Evaluation of the Choroid in Eyes With Retinitis Pigmentosa and Cystoid Macular Edema

Claudio Iovino,[1,2] Adrian Au,[1] Assaf Hilely,[1] Sara Violanti,[1,3] Enrico Peiretti,[2] Michael B. Gorin,[1] and David Sarraf[1,4]

[1]Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States
[2]Department of Surgical Sciences, Eye Clinic, University of Cagliari, Cagliari, Italy
[3]Department of Biomedical Sciences and Specialized Surgeries, School of Medicine, University Hospital of Ferrara, Ferrara, Italy
[4]Greater Los Angeles VA Healthcare Center, Los Angeles, California, United States

PURPOSE. To study the anatomical choroidal features associated with the presence of cystoid macular edema (CME) in eyes with retinitis pigmentosa (RP).

METHODS. A total of 159 eyes (from 159 patients) with a diagnosis of RP were enrolled in this retrospective cross-sectional case-control study and divided into two groups based on the presence (67 eyes) or absence (92 eyes) of CME. Retinal and choroidal features were evaluated on spectral domain optical coherence tomography including central macular thickness (CMT) and subfoveal choroidal thickness (CT). Total choroidal area (TCA), choroidal luminal area (LA), and choroidal stromal area (SA) were measured and the choroidal vascularity index (CVI) was calculated in all study eyes.

RESULTS. Average age was 49.2 ± 14.9 and 47.1 ± 15.5 years ($P = 0.40$) and logMAR Snellen visual acuity (VA) was 0.4 ± 0.6 (median 0.3, 20/40) and 0.2 ± 0.4 (median 0.1, 20/25) in the RP groups with and without CME, respectively ($P = 0.05$). Mean CMT was 334.1 ± 93.5 and 252.6 ± 47.6 μm in the RP groups with and without CME, respectively ($P < 0.001$). The subfoveal CT was significantly increased in the RP group with versus without CME (294.2 ± 110.9 μm vs. 198.1 ± 75.5 μm, respectively, $P < 0.001$). In patients with CME, the CVI was lower ($P < 0.001$) and the TCA, LA, and SA were all significantly higher ($P < 0.001$).

CONCLUSIONS. In patients with CME associated with RP, the choroid exhibited significantly greater subfoveal thickening and decreased CVI. The choroid may be an important factor to consider in the etiology of CME in patients with RP.

Keywords: retinitis pigmentosa, macular edema, optical coherence tomography, choroidal thickness, choroidal vascularity index

Retinitis pigmentosa (RP) is the most common inherited retinal dystrophy. Characterized by genetic and phenotypic heterogeneity, RP usually is classified into three subtypes according to the inheritance pattern: autosomal dominant, autosomal recessive, or X-linked.[1] The disease is remarkable for chronic progressive vision loss, including nyctalopia and centripetal vision field reduction caused by degeneration of photoreceptors, especially of the rod population.

Acute or subacute development of ocular complications, including cystoid macular edema (CME), can further reduce visual acuity at any stage of the disease.[2] The prevalence of CME in patients with RP ranges from 11% to 20% as detected by fluorescein angiography (FA)[3,4] and up to 50% as detected by spectral domain optical coherence tomography (SD-OCT).[5–9] The pathogenesis of CME in eyes with RP is not well understood and different mechanisms have been proposed, including vitreous traction, Müller cell degeneration, inner blood retinal barrier disruption, and RPE dysfunction.[10,11]

To date, there has been limited analysis of the choroid in relation to CME in patients with RP. We robustly analyzed the pathoanatomic features of the choroid in eyes with RP, using SD-OCT, and correlated these choroidal findings with the presence or absence of intraretinal cystic fluid or CME.

METHODS

This was a retrospective cross-sectional study of RP patients from the retinal practices of DS and MBG evaluated at the Stein Eye Institute, University of California, Los Angeles. The study protocol was approved by the University of California, Los Angeles institutional review board, adhered to the guidelines of the Health Insurance Portability and Accountability Act (HIPAA), and was performed in accordance with the tenets of the Declaration of Helsinki.

Study Population

The study included 159 patients with a diagnosis of RP from January 2014 to December 2018 who were divided into two groups based on the presence or absence of CME. In patients with bilateral CME, the eye with greater central macular thickness (CMT) was selected for analysis. In unilateral CME,

the affected eye was incorporated into the analysis and the nonaffected eye was excluded. In RP patients without CME, the right eye was selected for analysis. In a subanalysis of the eyes with unilateral CME, eyes with CME were compared to their non-CME eyes. A separate subanalysis was performed excluding patients on either topical or oral carbonic anhydrase inhibitors (CAI).

