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Diagnostic and Therapeutic Challenges Section of Retina

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Case Report

A 46-year old white male of Polish and Russian ancestry was initially seen in the Ophthalmology Department of the University of Illinois at Chicago in September 1990. He had been followed-up by one of the authors (GAF) since then. At his first examination in our clinic, he had no subjective visual complaints until two months prior to his visit when he received an Amsler grid in the mail and noticed a waviness in the left portion of the grid in his left eye and blurred areas in the upper right and lower right quadrants of his right eye. These patterns on the grid had not changed for a duration of two months. He did not complain of photoaversion, poor color vision, nyctalopia or poor central acuity. A general review of systems indicated a past history for a high-frequency hearing loss which he indicated was secondary to noise from jet engines. The patient was an air force pilot for 22 years and subsequently a commercial airline pilot.

A review of his prior ocular records stated that the patient's father had a history of impaired central vision associated with perifoveal pigmentary degenerative changes. His paternal grandparents were first cousins.

Vision was correctable to 20/15-3 OD with a $-1.25+0.50 \times 5$ and 20/15 OS with a $-1.50+0.75 \times 160$. External examination showed both eyes were orthophoric and there was full range of ocular motion in all directions of gaze.

The pupils were round and reacted normally. Ocular pressures measured by applanation tonometry were 17mmHg OD and 15mmHg OS. The left cornea showed a small scar from a presumed previous foreign body. The lenses and vitreous were clear. There was a Mittendorf dot OS.

Dilated fundus examination showed yellowish-white fleck-like lesions within the posterior pole of each eye. The lesions spared the foveola. The peripheral retina, optic discs, and retinal vessels were normal in each eye. Visual field examination was performed by Goldmann kinetic perimetry 940 (Haag-Streit AG, Switzerland), using II-2-e and II-4-e test targets. The testing showed no evidence of peripheral field restriction or central/paracentral scotomas in either eye.

A review of a previously obtained fluorescein angiogram (FA) showed no evidence for a dark choroid or apparent fluorescein leakage. There were regions of both hyper and hypofluorescence associated with the fundus flecks. On subsequent visits, the patient did not have any subjective visual complaints. Specifically, he did not complain of any difficulty with either central or peripheral vision, color vision or night vision. Previously he underwent dark adaptation testing with a Goldmann-Weekers dark adaptometer. The testing showed no abnormalities in the bleach recovery time or the final rod thresholds.

Nine years after the initial visit, the patient continued to maintain excellent central acuity with no abnormalities of his peripheral or mid-peripheral fields. Vision was still correctable to 20/15

in each eye. Dilated fundus examination showed moderately extensive fleck-like lesions

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Editor's Note: Drs. Genead and Fishman, and Martin Lindeman, COMT, have presented a 46-year-old man who was first seen in 1990 with good central vision and multiple yellowish flecks throughout the posterior pole of each eye, sparing each macula. He had no night blindness or dyschromatopsia. Long term follow-up showed no significant progression of fundus abnormalities.

Drs. Pennesi and Traboulsi have provided us with a differential diagnosis. Allowing for wide variation of phenotypes that can be associated with the same gene, the differential is as follows:

I. Gene Mutation

A. ABCA4

1. Stargardt's
2. Fundus flavimaculatus

B. PRPH2

1. Peripherin/RDS-related pattern dystrophies

C. ELOVL4

1. Autosomal dominant macular dystrophies

D. BEST1

1. Best's vitelliform dystrophy
2. Adult onset foveomacular vitelliform dystrophy
3. Autosomal dominant vitreoretinopathopathy (ADVIRC)

E. EFEMP1

1. Doyme's honeycomb dystrophy
2. Dominant drusen
3. Malattia Leventinese

II. Other Flecked Retina Syndromes

- A. Benign flecked retinal detachment
- B. Kandori's flecked retina
- C. Kjellin syndrome
- D. Alport's syndrome
- E. Fundus albipunctatus
- F. Retinitis punctata albescens

Dr. Pennesi notes that the yellowish fleck lesions bore a resemblance to fundus flavimaculatus caused by ABCA4 mutations, but cautions that PRPH2 mutations have also been shown to cause fundus flavimaculatus-like dystrophies. He states that the lack of dark choroid argues against an ABCA4 mutation, but warns that not all cases of ABCA4 mutation have dark choroids. At the end of the day, he feels this patient has a mutation in ABCA4 causing a fundus flavimaculatus appearance and preserved foveal function.

