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Sildenafil Citrate Induced Retinal Toxicity - ERG, OCT, and Adaptive Optics findings

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Abstract

Purpose—To report a case of persistent retinal toxicity associated with a high dose of sildenafil citrate intake.

Methods—Single retrospective case report.

Results—A 31-year-old Caucasian male with no previous medical history presented with complaints of bilateral multi-colored photopsias and erythropsia (red-tinted vision), shortly after taking sildenafil citrate —purchased through the internet. Patient was found to have cone photoreceptor damage, demonstrated by ERG, OCT, and adaptive optics imaging. The patient's symptoms and the photoreceptor structural changes persisted for several months.

Discussion—Sildenafil citrate is a widely used erectile dysfunction medication that is typically associated with transient visual symptoms in normal dosage. At high dosage, sildenafil citrate can lead to a persistent retinal toxicity is certain individuals.

Keywords

Sildenafil citrate; Viagra; Adaptive Optics; Retinal toxicity; Electroretinogram; ERG; optical coherence tomography; OCT

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Introduction

Sildenafil citrate is an oral phosphodiesterase-5 (PDE-5) inhibitor, widely used to treat male erectile dysfunction at an approved dosage range of 25-100 mg and pulmonary hypertension at a dosage range of 0.25 to 2 mg/kg every 4 to 8 hours[1]. In vitro studies have shown that sildenafil citrate also inhibits PDE-6, which is primarily found in the retinal photoreceptors and plays a key role in the phototransduction cascade. Sildenafil citrate's effect on PDE-6 is about 1/10 of the effect on PDE-5[2]. Nevertheless, that inhibitory effect on PDE-6 is believed to be responsible for the various sildenafil-induced visual disturbances including cyanopsia, a sense of blue-tinted vision, increased perception of brightness, blurred vision, photophobia, and transient electroretinogram (ERG) changes[2-3]. Other associated ocular side effects that have been reported including erythropsia, retinal vascular occlusion, anterior ischemic optic neuropathy, and central serous chorioretinopathy, are more likely to be secondary to the systemic or ocular hemodynamic changes[4-6]. Visual disturbances associated with sildenafil citrate are typically transient and usually resolve within 24 hours[1]. We report an unusual case of persistent retinal toxicity, characterized by structural and functional disturbances of the outer retinal, associated with high dose intake of sildenafil citrate.

Case report

A 31-year-old Caucasian male with no medical history presented to the New York Eye and Ear Infirmary urgent care clinic complaining of red-tinted vision in both eyes for the previous 2 days. He reported that his visual symptoms began shortly after taking a dose of liquid sildenafil citrate, he had previously purchased through the internet. He did not know the exact dose he took, since he had not used the measuring pipette provided, but instead had drunk the solution directly from the bottle. He believed that he consumed much more than 50 mg/ml that the measuring pipette would have delivered. A short while after ingesting the substance, the patient began to notice a red tint to his vision along with multi-color photopsias and a sense of decreased contrast. The following day, the photopsias resolved, but the decreased contrast and red-tinted vision remained.

At examination, his best corrected visual acuity was 20/20 in both eyes. His pupils were round, reactive to light, and no afferent pupillary defect was noted in either eye. Extraocular movements and confrontational fields were grossly normal. Intraocular pressure was 12 mm Hg in the right eye and 13 mm Hg in the left eye. Ishihara color plates were full in both eyes. The anterior segment exams were unremarkable. The posterior segment examinations revealed some mild pigment mottling in the macula, while the optic nerves appeared normal with sharp margins. The vitreous, retinal vessels, and peripheral retina were unremarkable in both eyes (Figure 1: A, B). Ultra-widefield fluorescein angiography was also unremarkable in both eyes (Figure 1: C, D). Fundus autofluorescence showed symmetric areas of hyperautofluorescence slightly temporal to the fovea, bilaterally (Figure 1: E, F). The scanning laser ophthalmoscopy near infrared reflectance (NIR) images revealed a bullseye pattern with concentric rings of hypo- and hyper-reflectivity, bilaterally, (Figure 2, A, C) and the optical coherence tomography (OCT) B-scans demonstrated diffused nodular thickening and irregularities of the central ellipsoid zone associated with thinning and poor delineation

