Ocular Tumor Update: Managing on the Front Lines
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• Optomap images obtained courtesy of a demo from Optos
• NIH: K08EY022672
• Ocular Melanoma Foundation: Scientific Advisor

Outline
• Uveal Melanoma
• Break
• Metastatic Disease
• Primary Lymphoma
• Widefield Imaging

Uveal Melanoma (UM)
• Most common primary intraocular eye cancer in adults.

What Is Uveal Melanoma?
• Cancer of the uvea:
  - Iris
  - Ciliary body
  - Choroid
• Melanocyte cells
• Blood vessel layer
Uveal Melanoma Epidemiology

• Most common primary intraocular cancer of adults.
• Age-adjusted incidence of 6/million people
• Median age at diagnosis 55 years

Ocular Melanoma – Risk Factors

• White race
  - Black patient have 1/8 risk of Caucasian patients
  - Low incidence in Asians
• Older Age
  - Incidence of 15/million in age 45-64
  - Incidence of 25.3/million in >65 yrs
• Environmental Exposure
  - Welding
  - Sunlight/UV-exposure: controversial; weak if any association
• Melanocytic conditions
  - Choroidal Nevus
  - Ocular/Oculodermal melanocytosis (Nevus of Ota)
  - Atypical mole syndrome; skin melanoma

What is a Nevus?

• "Freckle"—proliferation of melanocytes
• Found in choroid of about 6-10% of whites
• Can be a precursor of uveal melanoma
• Must be followed over time
  - Small percent become malignant

What About Hereditary Cancer Link?

• Increased risk for hereditary cancer predisposition in uveal melanoma patients (up to ~11%)
• Diverse range of cancers
• Recommend
  - Detailed cancer family history
  - Dermatology referral – skin melanoma most associated cancer

What are the symptoms of uveal melanoma?

• No symptoms—the most common
• Flashes/floaters
• Decreased or distorted vision
• Shadow in vision
• Brown spot on the eye
• Eye pain
• Headache

How is uveal melanoma diagnosed?

• Dilated eye exam is most important
  - Dilation recommended:
    - To detect other silent blinding conditions
    - At age 40
    - Vision problems, flashes, floaters, eye pain
    - Conditions such as diabetes
    - Family history
Clinical features of uveal melanoma

- Dome shaped or collar-button shaped mass
- Pigmented (most common), unpigmented (~25%) or both.
- May be associated with retinal detachment
- Presence of orange pigment (lipofuscin)

Uveal Melanomas
Pigmented
Amelanotic

Uveal Melanoma Mimics
Chorial hemorrhage
Melanocytoma
Choroidal nevus
Choroidal hemangiona

Choroidal metastasis
Pre-chemo
Post-chemo

Other testing to evaluate uveal melanoma

- Ocular photographs
  - Color
  - Autofluorescence
- Ocular ultrasound
- Fluorescein angiography
- OCT
- MRI

Tumor Ultrasound Characteristics

- Classic differences in tumors on A- and B-scan ultrasound
The Original Ultrasonographer

- 1793 Spallanzani: bats use sound to navigate
- 1920s: sonar war use
- 1950s: Ophthalmology
  - Keeney
  - Coleman
  - Purnell
  - Ossoinig
- Standardized Ultrasound 1960s

Uveal Melanoma: Ocular Imaging

- Ultrasound: most useful
  - B-scan: shows the tumor shape and dimensions
  - A-scan:
    - Indicates structural characteristics which can differentiate types of tumors
    - Height measurement

Ultrasound of Melanoma vs. Metastasis

**Melanoma**
- Dome or collar button
- Larger height-to-base
- Acoustic hollow zone
- Vascularity
- Choroidal excavation
- A-scan:
  - Low-medium internal reflectivity
  - Regularly structured

**Metastasis**
- Irregular, polygonal
- Smaller height-to-base
- Solid
- Minimal vascularity
- No choroidal excavation
- A-scan:
  - Medium-high internal reflectivity
  - Irregularly structured

Metastatic Lesion
- Medium internal reflectivity
- Irregular internal structure
- Smaller apical height than melanomas
- Polygonal surface
- No choroidal excavation

Figure 1. Comparison of metastases (open circles) and melanomas (closed circles) concerning reflectivity (%) and height-to-base ratio


