

Teaching Case Report

Subconjunctival Hemorrhage and Diabetes: A Lesson Learned

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Abstract

Every year in the United States more adults become legally blind due to diabetes than due to any other disease. This teaching case report reviews the etiology, pathophysiology, clinical presentation, management and treatment options of diabetic retinopathy. This case specifically highlights the need for detailed history-taking and adherence to an appropriate dilation schedule.

Key Words: subconjunctival hemorrhage, diabetes, diabetic retinopathy

Background

Diabetic retinopathy is the number-one cause of new cases of legal blindness in the United States among people who are 20 to 74 years old.^{1,2} Approximately 28.5% of U.S. diabetics over the age of 40 have some form of diabetic retinopathy and approximately 4.4% of those diabetics over 40 have vision-threatening diabetic retinopathy.² This correlates to 3.8% of the U.S. population having some form of diabetic retinopathy and 0.6% of the U.S. population having vision-threatening diabetic retinopathy.²

For the patient involved in this case, a crucial dilated exam may have been bypassed because the chief complaint had been properly identified, treated and explained without dilation. She presented with an acute subconjunctival hemorrhage, a common occurrence that often looks much worse than it really is. A brief history revealed recent fits of intense coughing and sneezing. Both are valsalva maneuvers that are common causes of subconjunctival hemorrhages.^{3,4,5,6} An in-depth history revealed that the patient was a poorly controlled diabetic, who had been diabetic for 15 years and had not had a dilated eye exam in the last 18 years, although she had had an eye examination without dilation two years prior. Dilated fundus exam revealed proliferative diabetic retinopathy.

This teaching case report discusses the importance of detailed history-taking and the need to treat the whole patient, not just the patient's chief complaint. This case specifically highlights taking a thorough patient history, including history of present illness, health history, social history and history of previous eye care. The eyecare provider can then use that information to properly identify and treat any and all conditions that fall within the scope of practice and efficiently refer the patient to the proper specialists if necessary.

Student Discussion Guide

Case presentation

10/27/2009

The patient, a 52-year-old Caucasian female, presented to the clinic complaining of a "blood red" left eye start-

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ing a couple of days ago. The patient noted a scratchy feeling and pain when moving the eye and reported no particular event associated with the beginning of the redness. However, she did report a recent bout with allergies causing excessive coughing and sneezing. The patient's last eye exam was about two years ago but her eyes were not dilated at that visit. Her last dilated exam was more than 18 years ago.

The patient's medical history was positive for type 2 diabetes, hypertension and seasonal allergies. The patient had been diabetic for approximately 15 years and reported "moderate" control with her most recent fasting blood sugar being 180 mg/dL and glycosylated hemoglobin A1C (HbA1c) being approximately 8.0%. The patient's current medications were metformin, valsartan, triamterene/hydrochlorothiazide and fexofenadine. She was unsure of the dosages for any of her current medications. The patient stated that she was allergic to penicillin, sulfa drugs, cats, dogs and dust.

At this point, the working diagnosis of subconjunctival hemorrhage was made based on patient history and external evaluation. However, because the patient was diabetic, had not had any form of eye exam in two years and had not had been dilated in more than 18 years, a comprehensive eye exam was performed.

The entering distance visual acuities, as measured with her habitual spectacle correction, were 20/40 OD with no improvement with pinhole (NIPH) and 20/50 OS with NIPH. Similarly, near acuities were 20/40 OD, OS. Extraocular muscles were full with pain OS when looking in direction of the redness. She reported no diplopia in any direction of gaze. Her pupils were equal, round and reactive to light with no afferent pupillary defect noted. No Amsler grid defects were reported in either eye. Slit lamp examination confirmed the working diagnosis of subconjunctival hemorrhage temporally OS. The rest of the anterior segment was within normal limits OU, with no neovascularization of the iris (NVI) noted. Intraocular pressures taken with Goldmann applanation tonometry were 14 mmHg OD and OS. Blood pressure measured on the right arm with the patient seated

was 140/82 mmHg.

The patient was dilated with 1.0% tropicamide and 2.5% phenylephrine. Fundus examination with 78D lens and binocular indirect ophthalmoscope revealed proliferative diabetic retinopathy OU. The patient had multiple dot and blot hemorrhages in all four quadrants OU, hard exudates OU, neovascularization in the posterior pole OU and a vitreous hemorrhage with tractional retinal detachment in the inferior peripheral retina OS. Optic discs had .3/.3 cup/disc ratios OU with possible neovascularization of the disc OU.

The patient was diagnosed with uncontrolled diabetes with ophthalmic complications, proliferative diabetic retinopathy OU, a tractional retinal detachment OS and subconjunctival hemorrhage OS. She was immediately referred to a retinal specialist for further evaluation and treatment of the diabetic retinopathy. The patient was educated on the benign and self-limiting nature

of the subconjunctival hemorrhage. The importance of advanced retinal care was stressed, as was the importance of tight control of her diabetes. The patient was scheduled to be seen by a retinal specialist on the following day. A referral letter was sent to the retinal specialist and an additional report was sent to the patient's internist updating them on the ophthalmic manifestations of the diabetes. **Table 1** summarizes the subsequent treatment the retinal specialist provided.

