Cancer and the Eye

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Cancer factoids
- Can affect any tissue or organ at any age
- All cancers begin with a defect in a single cell (monoclonal)
- This is followed by unrestrained growth

Cancer factoids
- A one cm. tumor contains one billion cells
- One trillion cells usually means a lethal tumor
- BENIGN tumors may damage local tissue by occupying space but they do not spread
- MALIGNANT tumors invade surrounding tissue and may metastasize

Cancer factoids
- Cell division is controlled by genes that promote it and genes that suppress it
- Cancer is the result of some combination of defects in this genetic functioning

Recent study
- Study of a 43 year old with skin cancer found 23,000 genetic mutations
- Study of a 55 year old with lung cancer found 33,000 genetic mutations
Cancer types

- General types of cancer include:
  - Melanomas (melanin)
  - Sarcomas (connective tissue)
  - Carcinomas (epithelial tissue)
  - Leukemias (bone marrow)
  - Lymphomas (lymphoid tissue)

- Adenocarcinoma: Glandular tissue

Leading cancers in US

- Men:
  1) Prostate
  2) Lung
  3) Colon
  4) Urinary
  5) Skin melanoma

- Women:
  1) Breast
  2) Lung (90% use tob.)
  3) Colon
  4) Uterine
  5) NHL lymphoma

- But the most common malignancy in humans is Basal Cell Carcinoma!

Skin cancer

- In the US 50% of all cancer is skin cancer, and 80% of skin cancer is BCC

- Did you know that patients that have had a kidney transplant are 20X more likely to develop ocular squamous cell carcinoma?

2013 American Cancer Society Report

- Overall in 2013:
  - 1,660,290 new cases of cancer excluding SCC and BCC
  - 13.7 million living Americans with a history of cancer (active or remission)
  - 580,350 deaths: 1,500/day

- Combined M & F Rank:
  - Prostate (238,590)
  - Breast (234,580)
  - Lung (228,190)
  - Colon (102,480)
  - Lymphoma (79,030)
  - Skin melanoma (76,690)

Cancer mortality in the US (combined M & F)

- 1) lung
- 2) colorectal
- 3) breast
- 4) pancreatic (# 12 in frequency)
- 5) prostate

Cancer in the future

- By 2020, the number of cancer patients and cancer survivors will increase by over 50% to an estimated 18.2 million
- There will be a projected shortage of 4000 oncologists
Cancer epidemiology

- Cancer screenings are driven by several factors............
  - 1) Is it a common cancer?
  - 2) Can we detect it?
  - 3) Can we treat it?
  - 4) How much does the screening cost?

- It is worth screening for prostate, colon, breast, cervical, and skin cancer.
- Cancer increases with age due to increased length of exposure to carcinogens.

Cancer screenings

- 1) Blood tests
- 2) Bone scans
- 3) Biopsies
- 4) X-ray, CT, MRI and other imaging
- 5) Observation

- It is worth screening for prostate, colon, breast, cervical, and skin cancer.
- Cancer increases with age due to increased length of exposure to carcinogens.

Cancer

- Leading cause of death worldwide
- It accounts for ¼ of deaths in the US......Only heart disease kills more.
- Economic toll of $895 billion......not counting the cost of treatment!

Cancer treatment

- CHEMOTHERPY:
  - Drugs that interfere with cell division
  - Multiple drugs available, oral and IV

- RADIATION:
  - Damages cellular DNA

- SURGERY:
  - Removes the tumor

- Chemotherapy targets all cells in the body that are actively dividing............abnormal and normal!
- Hair follicles > loss of hair
- Intestinal mucosa > diarrhea, vomiting, nausea
- Bone marrow > anemia

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Cancer treatment

- Radiation results in the damage of cellular DNA > cell death
- Need to be focal with treatment because all cells are affected
- Both radiation and chemotherapy can lead to retinal complications

Cancer treatment

- Treatment often consists of a combination of surgery, radiation and chemotherapy
- This depends on many factors (location, metastases, etc.)

Help from a tree?

