BREAKING THE RETINAL VASCULAR DA VINCI CODE

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DISCLOSURE INFORMATION

- Dr. Aaron Gold was previously on the Advisory Board for Regeneron. Dr. Marco Gonzalez, and Dr. Gary Sheinabum have no relevant financial relationship(s) with ineligible companies to disclose.
- All of the relevant financial relationships listed for this individual have been mitigated.

RETINA SPECIALIST'S ARSENAL

- Ancillary testing
  - Fundus photography/ultra-widefield retina imaging
  - OCT
  - Fundus autofluorescence
  - Ultrasonography
  - OCT-A
  - FA and/or ICG

RETINA SPECIALIST'S ARSENAL

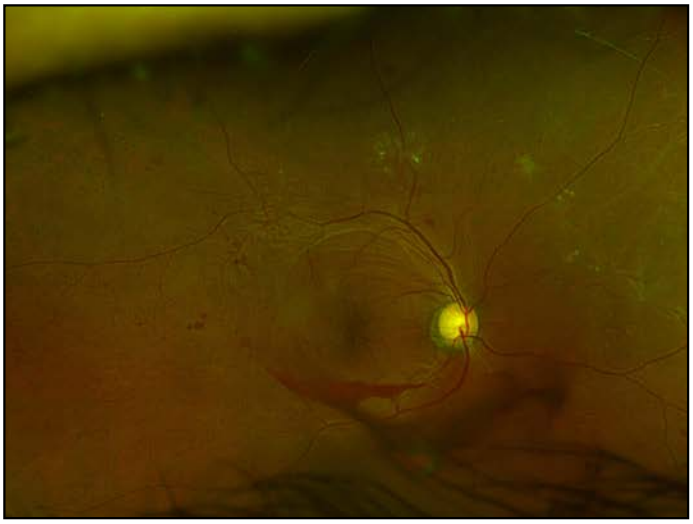
- Therapeutic Treatment Options
  - Intravitreal Injection Therapy
    - Anti-VEGF, Steroid, etc.
  - Laser therapy
    - Laser photocoagulation, PDT, TTT, Micropulse, etc.
  - Cryotherapy
  - Surgery
    - Vitrectomy, SB, Pneumatic retinopexy, etc.

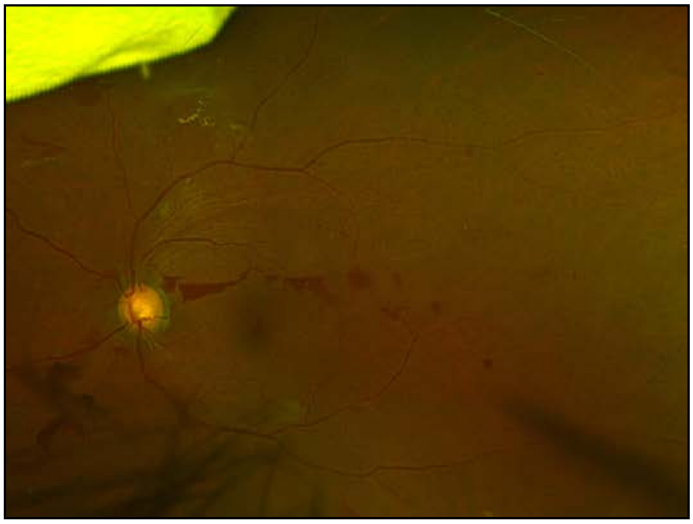
REFERRAL URGENCY

- Ocular Urgency
  - Retina Specialist within next few days
- Ocular Emergency
  - Straight to retina specialist or ocular ED
- Medical Urgency
  - Medical doctor/Specialist within next few days
- Medical Emergency
  - Straight to ED

CASE 1

- 46/B/F
- CC: Blurred vision OU
- HPI: Mild, central vision, worsening over years, was told she had “bleeding in the eyes”
- PMHx: HTN, NIDDM
- BCVA: 20/40- OD, 20/40- OS
- IOP: 16 mmHg OD, 15 mmHg OS
- Anterior Seg: Trace NS OU
- Posterior Seg: See Photos





DIABETIC RETINOPATHY

- Chronic hyperglycemia, capillary basement membrane thickening, pericyte loss, capillary nonperfusion, retinal ischemia, and eventual VEGF-driven neovascularization
- Vascular Mechanism: Retinal ischemia stimulates new vessel growth on disc and elsewhere
- PDR is the most severe form of diabetic retinopathy; affects both Type 1 & 2 DM; leading cause of vision loss in working-age adults
- Diabetes can also increase cataract development with or without DR

DIABETIC RETINOPATHY RISK FACTORS

- Length of time with diabetes
- Poor management of blood sugar
- Hypertension
- High Cholesterol
- Smoking
- Pregnancy
- Family history

DIABETIC RETINOPATHY

- Nonproliferative Diabetic Retinopathy (NPDR)
  - Mild NPDR
    - Microaneurysms
  - Moderate NPDR
    - Microaneurysms and/or hemorrhage WITH hard exudates, CWS, venous beading
  - Severe NPDR
    - 4-2-1 rule (many hemes in all 4 quadrants, venous bleeding in at least 2 quadrants, or any intraretinal microvascular abnormality)
- Proliferative Diabetic Retinopathy
  - NVD, NVE, Vitreous or preretinal hemes, tractional RD

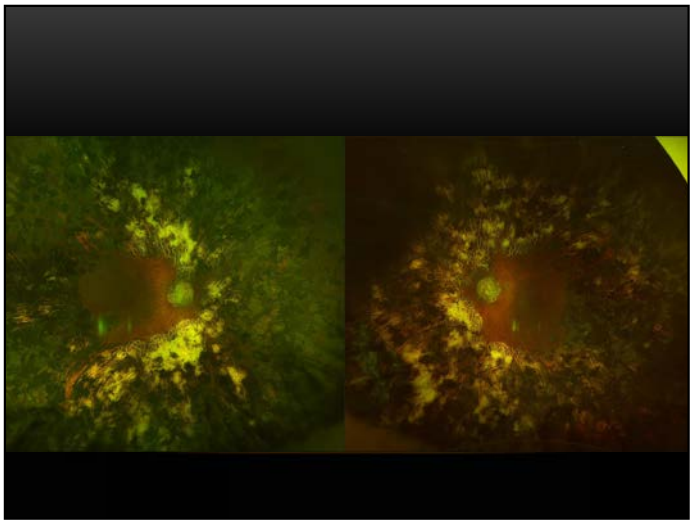
*DME may occur at any stage

ANCILLARY TESTING

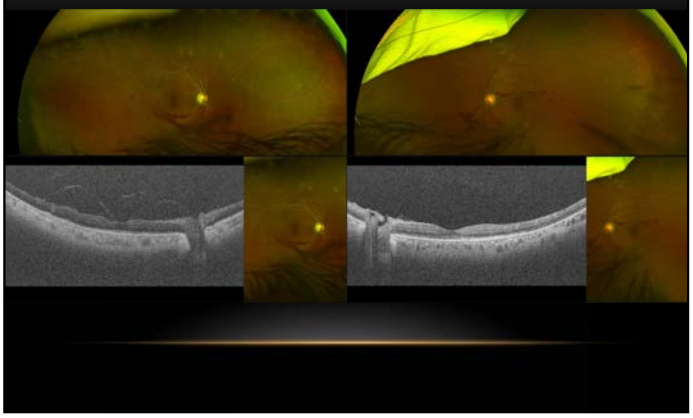
- Fundus Photography: Documents neovascularization and hemorrhages
- OCT: Detects coexisting diabetic macular edema
- OCT-A: ischemic zones and neovascular networks
- Fundus Autofluorescence (FAF): RPE damage
- Fluorescein Angiography (FA): Capillary dropout, leakage from neovascularization

PDR MANAGEMENT

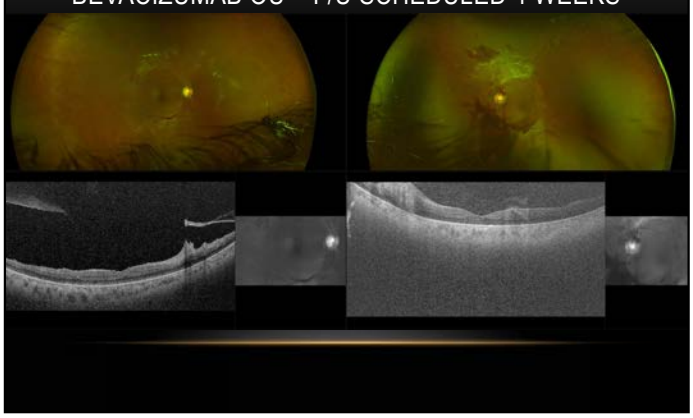
- Anti-VEGF therapy: treats NVE, NVD, DME, and early NVG
- Panretinal Photocoagulation (PRP): laser ablate the peripheral retina, reducing the retina's oxygen demand in that area and thus preventing NVE
- Surgery: Pars plana vitrectomy for non-clearing vitreous hemorrhage or tractional retinal detachment
- Systemic management: Tight glycemic, blood pressure, and lipid control



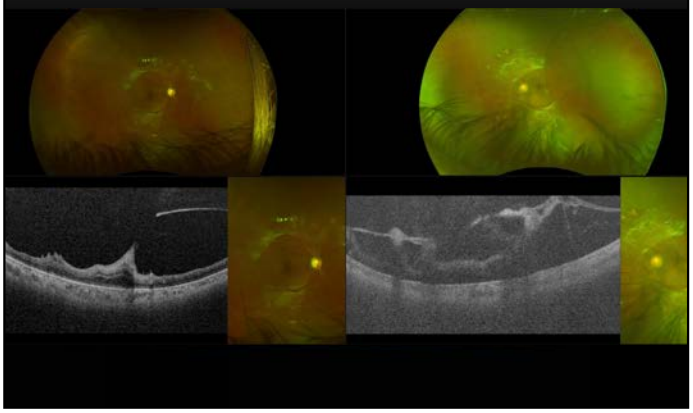
20/40- OD, 20/40- OS
BEVACIZUMAB OU – F/U SCHEDULED 4 WEEKS



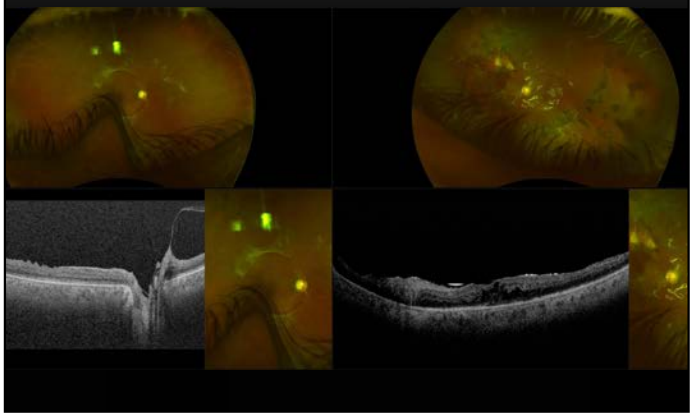
LOST TO F/U FOR 9 MONTHS
20/40- OD, 20/40- OS
BEVACIZUMAB OU – F/U SCHEDULED 4 WEEKS



