

Management of Proliferative Diabetic Retinopathy

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Brief summary of the literature

The detection and management of proliferative diabetic retinopathy (PDR) have dramatically changed in the past 55 years. The classical description by Matthew Davis of the changes noted clinically in PDR¹ has not been improved, although newer imaging methods such as OCT and wide-angle fluorescein angiography allow more effective documentation of what can be seen at the slit lamp and with indirect ophthalmoscopy. Simultaneously, the treatment of PDR has evolved from pituitary ablation² (abandoned in the 1960s), through laser panretinal photocoagulation (PRP),³ vitrectomy⁴, and intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs⁵, methods often used in combination. Which option to choose often depends on the severity of proliferations, the status of the fellow eye, the likelihood of follow-up, and socioeconomic factors.

The 3 prerequisites for development of proliferative diabetic retinopathy are:

- 1.) Presence of increased VEGF-A,
- 2.) Presence of viable retinal vessels, and
- 3.) Presence of a vitreous scaffold.⁶

The teaching point highlighted by this case is the importance of the third factor.

Issues raised by the case

1. The initial choice of therapy was dictated by the patient's assessment of his finances and his fear of immediate loss of peripheral vision and night vision with PRP.

The drug trial gave him regular, free access to an expensive anti-VEGF drug. The use of less expensive bevacizumab would have been his choice had he not been offered the drug trial option. Protocol S 5-year data showed that the eyes receiving ranibizumab progressively lost visual field in years 2-5 of the study, such that the difference in peripheral field compared to the PRP group that had existed at year 2 was halved. ⁷ Nevertheless, the concern regarding immediate loss with PRP is dispositive in some patients and outweighs the increased cost and visit burden associated with injection therapy as in this case.

2. The posterior vitreous detachment may have been induced by the 13 aflibercept injections.

This is impossible to prove, but simply injecting saline into human eyes can induce a posterior vitreous detachment.⁸

3. My choice of observation when the posterior vitreous detachment occurred was predicated on his documented record of perfect attendance at visits in clinic.

The hazards of nonadherence when anti-VEGF drugs have been chosen to treat PDR are published and are severe.⁹

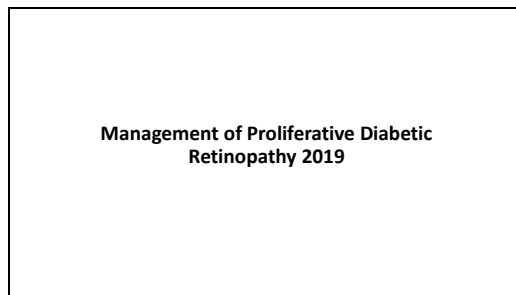
4. Although posterior vitreous detachment reduces the probability of vitreous hemorrhage, a residual risk exists due to abortive neovascular outgrowths (ANVOs).⁶ In addition, neovascularization of the iris and anterior hyaloidal fibrovascular proliferation are possible complications necessitating regular frequent follow-up.¹⁰

Probably the best way to identify ANVOs is with wide-angle fluorescein angiography. This was not available at the satellite office where the patient attended clinic.

