

Photodynamic Therapy for Focal Retinal Pigment Epithelial Leaks Secondary to Central Serous Chorioretinopathy

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Purpose: To report the use of photodynamic therapy with verteporfin as a treatment for patients with focal retinal pigment epithelial leaks secondary to central serous chorioretinopathy (CSC).

Design: Noncomparative, nonrandomized, retrospective interventional case series.

Participants: Nine eyes of 9 symptomatic patients with acute focal retinal pigment epithelial leaks secondary to CSC, confirmed with fluorescein angiography, evaluated at 1 of 3 referral retina practices.

Methods: Patients were treated with photodynamic therapy using verteporfin. Best-corrected visual acuity (VA) was recorded at presentation and follow-up visits.

Main Outcome Measures: Resolution of neurosensory detachment, status of fluorescein leakage, and VA.

Results: Neurosensory detachment and fluorescein leakage resolved in all patients within 1 month. Visual acuity improved from 1 to 6 lines in 7 eyes and remained unchanged in 2. At 6 months, there was a statistically significant improvement in mean VA ($P = 0.012$, Wilcoxon signed ranks test), and mean VA improved from 20/80 to 20/40. No patient lost vision or suffered any treatment-related complications.

Conclusion: The treatment of acute CSC with photodynamic therapy may result in prompt resolution of neurosensory detachment and fluorescein leakage, which can be associated with rapidly improved vision. Although this case series is limited in follow-up and number of patients, the encouraging results and lack of visually significant complications suggest that further investigation is warranted. *Ophthalmology* 2005;112:2088–2094 © 2005 by the American Academy of Ophthalmology.

Central serous chorioretinopathy (CSC) is a well-characterized disorder leading to serous neurosensory elevation of the central macula. The acute form of the disease is associated with focal leakage at the level of the retinal pigment epithelium (RPE) demonstrated with fluorescein angiography (FA).^{1–3} Fortunately, the disorder is self-limited in the majority of patients, who also regain excellent vision. Occasionally, the neurosensory detachment persists and leads to pigment epithelial and

photoreceptor damage with visual impairment. A thermal laser applied to the focal RPE leak has been shown to decrease the duration of disease in patients with acute CSC⁴; however, it may be associated with side effects, including stimulation of choroidal neovascularization, localized scotoma, and enlargement of the pigment epithelial atrophic scar over time.^{5–8} Chronic cases of CSC may yield further complications such as diffuse retinal pigment epithelial decompensation, subretinal precipitates,^{9,10} descending atrophic tracts,¹¹ dependent retinal detachments (RDs), cystoid macular edema, cystoid macular degeneration,¹² secondary choroidal neovascularization,⁶ and fibrous scarring. Although scatter thermal laser photocoagulation may shorten the duration of macular detachment in chronic CSC, the reported cases are few and lack long-term follow-up.⁴

The advent of indocyanine green angiography provided a means to identify CSC in quiescent or chronic stages when FA did not image focal RPE leakage. Indocyanine green angiography revealed multiple areas of choroidal vascular hyperpermeability in midstages of the study, suggesting a more generalized RPE or choroidal vascular disturbance.^{13–20}

Photodynamic therapy has been shown to reduce visual loss in patients with choroidal neovascularization secondary to age-related macular degeneration (AMD) and pathologic myopia.^{21,22} Extrapolating from these large clinical trials, retina specialists have also reported using photodynamic

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therapy to treat choroidal neovascularization secondary to CSC successfully.^{23–25} Unlike laser photocoagulation, photodynamic therapy works by selectively occluding choroidal neovascularization and superficial choroidal vessels with minimal effects on the overlying retina as well as deeper choroidal layers.^{26–29} Although choroidal neovascularization is not typically present in CSC, alteration of choriocapillaris blood flow by verteporfin may reverse or prevent fluid leakage beneath and beyond the RPE in patients with chronic CSC. Recently, researchers associated with several case series have reported favorable results when treating chronic CSC with indocyanine green–guided photodynamic therapy using verteporfin.^{30–34} Photodynamic therapy has also been performed for chronic CSC using fluorescein guidance with positive results.^{35,36}

Patients with acute CSC and focal leaks immediately under or adjacent to the fovea are seldom advised to have thermal laser because of potential visual disturbances, including central scotomata and the risk of associated choroidal neovascularization. On the other hand, chronic detachment of the fovea may lead to irreversible structural damage to the retina and permanent visual dysfunction. The purpose of this article is to report the use of photodynamic therapy as a treatment for patients with CSC and focal RPE leaks that are identified with FA.

