CNV Variations and Masqueraders

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Course Goal

- To provide useful clinical information about variations and masqueraders of CNV.
  - Classification, diagnosis, treatment/management

Evaluate the vitreoretinal interface routinely.

The Vitreoretinal Interface

retinalphysician.com
Persistent Vitreomacular Adhesions (VMA)

Anomalous PVD
• May hasten the Wet AMD process.

The Retina
• RPE
• Neurosensory
• 6 million Cones
  • Detailed vision
  • Color vision
• 120 million Rods
  • Peripheral retinal receptors
  • Great sensitivity to light

SD-OCT Healthy Macula

Jetrea (ocriplasmin)
Retina

- The Pigment Epithelium
  - Monolayer
  - Cuboidal cells
  - Function of RPE
  - Tight junctions form outer blood-retina barrier

RPE

Retinal Pigment Epithelium

- 120 million cells in monolayer
- Functions of RPE
  - Phagocytosis of renewable discs of PRs
  - O-2 diffusion to PRs
  - Provision of nutrients to PRs

Early AMD: Accumulation of Lipofuscin and Vitamin A Metabolites

Reduced degradation of cellular debris leads to the accumulation of lipofuscin, toxic vitamin A metabolites.

Drusen

Retina

- The Neurosensory Retina
  - The Photoreceptors
    - Structure and function of cones and rods
  - Inner and outer segment junction
    - Importance of structural integrity to visual function
  - Outer limiting membrane
  - Outer nuclei
  - Synaptic layer (plexiform)
Photoreceptors

- Inner nuclei
- Synaptic layer (plexiform)
- Ganglion cells
- Nerve fiber layer
- Internal limiting membrane

Retinal Vasculature

- 2 main sources of blood supply:
  - Choroidal BV
    - Supplies outer retinal layers, including PRs
  - CRA
    - 4 branches nourish inner retina
    - Run radially toward fovea

Retinal Capillaries

- Pericytes surround each endothelial cell
  - Provide support
- Tight junctions between endothelial cells
- Pericytes + tight junctions form inner blood-retinal barrier.

Retina

- Phototransduction
  - Conversion of light into an electrical impulse
- The retina is damaged by its own operation.
- Autoregulation of blood flow
Functional Anatomy: The Fovea

The Choroid

- Vascular layers
- Melanocytes
- Bruch’s membrane
- Sympathetic regulation of blood flow
- Function of choriocapillaris
  - Supply of nutrients
  - Absorption of light

Diagnostic Dilemma

Choroidal Neovascularization

Angiogenesis

Environmental factors

(hypoxia, pH)

Growth factors, hormones

(EGF, bFGF, PDGF, IGF-1, IL-1α, IL-6, estrogen)

Endothelial cell activation

VEGF-A binding and activation of VEGF receptor

VEGF-A = vascular endothelial growth factor A; EGF = epidermal growth factor; bFGF = basic fibroblast growth factor; PDGF = platelet-derived growth factor; IGF = insulin-like growth factor; IL = interleukin.


The Angiogenic Cascade is a Complex Process

CNV ---> FV Scar
CNV has several variations, causes, and masqueraders.

Choroidal Neovascularization
- Subjective symptoms
- Objective data
- Diagnostic Workup
- Making the diagnosis

Common Causes of CNV
- Exudative AMD
- Ocular Histoplasmosis
- High Myopia
- Angioid Streaks

Fundus Autofluorescence
- Wet AMD
Fluorescein Angiography

Indocyanine Green Angiography (ICGA)
- Uses digital imaging systems
- Dye properties
- “Sees” through blood
- Delineates choroidal circulation better than fluorescein angiography
- Boundaries of occult membranes imaged

Occult CNV

Classic CNV

Type I CNVM

Type II CNVM
CNV in subsensory space
ANGIOID STREAKS

- Note Angioid Streaks radiating from the optic discs and macular laser scarring

Differential Dx. of Angioid Streaks: PEPSI

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Key Clinical Features</th>
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<tbody>
<tr>
<td>Pseudoxanthoma</td>
<td>Redundant, “plucked chicken” skin hypertrophy</td>
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<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Blue sclera, joint hyperextensibility, fragile, elastic skin, eczema, bruising</td>
</tr>
<tr>
<td>Paget’s disease</td>
<td>Bone erosion and abnormal bone formation, osteosclerosis, hearing loss, vertigo, tinnitus, impaired speech, difficulty swallowing</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Hemoglobin SS (most commonly) anemia</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Skin and iris changes</td>
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Causes of CNV

- High Myopia in a 52 y/o WM
- CNV w/heme
48 y/o WM
-12.00D

Concave fundus, CNV, schisis

Causes of CNV

• OHS

Case

• 81 Year old Female with a history of arthritis.
• 7 year history of injections with Avastin or Lucentis
• PMH: AMD OU, Cataracts OU
• OcHx: Injections for AMD.

