Special Issue

Visualization of Changes in the Choriocapillaris, Choroidal Vessels, and Retinal Morphology After Focal Laser Photocoagulation Using OCT Angiography

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Purpose. To utilize optical coherence tomography (OCT) and OCT angiography (OCTA) to describe alterations in the retinal and choriocapillaris vasculature following remote laser photocoagulation. Lesions are classified on the basis of choriocapillaris alteration as evaluated on en face OCTA.

Methods. This was a retrospective, cross-sectional study analyzing 28 laser photocoagulation scars from 8 patients treated for diabetic macular edema. All eyes were analyzed using a combination of OCTA, en face and cross-sectional OCT, and fundus photography. Two masked readers scored images for alterations at the level of the retinal pigment epithelium (RPE), choroid, and choriocapillaris. Laser photocoagulation lesions were classified as deep if choriocapillaris alteration was present on OCTA; lesions were classified as superficial if no choriocapillaris alteration was present on OCTA.

Results. Optical coherence tomography angiography was found to be useful for evaluation of choriocapillaris alteration underlying regions of laser scarring. Of the 28 analyzed laser scars, 13 were classified as superficial and 15 were classified as deep.

Conclusions. Optical coherence tomography angiography can be used to visualize choriocapillaris alterations associated with focal laser photocoagulation treatment.

Keywords: laser photocoagulation, OCT angiography

Laser photocoagulation was previously a mainstay of office-based therapy for retinal disorders such as diabetic macular edema (DME), choroidal neovascularization (CNV), and retinal vein occlusion (RVO). However, the introduction of multiple antivascular endothelial growth factor (VEGF) agents, which have been shown to result in improved visual outcomes, has led to the decline of focal laser as a first-line therapy.[1–5] Nevertheless, focal laser photocoagulation may still be preferred in select clinical scenarios such as extrafoveal CNV, retinal artery macroaneurysms, and non-center-involved clinically significant macular edema.[6]

Structural changes in the retina and choroid induced by laser photocoagulation depend on laser parameters such as wavelength, power, exposure time, and spot size; patient factors, time interval following exposure, and individual physician treatment preferences. Focal laser for DME typically consists of small, light treatments applied either in a grid pattern over a region of DME or to select microaneurysms. Due to the high concentration of melanosomes, the RPE is the main target of the incident laser applied to the retina. Histopathology of autopsy eyes has demonstrated defects in the choriocapillaris beneath retinal laser lesions secondary to photocoagulation for proliferative diabetic retinopathy.[7] These lesions have been observed to expand circumferentially over time, especially in the posterior pole, and enlargement of RPE atrophy can cause significant, delayed visual loss.[8–10] In animal models, spectral-domain optical coherence tomography (SD-OCT) has been used to visualize disruptions in the RPE caused by laser treatment, as well as the subsequent proliferation of RPE cells associated with the postlaser healing process.[11,12] There are, however, limited studies detailing the in vivo changes that occur in the RPE and choriocapillaris following focal laser treatment.

Optical coherence tomography angiography (OCTA) enables noninvasive, depth-resolved visualization of the retinal and choroidal vasculature. Optical coherence tomography angiography images are generated through a repeated B-scan protocol whereby multiple B-scans are acquired in rapid succession from the same tissue location. As such, structural and angiographic data sets are intrinsically coregistered, allowing for simultaneous visualization of the structure and blood flow. Optical coherence tomography angiography has its origins in Doppler OCT, a set of phase-sensitive techniques that exploit the Doppler shift that occurs when the OCT beam is scattered by moving erythrocytes.[13] Since then, a number of related OCT-based techniques measuring the phase and intensity changes imparted by moving erythrocytes have been proposed.[14–20] Split-spectrum amplitude decorrelation angiography (SSADA), the algorithm used in this study, is an intensity-based technique

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that partitions the spectrum into multiple subspectrums, performs the repeated B-scan decorrelation separately for each subspectrum, and then averages the results. Split-spectrum ADA has been shown to increase the signal-to-noise ratio as compared to the single-spectrum approach.[19]

The central aim of this study was to assess the hypothesis that a combination of OCT and OCTA images can be used to assess changes in the retinal and choroidal vasculature, including the choriocapillaris, in patients who have a history of remote laser photocoagulation. Furthermore, in the process of assessing this hypothesis we developed a classification scheme that partitions lesions into "superficial" and "deep" categories.

