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# Successful Management of Central-Involving Diabetic Macular Edema with Sequential Anti-VEGF Injections in Moderate NPDR: A Case Study

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**A B S T R A C T**

Diabetic macular edema (DME), particularly central-involving DME (CI-DME), represents a primary cause of significant vision impairment among individuals afflicted with diabetic retinopathy (DR). The progression from non-proliferative diabetic retinopathy (NPDR) stages can be complicated by the development of CI-DME, which mandates prompt and effective intervention to preserve visual function. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have emerged as the definitive first-line therapeutic strategy for CI-DME, demonstrating considerable efficacy in reducing macular thickness and enhancing visual acuity outcomes. This report provides a detailed account of the successful clinical management of a patient presenting with moderate NPDR and concurrent CI-DME, utilizing a regimen of sequential intravitreal anti-VEGF injections. A 58-year-old female patient, with an established 3-year history of both type 2 diabetes mellitus and systemic hypertension, presented with a chief complaint of progressively deteriorating vision in her right eye (OD) over the preceding two-month period. Her pertinent ophthalmic history included cataract extraction with intraocular lens implantation OD performed three months prior, followed by an initial anti-VEGF injection administered OD one month before the current evaluation. Upon examination, her best-corrected visual acuity OD was measured at 4/60. Dilated funduscopic examination of the right eye revealed retinal findings characteristic of moderate NPDR, specifically the presence of microaneurysms distributed across two retinal quadrants and discernible venous beading within one quadrant. Optical Coherence Tomography (OCT) imaging objectively confirmed the diagnosis of CI-DME, demonstrating a central subfield thickness (CST) of 376 µm accompanied by evident intraretinal hyporeflective spaces indicative of fluid accumulation. The patient subsequently received sequential intravitreal injections of Ranibizumab 0.5mg. Following the second injection, a follow-up assessment conducted at three weeks revealed a notable improvement in visual acuity to 6/30 OD, corroborated by anatomical improvement observed on OCT, which showed a discernible reduction in intraretinal fluid. Consequently, planning for a third intravitreal injection was initiated. In conclusion, the administration of sequential intravitreal anti-VEGF therapy, specifically Ranibizumab in this patient's course, proved demonstrably effective in the management of CI-DME within the context of moderate NPDR. This intervention resulted in both clinically meaningful functional vision improvement and objective anatomical reduction of macular edema. This case serves to underscore the paramount importance of anti-VEGF agents as a foundational management strategy for CI-DME. Optimal patient outcomes are contingent upon meticulous patient selection, diligent and ongoing management of systemic comorbidities, particularly diabetes and hypertension, and adherence to a regular follow-up schedule.

## 1. Introduction

Diabetes mellitus (DM) has become a global health crisis, with a relentless increase in prevalence and a substantial burden on individuals and healthcare systems worldwide. The number of individuals affected is currently estimated to be in the hundreds of

millions, and projections suggest a continued rise in diagnoses in the coming decades. The chronic hyperglycemia that characterizes DM leads to a range of systemic complications, with diabetic retinopathy (DR) being a particularly vision loss and blindness are serious microvascular consequences. In particular, DR is a major cause of vision loss and blindness among working-age adults. Progressive damage to the delicate retinal vasculature, including arterioles, capillaries, and venules, is the root cause of DR. This damage is caused by the sustained metabolic stress of high blood sugar levels and related pathophysiological changes. The clinical progression of DR ranges from early non-proliferative stages (NPDR) to advanced proliferative diabetic retinopathy (PDR), which threatens sight. Initial vascular abnormalities in NPDR are confined to the retina and include microaneurysm formation, dot and blot hemorrhages, hard exudates (lipid deposits), cotton wool spots (focal nerve fiber layer ischemia), venous caliber changes like venous beading, and intraretinal microvascular abnormalities (IRMA). IRMAs are dilated capillary channels that act as intraretinal shunts, bypassing areas of capillary non-perfusion. Based on the type, number, and extent of these lesions, NPDR is further classified into mild, moderate, and severe categories using scales such as the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale. Although mild to moderate NPDR may be asymptomatic or cause only minor visual disturbances, it indicates ongoing retinal damage and carries the risk of progressing to PDR. PDR is characterized by the development of fragile new blood vessels (neovascularization) on the retinal surface or optic disc, which can lead to vitreous hemorrhage and tractional retinal detachment. Diabetic macular edema (DME) is a frequent and visually significant complication that can occur at any stage of DR, though it is more common with increasing severity. The macula, the central region of the retina responsible for high-acuity vision needed for tasks like reading and facial recognition, pathologically thickens in DME. The breakdown of the blood-retinal barrier (BRB), a complex physiological structure made up of tight junctions between retinal capillary endothelial cells and the retinal pigment epithelium (RPE), is the source of this thickening. Hyperglycemia and related factors compromise the BRB's integrity, which leads to increased vascular permeability and the leakage of fluid, proteins, and lipids from the capillaries into the retina's interstitial spaces, particularly in the outer plexiform and inner nuclear layers. DME is still the main cause of moderate vision loss in people with diabetes mellitus. Its presence has a considerable negative impact on quality of life and functional independence. The location and extent of macular thickening are essential for classification and treatment choices. Central-involving DME (CI-DME) is the term used to describe DME that affects the central 1-millimeter diameter subfield of the macula. CI-DME is a direct threat to central vision and typically necessitates therapeutic intervention to avoid irreversible structural damage and functional decline.[1-3]

