Case Report/Series

A case of mixed mechanism glaucoma: diagnostic and management challenges

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pISSN: 0853-1773 • eISSN: 2252-8083
https://doi.org/10.13181/mji.cr.258092
Med J Indones. 2025;34:285–92

Received: March 03, 2025
Accepted: November 20, 2025

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ABSTRACT
Mixed mechanism glaucoma occurs when secondary causes contribute to glaucoma in an eye with preexisting primary open-angle glaucoma (POAG) or primary angle-closure glaucoma. This study highlights its diagnostic and management challenges. A 63-year-old female presented with blurry vision and right eye pain for 2 months. She had undergone cataract surgery in the right eye 6 months earlier and developed elevated intraocular pressure (IOP) afterward. Her visual acuity in the right eye was hand movements, and IOP was 34 mmHg despite medications. Examination revealed signs of uveitis, leading to a diagnosis of secondary glaucoma. A glaucoma drainage device (GDD) was implanted, successfully controlling IOP. Follow-up revealed POAG signs in the left eye, prompting a revised diagnosis of mixed mechanism glaucoma in the right eye. GDD implantation was effective, but continued monitoring remained essential to maintain the target IOP.

KEYWORDS case management, case report, diagnosis, glaucoma

Mixed mechanism glaucoma occurs when secondary causes of glaucoma contribute to disease progression in eyes with existing primary open-angle glaucoma (POAG) or primary angle-closure glaucoma.[1,2] Glaucoma is the second leading cause of blindness, with the number of cases among individuals aged 40–80 years projected to increase from 76 million in 2020 to 111.8 million by 2040.[3,4] In Indonesia, the prevalence of glaucoma was 0.46% in 2007, with 80,548 new cases reported in 2017.[5] Diagnosing mixed mechanism glaucoma is complex and requires clinical history, calibrated intraocular pressure (IOP) measurement (as corneal thickness affects IOP measurement accuracy), corneal curvature assessment, gonioscopy, optic disc, retina, and retinal nerve fiber layer (RNFL) evaluation, visual field testing, and imaging such as optical coherence tomography (OCT). Because visual fields and RNFL thickness often correspond, interpreting these findings requires careful analysis, further complicating the diagnosis.

The main goal of current glaucoma management is to preserve visual function by reducing IOP with minimal adverse effects and the least impact on the patient's quality of life (QoL), including treatment costs. The target IOP must be individualized based on the patient's IOP and the severity of eye damage. More advanced disease at initial presentation requires a lower target pressure to minimize visual deterioration. Treatment options include topical medications, laser therapy, and glaucoma surgery. The benefits of any

intervention must outweigh the risks, considering both treatment-related complications and the consequences of disease progression on the patient's QoL.[2] This case report presents a challenging mixed mechanism glaucoma case, offering insights into its diagnosis and management. Following complete examinations, we identified uveitis as a contributing factor to glaucoma and, through assessment of the fellow eye, established a diagnosis of POAG.

CASE REPORT

A 63-year-old woman presented with a chief complaint of blurry vision and pain in her right eye, which had worsened over the past 2 months. She had undergone intracapsular cataract extraction (ICCE) without intraocular lens (IOL) implantation in the right eye 6 months earlier at another hospital.

Five months before admission, she underwent anterior vitrectomy and iridectomy for the right eye, with controlled IOP. However, 2 months prior to admission, she underwent secondary IOL implantation using a retropupillary iris-claw lens in the right eye. Following the surgery, she experienced pain, redness, and blurred vision in the right eye, with an elevated IOP of 40 mmHg. She was diagnosed with anterior uveitis and secondary glaucoma. Her medical history included diabetes and hypertension, both controlled with medication (glimepiride 1 mg and amlodipine 10 mg once daily). Other systemic diseases, such as heart disease, tuberculosis (Tb), or lung diseases, were excluded. She reported bilateral knee joint pain, but no systemic autoimmune symptoms such as red rashes, mouth ulcers, hair loss, or prolonged cough. Her family had no remarkable medical history.

At her first visit, her initial uncorrected visual acuity (VA) was counting fingers at half a meter in the right eye and at 3 meters in the left eye, both uncorrected with a pinhole. Her right IOP was 34 mmHg with the following medications: timolol 0.5% twice and brinzolamide 3 times daily, with a left IOP of 14 mmHg. In the right eye, a slight ciliary injection and multiple large keratic precipitates (KPs) were observed in the inferior quadrant, with a shallow anterior chamber, iris-claw IOL, and rubeosis iridis (Figure 1). Gonioscopy revealed peripheral anterior synechia (PAS) in the superior and temporal quadrants, with the inferior and nasal quadrants unremarkable.

