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Case Report

Multimodal Imaging in a Case with Bilateral Choroidal Folds

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Pattern dystrophy · Choroidal neovascularization · Choroidal folds · Aflibercept · Bevacizumab

Abstract
We highlight the use of multimodal imaging to diagnose and report what is, to our knowledge, a novel presentation of bilateral choroidal neovascularization (CNV) and prominent macular choroidal folds (CFs) in a patient with pattern dystrophy. An 81-year-old Caucasian male presented with painless, blurry central vision in both eyes. Color fundus photography, spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), fundus autofluorescence, and brightness scan ultrasonography supported the diagnosis of pattern dystrophy with bilateral CNV and CF. In the right eye, visually significant CNV worsened post-bevacizumab treatment but responded well to aflibercept. During 4-year follow-up, Snellen visual acuity remained excellent in both eyes at 20/20, including the treatment-naïve left eye. CFs remained markedly stable in both eyes.

Introduction

Pattern dystrophies of the retinal pigment epithelium (RPE) are a group of clinically heterogeneous, related diseases characterized by distinct patterns of pigment maculopathy due to the pathologic accumulation of lipofuscin, most prominently seen on spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), and fundus autofluorescence (FAF) [1]. Disruptions in the RPE and Bruch's membrane by lipofuscin have been attributed to choroidal neovascularization (CNV) and atrophy, which may result in a decline in Snellen visual acuity (VA). The serious threat of permanent vision loss due to CNV warrants

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close monitoring and treatment with anti-vascular endothelial growth factor agents to control CNV and reduce the risk of associated vision loss [2].

CFs are considered sequelae of compressive intra- or extraocular forces commonly summarized with the acronym "T.H.I.N. R.P.E.": choroidal tumors, hypotony, hyperopia, inflammation (posterior scleritis), contracting choroidal neovascular membrane, retrobulbar mass, papilledema (increased intracranial pressure), or extraocular hardware [3]. Angioid streaks and other disruptions of the RPE, including pattern dystrophy, have also been described to cause CFs [4].

We describe the novel presentation and yearslong course of our patient with pattern dystrophy and bilateral CNV with CF. CFs remained unchanged despite successful treatment of CNV. We present, in detail, the use of multimodal imaging to diagnose and follow our patient.

Case Report

An 81-year-old male presented with a complaint of painless, blurry vision in both eyes, right worse than left, of unknown duration. His only ocular history was uncomplicated cataract surgery in both eyes. On initial examination, despite VA measuring 20/20 in the right eye and 20/25 in the left eye, the patient noted subjective blurriness. There was no afferent pupillary defect, and intraocular pressure was within normal range in both eyes. The anterior segment was unremarkable other than well-positioned intraocular lenses. Dilated exam showed peripapillary yellow-white, creamy RPE pigmentary abnormalities in a reticular pattern extending from the optic nerve into the macula of both eyes, along with macular CFs bilaterally (shown in Fig. 1). No intraocular inflammation was observed in either eye. Ophthalmic imaging included color fundus photography, FA, FAF, SD-OCT, and brightness scan (B-scan) ultrasound during the initial visit. SD-OCT was repeated at all subsequent visits for 4 years.

SD-OCT of the right eye revealed central subretinal fluid (SRF) and intraretinal fluid (IRF) encroaching the fovea, while the left eye showed shallow peripapillary SRF and milder IRF (shown in Fig. 2a–d). In Figure 2c and f, peripapillary 5-line raster of both eyes revealed prominent CFs (infrared images) and IRF near both optic nerves, which did not emanate from a pigment epithelium detachment or optic nerve pit. Rather, we suspect the IRF resulted from significant peri- and juxta-papillary pigmentary changes and disruptions in Bruch's membrane with CNV, highlighted prominently in FA and FAF images (shown in Fig. 3, 4). Additionally, FA showed reticular-shaped hypofluorescence in the peripapillary regions of both eyes, although more pronounced in the left eye, corresponding to blockage from pigmentary changes seen on exam. The left eye also had an area of small occult leakage in the central macula. Both maculae on FA demonstrated an alternating pattern of hyper- and hypofluorescence, most visible in the superior and inferior macula, corresponding to CF seen on exam and SD-OCT (shown in Fig. 3). FAF had a striking pattern of peripapillary reticular hyperautofluorescence extending into the macula in the left eye. The right eye had a similar appearance, supporting the presence of excess lipofuscin, though less prominent than the left eye. CFs were also seen on FAF as wrinkles in the superior and inferior maculae of both eyes (shown in Fig. 4). Lastly, B-scan ultrasound and axial length measurements were obtained to rule out aforementioned causes of CFs. B-scan did not reveal retrobulbar masses or signs of scleritis, and axial length was within normal limits (shown in Fig. 5).

