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WALDENSTROM AND THE EYE

by Maureen Hanley, O.D.

Dr. Maureen Hanley is a living legend to readers of IWWMF-TALK. Whenever a question concerns the possible impact of WM on a patient's eye health there is certain to be a response from Dr. Hanley reflecting her training and experience as an eye care professional. A search of the TALK archives in preparation of this article produced no less than 152 such detailed answers to the concerns of other TALK participants. And whenever mention is made of an elevated level of serum viscosity there is sure to quickly follow the familiar, almost telegraphic, warning: "Be sure to get a dilated eye examination." In this article Dr. Hanley draws on considerable knowledge and experience to discuss specific ocular problems that a WM patient may encounter.

Many ocular problems can happen due to Waldenstrom's macroglobulinemia (WM). It is, however, important to remember that many things that happen to the eye are part of normal aging.

Focusing difficulties

In our forties or early fifties, for example, we begin to lose the ability to focus. This is called presbyopia. With WM, presbyopia may become more pronounced because one tends to become more fatigued. We may need bifocals to allow us to see at both distance and near.

Conjunctiva and Conjunctival Hemorrhages

The conjunctiva is a clear mucous membrane with fine blood vessels which lines the inside of eyelids and also covers the sclera (the white part of the eye). The conjunctiva can be affected by WM, and in this case the blood within the vessels of the conjunctiva may appear segmented and sluggish. The change in the conjunctiva can only be seen under an instrument called a slit lamp. Such changes also happen with almost all types of anemia.

Subconjunctival hemorrhages also occur commonly, whether or not the patients have WM. The hemorrhage occurs when a small blood vessel bleeds into the area of the eye between the sclera and the conjunctiva. When this happens, the sclera or whites of our eye look bright red. While a subconjunctival hemorrhage is usually harmless, if your eye looks abnormally red then you should certainly have it checked by your eye doctor. However, if you are taking Coumadin your INR (international normalized ratio – a clotting index) should be immediately checked and so, too, your CBC (complete blood count) values if they have been running low, especially your platelets. Also, you should notify your doctor if you have a bright red eye after plasmapheresis since your PT (prothrombin time – a test for clotting ability) and PTT (partial thromboplastin time) may be dangerously off.

Dry Eyes

Dry eyes are a very common problem. Approximately twenty percent of all Americans suffer from dry eye symptoms. Dry eyes are even more prevalent in post-menopausal women, and WM may make this problem worse because it may have an autoimmune effect on the lacrimal gland.

In 2010 there are many treatments that can reduce the symptoms of dry eye and provide relief, such as punctal plugs (silicon or collagen pieces) inserted in the tear ducts to reduce the flow of tears to the nose and to keep them on the eye and the drug Restasis (ophthalmic cyclosporine) used to increase tears. Low-dose steroid drops may also be of help, in addition to the standard variety of artificial tears. It has been reported that WM can be associated with incapacitating dry eyes because of the infiltration of the lacrimal gland associated with secondary Sjogren's syndrome (an autoimmune disease that causes dry mouth and eyes). While this is a serious condition, Sjogren's syndrome is fortunately uncommon among WM patients.

Because of dry eyes, WM patients should be very cautious if planning for refractive surgery. Many surgeons will not perform refractive surgery on patients with autoimmune diseases.

In some patients with WM a diffuse or focal immunoprotein deposit can occur on the posterior part of the stroma of the cornea, but again this is rare and does not affect vision.

Cataracts

A cataract is an opacity of the lens. The lens is part of the focusing mechanism of the eye. The Framingham study showed that the prevalence of cataracts occurring without vision loss was 41.7% in persons 55-64 years of age and 91.1% in those of ages 75-84. The prevalence of cataracts with vision loss was 4.5% in persons 55-64 years of age and 45.9% in persons of ages 75-84. Essentially, if we live long enough we all will develop a cataract.

However, some studies suggest that the most important factor in steroid-induced posterior subcapsular cataract formation may be individual susceptibility. Other studies suggest the cumulative amount of glucocorticosteroid taken is the determining factor. The use of ocular or inhaled steroids has also been linked to cataract formation but does not pose as great a risk for cataract formation.

Glaucoma

Systemic and ocular steroids can also raise the intraocular pressure in the eyes. A patient is designated a steroid responder if their eye pressure increases while taking either a systemic or ocular steroid. A steroid responder may have to take glaucoma medications when a steroid is prescribed. Steroids appear to alter the outflow mechanisms in the trabeculum meshwork, a porous tissue that drains aqueous humor from the eye.

