Published in final edited form as:

Semin Ophthalmol. 2013 March ; 28(2): 79–83. doi:10.3109/08820538.2012.760614.

Cystoid Macular Edema in Retinitis Pigmentosa Patients without Associated Macular Thickening

Ian R. Gorovoy¹, Denise S. Gallagher², Andrew W. Eller², Vera A. Mayercik², Thomas R. Friberg², and Joel S. Schuman²

¹University of California, San Francisco, Department of Ophthalmology, San Francisco, California, USA

²UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh School of Medicine, and The Eye and Ear Institute, Pittsburgh, Pennsylvania, USA

Abstract

Purpose—To describe the occurrence of cystoid macular edema (CME) in the setting of central foveal thickness (CFT) under 250 μm as measured by optical coherence tomography (OCT) in patients with retinitis pigmentosa (RP).

Methods—Stratus OCT was used to measure CFT in a total of 90 eyes from 46 patients with RP. Cross-sectional OCT images were also evaluated for CME, which was defined as cystoid changes in the macula seen on at least two linear scans.

Results—CME was identified in 13 of the 46 patients or in 22 of 90 eyes by OCT. In eyes with macular edema, CFT ranged from 224 to 718 μm (mean = $339 \pm 137 \mu\text{m}$). In eyes without macular edema, CFT ranged from 99 to 273 μm (mean = $184 \pm 40 \mu\text{m}$). Bilateral CME occurred in 9 of 13 patients (69%). CFT was considered “normal” in 7 of the 22 eyes (32%) with CME. Two patients had bilateral CME with normal CFTs, under 250 μm .

Conclusion—We demonstrate the occurrence of CME in RP patients without associated thickening, which has not been described. This concept likely is applicable to other diseases with retinal thinning.

Keywords

Cystoid macular edema; OCT; retinitis pigmentosa; retinal thinning

INTRODUCTION

Retinitis pigmentosa (RP) is a clinically variable and genetically heterogeneous group of hereditary retinal dystrophies in which abnormalities of the photoreceptors or retinal pigment epithelium (RPE) cause progressive retinal cell loss and dysfunction. With a

Correspondence: Andrew W. Eller, MD, 203 Lothrop Street, Room 819, Pittsburgh, PA 15213, USA. elleraw@upmc.edu.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. (New York, NY).

Dr. Schuman receives royalties for intellectual property licensed by MIT (Cambridge, MA) to Carl Zeiss Meditec, Inc. (Dublin, CA).

prevalence of approximately 1:4000 and a total of 1.5 million individuals affected worldwide, it is a significant cause of inherited blindness.^{1,2} RP initially affects the photoreceptor layer and the outer retina, but eventually the damage spreads to the inner retinal layers as well. The end result is thinning of multiple layers of the retina, with a characteristic progression from nyctalopia, to mid-peripheral vision loss, and finally to decreased central visual acuity.³

In addition to affecting the photoreceptors and RPE, RP causes visual impairment through a variety of other mechanisms including cataracts (classically posterior subcapsular), bulls-eye or cellophane maculopathy, epiretinal membrane formation, and cystoid macular edema (CME).⁴⁻⁹ The development of CME can decrease both visual acuity and contrast sensitivity and can be extremely debilitating in the face of an already restricted peripheral visual field. The prevalence of CME in RP is generally reported between 11–49%,¹⁰⁻¹² although this percentage is influenced by the diagnostic test chosen and more likely falls in the bottom half of this range.^{13,14} It is more common in moderately advanced stages of the disease; however, earlier occurrence is not uncommon and can be functionally devastating.¹⁵

Detection of CME in RP patients has traditionally been made by dilated fundus exam with fluorescein angiography used as an ancillary diagnostic test. Optical coherence tomography (OCT) has been a significant addition to the diagnostic armamentarium for CME since it is faster, less invasive, and more sensitive than fundus exam or fluorescein angiography.^{10,14,16-18} By measuring macular thickness and volume, OCT creates cross-sectional images of the retina that correspond closely to histology and reveal in-vivo retinal architecture.^{16,19} It has previously demonstrated increased sensitivity in the diagnosis of CME in a variety of vitreomacular disorders, such as subtle or non-leaking CME in diabetic retinopathy without discernible change on ophthalmoscopy or contact lens biomicroscopy.²⁰

In conditions which cause diffuse retinal thinning, such as RP,²¹ images from OCT can also be misleading because CME may be missed if background retinal thinning is not taken into account and the cross-sectional images are not examined. Traditionally, CME is believed to arise in the setting of macular thickening; however, we observed its presence in the setting of normal central foveal thickness (CFT) measurements suggesting that increased CFT alone is not an adequate surrogate of macular edema in conditions with retinal thinning.

