·Clinical Research·

Chronic macular edema associated with extrafoveal vitreoretinal traction

Aaron Trevino [1], *Michael R Martinez* [1], *Avinoam Ophir* [1,2]

[1] Division of Ophthalmology, Hillel-Yaffe Medical Center, Hadera, Israel
[2]The Ruth and Bruce Rappaport Faculty of Medicine, The Technion, Haifa, Israel
Correspondence to: Avinoam Ophir. Division of Ophthalmology, Hillel-Yaffe Medical Center, Hadera, Israel. ophthalmology@hy. health.gov.il
Received:2010-09-08 Accepted:2010-11-16

Abstract

• AIM: To describe an association between extrafoveal vitreoretinal traction and chronic macular edema, either diffuse (DiME) or cystoid (CME), by the use of optical coherence tomography (OCT).

• METHODS: Charts and OCT findings of two patients with persistent DiME or persistent DiME accompanied by CME, both associated with extrafoveal vitreous traction membranes were analyzed. Excluded were eyes that either had another vitreoretinopathy that could affect the analysis, had undergone pars plana vitrectomy or that had been treated by intravitreal medications. An age-matched normal control group for OCT (n =12) allowed for the quantification of the normal macular thicknesses.

• RESULTS: One patient (one eye) following perforating ocular injury and one patient (one eye) of idiopathic origin, both with chronic macular edema refractive to conventional treatment, were found to be associated with extrafoveal vitreoretinal traction in each eye. Retinal edema that was underlying the traction site in each eye was in continuum with the central macular edema, thus manifesting as diffuse macular edema. The automatic central 6-radial lines program in the OCT enabled the detection of the traction site in one eye, while in the other eye the diagnosis was achieved only with the additional use of the Line group program.

• CONCLUSION: Chronic diffuse macular edema might be related to extrafoveal vitreoretinal traction. Careful search with the diverse OCT programs should be made in order to detect extrafoveal traction sites. Further studies and a larger cohort are required to compare the efficacy of early vitrectomy or pharmacologic vitreolysis versus the current therapeutic approaches in these situations.

• KEYWORDS: extrafoveal vitreous traction; macular edema; optical coherence tomography; ocular perforation

DOI:10.3980/j.issn.2222-3959.2010.04.10

Trevino A, Martinez MR, Ophir A. Chronic macular edema associated with extrafoveal vitreoretinal traction. *Int J Ophthalmol* 2010;3 (4): 321-325

INTRODUCTION

Macular edema may appear in a diffuse and/or cystoid pattern and is related to diverse etiologies including ocular vascular diseases (i.e. diabetic retinopathy and retinal vein occlusion) as well as non-vascular circumstances such as pseudophakia, penetrating ocular injury and uveitis. The onset of macular edema has been associated with the breakdown of the blood-retinal barrier caused by diverse mechanisms like the expression of inflammatory mediators (e.g., prostaglandins) [1,2] and/or vascular endothelial growth factor (VEGF). Other documented causes of macular edema are those associated with tractional forces such as vitreofoveal traction[3] as well as vitreous traction membranes that are located extrafoveally [4,5], either retinal or at the optic nerve head (ONH; i.e. vitreopapillary traction). Epiretinal membranes (ERM) have also been found to be associated with macular edema[6].

Prompt treatment of macular edema is required since irreversible macular changes might occur if macular edema is present for a long time [7]. Various pharmacologic agents are commonly used for the treatment, including topical, sub-Tenon's, intravitreal and systemic corticosteroids, oral and topical nonsteroidal anti-inflammatory agents (NSAIDs), and antiangiogenic agents such as bevacizumab (Avastin) [8]. However not all patients respond to these therapies [9] or sometimes their benefit is only temporary [8,10]. Regarding surgery, pars plana vitrectomy (PPV) has been reported relatively beneficial for the reabsorption of macular edema in various conditions (diabetes, retinal occlusive disease, pseudophakia) [11]. Recently, pharmacologic vitreolysis has been reported efficacious in the treatment of macular edema of diverse origins. Sakuma *et al* [12] described marked improvement of macular edema and visual acuity associated with total posterior vitreous detachment (PVD) in 23 of 26 eyes with branch retinal vein occlusion (BRVO) after a single intravitreal injection of autologous plasmin enzyme.

