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Case Report

A Temporal Association between Regression of Pachydrusen and Use of Proprotein Convertase Subtilisin Kexin 9 Inhibitor: A Case Report

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Abstract
Introduction: We aim to report the clinical course of a patient with pachychoroidopathy who experienced regression of subfoveal drusen during cholesterol treatment using PCSK9 inhibitors. ***Case Presentation:*** A 62-year-old woman who was visually asymptomatic complained of recent visual loss in the left eye (OS). She was diagnosed with foveal pachydrusen (OS) that had remained stable for 10 years. Three months after starting cholesterol treatment with a PCSK9 inhibitor, the latest class of lipid-lowering medication, her vision improved in parallel with gradual regression of material deposited beneath the retinal pigment epithelium (RPE). Recurrence of drusen was observed after discontinuing the drug. ***Conclusions:*** Use of PCSK9 inhibitors may improve the retina's lipid homeostasis by increasing the number of RPE-LDL receptors and partly contribute to the improvement of ocular phenotypes associated with dysfunctional RPE in pachychoroidopathy.

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Introduction

Pachydrusen is characterized by discrete, yellowish subretinal pigment epithelium (RPE) deposits coinciding with adjacent choroidal thickening, often with overlying choriocapillaris atrophy. It belongs to a spectrum of pachychoroid diseases and can be misdiagnosed as basal linear deposits in non-neovascular age-related macular degeneration (AMD) [1].

The development of drusen in pachychoroid diseases is governed by a mechanism differing from that of conventional soft drusen in AMD. Prolonged exposure to engorged choroidal vessels in the Haller's layer creates discrete areas of choriocapillaris closure and subsequent complications including pachydrusen and other pathologies [2].

Dysfunctional RPE is a shared feature of pachychoroid diseases and AMD. Reduced phagocytosis of photoreceptor disks and disrupted choroidal blood flow to the RPE cells result in increased endogenous production of lysosomal lipofuscin fluorophore. Ultimately, there is an inhibition of the efflux of digested photoreceptors, leading to drusen formation [2]. On a histological level, the lesion deposits are expected to exhibit lipofuscin and a substantial amount of lipid-rich substances, resembling those seen in soft drusen resulting from AMD [3].

Currently, no treatment has been demonstrated to decelerate the progression of pachydrusen and it is unclear whether modification of the risk factors of pachychoroid variants can reduce such deposited material. Here, we report a case of a woman with pachychoroidopathy in whom foveal drusen resolved with visual improvement, after hypercholesterolemia treatment using evolocumab, a new agent in the proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor class.

Case Report

A 62-year-old woman was initially diagnosed with unilateral adult-onset foveomacular vitelliform dystrophy because of a solitary, subfoveal, drusen-like lesion in the left eye (OS) 10 years (2008) before the presentation. Her best-corrected visual acuity (BCVA) was 20/25 in both eyes (OU). In December 2018, she was referred to our clinic due to declining vision (OS), which was $20/40^{-2}$. The optical coherence tomography (OCT; CIRRUS™ 5000, ZEISS, Dublin, CA, USA) revealed a sub-RPE hyperreflective lesion extending to the photoreceptor layers, concurrent with choroidal pachyvessels (Fig. 1a) and having the largest horizontal dimension of 768 μm. A flimsy epiretinal membrane nasal to the fovea and detached posterior hyaloid were observed. Despite a subfoveal choroidal thickness of 259 μm (axial length, 24.10 mm), the diagnosis was changed from adult-onset foveomacular vitelliform dystrophy to pachydrusen because of the unilateral involvement and material predominantly located within the sub-RPE space, coinciding with choroidal pachyvessels underneath the lesion (Fig. 1a). Indocyanine green angiography revealed hyperpermeability of the large choroidal vessels in the perifoveal (OD) and parafoveal regions (OS). Blood test results for a mutation of the *BEST1, PRPH2, IMPG1*, and *IMPG2* were negative (MedGenome Labs Ltd.). Neither drusen nor RPE alteration was observed in the right eye. Past medical history included obesity (body mass index, 28.3 kg/m^2), dyslipidemia, and untreated obstructive sleep apnea. She indicated that her obstructive sleep apnea symptoms were unaffected by the seasons and her weight remained constant throughout the observation period. Due to the patient's intolerance to statin drugs, 2 weeks prior to the referral, her cardiologist recently prescribed evolocumab (Repatha, Amgen, Thousand Oaks, CA, USA) at a dose of 140 mg/1.0 cc subcutaneously every 2–4 weeks.