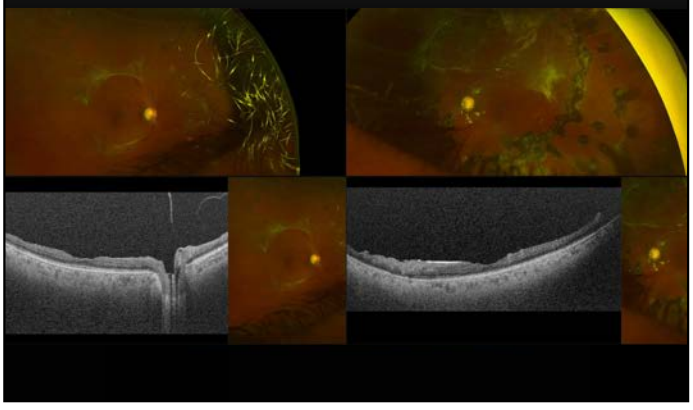
FOUR WEEKS LATER
TRD OS (20/60-)
PLAN: PPV/MP/EL/AFE/SO INSERTION



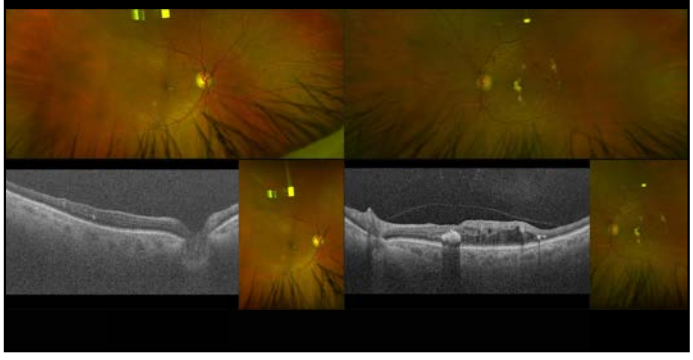
POM 2: 20/60- AVASTIN Q4-6WEEKS



MOST RECENT VISIT – 2 YEARS LATER
20/40 OD, 20/30 OS

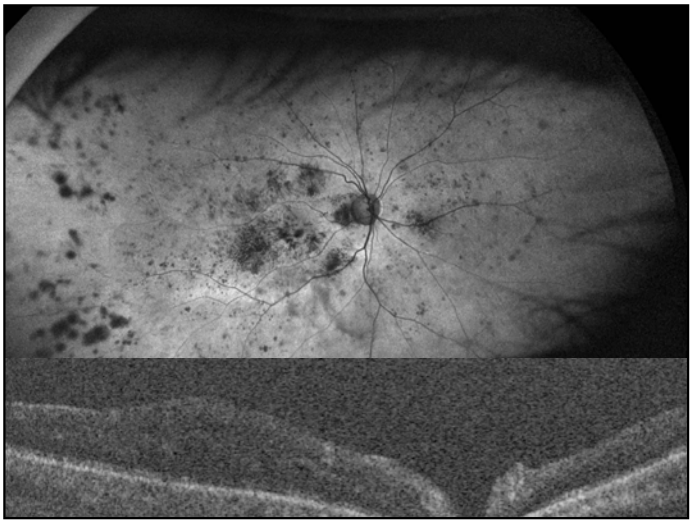


ANTI-VEGF FOR NPDR WITHOUT DME?



CASE 2

- 78/W/F
- CC: Blurred vision OD
- HPI: Severe, central vision suddenly decreased over the last 2 weeks
- PMHx: HTN, NIDDM
- BCVA: 20/400 OD, 20/30- OS
- IOP: 21 mmHg OD, 16 mmHg OS
- Anterior Seg: 2+ PEK OU, Pseudophakic OU
- Posterior Seg: OS unremarkable, OD – see photo



CENTRAL RETINAL VEIN OCCLUSION

- Thrombus formation at or near the lamina cribrosa that causes obstruction of central retinal vein which leads to increased hydrostatic pressure, hemorrhage, and ischemia
- Second most common retinal vascular disorder after diabetic retinopathy; usually unilateral

CRVO RISK FACTORS

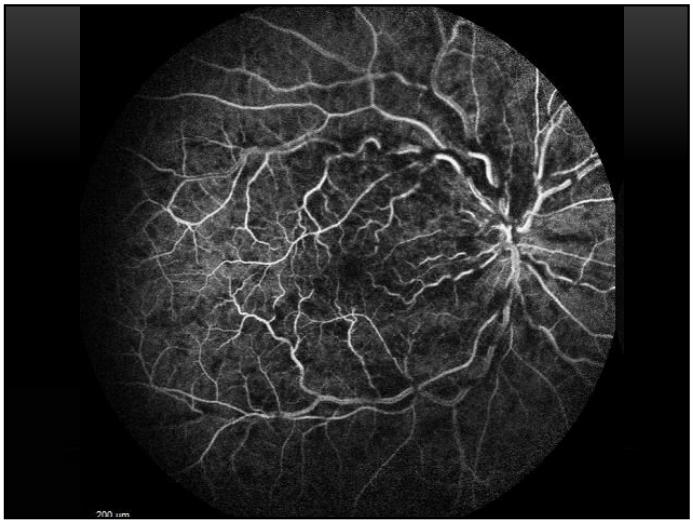
- Systemic hypertension
- Diabetes mellitus
- Elevated intraocular pressure
- Age >50 years
- Smoking, obesity

CRVO SIGNS

- Diffuse retinal hemorrhages (“blood and thunder” fundus)
- Dilated and tortuous retinal veins
- Cotton wool spots, disc swelling
- Macular edema (common cause of vision loss)
- Neovascularization of the iris or angle in ischemic CRVO

ISCHEMIC VS NONISCHEMIC CRVO

- Ischemic
  - Severe capillary nonperfusion
  - Poor VA - <20/200
  - More likely to present with macular edema
  - Significant risk of NVG
- Nonischemic
  - Minimal capillary nonperfusion
  - VA >20/200
  - Lower risk of NVG, but still may convert to ischemic CRVO

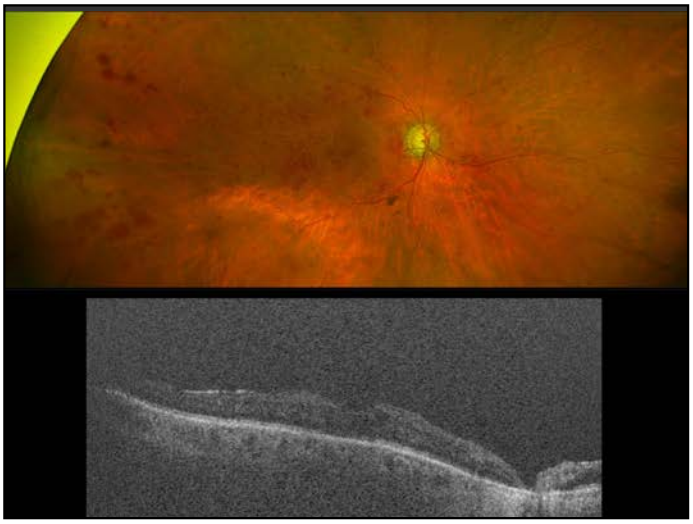


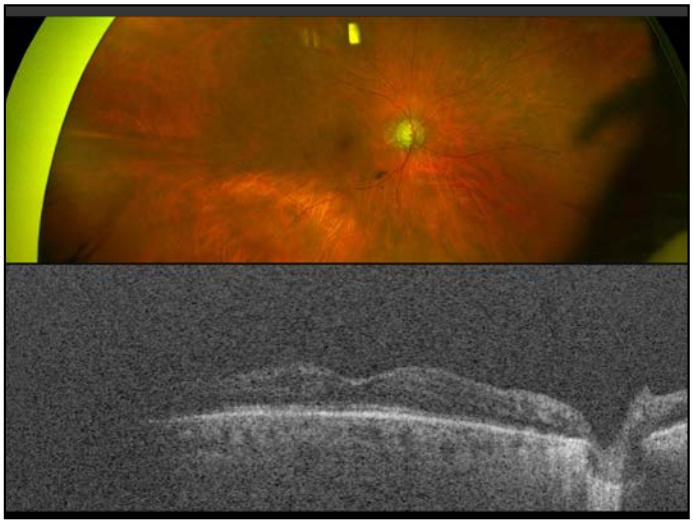
CRVO ANCILLARY TESTING

- OCT: macular edema and
- FA: Distinguishes ischemic from non-ischemic CRVO; shows delayed venous filling, capillary dropout, and leakage
- OCT-A: Visualizes nonperfusion areas and capillary network integrity

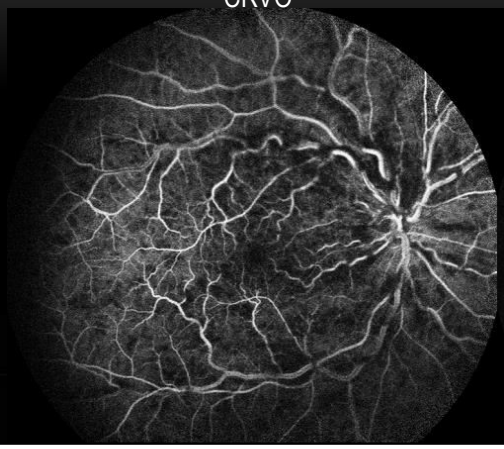
CRVO MANAGEMENT

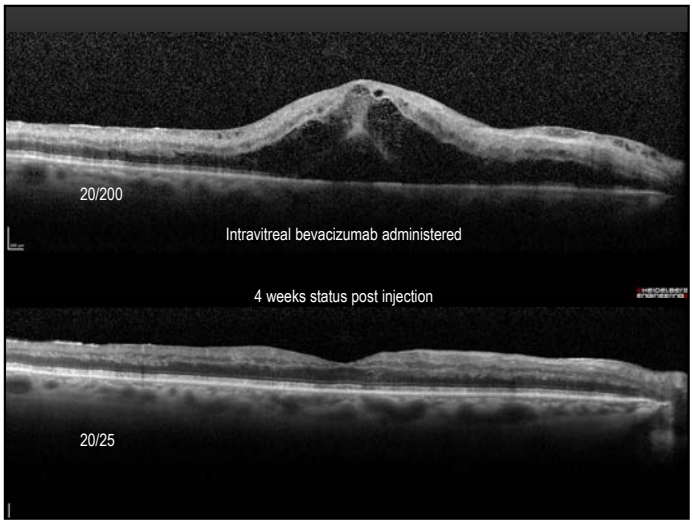
- Intravitreal Injection therapy for macular edema (Anti-VEFG or steroid)
- Ischemic CRVO with neovascularization:
  - PRP?
  - Continued anti-VEGF to control neovascular drive
- Systemic workup/management: Blood pressure, glucose, lipid panel, hypercoagulability screen if indicated
- Monitoring: Close follow-up for neovascular glaucoma development





