Waldenström and the Eye

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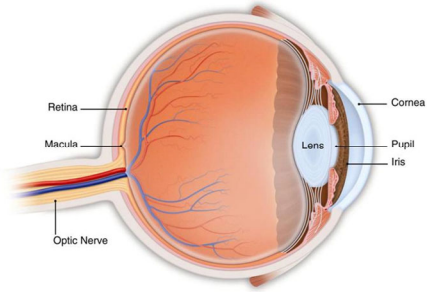
Lets talk eyes

- Normal aging versus Waldenstrom related issues.



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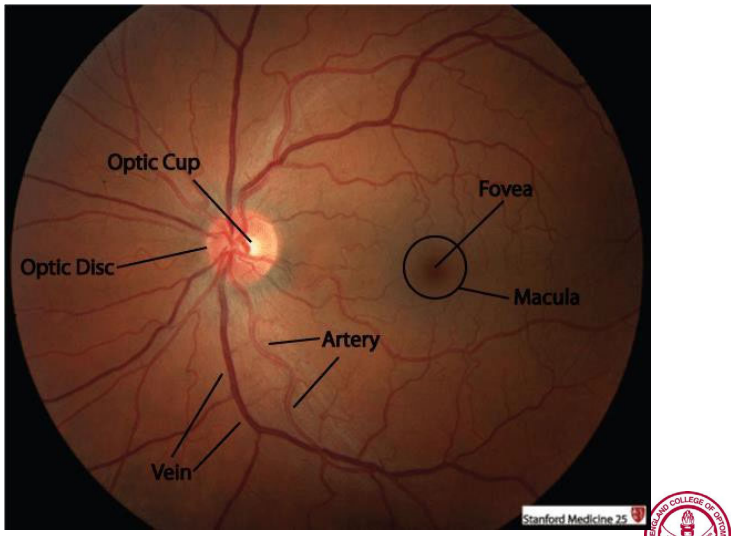

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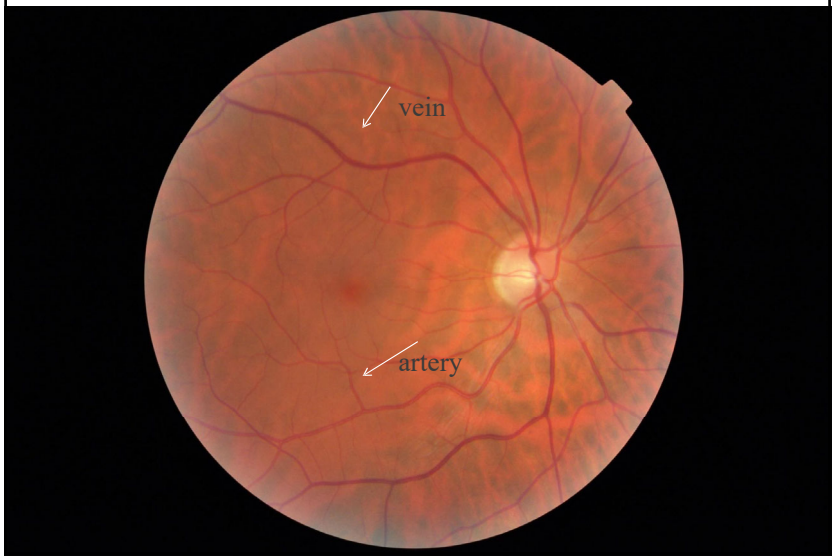
Normal Right Eye



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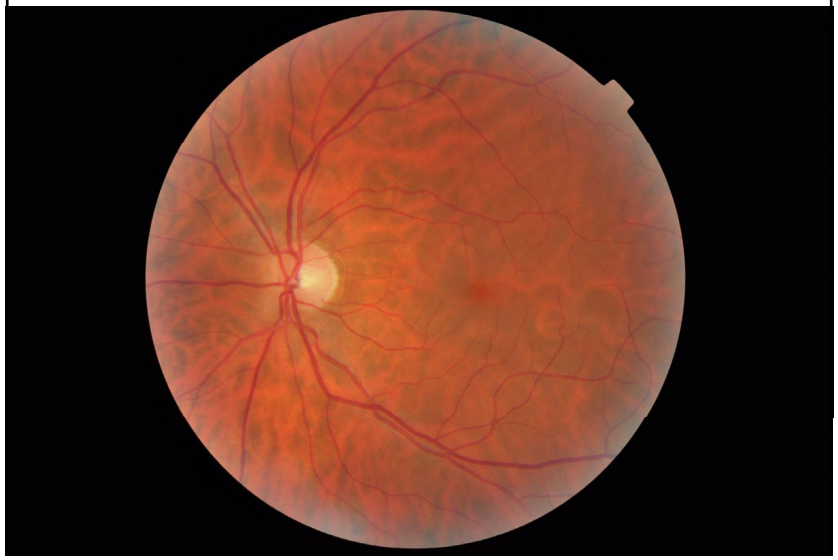
Normal Left Eye



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Retina

- 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.
- Diabetic retinopathy can also show signs of venous dilation and increased venous tortuosity.

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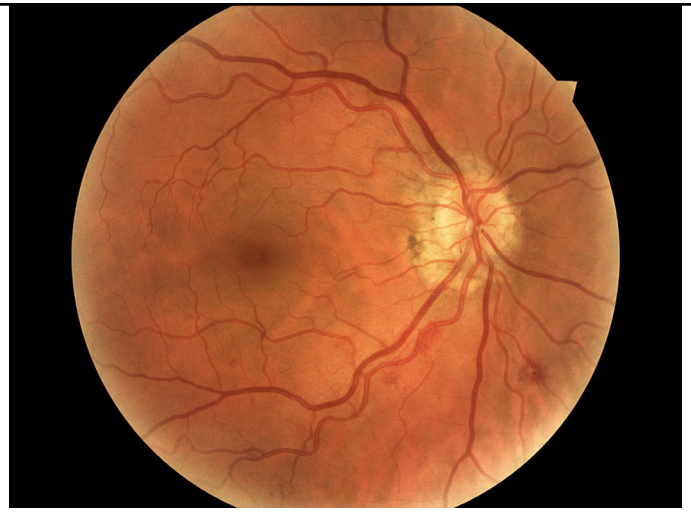

Eye with WM – IGM was 10,900

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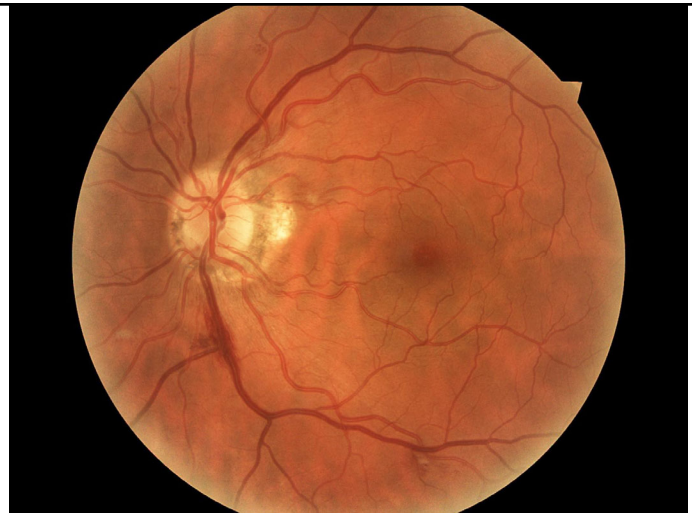

Eye with WM – IGM was 10,900

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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 in combination with thrombocytopenia (low platelets).
- The cause of the hemorrhages is secondary to the anoxic damage to the endothelial cells of the retinal capillaries
  - The decreased platelet counts may delay the sealing of the endothelial defect, causing a hemorrhage.

9

Retinal Hemorrhaging

- Thrombocytopenia by itself can cause retinal changes.
- Hypertension and diabetes can also cause retinal hemorrhaging in the eye, as can carotid artery blockage
- So many times if someone has diabetes and/or hypertension the WM or anemia may be missed because the retinal hemorrhaging may be assumed to be secondary to diabetes or hypertension etc.

10

Retinal Hemorrhages with Anemia

- Retinal hemorrhages from severe anemia may be flame shaped (occasionally with Roth's spots) or dot and blot hemorrhages.
- Roth's Spots are flame shaped hemes with white centers that are either cotton wool spots or white blood cells.
- Cotton wool spots, hard exudates and venous tortuosity may be present.

11

Severe Anemia

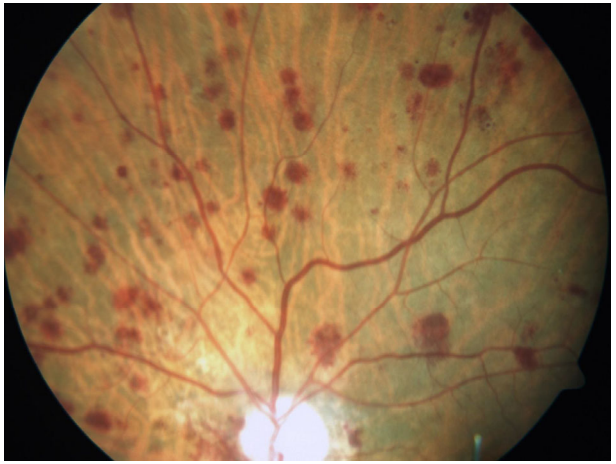

Photo by
Jeff Ho, OD

12

Severe Anemia

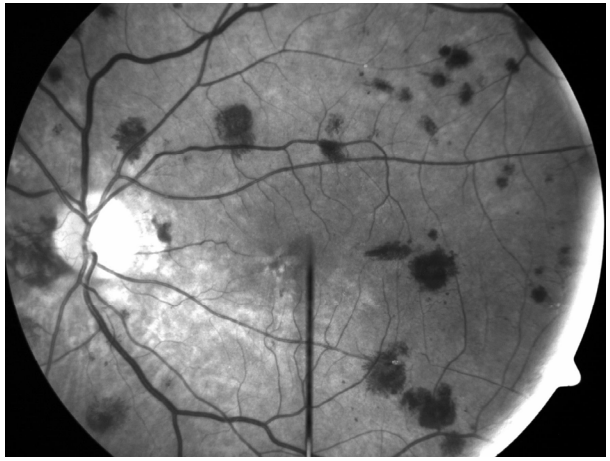

Photo by
Jeff Ho, OD

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Severe Anemia

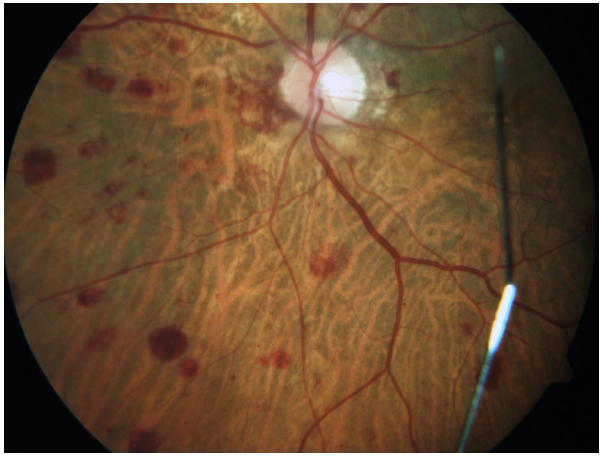

Photo by
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Roth spot - Slide courtesy of Dr. Bina Patel

