Tales from the Trenches: Posterior Segment
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Mark Dunbar: Disclosure
- Consultant for Allergan Pharmn
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  - Artic Dx
  - Alcon Nutrition

Speakers Bureau for:
- Allergan
- Carl Zeiss
- Artic Dx
- Alcon Nutrition

Mark Dunbar does not own stock in any of the above companies

Presented on Monday for a refraction
Blurry vision OU
RE: 20/50
LE: 20/20

Choroidal Melanoma
- How is this treated?
  - Enucleation vs. Plaque
- What is the likelihood that he will be alive in 5 years?

Treatment: Choroidal Melanoma
- Enucleation
- External beam radiation
- Plaque radiation
- Photocoagulation
Plaque Radiation (Ionizing Radiation)
- Iodine-125
- Seeds of radioactive material implanted into a plaque
- Sewn onto the globe and left on for 3 d
- Dosage: 8-10 rads reach apex, 40-50,000 reach the base

Plaque Radiation
- Survival rate is approximately equal to enucleation
- Rapid regression of melanoma post Tx is an unfavorable prognosis
  - Indication of tumors malignant potential

Collaborative Ocular Melanoma Study (COMS)
- International, multi centered randomized controlled clinical trial
- Supported by NEI: 32 centers
- Primary outcome: overall survival p Tx
  - Secondary: metastatic free survival, preservation of vision

Collaborative Ocular Melanoma Study (COMS)
Small Tumors
- Thickness: 1-3 mm in hgt
- > 5 mm in largest basal diameter
- Physician choice in Tx

Collaborative Ocular Melanoma Study (COMS)
Medium Tumors
- Thickness: 3-8 mm in hgt
- Basal diameter up to 16 mm
- Enucleation vs I-125 plaque

Collaborative Ocular Melanoma Study (COMS)
Large Tumors
- Thickness: > 8 mm hgt
- > 16 mm largest basal diameter
- Enucleation vs Ext beam Rad followed by Enucleation
### COMS: Results

#### Diagnostic Accuracy
- 1527 of 1532 enucleations resulted in correct Dx 99.7% Accuracy

#### Cell Type
- Spindle Cell = 9%
- Mixed Cell = 86%
- Epitheloid = 5%

Histopath Characterist. COMS Report #6 AJO June 1998

### COMS Results

#### Small Tumors
- 204 patients with small choroidal melanomas
- 8% were immediately treated at the time of diagnosis
- 33% were treated during the follow-up
- 6 deaths due to metastatic melanoma
- Small choroidal have a low 5 yr mortality


### COMS Results: Medium Tumors

#### Enucleation vs I\textsubscript{125} Brachytherapy
- 1317 Enrolled: 660 Enucleation 657 plaque
- 1072 (91%) followed for 5 yrs
  - 416 (32%) 10 yrs
- 364 pts died:
  - 188 Enuc (28%); 176 (27%) Plaque

Arch of Ophthalmol July 2001 119(7):969-982

### COMS Results: Medium Tumors

#### Unadjusted 5 yr survival: 81% vs 82%
- 5 yr adjusted rate of death from metastatic melanoma:
  - 11% Enucleation
  - 9% Plaque

Conclusion: Mortality rates do not statistically differ b/w the 2 treatments for up to 12 years
Arch of Ophthalmol July 2001 119(7):969-982

### Latest Research in Molecular Genetics of Ocular Melanomas

- Discoveries in molecular genetics have established that there are 2 classes of tumors with distinct molecular signatures
  - Class 1 -> carries a low risk of metastasis - less than 90%.
  - Class 2 -> greater than 90 percent chance of spreading to the liver.
**Molecular Genetics of Ocular Melanomas**

- Via fine needle biopsy transcriptomic profiling can be done which can accurately predict which tumors will likely go on to develop metastatic disease and which won’t...
- This risk may be independent of what type of treatment that patient may have had

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**Leonardo**

57 y/o Hispanic Male

- “Routine” exam
- Has had poor vision for ~ 25 yrs or so
- VA: 20/70 RE; 20/60 LE
- CVF: FTFC OU
- Pupils: EERR – No APD
- SLE – Tr NS

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**Leonardo**

Thoughts…?

Differential Diagnosisis?

