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Yellow corneal ring associated with vitamin supplementation for age-related macular degeneration

Andrew W Eller, MD, Ian R Gorovoy, MD, and Vera A Mayercik, AB

Retina Service, UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh School of Medicine, and The Eye and Ear Institute, Pittsburgh, Pennsylvania

Abstract

Purpose—To report the first described cases of peripheral yellow corneal rings secondary to vitamin supplementation for age-related macular degeneration (ARMD).

Design—Retrospective single-center case series.

Participants—The eyes of four patients taking vitamin supplementation for ARMD were examined at University of Pittsburgh Medical Center (UPMC) Department of Ophthalmology between January 2010 and April 2011.

Methods—We reviewed the medical records of four patients with peripheral corneal rings receiving vitamin supplementation for ARMD.

Main Outcome Measures—the presence of peripheral yellow corneal rings, skin findings, and serum carotene levels.

Results—Each patient had circumferential yellow peripheral corneal rings and exhibited subtle yellowing of the skin most notable on the palms. Serum carotene levels were normal in two of the three cases and markedly elevated in the last case in which it was measured.

Conclusion—It is unclear at this time how to counsel patients with this ocular finding. We suspect that these rings are more common than generally appreciated as they can have a subtle appearance or may be misdiagnosed as arcus senilis. We suggest that a formal study be performed on a cohort of patients taking macular degeneration vitamin supplementation that specifically screens for yellow rings and measures serum carotene levels when they are identified.

Peripheral Corneal Rings

The propinquity of the limbal circulation and its clarity predisposes the peripheral cornea to the deposition of pigment from the systemic circulation. Characteristic depth, color, and pattern of these deposited substances helps to direct the differential diagnosis. Heavy metals in particular have a propensity for accumulation in the peripheral cornea. An appropriate

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Correspondence: Andrew W. Eller, MD, 203 Lothrop Street, Room 822, Pittsburgh, PA 15213. Phone: (412) 647-2362; Fax: (412) 647-5119. (elleraw@upmc.edu).

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This article contains online-only material. The following should appear online-only: Appendix 1

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medical and occupational history is critical as findings on exam may overlap amongst various deposited materials. In many cases, corneal deposition is accompanied by visible and often irreversible changes in skin coloration as seen in argyrosis (silver), chrysiasis (gold), and chlorpromazine.¹

Ocular chrysiasis from gold, formerly used in the treatment of rheumatoid arthritis, has been associated with golden rings from gold precipitation in the peripheral anterior and middle stroma as well as the conjunctiva.² Silver deposition in the central and peripheral cornea and conjunctiva has been reported with exposure to topical and systemic organic silver salts.³ Silver has been found principally in the deep stroma and Descemet's membrane with confocal microscopy.⁴ Ocular hydragrya (mercury) causes greenish-gray deposits primarily in the cornea periphery, Descemet's membrane, and anterior lens capsule from chronic mercury exposure.⁵ Iron from intraocular foreign bodies in the anterior chamber may leave rust-colored deposits on the posterior corneal stroma and anterior lens capsule in a form of localized siderosis.

Greenish-gold Kayser-Fleisher rings, found in 60%–95% of patients with Wilson's disease, are the result of abnormal copper deposition at the level of Descemet's membrane.^{6,7} Wilson's disease is an autosomal recessive disorder which causes cirrhosis and neuropsychiatric disease due to elevated copper stores in the body secondary to an inability to excrete copper. Kayser-Fleisher rings are more common in Wilson patients with neuropsychiatric manifestations, which may reflect the higher levels of copper reaching the cerebral circulation. They appear first in the upper corneal limbus, followed by the lower limbus, and subsequently form a complete ring that expands centripetally.⁸ After copper chelation or liver transplantation, Kayser-Fleischer rings disappear in the opposite sequence in which they were deposited.^{9,10} Similar cases of copper deposition in Descemet's membrane and the anterior and posterior lens capsule from acquired systemic disorders with hypercupremia have also been reported.¹¹

Pigmented rings of the peripheral cornea are associated with other forms of advanced liver disease.¹² These pigmented rings are the result of increased serum bilirubin diffusing from the systemic circulation and depositing in the deep stroma and conjunctiva as scleral icterus. Arcus senilis is a gray to white opaque ring secondary to cholesterol deposits. It can be found in patients with normal or elevated lipid levels, although it is generally more pronounced and occurs earlier in patients with hyperlipidemia.