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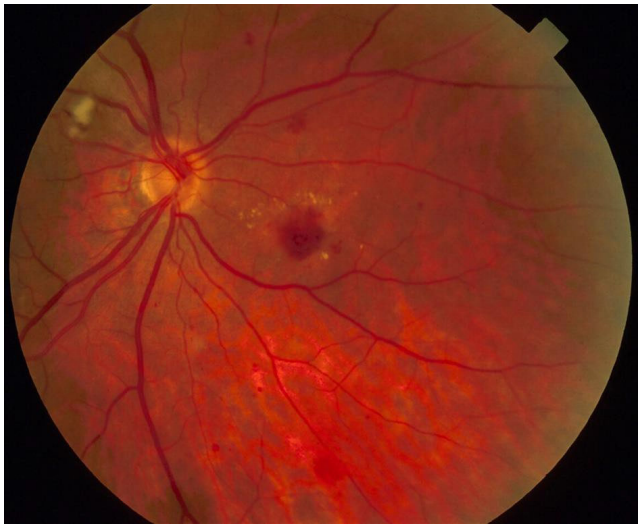
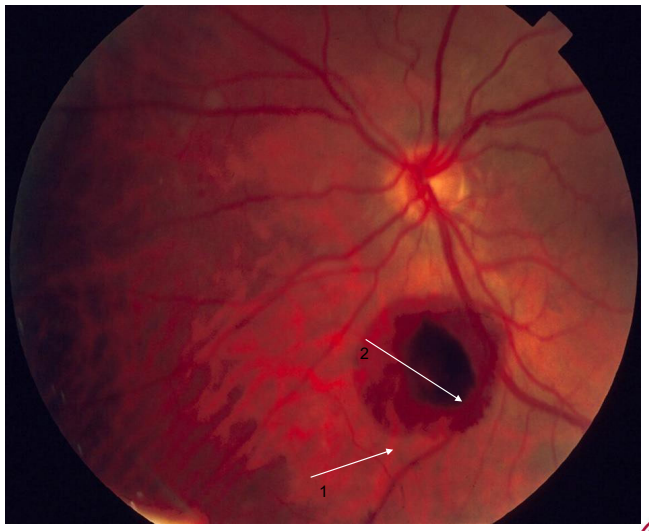


Leukemia retinopathy – exudates and large intraretinal heme

16



Leukemia retinopathy – 1.subretinal heme 2.sub RPE heme

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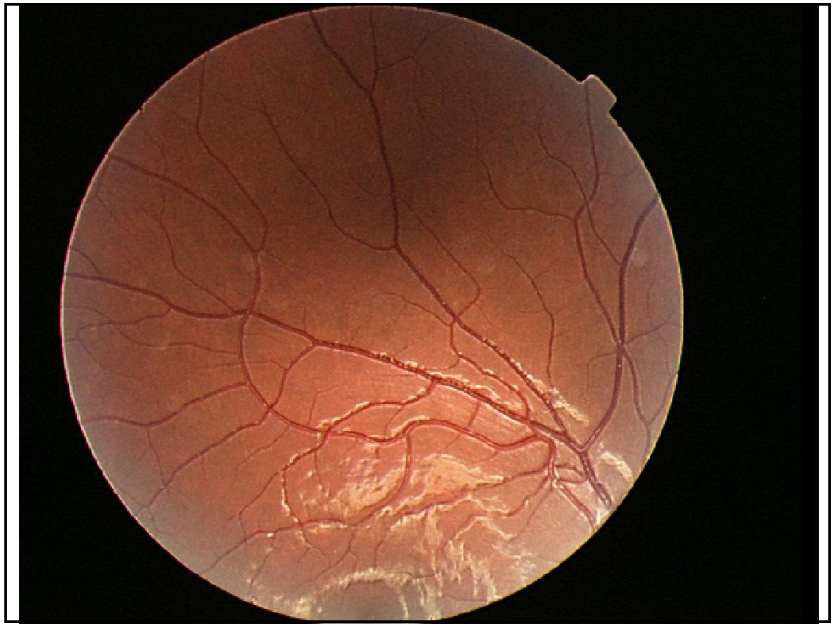

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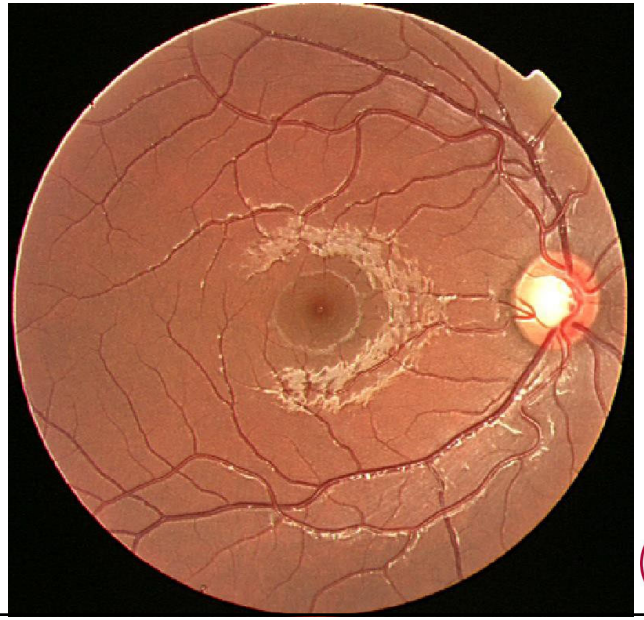

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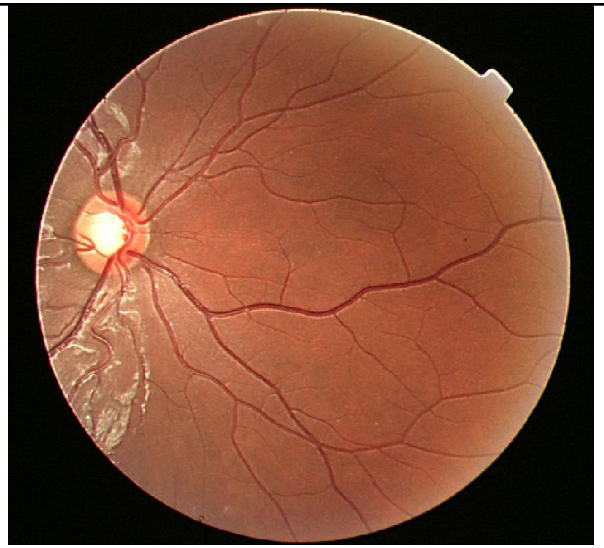

Hemorrhage from DM but could have been from WM

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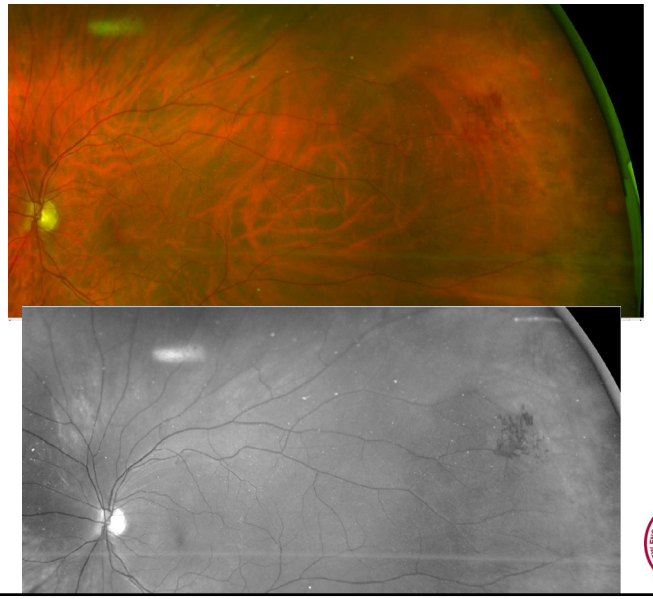

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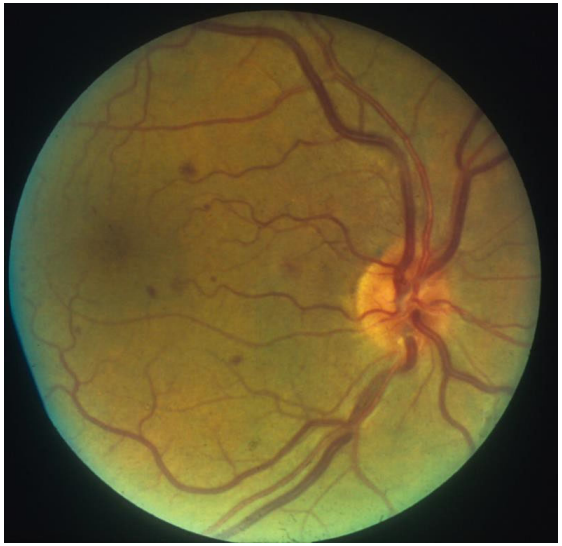

Courtesy of Dr. Bina Patel - again DM but could be WM

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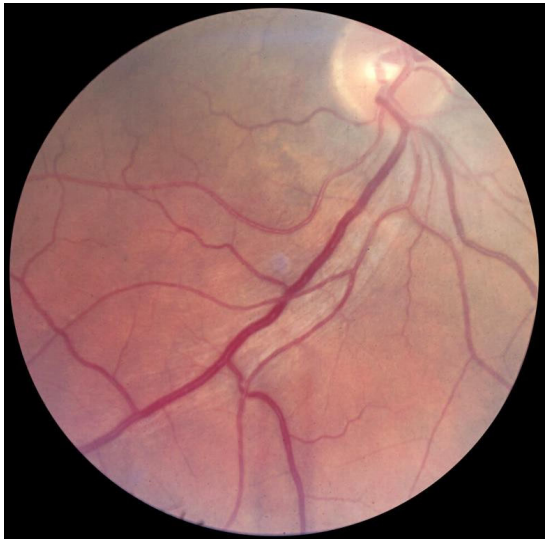