Similarly, Stalmans *et al* [13] reported a success rate of 58% in releasing vitreomacular adhesions that resulted from various etiologies and a reduction of macular edema after repeated intravitreal injections of microplasmin.

The optical coherence tomography (OCT), which provides an "optical biopsy" of the macula and the posterior pole in a near-histological level of resolution enables, by careful search, the detection of extrafoveal vitreoretinal traction sites among other macular abnormalities [4,5]. This study presents the OCT findings of two cases in which intractable chronic macular edema was found to be associated with extrafoveal vitreoretinal traction in each.

MATERIALS AND METHODS

Materials Patients were included in the study if the chronic macular edema (> 6 months) was related to vitreoretinal traction membranes. Exclusion criteria covered eyes that had: 1) another retinopathy that could affect the data analysis; 2) vitreoretinal adherence without signs of retinal traction or vitreous traction without macular edema; 3) undergone vitreoretinal surgery; 4) been treated by intravitreal administration of medication (s), or 5) eyes in which the OCT scans were of too low a quality for a proper diagnosis and measurements.

Methods In an institutional retrospective study, we analyzed the charts and OCT scans (OCT 2000, Humphrey Zeiss Inc., San Leandro, CA, USA) of two patients who had chronic macular edema associated with extrafoveal vitreoretinal traction. One patient had undergone a perforating ocular injury and the origin of the second patient was idiopathic. Clinical examination included Snellen best-corrected visual acuity (BCVA) and slit-lamp and fundus examinations. OCT examination of the eyes was thereafter performed through a dilated pupil by one of two trained examiners. With the OCT, each evaluation of macular edema was routinely initiated by using the Automatic 6-radial lines program directed to the fixation point and focused on the central macula each oriented 30° from one another. This was followed using the Line group program, which the examiner can control manually by focus, scan length and angle, as well as by site of examination that routinely included the ONH. Scans were taken at various angles and lengths (a shorter scan increases resolution) to search for a vitreous traction site at the area centralis (between the vascular arcades) away from the macula. When an extrafoveal vitreous traction was detected, that site was examined to determine whether its underlying retinal edema (or subretinal fluid) was in continuum with the central macular edema.

By OCT, cystoid spaces at the foveal region were defined as intraretinal round hyporeflective lacunae with well-defined boundaries and hyper-reflective septa separating the cystoid-like cavities. Diffuse macular edema was identified as an ill-defined and widespread, hyporeflective, increased retinal thickness that often attains the appearance of sponge-like cavities [10,23]. The fovea could be designated as edematous when cystoid spaces were located at its site, even if the tissue was not abnormally thickened, due to the fact that it could be thin due to atrophy or lamellar hole formation. Because the anatomical boundaries of the elevated edematous macula cannot often be precisely delineated, we designated vitreous traction at the central macula as "vitreofoveal traction", as previously described[11]. Vitreous traction at one site ("unifocal") away from the edematous central macula was designated as "extrafoveal traction", either at the area centralis ("extrafoveal vitreoretinal" traction) or at the ONH ("vitreopapillary" traction). When there were two or more traction sites, traction was designated as "multifocal". Evidence of traction required vitreous adherence to the retina or ONH associated with, 1) tissue elevation and deformity at the traction site, e.g., the shape of the inner retina at the exact site of traction changed its angle and thus was typically thicker than that of the adjoining edematous retinal tissue, and 2) the posterior hyaloid or vitreous strand terminated or changed its angle at that site. "Vitreous adherence" (without traction) related to those eyes in which the attachment of the vitreous was not associated with any vitreoretinal or vitreopapillary deformities of these tissues at that site.

