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Simulating Vascular Leakage on Optical Coherence Tomography Angiography

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Simulating Vascular Leakage on Optical Coherence Tomography Angiography

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Abstract

Purpose: To demonstrate a potential technique for using optical coherence tomography angiography (OCTA) to simulate leakage in eyes with diabetic macular edema and determine the sensitivity and positive predictive value of detecting leaking microvasculature on OCTA using fluorescein angiography (FA) as the comparative norm.

Methods: 6x6mm OCT angiograms were overlayed with the corresponding OCT thickness maps. Microvascular abnormalities on the OCT angiogram underlying areas of thickening on the OCT thickness map were assumed to be leaking. Two independent readers blindly read the OCTA overlay images then the FA images cropped to the same approximate region to delineate areas of leaking microvasculature. The results were compared to determine with sensitivity and positive predictive value of OCTA for detection of leaking vessels.

Results: 32 eyes of 22 diabetic patients were included. Each eye demonstrated an average of seven leaking microvascular abnormalities on the OCTA images compared with an average of 21 leaking vessels on the FA images. Sensitivity of leaking microvasculature detection by OCTA was 25.3% and positive predictive value was 71.3%. The correlation coefficient of the two readers' detection of leaking microvasculature was 0.583 for OCTA reads compared with 0.908 for FA.

Conclusion: OCTA as a whole can be used to simulate leakage but currently sensitivity of the technique is low. Further understanding of the OCTA technology may yield novel ways of detecting retinal pathology.

Introduction:

Diabetic retinopathy (DR) is the most common cause of severe vision loss in middle-aged patients in the developed world and diabetic macular edema (DME) secondary to DR is the leading cause of visual impairment in this population.[1] In DME, fluid accumulates from the hyperpermeable retinal vessels into the retina deforming the normally highly-organized retinal anatomy and leading to vision loss ranging from a subtle blur to significant vision loss.[2] DME is identified by binocular fundoscopic examination. However, ancillary imaging plays a significant role in detection and monitoring of the disease process.

Optical coherence tomography (OCT) and fluorescein angiography (FA) play an important part in diagnosis and management of DME. OCT provides in vivo images of the retinal layers and pathology, demonstrating DME as cystic spaces that may distort the adjacent retinal layers and disrupt the normal foveal contour.[3] Automated OCT retinal thickness maps have become a standard for monitoring DME and its response to treatment.[4] However, standard OCT provides only structural information, and therefore does not delineate blood flow from the retinal vasculature. FA is the gold standard for evaluation of the retinal vasculature in DR.[5] It is a minimally invasive dye-based technique, which demonstrates a dynamic series of images of the retinal blood flow over time.[6] FA therefore has the unique ability to directly demonstrate leakage from the retinal vasculature. The ability to show leakage is critical in determining which microvascular abnormalities are contributing to the DME. While clinicians often treat DME with intravitreal injections of anti-vascular endothelial growth factor (VEGF) or corticosteroids, focal laser still plays a role in targeting the leaking retinal vasculature to treat non-foveal clinically significant macular edema.

OCT angiography (OCTA) is a relatively new imaging modality that is gaining popularity due to its quick and non-invasive nature. In a matter of minutes, the technology creates a high-resolution en face OCT angiogram of the retinal vasculature that is automatically co-registered with an OCT thickness map and multiple corresponding OCT b-scans for simultaneous viewing of both structural and blood flow information of the retina.[7] Multiple previous studies have demonstrated the potential utility of OCTA in the diabetic eye exam for detection of microvascular changes, enlargement of the foveal avascular zone, and preretinal neovascularization.[8,9,10] Advocates of the technology believe that its high-resolution, fast, and non-invasive nature will make it a staple in future clinical practice. However, skeptics note that its greatest setback is that it shows, by design, a static image of retinal blood flow and therefore lacks the ability to show leakage. Since its advent, clinicians have repeatedly expressed concerns that without the ability to show leakage the utility of OCTA is limited and therefore may never replace the current gold standard for retinal angiographic imaging.

With any new technology there is a learning curve as to how to interpret the images and manipulate them to demonstrate what is needed to make clinical decisions. As OCTA provides both structural and blood flow information, using the OCTA in its entirety, as opposed to just using the OCT angiogram alone, should offer more information. We hypothesize that by overlaying the OCT angiogram and co-registered OCT thickness map, areas of thickening on the OCT thickness map may be correlated with microvascular abnormalities seen on the OCT angiograms. This may be able to simulate “leakage” by showing which vascular changes are actively causing retinal swelling. In this paper, we demonstrate a potential technique for using OCTA to simulate leakage in eyes with DME and determine the sensitivity and positive

predictive value of detecting leaking microvasculature on OCTA using FA as the comparative norm.

