Morphogenetic Model for Radial Streaking in the Fundus of the Carrier State of X-Linked Albinism

Ocular albinism is an X-linked disease characterized in affected males by poor vision, nystagmus, iris transillumination, hypopigmented fundus, foveal hypoplasia, and a decreased proportion of ipsilateral ganglion cell fibers at the optic chiasm. Mutation of the OA1/GPR143 gene on the X chromosome is responsible for this condition. The skin and hair pigmentation appears clinically normal, but skin histologic analysis reveals macromelanosomes in melanocytes. Carriers of the condition are rarely symptomatic but often have signs of their carrier status. Female carriers have macromelanosomes in the skin, although they are fewer in number than in affected males. The eyes of carriers often show iris transillumination (80%) and a mud-splattered appearance of the posterior pole with typical pigmenetary streaks in the peripheral fundus (92%). The pathogenesis of these streaks has not been understood.

Report of a Case. A 60-year-old woman was referred for evaluation of nonspecific visual complaints and abnormal fundus pigmentation. She was thought to have a possible retinal dystrophy. The patient’s symptoms were limited to difficulty seeing clearly while driving at night and difficulty seeing clearly at near. Both eyes were affected equally, and the symptoms had been present for several months. Her medical history was unremarkable for any chronic medical conditions, and she took no medications. The patient had no significant ocular history. Her family history was significant for a father and a son with ocular albinism. She therefore was an obligate carrier of this disease.

Her distance and near visual acuities were correctable to 20/20 OU. Pupillary reactions were normal, as were intraocular pressures, extraocular movements, confrontation visual fields, and oculor alignment. Slitlamp examination findings were remarkable only for moderate nuclear sclerosis in each eye. No iris transillumination was noted on careful examination. Dilated examination revealed clear media in each eye, pink optic nerves with normal cups, flat maculae, and normal retinal vessels bilaterally. The posterior pole appeared to have a splotchy pattern of pigmentation, as seen on fundus autofluorescence imaging (Figure 1). The peripheral fundus had alternating radial streaks of hyperpigmentation and hypopigmentation (Figure 2A) at the level of the retinal pigment epithelium (RPE), typical of the X-linked ocular albinism carrier state. Fluorescein angiography showed normal retinal vasculature with areas of blocking and window defects corresponding to hyperpigmented and hypopigmented regions, respectively (Figure 2B). Findings on optical coherence tomography of the macula and full-field electroretinography were normal in both eyes. Her visual symptoms were consistent with presbyopia and cataract.

Comment. Recent studies using 4-dimensional imaging with custom cell-tracking software and photoactivatable fluorophore labeling to determine the cellular dynamics underlying optic cup morphogenesis in the zebrafish shed light on the fundus pattern in our patient. Kwan et al identified 2 major RPE cell movements during eye development: pinwheeling and spreading. An initial pinwheel-like movement of RPE cells during the optic vesicle elongation phase gives rise to a discrete RPE domain that can be further subdivided within posterior, central, and anterior subdomains (corresponding to temporal, central, and nasal in humans). Immediately afterward, during optic vesicle invagination, RPE cells corresponding to the temporal and nasal domains undergo a posterior to anterior radial migration (spreading), while RPE cells located in the central domain maintain their relative central position. Kwan and colleagues replicated these studies on chick embryos and found similar movements, thereby suggesting that optic cup morphogenesis may be evolutionarily conserved across vertebrate species. Time-lapse photography (also available online at http://www.youtube.com/watch?v=VyJ4Mz1HEzY) demonstrates these dramatic movements and migration of RPE precursor cells.

Bodenstein and Sidman studied RPE development in mice using pigmented-albino mouse chimeras and X-inactivation mosaics. They found that posterior RPE precursors (corresponding to the central domain in zebrafish) become postmitotic sooner than in peripheral RPE precursors. Therefore, these posterior RPE precursors stay
relatively localized, allowing more “cell mixing.” Conversely, peripheral RPE precursors divide more, because they stay mitotically active longer, and add cells in an edge-biased fashion, producing less cell mixing and accounting for groups of clones in the peripheral fundus.

