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Case report

Amiodarone: A potential risk factor for retinal phototoxicity

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A B S T R A C T

Purpose: To report the only known case, to our knowledge, of amiodarone induced retinal phototoxicity following vitrectomy surgery.
Observations: A 66-year-old male presented with visual acuity of 20/150 OS secondary to an epiretinal membrane (ERM). Patient was on oral amiodarone for atrial fibrillation. Baseline spectral domain optical coherence tomography (SD-OCT) revealed an ERM with retinal thickening and schisis. The patient underwent an uncomplicated pars plana vitrectomy and membrane peel using standard vitrectomy settings and illumination. Triamcinolone was used to stain the ERM intraoperatively. ICG was not used. On post-operative day one, vision was count finger (CF) at 1′. At post-operative week one, vision was unchanged and SD-OCT showed macular edema. At post-operative month one, vision remained CF at 1′ and macular edema resolved with residual pigmentary changes and subretinal fibrosis resembling phototoxic damage. SD-OCT at one month showed resolution of macular edema, retinal pigment epithelium hyperplasia and an indistinct ellipsoid layer. Fluorescein angiography did not show any neovascularization. At three month follow-up, patient's vision, exam and OCT findings remained unchanged.
Conclusions and importance: Many pharmacologic agents have the ability to alter a patient's sensitivity to solar or artificial radiation. Drugs act as photosensitizers that lead to photochemical damage. Amiodarone has been reported to have such photosensitizing properties in humans. This report describes a case of retinal phototoxicity from intraoperative light exposure photosensitized by systemic amiodarone use.

1. Introduction

The eye is more vulnerable to phototoxicity than other organs in the body as the optics of the eye are designed to concentrate and focus light on the retina.[1] Retinal phototoxicity can occur through three mechanisms: photothermal, photomechanical and photochemical.[2] Many pharmacologic agents have the ability to change a patient's sensitivity to solar or artificial radiation. Drugs may act as photosensitizers leading to photochemical damage. Photosensitizing drugs deposit in the retina and when activated by light, release reactive oxygen species that cause oxidative damage to various cellular components.[3,4] We present here the only known case, to our knowledge, of retinal phototoxicity as a result of photosensitization from systemic amiodarone use.

2. Case report

A 66-year-old male presented with one-year history of progressive decrease in vision in his left eye. His past ocular history was significant for primary open angle glaucoma treated with bimatoprost in both eyes. He had a history of atrial fibrillation, mitral valve regurgitation and hypertension. His systemic medications included metoprolol 25mg, sildenafil 100mg, amiodarone Hcl 200mg, valsartan 320mg, dabigatran 150mg and amlodipine 5mg. Patient had been taking amiodarone for 9 years.

On examination his vision by Snellen visual acuity was 20/20 OD and 20/150 OS. There was no afferent pupillary defect. Intraocular pressure (IOP) was within normal limits OU. Slit lamp examination revealed corneal verticillata OU and 1 + nuclear sclerotic cataracts OU. Dilated fundus examination demonstrated a single micro-aneurysm temporal to fovea in the right eye and a prominent epiretinal membrane (ERM) in the left eye. Scleral depression of both eyes did not reveal any peripheral abnormalities. Initial spectral-domain optical coherence tomography (Heidelberg Spectralis HRA + OCT, Vista, CA SD-OCT) of the left eye revealed a

prominent ERM with thickening and loss of the normal foveal contour with intraretinal cystic changes (Fig. 1C and D). SD-OCT of the right eye was normal (Fig. 1A and B).

