Case Report

Macular Degeneration – A Spectrum of Disease

V502 Problem Based Learning

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A seventy-two-year-old white male patient presented for a comprehensive eye exam with a chief complaint of difficulty reading and seeing traffic signs. The patient notes the problem is worse in his right eye. The patient indicates that the lines of his crossword puzzles are wiggly. The patient does notice a cobweb-like floater in his right eye and denies flashes of light. His current medications are 20mg daily of Benicar and 20mg daily of Zocor. The patient states he has no allergies. The patient reports that his father became blind before his death at 85, but he does not know the origin of the blindness. His best-corrected visual acuities (BCVA) are 20/30 OD and 20/25 OS. Confrontational visual fields are normal. The anterior segment examinations are within normal limits except for a mild nuclear cataract in both eyes. Goldmann tonometry revealed IOP’s of 17 mmHg OD and 18 mmHg OS. An Amsler grid test revealed abnormalities in the patient’s central vision. Lastly, non-mydriatic direct ophthalmoscopy revealed white spots, likely lipofuscin, and a stippled appearance to the macula in both eyes. Based on the history and initial exam, the patient is suspected of posterior pole disease and will need follow-up.

The macula lutea is a circular shaped region of the retina roughly 5 to 5.5mm in diameter. The macula is temporal and slightly inferior to the optic disc in each eye. The macular area is typically darker in hue than the remainder of the retina due to an intrinsic yellow pigment called xanthophyll and the melanin of the underlying retinal pigment epithelium (RPE). The center of the macula, or fovea centralis, is responsible for high-resolution vision in photopic settings.

In ideal conditions with a perfectly emmetropic patient, best corrected visual acuity in the fovea is approximately 60 cycles per degree or 20/10. This prominent level of acuity is attained by four different contributing factors. First, the fovea, Latin for pit, is a defining characteristic of the macula. In this area, many layers of the retina are pushed aside to maximize exposure of the photoreceptors. Second, the fovea contains only cone photoreceptors, which have significantly higher spatial resolution than rods. Third, the foveal cones are remarkably compressed in a hexagonal array which allows for maximum cellular density. Fourth, arterioles and venules skirt around the central macula, creating the foveal avascular zone. This characteristic improves vision because blood vessels do not normally cross into the very center and as a result, will not interfere with the light reaching the foveolar cones.

Photoreceptors intrinsically possess an exceptionally high rate of metabolism. Also, oxygen does not diffuse readily within the retina. This combination creates a steep oxygen gradient within the tissue layers and particularly in the foveal avascular zone. The choriocapillaris lies below, and it is thickest in this area because it is the only metabolic support to the foveal region. In contrast, the rest of the retina has retinal circulatory support as well.

The patient has been previously prescribed 20mg of Benicar daily and 20mg of Zocor daily. A history of both hypertension and hyperlipidemia are potent risk factors for macular disease. Benicar, generic name olmesartan, is a potent anti-hypertensive medication, acting as an angiotensin II receptor antagonist. Angiotensin II is the body’s most powerful vasoconstrictor, and this drug acts to block it via the selective AT1 receptor found predominantly in the kidney. In summary, olmesartan reduces blood pressure by preventing the vasculature from constricting, which in turn lowers blood pressure and enhances blood flow.

Zocor, generic name simvastatin, is a statin drug used to lower cholesterol. As a group, statins inhibit a hepatic enzyme called HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase.
simvastatin, directly affect the liver’s rate-limiting step in the synthesis of cholesterol. This inhibition ultimately reduces low-density lipoproteins (LDL’s) in the blood serum and marginally increases good cholesterol, known as high-density lipoproteins (HDL’s).13 Statins are widely prescribed because they are very efficacious at improving lipid profiles.

Hypertension and hyperlipidemia adversely affect endothelial cells in blood vessels. When endothelial cells are sufficiently disrupted, it destroys the smooth lining of the vessel wall. Macrophages will attack excess LDL’s in the bloodstream, producing foam cells. Foam cells have been shown to be a precursor to atherosclerosis when under oxidative stress.14 Atherosclerosis is defined as a hardening and narrowing of the arteries and it results from prolonged insult to the vessels.15 The eye has microvasculature under persistent oxidative stress from light. These circumstances create vessels which are exceptionally susceptible to damage over time. Consequently, geriatric patients with high levels of HDL are at elevated risk for age-related macular degeneration (AMD).16