of the inter-digitation zone. The choroid appeared thickened. (Figure 2, B, D). Full-field ERG showed reduced cone amplitudes, normal rod responses, and normal implicit times in both eyes (Figure 3: A). Multifocal ERG revealed reduced amplitudes throughout the macula in both eyes (Figure 3: B). Adaptive optics scanning light ophthalmoscopy performed at 6 months following the incident revealed multiple dark spots in the photoreceptor mosaic consistent with loss or non-waveguiding cone photoreceptors. These correspond to the areas of outer retina disruption seen on OCT (Figure 4). OCT angiography demonstrated normal flow in the superficial and deep retinal capillary layers and choriocapillaris. (Figure 5: A-F).

Following presentation, the patient was treated with topical prednisolone acetate four times a day in both eyes, brinzolamide 1% three times a day in both eyes, and brimonidine tartrate twice daily in both eyes. The next day, the patient's symptoms were unchanged. A trial of oral prednisone 60 mg once a day for 3 days was initiated. However, there was no noticeable improvement, and the steroids were discontinued. At 3-months follow-up, visual symptoms remained unchanged. The outer retinal changes partially improved leaving some diffuse mottling of the ellipsoid zone layer with absence of the interdigitation zone layer on OCT scans. (Figure 6: A-D) The optic nerve scans showed normal values of retinal nerve fiber layer thickness. (Figure 6: E, F)

Discussion

Studies of sildenafil citrate at the approved dose for erectile dysfunction, have shown that visual side effects are transient, and ERG changes typically resolve within 24 hours. In a double-blind control study, Jagle demonstrated that 100 mg of sildenafil citrate in a healthy male subject resulted in transient ERG changes that returned to normal within 24 hours. Visual changes showed significant correlation with plasma concentration[7]. Additionally, in preclinical studies conducted by Pfizer, sildenafil citrate at a dose of 200 mg produced visual symptoms in almost 50 percent of the subjects. ERG tracings in these subjects also indicated a reduction in rod and cone function at the peak plasma level[8]. This finding suggests that sildenafil citrate's effect on the retina is dose-dependent.

In our case, we do not know how much sildenafil was ingested, but we believe that it was substantially higher than the recommended dose. The changes seen in our patient are consistent with photoreceptor toxicity, especially in the macula. The cone cells appear to be more vulnerable. The multifocal ERG showed a global depression in cone response that was consistent with the structural findings of cone disruption seen with adaptive optics. Kim et al. recently reported a case of retinal toxicity from high dose of sildenafil citrate ingestion.[9] The patient reportedly took 10 pills of 75 mg (750 mg) of sildenafil citrate and presented with complaints of blurred vision. His OCT demonstrated irregularities in the photoreceptor line and his full-field and multifocal ERG were reduced in amplitudes. As in our case, the patient consumed a high dose of sildenafil citrate just prior to the onset of the symptoms. The macula appeared to be most affected with damage localized to the cone photoreceptors. In the case reported by Kim, toxicity persisted for several months with ERG and the OCT changes returning to normal after one year.[9]

Nivison-Smith and colleagues showed that mouse carriers for the retinitis pigmentosa gene (rd1) are more susceptible to sildenafil citrate toxicity compared to normal wild type.[10] This is because rd1 mutation results in a deficiency in PDE-6 which blocks the breakdown of cyclic guanosine monophosphate (cGMP), involved in retinal phototransduction. Elevated cGMP is potentially toxic. In this study, mice received on average 29 mg/kg of sildenafil citrate, 20 times the recommended human dosage. Wild type mice had complete recovery of ERG function within 48hrs, but rd1 gene carrier mice did not recover. Asymptomatic rd1 gene carrier rate is estimated to be as high as 2% in human populations.[10] This may explain why certain patients may be more susceptible to sildenafil citrate toxicity. Notably, adaptive optics images of cone cells in our case of sildenafil toxicity appear remarkably similar to the images from patients with achromatopsia.

While previous studies have indicated that the visual changes associated with sildenafil citrate typically resolve within 24 hours, our case and the one reported by Kim et al suggest that higher doses of sildenafil can lead to persistent retinal damage. We also acknowledge that because the drug was acquired online from a non-pharmacy source, there are concerns about the purity of the active drug and the accuracy of the concentration—factors that might have contributed to the increased risk of toxicity.