Reference List

1. Davis MD. Vitreous contraction in proliferative diabetic retinopathy. Arch Ophthalmol 1965;74:741-51.
2. Speakman JS, Mortimer CB, Briant TDR, et al. Pituitary ablation for diabetic retinopathy. Canadian Medical Association Journal 1966;94:627-35.
3. The Diabetic Retinopathy Study Research Group. Preliminary Report on Effects of Photocoagulation Therapy. American Journal of Ophthalmology 81[4], 383-395. 1976.
4. Flynn Harry W, Chew EY, Simons BD, et al. Pars plana vitrectomy in the early treatment diabetic retinopathy study-ETDRS report number 17. Ophthalmology 1992;99:1351-7.
5. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006;113:1695-705.
6. Wong HC, Sehmi KS, Mcleod D. Abortive neovascular outgrowths discovered during vitrectomy for diabetic vitreous hemorrhage. Graefe's Arch Clin Exp Ophthalmol 1989;227:237-40.
7. Gross JG, Glassman AR, Liu D, et al. Five year outcomes of panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy. A randomized clinical trial. JAMA Ophthalmol 2018;136:1138-48.
8. Neffendorf JE, Kirthi V, Pringle E, Jacksn TL. Ocriplasmin for symptomatic vitreomacular adhesion (Review). Cochrane database of systematic reviews 2017.
9. Obeid A, Su D, Patel SN, et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti-vascular endothelial growth factor. Ophthalmology 2019;126:407-13.
10. Lewis H, Abrams GW, Williams GA. Anterior hyaloidal fibrovascular proliferation after diabetic vitrectomy. Am J Ophthalmol 104, 607-613. 1987.

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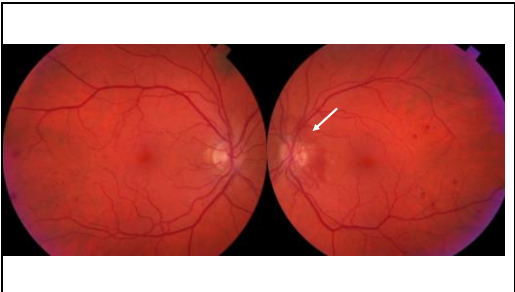


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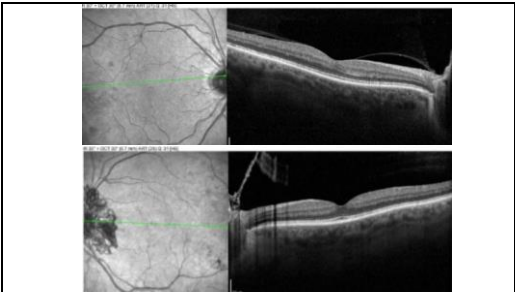
67 year old man with type 2 DM, insulin dependent, for 10 years and hypertension for 15 years. Referred by his optometrist for diabetic retinopathy. No complaints.

- 1/24/2017
- Vision 20/20 OU
- IOP 14 OU
- Pupils: No RAPD
- Slit lamp: PCIOL OU
- Fundus: as shown

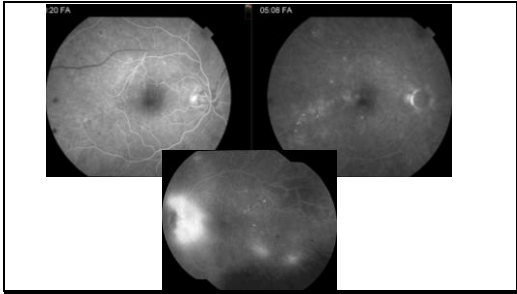
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Options

- Anti-VEGF
 - No field loss
 - Expensive
 - High visit burden
- Laser PRP
 - Potential for visual field loss
 - Less expensive
- Vitrectomy
 - Riskier
 - Effective
- Observation
 - Near certainty of vitreous bleeding

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His decision:

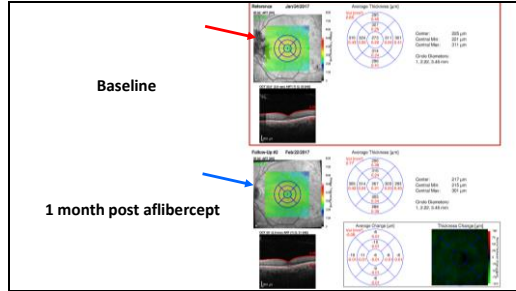
- Anti-VEGF
 - He enrolled in a drug study for the right eye
 - The study paid for aflibercept injections for the left eye

Figure 7. Changes in Cumulative Visual Field (CVF) Mean Values for the Control Group

Week	Panretinal Photocoagulation (Degrees)	Ranibizumab (Degrees)
0	100	100
120	95	75
180	90	65
240	85	55
300	80	50
360	75	45

Gross JG, et al. Five year outcomes of panretinal photocoagulation vs intravitreal Ranibizumab for proliferative diabetic retinopathy. JAMA Ophthalmol 2018; 136(10):1138-48.