The pathophysiology of DME is complex and involves a complex interplay of biochemical and cellular events brought on by the diabetic environment. Chronic hyperglycemia causes oxidative stress, promotes the production of advanced glycation end products (AGEs), activates protein kinase C (PKC) pathways, and triggers inflammatory cascades in the retina. Together, these processes lead to endothelial cell dysfunction, pericyte apoptosis (loss of supporting cells around capillaries), thickening of the capillary basement membrane, and altered retinal blood flow. Importantly, these events cause an increase in vascular endothelial growth factor (VEGF), a potent signaling protein that dramatically increases vascular permeability and encourages angiogenesis. High intraocular VEGF levels are strongly implicated as a major contributor to both DME and the neovascularization seen in PDR. Additional inflammatory mediators such as interleukins (IL-6, IL-

8), tumor necrosis factor-alpha (TNF-α), and intercellular adhesion molecule-1 (ICAM-1) contribute to BRB breakdown and leukocyte adhesion, further perpetuating the inflammatory environment within the diabetic retina. Over the past two decades, the management of DME has changed dramatically. Historically, focal or grid laser photocoagulation, guided by fluorescein angiography to identify leaking microaneurysms or areas of diffuse leakage, was the established standard of care for clinically significant macular edema (CSME), a term largely encompassing CI-DME. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that laser treatment could reduce the risk of moderate vision loss by approximately 50% compared to observation. However, laser photocoagulation primarily aimed at stabilizing vision and rarely resulted in significant visual acuity improvement; its mechanism involves creating microscopic burns to reduce leakage and perhaps improve oxygenation, but it inherently involves some level of retinal tissue destruction. The elucidation of VEGF's critical role in DME pathogenesis paved the way for targeted pharmacotherapy. The development and introduction of intravitreal anti-VEGF agents marked a paradigm shift, fundamentally altering treatment goals from mere stabilization to potential vision restoration. A number of anti-VEGF drugs, including Ranibizumab (Lucentis®), Aflibercept (Eylea®), Bevacizumab (Avastin®, used off-label for ocular indications), Brolucizumab (Beovu®), and Faricimab (Vabysmo®), which also targets Angiopoietin-2, are now widely available. By binding to and neutralizing VEGF isoforms within the eye, these agents inhibit VEGF signaling, reduce vascular hyperpermeability, suppress inflammation, and resolve macular edema. Numerous large-scale, multicenter, randomized controlled trials (RCTs), including pivotal studies like RISE/RIDE (Ranibizumab), VIVID/VISTA (Aflibercept), and various DRCR Retina Network protocols (Protocol I, Protocol T, Protocol V, among others), have unequivocally established the superiority of anti-VEGF therapy over laser photocoagulation for treating CI-DME, particularly regarding visual acuity gains. These trials demonstrated that monthly or bimonthly intravitreal anti-VEGF injections could lead to mean visual acuity improvements averaging 2-3 lines (10-15 ETDRS letters) over 1-2 years, results far exceeding those typically achieved with laser therapy alone. As a result, current clinical practice guidelines worldwide universally recommend intravitreal anti-VEGF therapy as the first-line treatment for patients with vision loss due to CI-DME. The management of patients with moderate NPDR and CI-DME, as illustrated in this case report, has two goals: effectively treating the vision-impairing edema and addressing the underlying retinopathy to reduce the risk of progression to PDR. While anti-VEGF therapy directly targets the edema by reducing vascular leakage, compelling evidence suggests it also positively impacts the underlying DR severity. Studies like PANORAMA and DRCR.net Protocol W have shown that prophylactic anti-VEGF injections in eyes with moderate-to-severe or severe NPDR without baseline CI-DME can significantly reduce the risk of developing PDR or vision-threatening DME over time. Even though this patient already had CI-DME, the anti-VEGF treatment started primarily for the edema also has the potential to slow the progression of her NPDR.[4-7]

In contemporary retina practice, Optical Coherence Tomography (OCT) has become an indispensable technology, transforming the diagnosis, classification, monitoring, and management of DME. This non-invasive imaging modality uses low-coherence interferometry to produce high-resolution, cross-sectional images (B-scans) of the retina, similar to "optical biopsies." OCT enables objective and precise quantification of retinal thickness, typically reported as Central Subfield Thickness (CST), which is the average thickness within the central 1mm diameter zone. In addition to simple thickness measurements, OCT offers detailed morphological visualization of