We propose that these morphogenetic movements of RPE precursors during eye development may constitute the basis of the characteristic radial-streaking phenotype observed in carriers of X-linked ocular albinism. This model is based on the premise that female carriers have a mixed population of both pigmented and nonpigmented RPE precursor cells due to lyonization of the X chromosome. During the early stages of optic vesicle development, this mixed population of RPE precursors will undergo pinwheel movements and give rise to temporal, central, and nasal RPE subdomains characterized by a pigmented and nonpigmented mosaic pattern. As development proceeds, the mud-splattered pattern of the posterior pole would originate from the central RPE subdomain through the generation of localized pigmented vs nonpigmented clones by relatively fewer cell divisions and less migratory activity. On the other hand, the radial streaks seen in the periphery would originate from the posterior to anterior migration of RPE cells from the temporal and nasal RPE subdomains as well as the edge-biased pattern and relatively increased mitotic activity of the peripheral clonal cell populations (Figure 3). A computer animation of the proposed model is presented in the video (http://www.jamaophth.com). Further molecular histopathologic analysis in human samples and experiments in knockout mice may lend further evidence in support of this model in mammalian species.

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A critical method of monitoring patients with neovascular age-related macular degeneration (AMD) being treated with anti–vascular endothelial growth factor (anti-VEGF) is optical coherence tomography (OCT), which uses low-coherence interferometry of light to examine the retina in vivo on a micrometer scale.1

Recent advances in spectral-domain OCT make visualization of the choroid feasible. Using image averaging and enhanced depth imaging, successful examination and measurement of choroidal thickness in normal and pathologic states have been reported.2-4

It has been hypothesized that anti-VEGF may affect choroidal vasculature.2 The goal of this study is to evaluate the effect of anti-VEGF on choroidal thickness using spectral-domain OCT in treatment-naive subjects.

Methods. Twenty-two patients (22 eyes) with neovascular AMD were identified prior to first-time treatment with anti-VEGF at New England Eye Center. All patients with concomitant ocular pathologies were excluded. Twenty age-matched healthy eyes were identified as a control group. This study was approved by the institutional review board of the Tufts Medical Center.

Patients were imaged with spectral-domain OCT prior to first-time treatment with anti-VEGF therapy and again at 3, 6, and 12 months (Figure 1). Control eyes were imaged at the time of identification and 6 months later. The scan pattern used was Cirrus high-definition 1-line raster (Carl Zeiss Meditec), which is a 6-mm line consisting of 4096 A-scans and 20 B-scans averaged together without tracking.

Choroidal thickness was manually measured at 500-µm intervals, 2500 µm temporal and nasal to the fovea. Measurements were performed by 2 independent observers with a strong interobserver correlation (r = 0.97; P < .001). Two-way analysis of variance with Tukey multiple test was applied using Prism Mac 5.0 statistical software (GraphPad Software, Inc).

Results. A total of 22 eyes of 22 patients (11 male, 11 female) were included. The mean age was 79 years (range, 66-88 years). Five patients were lost to follow-up. Anti-VEGF therapy was not delivered in a standard fashion. Most eyes were treated with a “treat and extend” protocol. Fifteen patients were treated with ranibizumab and 7 were treated with bevacizumab. The average number of anti-VEGF treatments was 6.9 (range, 2-12). No correlation was found between the number of treatments and a decrease in choroidal thickness.

The mean (SD) subfoveal choroidal thickness at baseline and 3, 6, and 12 months' follow-up was 207.4 (22.1) µm, 194.7 (21.9) µm (P > .05), 164.9 (18.0) µm (P < .05), and 171.8 (17.4) µm (P < .05), respectively (Figure 2). The mean (SD) subfoveal choroidal thickness in the control group was 253.5 (4.1) µm at the first measurement and 255.3 (4.2) µm at 6 months (P = .72).

Comment. This study demonstrates significant choroidal thinning after 6 and 12 months of anti-VEGF treatment for neovascular AMD. Control eyes demonstrated no decrease in choroidal thickness over 6 months.

Histopathology of AMD is characterized by attenuation of the Bruch membrane and degeneration of the choriocapillaris.5 This suggests that there may be a component of choriodopathy in neovascular AMD. If antiangiogenic therapy affects the choroid, treatment could potentially have unforeseen adverse effects.

It is unclear whether the observed decrease in choroidal thickness is a consequence of anti-VEGF treatment or a component of AMD. Greater numbers of subjects are nec-

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Figure 1. Spectral-domain optical coherence tomographic scans showing choroidal thicknesses of the same subject at 4 different times. Image averaging is used for choroidal visualization. Subfoveal choroidal thickness measurements were taken from the outer edge of the hyperreflective retinal pigment epithelium to the inner sclera. Red lines indicate subfoveal choroidal thickness. A, Before treatment with intravitreous anti–vascular endothelial growth factor. B, Three months after treatment with intravitreous anti–vascular endothelial growth factor. C, Six months after treatment with intravitreous anti–vascular endothelial growth factor. Note the decrease in choroidal thickness. D, Twelve months after treatment with intravitreous anti–vascular endothelial growth factor. Note the decrease in choroidal thickness.

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