Cystoid macular edema was defined as one or more fluid-filled, intraretinal cystoid spaces in the macula as detected by volumetric SD-OCT. RP was diagnosed by the presence of peripheral bone spicule migration of pigment into the retina as identified by retinal examination and wide field fundus photography or fundus autofluorescence. Preserved RPE and external limiting membrane (ELM) and ellipsoid zone (EZ) bands in the central 500 μm under the fovea, as determined by SD-OCT, were an additional inclusion criterion. A thorough chart review of the patient's medical history, family history, characteristic fundus appearance, multimodal imaging, and results of visual field (manual Goldmann or automated Humphrey) and electroretinography was performed to ensure a diagnosis of RP (i.e., rod cone dystrophy) and eligibility for this study. As the genetic characterization of RP was not available in all patients, this information was not included in the analysis and the diagnosis of RP (that is, rod cone dystrophy) was made according to aforementioned clinical criteria.

Exclusion criteria included the presence of any other retinal disease or ocular disorder that could affect choroidal thickness (CT) or could be associated with the development of CME (e.g., recent history of cataract and/or vitreoretinal surgery in the previous 6 months). Patients younger than 20 or older than 70 years of age and eyes with hyperopia or myopia >6 diopters were excluded. Pregnant patients also were excluded. Low quality OCT images due to optic media opacities that did not allow sufficient visualization of the choroid were excluded.

Clinical Examination

Patients underwent a comprehensive ophthalmologic evaluation that included clinical history, Snellen visual acuity (logMAR conversion was performed for statistical analysis), lens status, fundus examination, FA, fundus autofluorescence, and enhanced depth-OCT (FAF and EDI-OCT; Heidelberg Spectralis HRA + OCT; Heidelberg Engineering, Germany; Optos PLC, Dunfermline, Scotland, UK). FA was performed only in select cases. All imaging data were collected and analyzed by three examiners (CI, AA, AH), then selectively reviewed by the senior author (DS) to ascertain all retinal findings.

OCT Analysis of the Retina and Choroid

A horizontal 30° × 20° volume scan containing 25 or 61 B-scans was obtained for all study eyes. CMT and subfoveal CT were measured on the OCT B scan using the built-in automated software (Heidelberg Eye Explorer HEYEX; Heidelberg Engineering). Specifically, CMT was automatically displayed by the thickness profile module, whereas subfoveal CT was determined manually by measuring the subfoveal vertical distance between the Bruch's membrane interface and the sclerochoroidal junction using the caliper tool on the EDI-OCT B scan. If EDI-OCT scans were not available, only the eyes in which the entire choroid could be visualized from the Bruch's membrane to the sclerochoroidal interface were selected for the analysis. Presence of epiretinal membrane was evaluated and graded as suggested previously[12] and comparative analysis was performed between the two RP groups with and without CME.

The exact location of the cystoid spaces in the retinal layers and their maximum distance from the fovea were analyzed using horizontal linear OCT B-scans. Outer retinal band (ELM and EZ) integrity also was analyzed in the area under the intraretinal fluid. The preserved EZ length also was measured using the line tool of the ImageJ software.

OCT Analysis: Choroidal Vascular Index (CVI)

In all study eyes, macular B scan images were exported with a 1:1 pixel ratio and processed with ImageJ 1.50 software (National Institutes of Health, Bethesda, MD, USA) using the set scale tool to convert pixels to micrometers. The choroidal vascularity index (CVI) and the choroidal luminal and stromal areas (LA and SA, respectively) were measured and calculated as suggested previously.[13–15] SA/LA was calculated as a ratio of the stromal area divided by the luminal area. The central foveal OCT B scan was chosen for the analysis in all study eyes. Briefly, the polygon tool was used to select the region of interest (choroid) across the entire length of the OCT B scan. After converting the image into 8 bit, Niblack's auto-local threshold was applied to binarize the image and demarcate the LA and SA. LA was highlighted by applying the color threshold and then added to the region of interest (ROI) manager. The total choroidal area (TCA) and LA were measured and the CVI (defined as the ratio of LA to TCA) was calculated in every eye.

Correlation Analysis

Correlation analysis was performed between choroidal parameters versus age, visual acuity (VA), and CMT. The relationship of age to choroidal vasculature was evaluated to determine if choroidal changes were due to age versus the presence or absence of CME. Correlation of choroidal parameters with BCVA and CMT was performed to analyze functional outcomes that are relevant in the setting of CME. Specifically, correlation analysis was conducted between subfoveal CT, CVI, TCA, SA, LA, SA/LA versus age, VA, CMT, and EZ length.

Statistical Analysis

Statistical analyses were performed using R version 3.5.0 (available in the public domain at www.r-project.org). Results of descriptive analyses are expressed as counts and percentages for categorical variables, and as means ± SDs for quantitative variable. The χ^2 test was performed with ordinal or categorical variables (sex, eye, presence of ERM, ELM, and EZ disruption) while the 2-sample t-test was performed for interval variables (age, CMT, subfoveal CT, TCA, CVI, LCA, SA, SA/LCA, EZ length). Bonferroni correction was used for multiple pair-wise t-test analyses and $P < 0.006$ (0.05/8) was considered significant. Multivariable nonparametric correlation was performed with Spearman's rank test. Cohen's effect size was calculated for each correlation r value. As there were 24 different comparisons, a P value of 0.002 (0.05/24) was used to determine significance with regards to the correlation analysis.