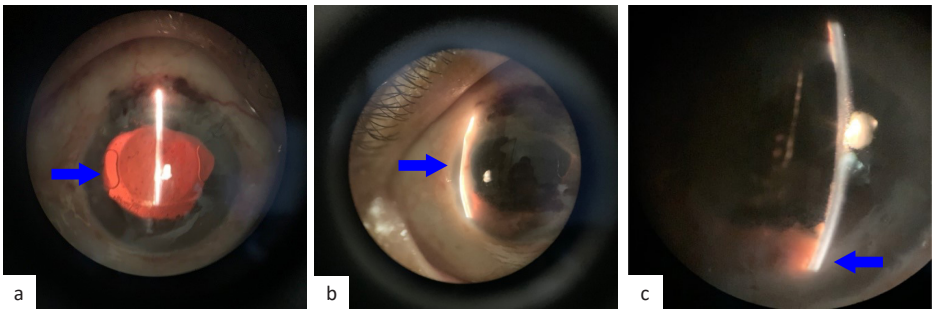

Figure 1. Initial presentation of right eye. (a) Right eye showed slight conjunctival and ciliary injection with iris-claw lens (blue arrow); (b) anterior chamber was shallow and there was PAS in the temporal and superior quadrant (blue arrow); (c) slit beam shows multiple large KPs mostly in the inferior quadrant (blue arrow). KP=keratic precipitate; PAS=peripheral anterior synechia

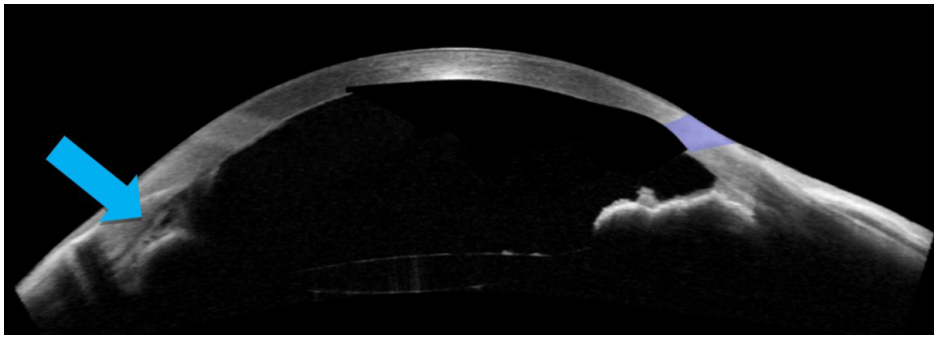

Figure 2. Anterior segment optical coherence tomography (AS-OCT) of the right eye showed blockage of the anterior chamber in the temporal quadrant (blue arrow)