Due to the excellent measured VA in both eyes, the patient was initially observed. However, 8 weeks after initial presentation, vision in the right eye decreased from 20/20 to 20/40 due to worsening foveal SRF and IRF (shown in Fig. 6a). The patient was treated with a bevacizumab intravitreal injection in the right eye. At 4-week follow-up, both SRF and IRF significantly

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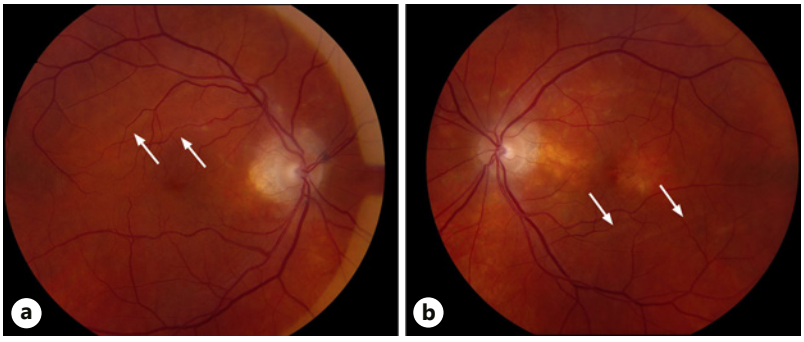

Fig. 1. Color fundus photographs of right eye (**a**) and left eye (**b**). Peripapillary creamy yellow RPE changes are present in both eyes. Pigmentary changes and mottling are present in the left macula. CFs are seen in both eyes (arrows). CF, choroidal fold; RPE, retinal pigment epithelium.

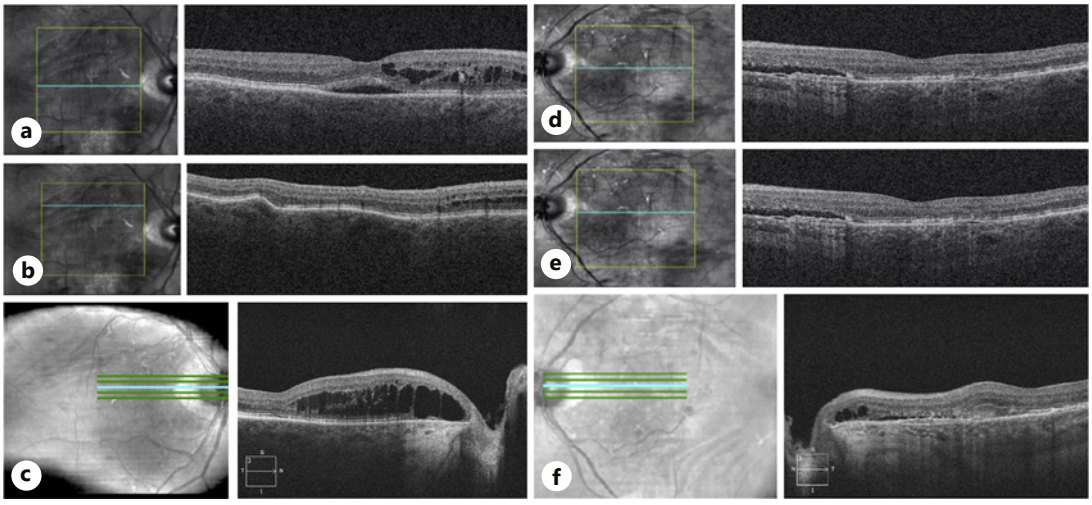

Fig. 2. SD-OCT of both eyes. **a** In the right eye, subfoveal SRF and nasal IRF encroaching the fovea are present. **d** In the left eye, shallow SRF is present. **c**, **f** IRF is seen in the juxta-papillary region in both eyes. **b**, **e** Choroidal folds are present in both eyes. CF, choroidal fold; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid; IRF, intraretinal fluid.