RESULTS

Study Population

Overall, a total of 600 eyes of 300 patients were screened using ICD-9/10 codes for retinal dystrophies, rod-cone dystrophy, or retinitis pigmentosa. Among the 300 patients 159 (53.4% male) met the strict inclusion criteria and were included in this retrospective study. Of the 141 patients excluded, 120 did not meet inclusion criteria. An additional 21 patients were excluded because of inadequate visualization of the choroi-

TABLE 1. Patient Characteristics and Comparison of Structural Retinal and Choroidal Characteristics Between RP Eyes With and Without CME

	Without CME, $N = 92$	With CME, $N = 67$	P Value
Age, avg ± STD	47.1 ± 15.5	49.2 ± 14.9	0.40**
Sex			0.80*
M, n (%)	50 (54.4)	35 (52.2)	
F, n (%)	42 (45.6)	32 (47.8)	
Pseudophakia	42 (45.6)	24 (35.8)	0.21*
Presence of epiretinal membrane, n (%)	27 (29.4)	29 (43.3)	0.07*
LogMAR VA, median, avg ± STD	0.1, 0.2 ± 0.4	0.3, 0.4 ± 0.6	0.05†
CMT, μm, avg ± STD	252.6 ± 47.6	334.1 ± 93.5	<0.001†
Subfoveal CT, μm, avg ± STD	198.1 ± 75.5	294.2 ± 110.9	<0.001†
TCA, mm², avg ± STD	3.1 ± 0.8	4.4 ± 0.7	<0.001†
CVI, %, avg ± STD	65.2 ± 3.2	62.9 ± 2.2	<0.001†
LA, mm², avg ± STD	2.0 ± 0.5	2.7 ± 0.4	<0.001†
SA, mm², avg ± STD	1.1 ± 0.3	1.7 ± 0.3	<0.001†
SA/LA, %,avg ± STD	0.5 ± 0.1	0.6 ± 0.1	<0.001†
EZ length, μm, avg ± STD	2698.4 ± 2133.1	2374.1 ± 1599.9	0.27

* χ^2 test; $P < 0.05$ indicates statistical significance.
† Two sample t-test; $P < 0.007$ indicates statistical significance.

doscleral junction due to optic media opacities or severe CME with shadowing effect.

Patients were divided into two groups based on the presence (67 eyes) or absence (92 eyes) of CME. The cystoid spaces were bilateral in 48 eyes (71.6%) and unilateral in 19 eyes (28.4%). The demographics and ocular characteristics of the study subjects are summarized in Table 1. Neither group exhibited any significant differences as pertains to sex or age. Average age was 49.2 ± 14.9 and 47.1 ± 15.5 years ($P = 0.4$) in the RP groups with and without CME, respectively. Mean Snellen VA in logMAR was 0.4 ± 0.6 (median 0.3, 20/40) and 0.2 ± 0.4 (median 0.1, 20/25 $P = 0.05$), respectively.

OCT Analysis of the Retina

Epiretinal membrane was detected in 29 RP patients with (43.3%) and in 27 without (29.4%) CME and no statistically significant difference was noted ($P = 0.07$). Of the patients with ERM, the average grade of ERM was 1.6 ± 0.8 in patients with (median 1) and 1.4 ± 0.6 without (median 1, $P = 0.90$) CME. No statistically significant differences were found between the two groups in regard to the lens status ($P = 0.21$).

Data for the retinal and choroidal analysis are summarized in Table 1. As expected, the mean CMT was significantly greater in the CME group. Mean CMT was 334.1 ± 93.5 and 252.6 ± 47.6 μm in the RP groups with and without CME, respectively ($P < 0.001$).

Cystoid macular edema location was analyzed. The intraretinal fluid was located exclusively in the inner nuclear layer in 47.8% of the total cohort. It was located only in the outer nuclear layer in 9.0% of eyes and in both nuclear layers in 43.3%. The mean maximal distance of CME from the fovea was 1036.7 ± 532.9 μm nasal and 1086.4 ± 532.9 μm temporal to the central fovea.

Analysis of the outer retinal bands under the CME revealed that the ELM was intact in 42 eyes (62.7%) and the EZ was preserved in 30 (44.8%). EZ length was slightly greater at 2698.4 ± 2133.1 μm without CME compared to 2374.1 ± 1599.9 μm with CME ($P = 0.27$). There was no statistically significant difference in EZ length between groups.

OCT Analysis of the Choroid

The average subfoveal CT was greater in the RP group with (294.2 ± 110.9 μm) versus without (198.1 ± 75.5 μm) CME and this was highly statistically significant ($P < 0.001$) (Table 1). In the RP group with CME, mean CVI was 62.9% ± 2.2% versus 65.2% ± 3.2% in the RP group without CME ($P < 0.001$). TCA, LA, and SA were all significantly greater in the RP group with CME ($P < 0.001$) (Table 1).