METHODS

This study was conducted at the University of Pittsburgh Medical Center (UPMC) Eye Center, Department of Ophthalmology at the University of Pittsburgh School of Medicine from June 2007 to January 2009. Approval for an Exempt Review was obtained from the Institutional Review Board of the University of Pittsburgh for this study and performed in accordance with the tenets of the Declaration of Helsinki. This was a retrospective chart review of RP patients. We queried the electronic health records of the UPMC Retina Service including UPMC Mercy Hospital and UPMC Eye and Ear Hospital to identify all patients with RP using the International Classification of Disease-9 (ICD-9) code for RP, 362.74.

Human Subjects

The diagnosis of RP was based on a history of nyctalopia, characteristic ophthalmoscopic appearance of bone-spicule pigment clumping, retinal vessel attenuation, and waxy pallor of the optic disc, impaired peripheral visual fields, and reduced or non-detectable electroretinographic rod and cone amplitudes with a lack of other ocular or systemic disease that might have led to a similar clinical appearance. Patients with other retinal pathology that could cause retinal thinning, such as previous trauma, glaucoma, or intraocular pressure greater than 21 mmHg, or diseases associated with macular edema, such as diabetic retinopathy, ocular inflammatory diseases, or primary retinal vascular diseases, were excluded from the study. All eyes were phakic and had non-glaucomatous optic discs. Patients had a refractive error between ± 6.00 so that variability in magnification secondary to variability in axial length was minimal.²²

The study included 90 eyes from 46 patients with two eyes excluded due to poor scan quality where distinct retinal layers could not be well visualized. As part of their exam, all patients received a complete eye examination with best-corrected visual acuity using the Snellen chart, dilated fundus exam by binocular indirect ophthalmoscopy and 78-D non-contact lens, anterior segment exam with slit lamp biomicroscopy, and intraocular pressure measurement by Goldmann applanation tonometry.

OCT Methodology

OCT images from RP patients seen by the Retina Service of UPMC Eye Center were identified and reviewed for cystoid changes by the three attending retina specialists listed in the authorship. OCT was performed with the Stratus High-Resolution OCT (Model 3000, Carl Zeiss Meditec, Dublin, CA) and analyzed with software version 3.0 (OCT3; Humphrey Instruments, San Leandro, CA) to measure central foveal thickness and evaluate cross-sectional images. The macular thickness map scan protocol was used to obtain six consecutive 6 mm macular scans centered on the fovea in a radial spoke pattern of 30° intervals. CFT was calculated as the mean thickness in the central 1,000 μm diameter as described in the Early Treatment Diabetic Retinopathy Study protocol.^{23,24} The scans were performed by trained technicians at the UPMC Ocular Imaging Center.

Each tomogram contained 512 A-scans with each A-scan consisting of 1024 data points which spanned a 2-mm depth. The location of the foveola in the OCT scan was centered by the examiner. It was occasionally difficult to confirm the precise centering of the foveola in the scan in eyes with CME, and in such cases the examiner relied on the patient's fixation. Cross-sectional OCT images were also examined for CME using the Stratus OCT mapping software. CME was defined as cystoid changes in the macula seen on at least two linear scans. Two scans, which occurred in patients with CME in the contralateral eye, were excluded due to poor scan quality.

Statistical Analysis

Stata 11 statistical software (Stata Corp., College Station, TX) was used for data analysis. Comparison of CFT between eyes with and without CME was made using a Student's *t* test. *p* values less than 0.05 were considered statistically significant.

RESULTS

Cystoid macular edema was identified in 13 of the 46 RP patients (28%) or in 22 of the 90 eyes (24%). In eyes with macular edema, CFT ranged from 224 μm to 718 μm (mean $339 \pm 137 \mu\text{m}$). In eyes without macular edema, CFT ranged from 99 μm to 273 μm (mean $184 \pm 40 \mu\text{m}$). These data are shown in Table 1.

Additionally, mean CFT in the RP eyes with and without CME was $184 \pm 40 \mu\text{m}$ and $239 \pm 10 \mu\text{m}$, respectively, which was a statistically significant difference ($p=0.02$, student's unpaired t test). However, in 10 of the 22 eyes with CME, CFT was lower than measurements in the eyes without CME illustrating the overlap of CFT measurements between these two groups. These data are shown in Figure 1. Out of the 13 total patients with CME, 9 had bilateral edema (69%).