The 6-mm Early Treatment Diabetic Retinopathy Study (ETDRS) macular maps and the OCT false-colors maps provided quantitative and qualitative information on the thickness of the retinal tissue at the site in question, respectively, and were based on our normative OCT (n=12) database of normal macular thickness in age-matched patients as controls. The macula was considered thickened when its central sub-field (CST) exceeded 200μm, similar to data previously reported [15,16]. Research adhered to the tenets of the Declaration of Helsinki, and the approval of the Institutional Review Board was obtained.

RESULTS

Two patients with chronic diffuse macular edema in which any other potential clinical cause for the edema was not detected, were diagnosed using OCT to have extrafoveal vitreoretinal traction sites in each eye. The first patient (Eye No. 1), a 53-year-old male, underwent perforating injury in his left eye 12 months prior to the OCT examination. His BCVA was 6/18 and the CST was 358μm. The centrally fixated Automatic 6-radial lines program enabled the diagnosis of the traction membrane (Figure 1) which was

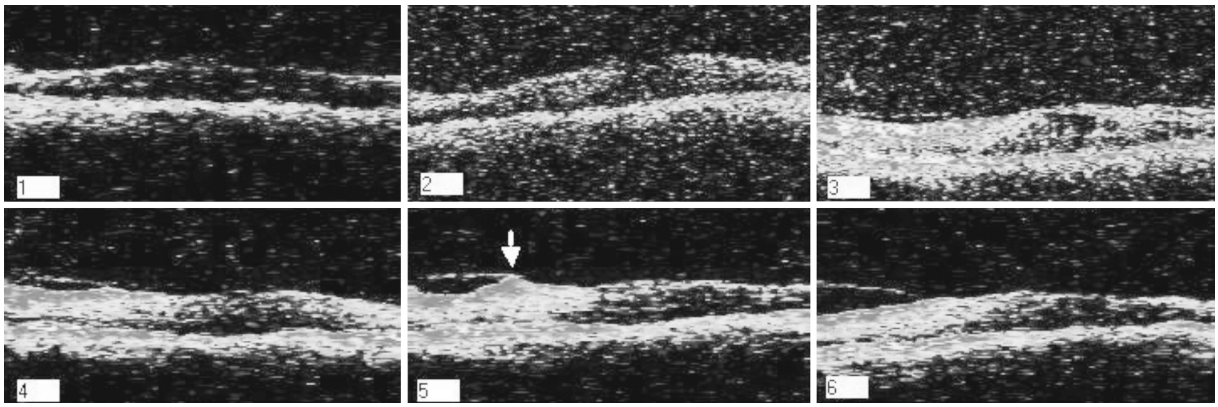

Figure 1 Diffuse macular edema in the left eye of a 53-year-old man after perforating ocular injury (Eye No. 1) in the automatic 6-radial lines program. A vitreoretinal extrafoveal traction strand is detected in scans 3-6 (arrow at scan 5) located nasal to the fovea in the papillomacular bundle zone. Diffuse edema is adjacent to the traction site and in continuum with the central macula

