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Response to treatment with intravitreal anti-vascular endothelial growth factors in bilateral exudative cuticular drusen

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ABSTRACT

Purpose: To present the response to treatment with anti-vascular endothelial growth factor (VEGF) agents of exudative cuticular drusen (CD) in a patient who developed temporary suspended scattering particles in motion (SSPiM) after injection in the symptomatic eye and full recovery of subretinal hyperreflective exudation (SHE) in the fellow eye by multimodal imaging modalities.

Observations: A 46-year-old patient was diagnosed with exudative CD associated with type I and II (mixed type) macular neovascularization (MNV) in the right eye, and quiescent type I MNV was detected in the left eye by en face optical coherence tomography angiography (OCTA). Bilateral flat irregular pigment epithelial detachments were found in both eyes by optical coherence tomography (OCT). A week after injection of intravitreal aflibercept (IVA), oval shaped hypersignals developed at Henle's fiber layer with a petaloid appearance and at the subfoveal space as detected by en face OCTA in the right eye. These oval hypersignals were considered as SSPiM. They disappeared 4 weeks later and did not recur. During follow-up of the patient, juxtafoveal SHE and disruption of the ellipsoid zone (EZ) were noticed in her left asymptomatic eye by OCT. Fluorescein angiography disclosed leakage at the location of the SHE. Choriocapillaris flow analyzed by cross-sectional OCTA disclosed time-dependent local alterations before and after the development of SHE. SHE recurred twice, and juxtafoveal type I MNV subsequently developed at the same location. Intravitreal ranibizumab (IVR) treatment was initiated because of distorted vision accompanied by the development of SHE and persistent subfoveal fluid accumulation, as documented by OCT during IVA treatment. Complete recovery of the EZ took place consistently in both eyes with stable vision over three years of follow-up.

Conclusions and Importance: Temporary SSPiM could be seen in the early period after IVA injection once but has not recurred up to three years' follow-up in the right eye of our patient with exudative CD. Prompt and appropriate treatment of SHE by intravitreal anti-VEGF agents (IVA and IVR) prevented the permanent deterioration of visual acuity in the left eye with type I MNV at her thirty-months follow-up.

1. Introduction

Cuticular drusen (CD), also known as basal laminar drusen (BLD), is considered as a unique subgroup of age-related macular degeneration (AMD).[1] Gass in 1977, speculated that uniformly small round drusen might be caused by the nodular thickening of the basement membrane of the retinal pigment epithelium (RPE).[1] However, various studies have shown that CD appears as numerous, uniform, round, yellow-white punctate accumulations under the RPE.[2,3,4] Drusen may be closely arranged in a tightly knit pattern giving the orange-peel display through the entire macular/paramacular area by fundus examination.[1] Drusen are more easily visualized during the early arteriovenous phase exhibiting the fundus a "stars-in-the-sky" or "milky-way" image by fluorescein angiography (FA).[1] Optical coherence tomography (OCT) analysis of the CD patients disclosed the region of the drusen between the Bruch's (BM) and the RPE.[2,3] Henceforth, CD is located external to the RPE, small with steep sides, and contain dense hyalinized contents as revealed by light microscopy, whereas electron microscopy shows that the CD contents are homogenous and electron dense, with small vacuoles attributed to extracted lipids distributed throughout.[4]

The heterogeneity of fundus features in CD patients points to a need for classification of the disease. Recently, Sakurada et al. classified eyes with CD into three phenotypes and longitudinally analyzed the risk of geographic atrophy (GA) and macular neovascularization (MNV).[3] Phenotype 1, the classical form of CD, includes bilateral, symmetrical, concentrated cluster of translucent and yellowish, small (25–75 μm)

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sub-RPE elevations. Phenotype 2 shows a scattered distribution of similar but less densely populated drusen in the posterior pole infrequently extending into the peripheral fundus. Phenotype 3 involves a mix of CD and large drusen (above 200 μm) presenting as colloidal/hyalinized in nature.[3] A strong association was found between CD (especially phenotypes 2 and 3) and GA/MNV, providing evidence that CD is likely to be a part of age-related macular degeneration (AMD).[3] It has been reported that throughout the five-year follow-up of CD patients, the estimated cumulative incidences of advanced AMD were 12.9% for phenotype 1 and 50.5% for phenotype 2, 53% for phenotype 3, respectively.[3] Thus, CD is a dependent risk factor for AMD progression leading to visual impairment.[2]

2. Case report

In September 2017, a 46-year-old woman was referred for decreased vision and metamorphopsia in her right eye which developed in the previous three months. She had no previous remarkable systemic or ophthalmic history. Her best corrected visual acuities were 6/20 in the right eye, and 20/20 in the left eye. The results of her biomicroscopic examination and tonometry recordings were normal.