CME with “Normal” CFT

In 7 of the 22 eyes (32%) with CME, CFT measured less than 250 μm . This form of CME with normal CFTs occurred in five patients with two patients having bilateral normovolemic CME, two patients having CME in the contralateral eye greater than 250 μm , and one patient having no evidence of CME in the contralateral eye. In this last eye, CFT measured 183 μm in the eye without CME.

DISCUSSION

Cystoid macular edema is considered a “final common pathway” that may result from a number of underlying conditions and is commonly reported in RP.^{10–14,25} Currently, OCT is considered the most sensitive diagnostic test as RP-associated CME may demonstrate little evidence of angiographic leakage or pooling of dye or cystic changes on contact-lens biomicroscopy.^{10,14,16–18} In addition to improving diagnostic sensitivity, OCT may be superior to angiography in monitoring the effectiveness of therapy in RP patients in part because of its superiority in detecting subtle changes in macular volume.¹⁶

A source of error in using OCT measurements is the use of a “normal” range that ophthalmologists have developed for evaluating macular thickness. We defined macular thickening as a CFT greater than 250 μm because this cut-off is approximately two standard deviations above the mean CFT as calculated by Chan et al. using healthy eyes on the Stratus OCT software ($212 \pm 20 \mu\text{m}$).²⁴ Although this assumption is useful in eyes with a normal baseline retinal thickness, CFT may appear to be within the “normal” range in patients with CME and underlying macular atrophy, falsely suggesting a normal study.

In our study, we found that 28% of our RP patients had CME, which supports its high prevalence in RP. Additionally, we found that 38% of RP patients (5 out of 13) with evidence of CME on cross-sectional OCT had a “normal” CFT. Using Stratus OCT, Jun et al. found the overall prevalence of this newly described entity to be 4.9% in their vitreoretinal practice over a two-month period using $<252 \mu\text{m}$ as the upper limit of normal for CFT.²⁶ Mean CFT for their patients with CME with normal CFTs was $201.4 \pm 29.4 \mu\text{m}$ compared to the healthy controls from Chan et al. ($212 \pm 20 \mu\text{m}$).²⁴ In our cohort, RP

patients without CME had a CFT of $184 \pm 40 \mu\text{m}$. Our RP patients with CME with CFTs within the normal thickness range had an increased mean CFT ($239 \pm 10 \mu\text{m}$) compared to this healthy control group but likely also had background retinal thinning for these CFTs to fall in the “normal” range. In disorders predisposed to retinal thinning such as advanced glaucoma, optic atrophy, macular diseases, and various retinal dystrophies, the prevalence of this form of CME likely is increased.

The mechanism of CME in RP is incompletely understood with several theories proposed. One hypothesis suggests that because RP is associated with an increased prevalence of anti-retinal antibodies, CME is the result of an autoimmune reaction.²⁷ This autoimmune phenomenon may explain the efficacy of steroids in the treatment of CME.²⁸ An alternative hypothesis proposes that dysfunction of the outer blood-retinal barrier at the RPE, perifoveal capillary plexus, or both increases vascular permeability causing fluid leakage in the macula.²⁹ Carbonic anhydrase inhibitors may treat CME by enhancing the pumping mechanism at the level of the RPE.^{17,30} In addition to its anti-inflammatory properties, steroids may also work at the level of the blood-retinal barrier in RP as it has been shown experimentally to reduce breakdown of the blood-retinal barrier in diabetic retinopathy.³¹ Lastly, it is possible that both mechanisms occur in concert: breakdown of the blood-retinal barrier allows release of retinal proteins into the circulation which are antigenic and create CME in addition to the anti-retinal antibodies seen in RP patients.^{27,32}

Although the mechanism of macular edema has not been elucidated, early treatment may prove to be most beneficial. Chung et al.¹⁷ suggest that chronic macular edema itself may hasten photoreceptor cell loss or cause some other irreparable functional impairment that may limit the response to carbonic anhydrase inhibitors. Besides serial monitoring with OCT, inheritance of RP also may be useful in raising suspicion for CME. Sandberg et al.³³ found that in 316 patients with RP, macular cysts were most common among dominantly inherited disease and not seen in patients with X-linked disease.