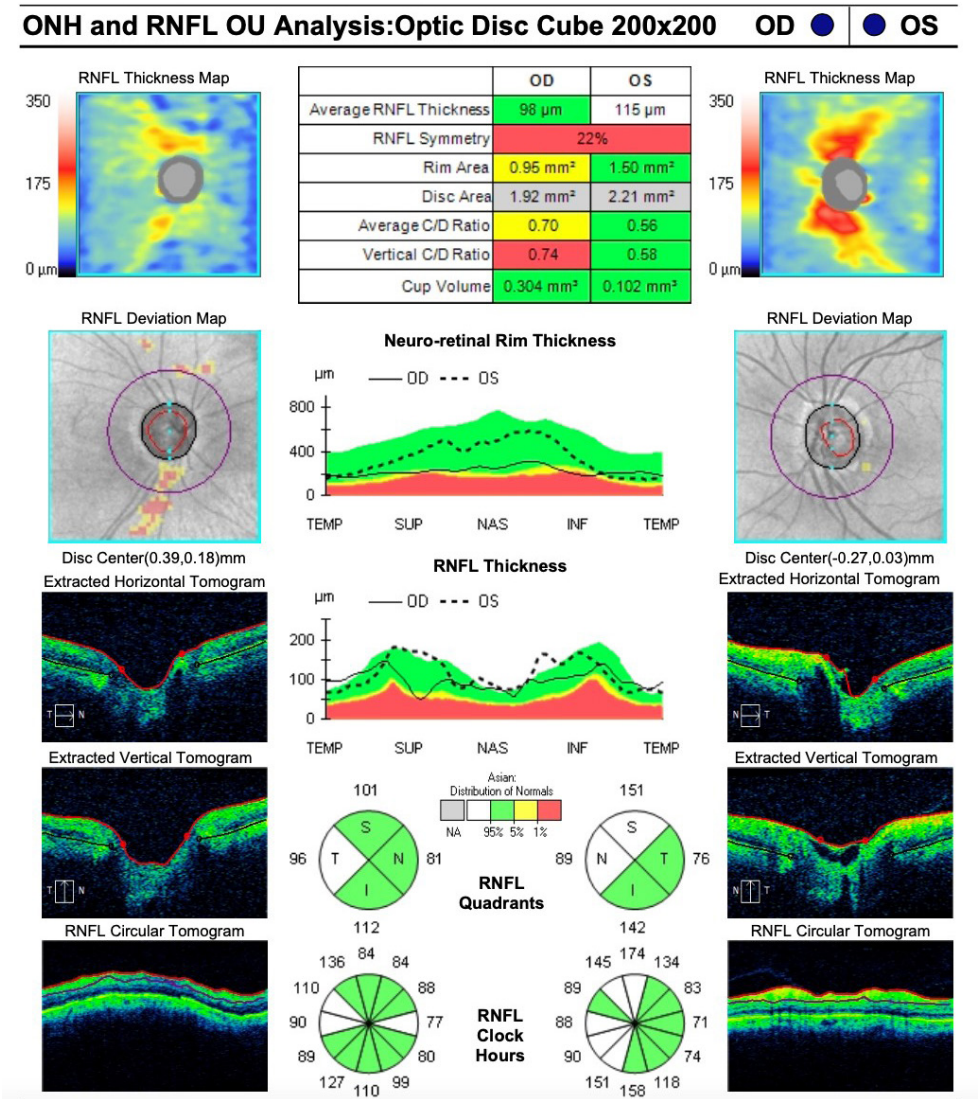

Figure 3. The ONH and OCT of both eyes show an enlarged C/D with still normal RNFL. C/D=cup-to-disc; INF=inferior; NA=not available; NAS=nasal; OCT=optical coherence tomography; OD=oculus dexter; ONH=optic nerve head; OS=oculus sinister; OU=oculus uterque; RNFL=retinal nerve fiber layer; SUP=superior; TEMP=temporal

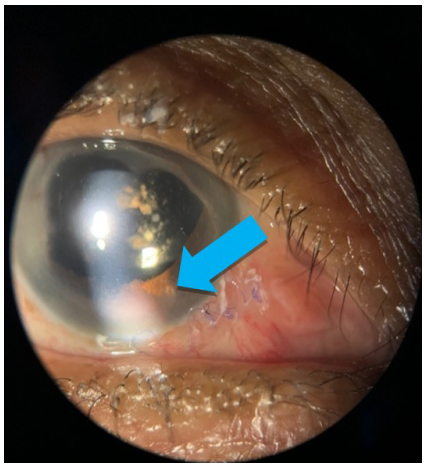

Figure 4. Presentation of right eye 1-month after surgery. The tube was still in the inferonasal quadrant (blue arrow) with intraocular pressure (IOP) of 15 mmHg

Her right eye fundoscopy revealed a round optic nerve head (ONH), but detailed evaluations were limited due to microcystic corneal edema and hazy vitreous. The anterior segment of the left eye was within normal limits. Laboratory tests revealed low hemoglobin and elevated creatinine levels. Anterior segment optical coherence tomography (AS-OCT) of the right eye revealed a blockage of the anterior chamber of the temporal quadrant (Figure 2). ONH OCT revealed a normal RNFL with an enlarged cup-to-disc (C/D) ratio, as illustrated in Figure 3. Specular microscope scans of the right eye showed a reduced cell density (CD) of 1,808 cells/mm^2, thin central corneal thickness (CCT) of 478 µm, reduced hexagonality (36%), and increased coefficient of variation (CV) of 53%. In contrast, the left

