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Reevaluating the Definition of Intraretinal Microvascular Abnormalities and Neovascularization Elsewhere in Diabetic Retinopathy Using Optical Coherence Tomography and Fluorescein Angiography

CECILIA S. LEE, **AARON Y. LEE**, **DAWN A. SIM**, **PEARSE A. KEANE**, **HEMAL MEHTA**, **JAVIER ZARRANZ-VENTURA**, **MARCUS FRUTTIGER**, **CATHERINE A. EGAN**, and **ADNAN TUFAIL**

Medical Retina Service (C.S.L., A.Y.L., P.A.K., H.M., C.A.E., A.T.) and National Institute for Health Research Biomedical Research Centre for Ophthalmology (D.A.S., P.A.K., J.Z.-V., C.A.E., A.T.), Moorfields Eye Hospital National Health Service Foundation Trust; and University College London, Institute of Ophthalmology (A.Y.L., D.A.S., P.A.K., M.F., A.T.), London, United Kingdom

Abstract

PURPOSE—To evaluate the agreement between clinical examination, spectral-domain ocular coherence tomography (SD OCT), and fluorescein angiography (FA) in diagnosing intraretinal microvascular abnormality (IRMA) and neovascularization elsewhere (NVE) and define the SD OCT features that differentiate NVEs from IRMAs.

DESIGN—Retrospective study.

METHODS—Data were collected from 23 lesions from 8 diabetic patients, seen from July 2012 through October 2013 at Moorfields Eye Hospital, United Kingdom. Main outcomes were SD OCT features and FA leakage of IRMA and neovascular complex. The agreement between 3 evaluations was analyzed by Fleiss' kappa.

RESULTS—The following 5 SD OCT features significantly differentiated IRMAs from NVEs: (1) hyperreflective dots in superficial inner retina ($P = .002$); (2) the outpouching of internal limiting membrane (ILM) ($P = .004$); (3) the breach of ILM ($P = .004$); (4) the breach of posterior hyaloid ($P = .0005$); (5) hyperreflective dots in vitreous ($P = .008$). The agreement was moderate between 3 evaluations ($\kappa = 0.48$, $P = 7.11 \times 10^{-5}$) but substantial between clinical and SD OCT

Inquiries to Adnan Tufail, Moorfields Eye Hospital National Health Service Foundation Trust, 162 City Road, London EC1V 2PD, United Kingdom; adnan.tufail@moorfields.nhs.uk.

Current affiliations of the authors: C.S. Lee, University of Washington, Seattle, Washington; A.Y. Lee, University of British Columbia, Vancouver, Canada.

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evaluation (κ = 0.72, P = .00055). There was no significant agreement between OCT evaluation and FA leakage (κ = 0.249, P = .232).

CONCLUSIONS—SD OCT will be a valuable adjunct in evaluating IRMA and NVE, since it can verify the histopathologic correlate. SD OCT provides subtle anatomic insights and may be more accurate than clinical examination or leakage on FA, our current method of diagnosing this important endpoint, which has implications in future trial design for proliferative diabetic retinopathy prevention.

Diabetic Retinopathy (DR) is the leading causes of blindness in working-age populations worldwide.[1] Initially described by Jaeger in 1855,[2] DR was mainly categorized into nonproliferative vs proliferative disease. Proliferative diabetic retinopathy or “diabetic retinitis proliferans” was first reported by Manz in 1876,[3,4] and the initial descriptions of diabetic neovascularizations have been largely based on histopathologic description of new blood vessels that grow into the vitreous through a break of the internal limiting membrane (ILM).[5–8]

The term intraretinal microvascular abnormality (IRMA) arose much later as a clinical definition in 1968 from the Airlie Classification of Diabetic Retinopathy.[9] Histopathologic description of IRMA predates the clinical definition,[10] but Airlie classification provided an early framework for a “common language” in staging DR in clinical practice and trials.[9,11] In 1981, Diabetic Retinopathy Study report No. 7[12] provided standard photographs 8A and 8B and subsequently, IRMA became defined as tortuous intraretinal vascular segments in fields 4–7, varying in caliber from barely visible to 31 μm per Early Treatment of Diabetic Retinopathy Study (ETDRS).[13] As histopathology is limited to examining a single time point of a lesion’s evolution, whether IRMAs are a direct precursor lesion of neovascularization elsewhere (NVE) has not been established, but the severity of IRMA was shown to be a risk factor for the progression into proliferative diabetic retinopathy (PDR).[14] In fact, IRMA became one of the defining characteristics of end-stage nonproliferative diabetic retinopathy and therefore an important clinical endpoint.[15]