Methods:

This study was approved by the Institutional Review Board of The University of Chicago at Illinois Hospitals Medical Center. The research adheres to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. This is a retrospective chart review of all diabetic patients with same-day FA and OCTA seen at the Illinois Eye and Ear Infirmary vitreoretinal surgery department between 1/1/2014 and 10/15/2017. Inclusion criteria was presence of DME on the date of the imaging as determined by the clinical exam and interpretation of FA and/or OCT by the retinal specialists (WFM, JIL, or PRVC). Exclusion criteria included other retinal/uveitic diseases, high myopia, and previous intraocular surgery other than cataract extraction. Eyes with OCTA images of poor quality were excluded; poor quality was defined as images with over 50% of the OCT angiogram obscured by artifact such as motion or poor signal strength. Data collected included age, race, gender, best corrected visual acuity (BCVA), disease stage, prior treatment and treatment type, lens status, HbA1c, and years since diagnosis of diabetes.

The AngioVue OCTA system (Optovue, Inc., Fremont, CA) was utilized for all OCTA images. It operates at 70,000 A-scans per second to acquire OCTA volumes consisting of 304x304 A-scans in a matter of seconds to create 6x6mm OCTA volumes of each eye. The OCT thickness map was overlayed over the OCT angiogram for each eye using Adobe Photoshop (Adobe Systems, San Jose, CA). The individual OCT angiogram, OCT thickness map, and one

corresponding OCT b-scan were provided in addition to the overlayed OCTA image to each reader for reference.

Two readers (TED, SZ) evaluated both of the retinal imaging modalities: an ophthalmology resident and clinical trial image reader who had previously worked as an OCT research fellow (TED) and a retina fellow (SZ) both with experience reading OCTA and FA images. The readers first independently read the OCTA overlay images to pinpoint and mark "leaking" microvasculature by correlating areas of thickening on the OCT thickness map with adjacent microvascular abnormalities such as a single microaneurysm or a cluster or microaneurysms, telangiectasias, and vascular dilatations on the underlying OCT angiogram. The readers were blinded to each other, the patient information, and the FA images. Microsoft Excel (Redmond, WA) was used to calculate the correlation coefficient between the two readers prior to adjudication and to create a Bland and Altman plot. Any discrepancies in the OCTA reads were then reconciled via open adjudication until a consensus was attained.

Over one week later, the readers were provided the FA images to ensure that the readers would not remember the vasculature seen on the OCTA images. An early-mid and a mid-late frame FA image of each eye was cropped to the approximate area of the 6x6mm OCTA and provided to the readers. The FA's were read independently by each reader to detect leaking microvasculature. The readers were blinded to each other, the patient information, and the OCTA images. Microsoft Excel was used to calculate the correlation coefficient between the two readers prior to adjudication and to create a Bland and Altman plot. Again any discrepancies were then reconciled via open adjudication until a consensus was attained. The leaking vascular abnormalities detected on the FA images were considered the comparative norm. The FA images

and OCTA images were then compared to determine the sensitivity and positive predictive value of OCTA for the detection of leaking vessels.

Results:

After five eyes were excluded for OCTA images of poor quality 32 eyes of 22 patients were included in the study. The patient population consisted of ten Hispanics, nine African Americans, two Asians, and one Caucasian. There were 11 men and 11 women included. The average HbA1c was 8.81% (range of 7.5-11%) and the average number of years since diagnosis of diabetes was 14.91 (range of 1-31). There were 16 right and 16 left eyes. The average BCVA was 0.26 (20/36) with a range of 0-1 (20/20-20/200). The majority of the eyes (23 eyes) had never undergone prior treatment but six eyes had had prior PRP and three eyes had underwent prior intravitreal anti-VEGF treatment (ranging from 4-26 prior injections). Twenty two eyes were phakic and 11 eyes were pseudophakic. The severity of DR ranged from six eyes with mild non-proliferative DR (NPDR), five eyes with moderate NPDR, three eyes with severe NPDR, and 18 eyes with proliferative DR.

The readers were able to come to a consensus on all OCTA and FA images so that no third reader was required to arbitrate. The readers demonstrated agreement in 51.2% of the detected leaking abnormalities on OCTA prior to adjudication. This is compared with about 71.2% agreement in delineating leaking abnormalities on FA prior to adjudication. The correlation coefficient between the two readers was 0.583 for OCTA reads versus 0.908 for FA reads. A Bland and Altman plot of number of detected leaking vessels on OCTA demonstrated that all but two data points fell within the 95% confidence interval of −6.24 to 5.67 with an average difference of -0.28 (Figure 1). This compares with one data point on the Bland and

Altman plot outside of the 95% confidence interval of -5.32 to 11.26 with an average difference of 2.97 for the FA reads (Figure 2). On average each eye demonstrated seven leaking microvascular abnormalities on the OCTA images compared with an average of 21 per eye seen on the FA images. The sensitivity of detection by OCTA was only 25.3%, however, the positive predictive value of OCTA was much higher at 71.3%. Figure 3 shows an example of one eye with 15 microvascular abnormalities noted to be "leaking" on the OCTA that correlate with leakage seen on FA.