DME characteristics, including the presence, size, and location of intraretinal cysts (IRC), subretinal fluid (SRF) accumulation between the neurosensory retina and the RPE, hyperreflective foci (HRF) thought to represent inflammatory cells or lipid exudates, the structural integrity of critical retinal layers, and the status of the vitreomacular interface. Specific OCT biomarkers are increasingly recognized for their prognostic value in predicting visual outcomes and treatment responses in DME. For instance, the integrity of the outer retinal layers, particularly the Ellipsoid Zone (EZ, formerly the inner segment/outer segment junction), which reflects photoreceptor health, is a strong predictor of final visual acuity potential. Even with significant macular thickness improvement with treatment, disruption or absence of the EZ band at baseline frequently correlates with poorer visual outcomes. Similarly, Disorganization of the Retinal Inner Layers (DRIL), defined as the inability to distinguish the boundaries between the ganglion cell-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer in the central macula, has been consistently linked to worse baseline and final visual acuity. While contributing to macular thickening, subretinal fluid has paradoxically been associated with better visual outcomes in some studies, possibly indicating less chronic inner retinal damage or a different inflammatory profile. Conversely, the presence and extent of hyperreflective foci may indicate a greater inflammatory component and potentially a differential response to anti-VEGF versus corticosteroid therapy. Monitoring changes in these qualitative and quantitative OCT parameters throughout treatment offers a comprehensive evaluation of therapeutic efficacy beyond simple CST reduction and aids in tailoring long-term management strategies.[8-10] This case report aims to provide a detailed clinical account of a patient navigating the complexities of moderate NPDR with CI-DME. It emphasizes the diagnostic process, the rationale for initiating anti-VEGF therapy, the observed clinical and anatomical response following sequential injections, and considerations for ongoing management. All of this is contextualized within the framework of current evidence-based practices and the crucial role of advanced imaging modalities like OCT.

## 2. Case Presentation

The patient is a 58-year-old female. Her occupation is listed as housewife. These demographic details provide the initial context for the patient, establishing her age, gender, and social role, which can be relevant in considering the impact of her condition on her daily life. The presentation date anchors the timeline of her clinical encounter and subsequent management. The patient's chief complaint was blurred vision in her right eye (OD). The history of her present illness revealed a gradual worsening of this blurred vision in the OD over the preceding two months. She also reported that she had noticed some initial issues approximately two years prior to this presentation. Importantly, she denied experiencing any associated redness, pain, diplopia (double vision), floaters, flashes, or curtain sensation in either eye. This absence of acute symptoms like pain or redness helps to steer the differential diagnosis away from conditions involving acute inflammation or infection. The lack of reports of floaters, flashes, or a curtain sensation is significant as it reduces the likelihood of acute retinal detachment or vitreous traction, which are ophthalmic emergencies. The gradual and progressive nature of the vision loss, however, points towards a chronic underlying process. Her past ophthalmic history included a cataract surgery with phacoemulsification and intraocular lens (IOL) implantation in the right eye (OD) three months prior to this presentation. She also reported having an intravitreal anti-VEGF injection in the OD one month prior. Notably, she has no history of glasses use or ocular trauma. The cataract surgery is a crucial piece of information, as it can be both a contributing factor and a complicating factor in the development or management of macular edema. The

prior anti-VEGF injection suggests that the patient was already under treatment for a retinal condition, likely macular edema, and the current presentation represents either a recurrence, persistence, or progression of that condition. The absence of a history of glasses use might suggest that her vision problems are of relatively recent onset or are not refractive in nature. The lack of ocular trauma history eliminates trauma as a direct cause of her current symptoms, directing focus to other etiologies. Her past medical history is significant, revealing that she has been diagnosed with type 2 diabetes mellitus for three years. She manages this condition with Metformin 500mg taken three times a day (TID). She also has a three-year history of systemic hypertension, which she manages with Amlodipine 10mg once daily (OD). Both diabetes and hypertension are major systemic diseases with well-established ocular manifestations, particularly diabetic retinopathy and hypertensive retinopathy. These conditions are critical to consider as they are significant risk factors for the development of macular edema and other retinal pathologies. The specific medications and dosages provide insight into the management of these systemic conditions, although the efficacy of this management will be further evaluated in the laboratory findings. Her general condition was described as good, alert, oriented, and cooperative, indicating that she was mentally competent and able to participate in the examination and provide a reliable history. Her vital signs were recorded as follows: blood pressure of 140/80 mmHg, heart rate of 92 beats per minute, respiratory rate of 22 breaths per minute, and temperature of 36.9°C. The blood pressure is at the higher end of the normal range, or slightly elevated, and warrants further evaluation and management, especially in the context of her existing hypertension. The heart rate and respiratory rate are within normal limits. The temperature is also within the normal range, suggesting the absence of any acute systemic infection. Her best-corrected visual acuity (BCVA) was 4/60 in the right eye (OD), and there was no improvement with pinhole testing. In the left eye (OS), the BCVA was 6/21, which improved to 6/12 with pinhole testing. Visual acuity is a fundamental measure of visual function. The significantly reduced vision in the right eye (OD) indicates substantial visual impairment. The lack of improvement with pinhole testing suggests that the vision loss is not primarily due to refractive error. In the left eye (OS), the vision is also reduced, but it improves with pinhole, indicating a refractive component. This difference between the two eyes is important for differential diagnosis. Her intraocular pressure (IOP) was 11.7 mmHg in the right eye (OD) and 13.2 mmHg in the left eye (OS). These values are within the normal range, suggesting that elevated intraocular pressure is not a primary factor in her vision problems. Ocular alignment and motility were described as orthophoria with full extraocular movements in both eyes (OU). This indicates that the eyes are properly aligned, and there are no restrictions in eye movements. The anterior segment examination of the right eye (OD) revealed unremarkable lids and conjunctiva, a clear cornea, normal depth anterior chamber (AC) with no cell or flare, a normal iris, a slightly oval pupil (likely post-surgical), and a well-centered posterior chamber IOL. The unremarkable lids and conjunctiva suggest no external inflammation or infection. The clear cornea is essential for clear vision. The normal depth AC and absence of cell or flare indicate no active intraocular inflammation. The slightly oval pupil is consistent with the history of cataract surgery. The well-centered posterior chamber IOL confirms the successful placement of the lens implant. The anterior segment examination of the left eye (OS) also showed unremarkable lids and conjunctiva, a clear cornea, normal depth AC with no cell or flare, and a normal iris. However, it also revealed a round and reactive pupil and significant lenticular opacities, described as an immature senile cataract. The round and reactive pupil indicates normal pupillary function in this eye.