During the landmark trials of the Diabetic Retinopathy Study and the ETDRS, IRMA and NVE were differentiated based on color stereoscopic photographs.[12,13] Although fluorescein angiography (FA) was used in ETDRS to evaluate the degree of macular edema and the severity of DR, it was not employed for the definition of IRMAs.[16] However, ETDRS did identify that the source of “fluorescein leakage” in DR included microaneurysms, dilated capillaries, and other evident vascular abnormalities such as IRMA and neovascularization.[16] Furthermore, it was revealed that diffuse leakage in the retina was predictive of progression of DR.[17] Thus, in the time of Airlie classification and consequent landmark trials, FA findings were to be used only as an adjunct to clinical examination and color photography, rather than as the source of defining stages of DR.[9,16] However, textbooks often state that IRMAs have no or minimal leakage on FA and that this is often how they are differentiated from NVEs.[18–20]

Optical coherence tomography (OCT) is a noninvasive imaging modality that allows the evaluation of the vitreous cavity, retinal layers, retinal pigment epithelium, and choroid.[21] The advent of spectral-domain (SD) OCT has allowed better sensitivity, increased depth of

penetration, and higher resolution of each image obtained.[22] Current commercially available SD OCT provides high-resolution images with an axial resolution of <5 μm.[22,23] As a result, OCT parameters are increasingly used in various clinical trials.[24–26] With commercially available OCT, it is now possible to evaluate the disruption of the ILM and the breach of the posterior hyaloid associated with NVE or neovascularization of disc (NVD).[27,28] However, whether IRMA and NVE can be distinguished on SD OCT has not been established.

In this study, we perform detailed characterization of the SD OCT features of IRMA and NVE/NVD, with comparison to clinical and FA findings. In particular, we evaluate the ability of SD OCT to show breach of the posterior hyaloid in support of previous histopathologic descriptions of NVE, with the objective of refining disease feature definitions for use as clinical endpoints.

SUBJECTS AND METHODS

INCLUSION CRITERIA AND DATA COLLECTION

Clinical and imaging data were collected retrospectively from patients attending medical retinal clinics at Moorfields Eye Hospital, London, United Kingdom from July 1, 2012 to October 31, 2013. All patients were assessed by medical retina specialists in the same institution. Approval for data collection and analysis were obtained from the Institutional Review Board at Moorfields Eye Hospital, London, United Kingdom and adhered to the tenets set forth in the Declaration of Helsinki.

Eight patients with a diagnosis of type 1 or 2 diabetes mellitus who had undergone concurrent FA and SD OCT scanning (Spectralis; Heidelberg Engineering, Heidelberg, Germany) for evaluation of PDR were included in the study. Patients with angiographic and SD OCT image sets of insufficient quality to allow grading of DM severity and segmentation of retinal and posterior hyaloid boundaries were excluded. No image manipulation was performed. Classification of IRMA and NVE were based on a clinical diagnosis using color and red-free photographs as part of the patients' standard of care.

ACQUISITION AND ANALYSIS OF FLUORESCEIN ANGIOGRAPHY

All angiographic images were acquired with a digital retinal camera system (Topcon TRC 50IX; Topcon Medical Systems, Inc, Paramus, New Jersey, USA). Macular centered FAs with peripheral sweeps were obtained.

QUALITATIVE ANALYSIS OF FLUORESCEIN ANGIOGRAPHY IMAGES

FA and any available fundus images were reviewed independently by 2 masked graders (C.L., A.L.). FA was interpreted as leakage or no leakage.

ACQUISITION AND ANALYSIS OF SPECTRAL-DOMAIN OCULAR COHERENCE TOMOGRAPHY IMAGE SETS

SD OCT images sets were obtained using a standard, commercially available SD OCT device. In each case, both macular and extramacular raster scan acquisition protocol were performed, centered on the fovea and the NVE, respectively. SD OCT images at the NVEs

were selected either with the vertical or horizontal scanning plane bisecting the NVE, and the image set size was adjusted accordingly in order to include the whole extent of the NVE, using equally spaced OCT B-scan sections, each composed of 50–100 averaged B-scans.

QUALITATIVE ANALYSIS OF SPECTRAL-DOMAIN OCULAR COHERENCE TOMOGRAPHY IMAGES

All SD OCT image sets were reviewed independently by 2 masked graders without correlating FA or fundus images. Each image set was assessed for the presence of the following vitreo-retinal features: (1) hyperreflective dots in superficial portion of inner retina without evidence of ILM breach; (2) the outpouching of ILM without disruption in the ILM layer; (3) the breach of ILM, defined as a disruption in the ILM; (4) the breach of the posterior hyaloid, defined as a connecting hyperreflective layer from the ILM to posterior hyaloid/vitreous cavity; (5) hyperreflective dots in the vitreous cavity; (6) presence of posterior vitreous detachment (PVD), defined as a fully detached posterior hyaloid seen as a thin hyperreflective layer above the ILM.

STATISTICAL ANALYSIS

The SD OCT and FA features of IRMA vs NVE were analyzed with Fisher exact test. The concordance between clinical examination, SD OCT evaluation, and FA leakage were analyzed with Fleiss' kappa. The intra- and intergrader correlation was assessed by kappa test. Significance was defined as P value <.05. Multiple comparisons were adjusted by the Bonferroni correction. All statistical analysis was performed using R (http://www.r-project.org/).

