HEMORRHAGIC RECURRENCE OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION NOT PREDICTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY

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Purpose: To report a case in which a patient with neovascular age-related macular degeneration developed a large submacular hemorrhage 2 days after spectral domain optical coherence tomography imaging, which revealed no intra- or subretinal fluid.

Methods: A noninterventional case report.

Results: A 93-year-old woman with neovascular age-related macular degeneration was seen for a regular follow-up examination 3 years after treatment with verteporfin photodynamic therapy in which lesion quiescence was achieved. Visual acuity was stable at 20/200, and spectral domain optical coherence tomography scans using 2 different instruments revealed no intra- or subretinal fluid. Two days after clinical examination and imaging, the patient presented with a large submacular hemorrhage and 5/400 vision.

Conclusion: Hemorrhagic exudation from choroidal neovascularization in age-related macular degeneration may occur suddenly, even in the absence of fluid detected by spectral domain optical coherence tomography.

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Advances in the treatment of neovascular age-related macular degeneration (AMD) have included photodynamic therapy (PDT) and the intravitreal antivascular endothelial growth factor (VEGF) drugs such as bevacizumab and ranibizumab.[1-4] In the TAP[1] and VIP[2] studies, patients received treatment with PDT if fluorescein angiography showed leakage from choroidal neovascularization (CNV). In contrast, in the ANCHOR[3] and MARINA[4] trials, patients were treated with intravitreal ranibizumab monthly for 2 years regardless of CNV activity. Because of the burden of monthly injections, additional studies have looked at alternative dosing strategies with the intention of reducing the number of treatments without compromising visual results. In the PIER trial,[5] when patients were switched from monthly to quarterly injections of ranibizumab, they subsequently lost the vision they had gained with monthly injections. However, the PrONTO trial[6] demonstrated that a variable dosing regimen using optical coherence tomography (OCT) as a guide for retreatment could potentially achieve the same visual results as monthly injections but with fewer treatments.[7] Another commonly used dosing regimen referred to as "treat and extend" is also guided by the presence of intra- or subretinal fluid on OCT. With this strategy, the time interval between injections is gradually extended as long as no fluid is seen (J. P. Levine et al, unpublished data). There have been questions of whether OCT is always a reliable measure of neovascular activity. For instance, OCT provides little information regarding the size of neo-

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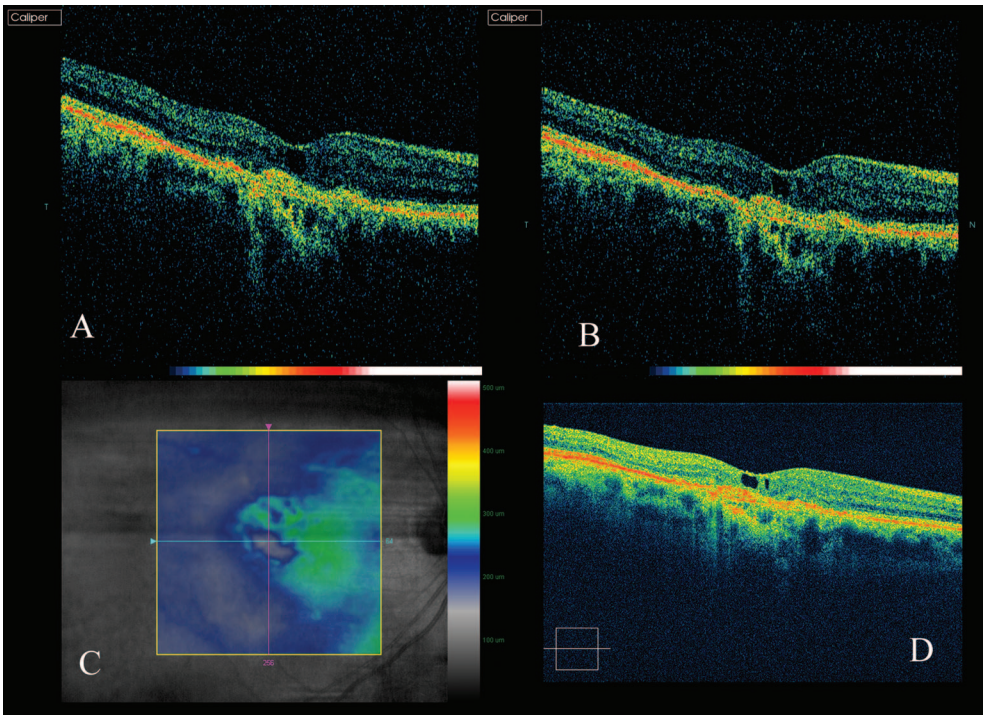