- Beta-lapachone from the South American lapacho tree
- Cytotoxic effects shown (due to induced apoptosis) to cancer cells: retinoblastoma, lung, breast, prostate, many others

Beta Lapachone

- Usefulness in humans limited thus far by toxicity
- Also has antibacterial and antiviral properties, including activity against HIV

Did you know………

- Metformin (Type II DBM drug) is proving to be very protective against lung cancer
- It activates an enzyme………. that inhibits a protein………. that is needed for the growth of cancer cells

Paraneoplastic syndrome

**CAR (cancer associated retinopathy)**

- Rare: antibody mediated
- Associated with many types of cancer
- Photopsia and progressive bilateral vision loss
- Normal fundus appearance then RPE changes, etc.
- Confirm with ERG

**MAR (melanoma associated retinopathy)**

- Rare, more common in males
- Associated with cutaneous melanoma
- Photopsia, night blindness, loss of vision
- Normal fundus appearance then RPE changes, etc.
- Antibodies target rods
Interferon chemotherapy
Cancer itself can cause CWS too.......

Case Report
A 55 year-old white female reported to our clinic with a complaint of blurry vision in her left eye for about one month
She also complained of dizziness, nausea, and a “pressure” behind her left ear
Her medical history was significant only for a family history of colon cancer

Case Report
An eye exam performed in our clinic three years prior was remarkable only for refractive error
Entering acuity with correction was 20/20 OD, 20/40 OS and BCVA was 20/20 OD, 20/25 “-” OS
Entrance testing was unremarkable as was the anterior segment OU

Case Report
DFE OD was remarkable for an isolated cotton-wool spot in the superior arcade
All other fundus findings OD were normal
DFE OS revealed a large (2.5 disc diameter) cream colored mass infero-temporal to the macula which was encroaching on the foveal region but did not involve the foveal center

Amelanotic Lesion OS (whitening in arcades is a camera artifact)

Case Report
Screening and threshold Matrix FDT VF results were normal OU
B-scan ultrasound of the left eye revealed a solid lesion with 1.5-2.0mm of elevation and moderately high internal reflectivity with no evidence of overlying retinal detachment
Systemic Work-up

- Due to the appearance of the retinal lesion, metastatic disease was strongly suspected
- The patient was counseled earnestly regarding this fear and referred for a consultation with a retinal oncologist

Systemic work-up

- A systemic work-up revealed previously undiagnosed large cell carcinoma of the lung with multiple lesions
- There were metastases detected in the liver, spleen, and kidneys
- Chemotherapy was begun at this time

Therapy

- The ocular lesion in the left eye continued to be problematic despite chemotherapy and the vision deteriorated to 20/100 over the course of one month
- The retinal surgeon decided to proceed with a course of external beam radiation ocular therapy in addition to the chemotherapy. Ultimately successful with acuity recovery to 20/25

Another example......

- The following set of pictures represent another patient
- Once again, the patient reported with a complaint of blurry vision OS and no known cancer
Multiple Metastatic Lesions OU

Early IVFA OS
- Note blocking of the background hyperfluorescence in multiple areas including large central lesion

Late IVFA
- Note late staining of large central lesion secondary to leakage from lesion’s blood supply

Another Example........
- In this case, systemic evaluation revealed multiple, subcutaneous adenocarcinomas with several intracranial metastases and lymph node involvement
- No primary tumor site was able to be identified
- Management with radiation and chemotherapy was undertaken and the ocular lesions responded well but ultimately the patient did not survive

Several weeks later....systemic chemo and radiation

Uveal Metastatic Lesions
- Most common intraocular tumor
- Number one primary site in women is the breast, in men it is the lung
- Choroid around 90%, ciliary body about 8%, iris 1-2%
- Up to 10% of cancer patients get uveal metastases: often not diagnosed
- Primary site is often never determined
Uveal Metastases
- Located in posterior pole (blood supply)
- Unilateral or bilateral (unilateral 3 to 1)
- Breast metastases most likely to be bilateral; lung unilateral
- Single lesion or multiple lesions
- RPE detachments
- Creamy yellow in color (may have orange hue)
- Oval to placoid
- Relatively flat (rarely break through Bruch's membrane)
- High internal reflectivity on ultrasound

Management of Metastatic Tumors
- Metastatic lesions tend to be detected sooner because their posterior pole location leads to earlier symptoms
- Systemic work-up is critical
- Average survival time of 9 months after Dx
- Systemic chemotherapy
- Radiation via external beam (outpatient) or plaque (hospital)
- PBT (protons)
- Photocoagulation
- Enucleation
- Anti-VEGF injections
- Must consider life expectancy

Differential Diagnoses of Metastatic Tumors
- Primary uveal melanomas
- Hemangiomas
- Osteomas
- Posterior scleritis
- Inflammatory disorders

Other Examples of Ocular Neoplasms
- Choroidal nevi
- Primary Choroidal / CB Melanomas
- Melanocytomas
- Iris melanomas

Choroidal nevi
- Possibly present in up to 30% of general population (90% clinically)
- 6.5% of whites in 2011 study
- Flat or minimally elevated (< 1.5 mm)
- < 6 mm in diameter; 95% are less than 2mm
- Melanotic or amelanotic
- Overlying drusen usually indicate longstanding inactivity; lipofuscin?
- Possible overlying serous RD
- RPE disturbance / atrophy over time
- Conversion to uveal melanoma: 1 in 4000-8000
- 10% will grow without undergoing malignant conversion. Recent 2011 study showed growth in 31% over 15 years.