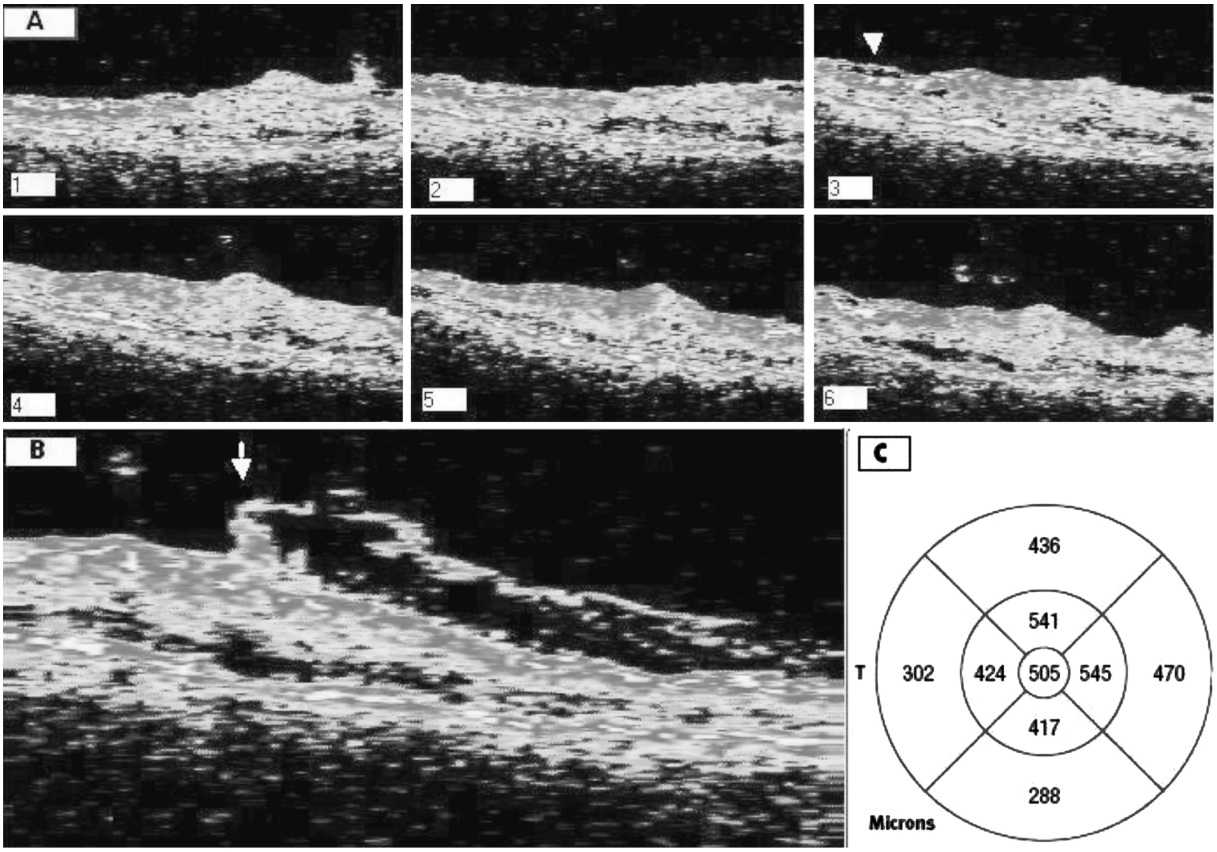

Figure 2 Diffuse macular edema in the right eye of a 74-year-old woman of idiopathic origin (Eye No. 2) in the automatic 6-radial lines program. A: A small epiretinal membrane is identified (arrowhead); B: Vitreous traction strand located superonasally to the fovea. Diffuse edema is adjacent to the traction site and is in continuum with the central macula; C: Macular map shows a thickened retina in most of the zones surrounding the fovea. T = temporal

located at the papillomacular bundle (PMB) zone. The retinal edema that underlined this site was in continuum with the central macular edema, thus attaining a pattern of diffuse macular edema. The second patient (Eye No. 2), a 74-year old female with a chronic intractable macular edema of idiopathic origin in her right eye, had a BCVA of 6/24 and CST of 505μm. A vitreoretinal traction membrane was identified superonasal to the fovea associated with diffuse macular edema and accompanied by cystoid spaces. The centrally fixated Automatic 6-radial lines program shows a small ERM (Figure 2A) but it did not enable a diagnosis of vitreoretinal traction membrane; rather it was detected only by the Line group program (Figure 2B). The retinal edema that underlined the traction site was in direct communication with the edema at the central macula. This association could be also depicted from the macular map (Figure 2C).