To evaluate the effects of CAI on the choroid, we compared choroidal parameters after removing patients on topical or oral CAI in the CME group (Table 2). There were 24 patients on CAI who were removed from the CME group. After removal, there was a decrease in the CMT and increase in the CT, but other parameters were minimally changed (Table 2). Comparison of patients with and without CME remained statistically significant for all choroidal parameters ($P < 0.001$, Table 2).

Subanalysis of choroidal characteristics in only those patients with unilateral CME was performed and summarized

TABLE 2. Comparison of Structural Retinal and Choroidal Characteristics Excluding Patients on Carbonic Anhydrase Inhibitors

	Without CME, $N = 92$	With CME, $N = 43$	P Value*
CMT, μm, Avg ± STD	252.6 ± 47.6	327.5 ± 89.2	<0.001
Subfoveal choroidal thickness, μm, Avg ± STD	198.1 ± 75.5	315.6 ± 103.4	<0.001
TCA, mm², avg ± STD	3.1 ± 0.8	3.7 ± 1.1	<0.001
CVI, %, avg ± STD	65.2 ± 3.2	62.8 ± 2.0	<0.001
LA, mm², avg ± STD	2.0 ± 0.5	2.3 ± 0.7	<0.001
SA, mm², avg ± STD	1.1 ± 0.3	1.4 ± 0.4	<0.001
SA/LA, %, avg ± STD	0.5 ± 0.1	0.6 ± 0.1	<0.001
EZ length, μm, avg ± STD	2698.4 ± 2133.1	2473.1 ± 1763.1	0.52

* Two sample t-test; $P < 0.007$ indicates statistical significance.

TABLE 3. Comparison of Structural Retinal and Choroidal Characteristics Within Unilateral CME Group

	Eye Without CME, $N = 19$	Eye With CME, $N = 19$	P Value*
CMT, μm, avg ± STD	250.3 ± 47.8	277.2 ± 64.0	0.02
Subfoveal CT, μm, avg ± STD	217.2 ± 100.5	240.9 ± 109.7	0.09
TCA, mm², avg ± STD	3.4 ± 0.3	4.0 ± 0.6	0.11
CVI, %, Avg ± STD	65.2 ± 2.2	64.7 ± 0.8	0.61
LA, mm², avg ± STD	2.2 ± 0.2	2.6 ± 0.4	0.09
SA, mm², avg ± STD	1.4 ± 0.4	1.5 ± 0.2	0.60
SA/LA, %, avg ± STD	0.6 ± 0.1	0.6 ± 0.1	0.97
EZ length, μm, avg ± STD	1814.4 ± 1097.2	1873.5 ± 1704.2	0.83

* Two sample *t*-test; $P < 0.007$ indicates statistical significance.

in Table 3. CMT, subfoveal CT, TCA, LA, and SA were all greater in RP eyes with versus without CME, but these differences were not statistically significant with the conservative Bonferroni correction. SA/LA ratio was the same between both groups. CVI was lower in RP eyes with versus eyes without CME ($P = 0.61$).

Table 4 summarizes the correlation analysis performed. In the CME group, there was a statistically significant and large negative correlation between CVI and logMAR VA, suggesting that lower CVI was associated with a worse VA ($r = -0.19$, $P = 0.02$, $d = 3.32$). This association also was noted when VA was compared to CVI in all patients, albeit to a lesser degree ($r = -0.17$, $P = 0.16$, $d = 4.20$).

Correlations between subfoveal CT, TCA, SA, LA, or SA/LA showed no statistically significant associations with age, VA, CMT, or EZ length in the CME group, although the CVI versus CMT analysis did display a large negative correlation in the CME group ($r = -0.29$, $P = 0.0003$, $d = -3.88$). When performing correlations between choroidal characteristics and the total patient cohort, there were statistically significant negative correlations with logMAR VA. Specifically, patients with higher TCA, SA, LA and lower CVI exhibited worse visual acuity ($P < 0.001$). Of note, there was a positive correlation with TCA ($P = 0.02$), SA ($P = 0.004$), and LA ($P = 0.03$) and negative correlation with CVI ($P = 0.0003$) versus CMT that did not reach significance when implementing the conservative Bonferroni correction.