The significant lenticular opacities, or cataract, are a likely cause of the reduced vision in the left eye, which improved with pinhole testing. The posterior segment/funduscopy of the right eye (OD) showed a clear view through the IOL, an optic disc with round and sharp margins, a pink rim, and a cup-to-disc ratio (C/D) of 0.3. The arteriovenous (A/V) ratio was 1:3. The retina showed moderate non-proliferative diabetic retinopathy (NPDR) with microaneurysms in two quadrants and venous beading in one quadrant. Diminished foveal reflexes were noted, and detailed retinal evaluation revealed observed retinal detachment. The clear view through the IOL is important for visualizing the retina. The optic disc findings are generally normal. The moderate NPDR is a critical finding, confirming the presence of diabetic retinopathy. Microaneurysms and venous beading are characteristic lesions of NPDR. The diminished foveal reflexes suggest macular involvement. The observed retinal detachment is a significant finding and requires further investigation and management. The posterior segment/funduscopy of the left eye (OS) had its view limited by the cataract. The optic disc appeared normal with a C/D ratio of 0.3 and an A/V ratio of 1:3. Diminished foveal reflexes were noted. A detailed retinal assessment was obscured by the cataract. The limited view due to the cataract makes a complete retinal evaluation challenging. However, the diminished foveal reflexes suggest potential macular issues in this eye as well. The glycated hemoglobin (HbA1c) level was 8.2%, indicating suboptimal glycemic control at the time of presentation. This is a critical finding, as it reflects the average blood glucose level over the past 2-3 months and is a key indicator of diabetes management. The elevated HbA1c strongly suggests that the patient's diabetes is not well-controlled, which is a major risk factor for diabetic retinopathy and macular edema. The fasting blood glucose level was 155 mg/dL. This elevated level further supports the finding of suboptimal glycemic control. The lipid profile revealed a total cholesterol of 210 mg/dL, LDL cholesterol of 130 mg/dL, HDL cholesterol of 45 mg/dL, and triglycerides of 180 mg/dL. These values indicate some abnormalities in lipid metabolism. The elevated total cholesterol and LDL cholesterol are risk factors for cardiovascular disease and can also contribute to the progression of diabetic retinopathy. The HDL cholesterol is within the normal range, and the triglycerides are mildly elevated. The estimated glomerular filtration rate (eGFR) was > 60 mL/min/1.73m$^2$. This indicates relatively preserved renal function. While diabetic nephropathy is a common complication of diabetes, in this case, the initial renal function appears to be within an acceptable range. The Optical Coherence Tomography (OCT) of the right eye (OD) was performed using a TOPCON 3D OCT device. Quantitative findings included a central subfield thickness (CST) of 376 µm, an average macular thickness of 282.3 µm, and a total macular volume of 7.98 mm$^3$. These quantitative measurements confirm the presence of significant macular thickening, which is a hallmark of macular edema. The elevated CST is particularly important as it directly affects central vision. Qualitative findings included central-involving macular edema, intraretinal hyporeflective spaces (cystoid changes), effaced foveal depression, mild disorganization of retinal inner layers (DRIL), irregular but intact ellipsoid zone (EZ), no vitreomacular traction (VMT), regular RPE/Bruch's membrane complex, and normal choroidal thickness. These qualitative findings provide a detailed morphological description of the macular edema. The intraretinal hyporeflective spaces are indicative of fluid accumulation within the retina. The effaced foveal depression reflects the disruption of the normal macular architecture. DRIL suggests some structural damage to the inner retinal layers. The irregular EZ indicates potential photoreceptor compromise. The absence of VMT rules out tractional forces on the macula. The regular RPE/Bruch's membrane complex and normal choroidal thickness provide information about these specific retinal

