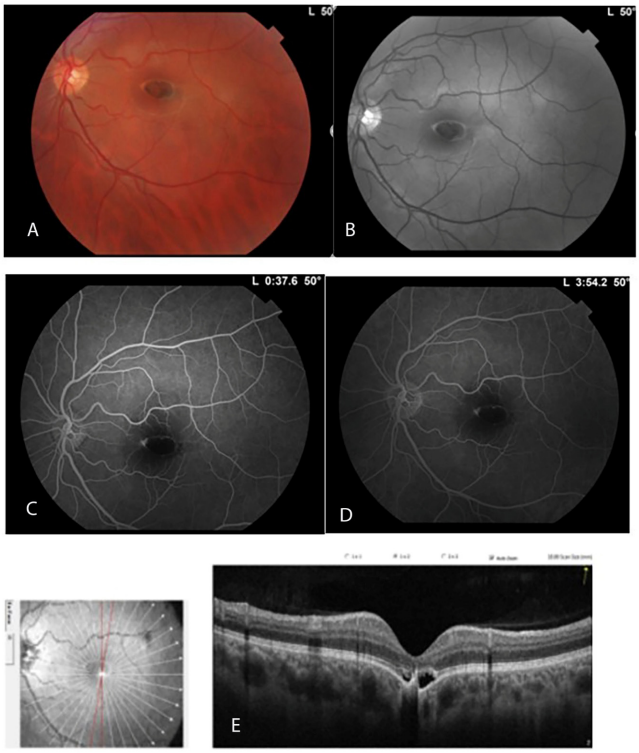

Figure 2. A) Color fundus photography of second case reveals a torpedo-shaped lesion at the center of the fovea in the left eye, characterized by a hypopigmented peripheral zone and a hyperpigmented center. B) FAF demonstrates a hypoautofluorescent lesion, surrounded by a hyperautofluorescent ring. C, D) FA shows hyperfluorescence nasal to the lesion due to a window defect. E) SD-OCT of the left eye demonstrated thickening of the ellipsoid zone and the presence of a cleft between the ellipsoid zone and the thinned RPE and inner choroidal excavation

DISCUSSION

TM is an uncommon macular anomaly characterized by a distinct, torpedo-shaped lesion within the RPE of the temporal macula. Its unique form features a rounded edge towards the temple and a pointed end directed towards the macula. It is typically asymptomatic, with an estimated occurrence of approximately 2 in every 100,000 people.[6] The exact cause of TM isn't fully understood. However, researchers suggest it's a congenital anomaly and they believe it stems from a persistent flaw in the development of the RPE within the fetal temporal bulge.[7]

The classic presentation of this lesion is a single, hypopigmented spot located in the temporal macula. Contrary to what is known, two cases of TM, both hyperpigmented, are presented here. One case is located in the fovea, and the other is located in the temporal macula. A previously unreported PSC is associated with the first case at a young age.

A few cases with hyperpigmented features have been published in the literature. Our first case has partially hyperpigmented tail in the temporal side of lesion like Yuan et al's[8] case whose explained choroidal structure characteristics. Another case whose hyperpigmentation pattern was similar to this case did not change its character and showed no progression during the 10-year follow-up.[9] In our second case, the macular lesion has a diffuse hyperpigmented center and a hypopigmented halo around it. These features are alike to the cases of Ranjith et al.[4] and Rohl et al.,[5] but while these lesions were located in the temporal macula, whereas our case was located right in the fovea. Wong et al.[10] classified OCT findings of TM into two categories: Type 1, characterized by outer retinal disturbance, and type 2, distinguished by outer retinal cavitation. In 2018, Tripathy et al.[11] defined type 3 TM by adding "inner retinal excavation" on OCT in addition to these classical TM findings. In terms of OCT characteristics, our first case exhibited type 1 TM features, while our second case displayed type 2 TM features.

