

# *Diagnostic and Therapeutic Challenges* \_\_\_\_\_ Edited by H. Richard McDonald

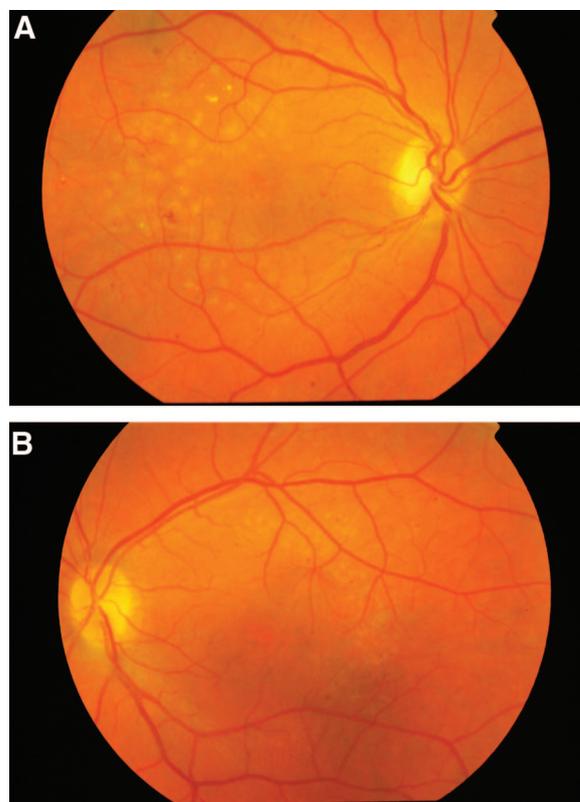
Submitted by Drs. Umut Aslı Dinç, Nursal Melda Yenerel, Ebru Görgün, and Huseyin Yetik; Commented by Drs. Gregg T. Kokame and Jennifer I. Lim

This case was submitted by Drs. Umut Aslı Dinç, MD,\* Nursal Melda Yenerel, MD,\* Ebru Görgün, MD,\* and Huseyin Yetik, MD,† of the \*Department of Ophthalmology, Yeditepe University Eye Hospital, Istanbul, Turkey; and †Ophthalmology Department, Cerrahpasa University School of Medicine, Istanbul, Turkey.

## Case Report

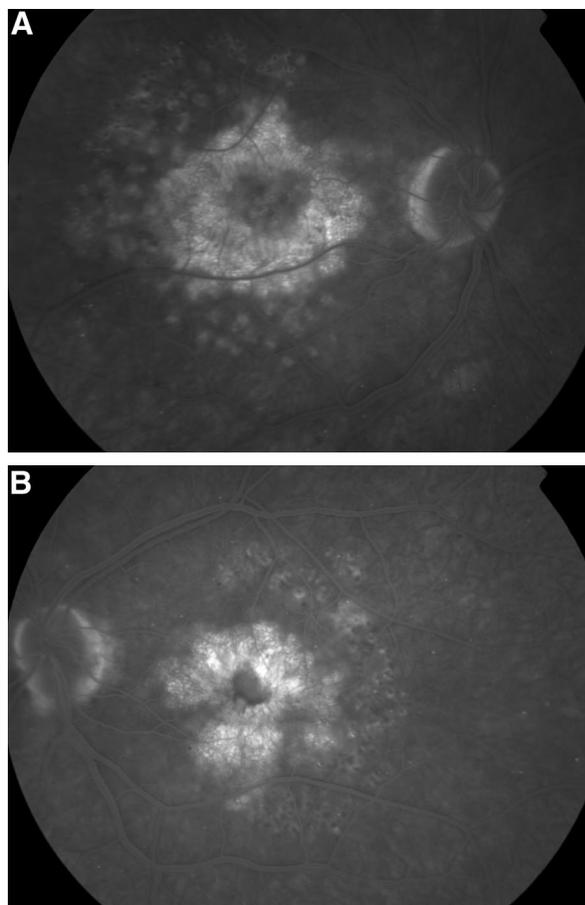
A 57-year-old man with known insulin-dependent Type 2 diabetes mellitus for 13 years was referred to our clinic with profound vision loss in both eyes for 1 year. He had undergone a coronary artery by-pass graft surgery 7 years ago because of myocardial infarction secondary to coronary artery disease. One year ago, grid laser photocoagulation and two sessions of intravitreal triamcinolone acetonide injections were administered to both eyes in another clinic. At the initial visit, best corrected visual acuity was found to be 20/400 in the right eye and 20/40 in the left eye. Anterior segment examination revealed mild nuclear sclerosis, and intraocular pressure (IOP) values were within normal ranges in both eyes. Fundus examination showed nonproliferative diabetic retinopathy and cystoid macular edema (CME) bilaterally (Figure 1, A and B). Leaking microaneurysms together with focal or diffuse diabetic macular edema (DME) were missing in fundus fluorescein angiography in the late phase. Solely, petaloid macular leakage pattern consistent with CME was evident in fundus fluorescein angiography (Figure 2, A and B). By optic coherence tomography (OCT, Stratus-OCT, Zeiss) severe CME with optically clear cystic cavities and bridging elements between the cysts were demonstrated (Figure 3, A and B). In the left eye, a subfoveal serous detachment was also apparent. Central foveal thickness was found to be 759 and 519  $\mu\text{m}$  in the right and left eyes, respectively. Posterior hyaloid traction was not obvious in OCT.