Most people think of glaucoma as high intraocular eye pressure (IOP) causing damage to the optic nerve. The most common type of glaucoma is called primary open angle glaucoma, and about two percent of adults over forty have this form. It is even more prevalent in African Americans.

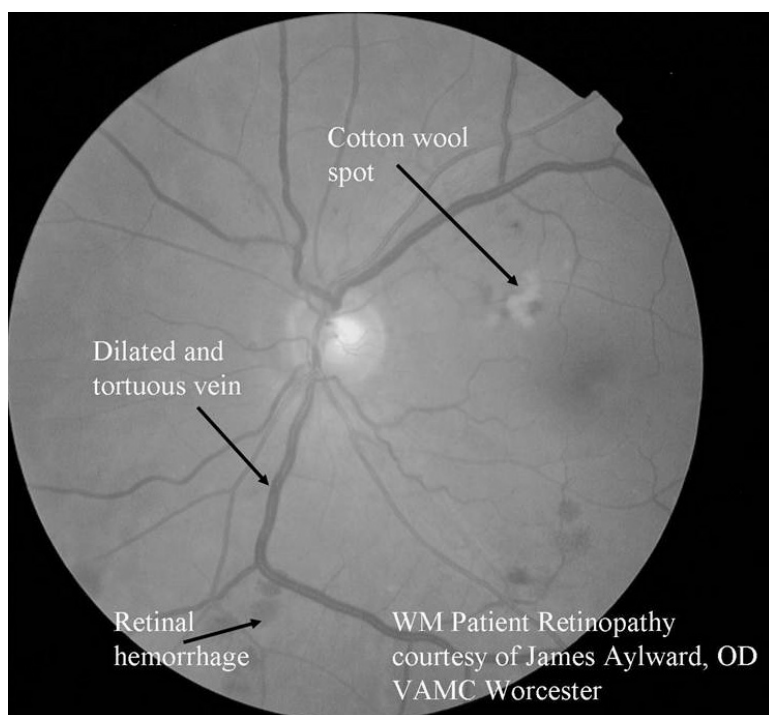
However, another type of glaucoma is called low tension or normal tension glaucoma. In this type of glaucoma the IOP is normal but the optic nerve develops the same type of neuropathy that is associated with high IOP glaucoma. Low tension glaucoma is thought to be a vascular problem of blood insufficiency or an autoimmune problem rather than a glaucoma resulting from increased IOP. Patients who are more prone to low tension glaucoma include patients who have systemic hypotension, anemia, cardiovascular problems, and sleep apnea. High serum viscosity (SV) also appears to be a risk factor.

High SV is thus a risk factor for both low tension and high pressure glaucoma. Research has also shown that about 30% of patients with low tension glaucoma have an autoimmune component. In general, low tension glaucoma patients have a much higher prevalence of monoclonal gammopathy compared with age-based normal individuals. The relation between monoclonal gammopathies and low tension glaucoma is a subject of current research. As of today, no research has been published on the reverse hypothesis: that is, if you have monoclonal gammopathy or WM, what is the risk of you developing low tension glaucoma? Whether or not low tension glaucoma is due to autoimmune neuropathy is also currently under investigation.

The Retina

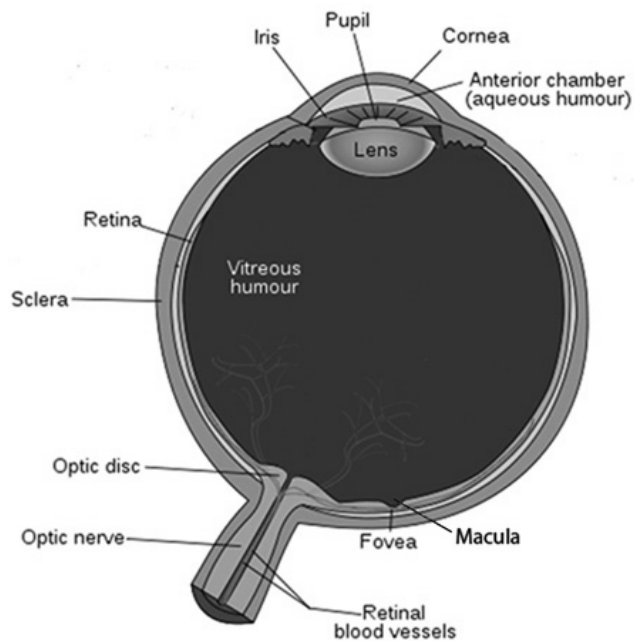
When eye doctors hear the term Waldenstrom they generally think of the retina. Before discussing the retinal impacts of WM, it is important to know that hemorrhaging in the eye can also occur if one's hematocrit (HCT) is 50% below normal, especially if it is combined with thrombocytopenia (low platelets). Hypertension and diabetes can also cause retinal hemorrhaging in the eye, as can carotid artery blockage problems. Many other vascular diseases are associated with retinal hemorrhages.