The prevalence of cataracts increases with age. In addition to age, several risk factors contribute to the development of posterior PSC. These include atopy, diabetes mellitus, glaucoma, hereditary disorders, hypoparathyroidism, ocular inflammation, trauma, myopia, obesity, retinal dystrophies, solar ultraviolet (UV) radiation, steroids, and vitrectomy.[12] Our case was 26 years old and had an increasing loss of vision in the last few years. We do not know whether PSC is present at birth or whether it is added to the disease later but she did not have any of the other risk factors we mentioned. To our knowledge, this is the first case in the literature to report the coexistence of TM and PSC with a young patient.

In fact, although TM is very rarely associated with choroidal neovascularization, they are generally stable and non-progressive lesions.[9] It is important to recognize TM and to differentiate it from more aggressive lesions such as malignant melanoma, choroidal nevus, congenital simple hamartoma of the retina, congenital hypertrophy of RPE, congenital Zika virus infection and congenital toxoplasmosis. Therefore, presenting TM cases with different characteristics, as in our cases, may contribute to easier diagnosis and differential diagnosis of these cases.

CONCLUSION

In this case report, contrary to popular belief, two hyperpigmented TM cases are presented with the help of multimodal imaging methods. In one of these cases, there was PSC association, which has not been previously reported in the literature. Recognizing atypical TM cases like ours is important in distinguishing them from similar lesions with more malignant characteristics.

ETHICAL DECLARATIONS

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Superior ophthalmic vein thrombosis following barosinusitis: a rare case report

Gülistan Oyur, Fatma Savur
Department of Ophthalmology, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkiye

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ABSTRACT

Superior ophthalmic vein thrombosis (SOVT) is a rare but potentially serious condition that can arise from various causes, including barotrauma. This case may represent one of the first reported instances of SOVT associated with barosinusitis, identified after exclusion of other potential etiologies. A previously healthy patient developed acute orbital symptoms shortly after exposure to sudden changes in ambient pressure during a flight. Clinical and radiological investigations revealed SOVT secondary to barosinusitis. Magnetic resonance imaging confirmed thrombosis of the superior ophthalmic vein and demonstrated paranasal sinus inflammation consistent with barosinusitis. The patient was successfully treated with anticoagulation and broad-spectrum antibiotics, resulting in rapid resolution of symptoms and radiologic improvement. Barosinusitis, although rare, should be considered a possible etiological factor for SOVT, especially in patients presenting with orbital symptoms after pressure-related activities. Early recognition and appropriate treatment can prevent potentially serious complications.

Keywords: Barotrauma, paranasal sinusitis, venous thrombosis

INTRODUCTION

Superior ophthalmic vein thrombosis (SOVT) is a very rare condition, with an incidence of only 3-4 cases per million each year, but it may lead to serious clinical consequences.[1]

SOVT may result from both septic and aseptic causes. Septic etiologies include orbital cellulitis, paranasal sinusitis, and septic cavernous sinus thrombosis (CST), while aseptic causes comprise facial trauma, spontaneous carotid cavernous fistula (CCF), hypercoagulable states, orbital tumors, and Tolosa-Hunt syndrome.[2,3]

Paranasal sinusitis, a common septic factor, may develop due to viral and bacterial infections, allergies, polyps, and-though rarely-barotrauma.[4] Barotrauma refers to tissue injury or inflammation caused by failure to compensate for changes in ambient pressure. Barosinusitis, a barotrauma-related sinus condition, typically occurs during flight or diving, when reduced barometric pressure leads to expansion of intrasinus air and a resultant pressure gradient between the sinus ostia and the nasal cavity. In cases of inflamed or obstructed sinuses, this imbalance results in a "reverse squeeze" effect, where the mucosa is compressed outward against the bony walls.[5] Although barosinusitis can occur in the absence of preexisting sinus pathology, it is more frequently observed in individuals with acute sinonasal inflammation.[6]