worsened, and VA further decreased to 20/60, which led to a transition in treatment to aflibercept. Following 3 monthly aflibercept injections in the right eye, SD-OCT revealed a nearly dry macula and improvement of vision by 4 lines to 20/20. However, with a trial of observation, IRF dramatically recurred, and vision worsened (shown in Fig. 6b–f). Aflibercept treatment was restarted, resulting in resolution of IRF and SRF and improvement in VA. The patient was successfully managed on a 6–8 week treat-and-extend regimen over 4 years of follow-up (shown in Fig. 7). Throughout this follow-up period, the left eye did not receive treatment, as fluid remained noncentral, and vision measured 20/20 (shown in Fig. 8).

Discussion

This case is a novel presentation and longitudinal follow-up of pattern dystrophy with CNV and CFs in both eyes, which we hypothesize are due to disturbances in Bruch's membrane. The visually striking nature and persistence of the CFs despite successful treatment of CNV

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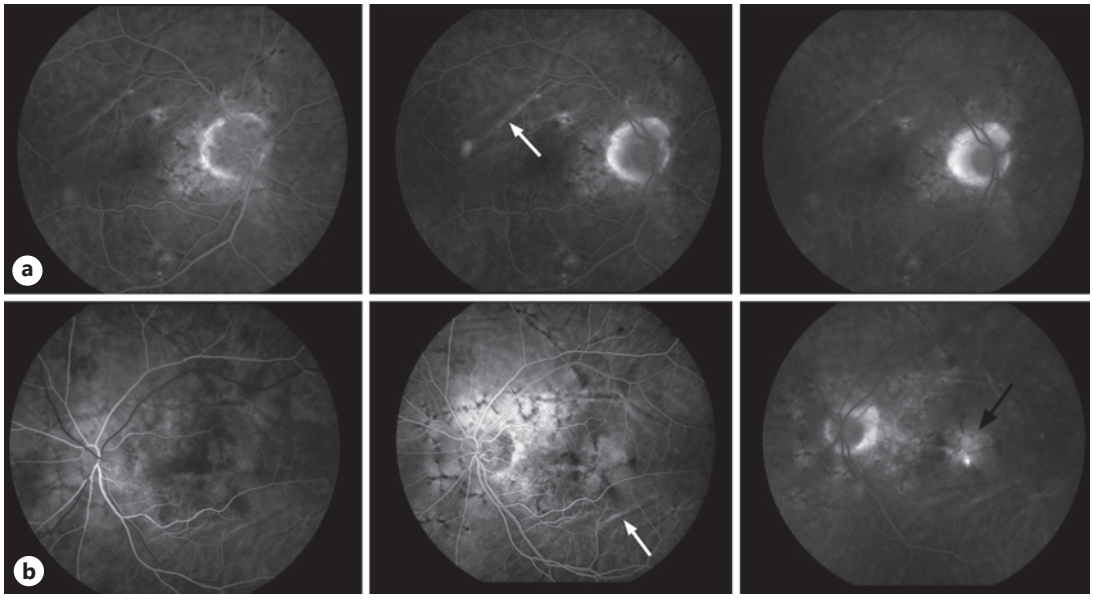

Fig. 3. FA of right eye (**a**) and left eye (**b**). Peripapillary hypofluorescence in a reticular pattern is seen due to blockage from lipofuscin in both eyes. Occult CNV (black arrow) is seen in the left eye, and choroidal folds are present in both eyes (white arrows). CNV, choroidal neovascularization; CF, choroidal fold; FA, fluorescein angiography.

