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Appearance of pediatric choroidal neovascular membranes on optical coherence tomography angiography

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Abstract

Purpose—Compared with fluorescein angiography (FA), the gold standard for diagnosing choroidal neovascularization (CNV) activity, optical coherence tomography angiography (OCTA) is non-invasive without risks associated with fluorescein dye use, and may be especially advantageous in the diagnosis and monitoring of children with CNV.

Methods—Eight eyes from eight patients aged 12 months to 18 years were imaged with the investigational Spectralis OCTA (version 6.9, Heidelberg Engineering, Heidelberg, Germany) and the RTVue XR Avanti (Optovue Inc., Fremont, CA, USA). Two patients were imaged during examination under anesthesia while six patients were imaged in the clinic. Demographic information, ocular characteristics, treatment history, and imaging studies (color photos, fluorescein angiography, OCT) were collected and reviewed.

Results—Three eyes had active CNV while five had quiescent CNV at the time of imaging. CNV was idiopathic or secondary to trauma, retinal vascular dysgenesis versus retinopathy of prematurity, pigmentary retinopathy, Best vitelliform macular dystrophy, panuveitis, morning glory disc anomaly, and optic disc drusen. OCTA of two active CNV demonstrated presence of a main trunk with multiple fine capillaries, vessel loops, and anastomoses. OCTA was repeated after treatment for two CNV and demonstrated a decrease in size with loss of fine capillaries, vessel loops, and anastomoses. For the third active CNV, OCTA verified flow in the CNV complex despite the uncertainty of FA hyperfluorescence in the setting of grossly abnormal retinal vasculature. The five quiescent CNV all lacked fine capillaries, vessel loops, and anastomoses on OCTA.

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Conflict of interest STH declares that she has no conflict of interest. SSO declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Duke University and Johns Hopkins University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study from Duke University. One participant was retrospectively included from Johns Hopkins University and no consent was obtained from this single case report.

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Conclusion—OCTA demonstrates morphological differences between active and quiescent pediatric CNV.

Keywords

Pediatric choroidal neovascularization; CNV in children; Optical coherence tomography angiography; OCTA

Introduction

Pediatric choroidal neovascularization (CNV) is a rare entity that can cause significant visual impairment. Although typically idiopathic, they can also occur as a consequence of inflammation, infection, trauma, pathologic myopia, angioid streaks, retinal dystrophies, optic nerve abnormalities, colobomas, and choroidal tumors [1, 2]. Histopathological examination demonstrates that pediatric CNV membranes most commonly consist of a combination of retinal pigment epithelium, fibrocytes, vascular endothelium, and collagen [3].

Dye leakage on fluorescein angiography (FA) remains the gold standard for diagnosing active CNV. However, the procedure is invasive and may be associated with nausea, urticaria, and rarely anaphylaxis. In children, general anesthesia is often required to acquire FA images with the contact lens–based Retcam (Clarity Medical Systems) since few children would tolerate a needlestick while awake. Ultra-wide field oral fluorescein angiograms with the Optos Panoramic 200MA system (Optos PLC), a non-contact system, have been reported to circumvent the need for intravenous access in infants and young children [4]. However, it is difficult to obtain arterial phase images from oral FA, which limits its usefulness in the evaluation of CNV or increase in leakage [5]. Moreover, Hara et al. found that itching, discomfort, and nausea still occurred in a small subset of patients after oral sodium fluorescein intake (1.7%), albeit at a lower rate when compared with subjects who received intravenous FA (3.0%) [5].

Optical coherence tomography angiography (OCTA) is a relatively new imaging method that captures three-dimensional angiograms of retinal and choroidal blood vessels and allows the detection of CNV. OCTA may be an especially useful tool in the diagnosis and monitoring of pediatric retinal vascular diseases [6–9] especially CNV since it is non-invasive and safe. To date, only two cases of pediatric CNV imaged with OCTA have been reported in the literature [10]. In this case series, we report OCTA findings in eight pediatric patients with CNV. To our knowledge, this represents the largest number of pediatric CNV examined on OCTA to date.

Methods

Eight eyes of 8 children (age range 12 months to 18 years) with CNV were imaged. Seven children were prospectively recruited into the study under a protocol approved by the Duke University Institutional Review Board following the tenets of the Declaration of Helsinki. One child was seen at Johns Hopkins University as part of routine clinical care and was included as a single case report.