It was concluded that the ERM was visually significant and the patient underwent an uncomplicated pars plana vitrectomy and membrane peel (PPV/MP) of the left eye. The surgery was performed under monitored intravenous anesthesia and sub-Tenon's block consisting of a 50:50 mixture of 0.75 bupivacaine and 2% lidocaine without epinephrine. A standard three port 23-gauge core and peripheral pars plana vitrectomy was performed using the Alcon Accurus 800cs vitrectomy machine at standard illumination setting of 38%. The illumination of the Leica operating microscope (Leica M844 C40) was set to a standard of 20%. Both of these settings were at the lower end of the illumination range. A 1:3 dilution of 40mg/ml triamcinolone acetonide to balanced salt solution was injected into the eye to stain the ERM. An edge of the ERM was elicited using a flexible loop internal limiting membrane scaper just inside the inferotemporal arcade. The ERM was easily removed using internal limiting membrane forceps extending to the superotemporal and inferotemporal arcades, to the temporal aspect of the nerve and several disc diameters temporal to the fovea. No tears or breaks were elicited. Of note, indocyanine green dye was not used. The total duration of the procedure from when the patient entered and exited the operating room was 1 hour and 21 minutes. The actual time for epiretinal membrane peeling was not recorded but of standard duration lasting less than 10 minutes.

On post-op day one, visual acuity was count finger (CF) at 1 ft in the left eye. IOP was normal. Fundus exam was significant for trace residual triamcinolone visible overlying the macula and inferiorly. Routine post-operative drops were initiated including prednisolone acetate 1% QID, gatifloxacin QID, atropine 1% BID and erythromycin ointment QHS.

At post-op week one, visual acuity remained at CF at 1 ft. Fundus examination revealed macular edema. SD-OCT demonstrated marked distortion of the foveal contour with retinal edema, retinal pigment epithelium (RPE) disruption, and intraretinal cystic changes (Fig. 2A and B). Prednisolone acetate 1% was increased to six times a day at this point to help reduce the macular edema.