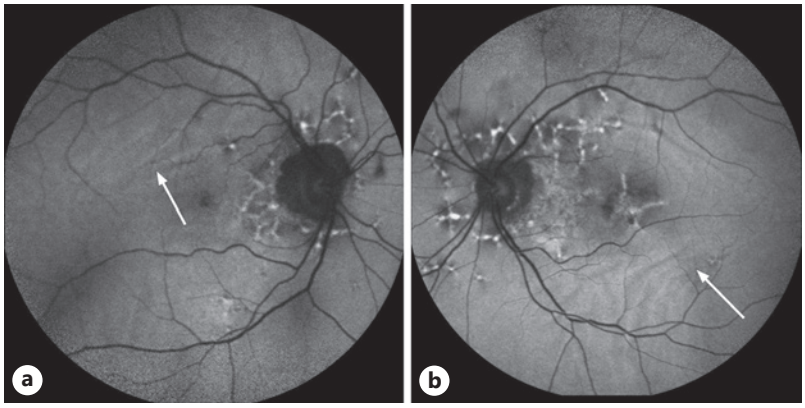

Fig. 4. FAF of right eye (**a**) and left eye (**b**). Hyperfluorescence corresponds to pigmentary changes seen on exam, mainly localized around the optic nerve head in both eyes and extending into the macula in the left eye. CFs are seen as subtle wrinkles in both eyes (arrows). CF, choroidal fold; FAF, fundus autofluorescence.

over several years are noteworthy. The right eye was treated with aflibercept, resulting in resolution of SRF and IRF and improved VA. The left eye did not require treatment due to nonprogressive, noncentral fluid, absence of retinal hemorrhage, and preserved vision, despite a more remarkable FA at presentation. CFs in both eyes remained stable at 4-year follow-up (shown in Fig. 7, 8). Genetic testing for pattern dystrophy was deferred, as multimodal imaging pointed to pattern dystrophy as the most likely diagnosis. Further, it was not necessary for clinical management.

At a glance, the pathology observed in this case seems to fit into common diagnostic heuristics. Bilateral pigmentary changes and CNV in this patient may lead to a diagnosis of age-related macular degeneration (ARMD) and/or central serous chorioretinopathy (CSCR).

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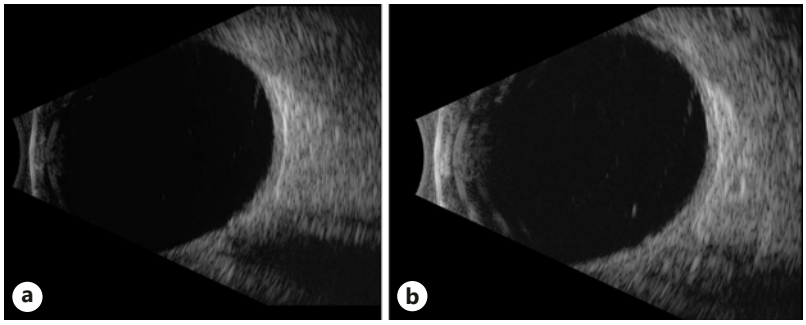

Fig. 5. B-scan of right eye (**a**) and left eye (**b**). No masses, choroidal thickening, or fluid in Tenon's capsule are seen in either eye. B-scan, brightness scan ultrasonography.