Key Concepts

1. Importance of a thorough patient history
2. Importance of treating the entire patient and not just the chief complaint
3. Management and care of subconjunctival hemorrhage
4. Pathophysiology, stages and management of diabetic retinopathy

Table 1
Summary of Care from a Retinal Specialist
Between 10/29/2009 and 08/31/2011

10/29/2009	Visual acuity was 20/40 OD, 20/50 OS Retinal specialist performed intravenous fluorescein angiography (IVFA) OU IVFA confirmed diagnosis of proliferative diabetic retinopathy (PDR) OU and led to further diagnosis of diabetic macular edema (DME) OU Intravitreal anti-vascular endothelial growth factor (VEGF) treatment, bevacizumab, was given OU Retinal specialist suspects the patient will eventually require significant panretinal photocoagulation (PRP) and possibly a vitrectomy in one or both eyes
12/02/2009	Visual acuity 20/30 OD, 20/50 OS Intravitreal bevacizumab injections performed OU
12/16/2009	PRP performed OS
04/14/2010	Visual acuity 20/30 OD, 20/30 OS PRP performed OD
09/14/2010	IVFA performed to monitor progress; test showed stable retinopathy, but that further treatment would be required
10/06/2010	IVFA and optical coherence tomography (OCT) performed; tests showed stable diabetic retinopathy, but that the patient had developed epiretinal membranes (ERMs) OU, with subsequent macular edema Visual acuity 20/40 OU Intravitreal bevacizumab injections performed OU
10/20/2010	PRP performed OD
10/27/2010	PRP performed OS Retinal specialist recommended the patient be monitored every 3 months by an optometrist; patient elected to see her original optometrist
03/29/2011	IVFA performed and showed that PDR and DME were stable Visual acuity 20/30 OD, 20/40 OS
04/27/2011	PRP performed OS Intravitreal triamcinolone acetonide injection performed OS
05/11/2011	PRP performed OD
08/23/2011	IVFA performed and showed that PDR was stable OU, but DME was worse OD
08/31/2011	Focal grid laser photocoagulation performed OD Intravitreal triamcinolone injection performed OD Retinal specialist recommended the patient have IVFA and OCT performed annually to monitor her diabetic retinopathy

5. Role of the primary care optometrist in the management of diabetes and diabetic retinopathy

Learning Objectives

1. To gain knowledge of subconjunctival hemorrhage, including causes, treatment and management options and indication for further testing including lab testing
2. To gain knowledge of diabetic retinopathy, including the grading of diabetic retinopathy, the use of ancillary testing in the management of diabetic retinopathy and when ancillary testing is warranted
3. To gain an understanding of the primary care optometrist's role in the management of systemic diabetes, specifically the questions to ask every patient with diabetes, the normal ranges for common diabetic test results, timing and frequency of dilated eye exams and the pertinent negatives of a diabetic eye exam
4. Introduction to some of the procedures performed by retinal specialists in the treatment of diabetic retinopathy
5. To understand the role that primary care optometrists play in properly monitoring sight-threatening diseases such as diabetes

Discussion Questions

1. Background knowledge of subconjunctival hemorrhage, diabetes and diabetic retinopathy
 - a. Describe the pathophysiology of a subconjunctival hemorrhage
 - b. List the risk factors for subconjunctival hemorrhage
 - c. Describe the retinal findings at each stage of diabetic retinopathy
 - d. Describe the pathophysiology of diabetes
 - e. Discuss why the eyes are affected by diabetes
 - f. List the pertinent negatives of a diabetic eye exam and describe why they are important
 - g. What are the different treat-

ments for diabetic retinopathy? What is the ultimate goal of all diabetic retinopathy treatment? Discuss how the different treatments achieve this goal

2. Primary care optometrist's role in the management of this patient
 - a. What was the appropriate treatment for this patient's chief complaint?
 - b. Discuss the need and the timing of a dilated eye exam after a patient has been diagnosed with diabetes. What accounts for the discrepancy between type 1 and type 2?
 - c. Discuss the need for yearly eye exams for diabetics. Should all diabetics be dilated even if they just need new glasses?
 - d. Discuss the role of the primary care optometrist in the management of patients with diabetes. What warrants communication with the patient's primary care physician or endocrinologist? What warrants referral to a retinal specialist?
 - e. Discuss the management of this patient. Was the referral appropriate and timely? What else, if anything, must be done to ensure this patient's ocular and systemic issues are properly addressed?
 - f. Discuss a primary care optometrist's role in the continued management and treatment of this patient
3. Critical thinking
 - a. Why would a patient present with a chief complaint as minor as a subconjunctival hemorrhage, but maybe not seek treatment for something as major as proliferative diabetic retinopathy?
 - b. What is the role of the primary care optometrist in the management of diabetes?
 - c. What do the patient's retinal findings indicate about the patient's systemic health?
 - d. What could have been done by

this patient's current optometrist, former optometrist and/or primary care physician that could have prevented this ocular progression of the patient's diabetes?

