PRESENTATION TITLE

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  - Castle Biosciences, Optos, SPARK, Arix Biosciences, ClearSight

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I AM AN OCULAR ONCOLOGIST

- Comprehensive care of cancerous, pre-cancerous and simulating conditions in and around the eye
- Impact of treatments of systemic cancers on the eye
- Spans all specialties in Ophthalmology

OCULAR IMPACT OF SYSTEMIC CANCERS

Prithvi Mruthyunjaya, MD, MHS

Mary M. and Sash A. Spencer Center For Vision Research
STANFORD OCULAR ONCOLOGY SERVICE

- Childhood:
  - Retinoblastoma
  - Conjunctival and Iris tumors
  - Posterior segment
    - Melanoma
    - Lymphoma
- Ocular complications of systemic cancers

OCULAR IMPACT OF SYSTEMIC CANCERS

- Metastatic tumors to the eye
  - Presentation
  - Treatment options
- Paraneoplastic conditions
- Ocular toxicity from systemic therapy

A BRIEF TOUR...

CLINICAL CASE

- 66 yo Caucasian male with gradual vision loss over 1 year.
- Now with choroidal lesion, left eye
- PMH
  - Resected cutaneous melanoma

METASTATIC SCREEN

- Multilobed right kidney mass
  - 5 X 7 X 4 cm lesion with calcifications and cyst
- Needle biopsy
  - renal cell carcinoma
- Laproscopic resection
OCULAR METASTASES FROM SYSTEMIC CANCER

- First reported in 1852
- Most common intraocular tumor
  - 8% of cancer patient eyes at autopsy
  - 8-30% precedes diagnosis of systemic cancer
  - Indicative of Stage IV disease, poor prognosis

WHY THE UVEAL TRACT?

CLINICAL PRESENTATION

- Blurred Vision 75%
- Photopsias 5-12%
- Pain 5-14%
  - NO symptoms 9-11%

CLINICAL FEATURES

- Yellow/white mass 94%
- Subretinal Fluid 73%
- Speckled RPE 45%
- “leopard spot”
- Bilateral, multifocal
- Orange color
  - Renal cell, thyroid, carcinoid

CHOROIDAL METASTASIS - TESTING

- Detailed cancer history
- Systemic evaluation tailored to clinical presentation
- Re-staging in known cancers
- MRI brain should usually be performed due to high incidence of CNS lesions (30%)4

TUMOR ORIGINS

<table>
<thead>
<tr>
<th>Cancer status</th>
<th>Known malignancy</th>
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<tbody>
<tr>
<td></td>
<td>No known malignancy</td>
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* Li and Mithunpunnoo 1st Eye Ophthal 2014
* Chen et al. Survey Ophthalmology 2011
* Shields et al. 2005
* Mathis et al. PRER 2019
* Mathis et al. PRER 2019

Pancreatic Adenocarcinoma

Chen et al. Survey Ophthalmology 2011
**BREAST CANCER OCULAR METASTASIS**

- Woman with known stage IV disease
  - 16% initial manifestation of breast CA
  - 3% first metastatic site
  - Mean 48 months after 1st diagnosis
- Treatment (regress/stable)
  - ERBT (93%)
  - Systemic therapy (88%)
- Survival after eye mets
  - 1 year 65%
  - 5 year 24%

*Demirci et al. AJO 2003*

**LUNG CANCER OCULAR METASTASIS**

- Men with unknown primary tumor
  - 44% initial manifestation of lung CA
  - Mean 31 months after diagnosis
- Treatment (regress/stable)
  - Chemotherapy (63%)
  - ERBT (86%)
- Mean survival from ocular met
  - 12 months

**TREATMENTS FOR OCULAR METASTASES**

- Optimizing systemic therapy
- Ocular therapy
  - Photodynamic Therapy
  - Radiation Therapy
  - Laser therapy
  - Anti-VEGF therapy