This is hypertension and arteriosclerotic retinopathy

23

Let's talk about WM retinopathy specifically

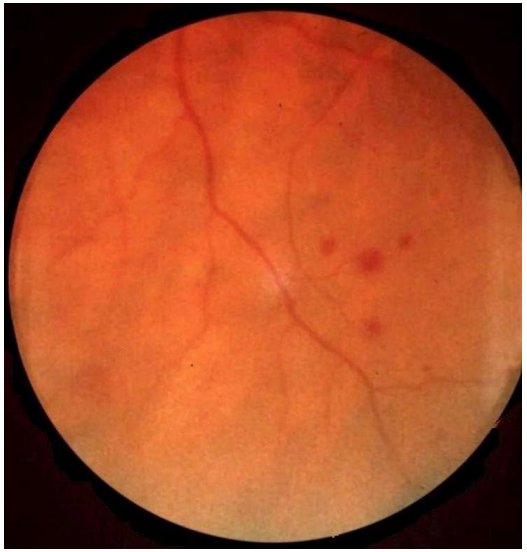
- Small B cell lymphoma secretes monoclonal Ig M which is a large protein molecule and increases the blood viscosity resulting in venous dilation, segmentation, tortuosity, and sludging. You can get superficial and deep hemorrhages and you can also get disc edema. Retinal artery and vein occlusions can result.
- Although it varies, patients with an IgM of over 3,000 are at risk for retinal bleeding but in some cases peripheral hemorrhaging has been noted with lower IGM.
- In the early stages of WM-related retinopathy, small hemorrhages in the peripheral retina are seen. Scleral depression is usually needed to see these peripheral hemorrhages.

24

www.meadowsretina.com

The earliest changes may be seen only with scleral depression looking at hemorrhages in the periphery

25



Hyperviscosity causing Peripheral Hemorrhages near the ora

However these can also occur in patients with diabetes and in patients with carotid artery stenosis

26

WM Retinopathy Progression

- As the WM-related retinopathy becomes more evident hemorrhages increase in number, appearing in the posterior pole. Exudates, and cotton wool spots can occur in addition to hemorrhages.
- The venous system becomes engorged via compression at arteriovenous crossings 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 central retinal vein occlusions.
- Not all individuals progress from one hemorrhage to a full-blown central vein occlusion.

27

Patient with Retinopathy From WM

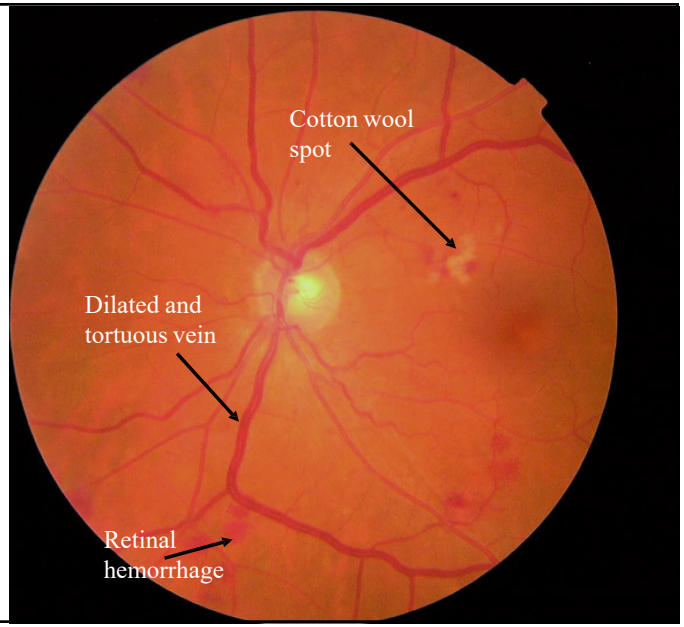
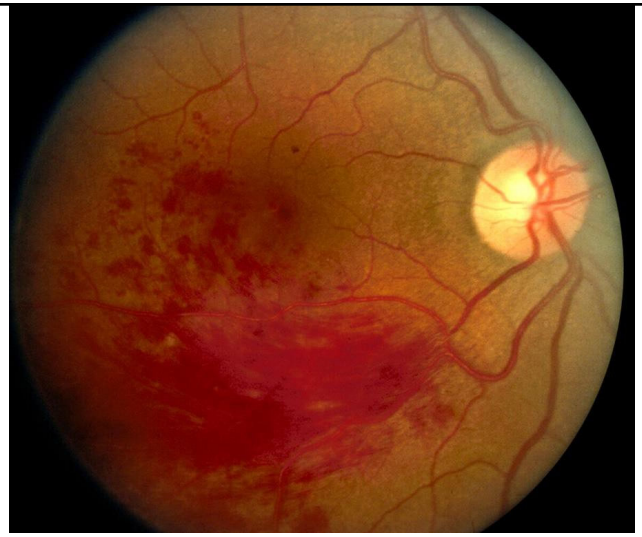


Photo courtesy of James Aylward, OD

28



Donated by Patti Landry,OD

29

Eye with WM

30

Serum Viscocity

- Normal serum viscosity is 1.4- 1.8 times that of water - in WM it can go > 6.
- Retinopathy has been noted as low as 2.1 (far periphery) however the average s.v. associated with retinopathy in the posterior pole is 5.6

Arch Ophthalmol. 2006 Nov;124(11):1601-6. ***Hyperviscosity-related retinopathy in waldenstrom macroglobulinemia.Menke et al***

31

Variability of WM

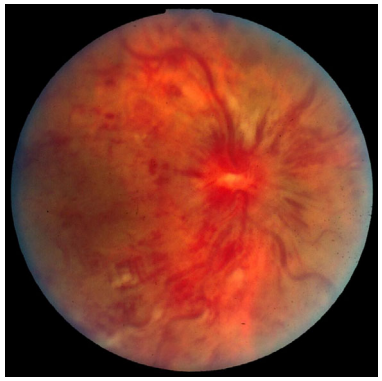
- Some individuals can have a clean retinal evaluation and later have a central vein occlusion in just weeks or months following the exam.
- It is very important to realize that while not everyone with WM will have retinal problems, it is estimated that about 40% will, and these cases appear to be related to SV, which in turn depends *somewhat* on the concentration of monoclonal IgM.
- However some patients can have a s.v. of 8 and not have retinopathy.

32

Central Retinal Vein Occlusion

- Thrombus of the Central Retinal Vein in the area of the lamina cribosa causing increased venous resistance

Patient could have been 20/20 before and now has counting-fingers vision
This needs to be avoided if at all possible



33

Hyperviscosity-Related Retinopathy in Waldenstrom Macroglobulinemia
Marcel N. Menke, MD; Gilbert T. Feke, PhD; J. Wallace McMeel, MD; Andrew Branagan, BS; Zachary Hunter, BS; Steven P. Treon, MD, PhD

- Patients with WM were evaluated using slit lamp biomicroscopy, indirect ophthalmoscopy with scleral depression, laser Doppler retinal blood flow measurements, and serum IgM and SV determinations.
- Hemodynamic findings were compared with those of a group of age-matched controls.
- A retinopathy severity scale was developed, and the associated IgM and SV values were related to particular morphologic changes.
- A total of 46 patients with WM and 14 age matched, healthy controls participated in the study.
- 24 patients 48% of the patients showed hyperviscosity syndrome

34

Study continued

- Retinal hemodynamics were assessed using a Canon Laser Doppler Blood Flow Meter (CLBF100; Canon Inc, Tokyo), an instrument that simultaneously measures the centerline red blood cell speed and the blood column diameter in individual retinal vessels. The retinal blood flow rate is automatically calculated at each measurement site. Only 3 of these machines in the world
- Venous diameter and venous blood flow

35

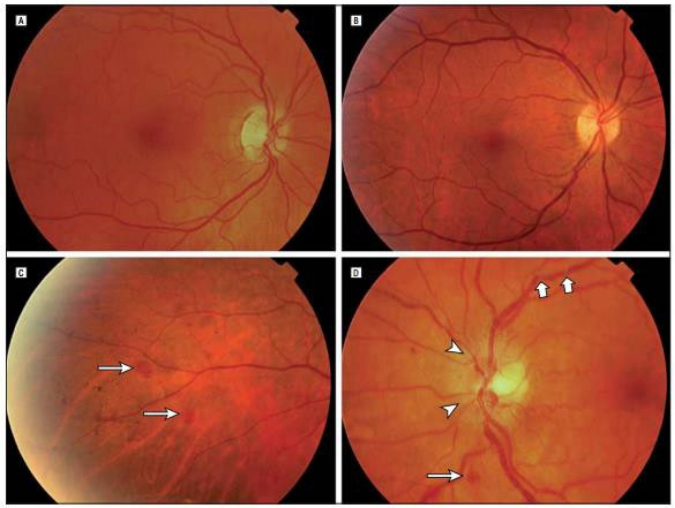


Figure 3. Fundus images of patients with Waldenström macroglobulinemia. A, No retinopathy (group 1); B, dilated veins (group 2); C, peripheral retinal hemorrhages in a group 2 patient (arrows); and D, central retinal hemorrhage (thin arrow), optic disc edema (arrowheads), and venous sausaging (thick arrows) in a group 3 patient.

