I HAVE WALDENSTROM MACROGLOBULINEMIA — WHY SHOULD I GET MY EYES CHECKED?

BY MAUREEN HANLEY, OD

Editor's Note: Dr. Maureen Hanley has been a longstanding faculty member at the New England College of Optometry. She is presently co-master of the Ocular Disease Principles Course. This is a one-year sequenced course in which she lectures on glaucoma, vascular disease, optic nerve abnormalities, pupils, cornea, cataracts, and visual fields. After earning her Doctor of Optometry from the New England College of Optometry, Dr. Hanley completed a residency in hospital-based optometry at the West Roxbury VA Medical Center. Dr. Hanley has practiced at many clinical sites, most recently at the Uphams Corner Community Health Center and the Boston Healthcare for the Homeless. She spent the majority of her patient care experience as an attending optometrist in the VA Boston Healthcare System.

This article is dedicated to the memory of Alice Riginos. Alice edited the first article I wrote, "Waldenstrom and the Eye," in the January 2011 *IWMF Torch*. You can find it online at *https://www.iwmf.com/sites/default/files/docs/publications/Hanley.pdf*. In 2018 she asked me to write a follow-up article. I said I'd be happy to when I had some time during my busy schedule. Unfortunately, that never happened before her passing, but Alice: here it is.

I suggest reading that first article before this update just to re-familiarize yourself with all the terms and the basics of eye findings in Waldenstrom macroglobulinemia (WM).

Let us look at a few cases. These are all real-life patients.

Patient 1:

A 53-year-old white male was diagnosed with WM with a symptom of fatigue. His IgM was approximately 10,000 mg/dL, and serum viscosity (SV) was 9.0 centipoise (cp). His vision was fine, but he went for an eye examination because he knew there was some risk to his eyes with WM.

Upon presentation, his vision was very good at 20/20 in his right and left eye, but retinal hemorrhaging and cotton wool spots were noted in both eyes. Cotton wool spots are caused by lack of oxygen to the top part of the retina, the nerve fiber layer. They are named this because they look like fluffy cotton or fluffy wool. As the concentration of IgM increases, the blood gets thicker, and this creates a rise in the intravascular pressure within the retinal venous circulation. Impairment in the retinal circulation produced his hyperviscosity-related retinopathy.

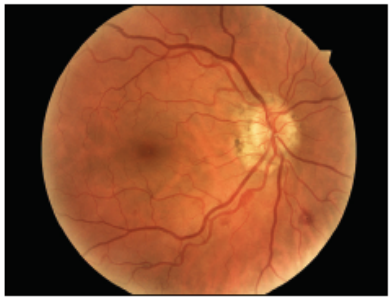

Figure 1. Right eye.

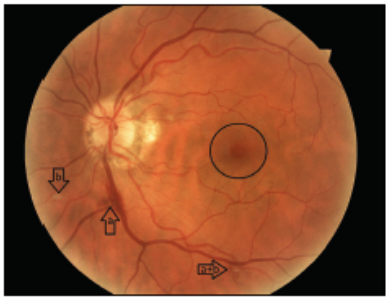

Figure 2. Left eye.

Note the retinal hemorrhaging (a) and cotton wool spots (b) in both eyes in Figures 1 and 2. The vision is still good because the macula region (the area in the black circle) is clear of retinopathy. The patient had retinal problems, but as he was asymptomatic, he was unaware of them.

Six weeks and five plasmapheresis treatments after Patient 1's first eye examination, his IgM had temporarily lowered to 2,600 mg/dL. You can see the large improvement in his retinal findings in Figures 3 and 4. Note that the diameter of the retinal veins (the darker colored vessels) are thinner and the amount of hemorrhaging is considerably less.