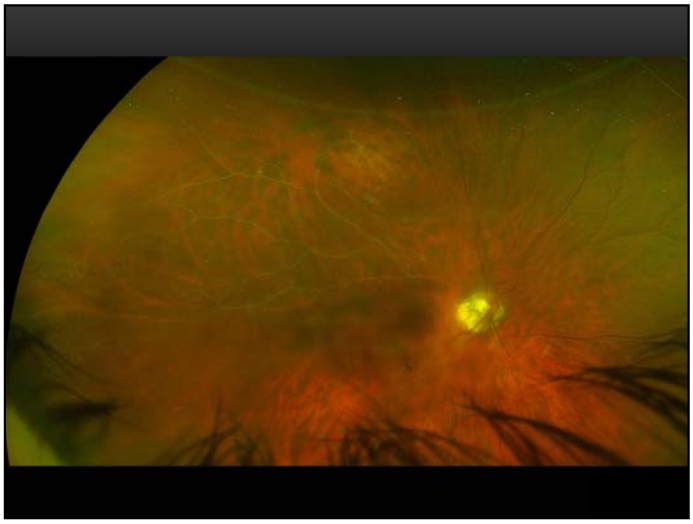
74/W/M
CRVO





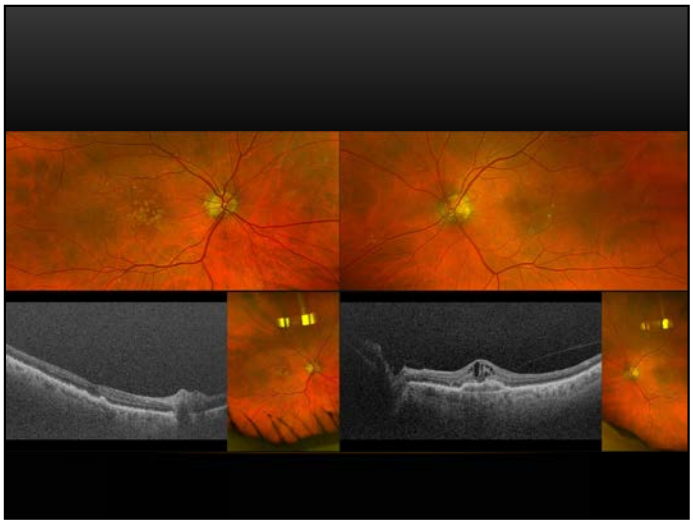
WHAT ABOUT CRAO/BRAO?

- Pathophysiology: Usually an embolic occlusion of the central retinal artery leading to cessation of inner retinal blood flow and ischemic infarction of the retina
- Epidemiology: Ophthalmic emergency; analogous to a retinal stroke
- Vascular Mechanism: Most emboli originate from carotid plaques or cardiac sources (atrial fibrillation, valvular disease)



CASE 3

- 85/W/M
- CC: Blurred vision OS>OD
- HPI: Blur OS, gradually getting worse over last several months, glasses not helping
- PMHx: HTN, Hyperlipidemia
- BCVA: 20/30 OD, 20/60- OS
- IOP: 13 mmHg OD, 12 mmHg OS
- Anterior Seg: 1+ PEK OU, Pseudophakic OU
- Posterior Seg: see photos



NEOVASCULAR AMD

- Degeneration of retinal pigment epithelium (RPE) and Bruch's membrane leading to choroidal neovascularization (CNV) subretinal fluid, intraretinal fluid, hemorrhage, and subretinal fibrosis
- Most common cause of severe central vision loss in adults >55 years

NEOVASCULAR AMD RISK FACTORS

- Age
- Family history/genetics
- Smoking (strongest modifiable risk factor)
- Cardiovascular disease, hypertension, obesity
- Light iris color and cumulative UV exposure
- More common in caucasians

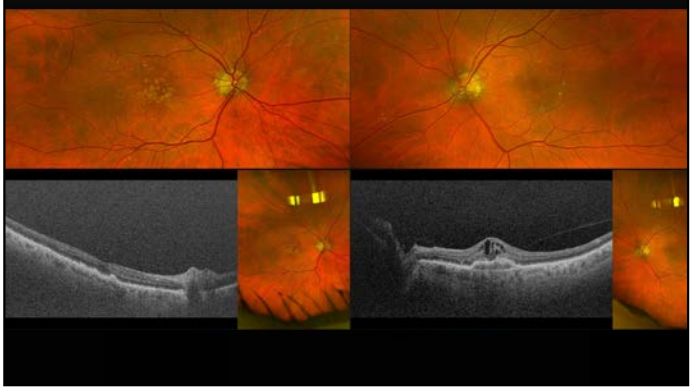
NEOVASCULAR AMD SIGNS AND SYMPTOMS

- Symptoms: Metamorphopsia, central scotoma, difficulty reading or recognizing faces
- Signs:
  - Subretinal or intraretinal fluid on OCT
  - Subretinal hemorrhage, CNV lesion
  - Disciform scar in advanced disease
  - Drusen coexistent

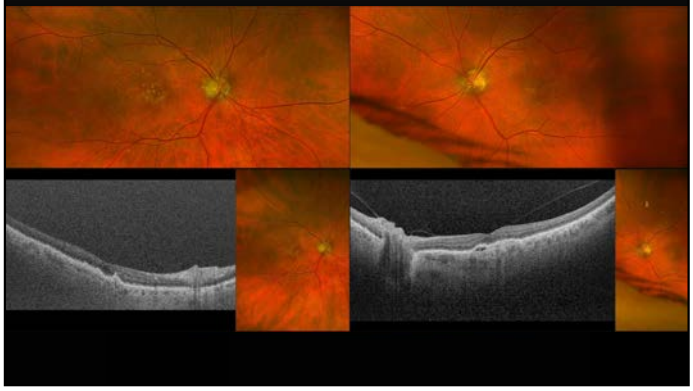
NEOVASCULAR AMD MANAGEMENT

- Anti-VEGF intravitreal injections:
  - Faricimab also has a second MoA: angiopoietin-2 (Ang-2) inhibitor
  - Regimen: Loading dose, treat-and-extend, and/or PRN
- Previously used treatments include PDT and grid laser

VA 20/30 OD, 20/60- OS



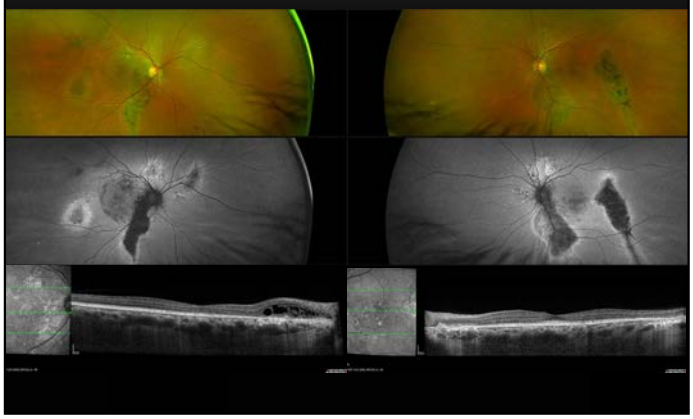
FARICIMAB OS Q4-6W FOR 6 MONTHS
VA 20/30 OD, 20/50+ OS

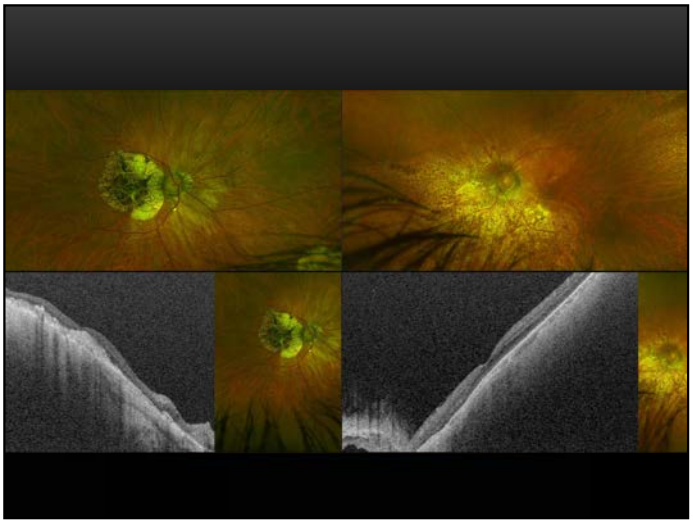


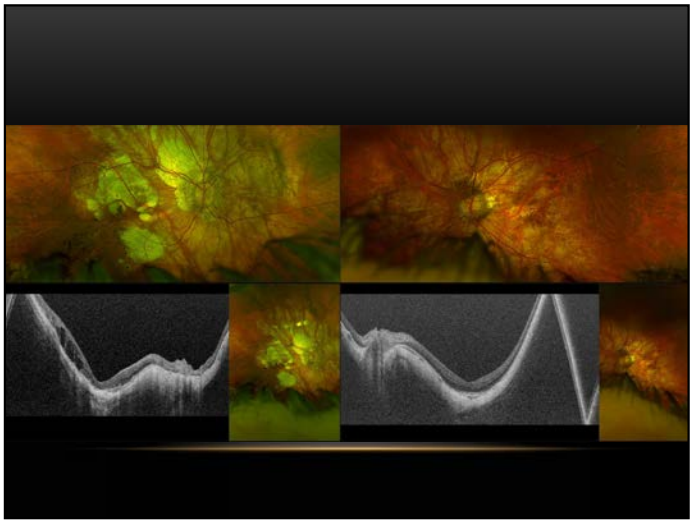
WET AMD VS CSR VS PPC VA MYOPIC DEG AND CHOROID APPEARANCE

- Wet AMD – typically normal thinner choroid on EDI
- CSR – Thickened (pachychoroid) on EDI
- PPV - balloon-like formations on ICG with corresponding thickening on EDI
- Myopic degeneration – Very thin on EDI (EDI not needed to appreciate)