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**28 y/o Hispanic Female**

33 Wks Pregnant: 3 Wk Hx of ↓VA

4/27/2009
28 y/o Hispanic Female
33 Wks Pregnant: 3 Wk Hx of ↓VA

- Seen 2 Wks Later with resolution of her serous detachments

35 y/o HIV (+) Male
CD4 ~ 400

- Patient first presented to BPEI in 3/99
- Normal findings noted
Idiopathic Central Serous Chorioretinopathy (ICSC)
- Condition of unknown etiology
- Localized detachment of sensory retina
- Anxious males: 3:1 to 10:1
  - Incidence doubles in women 30-40 vs 20-30 y/o
- History of emotional stress
- “Type A personality”
- Common Caucasians, Hispanics, Asians

Central Serous Chorioretinopathy (CSC)
- Condition 1st described by Albrecht von Graefe 1866
- Relapsing central leutic retinitis
- Several terms commonly used today
  - Idiopathic central serous chorioretinopathy
  - Central serous chorioretinopathy (CSC)
  - Central serous retinopathy (CSR)

Age of Onset
- Ages 30-55 y/o
- Europe 40-60 y/o
Corticosteroids and CSC
- Strong relationship with increased cortisol levels
  - Steroid users
  - Organ transplant
  - Medical conditions requiring steroid: SLE, RA
- Pregnant women
  - Increased levels of free circulating endogenous cortisol

ICSC
- Detachment of sensory retina
  - Due to leakage from small underlying PED
- Absence of foveal reflex
- Yellow dot in center of fovea: Xanthophil
- Vision rarely less than 20/25
- Patients often report micropsia

Fibrin with Atypical ICSC
- Some patients with ICSC can exude more of a fibrin response
- Recent studies suggest the fibrin may actually be fragments of the photoreceptor outer segments
  - They accumulate when the normal process of phagocytosis of the photoreceptor outer segments become disrupted due to the serous detachment of the retina

Central Serous Chorioretinopathy (CSC)
2 Main Types
- Common classic CSC
- More widespread alteration of the RPE with chronic shallow SRF
- Chronic CSC
- May be associated with chronic corticosteroid use

Pathophysiology of CSC
- Normal physiology
  - There is a balance in the tissue osmotic and hydrostatic pressures which results in fluid flow from the retina toward the choroid
  - Abnormal choroidal vascular hyperpermeability
  - Excessive tissue hydrostatic pressure in choroid leads to mechanical disruption of the RPE barrier -> damage to the RPE Cells -> egress of fluid under the retina

CSC: Treatment
- Argon laser directly to site of leakage (PED) if detachment persists > 6 months
- Do NOT use oral steroids
- PDT for chronic CSC
Who can tell me what “Sclopetaria” is?

Chorioretinitis Sclopetaria
- Closed globe injury that results from high velocity object bumping, but not perforating the sclera.
- Full-thickness defect in Choroid, Bruch’s membrane, and Retina, but Intact Sclera.
- Tissue replaced with dense fibrous connective tissue.
  

Chorioretinitis Sclopetaria
- Closed globe injury that results from high velocity “missile energy” bumping, but not perforating the sclera.
- Full-thickness defect in Choroid, Bruch’s membrane, and Retina, but Intact Sclera.
- Tissue replaced with dense fibrous connective tissue.


BB Gun Related Injuries
- Nearly 30,000 Americans present to ERs with BB- and pellet gun-related injuries each year.
- Most incidents are unintentional and typically occur in young males.
- CDC Surveillance report of 47,000 BB gun-related injuries between 1992-1995:
  - 50% of injuries occurred in children between 10 and 14 years of age.
  - 2,839 (6%) of patients suffered direct eye trauma.