TABLE 4. Correlation Between Choroidal Features and Outcomes

|	With CME, $N = 67$			All Eyes, $N = 159$		
	Correlation*	P Values	d Values	Correlation*	P Values	d Values
Subfoveal CT						
Age	−0.23	0.004	2.58	−0.28	0.02	3.09
VA	−0.19	0.02	3.30	−0.31	0.01	3.75
CMT	0.15	0.06	−0.52	0.08	0.54	−0.39
EZ length	0.03	0.74	1.83	0.21	0.09	1.7
CVI						
Age	−0.14	0.07	1.47	−0.02	0.85	1.20
VA	−0.19	0.02	3.32	−0.17	0.16	4.20
CMT	−0.29	0.0003	−3.88	−0.32	0.008	−4.14
EZ length	0.14	0.07	2.04	0.07	0.58	1.8
TCA						
Age	−0.18	0.02	−4.19	−0.14	0.25	−4.31
VA	−0.33	<0.001	2.69	−0.26	0.03	3.16
CMT	0.19	0.02	−4.95	0.12	0.33	−5.01
EZ length	0.12	0.117	2.10	0.12	0.31	1.87
Stromal choroidal area						
Age	−0.15	0.06	−4.36	−0.14	0.27	−4.55
VA	−0.28	<0.001	1.44	−0.25	0.04	1.70
CMT	0.22	0.004	−4.98	0.17	0.17	−5.03
EZ length	0.10	0.22	2.10	0.13	0.31	1.87
Luminal choroidal area						
Age	−0.19	0.01	−4.29	−0.14	0.25	−4.46
VA	−0.35	<0.001	2.29	−0.28	0.02	2.58
CMT	0.17	0.03	−4.97	0.10	0.41	−5.02
EZ length	0.13	0.09	2.10	0.14	0.27	1.87
SA/LA						
Age	0.09	0.50	−4.40	0.13	0.09	−4.61
VA	0.18	0.16	0.79	0.20	0.009	0.55
CMT	0.35	0.004	−4.98	0.28	<0.01	−5.04
EZ length	−0.14	0.07	2.10	−0.07	0.55	1.87

* Spearman's rank correlation.
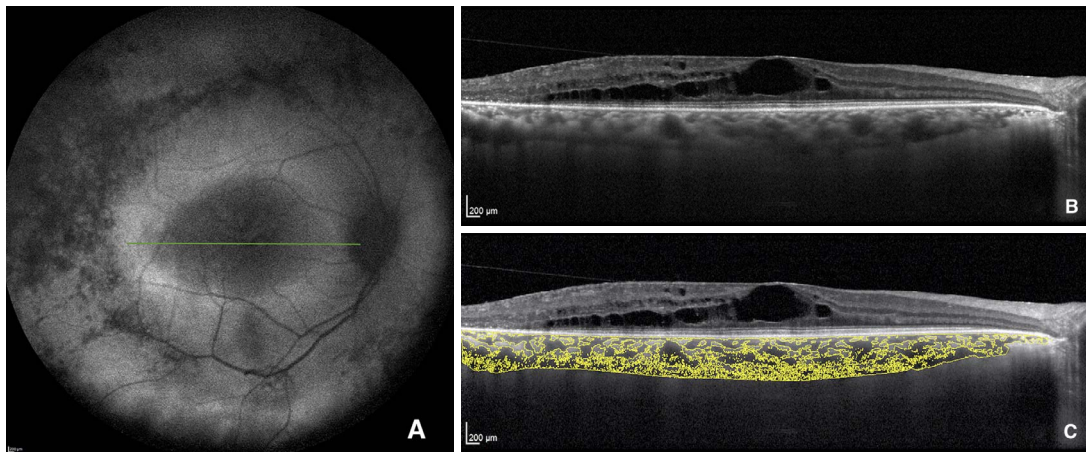
FIGURE 1. Multimodal retinal imaging of the right eye of a 48-year-old RP patient with CME. (**A**) Wide-field (55°) FAF illustrates 360° hypoautofluorescent pigmentary alterations in the mid-periphery classic for RP. (**B**) Cross sectional EDI-OCT displays CME with intraretinal fluid and underlying preserved EZ and ELM bands and an associated thickened choroid (408 µm). (**C**) Post-binarization image map of the LA and SA illustrates an increased TCA and SA.

DISCUSSION

Cystoid macular edema is a common complication in patients with RP. Various pathogenic mechanisms have been proposed, including breakdown of the inner or outer blood retinal barrier, RPE pump dysfunction, and Müller cell disruption. Although these mechanisms may work in aggregate, involvement of the choroid in the pathophysiology of CME has been discussed minimally in the literature. Our study provided evidence that CT may be associated with the development of CME in eyes with RP. Increased TCA, LA, and SA as well as increased subfoveal CT, were all significantly associated with CME in eyes with RP suggesting that hydrostatic and hemodynamic choroidal flow alterations may be driving the development of CME in eyes with RP.

Prior reports have illustrated inconsistent findings on the subject of CT in RP patients. Several investigators have reported reduced CT in RP patients versus healthy controls.[16–19] These findings are consistent with other studies that reported choroidal blood flow impairment in RP using ocular pulse amplitude,[20] confocal laser Doppler flowmetry,[21] high-resolution magnetic resonance imaging,[22] and laser speckle flowgraphy.[23] By contrast, Tan et al.[14] reported a greater mean subfoveal CT and a lower CVI in a cohort of 35 patients with RP compared to normal eyes.[14] None of these prior studies, however, investigated these alterations in RP eyes with CME and also failed to perform other robust markers of CT such as CVI (or TCA, LA, and SA) in RP eyes with and without CME.