DISCUSSION

The study presents two eyes with chronic macular edema that was associated with extrafoveal vitreoretinal traction in each. The retinal edema that underlined the traction site per eye was in continuum with the central macula, manifesting in each as diffuse macular edema. In the first patient (No. 1) the treatment was not efficacious in resolving the edema. The second patient presented with extrafoveal vitreous traction and diffuse macular edema of idiopathic origin. Of the possible idiopathic causes, the most common is an old, transient subclinical uveitis[26]. In such cases, macular traction and secondary macular edema, or tractional peripheral retinal tears have been reported. However, none of the uveitic studies related the dif fuse macular edema to an extrafoveal traction. In consideration of the potential treatment in these 2 eyes, PPV was found beneficial in the resolution of macular edema and improvement of BCVA in various conditions that are related to mediators such as in pseudophakic macular edema, but PPV is still controversial in other conditions such as diabetic macular edema (DME)[11,17]. La Heij *et al*[17] suggest that a delay of surgery (in addition to the harmful, sometimes repeated laser treatment for macular edema) in DME may partly explain the permanent reduced vision in spite of marked improvement in the edema in the earlier studies on DME. Other authors proposed to attribute the surgical success, in part, to the removal of growth factors associated with macular edema from the vitreous site [18]. Considering the potential risk that the PPV may imply, Sakuma *et al*[12] recently reported a high success rate of 88% (23 out of 26 eyes) that was achieved with a single intravitreal injection of autologous plasmin enzyme, which induced total PVD in cases of macular edema associated with BRVO. These findings suggest a major role of the vitreous in the persistence of macular edema in eyes with BRVO. In another study, Stalmans *et al*[13] reported a success rate of 58% in releasing vitreomacular traction from various etiologies after repeated intravitreal injections of microplasmin. However, in the aforementioned studies, the existence of extrafoveal vitreous traction was not mentioned or ruled out, and the cause of success or failure of the treatment was often ambiguous. The presence of extrafoveal vitreous traction in the current study may be relevant to these interventional approaches.

The centrally fixated Automatic 6-radial lines program of the OCT-2000 enabled diagnosis of the extrafoveal vitreous traction in eye No. 1 at the PMB zone (Figure 1). In contrast, in eye No. 2, only the Line group program enabled unequivocal diagnosis of the extrafoveal traction site, located superonasally to the fovea (Figure 2). As previously described, detection of extrafoveal traction sites may often be made only with the Line group or the Raster line programs [4]. This is due to the fact that the length of each scan in the Automatic 6-radial lines program is ~6mm and is separated from each other by a 30° of arc, and the OCT B-mode output is limited only to the 6 lines that are scanned. Furthermore the length of the arc between two adjacent radial lines at their most far point from the center is ~1.5mm [$2\pi R$; $(2\times3.14\times3=18.84)/12=1.57$mm]. Therefore, the Line scan program, or the Raster line program that includes several parallel lines, should fulfill the task only after covering the whole remaining area of interest. It is likely that hundreds of such scan lines are required to cover every point at the area centralis when search for an extrafoveal traction site is made. Consequently, many extrafoveal traction sites might be overlooked due to omission of vitreous adherence sites that are typically small. This drawback is coupled by progressive patient fatigue and the time-consuming searched that may be associated with gradual drying of corneal epithelium resulting in poor scan quality. Except for the potential for consideration of PPV in these eyes or further, when available, the use of intravitreal injection of microplasmin, the detection of extrafoveal traction should also be of importance if a therapeutic agent such as bevacizumab or triamcinolone acetonide (kenalog) is planned intravitreally, since it can result in worsening of traction and subsequent traction retinal detachment[19].

In conclusion, the study raises the possibility that diffuse macular edema may be associated with extrafoveal vitreoretinal traction in etiologies other than those previously described. The Line group program (or the Raster program) of the OCT should be used throughout the whole area centralis and the ONH site in addition to the centrally fixated Automatic 6-radial lines program in order to detect extrafoveal traction sites. Further studies and a larger cohort are required to compare the efficacy of early vitrectomy or pharmacologic vitreolysis versus the current therapeutic approaches in these situations.