JAMA. 1995 Jun 14;273(22):1749-54

Commotio Retinae
- Whitening of outer retinal layers.
- Shock waves traversing the eye.
- Cherry red spot and decreased vision in Berlin’s edema.
- Good prognosis.
Traumatic Macular Hole

- Knapp first described in 1869
- Now known to be less than 10% of full thickness macular holes
- 6% of pts suffering contusive injuries develop full thickness macular hole
- Develops from concussive forces in a countercoup manner

Intact hyaloid, mechanism likely traction / ILM rigidity
- Outward extension of the equator causes a flattening of the retina and tangential traction
- Hydration theory: dehiscence of the ILM disrupts hemostasis and causes intraretinal swelling -> leads to macular hole formation

Idiopathic Macular Holes

- VA 20/400 to 20/60
- 1/3 DD full thickness round hole
- Surrounding cuff of fluid
- Yellow deposits in the base of the hole
- Translucent operculum (anterior) 50%
- May have associated ERM (10-20%)

Pathogenesis
- Anterior-posterior vitreous traction
- 1989 Gass/Johnson:
  Tangential traction due to shrinkage and contraction of the prefoveal vitreous cortex

Stages of Macular Holes

- IA: Yellow spot or ring in macula
- IB: Loss of foveal depression
- II: Partial tear in the sensory retina
- III: Fully developed full thick mac hole
- IV: Macular hole with posterior vitreous separation

Vitreous Surgery for Macular Holes

  - 52 patients
  - PPV/Removal vitreous cort, Fld/Gass exchange
  - 58% anatomic success, 73% visual success
  - Overall 42% success rate
- Kelly, Wendel: Ophth Nov 1993
  - 170 patients

Macular Hole Surgery

- Patel/Wendel Sem Ophthal 1994, 152 pts
  - Macular hole < 3m duration 80% success
  - Macular hole > 3 mo – 2 yrs 74% success
  - Macular hole > 2 yrs duration 61% success

Macular Holes: Loss of Vision

- Loss of neurosensory retinal tissue
- Rim of subretinal fluid around the hole (microdetachment)

Macular Hole Surgery

Postoperative Period

- Face down for 2 weeks
- Has evolved to face down for 1 wk
- Silicone Oil sometimes for patients who need to travel on planes or over mountains

Intravitreal Gas Tamponade
Why Face Down Positioning (FDP)

- The mechanism by which the tamponade agent facilitates macular hole sealing is uncertain
- Two possible effects are:
  - Mechanically tamponade the macula
  - Isolate the healing macula from vitreous fluid
- Theory: provide a template over which the nascent bridging preretinal membrane can form

Vitreomacular Traction in the Era of OCT

- Not rare!
- A group of disorders caused by incomplete PVD
- Leads to persistent traction on the macula
- Produces in most cases CME and decreased visual acuity
- Can be idiopathic
- Can occur with ERM and macular hole

Future tx though Microplasmin injection

- Is a recombinant truncated form of human plasmin that is active
- Functions as a thrombolytic agent causing an enzyme induced pharmacological vitreolysis
  - The enzymatic agents alter the biochemistry of vitreous
    - Liquefaction of the vitreous occurs
    - LYSIS between vitreous cortex and ILM is the final outcome

Microplasm (ThromboGenics)

- Microplasmin is a proteolytic enzyme that has the potential to facilitate the development of PVD
  - Breaks down the protein structures, which join the vitreous to the retina
    - Results in liquefaction of the vitreous
    - LYSIS between vitreous cortex and
  - Microplasmin is a molecule created from plasminogen
  - Similar protein formations are also seen linking the vitreous to the retina in the eye
  - Microplasmin has evolved as a non-surgical treatment for focal vitreomacular adhesions and macular hole

MIVI-TRUST Results

- Largest interventional clinical trial ever performed to specifically evaluate the vitreoretinal interface in patients with retinal disorders
  - 652 pts at 90 centers in Europe and US randomized
  - 464 with Ocriplasmin, 188 with placebo

- 652 patients at 90 centers randomized to single intravitreal injection vs placebo injection
- 26.4% achieved resolution of their VMT by 28 days vs. 10.2% (182 pts) who received placebo
- 106 PTS with FT macular hole: 40.6% had closure vs. 10.6% (n47 pts) in the placebo
Do any of the medications that I am taking affect my eyes?

“I am having blurry vision – could this be from any of the medications that I am taking?”