Discussion:

Diabetes is a major cause of vision loss throughout the world. Consequently, increasing our understanding of this disease and facilitating the detection of DME and vascular abnormalities secondary to DR is important. At the present time, DME is most commonly treated with intravitreal anti-VEGF agents, and occasionally with intravitreal corticosteroids focal laser photocoagulation. The focal photocoagulation is still used particularly in non-foveal involving DME and cases where the patient is not a good candidate for anti-VEGF treatment. FA is currently the gold standard for detection of leaking microvascular abnormalities, which clinicians target for focal laser. However, FA can be time consuming and is invasive with the risk of the fluorescein dye ranging from nausea or local discomfort to anaphylaxis.[5,6] With the advent of OCTA, many clinicians are hopeful that it will provide an alternate method of investigating the retinal vasculature quickly and non-invasively. However, one main limitation of OCTA is its inability to directly demonstrate leakage. In this manuscript we described a method to simulate "leakage" from vascular abnormalities on OCTA and investigated its potential utility as compared with FA.

The OCTA software automatically provides multiple co-registered images within a matter of seconds: a segmentable OCT angiogram, an OCT thickness map, and multiple corresponding OCT b-scans. These images used as a whole can provide much more information than the OCT angiogram alone. However, currently most research investigators and clinicians use just the OCT angiogram in their analysis of the OCTA. By using the OCT angiogram and OCT thickness map in concert, areas of thickening on the OCT thickness map can be correlated with nearby microvascular abnormalities noted on the OCT angiogram. These adjacent vascular abnormalities can therefore be hypothesized and assumed to be the cause of the leakage. Using this method we noted a low sensitivity of OCTA, detecting only about one quarter of the leaking abnormalities noted on the FA images. However, the positive predictive value was significantly higher at 71.3%, suggesting that when evaluating the OCTA in this manor, areas of "leaking" microvascular abnormalities likely correspond to true leakage that would be seen on FA.

In this manuscript, we described overlaying the OCT angiogram and corresponding OCT thickness map. We chose this overlay technique to maintain blinding even though the OCTA software already allows simultaneously viewing of and correlation between the OCT angiogram and OCT thickness map. This is important to note as we recognize that it is not feasible to overlay images in clinic due to time constraints. However, by using the OCTA software, a clinician can quickly and easily adjust the cross-hairs to pinpoint pathology on the OCT angiogram that corresponds with areas of thickening on the OCT thickness map at the exact same location without needing to overlay the images. In this manor, the clinician would also benefit from being able to see the corresponding horizontal and vertical OCT b-scans as well in the location of the cross-hairs. This would provide even further information and potentially increase the sensitivity of detection of "leaking" vessels by giving an augmented ability to note

more subtle areas of thickening. Hopefully this information could be put to use to help make clinical decisions regarding treatment while the patient is still in clinic.

When we reviewed the areas of "leakage" noted on OCTA but that were not seen on FA, many of these areas showed subtle leakage on FA or were hidden by diffuse leakage so were not directly visualized with FA. This is a limitation of the retrospective nature of this paper. Many of the FAs were wide-field and therefore when cropped to the posterior pole region had decreased resolution, potentially masking more subtle areas of leakage. Furthermore, not all of the FAs had early frames captured of the study eye and therefore mid and late frames had to be used for analysis. Therefore, the FA images sometimes had large or diffuse areas of leakage that could hide underlying microvascular changes that the OCTA images were able to accurately delineate. Regardless, given the fairly high positive predictive value noted in this manuscript, areas of "leakage" seen on OCTA could potentially be lasered to treat the DME. Further prospective studies with more consistent early and mid phase FA images of the posterior pole would be important to more accurately determine the positive predictive value of OCTA for detection of "leakage" because we hypothesize that it could be higher than 71.3%.

The relatively low sensitivity of detection of "leakage" on OCTA, however, is notable and warrants further discussion. Often, the microvascular changes missed on OCTA were subtle changes nearby more obvious detected abnormalities, in very subtle areas of thickening on the OCT thickness map, or in the periphery of the OCTA image and thus were not readily noticed. As focal laser is sometimes performed in a small grid-like pattern, abnormalities not noted to be "leaking" but that are adjacent to the detected "leaking" microvasculature would likely be lasered as well. As to the overlooked leaking peripheral vessels, these may not always require treatment if the resulting DME is not clinically significant. However, very careful perusal of the

entire OCTA image could potentially improve detection of these vessels as many of these abnormalities were visible on the OCTA images once compared directly with the FA images after all official reads were completed. Again, this represents the learning curve for the OCTA technology. Sensitivity of detection should improve with continued usage and understanding of OCTA. Nonetheless, the low sensitivity of OCTA for detection of leaking vessels is a major limitation of this technique because focal laser to areas pinpointed by OCTA alone could potentially miss important leaking areas and therefore incompletely treat the DME.