At post-op week two, vision remained at CF at 1 ft. Fundus examination revealed decreased macular edema with pigmentary changes at the level of the RPE. SD-OCT showed pigmentary changes in the macula and loss of the ellipsoid layer (Fig. 2C and D). IOP was mildly elevated to 27 secondary to steroid response and a prednisolone taper was initiated. At post-op month one, vision was stable at CF and examination now showed subretinal fibrosis along with increase in pigmentary changes (Fig. 3C). SD-OCT showed pigmentary changes at the level of the RPE with loss of ellipsoid layer (Fig. 3A and B). A fluorescein angiogram was obtained showing window defects with late staining and blockage from pigment. No choroidal neovascularization was noted (Fig. 3D and E). At the latest follow-up at 3 months postop, the patient's vision, exam, and SD-OCT findings remained unchanged.
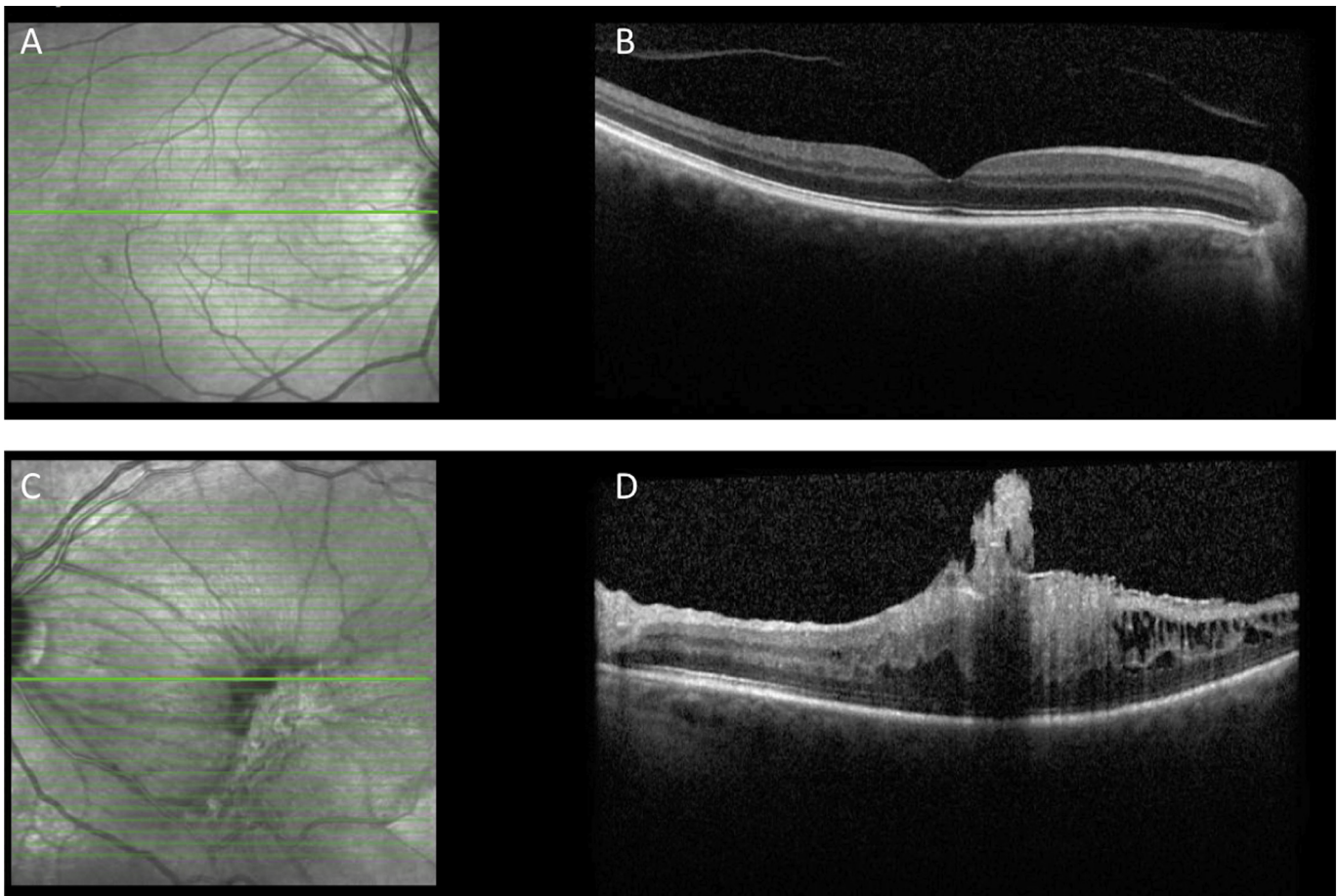