Hyperviscosity-Related Retinopathy in Waldenstrom Macroglobulinemia Marcel N. Menke, MD; Gilbert T. Feke, PhD; J. Wallace McMeel, MD; Andrew Branagan, BS; Zachary Hunter, BS; Steven P Treon, MD, PhD

36

- Patients were divided into 3 groups:
- Group 1: no retinopathy. Mean serum IgM 3569 +/-1767 and a mean s.v of 2.5 +/- .7 (24 patients)
- Group 2: dilated veins and/or peripheral hemorrhages; a mean serum IgM of 5,442 mg/dL +/- 1625 (range of 2,950 to 8,440 mg/dL) and a mean SV of 3.1 cp range was 2.1-4.7cp. (18 patients)
- Group 3: peripheral and central retinal hemorrhages accompanied by dilated veins, optic nerve head edema, and venous sausaging; a mean serum IgM of 8,515 mg/dL +/- 3241) (range of 5700 to 12,400 mg/dL) and a mean SV of 5.6 cp. Range 3.8 to 8cp 4 patients

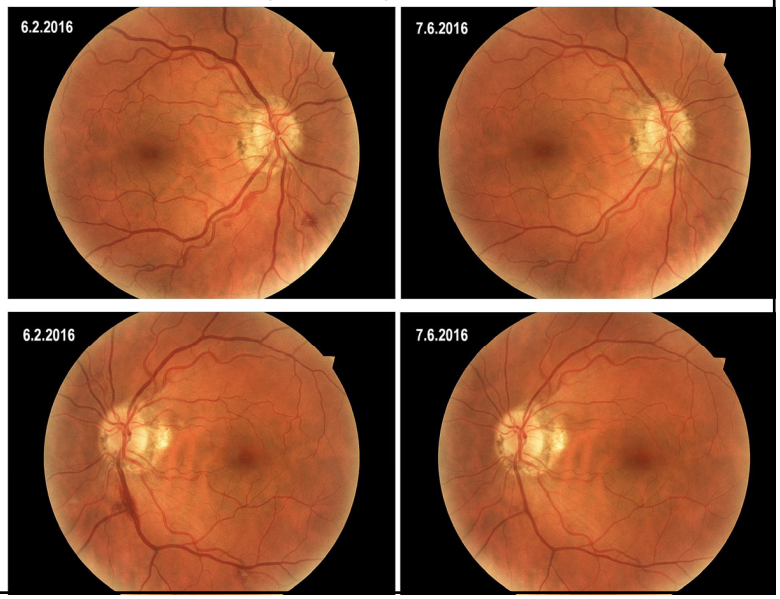
37

Study continued

- *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).*
- This study concluded that retinal changes were found in patients with SV values as low as 2.1; however, these changes did not produce any 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

38

Retina and OCT scans show dramatic improvement after 5 pheresis treatments. Optic nerve is normal.



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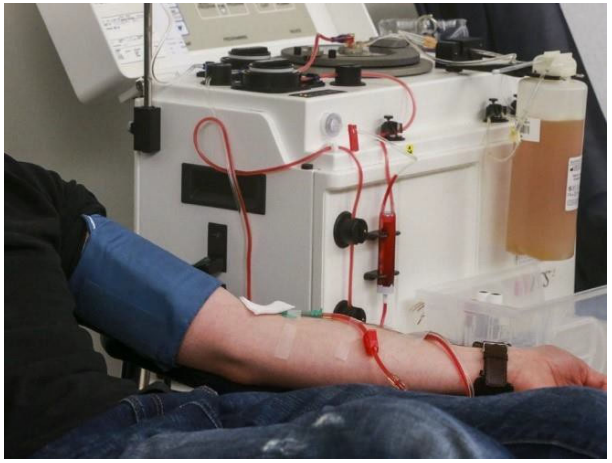
Plasmapheresis



40

Questions do we have the Answers???

- The question becomes, “Should a patient be treated if their IgM is 4,000 mg/dL, 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. What if a patient has an IgM concentration of 10,000 and both eyes look fine??????

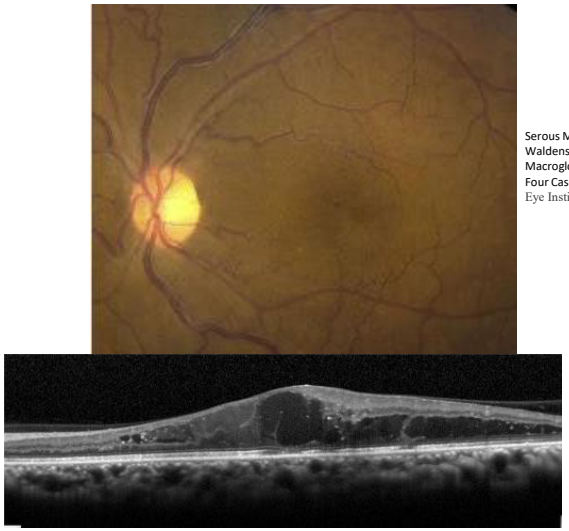
41

Also with Waldenstrom

- You can also get a “central serous type” maculopathy - a serous retinal detachment of the macula
  - It is believed that the high IGM may actually seep fluid out of the retina.
- Central Serous is the formation of a split is the sensory retina
- Other causes of this sensory detachment can be idiopathic, steroids, or subretinal neovascularization

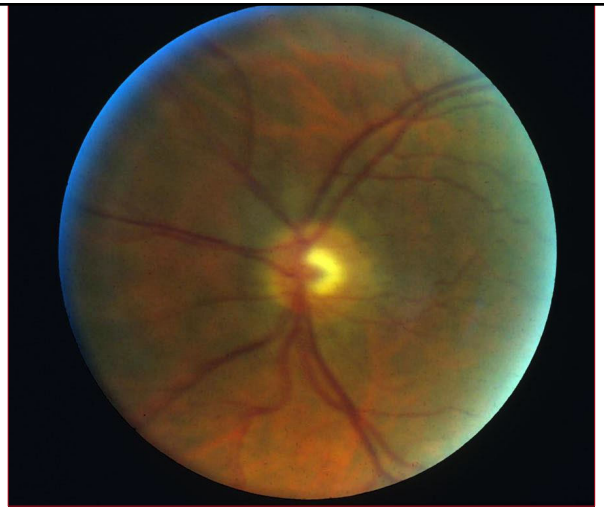
42

Serous Macular Detachment



Serous Macular Detachment in Waldenstrom Macroglobulinemia: A Report of Four Cases - Paul S. Baker Wills Eye Institute

43



Cataract

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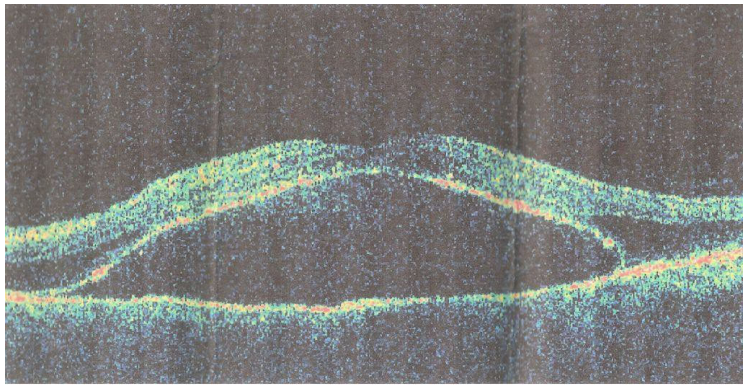

OCT of a serous macular detachment from a WM patient

OCT of a patient who actually was operated on for cataracts but indeed the patient had WM maculopathy

45

Pathophysiology

- Previous reports have shown that excess IgM is directly deposited in the neurosensory retina and subretinal space.
- The increased concentration of extracapillary protein in the neurosensory retina and the subretinal space would lead to increased osmotic pressure gradient toward the extracellular space.
- This may result in increased transudation of fluid from retinal capillaries and inhibition of RPE pumping of the excess subretinal fluid.
- Thus, the pathogenic mechanism of serous detachment of the macula in immunogammopathy is probably an inability of the RPE pump to overcome the osmotic gradientcreated by excess extracellular IgM.

IMMUNOGAMMOPATHY MACULOPATHY ASSOCIATED WITH WALDENSTRÖM MACROGLOBULINEMIA IS REFRACTORY TO CONVENTIONAL INTERVENTIONS FOR MACULAR EDEMA Cagri G. Besirli, MD, PhD, Mark W. Johnson, MD Fall 2013;7(4):319-24. doi: 10.1097/ICB.0b013e31828ef0dc

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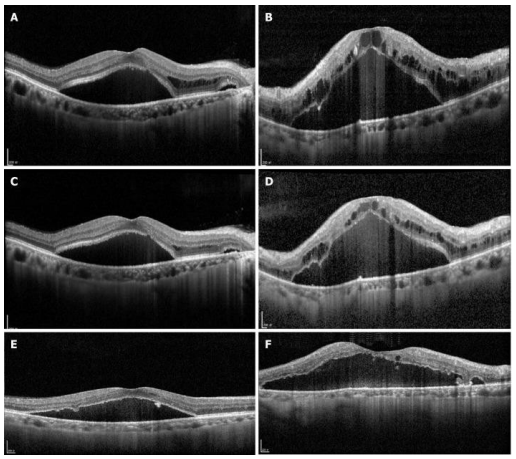


Optical coherence tomography angiography characteristics in Waldenström macroglobulinemia retinopathy: A case report.

Li J, Zhang R, Gu F, Liu ZL, Sun P.

World J Clin Cases. 2020 Dec 6;8(23):6071-6079. doi: 10.12998/wjcc.v8.i23.6071.

47

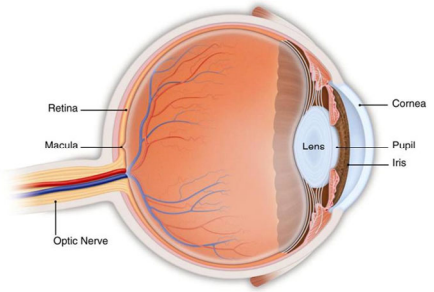
Discuss WM case

- 80 year old routine eye examination just wanted glasses
- Hemorrhage in far periphery
- HCT of 26.5 and living on transfusions
- Past HX of MGUS (monoclonal gammopathy of unknown significance)
- IGM 1990 and also IGG and IGA were low
- He was living on 80mg of steroids a day secondary to hemolytic anemia and had steroid induced diabetes
- I called oncologist- discuss results in lecture

48

Lets talk eye - front to back

- Normal aging versus Waldenstrom related issues.