CASE

A 25-year-old male patient travelling from Sydney to London via Singapore experienced increasing pain on the left side of his face during the first 8-hour flight from Sydney to Singapore. The pain subsided slightly during a 6-hour wait at Singapore Airport, then gradually became intense pain on the left side of his face during the flight from Singapore to London. The patient's pain became so severe, there was swelling around his eyes and vision decreased, in the 10th hour of the flight, so the plane had to make an emergency landing in İstanbul (**Figure 1**). He applied to the emergency department of Başakşehir Çam and Sakura City Hospital. In the ophthalmic examination, the right eye was normal, and the visual acuity of the left eye was 0.1. Swelling, subconjunctival hemorrhage and conjunctival hyperemia were seen in the left eye. Fundoscopic examination was normal. Pupillary light reflex and oculomotility were intact. CT and MR scan showed left maxillary sinusitis and left superior ophthalmic vein dilatation and filling defect (**Figure 2**). Additional laboratory and imaging studies were performed to exclude other potential etiologies of superior ophthalmic vein thrombosis. The patient's complete blood count, coagulation profile (prothrombin time, activated partial thromboplastin time, and D-dimer), inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), and autoimmune panel (antinuclear antibody and

Corresponding Author: Gülistan Oyur, gulistanoyur@hotmail.com

antiphospholipid antibodies) were all within normal limits. Blood cultures were negative. These findings, combined with the absence of systemic prothrombotic conditions or orbital trauma, supported the diagnosis of SOVT secondary to maxillary barosinusitis. The patient, who was thought to have septic thrombosis due to maxillary sinusitis, was given IV vancomycin and meropenem (since he was allergic to penicillin and clindamycin), heparin 2x6000 IU as anticoagulant therapy, and nasal decongestant therapy. On the first day of treatment, visual acuity reached 1.0 and periocular edema and hyperemia regressed. At the patient's first week follow-up, paranasal sinus CT and contrast-enhanced orbital MRI were performed due to the persistence of pain around the eye. Despite antibiotic treatment, advanced maxillary sinusitis was observed in the patient's paranasal sinus CT, and in the contrast-enhanced orbital MRI, it was observed that the left superior ophthalmic vein dilatation had regressed and there was no filling defect. During the otorhinolaryngologist examination, sinus antrostomy and functional endoscopic sinus surgery (FESS) surgery were recommended to the patient, but the patient did not accept this surgical treatment.

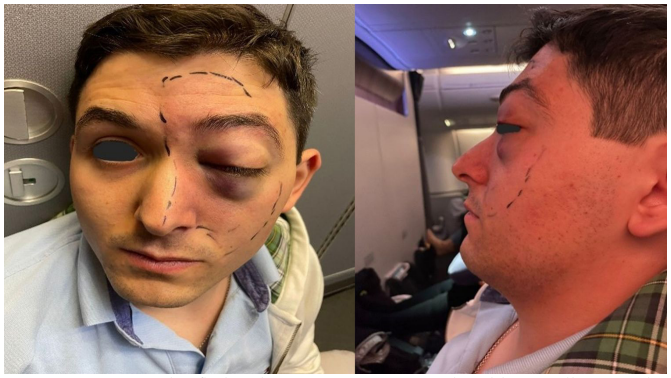

Figure 1. During the flight, the patient experienced sudden swelling on the left side of his face, ecchymosis and proptosis of the left eye, chemosis and hyperemia in the conjunctiva

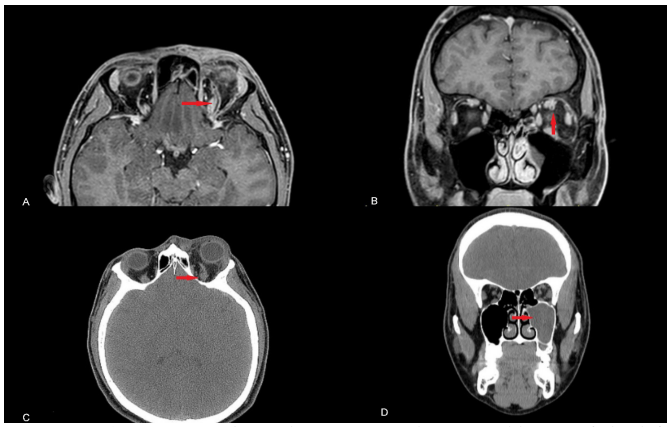

Figure 2. A) Contrast-enhanced MRI-T1-axial section dilation of the left SOV and a filling defect (red arrow), B) Contrast-enhanced MRI-T1-coronal section a filling defect in the SOV (red arrow), C) CT-axial section enlarged SOV (red arrow) and proptosis, D) CT-coronal section shows left maxillary sinusitis (red arrow)