Low Internal Reflectivity

Uveal Melanoma
- Low internal reflectivity

Low

Medium

High

Internal Reflectivity

Ultrasound B-scan

A-scan

Uveal Melanoma

Metastatic Lesion
**Choroidal hemangioma – High Reflectivity**

**Osteoma: Calcific Shadowing**

RG Waldron and TM Aaberg Jr.  
emedicine.medscape.com/article/1228865-overview

**Other Testing**

- Optical coherence tomography (OCT)  
  ✓ Can show subretinal fluid  
- Fluorescein angiography  
  ✓ Characteristic pattern of fluorescence  
  • Hot spots with late leakage  
  • Tumor blood vessels: “double circulation”  
- MRI:  
  ✓ Bright on T1, dark on T2 imaging


**Cases**

**Case 1:**  
84yo WM with shadow in vision OD x 3 months

**Fundus Photo OD**  
**Autofluorescence OD**
Case 1:

**Fundus Photo OD**

**Autofluorescence OD**

Orange pigment = Lipofuscin
Bright on Autofluorescence Photography

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**Case 1**

B-scan
A-Scan

Peripapillary Choroidal lesion 3.6mm height
Scleral excavation, subretinal fluid

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**What is this?**

- Choroidal nevus
- Choroidal melanoma
- Indeterminate

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**How would you manage patient?**

- Observe
- Refer for ocular oncology

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**Case 1**

- Pt was referred by new optometrist
- Choroidal tumor >2mm height
- Subretinal fluid
- Symptoms
- Orange pigment
- Margin near optic disc

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**Case 1**

- Diagnosed with small uveal melanoma
- Brachytherapy I125 notched plaque recommended
- Pt declined treatment and moved to Florida
Case 1: 8 months later...

- VA: CF
- IOP: 18
- RD
- Lesion increased from 3.6 to 9.3 mm height
- Low reflectivity

Case 1

- Metastatic work-up
  - No evidence metastatic disease
- Treated with enucleation
  - Pt delayed treatment 3 more months:
    - Growth from 9.3mm to 13.5mm ht

Small Uveal Melanomas

- Practically impossible to distinguish from atypical nevi

Finding Small Melanomas

- TFSOM Mnemonic
  - To: Thickness (>2mm)
  - Find: Subretinal Fluid
  - Small: Symptoms
  - Ocular: Orange Pigment
  - Melanomas: Margin (within 3mm of optic disc)

(Shields et al. Ophthalmology 1995; 102(9): 1351-61)
**TFSOM Mnemonic**

- **T**o: Thickness (>2mm)
- **F**ind: Subretinal Fluid
- **S**mall: Symptoms
- **O**cular: Orange Pigment
- **M**elanomas: Margin (within 3mm of optic disc)
- **U**sing **H**elpful: Ultrasound Hollowing
- **H**ints: Absence of Halo


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**Advantages for finding small melanomas**

- Preferable treatment options
- Better prognosis
  - "... at 5 years, metastasis occurs in 16% of patients with small choroidal melanomas (less than 4 mm thick), compared with 32% of those with medium-sized (4-8 mm thick) choroidal melanomas and 53% of those with large (more than 8 mm thick) choroidal melanomas"


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**Suspicious for Small Melanoma**

- Orange pigment
- SRF
- Orange pigment
- Margin at Optic nerve

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**B-Scan**

Acoustic hollowing from dense cellularity & homogenous tumor

Courtesy of BPEI ultrasound department
Case 2

• Diagnosis?
  - Choroidal nevus
  - Choroidal melanoma
  - Metastasis

Case 2: 1 year later

Case 2: Initial presentation

Case 2: OCT

Increased height
Subretinal fluid
**Case 2**

- Uveal melanoma diagnosed
- Metastatic work-up
- Brachytherapy

**Can OCT be helpful?**

- Helpful for detecting subretinal fluid
- Can detect increased size
- Not helpful for "looking in" the tumor

**Serial Observation Needed for all Choroidal Nevi**

- Serial color fundus photos
- Baseline ultrasound if >1 disc diameter
- +/- OCT
- Monitoring at least yearly
- Notify the patient

**Serial Observation for all Choroidal Nevi**

- 13 years
- 1 year

**Serial Observation Needed for all Choroidal Nevi**

- When to refer:
  - 2 disc diameters or greater
  - Mildly thickened
  - Near the nerve
  - Signs of small melanoma: (TFSOM)
  - Strong cancer family history
  - Multiple choroidal nevi
  - Anytime

**Uveal Melanomas**

- Malignant transformation of nevus
- Original nevus
Case 3: Uveal melanoma

- Large uveal melanoma
- Not amenable to brachytherapy
- Doing well s/p enucleation
- Metastatic work-up negative
- Following with melanoma oncology

Metastatic Work-up

- Imaging
  - CT Chest, Abdomen/pelvis, and MRI brain
  - Hepatic ultrasound and CXR
  - CMP, LDH, CBC
- Micrometastases form when tumor very small, lie dormant
- Lifelong surveillance—frequency depending on risk factors
What are treatment options for uveal melanoma?