One limitation of OCTA is the field of view. The 6x6mm OCTA image is significantly smaller than standard FA or wide-field FA. However, the 6x6mm region includes the entire posterior pole, which is where clinically significant macular edema occurs and would require treatment. As the current OCTA software uses the same number of OCT b-scans to create each of the different fields of view it offers, the larger the field of view, the lower the resolution of the image. This is because the software that creates the OCT angiograms interpolates between data points. Therefore, an OCTA image of 3x3mm has much finer detail (about 4x) than a 6x6mm image, which could possibly increase the sensitivity and positive predictive value of detection of "leaking" microvasculature. However, the 3x3mm OCTA provides such a small field of view and in an area where it is not as safe to use focal laser. A previously described montage technique using the 3x3mm OCTA images could be used to widen the field of view while maintaining the OCTA resolution especially if automated by the OCTA device.[11] Further studies using a montage of 3x3mm OCTA images could be interesting to determine if this would improve the detection of "leakage" on OCTA.

Another major limitation of OCTA is image quality. Five of 37 eyes (13.5%) were excluded in this study for poor OCTA quality. While OCTA is fast and noninvasive and

therefore can theoretically be repeated until better image quality is obtained, sometimes the quality may still be limited by patient movement due to musculoskeletal disease or inability to fixate, or signal quality secondary to media opacity such as cataracts. Although vitreoretinal interface diseases were not excluded in our study, a few eyes had epiretinal membranes (ERM) that made the images more difficult to interpret as the ERM altered the thickness maps and caused areas of thickening unrelated to DME. We chose not to exclude eyes with ERM from the study for two reasons: (1) there are varying degrees of ERM, many of which would not affect the data significantly, and (2) because ERM is common in diabetic eyes and therefore keeping eyes with ERM in the study would better simulate real-life data. Eleven eyes of eight patients had an ERM (mostly mild but one more severe case) causing puckering of the posterior pole. The sensitivity of detection of "leaking" vessels on OCTA was 21.9% for these eyes and the positive predictive value was 78.2% so comparable to the data as a whole. Figure 4 shows the eye with the most severe ERM, demonstrating a sensitivity of vessel abnormalities of 28.6% and a positive predictive value of 66.7% (limited in part by the diffuse leakage seen in the FA due to no available earlier phases).

Finally it is important to note that while this manuscript describes a potential way for OCTA to simulate leakage from microvascular abnormalities, OCTA does not directly show leakage and is still not capable of demonstrating the vasculitic leakage as seen on FA in inflammatory disease. FA remains the gold standard for directly showing leakage. However, this manuscript demonstrates that there is a learning curve for OCTA and that there are still ways that OCTA can be used and analyzed in novel ways to provide more information than previously thought possible. Importantly, the entire OCTA, not just the OCT angiogram, can be used for a myriad of new investigational techniques that may improve detection of vascular abnormalities

and increase our understanding of retinal and choroidal disease. As we described, OCTA can noninvasively demonstrate some “leaking” microvasculature. Further advancements in the technology and in our understanding of how OCTA works will increase the sensitivity and accuracy of this detection. With this advancement, in the future OCTA may be used an adjuvant to or in some cases in place of FA for imaging of retinal pathology.

Figure Legend

Figure 1. Bland and Altman plot of the number of leaking microvascular abnormalities noted by two independent readers using OCTA. All but two data points fall within the 95% confidence interval of −6.24 to 5.67 with an average difference of -0.28.

Figure 2. Bland and Altman plot of the number of leaking microvascular abnormalities noted by two independent readers using FA. All but one data point fall within the 95% confidence interval of -5.32 to 11.26 with an average difference of 2.97.

Figure 3. OCTA image of the OCT thickness map overlayed over the OCT angiogram (A1) in which 15 leaking vascular abnormalities are marked by yellow circles (A2). The mid phase (B1) and late phase (B2) FA demonstrate multiple areas of leakage. All 15 abnormalities noted on OCTA were also seen on the FA but an additional 14 irregularities were noted on the FA that were not delineated by the blinded reading by the independent readers. The sensitivity of OCTA was 51.7% and the positive predictive value was 100%.

Figure 4. OCTA image of the OCT thickness map overlayed over the OCT angiogram (A) in an eye with a signficiant ERM in which six leaking vascular abnormalities are marked by yellow circles. The corresponding OCT b-scan (B) shows puckering of the retinal layers. The mid phase (C1) and late phase (C2) FA show multiple areas of leakage as marked in green on the mid phase image in C3. The sensitivity of OCTA was 28.6% and the positive predictive value was 66.7%.

