A 48-Year-Old Female Referred for the Possibility of PDR and AMD

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Introduction:

A 48-year-old female initially referred to a retina practice for possible proliferative diabetic retinopathy and age-related macular degeneration in both eyes. The patient presented to the practice five years prior for possible diabetic macular edema but was lost to follow-up. Past medical history was significant for Type 1 Diabetes, deafness, hypertension, and hyperlipidemia. The patient had no prior past ocular history and past surgical history is non-contributory. Family history was notable for diabetes in multiple family members. At that time, the visual acuity was 20/25 OU with mild diabetic retinopathy without macular edema.

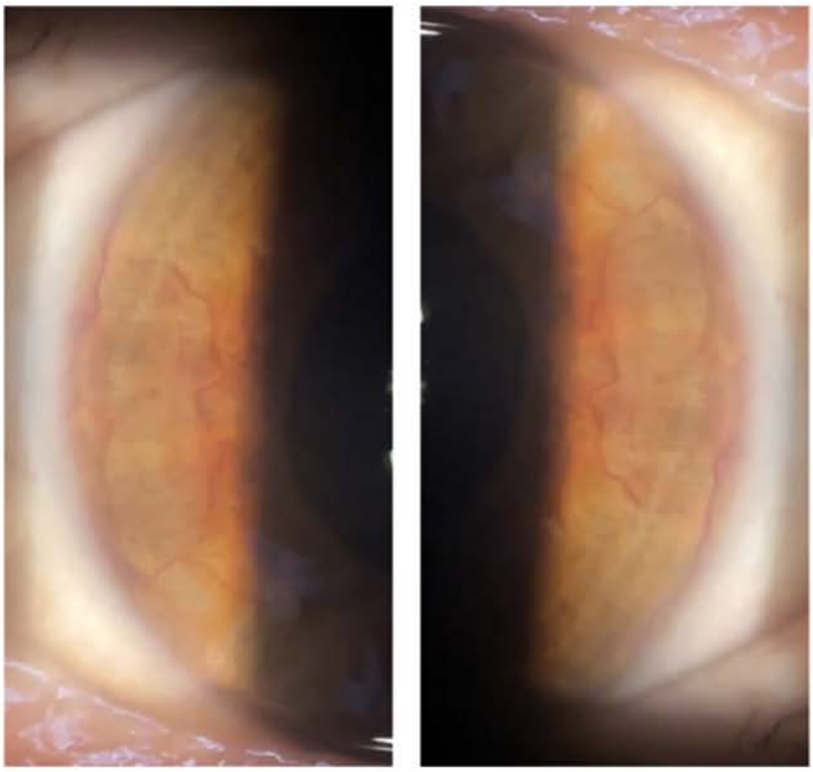

Figure 1: Neovascularization of the iris in both eyes.

Exam:

Upon initial examination at re-presentation, the patient had noted some vision loss in both eyes. Her uncorrected visual acuity was 20/200 OD and 20/50 OS with no improvement with pinhole. Her intraocular pressure was 21 mm Hg OD and 11 OS. Her slit lamp examination was notable for florid neovascularization of the iris in both eyes (OD>OS) and mild nuclear sclerotic cataracts (Figure 1). Dilated fundus examination revealed a clear vitreous, neovascularization of the disc OS, macular atrophy OU, arteriolar attenuation, and dot blot hemorrhages OU (Figure 2). Optical coherence tomography revealed complete retinal pigment epithelium and outer retinal atrophy (Figure 3). Fundus autofluorescence demonstrated hypoautofluorescence corresponding to the area of atrophy in both eyes (Figure 4)

The patient was injected with aflibercept in the right eye with plans to perform panretinal photocoagulation (PRP) in the right eye and inject aflibercept and perform PRP in the left eye at subsequent visits. In addition, the plan included completion of genetic testing given the presence of macular atrophy in both eyes.

Initial genetic testing was done with Invitae (San Francisco, CA) which revealed an uncertain test result. Testing showed a missense change in the FSCN2 gene that was of uncertain significance. Importantly, the genes included on this assay did not include

mitochondrial genes. Subsequent genetic testing was performed using the Blueprint Genetics (Seattle, WA) Panel. Testing revealed a pathogenic heteroplasmic (39.7%) MT-TL1 m.3243A>G variant. Upon further questioning, the patient revealed that her mother and one sister have a history of diabetes. In addition, one of her sisters passed away at a young age with all of her children testing positive for MELAS.