Treatments

- Radiation
  - Radioactive plaque brachytherapy
  - Proton beam radiation therapy
- Enucleation
  - (Transpupillary Thermotherapy): controversial

Brachytherapy: “radiation patch”

- Eye sparing therapy
- Small and medium-sized tumors
  - Excellent 5-year survival
  - Overall incidence of tumor recurrence at 5 years is about 10%
  - Ultrasound guidance to help place plaque may decrease recurrence
  - May combine with transpupillary thermotherapy (laser)

Proton Beam Radiation

- Good for small and medium tumors
- Potential advantages for tumors around the optic nerve/macula
- Higher rate neovascular glaucoma
- Few centers have this technology

Enucleation

- Permanent removal of the eye
- Best for large tumors
- Orbital implant placed
- Ocular prosthesis match eye
  - about 6 weeks later
Transpupillary Thermotherapy (TTT laser)
• Laser office procedure for small uveal melanomas
• Less effective as primary rx than brachytherapy
• Can lose as much vision as with brachytherapy
• May be considered in certain cases

How do we know what treatments to use?

The Collaborative Ocular Melanoma Study (COMS)
• Designed to clarify management options
• Large randomized, prospective, NIH-funded multicenter trial

COMS Medium Tumor Trial
• Outcomes of I-125 brachytherapy vs. enucleation
• 1,317 patients randomized (1987 – 1998)
• Treatments were equivalent in survival
  • Visual Acuity: Ambulatory vision after brachytherapy at 3 years
    57% ≥ 20/200
    Median 20/125

Why enucleation for large tumors?
• Higher rate of brachytherapy treatment failure for large tumors
• Eye may not withstand the large dose of radiation required for brachytherapy
  • After brachytherapy for large melanoma, many lose vision, develop glaucoma, or have the eye removed anyway
  • Brachytherapy can be considered for some large tumors

What is the 5 yr Melanoma specific mortality?

<table>
<thead>
<tr>
<th>Size</th>
<th>Small: &lt;2.5 x &lt;16 mm</th>
<th>Medium: 2.5 - 8 x &lt;16 mm</th>
<th>Large: 8+ x 16+ mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma specific 5yr mortality*</td>
<td>1%</td>
<td>10%</td>
<td>30%</td>
</tr>
</tbody>
</table>
**Why don’t we treat all nevi?**

- Vision is precious and treatment causes vision loss
- Only a small percentage with atypical nevi/small melanoma develop metastatic disease (1% 5yr)
- Low rate of choroidal nevus transformation
  - 9% 5yr, 13% 10 yr (out of 2514 eyes; Shields CL et al. Arch Ophthalmol. 2009;127(8):981-987)

**Do tumors need to be biopsied?**

- UM diagnosed clinically
- Biopsy useful in atypical cases
- Fine needle
- Recently considered for patients for prognostic genetic testing

**Uveal Melanoma Biopsy for Genetic Testing**

- Some controversy but now standard of care to offer to pt
- Some risk of invasive procedure: infection, bleeding, decreased vision, retinal detachment, local tumor recurrence
- Does not appear to increase risk of metastasis (Harbour)
- CBS Sunday Morning clip: [Video Link]

**Uveal Melanoma Biopsy at time of plaque**

- Reasons Ocular Oncologists cite against biopsy:
  - No treatment option
  - Risk of biopsy
- Reasons cited for biopsy:
  - To better screen high risk patients
  - To identify high risk patients for clinical trials
  - Patients want to know
  - For research

**Uveal Melanoma Metastases**

- Median survival: Very poor
  - After detection of metastases: 4 months
  - 1 year = 13%
- Sites
  - Liver (90-94%)
  - Lung (20-24%)
  - Bone, Skin, CNS (< 20%)

**Metastatic Work-up**

- Imaging
  - Initial
    - CT chest, abdomen, pelvis
    - MRI brain
    - MRI abdomen if liver disease suspected
  - Follow-up
    - Hepatic ultrasound +/- CXR
    - (MRI liver as needed)
- Bloodwork:
  - Comprehensive metabolic panel (includes liver function tests)
  - Lactate dehydrogenase (LDH)
Why should patients follow-up with a medical oncologist?
- Micrometastases form when tumor very small, lie dormant
- Lifelong surveillance—frequency depending on risk factors

Risk Factors for Metastases
Factors associated with increased risk
- Tumor Size
- Cell type (Epithelioid or mixed)
- Extrascleral extension
- Tumor Microvasculature
- Anterior location of the tumor
- Older patient age
- Higher number of mitoses