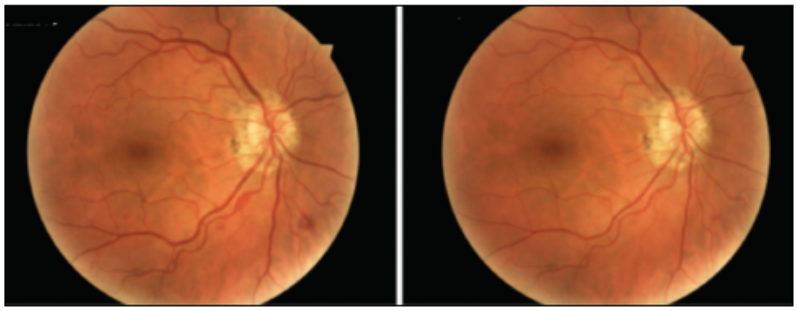

Figure 3. Right eye before plasmapheresis on left and six weeks after plasmapheresis on right.

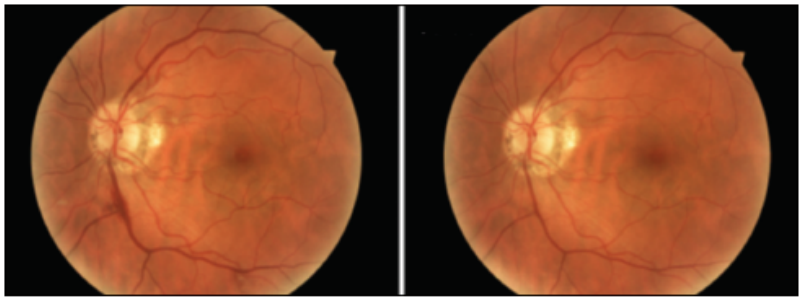

Figure 4. Left eye before plasmapheresis on left and six weeks after plasmapheresis on right.

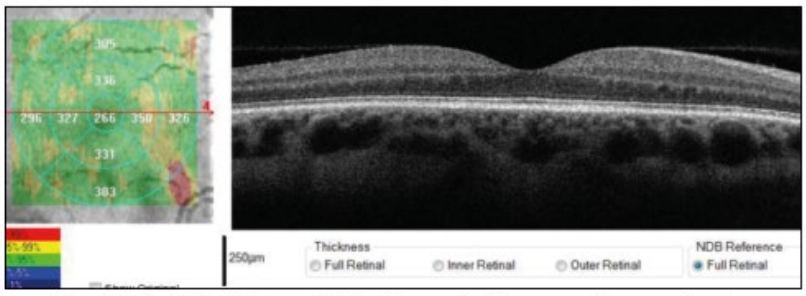

Figure 5. This is the OCT scan of Patient 1's macula. It has normal shape and contour.

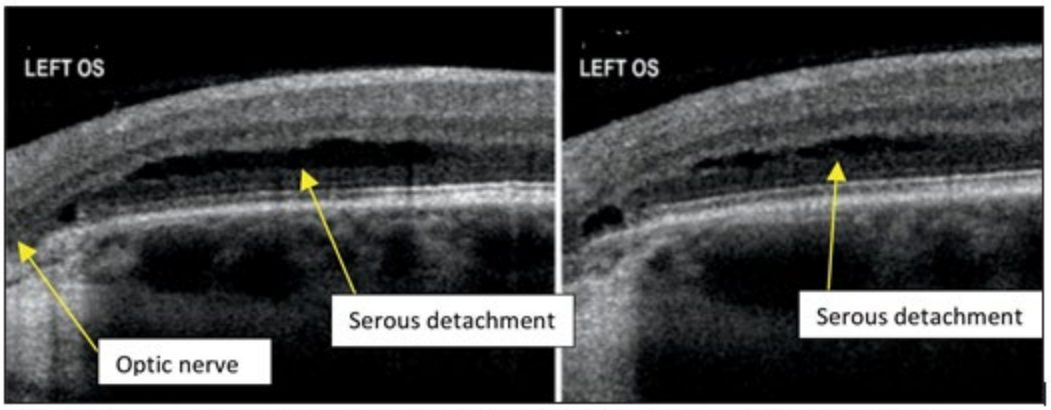

Figure 6. This is the OCT scan of Patient 1's optic nerve. The original left eye scan is on the left, and the one six weeks later is on the right.

