Proliferative Diabetic Retinopathy: A Case Review

Victoria Branca, OD; Rebecca Doyle, OD; Joseph Mega, OD; Paul B Greenberg, MD, MPH; Salvatore Loporchio, MD, MPH, JD; John Sellechio, OD

Abstract
Proliferative diabetic retinopathy (PDR) is the leading cause of preventable vision loss and visual disability amongst working-age adults in the United States. Complications include neovascularization of the iris, retina, and optic disc, which can lead to vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma. Treatment options for PDR include pan-retinal photocoagulation (PRP) and intravitreal anti-vascular endothelial growth factor (VEGF) injection. The case of a 48-year-old male Caucasian with PDR and associated complications is presented.

Introduction
According to the United States (US) Center of Disease Control and Prevention, an estimated 26.9 million Americans have diabetes mellitus (DM), and one-third have diabetic retinopathy (DR). In the US, DR is the leading cause of preventable vision loss and visual disability amongst working-age adults, and costs the healthcare system $48 billion annually. There are two primary types of DR: non-proliferative and proliferative. Non-proliferative diabetic retinopathy (NPDR) is defined by the presence of microvascular changes, venous/arterial changes, and accumulation of intraretinal deposits. Proliferative diabetic retinopathy (PDR) is defined by neovascularization (NV) of the retina, optic disc, and/or iris. The risk of complications from PDR increases significantly with disease duration. Anti-vascular endothelial growth factor (VEGF) intravitreal injections and pan-retinal photocoagulation (PRP) are common treatments for PDR. Herein, we present a case and review the management of PDR.

Case Presentation
A 48-year-old Caucasian male reported to the eye clinic complaining of a new “flickering” sensation and decrease in brightness of colors in both eyes as well as floater-like symptoms in the left eye for several weeks. The patient also noted that his vision tended to fluctuate with changes in blood glucose levels. The patient’s last eye examination (elsewhere) was 2 years ago; his previous ocular history was unremarkable. The patient’s medical history was significant for a 25-year-history of insulin dependent DM type II and hypertension. His most recent glycosylated hemoglobin was 8.3% (3 months prior to exam) and his BMI was 34.77 kg/m² (2 months prior to exam). The patient’s medications included dulaglutide 0.75mg injection pen, glargine insulin 42 units, losartan 100mg, and amlodipine 10mg.

On examination, his best-corrected visual acuity was 20/20 in the right eye and 20/30 in the left eye. Confrontation fields were intact, extraocular motilities were full and extensive and both pupils were equal, round and reactive to light without any afferent pupillary defects. Anterior segment examination was unremarkable in both eyes without iris NV. Intraocular pressures with Goldmann applanation tonometry were 17mmHg in the right eye and 16mmHg in the left eye. On dilated fundus examination, the cup-to-disc ratio was 0.45 horizontally and vertically with presence of 1/4 disc diameters (DD) of neovascularization of the disc (NVD) in the right eye and 2/3DD NVD in the left eye. Posterior segment findings (Figure 1) were significant for scattered microaneurysms and dot/blot hemorrhages in the maculae. In the periphery of both eyes, there were tortuous vessels, scattered microaneurysms with dot and blot hemorrhages, and multiple areas of neovascularization elsewhere (NVE) with several foci of vitreous traction. There were no vitreous hemorrhage (VH) or tractional retinal detachment (TRD) of either eye.

Spectral Domain Optical Coherence Tomography (OCT) revealed an epiretinal membrane (ERM) in the right eye and a blunted foveal contour with parafoveal cystic spaces, most likely secondary to vitreomacular traction (VMT). The left eye also had an ERM and blunted foveal contour secondary to vitreomacular adhesion (VMA).

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The patient was diagnosed with bilateral high-risk PDR and referred to the retina service for evaluation and treatment. Fluorescein angiography (FA) was performed. In the mid-phase in the right eye there was hyperfluorescence at the disc and along the inferior temporal arcade consistent with neovascularization (NV) with adjacent areas of nonperfusion (Figure 2a); in the later phases, there was prominent leakage from the areas of NV with pronounced nonperfusion in the periphery (Figure 2b). The mid-phase of the left eye showed marked leakage from NVD and foveal ischemia with broken parafoveal capillary ring (Figure 3a); in the later phases, there was marked nonperfusion with adjacent foci of leakage from NVE, as well as a blockage from pre-retinal hemorrhage in the periphery (Figure 3b).

The treatment plan for the patient’s PDR consisted of a series of intravitreal injections of bevacizumab (IVB) to stabilize the NV (Figure 4) followed by full PRP laser treatment in both eyes. The treating ophthalmologist did not find vitrectomy beneficial for initial treatment for this patient, as the risk for tractional retinal detachment was insignificant.