Materials and Methods

Patients were evaluated for the presence of acute CSC with visual disturbance, defined as idiopathic neurosensory elevation with complaints of vision changes in the presence of focal leaks at the level of the RPE on FA. Focal RPE leaks were characterized by discrete pinpoint areas of hyperfluorescence identified on early FA frames that increased in size and intensity throughout later frames. Each patient underwent best-corrected visual acuity (VA) measurements (Snellen or Early Treatment Diabetic Retinopathy Study charts), a dilated retinal examination, and FA. Selected patients also received indocyanine green angiography and/or optical coherence tomography (OCT). As part of standard practice patterns, patients were excluded from photodynamic therapy at these offices if they had significant liver disease, uremia, or known adverse reactions to fluorescein dye, or were pregnant.

Photodynamic therapy with verteporfin was applied in the same manner as the treatment for neovascular AMD in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy investigation.²¹ The location of laser light application was based on the judgment of the authors, who identified treatment zones based upon focal RPE leakage identified by FA. Selected patients (cases 2 and 7–9) received photodynamic therapy to areas of choroidal hyperpermeability demonstrated by indocyanine green, which surrounded and included the areas of focal RPE leakage. No treatments were given to areas of choroidal hyperpermeability that were separated from RPE leaks. Only focal leaks judged to be responsible for the macular detachment were selected for treatment. Treatment of the central macula was preferentially avoided when possible; however, it was included in treatment spots when necessary based upon location of fluorescein leaks (cases 1, 3, 7, and 8).

Statistical Methods

Data obtained were analyzed with frequency and descriptive statistics. Visual acuity was converted to logarithm of the minimum

angle of resolution (logMAR) for analysis. The Wilcoxon signed ranks test was performed to assess change in VA from baseline to the interval examination 6 months after treatment. SPSS software (version 12.0, SPSS, Inc., Chicago, IL) was used for data analysis.

Selected Case Reports

Case 1

A 42-year-old Caucasian physician presented with complaints of decreased vision in the left eye (LE) and inability to perform his work requiring excellent stereoscopic vision. Visual acuity measured 20/32, and retinal evaluation revealed a central macular neurosensory detachment (Fig 1A) with a solitary subfoveal focal leak at the level of the RPE on FA (Fig 1B). He was observed for 2 months without improvement. The area of leakage was judged to be too close to the center of the retina to risk the iatrogenic damage that might occur with laser photocoagulation. Treatment with photodynamic therapy utilizing a 1-mm spot size was suggested as a potential method of causing resolution of leakage with less damage to the overlying photoreceptor than might occur after laser photocoagulation, recognizing the limited evidence available regarding the precise risks and benefits of treating this case in this way. Two months after treatment, VA improved to 20/20, with resolution of symptoms, the neurosensory detachment (Fig 1C), and fluorescein leakage (Fig 1D). Five months after photodynamic therapy, VA remained 20/20; however, a central hypopigmented and hyperpigmented area of RPE disturbance was noted. Repeat FA showed a circumscribed area of staining corresponding to the hypopigmented area noted on clinical examination without evidence of fluorescein leakage. Both retinal examination results and VA (20/20) have remained stable for 6 additional months of follow-up.