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3. R.B. Rosen is a consultant for Optovue, NanoRetina, Regeneron, Ocata Therapeutics, Guardion Health, Glaucohealth, Allergan, Boehringer-Ingelheim, CellView and receives grant support from Genentech/Roche, Zeavision, and NanoRetina. None of these are relevant to this report.

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Summary statement

We present an unusual case of outer retinal toxicity with persistent visual impairment following a high dose of sildenafil citrate.

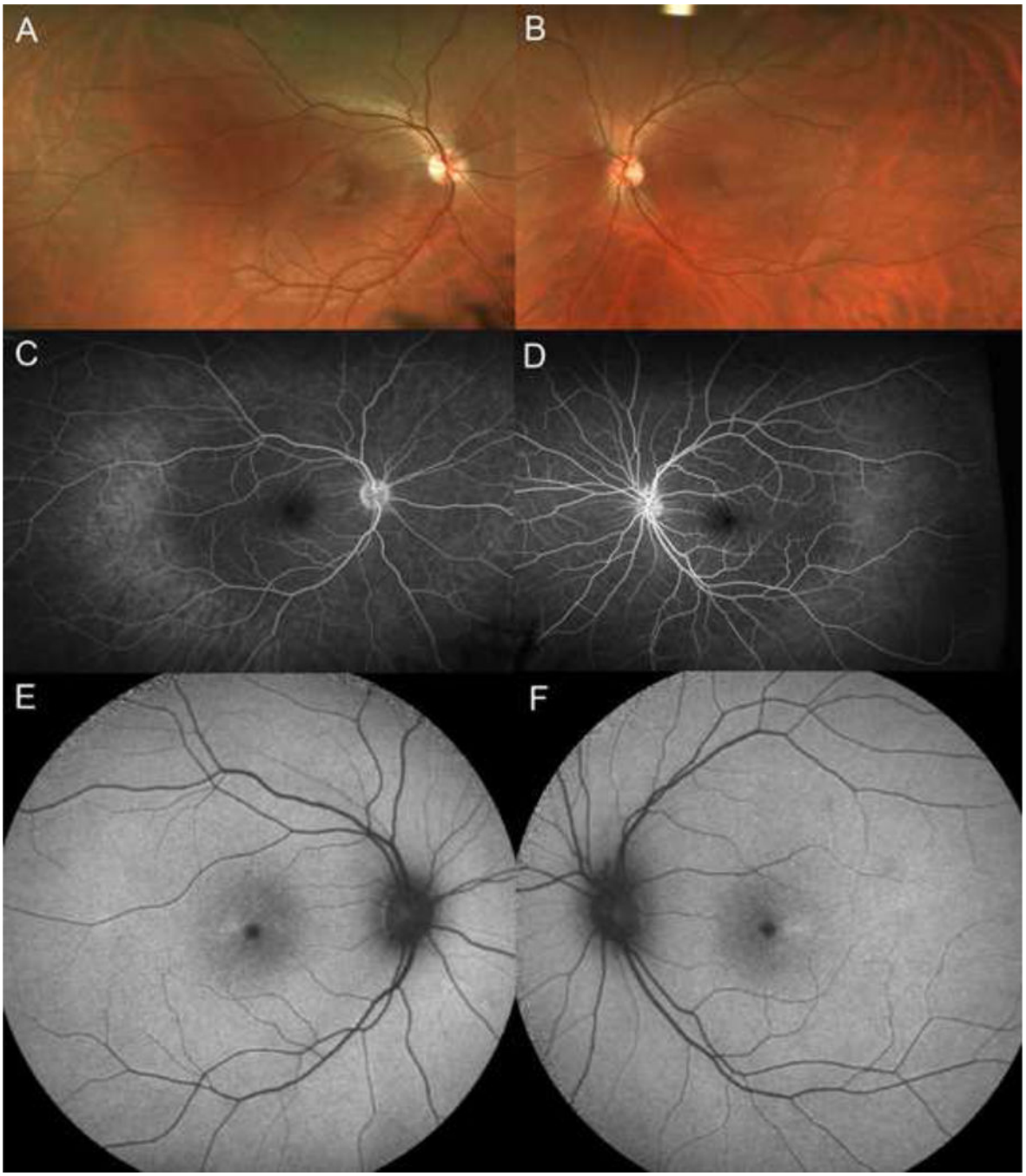

Figure 1.