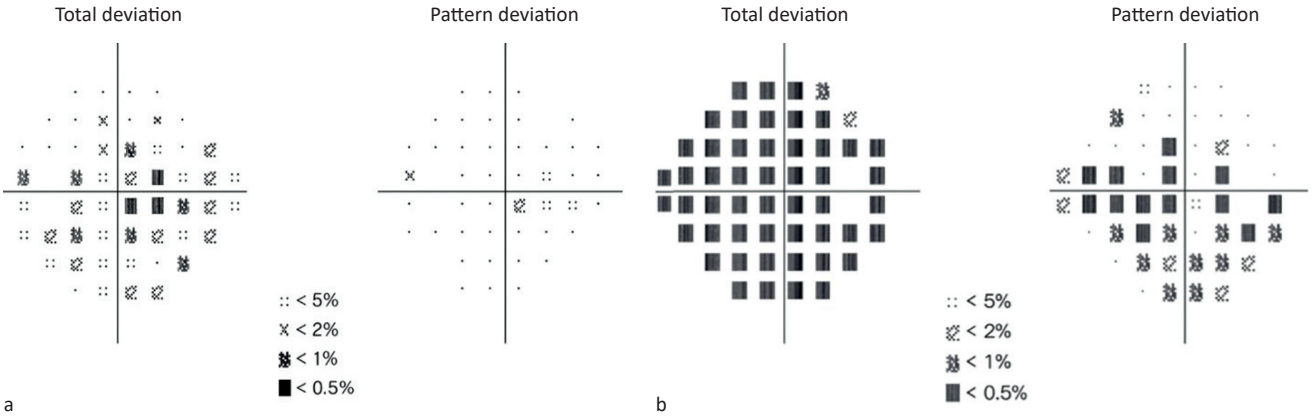

Figure 5. HVF result. (a) 24-2 field HVF test showed within normal limits for left eye; (b) GHT of outside normal limits for right eye. GHT=glaucoma hemifield test; HVF=Humphrey visual field