structures. The Optical Coherence Tomography (OCT) of the left eye (OS) showed quantitative findings of a central subfield thickness (CST) of 224 µm, an average macular thickness of 271.0 µm, and a total macular volume of 7.06 $mm^3$. These values are within the normal range or show only subtle changes, suggesting no significant macular edema in this eye. Qualitative findings included subtle intraretinal hyporeflective spaces, mild reduction in foveal depression, no significant edema or cystoid changes, no VMT, regular RPE/BM, and normal choroidal thickness. These findings indicate some minor abnormalities but no major structural changes consistent with significant macular edema. The clinical diagnosis for the right eye (OD) was: 1. Moderate Non-Proliferative Diabetic Retinopathy (NPDR), 2. Central-Involving Diabetic Macular Edema (CI-DME), and 3. Pseudophakia (Status Post Cataract Surgery). This diagnosis is supported by the funduscopy findings of microaneurysms and venous beading, the OCT findings of macular thickening and intraretinal fluid, and the history of cataract surgery. The clinical diagnosis for the left eye (OS) was: 1. Immature Senile Cataract (Visually Significant), and 2. Rule out mild NPDR (view limited). This diagnosis is based on the anterior segment examination revealing lenticular opacities and the limited funduscopy view due to the cataract, which makes a definitive assessment of the retina difficult. The term "rule out mild NPDR" suggests that while the view was limited, there might be some subtle signs suggestive of early diabetic retinopathy that require further evaluation once the cataract is addressed (Table 1).

In the patient's prior history, it is noted that she had a history of one prior intravitreal anti-VEGF injection in the right eye (OD). This injection was administered approximately in September 2024, and its purpose was for the treatment of diabetic macular edema (DME) following cataract surgery. Unfortunately, the detailed specifics regarding this prior injection, such as the agent used, the dosage, and the precise date, are unavailable. This lack of detailed information can present a challenge in fully assessing the patient's response to previous treatments and in tailoring subsequent management strategies. However, the knowledge that a prior anti-VEGF injection was administered does establish a precedent for this treatment modality in this patient and suggests that DME was a recognized issue prior to the current presentation. The context of post-cataract surgery DME is also clinically relevant, as cataract surgery itself can sometimes contribute to or exacerbate macular edema in susceptible individuals. The initial visit involved a comprehensive ophthalmic examination of both eyes (OD and OS) and Optical Coherence Tomography (OCT) imaging of both eyes. This thorough evaluation was crucial for establishing the patient's baseline ocular status and for formulating an appropriate treatment plan. The clinical findings in the right eye (OD) at this baseline visit were significant. The best-corrected visual acuity (BCVA) was measured at 4/60, indicating a substantial degree of visual impairment. The intraocular pressure (IOP) was 11.7 mmHg, which is within the normal range. Funduscopic examination revealed moderate non-proliferative diabetic retinopathy (NPDR), characterized by microaneurysms in two quadrants and venous beading in one quadrant. Additionally, diminished foveal reflexes were observed, suggesting macular involvement. The OCT findings in the right eye (OD) confirmed the presence of central-involving diabetic macular edema (CI-DME). The central subfield thickness (CST) was significantly elevated at 376 µm, indicative of macular thickening. Intraretinal cysts were noted, representing fluid-filled spaces within the retinal layers. The foveal contour was effaced, demonstrating the disruption of the normal macular architecture. Mild disorganization of the retinal inner layers (DRIL) was also observed, suggesting some structural compromise of the inner retina. The ellipsoid zone (EZ) was irregular but still intact, indicating some degree of photoreceptor

involvement. Notably, there was no vitreomacular traction (VMT). In the left eye (OS), the clinical findings were less severe. The BCVA was 6/21, improving to 6/12 with pinhole testing, suggesting a refractive component to the vision reduction. The IOP was 13.2 mmHg, also within the normal range. Based on these comprehensive findings, the plan of management for the right eye (OD) was determined. The immediate steps involved obtaining informed consent from the patient and proceeding with a second intravitreal anti-VEGF injection of Ranibizumab 0.5mg. Furthermore, the patient was to receive counseling on the importance of systemic control of her diabetes mellitus (DM) and hypertension (HTN). This multi-faceted approach addresses both the ocular pathology and the underlying systemic conditions that contribute to it. Anti-VEGF therapy directly targets the macular edema, while systemic control aims to mitigate the long-term progression of diabetic retinopathy. Shortly after the initial visit day, the patient underwent the second intravitreal injection in her right eye (OD). The procedure was performed under strict aseptic conditions to minimize the risk of infection. The preparation involved using Povidone-Iodine 10% for antiseptic preparation of the ocular surface. Topical anesthesia was achieved using Pantocaine to ensure patient comfort during the procedure. An eyelid speculum was carefully placed to maintain a stable ocular field. The injection site was precisely measured at 3.5-4.0 mm from the limbus in the inferotemporal quadrant to avoid critical ocular structures. Ranibizumab 0.5mg in 0.05mL was injected using a 30-gauge needle. Following the injection, post-injection pressure was applied with a cotton bud to prevent reflux. Finally, a combination of Levofloxacin ointment, a sterile pad, and a shield were applied to protect the eye and prevent infection. The procedure was reported to have been performed uneventfully, indicating that there were no immediate complications during the injection process. Post-operatively, the patient was prescribed medications to manage potential inflammation and prevent infection. These medications included Cefixime orally (PO), Paracetamol orally as needed (PRN), Fluorometholone eye drops (ED) four times a day (QID) in the right eye (OD), and Levofloxacin eye drops (ED) four times a day (QID) in the right eye (OD). This regimen is designed to promote healing and reduce the risk of post-injection complications. Approximately two weeks following the second intravitreal injection, the patient returned for a follow-up visit. This visit focused on assessing the initial response to the treatment and monitoring for any early complications. The key procedure at this visit was a follow-up ophthalmic examination. The clinical findings in the right eye (OD) revealed that the BCVA was 4/60, which was stable compared to the baseline measurement. The IOP was 14.1 mmHg, showing a slight increase but still within the normal range. The anterior segment was quiet, and the IOL was centered, indicating no signs of inflammation or IOL displacement. The fundus appearance was stable, with the moderate NPDR findings persisting. Importantly, OCT imaging was not performed at this particular visit. This decision was in accordance with the protocol or reporting standards being followed, which might have dictated the timing of OCT examinations at specific intervals. The plan of management at this visit was to continue the post-operative eye drops as prescribed and to schedule a follow-up visit in approximately 2-3 weeks, at which time a repeat OCT scan would be performed. This approach balances the need for ongoing monitoring with the practical considerations of patient visits and resource utilization. Approximately five weeks after the second intravitreal injection, the patient returned for her second follow-up visit. This visit involved a follow-up ophthalmic examination and a repeat OCT imaging of the right eye (OD) to assess the treatment's effectiveness. The clinical findings in the right eye (OD) showed a notable improvement. The BCVA had improved to 6/30, indicating a significant gain in visual acuity. The IOP was 13.1 mmHg, remaining