- Genetics
  - Cytogenetics: Chromosomal abnormalities: 3, 8, 6
  - Gene expression profiling: Class 2

Genetics
- Chromosomal abnormalities in uveal melanoma
  - Monosomy 3
    - Loss of one copy of chromosome 3
    - One of the strongest predictors of metastasis
- Metastases with normal chromosome 3 may have longer survival with metastatic disease

Genetics: Gene Expression Profile
- RNA-based test of tumor tissue
- Gene expression
  - Class 1 = low risk
  - Class 2 = aggressive

Commercially available

BAP-1 Mutation
- BRCA1 associated protein-1
- Associated with highly metastatic tumors
- May offer potential for treatments

- BAP1 inherited cancer syndrome
  - Uveal melanoma
  - Skin melanoma
  - Mesothelioma
  - Renal carcinoma
  - Other cancers

NIH: The Cancer Genome Atlas Project

- Detailed genetic analysis of 100 uveal melanomas
- Centers: OSU, CCF, MD Anderson, Liverpool, France
- Hope to identify biomarkers and novel treatment pathways

Clinical Trials For Metastatic Uveal Melanoma

- Many active trials
- Clinicaltrials.gov
- Hope on the horizon

Uveal Melanoma

- Early detection saves lives
- Refer early to ocular oncology
- Need lifelong monitoring
- Exciting developments in genetics
- Need to work on better treatments for metastatic disease

Resources

- CBS Sunday Morning (clip on genetic testing in uveal melanoma: “Your genetic crystal ball”)
  https://webmail.osumc.edu/OWA/redir.aspx?C=Wpp0PmrzgUGxQ8YiztQjjUhubb59wc9IVYiC
- Ocular Melanoma Foundation
  - EYE AM NOT ALONE (EANA)
- Melanoma Research Foundation
  - CURE Ocular Melanoma
- International Society for Ocular Oncology
  - http://www.isoo.info/
- Eye Cancer Network website
  - http://www.eyecancer.com/

Uveal Melanoma Team at OSU

- Ocular Oncology
  - Colleen Cebulla
  - Frederick Davidorf
- Radiation Oncology
  - Doug Martin
- Pathology
  - Lynn Schoenfield
  - Sara Peters
  - Nyla Heerema (FISH)
- Medical Oncology
  - Kari Kendra
  - Thomas Olencki
  - David Liebner
- Surgical Oncology
  - Mark Bloomston
  - Carl Schmidt
- Cancer Genetics
  - Mohamed Abdel-Rahman
  - Robert Pilarski

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Ocular Tumor Update: Managing on the Front Lines
Part 2

• Metastatic Lesions
• Lymphoma
• Widefield imaging

Metastatic Lesions

• Choroidal Metastases
• Retinal Metastases
• Intraocular Lymphoma
• Leukemia
  • Carcinomatosis Syndromes—Paraneoplastic
    • Cancer-associated retinopathy (CAR)
    • Melanoma-associated retinopathy (MAR)
    • Bilateral diffuse uveal melanocytic proliferation (BDUMP)

Metastatic Disease of the Eye

• First described by Perl (1872)
• Albert and Scheie (1967) and Bloch & Gartner (1971) suggested that metastasis, not choroidal melanoma, is most common intraocular malignancy
  • Incidence estimated at 4-12% in patients with solid tumors of all histologies (excluding lymphoma, leukemia, myeloma)
• Clinically apparent metastases may be increasing due to increased life span of patients from improved systemic therapies

Choroidal Metastasis

Most common intraocular malignancy
  • Often goes undiagnosed
• Choroid is the most common location for metastatic lesions
• Most cases are carcinomas
  • Sarcomas and melanomas are less common

Metastatic Disease of the Eye

• Metastasis to all subsites of eye and orbit have been reported
• Metastases are bilateral in 1/3 patients
  • Breast cancer accounts for nearly 2/3 bilateral cases
  • 30% patients have >1 deposit per eye
• Median life expectancy is 9 months (range 4-13 months)
  • Pts with breast cancer and carcinoid have slightly longer survival
Metastatic Disease of the Eye

- Most common subsite of metastatic disease is posterior uveal tract, particularly the choroid (posterior ciliary arteries)
- Mean age of patient with uveal metastasis is 60 years (75% between 40 and 75 years)
- Uveal metastases can become apparent before primary tumor is recognized in 28-46% patients
  - Lung cancer (35%) is primary site most commonly identified in these cases
  - Primary site may not be identified in up to 50% of these cases