When your eye doctor looks at the back of your eye (also known as the fundus) he or she can see the retina, the arteries and veins of the eye, and the optic nerve. In WM the earliest sign of a problem is usually venous dilation. Venous dilation and increased venous tortuosity can be difficult to recognize in their earliest state because many patients have congenital tortuous vessels. Congenital tortuosity is not associated with retinal hemorrhaging.



Left eye of a WM patient with retinopathy

In the early stages of WM-related retinopathy, one can see small hemorrhages in the peripheral retina. Scleral depression is usually needed to see these peripheral hemorrhages. Scleral depression involves putting gentle pressure on the eyelids with a small metal probe (a depressor) to gently push the far peripheral retina into focus. This procedure adds about 2-3 minutes to a regular dilated exam. As the WM-related retinopathy becomes more evident, hemorrhages increase in number, appearing in the posterior pole where the optic nerve and macula are located. Exudates (leakage of lipids) and cotton wool spots (microinfarctions of the nerve fiber layer that resemble cotton wool) can occur in addition to hemorrhages. The venous system becomes engorged via compression at arteriovenous crossings in the eye near the optic nerve. This can lead to branch-vein occlusions. Further engorgement or swelling of the veins can lead to optic nerve congestion and a central retinal vein occlusion. Not all individuals progress from one hemorrhage to a full-blown central vein occlusion. On the other hand, some individuals can have a clean retinal evaluation and later have a central vein occlusion in just weeks or months following the exam. It is



Schematic drawing of the human eye. This is a diagram from the [Wikimedia Commons](#).

very important to realize that while not everyone with WM will have the retinal problems, it is estimated that about 40% will, and these cases appear to be related to SV, which in turn depends on the concentration of monoclonal IgM.

A study by Menke evaluated 46 patients with WM along with 14 age-matched adults without WM. The mean IgM level of patients with the first indications of retinal change was 4,732 mg/dL and a mean SV of 3.0 cp (centipoise).

Patients were divided into 3 groups:

Group 1: no retinopathy.

Group 2: dilated veins and /or peripheral hemorrhages; a mean serum IgM of 5,442 mg/dL (range of 2,950 to 8,440 mg/dL) and a mean SV of 3.1 cp.

Group 3: peripheral and central retinal hemorrhages accompanied by dilated veins, optic nerve head edema, and venous sausageing; a mean serum IgM of 8,515 mg/dL (range of 5,700 to 12,400 mg/dL) and a mean SV of 5.6 cp.

This study concluded that retinal changes were found in patients with SV values as low as 2.1; however, these changes produced no symptoms for the patient since the hemorrhages were in the far periphery. Clinically, the hemorrhages represent structural damage secondary to hyperviscosity. The hyperviscosity-related changes in the eye become symptomatic when the posterior pole becomes involved; the average SV associated with that effect was 5.6 cp.

Another study by the same group showed that plasmapheresis helped reduce the hyperviscosity-related retinopathy.

The Macula

The other important retinal finding noted with WM is serous macular detachment. The macula, the most sensitive part of the retina, provides fine visual acuity. Plasmapheresis and lowering of the IgM appear to be the only effective treatment for resolving serous detachments secondary to WM. Optical coherence tomography (OCT) does an excellent job of mapping these lesions. The cause of these lesions is unknown but appears related to increasing monoclonal IgM concentration that causes the transfer (by osmolar pressure) of normal fluids from the retina and choroid. Reducing the level of IgM systemically often results in decreased pressure within the subretinal space, with normalization of subretinal fluid dynamics and flattening of the retina. If, however, the macula sits in this fluid too long, the visual function will not return even if the retina flattens.