A, B. Ultra-wide-field color images suggest subtle pigment mottling in the macula, with unremarkable vascular networks, optic nerves, and retinal periphery. C, D. Ultra-wide-field fluorescein angiography shows normal filling and no leakage. E, F. Fundus autofluorescence demonstrates symmetric areas of hyperautofluorescence slightly temporal to the fovea in both eyes

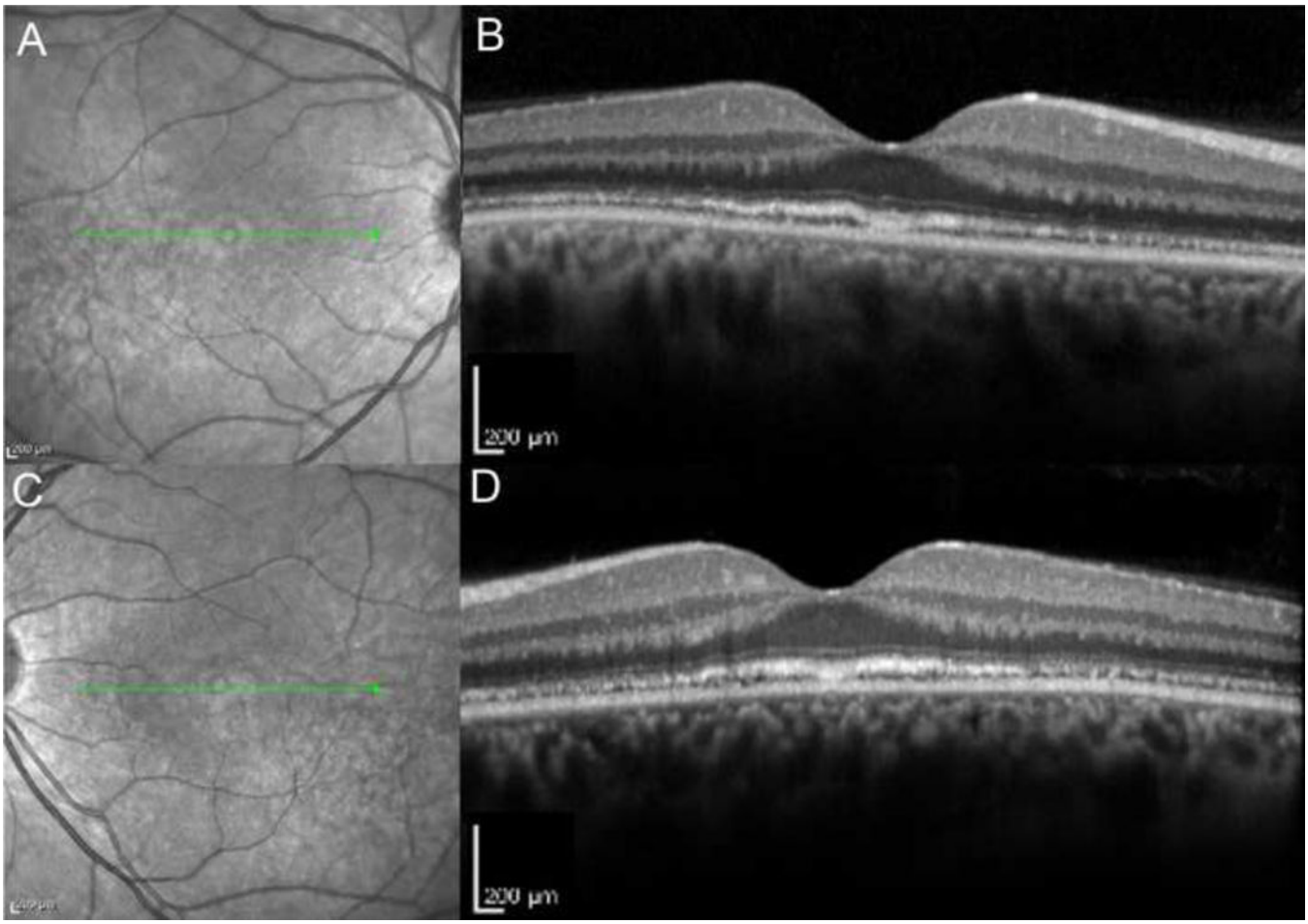

Figure 2.

