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Case report

Projection-resolved optical coherence tomography angiography exhibiting early flow prior to clinically observed retinal angiomatous proliferation

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ABSTRACT

Purpose: The purpose of this study is to analyze early retinal angiomatous proliferation (RAP) utilizing a novel imaging modality, Projection-Resolved Optical Coherence Tomography Angiography (PR-OCTA).
Observations: Five months prior to the diagnosis of a RAP lesion, cross-sectional PR-OCTA demonstrated flow in the outer retina contiguous with the deep retinal capillary plexus (DCP) and adjacent to a small pigment epithelial detachment. After development of a clinically visible RAP lesion, cross-sectional PR-OCTA demonstrated the RAP lesion connecting DCP and sub-retinal pigment epithelial neovascularization.
Conclusions & importance: This is the first report of PR-OCTA demonstrating abnormal flow in the outer retina prior to the development of a clinically detectable RAP lesion. PR-OCTA may be useful for surveillance and to help further characterize and stage RAP lesions.

1. Introduction

Retinal angiomatous proliferation (RAP) or type 3 neovascularization is a well-recognized variant of neovascular age-related macular degeneration (AMD) characterized by intraretinal hemorrhage (IRH) and cystic retinal edema.[1–6] Structural optical coherence tomography (OCT) may additionally demonstrate the presence of accompanying pigment epithelial detachment (PED) or intraretinal pigment migration.[3]

Optical coherence tomography angiography (OCTA) is a novel functional extension of OCT that enables non-invasive visualization of separate retinal capillary plexuses as well as choroidal neovascularization.[7–12] One limitation of OCTA is that moving red blood cells in the inner retinal vessels project fluctuating shadow artifact onto the deeper layers of the retina creating artificial flow signals. On cross-sectional OCTA, projection artifact appears as "tails" below *in situ* flow most prominent on hyperreflective structural regions, and *en face* images contain artificial inner retinal vasculature visible in deeper retinal tissue.

A recent image processing algorithm termed projection-resolved OCTA (PR-OCTA) mitigates projection artifact by resolving the ambiguity between true flow signal and projection artifacts.[10] PR-OCTA detects voxels with *in situ* flow as those where intensity-normalized decorrelation values are higher than all shallower voxels in the same axial scan line, providing artifact resolution for both *en face* and cross sectional OCTA. In commercial OCT angiography, the flow projection artifact is suppressed with a slab-subtraction (SS) algorithm. A notable limitation of the SS algorithm, in contrast to PR-OCTA, is the failure to remove prominent tail artifacts on cross-sectional OCT angiograms. Adequate resolution of these artifacts is particularly necessary to capture axially directed flow which is characteristic of RAP. We herein present OCTA and PR-OCTA findings of a RAP lesion prior to diagnosis, at clinical diagnosis, and with subsequent therapy.

2. Materials and methods

Following Institutional Review Board approval, multimodal retinal imaging including structural OCT, color fundus photography,

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and fluorescein angiography was retrospectively reviewed. OCT angiograms were acquired using the commercially available scan protocols with the spectral domain OCT (RTVue-XR Avanti) based on the split-spectrum amplitude decorrelation angiography (SSADA) algorithm.[8] These images were subsequently exported to the Casey Eye Reading Center for application of PR-OCTA algorithm and semi-automated segmentation.[10] The deep capillary plexus (DCP) of the retina was defined as flow between the outer half of inner nuclear layer and the outer boundary of the outer plexiform layer (OPL). Outer retinal flow was localized between the outer boundary of the OPL and Bruch's membrane (BM). Purple segmentation lines were utilized to depict the inner limiting membrane, yellow lines the interface of OPL and outer nuclear layer, and green lines the interface of retinal pigment epithelium (RPE) and BM. Inner retinal flow was depicted as purple, outer retinal flow as yellow, and choroidal flow as red.