RESULTS

BASELINE CHARACTERISTICS

Twelve eyes (8 patients) were included, and a total of 23 lesions were examined. Six lesions in 1 patient were followed for 14 months. The baseline demographics and clinical characteristics of the study patients are summarized in Table 1. The mean age was 46.1 years (SD = 15.1) and 6 patients were male. Two patients had type 1 diabetes. Two patients had previous panretinal photocoagulation. Out of 18 eyes, 7 had a single lesion and 2 had more than 2 lesions.

CHARACTERISTIC SPECTRAL-DOMAIN OCULAR COHERENCE TOMOGRAPHY FEATURES IN CLINICALLY DIAGNOSED INTRARETINAL MICROVASCULAR ABNORMALITIES VS NEOVASCULAR COMPLEX (NEOVASCULARIZATION ELSE-WHERE OR OF DISC)

Clinically diagnosed IRMA and NVE were based on the clinician's best judgment at the time of evaluation, assisted by color photographs when available. SD OCT images were graded without prior knowledge of clinical diagnosis. No patient had a complete PVD on OCT. All 5 SD OCT features significantly differentiated IRMAs from NVEs even after adjustment for multiple comparisons (Table 2). First, hyperreflective dots in the inner retina, without breach of the ILM (Figure 1, Top left), were seen in 70% (7/10) of clinically diagnosed IRMAs but in none (0/13) of the NVEs (P = .002). Second, outpouching of the

ILM without disruption of this layer was observed in 80% (8/10) of clinically diagnosed IRMAs but in only 7.7% (1/13) of NVEs ($P = .004$) (Figure 1, Top middle). Third, disruption of the ILM without breach of the posterior hyaloid (Figure 1, Top right) was observed in 20% (2/10) of clinically diagnosed IRMAs and in 92.3% (12/13) of NVEs ($P = .0007$). Fourth, breach of the posterior hyaloid was seen in 20% (2/10) of clinical IRMAs and 100% (13/13) of NVEs (Figure 1, Bottom left). Several lesions had multiple areas of breach and a horizontal growth pattern (Figure 1, Bottom middle). Lastly, hyperreflective dots in the vitreous were observed adjacent to 10% (1/10) of clinically diagnosed IRMAs and 69.2% (9/13) of NVEs ($P = .002$) (Figure 1, Bottom right).

ASSESSMENT OF INTRARETINAL MICROVASCULAR ABNORMALITIES VS NEOVASCULAR COMPLEX (NEOVAS-CULARIZATION ELSEWHERE OR OF DISC)

Based on clinical examination, 10 of 23 lesions (43.5%) were IRMAs and 13 of 23 (56.5%) neovascular complexes (2 NVDs, 11 NVEs). Using the SD OCT evidence of the breach of the ILM as the defining criterion of NVE, 8 of 23 (34.8%) were IRMAs and 15 of 23 (65.2%) were neovascular complexes (2 NVDs, 13 NVEs). Figure 2 (Top left) shows an example of a clinically defined IRMA that has a clear disruption of the ILM on OCT (Figure 2, Top right), but that did not leak on FA (Figure 2, Bottom). Five out of 10 clinically defined IRMAs (50%) and 12 out of 13 clinically defined NVDs or NVEs (92.3%) showed leakage on FA. Figure 3 shows 3 clinically defined IRMAs and their SD OCTs, respectively (Figure 3, Top left and Bottom row). There is diffuse leakage from all 3 lesions on FA (Figure 3, Top middle and Right).

AGREEMENT BETWEEN CLINICAL EXAMINATION, SPECTRAL-DOMAIN OCULAR COHERENCE TOMOGRAPHY EVALUATION, AND FLUORESCEIN ANGIOGRAPHY RESULTS

The agreement between 3 evaluations (clinical, SD OCT, FA) was moderate, with kappa value (κ) of 0.48 ($P = 7.11 \times 10^{-5}$). There was substantial agreement between clinical examination and SD OCT evaluation of NVE, with the highest κ of 0.72 ($P = .00055$). The agreement between clinical examination and FA leakage in evaluation of NVE was fair ($\kappa = 0.25$ $P = .042$). There was no significant agreement between SD OCT evaluation of NVE and FA leakage ($\kappa = 0.249$, $P = .232$). Reproducibility of grading of all images between 2 graders was substantial, with a weighted $\kappa = 0.87$ (SE = 0.09).

CASE STUDY

A 25-year-old white man with type I diabetes was referred to our medical retina clinic from the United Kingdom national diabetic retinopathy screening program. On initial examination, he had proliferative changes in both eyes and several IRMAs in both eyes. There were a total of 5 IRMAs that were clinically noted in the left eye and the diagnosis was supported by the absence of the ILM breach on SD OCT (Figure 4, First row, left). Four out of 5 IRMAs showed severe leakage on the FA. This patient underwent panretinal photocoagulation in both eyes and was followed every 2–3 months for 18 months, during which he received 2 additional fill-in laser therapies.