Choroidal Nevi
- Photodocument
- B-scan
- If small follow annually
- If suspicious, more frequent observation
- Significant elevation rare with nevi
Choroidal Nevi

Peripheral choroidal nevus

Longstanding, Large Choroidal Nevus
- Overlying PED / RD
- B-scan revealed no growth compared to baseline: retinal oncologist chose to monitor closely

B-Scan

Melanoma
- Later, decision was made that malignant transformation had occurred
- Treatment was undertaken with brachytherapy
Primary Uveal Tumors
- Unilateral & solitary
- Pigmented but may be amelanotic
- Relatively elevated
- Can break through Bruch's membrane... "Collar Button"
- Rare in non-caucasians
  (C:19 X AA; H Bx AA)
- Low internal reflectivity with ultrasound
- Can be located anywhere... no posterior pole predilection
- About 2000 new cases per year in US

Melanoma vs. nevus
- Important risk factors for possible malignant transformation...
- Thickness > 2mm
- Symptoms
- Orange Pigment
- New onset of subretinal fluid / serous RD, especially in the absence of drusen
- Ultrasound hollowness / no halo
- Location within 8mm of ONH
- Diameter of 12mm or more

Shields
- "To find small ocular melanomas"
- Thickness > 2mm
- Fluid
- Symptoms
- Orange Pigment
- Margin near ONH (3mm)

EDI SD-OCT feature of small melanomas vs. nevi
- Shaggy photoreceptors
- Loss of PIL
- Disruption of IPL, GCL
- Loss of ELM

Primary uveal tumors
- Can metastasize (up to 50%, but often not yet detectable at the time that the ocular tumor is found). 75% to the liver first
- Gene mutation that causes metastasis has been discovered (Dr. Harbour, Washington University, and others. Dr. Harbour now at Bascom Palmer)
- Systemic work-up a must. but not common to find metastases at time of diagnosis
- 2X risk of colon cancer compared to general population

Radiation risk
- For a 50 year old diagnosed with an ocular melanoma, the cancer risk from 10 years of radiation exposure with abdominal scans is.....
- CT scan around 1% lifetime risk
- CT plus PET scan around 2% lifetime risk
- This is average for both sexes, women slightly higher risk
Pathology

- Three main tumor types based upon cell morphology...
  - Spindle (relatively benign)
  - Epithelioid (most large tumors)
  - Mixed

Small Choroidal Melanoma with Lipofuscin and Elevation

Choroidal Melanoma With Intravitreal Extension

Early choroidal melanoma

“Collar Button” Melanoma

Bile Duct Liver Cancer with no ocular history

Lesion edge

Atrophic area and border
Could the liver cancer have been metastatic from the eye?

Sub-retinal hemorrhage

Treatment options for tumors
- Systemic radiation / chemo if metastatic disease involved
- Brachytherapy (radioactive plaque): requires two surgeries and sometimes a hospital stay. Local recurrence rate of 10% @ 5 years. 12.5% end up enucleated
- Photocoagulation- replaced by TTT. 20% recurrence rate, but limited "down side"
- Cryotherapy, stereotactic radiotherapy
- Enucleation

EBRT (external beam radiation therapy)
- 3-4 weeks of daily treatment

PBT (proton beam therapy)
- Two treatment sessions only
- Less readily available
- Lowest local recurrence rate: 3.5% @ 5 years, 5% @ 10 years

PBT in Scotland
- 2012 retrospective study
- 147 patients who had medium and large uveal (most all choroidal) melanomas
- Treated with PBT between 1993 and 2008
- 23% eventually required enucleation
- Disease specific 5 year survival rate of 88%
- Most common reasons for eventual enucleation were tumor recurrence and NVG

Treatment side effects
- Main side effect of focal ocular treatment is...........
- Radiation retinopathy!
- NVD / NVE
- Exudative changes
- Macular edema
- Occurs several weeks to months after therapy
Treatment options

- Rapid shrinkage of the tumor with treatment may be bad news. Indicates substantial malignant (and metastatic) potential.