Ophthalmic Exam

• VA:
  - OD: 20/400  OS: 20/80
• IOP
  - OD: 11  OS: 12
• SLE:
  - OD: NS +1  OS: NS + 1
• DFE:
  - PED OD  and Geo Atrophy OS

OCT

After Switching to Eyelea
Variations and Masqueraders of CNV

- Polypoidal Choroidal Vasculopathy (PCV)
- Retinal Angiomatous Proliferation (RAP)
- Masqueraders of CNV
  - Choroidal Neoplastic Disease
  - Primary Tumors of the Choroid
    - Nevus vs. melanoma
  - Metastatic Tumors to the Choroid
  - Common primary sites
    - Breast
    - Lung
  - Central Serous Chorioretinopathy (CSC)

ICG Angiography

AMD vs PCV

SUSPICIOUS POLYPOIDAL

AMD - SUBRETINAL HEMORRHAGE
Retinal Angiomatous Proliferation

- Sub retinal neovascularization ensues.

Retinal Angiomatous Proliferation

- First described by Yannuzzi in 1991, RAP is a retino-choridal anastamosis.
- Intraretinal capillary proliferation, which extends throughout the sensory retina and then into the sub retinal space.

Retinal Angiomatous Proliferation

- 10-20 % of neovascular AMD patients start with RAP.
- The age group is thought to be slightly older.
- ICGA aids in confirming diagnosis, identifying “hot spots” of ICG dye pools in the sub retinal space.

82 y/o WM w/drusen
RAP Stage I: intraretinal neovascularization.

RAP Stage II: subretinal NV w/retinal-retinal anastomosis.

RAP Stage III: subretinal NV w/vascularized RPED and retina-choroid anastomosis.
RAP: Current Treatment Options
- Thermal Laser
- Photodynamic Therapy
- Anti VEGF Therapy

CNV Masquerador:
Neoplastic Disease

CNV or Mass?

CNV Masquerador:
Central Serous Chorioretinopathy

Mystery Macula
- Subjective
  - 35 y/o WM
  - sudden, unilateral blur OD
  - no pain or trauma
  - "Type A"
- Objective
  - VA
    - OD 20/60
    - OS 20/20
    - Hyperopic shift
Describe That Fundus!

- DFE shows large, serous elevation
- Focal detachment of sensory retina

What other tests would you like to perform?

OCT
(Idiopathic) Central Serous Chorioretinopathy (ICSC)

Patient Outcome

- VA recovered to 20/25 at week 12
- Reduction of fluid, 20/40 VA at week 6

Central Serous Chorioretinopathy
- 36 y/o WM
- CC: Sudden central blur OS
- VA OD 20/20
- VA OS 20/200

ICSC

- Objective
  - Breakdown of outer blood-retina barrier
  - FA shows classic “smoke-stack”
    - Pooling beneath RPE detachment
    - Dye ascends vertically, then laterally in SRS
- Differential Diagnosis
  - Tumor
  - RPE detachment/CNVM
  - Steroid-induced CSC
ICSC

Plan

- Observation
  - 60% regain 20/20 w/no intervention
  - monitor q4wks for 6 mon
- Focal Laser
  - Unresolved after 4-6 mon
  - Recurrent
  - Focal, direct treatment
  - Leak must be outside FAZ (500 um)

Treatments for CSC

- Thermal laser
- Photodynamic Therapy
  - Visudyne (Verteporfin)
  - A light-activated drug

Photodynamic Therapy for CSC

- Serous detachment before PDT.
- Resolution of detachment with residual RPE mottling after PDT.

What’s new in CSC Treatment?

- Intravitreal bevacizumab (Avastin) has shown some benefit in small case series.

Low-fluence PDT

ICGA-guided, lower flow, lighter dosage resulted in less hypoperfusion of the choriocapillaris
Current and Future Treatment of CNV

- Laser
  - Now reserved for extrafoveal disease
  - Ectopic disciform
  - Polypoidal demarcation

Limitations of Laser

PDT
- Polypoidal choroidal vasculopathy
- Used in conjunction with anti VEGF
- Central Serous Chorioretinopathy

Photodynamic (Visudyne) Therapy: A 2-Step Process

- **Step 1**
  - 10 Min Infusion

- **Step 2**
  - 83 Sec Activation
Vascular endothelial growth factor (VEGF)

- VEGF was found to be essential in normal and pathological angiogenesis.
- Hypoxia (ischemia) and inflammation induce secretion of VEGF.
- VEGF binds to its receptors, promoting endothelial cell migration and proliferation, which are required to develop new vessels.
- VEGF breaks down the blood-retina barrier which increases vascular permeability (edema).
- Maximum expression of VEGF at border of vascular and avascular tissue.