Methods

Subjects

This was a retrospective cross-sectional study evaluating eyes with a remote history of macular laser photocoagulation. The study was performed at the New England Eye Center (Boston, MA, USA), and the study protocol was approved by the Tufts Medical Center Institutional Review Board (IRB). The research adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act of 1996. Written informed consent was obtained before OCTA examination in accordance with the Tufts Medical Center IRB.

Patients with active DME were excluded from the study; patients with color fundus and/or en face images without clearly identifiable laser photocoagulation lesions in the macular region were also excluded. To distinguish between true flow impairment and OCTA thresholding artifacts caused by low OCT signals, en face OCTA images were jointly viewed with en face and cross-sectional OCT images using ImageJ (National Institutes of Health, Bethesda, MD, USA [in the public domain]). This technique has been previously described.[21,22]

All lesions included in this study were a result of laser photocoagulation treatments occurring at least 1.5 years prior to OCTA imaging. A chart review was performed to determine laser settings. Traditional Early Treatment Diabetic Retinopathy Study (ETDRS) parameters were used with a spot diameter of 50 μm, exposure time of 0.1 seconds, and power of 50 to 150 mW.

OCTA System

Subjects were imaged at the New England Eye Center between September 2014 and July 2015 on the RTVue XR Avanti AngioVue OCTA system (Optovue, Inc., Fremont, CA, USA). This spectral-domain system operates at 70,000 A-scans per second and acquires OCTA volumes of 304 A-scans × 304 A-scans. The central wavelength of the device is 840 nm with an axial resolution of 5 μm and a transverse resolution of 15 μm.

Qualitative Analysis

Two masked Boston Image Reading Center readers (EDC, EAN) correlated the location of laser lesions on the color fundus photographs, en face OCTA images, and en face and cross-sectional OCT images. The OCTA images were manually segmented and evaluated for changes at the level of the choriocapillaris. The manual segmentation of the choriocapillaris was achieved by first viewing the choriocapillaris slab segmentation automatically generated by the AngioVue software. The position of this slab was manually adjusted by scrolling up or down in the corresponding B-scan, and the slab thickness was adjusted so as to minimize decorrelation tail artifacts. The slab was considered to be at the level of the choriocapillaris when the background of the slab (not including the laser marks) was a dense, homogenous layer, consistent with choriocapillaris morphology. En face structural OCT images were automatically fit to the RPE contour using the Optovue software. En face images were analyzed at the level of the RPE and choroid; corresponding OCT B-scans were also used to assess OCT signal levels.

Laser photocoagulation lesions were classified as deep if OCTA showed choriocapillaris alterations (red circles, Figs. 1, 2), and superficial if no visible choriocapillaris alterations were visible on OCTA (yellow circles, Figs. 1, 2).

Photocoagulation lesions were classified as having choriocapillaris alteration if the two readers agreed that OCTA revealed a focal choriocapillaris alteration at the laser spot. Retinal pigment epithelium changes were considered present if the corresponding en face OCT and/or cross-sectional OCT images, segmented at the level of the RPE, showed disruption of the linear RPE above the area of choriocapillaris alteration.

Results

Eight eyes with 28 laser lesions from prior focal laser for DME in the macular region met the inclusion criteria for this study. Baseline characteristics of the patients were as follows: mean age was 65.3 ± 6.8 years, 6 of 8 patients were male, and 5 of 8 patients were Caucasian. All focal laser treatments were performed between 1.5 to 9 years (mean 3.9 ± 2.7 years) prior to OCTA imaging. Of the 28 laser lesions, 15 were classified as deep and 13 as superficial lesions.