Consequently, the patient was offered intravitreal bevacizumab injection bilaterally. After a detailed informed consent was ob-



**Fig. 1.** Color photos reveal nonproliferative diabetic retinopathy in right (A) and left eyes (B).

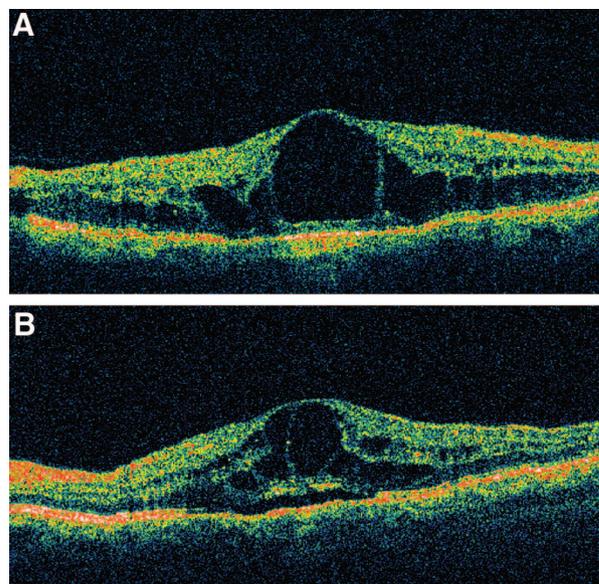
tained, intravitreal bevacizumab injection of 1.25 mg was applied to both eyes. In the first month follow-up control, best corrected visual acuity rose to 20/200 in the right eye and 20/25 in the left eye. Central foveal thickness decreased to 444 and 224  $\mu\text{m}$  in the



**Fig. 2.** Fluorescein angiography of right (A) and left (B) eyes reveals severe retinal vascular leakage and cystoid macular edema. Note previous laser scars.

right and left eyes, respectively (Figure 4, A and B), whereas in the right eye CME persisted. Afterwards, intravitreal triamcinolone acetonide injection of 4 mg/0.1 mL was applied to the right eye. At the end of 3 months, no recurrence of CME was detected in the right eye with a central foveal thickness of 200  $\mu\text{m}$  and final best corrected visual acuity was found to be 20/200.

