Recalcitrant Diabetic Macular Oedema: Therapeutic Options

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A 63 year old gentleman with history of diabetes mellitus of 10 years duration presented to us with defective vision in both eyes of 6 months duration on November 23rd 2004. There was no previous treatment history of diabetic retinopathy, no history of associated hypertension or ischaemic heart disease. Metabolic control of diabetes was adequate. No abnormal lipid parameters. On examination best corrected visual acuity was 6/18 N8 in the right eye and 6/36 N12 in the left eye. Intra ocular pressure was normal with applanation tonometry. Biomicroscopic examination of macula in both the eyes showed bilateral clinically significant macular oedema. He underwent digital fundus fluorescein angiography (Figure 1). Based on FFA he received bilateral perifoveal laser photocoagulation on 1st December 2004. He was reviewed 3 months following laser photocoagulation when his visual acuity was stable at 6/12 N6 in right eye and 6/36 N12 in the left eye. Optical Coherence Tomography of the left eye showed persistent macular edema with cystoid changes.

Fig. 1. Dfa of LE : early & late phase

Fig. 1. Dfa of RE: early and late phase

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He was therefore advised Intravitreal Triamcinolone injection in the left eye. This was performed on 21\textsuperscript{st} March 2005. He received one more injection of Intravitreal Triamcinolone to the left eye on 26\textsuperscript{th} September 2005 and was reviewed in December 2005. Visual acuity in the right eye was 6/18 N6 and the left eye had improved to 6/24 N6. OCT showed near normal central macular thickness in the left eye (figure 2). The right eye received Intravitreal Triamcinolone Injection. However he reported in May 2006 with further decrease in vision. Visual acuity was 6/36 N12 in the right eye and 3/60 in the left eye. He underwent digital fundus
fluorescein angiography and OCT (figure 3 & 4). OCT of the right eye showed central macular thickness of 659 microns with cystoid changes and left eye 604 microns with cystoid changes.

We would like your comments regarding what has been done till now and how you will proceed with further management of this case.

Cyrus M Shroff

After going through the complete case report these are my comments as far as the treatment that has been undertaken till now. Focal laser photocoagulation could have been combined with Intravitreal Triamcinolone Injection. After giving Intravitreal Triamcinolone once the macular oedema has reduced, focal treatment could have been given to the micro aneurysms or a grid laser. This might have helped in better resolution.

As far as the present management is concerned the patient has bilaterally significant macular oedema. I would

a. Reassess metabolic status
b. Repeat Intravitreal Triamcinolone if intraocular pressure continues to be stable and metabolic status is satisfactory.

c. Perform laser once macular thickness comes down to around 300 microns.

d. Consider Anti VEGF Therapy if there is no response to Triamcinolone.

e. In this case based on OCT pictures vitreous surgery does not appear to be an option as there is no tractional component.

N S Muralidhar

The management of the macular edema has been done on well-accepted clinical practice. Initially grid laser followed by IVTA has produced reduction in the edema. Recurrence of macular edema is common and continues to be a major challenge. It is interesting to see that the last FFA shows some leakage in the right eye but not much leakage in the left eye. OCT shows possible ERM in the right eye but no ERM in left eye. I suggest reevaluation of the systemic factors, especially control of diabetes and renal failure, as it is nearly 18 months from the first presentation. Management options are a. Repeat IVTA b. Intravitreal Avastin. c. Combined with grid laser.

In the left eye, prognosis is poor as there is not much leakage on FFA, and the patient may be going for Cystoid degeneration. Vitrectomy with peeling of ILM is an option, but the outcome is uncertain.

R. Narayanan

This illustrated case of chronic diabetic macular edema is probably encountered by all ophthalmologists in their
practice. Such cases also pose a challenge to the treating ophthalmologist as it is not uncommon for the patient to have multiple sessions of treatment, laser photocoagulation or Intravitreal injections, and still have recurrences.

The patient in this case had been investigated and treated as per the best practice procedure. Metabolic control of diabetes and altered serum lipid profile had been appropriately investigated as these can have significant impact on macular edema and presence of hard exudates. Also, the importance of near visual acuity cannot be over-emphasized and had been recorded in this particular case. Fundus fluorescein angiography guided focal laser treatment was performed, as it still remains the standard of care for diabetic CSME. In the Early Treatment Diabetic Retinopathy Study, immediate focal laser photocoagulation in cases of CSME showed a 50% reduction in severe visual loss compared to the control group of untreated patients. However, OCT was not available at the time when the ETDRS study was conducted. In a recent study published by the Diabetic Retinopathy Clinical Research Network (DRCR.net), modified macular grid laser reduced the central retinal thickness by an average of 88 microns as measured by OCT. In our case, at the follow-up visit 3 months after laser, OCT showed persistent macular edema in the left eye. It is important to rule out vitreomacular interface abnormalities and OCT is an excellent diagnostic tool to detect subtle traction. As OCT ruled out VMT in our case, one has to again evaluate the systemic conditions. Renal function test to rule out azotemia and blood counts with hematocrit should be performed to rule out anemia. Impaired renal function and anemia are known to cause not just a worsening of the severity of the retinopathy, but also aggravation of macular edema. Treatment of anemia and azotemia can improve the macular edema in many cases without any further intervention.