Notably, there were no visible retinal vascular changes on OCTA in the superficial and deep plexuses of retinal vasculature with manual and automated segmentation. Corresponding OCT B-scans of the deep lesions showed destruction and irregularity involving the retinal pigmented epithelium (RPE), cone outer segment tip (COST) line, inner segment-outer segment (IS/OS), outer limiting membrane (OLM), outer nuclear layer (ONL), and, in some cases, outer plexiform layer (OPL) (Figs. 1E, 2E). Superficial lesions showed less severe structural changes, and alterations were visible only at the level of the RPE, COST line, IS/OS, and OLM (Figs. 1F, 2F).

All superficial and deep lesions showed areas of increased OCT signal on en face OCT segmented at the level of the choroid; the areas associated with the deep lesions were larger than those associated with the superficial lesions (Figs. 1C, 2C). Nine of the 13 superficial scars had both regions of low and high OCT signal on en face OCT segmented at the level of the RPE; the remaining 4 lesions were associated only with increased OCT signal. All deep lesions had both regions of low signal and regions of high signal on en face OCT segmented at the level of the RPE (Figs. 1B, 2B).

Discussion

Visualizing laser lesions with a combination of OCT and OCTA showed focal RPE loss and choriocapillaris alteration associated with regions previously treated with laser photocoagulation, which is consistent with histopathology literature.[7–10] Furthermore, OCTA showed that some laser lesions were associated with choriocapillaris alterations while others were not, which may suggest variations in laser energy delivered to the RPE.

Postmortem analysis of eyes treated with argon laser photocoagulation for proliferative diabetic retinopathy have found choriocapillaris filling defects. These changes, as seen on antemortem fluorescein angiography, corresponded to histopathologic disruption of the choriocapillaris associated with fibrosis and nonperfusion.[7,23]

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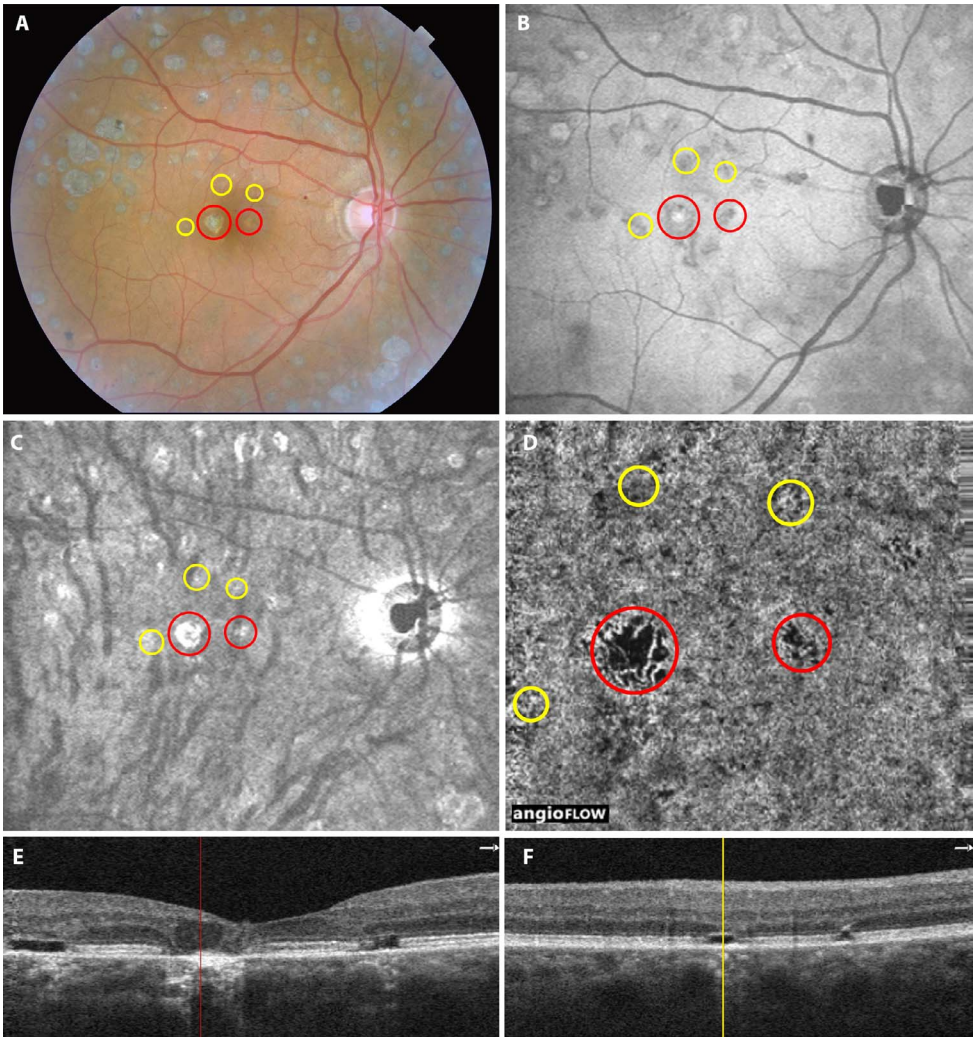