Upon consultation after diagnosis of PDR, the patient’s primary care physician increased dosage of his medications of dulaglutide 0.75mg to 1.5mg and glargine 42 units to 50 units, but decided against switching to an automated insulin pump. This regimen improved the patient’s glycosylated hemoglobin from 8.3% to 6.5% within 5 months’ time.
Discussion
The progression of NPDR to PDR is defined by the presence of neovascularization of the retina, optic nerve head and/or iris. Often PDR is asymptomatic; however, symptoms of blurred or distorted vision, sudden partial or total vision loss, and flashes and floaters in vision may occur secondary to diabetic macular edema (DME), VH, or TRD.

a. Etiology
There are many evolving theories on the pathophysiology and progression of diabetic retinopathy. An important pathogenic factor is the effect of chronic hyperglycemia on microvasculature and proinflammatory mediators. Hyperglycemia leads to the activation of alternative pathways involved in glucose metabolism, including the polyol pathway, increased oxidative damage, activation of protein kinase C, and increase in advanced glycation end products. These pathways lead to the activation of pro-inflammatory cytokines, upregulation of growth factors including VEGF, death of pericytes, and dysfunction of vascular endothelial cells. This disruption causes increased vascular permeability and microvascular occlusion, causing neovascular growth secondary to hypoxia. The development of PDR is dependent on factors such as duration of disease and age of diagnosis. The prevalence of PDR and the risk of PDR-related complications is significantly higher in type I versus type II DM.

b. Diagnostic Testing
Auxiliary testing for PDR aids in diagnosis, documentation and management. Fundus photography is useful for objectively monitoring disease progression. Fluorescein Angiography aids in locating areas of retinal ischemia, differentiating IRMA and collaterals from NV, and highlights subclinical NV.
Coherence Tomography (OCT) is necessary to evaluate for diabetic macula edema. Optical Coherence Tomography Angiography (OCT-A) helps generate similar images as FA without injecting dye and is especially useful in patients with kidney disease as well as those with allergies to dyes. B-scan ultrasonography is helpful to evaluate the posterior segment when the media is hazy secondary to VH and/or TRD.

c. Treatment
Panretinal photocoagulation is an important treatment of PDR. Risks of PRP include worsening of visual acuity, loss of peripheral vision, DME, vascular occlusion, choroidal detachment, exudative retinal detachment, and formation of choroidal neovascular membrane. The addition of intravitreal anti-VEGF therapy or intravitreal steroid therapy can aid in regressing active neovascularization, reducing preretinal and vitreous hemorrhages, and may lead to conservation of the visual potential compared to PRP alone.

The below table outlines the outcomes of various treatments for PDR as well as how these treatments are helpful in PDR cases complicated by neovascular glaucoma, dense vitreous hemorrhages, and fibrovascular proliferation (Table 1).

Several novel drug delivery strategies are currently being studied in attempt to decrease the therapeutic burden of monthly intravitreal injections. They include non-biodegradable and biodegradable polymeric drug delivery systems, nanoparticle-based drug delivery systems, ocular injection devices which aid in a concealed and sustained release of a drug, and sustained release refillable devices.

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<th>Table 1. Selected PDR Treatment Studies</th>
<th>Methodology</th>
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| **5 Year outcome of PRP vs intravitrean ranizumab for PDR: a randomized clinical trial (Gross et al. 2018)** | PRP alone vs intravitreal ranizumab (IVR; Lucentis) alone                   | • Occurrences of TRDs and VHs were greater in the PRP groups vs the IVR group  
• IVR resulted in lower rates of vision impairing DME  
• PRP increases risk of secondary DME          |
| Structural and functional assessment of macula in patients with high-risk proliferative diabetic retinopathy submitted to panretinal photocoagulation and associated intravitreal bevacizumab injections: a comparative, randomized, controlled trial (Preti et al. 2013) | Intravitreal injections before PRP vs PRP alone                           | • IVR injections as adjunct therapy with PRP reduces the risk of visual acuity loss vs PRP alone |
| The diabetic retinopathy clinical research network (George et al. 2011)   | IVR vs IVTA                                                                 | • Lower occurrences of TRDs and VHs in IVTA group vs IVR  
• Both IVTA and IVR are equally safe and effective in patients who receive PRP and focal/grid laser |
| Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy (Cho et al. 2010) | PRP alone vs intravitreal bevacizumab (IVB, Avastin) & PRP vs intravitreal triamcinolone (IVTA) & PRP | • Both IVB & IVTA minimize risk of PRP induced macular edema and vision loss |
| Intravitreal bevacizumab for prevention of early post vitrectomy hemorrhage in diabetic patients: randomized clinical trial (Amadieh et al. 2009) | Effectiveness of preoperative IVB prior to vitrectomy vs sham injection | • IVB 1 week before vitrectomy reduced the incidence of early post VH in diabetic patients.  
• IVB pre-vitrectomy decreases the rates of repeat vitrectomy |

d. Control of Systemic Disease
Collaboration of patient care between eyecare providers, primary care, and endocrinology are key to PDR prevention and management. Providers working together can assist patients with diet control, physical activity, and medication compliance, all of which aid in good systemic control of glycated hemoglobin, blood pressure, triglyceride and cholesterol levels. Low and controlled levels decrease microcirculatory damage, delaying risk of development of PDR as well as decreasing risk of further progression.

e. Visual Outcome
PRP when greatly extensive can result in restricted visual fields, nyctalopia and poor light and dark adaptation, which can potentially cause difficulty with driving, orientation and mobility. Referral for vision rehabilitation may be greatly beneficial in these instances and should be initiated as soon as possible after extensive therapy to aid in adaptation to decreased visual efficiency. Occupational therapy may involve instruction in orientation and mobility, activities of daily living, occupational training, insulin management and self-care.

Conclusion
Proliferative diabetic retinopathy is a sight threatening disease and is a leading cause of vision loss in the US. Regular dilated fundus examinations in conjunction with the judicious use of diagnostic imaging can lead to prompt diagnosis and treatment. Improved control of diabetes mellitus and systemic comorbidities along with anti-VEGF and/or PRP, can prevent long term vision impairing complications such as NVG, VH, and TRD can be prevented.
References

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