Three months later (March 2019), her vision improved to $20/32^{-2}$, and the lesion's dimension shrank to 684 μm (Fig. 1b). The initial high-density lipoprotein (HDL-C) levels

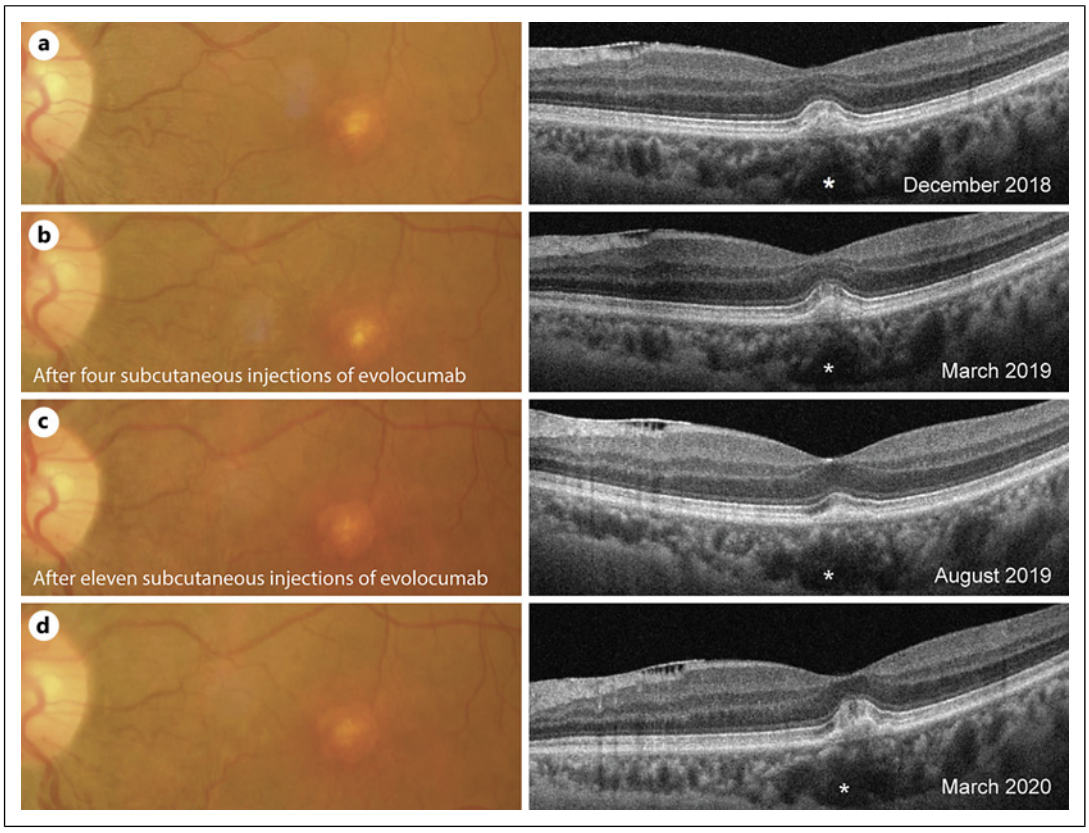

Fig. 1. Clinical course of pachydrusen, as illustrated by color fundus photography and optical coherence tomography (OCT). The patient presented with subfoveal yellowish lesions, with a halo of retinal pigment epithelium (RPE) alteration in the left eye (OS). Corresponding OCT showed a poorly defined RPE layer with sub-RPE hyperreflective material that extended to the ellipsoidal zone. **a** Enlarged choroidal hyporeflective lumens (pachyvessels) were observed in the Haller's layer underneath the fovea (asterisk). A decrease in lesion size with partial resolution of drusenoid appearance was observed at 3 (**b**) and 8 (**c**) months, after initiation of evolocumab cholesterol-lowering treatment. **d** A noticeable deposit of newly assembled material in the RPE basal extracellular space was detected 8 months after drug discontinuation. All OCT images are not provided with their concurrent infrared scans since the 21-HD scan mode was utilized to acquire and export them.

were 62 mmol/L. After eleven injections (August 2019), her low-density lipoprotein (LDL-C) decreased from 179 mmol/L at baseline to 65 mmol/L; however, the patient opted to discontinue the treatment due to an urticarial rash at the injection site. Funduscopy identified a slight decrease in the yellowish deposit in the central areas surrounded by a mottling appearance of the lesion. A corresponding OCT image revealed the lesion only remaining in the sub-RPE pocket of the foveolar regions and partial restoration of ellipsoid and interdigitation zones without pigmentary migration (BCVA, $20/20^{-2}$ OS) (Fig. 1c). Subfoveal choroidal thickness (OS) ranged between 249 and 274 μm over the follow-up period. Eight months after drug discontinuation, her vision deteriorated to 20/40, consistent with her baseline visual acuity, and the OCT scans indicated a recurrence of subretinal deposits extending to the myoid zone (Fig. 1d).