CHRONIC CSR

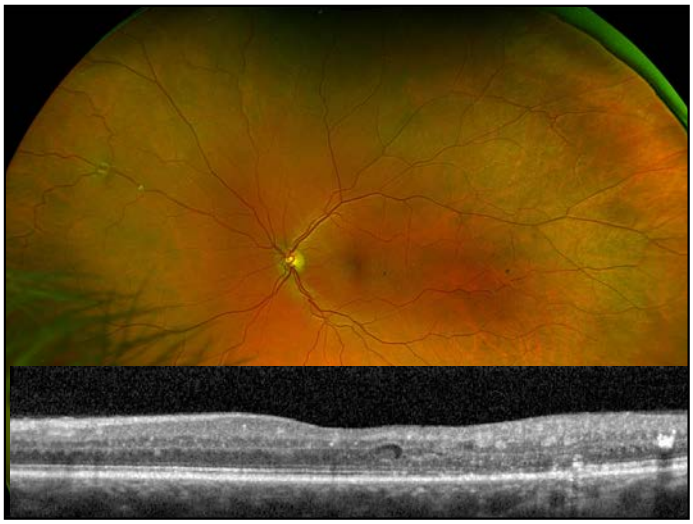






CASE 4

- 46/W/M
- CC: Mild blurred vision OS
- HPI: Mild, central vision, patient is a pilot in the USAF and needs to be cleared to fly – first appointment, arrived to clinic with a military physician
- PMHx: unremarkable
- UCVA: 20/15 OD, 20/20+1 OS
- IOP: 14 mmHg OD, 15 mmHg OS
- Anterior Seg: unremarkable
- Posterior Seg: OD unremarkable, OS - See imaging



MACULAR TELANGIECTASIA (MACTEL)

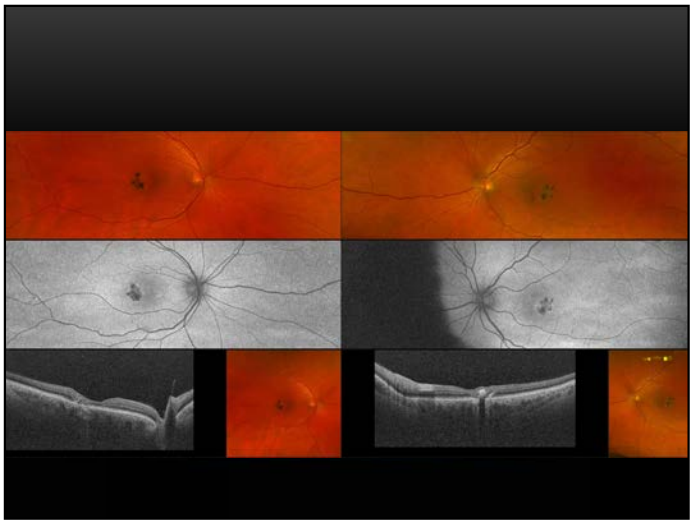
- Pathophysiology: Abnormal parafoveal capillary network and Müller cell dysfunction causing vascular leakage
- Classification:
  - Type 1: Unilateral, aneurysmal telangiectasia (usually male)
  - Type 2: Bilateral, idiopathic parafoveal telangiectasia
- Type 2 usually affects middle-aged to older adults; often misdiagnosed early as macular edema or early AMD

MACTEL RISK FACTORS

- Type 1: Often idiopathic; occasionally associated with systemic vascular disorders
- Type 2:
  - Age (5th–6th decade)
  - Diabetes (without DR), or hypertension (associations)
  - No strong genetic link identified
  - Possible link with abnormal Müller cell metabolism

MACTEL SIGNS

- Temporal foveal reflex blunting
- Microaneurysms (more common in type 1)
- Right-angled venules
- Parafoveal telangiectatic vessels
- Intraretinal crystalline deposits
- Retinal pigment hyperplasia and neovascularization in late stages

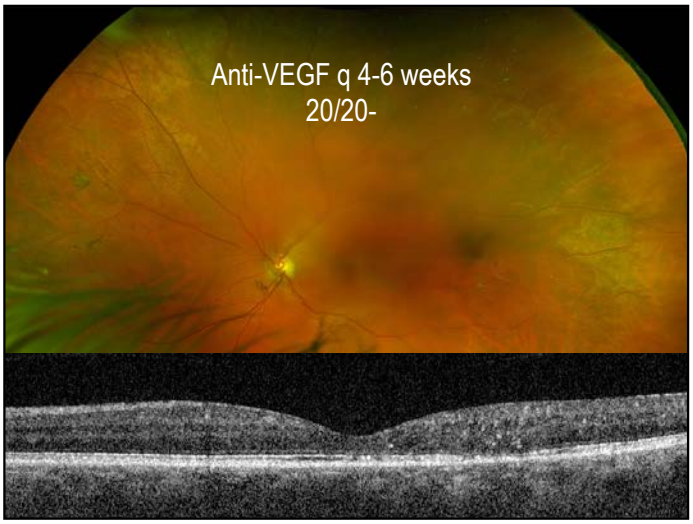


MACTEL ANCILLARY TESTING

- OCT:
  - Hyporeflective cavities and hyperreflective deposits in the inner retina
- FA:
  - Late leakage in juxtafoveal area (temporal > nasal)
- OCT-A:
  - Dilated parafoveal capillary network and telangiectatic vessels
- Fundus Autofluorescence (FAF):
  - Increased signal temporally (due to loss of macular pigment)

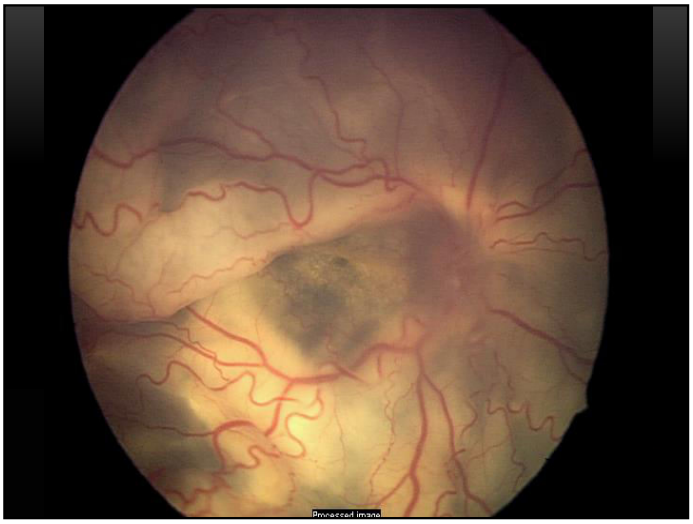
MACTEL MANAGEMENT

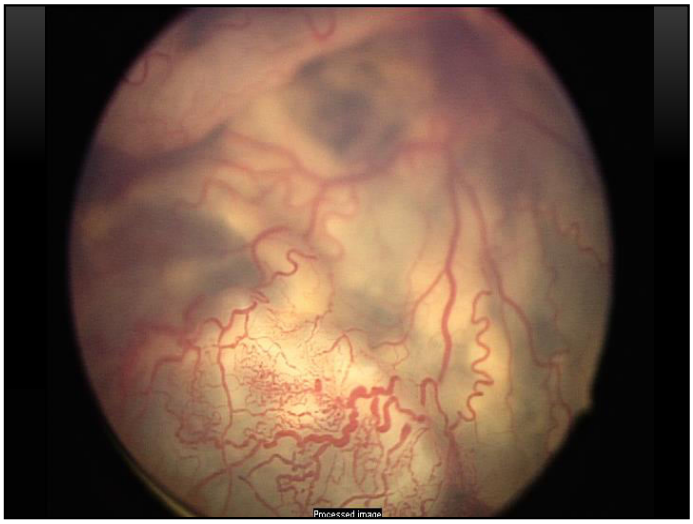
- Monitor
- Laser photocoagulation to leaking telangiectatic vessels
- Anti-VEGF?



COATS DISEASE

- Idiopathic retinal vascular telangiectasia leading to lipid-rich subretinal exudation and possible exudative retinal detachment
- Rare, nonhereditary, usually unilateral
- Primarily affects young males (average onset: 8–16 years)



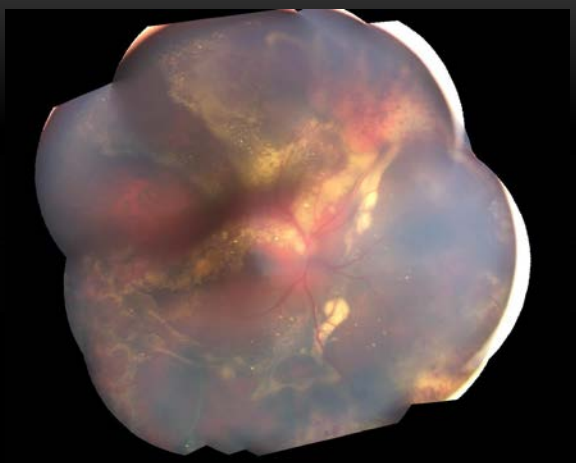


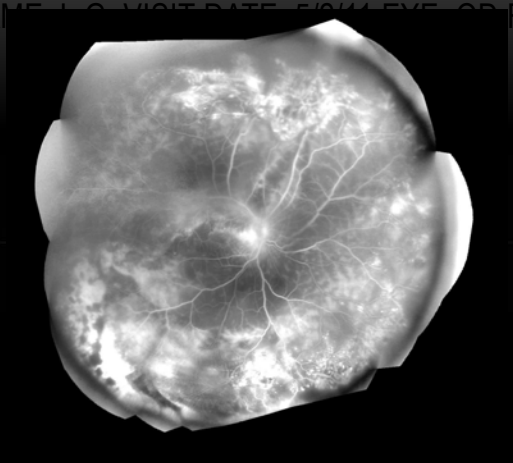
COATS DISEASE SIGNS

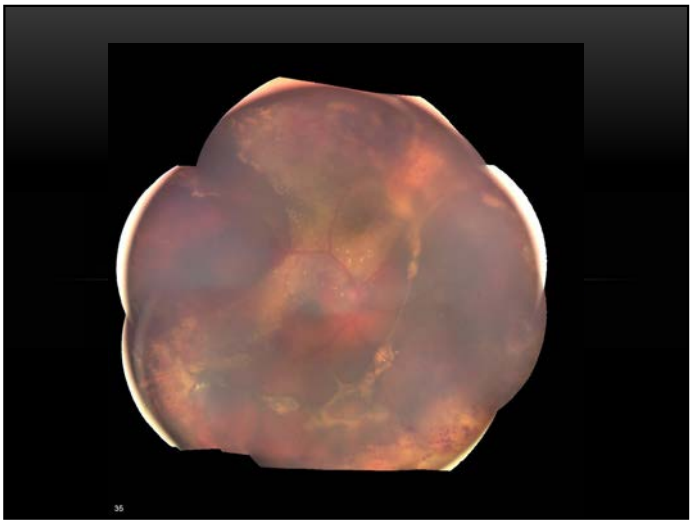
- Telangiectatic vessels
- Venous dilation
- Microaneurysms
- Fusiform capillary dilation
- No intraocular inflammation
- Typically absence of neovascularization