Antiangiogenic Drugs: VEGF Inhibitors

- VEGF binds to receptor

Anti VEGF

- The mainstay of CNV treatment at this point
- Requires intravitreal injection
- Post operative care

Pathogenesis of CNVM

- Breaks in Bruch’s Theory
  - Diffuse thickening of Bruch’s w/soft drusen
  - Predisposes Bruch’s to breaks
  - New BV’s from CC grow and proliferate

Wet AMD Pathology

- Post-PDT Events in The Retina
- *Vascular occlusion*
- *Up-regulation of VEGF*
- *Inflammatory response*
- *Up-regulation of PEDF*
### Anti VEGF Treatment
- Concept of antiangiogenesis was first proposed by Judah Folkman as a cancer treatment
- The concept has been extended to ocular proliferative retinopathies
- Three anti-VEGF treatments currently being used (Avastin, Lucentis, Eyelea)

### VEGF-A
- VEGF-A has 3 isoforms which differ in their solubility and receptor binding properties
  - VEGF 121
  - VEGF 188
  - VEGF 165

### VEGF Inhibition for Wet AMD

<table>
<thead>
<tr>
<th>VEGF Inhibitors</th>
<th>Details</th>
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</table>
| Pegaptanib sodium-**Macugen** (Pfizer/Eyetech) | FDA Approved  
  - Aptamer (decoy): inhibits protein activity  
  - RNA aptamer (decoy) that binds the isoform VEGF 165  
  - First ocular VEGF therapy - Seldom used today  
  - Received FDA approval in December 2004 for treatment of neovascular macular degeneration |
| Ranibizumab-**Lucentis** (Genentech) | FDA Approved  
  - Antibody-based  
  - Compared favorably to PDT in ANCHOR study  
  - Binds and inactivates all 3 isoforms of VEGF  
  - FDA approved in June 2006 for treatment of neovascular macular degeneration |
| Bevacizumab-**Avastin** (Genentech) | Off label  
  - Anti-neoplastic  
  - Intravitreal injection  
  - 1 injection/mon x 3 mon |

### VEGF Inhibitors
- Macugen (Pfizer)
- RNA aptamer (decoy) that binds the isoform VEGF 165
- Received FDA approval in December 2004 for treatment of neovascular macular degeneration
- First ocular VEGF therapy
  - Seldom used today

### Ranibizumab
- Lucentis (Genetech, Inc.)
- Recombinant humanized monoclonal antibody fragment
- Low molecular weight for better retinal penetration
- Binds and inactivates all 3 isoforms of VEGF
- FDA approved in June 2006 for treatment of neovascular macular degeneration
Bevacizumab

- Avastin (Genetech, Inc.)
- Full length humanized monoclonal antibody
- Binds all 3 isoforms of VEGF and inhibits its interaction with receptors on endothelial cells
- FDA approved for IV treatment of metastatic colorectal cancer in 2004
- Used off label for ocular neovascularization
- Less expensive than Lucentis
- Longer half life than Lucentis due to larger molecule weight

Pre and Post Avastin Treatment

![VA 55 L](image)

![VA 78 L](image)

Treatment Studies

- VISION => VEGF Inhibition Study in Ocular Neovascularization
- MARINA => Minimally Classic/Occult Trial of the Anti VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD
- ANCHOR => Anti VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD Study
- PrONTO; CATT (ongoing), SAILOR, and more

Intravitreal Injections for Wet AMD

**Anti-VEGF Agents**

**Antiangiogenic therapy**

- Pegaptanib (Macugen)
  - Dec 2004, for neovascular (wet) AMD
- Bevacizumab (Avastin)
  - For metastatic colorectal cancer
- Ranibizumab (Lucentis)
  - June 2006, for neovascular (wet) AMD

AMD = age-related macular degeneration; VEGF = vascular endothelial growth factor.

