Clinical Case Study

- 56-year-old American Indian/Native American man with 25-year history of diabetes
- Intraocular pressures of 48 mmHg OD and 17 mmHg OS
- Anterior segment examination shows iris and angle neovascularization OD
- Fundus examination shows proliferative diabetic retinopathy in both eyes

Question 1

What is the third most common cause of neovascular glaucoma?
- a. Diabetic retinopathy
- b. Central retinal vein occlusion
- c. Carotid artery occlusive disease
- d. Carotid-cavernous fistula

Evidence-based Recommendations for the Diagnosis and Treatment of Neovascular Glaucoma

Introduction

- First described in 1866 after central retinal vein occlusion
- Rubeosis iridis: iris neovascularization
- Neovascular glaucoma: glaucoma associated with iris neovascularization
- Generally associated with retinal ischemia
Predisposing Disorders

- Diabetic retinopathy
- Retinal vascular occlusions
- Carotid artery obstructive disease: probably third most common cause of neovascular glaucoma
- Carotid-cavernous fistula
- Uveitis

Predisposing Disorders

- Other retinal disorders
  - Chronic retinal detachment
  - Retinal detachment in malignant melanoma
  - Retinoblastoma
  - Coats' exudative retinopathy
  - Retinopathy of prematurity
  - Sickle cell retinopathy
  - Syphilitic retinal vasculitis
  - Retinoschisis
  - Stickler's syndrome

Diabetic Retinopathy

- Diabetes accounts for one-third of neovascular glaucoma
- Rubeosis and neovascular glaucoma usually associated with proliferative diabetic retinopathy

Diabetic Retinopathy

- Iris neovascularization not invariably followed by neovascular glaucoma
- Vitrectomy and lensectomy may be associated with rapid progression of iris neovascularization

Retinal Vascular Occlusive Disorders

- Central retinal vein occlusion second most common cause of neovascular glaucoma
- 30% of patients over age 40 with central retinal vein occlusion develop neovascular glaucoma
- Rubeosis strongly correlated with degree of retinal ischemia; develops in 60% of ischemic central retinal vein occlusions
Retinal Vascular Occlusive Disorders

• Neovascular glaucoma in central retinal vein occlusion may progress more rapidly than in diabetes
• Neovascular glaucoma may be seen after central retinal artery occlusion and branch retinal vein occlusions

Onset of Neovascular Glaucoma in Central Retinal Vein Occlusion

• Two weeks to years
• Usually within first 12 months; 80% within 6 months
• Difficult to predict onset of neovascular glaucoma in individual cases

Classification of Central Retinal Vein Occlusion

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<tr>
<td>Nonischemic</td>
<td>75−80%</td>
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<tr>
<td>Ischemic</td>
<td>20−25%</td>
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<td>Nonischemic to Ischemic</td>
<td>8%</td>
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Signs of Retinal Ischemia

• Extensive retinal capillary nonperfusion on fluorescein angiography
• Decreased vision
• Ten or more cotton wool spots
• Significant relative afferent pupillary defect
• Reduced b/a wave ratio (<1.2) on electroretinography

Relative Afferent Pupillary Defect in Central Retinal Vein Occlusion

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<tr>
<td>Nonischemic</td>
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<tr>
<td>97%&lt;0.6LU</td>
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<tr>
<td>Ischemic</td>
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<tr>
<td>91%&gt;1.2LU</td>
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*LU = log units
Theories of Neovascularogenesis

- Angiogenesis theory: hypoxic retinal tissue releases angiogenic factor (e.g., vascular endothelial growth factor, an angiogenic peptide, and/or basic fibroblast growth factor), which diffuses forward and causes new vessel formation.

- Iris neovascularization in animal model inhibited by administration of neutralizing anti-VEGF monoclonal antibody.

- Vitreous and lens may act as barriers to angiogenic factors or may possess vasoinhibitory abilities.

Pathophysiology of NVG

Vascular Endothelial Growth Factor in Neovascular Glaucoma

- Compared aqueous humor concentrations of VEGF in patients with neovascular glaucoma, primary open-angle glaucoma, and cataract.
- VEGF detected in:
  
<table>
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<tr>
<th>Samples</th>
<th>Concentration</th>
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<tr>
<td>NVG</td>
<td>12 of 12</td>
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<tr>
<td>POAG</td>
<td>15 of 28</td>
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<tr>
<td>Cataract</td>
<td>4 of 20</td>
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Vascular Endothelial Growth Factor in Neovascular Glaucoma

- Mean concentration of VEGF in neovascular glaucoma 40- and 113-fold higher than in POAG and cataract, respectively.


Neovascular Glaucoma:
Clinical Stages

- Iris neovascularization without glaucoma
- Open-angle glaucoma
- Angle-closure glaucoma

Iris Neovascularization Without Glaucoma

- Clinically, first see dilated tufts of vessels at pupil margin; progress toward iris root.
- May or may not see angle vessels.
- In Central Vein Occlusion Study, 10% of eyes with nonischemic CRVO and 6% with ischemic CRVO showed angle neovascularization without iris neovascularization.
New Vessels versus Engorged Vessels

- Engorged normal vessels
  - Uniform size and radial course
  - Do not branch within iris
  - Vessels lie in iris stroma
- New vessels
  - Irregular size and course
  - Branch frequently
  - Lie on iris surface

Open-Angle Glaucoma

- More extensive iris neovascularization
- May see anterior chamber reaction and hyphema
- Angle “open” with intensive neovascularization
- Fibrovascular membrane covers angle and anterior iris surface