Case 2

A 55-year-old male professional musician with a history of CSC complained of worsened vision in the right eye (RE) for 2 months that interfered with his livelihood. Central serous chorioretinopathy was diagnosed 18 months prior, and VA improved with observation after resolution of the original episode; however, it did not return to baseline. Visual acuity at the time of presentation for the recent exacerbation measured 20/50 (RE) and 20/20 (LE). Fluorescein angiography revealed a focal RPE leak just inferior to the fovea in the RE (Fig 2A, B) with surrounding neurosensory detachment confirmed with OCT (Fig 2D). Indocyanine green angiography showed choroidal hyperpermeability in the central macula including the area of the RPE leak seen on FA. Photodynamic therapy was performed for the focal FA leak without complication. Visual acuity improved to 20/40 plus 2, with resolution of both fluorescein leakage (Fig 2C) and neurosensory detachment (Fig 2E) associated with a marked improvement in quality of reading vision and work proficiency at 6 months' follow-up.

Case 4

A 56-year-old male with a 10-year history of recurrent episodic CSC exacerbated by use of a corticosteroid nasal spray complained of new distortion in both eyes, and VA was 20/200 in both eyes. Examination revealed neurosensory elevation of the central and inferior macula with a juxtafoveal circular hypopigmented area possibly containing fibrin exudation (RE) and large neurosensory detachment (LE) with fibrin and lipid exudation. Angiography showed a single RPE leak superior to the fovea on FA (Fig 3A), with corresponding choroidal hyperpermeability on indocyanine

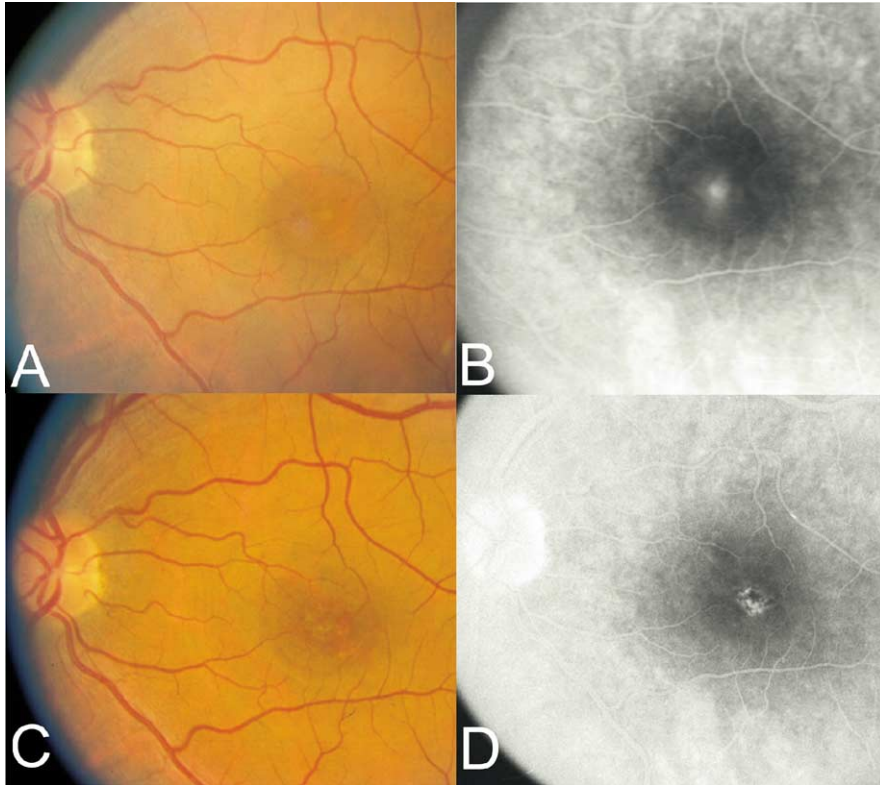


Figure 1. A, Color fundus photograph of the left eye upon presentation with central neurosensory detachment and visual acuity of 20/32. B, Late-phase frame of a fluorescein angiogram (FA) showing a focal leak at the level of the retinal pigment epithelium. C, Color fundus photograph with resolution of macular detachment and return of vision to 20/20 6 months after treatment with photodynamic therapy. D, Late-phase FA after treatment, revealing mild retinal pigment epithelial disturbance without fluorescein leakage.