COMS and other studies

- Five year survival rates for:
  - Small melanomas (< 10 mm): 94%
  - Medium melanomas (10-15 mm): 70-90%
  - Large melanomas (> 15 mm): 40-60%
- Enucleation does NOT appear to increase metastatic risk.

Choroidal Melanoma (“George”)
Post Photocoagulation Therapy

Melanoma: photos courtesy of Dr. Vic Malinovsky

Melanoma

Radiation retinopathy

- Avastin may be effective at reducing retinopathy and stabilizing vision.
- What about silicone oil? May reduce radiation retinopathy risk, but can cause other issues.
Another example of RR

What if...........

- Fine needle biopsies of melanomas are yielding amazing info with RNA transcriptomic profiling
- Essentially two types of tumors that can be identified with over 90% accuracy
- Class one signature: almost never metastasizes;
  Class two almost always does (monosomy-3)
- What are the implications of this?

Possible intervention

- New research by Dr. Harbour indicates that a certain class of seizure drugs......HDAC inhibitors........may help
- Cancer cells that have metastasized from the eye to other sites are inhibited and made less aggressive by these drugs. May be able to keep disease “at bay” for an extended period

More genetics........

- 80% of uveal melanoma patients have mutations in either GNA11 or GNAQ
- But.............this mutation alone does not result in melanoma formation. Must have mutation plus other factors (as of now not known)

Iris Melanomas

- Around 5% of all uveal tumors
- Located inferiorly secondary to sun exposure
- Only metastasize in about 8% of cases after 16 years.
- Found mostly in light colored irides (therefore Caucasians)
- Can have satellite lesions
- Can seed tumor cells into the TM causing elevated IOP
- May be melanotic or amelanotic
- Can irradiate or surgically excise

Differential diagnoses

- Be suspicious if...........
  > 3mm
  Increased IOP
  Distorted pupil
  Rapid growth
  Secondary cataract

- Neurolemmoma
- Xanthogranuloma
- Nevus
- Iris cyst
- Lisch nodule
- Melanocytoma
Amelanotic Iris Melanoma

Another iris melanoma

Melanocytomas
- Jet black lesion consisting of melanocytes
- Most often on ONH, but can rarely affect the conjunctiva or uveal tract
- Usually involves less than half of the disc but may cover the entire ONH
- Can have concomitant juxtapapillary choroidal nevus

Melanocytoma
- Very little potential for malignant transformation
- Very slow growing
- Usually little or no effect on vision but can cause VF defects including an enlarged blind spot
- May also cause an APD

Differential diagnoses
- Malignant melanoma
- Juxtapapillary choroidal nevus
- Optic disc meningioma

Melanocytomas
Melanocytoma

Multiple CHRPE / Bear tracks

A ticket for.............. Colonoscopy!

Familial Adenomatous Polyposis

FAP
- 1 / 8000 people
- Associated with RPE hypertrophy
- Colon polyps with a chance for malignant transformation

Gardner’s Syndrome
- A variant of FAP, but also has.....
- Osteomas of the jaw
- Soft tissue benign tumors
- Dental abnormalities
- Polyps have nearly 100% chance of malignant transformation
- 1 / 1,000,000 people

What’s this?

Conjunctival Intraepithelial Neoplasia (CIN)
Melanocytoma

Osteoma

Syphilitic chorioretinitis

Retinoblastoma
- Malignant, congenital tumor
- Derived from retinoblasts
- Most common intraocular tumor in infants/children
- 70% unilateral
- 1/15,000 children
- 200-300 US cases/yr
- No racial or sexual predilection
- Two types:
  1) Inherited (AD), less than 10% of cases, frequently multifocal and bilateral
  2) Sporadic, usually unilateral
- Can metastasize and be fatal if detected too late
- Survival rate 90+% if detected early (typical age of diagnosis is around 18 months)
- LEUKOCORIA
- Strabismus
- Poor VA
- Involvement of ONH is ominous
- Many treatment options depending on multiple factors
- IV chemo?

Genetics
- RB survivor with inherited type: 50% chance of transmitting to their children
- Healthy parents: one child with RB; 6% chance of another; two or more children with RB; 50% of another

OCT
Leukocoria differentials

- Retinoblastoma
- Coats' disease
- Toxocariasis
- Toxoplasmosis
- Congenital cataract
- PHPV
- coloboma

Coloboma

Retinoblastoma

The End!