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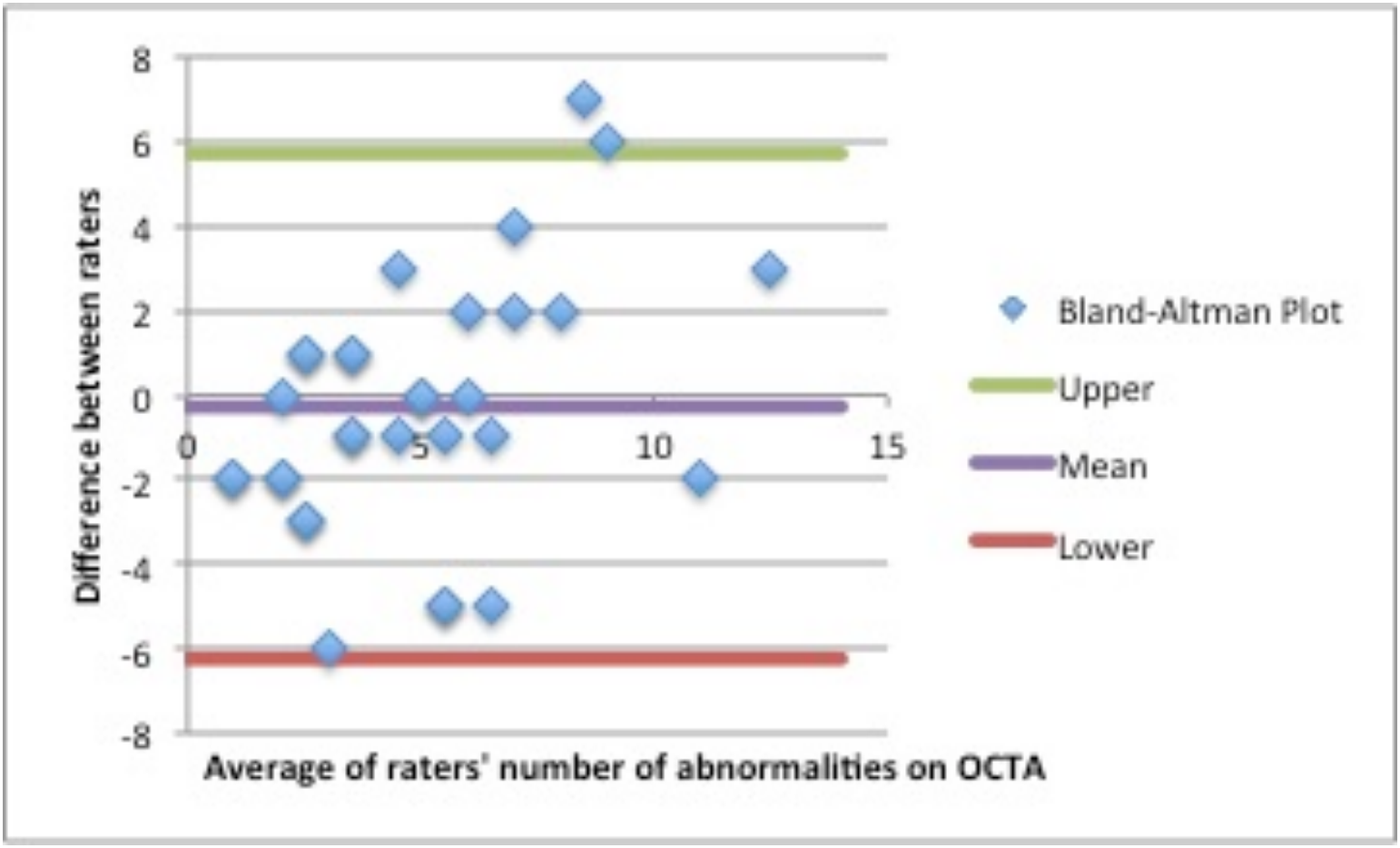
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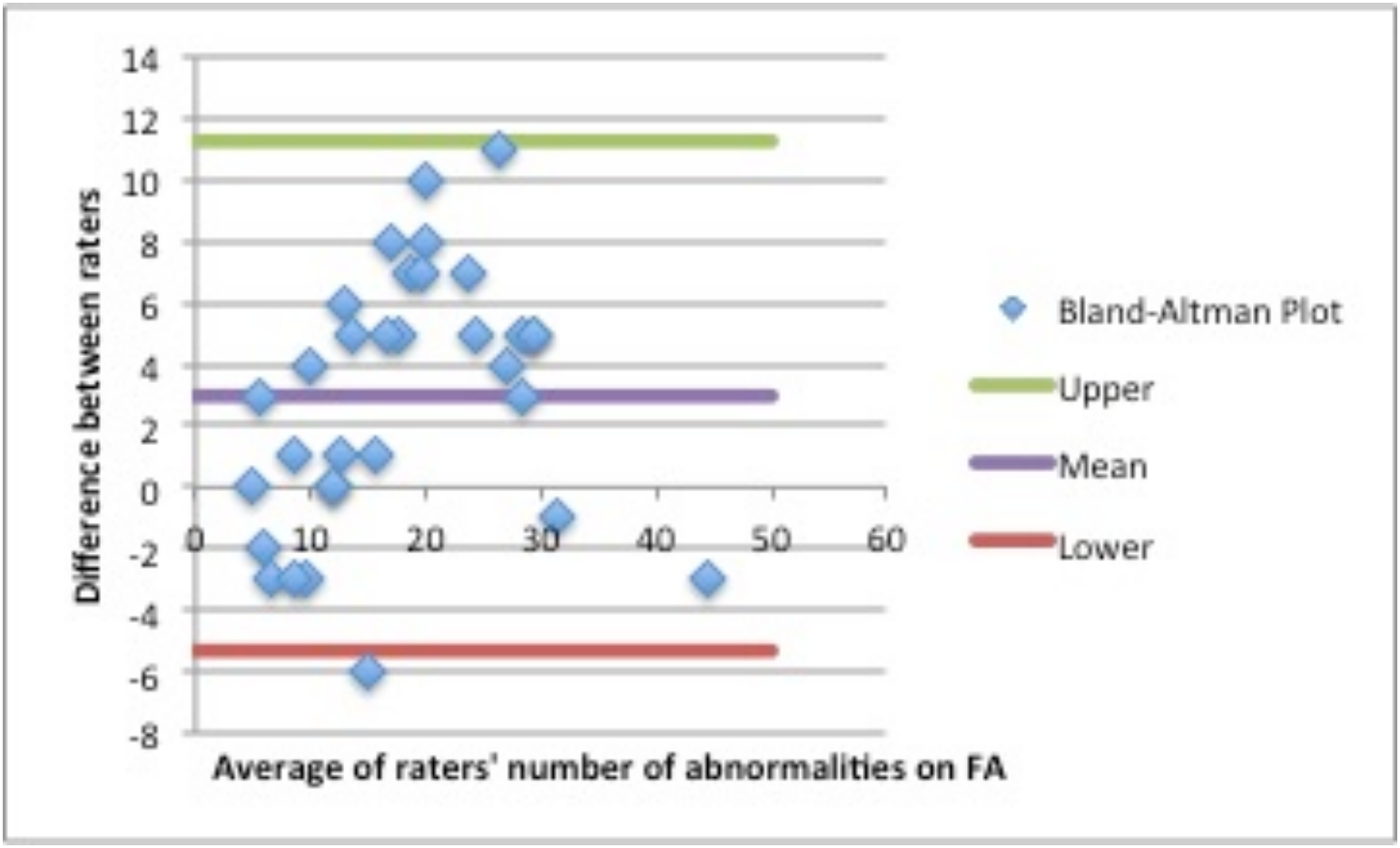