Fundus examination (Kowa VX-20; Kowa Company Ltd, Japan) disclosed features of CD in both eyes and severe macular edema in the right eye (Fig. 1A). Fluorescein angiography (FA; Kowa VX-20; Kowa Company Ltd, Japan) clearly outlined late leakage from the MNV and macular edema in the right eye (Fig. 1B). The stars-in-the-sky (milky way) appearance caused by CD on FA was prominent (Fig. 1B). OCT (RTVue XR Avanti; Optovue, Inc, Fremont, CA) disclosed subfoveal hyperreflective material corresponding to mixed type (types 1 and 2) MNV with intrafoveal hyporeflective cysts (Fig. 1C). Flat irregular retinal pigment epithelial detachment (FIRPED) was located at the temporal macula seen as double-layer sign (Fig. 1C). A 6-mm en face optical coherence tomography angiography (OCTA) choriocapillaris slab (AngioVue RTVue XR Avanti; Optovue, Inc, Fremont, CA) disclosed mixed type subfoveal MNV in the right eye (Fig. 1D). Intravitreal aflibercept (IVA) injection (2 mg in 0.05 mL) was administered via pars plana into the right eye. We observed perifoveal weak hypersignals at the deep capillary plexus at Henle's fiber layer (HFL) in the right eye on 2-mm en face OCTA slabs (Fig. 1E). A week after the first injection of IVA into the right eye, en face OCTA revealed several ovoid hypersignals with a flower petal arrangement perifoveally at the deep capillary plexus slab at HFL and at the subfoveal location (Fig. 1F). Four weeks after injection of IVA, the hypersignals located at HFL and the subfoveal space disappeared and did not recur (not shown). A total of three repetitive injections of IVA were administered into the right eye four weeks apart, and her visual acuity in the right eye increased to 20/20, however metamorphopsia was not resolved.

At a follow-up examination in January 2018, her visual acuity was stable in the right eye. The macular edema was resolved, but there was minor subfoveal fluid accumulation in the right eye by OCT (not shown). Her left eye was asymptomatic; however, fundus examination of the left eye revealed cream-colored circular juxtafoveal exudation (Fig. 2A). The margin of the exudation was sharp (Fig. 2A). During FA, leakage was observed at the late phase in the left eye (Fig. 2B). Subretinal hyperreflective exudation (SHE) was noticed on OCT (Fig. 2C). The external limiting membrane (ELM) was intact (Fig. 2C). IVA injection was