Fig. 1. Preoperative SD-OCT. A: Pre-operative Infrared Reflectance (IR) image of right eye designating the spectral domain optical coherence tomography (SD-OCT) cross section in B. **B**: SD-OCT of the right eye is normal. **C**: Pre-operative IR image displaying the epiretinal membrne (ERM) and designating the location of the SD-OCT cross section in D. **D**: Preoperative SD-OCT of left eye showing ERM with marked distortion of foveal contour, retinal thickening and intraretinal cystic changes.
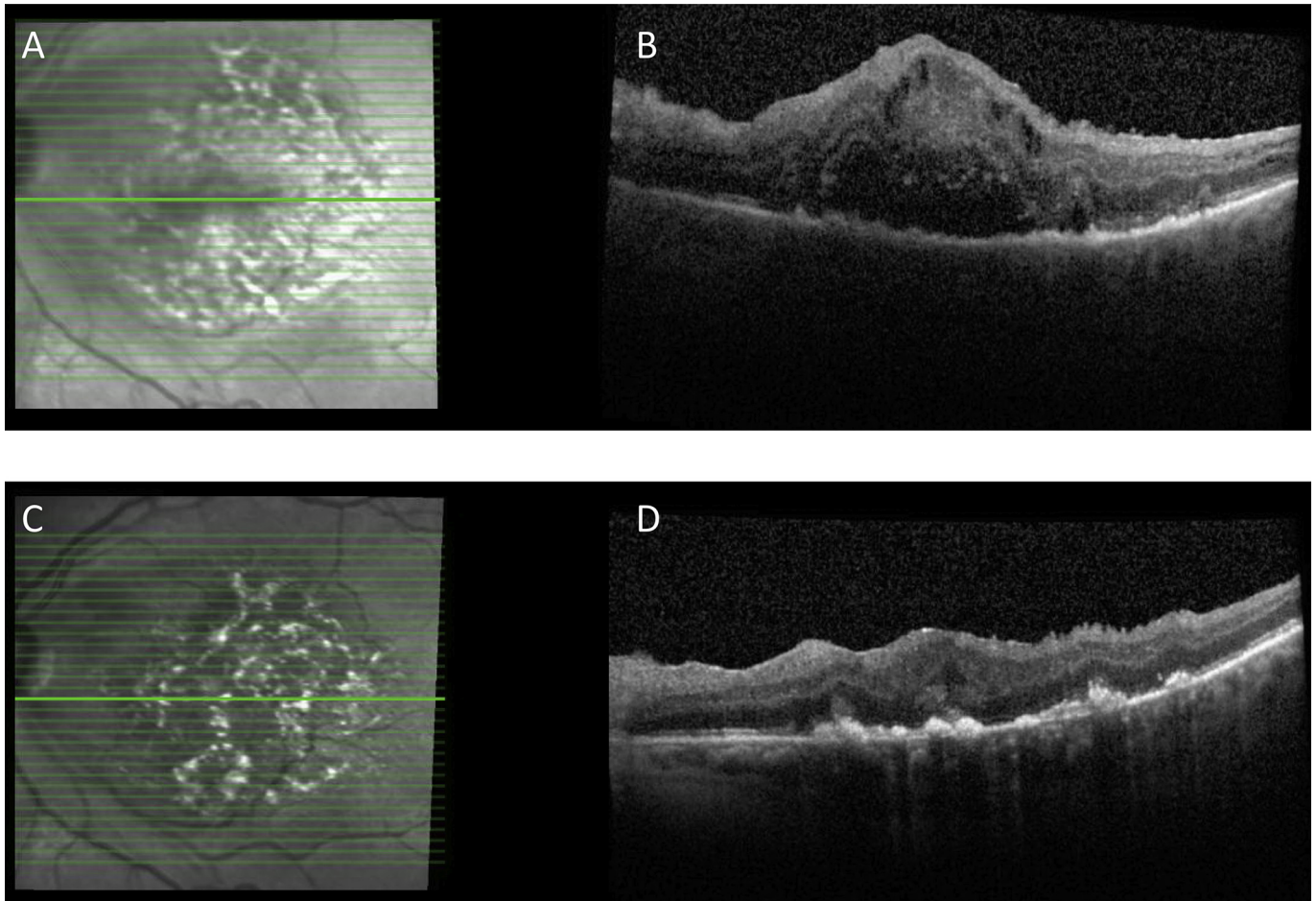
Fig. 2. Postoperative SD-OCT. A and B: Infrared Reflectance (IR) image and spectral domain optical coherence tomography (SD-OCT) respectively at post-op week one showing distortion of foveal contour with retinal edema, retinal pigment epithelium disruption, and intraretinal cystic changes. **C and D**: IR image and SD-OCT respectively at post-op week two showing decrease in macular edema with retinal pigment epithelium elevations/hyperplasia and indistinct ellipsoid layer. Foveal contour remains distorted.