DCP and outer retinal e*n face* angiograms consisted of maximal flow projection along axial (Z) dimension. Thick (100 μm) cross-sectional OCT angiograms consisted of 10 axial frames. Cross-sectional structural OCT images were represented by the reflectance signals in the middle of the thick cross-sectional OCTA (Fig. 2A,D).

2.1. Case report

A 79-year-old male with neovascular AMD in the right eye presented with vision loss in the left eye. Visual acuity measured 20/40, IRH was detected superior to the fovea by fundus exam and was associated with leakage on fluorescein angiography (Fig. 1A–B). Cross-sectional OCTA showed intra-retinal fluid (IRF) and abnormal flow in the outer retina, however projection artifact is present on retinal pigment epithelium (RPE) and artifact "tails" of *in situ* flow limit depth discrimination (Fig. 1C). With cross-sectional PR-OCTA, projection artifact is removed allowing easier discrimination of RAP lesion depth (Fig. 1D). Three-dimensional volume rendering of OCTA illustrates axially directed flow within the RAP lesion (Supplementary Video).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ajoc.2017.10.001.

Five months prior, the patient had received OCTA imaging of the left eye as part of routine evaluation. Scans were reviewed focusing on the region superior to the fovea: *en face* PR-OCTA of DCP showed a single vessel that was slightly dilated and brighter compared to surrounding DCP (Fig. 2A). Flow could not be confirmed by conventional OCTA due to tail artifact (Fig. 2B). Cross-sectional PR-OCTA detected flow in the outer retina associated with a very small PED and no IRF was present (Fig. 2D). Thick cross-sectional OCTA revealed outer retinal flow was contiguous with DCP without extension into the sub-retinal pigment epithelial (RPE) space (Fig. 3). The axially oriented RAP lesion appeared small with *en face* OCTA (Fig. 3).

At the time of RAP diagnosis, monthly treatment with aflibercept was initiated. After three injections, treatment interval was extended to every six weeks. Serial PR-OCTA demonstrates RAP

