

A UNILATERAL FOVEAL VITELLIFORM LESION IN A CHOROIDEREMIA CARRIER

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Purpose: To describe a unilateral foveal vitelliform lesion associated with subnormal visual acuity in a choroideremia carrier.

Methods: A retrospective case report, assessment of the best-corrected visual acuity, fundus photography, wide-angle scanning laser ophthalmoscopy, optical coherence tomography, and microperimetry.

Results: A 37-year-old woman with a pathogenic 907C>T mutation in the choroideremia gene encoding Rab escort protein-1 presented with blurred vision in her left eye. The Snellen best-corrected visual acuity was 20/20 in the right eye and 20/32 in the left eye, a unilateral decrease because it was 20/20 in both eyes at the most recent examination nine years earlier. In the left eye, a large vitelliform lesion with a diameter of 1,300 μm had developed in the fovea, whereas in the right eye, a smaller similar lesion was seen close to the fovea. Both eyes showed classical radial patterns of multiple bright fundus patches with associated autofluorescence defects and focal drusenoid lesions of the outer retina.

Conclusion: With its large size and foveal location the vitelliform lesion in this patient's left eye is an unusual manifestation in an otherwise common Rab escort protein-1 mutation carrier state, and its unilaterality fits the assumption of random X-chromosome inactivation.

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Choroideremia is an X-linked recessive eye disease characterized by progressive degeneration of the

choroid, the retinal pigment epithelium (RPE), and the photoreceptors. It is caused by mutations in the choroideremia gene encoding Rab escort protein-1 which is involved in intracellular trafficking.¹ Beginning in the periphery of the fundus, choroideremia is associated with the gradual development of symptomatic visual field constriction in adulthood, progressing to tunnel vision and legal blindness.²

Women who carry a mutated allele on one X-chromosome usually have gradually progressing carrier traits in the form of patches of fundus hypopigmentation, pigment clumps, and patchy outer retinal atrophy,³ all of which tend to spare the fovea. Some choroideremia carriers, mainly in their later years, have symptoms of night blindness, photophobia, and symptomatic visual field loss.² Carrier retinopathy, however, rarely leads to the debilitating levels of visual loss seen in men with choroideremia.⁴

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Case Report

A woman aged 37 years with a pathogenic 907C>T mutation in the choroideremia gene encoding Rab escort protein-1 presented for

evaluation of blurred vision in her left eye. She had only mild subjective visual discomfort but was concerned about her driver's license. The patient had psoriasis since childhood and had been treated with methotrexate and supplements of folic acid and hydroxocobalamin for a period that ended two years earlier. In addition, the patient had been exposed to tuberculosis six months earlier, confirmed by a positive QuantiFERON-TB test (Qiagen, Venlo, Netherlands), for which she had been treated with isoniazid two months before the eye examinations although the treatment aggravated the patient's itching. She was a current smoker and had a smoking history of 10 pack-years. Her parents were not consanguineous.

At presentation, refraction was +2.25 -2.25/115 in the right eye and +1.0 -1.0/65 in the left eye. The best-corrected visual acuity was found to be Snellen 20 of 20 in her right eye and 20 of 32 in her left eye, a unilateral decrease compared with having had 20 of 20 in both eyes nine years earlier corresponding to a loss of 10 Early Treatment Diabetic Retinopathy Study letters in the left eye.

Common carrier traits were visible in both fundi. A radial pattern of multifocal bright fundus patches seen on color fundus photographs (TRC-50DX; Topcon Corporation, Tokyo, Japan) (Figure 1) was associated with autofluorescence defects on wide-angle scanning laser ophthalmoscopy (Optos; model California; Nikon, Dunfermline, Scotland) (Figure 2). Optical coherence tomography (Spectralis HRA + OCT2, Heidelberg Engineering, Heidelberg, Germany) showed multiple focal drusenoid lesions of the outer retina in both eyes that were associated with focal photoreceptor loss and hyperreflectivities of Henle's fibers above (Figure 2). Subfoveal choroidal thickness was considered normal (270 μm in the right eye and 264 μm in the left eye).

In the left eye, a large crescent-shaped vitelliform lesion with a diameter of 1,300 μm was seen in the fovea above the retinal pigment epithelium (DRI OCT Triton, Topcon Corporation, Japan) (Figure 3). The outer nuclear layer was attenuated over the lesion along with disruptions of the external limiting membrane and the junctions between the photoreceptor's inner and outer segments. There were neither evidence of subretinal fluid as a sign of underlying drusen nor focal hyperreflective thickenings of the RPE band as sign of clustering of pigment-laden retinal pigment epithelium cells or macrophages.⁵ In the



Fig. 1. Color fundus photograph of the left eye of a 37-year-old woman with a choroideremia mutation on one X-chromosome and thus a carrier of choroideremia. As seen, there is a classical radial pattern of multifocal bright fundus patches. Remarkably, a very large version of these patches is seen in the middle of the macula (yellow arrow).

right eye, a smaller similar vitelliform lesion with a diameter of 500 μm was seen only 500 μm from the center of the fovea (Figure 3).