His infrared and OCT images of the initial evaluation showed an IRMA located superotemporal to the disc in the left eye (Figure 4, First row). The initial outpouching of the ILM became more prominent 4 and 9 months later (Figure 4, Second row and Third row). Eventually, this IRMA progressed into an NVE 14 months after the initial evaluation (Figure 4, Fourth row). During his follow-up, 3 out of 5 IRMAs breached the ILM and became NVEs in a similar fashion.

DISCUSSION

This study has reviewed the initial histopathologic descriptions of neovascularization in DR, and demonstrated the potential use of SD OCT in evaluating the vitreoretinal characteristics of aberrant neovascular structures for the purpose of distinguishing between NVEs and IRMAs. FA is an important imaging modality and is useful for assessing macular edema and the DR severity. Although helpful in determining the activity of the NVEs, leakage in FA alone may not be sufficient for differentiating NVEs from IRMAs. This is because FA leakage can occur in other settings, such as in dilated capillaries and vascular abnormalities other than with NVE. Furthermore, FA is an invasive test and is time consuming, making it less than ideal for frequent use in routine disease monitoring.

The current gold standard of differentiating IRMA from NVE is by clinical examination. IRMAs were defined by the tortuosity and the caliber of vessels on standard photographs.[9,12,13] The histopathologic definition of NVE states that breach of the ILM and growth into posterior hyaloid should occur only in NVEs and never in IRMAs. With current SD OCT technology, it is possible to noninvasively evaluate a cross-section of the vitreous and retinal layers, thereby confirming or refuting the breach of ILM or posterior hyaloid. In accordance with early histopathologic definitions, posterior hyaloid breach on SD OCT was used as the defining diagnostic criterion for NVE in our study. The SD OCT diagnosis of neovascularization was in agreement with clinical diagnosis in 84.6% of our cohort. It is interesting that in 15.4% of cases, there was disagreement between both methods. Although the gold-standard clinical definition of IRMA and NVE (with standard photographs) is what has been used in daily clinical settings and in major clinical trials such as ETDRS, it is the SD OCT characteristics that more parallel the original definition of NVE. Therefore, it is difficult to determine which diagnosis to accept when 2 modalities do not agree. It may be that SD OCT findings should be incorporated into current definitions of both IRMA and NVE. However, we recognize that the validity of this additional test can only be answered in large-scale studies.

The identity of hyperreflective dots in the inner retina has been suggested to be either microglia-activated cells[29] or new vessels.[30] It has been hypothesized that there may be inflammation around retinal capillaries mediated by the surrounding microglia.[31] Furthermore, these dots have been described in both inflammatory retinal conditions and other retinal vascular pathology.[32] In our study, they were present in IRMAs and active NVEs but not in inactive NVE that was fibrosed and did not leak on FA. We think that hyperreflective dots may represent initial changes in the earliest stage of IRMA that persist until the IRMAs or NVEs are no longer active. Although nonspecific, the presence of hyperreflective dots on SD OCT in the area of suspicious vascular lesions may be used in

clinical practice to indicate that the patient requires close monitoring. Further studies with comparative histopathology would be useful to validate these features.

It is well known that moderate to severe IRMA increases the risk of developing PDR.[14] However, the notion that IRMAs are direct precursors of NVE is controversial. In our study, only 3 IRMAs progressed to NVEs while they were being followed longitudinally (Figure 4). We observed that the transition from IRMA to NVE commenced with an initial outpouching of the ILM without the disruption of this layer. It has been suggested that once there is a disruption of the ILM, the early neovascular complex grows into the potential space between the ILM and the posterior hyaloid.[33,34] The underlying mechanism is thought to be attributable to leakage from the vessels that creates a focal detachment of the vitreous into which new vessels can grow.[33,34] In our study, we similarly observed that once there was a breach into the posterior hyaloid, NVE grew across the horizontal plane of the posterior hyaloid. Once this potential space was created, it was common to observe multiple breaches across the posterior hyaloid face as the NVE became larger. Given our small cohort, whether IRMA and NVE originate from the same pathologies is still unanswered. However, to our knowledge, this is the first time that the possible progression from IRMA to NVE has been shown on SD OCT. Further studies with larger cohorts with serial imaging will be needed to better understand the pathophysiology of neovascular progression.