A, C. Near-infrared reflectance shows a bullseye pattern with concentric rings of hypo- and hyperreflectivity in both eyes. B, D. Optical coherence tomography B-scans show a diffused nodular thickening and irregularities of the central ellipsoid zone associated with thinning and poor delineation of the inter-digitation zone in both eyes. The choroid appears thickened in both eyes

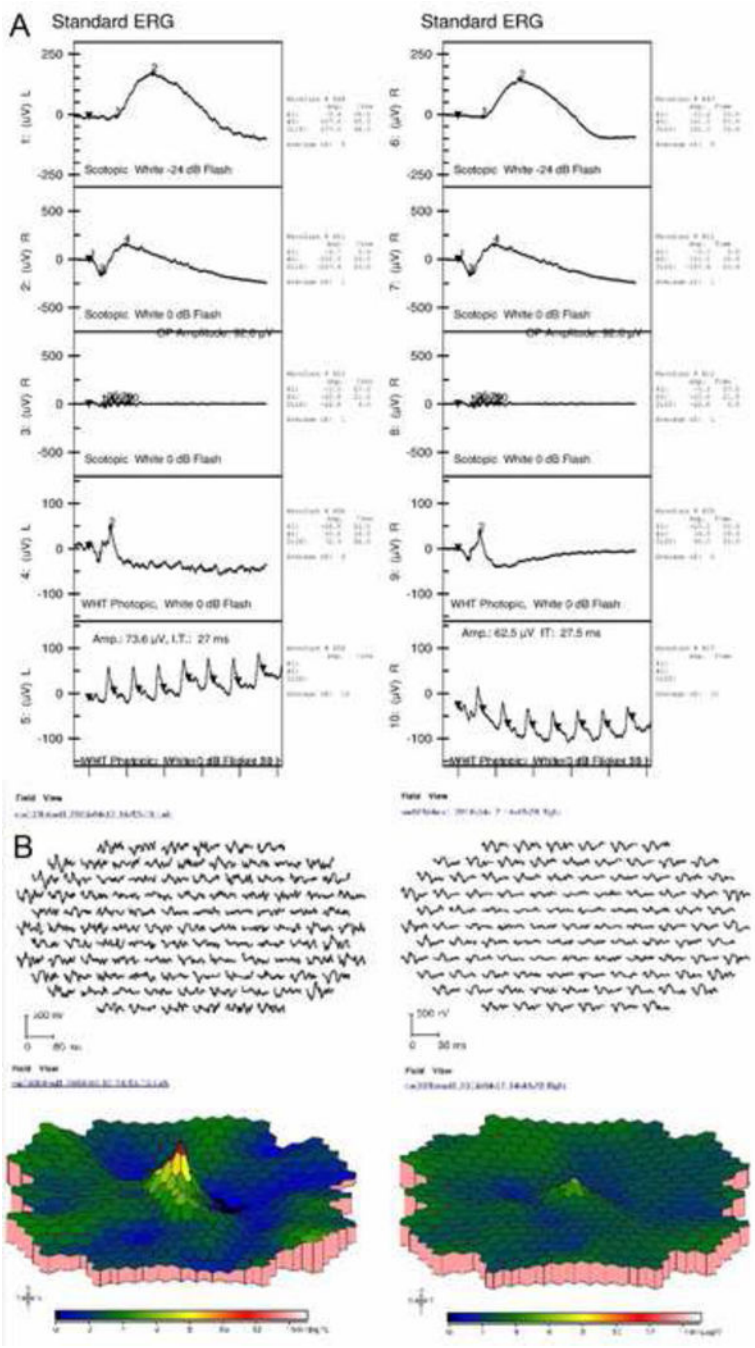

Figure 3.