Features of Uveal Metastases

<table>
<thead>
<tr>
<th>Location (%)</th>
<th>Ferry &amp; Font (1974)</th>
<th>Shields et al. (1997)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroid/Posterior segment</td>
<td>56.5</td>
<td>98</td>
</tr>
<tr>
<td>Iris/Anterior segment</td>
<td>18.6</td>
<td>8</td>
</tr>
<tr>
<td>Orbit</td>
<td>17.6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Unilateral</td>
<td>90</td>
<td>76</td>
</tr>
<tr>
<td>Bilateral</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Right eye</td>
<td>38.8</td>
<td>48</td>
</tr>
<tr>
<td>Left eye</td>
<td>38.8</td>
<td>52</td>
</tr>
<tr>
<td>Median age, years</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>% Female</td>
<td>51</td>
<td>67</td>
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</table>

Features of Uveal Metastases

<table>
<thead>
<tr>
<th>Primary cancer - %</th>
<th>Ferry &amp; Font (1974) - %</th>
<th>Shields et al. (1997) - %</th>
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<tbody>
<tr>
<td>Breast</td>
<td>39.7</td>
<td>47</td>
</tr>
<tr>
<td>Lung</td>
<td>29.5</td>
<td>21</td>
</tr>
<tr>
<td>GI</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td>Renal</td>
<td>4.0</td>
<td>2</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.3</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>0</td>
<td>&lt;1</td>
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<tr>
<td>Skin melanoma</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>18.3</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>3.5</td>
<td>4</td>
</tr>
</tbody>
</table>

Symptoms

- Symptoms (Stevens and Shields, 1979)
  - 80% report decreased vision, often to 20/200 or worse
    - Due to EXUDATIVE RD
  - Photopsias (13%) and floaters (7%)
  - Pain 14%
    - More associated with lung or unknown primary
  - Red eye 7%
  - VF defect 3%
  - Photophobia 1%
  - Asymptomatic 8%
- Ophthalmoscopic findings
  - Creamy yellow plateau or dome-shaped lesion, often associated with serous retinal detachment
  - Occasionally brown (metastatic melanoma, breast, lung, GI) or orange (carcinoid, renal cell, thyroid)

Findings

- Unilateral or Bilateral (20-40%)
- Solitary or Multifocal (20%)
- Predominantly posterior pole involving
- Yellow or yellow-white
- Flat
- Serous retinal detachment
  - Typically out of proportion to the tumor size
  - Tumor may be difficult to see on slit lamp exam leading to misdiagnosis

Case 1

- 56yo WF
- "Trouble with contacts"
- Blurry x 1mo
- Under stress
- Diagnosed with RD
- VA 20/40
- IDP 15
Case 1: What is diagnosis?

- Central Serous
- Wet AMD
- Rhegmatogenous Retinal Detachment
- Other

Widefield Imaging

Widefield Imaging

Lesion

SRF

Color Photo

OCT—Over lesion
Choroidal location

AF Photo

Fluorescein Angiogram

Early mild hypo fluorescence, mild later hyperfluorescence

Case 1

- Hx of triple negative breast cancer s/p radiation and chemo
- Previously cancer free x 5 years
- Metastatic work-up revealed pulmonary masses, biopsy proven breast carcinoma
- Eye treated with EBRT, systemic chemo
Case 1

**Pre-EBRT**

1.5y post EBRT

**Primary Site - Male**

- Lung 40%
- Unknown 29%
- GI 9%
  - "LUG" mnemonic
- Prostate 6%
- Renal 6%
- Skin 4%
- Breast 1%
- Other 4%

**Primary Site - Female**

- Breast 68%
- Lung 12%
- Unknown 12%
  - "BLU" mnemonic
- GI 2%
- Skin 1%
- Renal <1%
- Other 4%

**Choroidal Metastases**

Why here?
Greater overall blood flow; Tumor emboli are large and flow along vessel walls, leading to branching off early

- Internal Carotid Artery
- Ophthalmic Artery
- Short Posterior Ciliary Artery (10 – 20) to Posterior Choroid
- Long Ciliary Artery (2) to Anterior Choroid
- Central Retinal Artery (1) to Retina

Shields et al, Ophthalmology 1997
Diagnostic Tests

- **Fluorescein angiography**
  - Recent lesions:
    - Mild early hypofluorescence
    - Mild late hyperfluorescence
  - Later RPE alterations produce mottled hyperfluorescence

Fluorescein Angiogram

- **Ultrasonography**
  - A-scan echography shows irregular and medium-to-high reflectivity
  - B-scan shows acoustic solidity, no choroidal excavation