**CHOROIDAL METASTASIS - PHOTODYNAMIC THERAPY**

- Long duration infrared “cold” laser + photosensitizer (verteporfin)
- Generates free radicals leading to vasoconstriction, thrombosis, and immune reaction
- Initially introduced for therapy of wet-AMD
- 77-100% reduction in tumor size
  - Marks et al. PRDR 2019
**HISTORY OF PRESENT ILLNESS**

- 71 year old female, referred for retinal lesion in the left eye
- Notes transient darkening of peripheral visual field, occasional photopsias for the past few weeks

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**PAST MEDICAL HISTORY**

- June-October 2017 - persistent cough, right hip pain, weight loss
  - MRI of lumbar spine, T1/T2 hypointense lesion in sacrum
  - CT chest shows left hilar and lung mass with innumerable lung nodules in both lungs
- EGFR mutation exon 20

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**PAST MEDICAL HISTORY**

- Oct 2017 - Biopsy of sacral lesion c/w metastatic non-small cell lung adenocarcinoma
- Oct 2017 - Brain MRI shows 5mm frontal and parietal mass
- Nov 2017 - Radiotherapy to brain and sacral lesions

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**PAST MEDICAL HISTORY**

- Normal Right eye exam and OCT
- Abnormal Left eye
  - Subretinal fluid under fovea
  - Lumpy choroidal infiltration
ASSESSMENT

- Primary non-small cell lung adenocarcinoma, stage IV, with bone, brain and symptomatic choroidal metastases

- Options
  - External beam radiation
  - Systemic chemotherapy (non target mutation)
  - Photodynamic therapy

VERTEPORFIN PHOTODYNAMIC THERAPY

3 months later: 20/20
Presentation: 20/50

CHOROIDAL METASTASIS - RADIOTHERAPY

- External beam radiation
  - 20-40 Gy in fractions
  - 66-84% improved/stabilized
- Stereotactic radiosurgery
- Proton Beam radiation
- Plaque Brachytherapy

ANOTHER CASE

- 44 yo Asian woman with ductal breast carcinoma
  - s/p radiation and chemotherapy 1 year ago
  - Stable regional metastatic disease
  - 2 month history of blurry vision in the right eye
  - Associated headaches
  - No prior ocular history or surgery
ON EXAMINATION

- Vision 20/400 right eye
- 13 x10mm amelanotic choroidal mass
- Extensive retinal detachment
- Normal left eye

BIOPSY OF CHOROIDAL TUMOR

- Metastatic breast carcinoma
- Concurrent CNS metastasis

- Treated with 30 Gy EBRT in 15 fractions
  • Brain and orbit

EXCELLENT RESOLUTION OF LESION AND FLUID

ERBT: COMPLICATIONS

- Anterior segment
  • Skin excoriation, lash loss
  • Keratopathy
  • Cataract
  • Secondary glaucoma

- Posterior segment
  • Retinopathy
  • Optic neuropathy
  • Neovascularization

- Plaque vs. ERBT
  • Technique
  • Timing
  • complications
TARGETED THERAPY

ANOTHER CASE...

- 45 yo white male with acute vision loss in the right eye
- No prior ocular history
- PMH: healthy, non smoker
- Family history: no malignancy

25-gauge transvitreal choroidal biopsy
**BIOPSY CONFIRMED**

- Adenocarcinoma of lung
  - S-100 negative
  - CK7 and TTF-1 reactive
  - EGFR mutation positive **(SURPRISE!)**
- Erlotinib therapy initiated

**3 WEEKS AFTER TREATMENT**

**EGFR MUTATION POSITIVE LUNG CA**

- 5% of adenCA cases harbor EGFR mutations
- Erlotinib TKI approved in May 2013
- Outcomes (erlotinib vs. platinum based chemo)
  - PFS: 10 vs 5 months
  - Overall survival: 23 vs 20 months
  - Objective response: 65% vs. 16%
- 3 cases in literature using TKI for choroidal met
PALLIATIVE CARE: WHEN TO TREAT AND WHY?