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From 1/24/2017 to 1/24/2019

- 13 aflibercept injections OS
- 1/24/2019
 - Last injection aflibercept
 - Study ends
 - No more free shots
 - VA 20/20

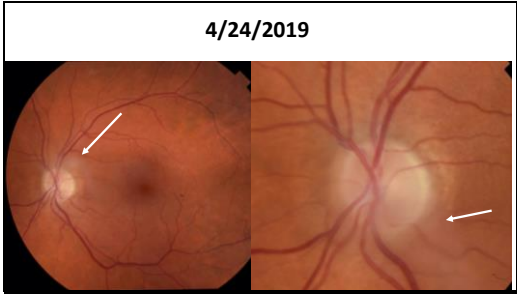
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4/24/2019

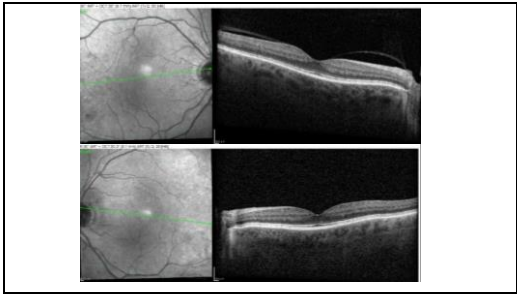
No new symptoms since 1/24/2019

- A1C 6.8
- BP 165/84
- VA R-20/25, L-20/20
- IOP 15 OU
- Slit lamp normal PCIOL OU, no NVI OU
- Fundus-as shown

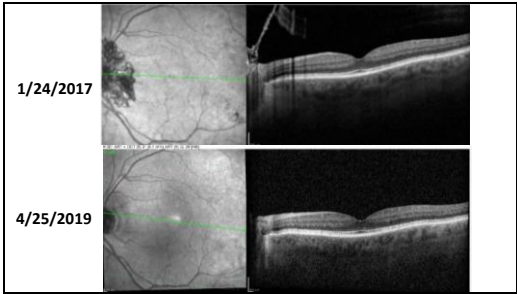
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What would you do?

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Options

- Intravitreal anti-VEGF drug
- Laser PRP
- Vitrectomy
- Observe

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What I did

- Observation

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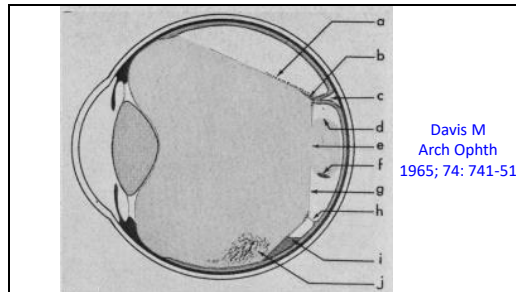
Neovascularization and the Vitreous Scaffold

- "...the vitreous "membrane" of principle importance in proliferative diabetic retinopathy is actually the detached posterior surface of the formed vitreous ... the new vessels associated with it have not grown actively forward into the vitreous, but rather have been pulled passively forward during vitreous contraction by adhesions to the vitreous framework. Vitreous contraction thus assumes an importance in proliferative diabetic retinopathy equal to that of the new vessels themselves."
- [Davis M. Arch Ophthalmol 1965; 74:741-51](#)

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- "After completion of vitreous detachment, a remission in the retinopathy often took place, with reduction in number of retinal hemorrhages, decrease in venous dilatation and beading, regression of new vessels, thinning of fibrous proliferations, and clearing of vitreous hemorrhage."
- [Davis M. Arch Ophthalmol 1965; 74:741-51](#)