The patient was lost to follow-up due to the pandemic and returned to our clinic in May 2022 with declining vision (OU) (BCVA, 20/40 OD; 20/50 OS). Ocular examination revealed perifoveal pachychoroid pigment epitheliopathy inferonasal to the fovea (Fig. 2a) with significant cataract (OD) and non-ischemic branch retinal vein occlusion affecting the inferonasal

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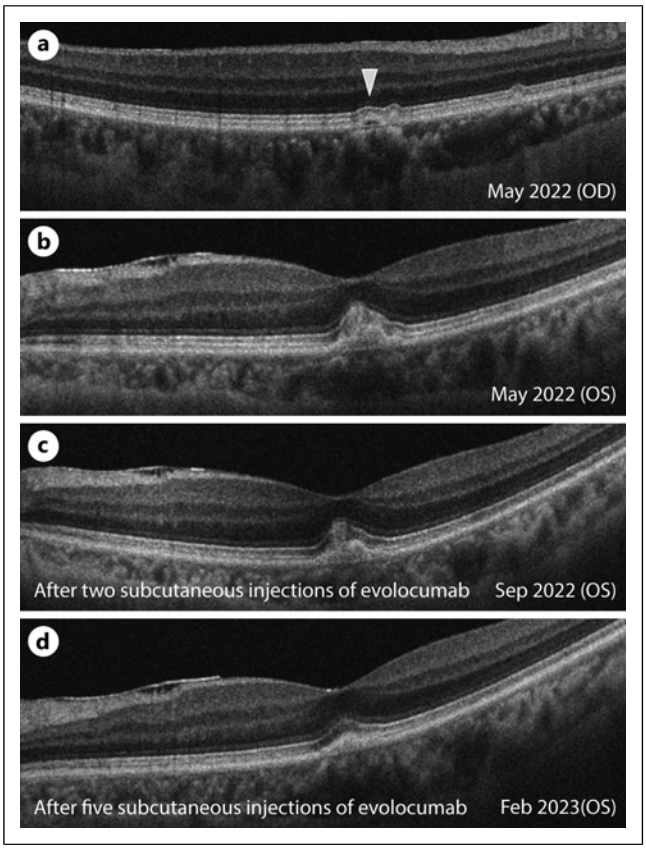

Fig. 2. PPE and the patient's clinical responses during a second course of cholesterol therapy. **a** The patient later developed serous pigment epithelial detachment (white arrowhead) inferonasal to the fovea, corresponding with pachyvessels and overlying collapsed choriocapillaris in the right eye. The recurrent lesion in the left eye (**b**) was reabsorbed again, starting from the subretinal space, and progressing outward, at 2 (**c**) and 7 (**d**) months after restarting evolocumab.

branch (OS). Increased subfoveal deposits with overlying disintegrated photoreceptor layers were observed (OS) (Fig. 2b). She had recently started taking 20 mg rosuvastatin (Vivacor, Sandoz, Basel, Switzerland) once every 2 days for cholesterol treatment. Two months later (July 2022), the cardiologist prescribed evolocumab at 6-week intervals (with a pre-injection of antihistamine) for uncontrolled LDL-C. After five injections (February 2023), the material was substantially reabsorbed, beginning from the subretinal space (Fig. 2c), but the photoreceptor layers remained disintegrated, and OCT angiography revealed no macular neovascularization (LDL-C, 70 mmol/L) (Fig. 2d). She underwent cataract surgery (OD), while branch retinal vein occlusion OS spontaneously resolved without macular edema (BCVA, 20/20 OD; $20/40^{-2}$ OS). Her echocardiogram and carotid Doppler ultrasonography results were normal.

There was no history of prolonged steroid use. She had no family history of ocular problems. No major adverse events from evolocumab occurred and her liver function profile remained normal throughout the treatment course.

Discussion

This patient with pachydrusen showed improvement during PCSK9 inhibitor treatment and worsened in parallel with drug discontinuation. Despite the patient's characteristics not being completely consistent with the sharply delineated lesions with eroded or complex outer contour previously described in pachydrusen cases [1], the position of the material, i.e., beneath the RPE and coinciding with the adjacent hyperpermeable pachyvessels (OS), and continuous progression of the pachychoroid diseases, as evidenced by the emergence of

pachychoroid pigment epitheliopathy (OD), support the diagnosis of pachychoroid-related maculopathies [4].