- e. Recreate this situation and give an example of proper patient education for the patient

Educator's Guide

The educator's guide contains the information needed to discuss the case. Individual educators should tailor the information to a level appropriate for students in the first and second year of optometric education.

Subconjunctival hemorrhage

Subconjunctival hemorrhages, such as the one that initially prompted this patient to present to our eye clinic, are diffuse or local areas of focal blood underneath the conjunctiva.³⁻⁵ The area of blood appears bright red and is visually alarming to the patient, but patients are usually otherwise asymptomatic. The blood can completely obstruct the view of the underlying sclera, and 65.1% of all subconjunctival hemorrhages are located inferior-temporally.⁷ The prevalence of subconjunctival hemorrhage increases with age, largely due to the increased prevalence of risk factors.⁸ It is estimated that approximately two-thirds of subconjunctival hemorrhages occur after the patient rises from a sitting or resting pose.⁹ The primary risk factors and/or underlying etiologies include hypertension, diabetes, high cholesterol, anti-coagulative therapy, surgery, bleeding disorders, trauma or valsava maneuvers.^{3-5,9}

The clinical examination should begin with a detailed history of present illness, including any present allergies or flu symptoms (i.e., sneezing, coughing), any recent strenuous activity or valsava maneuvers, anti-coagulative medications, bleeding disorders and history of recurrences.^{3,4} Further examination should include an in-office blood pressure measurement, biomicroscopic evaluation and, in some cases, a dilated fundus examination if the underlying etiology of the condition cannot be determined based on the history.^{3,4}

Subconjunctival hemorrhages start off bright red and gradually change to a

yellowish-green color as they resolve, much like a bruise.⁶ Rarely, permanent conjunctival or limbal blood staining can occur.⁶ Usually no treatment is required and they will resolve on their own within 2-3 weeks.³⁻⁶ Artificial tears and cold compresses can be used to alleviate any mild ocular irritation.³⁻⁵ If appropriate, the use of blood thinning medications, vitamins and herbal supplements should be discontinued. Anti-platelet or anti-coagulant medications prescribed by a patient's medical doctor should not be discontinued. If the use of an analgesic is necessary, then over-the-counter acetaminophen should be recommended because it has analgesic properties without the anti-coagulant properties of other over-the-counter analgesics. Heavy lifting or other strenuous activities should be avoided.³ If the hemorrhage lasts for longer than three weeks or recurs, the patient should be referred to his or her primary care provider for further evaluation to rule out underlying conditions such as blood clotting disorders or other systemic blood disorders.^{5,6} As our patient's presentation was most likely related to her uncontrolled diabetes in addition to her history of sneezing and coughing, the remainder of this discussion focuses on diabetes and diabetic retinopathy.

Diabetic retinopathy

Diabetic retinopathy is the leading cause of preventable blindness in adults aged 20 to 74 in the United States.^{1,2} Some degree of diabetic retinopathy occurs in nearly all of those who have been diabetic for more than 15 years.¹ Among U.S. diabetics, the prevalence of retinopathy is greater in men than women, with 31.6% of males and 25.7% of females having some degree of diabetic retinopathy. Diabetic retinopathy is more common in minorities in the United States with 38.8% of diabetic, non-Hispanic blacks developing retinopathy, 34.0% of diabetic Mexican Americans developing retinopathy and 26.4% of non-Hispanic whites developing retinopathy.² Other estimates indicate that the prevalence of diabetic retinopathy can be as high as 50% of those with type 2 diabetes, and up to 86% of those with type 1 diabetes.¹⁰ The prevalence of diabetic retinopathy is slowly decreasing in developed coun-

tries due to improved control of the risk factors. Unfortunately, the prevalence of diabetic retinopathy is increasing worldwide in developing countries due to changing lifestyles.¹⁰

The main risk factors for developing diabetic retinopathy include increased duration of diabetes, hypertension, elevated blood glucose levels, high cholesterol and insulin dependence.^{2,10,11} Reduction of blood glucose levels, blood pressure and serum lipid levels is likely to reduce the incidence of diabetic retinopathy.^{2,10,11} Conversely, while controlling these factors may increase life expectancy, this increased longevity increases patients' chances of developing diabetic retinopathy over their lifetime.¹⁰