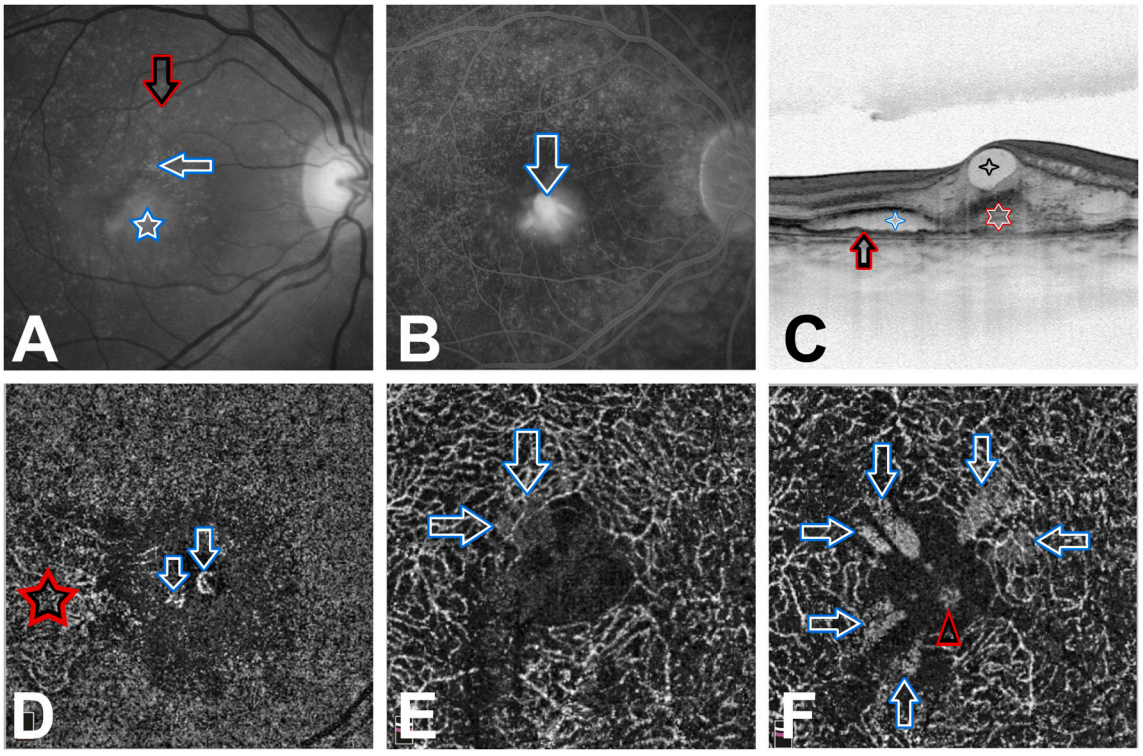

Fig. 1. Red-free fundus photograph (**A**) discloses macular edema (blue star), tiny hard exudates (blue arrow), and SDD (red arrow) in the right eye. Fluorescein angiography (**B**) shows late (11min 20sec) fluorescein leakage, indicating macular edema associated with subfoveal CNV (blue arrow) and a milky way appearance, particularly around the paramacular region. OCT (**C**) demonstrates hyperreflectivity of mixed type MNV (types I and II; six-point red star), an intrafoveal hyporeflective cyst (four-point black star), and subfoveal hyporeflective fluid (four-point blue star) and flat irregular retinal pigment epithelial detachment (red arrow). A 6-mm en face OCTA choriocapillaris slab (**D**) reveals subfoveal hypersignals, indicating mixed type MNV (blue arrows) and type I MNV (red star). En face OCTA of a 2-mm deep capillary plexus slab before injection of IVA (**E**) illustrates a distorted vortex pattern and two weak perifoveal hypersignals (blue arrows) as SSPiM. One week after IVA (**F**), en face OCTA of the deep capillary plexus discloses a restored vortex pattern, and several perifoveal SSPiM hypersignals (blue arrows) appear as flower petals. The red triangle at the umbo indicates a subfoveal SSPiM hypersignal (**E**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