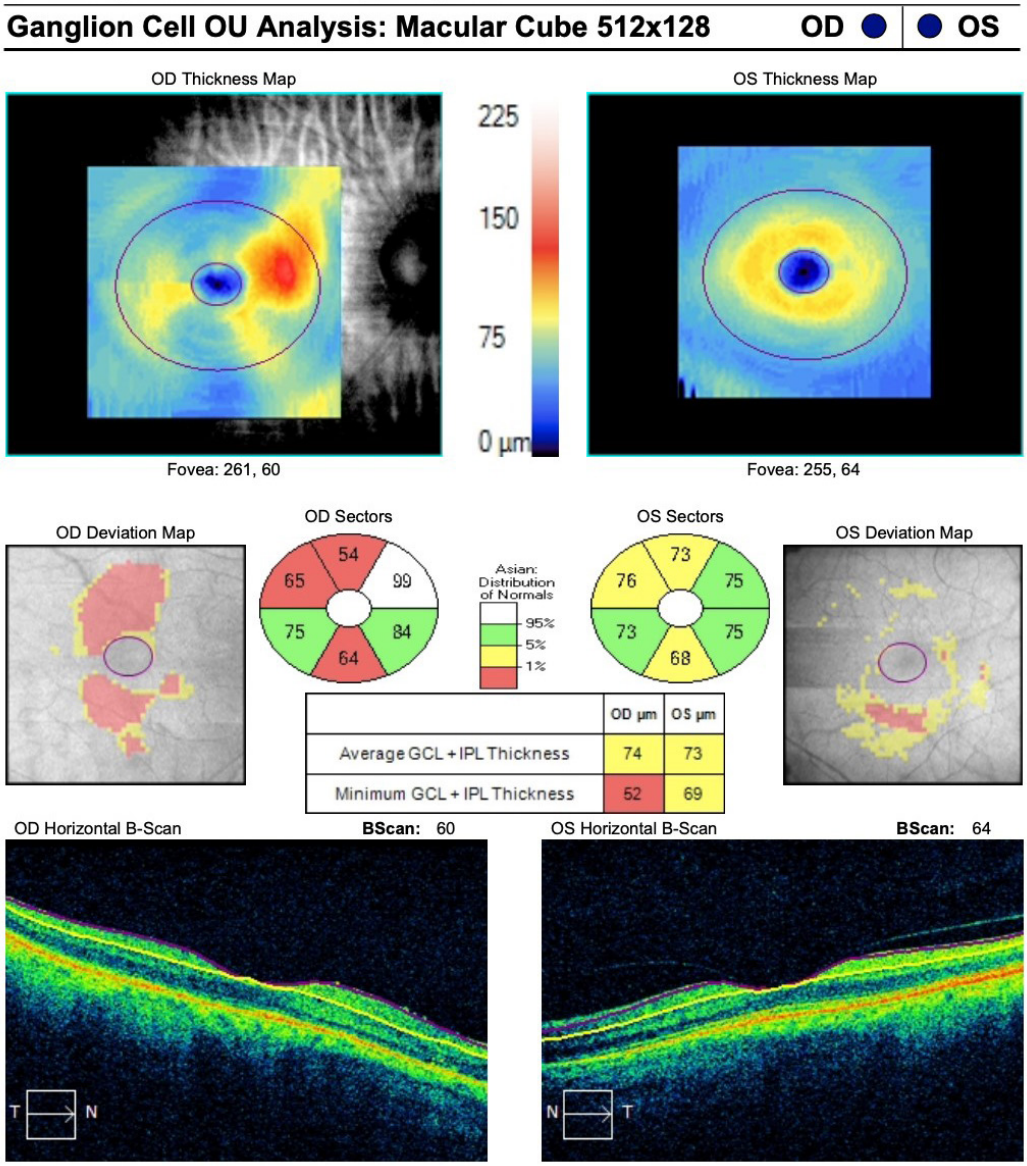

Figure 6. OCT showed moderate thinning of GCIPL in right eye and mild thinning of GCIPL in left eye. GCIPL=ganglion cell-inner plexiform layer; OCT=optical coherence tomography; OD=oculus dexter; OS=oculus sinister; OU=oculus uterque

eye showed a normal CD (2,740 cell/mm^2), thin CCT (485 µm), normal hexagonality (50%), and increased CV (50%).

Despite receiving maximum medication (acetazolamide 250 mg 4 times daily, timolol 0.5% eye drops twice daily, brinzolamide 3 times daily, and latanoprost once daily) for the right eye, the IOP remained at 28 mmHg. Acetazolamide was discontinued due to impaired kidney function. A glaucoma drainage device (GDD) was implanted using the Virna Glaucoma Implant® (Rohto Laboratories Indonesia, Indonesia) 1 month after her first visit. The tube was fixed in the inferonasal quadrant because PAS was present in the superior quadrant. On postoperative Day 1, she reported reduced pain in her right eye. The IOP decreased from 28 mmHg preoperatively to 10 mmHg. On postoperative Day 11, the IOP remained low (8 mmHg) with minimal pain. The bleb was elevated and the tube was placed in the anterior chamber and inferonasal quadrant (Figure 4).

Given her history of inflammation and the clinical findings, she was referred to the Ocular Infection and Immunology clinic for suspected uveitis. Her uveitis workup was positive for anti-toxoplasma IgG 525.4 IU/ml (non-reactive: <1 IU/ml), anti-herpes simplex virus (HSV)-1 IgG 3.29 cut-off (non-reactive: <0.90 cut-off), and anti-cytomegalovirus (CMV) IgG 883.3 U/ml (non-reactive: <0.5 IU/ml). Based on these results, she was diagnosed with toxoplasmosis-related posterior uveitis of the right eye and was administered an azithromycin loading dose of 500 mg once, followed by azithromycin 250 mg once daily for 3 weeks.

At the 1-month follow-up, she reported no pain in the right eye. The tube remained patent and was placed in the anterior and inferonasal quadrants (Figure 5). The IOP was stable at 15 mmHg. Her microcystic edema resolved, and a posterior segment examination revealed a round, pale ONH with a tigroid retina. A chorioretinal scar was observed in the inferotemporal quadrant, which supported the diagnosis of toxoplasmosis. The left eye underwent phacoemulsification with IOL implantation, and her VA increased from 3/60 to 6/7.5. Fundus examination of the left eye revealed that the posterior segment showed an enlarged C/D ratio of 0.5–0.6 with a tigroid retina, but no other abnormalities were observed in the left eye. She regained independence in daily activities and her pain-free condition enabled greater family interactions, resulting in an improved QoL.

At the 3-month follow-up, she reported no complaints. Timolol maleate 0.5% twice daily was administered to the right eye to maintain an IOP below 15 mmHg. Humphrey visual field (HVF) examination revealed a reduced visual field index (VFI) for the right eye (66%), and the results of the glaucoma hemifield test (GHT) were outside normal limits (Figure 5). In contrast, the left eye remained within normal limits (VFI 97%, GHT within normal limits). At the 4-month follow-up, the IOP was maintained at 12 mmHg, and timolol use was continued.