MRI-T1: T1-weighted three-dimensional structural magnetic resonance imaging, SOV: Superior ophthalmic vein, CT: Computed tomography

DISCUSSION

Superior ophthalmic vein, a vein without valves, plays a key role in draining the majority of venous blood from the orbit. SOVT arises from disrupted venous blood flow, which may occur due to blood flow stasis, vessel wall injury, or hypercoagulable conditions. SOVT can have both septic and aseptic origins. Aseptic causes are attributed to changes in blood flow, driven by either anatomical abnormalities or systemic factors.[2] Septic causes of SOVT include infections originating from the paranasal sinuses, orbit, teeth, and face. According to the literature, paranasal sinusitis is the most frequently reported cause of septic SOVT.[7]

In the clinical presentation of SOVT, symptoms result from impaired orbital venous drainage and include orbital swelling, pain, chemosis, eyelid edema, proptosis, restricted ocular motility, with or without fundus abnormalities, and reduced visual acuity.[2] This patient experienced severe pain on the left side of his face that began on his first connecting flight and worsened on the second flight. During air travel, he developed periorbital edema, ecchymosis, proptosis, conjunctival chemosis, and hyperemia, along with limited ocular motility and decreased vision. (**Figure 1, 2**).

The diagnosis is established through magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) scans.[1] CT imaging reveals thickening and dilation of the superior ophthalmic vein, often accompanied by an intraluminal filling defect. Similarly, MRI identifies a filling defect within the vessel lumen.[1,2] MRI is considered superior to CT in detecting SOVT and cavernous sinus thrombosis, particularly in the early stages, as CT may fail to identify SOVT during this period.[8] In this patient, we detected thickening and dilatation of the superior ophthalmic vein accompanied by an intraluminal filling defect in the CT and MRI imaging and the patient had deformity in the left maxillary sinus, which may be secondary to chronic sinusitis, thickening of the sinus wall, decreased ventilation, left venous enlargement with an intraluminal thrombus (**Figure 3**). Because the patient's symptoms developed during a long connecting flight, we interpreted the case as superior ophthalmic vein thrombosis, which probably developed secondary to barosinusitis due to barotrauma that developed on the basis of chronic sinusitis.

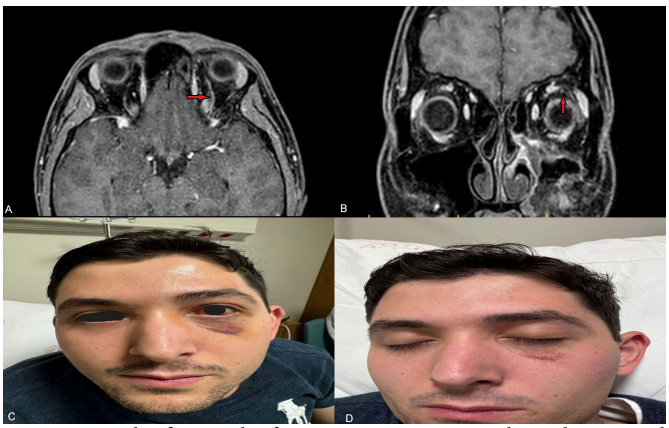

Figure 3. In the first week after treatment; contrast-enhanced computed tomography axial (A) and coronal (B) sections show normal blood flow in the superior ophthalmic vein (red arrow), edema and ecchymosis around the patient's left eye regressed, and proptosis resolved (C, D)

Barosinusitis is defined as acute or chronic inflammation of the paranasal sinuses resulting from barometric pressure differences between the atmosphere and the air inside the sinuses.[9] Barosinusitis due to barotrauma, reverse impingement or compression injury, can occur in an inflamed or partially obstructed sinus when air expands and increases intrasinus pressure during ascent. Without pressure compensation, this leads to an outward compression injury in which the sinus mucosa is pushed against the bony walls.