REFERENCES

1 Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. *Surv Ophthalmol* 2002;47(Suppl 1):S203-218

2 Kent D, Vinores SA, Campochiaro PA. Macular oedema: the role of soluble mediators. *Br J Ophthalmol* 2000; 84(5):542-545

3 Catier A, Tadayoni R, Paques M, Erginay A, Haouchine B, Gaudric A, Massin P. Characterization of macular edema from various etiologies by optical coherence tomography. *Am J Ophthalmol* 2005;140(2):200-206

4 Ophir A, Trevino A, Fatum S. Extrafoveal vitreous traction associated with diabetic diffuse macular oedema. *Eye (Lond)* 2010;24(2):347-353

5 Fatum S, Trevino A, Ophir A. Non-diabetic diffuse macular edema associated with extrafoveal vitreous traction. *Isr Med Assoc J* 2009;11(5):286-290

6 Yamamoto T, Akabane N, Takeuchi S. Vitrectomy for diabetic macular edema: the role of posterior vitreous detachment and epimacular membrane. *Am J Ophthalmol* 2001;132(2):369-377

7 Reis A, Birnbaum F, Hansen LL, Reinhard T. Successful treatment of cystoid macular edema with valdecoxib. *J Cataract Refract Surg* 2007;33(4):682-685

8. Arevalo JF, Maia M, Garcia-Amaris RA, Roca JA, Sanchez JG, Berrocal MH, Wu L. Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. *Ophthalmology* 2009;116(8):1481-1487

9 Rho DS. Treatment of acute pseudophakic cystoid macular edema: diclofenac versus ketorolac. *J Cataract Refract Surg* 2003;29(12):2378-2384

10 Spitznat MS, Ziemssen F, Petermeier K, Aisenbrey S, Szurman P. Efficacy of intravitreal bevacizumab in treating postoperative pseudophakic cystoid macular edema. *J Cataract Ref Surg* 2008;34(1):70-75

11 Dillinger P, Mester U. Vitrectomy with removal of the internal limiting membrane in chronic diabetic macular oedema. *Graefe's Arch Clin Exp Ophthalmol* 2004;242(8):630-637

12 Sakuma T, Mizota A, Inoue J, Tanaka M. Intravitreal injection of autologous plasmin enzyme for macular edema associated with branch retinal vein occlusion. *Am J Ophthalmol* 2010;[Epub ahead of print]

13 Stalmans P, Delaey C, de Smet MD, van Dijkman E, Pakola S. Intravitreal injection of microplasmin for treatment of vitreomacular adhesion: results of a prospective, randomized, sham-controlled phase II trial (the MIVI-IIT trial). *Retina* 2010;30(7):1122-1127

14 Yamamoto S, Yamamoto T, Hayashi M, Takeuchi S. Morphological and functional analyses of diabetic macular oedema by optical coherence tomography and multifocal electroretinograms. *Graefe's Arch Clin Exp Ophthalmol* 2001;239 (2):96-101

15 Massin P, Vicaut E, Haouchine B, Erginay A, Paques M, Gaudric A. Reproducibility of retinal mapping using optical coherence tomography. Arch Ophthalmol 2001;119(8):1135-1142

16 Sayanagi K, Sharma S, Kaised PK. Comparison of retinal thickness measurements between three-dimensional and radial scans on spectral-domain optical coherence tomography. *Am J Ophthalmol* 2009;148(3):431-438

17 La Heij EC, Hendrikse F, Kessels AG, Derhaag PJ. Vitrectomy results in diabetic macular oedema without evident vitreomacular traction. *Graefe's Arch Clin Exp Ophthalmol* 2001;239(4):264-270

18 Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J, Zimmer-Galler I, Do DV, Campochiaro PA. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. *Am J Ophthalmol* 2006;142 (6): 961-969

19 Arevalo JF, Maia M, Flynn HW, Jr Saravia M, Avery RL, Wu L, Eid Farah M, Pieramici DJ, Berrocal MH, Sanchez JG. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008;92(2):213-216