Optical coherence tomography (OCT) is a non-invasive imaging test. OCT uses light waves to take cross-sectional pictures of your retina. It takes less than a minute per eye to get a wonderful image of the deep structures in the eye.

Although the OCT scan of the macula region in Figure 5 was fine at his first eye examination, the OCT scan of Patient 1's optic nerve in Figure 6 showed a serous detachment adjacent to the optic nerve, which was markedly improved after six weeks.

So we ask, what did this patient gain from having an eye examination? If he had not had treatment for WM, his eyes could have developed a full blown central retinal vein occlusion, possibly resulting in permanent vision loss. Lowering the serum viscosity decreased the stagnation of blood in the retinal vessels and allowed the hemorrhages to reabsorb before permanent damage could result.

Patient 2:

This 62-year-old white male with no prior diagnosis of WM went to his optometrist for a routine eye examination for a new pair of glasses. To the patient's surprise, upon dilating his eyes the optometrist saw hemorrhages in the periphery of his retinas as seen in Figures 7a and 7b. The optometrist was able to see the hemorrhages on the wide field Optomap—a camera used to image the peripheral retina. When an eye doctor sees peripheral retinal hemorrhaging, WM is not the first thing that comes to mind. Diabetes, anemia, and carotid issues are usually the primary causes for peripheral hemorrhaging in a 62-year-old male. The eye doctor called the patient's primary doctor to discuss the patient's findings, and routine tests were ordered to determine the cause.

These tests include checking blood pressure, a CBC with differential, fasting blood sugar levels, hemoglobin A1C, sedimentation rate, C reactive protein, a cholesterol panel, and usually a basic metabolic panel looking at renal, liver, heart, and bone function. If those come back normal, we think of a second line of testing, which usually includes inflammatory markers, coagulation markers, serum electrophoresis, and possibly a carotid Doppler test. Which tests we order really depend on the patient. Certainly, each doctor may have a different order of testing or may order additional tests.

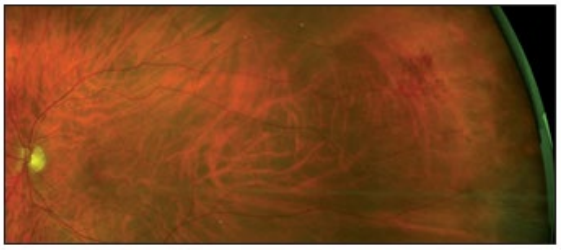

Figure 7a. Optomap of Patient 2 with hemorrhage in the far periphery.

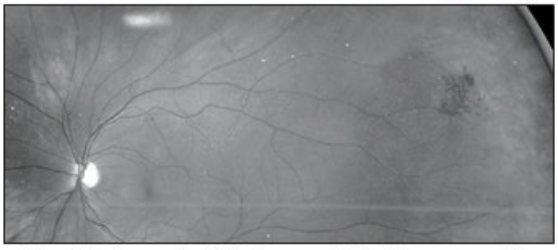

Figure 7b. Same patient but using a special autofluorescence filter.

Naturally we ask about trauma and if the patient is on any medications associated with retinal hemorrhaging, like interferon and anticoagulants. This patient had all these tests and they were normal—until the serum protein electrophoresis was performed, and it was discovered that the patient had an IgM of 5,600 mg/dL. After a bone marrow biopsy confirmed the diagnosis, the patient was treated for WM.

Going for an eye exam helped him get diagnosed and treated before more serious problems with hyperviscosity could occur.

Patients 1 and 2 both had high IgM and high serum viscosity. Normal serum viscosity (SV) is 1.4-1.8 cp. For reference, the SV of water is 1.