This causes mucosal swelling and tearing.[5] According to the literature, acute barosinusitis typically affects a single sinus, with the frontal sinus being the most commonly involved (reported in 68-100% of cases across various studies).[10] This is followed by the maxillary sinus and, less frequently, the sphenoid sinus.[11,12]

Vaezeafshar et al.[5] defined acute barosinusitis, the most common form, as a singular episode of sinus-related pain and inflammation occurring within hours to days after exposure to a known cause of changes in ambient air pressure. Although acute barosinusitis can occur without prior sinus pathology, studies suggest that it is significantly more common in the context of preexisting acute sinonasal inflammation.[6] From the patient's history, we learned that he had been treated for sinusitis in previous years, which may have predisposed him to this condition.

The most commonly reported symptom of acute barosinusitis is a sudden onset of pain, which is often distinctly localized to the affected sinus.[5] This patient also had pain that started when the plane started to climb and gradually increased during the flight. On the second flight, he experienced pain accompanied by periorbital edema and decreased vision. Another common complication of barosinusitis is epistaxis, which has been reported at rates ranging from 33% to 66% in different series, but this finding was not present in our patient.[13] Considering these symptoms, clinical history, and radiological findings, barosinusitis due to barotrauma was considered the most plausible explanation, leading to superior ophthalmic vein thrombosis as a complication of sinusitis.

Management

Due to the rarity of SOVT, its management lacks consensus. Treatment is guided by the underlying pathology. Medical therapy may include antibiotics, steroids, and anticoagulant therapy (ACT) with antibiotics being specifically indicated in cases of septic SOVT. The selection of antibiotics should target pathogens commonly associated with the suspected source of infection while awaiting culture results. The duration of antibiotic therapy remains undefined because of limited consensus.[2] Because the patient was allergic to penicillin, IV vancomycin, meropenem, and nasal decongestant treatment was started.

The use of corticosteroids has been reported; however, their role remains controversial and not well-defined. Corticosteroids are considered effective in aseptic SOVT caused by autoimmune or inflammatory diseases, as they help reduce inflammation, edema, and orbital congestion, and may alleviate proptosis.[14] Among 88 cases of septic cavernous sinus thrombosis reported by Weerasinghe et al.,[15] 15 patients received corticosteroids for various indications, such as reducing cranial and orbital inflammation, providing replacement therapy, or managing associated conditions like lupus, meningitis, or temporal arteritis. Outcomes were comparable between those who received corticosteroids and those who did not, with no clear overall benefit in recovery, disability, or mortality. Similarly, Mandic et al.[8] advocated that corticosteroids should be avoided, especially during the acute phase of infection, due to potential worsening of the septic process. Based on these findings, we did not administer corticosteroids to our patient, who was considered to have septic thrombosis.

Concerns about hemorrhagic complications initially made ACT a topic of controversy. In their study on cavernous sinus thrombosis, Weerasinghe et al.[15] reported that ACT was associated with decreased mortality in these patients. Although current evidence supports the use of ACT, the optimal dose and duration remain uncertain.[2] Our patient was started on low-molecular-weight heparin (2×6000 IU) as anticoagulant therapy. Follow-up imaging performed in the first week showed resolution of the thrombus and restoration of normal blood flow.