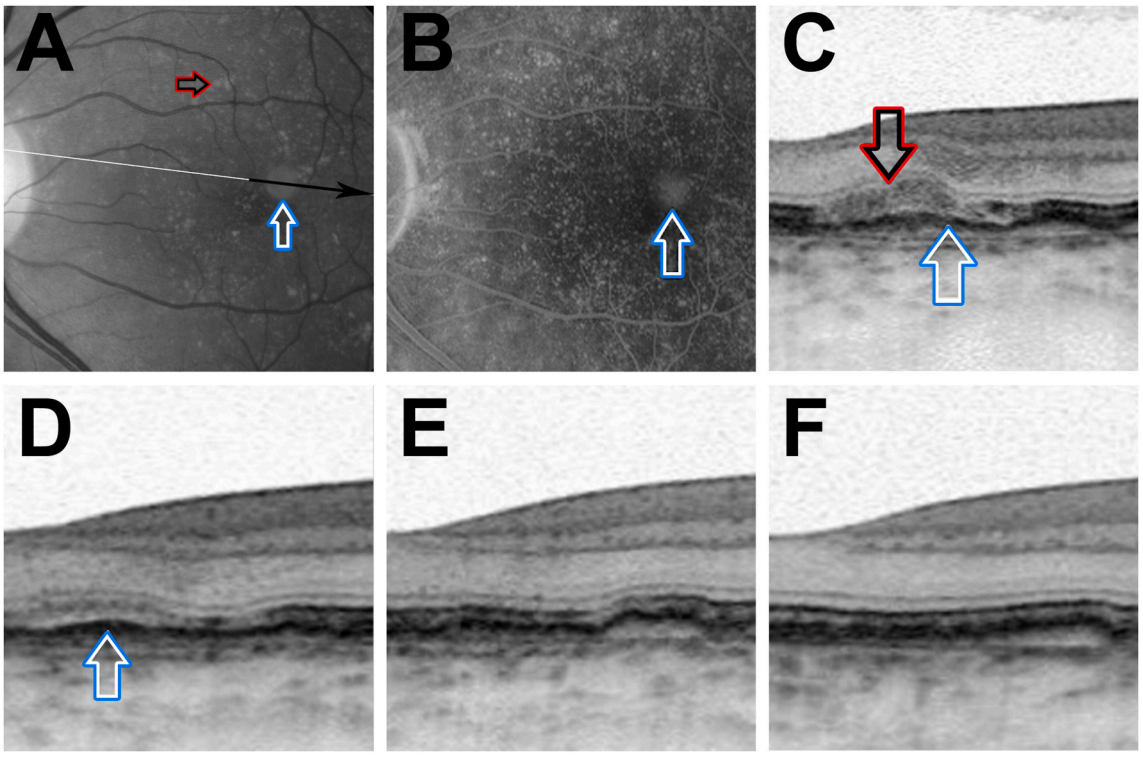

Fig. 2. A red-free fundus photograph (**A**) discloses a circular lesion with a sharp margin (blue arrow) juxtafoveally in the left eye. SDD is apparent superior to the macula (red arrow). The white line indicates the axis of the OCT scan, and the black arrow indicates sections (**C**) to (**F**). Fluorescein angiography (**B**) shows late (11min 17sec) fluorescein leakage at the juxtafoveal location (blue arrow) and paramacular milky way appearance. (**C**) Subretinal hyperreflective exudation (SHE) (red arrow) is located above the flat irregular retinal pigment epithelial detachment (FIRPED) (blue arrow). One week after injection of intravitreal aflibercept (IVA), SHE had disappeared (**D**), the ellipsoid zone (EZ) was recovered, and the FIRPED was shallow (blue arrow). Four weeks after injection of IVA (**E**), the EZ was fully reconstituted and FIRPED had increased. A year after the first injection of IVA (**F**), the stability of the EZ is remarkable. There is no subfoveal scar hyperreflectivity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

administered on the same day because of juxtafoveal SHE in the left eye. The patient was monitored by fundus photos (not shown), OCT, and OCTA at one week (Fig. 2D) and four weeks (Fig. 2E). Two more consecutive injections of IVA were administered to the left eye four weeks apart. The results at her one-year follow-up after the first IVA injection are shown in Fig. 2F.

En face and cross-sectional OCTA focusing on choriocapillaris findings from September 2017 until January 2019 in the left eye are shown in Fig. 3A–F. Quiescent type I MNV was noted below RPE and above Bruch's membrane, which was the location of FIRPED in the left eye at the first referral date in September 2017 (Fig. 3A). Four weeks later in October 2017, quiescent type 1 MNV remained stable (Fig. 3B). Two months later in November 2017, the choriocapillaris flow void area (CCFVA) and vacuolization at the level of RPE were noticed (Fig. 3C). In January 2018, SHE was apparent with neovascular hypersignal (Fig. 3D). Consecutive recordings were taken in the left eye one week after the first IVA injection (Fig. 3E), four weeks after the first IVA injection (Fig. 3F), six months after the first IVA injection (Fig. 3G), and one year after the first IVA injection in January 2019 (Fig. 3H). Later, the patient noticed distorted vision in her left eye in June 2020, six weeks after IVA injection. The cross-sectional OCTA disclosed prominent SHE and subfoveal fluid accumulation (Fig. 4A and B). The remarkable type I MNV signal was also noticed by en face OCTA (Fig. 4A and B). Three monthly injections of intravitreal ranibizumab (IVR) (0.5 mg in 0.05 mL) were administered via pars plana into the left eye. In September 2020, the patient was asymptomatic, and the visual acuities were 20/20 in both eyes. En face and cross-sectional OCTA (Solix; Optovue, Inc, Fremont, CA) recordings in the left eye in September 2020 were shown in Fig. 5. The SHE disappeared, but subfoveal fluid was present with diminished neovascular signal (Fig. 5). Complete recovery of the ellipsoid zone (EZ) took place (Fig. 5).