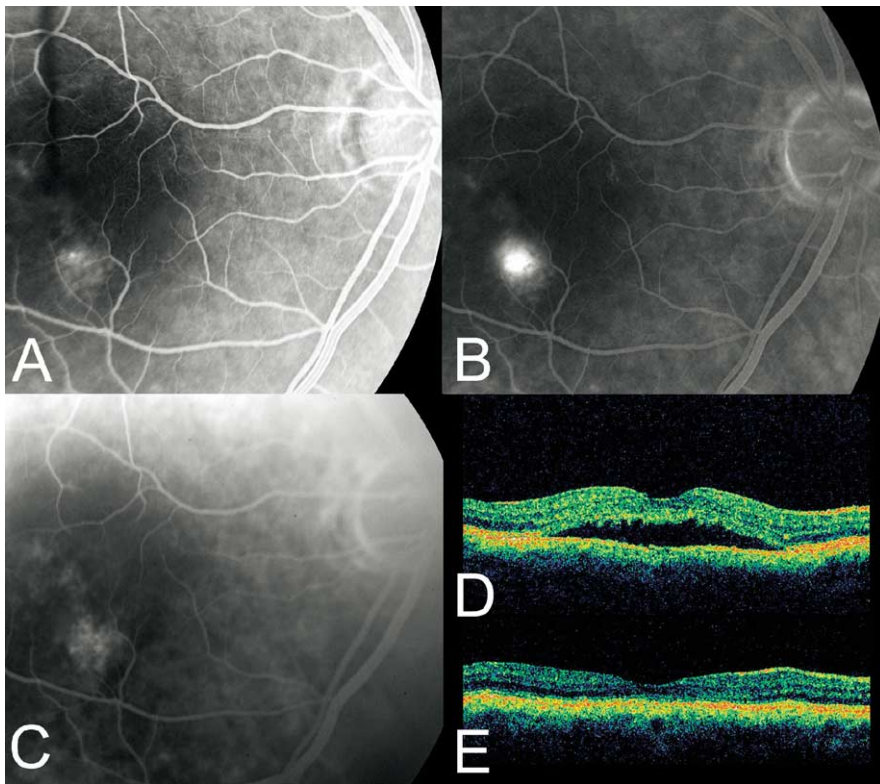


Figure 2. A, Early-phase fluorescein angiogram (FA) before treatment showing a focal leak at the level of the retinal pigment epithelium inferior to the fovea. B, Late-phase FA revealing further leakage inferior to the fovea. C, Late-phase FA after treatment showing mottled hyperfluorescence, consistent with a window defect without focal leakage. D, Vertical-line optical coherence tomography (OCT) before treatment showing subfoveal neurosensory detachment. E, Post-photodynamic therapy vertical-line OCT showing resolution of retinal detachment.