Other risk factors for diabetic retinopathy include intravascular fluid overload, hypoalbuminemia and anemia. Intravascular fluid overload secondary to congestive heart failure or renal failure causes increased vascular hydrostatic pressure. Hypoalbuminemia due to renal loss of albumin or decreased albumin production can cause decreased vascular osmotic pressure. Anemia causes further retinal hypoxia, which exacerbates diabetic retinopathy.¹¹ Often these factors are not considered when taking a diabetic history. It is important to ask diabetic patients about any heart failure and about serum lipid levels, and to check for ankle swelling, measure blood pressure and evaluate retinal vessel caliber for hypertensive changes.¹¹

Pathophysiology of diabetic retinopathy

The blood vessels, neurons and glial cells of the retina are made up of a variety of different cell types, which help comprise the blood-brain barrier. Diabetic damage to these cells can result in retinopathy from a breakdown of the blood-brain barrier.¹¹

In diabetes, endothelial cells and pericytes of the retinal blood vessels can become damaged and lead to diabetic retinopathy.¹¹ Endothelial cells comprise most of the blood-retinal barrier and help regulate homeostatic blood flow.¹¹ Pericytes, located between the endothelial cells, are modified smooth muscle cells that aid in dilation and contraction of retinal blood vessels to accommodate blood flow.¹¹ Diabetic damage

to the tight junctions between the vascular endothelial cells causes increased vascular permeability and a degradation of the blood-brain barrier.^{10,11} The blood-brain barrier prevents the retinal tissue from coming in contact with the inflammatory and cytotoxic elements found in blood.¹¹

The blood-brain barrier is comprised of special proteins called occludins and claudins, which act like adhesive material between the endothelial cells that make up the functional barrier.¹¹ These proteins span the entire plasma membrane and restrict the flow between endothelial cells. Studies have shown that diabetes can reduce the number of these proteins and cause a breakdown of the blood-brain barrier.¹¹

Müller cells and astrocytes are two main types of glial cells of the retina.¹¹ Glial cells are support cells that help regulate retinal metabolism and modulate the functions of neuroretinal cells and retinal blood vessels. They are similar to tissue macrophages in that they are very sensitive to changes in retinal homeostasis and can rapidly become phagocytic when this homeostasis is altered, as in diabetic retinopathy.¹¹ Müller cells span the entire retinal thickness and act to regulate extracellular ionic balance, glutamate metabolism and overall neuronal function.¹¹ Astrocytes are located within the retinal nerve fiber layer and have end feet that wrap around retinal blood vessels and ganglion cells to provide them with support. Astrocytes also express tight junction proteins that contribute to the blood-retinal barrier.⁸ Diabetic damage also causes a reduction in glial fibrillary acidic protein (GFAP), altering the structural stability of astrocytes and affecting retinal vascular function. This is thought to exacerbate vascular permeability and cause changes in blood flow.^{1,11} Diabetes can also alter Müller cells, causing them to proliferate and form an epiretinal membrane.¹¹

Neuronal cells are cells that perform phototransduction, the formation and transduction of nerve impulses from visible light.¹¹ There are four main types of neuronal cells in the retina: photoreceptors, bipolar cells, amacrine cells and ganglion cells.¹¹ In states of distress, these neuronal cells can become altered and/or reduced. This reduction of cells

manifests as vision changes that precede the vascular changes detected on fundoscopic examination. Early electroretinogram (ERG) changes can be seen in those with diabetes before any clinical retinopathy is present.^{1,11} Changes in color vision and contrast sensitivity can also occur before clinical retinopathy is present; these changes are especially present with blue-yellow contrast and in low-light conditions.¹ Some believe these changes can predict a future progression of retinopathy better than clinical characteristics.¹ Early diabetic damage causes apoptosis of retinal ganglion cells, reducing the number of ganglion cells and decreasing the thickness of the inner retina.^{1,11} Further diabetic damage results in retinal swelling, which causes the thickening of the inner retina seen in diabetic edema. It was once thought that diabetic retinopathy was solely a vascular disease, but the early damage that precedes any vascular events proves diabetic retinopathy is both a vascular disease and a neurodegenerative disease. After macular edema has resolved, many patients with diabetic retinopathy continue to have decreased vision and this neurodegenerative component of the disease accounts for some of this decreased vision.¹

The retina has a higher metabolic demand than any other part of the central nervous system. This high oxygen demand combined with the delicate nature of the retinal vasculature causes the retina to be very susceptible to hypoxia.¹⁰ When areas of the retina become hypoxic, a cytokine called vascular endothelial growth factor (VEGF) is expressed by the neurons and glial cells of the retina.^{1,10,11} This cytokine is a potent biogenic permeability factor that causes a reduction in the number of occludins and claudins.^{1,10} This reduction in proteins results in an increase in vascular permeability, which is designed to be a survival factor for neurons.¹ The vessels become leaky in the body's attempt to deliver more blood to the hypoxic areas. VEGF also induces endothelial cell proliferation, promotes cell migration and inhibits apoptosis by reducing tumor necrosis factor. These processes result in the formation of new capillaries bringing more blood to the hypoxic area.¹ This angiogenesis, or neovascularization, results in new vessels that

are very permeable and rupture easily, causing further retinal hemorrhaging and microaneurysms. The angiogenic vessels can also form fibrovascular membranes that cause tractional forces on the retina and create the potential for a tractional retinal detachment.¹⁰