within the normal range. The anterior segment remained quiet, and the IOL was centered. The fundus appearance was stable, with the moderate NPDR findings persisting. The OCT findings in the right eye (OD) demonstrated significant anatomical improvement. The CST had decreased to 305 µm, confirming a reduction in macular edema. There was a marked reduction in intraretinal cysts, indicating decreased fluid accumulation within the retina. Resolution of subretinal fluid (SRF) was observed. The mild DRIL was slightly less prominent, suggesting some structural improvement. The ellipsoid zone (EZ) remained irregular but stable. There was no VMT. Based on these positive findings, the diagnosis was "Post-Injection Status Moderate NPDR with improving CI-DME OD." The plan of management was to obtain informed consent from the patient and proceed with a third intravitreal anti-VEGF injection of Ranibizumab 0.5mg in the right eye (OD). This decision reflects the ongoing need for anti-VEGF therapy to further consolidate the gains and achieve maximal resolution of the macular edema (Table 2).

**3. Discussion**

Diabetic macular edema (DME) is a complex and multifactorial complication of diabetes mellitus that represents a leading cause of vision loss in the working-age population. Its pathophysiology is characterized by a breakdown of the blood-retinal barrier (BRB), a critical structure that maintains the delicate homeostasis of the retinal environment. This barrier, composed of tight junctions between retinal capillary endothelial cells and the retinal pigment epithelium (RPE), normally prevents the leakage of plasma constituents into the retinal tissue. In diabetes, chronic hyperglycemia initiates a cascade of biochemical events that compromise the integrity of the BRB. These events include increased oxidative stress, the formation of advanced glycation end products (AGEs), the activation of protein kinase C (PKC) isoforms, and the upregulation of various inflammatory mediators. Oxidative stress, resulting from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant capacity of the retina, damages endothelial cells and pericytes, the cells that support capillary structure and function. AGEs, formed through the non-enzymatic glycation of proteins and lipids, accumulate in retinal tissues and further disrupt cellular function and increase vascular permeability. Activation of PKC isoforms leads to alterations in blood flow, increased permeability, and the production of pro-angiogenic factors. Inflammatory mediators, such as interleukins, tumor necrosis factor-alpha (TNF-α), and intercellular adhesion molecule-1 (ICAM-1), contribute to leukostasis (the sticking of white blood cells) and further BRB breakdown. A central player in the pathogenesis of DME is vascular endothelial growth factor (VEGF). VEGF is a potent angiogenic and permeability-enhancing cytokine whose expression is upregulated in the diabetic retina. It binds to receptors on endothelial cells, triggering signaling pathways that lead to increased vascular permeability, the formation of new, leaky blood vessels, and the accumulation of intraretinal fluid, all hallmarks of DME. The resulting macular thickening disrupts the normal retinal architecture, particularly in the central macula, or fovea, which is responsible for sharp, detailed vision. This disruption leads to visual distortion and a reduction in visual acuity, the primary symptoms experienced by patients with DME.[11-13]

Central-involving diabetic macular edema (CI-DME), as observed in the presented case, carries particular clinical significance due to its direct impact on central vision. The macula, the central portion of the retina, is responsible for high-acuity vision, enabling tasks such as reading, driving, and facial recognition. CI-DME, defined as macular edema involving the central 1-mm subfield, directly affects this critical area, leading to a rapid decline in visual acuity and significant functional impairment.