Eylea (Regeneron)

- Aflibercept intravitreal injection
- Approved for CNV/AMD.
- Binds all forms of Vascular Endothelial Growth Factor-A (VEGF-A) and Placental Growth Factor (PIGF).
- Binds tightly to VEGF receptors
- Rapid decrease in foveal thickening, improved visual function.
Wet AMD Treatments on the Horizon

VEGF Inhibitors
- Squalamine lactate- *Envizon* (Genaera): Phase II
  - Isolated from dogfish shark tissue
  - Originally developed for oncology
  - Aminosterol
    - Inhibits plasma membrane ion channels
    - Blocks proliferation of endothelial cells
  - Administered Intravenously
  - Weekly x 4 wks
  - Small sample showed improved or stabilized VA
  - Low systemic toxicity
  - Topical drug delivery??

Squalamine lactate- *Envizon* (Genaera)
Squalamine works INSIDE endothelial cells to block multiple intracellular pathways generated by the binding of VEGF and PDGF to receptors.

Fovista (Ophthotech)
- Anti-PDGF
  - Platelet derived GF
  - To be used with Anti-VEGF
  - Decreases size of CNV when used w/Lucentis
  - Better efficacy than Lucentis alone
  - No adverse events at 6 mon
  - Phase 3 under way

Conversion to Exudative AMD
Can we prevent this?
Dry AMD Treatments on the Horizon

Future Dry AMD Treatments?
- Neuroprotection
- Prevention of oxidative stress/damage
- Inflammation inhibition

Future Dry AMD Treatments?
- Ciliary neurotrophic factor (CNTF) delivered via intraocular encapsulated cell technology implant.
- CNTF retards PR loss.
- Right, an 84 y/o subject with GA.

OT-551 (Othera)
- Topical Anti-
  - oxidant
  - inflammatory
  - angiogenic
- Tested in combo w/L & Z

Future Dry AMD Treatments?
- Fenretinide po
  - Synthetic Vitamin A derivative
  - Reduces amount of lipofuscin accumulation
Future AMD Treatments

- Visual Cycle Modulation:
  - ACU - 4429 (Acucela and Otsuka) - can modulate, slow down, the visual cycle. Oral drug targets the rod system by inhibiting a key enzyme. Does not affect the cones.
  - Reduces the amount of A2E and lipofuscin accumulating in the RPE.
  - Fenretinide aka RT-101 (Sirion Therapeutics) - reduces the amount of A2E and lipofuscin by modifying the visual cycle. Oral administration.

Future Dry AMD Treatments?

- Neuroprotection
- Prevention of oxidative stress/damage
- Inflammation inhibition

Future Dry AMD Treatments?

- Complement inhibition:
  - Intravitreal (ARC 1905)
  - Sub-conj (Soliris)
- Toxic RNA (Alu RNA) inhibition
- Increase “Dicer” enzyme

Future AMD Treatments

- Complement Inhibition:
  - POT-4 (Potentia Pharmaceuticals)
  - Inhibits complement component C3. Single intravitreal injection
- Neuroprotection:
  - NT-501 intraocular implant (Neurotech)
  - Delivers human cells that have been genetically modified to secrete ciliary neurotrohic factor (CNTF).
    - CNTF is a neuroprotectant cytokine under investigation for neurodegenerative diseases like ALS.

A Nutritional Approach

AMD Risk Factors

- Age
  - Gender - F > M
- AMD Family History
- Smoking
- Iris Color - lighter iris
- Obesity
- CV Disease
- Poor nutrition
- Dietary and Serum Levels
  - Complex analyses (most, but not all) show a relationship.
- Low Macular Pigment
  - MPOD- Most (but not all) studies have shown reduced MPOD in AMD (by multiple measurement techniques).
Macular Pigment Optical Density (MPOD)

HFP

Risk assessment, early detection and monitoring of AMD
- Macular Pigment Optical Density
  - MPOD

Xanthophylls and AMD
- Lutein and zeaxanthin form the macular pigment
- Dietary sources include green leafy vegetables and orange-yellow fruits
- Act as antioxidants or light screening compounds

Macular Pigment Optical Density (du)

<table>
<thead>
<tr>
<th>Low</th>
<th>Average</th>
<th>High</th>
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<tbody>
<tr>
<td>0.1-0.25</td>
<td>0.25-0.45</td>
<td>&gt; 0.45</td>
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</table>

Lutein

Zeaxanthin
Dietary Lutein and Zeaxanthin: Eggs

AREDS 1 and 2

Daily Dosage in AREDS 1
Supplements were manufactured to have the following minimum contents:

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td>Antioxidants</td>
<td></td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>15 mg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
</tr>
<tr>
<td>Essential Trace Elements</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>2 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>80 mg</td>
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</table>

AREDS Grading Scale

1. No drusen or a few small drusen.
2. Pigment abnormalities or non-extensive small or intermediate drusen.
3. Extensive intermediate drusen or any large drusen or non-central atrophy.
4. Good acuity and no advanced AMD in the study eye. Advanced AMD in the fellow eye (choroidal neovascularization or geographic atrophy).