Dr. Traboulsi presumes that the patient's father has the same genetic disorder and concludes that a dominant mode of inheritance is probable, indicating either dominant radial drusen or pattern dystrophy. He notes that though there are rare families with dominant Stargardt's disease, the vast majority are autosomal recessive and are due to mutations in the ABC4A gene. He concludes that the diagnosis is that of a pattern dystrophy, most likely due to a mutation in the peripherin/RDS gene.

Follow-up

A blood sample was drawn and sent for genetic molecular analysis. The patient's DNA contained a mutation within the peripherin/RDS gene (CAG to TAG nucleotide substitution) in the coding sequence of exon 3 of the peripherin/RDS gene resulting in an amino acid change from glutamine to a stop codon at codon 331- compatible with the diagnosis of pattern dystrophy.

The genetic results, absence of a dark choroid on FA, absence of relative peripapillary sparing of pigmentary changes (as noted in Stargardt disease), and the positive family history of a paternal central retinal pigmentary degeneration (the latter suggestive of autosomal dominant disease), are collectively most consistent with the diagnosis of pattern dystrophy.

throughout the posterior pole and mid-peripheral retina which continued to spare the foveola. The flecks were more extensive than those noted on prior exams.

At his most recent visit, which was 29 years after the initial visit, subjectively the patient still did not notice any changes in his central or peripheral vision, night vision or color vision.

Visual acuity was correctable to 20/20-1 OD with a $-0.25+0.75\times 180$ and 20/20 OS with a $-0.50+1.25\times 165$. He read J1 for near at 14 inches with a $+2.25$ add.

The corneas and anterior chambers were clear while the lenses showed trace nuclear sclerosis in each eye. Ocular pressures were 13mmHg OD and 14mmHg OS.

Dilated fundus examination showed diffuse flecks throughout the posterior pole and mid-peripheral retina with a relative sparing of the foveola. The peripheral retina, optic discs, and retinal vessels were normal (Figure 1A–B).

Fundus autofluorescence (AF) testing was performed. The AF and Infrared (IR) images were obtained with a confocal scanning laser ophthalmoscope (cSLO) (Heidelberg Retina Angiograph (HRA), Heidelberg Engineering, Heidelberg, Germany). AF images showed diffuse foci of hyper-autofluorescence scattered throughout the posterior pole and mid-peripheral retina associated with the fundus flecks. There were also scattered foci of hypo-autofluorescence within the posterior pole (Figures 1C–F).

The most recent visual field testing by Goldmann kinetic perimetry showed small paracentral scotomas to a II-2-e target which were not apparent on his prior visual field tests.

Spectral-domain OCT (SD-OCT) was performed by imaging with Spectralis HRA+OCT technology (Heidelberg Retina Angiograph (HRA), Heidelberg Engineering, Heidelberg, Germany). The OCT scans showed several rounded-oval elevated lesions at the level of retinal pigment epithelium (RPE), which extended into the inner segment/outer segment junction of the photoreceptors, external limiting membrane and the outer nuclear layer as well. Additionally, the OCT scans showed focal areas of the photoreceptor layer disruption within the posterior pole of the fundus (Figures 2A–F).

Questions for Discussants

1. What would be the differential diagnosis of the ocular disease in this patient?
2. What findings on history, clinical fundus features, fundus imaging, and/or genetic testing would be most useful in leading to the correct diagnosis?
3. What is the most likely diagnosis in this patient?

We asked several experts for their opinion.