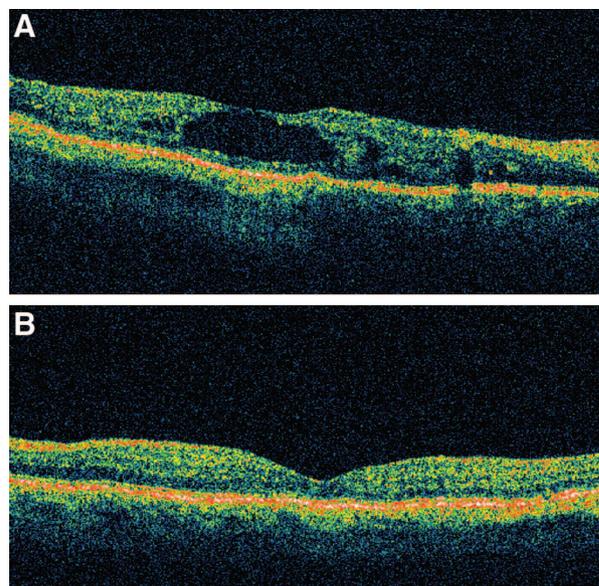
In the left eye, IOP increase that was responsive to topical antiglaucomatous medication developed after intravitreal bevacizumab injection. At the third month control of intravitreal bevacizumab injection, best corrected visual acuity was 20/25 and macular anatomy was normal (Figure 5). Surprisingly, 3 days later the patient returned with sudden vision loss in the left eye. Best corrected visual acuity dropped to 20/50. Cystoid macular edema reoccurred in the left eye with a mean central foveal thickness of 480  $\mu\text{m}$  (Figure 6). As secondary glaucoma had already occurred, an additional intravitreal triamcinolone injection was avoided. Also pars plana vitrectomy for refractory macular edema was deferred because of severe cystoid appearance in OCT. Consequently, topical brinzolamide twice daily and oral acetazolamide 500 mg three times daily were started. After 2 weeks of medical treatment, CME dramatically disappeared with central foveal thickness of 211  $\mu\text{m}$  (Figure 7). Therefore, systemic acetazolamide was tapered gradually to 500 mg one times daily. Unpredictably, severe CME promptly developed within 10 days and central foveal thickness raised to 670  $\mu\text{m}$  (Figure 8). Oral acetazolamide was again pre-



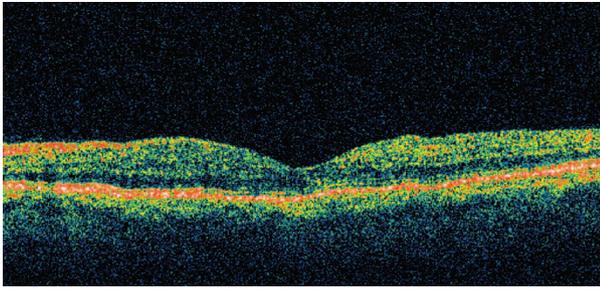
**Fig. 3.** Optical coherence tomography of right (A) and left (B) eyes reveals massive CME. Note the subretinal fluid in the left macula. The central foveal thickness was 759  $\mu\text{m}$  in the right eye; 519  $\mu\text{m}$  in the left eye.

scribed in a dose of 500 mg three times a day. Cystoid macular edema again regressed and disappeared rapidly after 10 days. Final visual acuity was 20/32 in the left eye. All cystic cavities disappeared in OCT. Since then, our patient is receiving topical brinzolamide and oral acetazolamide 500 mg twice daily.

Rapid development and resolution of CME in the left eye led us to investigate total blood count, sedimentation rate, C-reactive protein, serum immunoglobulin levels (IgA-IgE), antinuclear antibody and anti ds-DNA antibody in order not to overlook any



**Fig. 4.** After intravitreal bevacizumab injection in each eye, the central foveal thickness decreased to 444  $\mu\text{m}$  in the right eye (A) and 224  $\mu\text{m}$  in the left eye (B).



**Fig. 5.** Three months after intravitreal bevacizumab injection in the left eye, vision was 20/25 and the macular anatomy was normal.

