The spectrum of central serous chorioretinopathy: clinical characteristics, genetic associations and outcome of treatment

Mohabati, D.

Chapter 2.3

Clinical characteristics and outcome of posterior cystoid macular degeneration in chronic central serous chorioretinopathy

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ABSTRACT

Purpose: To assess clinical characteristics and visual outcome in chronic central serous chorioretinopthy (cCSC) patients with posterior cystoid retinal degeneration (PCRD).

Methods: Patients' medical records were reviewed retrospectively in 62 cases (83 eyes, mean age = 59 years, 88% male). Data were collected at CSC diagnosis, at PCRD manifestation, and at final visit. All treatment modalities were reviewed. Main Outcome measures were treatment efficacy in achieving PCRD resolution, and final best corrected visual acuity (BCVA).

Results: In 63 eyes (76%) subretinal fluid (SRF) was present at first PCRD manifestation, while fluorescein angiography showed active focal or diffuse leakage in 65 eyes (78%). Seventy-six eyes (81%) received treatment, and PCRD had resolved completely in 31 eyes (37%) at the final visit. Photodynamic therapy (PDT) was most successful in achieving a complete PCRD resolution. BCVA did not improve, even after complete PCRD resolution (mean baseline BCVA = 69 ±19, and mean final BCVA = 67 ±20 ETDRS letters (20/40 and 20/50 in Snellen equivalent respectively), $P = 0.354$).

Conclusions: PCRD is a relatively common finding in cCSC, which is often accompanied by active SRF leakage. Treatment may be beneficial to stop the SRF leakage component, but is less likely to result in a complete PCRD resolution and/or a BCVA improvement.

INTRODUCTION

Chronic central serous chorioretinopathy (cCSC) is characterized by a persistent or intermittent subretinal serous leakage, presence of a serous neuroretinal detachment, and diffuse irregularities and atrophy of the retinal pigment epithelium (RPE).[1] Patients with cCSC may have a decreased vision-related quality of life and the disease is associated with progressive vision loss.[2, 3] Variability exists in the anatomical abnormalities among patients with cCSC, which may reflect the progression or stage of the disease.[4] Besides chronic subretinal fluid (SRF) leakage, most cCSC patients show more extensive and/or multifocal RPE detachments and atrophic RPE changes in comparison to acute, self-limiting CSC.[5] In contrast, acute central serous chorioretinopathy (aCSC) is characterized by an acute onset of a neurosensory detachment that often shows spontaneous resolution with a full recovery of vision, with little atrophic RPE changes.

A considerable number of cCSC patients show an extensive and presumably severe disease phenotype with diffuse atrophic RPE alterations (DARA), numerous 'hot spots' of leakage on fluorescein angiography (FA), subretinal fibrin deposits, and/or occasionally posterior cystoid retinal degeneration (PCRD) at first presentation.[6-10] These severe cCSC cases seem to form a distinct entity within the spectrum of CSC with the worst visual prognosis.[6] PCRD, first described by Piccolino et al. in 2008,[10] in particular was shown to be present in up to 35% of severe cCSC cases.[6]

In contrast to cystoid macular edema (CME), which is generally associated with vascular hyperpermeability and active leakage, presence of PCRD as seen in cCSC may have a more degenerative origin related to the primary choroidopathy and RPE dysfunction.[9] For example, in contrast to retinal vascular diseases with secondary CME, there seems to be no vascular endothelial growth factor (VEGF) driven mechanism involved in PCRD, as anti-VEGF medication was shown to be ineffective in PCRD.[11] The recently described entity of "peripapillary pachychoroid syndrome", which is characterized by peripapillary intraretinal cystoid changes, belongs to the pachychoroid disease spectrum just like CSC, with involvement of hyperpermeable choroidal vessels, that do not respond to intravitreal anti-VEGF either.[12]

Little is known about the etiology of PCRD. The development of PCRD may be explained at least partially by the hyperpermeability of choroidal vessels and the dysfunctional outer blood-retina barrier of the RPE, which is a characteristic of cCSC and other pachychoroid associated disease, even though PCRD can occur in absence of active SRF leakage.[9, 10] As PCRD has been associated with a severely reduced visual acuity, resolution of PCRD is desirable.[9, 11] However, at present only a few relatively small studies are available on the clinical characteristics and treatment of PCRD in cCSC.[9-11, 13, 14]

The purpose of the present study is to describe the clinical characteristics on multimodal imaging in cCSC patients with PCRD, to review the outcome of treatments, especially for PDT, and to assess the final visual outcome.