Table 1. Summary patient's clinical findings.

| Category | Finding | Details |
|---|---|---|
| **Demographics** | **Age** | 58 years |
| | **Gender** | Female |
| | **Occupation** | Housewife |
| | **Presentation Date** | October 30th, 2024 |
| **Anamnesis (History)** | **Chief Complaint** | Blurred vision, Right Eye (OD) |
| | **History of Present Illness** | Gradual worsening of blurred vision OD over 2 months; initial notice ~2 years prior. No associated redness, pain, diplopia, floaters, flashes, or curtain sensation. |
| | **Past Ophthalmic History** | - Cataract Surgery (Phacoemulsification + IOL) OD: 3 months prior. - Intravitreal Anti-VEGF Injection OD: 1 month prior. - No history of glasses use or ocular trauma. |
| | **Past Medical History** | - Type 2 Diabetes Mellitus: Diagnosed 3 years prior. Medication: Metformin 500mg TID. - Systemic Hypertension: Diagnosed 3 years prior. Medication: Amlodipine 10mg OD. |
| **Physical examination (Systemic)** | **General Condition** | Good, alert, oriented, cooperative (Compos Mentis). |
| | **Vital Signs** | - Blood Pressure: 140/80 mmHg - Heart Rate: 92 bpm - Respiratory Rate: 22 breaths/min - Temperature: 36.9°C |
| **Ophthalmology examination** | **Visual Acuity (BCVA)** | - OD: 4/60 (No improvement with pinhole) - OS: 6/21 (Improves to 6/12 with pinhole) |
| | **Intraocular Pressure (IOP)** | - OD: 11.7 mmHg - OS: 13.2 mmHg |
| | **Ocular Alignment & Motility** | Orthophoria, Full extraocular movements OU. |
| | **Anterior Segment (OD)** | Unremarkable lids & conjunctiva; Clear cornea; Normal depth AC, no cell/flare; Normal iris; Slightly oval pupil (post-surgical), reactive; Well-centered posterior chamber IOL. |
| | **Anterior Segment (OS)** | Unremarkable lids & conjunctiva; Clear cornea; Normal depth AC, no cell/flare; Normal iris; Round, reactive pupil; Significant lenticular opacities (Immature Senile Cataract). |
| | **Posterior Segment / Funduscopy (OD)** | Clear view through IOL; Optic Disc: Round, sharp margins, pink rim, C/D 0.3; A/V ratio 1:3; Retina: Moderate NPDR - Microaneurysms (2 quadrants), Venous Beading (1 quadrant); Diminished foveal reflex. |
| | **Posterior Segment / Funduscopy (OS)** | View limited by cataract; Optic Disc: Appears normal (C/D 0.3, A/V 1:3); Diminished foveal reflex; Detailed retinal assessment obscured. |
| **Laboratory findings** | **Glycated Hemoglobin (HbA1c)** | 8.2% (Indicating suboptimal glycemic control at presentation) |
| | **Fasting Blood Glucose** | 155 mg/dL |
| | **Lipid Profile** | - Total Cholesterol: 210 mg/dL - LDL Cholesterol: 130 mg/dL - HDL Cholesterol: 45 mg/dL - Triglycerides: 180 mg/dL |
| | **Renal Function** | Estimated Glomerular Filtration Rate (eGFR): > 60 mL/min/1.73m² |
| **Imaging (OCT - OD Baseline)** | **Device** | TOPCON 3D OCT |
| | **Quantitative Findings** | - Central Subfield Thickness (CST): 376 µm - Average Macular Thickness: 282.3 µm - Total Macular Volume: 7.98 mm³ |
| | **Qualitative Findings** | - Central-involving macular edema - Intraretinal hyporeflective spaces (cystoid changes) - Effaced foveal depression - Mild Disorganization of Retinal Inner Layers (DRIL) - Irregular but intact Ellipsoid Zone (EZ) - No Vitreomacular Traction (VMT) - Regular RPE/Bruch's Membrane complex - Normal choroidal thickness |
| **Imaging (OCT - OS Baseline)** | **Quantitative Findings** | - Central Subfield Thickness (CST): 224 µm - Average Macular Thickness: 271.0 µm - Total Macular Volume: 7.06 mm³ |
| | **Qualitative Findings** | Subtle intraretinal hyporeflective spaces; Mild reduction in foveal depression; No significant edema or cystoid changes; No VMT; Regular RPE/BM; Normal choroid. |
| **Clinical diagnosis** | **Right Eye (OD)** | 1. Moderate Non-Proliferative Diabetic Retinopathy (NPDR) 2. Central-Involving Diabetic Macular Edema (CI-DME) 3. Pseudophakia (Status Post Cataract Surgery) |
| | **Left Eye (OS)** | 1. Immature Senile Cataract (Visually significant) 2. Rule out mild NPDR (view limited) |

Table 2. Treatment procedures and follow-up.