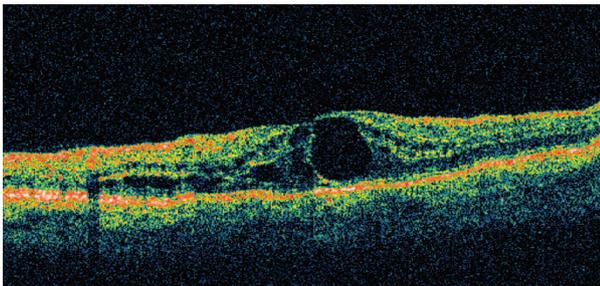
additional inflammatory pathology that might lead to CME other than diabetes. HemoglobinA1C level was 5.2 mg/dL. All laboratory evaluations were found to be within normal limits. Endocrinology consultation revealed regulated diabetes mellitus with insulin treatment and no evidence of insulin resistance.

This case is presented for discussion concerning further management. We asked several experts for their opinion.

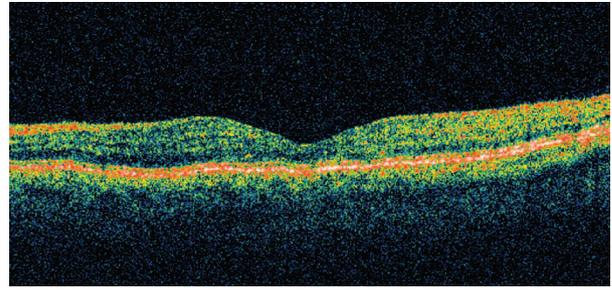
**Dr. Gregg T. Kokame (Aiea, Hawaii):** \_\_\_\_\_

This 57-year-old diabetic patient with excellent blood sugar control (HgbA1c—5.2 mg/dL) initially presented with bilateral diffuse DME, which persisted after previously placed grid laser photocoagulation and two prior treatments with intravitreal triamcinolone in both eyes. Persistent severe edema without vitreofoveal traction was noted on OCT in both eyes, and serous retinal detachment was noted in the left eye. Serous retinal detachment has been noted with increasing frequency in macular edema due to retinal vascular disease in the era of OCT, and may be a negative prognostic factor in some retinal vascular diseases.<sup>1</sup>

Although blood sugar is under control, and endocrinology consultation was obtained, we are not informed of systemic medications. Recently, commonly used glitazone oral medications, such as pioglitazone (Actos) and rosiglitazone (Avandia), which are used to increase sensitivity to insulin and decrease blood sugars, have been associated with worsening macular



**Fig. 6.** OCT of left eye. Three days after the OCT in Figure 5, the vision dropped to 20/50 and the OCT revealed a mean foveal thickness of 480  $\mu$ m. Note the return of significant cystic changes.

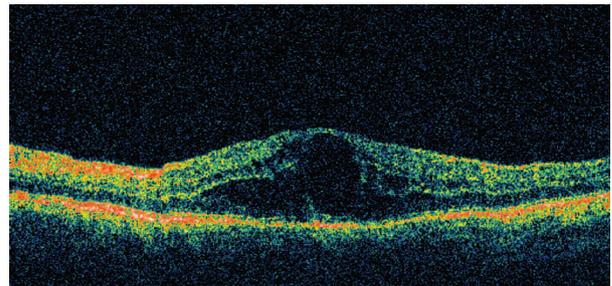


**Fig. 7.** Topical brinzolamide and oral acetazolamide were started and the CME dramatically disappeared. The central foveal thickness was 211  $\mu$ m.

edema. We do not have information on systemic medications, but discontinuation of these oral medications have been associated with reduction of DME.<sup>2</sup>

Diabetic macular edema is a multifactorial process, and treatment goals include not only reducing breakdown of the blood retinal barrier, but also decreasing inflammation and decreasing the effects of vascular endothelial growth factor (VEGF). Because VEGF is one of the major factors in the development of DME, the authors subsequently used intravitreal bevacizumab to treat both eyes. Although this was effective in the left eye, the right eye had persistent macular edema and cystic changes. Intravitreal triamcinolone was placed subsequent to the intravitreal bevacizumab in the right eye, and was effective at resolving DME without recurrence. This right eye highlights the potential of combination therapy to treat the multifactorial pathophysiology of DME in cases unresponsive to monotherapy. However, vision remained poor despite resolution of macular edema, also highlighting the inconsistent relationship of vision improvement with resolution of macular edema.