MATERIALS AND METHODS

Patients were included for this study from three Dutch tertiary referral centers: the Department of Ophthalmology at Leiden University Medical Center (Leiden, the Netherlands), the Rotterdam Eye Hospital (Rotterdam, the Netherlands), and Radboud University Medical Center (Nijmegen, the Netherlands). This study was approved by the respective institutional review boards at the participating centers and was performed in accordance with the tenets of the Declaration of Helsinki.

Patients were included when visual complaints existed for over 6 months. Chronic CSC was defined according to a previous definition: evidence of persistent SRF for at least 3 months, RPE window defects and at least one "hot spot" of focal leakage on FA, and corresponding hyperfluorescent zones on indocyanine green angiography (ICGA) when available.[3] All cases had cCSC-associated PCRD at some point during follow-up. PCRD was recognized on OCT according to a previous definition by Piccolino et al, as intraretinal spaces separated by reflective tissue from the RPE which were detected within the temporal vascular arcades.[10] Patients were excluded when intraretinal cystoid abnormalities were caused by other retinal or choroidal vascular abnormalities, such as (secondary) choroidal neovascularization (CNV). We also excluded patients with cystoid degeneration caused by trauma, evident epiretinal membrane, retinoschisis, and degeneration due to previous thermal laser treatment.

The medical charts were evaluated and information was collected concerning general medical background and steroid use, as well as diagnosis-related data including: date of CSC diagnosis, date of PCRD determination, fellow eye diagnosis, follow-up duration, treatment modalities and treatment effect, and best corrected visual acuity (BCVA) at diagnosis and at final visit. BCVA which was originally assessed with a Snellen chart was converted to early treatment of diabetic retinopathy study (ETDRS) letters for further analysis.[15] The location of PCRD was assessed and reported as: adjacent to the temporal side of the optic disc (peripapillary region), between the optic disc and the foveal region without peripapillary or foveal involvement (papillomacular region), covering the fovea, and elsewhere in the posterior pole. Treatment was considered effective only when there was a complete resolution of SRF and PCRD.

Clinical examinations

Subjects were included when ophthalmological and multimodal imaging examinations were available at diagnosis and during follow-up. Minimum available multimodal imaging examination included either time-domain OCT (Cirrus HD-OCT, Carl Zeiss Meditec or OCT-HS100, Canon Inc., Tokyo, Japan) or spectral-domain OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) at the moment of PCRD manifestation and at final visit; and a FA (Topcon Corp., Spectralis HRA+OCT, or Carl Zeiss Meditec) after PCRD manifestation. ICGA (Topcon Corp., Heidelberg Spectralis HRA+OCT, or Carl Zeiss Meditec) was performed when a CNV had to be ruled out. The following characteristics were determined on FA imaging: presence of active leakage, type of leakage (focal vs. diffuse), and the area of DARA associated with PCRD. The extent of DARA area was quantified by using available caliper measurement tools on FA equipment and expressed in number of optic disc diameters (DD).

Statistical analysis

Statistical analyses were performed using IBM SPSS software for Windows, version 23 (IBM Corp., Armonk, NY, USA). Continuous numerical data were compared using a paired or unpaired Student's *t*-test. Categorical data were analyzed using a chi-square test. A COX proportional hazard model was computed to predict the effect size of multiple clinical and patient characteristics on complete resolution of PCRD. Hazard ratios (HR) and 95% confidence intervals (CI) are reported for each risk factor according to an univariate and a multivariate analysis. For all tests, a *P*-value of <0.05 was considered significant.

RESULTS

In total, 62 patients (83 eyes, 73 (88%) male) were included for analysis (Table 1). The mean age at first documented PCRD manifestation was 59 years (range: 36-80 years). The mean time between cCSC diagnosis and PCRD manifestation was 61 months (range: 0-347 months). Twenty-one cases had bilateral PCRD. General medical background in the study cases was as follows: cardiovascular (coronary artery obstruction, hypertension, transient ischemic attack, etc.) in 26 cases (31%), diabetes mellitus without diabetic retinopathy in 8 cases (10%), and autoimmune disorders in 6 cases (7%). The baseline demographic characteristics are summarized in Table 2.