Images were acquired using the Spectralis SD-OCT tabletop and investigational portable Flex modules integrated with the OCTA software (version 6.9, Heidelberg Engineering, Heidelberg, Germany) for seven patients, and the Food and Drug Administration (FDA)–approved tabletop RTVue XR Avanti (Optovue Inc., Fremont, CA, USA) for one patient. Informed consent was prospectively obtained for images obtained using the investigational Spectralis system. The FDA-approved RTVue XR Avanti was used as part of routine clinical care for imaging in one participant whose images were included in this report.

Two patients were imaged supine in the operating room while undergoing exams under anesthesia (EUA) using the Spectralis Flex module as previously reported [7] (patients 3 and 6), five patients were imaged sitting upright in clinic using the Spectralis tabletop unit (patients 1, 4, 5, 7, 8), and one patient was imaged sitting upright using the RTVue XR Avanti tabletop unit (patient 2).

With the investigational Spectralis OCTA, $10 \times 10^\circ$ and $20 \times 20^\circ$ images, each comprised of 512 A-scans per B-scan and 512 B-scans of the macula, were captured. With the RTVue XR Avanti, 3×3 mm and 6×6 mm images, each made up of two orthogonal OCTA volumes with each OCTA volume having 304 A-scans per B-scan and 304 uniformly spaced B-scans, were obtained. OCTA images were automatically segmented and rendered by the intrinsic Spectralis and AngioVue software. CNV was identified in the avascular layer, defined as from the bottom boundary of the outer plexiform layer (OPL) to Bruch's membrane for the Spectralis system and defined as from $10 \mu\text{m}$ below the OPL to $10 \mu\text{m}$ above Bruch's membrane for the RTVue system. Projection artifact removal was automatically applied in both systems. Trained graders (S.S.O., S.T.H.) reviewed the automated segmentation of the retinal layers and manually corrected the segmentation.

Results

Table 1 lists the demographic characteristics of all eight patients, as well as the etiology and location of the CNV; at presentation, the CNV status and best correct visual acuity (BCVA); treatment received prior to the imaging visit; interval between presentation and imaging visit; and at the time of imaging, the CNV status and BCVA. CNV status (active or quiescent) was determined based on presence of leakage on fluorescein angiography. If fluorescein angiography was not available, other clinical features including presence of hemorrhage and subretinal fluid on dilated exam and/or optical coherence tomography were utilized to determine CNV activity.

Patient 1

An 11-year-old boy presented for follow-up and management of idiopathic CNV in the right eye (Fig. 1a, b). He had previously been treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections. He returned with new complaints of decreased vision in the right eye. Exam showed BCVA had decreased from 20/20 to 20/30, and there were new subretinal heme and subretinal fluid by the CNV. OCT demonstrated subretinal fluid and subretinal hyperreflective material corresponding to hemorrhage. FA demonstrated occult leakage (Fig. 1c, d). *En-face* OCTA illustrated a large circular CNV complex with a main trunk, multiple dense thin capillaries branching from the main trunk in a tree-like manner

and frequent anastomoses (Fig. 1f), while cross-sectional OCTA showed flow in the sub-RPE type 1 CNV membrane (Fig. 1g). He received intravitreal anti-VEGF therapy in the affected eye. Two months later, BCVA had improved to 20/20; the *en-face* OCTA showed that the CNV complex had decreased in size with decreased thin capillaries and vascular loops (Fig. 1h) while the cross-sectional OCTA/structural OCT showed decreased flow and height of the sub-RPE lesion, and resolution of subretinal fluid and subretinal hyperreflective material (Fig. 1i).