In addition to the hyperpermeability of retinal vasculature and vascular angiogenesis, retinal hypoxia can also be caused by microthrombosis.¹⁰ Thrombus and/or embolus formation can occur in retinal capillaries and lead to retinal non-perfusion. Thrombosis can be induced by changes in the vascular wall structure, changes in blood components and changes in blood flow.¹⁰ Diabetes can cause abnormal blood flow, coagulation and fibrinolysis, promoting clot formation. Platelets, fibrin, and leukocytes all play an important role in this clot formation, and their expression is altered in diabetes.¹⁰

Diabetic retinopathy also has an inflammatory component. Chronic inflammation is inflammation of prolonged duration in which active inflammation, tissue destruction and gliosis occur simultaneously.¹¹ Non-proliferative diabetic retinopathy (NPDR) is characterized by vasodilation, increased blood flow, tissue edema and increased vascular permeability followed by neovascularization and gliosis.¹¹ Thus, NPDR meets most criteria for chronic inflammation. It is not currently known why diabetes inflicts an inflammatory response in the retina, but it is important to realize that this is occurring so proper treatment, such as corticosteroids, can be administered.¹⁰

Clinical presentation of diabetic retinopathy

The clinical signs of diabetic retinopathy include a wide array of hemorrhages, new vessel growth and retinal edema. The main symptom of diabetic retinopathy is reduced vision, but this generally doesn't manifest until the retinopathy is advanced and irreversible damage has already occurred.^{1,10-12}

The least severe vascular lesions are the microaneurysms and dot/blot hemorrhages. Microaneurysms are focal dilations of the retinal veins, which occur in the inner nuclear or outer plexiform layers of the retina.^{12,13} If the microaneurysms rupture they produce dot/blot

hemorrhages.¹⁴ Microaneurysms and dot/blot hemorrhages are small and confined to a specific location by intraretinal compression. Because dot/blot hemorrhages are located deep in the retina relative to other types of hemorrhages, they may take slightly longer to resolve.¹³ Both are associated with microvascular edema and are caused by defects of the pre-venular retinal capillaries.¹³ These lesions can be easily detected via dilated fundus examination. The use of a red-free filter may help improve contrast of the blood against the retina to ease detection of small hemorrhages.

Another relatively minor form of retinal hemorrhage is the "flame-shaped" hemorrhage.^{12,13} They are sometimes termed nerve fiber layer (NFL) hemorrhages because they occur in the nerve fiber layer of the retina. These hemorrhages reflect the structure and organization of the nerve fibers because the blood is being squeezed within the axons of the ganglion cells, which causes them to take on a characteristic flame-shaped appearance.¹³ These hemorrhages are associated with pathology affecting the superficial and peripapillary capillary beds and usually resolve within six weeks. Flame hemorrhages are also commonly found in hypertensive retinopathy.¹³ Flame hemorrhages can also be easily detected by fundoscopic examination.

Other hemorrhages that can occur in diabetes are sub-hyaloid hemorrhages and pre-retinal hemorrhages. Sub-hyaloid hemorrhages are located on the surface of the retina, between the posterior vitreous face and the interior limiting membrane of the retina. Pre-retinal hemorrhages are located posterior to the interior limiting membrane, but anterior to the nerve fiber layer, thus contained within the retina.¹³ However, it is often difficult to discern exactly where the blood is lying, so these terms are used interchangeably. These hemorrhages are often called "boat-shaped" or "D-shaped" hemorrhages because the blood is pulled inferiorly by gravitational forces and contained by the structure of the curved retinal vessels, taking on a characteristic rotated-D or boat-hull appearance.¹³ These types of hemorrhages are associated with pathology affecting the major

retinal blood vessels or superficial capillary beds. Sub-hyaloid and pre-retinal hemorrhages typically result from the rupture of new vessels that are formed in angiogenesis.¹³ These hemorrhages usually clear up relatively quickly, but the underlying neovascularization and fibrosis remain.¹³ These hemorrhages can be detected by fundoscopic examination, but utilization of optical coherence tomography (OCT) technology may help determine their exact location.