In cases where the systemic condition is normal, Intravitreal injection of Triamcinolone has been shown to be beneficial and can cause dramatic reduction in the macular edema. Periocular steroids have been shown to be ineffective in large prospective studies. The effect of Intravitreal Triamcinolone can be seen for up to 3 to 6 months, and there is usually a tendency for the macular edema to recur once the effect of the steroid has waned off, as happened in this case. Hence, a second injection of Triamcinolone was appropriate. However, an additional sitting of laser photocoagulation 2 weeks after the steroid injection may stabilize the macular edema and may reduce the need for repeated injections although there is no evidence from large randomized studies. Intravitreal Triamcinolone has significant adverse effects, mainly glaucoma and cataract. Recently, with the introduction anti-VEGF agents in the market, ophthalmologists have especially found the off-label use of Intravitreal Bevacizumab (Avastin, Genentech, USA) helpful in reducing the macular edema. However, a recently published phase II trial of Avastin alone or combining with laser did not show any significant advantage over focal laser, both in terms of visual acuity and retinal thickness. However, this was only a phase II study with a small sample size and a short follow-up. At this point of time, when the patient was seen again in December 2005, 3 months after the second Intravitreal injection, the lens status should be known as steroids can cause cataract.

The patient was next seen after a year in May 2006 when the visual acuity deteriorated in both eyes. Was there any cataract at this time? Fundus fluorescein angiography was appropriately performed to rule out any macular ischemia, and OCT showed significant macular thickening. This is mainly due to the fact that the effect of Triamcinolone is no longer present, and there has been a recurrence of macular edema. At this time, our objective would be to first stabilize the vision and reduce the macular edema. The options include Intravitreal injection of anti-VEGF agent combined with modified grid laser photocoagulation. Although Bevacizumab is inexpensive, it is used as off-off-label, whereas Pegaptinib (Macugen, Pfizer, USA) and Ranibizumab (Lucentis, Genentech, USA) may be used as off-label. Anti-VEGF agents do not have the adverse effect profile of steroids, such as glaucoma and cataract, although the risk of endophthalmitis is similar. Currently, all three of the above drugs are being studied in phase III trials for CSME. Other steroids, such as dexamethasone (Posurdex, USA), fluocinolone acetoni de (Alameira Sciences, USA) are under investigation in phase III trials, and these may be useful additions to our armamentarium against CSME. There are reports of improvement in macular edema in
intractable cases with triple therapy of vitrectomy with or without ILM peeling, Intravitreal Triamcinolone and focal laser. However, evidence for this approach is limited to small non-randomized prospective and retrospective studies. In conclusion, this case has shown that intractable diabetic macular edema can pose serious challenges to the ophthalmologist. A thorough systemic evaluation along with a combination approach may be the only available option in such cases. Laser photocoagulation still remains the standard of care and the first line of treatment.

Biju Raju

From the clinical picture, fluorescein angiography and OCT of this patient, it is obvious that the patient has ischemic diabetic maculopathy and cystoid changes. The ischemia becomes obvious in the angiograms taken after IVTA. From the description, it is presumed that the renal parameters were normal. With IVTA, the macular thickness did return to normal in the left eye, but the resolution was short lived due to the ischemic nature of the maculopathy. The right eye responded initially to laser photocoagulation but from the OCT it is obvious that the edema still persisted despite the marginal symptomatic improvement. The presence of macular ischemia makes this a challenging case to treat. Repeat intravitreal triamcinolone acetonide followed by additional photocoagulation under angiographic control to the leaking micro aneurysms and non-ischemic areas, avoiding the Perifoveal areas of ischemia, once the retinal thickness approaches normal may work in this case. If there is further recurrence then as a last resort, vitrectomy with induction of posterior vitreous detachment may be attempted. But it may not be successful in complete resolution of the edema as OCT does not give any strong evidence of vitreo macular traction. However, right eye shows a hyper reflective layer suggestive of a thickened posterior hyaloid. The role of ILM peeling over such ischemic and bogg macula is controversial as is the role of VEGF inhibitors.

Gopal Pillai

Recurrence of macular edema following treatment is a very common problem that all medical retina specialists face during their diabetic retinopathy practice. The basic reason for such an occurrence is not a treatment failure, but it is due to the fact that diabetes is a multifaceted disease with no cure, but only control. Apart from diabetic macular leakages on fluorescein angiography and patterns of macular edema on OCT, there are many unknown factors, which may decide the progression or regression of diabetic macular edema following treatment.