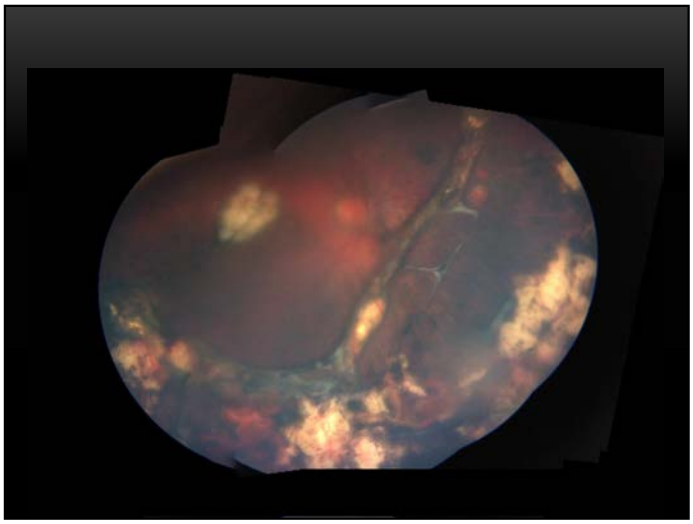
COATS DISEASE MANAGEMENT

- Early disease:
  - Laser photocoagulation to telangiectatic vessels
  - Possible cryotherapy for more peripheral lesions
- Advanced disease (exudative detachment):
  - Drainage of subretinal fluid and/or vitrectomy if necessary
  - Anti-VEGF may be used adjunctively to reduce exudation
- Severe end-stage:
  - Enucleation if painful blind eye or RB can't be ruled out

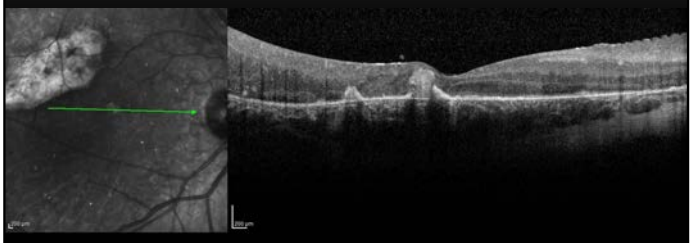








VA 20/40
EXTENDED FOLLOW-UP: 32 MONTHS



RB PRESENTING SIGNS & SYMPTOMS

- Leukocoria – 50-60%
- Strabismus – 20%
- Red, painful eye – 7%
- Well baby examination – 3%
- Other – 10%

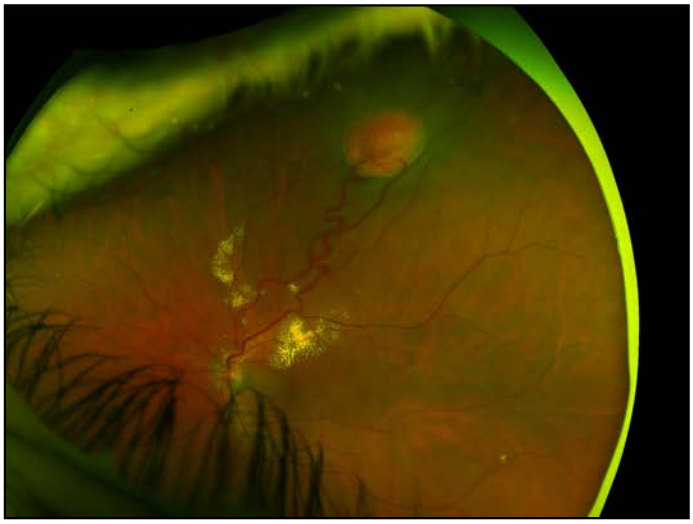
STAGING

- The International Classification for Intraocular Retinoblastoma
  - Group A
    - Small tumors (3 millimeters [mm] across or less) that are only in the retina and are not near optic disc or foveola.
  - Group B
    - All other tumors (either larger than 3 mm or small but close to the optic disc or foveola) that are still only in the retina.
  - Group C
    - Well-defined tumors with minimal subretinal seeding or vitreous seeding.
  - Group D
    - Large or poorly defined tumors with widespread vitreous or subretinal seeding and/or retinal detachment.
  - Group E
    - The tumor is very large, extends near the front of the eye, presents with AC seeding, spontaneous hyphema or causing glaucoma.

(2015, March 12). Retrieved from https://www.cancer.org/cancer/retinoblastoma/detection-diagnosis-staging/staging.html

CASE 5

- 28/W/M
- CC: Floaters OS
- HPI: Mild, sporadic floaters without flashes; present for 2-3 months
- PMHx: unremarkable
- BCVA: 20/20 OD, 20/20- OS
- IOP: 15 mmHg OD, 16 mmHg OS
- Anterior Seg: unremarkable
- Posterior Seg: OD unremarkable, OS – see photo

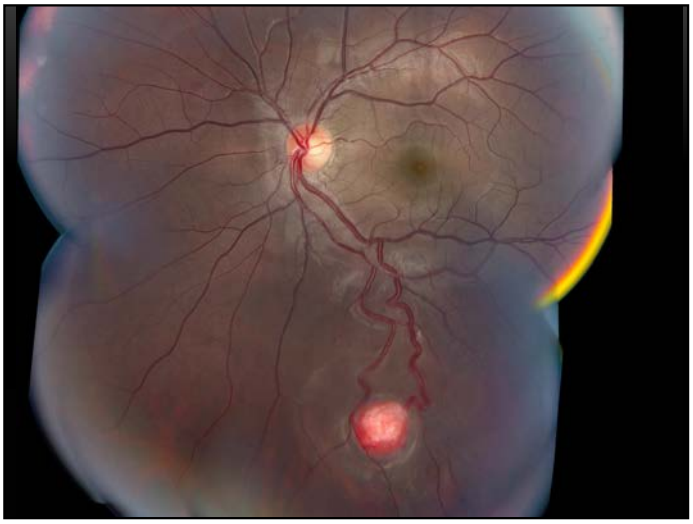


RETINAL CAPILLARY HEMANGIOMA

- Orange–red vascular tumors within the retina with feeder vessels
- Can occur sporadically or in association with von Hippel–Lindau (VHL) disease
- VHL diagnosed at around 20 years of age
- Sporadic tumors present later in life, at around 30–40 years of age

CAPILLARY HEMANGIOMA

- Large lesions produce intra- and subretinal exudates in the surrounding part of the fundus and at the macula
- Advanced lesions give rise to vitreous membranes, which cause tractional retinal detachments
- Severe exudative retinal detachment can also occur
- In the advanced stages, secondary glaucoma and uveitis commonly occur

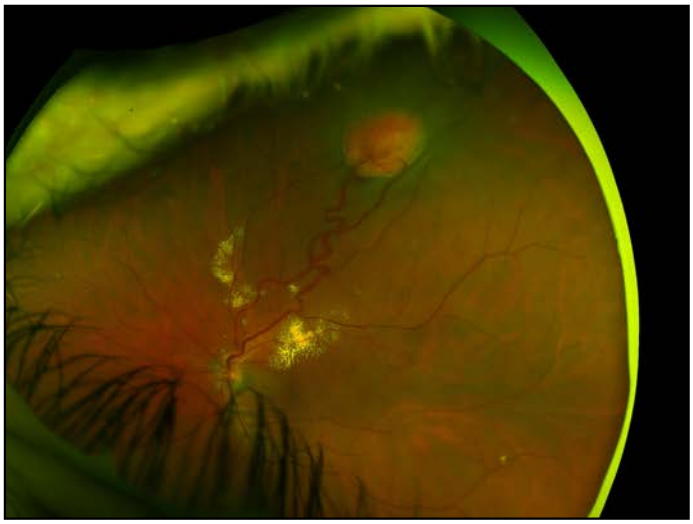


CAPILLARY HEMANGIOMA TREATMENT

- Determined by the size, number, and location of the hemangioblastomas, as well as any secondary effects
- Dormant lesions are usually treated if peripherally located and monitored if located juxtapapillary

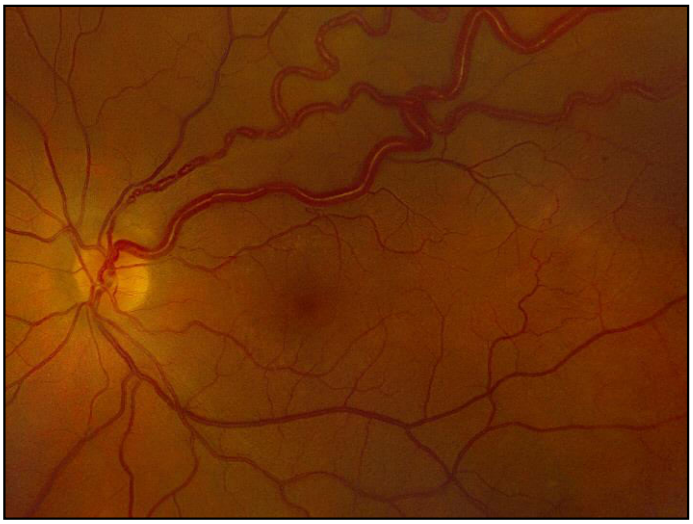
CAPILLARY HEMANGIOMA TREATMENT

- Treatment options:
  - Observation
  - Vascular endothelial growth factor receptor inhibitor
  - Photodynamic therapy
  - Radiotherapy (for larger tumors)
    - EBRT
    - Plaque brachytherapy
    - Proton beam radiotherapy
  - Cryotherapy (less than 5mm thick)
  - Laser photocoagulation (1.5mm – 4mm diameter)
  - Vitreoretinal surgery



IN ADDITION TO TREATMENT…

- Patients must still be screened for VHL
  - Multiple retinal hemangioblastomas are diagnostic for VHL
  - 50% of solitary retinal hemangioblastomas are associated with VHL
- Screenings include:
  - Physical examination
  - Imaging of the abdomen and brain
  - Genetic testing
- Relatives should also be screened