OCT of the ganglion cell-inner plexiform layer (GCIPL) demonstrated moderate thinning in the right eye and mild thinning in the left eye, suggestive of mild glaucoma defect in the left eye, showing signs of POAG (Figure 6). Thus, she was diagnosed with glaucoma mixed mechanism (POAG, uveitic, and neovascular) in the right eye, as well as POAG and pseudophakia in the left eye. Informed consent was obtained from the patient.

DISCUSSION

Diagnosing and managing mixed mechanism glaucoma is challenging because of its multifactorial etiology. In this case, the patient presented with blurry vision, pain, redness in the right eye, and a high IOP despite the use of topical antiglaucoma medications. She received ciliary injections, multiple large KPs, PAS in the temporal and superior quadrants, and rubeosis iridis, suggestive of secondary glaucoma caused by uveitis and neovascular diseases.

Uveitic glaucoma is a secondary type of glaucoma that combines open-angle and angle-closure diseases. The elevation in IOP may result from trabecular meshwork (TM) edema, TM endothelial dysfunction, fibrin and inflammatory cells blocking outflow through the TM or Schlemm's canal, corticosteroid-induced reduction in outflow, PAS formation, or prostaglandin mediated breakdown of the blood-aqueous barrier.[2,6] The wide range of differences in individuals' underlying TM function complicates the understanding of uveitis. Interestingly, older age is a risk factor for increased IOP in uveitis patients. While younger people may have optic nerves that can tolerate high pressure longer, older patients seem to suffer severe optic nerve damage and resulting visual impairment even from brief periods of elevated IOP.[6]

The patient was further evaluated for the underlying cause of her uveitic glaucoma. Physical

examination revealed a cicatrix in the inferotemporal quadrant on right eye fundoscopy. The workup revealed nonreactive results for HIV, syphilis, Tb, and rheumatoid factors, while toxoplasma IgG, HSV-1 IgG, and CMV IgG were all reactive. Owing to the presence of vitreous opacity, a trial of cotrimoxazole was planned. However, she experienced gastrointestinal discomfort, necessitating a switch to azithromycin, which was well-tolerated. During the follow-up, no recurrence of uveitis was observed. Kalogeropoulos and Sung[7] reported an increased IOP in 10–30% of patients with active ocular toxoplasma lesions, leading to glaucoma.[8]

We identified rubeosis iridis in the right eye even without gonioscopy. The iris displays an extreme and rapid sensitivity to an extended or even transitory state of retinal ischemia.[9] Elevated IOP causes oxidative stress, inflammation, and tissue damage in the retina and optic nerve.[10] Retinal ischemia and hypoxia stimulate the production and secretion of multiple vasoproliferative growth factors (e.g., vascular endothelial growth factor, insulin-like growth factor-1), inflammatory cytokines (e.g., interleukin-6, endothelin-1, or nitric oxide), and the expression of platelet-derived growth factor-C, transforming growth factor beta 1 and beta 2, and other angiogenic factors, which trigger the release of a cascade of angiogenic factors that promote the development of iris and anterior chamber angle neovascularization. Neovascular glaucoma (NVG) results in fibrovascular membrane (FVM) formation on the anterior iris surface, which extends to the iridocorneal angle before the IOP increases. The trabecula is occluded by an FVM that is gradually drawn forward to close the angle. Fibrovascular proliferation of the anterior segment ultimately causes PAS formation, which progressively closes the anterior chamber angle and produces an intractable increase in the IOP. TM obstruction by the FVM and associated inflammation are implicated in the pathogenesis of NVG.[9–11] In this case, the prolonged elevation of IOP and uveitis may have contributed to the development of rubeosis iridis and NVG.