Observe
- Poor status
- New therapy

Bilateral disease
- Systemic therapy
- EBRT

Unifocal, vision involved
- PDT, ERBT, plaque, laser
Blind/painful eye
- enucleate

Systemic Status
Tumor Status
- # of tumors
- Location
- Laterality
Patient Preference

OCULAR TOXICITY FROM CANCER THERAPIES

- >50 approved anti-cancer therapies since 2008
  - 34 were antibodies or kinase inhibitors
- Often overlooked or underreported side effects
  - 7% with permanent vision loss

Fu et al. Oncotarget 2017; Kundler et al. Graefe’s Archives Ophthalmol, 2019

ANOTHER CASE

- 54 yo Vietnamese man with metastatic malignant melanoma
- s/p ipilimumab therapy without response
- Started on interferon infusion therapy
  - Moderate initial response
- Noted vision alterations in both eyes

BILATERAL COTTON WOOL SPOTS

Right eye fundus Left eye fundus

During interferon

3 months after stopping interferon
**INTERFERON RETINOPATHY**

- Recombinant protein used in lymphoma, melanoma, and leukemia therapy
- Ischemic retinopathy
  - Cotton wool spots, hemorrhage in 16-84%
  - Leukocyte dysfunction and endothelial damage
- Drug cessation may reverse

**OCULAR TOXICITIES FROM TARGETED AGENTS**

- Of 46 targeted agents, 20 with FDA label of ocular toxicity
  - 40% of small molecules
  - 25% of monoclonal antibodies
- Most common FDA label notes
  - Conjunctivitis, iritis, eye irritation, blurry vision, dry eyes,
  - Fu et al. Oncotarget 2017

**OCULAR SAE TARGETED AGENTS**

- Most common: conjunctivitis (20%), blurred vision (21%)
- Imatinib: 3% of patients with Grade 3+ periorbital edema
  - Imatinib (70%) and crizotinib (62%) experience any toxicity
- Acute vision threatening toxicities
  - Vascular occlusions, corneal ulceration, retinal findings
    - 5 drugs: erlotinib, gefitinib, trametinib, vemurafenib, ipilimumab

**EGFR INHIBITION PRODUCES TRICHOMEGALY**

**IMMUNE CHECKPOINT INHIBITOR TOXICITY**

- Dry Eye 1-24%
- Uveitis 1%
- Myesthenia 1%
- Managed with steroids
- Artificial tears
- Rarely discontinue

- Fu et al. Oncotarget 2017

- Fu et al. Oncotarget 2017

- Dalvin et al. Retina 2019
CHECKPOINT INHIBITOR OCULAR SIDE EFFECTS

- Dalvin et al. Retina 2019

MEK ASSOCIATED RETINOPATHY

- Subretinal fluid with binimetinib therapy
  - 90% during phase 1b/2 studies
  - 78% after first dose
- Bilateral, multifocal and visually symmetric: 10%
- Improved with dose reduction/withdrawal

Weber et al. JAMA Ophthalmology 2016; Mendez-Martinez et al. Retina 2018

TARGETED AGENTS:

- Recommend pre-treatment ophthalmic examinations
- Interferon therapy
- EGFR inhibitors
- MEK inhibitors (trametinib, selematinib)
- Tyrosine kinase inhibitors (ibrutinib)
- Anti–CTLA4 antibodies (ipilimumab)
- BRAF inhibitors (vemurafenib)

- Most visual complaints in cancer patients are minor
- Toxicities can be supported but may require discontinuation

STAGE IV DISEASE WITH OCULAR INVOLVEMENT

- This is PALLIATIVE care
- Little impact on the primary tumor
- Major impact on vision and quality of life

STANFORD OCULAR ONCOLOGY SERVICE

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Figure 1

Figure 2

**METASTATIC IRIS LESIONS**

- Rare, but important to recognize
- 5-10% of uveal metastases
- In 1/3 cases, NO known primary
- In ½ cases, first sign of metastasis
- Very poor prognostic sign

*Am. J. Ophthalmol. April 1995*
**IRIS METASTASES: CLINICAL FEATURES**

- Unilateral
- Solitary
- Epibulbar injection
- Secondary glaucoma
- Hyphema
- Pseudo-hypopyon
- Associated choroidal metastases