Systemic Interactions
- Medications may cause alteration of the pigment
  - Plaquinil -> Bull’s eye maculopathy
- Pharmacologic toxicity can occur leading to cell death and loss of function
  - Can affect the optic nerve
- Patient variability may influence and cause unexpected effects
  - Pharmaceutical studies provide statistical evidence supporting appropriate dosage for meds, however individual variation can result in unexpected results

What are your/our obligations in deciding if certain medications that a patient is taking are affecting the patients vision?
How About This One…

- 37 y/o Hispanic female presented with a recent onset of blurred vision OU X 1 mo
- Currently taking Rifampin, Ethambutol, Clarithromycin 5 mo prior for MAC (TB)
- BCVA: 20/20 RE; 20/20 LE
- CVF: FTFC OU, Pupils: Normal
- Very low hyperopic correction (+0.25)
- Normal fundus exam

Ethambutol

- TB regimens begin at either 50 mg/kg/day (maximum 4 grams) for 2 weeks or 25-30 mg/kg/day (maximum 2 grams) for 3 weeks, and then maintained at 15-20 mg/kg/day (max 2 grams)
- For MAC regimens the maintenance dose is 15 mg/kg/day (maximum 2.5 grams).
  - Depending on the species of mycobacteria pts, may be treated with a loading dose of 25 mg/kg/day for the first two months of therapy (Mandell et al., 2005; Micromedex 2007).

Ethambutol Toxic Neuropathy

- 1st described by Leibold in the 1960’s
- Dose dependent
- Risk is 6-18% for pts with dose > 30 mg/kg/day (18% at 35 mg/kg/day)
- Develops in 1-3% at dose 15-25 mg/kg/day

57 y/o White Female

- Presented on 2/29/08 with decreased vision, near > distance
- 2nd CC: can my medicine affect my eyes?
- LEE: 1970’s

Patient History

Meds
- Pegasys
- Copegus
- Visine prn

Social Hx
- 1 pack/day tobacco usage X 40 yrs
- 20 drinks/day x 40 yrs, quit 2007 in AA

Family Hx
- None

Interferon Retinopathy

- 1990: Ikebe reported the first case
- 1992: IFN therapy widely used in Japan for hepatitis C patients
- 1993: Ocular complications from IFN increasingly reported from Japan
- 1998: Review of early reports by Hayasaka
**Review of Early Reports**

**Typical Findings**

- CWS
- Hemorrhages: flaming shaped or white centered
- Posterior pole or around the optic disc
- Occurred alone or together
- Unilateral or bilateral
- Subjective complaints are uncommon
- Visual acuity not usually impaired

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**57 y/o Hispanic Female**

- Was told by her rheumatologist to have her eyes checked
  - He wants to put her on a new medication but told her it can affect her eyes.
- Medical history of severe rheumatoid arthritis
  - Currently on Prednisone 20 mg/day
  - Wants to start her on plaquenil

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**What are your obligations for managing a patient on plaquenil?**

- What is the risk of having ocular problems from plaquenil?
- What testing is necessary?
- How often do you need to follow her?

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**Plaquenil (Hydroxychloroquine)**

- Prescribed in 200 mg tablets
  - Dose is 200mg or 400mg daily
- Risks for macular damage include
  - Cumulative dose of 1000g
  - 5-7 years or more of use
    - 1% risk after 1000g total dose (7 years)
  - Renal or hepatic dysfunction (both)
  - Pre-existing macular pathology
  - Short stature / obesity Age

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**Plaquenil Screening: Traditionally**

- Baseline macula photos
- Color vision testing
- Amsler grid
- 10-2 Visual fields
- Yearly exams
Revised Recommendations on Screening for Plaquenil Toxicity

- Amsler grid testing removed as an acceptable screening technique
  - NOT equivalent to threshold VF testing
- Strongly advised that 10-2 VF screening be supplemented with sensitive objective tests such as:
  - Multifocal ERG
  - Spectral domain OCT
  - Fundus autofluorescence

Tests Not Recommended for Screening:
- Fundus photography
- Time domain OCT
- Fluorescein angiography
- Full-field ERG
- Amsler grid
- Color vision screening
- EOG

Parafoveal loss of visual sensitivity may appear before changes are seen on fundus evaluation
- Many instances where retinopathy was unrecognized for years as field changes were dismissed as “non-specific” until the damage was severe
- 10-2 VF should always be repeated promptly when central or parafoveal changes are observed to determine if they are repeatable

Mild Retinopathy

Older literature focused on daily dose/kg
- Newer literature emphasizes cumulative dose as the most critical factor
- Initial baseline
  - Within 1 year of beginning medication
  - After 20 years of therapy