Fig. 1. Optical coherence tomography scan through the right fovea with the Topcon 3D-OCT 1000 (**A** and **B**) and Cirrus HDOCT (**C** and **D**) showing a chronic intraretinal cavitary space with no subretinal fluid.

vascular lesions and cannot differentiate certain lesion components such as polypoidal neovascularization or subretinal fibrosis from actively proliferating well-defined Type 2 (subretinal) neovascularization. With these concerns in mind, we report a patient with neovascular AMD, stable for 3 years after PDT, who developed a large submacular hemorrhage 2 days after a clinical examination, and spectral domain OCT revealed stable findings and no intra- or subretinal fluid.

Case Report

In September 2005, a 90-year-old woman presented with bilateral neovascular AMD. There was a history of hypertension controlled with enalapril. She was not taking aspirin or any other anticoagulants. Visual acuities were 20/400 and 20/200 in the right and left eyes, respectively. Fluorescein angiography showed bilateral Type 3 neovascularization (retinal angiomatous proliferation) of less than 1 disk diameter in size. Two bilateral verteporfin PDT treatments combined with intravitreal triamcinolone acetonide injections were performed in each eye. After treatment, the right eye stabilized with no recurrent angiographic leakage or fluid noted on OCT. The left eye experienced continued exudation and was treated with multiple intravitreal injections of anti-VEGF agents, including bevacizumab and ranibizumab. On a routine evaluation 3 years after the second PDT treatment, visual acuity was 20/200 bilaterally with a small area of clinically inactive, subfoveal subretinal fibrosis in the right eye. There was no fluid, lipid, or hemorrhage detected clinically or on fundus photography.

A small amount of subretinal fluid overlying a similar lesion was noted in the left eye. High-density 6 × 6-mm raster scans were performed centered on the fovea with a resolution of 512 × 128 A-scans using 2 different spectral domain OCT instruments: Cirrus HD-OCT (Model 3000, Carl Zeiss Meditec, Dublin, CA) and the Topcon 3D-OCT 1000 (Topcon, Tokyo, Japan). In addition, 5 high-resolution (4096 A-scan) horizontal line scans centered at the fovea were performed on the Cirrus HD-OCT unit. Foveal thickness in the right eye measured 139 μm on the Topcon instrument, which was unchanged from the measurement of 141 μm on the patient's visit 10 weeks earlier. Review of all OCT cuts revealed a stable, small, focal intraretinal cavitary space in the right eye (Figure 1). This space was not considered to represent active leakage but rather loss of retinal tissue, because reduced retinal thickness and loss of the nuclear and plexiform layers were seen on OCT; it was unchanged from multiple prior OCT scans during a 3-year period, including the prior visit, and there was no leakage on previous fluorescein angiography. The left eye was retreated with intravitreal ranibizumab for a small amount of subretinal fluid detected on OCT. Two days later, the patient returned with rapidly worsening vision in the right eye. Visual acuity was 5/400, and examination revealed a large submacular hemorrhage consistent with recurrence of CNV (Figure 2).

Discussion

The advent of PDT and antivasogenic treatments for neovascular AMD has greatly improved visual outcomes compared with thermal laser photocoagulation. However, the best criteria to use for retreatment remain uncertain. Using OCT to assess CNV activity and direct treatment has become a common approach in the management of neovascular AMD, in part because of the noninvasive nature of this form of imaging and the ease and speed of obtaining this data. Also, unlike fluorescein angiography, in which interpreta-

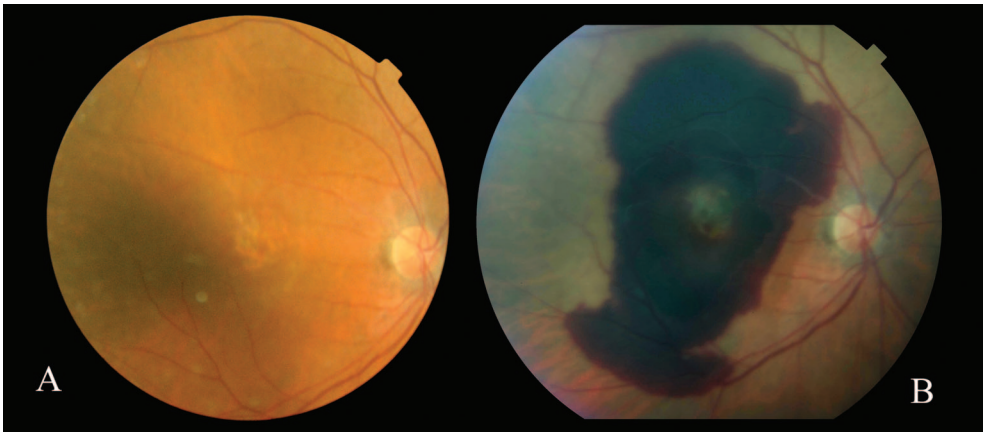

Fig. 2. Color photographs of the right eye showing a small area of clinically inactive subfoveal fibrosis (**A**) 2 days before development of a large submacular hemorrhage (**B**).