Table 1 Patient Selection

	Exclusion due to	Patients (Eyes)
cCSC eyes evaluated for the study		83 (106)*
	PCV	1 (1)
	AMD	1 (1)
	Diabetic macular edema	1 (1)
	Paraneoplastic syndrome	1 (1)
	Choroidal naevus	1 (1)
	Central retinal vein occlusion	1 (1)
	Retinoschisis	1 (1)
	Occult CNV	8 (10)
	PCRD induced by thermal laser	6 (6)
cCSC eyes included in the study		62 (83)†

*In a cohort including 1811 CSC patients, 83 patients were identified with a chronic disease and PCRD on OCT imaging.
†Twenty-one cases had bilateral and 41 cases had unilateral PCRD. 18 fellow eyes in unilateral cases showed active CSC, 7 fellow eyes had signs of CSC without active leakage on FA, 10 fellow eyes had mild RPE changes compatible with pachychoroid pigment epitheliopathy without active CSC, and 3 fellow eyes were completely normal. Three fellow eyes had other diseases (1 CNV, 1 retinal venous obstruction, 1 uveitis).
AMD, age-related macular degeneration; CNV, choroidal neovascularization; PCV, polypoidal choroidal vasculopathy.

Table 2 Patient demographics and clinical features

Features	Value
Eyes (Patients)	83 (62)
Male gender, No. (%)	73 (88)
Age at CSC diagnosis in years, mean ± SD	54 ± 12
Age at PCRD presentation in years, mean ± SD	59 ± 10
Caucasian, No. (%)	68 (82)
Recent steroid use, No. (%)	20 (24)
BCVA at diagnosis, in ETDRS letters, mean ± SD	68 ± 19* (20/40 in Snellen equivalent)
Time from CSC diagnosis until PCRD presentation in months (range)	61 (0-347)
Mean follow-up duration form CSC diagnosis in months (range)	95 (4-373)

*Two patients (2 eyes) could only recognize hand movements
ETDRS, Early Treatment Diabetic Retinopathy Study

Characteristics on OCT imaging

In 63 eyes (76%), active SRF leakage was present on OCT at first PCRD manifestation (Table 3). In 45 eyes (54%), PCRD was overlying a dome-shaped (15 eyes, 18%) or a flat irregular RPE detachment (30 eyes, 36%) (Table 3). In most cases PCRD was present in the peripapillary region (32 eyes, 39%) or in the papillomacular region (35 eyes, 30%), while the fovea was involved in 15 eyes (18%). Eleven eyes (13%) showed PCRD outside these regions and without foveal involvement (Figure 1). PCRD could be localized in the inner nuclear layer (INL) of the retina, the outer nuclear layer (ONL), the ganglion cell layer, but was most frequently observed to be present in multiple layers as summarize in Table 3. In 24 eyes (29%) large cystoid changes were observed which penetrated multiple retinal layers (Figure 2, F and H).

At final available visit, on average 35 ±29 months after the first PCRD manifestation, PCRD had completely resolved in 31 eyes (37%). PCRD was reduced in 17 eyes (21%), remained unchanged in 30 eyes (36%), and showed an increase in 5 eyes (6%) as compared to baseline. SRF in this cohort had resolved completely in 68 eyes (82%) at final visit.

Characteristics on FA imaging

The first FA imaging after PCRD manifestation showed active (multi)focal fluorescein leakage in 29 eyes (35%) (on average: 2.4 focal 'hot spots' of leakage, range: 1-7 'hot spots'), while 36 eyes (43%) showed more diffuse leakage, attributed to SRF. In 18 eyes (22%), there was no fluorescein leakage (Table 3). In 50 eyes (60%), the area of leakage was associated with the location of PCRD. The mean cumulative area of DARA on FA was 7.1 DD (range: 0-20 DD), and in 69 eyes (83%) DARA included the location of PCRD (Table 3).

Treatment outcome and PCRD resolution

Among all eyes included in this study, 27 eyes (32%) had previous treatment for cCSC prior to PCRD manifestation, while 56 eyes (68%) were treatment-naive (Table 4). Sixty-seven study eyes (81%) were treated after PCRD manifestation, of which 21 eyes (21/67, 31%) had previously received treatment prior to PCRD manifestation. Out of a total of 67 treated eyes, 36 eyes (54%) had a complete resolution of PCRD. Complete resolution occurred after a single treatment in 27 eyes (33%) (of which PDT in 25 eyes, 30%), and after multiple treatments in 7 eyes (9%). In 2 eyes (2%), PCRD resolved independent of treatment (Figure 2, Table 4, and Table 5). Among cases with foveal involvement of PCRD which were treated (14/67, 21%), 8 eyes (8/14, 57%) had a complete PCRD resolution. Forty-nine study eyes (49/67, 73%) had received PDT as first treatment option, among which 23 eyes (23/49, 47%) showed a complete resolution of PCRD after this first PDT. Recurrence of PCRD was observed in 4 eyes (4/23, 17%) with an initial PCRD resolution after first successful PDT treatment.