A. Full-field ERG shows reduced cone amplitudes, normal rod responses, and normal implicit times in both eyes. B. Multi-focal ERG shows reduced amplitudes throughout the macula in both eyes

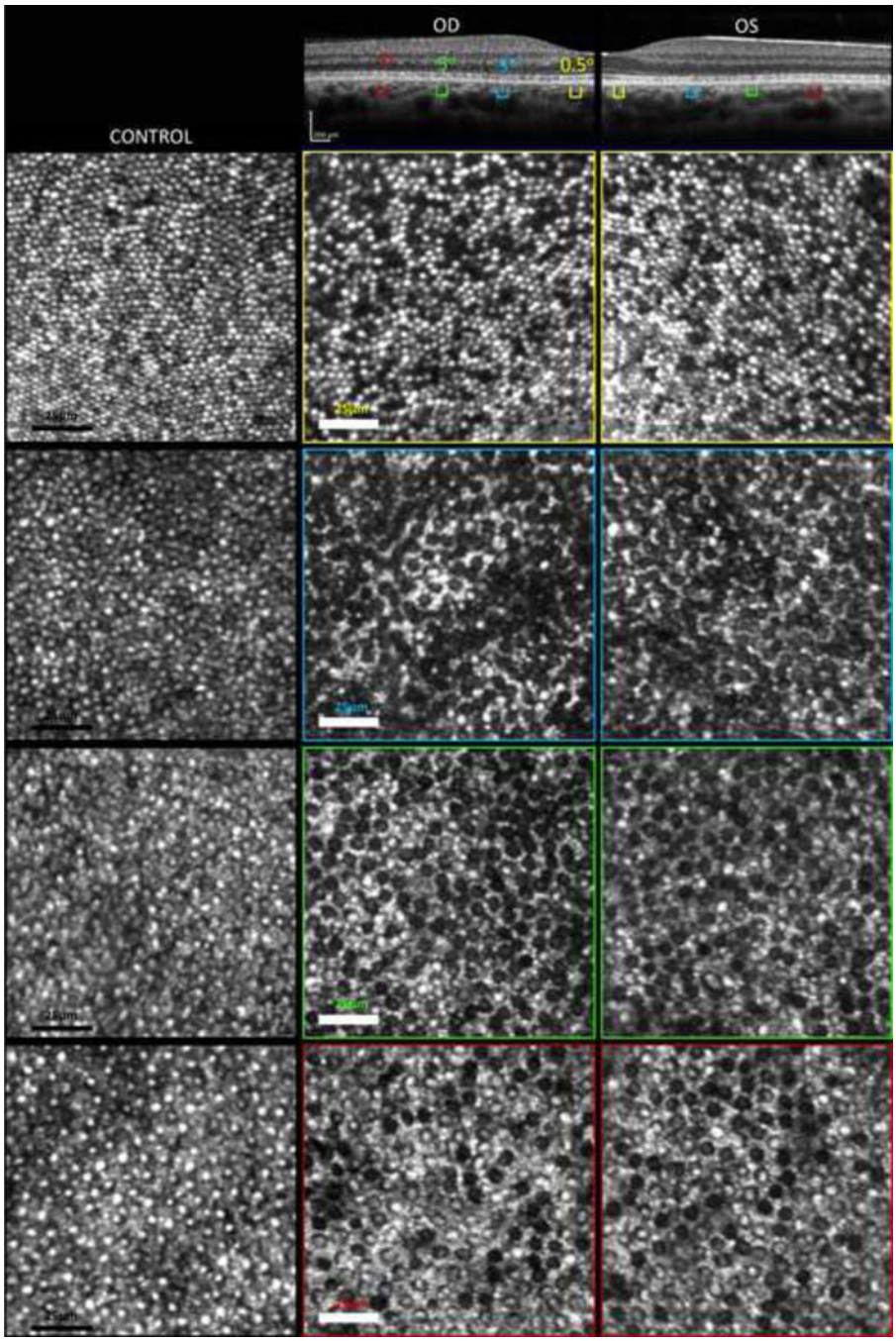

Figure 4.

Adaptive optics scanning light ophthalmoscope images of the patient reveal multiple dark spots in the cones mosaic, not seen in the controls, consistent with loss or non-waveguiding photoreceptors at increasing eccentricities from the foveal center in both eyes (0.5, 3, 5, 7 degrees from Umbo).