In this case, the otorhinolaryngology team recommended functional endoscopic sinus surgery (FESS) to address the persistent maxillary sinusitis that had contributed to the septic thrombosis. However, the patient declined surgical intervention. FESS is considered the standard surgical approach for refractory or complicated sinus disease, including barosinusitis-related complications, as it allows direct drainage and ventilation of the affected sinus and reduces the risk of recurrence.[5] Despite the absence of surgical treatment, our patient responded favorably to prompt medical therapy, underscoring that early recognition and appropriate management can sometimes obviate the need for surgery in selected cases

CONCLUSION

This case illustrates a rare presentation of superior ophthalmic vein thrombosis secondary to barosinusitis, an uncommon but clinically important complication of barotrauma. Early recognition and appropriate medical management, including antibiotic and anticoagulant therapy, led to full recovery. Clinicians should consider SOVT in patients presenting with orbital symptoms following pressure-related events, particularly in those with a history of sinus disease.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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The great masquerade-a case of squamous cell carcinoma of tarsal conjunctiva after a prompt diagnosis and good margin controlled excision

Thangjam Amit Singh, Sakshi Kumar, Alka Tripathi, Rohit Kumar
Department of Ophthalmology, India Institute of Medical Sciences Gorakhpur, Uttar Pradesh, India

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ABSTRACT

A 70-year-old man complained to us of a big, friable mass from the upper lid of the left eye. The mass was gradually increasing in size and was causing drooping of the upper eyelid. The excision of the mass was planned and sent for biopsy and it was found to be squamous cell carcinoma . The presentation was atypical due to its location, so we chose to present this case.

Keywords: Squamous cell carcinoma, MMC, mitomycin-C, excision biopsy

INTRODUCTION

Conjunctival squamous cell carcinoma (SCC) is the most common non-pigmentary malignancy of the ocular surface. It has higher incidence in the African population.[1]

SCC is diagnosed by performing histopathological evaluation following excisional biopsy.

After resection mostly patients are kept on topical mitomycin C (MMC) and seems to be safe and effective therapy for conjunctival and corneal SCC.[2]

Conjunctival tumors encompass a broad range of diagnosis. The 3 most important malignant tumors include ocular surface squamous neoplasia (OSSN) 14%, melanoma 12%, and lymphoma 7%. Common benign eyelid tumors include nevi (moles), papillomas (similar to skin tags), seborrheic keratoses (wart like growths), and xanthelasmas (fat deposits).

Common malignant tumors include basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma and melanoma.[3]

CASE

A 70-year-old male came to us with the complain of swelling of left upper lid from past 4 weeks. The swelling initially presented as a small nodule which had gradually progressed into a fleshy mass and was protruding from the upper lid of the left eye (**Figure 1 a, b**).

The swelling was associated with watering, pain, irritation and redness in left eye. The visual acuity in the right eye was 6/18p and left eye was 6/60. The lids and adnexa of right eye were within normal limit. The left eye showed lobulated, pink, friable mass of about 18 mm x14 mm arising from the tarsal conjunctiva of the upper lid (**Figure 1 c**) which led to mechanical ptosis of left upper lid.