3. Discussion

Retinal imaging in CD is of special interest in the ophthalmic literature.[1–4] FA, FAF, and OCT identify CD with a high degree of sensitivity/specificity and those multimodal imaging techniques for the definitive diagnosis and phenotyping.[3] The diagnosis of CD was based on "stars-in-the-sky" (or "milky-way") pattern by FA, "saw-tooth" pattern by OCT, and finally the punctate hypoautofluoresecence on FAF.[3]

In a recent article, clinical grouping was suggested for different phenotypes with CD.[3] The first phenotype is characterized by concentrated densely populated CD in the macular/paramacular area. The second phenotype showed scattered CD in the posterior fundus. Phenotype 3 included CD mixed with large drusen exceeding 200 μm. According to this study,[3] our case was considered as phenotype 3 CD with large clusters of drusen manifesting as bilateral MNV.

In our case, the suspended scattering particles in motion (SSPiM) phenomenon appeared temporarily, one week after the first IVA injection in the right eye (Fig. 1F). This is the first report of attenuated SSPiM in a patient with CD after IVA in the literature. Recently, SSPiM has been reported in various exudative maculopathies as revealed by OCTA.[5] SSPiM presumably developed as an extravascular hypersignal located at the edge or border of a vascular plexus at an avascular-vascular junction, but not in the subretinal space.[5] Here, we report the appearance of SSPiM that was provoked one week after the IVA injection (Fig. 1E and F). In our case, SSPiM was not only observed at the HFL (the edge or border of the vascular plexus at an avascular-vascular junction), but also at the subfoveal space (Fig. 1F). Kashani et al. stated that lipid