Central visual field function was assessed using microperimetry (Nidek MP-1; Nidek Technologies, Padova, Italy, photopic and scotopic, and MAIA, Centervue, Padova, Italy, photopic). The mean sensitivities of the entire fields on photopic (16.7/16.1) and scotopic (5.2/6.3) examinations were within the normal range in both eyes (Nidek MP-1), but a local reduction in photopic sensitivity was seen inferotemporal of the fovea in both eyes, corresponding to the vitelliform lesions (Nidek MP-1 and MAIA).

The appearance of the vitelliform lesions gave rise to consideration of the theoretical possibility that two retinal diseases might be present simultaneously, but no defects were found by next-generation sequencing of the genes PRPH2, BEST1, and ABCA4 which are considered relevant in this context (Prof. Robert McLaren, personal communication). Serum retinol was normal.

Discussion

This retrospective case report demonstrates that symptomatic visual acuity reduction secondary to a unilateral foveal vitelliform lesion may occur in a choroideremia carrier. This lesion located in the left eye appeared to be a very large version with an unusual location of the small extrafoveal drusenoid lesions seen outside the fovea in both eyes of our patient. A similar, but smaller vitelliform lesion was seen in the right eye in proximity to but not involving the fovea. This variable disease manifestation in the eyes of our patient fits the random distribution of X-chromosome inactivation described by Lyon.⁶ It remains to be seen whether her right fovea will sustain a normal visual acuity protected by a favorable, fovea-sparing lyonization pattern, or if it will be affected by worsening over time by degeneration that spreads from an adjacent affected area.^{7,8}

In a group of 11 choroideremia carriers, Murro et al¹ described four fundus patterns according to different locations of the RPE dystrophy: 1) midperipheral retina alone, B-D) peripheral retina and posterior pole with; 2) small hypopigmented RPE areas; 3) small yellowish, well-defined dots; and 4) yellowish, well-defined dots and large hypopigmented RPE areas.¹ The overall fundus pattern in our patient fits the D pattern with the addition of the foveal involvement.

Formation of a vitelliform lesion in a setting of widespread RPE abnormalities has been described in several retinal diseases, for example, age-related macular degeneration, central serous chorioretinopathy, and vitreomacular traction.^{5,9} A vitelliform lesion consists mainly of shed photoreceptor outer segments that have accumulated extracellularly in the subretinal space because of an impaired phagocytosis by the RPE cells.^{5,9} Proposed mechanisms behind the RPE dysfunction include inflammation, impaired lipid transport leading to accumulation of basal linear deposit, and an