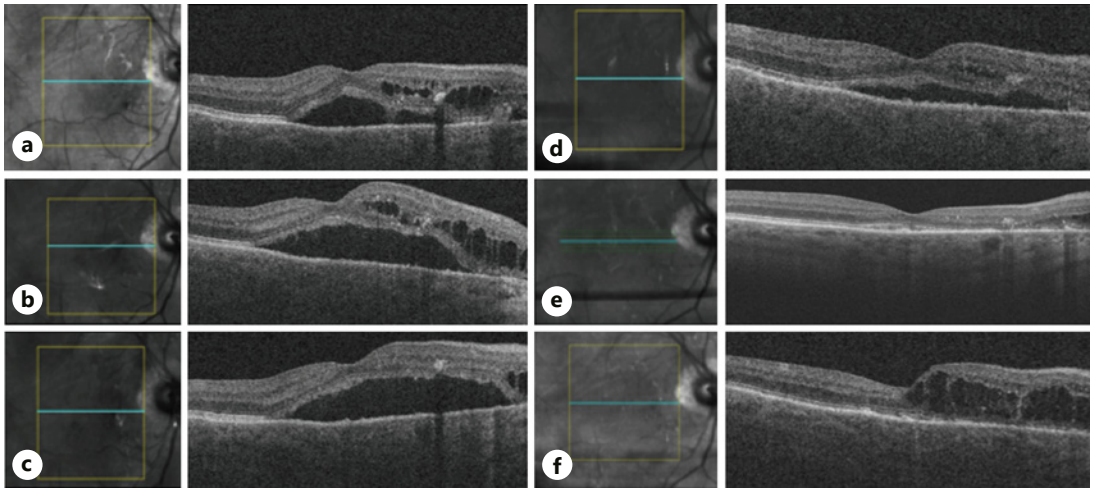

Fig. 6. Time-course imaging series of SD-OCT, right eye. **a** 8 weeks following presentation. VA decreased to 20/40. Worsening macular SRF and IRF. Received bevacizumab. **b** 4 weeks after bevacizumab. VA decreased to 20/60. Worsening macular SRF and IRF. Received aflibercept #1. **c** 4 weeks after aflibercept #1. VA improved to 20/50. Reduced macular SRF and IRF. Received aflibercept #2. **d** 4 weeks after aflibercept #2. VA improved to 20/40. Further reduction in fluid. Received aflibercept #3. **e** 4 weeks after 3 monthly aflibercept. VA improved to 20/20. Fluid nearly resolved. Observed, aflibercept held. **f** Recurrence of SRF and IRF following observation. SD-OCT, spectral-domain optical coherence tomography; VA, visual acuity; SRF, subretinal fluid; IRF, intraretinal fluid.

There are changes to FA and FAF as expected with ARMD and CSCR; however, there is an absence of drusen as seen in ARMD, and the choroid is not thick as would be expected in CSCR. FAF demonstrates hyperautofluorescence, supporting the presence of excess lipofuscin characteristic of pattern dystrophies. Based on the pattern of the pigment distribution, our case is most consistent with butterfly-shaped or reticular PD. The etiology of the CFs was evaluated, and B-scan was negative for retrobulbar mass, posterior scleritis, and short axial lengths. We hypothesize that the CFs formed due to the extensive PD-related pigmentary changes seen in our patient and expanding and contracting forces seen with CNV development within Bruch's membrane. PD and other disruptions of the RPE have been previously described to lead to CFs [4]. Notably, pigmentary changes were most remarkable superior and inferior to the nerve, corresponding to the location of CFs in the superior and inferior macula of both eyes.

It is worth noting that angioid streaks are also on the differential diagnosis due to the peripapillary distribution of creamy linear pigmentary changes. However, FA and FAF findings

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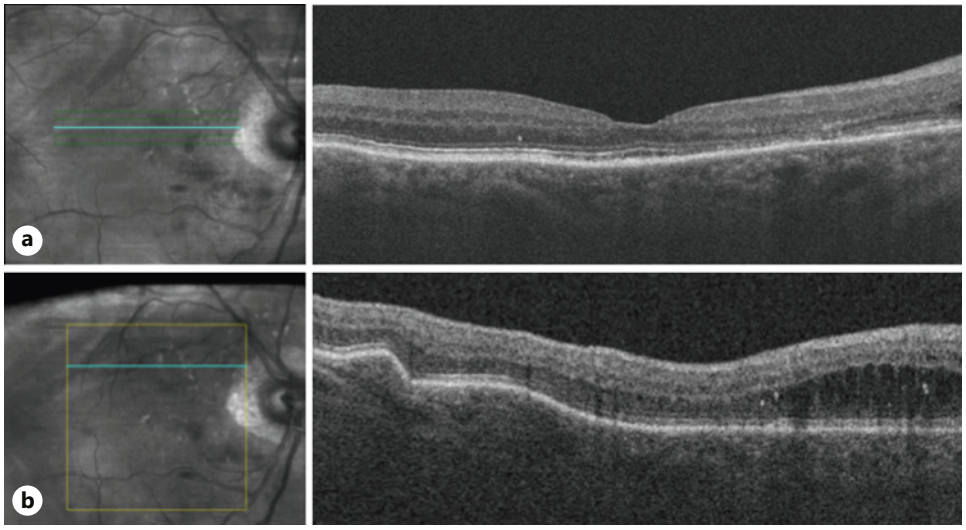

Fig. 7. SD-OCT of right eye at 3 years. **a** Macular SRF and IRF is well controlled. **b** Persistent but stable CFs in the macula. CF, choroidal fold; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid.