In light of the findings from this study, we propose the following SD OCT features, which defined the different stages of IRMA and NVE, in Table 3. Stage I of IRMA is defined by early vascular or inflammatory changes noted as hyperreflective dots in inner retina, but no breach or outpouching of the ILM. They may correspond to microglia-activated retinal capillary changes indicative of the activity of retinopathy.[29] Stage II of IRMA is defined by the outpouching of the ILM (Figure 4, First row). As the size of vascular abnormalities enlarges, the outpouching area enlarges accordingly (Figure 4, Second row). Finally, if these vessels are observed to grow outward towards the vitreous—the site of least resistance—this distinguishes an IRMA from a stage I NVE. At this point, although there is a breach of the ILM, the lesion does not extend into the vitreous cavity, and the hyperreflective posterior hyaloid layer appears intact despite the presence of the NVE through the break of the ILM (Figure 1, Top right). Stage II NVE is defined by the growth along the posterior hyaloid. The time period between stages I and II of NVE is likely minimal, given that it was rare to find an NVE lesion that had only ILM breach without the breach of the posterior hyaloid in our study. Stage III of NVE appears to involve multiple areas of breach (Figure 1, Bottom middle) and linear growth along the horizontal plane of the posterior hyaloid. However, some NVEs may grow vertically into the vitreous cavity (Figure 1, Bottom left), and the significance of different growth patterns is unclear. Once the NVE is firmly established in connection with vitreous, it appears to cause some contraction and cleavage in the vitreous cavity.

The vitreous appears to provide a scaffolding for NVE's growth[35] and a complete PVD has been shown to lower the risk of PDR.[35] Indeed, none of our patients had a complete PVD. It has been suggested that an iatrogenic PVD, either surgical or chemical, may decrease the risk of developing PDR.[35] However, it is noteworthy that a developing PVD is also an important factor in precipitating a vitreous hemorrhage by the disruption of both active and

inactive neovascular complexes. In fact, hyperreflective vitreous dots, as seen in SD OCT, may represent a previous vitreous hemorrhage[27] or be related to the increased vascular permeability of active neovascular complex lesions. Therefore, SD OCT could not only aid in the diagnosis of low-vs high-risk PDR, but may also be used to evaluate any suspicious vascular lesions before the use of a vitreolysis agent.

There are several limitations of the study inherent to a retrospective study of a small cohort. However, the study poses important questions regarding current methods of defining IRMA and NVE. The study advocates for SD OCT features as adjunct criteria for IRMA and NVE. Clinical examination with or without standard or stereo photographs can be difficult, and the agreement in interpreting the photographs and the leakage on FA can vary between the examiners and the readers in reading centers.[16] Firstly, our study did not include stereo photographs used in the original Airlie classification. However, stereo imaging for the assessment of “depth” in the retina has all but disappeared from clinical practice since the advent of OCT, which provides detailed cross-section information from the vitreous and retina. Secondly, this study excluded patients who had low-quality images and therefore cannot assess the feasibility of obtaining adequate images in busy clinic settings. In fact, peripheral retinal NVEs are not easily scanned with OCT. However, this may change with the use of “swept-source” OCT systems with “wide-field” image acquisition. In addition, we note that the density of B-scans when reviewing NVE using the SD OCT is critical. It is possible to misinterpret the OCT definitions of NVE or IRMA if only viewing a single scan —that is, one scan may only show the outpouching of the ILM (OCT—definition of a stage II IRMA) while the adjacent scan may reveal a breach of the ILM (OCT—definition of a stage I NVE). Finally, the small number of patients may overestimate the power of the significance shown in our study. Future studies with larger cohorts are needed to better study the importance of the OCT characterizations.

In this study, we identified several OCT-derived parameters that distinguish IRMAs and NVEs. We suggest that current clinical and FA definitions of IRMA vs NVE should be supported with SD OCT findings. If these parameters are successfully validated in a prospective cohort, it may serve as important endpoints to clinical trials and direction of future studies, in particular with the introduction of vitreolysis agents and its possible role in the prevention of DR progression. Further investigations on the utility of SD OCT evaluation may also enable clinicians to more closely monitor patients without the need for FA and to consequently tailor management decisions according to the individual’s response to treatment.

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Biography

Cecilia S. Lee, MD, is currently an Acting Instructor of Ophthalmology at University of Washington in Seattle, Washington. She completed her residency at Emory University in Atlanta, Georgia, followed by a fellowship in uveitis at Washington University in St. Louis and in medical retina at Moorfields Eye Hospital in London, UK. Her research interests include non-invasive imaging in medical retina and uveitis and the ocular surface microbiome.