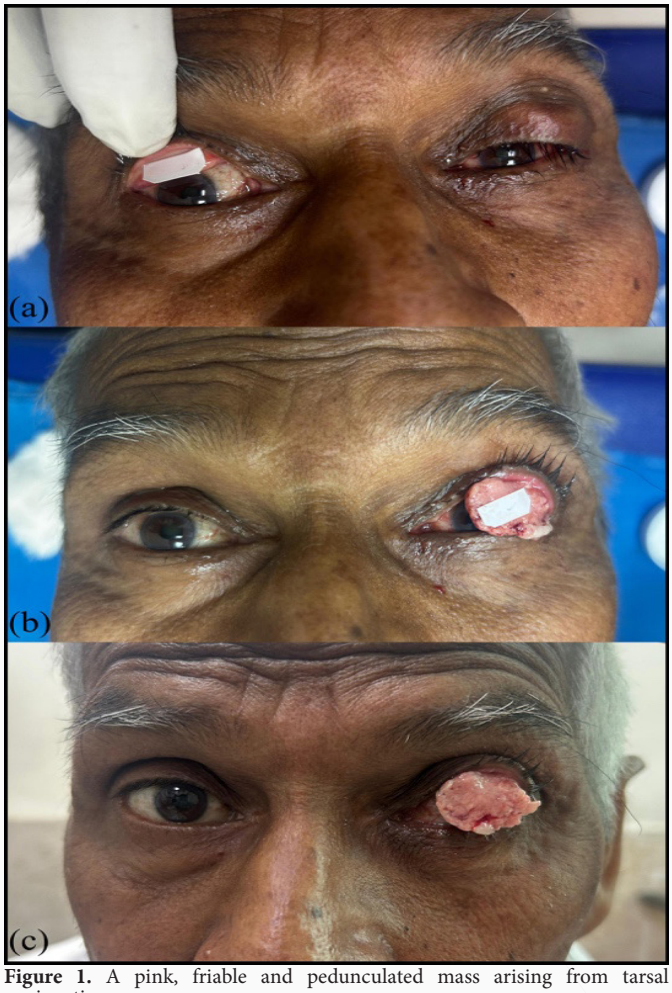

Figure 1. A pink, friable and pedunculated mass arising from tarsal conjunctiva

Corresponding Author: Sakshi Kumar, saks.rocks12@gmail.com

The anterior segment showed cataractous changes in both eyes and fundus was within normal limits. The patient was a known hypertensive with no other systemic illness.

He was a farmer by occupation with no history of any trauma to the eye or any ocular surgery or any similar lesions in the body.

A non-contrast computerised tomography of the brain and orbits gave no evidence of intra-orbital extension or bony erosion with an incidental finding of diffuse cerebral/ cerebellar atrophy.

Impression cytology showed highly cellular smears with dysplastic squamous cells showing high N:C ratio, hyperchromatic nuclei, coarse granular chromatin, prominent nucleoli and scant amount of cytoplasm. Overall cytomorphological features were suggestive of high grade dysplasia consistent with ocular surface squamous neoplasia. Excision biopsy was planned for this patient.

The lesion was a pedunculated mass and it was excised was planned from the base of the peduncle. Under local infilteration anesthesia, a moderate dissection was required for the tarsal conjunctiva to excise the entire mass. Hemostasis was achieved with electrocautery a good margin of about 2 mm was also excised around the peduncle. Cryoablation was done at the base to prevent the recurrence.

After the excision was done a sample measuring 2.8 cm x1.2 cm x0.6 cm was sent for histopathological evaluation and the patient was kept on topical interferon alpha drops.

Section examined showed tumour cells arranged in nodules, nests, lobules and islands. Individual tumour cells were moderately pleomorphic having high nucleus to cytoplasmic ratio, hyperchromatic nucleus, irregular nuclear membrane prominent nucleoli with scant eosinophilic cytoplasm (**Figure 2 a-f**). Mitosis is frequent with atypical mitotic figure is also identified. Features are suggestive of Basaloid squamous cell carcinoma (**Figure 2 a-f**). The patient reviewed with us weekly and no recurrence was noted (**Figure 3**).