| Time point / Visit | Key procedures / Assessments | Clinical findings (OD) | OCT findings (OD) | Plan / Management |
|---|---|---|---|---|
| **Prior history** | N/A | History of one prior Intravitreal Anti-VEGF injection OD (~Sept 2024) for DME post-cataract surgery. Details unavailable. | N/A | N/A |
| **Baseline visit** | Comprehensive Ophthalmic Examination; OCT Imaging OD & OS. | BCVA: 4/60; IOP: 11.7 mmHg; Moderate NPDR (Microaneurysms 2Q, Venous Beading 1Q); Diminished foveal reflex. | CI-DME; CST: 376 µm; Intraretinal cysts; Effaced foveal contour; Mild DRIL; Irregular but intact EZ; No VMT. | Obtain informed consent; Proceed with 2nd Intravitreal Anti-VEGF (Ranibizumab 0.5mg) injection OD; Counsel on systemic control (DM, HTN). |
| **Intervention** | **Second Intravitreal Injection OD; - Aseptic prep (Povidone-Iodine 10%); - Topical anesthesia (Pantocaine); - Eyelid speculum placement; - Injection site measured (3.5-4.0 mm from limbus, inferotemporal); - Ranibizumab 0.5mg/0.05mL injected via 30G needle; - Post-injection pressure with PVI cotton bud; - Levofloxacin ointment, sterile pad & shield** | Procedure performed uneventfully. | N/A | Post-operative medications prescribed: Cefixime PO, Paracetamol PO PRN, Fluorometholone ED QID OD, Levofloxacin ED QID OD. |
| **Follow-up visit 1 (~2 weeks post-2nd Injection)** | Follow-up Ophthalmic Examination. | BCVA: 4/60 (stable); IOP: 14.1 mmHg; Quiet anterior segment; Centered IOL; Stable fundus appearance (Moderate NPDR). | OCT not performed at this visit (per protocol/report). | Continue post-op eye drops; Follow-up in ~2-3 weeks with repeat OCT. |
| **Follow-up visit 2 (~5 weeks post-2nd Injection)** | Follow-up Ophthalmic Examination; Repeat OCT Imaging OD. | BCVA: 6/30 (Improved); IOP: 13.1 mmHg; Quiet anterior segment; Centered IOL; Stable fundus appearance (Moderate NPDR). | Anatomical Improvement: CST decreased to 305 µm; Marked reduction in intraretinal cysts; Resolution of SRF; Mild DRIL slightly less prominent; Persistent EZ irregularity but stable; No VMT. | Diagnosis: Post-Injection Status Moderate NPDR with improving CI-DME OD. Plan: Obtain informed consent; Proceed with 3rd Intravitreal Anti-VEGF (Ranibizumab 0.5mg) injection OD. |

Even relatively small amounts of fluid accumulation in this region can distort the delicate photoreceptor arrangement and disrupt neural signaling, resulting in substantial vision loss. The prompt recognition and treatment of CI-DME are therefore essential to preserve central vision and maintain the patient's quality of life. The Early Treatment Diabetic Retinopathy Study (ETDRS) highlighted the importance of timely intervention in clinically significant macular edema (CSME), a

category that largely overlaps with CI-DME, to reduce the risk of further vision loss. Modern management strategies, primarily centered on anti-VEGF therapy, have shifted the focus from merely preventing further deterioration to actively improving visual acuity in patients with CI-DME.[14-16]

The introduction of intravitreal anti-VEGF agents has revolutionized the treatment of DME. These agents, including Ranibizumab, Aflibercept, Bevacizumab, Brolucizumab, and Faricimab, target the elevated levels of VEGF in the diabetic eye. By binding to and neutralizing VEGF, these drugs inhibit its signaling pathways, leading to a reduction in vascular permeability, decreased fluid leakage, and subsequent resolution of macular edema. Clinical trials have consistently demonstrated the efficacy of anti-VEGF therapy in improving visual acuity and reducing macular thickness in patients with DME. The RISE and RIDE studies established the benefits of Ranibizumab, while the VIVID and VISTA trials confirmed the efficacy of Aflibercept. The DRCR.net Protocol T study further compared the effectiveness of Ranibizumab, Aflibercept, and Bevacizumab, providing valuable insights into their relative efficacy. These studies have shown that anti-VEGF therapy can lead to significant gains in visual acuity, often exceeding those achieved with previous treatments like laser photocoagulation. As a result, intravitreal anti-VEGF injections have become the standard of care for CI-DME, offering the potential for both stabilizing and improving vision in affected individuals.[17,18]

The selection of the specific anti-VEGF agent for treatment is an important clinical consideration. While Ranibizumab, Aflibercept, and Bevacizumab have been the most commonly used agents, newer drugs like Brolucizumab and Faricimab have emerged with potential advantages. Ranibizumab and Aflibercept are specifically designed for ocular use, while Bevacizumab is an off-label option. Aflibercept has demonstrated superior efficacy in some studies, particularly in eyes with worse baseline visual acuity, possibly due to its higher binding affinity for VEGF. Brolucizumab and Faricimab offer the potential for less frequent injections, which can reduce the treatment burden for patients. However, Brolucizumab has been associated with a higher risk of intraocular inflammation, requiring careful monitoring. Faricimab, with its dual mechanism of action targeting both VEGF-A and Angiopoietin-2, shows promise but requires further long-term evaluation. In this case, the use of Ranibizumab was a reasonable choice, given its established efficacy and safety profile.[19,20]

## 4. Conclusion

The presented case illustrates the successful management of CI-DME secondary to moderate NPDR with sequential intravitreal anti-VEGF injections. This therapeutic approach led to a clinically significant improvement in visual acuity and a corresponding reduction in macular edema, as confirmed by OCT imaging. The findings of this case underscore the efficacy of anti-VEGF therapy as a cornerstone in the treatment of CI-DME. The rapid visual and anatomical improvement observed following treatment highlights the importance of prompt intervention in preserving visual function in patients with diabetic macular complications. Furthermore, this case emphasizes the necessity of a comprehensive management strategy that includes not only addressing the ocular manifestations of diabetes but also optimizing systemic control of the underlying metabolic and vascular abnormalities.

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