The patient expressed that the lines in his crossword puzzles were “wiggly”. The crossword puzzle served as a provisional Amsler grid. His presenting complaint of the disrupted lines is classic for macular degeneration. Swiss ophthalmologist Marc Amsler developed the Amsler grid in 1947 to detect early symptoms of maculopathy.17 The Amsler grid comes in many variations, but the typical grid is a ten cm by ten cm square that resembles graph paper. Amsler described two visual phenomena that the grid is designed to detect. These defects are described by Amsler as metamorphomas and relative scotomas. Metamorphomas are distinct regions where the grid’s lines are not straight, parallel and equidistant. Relative scotomas are defects in the patient’s vision where the grid seems veiled or disconnected.18,19

Nuclear sclerosis (NS) is the yellowing, opacification and hardening of the central area of the eye’s crystalline lens.20 NS is the most common type of cataract, often developing slowly over many years causing a gradual opalescence in the lens.21 Browning, or brunescence, is often associated with a nuclear cataract fueled by chromophore concentration from oxidative stress. The hardening of the lens diminishes accommodation, and the clouding of the lens increases light scatter in the eye.22 A mature NS cataract can unquestionably cause decreased visual acuity, but it is doubtful in this patient’s situation because the cataract is classified as mild.

The patient returned to the clinic for a dilated fundus exam. Posterior pole examination reveals a Weiss ring and yellow deposits scattered in the macular areas OU. There were no signs of retinal hemorrhages, pigment changes or signs of obvious retinal elevation. The rest of retinal exam is WNL OU. Fundus photography and spectral domain OCT are performed for later review and analysis of changes. Based on the findings, the patient is diagnosed with bilateral macular drusen, likely early dry age-related macular degeneration. The patient is carefully educated on his condition, the importance of regular Amsler grid self-monitoring, and the role of “eye vitamins.” A follow up dilated fundus exam is set for six months.

A Weiss ring, also known as a senile annular ring, is often visible on the posterior vitreous surface consistent with its previous attachment to the optic disc.24,25 A full, or often partial, Weiss ring is often a sign of posterior vitreous detachment (PVD).23 A Weiss ring is a widespread objective finding in elderly patients, seen in nearly two-thirds in those over the age of 65. Flashes and floaters are the most common accompanying complaints with PVD. If pigment is also found in the vitreous, then there must be careful investigation of a potential vitreous hemorrhage or retinal tear because the RPE is likely disturbed.25
The patient was diagnosed with bilateral macular drusen. Drusen are localized yellowish accumulations of extracellular remnants, metabolic waste and lipids from the retina and its supporting structures. More specifically, drusen contain a variety of byproducts from the breakdown of photoreceptor outer segments. The majority of these are lipids, complement factors and cholesterol, both esterified and unesterified. Drusen accrue on or within the underlying metabolically active RPE and Bruch’s membrane. Bruch’s membrane is normally 2-4 microns thick and lies above the choriocapillaris and below the RPE. Cellular garbage in this area results in a decline in the permeability. If debris accumulation becomes proliferative, substantial visual consequences ensue. Waste products from intraocular structures will backload and may cause detachments and atrophy.

The current theories are that drusen arise in the retina mainly from chronic oxidative stress, hypoxia and inflammation. Three broad types of drusen present in the peripheral retina and posterior pole. Hard drusen are commonly smaller, solid, sphere-shaped and distinct. Generally, soft drusen are bulkier ill-organized clusters which lack a definite border. Compound drusen have intermediate characteristics of both hard and soft variants. Higher numbers of drusen, particularly soft drusen, are associated with macular degeneration because they attract inflammation and lower the permeability of supportive tissues.

Optical coherence tomography (OCT) is a ubiquitous modern ophthalmic technique employed to observe the retina and other ocular structures. A two-dimensional cross-sectional image is produced from a non-invasive scan. These high detail depictions, often with an artificial coloring of retinal layers, are created by measuring interference differences from light waves. The mechanism is akin to measuring ultrasound echo but uses light waves as a substitute to sound waves. This mechanism enables OCT to realize a very high level of resolution, operating in a resolution range of one to fifteen microns.

If available, an OCT should always be performed on a patient with AMD because retinal and sub-retinal deviations can be examined in microscopic detail over time. Monitoring changes in the neural retina, RPE and Bruch’s membrane are indispensable for the eye care professional treating retinal disease. Questionable deposits, detachments, elevations, fluid abnormalities, pigment focalizations, scars, and neovascularization are quantitatively scrutinized via OCT better than any other examination technique.