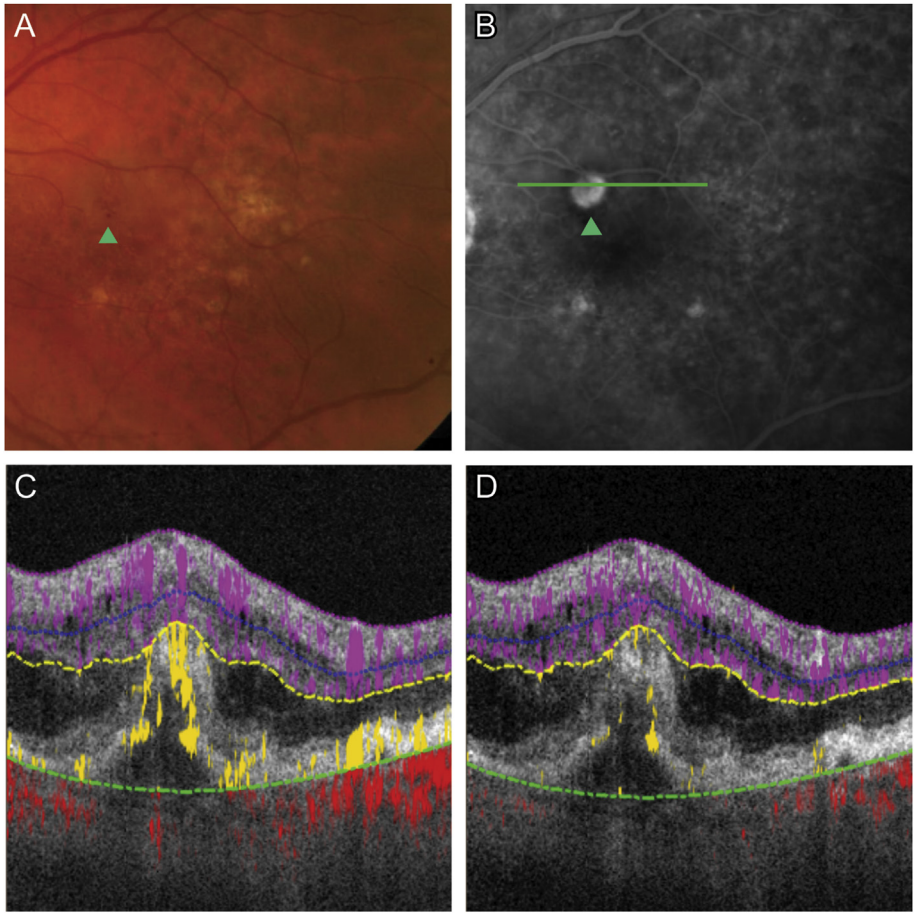

Fig. 1. Retinal angiomatous proliferation (RAP) at the time of diagnosis.
(**A**) Color photo and (**B**) fluorescein angiography of RAP lesion (green arrow). (**C**) Cross-sectional (corresponds to green line in B) optical coherence tomographic angiography (OCTA) revealed abnormal flow in the outer retina (yellow), however projection artifact is present. With cross-sectional PR-OCTA, projection artifact is removed allowing easier discrimination of RAP lesion depth (**D**). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