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- Many instances where retinopathy was unrecognized for years as field changes were dismissed as “non-specific” until the damage was severe
- 10-2 VF should always be repeated promptly when central or parafoveal changes are observed to determine if they are repeatable
HIGH RISK PATIENTS

<table>
<thead>
<tr>
<th>Factors Increasing Risk of Retinopathy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use</td>
<td>&gt; 5 years</td>
</tr>
<tr>
<td>Cumulative Dose</td>
<td>&gt; 1000 g (total) = 400x365x7 yr</td>
</tr>
<tr>
<td>Daily Dose</td>
<td>&gt; 400 mg/day</td>
</tr>
<tr>
<td>Age</td>
<td>Elderly</td>
</tr>
<tr>
<td>Systemic Disease/high BMI</td>
<td>Kidney or liver dysfunction</td>
</tr>
<tr>
<td>Ocular Disease</td>
<td>Retinal disease or maculopathy</td>
</tr>
</tbody>
</table>

Previously believed highest risk of maculopathy was based on low body mass was 6 mg/kg/day

25 y/o AA Female
Type I DM

28 yo Jeweler
- Referred by another jeweler who is friends with my wife
- Blurred vision RE > LE X 1 mo
  - Also red eyes OU
- PHx: RK done 10 yrs ago
  - Saw the RK Dr 1-2 mo ago – told “dry eyes”, quite smoking!
- Reports to be in good health

28 yo Jeweler
- VA: 20/40 RE; 20/20 LE
- CVF: FTFC OU
- Pupils – Equally reactive, NO APD
- No preauricular adenopathy
- Diffuse injection OU
28 yo Jeweler

- **Anterior Segment**
  - RK Scars OU
  - AC: 1 + C/F RE; 3 + C/F LE
  - Iris:
    - RE: organized fibrin membrane around the pupil – no synechia
    - Nodule inferior
    - LE: No fibrin, No nodule
  - Lens: fibrin, debris, pig ant cap R>L

28 yo Jeweler

- As he is dilating -> More history
- 3 Vices
  - Alcohol – 10 scotches/night
  - Very promiscuous – loves women
  - Smokes
- 20 lb weight loss over the holidays
  - Attributes this to work and not eating

28 yo Jeweler

- Panuveitis with Retinal Vasculitis
  - Periphlebitis
  - Vascular occlusions
- Iridocyclitis with iris nodules
- Moderate vision loss RE

What is the etiology?

Sarcoidosis

- Multisystem granulomatous disorder of unknown etiology characterized by intrathoracic involvement
- World wide distribution - more common in developing countries
- Multiple theories considered including infectious agents, allergies, hypersensitivity's: none conclusive

Sarcoidosis

- All races affected, blacks more in US
- Females more common 60/40
- 75% < 40, Children uncommon
- Area of active disease is Lung

Joanne: 50 y/o White Female

- Grew up in the Wisconsin
- Always “pretty highly myopic”
- Began having eye problems in early 20’s that ultimately required laser treatment
- Lost her central acuity in RE, but did “well” in the LE
Ocular Histoplasmosis

- Condition caused by mild or subclinical systemic infection with Histoplasma capsulatum
- Predominantly found in the eastern half of the U.S., especially the Ohio River Valley
- 2,000,000 people who live (have lived) in endemic areas have “histo spots”
  - 100,000 will lose vision in 1 or both eyes

Ocular Histoplasmosis

- Multiple "punched out" chorioretinal scars
- Peripapillary atrophy
- Lesion involving the macula -> NVM

Ocular Histoplasmosis

- Most frequent finding assoc with CNVM:
  - Localized serous or hemorrhagic detachment of retina
  - Poorly defined, round/oval, light gray, subretinal lesion
  - Subretinal blood, or exudate
- Bleeding/exudate occurs beneath the retina not beneath the RPE
Ocular Histoplasmosis

- Laser photocoag proven beneficial by MPS
  - Extrafoveal
    - 5 yrs: SVL 12% Tx vs 42% NonTx
    - 60-70% had VA > 20/40
  - Juxtafoveal
    - 5 yrs: SVL 12% Tx vs 28%
    - Adequately Tx eyes averaged 20/40
- Natural Hx: 14-23% of NonTx ≥ 20/40