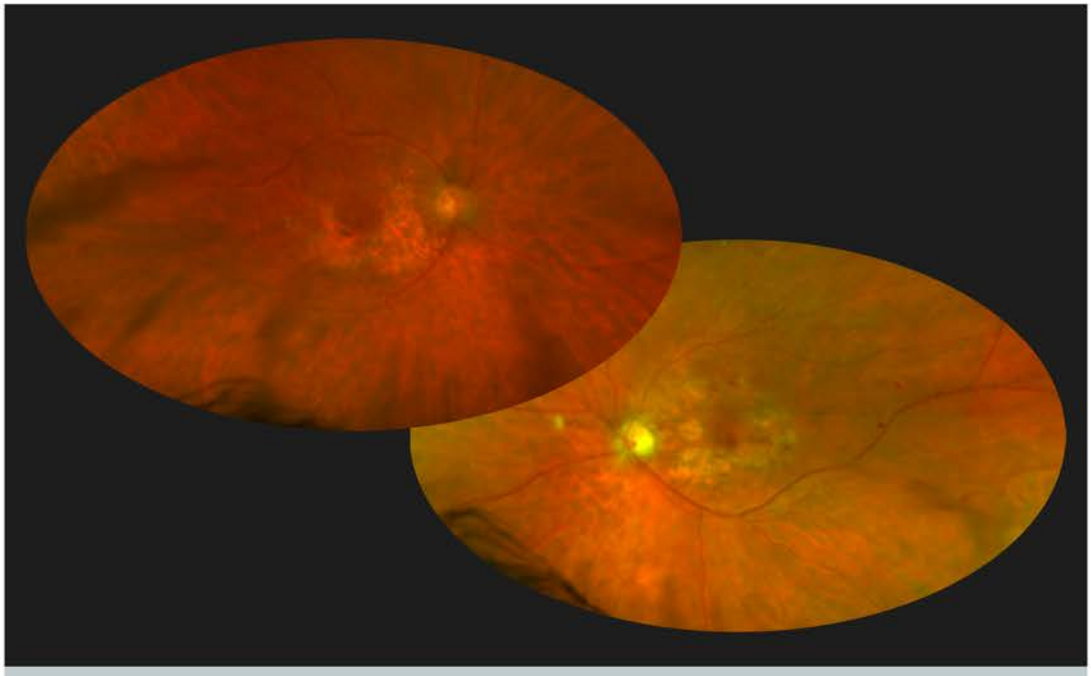

Figure 2: Fundus photos demonstrate macular atrophy sparing the fovea with dot blot hemorrhages with arteriolar attenuation in both eyes.

Discussion:

Our patient with hearing loss and type 1 diabetes represented after five years with florid neovascularization of the iris in both eyes and macular atrophy. The diagnosis of MELAS complicated by neovascular glaucoma was made given the results of the genetic testing and family history of MELAS. It has previously been reported that the prevalence of m.3243A>G carriers increases to over 5% in patients with diabetes who have deafness of a family history of deafness.[1,2] However, a previous case-control study reported that prevalence of diabetic retinopathy in these patients was low, suggesting possible protective factors against diabetic retinopathy in patients with maternally inherited diabetes.[3]