3. Discussion

Retinal phototoxicity can occur through three mechanisms: thermal, mechanical and chemical. There can be overlap between mechanisms and the type of damage depends on the wavelength and duration of exposure which are correlated with the rate of energy deposition.[2] If the rate of energy deposition exceeds the rate of thermal diffusion, thermal damage occurs. Thermal damage to the retina occurs if temperature is raised 10 °C above ambient. When this occurs proteins are denatured and there is decomposition of cell membranes leading to cell death and tissue damage. If the rate of energy deposition exceeds rate of mechanical relaxation then mechanical damage occurs. In mechanical damage, tissue is destroyed by shear forces or by formation of cavitation bubbles, which are lethal to the RPE. Finally, if the rate of energy deposition is too slow, photochemical damage occurs. Energetic photons are absorbed by cells and cause oxidative damage.[2]

Many pharmacologic agents cause phototoxicity mainly by photochemical damage. Drugs deposit in the retina and when activated by light, release reactive oxygen species that cause oxidative damage to various cellular components. Drugs such as phenothiazine and chloroquine are well known for their photosensitizing effects on the retina.[3]

Amiodarone is a drug that is commonly used as an anti-arrhythmic agent and is known to have photosensitizing effects on the skin.[5,6] Hyperpigmentation and slate-grey appearance of

sun-exposed skin is noted in patients with prolonged treatment with amiodarone.[5] Photosensitivity can develop after a minimal total dose of 40g after 4 months of continuous treatment.[7] The mechanism of damage is thought to be from creation of reactive species which lead to destruction of DNA, cell membranes and oxygenation of lipids.[5]

We hypothesize that our patient's postoperative findings are consistent with phototoxicity as a result of photosensitising effects of amiodarone. Amiodarone has well-known ocular side effects such as corneal verticillata, lens opacities and less commonly optic neuropathy. Histopathology studies show that during therapy, intracytoplasmic deposits of amiodarone can be found in the cornea, lens, optic nerve as well as the retina.[8] Previous studies have failed to show any retinal side effects of amiodarone in vivo.[9,10] In vitro studies have, however, demonstrated that RPE cells treated with amiodarone have decreased survival when exposed to UV radiation.[11] Therefore, given that amiodarone deposits are found in retinal pigment epithelial cells and ganglion cells, and that amiodarone has photosensitizing properties on the skin and in RPE cells in vitro, there is a theoretical risk of retinal phototoxicity.