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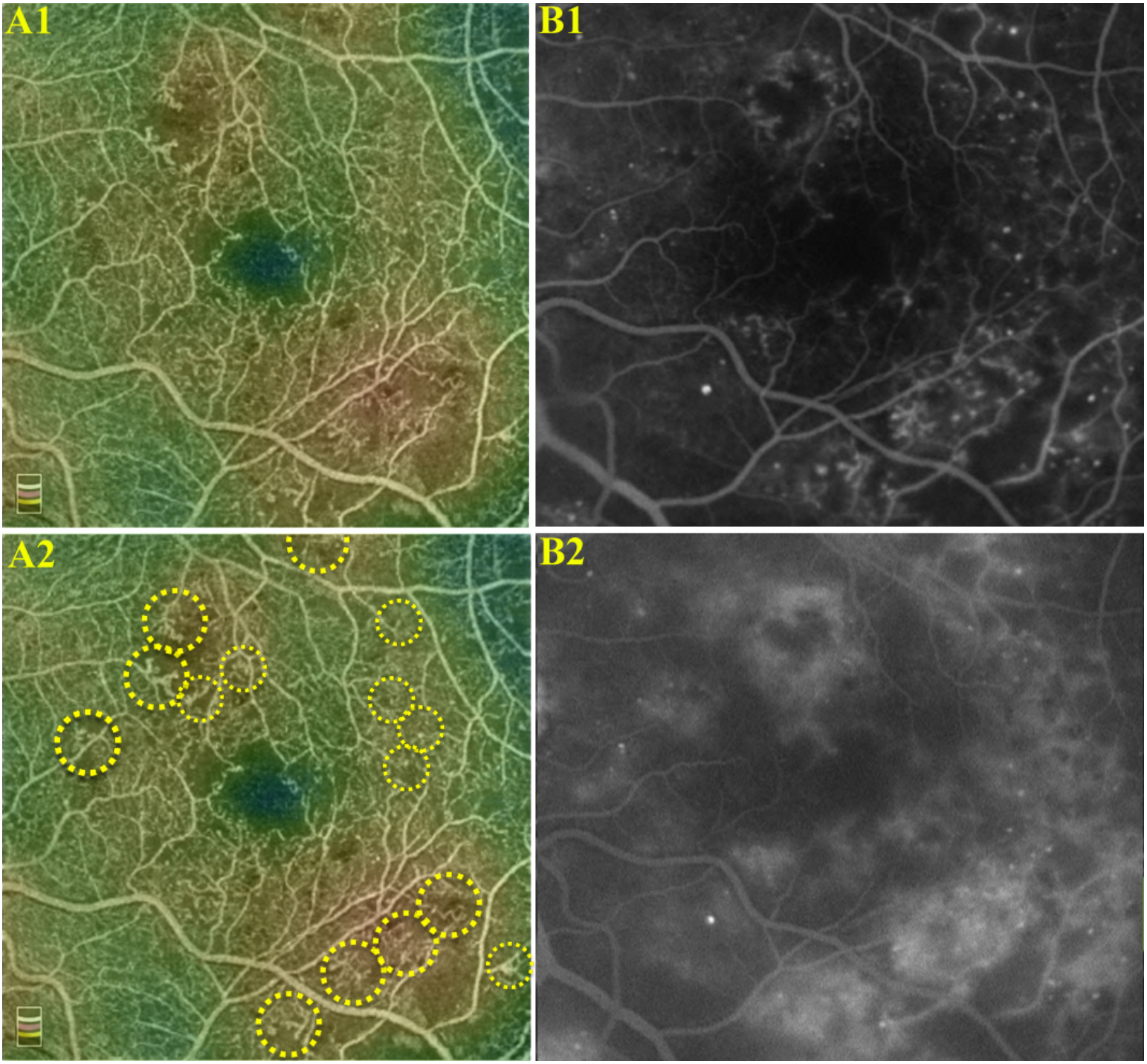
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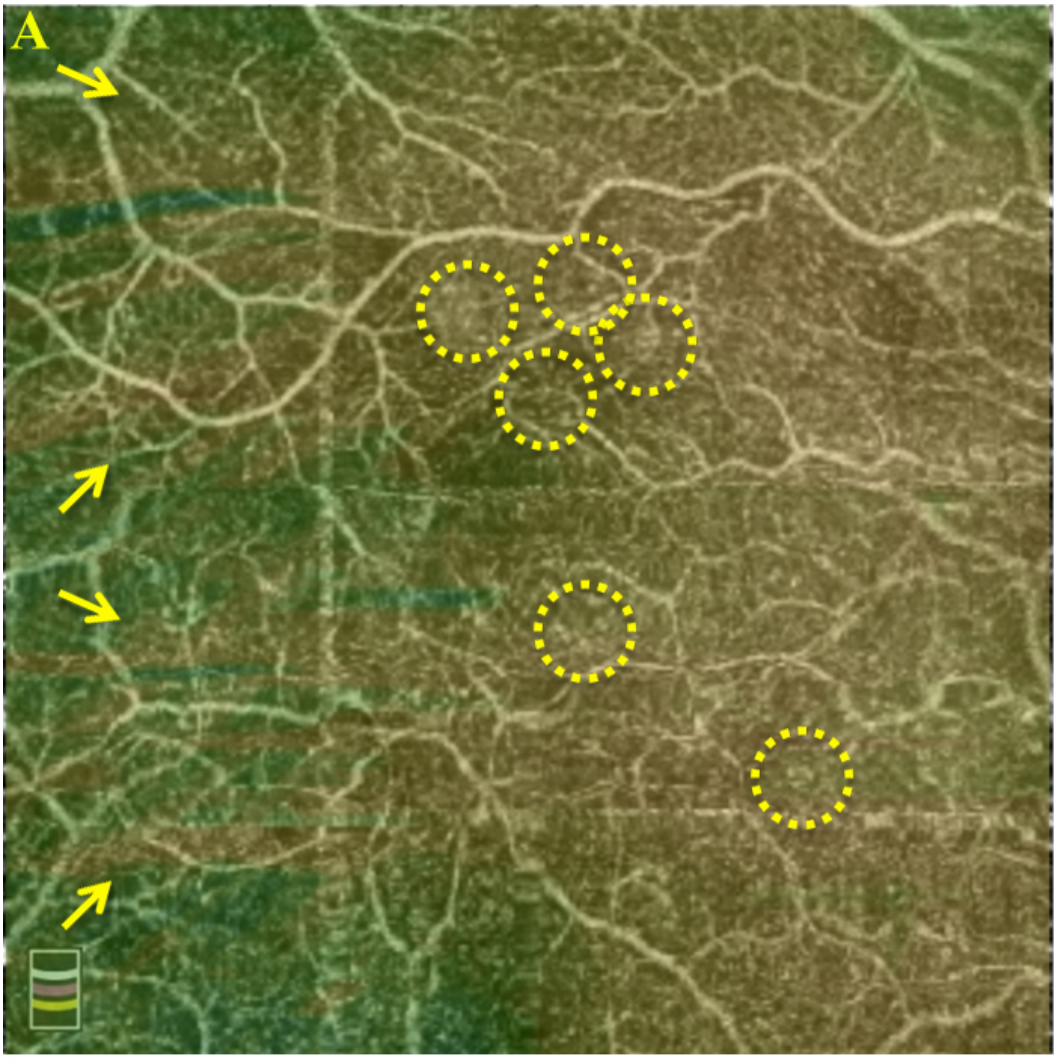