Table 3 Findings on multimodal imaging in patients with cCSC and secondary PCRD manifestation

Imaging	Features		No. of eyes (%/SD)
OCT at first PCRD manifestation	SRF	Subfoveal	52 (63)
		Peripheral	11 (13)
		No SRF	20 (24)
	PCRD association with PD	Dome-shaped	15 (18)
		Irregular flat	30 (36)
		No PD association	38 (46)
	PCRD location in posterior pole	Peripapillary region	32 (39)
		Papillomacular region	35 (30)
		Foveal	15 (18)
		Other *	11 (13)
	PCRD location in retinal layers †	ONL	16 (19)
		INL, ONL	61 (74)
		INL, OPL, ONL	5 (6)
		GCL, INL, ONL	1 (1)
OCT at final visit	SRF	Subfoveal	9 (11)
		Peripheral	6 (7)
		Complete resolution	68 (82)
	Presence of PCRD	Complete resolution	31 (37)
		Reduced	17 (21)
		Increased	5 (6)
		Unchanged	30 (36)
FA after PCRD manifestation	Fluorescein leakage	Focal	29 (35)
		Diffuse	36 (43)
		No leakage	18 (22)
	Leakage associated with PCRD		50 (60)
	Area of RPE atrophy in DD		7.1 (SD = 4)
	RPE atrophy associated with PCRD		69 (83)

* Other PCRD locations without foveal involvement included: 5 eyes (6%) temporal and nasal to fovea, 3 eyes (4%) temporal to fovea, 2 eyes (2%) inferior to fovea, 1 eye (1%) in papillomacular region and temporal to fovea.
† The cystoid changes were larger and more prominent in the ONL in 70 eyes (84%), in 9 eyes (11%) in the INL, and in 4 eyes (5%) cystoid changes were equally prominent in the INL and ONL.
DD, optic disc diameter; ETDRS, Early Treatment Diabetic Retinopathy Study; GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; PD, RPE detachment.

Table 4 Treatment strategies and treatment efficacy in eyes with cCSC and secondary PCRD

Treatment		Eyes (%/range)
Treatments before PCRD manifestation	Previously treated eyes	27 (32)
	Mean number of treatments	2 (range = 1-8)
	Previously untreated eyes	56 (68)
Treatments after PCRD manifestation	Treated eyes	67 (81%)
	Mean number of treatments	2 (range = 1-10)
	Untreated eyes	16 (19)
Treatment effect after PCRD manifestation	Resolution after mono treatment	27 (33)
	Resolution after multiple treatments	7 (9)
	Resolution independent of treatment	2 (2)
	No resolution despite treatment	31 (37)
	Not treated and no resolution	16 (19)

Table 5 Frequency of all applied treatments in eyes with cCSC with secondary PCRD manifestation

Treatment	Specifications	Eyes (%/range)
PDT	Total number	82 (59)
	Half -dose PDT	56 (68)
	Half-time PDT	10 (12)
	Half-fluency PDT	2 (3)
	Full-dose PDT	5 (6)
	Unknown settings	9 (11)
	Successful treatment*	32 (39)
SML	Total number	25 (18)
	Successful treatment*	1 (4)
Conventional thermal laser	Total number	18 (13)
	Successful treatment*	1 (6)
Anti-VEGF injections	Total number	14 (10)
	Bevacizumab	10 (72)
	Aflibercept	3 (21)
	Combination	1 (7)
	Mean number of injections	2.9 (range = 2-6)
	Successful treatment*	2 (14)

*Successful treatment = complete resolution of PCRD
VEGF, vascular endothelial growth factor; SML, subthreshold micropulse diode laser.