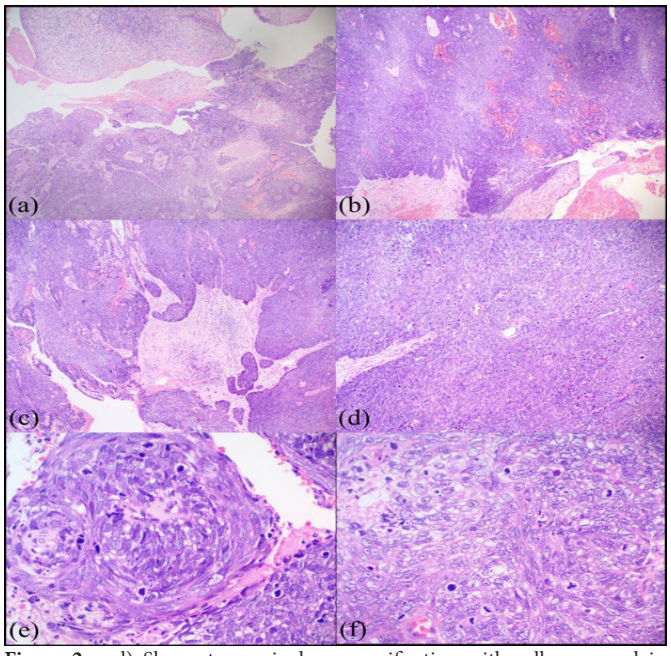

Figure 2. a-d) Shows tumor in low magnification with cells arranged in nests, lobules, islands and nodules, e, f) Shows tumour in high magnification displaying moderately pleomorphic tumour cells, having high nuclear to cytoplasmic ratio, hyperchromatic nucleus with irregular nuclear contour and scant eosinophilic cytoplasm. Frequent mitotic figure along with few atypical mitoses are seen

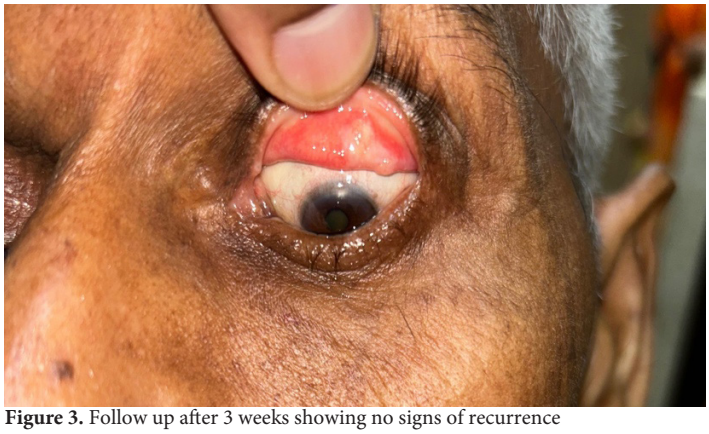

Figure 3. Follow up after 3 weeks showing no signs of recurrence

DISCUSSION

Ocular surface squamous neoplasia is a spectrum of conjunctival squamous cell dysplasia.[4] Squamous cell carcinoma of the conjunctiva is an uncommon tumour. There are two patterns in this tumour.[4] First pattern is observed in young patients who have HIV infection. The second trend is observed in older individuals, primarily men, who do not have HIV and reside close to equator.

The corneal limbus within the interpalpebral fissure is where this tumour frequently occurs.

UV-B radiation exposure is the most well-documented risk factor.

Atopic disorders, xeroderma pigmentosum and medical immunosuppression are immunodeficiencies linked to squamous cell carcinoma.

There has been a role of Human papilloma virus in other lesions of eye such as conjunctival papilloma , lacrimal sac neoplasia and squamous cell carcinoma of skin as such there has been a lot of studies to prove the relation with squamous cell carcinoma of conjunctiva but no definite relation has been associated till date.[4]

As per Tobias et al.,[5] a 33-year-old female presented with tumorous lesion of nasal bulbar conjunctiva. She was kept on topical mitomycin 0.02% after excision of the squamous cell carcinoma. It was atypical because of the gender and age of the patient.

In our case patient gave no history of any trauma or surgery, he had no systemic illness. He was farmer by occupation so he had exposure of UV rays but the location of the tumour was below the upper lid of left eye hence the location was atypical in terms of sun exposure.

As per Santoni et al.,[6] patient presented with squamous cell carcinoma in the mean age of 68 years and exposure to ultraviolet rays was the main reason for causing the squamous cell carcinoma.

CONCLUSION

We can conclude that squamous cell carcinoma of conjunctiva and tarsal plate is uncommon but clinically significant because benign masquerades delay diagnosis and increase the risk of orbital invasion. This case demonstrates that a high index of suspicion and early biopsy are pivotal for any persistent lesion in elderly and sun-exposed patients. A good margin controlled excision can achieve tumour free margins and good functional outcomes when performed promptly.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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