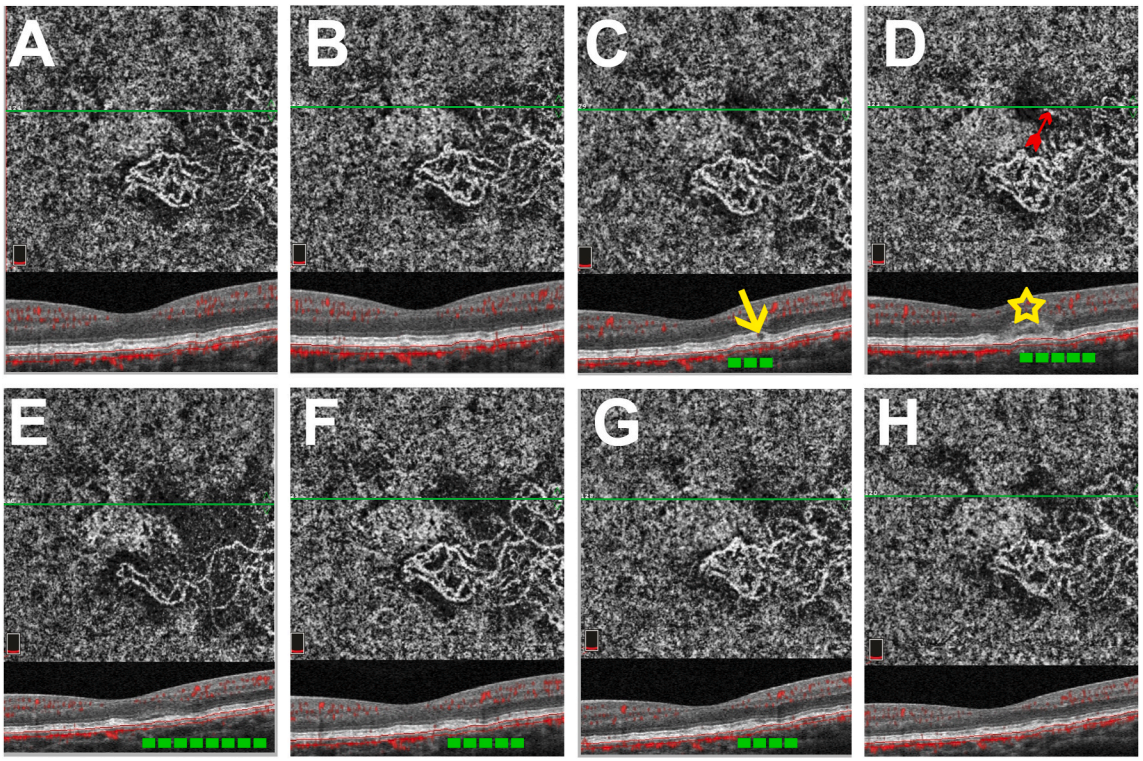

Fig. 3. A 3-mm en face OCTA choriocapillaris slab disclosed the quiescent type I MNV temporal macular region in (**A**)–(**H**): (**A**) September 2017; (**B**) October 2017; (**C**) November 2017; (**D**) January 2018; (**E**) 1 week after (**D**); (**F**) 4 weeks after (**D**); (**G**) 6 months after (**D**); (**H**) 1 year after (**D**). The thin green line at the center of each en face OCTA frame indicates the location of cross-sectional OCTA. The thick green dashed line below the cross-sectional OCTA in (**C**)–(**G**) indicates the width of the choriocapillaris flow void area (CCFVA). The CCFVA appeared six weeks before subretinal hyperreflective exudation (SHE) when RPE vacuolization (yellow arrow) was found (**C**). The red arrow shows the choroidal neovascular hypersignal inside the CCFVA (**D**). SHE is remarkable (yellow star in **D**). The width of the CCFVA was maximum one week after the first injection of IVA (**E**). Thereafter, the CCFVA gradually decreased: (**F**) after four weeks and (**G**) after six months. The CCFVA had disappeared one year after the first injection of IVA (**H**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

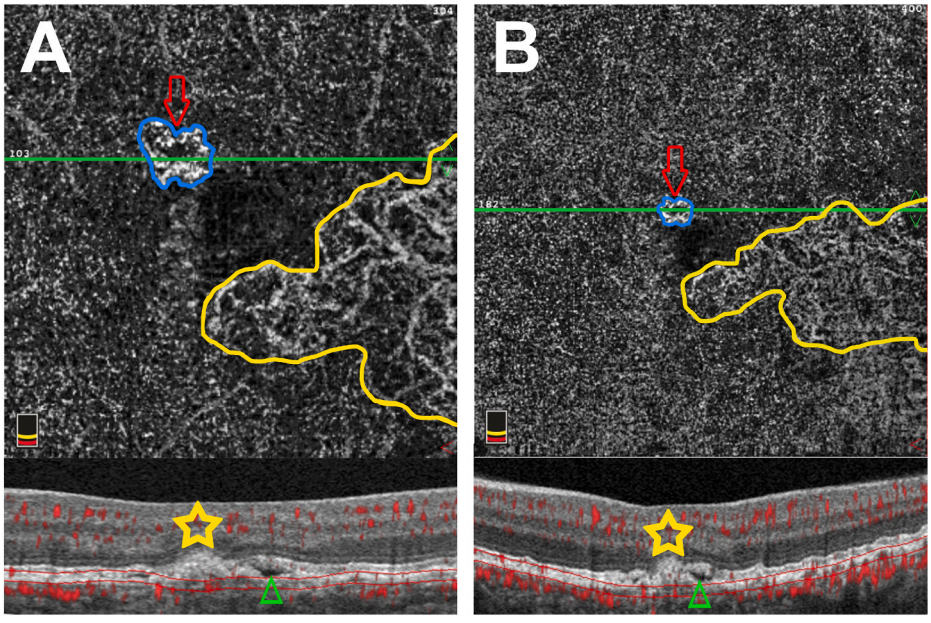

Fig. 4. In June 2020, before IVR injection, 3-mm and 6-mm en face OCTA (RTVue XR Avanti; Optovue, Inc, Fremont, CA) choriocapillaris slab disclosed hypersignal flow at juxta-foveal type I MNV (blue outlined) and the quiescent type I MNV temporal macular region (yellow outlined) in **A** and **B,** respectively. The red arrow shows that the type I MNV hypersignal is prominent. SHE was remarkable in cross-sectional OCTA recordings (yellow star). The subfoveal fluid was also noticed (green triangle). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

aggregates, a key component of the suspended particles in SSPiM, could generate hypersignals that are frequently located in HFL rather than the inner nuclear layer but not in the subretinal space.[5] It has been hypothesized that the initial formation of hyalinized protein-rich small nodules, remodeling, regressing, or increasing in size and number and then eventually accumulating under the RPE to prevent trafficking of the vital molecules between choriocapillaris, might summarize the life cycle of CD.[2] Curcio et al. indicated that RPE is a polarized/bidirectional