We proceeded with GDD implantation in the right eye because the patient's IOP remained at 28 mmHg despite maximum medication. GDDs are broadly classified into valved and non-valved types. Valved devices, such as the Ahmed glaucoma valve, incorporate flow-limiting mechanisms that allow or earlier IOP control and help prevent postoperative complications such as hypotony. In contrast, non-valved devices, such as the Baerveldt glaucoma implant (BGI), do not contain a valve; thus, they do not rapidly decrease IOP but are associated with stable IOP in the later period.[12]

The Virna glaucoma implant, a non-valved GDD similar to the BGI, may provide better long-term IOP reduction and a higher rate of complete success. Studies comparing valved and non-valved implants suggest that non-valved implants may achieve sustained drainage and lower IOP over time compared with valved options.[12] However, valved devices can provide competitive long-term outcomes. The Ahmed *versus* Baerveldt study reported that at 5 years, the Ahmed valve effectively reduced IOP, but was associated with a higher cumulative failure rate than Baerveldt (53% *versus* 40%); however, the complications and intervention rates were comparable, underscoring that valved devices may remain a viable choice under appropriate conditions.[13] Furthermore, a long-term review of glaucoma drainage implant surgery found that mixed-valve/non-valve cohorts achieved sustained glaucoma control in 73% of eyes at 10 years, reinforcing that device choice is not necessarily a determinant of ultimate success.[14]

The GDD was implanted in the inferonasal quadrant due to PAS involving the temporal and superior quadrants, as confirmed by AS-OCT. The superior PAS was likely caused by ICCE and aggravated by uveitis. During the postoperative follow-up, the IOP dropped to 10 mmHg, remained low in the 2nd month, and increased again in the 3rd month to 20 mmHg. We suspected that the increase in IOP was due to the hypertensive phase; therefore, timolol was administered twice daily. This phase typically occurs 1–3 months after surgery,[15,16] and poses a risk of further optic nerve damage in advanced refractory glaucoma. Therefore, we continued additional antiglaucoma medication to maintain the IOP below 15 mmHg, as she had already experienced severe glaucoma damage to her right eye. HVF examination showed severe glaucomatous damage of the right eye according to the Hodapp–Parrish–Anderson criteria, supported by thinning of the GCIPL.[2,17]

A specular microscopy scan of the right eye showed reduced CD, increased CV, reduced hexagonality, and thin CCT. These changes may have resulted from the prolonged duration of high IOP, extended use of antiglaucoma medications, and numerous surgeries. Endothelial cell loss alters the cell size and shape as

the remaining cells enlarge or migrate to compensate, leading to reduced transparency, corneal edema, bullous keratopathy, and impaired VA. Endothelial cell loss is associated with both glaucoma and its treatment, which is aimed at lowering IOP. Possible mechanisms include direct compression from elevated IOP and cell toxicity from prolonged exposure to preservatives in ocular hypotensive drugs.[18] Yu et al[18] also reported endothelial cell loss following glaucoma surgery in patients who received antiproliferative medications during filtration surgery or aqueous shunt implantation.

After the patient's right eye condition improved, we performed phacoemulsification with IOL implantation in the left eye to assess possible infection, which was suspected in the right eye and could potentially manifest in the left eye. This surgery may also therapeutically improve her visual function. The posterior segment of her left eye showed an enlarged C/D ratio of 0.5–0.6 with a tigroid retina. ONH OCT and HVF revealed normal structures and function. However, mild thinning on GCIPL OCT revealed early signs of glaucomatous damage. Lee et al[19] found that the GCIPL thinning rate on OCT was significantly higher in patients with glaucoma with progression than in those without. Ultimately, she was diagnosed with mixed mechanism glaucoma caused by a combination of POAG, uveitis, and neovascular disease.

This study illustrates a comprehensive diagnostic approach, beginning with the identification of uveitis as the etiology in the right eye and the detection of GCIPL thinning in the left eye. Furthermore, the successful IOP control in the right eye and visual rehabilitation in the left eye contributed to a significant improvement in the patient's overall QoL. This study has some limitations, primarily the short follow-up duration of only 4 months. She lived far from our center and preferred to continue her follow-up closer to home. Given that her IOP and VA were stable, follow-up was advised every 3 months. However, she did not return for subsequent evaluations.

Diagnosing mixed mechanism glaucoma is challenging because it requires comprehensive history-taking and thorough examinations. Multiple mechanisms and etiologies may contribute to the patient's current eye condition, and several ancillary examinations are required to confirm the etiology. An appropriate approach must be determined to achieve the target IOP, using the most effective medical or surgical modalities to optimize her QoL. The choice of GDD implantation site is important, considering its availability, risks, and benefits. Routine visits are necessary as patients must be informed that the goal of therapy is to preserve visual function by lowering IOP.

Conflict of Interest

The authors affirm no conflict of interest in this study.

Acknowledgment

None.

Funding Sources

None.

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