Other serious types of hemorrhages that can occur in the retina are sub-retinal or sub-retinal pigment epithelium (RPE) hemorrhages. Sub-retinal hemorrhages are located in the space between the neurosensory retina and the RPE. Sub-RPE hemorrhages are located between the RPE and Bruch's membrane.¹³ They are easy to differentiate from sub-hyaloid or pre-retinal hemorrhages because they have a much darker coloration and the retinal vessels can often be clearly seen running over the hemorrhage.¹³ Sub-retinal hemorrhages usually have a poorly defined, amorphous shape due to the absence of firm attachments in the space between the neurosensory retina and the RPE, whereas sub-RPE hemorrhages tend to have well-defined borders due to the tight junctions between RPE cells.¹³ These types of hemorrhages are of significant concern because they can cause neurosensory or RPE detachments. They resolve very slowly and often cause structural changes in the photoreceptors, which results in permanent loss of vision.¹³ These hemorrhages are most commonly caused by choroidal neovascular membranes (CNVM), which arise from the underlying choroidal vascular supply.¹³ These hemorrhages can also be detected by fundoscopic examination, but use of OCT is also beneficial to determine the location of the hemorrhage. Intravenous fluorescein angiography (IVFA) can be used to determine whether a CNVM is present, but OCT has limited the need for this procedure because it is faster, easier and less invasive than IVFA.

Non-hemorrhagic findings in diabetic retinopathy include cotton wool spots (CWS) and hard yellow exudates (HYE).¹⁴ CWS are a result of capillary occlusion in the retinal nerve fiber lay-

er. They cause a reduction in axoplasmic flow in the nerve fibers, resulting in the swelling of and then the ischemic death of neural tissue.¹⁴ They have a characteristic fluffy, white, cotton-like appearance and are usually less than 1 disc diameter in size, but can be up to 2 to 4 disc diameters in size.¹⁴ CWS are almost always found adjacent to a major retinal vessel, and are commonly seen in hypertensive patients in addition to diabetic patients. The presence of CWS could indicate rapid progression of retinopathy.¹⁴ HYE are accumulations of serum lipoproteins that have leaked out of damaged retinal vasculature and are condensed in the outer plexiform layer of the retina.¹⁴ As these accumulations become more concentrated, they take on a characteristic hard, waxy appearance. Microaneurysms are the principal source of this fluid plasma leakage into the retina. It is thought that the attachments between Müller cells are the reason that this concentration of lipoproteins occurs.¹⁴ These inter-photoreceptor adhesions restrict the movement of larger molecules, such as lipids and proteins, but allow water to pass towards the choroid so it can become resorbed into circulation, leaving behind the plasma byproducts. It is possible for HYE to become reabsorbed, either spontaneously via phagocytosis by macrophages or following laser photocoagulation treatment.¹⁴

Other clinical signs of diabetic retinopathy include vascular changes. Early changes include vessel tortuosity and dilation in response to reduced retinal circulation. These changes can be important indicators of potential proliferative disease.¹⁴ Venous beading can occur in conditions of increased retinal hypoxia. More serious vascular changes include intra-retinal microvascular abnormalities (IRMA) or neovascularization.¹⁴ IRMA are the hallmark sign of severe NPDR. IRMA are essentially new vessels that are contained within the retina and have not penetrated the internal limiting membrane of the retina.^{14,15} They form secondary to progressive vessel damage, which causes blood to be shunted through small capillary networks that were not intended for such high blood flow.¹⁴ This results in distension and irregularity of these capillaries. If the new vessel penetrates the

internal limiting membrane, it becomes true neovascularization, which is the defining trait of proliferative diabetic retinopathy (PDR).^{14,15} If this new vessel growth is located on or within 1 disc diameter of the optic nerve head, it is termed neovascularization of the disc (NVD). If this new vessel growth is expressed elsewhere throughout the fundus, it is simply called neovascularization elsewhere (NVE).¹⁴ In conditions of global ischemia, neovascularization can extend anteriorly to the anterior angle or pupillary margin and grow over the surface of the iris; this is called neovascularization of the iris (NVI) or iris rubeosis.¹⁴ These different classifications of new vessel growth all have a similar delicate, wispy appearance, and are sometimes difficult to differentiate from IRMA without utilization of IVFA.^{3,4,15}

Given the complexity of diabetic retinopathy, it is difficult to classify its severity. The Early Treatment Diabetic Retinopathy Study (ETDRS) provided the gold standard in classification of diabetic retinopathy. The classification ranges in severity from mild NPDR to high-risk PDR, with several stages of severity in between. **Table 2** summarizes this classification.

Diabetic macular edema (DME) is the primary cause of vision impairment in diabetic retinopathy.^{1,10,11,14} As mentioned previously, increased permeability of retinal vessels causes a leakage of plasma fluid. This fluid initially accumulates in the outer-plexiform and inner-nuclear layers of the retina and eventually disperses throughout the entire retina.¹⁴ The underlying cause of DME is no different than the underlying cause of NPDR, but it is classified differently given the specialized structure and function of the macula.¹⁴ DME is more prevalent in type 2 than in type 1 diabetes, but the risk for diabetic macular edema for any diabetic is 30% after having the disease for 20 years.¹⁴ Macular edema is difficult to detect via direct ophthalmoscopy without the depth perception provided by fused binocular vision. Utilization of a diagnostic aspheric lens along with a slit lamp biomicroscope can aid in detecting this condition.¹⁴ If macular edema is suspected, IVFA or OCT should be performed to confirm the diagnosis.