We report the occurrence of a yellow peripheral corneal ring that we believe is secondary to the carotenoids found in vitamin supplementation for the treatment of age-related macular degeneration (ARMD).¹³ To the best of our knowledge, peripheral corneal rings secondary to standard recommended vitamin doses for ARMD has not been previously described in the Pubmed literature or in clinical trials with β -carotene supplementation. (Yoser DSL, Heckenlively JR. The appearance of retinal crystals in retinitis pigmentosa patients using beta carotene. Invest Ophthalmol Vis Sci 1989; 30:305.)¹⁴

Report of cases

Case 1

An 85 year-old female was treated with laser photocoagulation for a peripapillary choroidal neovascular membrane in her right eye. Her ophthalmic history was significant for Terrien's marginal degeneration and cataracts. Her past medical history was remarkable for controlled hypertension and hyperlipidemia. In addition to Centrum Silver® (see Appendix 1, available at <http://aaojournal.org> for formulation), she was taking simvastatin and chlorthalidone.

She was enrolled in the Age-Related Eye Disease Study 2 (AREDS 2) trial and, in accordance with the protocol, she was randomized to a masked treatment arm. Based on the randomization for AREDS 2, she has the potential to be taking β -carotene, 15 mg; and/or lutein, 10mg; with zeaxanthin 2 mg in addition to vitamin C, 500 mg; and zinc oxide, 80 mg. She may also be taking 350 mg docosahexaenoic acid (DHA) and 650 mg eicosapentaenoic acid (EPA). Three years later on a routine AREDS 2 study visit she was found to have 20/40 vision in each eye while her intraocular pressure was in the normal range.

Slit lamp examination showed a prominent yellow ring in the peripheral cornea, adjacent to the limbus (Figure 1). Her peripheral corneal thinning was noted to be stable. Fundus exam showed a peripapillary laser scar, and some central macular pigmentary changes in the right eye. Several large drusen were noted in the macula of the left eye. Her palms had a subtle but definite yellow tinge. A serum carotene level measured 259 mcg/dl (reference range 6–77 mcg/dl). The carotenoids included in this lab assay for all patients include: β -carotene, alpha-carotene, lutein, and zeaxanthin.

Case 2

A 77 year-old white female was referred for evaluation of nonexudative macular degeneration. Her past medical history was significant for Hashimoto's thyroiditis treated with levothyroxine, mild hyperlipidemia treated with low dose simvastatin, borderline diabetes mellitus controlled with diet for 3 years, and osteoarthritis. The patient's ocular surgical history was significant for bilateral cataract surgery with implant lenses 15 years prior. As in case 1, she was also enrolled in the AREDS 2 trial.

After three years in the AREDS 2 study she returned for routine follow-up study exam. Her best-corrected visual acuity was 20/20 OD (oculus dexter) and 20/25 OS (oculus sinister), while intraocular pressures were within normal range. On slit lamp examination, a circumferential yellow peripheral corneal ring was apparent (Figures 2 and 3). The discoloration was most prominent in the stroma. It extended 2 mm from the limbus and was more distinct superiorly and inferiorly. There was no clear zone separating the limbus, no evidence of corneal neovascularization or edema, and no anterior capsule pigment deposition. The central cornea was clear. The remainder of the eye exam was significant only for pseudophakia and nonexudative macular degeneration. There was no evidence of diabetic retinopathy. Mild yellowing of the palms was noted.

Laboratory evaluation including complete blood count (CBC), thyroid stimulating hormone (TSH), basic metabolic panel (BMP), and hepatic function panel (HFP) were unremarkable. A serum carotene level was normal at 46 mcg/dl.

Case 3

An 87 year-old female was referred for treatment of neovascular AMD in her right eye. She had been placed on Ocuvite® PreserVision Soft Gels® (Bausch & Lomb) (see Appendix 1, available at <http://aaojournal.org> for formulation), twice a day, three years earlier. On examination, her vision was 20/70 OD and 20/50 OS. Slit lamp exam was remarkable for a prominent, peripheral yellow corneal ring, and pseudophakia (Figures 4 and 5). Fundoscopy revealed extensive, large drusen with pigmentary changes in each eye.