**PRIMARY TUMOR LOCATION**

- Breast
  - Previously known history
- Lung
  - Previously unknown history
  - Biopsy proven
- Carcinoid tumors
- Other sites (rare)

**ULTRASOUND**

- High internal reflectivity
- Less vascularity

**SOMETIMES YOUR FIRST TREATMENT MAY NOT BE THE BEST...**

- 60 yo gentleman referred for ocular melanoma evaluation
  - Otherwise healthy

**AFTER EBRT**

Tumor growth noted

**Choroidal biopsy + for renal cell carcinoma**
PARANEOPLASTIC SYNDROME:
THE STORY BEGINS...

- 56 yo wm presents to fantastic local retinal specialist with right iridociliary mass
  - Asymptomatic
  - Incidental finding on CT/MRI
- Confirmed findings, initiated metastatic screening

ON PRESENTATION...

ON PRESENTATION...
**INCIDENTAL MRI FINDING?**
- Admitted 1 month earlier with psychotic episode
- Prior pulmonary embolism
- Chronic pericardial effusion: spiral CT-angio
  - Increasing effusion
  - Stable 1.2mm paratracheal nodes
  - Patchy lung opacity, atelectasis vs. consolidation
- No evidence of liver or CNS disease

**DIFFUSE MELANOMA VS. MELANOCYTIC HYPERPLASIA**

**AT THE SAME TIME..**
- Ill appearing male, no systemic malignancy
- Differential:
  - Ring melanoma
  - Diffuse infiltrating melanoma
  - Metastatic disease

**RIGHT LUNG BIOPSY: NON-SMALL CELL CARCINOMA**
- Spindle cells, rarely epithelioid
- Benign melanocytic hyperplasia
- Rare mitoses
- Panuveal involvement
- Widely misreported as diffuse melanoma

**HISTOPATHOLOGY FINDINGS**
- Low power tumor growing in nests and along alveolae
- High power shows large highly atypical epithelioid cells in nests
Intraalveolar nests of tumor
Focal suggestion of gland formation

Cytokeratin-7 (confirms carcinoma, typically + in lung adenocarcinomas)

TTF-1 (70% adenocarcinomas of lung + for TTF1)

NOT A PRIMARY MELANOMA

HMB45 negative
S100 negative

PERICARDIAL BIOPSY: NEGATIVE FOR TUMOR
**Paraneoplastic Disease**

- Cause of significant vision loss
- Often may unmask underlying malignancy
- Delayed diagnosis
  - Overlap with numerous retinal conditions

**Autoimmune Retinopathy**

- Symptoms: photopsias, visual field change
- Signs: arteriolar changes, disc pallor, vitritis, ERG loss, scotoma, BDUMP

**Diffuse Uveal Melanocytic Proliferation**

- Paraneoplastic syndrome
- 60 year old patient (male=female)
- Early: subtle to few ocular signs
- Late: vision loss, serous RD, cataract (75%)
- Death in <1 year

**BDUMP: 41 Reported Cases**

<table>
<thead>
<tr>
<th>Females</th>
<th>Males</th>
</tr>
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<tbody>
<tr>
<td>GU malignancies</td>
<td>Lung</td>
</tr>
<tr>
<td>(pancreas)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

All tumors with known paraneoplastic associations
---CAR, hypercalcemia, Cushing’s syndrome

Presentation to death: 1 to 51 months (mean 15 m)
71-YEAR-OLD MAN WITH BLURRY VISION IN BOTH EYES

- 4 months vision loss in both eyes, vitritis OU
- Uveitis workup was sent. On chest X-ray, he was found to have incidental right upper lobe lung mass.
- Slit-lamp exam was notable for 1-2+ AC cells OU and 1+ vitreous haze and inferior

Walter, ... Mruthyunjaya, et al. JAMA Ophthalmology 2017

After plasmapheresis

OD: 20/100-
OS: 20/100-

OD: 20/25
OS: 20/30

After plasmaphoresis 3x

Walter, ... Mruthyunjaya, et al. JAMA Ophthalmology 2017