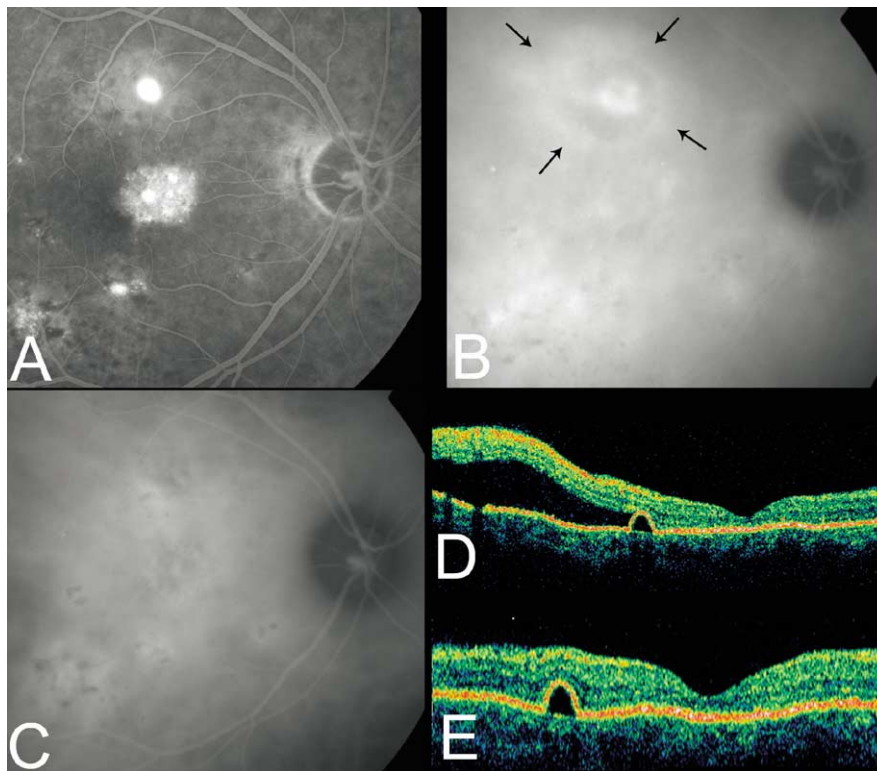


Figure 3. A, Early-phase fluorescein angiogram (FA) before treatment showing a focal leak at the level of the retinal pigment epithelium (RPE) superior to the fovea as well as additional areas of window defect representing previous activity. B, Midphase indocyanine green angiogram before treatment displaying hyperfluorescence (arrows) in the region surrounding the focal leak on FA. C, Midphase indocyanine green angiogram 9 months after treatment showing resolution of choroidal hyperpermeability in the treatment area. D, Vertical-line optical coherence tomography (OCT) before treatment showing RPE detachment adjacent to the site of the fluorescein leak on FA and overlying retinal detachment (RD). E, Post-photodynamic therapy vertical-line OCT showing resolution of RD with persistence of RPE detachment.

green angiography (RE) (Fig 3B), whereas the LE showed several areas of choroidal hyperpermeability without focal RPE leaks on FA. Optical coherence tomography showed shallow detachment of the fovea with an RPE detachment superiorly in the location of the focal leak (RE) (Fig 3D). This patient was enrolled in a study using photodynamic therapy to treat chronic CSC, and photodynamic therapy was applied to the RE with a 1-mm spot to the area of the fluorescein leakage. Subsequently, the central macula flattened, as demonstrated on OCT (Fig 3E), with resolution of the FA leak and resorption of inferior subretinal fluid (SRF). Cystoid macular degeneration and subfoveal RPE pigment changes developed in the fovea, with vision stabilized at 20/150 for 24 months' follow-up.

Results

Nine eyes of 9 patients (8 men, 1 woman) with focal RPE leaks secondary to CSC were treated with photodynamic therapy. The age at the time of treatment ranged from 34 to 61 years (mean, 49.8). Although all patients either stopped or did not have a history of corticosteroid use before photodynamic therapy, 1 patient (case 3) had used systemic corticosteroids as recently as 2 months before treatment, and 1 additional patient (case 4) used inhaled corticosteroids as recently as 6 months. Pretreatment VA ranged from 20/32 to 20/400 (median, 20/80). All patients had recent exacerbation of visual changes for at least 2 months before receiving photodynamic therapy, and no patients received prior photodynamic or thermal photocoagulation (Table 1).

All patients had one or more focal RPE leaks responsible for neurosensory detachment, identified as pinpoint areas of hyperfluorescence on early FA frames that increased in size through later frames. Five of 8 eyes demonstrated a single RPE leak on FA, whereas 4 eyes showed multiple active RPE leaks. Eight patients underwent indocyanine green angiography, which demonstrated midframe hyperfluorescence overlying areas where focal RPE leaks were seen on FA. Optical coherence tomography was also done on patients 2 to 9 and confirmed neurosensory detachment of the central macula in these patients; in addition, a localized RPE detachment was noted in case 4. All patients also underwent follow-up fluorescein and/or indocyanine green angiography as well as OCT imaging.

Treatments were performed based solely on location of FA leakage in 5 of 9 eyes (cases 1, 4–6, and 9), whereas 4 (cases 2 and 7–9) were treated based upon both FA and indocyanine green results where the area of choroidal hyperpermeability surrounding the FA leak as suggested by indocyanine green was also placed within the treatment zone. No areas of hyperpermeability distant from the RPE leak were included in treatments. Spot size ranged from 1 to 5.9 mm (mean, 2.6). A 1-mm spot size was used for 3 of 9 eyes (cases 1, 2, and 4). All patients were treated with a single application of photodynamic therapy, with the exception of case 6, who received 2 nonoverlapping light applications during a single treatment session to cover separate areas of fluorescein leakage.