49

Conjunctiva

- Clear mucous membrane with fine blood vessels
  - Lines the inside of eyelids
  - Covers the sclera (the white part of the eye)
- Can be affected by WM
  - Blood within the vessels of the conjunctiva may appear segmented and sluggish
  - Can only be seen under an instrument called a slit lamp.
- Such changes also happen with almost all types of anemia

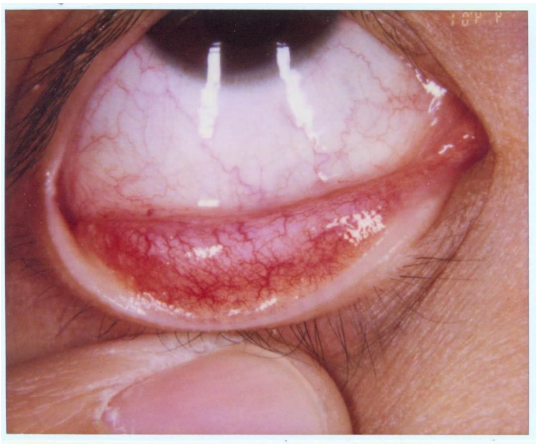
50

Conjunctival Pallor

- May be a simple screen for the presence of anemia although studies vary on sensitivity and specificity
- You can actually see gaps in between erythrocytes (red blood cells) when you do a careful slit lamp examination

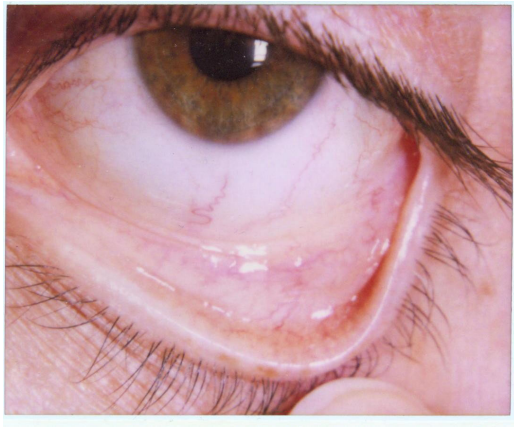
51

Normal Conjunctival Coloring



52

Anemic Conjunctiva (Pallor)



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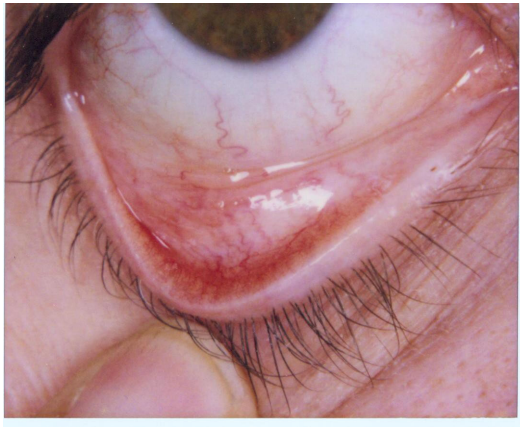
Anemic Conjunctiva (Pallor)



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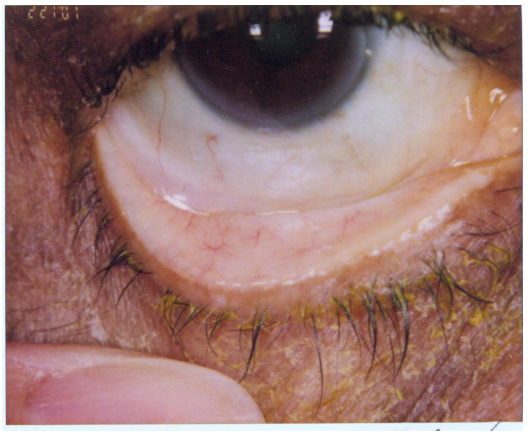
Anemic Conjunctiva (Pallor)



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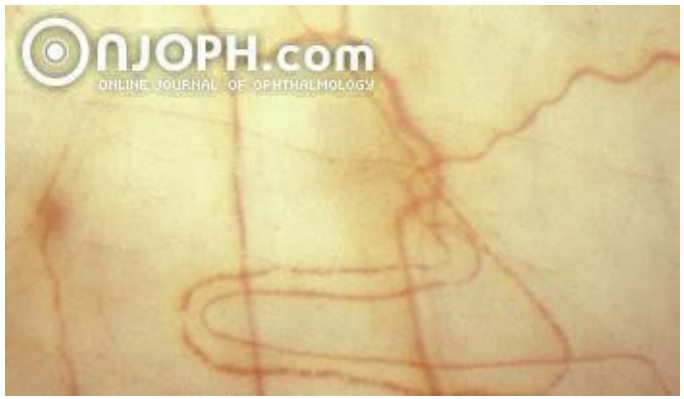
Anemic Conjunctiva (gaps between RBCs)



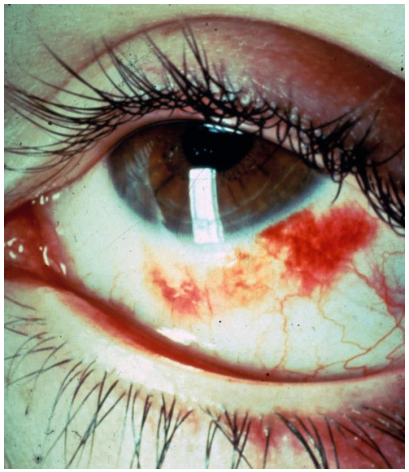
56

Subconjunctival Hemorrhages

- Common, whether or not you have WM
- Occur 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.
- Usually harmless, however, recurrent ones usually indicate a systemic issue
- Traumatic SCHs always need to be addressed
- **Call your doctor <u>immediately</u> if:**
  - **You are on blood thinners such as coumadin or your platelet counts are low**
  - **If your vision is ever down from a subconjunctival hemorrhage**

57

Sub-conjunctival Hemorrhage



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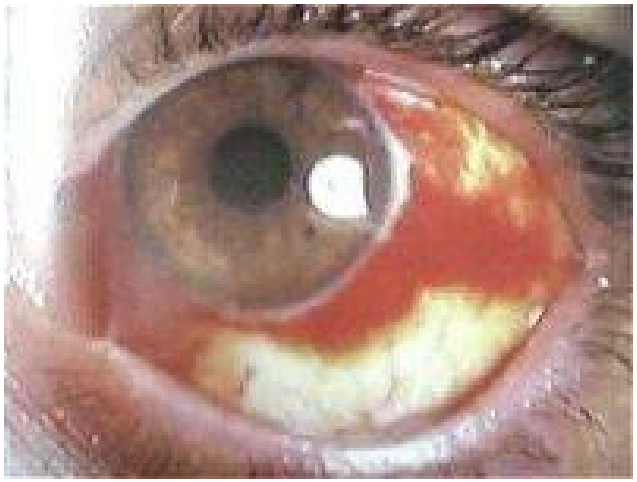


59

Plasmapheresis

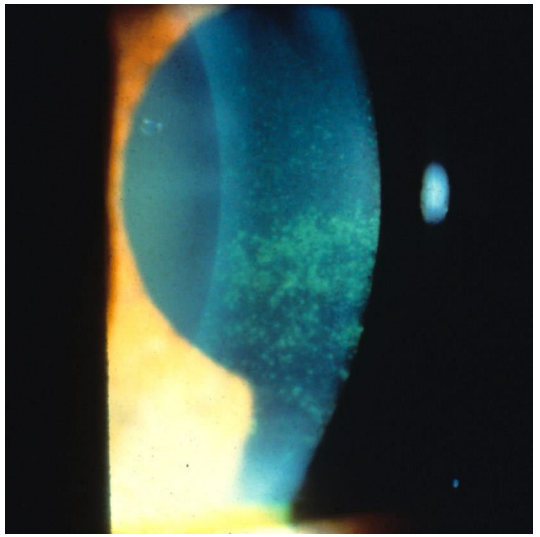
- Notify your doctor if you have a bright red eye after plasmapheresis since your PT (prothrombin time – a test for clotting ability) and PTT (partial thromboplastin time) may be dangerously off.
- This can not only cause a SCH but serious bleeding in the orbit which can lead to permanent vision loss

60

Dry Eye

- 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

61



62

What can be done for a dry eye?

- Find out what type of dry eye you have from your eye doctor and proceed from there
- Evaporative Dry
- Aqueous Deficient
- Mixed Etiology
- Systemic Medications

63

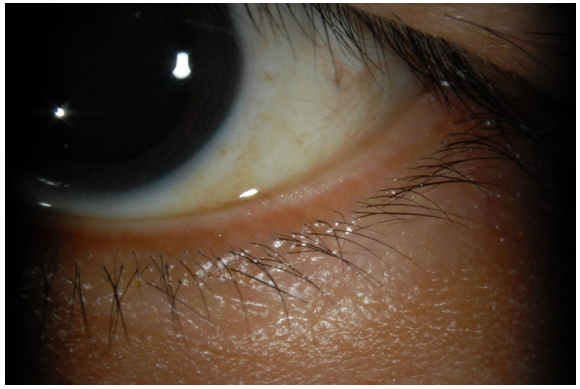
Treatment for Dry Eye

Varies **depending of type of dry eye – potential options:**

- Artificial Tears
- Warm compresses and lid scrubs
- Lipiflow
- Moisture chamber spectacles
- Restasis, Xiidra
- Low dose steroid drops
- Punctal Plugs
- Scleral contact lenses
- Autologous serum tears made from the plasma of your blood
- Amniotic membrane

64

Meibomitis



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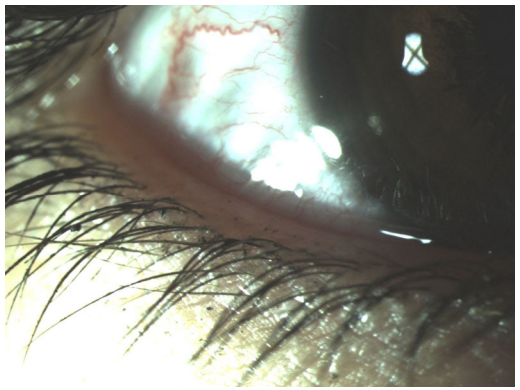
Make up

66

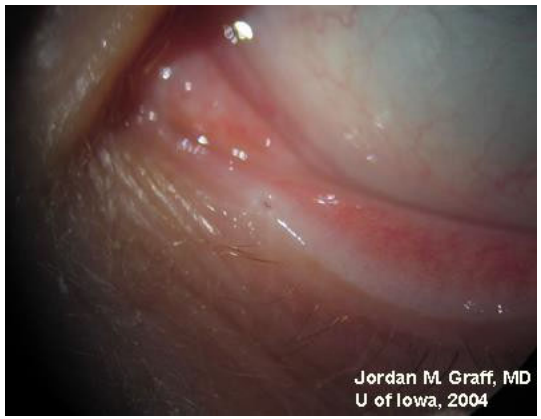
Makeup on lower lid



Patient Education

67

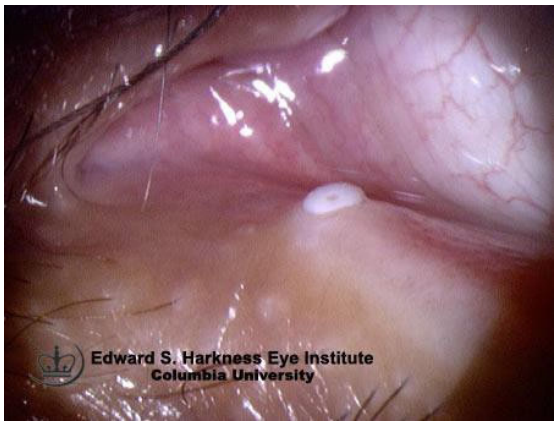
Inferior Puncta



68

Inferior Puncta with a Punctal Plug

Why would we want to do this?