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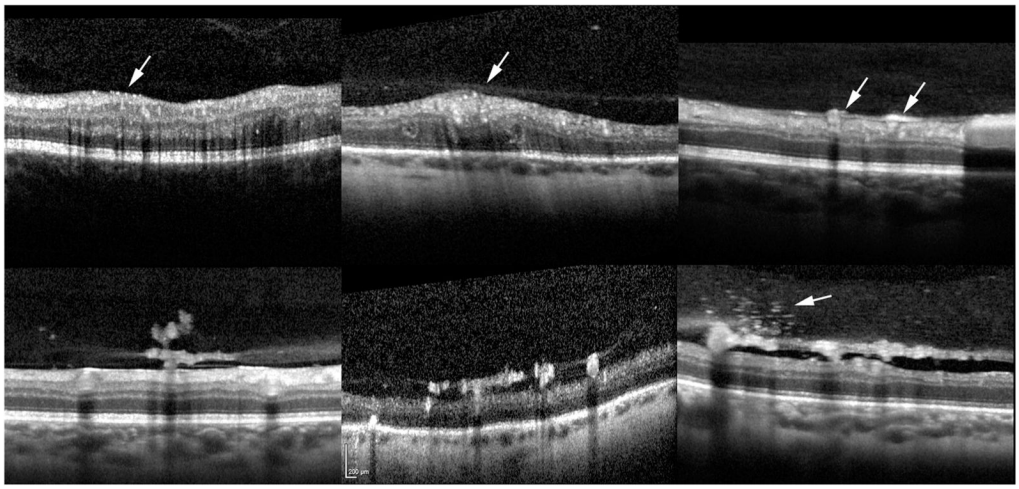

FIGURE 1.

Spectral-domain optical coherence tomography characteristics found in intraretinal microvascular abnormalities and/or neovascularization elsewhere in diabetic retinopathy. The top row illustrates different characteristics of intraretinal microvascular abnormalities on spectral-domain optical coherence tomography and the bottom row shows those of neovascularization elsewhere. (Top left) There are hyperreflective dots (arrow) in the inner retina without breach of the internal limiting membrane (ILM). (Top middle) There is an outpouching of the ILM without disruption of the layer (arrow). The contour of the ILM remains smooth. (Top right) There are 2 areas of ILM breach (arrows) without the breach of posterior hyaloid or further growth into the core vitreous. The posterior hyaloid membrane is placed over 2 lesions. (Bottom left) There is a breach of posterior hyaloid and the lesion grows into the core vitreous. (Bottom middle) The lesion shows multiple breaches of posterior hyaloid and linear growth along the horizontal plane of the vitreous cortex. (Bottom right) There are multiple hyperreflective dots in the vitreous near the neovascularization elsewhere lesion (arrow).

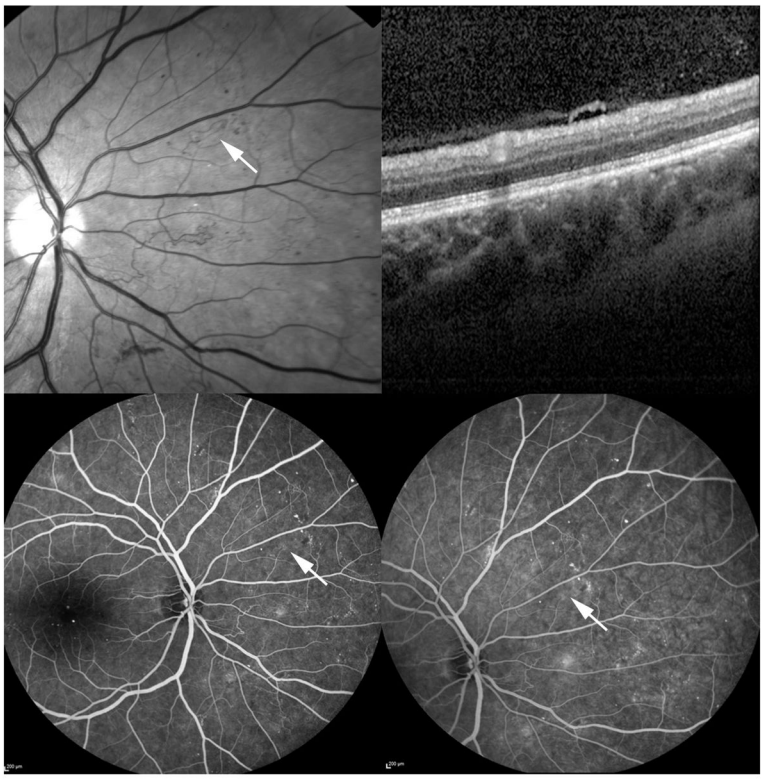

FIGURE 2.

Discrepancy between clinical grading and spectral-domain optical coherence tomography (SD OCT) imaging in defining intraretinal microvascular abnormality vs neovascularization elsewhere in diabetic retinopathy. (Top left) A red-free photograph of clinically defined intraretinal microvascular abnormality (IRMA). (Top right) Even though this lesion is diagnosed as IRMA based on clinical grading, the same lesion on SD OCT shows disruption of the internal limiting membrane and growth into the posterior hyaloid. Thus, this is defined as neovascularization elsewhere on SD OCT. (Bottom) The lesion shows no leakage on the mid (Bottom left) or late (Bottom right) phase on fluorescein angiography.