In our study of RP eyes, an increased average subfoveal CT was noted in the group with CME (mean, 294.2 ± 110.9 µm), which was significantly greater ($P < 0.001$) than the average value in the RP group without CME (198.1 ± 75.5 µm). After removal of patients on CAI treatment, subfoveal CT increased (315.6 ± 103.4 µm), suggesting that CAI treatment reduces CT, as previously reported.[24] Similar trends were also present, albeit to a lesser extent in the eyes with unilateral CME (i.e., CT, TCA, SA, and LA were all increased in the RP eye with unilateral CME versus the fellow eye without CME).

We computed CVI, a relative novel parameter to analyze choroidal structure and measured as a ratio of LA over TCA. The semi-automated tool used to measure CVI provides the capability to calculate quantitative parameters of the choroid and stratify the stromal and vascular components. In eyes with

CME, a thicker choroid implies a larger TCA; as a result, this may explain the lower CVI in CME patients and higher CVI in non-CME patients (Figs. 1, 2). Alternatively, an increased SA may explain the increase in the TCA and resultant decrease in the CVI. This increase in SA could be explained by choroidal vascular leakage (note that the LA or luminal choroidal area also was significantly increased in RP eyes with CME in our study) or by chronic fibrotic remodeling of the choroidal compartment. Either way, alterations in the hydrostatic and hemodynamic mechanisms of the choroid may be driving the development of CME in eyes with RP.

Varied reports exist on the correlation between CT and clinical function in RP patients (with and without CME). Some investigators have linked reduced visual acuity with decreased CT.[16] Our study showed that patients with CME with higher TCA, LA, and SA, and lower CVI exhibited a worse visual acuity. Across our total cohort (i.e., RP patients with and without CME), there was a positive correlation of quantitative choroidal parameters (TCA, SA, LA) versus CMT. These were not statistically significant with the conservative Bonferroni correction, but may implicate that alterations in these choroidal features may be associated with CME.

In our study, intraretinal fluid was mostly located within the inner nuclear layer where the cell body of Müller cells reside, suggesting that Müller cell dysfunction versus leakage from the deep retinal capillary plexus, in addition to choroidal hemodynamic mechanisms, may contribute to the development of CME. ERM presence and severity were similar in both groups without significant differences ($P = 0.07$) indicating that vitreous traction is less likely to explain the development of CME in RP patients. Interestingly, some investigators have demonstrated an increase in the intraocular production of proinflammatory molecules (IL-2, IL-6, MCP-1, and so forth) in RP patients (with and without CME) and have suggested that inflammation may have a role in the disease pathogenesis.[25] Based on this concept, it may be speculated that the thicker choroid in RP patients with CME may result from locally increased blood flow secondary to intraocular inflammation, leading to the development of CME. Supporting this hypothesis, several investigators have shown the efficacy of off-label intravitreal triamcinolone[26,27] and dexamethasone implantation for the treatment of CME secondary to RP[28–30] and have reported a significant reduction of CMT associated with an improvement in visual acuity.
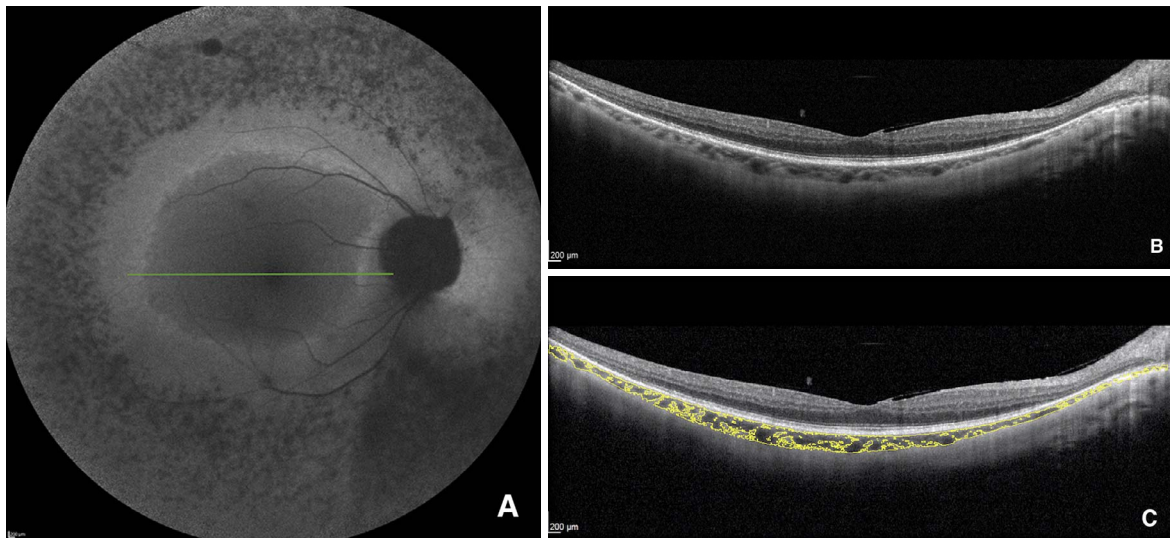
FIGURE 2. Multimodal retinal imaging of the right eye of a 57-year-old RP patient without CME. (A) Wide-field (55°) FAF displays 360° hypoautofluorescent peripheral pigmentary alterations classic for RP. (B) Cross-sectional EDI-OCT illustrates preserved ELM and EZ within 1000 μm from the fovea bilaterally and the presence of an epiretinal membrane. Note the thinner choroid (145 μm) in this RP case without CME. (C) Post-binarization image map of the LA and SA of the choroid in both eyes illustrates a decreased TCA.