FIGURE 1. Multimodal imaging of superficial (*yellow*) and deep (*red*) laser photocoagulation lesions. (**A**) Fundus photograph and (**B**) en face structural OCT segmented at the level of the RPE. (**C**) En face OCT segmented at the level of the choroid. (**D**) OCTA image segmented at the level of the choriocapillaris. Deep lesions exhibit choriocapillaris alteration, while superficial lesions do not. (**E**) OCT B-scan from a deep laser mark shows increased light penetration due to RPE disruption with overlying external neuroretinal atrophy. (**F**) OCT B-scan from a superficial laser mark shows comparably mild RPE and IS/OS changes.

The photoreceptor layer, RPE, and choriocapillaris are known to have a mutualistic relationship, and histopathologic studies of eyes with nonexudative age-related macular degeneration (AMD) have found that RPE atrophy is closely associated with choriocapillaris degeneration.[24,25] Changes in the choriocapillaris underlying areas of RPE disruption have also been observed in other diseases including exudative AMD, Stargardt disease, and retinitis pigmentosa.[26,27] In addition, recent OCTA studies have suggested decreased choriocapillaris vascular density associated with some diabetic patients, both with and without retinopathy (DA Salz et al., manuscript submitted, 2015). While it is possible that some of the choriocapillaris changes seen in this study were caused by diabetic damage and not laser treatment, the focal nature of the alterations suggests otherwise.

Spectral-domain OCT findings on human and rabbit eyes treated with panretinal laser photocoagulation (PRP) for diabetic retinopathy have been previously reported. The reported changes include reduced choroidal thickness, depression of the inner retinal surface corresponding to focal shrinkage of the ONL, and destruction of the choriocapillaris, RPE, photoreceptors, and outer portions of the retina.[28,29] In our study we found no depression of the retinal tissue above superficial or deep lesions nor was there retinal thinning, which is likely due to the remote history of laser treatment in the study patients. The extended time period (median 3.65 ± 2.9 years) between focal laser photocoagulation and OCTA imaging may explain why both superficial and deep plexuses of the retinal vasculature appeared unaffected. Previous studies have shown that retinal morphology can be restored after laser photocoagulation. Kriechbaum and associates[30] used OCT to monitor healing response of human eyes in vivo after PRP and showed that after 3 to 6 months, lesions were characterized by a stable defect in the RPE and the ONL remained thinned at the lesion center.