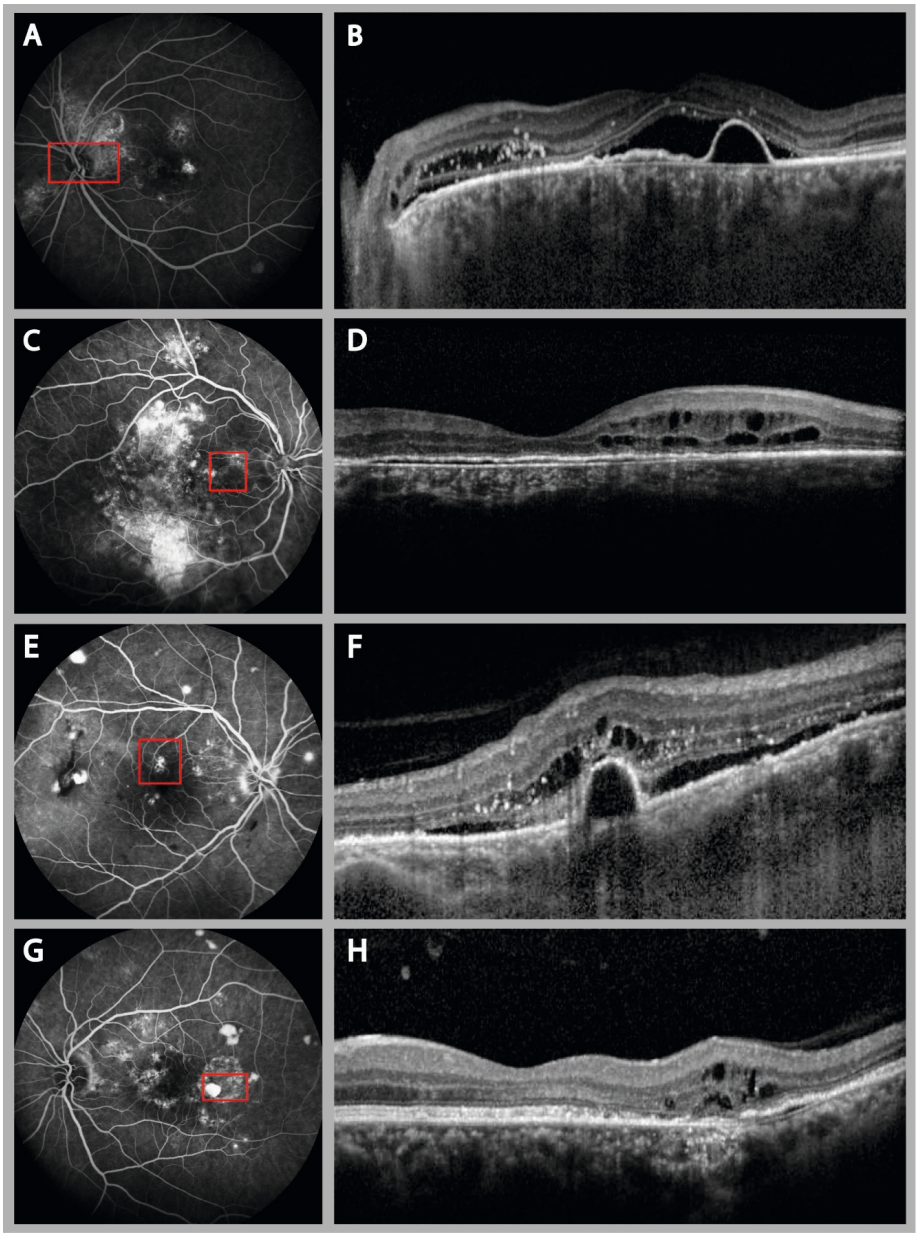

Figure 1. Fluorescein angiography (FA) (A, C, E, G) and optical coherence tomography (B, D, F, H) imaging in four cases of chronic central serous chorioretinopathy (cCSC) with secondary posterior cystoid retinal degeneration (PCRD). Figure depicts four locations of PCRD lesions in posterior pole, including the peripapillary region (A, B), the papillomacular region without peripapillary or foveal involvement (C, D), the foveal region (E, F), and outside papillomacular intersection, in this case temporal to the fovea (G, H). The red square in each FA imaging illustrates the distribution area of cystoid lesions. The cystoid lesions were most prominently located in the outer nuclear layer (ONL) (B, F) of the retina, and to a lesser degree also in the inner nuclear layer (INL) (D, H).