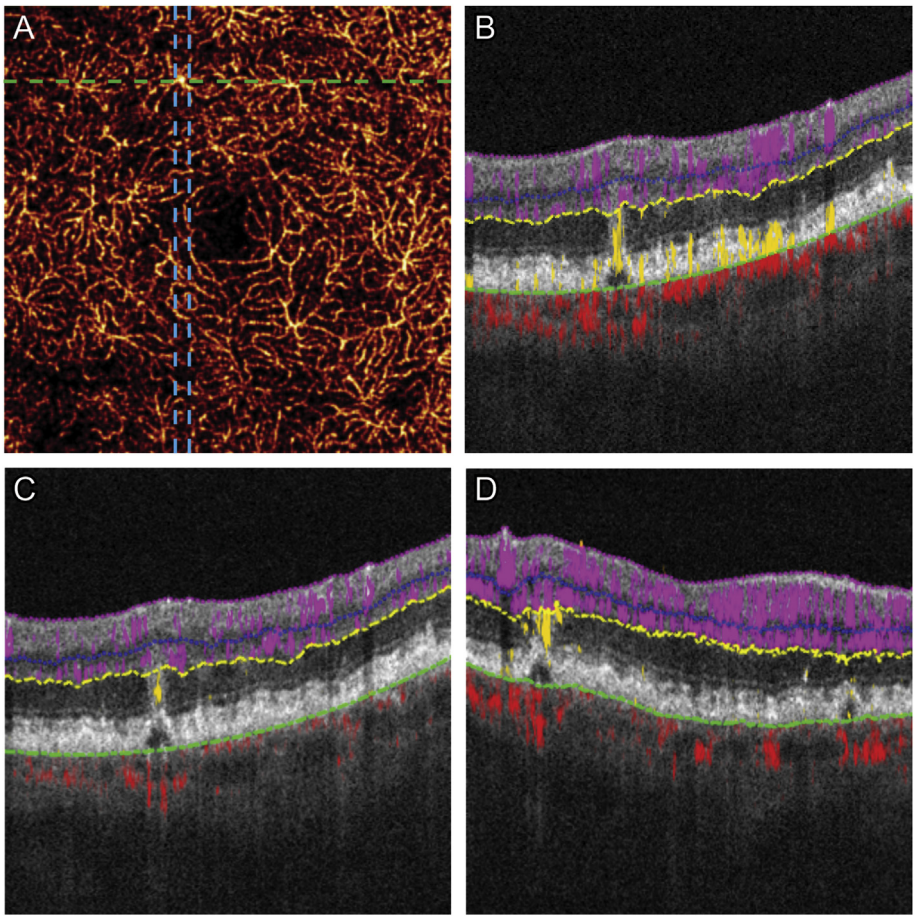

Fig. 2. Outer retinal flow detected five months prior to clinical diagnosis of retinal angiomatous proliferation (RAP).
(A) 3 × 3 mm projection-resolved optical coherence tomography (PR-OCTA) showing a single vessel that was slightly dilated and brighter compared to surrounding deep capillary plexus (**B**) Conventional OCTA does not clearly depict whether flow is associated with the pigment epithelial detachment (PED) due to extension of tail artifact to the PED (**C**) Cross-sectional PR-OCTA, in contrast, clearly detected flow in the outer retina associated with the very small PED. (**D**) Flow was confirmed on thickened perpendicular cross-sectional OCTA composed of 10 axial cross-sectional frames, corresponding to frames between the blue lines in (A). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lesion evolution and response to treatment. *En face* DCP PR-OCTA shows enlargement of the DCP vessel compared to five months prior to clinical appearance of RAP lesion (Fig. 3A). One month after treatment, the vessel appears less dilated (Fig. 3D). Six months following initiation of treatment and during longer treatment interval, the DCP vessel becomes more dilated and prominent (Fig. 3J). *En face* outer retinal PR-OCTA reveals growth of neovascularization and lesion persistence while under treatment (Fig. 3 B,E,H,K). Serial thick cross-sectional PR-OCTA reveals extension of outer retinal flow into the sub-RPE space leading up to RAP diagnosis (Fig. 3C,F). One month following treatment, despite resolution of IRF, flow persists above and below the PED (Fig. 3I). Subsequent to extension of treatment interval, the PED enlarges and IRF reoccurs. Thick cross-sectional PR-OCTA demonstrates persistent sub-RPE flow consistent with neovascular tissue.

3. Discussion

This is the first case report using PR-OCTA demonstrating the development of a RAP lesion prior to symptoms and classically described clinical features. Vessels in early RAP lesions are small and primarily axially oriented, rendering them difficult to detect with *en face* OCTA (Fig. 1B); cross-sectional OCTA is particularly useful in this setting. Further, RAP lesions often have associated hyper-reflective material and pigment migration in the outer retina.[1–5] These features are highly susceptible to projection artifact and potentially may lead to false positive flow detection in the outer retina. Previous studies utilized slab subtraction projection artifact removal in which *en face* superficial retinal vessel slab is subtracted from outer retinal slab.[13] This technique removes large vessel projection artifact for *en face* images only, whereas PR-OCTA mitigates artifact in both *en face* and cross-sectional OCTA. PR-OCTA in this case improved interpreter confidence to recognize true flow signal from projection artifact with cross-sectional OCTA, an invaluable strength of the PR algorithm (Fig. 1C-D). A single cross-sectional PR-OCTA frame reveals a fine cut through the RAP lesion, whereas thick cross-sectional OCTA aided in identifying the extent of the lesion (Fig. 2C-D).

Previous reports have described RAP with conventional *en face* OCTA.[7,11,12] At the time of clinical diagnosis and while under treatment, our case had a curvilinear morphology as previously described.[12] Two previous studies demonstrated reduction of flow after treatment of RAP lesions[11,12] In our case, the sub-RPE component of the RAP lesion appeared less responsive to treatment at one month (Fig. 3F,I) compared to the DCP component of the RAP lesion (Fig. 3D,G). The DCP component of the RAP lesion enlarged while the treatment interval was extended. Further longitudinal study with PR-OCTA is needed to determine if RAP lesion