The etiology of retinal thinning in RP is secondary to thinning of the photoreceptor layer.³³ Walia et al.¹ found that 40% of RP patients had abnormal thinning of the peripapillary retinal nerve fiber layer (RNFL) compared to healthy controls as measured by OCT. Witkin et al.²¹ found that the foveal outer segment/RPE (FOSPET) was statistically thinner in RP patients compared to normal subjects. CFT was also thinner in their RP patients; however, it was not statistically significant, although this may prove to be a function of the small sample size (9 RP patients). Interestingly, some authors have found that RNFL thinning was more common in X-linked RP compared to autosomal dominant disease,^{1,34} although other studies have disagreed with this finding.^{6,35}

Our study was limited by patient sample size and difficulty in obtaining good quality scans in certain patients. These scans were excluded. Additionally, although retinal thinning was supported by a statistically significant thinning in CFT in our group of eyes without CME compared to a control group by Chan et al. ($p=0.03$, student's unpaired t test),²⁴ we did not specifically use another measure of retinal thickness to confirm that eyes with normovolemic CME had background retinal thinning. In the future, it may be possible to recalibrate the

“normal” range of central foveal thickness according to some measure of background photoreceptor thinning.

With the expanded use of ultrahigh-resolution OCT, it is likely that this new form of subclinical CME, which is only detectable on cross-sectional images, will be increasingly recognized. It is likely that newer OCT models with greater resolution will detect more cases of CME with normal CFTs than seen with Stratus OCT. This entity has only been recently described and has been identified in a myriad vitreomacular diseases such as macular degeneration, retinal vein occlusions, diabetic retinopathy, and tractional disorders.²⁶ The clinical significance of this form of CME requires further investigation as it is increasingly recognized.

References

1. Walia S, Fishman GA, Edward DP, Lindeman M. Retinal nerve fiber layer defects in RP patients. *Invest Ophthalmol Vis Sci*. 2007 Oct; 48(10):4748–4752. [PubMed: 17898300]
2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *Lancet*. 2006; 368:1795–1809. [PubMed: 17113430]
3. Bunker CH, Berson EL, Bromley WC, et al. Prevalence of retinitis pigmentosa in Maine. *Am J Ophthalmol*. 1984 Mar; 97(3):357–365. [PubMed: 6702974]
4. Berson, EL. Retinitis pigmentosa and allied retinal diseases. In: Tasman, W., Jaeger, EA., editors. *Duane's Clinical Ophthalmology*. Lippincott, Williams & Wilkins; Philadelphia, PA: 2006.
5. Pagon RA. Retinitis pigmentosa. *Surv Ophthalmol*. 1988; 33:137. [PubMed: 3068820]
6. Pruett RC. Retinitis pigmentosa: clinical observations and correlations. *Trans Am Ophthalmol Soc*. 1983; 81:693. [PubMed: 6676982]
7. Weleber, RG., Gregory-Evans, K. Retinitis pigmentosa and allied disorders. In: Ryan, SJ., editor. *Retina*. Elsevier, Mosby; St. Louis, MO: 2006. p. 395
8. Berson EL. Retinitis pigmentosa: the Friedenwald lecture. *Invest Ophthalmol Vis Sci*. 1993; 24:1659–1676.
9. van Soest S, Westerveld A, de Jong PT, et al. Retinitis pigmentosa: defined from a molecular point of view. *Surv Ophthalmol*. 1999 Jan-Feb;43(4):321–334. [PubMed: 10025514]
10. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystic macular oedema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. *Br J Ophthalmol*. 2008 Aug; 92(8):1065–1068. [PubMed: 18653601]
11. Coscas G, Gaudric A. Natural course of nonaphakic cystoid macular edema. *Surv Ophthalmol*. 1984; 28:471–484. [PubMed: 6463848]
12. Adackapara CA, Sunness J, DiBernardo CW, et al. Prevalence of cystoid macular edema and stability in OCT retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. *Retina*. 2008; 28:103–110. [PubMed: 18185146]
13. Fishman GA, Maggiano JM, Fishman M. Foveal lesions seen in retinitis pigmentosa. *Arch Ophthalmol*. 1977; 95:1993–1996. [PubMed: 921578]
14. Hirakawa H, Iijima H, Gohdo T, Tsukahara S. Ocular coherence tomography of cystoid macular edema associated with retinitis pigmentosa. *Am J Ophthalmol*. 128:185–191. 199.
15. Tranos PG, Wickremasinghe SS, Stangos NT, et al. Macular edema. *Surv Ophthalmol*. 2004; 49:470–490. [PubMed: 15325193]
16. Apushkin MA, Fishman GA, Janowicz MJ. Monitoring cystoid macular edema by optical coherence tomography in patients with retinitis pigmentosa. *Ophthalmology*. 2004; 111:1899–1904. [PubMed: 15465554]
17. Chung H, Hwang J, Kim J, Yoon YH. Optical Coherence Tomography in the diagnosis and monitoring of cystoid macular edema in patients with retinitis pigmentosa. *Retina*. 2006; 26:922–927. [PubMed: 17031294]