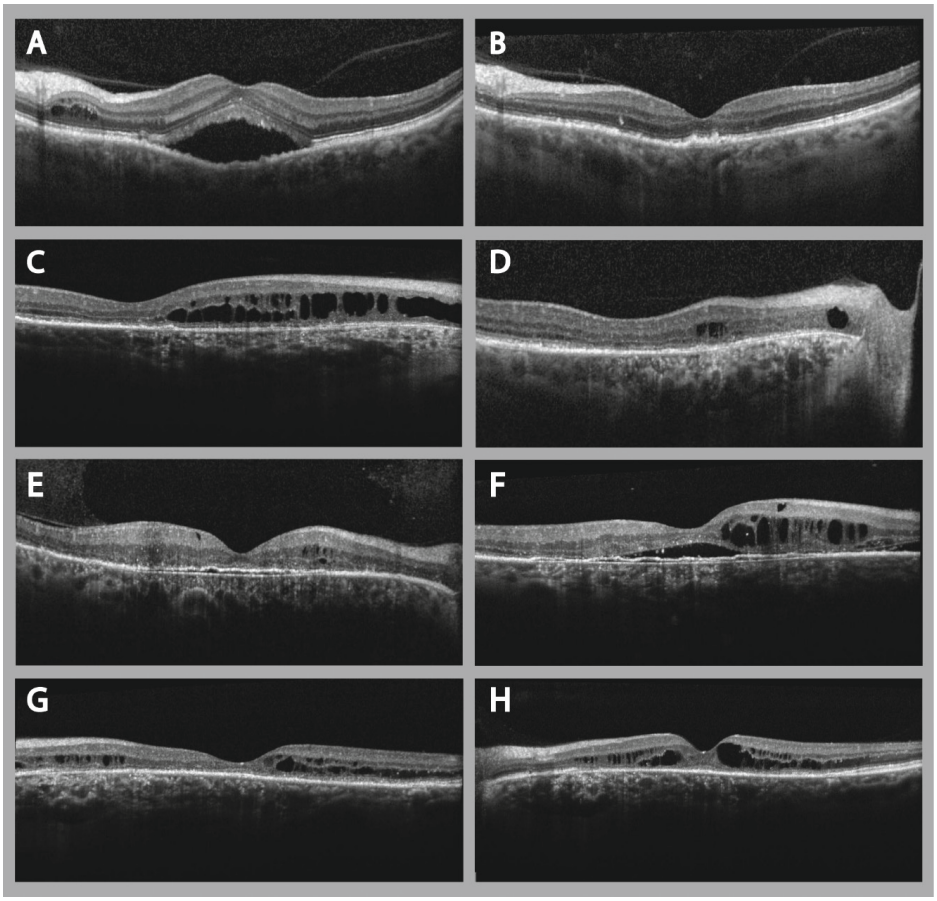

Figure 2. Optical coherence tomography imaging showing variable treatment response in four cases of chronic central serous chorioretinopathy (cCSC) with secondary posterior cystoid retinal degeneration (PCRD) (A-H). Four patterns of PCRD progression are illustrated during follow-up and until the final available visit. Complete resolution of PCRD and subretinal fluid (SRF) occurred in the left eye of a 62-year-old male patient, after one treatment with half-dose photodynamic therapy (PDT) (A and B). PCRD at final visit had decreased but not resolved in the right eye of a 67-year-old male patient, who was treated with three half-dose PDT sessions and two intravitreal injections of bevacizumab (C and D). In a 62-year-old male patient (E and F), PCRD showed an increase in volume in the right eye, despite multiple treatments (3 PDT treatments, 1 focal thermal laser, 1 subthreshold micropulse diode laser). The macula of a 42-year-old male, who was treated with focal thermal laser and 3 PDT treatments showed fluctuations of PCRD without a clear response to treatment (G and H).

BCVA Outcome

The mean baseline BCVA in the entire group was 69 ±19 ETDRS letters (20/40 in Snellen equivalent), reducing slightly to 67 ±20 ETDRS letter (20/50 in Snellen equivalent) at final visit (*P* = 0.354). Final BCVA outcome did not differ significantly among eyes with and without PCRD resolution (64 ±23 and 67 ±20 ETDRS letters respectively (20/50 and 20/40 in Snellen equivalent respectively), *P* = 0.499). The follow-up duration after PCRD manifestation was comparable in eyes with and without complete PCRD resolution (36 ±32 and 32 ±23 months respectively, *P* = 0.515). BCVA improvement after a complete PCRD resolution was variable depending on the location of PCRD (Table 6).

Table 6 Visual outcome in patient with cCSC and secondary PCRD during follow-up.

Groups	n	Baseline BCVA ±SD in ETDRS letters (Snellen equivalent)	Final BCVA ±SD in ETDRS letters (Snellen equivalent)	P
Entire group	83	69 ±19 (20/40)	67 ±20 (20/50)	0.354
Eyes with resolved PCRD	30	64 ±22 (20/50)	64 ±23(20/50)	0.083
Foveal location	6	46 ±24 (20/125)	47 ±25 (20/125)	0.691
Peripapillary location	6	77 ±10 (20/32)	81 ±5 (20/25)	0.524
Papillomacular location	13	62 ±23 (20/63)	68 ±21 (20/40)	**0.039**
Other locations	3	78 ±8 (20/25)	74 ±9 (20/25)	0.520
Eyes with no PCRD resolution	49	72 ±16 (20/40)	67 ±20 (20/50)	0.087

ETDRS, Early Treatment Diabetic Retinopathy Study.