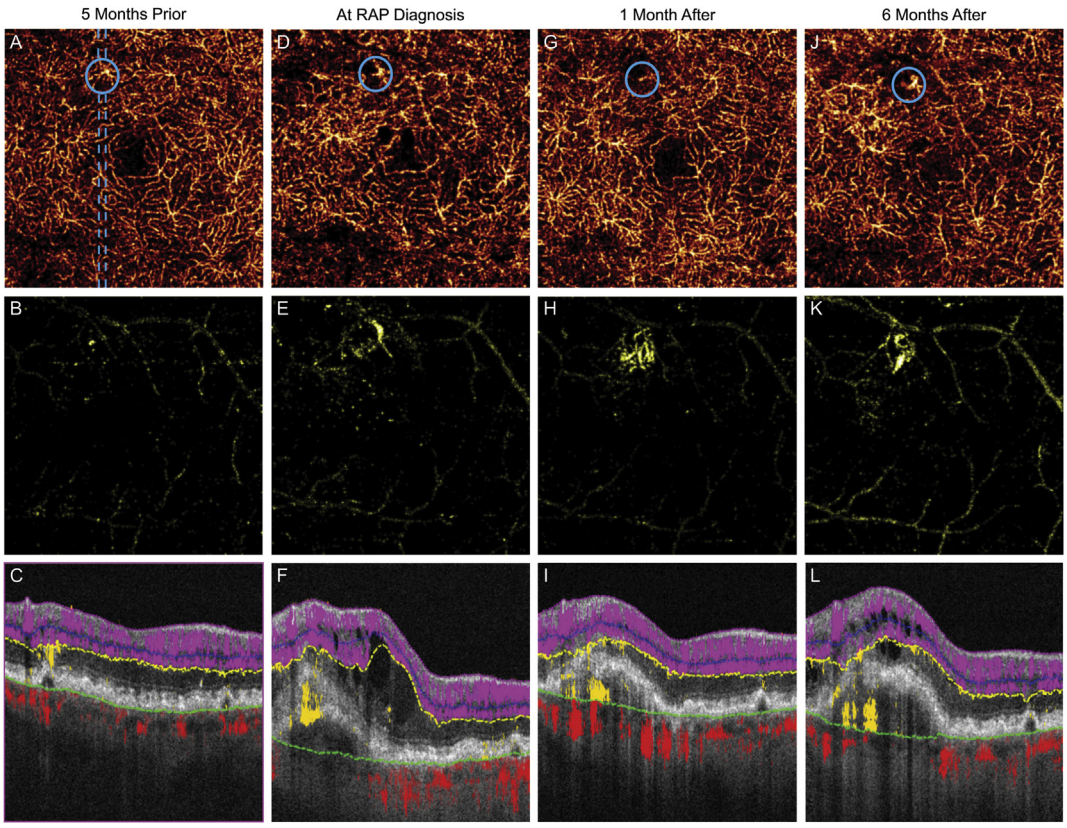

Fig. 3. Optical coherence tomography angiography (OCTA) in an evolving retinal angiomatous proliferation (RAP) lesion.
(**A**,**D**,**G**,**J**) Serial projection-resolved OCTA (PR-OCTA) of the deep capillary plexus reveals evolution of a dilated vessel (blue circles). *En face* outer retinal slab (**B**,**E**,**H**,**K**) and cross-sectional OCT/PR-OCTA (**C**,**F**,**I**,**L**) corresponding to dashed blue line demonstrate axial neovascular flow continuous with the dilated DCP vessel. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

flow changes under anti-vascular endothelial growth factor may be useful for clinicians attempting to optimize treatment intervals.

The origin and evolution of RAP lesions is controversial. It has been suggested with some histopathological evidence that RAP arises from the DCP with subsequent extension into the sub-RPE space, while others have postulated a choroidal origin.[1,2,5,6] In this longitudinal OCTA series, abnormal flow was clearly detected initially in the outer retina and contiguous with a small dilated vessel in the DCP. A small PED was present, but no sub-RPE flow was identified, suggesting potential origin from DCP. Further, progression over time depicted extension of flow into the sub-RPE space. RAP lesions are commonly bilateral, and frequent scanning of asymptomatic fellow eyes with PR-OCTA may help determine the origin and further define RAP pathogenesis.

4. Conclusions

Projection-Resolved OCTA improves depth discrimination by removing artifact. In this case, a RAP lesion arising from the deep capillary plexus was confirmed by PR-OCTA when adequate artifact resolution could not be obtained with conventional OCTA (SS algorithm). This case clearly demonstrates extension of flow initiating from the outer retina into the sub-RPE space over time.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Conflict of interest

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