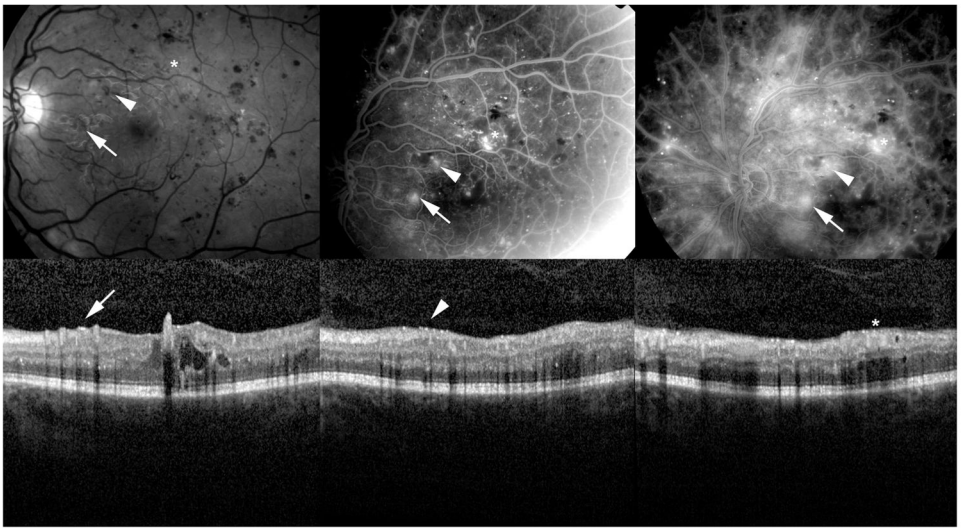

FIGURE 3.

Leakage on fluorescein angiography and spectral-domain optical coherence tomography (SD OCT) imaging of clinically defined intraretinal microvascular abnormalities (IRMAs) in diabetic retinopathy. (Top left) A red-free photograph of 3 clinically defined IRMAs shown with arrow, arrowhead, and asterisk. (Top middle) Fluorescein angiography shows early hyperfluorescence of 3 IRMAs. (Top right) Fluorescein angiography shows diffuse late leakage, including from 3 IRMAs, despite the commonly accepted idea that “IRMAs do not leak.” (Bottom) All 3 lesions were defined as IRMAs on SD OCT, supporting the clinical diagnosis. (Bottom left) SD OCT of IRMA indicated with arrow reveals multiple outpouchings of the internal limiting membrane (ILM). (Bottom middle) SD OCT of IRMA lesion indicated with arrowhead shows hyperreflective dots in the inner retina. (Bottom right) SD OCT of IRMA lesion marked with asterisk shows hyperreflective dots in inner retina and slight outpouching of the ILM.

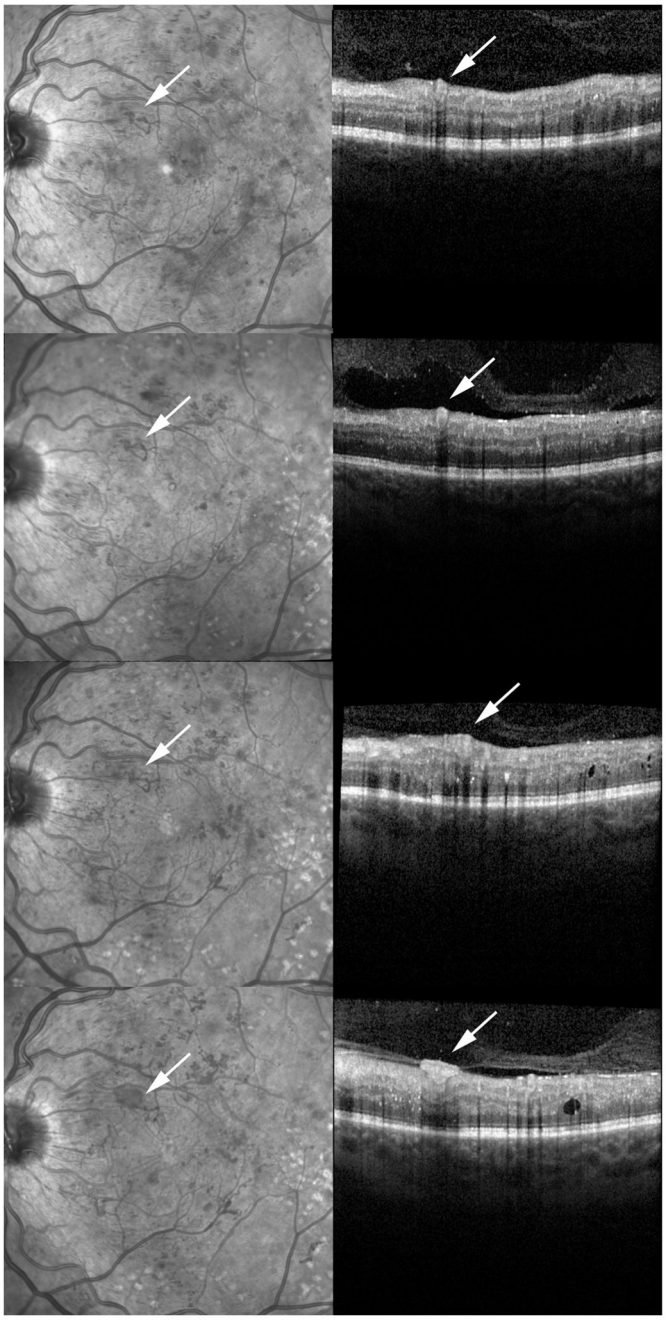

FIGURE 4.