Diagnostic Tests

Choroidal Metastasis
- Mod-high internal reflectivity
- Irregular internal structure
- Smaller apical height than melanomas
- Polygonal surface
- No choroidal excavation

Uveal Melanoma – Low Reflectivity

Choroidal hemangioma – High Reflectivity
Diagnostic Tests
- Optical coherence tomography
  - Can identify tumor and subretinal fluid
- CT scan and MRI of Orbits
  - Visualizes orbital and intracocular masses, but differentiation of masses may not be possible

Differential
- Choroidal Melanoma
- Choroidal Osteoma
- Choroidal Hemangioma
- Lymphoma
- Sclerochoroidal Calcification
- Inflammatory Conditions
  - VKH, uveal effusion, posterior uveitis, sarcoid, TB

Ocular Evaluation
- Evaluate other eye (mets often bilateral)
- Document lens status and diabetic retinopathy
- Affected by radiation treatment
- Obtain history of cancer, smoking, family hx
- Obtain photos and OCT
- Refer to Ocular Oncology early

Common Pitfalls
- Subretinal fluid thought to be due to central serous or other condition and observed
- Actual lesion difficult to see on slit lamp
- Not referred early

Metastatic Lesions
- Can develop rapid growth
- Prompt referral helpful
Therapeutic Options

- Goal of treatment: improve quality of remaining life by preserving vision, avoiding development of painful eye
- Treatment options
  - Observation
  - *Chemotherapy and systemic hormonal therapy*
  - *External beam radiotherapy*
  - Stereotactic radiotherapy
  - Plaque radiotherapy
  - Gamma knife stereotactic radiosurgery
  - Transpupillary thermotherapy
  - Excision
  - Enucleation

*Most common and helpful

Ocular and periocular side effects of EBRT

- 12% get side effects (Rudoler 1997)
- Dry eye, epi defects
- Posterior subcapsular cataract (2%).
- Radiation damage to retina/nerve (avg onset 18-24mo)(1.9%). Radiation retinopathy risk increased by preexisting retinal vasculopathy (DM), so close attention should be paid initially to vasculature.
- Lid edema/dermatitis
- Dry skin (exacerbated by concurrent adriamycin)

Prognosis

- Most tumors respond to treatment
- Tumor flattening and pigmentary proliferation
- Rarely may develop RPE tear or exudative retinal detachment
- Excellent prognosis for globe conservation
- Good chance of retaining vision
- Poor systemic prognosis

Iris Metastases

- One or more yellow, white, or pink nodules in the iris stroma
- Primary:
  - Breast
  - Lung
  - GI
  - Carcinoid *(orange)*
  - Melanoma *(black or brown)*

Iris Metastases

- Can be friable and seed cells into the aqueous
- Secondary glaucoma may occur

Ciliary Body Metastases

- Typically present as a solitary mass
- Difficult to detect on exam
Case

- 47yo WM
- Photophobia right eye
- Blurry x 2wk
- Cell and flare on exam, iris abnormality

- Concern for TB uveitis on original presentation to ER
- Work-up revealed new diagnosis small cell lung cancer
- Metastasis to iris, ciliary body, choroid
- Secondary inflammation and elevated IOP

Original Presentation 2 weeks later

Anterior high resolution ultrasound

- Iris involvement
- Ciliary body and choroid

Pt treated with chemotherapy
- Steroids and IOP drops
- Radiation treatment initiated but held due to improvement
- Observed very closely and tumor regressed well

6 days after chemo 4 months on chemo
9/12/2014

Lymphoma

6 days post Rx  4 months post Rx

Lymphomas

Hodgkin's Lymphoma

"...enlargement of the glands appeared to be a primitive affection of the bodies, rather than the result of irritation or inflammation..."
Thomas Hodgkin, 1832

non-Hodgkin's Lymphoma

"Lymphoma classified into three groups based on cellular morphology: Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma"
Henry Rappaport, 1956, 1966

Lymphoma

Primary
- Primary vitreoretinal
- Primary CNS
- Primary Uveal

Metastatic
- Originate outside CNS/eye

Primary Intraocular Lymphoma

Epidemiology

- Diagnosis in the 6th or 7th decade of life
- Slight male predominance
- Around 200 new cases per year
- Less than 1% of intraocular tumors
- 85% of PIOL is bilateral
- ~76% of those with PIOL develop CNS lymphoma in ~29 months

Risk factors

- Immunosuppression
- HIV-related, congenital or iatrogenic
- PCNSL develops in 6% of patients with AIDS
- Possibly secondary to EBV infection

Levy-Clarke, Hem Onc Clin N. Am. 2005
Bardenheier, Cancer Control, 1998
Mittra et al. 1999, Retina
Clinical Presentation