Optical coherence tomography angiography enables noninvasive, high-resolution imaging of the retinal and choroidal vasculature.[31–34] Of particular relevance to the current study is the capability of OCTA to visualize the choriocapillaris, which, when healthy, has a thin, dense, monolayer morphology.[26] Optical coherence tomography angiography visualization of the choriocapillaris is complicated by the possibility of "thresholding" artifacts. Thresholding occurs when regions of the OCTA signal that are associated with low OCT signal

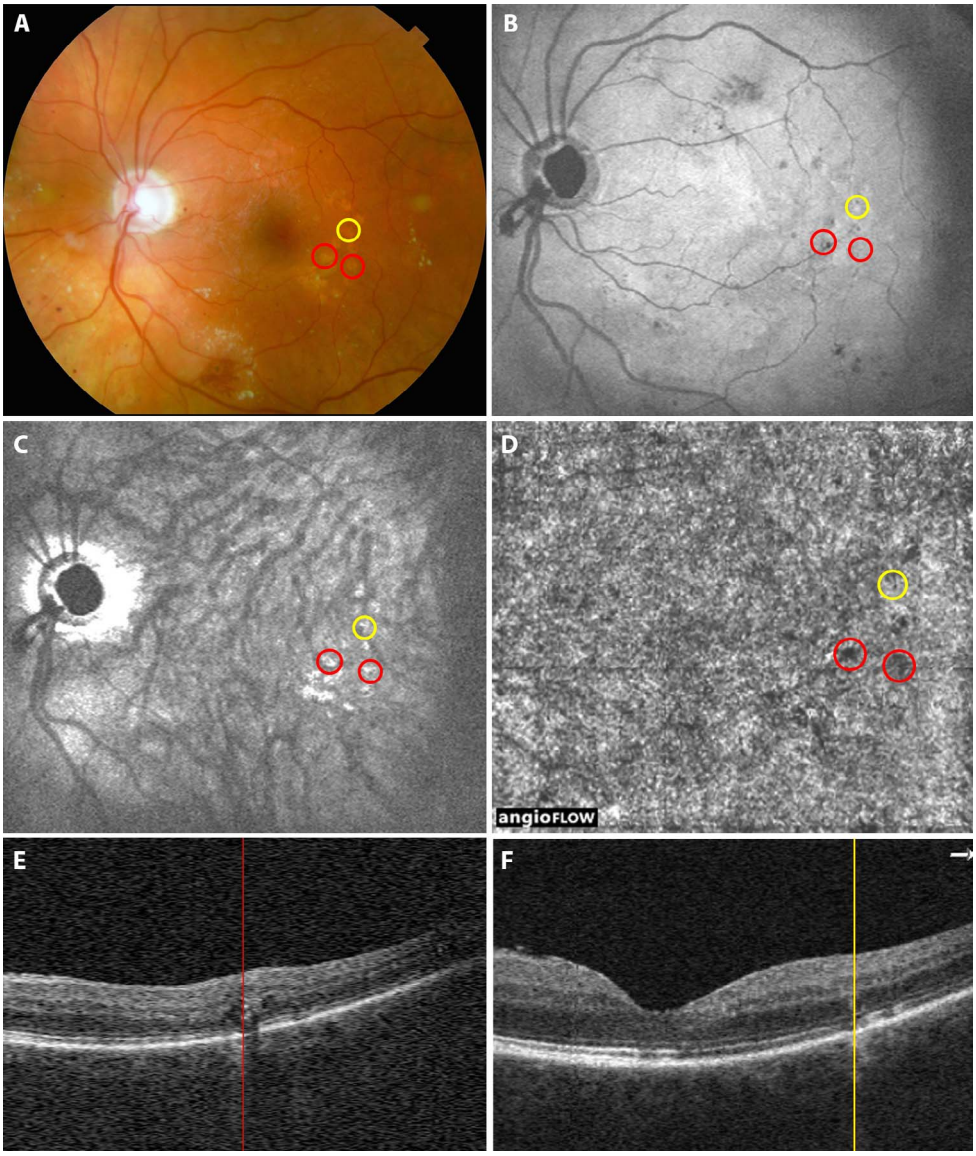

FIGURE 2. Multimodal imaging of superficial (*yellow*) and deep (*red*) laser photocoagulation lesions. (**A**) Fundus photograph and (**B**) en face structural OCT segmented at the level of the RPE. (**C**) En face OCT segmented at the level of the choroid. (**D**) Optical coherence tomography angiography image segmented at the level of the choriocapillaris. Deep lesions exhibit choriocapillaris alteration, while superficial lesions do not. (**E**) Optical coherence tomography B-scan from a deep laser mark shows increased light penetration due to RPE disruption with overlying external neuroretinal atrophy. (**F**) Optical coherence tomography B-scan from a superficial laser mark shows comparably mild RPE changes, indicated by increased signal penetration, and IS/OS and ELM changes.

