Waldenstrom Macroglobulinemia and the Eye: A Case Report and Review

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Abstract

Waldenstrom macroglobulinemia (WM) is a rare, malignant lymphoproliferative B-cell disorder that causes an excessive buildup of monoclonal protein. WM is associated with an excessive buildup of immunoglobulin M (IgM), which can cause blood hyperviscosity and damage many organ systems. This case report describes a patient who was followed annually but rapidly developed posterior pole and significant midperipheral hemorrhages secondary to a hyperviscosity condition of the retina. Ocular manifestations associated with WM will be reviewed and management suggestions will be presented. Management of this condition is dependent on macular involvement and requires co-management with an oncologist.

KEY WORDS:
Hyperviscosity retinopathy, Waldenstrom Macroglobulinemia

INTRODUCTION

Waldenstrom macroglobulinemia is a malignant lymphoproliferative B-cell disorder that causes an increased production of immunoglobulin M (IgM).[1] Buildup of IgM will manifest in many organ systems, and 17% of patients show symptoms of hyperviscosity syndrome.[2] Hyperviscosity retinopathy is a type of manifestation in the eye. Consequently, WM should be co-managed with an oncologist and retina specialist. The earliest retinal presentation will be bilateral dilated veins and midperipheral hemorrhages. As IgM levels increase, the retina may show posterior pole hemorrhages, macular edema and/or detachments, optic nerve edema, and retinal vein occlusions. These findings mimic more common retinal conditions such as diabetic retinopathy and ocular ischemic syndrome. When hyperviscosity retinopathy is suspected, laboratory testing and closer follow-up care are recommended.

CASE DESCRIPTION

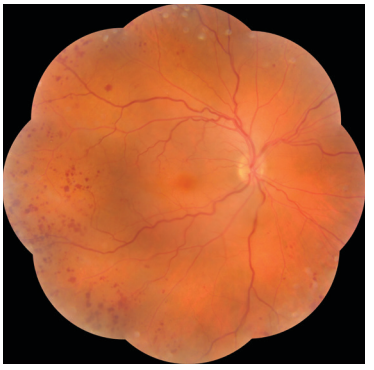
A 69-year-old Caucasian male presented to the clinic for a six-month follow-up appointment secondary to mild non-proliferative diabetic retinopathy (NPDR). His previous retinal exam findings included two perimacular hemorrhages in the right eye and one perimacular hemorrhage with one dot hemorrhage in the temporal periphery of the left eye. The patient had been diagnosed with Type 2 diabetes 27 years previously. He reported good compliance with his metformin HCl, dapagliflozin, and exenatide. His last glucometer reading was 141 mg/dl, while his last HbA1c was 7.1%. He also had hyperlipidemia treated with atorvastatin. His oncologist followed him for Waldenstrom macroglobulinemia and reported that the patient had received chemotherapy treatment 10 years previously. His ocular history included bilateral cataract surgery and dry eye syndrome.

His best corrected visual acuity was 20/20 in both eyes. Amsler grid findings did not exhibit any metamorphopsia or scotomas in either eye. The pupils were 4 mm in dim illumination without an afferent pupillary defect. Confrontations were full to finger count right and left eye, and extraocular motilities were normal.

His anterior segment showed mild superficial punctate keratitis and bilateral temporal incision scars in the cornea. Intraocular pressures were 18 mm Hg in both eyes. Dilation revealed bilateral posterior vitreous detachments. The cup-to-disc ratio was 0.20 right eye and 0.25 left eye. Both optic nerves were round,

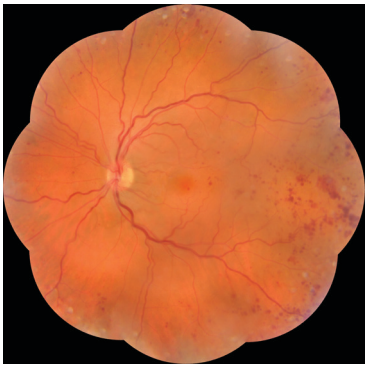
healthy, distinct and without disc edema or neovascularization. The macula was clear in the right eye, while the left eye had one perimacular dot hemorrhage inferior. There was no evidence of retinal thickening or exudates in either macula. Veins in both eyes were moderately dilated and tortuous. The right eye posterior pole had a few scattered dot hemorrhages in all quadrants and two flame hemorrhages nasal to the optic nerve, however the midperiphery to periphery had multiple dot and blot hemes in all quadrants.

Figure 1: *Right eye. Note dilated and tortuous veins. Significant dot, blot and flame hemorrhages in midperiphery.*



The left eye posterior pole had a few scattered dot hemorrhages in all quadrants, one large blot hemorrhage temporal to the macula, and one flame hemorrhage between the macula and optic nerve, with most dot and blot hemorrhages in the midperiphery to periphery.