Factors influencing PCRD resolution

Univariate COX regression analysis indicated that presence of SRF as a sign of active leakage at first PCRD manifestation (HR = 4.09, CI = 1.23-13.54, *P* = 0.021), and older age at initial cCSC diagnosis (HR = 1.05, CI = 1.02-1.09, *P* = 0.004), increased the probability (hazard) of PCRD resolution. On the other hand, a larger surface of DARA (HR = 0.86, CI = 0.77-0.96, *P* = 0.005) decreased the probability (hazard) of PCRD resolution (Table 7). After performing a multivariate analysis of hazard ratios, SRF leakage at first PCRD manifestation (HR = 2.47, CI = 0.65-9.45, *P* = 0.186), and the size of DARA surface (HR = 0.90, CI = 0.81-1.01, *P* = 0.065), although still indicative, lost statistical significance as predictive factors for PCRD resolution. Older age at initial cCSC diagnosis (HR = 1.05, CI = 1.01-1.09, *P* = 0.025) remained a statistically significant predictor (Table 7).

Table 7 Hazard ratios of factors predicting complete resolution of PCRD in cCSC patients

Characteristics	Univariate analysis*		Multivariate analysis*	
	HR (95% CI)	P	HR (95% CI)	P
Male gender	1.02 (0.36-2.86)	0.967	1.16 (0.36-3.71)	0.807
Caucasian ethnicity	1.60 (0.70-3.65)	0.262	0.39 (0.14-1.07)	0.068
Steroid use	1.08 (0.47-2.52)	0.852	0.64 (0.22-1.88)	0.420
SRF leakage at PCRD manifestation	4.09 (1.23-13.54)	**0.021**	2.47 (0.65-9.45)	0.186
SRF leakage under PCRD	0.46 (0.62-2.83)	0.464	1.35 (0.52-3.56)	0.540
Foveal location of PCRD	2.24 (0.98-5.12)	0.055	1.78 (0.73-4.32)	0.205
DARA surface	0.86 (0.77-0.96)	**0.005**	0.90 (0.81-1.01)	0.065
Age at cCSC diagnosis	1.05 (1.02-1.09)	**0.004**	1.05 (1.01-1.09)	**0.025**

* The overall model was statistically significant with a Chi-square *P* of 0.003
DARA, diffuse atrophic RPE alteration.

DISCUSSION

PCRD is a common feature in patients with advanced cCSC and can be viewed upon as a sign of more severe disease.[6, 9] In the present study, most PCRD cases also showed active leakage on FA, serous neurosensory detachment, and associated RPE atrophy. While treatment led to a complete resolution of SRF in 82% of the cases, less than half of the cases showed resolution of PCRD. Interestingly, the probability (hazard) of PCRD resolution was most strongly associated with coexistence of active SRF leakage. BCVA outcome was relatively poor as compared to uncomplicated cCSC and did not change during follow-up, even in cases with PCRD resolution.

The pathogenesis of PCRD is unclear. A complex hemostatic equilibrium maintains a dehydrated state, and thereby the transparency and functionality of the retina.[16] An imbalance in fluid entry and/or drainage can therefore lead to retinal edema.[16] While the inner blood-retinal barrier prevents serum passage by the act of the intercellular junctions of the endothelial cells and transendothelial transport, the outer-retinal barrier regulates fluid drainage through the intercellular tight junction complex of the RPE cells and the external limiting membrane (ELM).[16-18] Dysfunctionality of these natural barriers contributes to an increased fluid entry in the retina or subretinal space. Leukostasis, which may arise as a result of local ischemia or an inflammatory process, was suggested as a possible cause of reduced capillary flow in the deep retinal plexus in the sites of retinal edema.[17] This may in turn prevent a normal fluid drainage by the deep capillary plexus.[17] Furthermore, an impairment in the natural pumping function of the RPE cells and the Müller cells is suggested to contribute to insufficient fluid drainage, and subsequent subretinal and intraretinal fluid accumulation.[16, 17, 19] This loss of pumping function may occur through structural cell damage, cell disorganization, and cell death by atrophy.[19] All these factors contribute to the

appearance of cystoid macular edema. Cystoid maculopathy is most frequently associated with retinal vasculopathies.[20] However, cystoid maculopathies may also occur in diseases originating in the choroid, such as chronic CSC.[20, 21] The mechanism of PCRD in cCSC may be predominantly related to outer blood-retinal barrier breakdown and decreased active fluid drainage, which are both the result of a dysfunctional RPE layer.[21, 22] Our observations in the present study support this theory, as presence of DARA directly underneath PCRD was observed in 83% of our cases. Previous studies on cCSC-associated PCRD also reported that the largest cystoid spaces were often close to the atrophic RPE lesions.[10, 12]