Patient 2

A 14-year-old girl presented with persistent blurry vision in the right eye 3 months after suffering a right orbital fracture in a motor vehicle accident. The orbital fracture had been repaired during her initial hospitalization. BCVA was 20/50. Exam showed a subfoveal gray-green lesion (Fig. 2a). FA demonstrated early lacy hyperfluorescence with late leakage seen in classic CNV (Fig. 2b, c). *En-face* OCTA showed a main trunk transversing a rectangular CNV complex with branching thin capillaries and frequent anastomoses on either side of the main trunk (Fig. 2d), while cross-sectional OCTA/structural OCT demonstrated flow in the pre-RPE type 2 CNV membrane and the presence of subretinal fluid (Fig. 2e). She was treated with intravitreal anti-VEGF twice. Six weeks after her second intravitreal injection, BCVA had improved to 20/20. The *en-face* OCTA demonstrated a smaller consolidated CNV complex with loss of branching thin capillaries, vessel loops, and anastomoses (Fig. 2f), while the cross-sectional OCTA/structural OCT demonstrated decreased flow in the subretinal lesion, and resolution of subretinal fluid (Fig. 2g).

Patient 3

A 12-month-old girl previously born at 28 weeks with birth weight of 815 g was diagnosed with bilateral retinal vascular dysgenesis versus retinopathy of prematurity in the setting of a chromosomal abnormality (19q13.12 duplication). By age 3 months, she had undergone two vitreoretinal surgeries for vitreous hemorrhage and tractional retinal detachment in the left eye (Fig. 3a). At age 12 months, she underwent an EUA (Fig. 3b) and FA revealed two areas of hyperfluorescence concerning for leakage in the left eye (Fig. 3c, d). OCT showed presence of intraretinal fluid. The severe retinal vascular dysgenesis made it very challenging to properly segment the *en-face* OCTA (Fig. 3f, g). However, the cross-sectional OCTA demonstrated flow in the pigment epithelial detachment (Fig. 3h), thereby confirming presence of a type 1 CNV lesion. CNV treatment options were discussed with the parent and a decision was made to monitor the lesion since the affected eye had limited visual potential.

Patient 4

An 18-year-old male with bilateral pigmentary retinopathy was followed for management of a type 2 CNV in the right eye. A pre-RPE CNV with surrounding subretinal fluid disrupting the fovea was first noted on exam and OCT when he was 11 years old. FA at the time of diagnosis demonstrated leakage consistent with a classic neovascular complex. Over the years, he received multiple anti-VEGF injections and one session of photodynamic therapy. At the most recent follow-up, which was 2 months after his last anti-VEGF injection, he reported stable vision, and exam revealed a stable fibrotic scar without fluid accumulation. FA showed no leakage and OCT demonstrated no intraretinal or subretinal fluid. *En-face*

OCTA showed a main vessel trunk traversing the CNV complex with several large branching vessels and a lack of fine capillaries with anastomoses and vessel loops while cross-sectional OCTA verified residual flow in the quiescent pre-RPE CNV membrane (Fig. 4a).

Patient 5

A 10-year-old girl with Best vitelliform macular dystrophy was followed for management of a type 1 CNV membrane she had developed in the left eye at age 7. After four monthly anti-VEGF injections followed shortly by photodynamic therapy, the CNV remained quiescent and she did not require any further treatment. Her most recent FA demonstrated no leakage. Despite the absence of FA leakage, OCT showed persistence of an optically clear subretinal cleft [11]. *En-face* OCTA revealed two main trunks, one superior and one inferior, with a lack of small capillaries, anastomoses, and vessel loops. The cross-sectional OCTA verified residual flow in the quiescent sub-RPE CNV lesion (Fig. 4b).

Patient 6

A 5-year-old girl with a history of panuveitis and exudative subretinal deposits and extensive snowbanks with a negative infectious and inflammatory workup was found to have a mixed type 1 and 2 CNV membrane in the left eye during EUA. The child then received two intravitreal anti-VEGF injections a month apart. At the 3-month follow-up, FA demonstrated no leakage and OCT showed absence of intraretinal and subretinal fluid. *En-face* OCTA revealed a consolidated CNV lesion with large vessels and distinct margins while cross-sectional OCTA verified residual flow in the quiescent mixed sub-RPE with pre-RPE component CNV membrane (Fig. 4c).

Patient 7

A 6-year-old girl with morning glory disc anomaly in the left eye was followed for a peripapillary type 1 CNV membrane. The CNV membrane was first diagnosed at age 2. She was subsequently treated with two intravitreal anti-VEGF injections. At the most recent EUA, there was a lack of angiographic leakage; therefore, no further anti-VEGF therapies was given. OCT showed absence of intraretinal and subretinal fluid. *En-face* OCTA showed several large caliber vessels and a lack of small capillaries, anastomoses, and vessel loops while the cross-sectional OCTA verified residual flow in the quiescent sub-RPE CNV lesion (Fig. 4d).