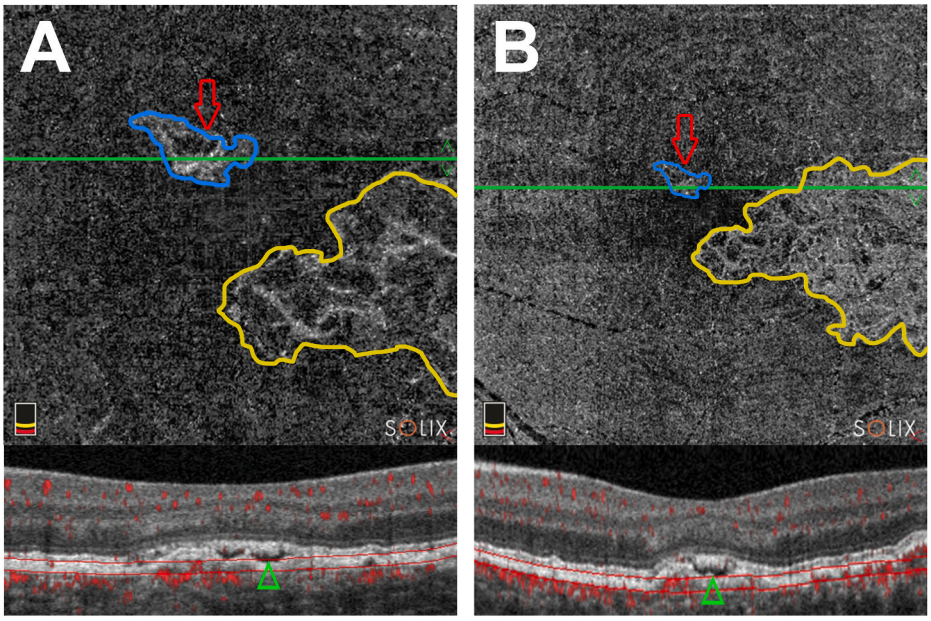

Fig. 5. In September 2020, after three monthly IVR injections, 3-mm and 6-mm en face OCTA (Solix; Optovue, Inc, Fremont, CA) choriocapillaris slab disclosed reduced hypersignal at juxta-foveal type I MNV (blue outlined) and the quiescent type I MNV temporal macular region (yellow outlined) in **A** and **B,** respectively. The red arrow shows that the type I MNV hypersignal is diminished. SHE disappeared and complete recovery of the EZ took place, which was noticed in cross-sectional OCTA recordings; however, the subfoveal fluid was persistent (green triangle). En face concentric micro-waves are remarkable in Figure **B**. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

secretor of lipoproteins, and high-density lipoprotein-associated molecules are present in subretinal space.[6] Thus, in our CD patient, altered lipoprotein turnover in the subretinal space during the healing period after IVA injection might have provoked enhancement of SSPiM in HFL and the subretinal space. Indeed, the avascular ovoid hypersignals appearing at HFL and the subfoveal space in the right eye during the acute phase of the healing period could be considered as pseudoflow. Following IVA injection, the rapid healing of macular edema followed by the increased accumulation of lipoproteins perifoveally might be responsible for the propagation of SSPiM during early post-injection period in the right eye. We observed that the development of SSPiM was temporary in the right eye, and no recurrence was found throughout the follow-up period of up to three years.