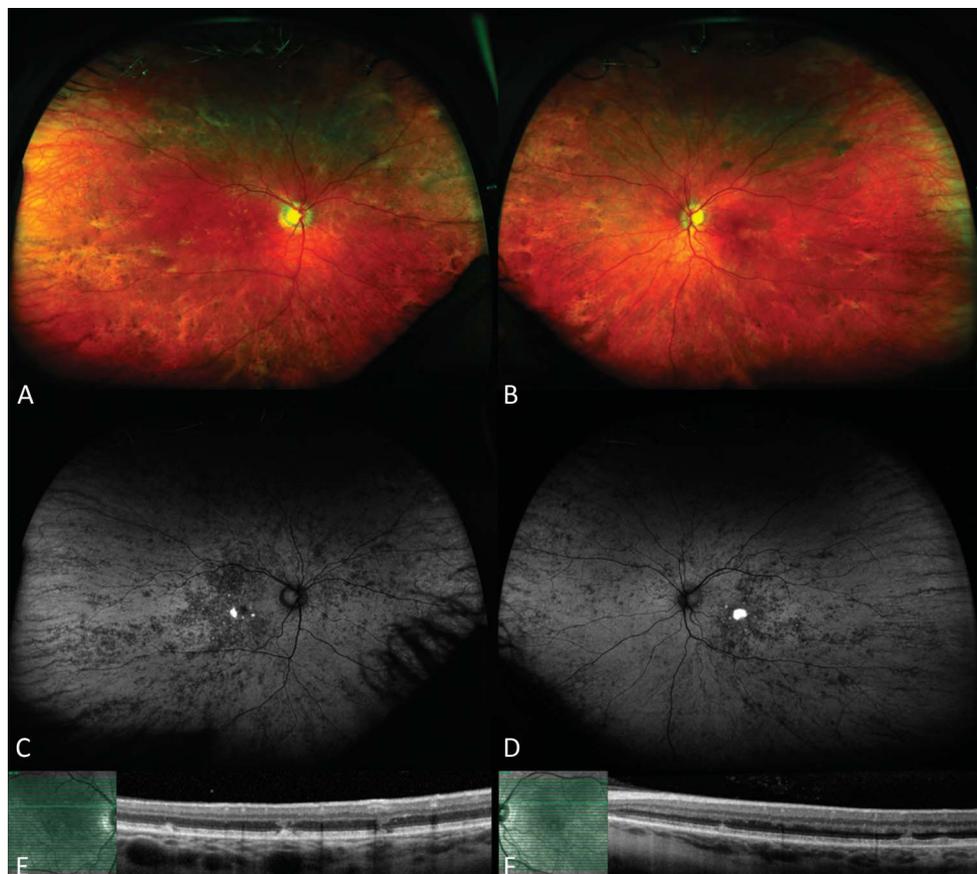


Fig. 2. Wide-angle scanning laser ophthalmoscopy color fundus images of the right (A) and left (B) eye show classical granular hyperpigmentation of the peripheral fundus. The corresponding autofluorescence images of both eyes (C and D, respectively) show multifocal granular hypoautofluorescence throughout the fundus, most densely in the macula. The central bright spot in the left eye comes from the foveal vitelliform lesion seen on optical coherence tomography (Figure 3). A smaller lesion of the same type located 500 μm temporal from the centrum of the fovea was seen in the right eye. The difference in size and location of these lesions illustrates the variable phenotype associated with mosaicism in the choroideremia carrier state. Sections of optical coherence tomography scans through the superior part of the macula corresponding in location to the green line in the infrared images of the right eye (E) and the left eye (F) show examples of extrafoveal drusenoid lesions of the photoreceptor and pigment epithelium layers.

increased content of lipofuscin or its components in the RPE cells.⁹ The phagocytosis will be further impeded by a loss of apposition between the photoreceptor tips and the apical surface of the RPE.⁵ The yellow appearance and hyperautofluorescence of vitelliform lesions are derived from the content of the outer

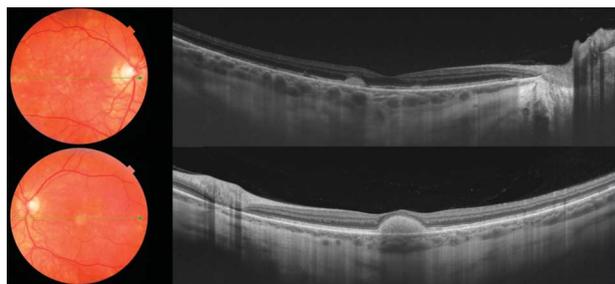


Fig. 3. Optical coherence tomography scans (right) through the fovea of the right (above) and left eye (below) corresponding in location to the green horizontal lines in the color fundus photographs (left) show vitelliform lesions interspersed between the retinal pigment epithelium and the photoreceptors in a female carrier of choroideremia who has otherwise milder pathological fundus changes than seen in affected men of comparable age. The lesions are of a focal nature with different size and locations in the two eyes corresponding to the patterns of presumed random X-chromosome inactivation. The outer nuclear layer is attenuated over the lesions. Only the foveal vitelliform lesion of the left eye is associated with a visual acuity reduction to Snellen 20/32 from being 20/20 in both eyes nine years earlier.

segments, including retinoids¹⁰ and other precursors of lipofuscin, for example, A2E and A2-rhodopsin,⁵ as well as from material containing cholesterol and cholesterol esters.¹⁰ Besides the lesion size, visual acuity reduction may be correlated with the disruptions of the photoreceptor outer segments, represented by the loss of a discernible junction between the inner and outer segments and the external limiting membrane, rather than the loss of photoreceptors, represented by the attenuation of the outer nuclear layer⁵ (Figure 3).

In conclusion, this case report describes the clinical findings of an unusual symptomatic foveal lesion in a choroideremia carrier of 37 years illustrating the variable phenotype associated with mosaicism because of random X-chromosome inactivation. The experience from this single case should be expanded by longitudinal multimodal studies of choroideremia carriers.

Key words: choroideremia, female carrier, visual acuity, vitelliform lesion, X-chromosome inactivation.

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