Limitations

Limitations of the study included the retrospective analysis and the lack of genetic categorization of RP patients. Moreover, this was a cross-sectional study and longitudinal analysis was not performed. This study did not prove causality. It is possible that increased CT and increased TCA (and LA and SA) may be associated with CME in RP patients due to an unidentified factor (e.g., inflammation). Another mechanism to consider could be related to RPE pump removal of fluid from the retina leading to an increase in all the choroidal parameters.[31] In this scenario, increased CT is the result and not the cause of CME. To definitively conclude causality, a prospective study is necessary. The readers (CI, AA, AH) were not masked to the presence or absence of CME. In an attempt to reduce these forms of bias, measurements were made strictly on localizing the specified structures. The volume of B-scans was limited in a small number of eyes to 25 B-scans and with this density small cysts may be missed.[32] Lastly, we excluded high myopic and hyperopic patients from our analysis, but cannot exclude the correlation between axial length and refractive status with the choroidal parameters. A prospective study that will include axial length analysis in all patients will be important to validate our results to ensure CT difference between the two groups is not the result of axial length differences.

CONCLUSIONS

In conclusion, our study demonstrated a significant association of various choroidal features with CME in RP patients. Specifically, increased subfoveal CT, decreased CVI, and increased TCA, LA, and SA were all noted in RP eyes with versus those without CME. These associations provide insight into the development of CME in RP patients and potential biomarkers of visual prognosis. These choroidal findings indicate the possible importance of choroidal hemodynamic alterations in the development of CME in RP eyes, but further studies evaluating choroidal alterations prospectively and after treatment are warranted. Carbonic anhydrase inhibitors have been used successively to mediate RPE fluid transfer across the outer blood–retinal barrier and this may further support the choroid as an important therapeutic target in eyes with RP and CME.[33,34] Further insight into the mechanisms of disease may facilitate the development of even more efficacious treatment strategies.[35]

References

1. Parmeggiani FS, Sorrentino F, Ponzin D, Barbaro V, Ferrari S, Di Iorio E. Retinitis pigmentosa: genes and disease mechanisms. *Curr Genomics*. 2011;12:238–249.

2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *Lancet*. 2006;368:1795–1809.

3. Piermarocchi S, Segato T, Midena E. Retinal fluorescein leakage in retinitis pigmentosa. *Am J Ophthalmol*. 1986; 102:674–675.

4. Pruett RC. Retinitis pigmentosa: clinical observations and correlations. *Trans Am Ophthalmol Soc*. 1983;81:693–735.

5. Adackapara CA, Sunness JS, Dibernardo CW, Melia BM, Dagnelie G. 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.

6. Hagiwara A, Yamamoto S, Ogata K, et al. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. *Acta Ophthalmol*. 2011;89:e122–e125.

7. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. *Br J Ophthalmol*. 2008;92: 1065–1068.

8. Makiyama Y, Oishi A, Otani A, et al. Prevalence and spatial distribution of cystoid spaces in retinitis pigmentosa: investigation with spectral domain optical coherence tomography. *Retina*. 2014;34:981–988.

9. Triolo G, Pierro L, Parodi MB, et al. Spectral domain optical coherence tomography findings in patients with retinitis pigmentosa. *Ophthalmic Res*. 2013;50:160–164.

10. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. *Br J Ophthalmol*. 2017;101:31–37.

11. Strong SA, Hirji N, Quartilho A, Kalitzeos A, Michaelides M. Retrospective cohort study exploring whether an association exists between spatial distribution of cystoid spaces in cystoid macular oedema secondary to retinitis pigmentosa and response to treatment with carbonic anhydrase inhibitors. *Br J Ophthalmol*. 2019;103:233–237.

12. Govetto A, Lalane RA, Sarraf D, Figueroa MS, Hubschman JP. Insights into epiretinal membranes: presence of ectopic inner foveal layers and a new optical coherence tomography staging scheme. *Am J Ophthalmol*. 2017;175:99–113.

13. Wei X, Ting DSW, Ng WY, Khandelwal N, Agrawal R, Cheung CMG. Choroidal vascularity index: a novel optical coherence tomography based parameter in patients with exudative age-related macular degeneration. *Retina*. 2017;37:1120–1125.