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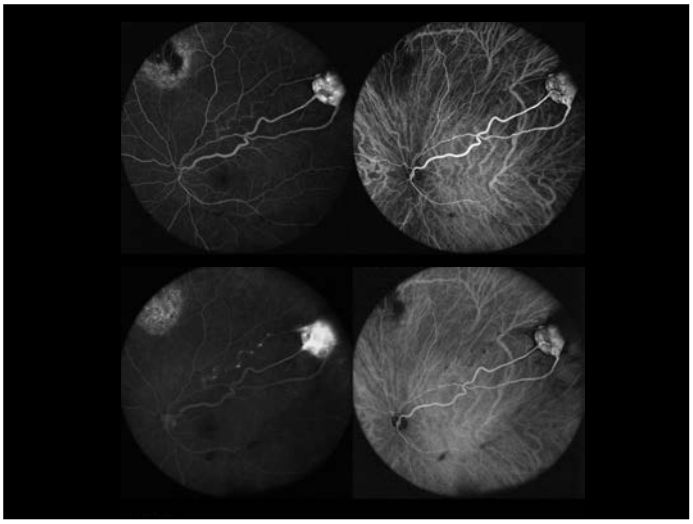


VHL

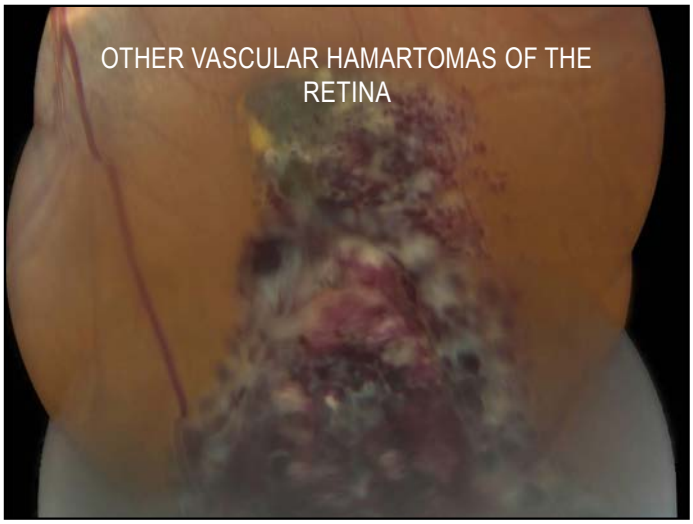
- Autosomal dominant
- Benign and malignant tumors and cysts may develop in several organs
- Caused by mutations of the VHL gene on chromosome 3p25-26
- Tumor cells show increased expression of vascular endothelial growth factor (VEGF)

VHL

- In a large series of 327 patients published by Neumann et al, the most common lesions were:
  - hemangioblastoma of the central nervous system (52% of affected patients)
  - retinal hemangioblastoma (48%)
  - renal cysts (33%)
  - pheochromocytoma - tumor of the medulla of the adrenal glands (33%)
  - pancreatic cysts (22%)
  - renal cell carcinoma (22%)

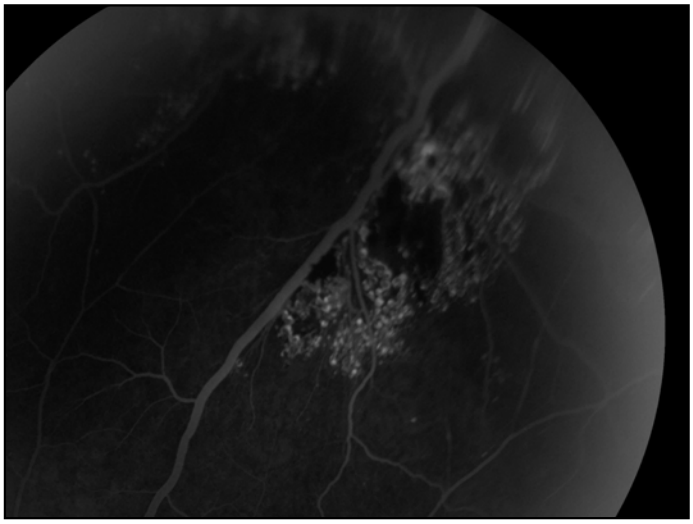
MURRAY

OTHER VASCULAR HAMARTOMAS OF THE RETINA

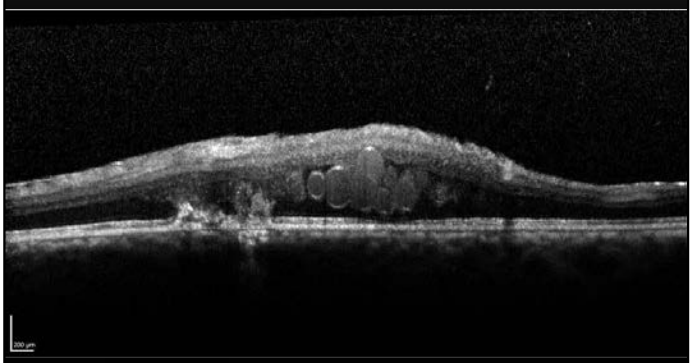


CAVERNOUS HEMANGIOMA

- Clusters of dark-red, saccular aneurysms within the inner retina
- May occur sporadically or can be inherited (autosomal dominant)
- May be associated with cerebral, spinal, and cutaneous angiomas, and aneurysms
- Usually be found away from the posterior pole (but rarely juxtapapillary and macular)
- Normal endothelial cell lining, therefore not associated with exudation
- Fluorescein angiography typically shows slow filling of the aneurysms with little or no leakage and late 'capping' of the dye in the superior half of the aneurysms as a result of settling of red blood cells

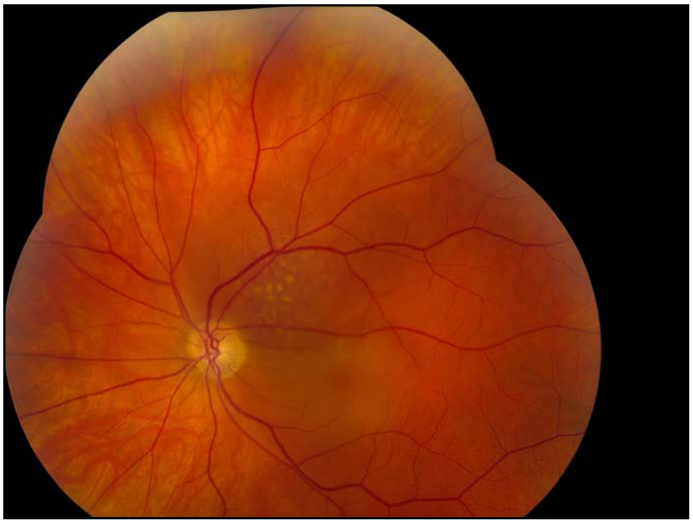


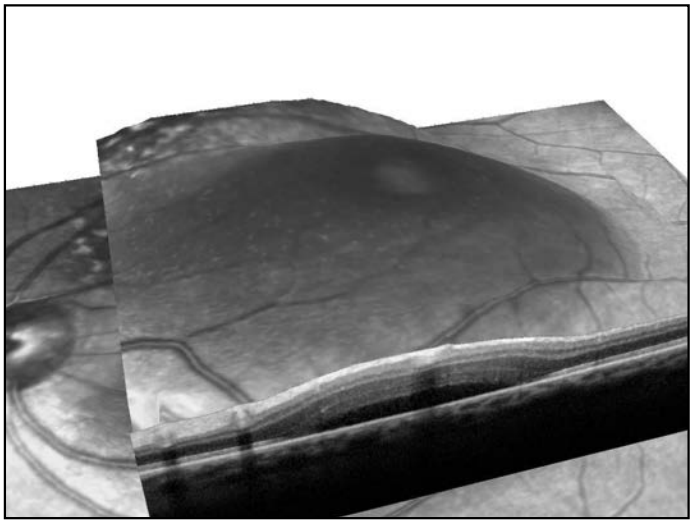
OCT OF CAVERNOUS HEMANGIOMA



CASE 6

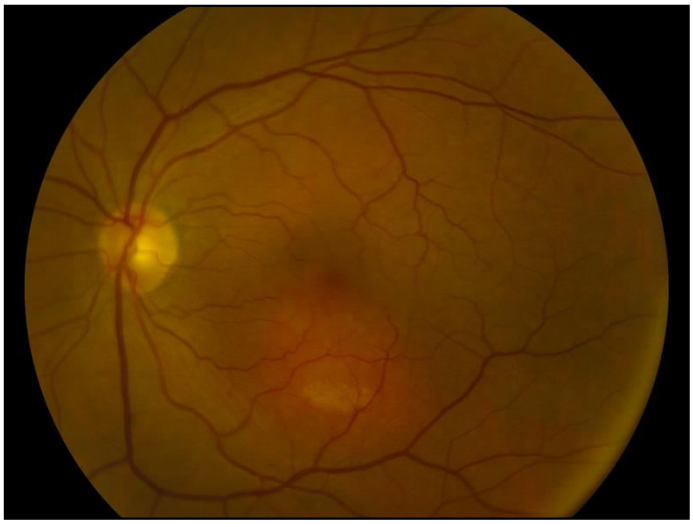
- 57/W/M
- CC: Blurred vision OS
- HPI: Moderate, central vision, worsening over several weeks, was told he might have a tumor in the eye
- PMHx: HTN
- BCVA: 20/20 OD, 20/60 OS
- IOP: 12 mmHg OD, 12 mmHg OS
- Anterior Seg: NS OU
- Posterior Seg: OD unremarkable, OS - See Photo and OCT





CIRCUMSCRIBED CHOROIDAL HEMANGIOMA

- Rare, benign, intraocular tumors of the choroid
- Often mistaken for choroidal metastases and melanomas
- Characteristic appearance consists of an indistinct round-to-oval, orange-pink swelling at the posterior pole, often involving the optic disc, macula, or both
- Likely congenital -- macular hemangiomas are usually associated with amblyopia, most likely occurring as a result of hyperopia



CIRCUMSCRIBED CHOROIDAL HEMANGIOMA

- May remain asymptomatic throughout life
- However, visual symptoms may present between the second and fifth decades
  - Caused by secondary, exudative retinal detachment and macular edema.
- If left untreated, many patients eventually develop severe retinal detachments with secondary neovascular glaucoma.