Dr. Mark Pennesi, Portland, Oregon

In this case, we are presented with a 46-year-old white male, who has good central visual acuity, mild visual disturbances as measured with an Amsler grid, and multiple yellowish-white fleck-like lesions in the posterior pole of each eye, which spare the fovea. Twenty-nine years after the first visit, the patient still only manifests mild visual disturbances; in spite of the worsening of the flecks in the posterior pole. Pertinent negatives include a lack of photophobia, color vision defects, or nyctalopia. The patient also has a notable family history for paternal grandparents who were first cousins and a father with perifoveal pigmentary changes with impaired central vision.

The bilateral and symmetric nature of the disease and the family history is suggestive of a genetic cause for these findings. The history of consanguinity would raise the risk for a recessively inherited disease. If we assume the patient indeed harbors the same mutation as his father, then x-linked or mitochondrial inheritance can be ruled out. Two possibilities remain: dominant inheritance or autosomal recessive with pseudo-dominant inheritance. In the case of dominant inheritance, the patient's father would have a new mutation, which the patient received. In pseudo-dominance, the patient's father would have received one recessive mutation from each parent and subsequently pass one copy to the patient. In addition, the patient's mother would have to be a carrier of the same recessive mutation, which was also passed on to the patient.

The differential for retinal flecks and pigmentary disturbances is broad and includes mutations in several characterized genes such as: ABCA4, PRPH2, ELOVL4 and BEST1. Several less common syndromes can also cause retinal flecks such as: benign fleck retina, flecks of Kandori, Kjellin syndrome, Alport syndrome, fundus albipunctatus, and retinitis punctata albescent. Several of these can be ruled out based on the lack of systemic findings and appearance. Benign fleck retina and flecks of Kandori present with flecks in the periphery and do not involve the macula as seen with this patient. Kjellin syndrome presents with the constellation of fleck lesions, spastic paraplegia, mental retardation, and amyotrophy. Alport syndrome is usually X-linked, although a minority of cases can be inherited autosomal recessively. The patient does have high frequency hear loss, which can be seen in Alport's, but we are led to believe that this is secondary to his occupation. Furthermore, there is no evidence to support a history of nephritis or anterior lenticonus, which is typical in Alport syndrome. The normal dark adaptation and the appearance of the flecks make fundus albipunctatus unlikely. The lack of peripheral visual field loss and nyctalopia also eliminate retinitis punctata albescent.

Distinguishing between diseases that can cause flecks is challenging due to the wide variation of phenotypes that can be associated with the same gene. For example, mutations in ABCA4 often present with the features of Stargardt disease such as yellowish-white pisciform flecks, macular atrophy, dark choroid on fluorescein, and diminished central sensitivity on visual fields and decreased multifocal ERGs. However, mutations in ABCA4 can also present with flecks without macular atrophy (often referred to as fundus flavimaculatus), or in some cases as a generalized cone-rod dystrophy with pigmentary changes and no flecks. An additional gene to consider is ELOVL4, which presents with similar phenotypic characteristics as ABCA4, but is inherited dominantly, presents later in life, and less commonly shows a dark choroid. Mutations in PRPH2 (which codes for peripherin/RDS) can also cause a spectrum of phenotypic features that range from barely noticeable pigmentary changes in the macula with a vitelliform appearance to larger intricate reticular or butterfly patterns of RPE disturbance which has given rise to the term "pattern dystrophy". Additionally, some mutations in PRPH2 can result in a widespread rod-cone dystrophy with pigmentary changes. Mutations in BEST1 (which codes for bestrophin1) typically present with the classic vitelliform lesion in the central macula. However, mutations in BEST1 can also manifest more subtly as adult onset foveomacular vitelliform dystrophy, as autosomal dominant vitreoretinopathopathy (ADVIRC), or as multifocal vitelliform lesions. Interestingly, mutations in PRPH2 can also present with as an adult onset foveomacular vitelliform dystrophy.