Patient 8

A 12-year-old girl was seen for follow-up of peripapillary type 1 CNV associated with optic disc drusen in the left eye. The CNV was first diagnosed at age 10. The child underwent multiple anti-VEGF injections and photodynamic therapy. At the most recent visit, exam demonstrated a stable lesion without subretinal fluid while FA did not demonstrate leakage. OCT showed trace intraretinal cystoid spaces overlying atrophy and no subretinal fluid. *En-face* OCTA illustrated two large caliber vessels and a lack of fine capillaries, anastomoses, and vessel loops while the cross-sectional OCTA revealed residual flow in the inactive sub-RPE CNV lesion (Fig. 4e).

Discussion

To our knowledge, this is the largest and youngest case series published to date of pediatric CNV imaged on OCTA. OCTA revealed vascular flow in CNV complexes in eight patients aged 12 months to 18 years. CNV was idiopathic or secondary to trauma, retinal vascular dysgenesis versus retinopathy of prematurity, pigmentary retinopathy, Best vitelliform macular dystrophy, panuveitis, morning glory disc anomaly, or optic nerve drusen. At the time of imaging, three children had active CNV while five had quiescent CNV. The CNV was type 2 (pre-RPE) in two children, type 1 (sub-RPE) in five children, and mixed (pre- and sub-RPE) in one child.

The active CNV complexes in patients 1 and 2 were observed to have numerous dense, fine capillaries with frequent anastomoses and vessel loops (Figs. 1f and 2d). After treatment in both cases, there was a lack of angiographic leakage and the *en-face* OCTA demonstrated a loss of fine capillaries, anastomoses, and vessel loops when compared with imaging before treatment (Figs. 1h and 2f). In addition, the structural OCT images revealed resolution of subretinal hyperreflective material corresponding to hemorrhage and subretinal fluid after treatment (Figs. 1i and 2g). In comparison, the quiescent CNV complexes in patients 4 to 8 were made up of mature trunks made up of large caliber vessels with low capillary density, and lacking anastomoses and vessel loops (Fig. 4a–e). The difference in morphological features between active and quiescent CNV in this report is consistent with findings from previous studies examining adult CNV [12, 13].

Given the morphological changes on OCTA that occur when a CNV is no longer active, OCTA could be used to dynamically monitor the evolution of CNV after treatment. Since OCTA is non-invasive and safe, it can be performed frequently. This is an especially important advantage in the pediatric population. In this population, FA is usually obtained at the initial visit for diagnosis but not repeated unless there is a strong suspicion for recurrence since the procedure is invasive, frequently requires an EUA, and can be associated with nausea, urticaria, or, rarely, anaphylaxis. In contrast, for children who can cooperate for tabletop OCTA, serial OCTA can be safely acquired at every visit to determine if there is any recurrence of CNV activity after treatment. Children whose OCTA demonstrates changes suspicious of CNV recurrence may then undergo FA to confirm CNV recurrence. OCTA changes have previously been shown to precede fluid reaccumulation in recurrence of CNV activity [14]. Serial OCTA may therefore increase the likelihood that any CNV recurrence will be detected and treated promptly, even before subretinal fluid and hemorrhage are observed on exam and OCT.

As shown in patient 3, OCTA can also be useful when grossly abnormal retinal architecture makes CNV detection challenging even with the use of FA. In patient 3, hyperfluorescence was observed but it was difficult to ascertain if it represented leakage from a CNV or staining from a fibrotic scar. The cross-sectional OCTA, which overlaid the information regarding blood flow over the structural OCT, was helpful in this case in diagnosing CNV by demonstrating flow. Cross-sectional OCTA in combination with *en-face* OCTA has previously been shown to increase the sensitivity and specificity of CNV detection when compared with the use of *en-face* OCTA alone. With *en-face* OCTA only, sensitivity of CNV

detection ranged between 50 and 86.5% while specificity ranged between 67.6 and 100% [15–20]. With both *en-face* and cross-sectional OCTA, sensitivity and specificity improved to 100% and 97.5–100%, respectively [21].