Figure 2: *Left eye. Note dilated and tortuous veins. Significant dot, blot and flame hemorrhages in midperiphery.*



Neither eye showed any signs of neovascularization, cotton wool spots, exudates or intraretinal microvascular abnormalities. Stratus time domain optical coherence tomography showed a central thickness of 207 microns in the right eye and 214 microns in the left eye. Neither eye exhibited any signs of edema or retinal pigment epithelial damage.

Based on the clinical presentation, it was determined that he had mild NPDR without macular edema in both eyes, but also exhibited retinal findings characteristic of hyperviscosity syndrome. The hyperviscosity retinopathy was likely secondary to WM. He was informed to return in four months for repeat dilation, fundus photography, and spectral domain OCT (SD-OCT), and was told to bring his most recent bloodwork including complete blood count, serum protein electrophoresis and IgM records from his oncologist.

The patient's IgM value was elevated to 2,870mg/dL (Table 1). His serum protein electrophoresis showed elevated total protein of 8.5g/dL, increased gammaglobulin of 2.39g/dL, and an M spike of 19.5% (Table 2). His serum viscosity was measured at 2.0 centipose. Despite mildly elevated lab findings, the oncologist restarted him on chemotherapy with bendamustine and rituximab, after learning of his ocular manifestations. His serum protein electrophoresis three months after chemotherapy (Table 2) indicated no M-spike, normal gammaglobulin and a decrease in IgM to 178mg/dL (Table 1). He never returned to the eye clinic for follow-up. However, in a follow-up phone call, he reported that he was being managed by an outside retina specialist who did not recommend any macular treatment and that the retinal bleeding had also improved.

Table 1: *IgM values*

	1 month prior to evaluation	Initial visit	2 months after treatment	3 months	6 months	1 year
Immunoglobulin M *Standard Range 50 - 300 mg/dL*	2,700	2,870	1,010	178	83	53

Table 2: *Serum protein electrophoresis values*

Component	Standard Range	Initial visit	3 months post-chemotherapy
Total Protein Electrophoresis	*6.0 - 8.0 g/dL*	8.5 g/dL	7.4 g/dL
Albumin Concentration	*3.50 - 4.70 g/dL*	4.02 g/dL	4.87 g/dL
Albumin %	*50.0 - 78.0 %*	47.3 %	65.8%
Alpha 1	*0.20 - 0.40 g/dL*	0.28 g/dL	0.12 g/dL
Alpha 1 %	*0.6 - 6.0 %*	3.3 %	2.5%
Alpha 2	*0.40 - 0.80 g/dL*	1.05 g/dL	0.81 g/dL
Alpha 2 %	*6.0 - 14.0 %*	12.4 %	11%
Beta	*0.50 - 1.00 g/dL*	0.76 g/dL	0.77 g/dL
Beta 1 %	*5.0 - 14.0 %*	8.9 %	10.4%
Gamma Concentration	*0.60 - 1.20 g/dL*	2.39 g/dL	0.76 g/dL
Gamma %	*9.0 - 18.0 %*	28.1 %	10.3%
M Spike	*g/dL*	1.66 g/dL	Not detected
M Spike %	*%*	19.5 %	Not detected

DISCUSSION

Hyperviscosity syndrome can be caused by a large increase in the cellular or acellular components of blood. Conditions with cellular component problems of the blood include polycythemia vera, thrombocytosis, and leukemia. Deformed blood cells in sickle cell anemia or spherocytosis can also cause hyperviscosity. Increased acellular components such as protein are found in WM, multiple myeloma and cryoglobulenemia. WM and multiple myeloma are most likely to cause hyperviscosity syndrome, and in turn hyperviscosity retinopathy.[3] Hyperviscosity retinopathy presents as midperipheral dot and blot hemorrhages along with dilated retinal veins in both eyes. In advanced cases, the retina will exhibit signs of posterior pole hemorrhages, tortuous blood vessels with venous sausaging, optic disc edema and serous macular detachments.[4] This case is interesting in that it presented very similarly to severe NPDR. Severe NPDR is classified as four quadrants of intraretinal hemorrhages, two quadrants of venous beading, or one quadrant of intraretinal microvascular abnormalities.[5] Diabetics may also exhibit signs of diabetic macular edema. NPDR, unlike hyperviscosity retinopathy, presents more in the posterior pole and extends peripherally. Also, patients with severe NPDR would also have a higher HbA1c value.[6] Another differential is ocular ischemic syndrome (OIS), which typically presents with unilateral mid-peripheral retinal hemorrhages and dilated non-tortuous veins. These patients may complain of decreased vision, transient monocular vision loss and/or ocular pain. OIS can present with anterior segment findings including rubeosis irides, anterior segment inflammation, or episcleral congestion. The clinical presentation of this case also mimics a non-ischemic central retinal vein occlusion (CRVO) due to the presence of retinal hemorrhages in all four quadrants and dilated tortuous retinal veins. However, patients with CRVO typically have diffuse flame and/or blot hemorrhaging in the posterior pole which extend peripherally, reduced vision, and associated macular edema. Bilateral CRVO is a rare clinical manifestation, but has been noted in hyperviscosity syndromes such as WM.[7] Hyperviscosity retinopathy was the likely diagnosis based on good visual acuity, tortuous venous dilation and multiple midperipheral dot and blot hemorrhages. Due to retinal presentations similar to diabetes, CRVO and OIS, it is important to order ancillary testing including CBC with differential, glucose