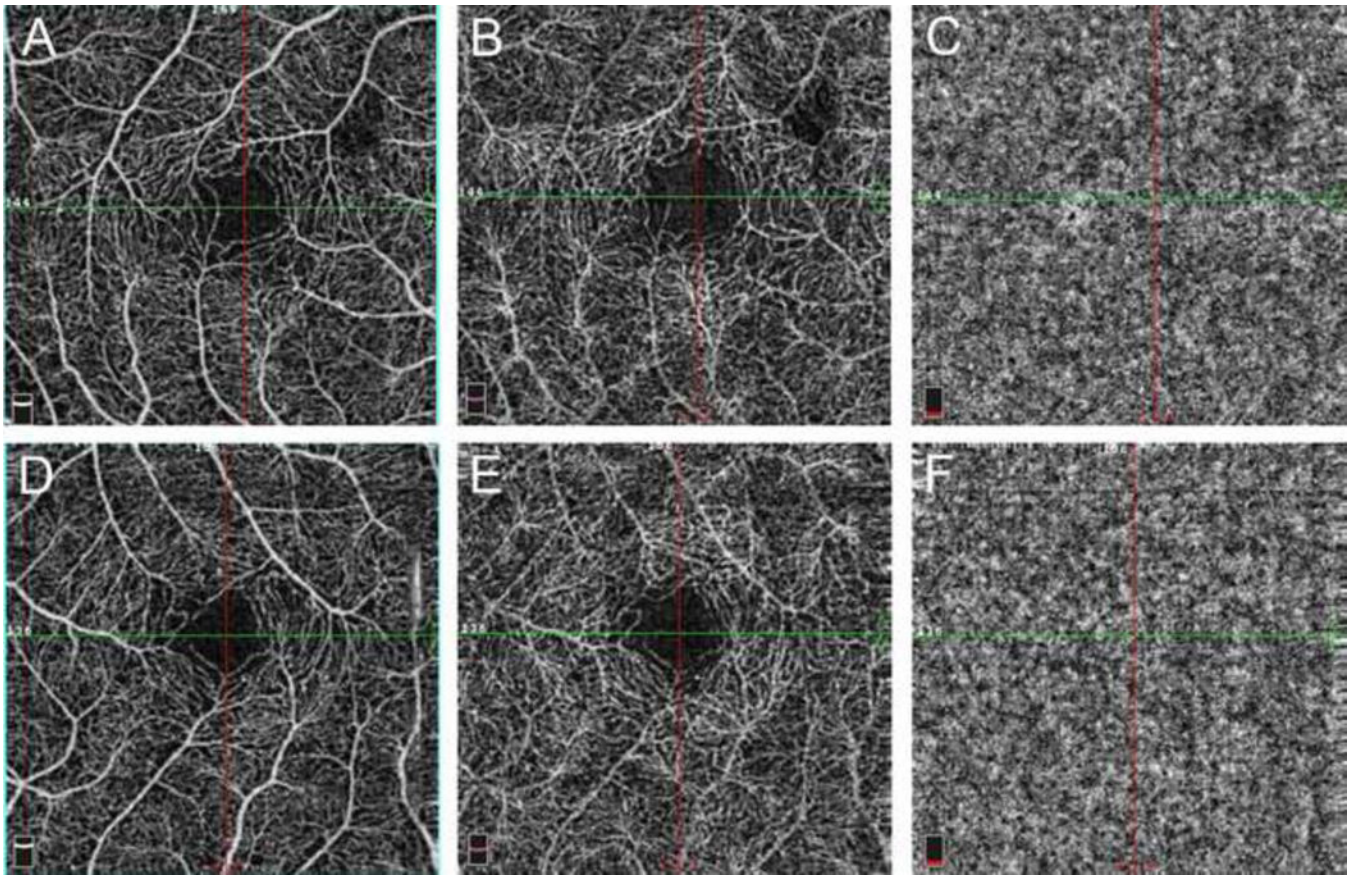

Figure 5.

En face OCT angiography (OCT-A) of the central 3×3 mm taken at 1-week follow-up shows normal microvasculature in the right eye (A, B, C) and the left eye (D, E, F). A and D are segmented at the level of the superficial retinal capillary plexus. B and E are segmented at the level of the deep retinal capillary plexus. C and F are segmented at the level of the choriocapillaris.