The fundus images in this patient show yellowish fleck like lesions that bare resemblance to fundus flavimaculatus caused by ABCA4 mutations. However, it should be noted that PRPH2 mutations have also been shown to cause fundus flavimaculatus-like dystrophies. The lack of a dark choroid argues against an ABCA4 mutation, but caution must be taken because not all cases of ABCA4 mutations will have a dark choroid and modern fluorescence cameras allow contrast correction, which can mask or artificially produce a dark choroid based on the settings. The speckled autofluorescence is often seen in Stargardt disease where the hypofluorescent

areas represent RPE loss and the hyperfluorescent areas indicate accumulation of lipofuscin. The OCT demonstrates loss of the IS/OS junction outside of the fovea, but shows preservation of this band within the fovea.

In some cases electrophysiology can be useful in narrowing down which genes to test. A normal EOG would make a mutation in BEST1 unlikely. Mutations caused by ABCA4 more typically have decreased amplitudes and timing delays on multifocal ERGs than PRPH2. Full-field ERGs can be normal, show decreased cone responses or decreased rod and cone activity in patients with ABCA4 mutations.

In conclusion, this patient likely has a mutation in ABCA4 causing a fundus flavimaculatus appearance and preserved foveal function. The inheritance in this case would be autosomal recessive with a pseudo-dominant pattern. Alternatively, the patient could have a dominant PRPH2 mutation causing a fundus flavimaculatus-like appearance. Genetic testing offers the best chance of determining the exact etiology of this disorder. Testing of ABCA4 and PRPH2 are likely to be the most beneficial tests.

Dr. Elias I. Traboulsi , Cleveland, Ohio

Genead, Fishman and Lindeman present the case of a 46 year-old patient with metamorphopsia, but no night blindness, dyschromatopsia, or reduced visual acuity. There are no associated systemic abnormalities. His father had macular degeneration and his grandparents were first cousins. There was no significant high error of refraction or other ocular abnormalities. The visual fields were full and there was a maculopathy with subretinal flecks that spared the fovea. Long-term follow-up did not show any significant progression of the fundus abnormalities and the retinal findings remained stable. Diffuse autofluorescence as well as small foci of hypofluorescence were found in the posterior pole and fundus midperiphery. OCT revealed focal excrescences at the level of the RPE and outer retina.

The differential diagnosis in this patient includes Stargardt disease, dominant drusen (malattia Leventinese), and pattern dystrophy (peripherin/RDS related disease). The absence of night blindness, dyschromatopsia and the normal dark adaptation study indicate an absence of photoreceptor dysfunction, even if a formal electroretinogram has not been performed. Although there are rare families with dominant Stargardt disease¹, the vast majority of cases are autosomal recessive and are due to mutations in the ABCA4 gene.² We presume that the patient's father has the same genetic disorder, hence a dominant mode of inheritance is probable, indicating either dominant radial drusen or pattern dystrophy. Dominant radial drusen result from mutations in EFEMP1 and are typically oriented in a radial fashion from the fovea and frequently involve the optic disk.³ The appearance of the flecks and the fluorescein angiographic findings in the present case are most suggestive of a pattern dystrophy.⁴⁻⁶ The relatively mild clinical abnormalities and the fairly stable clinical course over more than two decades are also compatible with this spectrum of clinical disorders.⁵

My clinical diagnosis is that of a pattern dystrophy, most likely due to a mutation in the peripherin/RDS gene. The same mutation would be responsible in this patient's father's macular disease. Mutation analysis of this gene will confirm the clinical diagnosis.

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Figure 1.

Color fundus photographs (top panel) of the right (A) and left (B) eyes show fundus flecks within the posterior pole and anterior to the vascular arcade. Infrared (IR) images (middle panel) highlighting the pigmentary degenerative changes of the right (C) and left (D) eyes. Autofluorescence (AF) images (bottom panel) show diffuse foci of hyper and hypo-autofluorescence scattered throughout the posterior pole associated with the fundus flecks of the right (E) and left (F) eyes.

Figure 2. Spectral-domain OCT (SD-OCT) in the right (A, C, E) and left (B, D, F) eyes allow for visualization of focal disruption in distal retinal structures and in regions which correspond to dome-shaped deposits located in the inner part of the retinal pigment epithelial cell (RPE) layer.