Table 1. Clinical manifestations of primary uveal melanoma based on history, ophthalmoscopy and fundus imaging

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Ocular Finding</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision loss</td>
<td>Decreased visual acuity</td>
<td>MRI with contrast of head and orbits</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Increased opacity</td>
<td>CT/PET of chest, abdomen, pelvis</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Elevated intraocular pressure</td>
<td>Consider testicular ultrasound of elderly men</td>
</tr>
<tr>
<td>Retinal edema</td>
<td>Enlarged retinal vessels</td>
<td>BM biopsy</td>
</tr>
<tr>
<td>Subretinal fluid</td>
<td>Accumulation of fluid between retina and pigment epithelium</td>
<td>To rule out systemic lymphoma</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>Blood in retina or choroid</td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Choroidal neovascularization</td>
<td>New growth of blood vessels in the choroid</td>
<td>Cytology</td>
</tr>
</tbody>
</table>

Possible ophthalmologic manifestations

DFE findings

Oncology Workup – Staging

Referral to Ocular Oncology
Referral to Neuro Oncology

Pars plana Vitrectomy: vitreous biopsy

Imaging:
- MRI with contrast of head and orbits
- CT/PET of chest, abdomen, pelvis
- Consider testicular ultrasound of elderly men

BM biopsy
- To rule out systemic lymphoma

Lumbar Puncture
- Cytology

Other:
- HIV
- CBC, SPEP, LDH, Chem 7, LFTs
**Diagnostic Testing: Cytology, Flow Cytometry, Cytokines, Molecular Studies**

- **Light microscopy**
  - Large, pleomorphic cells with high nuclear to cytoplasm ratios

- **Immunophenotype**
  - B-cell disorders: CD19, CD20, CD22, CD79
  - T-cell disorder (less common) CD3 and CD4

- **Cytokine analysis**
  - IL-10: IL-6 ratio > 1 “Strongly suggestive”

- **Molecular analysis**
  - "Strong evidence"

---

**Treatment of monocular PVRL without CNS involvement:**

- Intravitreal chemotherapy (Methotrexate, Rituximab)
- External Beam Radiation Treatment (30-35 Gy external beam)
- High Chance of CNS disease development

---

**Treatment of PCNSL**

- Intravitreal (debatable)
  - None
  - Intravitreal chemotherapy

- **Systemic Chemotherapy**
  - High-dose methotrexate based therapy (IV or intrathecal)
  - Systemic rituximab
  - Relapsed or recurrent: Intense chemotherapy

- **Whole Brain radiation**
  - Delayed Neurotoxicity (cognitive decline, ataxia etc)
  - Better response rate but higher toxicity
  - Often avoided

---

**PCNSL Take Home Messages:**

- Mimics chronic relapsing, steroid-resistant uveitis
- Mimics drusen
- Refer atypical cases early
- Typical RPE changes and subretinal infiltration

---

**Widefield Imaging Update**

Two Open Randomized Clinical Trials in progress (sponsored by National Cancer Institute)

- Standard Chemo VS Combination of Chemo and autologous transplantation
- MTX/ Rituximab/ Vincristine/Cytarabine/Procarbazine with or without radiation therapy

---

**References:**

Casady et al. Retina, 2013
Vosganian, J Neurooncol 2011
Financial Disclosures

• Optomap images obtained courtesy of demo from Optos

Widefield Imaging

• Widefield imaging technologies growing in popularity
• Can enhance evaluation of intraocular lesions but carries limitations

What Are Widefield Imaging Options?

• Montage photograph: 7- or 9-field photograph montage
  - E.g., Cannon 60 degree, Topcon 50 degree fundus camera
  - Montage software
  - Noncontact
  - Dilation
  - FA, ICG, AF, RF

What Are Widefield Imaging Options?

• Heidelberg Spectralis HRA
  - Confocal SLO
  - 30 or 55 degree lens + widefield module = 120 degrees
  - FA, ICG, RF, AF, infrared, video, OCT
  - Small pupil

Heidelberg HRA

Diabetic Retinopathy  Vasculitis
What Are Widefield Imaging Options?

- Staurenghi lens:
  - Contact lens
  - 150 degrees
  - Only used with Scanning Laser ophthalmoscope (e.g., Heidelberg HRA/Spectralis; can obtain video)
  - Not compatible with standard fundus cameras

Panoret (Medibell) (External light source contacts eye
- Large camera non-contact
- Supine position

Optos Optomap
- Scanning laser ophthalmoscope
- Noncontact
- 200 degree view
- Small pupil
- FA, AF, RF

Scanning Laser Ophthalmoscopy
- Coherent laser light
  - Green lasers (488 and 532nm) scan from the sensory retina to the pigment epithelial layers
  - Red laser (633nm) scans from the RPE to the choroid

Widefield Imaging vs. ETDRS

Nonmydriatic ultrawide field retinal imaging compared with dilated standard 7-field 35-mm photography and retinal specialist examination for evaluation of diabetic retinopathy.