The left eye developed steroid responsive glaucoma controlled with topical medications and a sudden, rapid recurrence of DME 3 months after intravitreal bevacizumab. Steroid-induced glaucoma had already developed, so further intravitreal triamcinolone was



**Fig. 8.** After the tapering off of acetazolamide, severe CME developed. The central foveal thickness increased to 670  $\mu$ m and massive cystic change was noted.

avoided with a therapeutic shift to carbonic anhydrase inhibitors (CAIs) both topically (brinzolamide) and orally (acetazolamide). The left eye DME showed an on-off response to this therapy, and the patient continues on this regimen at the end of available follow-up. Although oral CAIs may sometimes significantly decrease macular edema, the response is variable, and long-term therapy may be limited by side effects, including generalized malaise, paresthesias, stomach upset, and electrolyte imbalance. However, if this patient currently tolerates this therapy with good vision, then it is reasonable to continue carbonic anhydrase therapy. An alternative to this therapy would be repeat intravitreal bevacizumab injections, as the left eye responded well to this in the past, and could be considered should the patient not tolerate oral CAIs.

Although OCT did not show evidence of vitreomacular traction, pars plana vitrectomy with removal of the cortical vitreous and possibly the internal limiting membrane may still allow persistent and long-term resolution of edema in eyes which have failed all available or tolerated medical therapies.

In regards to future management, both eyes are phakic and will invariably develop cataracts after multiple intravitreal triamcinolone injections. In addition, steroid responsive glaucoma can become a delayed problem with worsening, uncontrollable IOPs. If there is recurrent macular edema despite all available medical therapies, worsening cataract, and poorly controlled and elevated IOP despite medical management, then combination surgical procedures using cataract removal and intraocular lens implantation, placement of a tube shunt in the anterior chamber or pars plana, and vitrectomy with membrane peeling with possible intravitreal triamcinolone injection have been helpful in long-term stabilization of vision and management of these multiple medical problems in one procedure.

**Dr. Jennifer I. Lim (Chicago, Illinois):** \_\_\_\_\_

Doctors Dinç and coworkers present an interesting case of a 57-year-old man with a history of Type 2 insulin-dependent diabetes, cardiac disease (status post bypass graft surgery and myocardial infarction) with bilateral macular edema previously treated with bilateral laser grid therapy twice and bilateral intravitreal steroid administration. A fluorescein angiogram showed diffuse edema with CME and a paucity of microaneurysms. Optic coherence tomography showed bilateral cysts and subfoveal fluid in the left eye. Doctors Dinç and coworkers administered bevacizumab intravitreally. The patient showed an initial response in visual acuity with decreased OCT thickness. They then chose to use intravitreal triamcinolone

in the right eye. Although the CME disappeared, the visual acuity failed to increase beyond 20/200. Doctors Dinç and coworkers treated the left eye with topical brinzolamide twice daily and oral acetazolamide 500 mg three times a day. The CME disappeared in the left eye. Severe CME returned 10 days after stopping therapy. The patient was restarted on topical brinzolamide and oral acetazolamide and maintained on 500 mg twice daily.

First of all, the lack of significant visual improvement in the right eye after resolution of CME is not surprising and consistent with ischemic retinal damage. In a patient with diabetes mellitus and systemic cardiovascular disease, this ischemic damage is not unexpected. The fluorescein angiogram shows hypoperfusion centrally.

As for the left eye, there are a few microaneurysms visible and evidence of laser photocoagulation. The response to the anti-VEGF in the left eye is reasonable—given that VEGF levels are high in diabetic retinopathy. It is well-established that VEGF mediates leakage and angiogenesis. The Macugen DME study group first demonstrated a response to VEGF-165 inhibition in treated patients when compared with sham therapy. Since then many reports have presented response of DME to anti-VEGF drugs. What is not expected with anti-VEGF therapy is IOP elevation. In this patient, I presume that the IOP rise stems from intravitreal steroid previously given to this patient. I personally would not have eliminated anti-VEGF drug therapy.