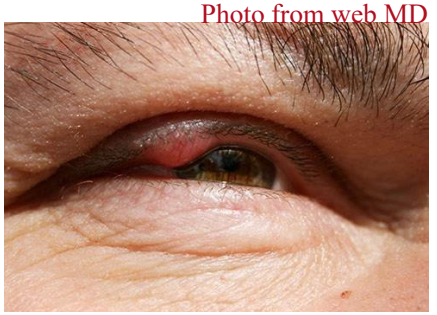


69

Bortizamab (Velcade)

- Proteasome inhibitor
- Associated with Chalazia

Photo from web MD



- Research article
- Open Access
- Published: 14 May 2019
- Management and outcomes of proteasome inhibitor
- associated chalazia and blepharitis: a case series
- Bonnie A. Sklar, Kalla A. Gervasio, Siyang Leng, Arnab
- Ghosh, Ajai Chari & Albert Y. Wu
- BMC Ophthalmology volume

70

Cornea

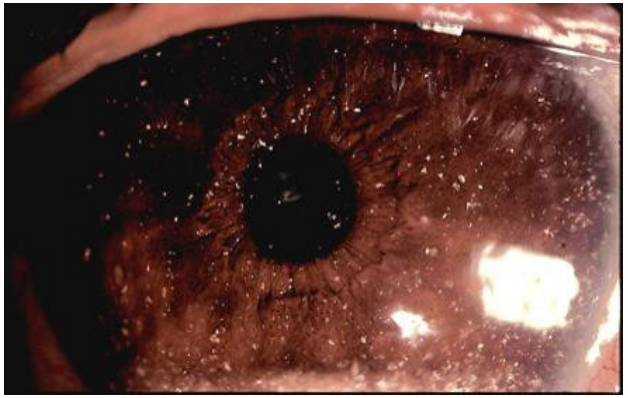
- Corneal crystalline deposits can occur
  - This is very rare
- Can happen in Multiple Myeloma and also just in MGUS

Corneal Crystals Secondary to
Lymphoplasmacytic Lymph
Ryan Petrucci, BSc (H...

71

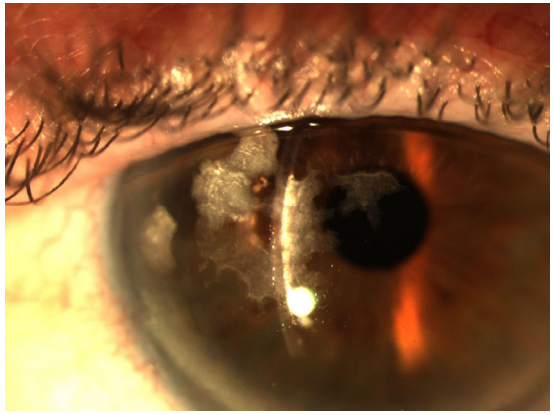
Corneal crystalline deposits

Courtesy of Joseph P. Shovlin, OD, FAAO



72

Corneal crystalline deposits

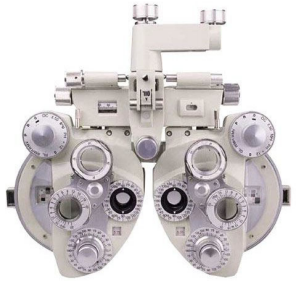


Courtesy of Joseph P. Shovlin, OD, FAAO

73

Refractive

- Going from front to back we next have the lens
- Increased blood sugar levels can change your refractive error
  - Usually becoming more near sighted (myopic) but some individuals can become more far sighted (hyperopic)
- High dose steroids can change blood sugar levels in some patients and lead to changes in refractive error
- Happens to both eyes at the same time
  - Unless you have had cataract surgery



74

The Lens

- Focusing - In our forties or early fifties 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 but we do not become presbyopic because of Waldenstrom.
- Anti-emetic medications, antihistamine drugs like Benadryl also decrease our ability to focus

75

The Lens - Cataracts

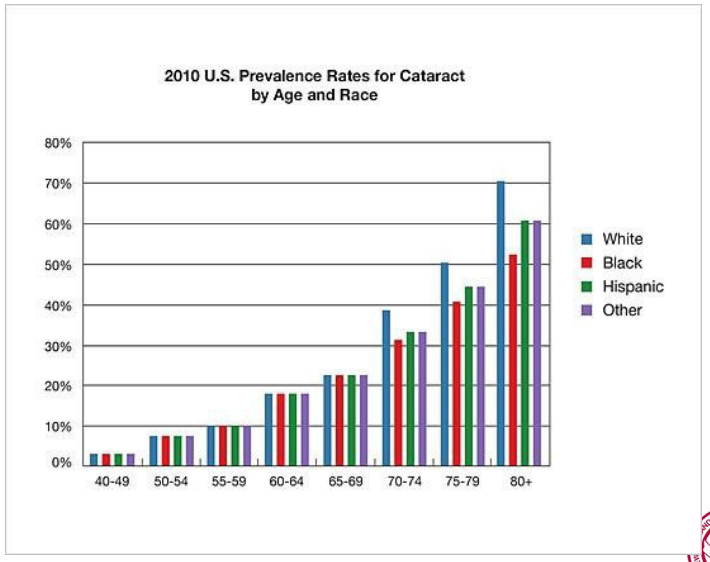
Framingham study showed:

- Prevalence of cataracts with vision loss
  cataract was defined as an opacity with dilated pupil and VA 20/30 or worse

  4.5% in persons ages 52-64
  18% in persons ages 65-74
  45.9% in persons ages 75-84

- Prevalence: 5.5 million people have cataracts interfering with their vision in the US (Research to Prevent Blindness)
- Incidence: 400,000 new cases of sight-reducing cataracts per year in the US (Research to Prevent Blindness)
- By the time they're 80 years old, more than half of Americans will have cataract or have had cataract surgery

76



NEI

77

Different Kinds of Cataracts

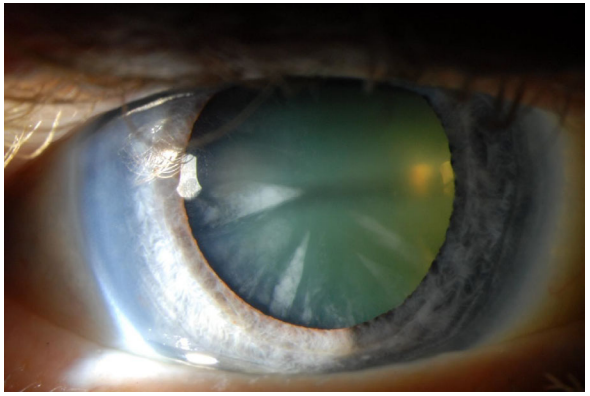
The three main age related cataracts are:

- Cortical
- Nuclear Sclerosis
- Posterior Subcapsular

78

Anterior Cortical and Nuclear Sclerotic Cataract

Photo courtesy of Mike Barlow, OD



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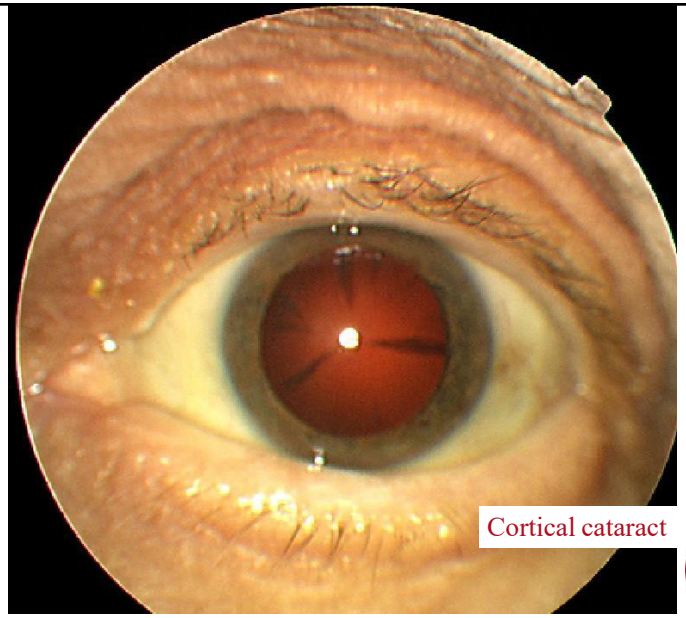
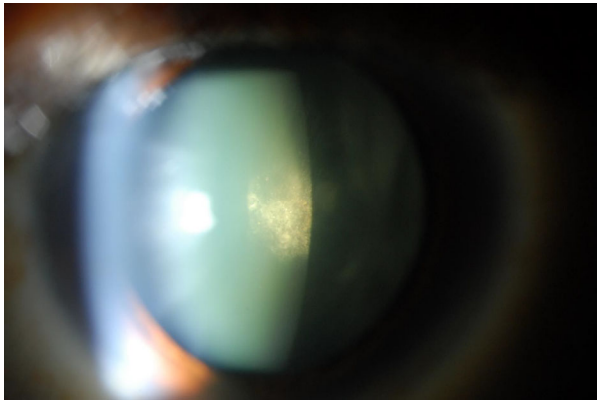


80

Nuclear Sclerotic and Posterior Subcapsular Cataract
Photo courtesy of Mike Barlow, OD



81

Cataracts: Posterior Subcapsular

Clinical Findings
- Dense granular appearance of posterior layers of lens cortex
- Early appearance described as iridescent sheen, which later becomes more granular and plaque-like
- Central opacities and vacuoles
- Often located along visual axis

Pathophysiology
- Epithelial cell proliferation at pole with fluid filled areas within
- Associated with UV exposure and steroids
- Occurs earlier than NS or cortical

- Most visually distressing type
- Reduced acuity at near because as you age or read, the pupil gets small (Miosis effect) and with miosis many times you are looking right through the cataract

82

Posterior Subcapsular Cataracts (PSC) Controversial

- A study found that 75% of the patients receiving more than 15 mg/day of prednisone for more than one year have PSC. JAMA 1960:174:166- 171
- Certainly other studies vary in percentage to as low at 11%
- 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 of a risk for cataract formation.