Cysts

Pars plana cysts may also develop in Waldenstrom's patients at the far periphery of the eye. Although shown by histopathological studies to contain IgM, these cysts do not affect vision. They may, in fact, be an aid in the diagnosis of WM or multiple myeloma (MM) since cysts of this type can develop in patients of both diseases.

Guidelines to Vision Health

As patients, we all want guidelines on how to protect our eyes from problems associated with WM. However, due to the rarity of WM, long-term clinical studies comprising large patient bases are unavailable and a firm set of guidelines for treatment protocol has yet to be established. By contrast, diabetic retinopathy has very specific guidelines concerning when to treat and when not to treat. The guidelines for diabetes were accomplished by studying over 3,000 patients for many years. In diabetic retinopathy the eye doctor does not use a laser to treat one or two hemorrhages but uses this technique exclusively to treat and diminish new blood vessel growth called proliferative retinopathy.

Years ago patients with eye pressures over 21 mm were regularly given eye drops to "treat glaucoma." Today only about 1 in 10 of patients with a pressure between 22-30 mm actually develops glaucoma. This was concluded from another large clinical trial called the Ocular Hypertension Treatment Study.

If a patient has posterior pole WM retinopathy or hyperviscosity maculopathy, most oncologists would treat the patient on the basis of these symptoms. The question becomes, "Should a patient be treated if their IgM is 4,000 mg/dL and there are only one or two retinal hemorrhages observed at the far periphery by scleral depression and the patient has no other signs or symptoms?" It appears that doctors have no consistent answer to this question of whether to treat or not under the circumstances described. What if a patient has an IgM concentration of 10,000 and both eyes look fine? Why does this patient not have retinopathy? Are they sitting on a "time bomb" and will this patient awake one morning with markedly reduced vision from a vein occlusion? Or, is there something unique to this individual that allows his or her venous system to tolerate the high IgM without an occlusion or hemorrhage? If I were the doctor of anyone with an IgM of 10,000 I would recommend some form of treatment to reduce the risk of eye damage from hyperviscosity effects and from all the other physical effects described in this article that could seriously and permanently cause vision loss.

So what can you do in 2011 to protect your vision if you have WM?

1. Get an annual or semi-annual complete dilated eye exam with a doctor who is comfortable examining a WM patient. Most doctors who see many diabetics should have no problem examining a WM patient since possible hemorrhages or tortuosity will appear very similar to what is seen with diabetics. It may take the doctor a few minutes to review a reference to vision problems associated with WM prior to the eye exam. The doctor may not be familiar with new findings related to employing scleral depression for peripheral hemorrhaging in addition to checking for macular serous detachments. The occurrence of so many possible eye diseases, coupled with the rarity of WM, explains why eye doctors, just like hematologists, may have little direct experience with WM.

2. Call ahead and ask before you make your appointment to be sure the doctor is comfortable seeing a patient with WM. If he or she is not, ask for a recommendation. If your oncologist is knowledgeable about WM they may be able to refer an eye doctor who is more experienced, especially if the oncologist has been referring other WM patients to the same eye doctor.
3. If possible, obtain retinal photographs. They are valuable, though not essential, to monitor changes in venous tortuosity over time.
4. Remember that you may be prone to low tension glaucoma even if your IgM is not high. Your optic nerve should be carefully examined, and if there is any question a visual field should be done that tests the sensitivity of your central and peripheral field of vision.
5. Be sure your eye doctor sends a report of your exam to your oncologist and encourage both to continue to communicate about WM and potential vision problems.

A final word from the wise: if you have any sudden changes in vision do not e-mail IWMF-TALK or try to self-diagnose. Go to or call your eye care provider immediately!

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Immediately after earning her doctor of optometry from the The New England College of Optometry in 1981, Dr. Hanley completed a residency in hospital-based optometry at the West Roxbury V. A. Medical Center. Dr. Hanley has practiced at many clinical sites; most recently she was a clinical preceptor and attending optometrist in the V.A. Boston Healthcare System for 12 years. Dr. Hanley has also been a certified reader of digital retinal images for the Joslin Diabetes Center in Boston. Since 2010 Dr. Hanley is in charge of vision services at the Jean Yawkey Place, providing eye care to homeless men and women.

In addition to her responsibilities with the college, Dr. Hanley frequently gives continuing education lectures to optometrists in the areas of visual fields, glaucoma, and ocular disease. Dr. Hanley is a member of both the American Optometric Association and the Massachusetts Society of Optometrists.

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