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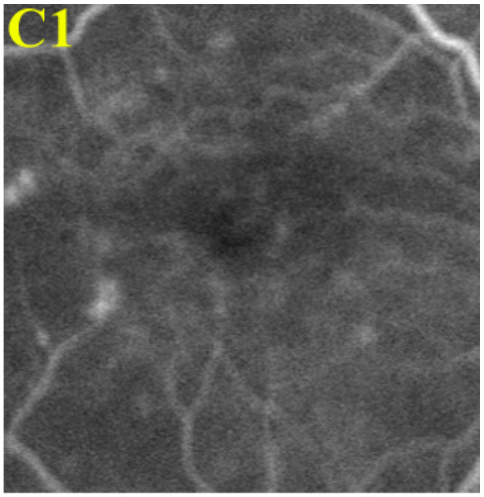
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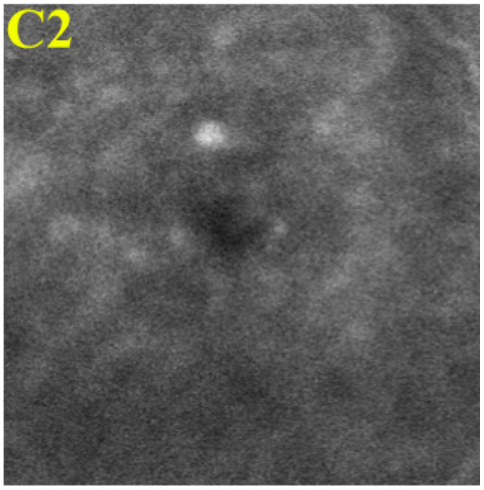
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