"AREDS 1 resulted in a formulation of vitamin C, beta carotene, zinc, and vitamin E that reduced the risk of progression of advanced disease by 25%" at 5 years."

Emily Chew, MD, from the National Eye Institute in Bethesda, Maryland,
**AREDS 2: NEI Trial Overview**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To evaluate the effect of high-dose vitamin supplementation on age-related macular degeneration (AMD) progression and visual acuity.</td>
</tr>
<tr>
<td>Design</td>
<td>Double-masked, randomized, placebo-controlled trial</td>
</tr>
<tr>
<td>Population</td>
<td>3640 high risk patients (55-80 years)</td>
</tr>
<tr>
<td>Duration</td>
<td>6.3 years supplementation and follow up</td>
</tr>
</tbody>
</table>

**AREDS 2**

- Lutein (10mg)
- Zeaxanthin (2mg)
- Omega-3 fatty acids (350 mg DHA, 650 mg EPA)
- With and without β-carotene (15 mg vs 0 mg)
- High vs low zinc levels (80mg vs 25mg)

**Lutein/Zeaxanthin**

- Antioxidant activity
  - Prevent free radical damage in the retina
  - More effective than Beta-carotene
- Filter blue light
  - Most damaging type of light due to its short wavelength
- Selectively binds to tubulin
  - Improves structure integrity
  - Maintains eye health and quality of vision

**AREDS 2 2006-2012**

4203 participants aged 50 to 85 with bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye.
AREDS 2: Purpose

- To determine if adding lutein/zeaxanthin, omega-3s, or a combination could improve upon the positive results found in the AREDS 1.
- To evaluate the effect of eliminating beta carotene, lowering zinc, or both.

AREDS 2 Design

- 4,203 participants were randomized to placebo with no additional supplementation or to 1 of 3 treatment groups:
  - Group 1: tablet w/10 mg L + 2 mg Z
  - Group 2: gel cap w/350 mg DHA + 650 mg EPA
  - Group 3: both the tablet and gel cap
- On a daily basis

AREDS 2: Primary Study Outcome

- An additional 25% decrease in the risk of progression to advanced AMD in the three treatment groups over the study subjects taking the original AREDS1 supplement.

Study Subjects:
AREDS 1 vs AREDS 2

- All stages of AMD
- Average age = 69
- 67% took Centrum (no L)
- Varied diets
- Varied serum L and Z
- More advanced stage
- Average age = 74
- 89% taking Centrum Silver (w/minimal L)
- Diet high in carotenoids and vegetables
- Higher serum L and Z

These differences could impact the ability to detect a more significant reduction in progression!

AREDS 2 First Results

"In the overall analysis, using 3 treatment groups, we found no significant difference in rates of macular degeneration," Dr. Chew said.
AREDS 2 Sub-group Analysis

- 10% reduction in progression to advanced AMD w/ L & Z compared to no L & Z
- 18% reduction in progression in subjects who received L & Z + AREDS 1 supplement (without beta carotene) compared to those who took the original AREDS 1 supplement with beta carotene
- 26% reduction in progression in the participants taking L & Z that were in the lowest quintile of dietary L & Z intake

AREDS 2 Conclusions: First, the Bad News

- Overall, the addition of 10 mg L and 2 mg Z, 1 g DHA + EPA, or both to the AREDS formulation did not further reduce risk of progression to advanced AMD.

AREDS 2 Conclusions

- Results reaffirm previous epidemiological data that high dietary intakes of L & Z reduce the risk of AMD.
- Results support the safety and treatment benefits of substituting 10 mg L and 2 mg Z for beta carotene in AREDS formulations.

What about omega-3 EFAs?

- Fish oil supplement did not significantly alter the progression of AMD in AREDS 2.

AREDS 2 Limitations

- A greater reduction in AMD progression may have been demonstrated if the subject’s diet had been more representative to that of the general US population.
- Inability to determine if the null findings are attributable to lack of efficacy of the supplements, inadequate dosing, inadequate Tx. duration, or a combination of these.

Conclusions

- Choroidal Neovascularization (CNV) is a leading cause of vision impairment worldwide.
- An understanding of the functional anatomy of the posterior segment is essential in understanding CNV.
- CNV has several causes, variants, and masqueraders.
- Early diagnosis of CNV enables early treatment with today’s effective therapies, thereby preserving visual function.
Thank you!

Carlo and Joe

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