The ETDRS group has defined DME vs. clinically significant macular edema (CSME).¹⁶ **Table 3** summarizes these characteristics.

Optometrist's role in diabetes management

As a primary eyecare provider, optometrists play an important role in the management of diabetes and monitoring for diabetic changes in the eye. Frequently, endocrinologists or general practitioners refer their diabetic patients to optometrists for a dilated fundus examination. This method of examination serves as a non-invasive way to view the retina and the retinal vasculature in real time. The status of the retinal vasculature is a valuable snapshot of the overall systemic control of the patient's diabetes. The presence of diabetic retinopathy may indicate microvascular dysfunction in other organ systems.²

A comprehensive diabetic eye examination should always start with a thorough history.^{3,4} The doctor should ask what type of diabetes the patient has, and when he or she was first diagnosed. This is important because, as we know, the duration of diabetes is a major risk factor for diabetic retinopathy.^{2,10,11} Up to 21% of patients with type 2 diabetes have retinopathy at the time the diabetes is diagnosed. Therefore, it is recommended that type 2 diabetics have comprehensive eye exams within 1 year of diagnosis and yearly thereafter. Type 1 diabetics over age 10 should have at least one comprehensive eye exam within 3-5 years of initial diagnosis and on a yearly basis thereafter. It is very rare for type 1 diabetics to have retinopathy within the first 3-5 years of diabetes or before puberty, but during the first 20 years of the disease nearly all type 1 diabetics develop retinopathy.¹⁷

The optometrist should ask what the patient's fasting blood sugar and glycosylated hemoglobin (HbA1c) readings are and when each was last measured. It is important to know what the expected ranges of blood glucose levels are in order to know how controlled the disease is. (**Table 4**). It is also beneficial to inquire about other systemic factors such as medications, blood pressure, cholesterol levels and renal function.¹⁷

Four "pertinent negatives" should al-

Table 2
Classification of Diabetic Retinopathy
from the Early Treatment Diabetic Retinopathy Study

Diabetic Retinopathy Classification	Findings / Characteristics
Mild NPDR Recommended follow-up 6-12 months ¹¹	<ul style="list-style-type: none"> At least one microaneurysm, BUT not severe enough to fall into a more severe classification (see below)
Moderate NPDR Recommended follow-up 6 months ¹¹	<ul style="list-style-type: none"> Hemorrhages and/or microaneurysms that are greater than or equal to "Standard Photograph 2A," and/or soft exudates, and/or venous beading, BUT not severe enough to fall into a more severe classification (see below)
Severe NPDR Recommended follow-up 2-4 months ¹¹	<ul style="list-style-type: none"> "4-2-1 Rule" Hemorrhages and/or microaneurysms present in all 4 quadrants on funduscopy view OR venous beading present in 2 quadrants OR intraretinal microvascular abnormality in 1 quadrant, BUT not severe enough to fall into a more severe classification (see below)
Early PDR (proliferative retinopathy that does not meet the high-risk characteristics listed below) Referral to retinal specialist indicated ¹¹	<ul style="list-style-type: none"> New vessel growth BUT not severe enough to fall into a more severe classification (see below)
High-Risk PDR Referral to retinal specialist indicated ¹¹	<ul style="list-style-type: none"> New vessel growth 1 disc diameter in size, within one disc diameter of the optic disc (NVD) Vitreous and/or pre-retinal hemorrhage accompanied by any new vessel growth at optic disc, or with new vessel growth of ½ disc area or larger anywhere else

Table 3
Classification of Macular Edema
from the Early Treatment Diabetic Retinopathy Study

Macular Edema Classification	Findings / Characteristics
Diabetic Macular Edema (DME)	<ul style="list-style-type: none"> Hard yellow exudates (HYE) and retinal thickening that involves the macular area
Clinically Significant Macular Edema (CSME)	<ul style="list-style-type: none"> Retinal thickening at or within 500 µm of the center of the macula, OR: HYE at or within 500 µm of the center of the macula, IF they are associated with adjacent retinal thickening, OR: An area of retinal thickening 1 disc area in size, at least part of which is within 1 disc diameter of the center of the macula The presence of any ONE of these criteria is sufficient for diagnosis of CSME

Table 4
The American Diabetes Association Recommended Blood Glucose Levels for Patients with Diabetes

	Recommended Range For Patients with Diabetes
Fasting Blood Sugar	70-130 mg/dL
HbA1c	< 7.0%, but more or less stringent goals may be appropriate on an individual basis

ways be noted in a diabetic eye exam. These clinical signs are pertinent negatives because their presence indicates diffuse ischemia, PDR and the potential for permanent blindness.¹⁷ These signs include CSME, NVI, NVD and NVE.