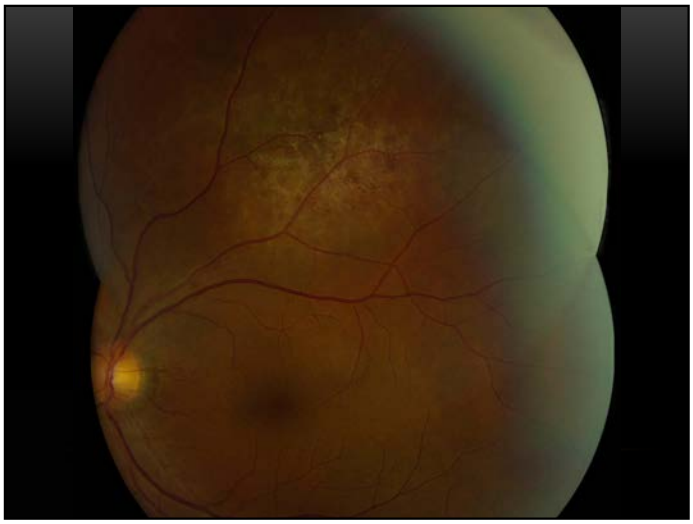
DIAGNOSTIC FEATURES

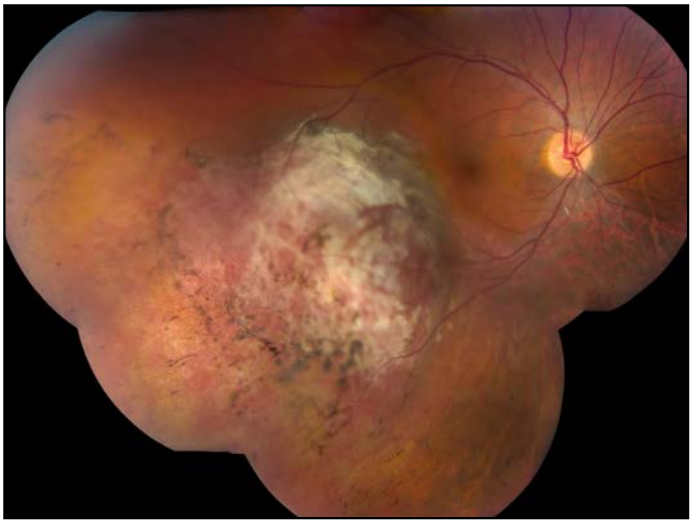
- Ultrasonography shows acoustic solidity with a high internal acoustic reflectivity
- Fluorescein angiography shows a highly vascularized choroidal lesion that typically fills rapidly, simultaneously with the normal choroidal vessels
- OCT can identify and quantify any associated macular edema and exudative retinal detachments

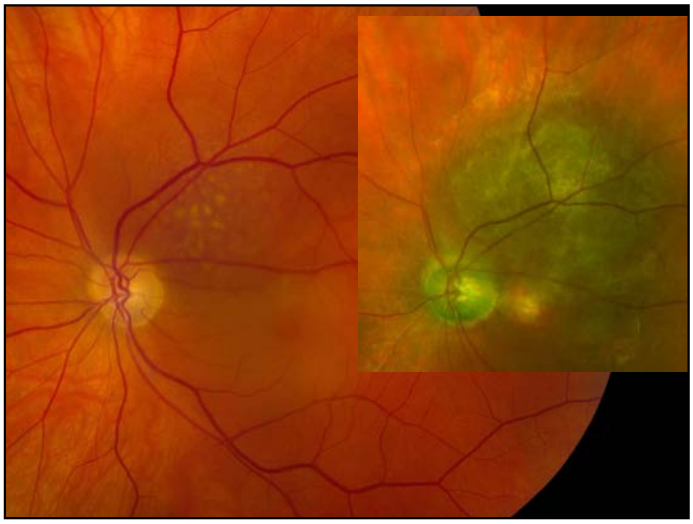
CIRCUMSCRIBED CHOROIDAL HEMANGIOMA TREATMENT

- Indicated for symptomatic patients due to:
  - Exudative retinal detachment
  - Macular edema
  - Severe exudative retinal detachment threatening to cause neovascular glaucoma
- PDT has been an effective treatment
- Other treatment modalities include:
  - Anti-VEGF therapy
  - External beam or proton beam radiotherapy
  - Transpupillary thermotherapy or laser photocoagulation

MURRAY

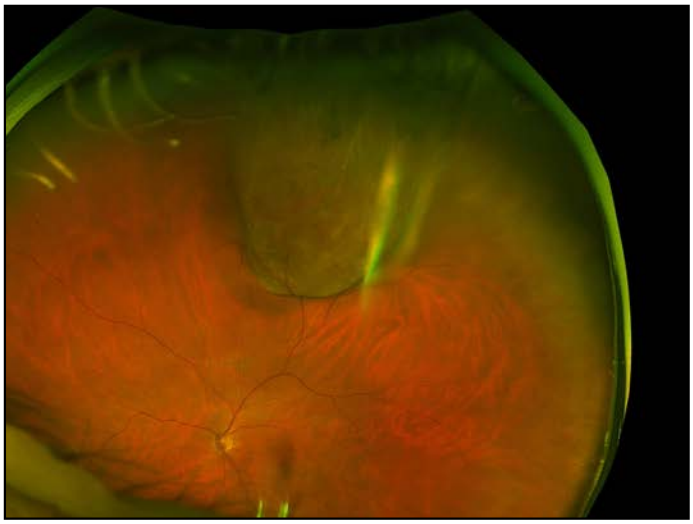






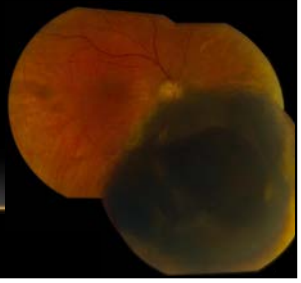
LAST CASE

- 57/W/F
- CC: Mild blurred vision OU
- HPI: Mild, decrease of vision while reading, went to her local eye doctor and was told she has a lesion in her right eye
- PMHx: unremarkable
- BCVA: 20/25 OD, 20/25 OS
- IOP: 14 mmHg OD, 12 mmHg OS
- Anterior Seg: NS OU
- Posterior Seg: OD unremarkable, OS - See Photo

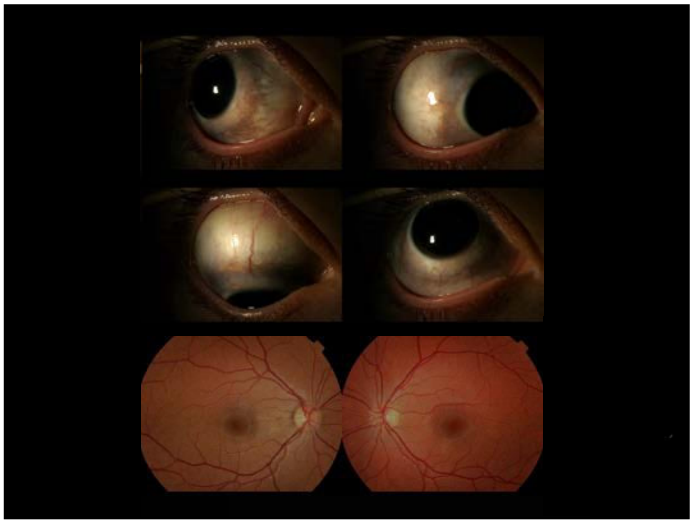


CHOROIDAL MELANOMA

- Most common primary intraocular neoplasm in adults
- Incidence of ~4-6 per million per year in the US
- Risk factors include
  - Iris and Skin color
  - European ancestry
  - Age
  - Oculodermal Melanocytosis (Nevus of Ota)
  - Environmental factors (less understood)



MURRAY

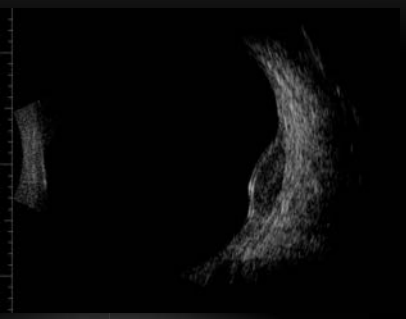


CHOROIDAL MELANOMA

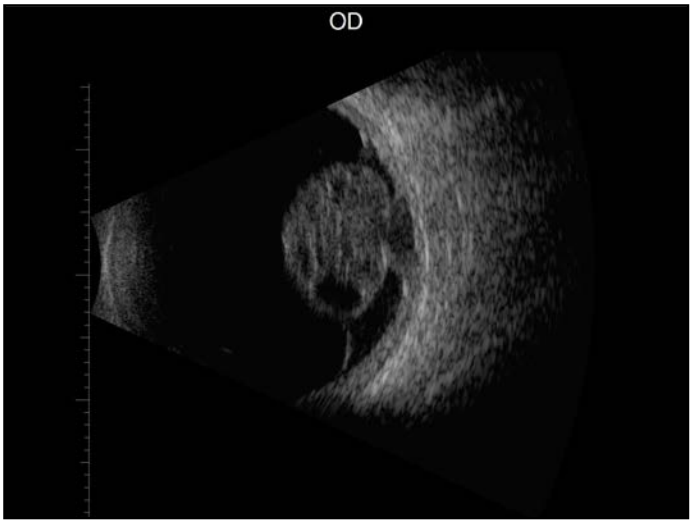
- Typically present as elevated choroidal lesions that may be pigmented or amelanotic
- Favored metastatic sites are the liver and lungs
- Diagnosis is made primarily by physical exam
  - Indirect ophthalmoscopy
  - Echography
- FA may show dual circulation pattern

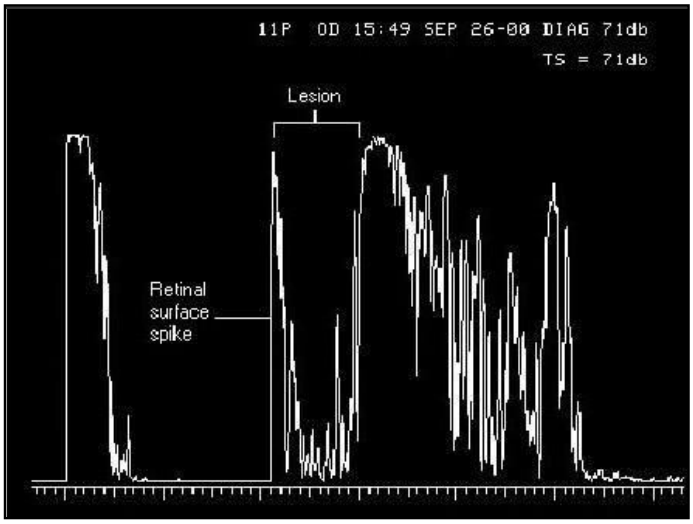
ECHOGRAPHY

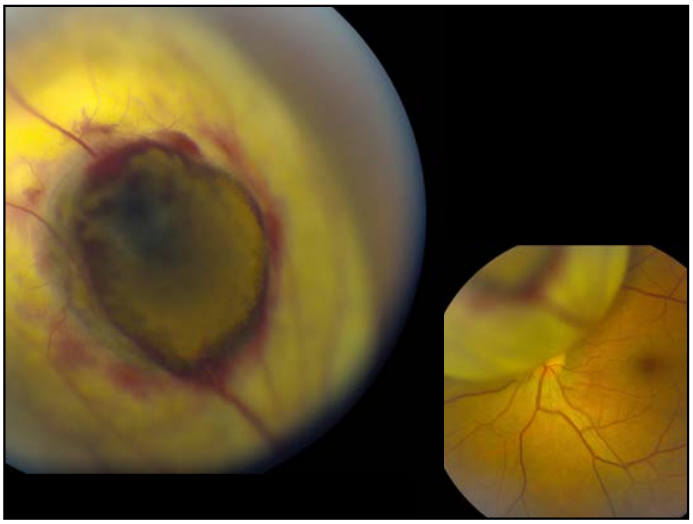
- Acoustic hollowing
- Choroidal excavation
- Orbital Shadowing
- Collar-button configuration