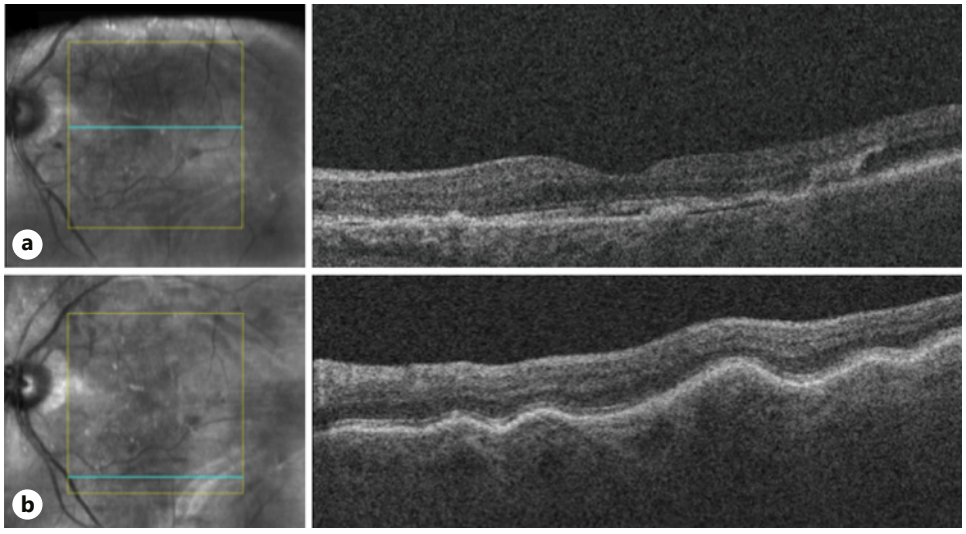

Fig. 8. SD-OCT of left eye at 3 years. **a** Macular SRF and IRF is well controlled. **b** Persistent but stable CFs in the macula. CF, choroidal fold; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid; IRF, intraretinal fluid.

in our case are the opposite of findings suggesting angioid streaks. On FA, angioid streaks are seen as peripapillary hyperfluorescence due to window defect, whereas PD pigmentary abnormalities appear hypofluorescent due to blockage from lipofuscin, as shown in Figures 3 and 4. Furthermore, on FAF, angioid streaks appear as areas of peripapillary hypoautofluorescence due to atrophic changes whereas PD is classically hyperautofluorescent due to lipofuscin accumulation, also shown in Figures 3 and 4.

Though relatively uncommon, patients with PD may have reduced VA if pigmentary changes in the central macula progress to atrophy or if CNV develops [1]. Treatment options include laser photocoagulation and photodynamic therapy but are not first-line as visual outcomes are suboptimal [5]. Currently, treatment of CNV using anti-vascular endothelial growth factor agents is first-line and has previously been shown to be effective in controlling

CNV activity and stabilizing or improving vision [2]. Intravitreal bevacizumab used to treat subfoveal CNV in PD for a period of >2 years showed significant and sustained improvement of best-corrected VA and retinal thickness [6]. Additionally, intravitreal ranibizumab seems to be an effective and safe option for the treatment of subfoveal CNV in patients with butterfly-shaped PD [7].

In our patient, transition from bevacizumab to aflibercept in the right eye led to resolution of macular SRF and IRF along with an improvement in vision. However, with observation, fluid returned and vision worsened, leading to retreatment with aflibercept and a successful treat-and-extend regimen to maintain 20/20 vision and well-controlled CNV activity over 4-year follow-up. The left eye preserved 20/20 vision without intervention, as SRF and IRF remained noncentral despite more impressive pigmentary changes observed during initial exam and multimodal imaging, particularly FA and FAF. Although a single case, our patient demonstrates evidence for successful long-term treatment of CNV in PD with aflibercept.

The rare incidence of PD, CF, and CNV in both eyes, all within a single patient, warrants further discussion to elucidate a relationship between all 3 findings if any. An important distinction is whether CNV or CF appeared first in this patient with pattern dystrophy. This is significant because of the implied relationships between the findings. A fortuitously timed OCT showing the presence of either CF or CNV alone would give the best evidence in determining their order of appearance and commentary on a potential causal relationship between CNV and CF in PD. However, the patient was referred to our retina subspecialty clinic when both findings were already present. Nonetheless, we are still able to have an educational discussion about the different scenarios this case presents.