Spontaneous resolution of PCRD in our cohort was rare, and treatment was therefore often used. Currently no standard treatment exists for cCSC-associated PCRD, and small case series have reported inconsistent results.[11-13, 21] PCRD in our cohort was accompanied by active SRF leakage in most cases, and 81% of these eyes received treatment. A large variety in treatment strategies and treatment frequency was used in the present study. Therefore, evaluating treatment efficacy in PCRD cases was challenging. Nevertheless, 54% of the cases showed a complete resolution of PCRD, often after a single PDT treatment with reduced settings for the presence of SRF. Overall, PDT was the most frequently used treatment with the relatively highest rate of complete PCRD resolution after treatment (39%) compared to the other used treatments. This rate of complete PCRD resolution after PDT is relatively high in comparison to previous smaller studies on PCRD.[14, 23] Still, the success rate for PDT on resolution of PCRD fluid, which is located intraretinally, is considerably lower than the reported success rates of 67-100% in resolving SRF in cCSC.[23-26] PCRD thus appears to be more therapy-resistant than SRF in cCSC. Also, BCVA in our PCRD cases showed no overall changes during follow-up even after PCRD resolution, presumably due to irreversible retinal cell loss. Treatment of cCSC before the occurrence of PCRD may therefore be advisable.

We showed that cases with active SRF leakage in conjunction with PCRD manifestation had a higher probability of PCRD resolution after treatment (often PDT). This indicates that PCRD is at least partly dependent on the underlying active choroidal/RPE leakage process, and therefore may resolve well when this process becomes more quiescent after treatment. The group of PCRD without SRF leakage was less likely to show resolution after treatment, indicating that this subgroup is less dependent on underlying choroidal/RPE leakage and more degenerative in nature. These observations suggest that the mechanism

in PCRD manifestation consists of a variable contribution of two components: 1) a homeostatic fluid imbalance component, leading to intraretinal fluid (PCRD) and SRF. This component appears more likely to respond to (PDT) treatment. 2) a degenerative component, leading to tissue loss and intraretinal cystoid cavity formation. This component is less likely to respond to treatment. A degenerative loss of tissue, especially loss of Müller cells, have been previously suggested in the occurrence of macular edema.[19] Müller cells may die presumably due to intracytoplasmic edema, and leave a cystoid space behind.[19] A similar process may explain the degenerative component of PCRD in our study.

In the current study PCRD was located peripapillary in more than a third of patients. This pattern of extra-foveal localization, which was also observed in previous studies,[10, 12] may distinguish PCRD from macular edema in the context of other retinal vasculature abnormalities.[20] The recently described clinical picture of peripapillary pachychoroid syndrome (PPS), which like PCRD is also characterized by peripapillary intraretinal cystoid changes in association with hyperpermeable choroidal vessels, shares many features that we also observed within the spectrum of cCSC with PCRD.[12] SRF leakage for instance, was frequently observed in both PPS cases (74%) and in our cohort (76%).[12] Atrophic RPE associated with cystoid changes were observed in 100% of PPS cases,[12] while PCRD associated DARA was present in 83% of our cases. Due to the similarities, PPS may be regarded as a peripapillary form of cCSC with PCRD. However, unlike PPS cases, BCVA outcome in our PCRD cases was poor, and showed no overall changes during follow-up even after PCRD resolution. This lack of reversible visual acuity is another characteristic of PCRD in comparison with other forms of retinal edema or PPS, where BCVA may improve more significantly once edema is resolved.[11, 12]

In this study, some of our observations may have been subject to bias due to the retrospective study design and limitations in availability of certain data. For instance, the follow-up duration and treatment regimens were variable. Also, no suitable control group was available in order to compare treatment outcome (especially after PDT treatment) in cCSC cases with and without PCRD manifestation. Nevertheless, important conclusions can still be drawn. Our study suggests that PCRD in cCSC is a sign of retinal cell loss, as treatment was less successful in resolving PCRD compared to SRF resolution, and since final BCVA outcome remained poor. Further studies are needed to assess if earlier treatment of cCSC may prevent the development of PCRD and the associated irreversible vision loss, and to assess the best treatment options for PCRD.

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Conflict of interest

The authors report no conflicts of interest in this work.

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