testing, blood pressure measurement and a carotid Doppler. If hyperviscosity retinopathy is suspected, additional laboratory testing including quantitative immunoglobulins, serum protein electrophoresis, and serum viscosity should be requested to properly diagnose the systemic etiology and refer accordingly.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Waldenstrom macroglobulinemia is a type of non-Hodgkin Lymphoma. It is considered a malignant lymphoproliferative B-cell disorder resulting in elevated IgM production and corresponding monoclonal protein in the blood. Buildup of protein in the body can lead to blood hyperviscosity and corresponding systemic conditions including excessive bleeding, visual ailments and nervous system problems.[8] The International Workshop Criteria for the diagnosis of WM are as follows: (1) IgM monoclonal gammopathy of any concentration, (2) bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation, and (3) intertrabecular pattern of bone marrow infiltration.[9] While the exact cause is unknown, 90% of patients with WM have been seen to have a mutation in the MYD88 gene.[10] Also, excess production of interleukin-6 by bone marrow dendritic cells appears to play a role in the development of WM.[11]

WM is a rare disease with an incidence of 3 cases per million people per year in the US. Approximately 1,000 to 1,500 Americans are diagnosed each year. Most of these patients are Caucasian males over the age of 70.[11]

Ocular complications are relatively common in patients with WM.[12] Anterior segment changes such as sluggish or segmented blood flow through the conjunctival blood vessels may be seen. Consequently, subconjunctival hemorrhages may occur.[13] WM can also have an autoimmune effect on the lacrimal gland causing dry eye syndrome. Fundoscopic abnormalities are found in approximately 30-40% of patients with WM.[14] Common exam findings include bilateral venous congestion, retinal vein dilation, venous tortuosity, intraretinal hemorrhages, microaneurysms, flame-shaped hemorrhages, retinal vein occlusions, optic disc edema and serous macular detachments.[8,12]

Retinal changes can be correlated with lab tests. Mean serum viscosity of 3.1 centipose and an IgM level of 5,442 mg/dL will be the first indications of retinal change. Symptomatic retinal changes involving the posterior pole occur with an average serum viscosity of 5.6 centipose.[15] Pars plana cysts may also develop in patients with WM.[13] There is no characteristic macular OCT pattern in WM, but scans have shown harmonious and regular cystoid pattern and deposits around photoreceptors,[16] which may appear hyper-reflective. Fluorescein angiography (FA) in WM patients with serous retinal detachments do not show leakage.[17] The current hypothesis behind the formation of these detachments is that venous congestion in the choroid and retina will cause choroidal hyperpermeability. This, in turn, will cause breakdown of the blood-RPE barrier, small tears of the RPE, and leakage of fluid into the subretinal space.[18] The retinal detachments have been treated with intravitreal injections of anti-VEGF antibodies and dexamethasone implants, without much change in the subretinal fluid.[14, 19] Retinal improvement is mainly seen when treatment is targeted toward IgM reduction. Currently, the two main ways oncologists treat WM are chemotherapy and/or biologic therapy. Biologic therapy drugs assist the body's immune system to fight the cancer.[11]

CONCLUSION

Waldenstrom macroglobulinemia is a rare systemic disease that causes hyperviscosity of the blood. This can manifest in the eye in multiple ways, including subconjunctival hemorrhages, dry eye syndrome, and hyperviscosity retinopathy. This mimics common retinal conditions such as those caused by diabetes or hypertension. Patients with bilateral tortuous dilated veins and significant hemorrhages seen more in the midperiphery than the posterior pole should be managed carefully, with special attention to hyperviscosity syndrome as a differential diagnosis. If hyperviscosity syndrome is suspected, laboratory tests including a CBC with differential, quantitative immunoglobulins, serum protein electrophoresis and serum viscosity should be ordered. If the results are abnormal, the patient should be co-managed with the proper specialist. In patients with suspected or confirmed WM, SD-OCT should be performed to rule out small serous retinal detachments, optic disc edema or macular edema. Although anti-VEGF has minimal effectiveness in improving subretinal fluid related to WM, co-management with a retinal specialist would be beneficial as FA may aid in visualizing leakage and assist in differentiating other retinal diseases. While there are no formal guidelines for the required frequency of retinal exams for patients with WM, we suggest that examinations every 3-4 months would be reasonable. At each visit, patients should have their IgM levels monitored, undergo a dilated eye exam with a SD-OCT, and be co-managed with their oncologist. ●

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