tion is often based on subjective interpretations, OCT technology provides quantitative measures of retinal thickness and subretinal fluid. The retreatment criteria chosen for the PrONTO trial were largely based on a clinical impression that OCT could detect the earliest signs of recurrent fluid in the macula (macular cysts or subretinal fluid) after the ranibizumab injections were stopped.[6] However, even in the PrONTO trial, two of the four criteria for retreatment required no OCT guidance: appearance of new classic CNV and new-onset hemorrhage. These elements accounted for 20% of the reinjections performed in this study. The TAP and VIP trials of verteporfin PDT were performed before the widespread use of OCT technology, and retreatment guidelines relied on fluorescein angiographic evidence of leakage.[1,2] High-resolution OCT is reported to have almost 100% sensitivity for cystoid macular edema and almost always correlates with leakage seen on fluorescein angiography.[8-10] However, a discrepancy between OCT and angiography in the detection of macular edema has been reported in up to 5% of cases.[10] Eter and Spaide[11] reported that some patients who had PDT for neovascular AMD had leakage by fluorescein angiography that did not correspond to any observable fluid on OCT. It is, therefore, conceivable that both OCT instruments used in our patient failed to detect early changes that may have predicted the submacular hemorrhage that occurred.

The PrONTO trial demonstrated visual outcome data similar to the MARINA and ANCHOR trials of ranibizuamb while reducing the total number of injections by ~50%. It is potentially significant that most clinical practices deviate from the rigorous testing of visual acuity with the Early Treatment Diabetic Retinopathy Study chart as was used in the PrONTO study. Clinicians have taken the PrONTO results a step further and are commonly implementing a "treat and extend" strategy. In this regimen, the time interval between examinations and intravitreal injections is gradually increased by 1- to 2-week increments as long as there are no signs of reexudation either clinically or on OCT. This interval is gradually extended to a maximum of 8 weeks to 12 weeks with the goal of finding a stable maintenance interval that keeps the macula "fluid-free."

When treating patients on an "as-needed" basis with either anti-VEGF monotherapy or combination approaches, we observed a subset of patients who experienced recurrent exudation with submacular hemorrhage shortly after a stable eye examination in which the Stratus OCT (Carl Zeiss Meditec) did not detect fluid before the event (J. P. Levine et al, unpublished data). Although angiography was not performed, the presence of a large submacular hemorrhage implied active CNV. This finding suggested that we were missing fluid present in the intervals between the six radial cuts that are often used with the time-domain Stratus OCT device. The current report demonstrates that severe recurrent hemorrhagic exudation can occur shortly after imaging showing absence of fluid detected with the much higher resolution and scan densities of the new spectral domain OCT technology. This is particularly concerning given that recurrent exudation after discontinuation of intravitreal anti-VEGF therapy is to be expected. Also, as many as 33% of eyes previously treated with PDT will have a recurrence of CNV within 18 months after their last treatment.[12] Perhaps there are certain patients such as those with preserved foveal function, juxtafoveal lesions, or poor vision in the fellow eye who would do better on a maintenance regimen even in the absence of fluid detected by OCT to reduce the risk of sudden and catastrophic recurrences. However, even with monthly dosing of ranibizumab, loss of visual acuity occurred in 5% to 10% of patients in the ANCHOR and MARINA studies. There are currently no published prognostic factors that are used to identify

patients at high risk for treatment failure, and there is no way to predict whether anti-VEGF treatment would have prevented the submacular hemorrhage that occurred in our patient.

The case presented highlights two important limitations to our current understanding of the pathophysiology of neovascular AMD and its optimal treatment. First, what is the earliest sign of CNV recurrence, and how is it best detected? Although OCT is currently used to detect fluid and direct treatment, other factors such as visual acuity or angiography may be more predictive in certain patients. Second, should treatment be administered only if CNV activity is detected or should maintenance therapy be given even without signs of neovascular activity? Future studies may help answer these questions and identify patients who are at risk for CNV recurrence.

Key words: age-related macular degeneration, optical coherence tomography, recurrence, submacular hemorrhage.

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