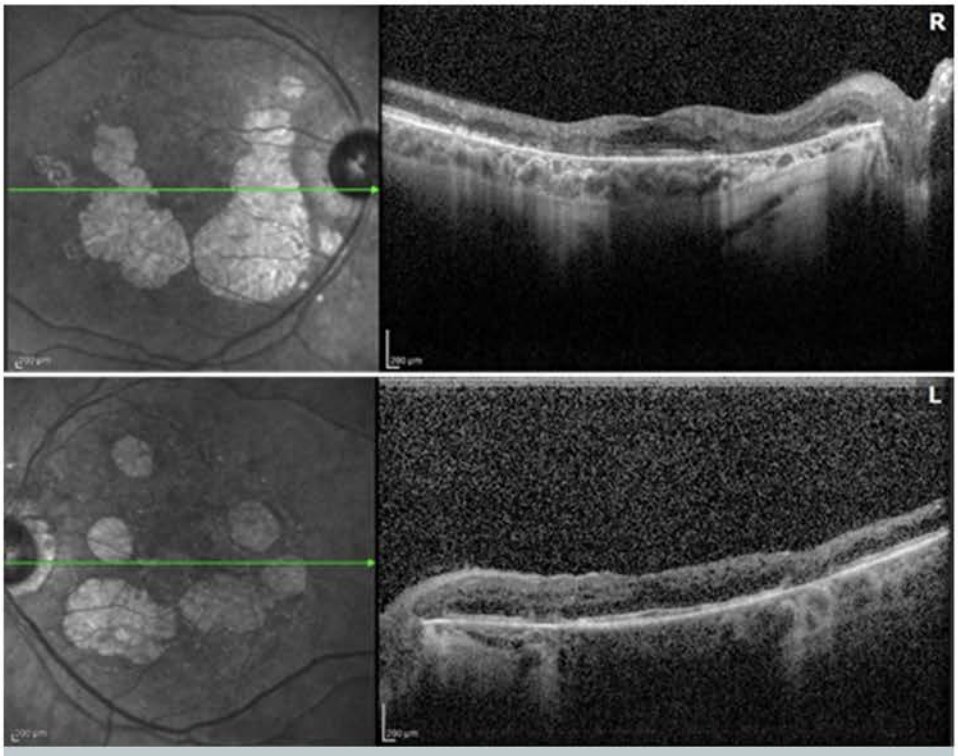

Figure 3: Optical coherence tomography demonstrates complete RPE and outer retinal atrophy of both eyes sparing the fovea. The near infrared photo demonstrates hyperautofluorescence corresponding to areas of atrophy.

Maternally inherited diabetes and deafness (MIDD) is another diagnosis that should be considered, especially considering the most common variant (seen in this patient) is commonly associated with MIDD as well.[4] It is hypothesized that these two entities are on the same disease

spectrum, with MELAS often representing a more severe manifestation of this disease. Previous reports have hypothesized a possible evolution of MIDD to MELAS.[4] Another study examined the correlation between heteroplasmy levels and severity of macular dystrophy, finding no correlation.[5]

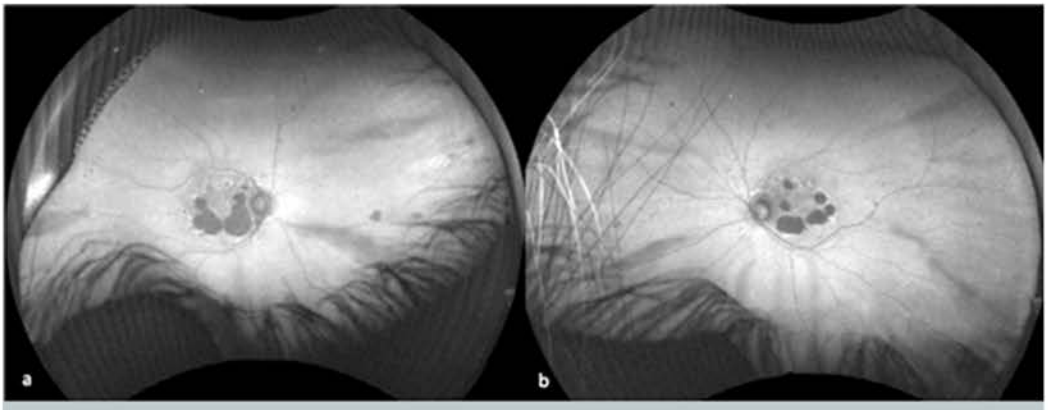

Figure 4: Fundus autofluorescence demonstrates hypoautofluorescence corresponding to areas of atrophy sparing the fovea in both eyes.

To our knowledge, there have been no reports of neovascular glaucoma in the setting of MELAS or other mitochondrially-inherited retinal dystrophies. Though prevalence of diabetic retinopathy in these patients is low, there should be a high index of suspicion of inherited retinal disease given the constellation of symptoms. It is important to keep this diagnosis on the differential due to the severity of other systemic manifestations of these diseases. Finally, genetic testing is useful in making the diagnosis, but ensuring the assays include mitochondrial genome testing is critical as not all inherited retinal disease panels have this.

References:

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