14. Tan R, Agrawal R, Taduru S, Gupta A, Vupparaboina K, Chhablani J. Choroidal vascularity index in retinitis pigmentosa: an OCT study. *Ophthal Surg, Lasers Imag Retin*. 2018; 49:191–197.

15. Giannaccare G, Pellegrini M, Sebastiani S, et al. Choroidal vascularity index quantification in geographic atrophy using binarization of enhanced-depth imaging optical coherence tomographic scans [published online ahead of print January 22, 2019]. *Retina*. doi:10.1097/IAE.0000000000002459.

16. Ayton LN, Guymer RH, Luu CD. Choroidal thickness profiles in retinitis pigmentosa. *Clin Exp Ophthalmol*. 2013;41:396–403.

17. Dhoot DS, Huo S, Yuan A, et al. Evaluation of choroidal thickness in retinitis pigmentosa using enhanced depth imaging optical coherence tomography. *Br J Ophthalmol*. 2013;97:66–69.

18. Adhi M, Regatieri CV, Branchini LA, Zhang JY, Alwassia AA, Duker JS. Analysis of the morphology and vascular layers of the choroid in retinitis pigmentosa using spectral-domain OCT. *Ophthal Surg Lasers Imag Retina*. 2013;44:252–259.

19. Sodi A, Lenzetti C, Murro V, et al. EDI-OCT evaluation of choroidal thickness in retinitis pigmentosa. *Eur J Ophthalmol*. 2018;28:52–57.

20. Langham ME, Kramer T. Decreased choroidal blood flow associated with retinitis pigmentosa. *Eye*. 1990;4:374–381.

21. Falsini B, Anselmi GM, Marangoni D, et al. Subfoveal choroidal blood flow and central retinal function in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2011;52:1064–1069.

22. Zhang Y, Harrison JM, Nateras OSE, Chalfin S, Duong TQ. Decreased retinal-choroidal blood flow in retinitis pigmentosa as measured by MRI. *Doc Ophthalmol*. 2013;126:187–197.

23. Murakami Y, Ikeda Y, Akiyama M, et al. Correlation between macular blood flow and central visual sensitivity in retinitis pigmentosa. *Acta Ophthalmol*. 2015;93:e644–e648.

24. Brandl C, Helbig H, Gamulescu MA. Choroidal thickness measurements during central serous chorioretinopathy treatment. *Int Ophthalmol*. 2014;34:7–13.

25. ten Berge JC, Fazil Z, van den Born I, et al. Intraocular cytokine profile and autoimmune reactions in retinitis pigmentosa, age-related macular degeneration, glaucoma and cataract. *Acta Ophthalmol*. 2019;97:185–192.

26. Saraiva VS, Sallum JMF, Farah ME. Treatment of cystoid macular edema related to retinitis pigmentosa with intravitreal triamcinolone acetonide. *Ophthalmic Surg Lasers Imag*. 2003;34:398–400.

27. Scorolli L, Morara M, Meduri A, et al. Treatment of cystoid macular edema in retinitis pigmentosa with intravitreal triamcinolone. *Arch Ophthalmol*. 2007;125:759–764.

28. Srour M, Querques G, Leveziel N, et al. Intravitreal dexamethasone implant (Ozurdex) for macular edema secondary to retinitis pigmentosa. *Graefe's Arch Clin Exp Ophthalmol*. 2013;251:1501–1506.

29. Sudhalkar A, Kodjikian L, Borse N. Intravitreal dexamethasone implant for recalcitrant cystoid macular edema secondary to retinitis pigmentosa: a pilot study. *Graefe's Arch Clin Exp Ophthalmol*. 2017;255:1369–1374.

30. Saatci AO, Selver OB, Seymenoglu G, Yaman A. Bilateral intravitreal dexamethasone implant for retinitis pigmentosa-related macular edema. *Case Rep Ophthalmol*. 2013;4:53–58.

31. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. *Br J Ophthalmol*. 2017;101:31–37.

32. Barañano AE, Keane PA, Ruiz-Garcia H, Walsh AC, Sadda SR. Impact of scanning density on spectral domain optical coherence tomography assessments in neovascular age-related macular degeneration. *Acta Ophthalmol*. 2012;90: e274–e280.

33. Bakthavatchalam M, Lai FHP, Rong SS, Ng DS, Brelen ME. Treatment of cystoid macular edema secondary to retinitis pigmentosa: a systematic review. *Surv Ophthalmol*. 2018;63: 329339.

34. Huang Q, Chen R, Lin X, Xiang Z. Efficacy of carbonic anhydrase inhibitors in management of cystoid macular edema in retinitis pigmentosa: a meta-analysis. *PLoS One*. 2017;12:e0186180.

35. Moldow B, Sander B, Larsen M, et al. The effect of acetazolamide on passive and active transport of fluorescein across the blood-retina barrier in retinitis pigmentosa complicated by macular oedema. *Graefes Arch Clin Exp Ophthalmol*. 1998;236:881–889.