In Veronese and colleagues' case series of two pediatric CNV, they had described the type 1 or occult CNV complex to appear "glomerular" with a lack of a main vessel, and the type 2 or classic CNV complex to be "tree-like" with a large main central feeder vessel on OCTA [10]. In contrast, in our case series, a main trunk is identified in both types of CNV. Patient 1 had an active type 1 CNV while patient 2 had an active type 2 CNV. While the active type 1 CNV appeared more circular or globular in shape, the active type 2 CNV appeared more oblong or rectangular. In the type 1 CNV, the main trunk branches into dense smaller caliber vessels in a tree-like manner similar to that seen in lung branching morphogenesis. After treatment, the smaller capillaries resolved, leaving behind the main trunk and larger caliber vessels. In the type 2 CNV, the main trunk is observed transversing the entire CNV with branching capillaries growing on either side of the trunk. After treatment, the CNV complex appeared smaller and consolidated with loss of branching capillaries.

In our case series, two patients underwent OCTA during EUA (ages 1 and 5) while the rest underwent tabletop OCTA while awake in the clinic (ages 7 to 18). Compared with structural OCT imaging, OCTA requires longer acquisition times and is exquisitely sensitive to motion artifacts. Microsaccades can appear as bright streaks on *en-face* OCTA [22]. These limitations make OCTA imaging of young children while awake challenging. A child would need to be able to rest his or her chin at the tabletop device, remain still, and fixate at the target for at least 3 s even with the fastest systems [23]. Therefore, in younger children who are not able to cooperate for an OCTA while awake, OCTA may only be performed during EUA, which limits its usefulness as a non-invasive device.

In summary, OCTA is a non-invasive device that can demonstrate differences in morphological characteristics between active and quiescent CNV. Therefore, OCTA can be a useful tool to monitor intra-individual changes in CNV morphology across time. This can be especially helpful in the early detection of CNV recurrence in children who can cooperate for tabletop OCTA. When there is suspicion for CNV recurrence, EUA with FA can then be planned to definitively diagnose CNV recurrence and plan treatment. FA remains the gold standard in diagnosing CNV and CNV activity. However, as this report demonstrates, OCTA is a useful adjunct that can add to the diagnostic armamentarium available to clinicians managing pediatric CNV.

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Fig. 1.

Type 1 idiopathic CNV in patient 1. **a** At presentation, color photo demonstrates a hyperpigmented CNV complex with hemorrhage just inferonasal to the foveal center. **b** OCT shows the subretinal pigment epithelium CNV complex. The patient was treated with intravitreal anti-VEGF injections. **c** One year after presentation, the patient had a recurrence of CNV activity. **c** Early and **d** late frames of fluorescein angiography illustrate occult leakage of the CNV complex, blocked fluorescence from hemorrhage, and circumferential window defect from retinal pigment epithelium atrophy. A feeder vessel is also visible (red arrows). **e** The green box and green arrow in the infrared image depict the area captured by the *en-face* (**f**) and cross-sectional (**g**) OCTA, respectively. **f** *En-face* OCTA shows a large circular CNV complex with a main trunk (yellow arrow), multiple dense thin capillaries branching from the main trunk in a tree-like manner, and frequent anastomoses in the segmented avascular cube. **g** Cross-sectional OCTA illustrates flow (arrows) in the CNV

complex. **h** *En-face* and **i** cross-sectional OCTA were repeated after anti-VEGF therapy and demonstrate a CNV complex that has decreased in size with loss of thin capillaries and vascular loops

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Fig. 2.

Type 2 traumatic CNV in patient 2. **a** Color photo shows a subfoveal CNV complex. **b** Early and **c** late frames of fluorescein angiography demonstrate early lacy hyperfluorescence with late leakage typical for classic CNV. A feeding vessel (red arrows) can also be seen. **d** *En-face* OCTA demonstrates a CNV complex with a main trunk (yellow arrow) transversing the entire CNV complex with branching capillaries on either side, vessel loops, and anastomoses. **e** Cross-sectional OCTA shows flow (white arrows) in the CNV. **f** *En-face* and **g** cross-sectional OCTA after two intravitreal bevacizumab injections show a smaller consolidated CNV complex with loss of branching capillaries, vessel loops, and anastomoses

Fig. 3.