The first scenario is that CF appeared first. If CF were present prior to CNV, CNV could have developed secondary to either the folds themselves, PD, or formed idiopathically which is unlikely in this setting [8]. Although very rare, CNV secondary to CF has been reported [8]. PD would exist within this scenario with 2 dispositions. The first disposition is that PD is a spectator, related only temporally and without association to the formation of CF, meaning ours is a case of CNV secondary to idiopathic CF, with PD existing in the background by chance. The second disposition is that our case illustrates a previously mentioned but not well-described or established, causative relationship between PD and CF [4].

The second scenario is that CNV appeared first. If CNV was present prior to the CF, CF could be attributable to the CNV itself, PD, or formed idiopathically. CNV leading to CF is a well-established relationship and has been described previously [9, 10]. The role of PD is either again as a spectator in the background related only temporally, or more likely, PD provides an environment in which disruptions in the RPE and Bruch's membrane by lipofuscin may lead to CNV formation [1, 2, 11, 12]. In our case, we believe the pronounced bilateral pigmentary changes from PD led to the development of CNV and may have also independently led to CF, which persisted throughout the extensive follow-up period and will be discussed shortly.

The third scenario is that PD led to both CF and CNV independently. Hypothetically, pigmentary changes in the RPE seen in PD may lead to CNV development. Conversely, CFs may form in an environment with compressive forces and pigment migration, attributable to CNV or not. However, as stated earlier, the current literature describing a relationship between PD and CF is not well-established.

The directionality of the CF is also an important point to review. Gass and Lindblom described cases with *radial* CFs that formed after CNV development, suggesting they develop due to contraction of a sub-RPE fibrovascular membrane adherent to the inner aspect of Bruch's membrane, causing a wrinkling of the underlying choroid with folds radiating outward from the borders of the contracted CNV and fibrotic scar [9–11]. In contrast, our case had linear or curvilinear CF bilaterally rather than a radial pattern. An important difference,

however, is that our patient did not have drusen, pigment epithelial detachments, or fibrosis, whereas their cases had these findings. Our patient's exam and imaging supported a diagnosis of PD, so there may have been a different mechanism of CF formation at play, potentially affecting CF directionality. Perhaps a lack of pigment epithelial detachment and drusen and instead presence of extensive peripapillary and macular pigmentary changes led to a more linear pattern of folds corresponding in location to the most marked of these pigment changes. It remains unclear, still, if CF or CNV came first, as we do not have an SD-OCT predating the formation of either.

The stability of CF in our case throughout the several-year follow-up period is worth mention. As discussed, CFs can develop in association with CNV-induced compressive stress within the choroid, Bruch's membrane, or the entire retina, to force these tissues to buckle. If so, one might expect CF to change in appearance as CNV is controlled or reactivates. We did not observe any change in CFs as CNV activity fluctuated, so it could be that they were present prior to the development of CNV and instead formed due to PD. Perhaps PD-associated pathology of Bruch's membrane creates an environment conducive to or opportune for both CF and CNV to form independently. The current literature consists of numerous reports of PD leading to CNV [9, 12] and is more established than PD leading to CF and/or the rare occurrence of idiopathic CF leading to CNV [10].

Our case of PD, a disease of Bruch's membrane, CF, a condition that can be caused by stress within Bruch's Membrane, and CNV, a vascular growth permeating Bruch's Membrane, poses interesting questions regarding causal or sequential relationships but cannot fully answer them. To our knowledge, the coexistence of these findings bilaterally throughout the follow-up period is unique. Multimodal imaging utilized for diagnosis, yearslong follow-up, controlled CNV, and stable CF with maintenance of excellent VA throughout the reported period is noteworthy, and we hope that our case contributes to the understanding and discussion of PD and associated complications.

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Statement of Ethics

This research was done ethically and in accordance with the World Medical Association Declaration of Helsinki. The patient has given their written informed consent to publish their case and associated images.

Conflict of Interest Statement

There are no proprietary interests or conflicts of interest by any author.

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Author Contributions

David Xu, MA, has made substantial contributions to the conception or design of the work, the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, gave final approval of the version to be published, and is in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authorship has been determined in accordance to ICMJE recommendations. Ambar Faridi, MD, made substantial contributions to the conception or design of the work, the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, gave final approval of the version to be published, and is in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authorship has been determined in accordance to ICMJE recommendations.

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