The mean follow-up period was 10 months (range, 6–25). All patients had complete resolution of fluorescein leakage as well as

Table 1. Results

Patient No.	Age (yrs)	Gender	Eye	Episode Duration (mos) before PDT	No. of RPE Leaks	Spot Size (mm)	VA before Treatment	VA at 1 mo	VA at 3 mos	BCVA at 6 mos	VA at 9 mos	BCVA at 12 mos	Follow-up
1	42	M	L	2	1	1	20/32			20/30			6
2	55	M	R	18	1	1	20/50	20/30		20/40			6
3	55	M	R	2	Multiple	4.2	20/70	20/40		20/40		20/40	11
4	56	M	R	6	1	1	20/200	20/200	20/200	20/200	20/100	20/200	25
5	34	M	L	2	1	4.3	20/400	20/400	20/400	20/100	20/100	20/40	25
6	51	M	R	4	Multiple	2.3, 1.8	20/200	20/100	20/100	20/125	20/125	20/125	12
7	42	M	L	2	Multiple	5.9	20/125	20/125	20/100	20/100	20/100		9
8	61	W	L	2	Multiple	3.3	20/80	20/32	30/32	20/32	20/32	20/32	12
9	48	M	L	5	1	1.2	20/30	20/25		20/25			6

BCVA = best-corrected visual acuity; F = female; L = left; M = male; PDT = photodynamic therapy; R = right; RPE = retinal pigment epithelium; VA = visual acuity.

anatomic resolution of macular fluid by 1 month. Visual acuity improved ≥ 2 lines in 4 patients (44%) at 6 months. Mean pre-treatment logMAR VA was 0.67 and improved to 0.47 at 6 months' follow-up, which was statistically significant ($P = 0.012$, Wilcoxon signed ranks test). The median VA also improved from 20/80 to 20/40 over the same period. One patient (case 4) developed cystic retinal changes and did not improve in VA despite resolution of neurosensory detachment and fluorescein leakage. A second patient, case 5, developed a region of well-demarcated chorioretinal atrophy within the photodynamic therapy treatment zone that was outside the fovea and did not affect central VA. No patient lost vision or suffered any visually significant treatment-related complications.

Discussion

Many individuals with CSC may experience spontaneous resolution of their neurosensory detachment and may regain good VA. Those with persistent detachment of the fovea, however, may experience atrophic degeneration of the retina and RPE with limited improvement of vision, even after resolution of the macular detachment; individuals with pre-existing pigment epithelial degeneration and cystic intraretinal edema may also have limited improvement of vision. Some authors have reported that laser photocoagulation shortens the duration of disease and reduces the recurrence rate,³⁷⁻⁴⁰ whereas others maintain that it does not improve final vision,^{6,41} recurrence rates,^{6,42} or progression to chronic CSC.⁴³ Furthermore, laser photocoagulation is associated with permanent scotomata, which may enlarge over time with RPE scar expansion^{7,8} as well as the possible development of choroidal neovascularization.^{5,40,44} Although there is no definitive evidence that laser photocoagulation benefits patients with CSC, most retinal specialists tend to consider a thermal laser for extrafoveal leaks with persistent detachment of the macula. Patients with multiple causative focal leaks under or adjacent to the fovea are therefore poor candidates for thermal laser. Various medical treatments have also been attempted for this disorder, including acetazolamide, β -blockers, vitamins, and nonsteroidal antiinflammatory medications without decisive benefit.⁴⁵

Recently, several case series have reported the use of indocyanine green-guided photodynamic therapy to treat chronic CSC, defined as >6 months' duration of disease with diffuse decompensation of the RPE, but lacking focal FA leaks.³⁰⁻³⁴ In the course of one of these studies, the authors encountered a patient (case 4 in the current series) with an acute exacerbation of chronic CSC and an extrafoveal focal RPE leak in the fellow eye of an enrolled patient. As part of the chronic CSC study protocol, the excitation light was applied to the choroidal hyperpermeability demonstrated with indocyanine green, which included the focal RPE leak shown on FA; however, this eye was excluded from the study because the neurosensory detachment was not present for 6 months. The treatment yielded closure of the RPE leak as well as rapid resolution of SRF. Despite limited visual improvement secondary to cystoid macular degeneration and subfoveal RPE changes, this result provided the proof of principle for the current study and prompted further exploration of the technique.