18. Nussenblatt RB, Kaufman SC, Palestine AG, et al. Macular thickening and visual acuity measurement in patients with cystoid macular edema. *Ophthalmology*. 1987; 94:1134–1139. [PubMed: 3684231]
19. Puliafito CA, Hee MR, Lin CP, et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995; 102:217–229. [PubMed: 7862410]
20. Hee MR, Puliafito CA, Wong C, et al. Quantitative assessment of macular edema with optical coherence tomography. *Arch Ophthalmol*. 1995; 113:1019–1029. [PubMed: 7639652]
21. Witkin AJ, Ko YH, Fujimoto JG, et al. Ultra-high resolution optical coherence tomography assessment of photoreceptors in retinitis pigmentosa and related diseases. *Am J Ophthalmol*. 2006 Dec; 142(6):945–952. [PubMed: 17157580]
22. Pach J, Pennell DO, Romano PE. Optic disc photogrammetry: magnification factors for eye position, centration, and ametropias, refractive and axial; and their applications in the diagnosis of optic nerve hypoplasia. *Ann Ophthalmol*. 1989; 21:454–462. [PubMed: 2627096]
23. Early Treatment Diabetic Retinopathy Study Research Group. ETDRS report number 7: early treatment diabetic retinopathy study design and baseline patient characteristics. *Ophthalmology*. 1991; 98:741–756. [PubMed: 2062510]
24. Chan A, Duker JS, Ko TH, et al. Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. *Arch Ophthalmol*. 2006 Feb; 124(2):193–198. [PubMed: 16476888]
25. Fu, A., Ahmed, I., Ai, E. Cystoid macular edema. In: Yanoff, M., Duker, JS., editors. *Ophthalmology*. Mosby; St. Louis, MO: 2004.
26. Jun JJ, Duker JS, Bauman CR, et al. Cystoid macular edema without macular thickening: a retrospective optical coherence tomographic study. *Retina*. 2010 Jun; 30(6):917–923. [PubMed: 20168270]
27. Heckenlively JR, Jordan BL, Aptsiauri N. Association of antiretinal antibodies and cystoid macular edema in patients with retinitis pigmentosa. *Am J Ophthalmol*. 1999; 127:565–573. [PubMed: 10334350]
28. Hakan O, Murat K, Serra K. Intravitreal triamcinolone acetonide for treatment of cystic macular edema in patients with retinitis pigmentosa. *Acta Ophthalmol Scand*. 2005; 83:248–251. [PubMed: 15799743]
29. Newsome DA. Retinal fluorescein leakage in retinitis pigmentosa. *Am J Ophthalmol*. 1986; 101:354–360. [PubMed: 3953729]
30. Fishman GA, Gilbert LD, Fiscella RG, et al. Acetazolamide for treatment of chronic macular edema in retinitis pigmentosa. *Arch Ophthalmol*. 1989; 107:1445–1452. [PubMed: 2803090]
31. Wilson CA, Berkowitz BA, Sato Y, et al. Treatment with intravitreal steroid reduces blood-retinal barrier breakdown due to retinal photocoagulation. *Arch Ophthalmol*. 1992; 110:1155–1159. [PubMed: 1497531]
32. Heckenlively JR, Solish AM, Chant SM, Meyer's-Elliott RH. Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings. *Br J Ophthalmol*. 1985; 69:758–764. [PubMed: 4052361]
33. Sandberg MA, Brockhurst RJ, Gaudio AR, Berson EL. Visual acuity is related to parafoveal retinal thickness in patients with retinitis pigmentosa with macular cysts. *Invest Ophthalmol Vis Sci*. 2008; 49:4568–4572.
34. Humayun MS, Prince M, de Juan E Jr. Morphometric analysis of the extramacular retina from postmortem eyes with retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1999; 40:143–148. [PubMed: 9888437]
35. Oishi A, Otani A, Sasahara M, et al. Retinal nerve fiber layer thickness in patients with retinitis pigmentosa. *Eye (Lond)*. 2009 Mar; 23(3):561–566. [PubMed: 18344951]

FIGURE 1.

Distribution of central foveal thickness (CFT) within cystoid macular edema (CME) and non-CME groups. Ten of 22 eyes with CME had CFTs which were lower than measurements in eyes without CME. The CME group totals 101% due to rounding.

TABLE 1

Central foveal thickness of eyes with and without CME.

	Non-CME Eyes	CME Eyes
Number of eyes (% of the 90 eyes)	68 (76%)	22 (24%)
Mean CFT (μm) 3SD	$184 \pm 40 \mu\text{m}$	339 ± 137
Confidence Interval (at 95% CI)	174–195 μm	281–396 μm

CME =cystoid macular edema; CI =confidence interval.