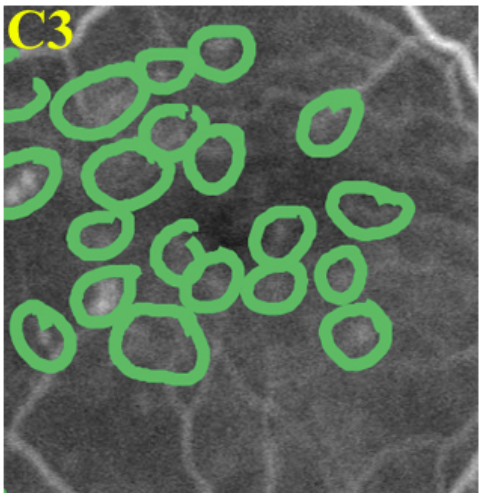
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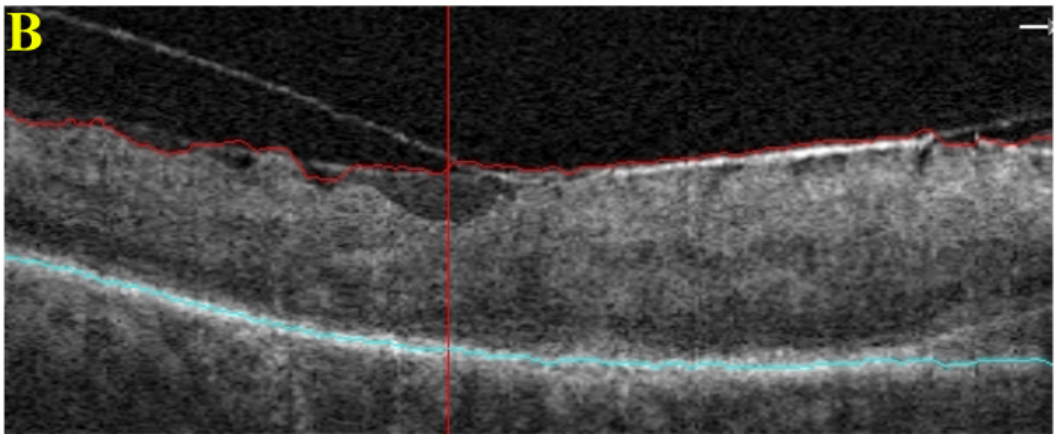
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