Our patient's post-operative exam and imaging findings are consistent with retinal phototoxicity. The operative time and illumination settings were all within normal range and there were no known intra-operative factors or complications that could otherwise explain the post-operative course. We presume that the use of
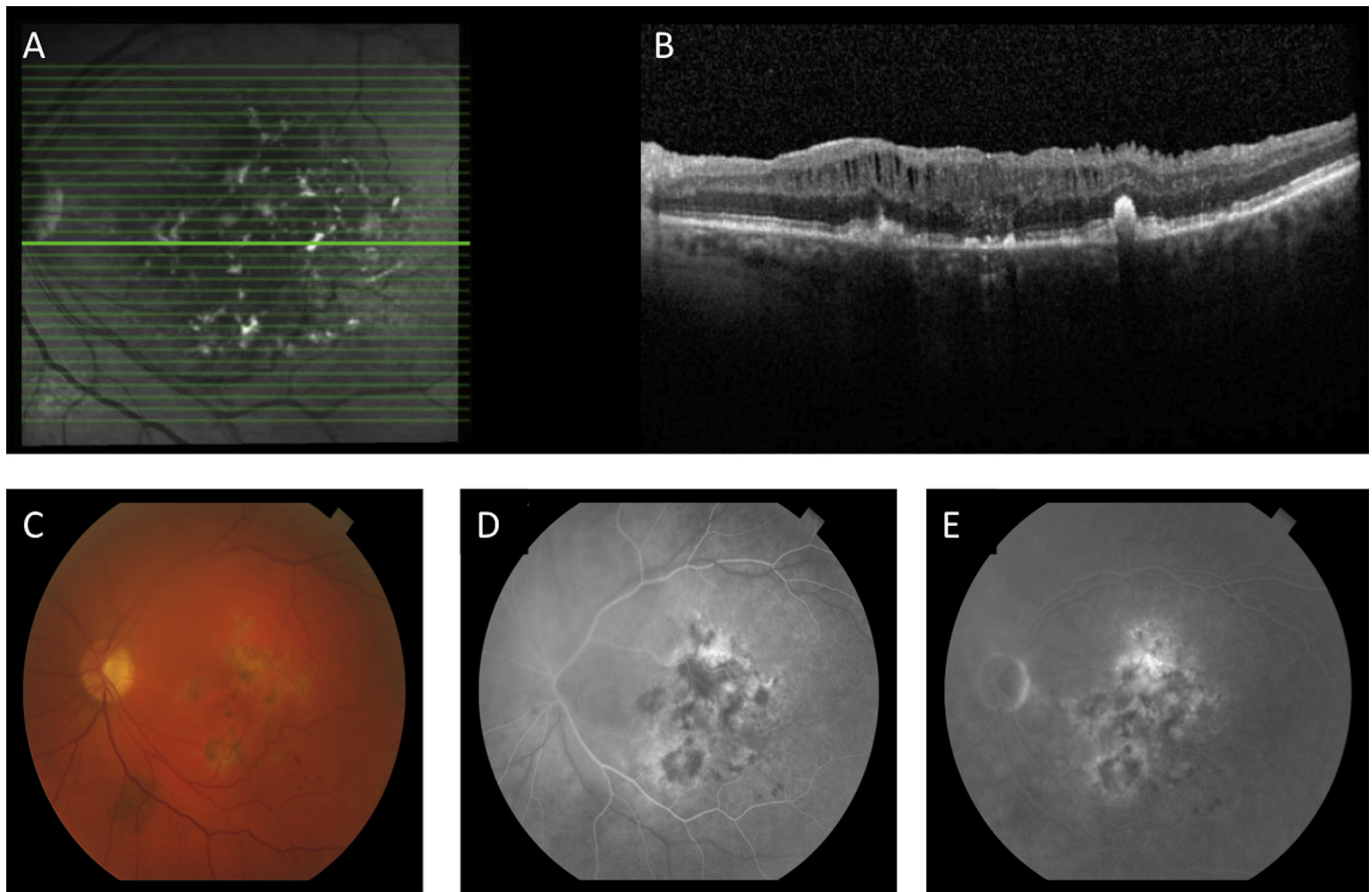
Fig. 3. Postoperative month one. A: Infrared reflectance (IR) image at post-op month one showing pigmentary changes and designating the location of the spectral domain optical coherence tomography (SD-OCT) cross section in B. **B**: SD-OCT of the left eye showing pigment clumping, fibrosis, and intraretinal cystic changes with loss of the ellipsoid layer. **C**: Color fundus photograph showing subretinal fibrosis along with pigmentary changes within the macula. **D and E**: early and late frames of fluorescein angiogram respectively. Early patches of hypofluoresecence in the macula with surrounding hyperfluorescence with staining in late frames. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

systemic amiodarone may have predisposed our patient to retinal phototoxicity. It is possible that the mechanical disruption of the retina from the ERM also contributed to the susceptibility of the retina to the photosensitizing effect of amiodarone.

4. Conclusion

While a cause and effect relationship has not been proven in the literature,[10] we believe that retinal surgeons should be cautious when performing pars plana vitrectomy and membrane peel surgery on patients using amiodarone because of its potential photosensitizing effects. The possibility of retinal phototoxicity should be discussed with the patient pre-operatively and an attempt to minimize operative time, and exposure to light should be made. Some vitrectomy machines have filters that can be used to increase the wavelength of light and therefore decrease the amount of blue and UV light exposure.[12] This maybe an option for patients on amiodarone. As this is the first case report of its kind, we are reluctant to conclude that vitrectomy should be avoided all together in patients on systemic amiodarone but rather surgeons should have a heightened awareness of the potential for this complication. Further studies are needed to better understand the incidence of retinal photosensitization from amiodarone and the mechanism by which this occurs.

Patient consent

Personal identifying information has not been included in this report because consent to publish such information was not obtained.

Conflict of interest

The following authors have no financial disclosures: KJ and MG.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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