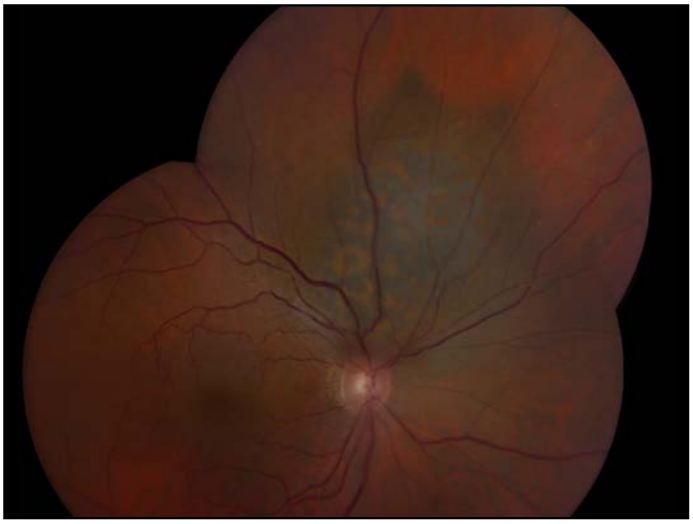


MURRAY





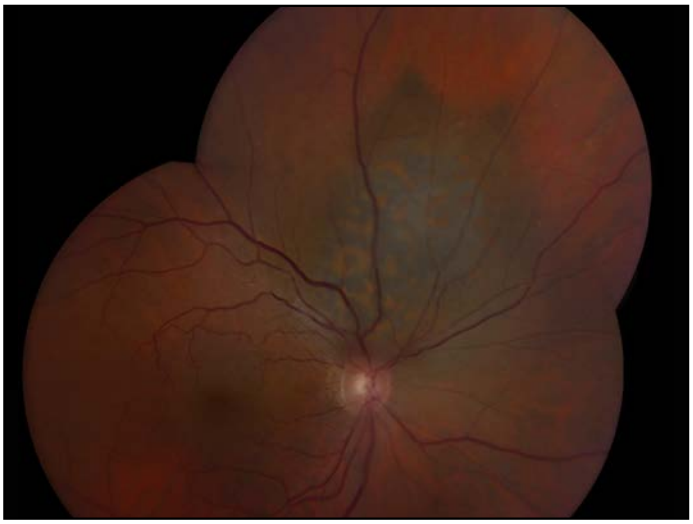




MOLES

- **M**ushroom shape
- **O**range pigment
- **L**arge size
  - Thickness: <1.0 mm vs 1.0-2.0 mm vs >2.00 mm
  - Diameter: <3DD vs 3-4DD vs >4DD
- **E**nlarging tumor
- **S**ubretinal fluid

- Scoring system: Absent = 0 points, Unsure/Borderline = 1 point, Present = 2 points
  - *total points of 3 or greater prompt urgent referral for probable melanoma



PRIMARY MELANOMA TREATMENT

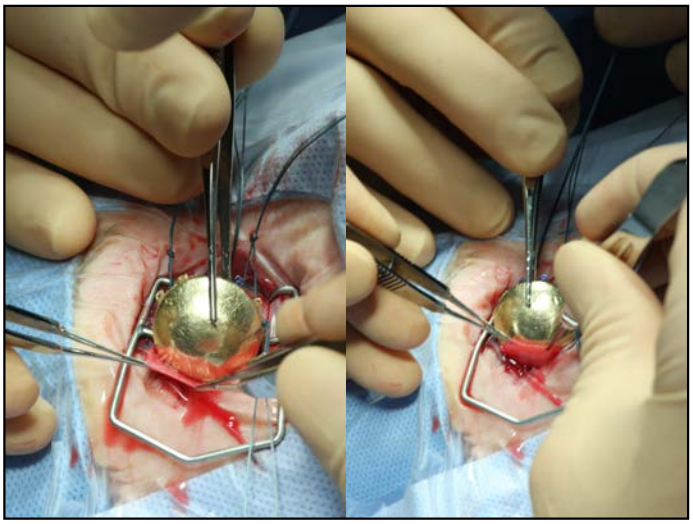
- Enucleation
- Radiation Therapy
  - ^{125}I plaque brachytherapy
  - Proton beam therapy
  - Gamma Knife and other Stereotactic Radiosurgery
- Transpupillary Thermotherapy (with radiation)

OTHER TREATMENTS EMPLOYED (WITH LESS SUCCESS)

- Microsurgical Resection
  - External Trans-Scleral Resection
  - Transvitreal Endoresection
- Laser Photocoagulation
- Photodynamic Therapy
- Hyperthermia
- Cryotherapy

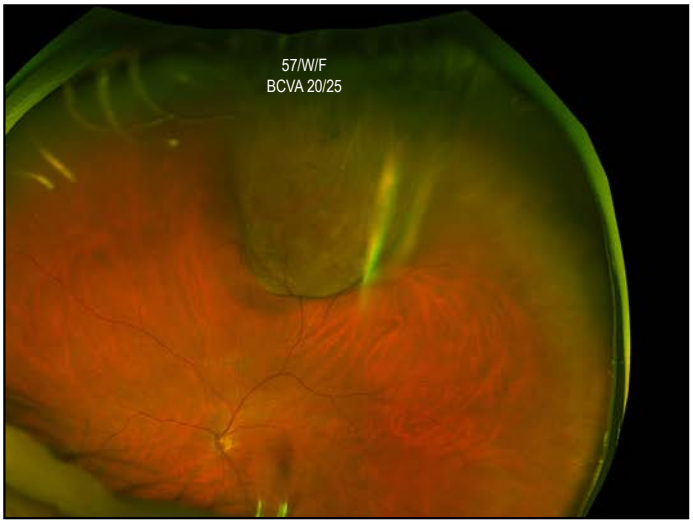
^{125}I PLAQUE BRACHYTHERAPY

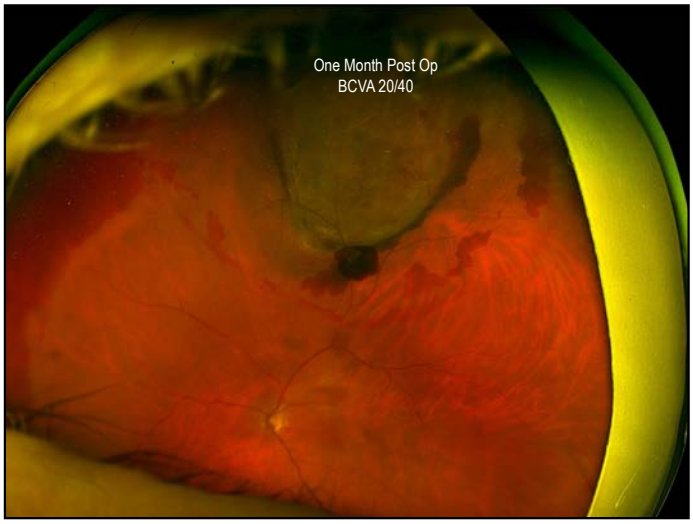
- Currently most widely used treatment for choroidal melanoma
- Small "rice-sized" radioactive seeds are attached within a gold bowl – the plaque
- Plaque sewn onto sclera using intraoperative echography to guide positioning
- Patient remains in the hospital for four days
- Day 3, plaque is removed
- Day 4, patient goes home



^{125}I PLAQUE BRACHYTHERAPY COMPLICATIONS

- Radiation retinopathy
- Radiation papillopathy (or radiation optic neuropathy)
- Cataract
- Vitreous hemorrhage
- Exudative RD
- Neovascular Glaucoma



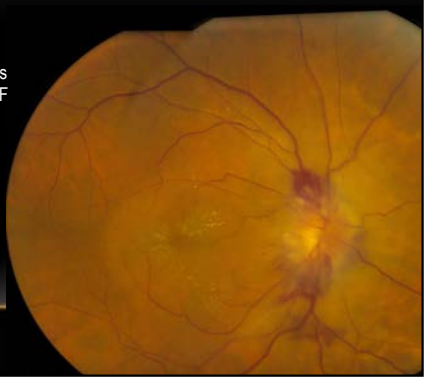


CURRENT MANAGEMENT OF RADIATION RETINOPATHY

Intravitreal injections
- Anti-VEGF
- Steroid

Vitrectomy

Enucleation



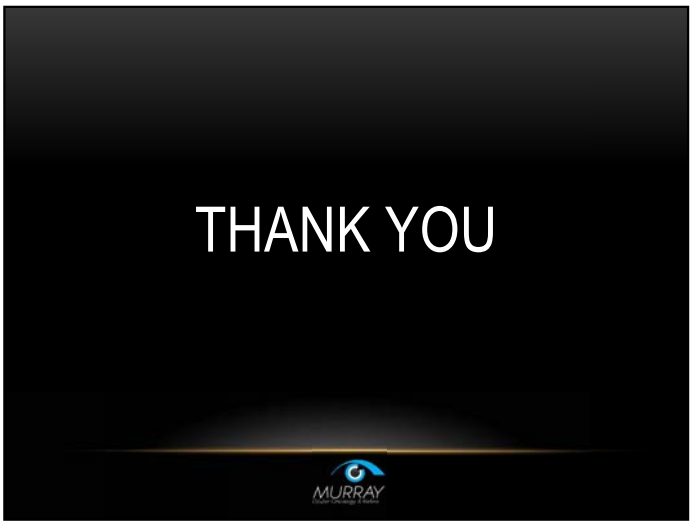
METASTATIC SCREENING WITH UVEAL MELANOMA

- **Abdominal MRI**
  - With liver function panel
- Chest X-ray
- CBC with differential
- SMA-20

- **Genomic testing**
  - Gene Expression Profiling

QUESTIONS?

MURRAY


THANK YOU
MURRAY