Fundus photography is another valuable tool for treating patients with macular degeneration, as well as other ocular and systemic diseases. Fundus photography is colored, which OCT is not, and provides a large-scale view. The most prominent causes of blindness in the developed world all show signs in the retina. Imaging the retina is an important analytical tool and provides valuable documentation to see a progression, or lack of, over time.

AMD is a neurodegenerative disorder that affects the retina. The macula is especially sensitive to this damage. In turn, an incidence of drusen, particularly the soft type, near the posterior pole is a significant risk factor. In developed countries, macular degeneration is the foremost cause of vision impairment and irreversible blindness in patients 65 and older. AMD is a complex disease process with a multitude of environmental and genetic associations. Some additional risk factors include smoking, hypertension, hyperopia, family history, female sex, Caucasian race, high ultraviolet light exposure and diet. Specially formulated supplements have been used to mitigate the risk of AMD progression. These nutritional supplements contain the AREDS formula of vitamins C, E, beta-carotene, zinc, and copper.
There is ongoing disagreement about how much the supplements aid; on the other hand, a “can’t hurt” approach is taken by most clinicians.\textsuperscript{43}

The patient fails to return to the clinic until two years later. His BCVAs are worsening, OD 20/50 and OS 20/25. DFE of the right macula at this time exposes a suspect region of retinal elevation and a slight retinal bleed. Spectral domain OCT confirms an irregular area of retinal elevation OD. The patient is asked to return for a one-month follow-up, but he did not return for three months. At this visit BCVAs are unchanged; however the patient notices additional distortion. SD-OCT now depicts an observable area of retinal fluid, which is likely stimulating the distortion. At this point, the disease has progressed to neovascular macular degeneration in the right eye and the left eye is likely on a three to four-year lag.\textsuperscript{44} As evidenced by this patient, there are two broad categories of AMD, exudative, or “wet”, and atrophic, or “dry”.\textsuperscript{40} Approximately 10-20\% of dry AMD patients eventually develop wet AMD.\textsuperscript{45} The patient is immediately referred to a retinal specialist, due to the sight-threatening nature of wet AMD and the patient’s history of non-compliance.

The retinal specialist is likely to treat his condition with an injection of anti-vascular endothelial growth factor (anti-VEGF). Intravitreal injection of anti-VEGF is the modern therapy for patients with wet AMD, diabetic retinopathy, and macular edema secondary to retinal vein occlusion.\textsuperscript{46} Bevacizumab, ranibizumab, aflibercept are the three angiogenesis inhibitors commonly used to prevent choroidal neovascularization.\textsuperscript{47} These new vessels arising from the underlying choroid are second-rate quality and too permeable, which is the source of the edema. Since the advent of these therapies, AMD incidence has virtually halved the incidence of wet AMD associated blindness.\textsuperscript{48}

Intravitreal injections involve an intentional needle wound to the globe to deliver medication near the retino-vitreous interface for maximum efficacy.\textsuperscript{46,47} The most prominent side effects of the anti-VEGF medications are related to its method of delivery. Any puncture to the globe increases the risk of infectious endophthalmitis, significant intraocular inflammation, rhegmatogenous retinal detachment and IOP elevation.\textsuperscript{48} Systemic cardiovascular side effects have been linked to the drugs but are extraordinarily rare due to the eye-blood barrier and the bulkiness of the therapy molecules.\textsuperscript{46,48}

Appropriate surgical procedure by the ophthalmologist increases positive outcomes rates. First and foremost, the site of injection is precise to minimalize risk of blood vessel insult, 3-3.5 mm posterior to the limbus for an aphakic or eye with an IOL implant, and slightly further, 3.5-4 mm posterior to the limbus for an eye with a natural lens. Second, a povidone-iodine solution is commonly used pre- and post-injection to counteract potential bacterial infection.\textsuperscript{46} There are other supplementary measures, but these seem to have the greatest prophylactic effect.

The provisional prognosis for this patient’s AMD is positive, contingent upon compliance and careful disease management. The long-term prognosis is unknown due to longitudinal studies proving difficult as study subjects tend to die before a longstanding observation can be made. Supplemental treatments may be necessary, and the doctor will need to educate the patient about the necessity of continuing to deliver intravitreal injections, take eye vitamins and have recurrent eye exams. Finally, many patients’ vision improves because of a reversal in macular edema and residual clearing of debris as a result reestablished RPE function.\textsuperscript{50,51} New pharmaceuticals with more attractive delivery methods and the use of statin drugs to help treat dry AMD are areas of intense research going forward.\textsuperscript{52,53}
References