Although no studies have explored the association between pachydrusen and dysregulated lipid metabolism, the patient's clinical patterns may partly be explained through lipid research into macular disorders like AMD since both pachydrusen and soft drusen share some underlying pathways involving increased intra-lysosomal lipofuscin and impaired RPE functions [5]. Histologically, the difference in contents between plasma apolipoproteins and drusen indicates that the lesions are endogenously produced rather than being deposited directly from circulating blood cholesterol [6]. Furthermore, the effects of cholesterol on drusen progression were opposite to those observed on cardiovascular risk, where AMD risk was higher among those with elevated HDL-C or low VLDL-C levels [7]. Therefore, no significant association has been detected between statin use and drusen progression risk [8, 9].

Evolocumab is a monoclonal antibody that belongs to a new class of cholesterol-lowering agents called PCSK9 inhibitors, which neutralize PCSK9 proteins that naturally mediate LDL receptors (LDLR) degradation. This allows more recycled LDLR to remove cholesterol more efficiently on the hepatocellular surface. Such mechanism aligns better with normal lipid homeostasis than statins do since blocking of cholesterol synthesis through modification of HMG-CoA reductase activity up-regulates PCSK9 activity [10].

RPE cells meet their high energy demand through several pathways, including phagocytosis of photoreceptors and uptake of plasma lipoproteins via their class B scavenger receptors and LDLR [11]. Given that PCSK9 proteins have been detected circulating throughout the body including in liquified vitreous in eyes with retinal detachment [12], they are likely to reach areas with a plethora blood flow, such as choroid. We speculate that reducing circulating PCSK9 proteins should allow more LDLR on the degraded RPE cells, maintaining a steady supply of energy from plasma apolipoproteins that reinforces their macrophage activities (phagocytosis) and shuttling of the digested photoreceptors into the choroid [10, 11].

The importance of LDLR activity is supported by studies indicating that LDLR deficiency results in the foamy appearance of RPE cells similar to that observed in their hypoxic state [13]. In the AMD model, macular neovascularization was considered a compensatory mechanism stimulated by choriocapillaris insufficiency and outer retina hypoxia [14]. Interestingly, these neovascular choroidal vessels were observed to have substantial LDLR (used as a verteporfin target) that further down-regulated vascular endothelial growth factors. These findings may emphasize the importance of LDLR in sustaining the health of RPE cells under both normal and pathological conditions [15].

This report overcame the challenge of isolating the impact of PCSK9 inhibitors from other cholesterol treatments because cardiology guidelines recommend these drugs as an adjunct in patients taking the maximum treatment of a statin plus ezetimibe. This case report had some limitations, including variable treatment intervals, lack of serial autofluorescence images, incomplete regression of vitelliform-like material, and unidentifiable systemic confounders. Nonetheless, the treatment-response associations should increase the integrity of the observed effect, which appeared to act against the natural course of the disease. A prospective study with measurement of serum PCSK9 levels should be conducted to confirm this observation. To create an agent that has the potential to impede the progression of early-stage AMD, it is essential to conduct translational research in the human RPE cell line (ARPE-19 cells) to investigate how recombinant human PCSK9 protein affects the uptake of LDL-C and VLDL-C via LDLR, VLDLR, and cluster of differentiation 36 (CD36) receptors, along with the expression of LDLR post-evolocumab treatment. These studies are designed to uncover the relationship between PCSK9 proteins and RPE functions in regulating the internalization and degradation of LDLR. Proceeding to the clinical-level studies, local treatment is recommended because systemic PCSK9 inhibitor therapy may impact overall cholesterol levels,

which could interfere the assessment of RPE health and drusen formation. To reach the specific receptors at basal membranes of the RPE cells, a nanobody antibody fragment capable of inhibiting the interaction between PCSK9 and LDLR should be created to enable its traversal through the zonula occludens. Incorporating this nanobody into a drug delivery system will prolong the duration of medication effects.

In summary, the temporal association between the use of a PCSK9 inhibitor and reabsorption of pachydrusen can aid in the development of potential treatments targeting enhanced RPE-LDLR for lipid-associated maculopathies including AMD. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540014).

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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. No identifying information is included. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

This work was carried out at Vajira Hospital and has not been presented at any prior meetings. No authors have a financial or proprietary interest in any materials or methods mentioned.

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Author Contributions

Dr. Kriengsak Funilkul: examining patients, documenting the course of treatment, and reviewing the manuscript. Dr. Yodpong Chantarasorn: examining patients, documenting the course of treatment, conceptualizing, and writing the manuscript. All the authors have read and approved the final manuscript.

Data Availability Statement

The datasets generated during the current study are not publicly available due to protection of the patient's personal information but are available from the corresponding author on request.

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