Case 4

An 84 year-old female presented with a history of AMD. She had been taking Quantum Eye Complex® (Premier Research Labs) (see Appendix 1, available at <http://aaojournal.org> for formulation), for the past 4 years. Each capsule contains Zeaxanthin 6,000 mcg and lutein 3,500 mcg from a marigold source. On exam, her vision was 20/100 OD and 20/200 OS. Slit

lamp exam showed a peripheral yellow ring with pseudophakia (Figure 6). Fundus exam demonstrated a drusenoid pigment epithelial detachment in the right eye, and geographic atrophy in the macula of the left eye. Serum carotene was 50 mcg/dl with this lab reporting levels between 4 and 51 mcg/dl as normal.

Discussion

In our patients, the lack of heavy metal exposure and the absence of scleral icterus excluded metalloemia or liver disease as the cause of peripheral corneal pigmentation. These patients also denied previous intraocular foreign bodies or exposure to medicines such as phenothiazines, which have been associated with ocular pigmentation. In addition to vitamin supplementation for AMD, they reported a typical American diet. Specifically, the patients denied excessive consumption of foods or supplements with high levels of carotenoids or vitamin A.

Based upon the history of vitamin supplementation and the color and distribution of the corneal rings, the etiology of the rings is most consistent with carotenoids. The location and color of the corneal rings are similar to those reported in three patients with hypercarotenemia secondary to massive β -carotene consumption with serum levels of β -carotene ranging from two to eight times the upper limit of normal by Rahmani *et al.*¹⁵ Previously, peripheral corneal rings have not been reported in clinical trials with β -carotene supplementation (Yoser DSL, Heckenlively JR. The appearance of retinal crystals in retinitis pigmentosa patients using beta carotene. Invest Ophthalmol Vis Sci 1989; 30:305.).¹⁴

Similar to our patients, all three of the patients described by Rahmani *et al.* had mild yellowing of the skin, although in our patients it was only subtly apparent on their palms. Two of their patients had associated retinal paramacular crystal deposition, and the third patient had diffuse yellow-brown discoloration of the anterior lens capsule bilaterally. This third patient had a lower serum carotene level, which may be the reason why perifoveal crystals did not form. Our patients all have AMD, which may obfuscate perifoveal crystals.

Retinal paramacular carotenoid crystals have been described in patients using canthaxanthine, which is another carotenoid used in artificial tanning, and high dose β -carotene for the treatment of retinitis pigmentosa.^{16–18} In one of our cases, the serum carotene level was markedly elevated to four times the upper limit of normal, while serum carotene levels fell in the high normal range for the other two cases in which it was measured. However, this may be spurious as ultraviolet light can denature the sample and give a falsely normal reading. The breakdown of carotenoid pigmentation by light may also explain the prominence of these rings superiorly and inferiorly where the eyelids protect the pigment.¹⁹

Vitamin A is a fat-soluble compound derived from two sources—provitamins from vegetable sources and preformed vitamin A from animal sources. Carotenoids, including β -carotene, β -cryptoxanthin, lycopene, lutein, and zeaxanthin, are provitamins that serve as the principle source of dietary vitamin A and are found mostly in colored and leafy green vegetables.²⁰ Preformed vitamin A is the most active form and comes from animal sources and includes retinol, retinal, retinoic acid, and retinyl ester.

β -carotene is absorbed in the small bowel and is stored in liver and adipose tissue. Because it is stored in these tissues, serum levels may not adequately reflect whole body stores. The initial steps in the metabolism of β -carotene are highly regulated, ensuring that excessive β -carotene intake is able to raise serum levels but unable to cause hypervitaminosis A. Hypervitaminosis A is characterized by gastrointestinal symptoms culminating in fulminant liver failure, intracranial hypertension, and cracking and yellowing of the skin. As vitamin A levels rise above the normal range, the process of converting β -carotene to vitamin A is also

down-regulated, suggesting that high doses of β -carotene are safe even in the setting of high levels of vitamin A.²¹ This mechanism has not been well described with the other carotenoids, but it is hypothesized that a similar process exists.