Silva PS, Cavallerano JD, Sun JK, Noble J, Aiello LM, Aiello LP.
- ETDRS protocol seven standard field 30-degree color fundus photo vs. non-dilated optomap images
  - Compared favorably with dilated ETDRS photos and DFE in determining clinical severity of diabetic retinopathy and diabetic macular edema.
  - Matched clinical level of diabetic retinopathy 84%
  - Within one level of agreement in 91%
  - Sensitivity and specificity of ultra-widefield images for detecting the presence or absence of diabetic retinopathy diagnosed on ETDRS photos were 99 percent and 100 percent

Cases
Giant Retinal Tear with RD

Uveal Melanoma

Massive subretinal hemorrhage

Massive subretinal hemorrhage
Late Fluorescein Angiogram

Dr. Havener’s scleral buckle from age 5

Kpro patient
Widefield imaging systems

- Limitations
  - Cost $$$$$$$
  - Less user friendly
  - 200 degrees horizontally, not vertically
  - Could miss more peripheral pathology
  - Not 3-D view
- Benefits
  - Dilation and directing eye movement enhance visualization of peripheral lesions

Is Widefield Imaging a Substitute for DFE?

- How Often Do You Dilate?
- Fewer than two-thirds of adults with diabetes get an annual dilated eye exam. By that measure, many patients aren’t dilated often enough.

- Review of Optometry 11/8/2010
- John Murphy, Managing Editor

- This 43-year-old patient presented with an amelanotic melanoma at his first eye exam.
- “He went from his first eye exam to enucleation in three weeks,” Dr. Bearden says. “I’m pretty sure a dilated eye exam [performed earlier] could have saved his eye.”

Review of Optometry 11/8/2010
Why Do Patients Refuse DFE?

- Blur
- Trouble driving/working
- Photophobia
- Drops sting

What Are Strategies to Encourage Dilation?

- Phenylephrine 2.5%
- "Usually when people refuse, I put on a video for them to watch," Dr. Bearden says. The video, also available through Dr. Bearden’s website (www.visionaryeyecareonline.com) and on the practice’s YouTube channel (www.youTube.com/...), is a convincing patient testimonial from a woman named Starlene Carter.

"I did not want to get dilated," Ms. Carter tells the camera. But Dr. Bearden eventually convinced Ms. Carter. Upon dilation, Dr. Bearden discovered a large horseshoe retinal tear, and referred Ms. Carter to a retinal surgeon for laser treatment. ("It's always the patients who give you a hassle, they're the ones you find problems with," Dr. Bearden says.)

"Testimonials from other patients hold a lot of weight."

Review of Optometry 11/8/2010

Front Lines of Eye Care

- DFE is important and should be recommended
  - Stereo
  - Periphery
- Widefield imaging
  - Assists in documentation, evaluation
  - ? increase sensitivity of pathology detection

Ocular Melanoma Foundation

- Informal poll ~114 patients with uveal melanoma and caregivers
  - 1% Never had eye exam prior to the diagnosis
  - 75% Evaluated by an eyecare professional within 1 year of diagnosis

How can all eyecare professionals increase sensitivity of (early) detection?

Early Detection Saves Lives

- Nevi: precursor to melanoma
- Nevi: color difficult to see with 90D
  - Better sensitivity with indirect ophthalmoscope
  - Better sensitivity with fundus photography
  - Peripheral lesions more difficult to detect
Early Detection Saves Lives

- Dilation, widefield photos
- Photograph all nevi
  ✓ even 1DD nevi can become melanoma
- Refer all suspicious nevi early

Thank you for saving lives!

- Thanks to American Academy of Optometry
- Ocular Melanoma Foundation

Uveal Melanoma Team at OSU

- Ocular Oncology
  - Colleen Cebulla
  - Frederick Davidorf
- Radiation Oncology
  - Doug Martin
- Pathology
  - Lynn Schoenfield
  - Sara Peters
  - Nyla Heerema (FISH)
- Medical Oncology
  - Kari Kendra
  - Thomas Olencki
  - David Liebner
- Surgical Oncology
  - Mark Bloomston
  - Carl Schmidt
- Cancer Genetics
  - Mohamed Abdel-Rahman
  - Robert Pilarski

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