83

Steroids

- Intravitreal
- Topical steroids
- Oral
- Inhaled

- Naturally dose and duration are important
- Steroids are associated with PSCs

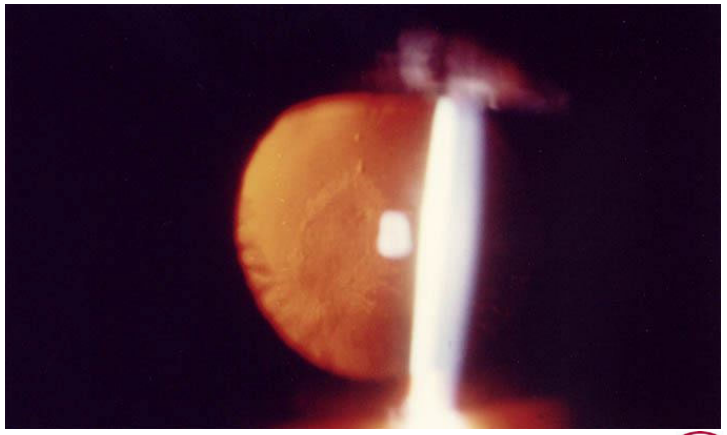
84

Steroids – Pathophysiology of PSC

- Lens epithelial cells seem to express a steroid binding protein and then gene expression occurs which appears to lead to:
  - Cell proliferation
  - Cell differentiation
  - Cell apoptosis
  - Modulation of glucose metabolism
  - Modulation of membrane channels
  - Direct and indirect modulation of signal transduction
- In summary the etiology of steroid induced cataracts may be secondary to transactivation and transrepression of genes as well as modulation of the activity of proteins
- *Ocular Disease Mechanism and Management Levin*

85

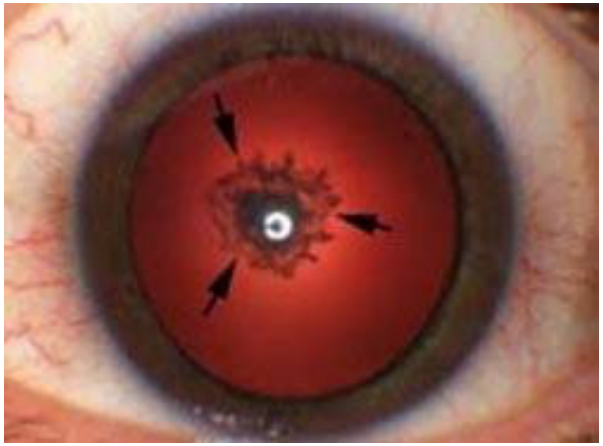
Cataracts: Posterior Subcapsular



www.eyeweb.org/cataract.htm

86

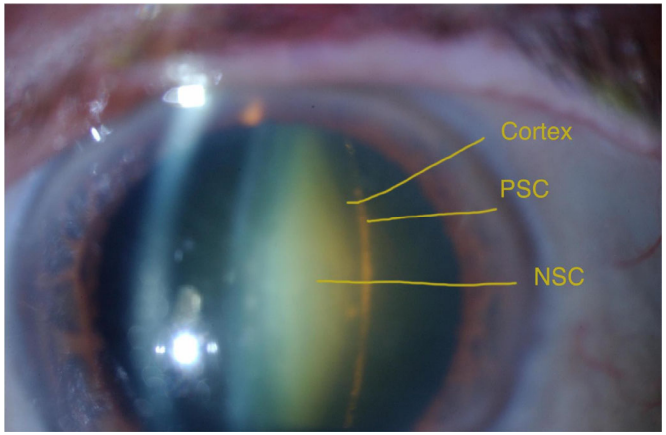
Cataracts: Posterior Subcapsular



Riley

87

Combination Cataract



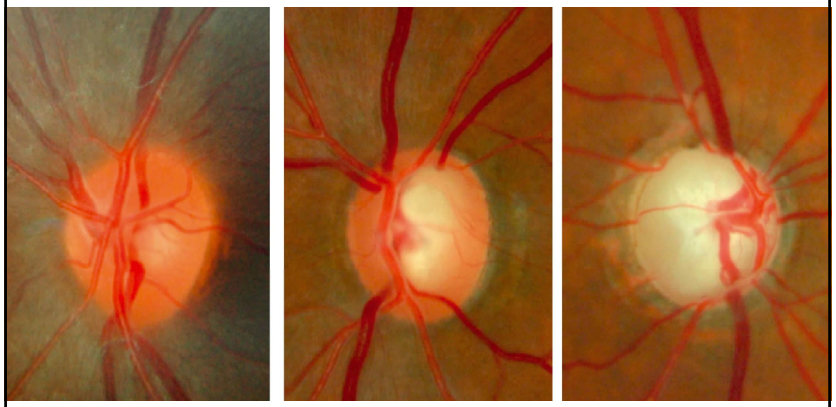
88

Glaucoma

- 2% of patients over 40 have glaucoma
- About 1/3 of patients on steroids will have an increase in eye pressure
- Low tension glaucoma is thought to be a vascular problem of blood insufficiency or an autoimmune problem rather than glaucoma resulting from increased IOP.
- Patients who are more prone to low tension glaucoma often have systemic hypotension, anemia, cardiovascular problems, and sleep apnea. High serum viscosity (SV) also appears to be a risk factor
- ?? Low tension and autoimmune neuropathy

89

Let us discuss these nerves



. © Heiko Philippin (left and middle), Rupert Bourne (right)

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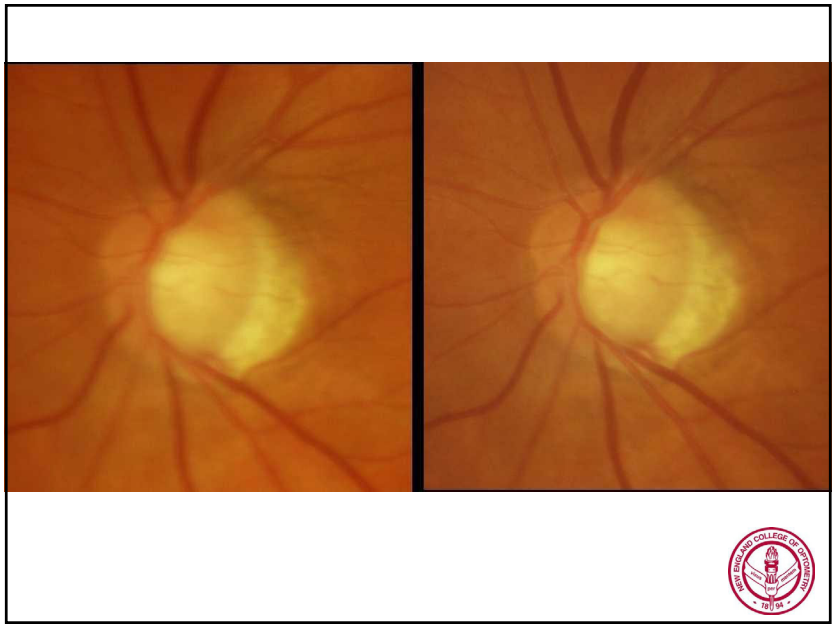

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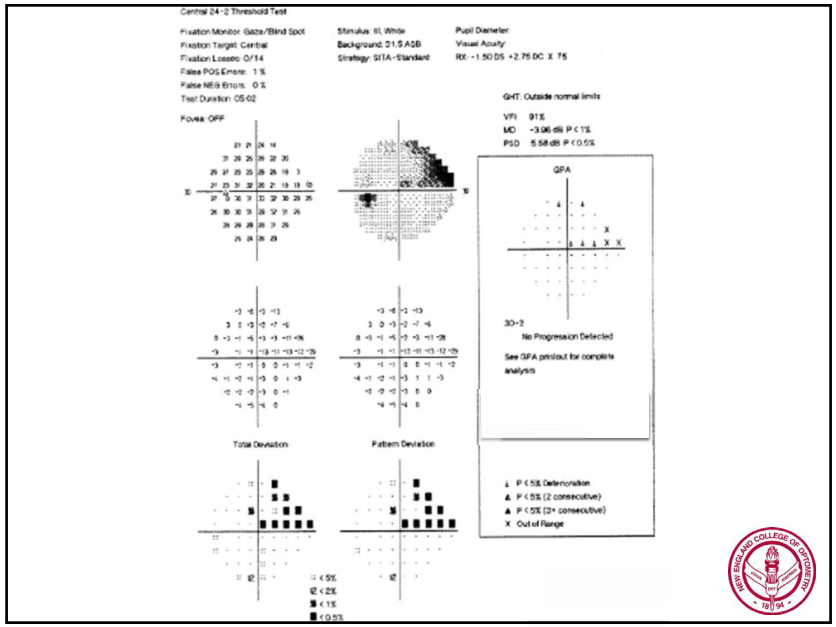
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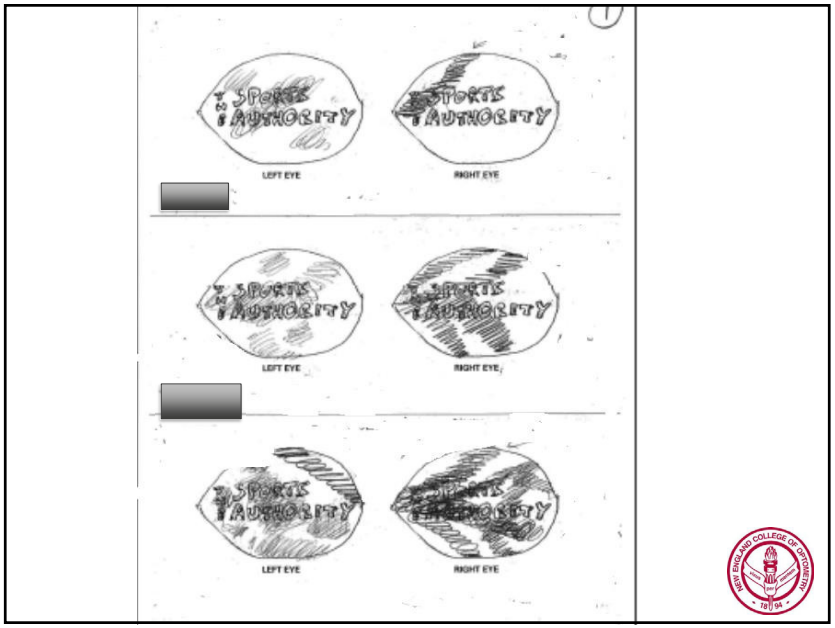
Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/14
False POS Errors: 1 %
False NEG Errors: 0 %
Test Duration: 05:02
Fovea: OFF
Stimulus: III, White
Background: 31.5 ASB
Strategy: SITA-Standard
Pupil Diameter:
Visual Acuity:
RX: -1.50 DS +2.75 DC X 75
GHT: Outside normal limits
VFI 91%
MD -3.06 dB P < 1%
PSD 5.58 dB P < 0.5%
GPA
30-2
No Progression Detected
See GPA printout for complete analysis
Total Deviation
Pattern Deviation
P < 5% Deterioration
P < 5% (2 consecutive)
P < 5% (3+ consecutive)
X Out of Range
< 5%
< 2%
< 1%
< 0.5%