Temporal progression of intraretinal microvascular abnormality (IRMA) to neovascularization elsewhere (NVE) of a single lesion in diabetic retinopathy over a 14-month period. (First row, left) Infrared image shows an IRMA. (First row, right) Concurrent spectral-domain optical coherence tomography (SD OCT) shows slight outpouching of the internal limiting membrane (ILM) with hyperreflective dots in the inner retina. (Second row, left) Infrared image taken 4 months after image in first row. (Second row, right) On concurrent SD OCT image, there is more distinctive outpouching of the ILM without disruption. (Third row, left) Infrared image taken 5 months after image in second row. (Third

row, right) The area of outpouching is larger without disruption of the ILM. (Fourth row, left) Infrared image taken 5 months after image in third row shows fine vessels characteristic of neovascularization. (Fourth row, right) SD OCT image shows evidence of NVE with a breach of the ILM and growth into the posterior hyaloid.

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TABLE 1

Demographics and Clinical Characteristics of Study Patients With Diabetic Retinopathy and the Diagnoses of Their Retinal Lesions Defined by Clinical Evaluation, Spectral-Domain Optical Coherence Tomography, and Fluorescein Angiography

Patient	Age	Sex	Type DM	Lesion No.	Laterality	Clinical Dx	OCT Dx	FA Leakage[a]	Previous PRP
1	47	M	2	1	OD	NVE	NVE	+	Yes
				2	OS	IRMA	IRMA	−	Yes
2	57	M	2	3	OS	IRMA	IRMA	−	No
				4	OS	NVE	NVE	+	No
				5	OS	NVE	NVE	+	No
				6	OS	NVE	NVE	+	No
				7	OS	NVE	NVE	+	No
3	25	M	1	8	OD	NVE	NVE	+	No
				9	OS	IRMA	IRMA	+	No
				10	OS	IRMA	IRMA	+	No
				11	OS	IRMA	IRMA	+	No
				12	OS	IRMA	IRMA	+	No
				13	OS	IRMA	IRMA	−	No
4	26	F	1	14	OD	IRMA	NVE	−	No
				15	OD	NVE	NVE	+	No
				16	OS	NVE	NVE	+	No
5	44	M	2	17	OD	NVD	NVD	−	Yes
				18	OD	NVE	NVE	+	Yes
				19	OS	NVE	NVE	+	Yes
6	65	M	2	20	OS	IRMA	IRMA	−	No
7	62	F	2	21	OD	NVE	NVE	+	No
				22	OD	NVD	NVD	+	No
8	43	M	2	23	OS	IRMA	NVE	+	No

DM = diabetes mellitus; Dx = diagnosis; FA = fluorescein angiography; IRMA = intraretinal microvascular abnormality; NVD = neovascularization of disc; NVE = neovascularization elsewhere; OCT = optical coherence tomography; PRP = panretinal photocoagulation.

[a] + indicates FA leakage; - indicates no FA leakage.

TABLE 2

Analysis of Spectral-Domain Optical Coherence Tomography Features in Evaluating and Distinguishing Clinically Diagnosed Intraretinal Microvascular Abnormality vs Neovascularization Elsewhere in Diabetic Retinopathy

	IRMA (n)	NVE (n)	*P* Value	Adjusted *P* Value
Hyperreflective dots in inner retina	7	0	.00049	.0024
ILM outpouching	8	1	.00073	.0036
ILM breach	2	12	.00073	.0036
Posterior hyaloid breach	2	13	.000092	.00046
Vitreous dots	1	9	.0017	.0084

ILM = internal limiting membrane; IRMA = intraretinal microvascular abnormality; NVE = neovascularization elsewhere.

TABLE 3

Proposed Stages of Intraretinal Microvascular Abnormality and Neovascularization Elsewhere Based on Spectral-Domain Optical Coherence Tomography Features in Diabetic Retinopathy

Stage of Vascular Abnormality	SD OCT Features
Intraretinal microvascular abnormality	
Stage I	Hyperreflective dots in inner retina
Stage II	Outpouching of ILM
Neovascularization elsewhere	
Stage I	Disruption of ILM
Stage II	Horizontal growth along posterior hyaloid
Stage III	Multiple breach of posterior hyaloid and linear growth

ILM = internal limiting membrane; SD OCT = spectral-domain optical coherence tomography.