levels (as determined by the coregistered OCT volume) are assigned low (dark) pixel values. This thresholding step introduces an ambiguity: Areas of low OCTA signal may be caused by low flow, low OCT signal, or both. Areas of low OCT signal are especially likely to occur beneath the RPE, due to its melanin content; additionally, sensitivity roll-off in spectral-domain OCT will also reduce the OCT signal toward the bottom of the image (when using a standard imaging configuration). Both of these factors make OCTA of the choriocapillaris particularly susceptible to thresholding artifacts. To avoid misinterpretation, it is necessary to evaluate OCTA images in conjunction with a combination of en face and cross-sectional OCT images. Additionally, due to limitations of the axial and lateral resolution of the AngioVue system, it is not possible for the segmented choriocapillaris slab to consist of solely choriocapillaris vessels; it may also include vessels from adjacent choroidal layers. However, it is likely that the laser photocoagulation induces damage not only in the choriocapillaris vessels but also in adjacent choroidal vessels.

The ability of OCTA to visualize choriocapillaris alterations suggests that a combination of OCT and OCTA may be useful for titrating laser power so as to reduce the probability of retinal and choroidal damage, as well as permanent disorganization and scarring in the photoreceptor layer. Strategies such as micropulse laser have been developed that may minimize tissue damage, especially in the macula.[12,35] Recently, Koinzer and associates[36] demonstrated in an animal model that automatic, temperature-controlled laser photocoagulation can predictably induce subvisible, mild, or moderate lesions without manual power titration. Application of fundus temperature measurements during laser photocoagulation would enable clinicians to perform laser photocoagulation while minimizing damage to retinal tissue.[17,36]

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The repeated B-scan protocol required for OCTA imaging limits the size of the field of view; the system used in this study is able to generate OCTA images of up to 6 × 6 mm. It is important to note that larger field sizes correspond to sparser sampling, which can be problematic, particularly when one is trying to interpret the choriocapillaris vasculature. The limited field of views on commercial OCTA systems prevents the acquisition of a single OCTA image covering the entire region of laser treatment. This limitation can be, in part, overcome by forming montages from multiple OCTA images. However, montage-based approaches result in significantly increased acquisition times because multiple smaller field-of-view OCTA images must be acquired in an overlapping fashion.[37,38] Moving forward, advances in high-speed imaging systems will likely enable wide-field OCTA imaging while maintaining clinically feasible imaging times; for example, Blatter et al.[39] have described a high-speed swept-source OCT system capable of generating ∼48° OCTA images from a single acquisition.

As we have tried to emphasize throughout this paper, caution should be exercised when interpreting OCTA images, particularly when visualizing vasculature lying beneath the RPE, such as the choriocapillaris. In addition to the previously discussed thresholding artifacts, there are a variety of other artifacts that merit consideration; these include the limited ability of OCTA to visualize low flow vessels, segmentation-related errors when viewing en face OCTA images, and artifacts resulting from patient motion. As a thorough discussion of OCTA artifacts is beyond the scope of this paper, we refer the reader to the study by Spaide et al.[21] for a detailed discussion.

The results of our current study are twofold. First, we demonstrated that OCTA can be used to visualize choriocapillaris alterations associated with laser scars. Second, we found that laser scars can be partitioned into two categories: deep laser scars, which have associated choriocapillaris alteration, and superficial laser scars, which have no associated choriocapillaris alteration. These results suggest that OCTA may develop into a useful tool for assessing choriocapillaris alteration resulting from focal laser photocoagulation.

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