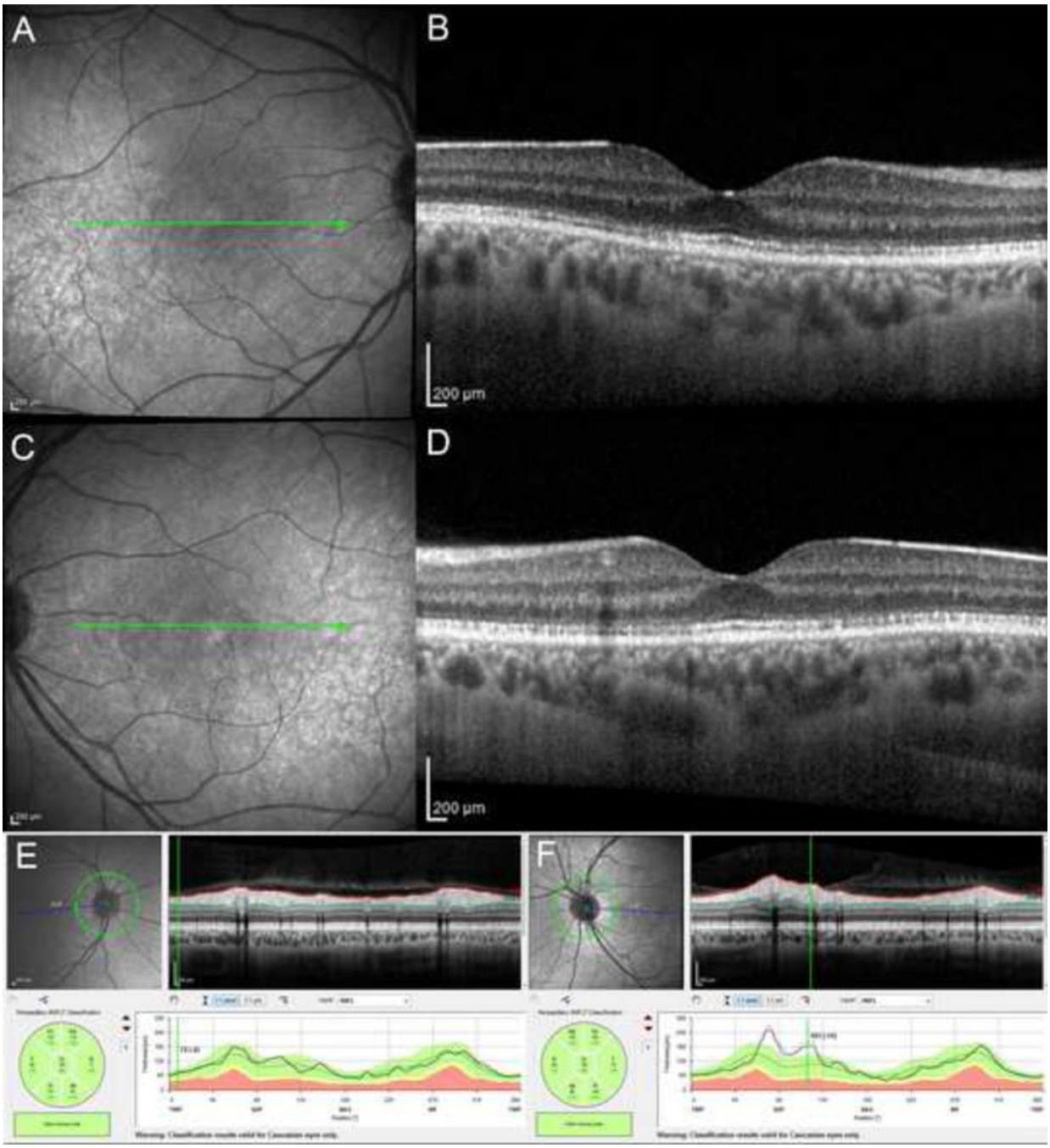

Figure 6. Examination 3 months following presentation

A, C. Near infrared reflectance (NIR) of the right eye (A) and the left eye (C) B, D. The OCT B-scans at the level of the corresponding area on panels A and C (green lines) evidence partial restoration of the ellipsoid zone with residual mottling. E, F. The optic nerve OCT scans demonstrate normal nerve fiber layer thickness in both eyes.