Treatment and management of diabetic retinopathy

Much of the damage done by diabetic retinopathy, especially the early neurodegenerative damage, is irreversible; therefore, the best treatment is preven-

tion.^{1,10} The primary preventative treatment for diabetes and diabetic retinopathy is tightly controlled blood glucose levels through a careful diet and regular exercise.^{2,10} Early diabetic retinopathy is often asymptomatic but its presence indicates the need for tighter control through medication and healthier living. Maintaining an HbA1c of less than 7% significantly reduces the risk of diabetic retinopathy.¹⁰ The risk is not eliminated, but the United Kingdom Prospective Diabetes Study (UK-

PDS) showed that for 1% reduction in HbA1c there is a 30-40% diabetic retinopathy risk reduction.^{10,17} The UKPDS also showed that tight glucose control reduces the risk of legal blindness due to diabetes by 16%.¹⁰

Other systemic risk factors include high blood pressure and elevated serum lipid levels. Hypertension can exacerbate diabetic retinopathy by means of increased blood flow and mechanical damage to the retinal vasculature, which consequently causes an increase in VEGF expression.^{10,11} Elevated serum lipid levels are a risk factor for hard exudates and diabetic retinal edema. Retinal lipid deposition also impairs retinal function. The Diabetes Control and Complications Trial (DCCT) showed that the severity of diabetic retinopathy was directly related to increased triglyceride levels and was inversely associated with “good” high-density lipoprotein (HDL) cholesterol levels.¹⁰

Control of systemic risk factors does not always prevent the development of diabetic retinopathy. If retinopathy becomes severe, medical and surgical intervention is required to preserve vision.^{10,14} Laser photocoagulation, anti-VEGF treatment, steroid treatment and surgical vitrectomy can all be used, either standalone or in concert, to treat vision-threatening retinopathy.

Laser photocoagulation is a process in which a laser is used to destroy areas of retina where hypoxia and neovascularization are occurring in order to reduce further angiogenesis. This process causes a reduction in retinal neovascularization and reduces central macular thickening/swelling.¹⁰ Laser photocoagulation has been shown to halt the course of diabetic retinopathy in approximately 50% of cases but often has to be repeated multiple times.¹ The ETDRS indicated that laser photocoagulation could reduce the risk of moderate vision loss by up to 50%.¹⁰

Intravitreal injection of VEGF-inhibitors can also be used in treatment for retinal angiogenesis. Two common anti-VEGF drugs that are used for intravitreal injections are bevacizumab (Avastin) and ranibizumab (Lucentis).¹⁰ Bevacizumab is a humanized antibody derived from mice that was FDA-approved for metastatic colorectal cancer

in 2004, but it is frequently used off-label as an intravitreal injection to treat DME.¹⁰ Ranibizumab is derived from bevacizumab and is specifically formulated for ocular injection. Ranibizumab has a much smaller molecular weight than bevacizumab, which enables it to penetrate the retina much faster.¹⁰ The injection of these drugs into the vitreous humor of diabetic eyes is intended to reduce the expression of VEGF, reducing angiogenesis and ultimately reducing retinal hemorrhages and edema. It is possible for a patient with DME to gain at least 10 letters of visual acuity in a 1-year span, but the patient may need multiple injections.¹⁰

Steroid treatment is also commonly used to control DME. Sub-Tenon’s or intravitreal steroid injections and intravitreal steroid implants have been shown to reduce DME and diabetes-related retinal inflammation.¹⁰ The mechanism is not fully understood, but studies have shown that hydrocortisone can increase the amount of tight junction proteins that line retinal endothelial cells.^{10,11}

Vitrectomy is a last resort for preserving vision in patients with diabetic retinopathy. It is considered when the patient has had recurrent or persistent vitreous hemorrhages or in cases of tractional retinal detachments.¹⁰ The vitreous and any associated hemorrhages, proliferative membranes, various cytokines and growth factors are surgically removed from the eye.¹⁰ Laser photocoagulation is often administered to the peripheral and mid-peripheral retina at the same time in order to reduce the angiogenesis after vitrectomy. The Diabetic Retinopathy Vitrectomy Study (DVRs) indicated that performing a prompt vitrectomy in type 1 diabetic patients with severe vitreous hemorrhage resulted in improved visual acuity.¹⁰

It is very important to perform yearly dilated fundus examinations on all patients but especially on diabetic patients. Follow-up intervals including dilation may be more frequent if retinopathy appears to be advancing or if blood glucose levels are not controlled. As an example, patients with CSME should be referred for treatment and then followed every 3-4 months after treatment. If treatment is deferred by the retinal specialist, generally patients

are followed within 3 months.¹⁹ The potential consequence of unmonitored diabetes is irreversible vision loss that could have been prevented and as such careful monitoring is crucial.

Conclusion

The detailed history-taking and wise decision-making of the primary care optometrist likely helped preserve this patient’s vision. Cases like this serve as a reminder of the importance of yearly dilated exams for all diabetic patients. If a diabetic patient is not compliant with keeping yearly appointments but presents in the optometrist’s office for other reasons, the opportunity should be used to emphasize the importance of retinal health assessment, even if the present chief complaint can be solved without dilation.

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