Individuals who consume a diet rich in carotenoids have lower mortality rates from chronic disease and a decreased incidence of some forms of cancer.^{22,23} Carotenoids and other antioxidants have been used in a large number of clinical trials in an attempt to treat a wide number of conditions ranging from heart disease to macular degeneration with generally favorable results. In particular, there is evidence that antioxidants with zinc supplementation are effective in preventing the progression of dry age-related macular degeneration.¹³ Two studies, however, have found a paradoxical increase in the incidence of lung cancer in smokers who take β -carotene supplements.^{14,24} The Food and Drug Administration has approved the use of carotenoids as a dietary supplement and dye additive.²⁵

The classic clinical symptom of increased levels of carotenoids is carotenoderma, also known as xanthoderma, which is considered to be a benign and reversible yellowish-orange discoloration of the skin. It is especially prominent in areas with an abundance of sweat glands—the palms, soles, and nasolabial folds—but spares the sclera as seen in jaundice. Other non-carotenoid causes for yellowing of the skin include endogenous sources such as hyperbilirunemia and riboflavinemia, or the ingestion of saffron, quinacrine, or flourscein. Carotenoid pigmentation has also been described in the liver, reflecting the systemic nature of pigment deposition.²⁶

Carotenoderma has many previously identified causes. Infants are especially prone to carotenoderma as even a single 2.5-ounce jar of sweet mashed potatoes contains 400% of an infant's recommended daily carotene.²⁷ Carotenoderma also often occurs in the treatment of erythropoietic protoporphyria where β -carotene is used in quantities that yellow the skin.²⁸ Excessive consumption of lycopene, a bright red carotenoid plant pigment present especially in tomatoes, can cause a deep orange discoloration of the skin.

Regardless of the etiology, carotenoderma is thought to be harmless and does not require treatment. It is still unclear how patients with this ocular finding should be counseled. We suspect that these rings are more common than generally appreciated as they may have a subtle appearance, be misdiagnosed as arcus senilis, or masked by topical fluorescein dye. It also is possible that in some cases these rings represent carotenoid staining of older arcus senilis. Furthermore, these rings do not appear to cause or be a marker for corneal dysfunction.

We propose several hypotheses about the significance of these corneal rings. These rings may simply indicate that the patient is compliant with the medication, as in the case of corneal verticillata ascribed to the use of amiodorone.²⁹ The presence of the rings described here may also imply that the patient has had appropriate serum carotenoid levels over sufficient time to treat macular degeneration. Taking this thought one step further, it may be appropriate to dose AREDS supplementations until these rings appear.

Another possibility is that these rings may be a marker for underlying systemic diseases such as hypothyroidism, hyperlipidemia, diabetes mellitus, nephrotic syndrome, or liver disease, which are known to cause hypercarotenemia through the impaired conversion of β -carotene into retinol and an associated increase in serum lipids.³⁰ One of our patients did suffer from the first three conditions. The correlation, however, may not be strong as it is also known that both the absorption and conversion of carotenoids to vitamin A between individuals is variable, suggesting a more benign etiology.²⁰

We believe that the rings are probably non-toxic due to down regulation of carotenoid conversion to vitamin A when levels are too high. Nonetheless, we should question whether or not this form of vitamin supplementation is safe. The use of megadoses of vitamins may ultimately prove to be harmful to patients or select subsets of patients. Leo *et al.* found that animals fed a very high β -carotene diet potentiated alcoholic hepatitis.³¹ Furthermore, epidemiological studies with smokers also suggest a mutagenic potential for β -carotene. We suggest that a formal study be performed on a cohort of patients taking macular degeneration vitamin supplementation that specifically screens for yellow rings and measures serum carotene levels when they are identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Slit lamp image of the left eye in a Patient 1 demonstrating an orange-yellow ring in the corneal periphery with prominence especially superiorly.

Figure 2. Slit lamp image of the left eye of patient 2 demonstrating an orange-yellow ring in the corneal periphery which is most distinct inferiorly and superiorly.

Figure 3.
Oblique slit lamp image of the right eye of patient 2 highlighting the prominence of the orange-yellow peripheral corneal ring.

Figure 4. Slit lamp image of the left eye of patient 3 demonstrating an orange-yellow ring in the corneal periphery extending towards the visual axis.

Figure 5. Slit lamp image of the left eye of patient 3 demonstrating an orange-yellow ring in the corneal periphery extending towards the visual axis.

Figure 6. Slit lamp image of the left eye of patient 4 demonstrating an orange-yellow ring in the corneal periphery extending towards the visual axis.