Angle-Closure Glaucoma

- Iris stroma flattened with smooth appearance
- Ectropion uvea frequently present; pupil often dilated
- Contracture leads to synechial closure of angle
- Secondary glaucoma typically severe
- Histopathologically, superficial layer of myofibroblasts overlies new vessels; may be responsible for tissue contraction
Differential Diagnosis

- Acute angle-closure glaucoma
- Uveitic glaucoma
- Fuchs heterochromic iridocyclitis

Medical Management

- Aqueous suppressants: beta-blockers, carbonic anhydrase inhibitors, and alpha-2 adrenergic agonists
- Miotics rarely helpful; should be avoided in presence of neovascularization
- Role of prostaglandin analogs unclear
- Topical corticosteroids
- Cycloplegic agents

Management: Retinal Ablation

- Panretinal photocoagulation to eliminate or reduce anterior segment neovascularization
- In vein occlusion and diabetes, treatment indicated if iris and/or angle neovascularization develops
- Panretinal cryoablation alternative therapy when media precludes panretinal photocoagulation
- Ablation presumably reduces retinal oxygen demand and stimulates for release of angiogenesis factor

Prophylactic Treatment of CRVO

- In past, many surgeons advocated prophylactic panretinal photocoagulation of all ischemic central retinal vein occlusions
- Central Vein Occlusion Study has shown that
  - Prophylactic PRP does not totally prevent anterior segment neovascularization
  - Prompt regression of neovascularization to PRP is more likely in eyes that have not been treated previously

Prophylactic Treatment of CRVO

- Authors therefore recommend careful and frequent follow-up (including undilated slit lamp examination of iris and gonioscopy) in the early months after ischemic CRVO and prompt PRP if new vessels develop
Future Management

- If no adverse effects, specific inhibition of vascular endothelia growth factor may be useful in treatment of retinal ischemia-associated ocular neovascularization

What is Bevacizumab (Avastin)?

- Anti-VEGF monoclonal antibody which is FDA approved for adjunct use with 5-FU in patients being treated for colon cancer
  - Full monoclonal antibody unlike ranibizumab (antibody fragment, Lucentis)
  - Provides pan-VEGF blockade unlike pegaptanib (Macugen)
  - Longer half life than either ranibizumab or pegaptanib
  - Penetrates entire retinal thickness

Bevacizumab’s Role in Ophthalmic Disease?

- Currently not FDA-approved for ophthalmic intravitreal use (off-label use)
- Gaining popularity in the treatment of exudative AMD
- Some small series, including series from Dean McGee Eye Institute, reporting improved outcomes when used in treating neovascular glaucoma
- Usual dose: 1.25 mg in 0.05 cc
- Further investigation in larger series appears warranted

Bevacizumab’s Role in Neovascular Glaucoma?

- General review of literature regarding the effects of bevacizumab in management (including surgical management) of neovascular glaucoma suggests:
  - Decrease in aqueous levels of VEGF
  - Decrease in anterior segment neovascularization
  - Decreased hyphema with surgical interventions
  - Similar surgical success rates with or without use of bevacizumab, but possibly lower overall IOPs and dependence on postoperative medical treatment

Surgical Management: Filtering Procedures And Tube Shunts

- Prognosis often poor due to intraoperative bleeding and postoperative progression of fibrovascular membrane
- With successful retinal detachment, careful hemostasis, and adjunctive antiproliferative therapy (e.g., mitomycin), improved success rates may be achieved, at least initially
- Placement of tube shunts (e.g., Molteno, Baerveldt, or Ahmed implants); 62-79% success at one year in some series

Diode Laser Cyclophotocoagulation

- Less discomfort than cyclocryotherapy
- Postoperative intraocular pressure rise less likely
- Decreased incidence of phthisis
- My personal choice in presence of active, florid neovascularization
Tube Shunt Surgery versus Cyclophotoocoagulation in Neovascular Glaucoma

- In series of 48 patients with neovascular glaucoma, 24 underwent noncontact cyclophotoocoagulation, and 24 underwent tube-shunt procedure.
- Satisfactory IOP control was achieved in 37.5% of eyes treated with CPC versus 66.7% with tube-shunt procedure.
- Visual loss greater in CPC group.
- Complication rate higher in tube-shunt group.

Summary and Conclusions

- With appropriately aggressive treatment, there is hope for eyes with neovascular glaucoma.

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Question 2

What proportion of central retinal vein occlusions are ischemic?
- a. 75%
- b. 50%
- c. 25%
- d. 5%

Surgical Management: Summary

- Prompt bevacizumab and panretinal photoocoagulation
- If significant active neovascularization, consider cyclophotoocoagulation versus aqueous shunt.
- If regressed or regressing neovascularization, consider aqueous shunt versus trabeculectomy with mitomycin.
- In eyes with poor visual potential, cyclophotoocoagulation still an option.
- Randomized clinical trial of surgical options needed.

Thank You Very Much!
Disclosure Statement

- Dr. Skuta currently serves on the Finance and Claims Committees for the Ophthalmic Mutual Insurance Company.
- He has served as an investigator for the Collaborative Normal Tension Glaucoma Study, the Advanced Glaucoma Intervention Study, the Collaborative Initial Glaucoma Treatment Study, and the Tube versus Trabeculectomy Study.
- He also has served on the Data and Safety Monitoring Committee for the Ocular Hypertension Treatment Study.