92



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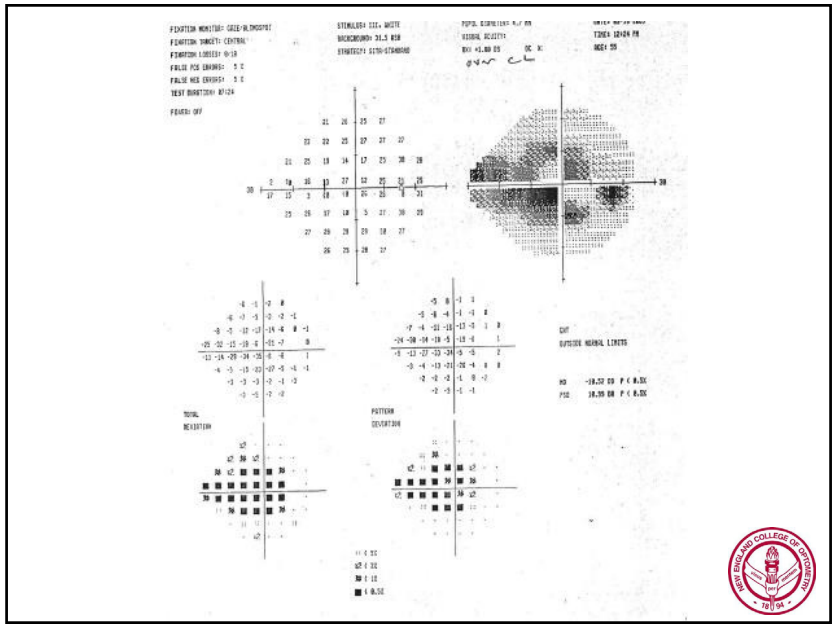

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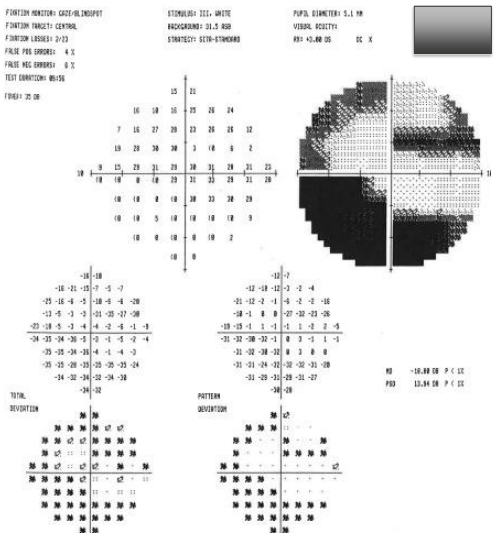


95

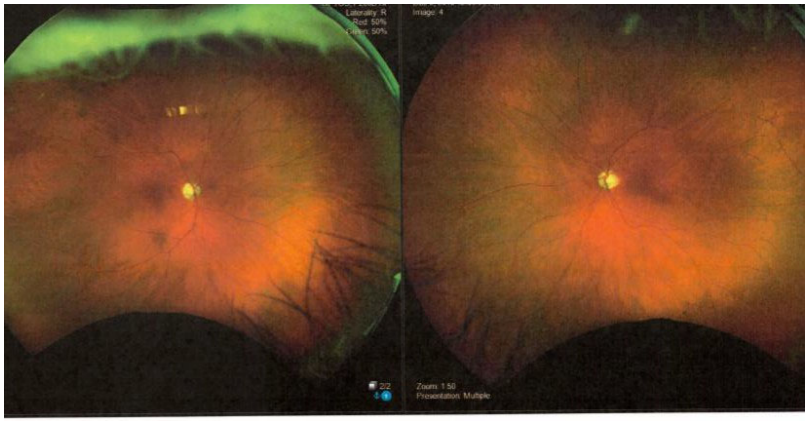
- Bing Neel Syndrome , a rare complication of WM, results from tumor cell infiltration of the CSF or the deposition of WM-associated IgM within the brain and spinal cord
- Ocular
  - Nerve palsies, optic atrophy, orbital involvement

96

Nerve Palsies

- This can result in binocular diplopia (double vision).

97



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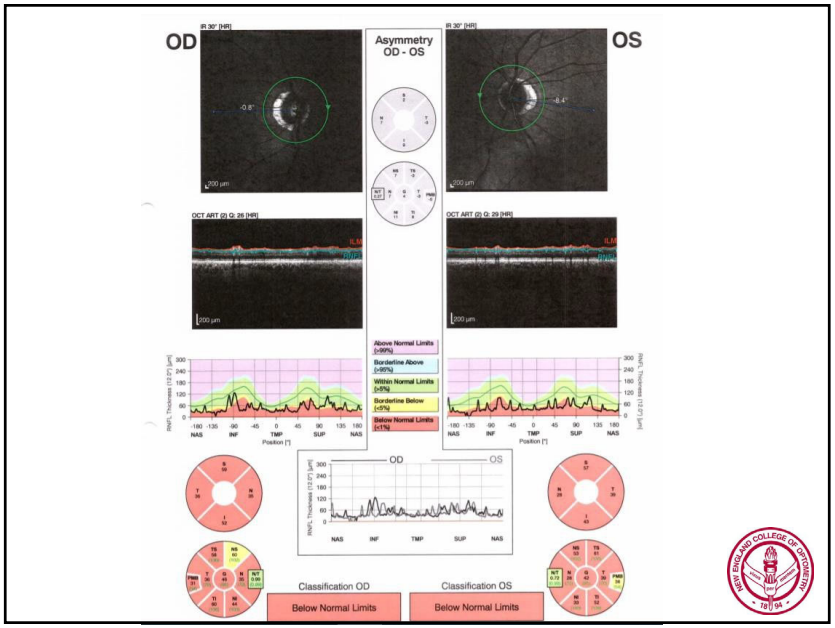
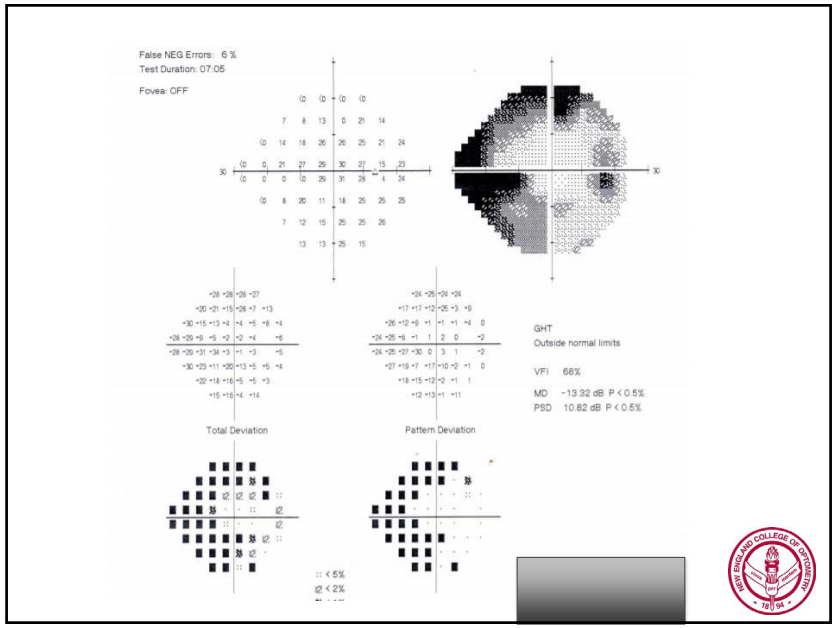

OD
OS
Asymmetry
OD - OS
Above Normal Limits (>99%)
Borderline Above (>97%)
Within Normal Limits (>5%)
Borderline Below (<5%)
Below Normal Limits (<1%)
Classification OD
Below Normal Limits
Classification OS
Below Normal Limits

99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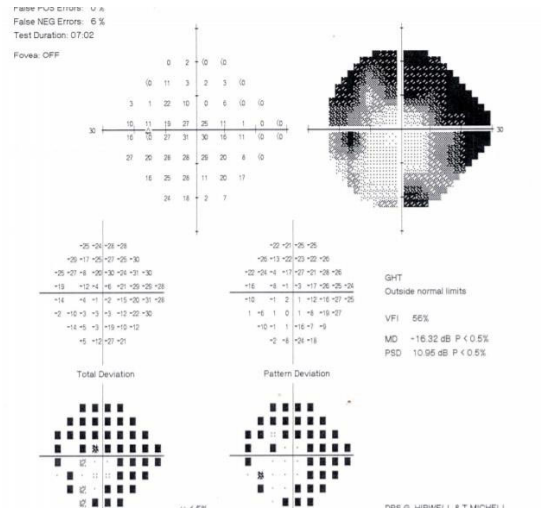
Test Duration: 07:05
Fovea: OFF
GHT
Outside normal limits
VFI 68%
MD -13.32 dB P < 0.5%
PSD 10.82 dB P < 0.5%
Total Deviation
Pattern Deviation

100



101

My Recommendations regarding Eye Care for Patients with WM

- Get an annual or semi-annual complete dilated eye exam with a doctor who is comfortable examining a WM patient
- Try to get a digital copy of retinal photos
- 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 glaucoma workup should be done.
- Have an OCT before cataract surgery
- WM patients with elevated IgM, certainly above 3,000 mg/dL, should have an OCT of the macula region, especially if they have unexplained visual acuity loss.
- Any sudden loss of vision call your eye doctor immediately

102

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105

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106