Type 1 CNV in patient 3 with retinal vascular dysgenesis versus retinopathy of prematurity. At age 2 months, color photos of the **a** left eye demonstrate vitreous hemorrhage and tractional retinal detachment, and the child underwent vitreoretinal surgery. One month later, she underwent surgery again in the left eye for a recurrent vitreous hemorrhage. At age 12 months, color photo of the **b** left eye shows attached retina with extensive panretinal photocoagulation endolaser scars. **c** Early and **d** late frames of fluorescein angiography in the left eye show two areas of hyperfluorescence in the macula suspicious for leakage (white arrows). **e** Infrared image with the green box depicting the *en-face* OCTA shown in **f** and **g** and the green arrow depicting the cross-sectional OCTA shown in **h**. **f** *En-face* OCTA of the entire retina shows grossly abnormal vasculature and a possible CNVM complex (red arrow). **g** Segmentation of the avascular cube was challenging given the abnormal

vasculature but shows a possible CNVM complex (red arrow) which is confirmed on **h** cross-sectional OCTA which shows flow in the pigment epithelial detachment (white arrow)

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Fig. 4.

Patients 4 to 8. From left to right: fundus photo, late fluorescein angiography, infrared, *en-face* OCTA, and cross-sectional OCTA. The green box in the infrared image delineates the area captured by the *en-face* OCTA while the green arrow demonstrates the scan shown by the cross-sectional OCTA. Quiescent CNV complexes in children with pigmentary retinopathy (**a**), Best vitelliform macular dystrophy (**b**), panuveitis (**c**), morning glory disc anomaly (**d**), and optic nerve drusen (**e**). The *en-face* OCTAs show that the CNV complexes in these children lack fine capillaries, vessel loops, and anastomoses while the cross-sectional OCTAs confirmed residual flow in the pre-RPE type 2 (**a**), sub-RPE type 1 (**b**, **d**, **e**), or mixed with predominantly type 1 component (**c**) CNV complexes

Patient demographics and choroidal neovascular membrane characteristics at presentation and at time of optical coherence tomography angiography imaging

Table 1

Case	Patient age (years)/sex/race	Etiology	Location	CNV type	CNV status at presentation *	Best corrected visual acuity at presentation	Treatment received prior to imaging visit	Interval between presentation and imaging visit	CNV status during imaging visit *	Best corrected visual acuity at imaging visit
1	11/M/white	Idiopathic	Subfoveal	1	Active	20/1250	Bevacizumab × 1, Aflibercept × 1	9 months	Active	20/30
2	14/F/black	Trauma	Subfoveal	2	Active	20/50	None	None	Active	20/50
3	1/F/Hispanic	Retinal vascular dysgenesis vs. retinopathy of prematurity	Juxtafoveal	1	Active	Unavailable	None	None	Active	Unavailable
4	18/M/black	Pigmentary retinopathy	Subfoveal	2	Active	20/160	Bevacizumab × 5, Aflibercept × 2	7 years	Quiescent	20/250
5	10/F/white and Asian	Best vitelliform macular dystrophy	Subfoveal	1	Active	20/320	Bevacizumab × 3, Aflibercept × 1, PDT × 1	2 years	Quiescent	20/125
6	5/F/black	Inflammatory	Juxtafoveal	1+2	Active	20/100	Bevacizumab × 2, Periocular and topical steroid, nonsteroidal immunomodulators	2 years	Quiescent	Unavailable
7	6/F/white	Morning glory disc anomaly	Juxtaperipapillary	1	Active	20/100	Bevacizumab × 2	3 years	Quiescent	20/100
8	12/F/black	Optic disc drusen	Juxtaperipapillary	1	Active	20/250	Bevacizumab × 3, Aflibercept × 1	15 months	Quiescent	20/100

F, female; M, male; CNV, choroidal neovascularization.

* CNV activity was determined based on presence of leakage on fluorescein angiography. If fluorescein angiography was not available, other clinical features including presence of hemorrhage and subretinal fluid on dilated exam and/or optical coherence tomography were utilized to determine CNV activity