Taban et al retrospectively studied 5 patients treated with photodynamic therapy based upon FA findings for chronic CSC and diffuse RPE leakage. Although all patients had relatively large areas of RPE leakage, they noted cessation of fluorescein leakage and visual improvement after treatment.³⁶ Canakis et al also reported on FA-guided photodynamic therapy for diffuse retinal pigment epitheliopathy in a single patient with multiple punctate RPE leaks and a shifting bullous RD. Photodynamic therapy was applied to 3 areas, resulting in resolution of fluorescein leakage and neurosensory detachment with improvement in vision.³⁵

It has been proposed that the earliest manifestation of acute CSC is an increase in hydrostatic pressure within the inner choroid secondary to choroidal vascular hyperpermeability that, over time, may lead to serous detachment of the RPE. Ultimately, the RPE monolayer may develop a disruption within the RPE detachment, manifest as a focal leak on FA, when the shear stress from the hydrostatic pressure on the distorted cell arrangement overcomes intercellular adhesion forces. This focal RPE defect allows fluid to flow from the choroid to the sub-

retinal space, yielding a serous RD, which is the characteristic sign of the disorder.^{17,19,46}

The mechanism by which photodynamic therapy ameliorates focal RPE leaks in CSC is unknown. In AMD, it is believed that verteporfin binds to low-density lipoprotein receptors on endothelial cells, which are expressed in greater numbers within neovascularization, thereby allowing selective destruction of choroidal neovascularization. Excitation of the verteporfin, a photosensitizer, initiates a photochemical reaction involving singlet oxygen and reactive oxygen intermediates that damage endothelial cells lining the choroidal neovascularization and lead to thrombosis of the choroidal neovascularization.⁴⁷ Larger choroidal vessels, neural structures, photoreceptors, retinal capillaries, and the RPE generally are spared these destructive effects at normal light and drug doses.²⁶ In CSC, however, there is no choroidal neovascularization; therefore, the therapeutic effect presumably derives from light activation of verteporfin bound to choriocapillaris endothelial cells. Thrombosis of the inner layers of the physiologic choroid—especially the choriocapillaris—after photodynamic therapy has been shown with both histopathology and indocyanine green angiography.^{26–29} The coagulation may have the desired effect in patients with CSC of reducing blood flow to the area with increased choroidal permeability, thus preventing exudation and breaking the chain of events leading to neurosensory detachment.

Although this case series demonstrates successful treatment of acute CSC with photodynamic therapy, it is limited by its retrospective nature and small number of patients, so the 95% confidence interval around the point estimates regarding risks and benefits is quite wide. None of the patients in this series experienced a visually significant adverse event; however, our total of 9 patients dictates approximately a 33% chance that a major adverse event would not have been detected.⁴⁸ In addition, the relatively short follow-up period in several cases does not allow one to determine if the effects of photodynamic therapy are sustained over a long time. Furthermore, individuals with CSC may experience spontaneous resolution of their symptoms and leakage; our lack of a control group also does not allow one to determine if the resolution of the RPE leaks in our 9 cases was actually a result of photodynamic therapy or was due to the natural history of the disease.

In this small case series, we have demonstrated that photodynamic therapy with verteporfin in patients with focal fluorescein leaks secondary to CSC can have prompt resolution of leakage from CSC, which can be associated with rapidly improved vision. The temporal course suggests that the improvement likely is due to the photodynamic therapy. Although these results are promising, further investigations would be helpful to understand more precisely the risks and benefits of this therapy for patients with CSC.

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