Initially, we found that SHE responded well to the injection of IVA in a short period of time with a long-term treatment effect in the left eye (Fig. 2C–F). SHE disappeared a week after IVA (Fig. 2D). We observed no signs of juxtafoveal scar formation after the disappearance of SHE (Fig. 2D-F). SHE might be composed of fibrin, high molecular weight proteins, lipoproteins, and extracellular matrix.[7] Early and frequent treatment of patients with anti-VEGF might eliminate the signs of SHE rapidly.[7] It has been shown that early subcutaneous injection of aflibercept prevented the development of progressive leukocyte infiltration and fibrosis associated with choroidal neovascularization (CNV) in an experimental model of CNV.[8] In our case, it is also striking that the disrupted EZwas rapidly and fully reconstituted after IVA injection in the left eye (Fig. 2D and E). The outer retinal layers and the ELM were intact and did not lose its integrity up to thirty months after the first IVA injection in the left eye (Fig. 5). Coscas et al. reported that information on the status of the ELM, as a marker of photoreceptor integrity, might be useful for determining the future prognosis in exudative AMD.[9] It was also intriguing that in our case, the CCFVA became evident six weeks before the appearance of SHE, which is recognized as a sign of neovascular activity[7] (Fig. 3C and D). McLeod et al. speculated that the driving mechanism for development of neovascularization might be hypoxia/ischemia as analyzed by morphometrical/electron microscopical methods in postmortem choroids of GA and MNV AMD subjects.[10] Laser Doppler flowmetry results in non-exudative AMD patients uncovered the association between increased drusen content and decreased choroidal blood volume/flow suggesting the presence of foveolar ischemia.[11] In our case, the CCFVA was larger one week after the first IVA injection (Fig. 3E), decreased at six months (Fig. 3G), and recovered one year after the first IVA injection (Fig. 3H). However, remarkable type I MNV hypersignal was developed at the same location in June 2020 (Fig. 4). Anti-VEGF agent shift from IVA to IVR in the left eye disclosed efficient result (Fig. 5). The stability of visual acuities, and the preservation of the morphologic retinal structures, as noticed by OCT in both eyes of our phenotype 3 CD patient, could be related with close follow-up and performing appropriate anti-VEGF treatment when needed.

4. Conclusions and Importance

In conclusion, we would like to emphasize the importance of detailed fundus examination of the fellow eye and performing OCT, and OCTA at every visit of patients with exudative AMD who have received intravitreal anti-VEGF injections. Therefore, the close follow-up and prompt/appropriate treatment following early diagnosis of exudation in the asymptomatic stage in eyes with exudative AMD may result in a favorable outcome. In addition, OCTA, a dye less, non-invasive retinal imaging technique, was found to be safe, reproducible, repeatable, and reliable during follow-up of our patient with CD after injection of anti-VEGF agents.

Patient consent

Written consent to publish this case report has been obtained from the patient. This case report does not include any personal information that could lead to the identification of the patient.

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Authorship

The author attests that he meets the current ICMJE criteria for Authorship.

Declaration of competing interest

The author declares that there are no financial other conflicts of interest.

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References

1. Gass JDM. Stereoscopic atlas of macular diseases. Diagnosis and treatment. *St. Louis 4th Ed.* 1997:106–111.
2. Balaratnasingam C, Cherepanoff S, Dolz-Marco R, et al. Cuticular drusen: clinical phenotypes and natural history defined using multimodal imaging. *Ophthalmology*. 2018;125:100–118.
3. Sakurada Y, Parikh R, Gal-Or O, et al. Cuticular drusen: risk of geographic atrophy and macular neovascularization. *Retina*. 2020;40:257–265.
4. Spaide RF, Curcio CA. Drusen characterization with multimodal imaging. *Retina*. 2010;30:1441–1454.
5. Kashani AH, Green KM, Kwon J, et al. Suspended scattering particles in motion: a novel feature of OCT angiography in exudative maculopathies. *Ophthalmol Retina*. 2018;2:694–702.
6. Curcio CA, Messinger JD, Sloan KR, et al. Subretinal drusenoid deposits in non-neovascular age-related macular degeneration: morphology, prevalence, topography, and biogenesis model. *Retina*. 2013;33:265–276.
7. Shah VP, Shah SA, Mrejen S, Freund KB. Subretinal hyperreflective exudation associated with neovascular age-related macular degeneration. *Retina*. 2014;34:1281–1288.
8. Cao J, Zhao L, Li Y, et al. A subretinal matrigel rat choroidal neovascularization (CNV) model and inhibition of CNV and associated inflammation and fibrosis by VEGF trap. *Invest Ophthalmol Vis Sci*. 2010;51:6009–6017.
9. Coscas F, Coscas G, Lupidi M, et al. Restoration of outer retinal layers after aflibercept therapy in exudative AMD: prognostic value. *Invest Ophthalmol Vis Sci*. 2015;56:4129–4134.
10. McLeod DS, Grebe R, Bhutto I, et al. Relationship between RPE and choriocapillaris in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2009;50:4982–4991.
11. Berenberg TL, Metelitsina TI, Madow B, et al. The association between drusen extent and foveolar choroidal blood flow in age-related macular degeneration. *Retina*. 2012;32:25–31.