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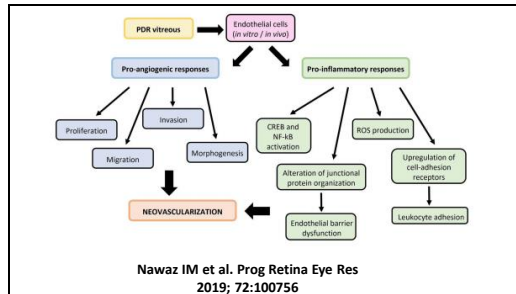
Davis M
Arch Ophth
1965; 74: 741-51

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Neovascularization and the Vitreous Scaffold

- To have elevated NV, VEGF is necessary but not sufficient
- Also need the vitreous scaffold
- Also need some viable retinal vessels
- Vitrectomy removes the vitreous scaffold, and elevated NV does not come back, even without PRP
- Post vitrectomy eyes without PRP do get NVI, so one normally does PRP
- In this case, he developed a PVD and lost his scaffold
- May not need any further aflibercept (or bevacizumab, given cost)
- Will need to watch for NVI

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What do you predict happened in subsequent follow-up?

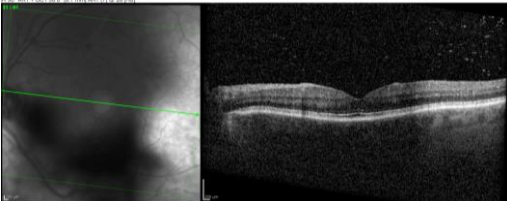
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5/23/2019
1 day of new floaters OS and blurring

- VA R-20/25, L-20/50
- IOP 15 OU
- Slit lamp normal PCIOL OU, no NVI OU
- Fundus-as shown

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New vitreous hemorrhage



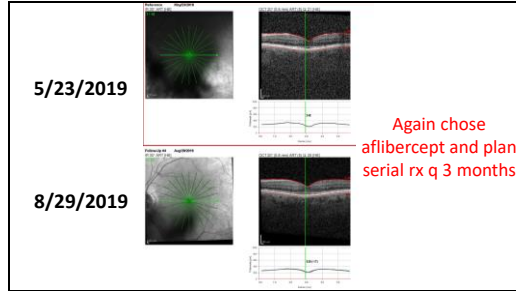
Patient chose aflibercept

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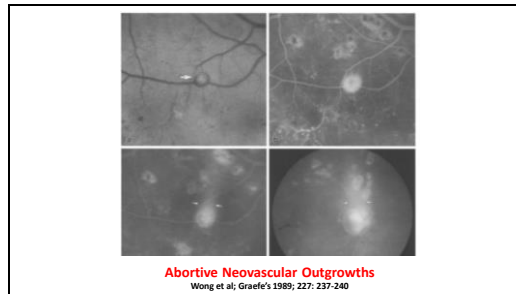
8/29/2019
Vision nearly back to normal

- A1C 7.2
- BP 140/75
- VA R-20/25, L-20/50
- IOP 15 OU
- Slit lamp normal PCIOL OU, no NVI OU
- Fundus-as shown

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References

- Davis MD. Vitreous contraction in proliferative diabetic retinopathy. Arch Ophthalmol 1965; 74:741-51
- Machemer R. Pathogenesis of proliferative neovascular retinopathies and the role of vitrectomy. A hypothesis. Int Ophthalmol 1978; 1:1-3
- Wong HC; Sehmi KS; McLeod D. Abortive neovascular outgrowths discovered during vitrectomy for diabetic vitreous haemorrhage. Graefes Arch Clin Exp Ophthalmol 1989;227:237-40.
- Nawaz IM et al. Human vitreous in proliferative diabetic retinopathy: characterization and translational implications. Prog Retin Eye Research 2019; 72: 100756