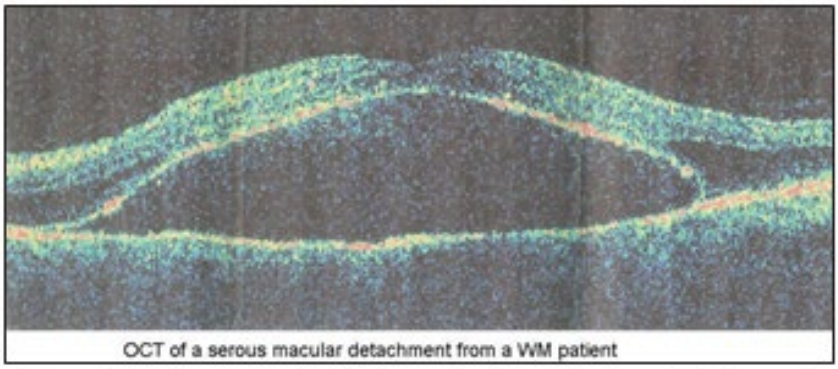

Figure 8. WM patient with WM maculopathy. Note how this does not look like the normal macula in Figure 5.

Marcel Menke (Menke et al., 2006) showed that retinopathy has been noted in patients with SV as low as 2.1 cp, but on average the peripheral retinal hemorrhages and dilated vessels were noted with a mean IgM 5,442 mg/dL and mean SV of 3.1 cp. Retinopathy in the posterior pole (the area where the macula and optic nerve rest) had a mean IgM of 8,515 mg/ dL and a mean SV of 5.6 cp. The conclusion was: on average the higher your IgM, the greater your chances of having retinopathy.

In Menke's study the highest IgM reported without retinopathy was approximately 5,500 mg/dL.

All WM patients are different. There are patients who can have IgMs above 6,000 mg/dL, and we have not been able to detect retinopathy even with scleral depression of the peripheral retina.

You may ask, what has changed since 2011 when the first *Torch* article on WM and the eyes was written?

1. The basics are still the same, but ocular imaging has greatly improved, and OCT is now present in almost all eye care practitioners' offices. The image quality of these diagnostic tests has also greatly improved, though scleral depression is still the best way to see the most peripheral of retinal hemorrhages.
2. The maculopathy of WM can cause a serous detachment in the macula and lead to moderate or severe vision loss. Compared to ten years ago, many more cataract surgeons are doing OCT of the macula on their pre-op exams for cataract surgery. Certainly, every cataract patient with WM should have an OCT of the macula to make sure that vision loss is from the cataract and not from WM maculopathy. This maculopathy is very hard to detect unless you have an OCT, and occasionally it can occur with few or no hemorrhages.

   It is my professional opinion that all WM patients with elevated IgM, certainly above 3,000 mg/dL, should have an OCT of the macular region, especially if they have unexplained visual acuity loss. The best way to treat WM maculopathy is to treat WM.
3. Bortezomib (Velcade), a proteasome inhibitor, was thought to be associated with meibomian gland dysfunction. Meibomian glands are located in the eyelids, and their openings or orifices are along the rims of the eyelids. The glands produce an oily/lipid substance that helps prevent evaporation of the eye's tear film. We now know that Velcade causes a marked increase in chalazions (bumps on the eyelid caused by blocked meibomian glands) and blepharitis (inflammation of the eyelids). Some patients WM retinopathy and/or WM maculopathy have been treated with anti-vascular endothelium growth factor (anti-VEGF) intra-vitreal injections, such as bevacizumab (Avastin). The literature shows mixed results; some patients have had fair results, but others have been totally refractory. Treating the WM itself remains the first-line treatment when it comes to WM-related retinopathy.
4. A retrospective study in Sweden by Kari Hemminki (Hemminki et al., 2016) confirmed that WM patients have a higher incidence of glaucoma (2.1 times) and cataracts (1.85 times), something that was always suspected but not actually confirmed.
5. Many WM patients also suffer from dry eye, and there are now many more treatments and diagnostic tests for this condition.
6. We also know a lot more about Bing Neel syndrome (occurring in about 1% of WM patients), a condition in which the WM cells invade the central nervous system (the brain and spinal cord). Eye doctors are more frequently watching for signs and symptoms of Bing Neel, including optic atrophy, facial nerve problems, eye movement problems, and neurological visual field defects.

As I am writing this, we are in the middle of a COVID-19 pandemic, and conjunctivitis can be a first sign of COVID-19, or the red eye can be "regular old" conjunctivitis. So, my last bit of advice is for everyone to stay safe and call your eye doctor if you have any ocular problems.

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