Nonetheless, the authors chose to use oral and topical CAI treatment. The patient did respond to this alternative therapy. Interestingly, this patient exhibited resolution of his diffuse macular edema with topical and oral CAI therapy. Similar good responses to CAIs have been reported in patients with retinal degeneration (retinitis pigmentosa) and with juvenile X-linked retinoschisis. There has also been one study showing response to CAI therapy in DME patients.<sup>3</sup> In that study, 12 diabetic (five Type 1 and seven Type 2) patients received either oral acetazolamide or placebo. Fluorescein-angiographic findings improved significantly ( $P < 0.01$ ) in the acetazolamide-treated cases compared with the controls ( $P > 0.01$ ), although the visual acuity varied only slightly.

The possible mechanisms of action of CAI are interesting. Wolfensberger has commented on possible mechanism.<sup>4</sup> Carbonic anhydrase inhibitor may have direct effects on retinal and retinal pigment epithelial cell function by inducing an acidification of the subretinal space, a decrease of the standing potential and an increase in retinal adhesiveness. Acidification of the subretinal space may be responsible for the

increase in fluid resorption from the retina through the retinal pigment epithelium into the choroid.

Of course, with diffuse CME, other considerations include recent surgery (none in this case), inflammation, dominant CME, mechanical traction, systemic and topical medication, and renal failure. The authors ruled out these other possibilities of inflammation, mechanical traction, or metabolic abnormalities with testing. The scenario does not fit dominant CME. Another consideration is choroidal neovascularization after laser therapy. However, there was no evidence of hemorrhage or lipid although there was some subretinal fluid in one scan before treatment. The fluorescein angiogram also did not reveal any choroidal neovascularization lesion. Finally, one should always check the periphery for the presence of any retinal pathology (retinal holes, tumors) that are also known to be associated with CME.

#### Editor's Note:

Drs. Dinç, Yenerel, Görgün, and Yetik present a 57-year-old man with diabetic retinopathy and decreased vision in one eye. He has undergone previous grid laser treatment and two intravitreal triamcinolone injections in each eye.

Each eye was massively thickened and given Avastin injections (two in the right eye, one in the left eye) which thinned each macula on OCT and resulted in an absence of CME at 3 months. However, edema returned and the patient was treated with CAIs. When the inhibitors were stopped the edema returned, so the systemic drugs were restarted.

Drs. Kokame and Lim have commented on this all too frequent and frustrating problem. Dr. Kokame notes the possibility that the oral medications, Actos and Avandia, might have been given and that discontinuation of these drugs has been associated with reduction of DME. He notes the inconsistent relationship of vision improvement with OCT-measured improvement of macular edema. His experience with oral anhydrase inhibitors is a common one, where DME may be decreased, but with variable success complicated by side effects. He mentions that vitrectomy, though more effective with documented vitreo-

macular traction, might result in resolution of edema that has failed all previous medical therapies.

Dr. Lim notes that the lack of visual acuity improvement after CME resolution is not surprising given the degree of foveal hypoperfusion noted on the angiogram. She also makes a case for anti-VEGF medication in the management of diabetic edema, as VEGF levels are high in diabetic retinopathy. She states clearly she would have continued anti-VEGF therapy. She reviews the only study showing a beneficial response of DME to CAIs and postulates on possible mechanisms of action.

We all have been in this position of having too few weapons against chronic macular edema secondary to diabetic retinopathy. Most of the medications we use, triamcinolone and CAIs, surely are fraught with side effects and complications. The anti-VEGF medications show promise and clinical trials are underway to test their efficacy. I was impressed with the patient's current level of diabetic control. A hemoglobin A1c of 5.2 mg/dL is impressive. One can only wonder what the patient's ocular condition would be if someone had talked him into that level of control 10 years ago.

We thank Drs. Dinç, Yenerel, Görgün, and Yetik for presenting this case to us, and Drs. Kokame and Lim for sharing with us their opinions.

#### References

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