Comment on previous treatment

To start with, this gentleman had a fluorescein angiography suggestive of diffuse diabetic macular edema in the left eye with a probable CME pattern on OCT (The OCT picture is not available) When ever we encounter a CME pattern on OCT, we should rule out a systemic cause for it like an acute change in blood pressure, recent onset of renal failure or a recent change in anti diabetic medication. However systemic evaluation of this patient was normal in 2004. Prior to the advent of anti VEGF treatment including triamcinolone, we were all doing grid laser therapy to these patients with diffuse diabetic macular edema. In many cases, I have personally felt that macular grid in such patients actually worsened the edema. So after triamcinolone was popular, I used to treat these patients with triamcinolone to reduce the edema and then, when the edema comes down, laser the focal microaneurysms. The advantage it offered was that with less fluid and edema in the macula, we could use lower laser power settings to achieve the same effect than in an edematous macula. We could also define the microaneurysms very well in a less edematous retina. I have always felt that in DDME, if we lasered first, we would kick off the vicious cycle leading to more edema formation.

Comments on future treatment

Triamcinolone is a drug, which we find it difficult to use multiple times in the same eye for fear of secondary glaucoma and cataract. In 2006, Bevacizumab and the newer anti VEGF, pegaptanib and ranibizumab made its entry. However the edema reduction with Bevacizumab was found to be lesser than with triamcinolone. The usefulness of these drugs lay in the
fact that they can be injected multiple times. Many reports of a combination of Bevacizumab and dexamethasone for the effective reduction of macular edema are now on.

Recurrence of CME in diabetic macular edema should be again evaluated medically to rule out any systemic pathology. Provided, all the systemic factors are under control, this gentleman with >600 microns of CME in both eyes can be offered Bevacizumab/ Pegaptanib/ Ranibizumab with dexamethasone and it can be repeated if necessary. If the macular thickness reduces to less than 300 microns, then I will repeat a fluorescein angiography and if possible laser the leaking microaneurysms. If at the end of 4-6 months/ 3 injections, the adequate reduction of edema is not achieved, it may be necessary to undertake a vitrectomy with PVD induction and ILM peeling for this patient. Many studies have found good results for vitrectomy and ILM peeling in recalcitrant diabetic macular edema.

Most importantly, a relapse of edema is not to be taken as a failure of treatment. It is part and parcel of diabetic retinopathy. It may be our mindset that requires a change. Just like one injection of insulin cannot take care of diabetes, and daily injections are the rule, one or two intravitreal injections may not take care of the diabetic macular edema. We may have to be mentally prepared to tell the patients that repeat injections may be necessary to keep the macular edema under control and control is what we strive to achieve. Cure of diabetic macular edema may be as elusive as the cure of diabetes mellitus.

A Giridhar

We have presented a case of chronic recalcitrant diabetic macular oedema resistant to all forms of intervention. Although, there are certain patients who respond very well to treatment with long-term stabilization of vision, there are few cases wherein the macular oedema is recalcitrant and resistant to treatment. The experts in this panel have highlighted some of the important points to consider in such cases. The most important aspect, which has been highlighted by all the experts, is to reassess metabolic control. In this patient we have reassessed the metabolic control on multiple occasions and found the control of diabetes to be satisfactory and also the lipid parameters. Another important point high

lighted by many of the experts is combination treatment that is combining the use of Intravitreal Agent along with laser photocoagulation. In this particular case one probable reason why we did not do this treatment was because there were not many leaking micro aneurysms. It was more of diffuse oedema. Probably we could have combined Intravitreal Agent with grid laser photocoagulation in the second stage of management. Regarding the use of Anti VEGF Agent it had not entered our clinical armamentarium when we first saw the patient in the year 2004. I would like to high light as what happened to this patient after May 2006 when he had presented with significant macular oedema in both the eyes. He received one more Injection of Intravitreal Triamcinolone combined with focal laser photocoagulation to the macula of right eye and he underwent cataract surgery with IOL implantation with Vitrectomy and PVD induction and ILM peeling in the left eye. The reason why we undertook a Vitrectomy was since the cataract was dense and he required a surgical procedure, we thought that vitreous surgery would be worthwhile. Surprisingly following the surgical procedure his visual acuity improves to 6/60 N12 when he was examined here on 10.08.06. The right eye also showed a visual acuity improvement of 6/24 N10 following re-injection of Triamcinolone along with focal laser photocoagulation. He reported in February 2007 4 months later with recent drop in visual acuity. OCT at this time showed significant macular oedema and he also underwent fundus fluorescein angiography. At this moment he received further Perifoveal laser to the left macula along with Intravitreal Injection of Avastin. HbA1c done at this time was 7.4. Subsequent to this treatment he was lost for follow up as he gone abroad to spend some time with his son. He reported back to us on 29.09.07 with poor vision in both the eyes. During his stay in UK he underwent cataract surgery with IOL Implantation in the right eye. Unfortunately he had a PC rupture in UK during cataract surgery and AC IOL was implanted. This eye had very low intra ocular pressure and uveitis with visual acuity of counting fingers 2 mtrs. Visual acuity in the left eye was stable at 3/60 N8. Concluding, we have presented a classic case of recalcitrant diabetic macular oedema wherein all modalities of treatment have been attempted. It is very obvious that in certain case of diabetic macular oedema multiple factors operate.