Ocular Cancer Clues
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REVISED SEPTEMBER 2012

Conditions Discussed
— Horner's Syndrome
— Carney's Complex
— Multiple Myeloma
— Myesthenia Gravis
— Cowden's Syndrome
— von Hippel-Lindau
— Gardner's Syndrome
— Multiple endocrine neoplasia, Type IIb

Definitions
Association - nonrandom occurrence of multiple anomalies not known to be a polytopic field defect, sequence, or syndrome
Malformation Syndrome – repetitive pattern of multiple non-sequential distinctive anomalies. (e.g. Trisomy 21)
Malformation Sequence - pattern of multiple anomalies with a presumed or proven common etiology, localized to a single morphogenetic field, with a related formal pathogenesis. (e.g. classic Potter's Sequence)
Hamartoma - proliferation of normal mature tissue in a normal anatomic location (hemangioma = skin)
Choristoma - heterotopic proliferation of normal mature tissue in an abnormal anatomic location (tooth = orbit)
Paraneoplasia - symptom complexes in cancer-bearing patients which cannot be explained by local or distant tumor spread
Neoplasm - “new growth” an abnormal mass of autonomous tissue serving no useful function, the growth of which exceeds and is uncoordinated with that of normal tissues. Neoplasms usually grow at the expense of the host organ.
Cancer - malignant neoplasm accompanied by abnormal cell division, invasion of surrounding tissues, and distant metastasis.
Some Generalities Regarding Carcinogenesis

- Defects in DNA repair increase susceptibility
- Numerous carcinogens are mutagens
- Tumors contain mutated oncogenes
- Early and late gene rearrangements are key to disease course
- Several human malignancies contain mutations in the germline and are inherited as other genetic traits.

USA Cancer Update

Mortality demographics

All age groups: #1 Heart diseases, #2 Cancer, #3 Accidents
Children: #1 Diseases of infancy, #2 Congenital anomalies, #3 Accidents, #4 Cancer
Adult males: #1 Heart diseases, #2 Cancer, #3 Cerebrovascular diseases
Adult females: #1 Cancer, #2 Heart diseases, #3 Cerebrovascular diseases

Leading cancer deaths

Children: #1 Leukemia, #2 Brain & CNS [incl eye], #3 Endocrine
Adult men: #1 Lung, #2 Prostate, #3 Colorectal
Adult Women: #1 Lung, #2 Breast, #3 Colorectal

Leading cancer diagnoses

Male: Prostate (25%), Lung (15%), Colorectal (10%)
Female: Breast (27%), Lung (14%), Colorectal (10%)

2012 Cancer estimates:

Total new US cancer cases, all ages 1,638,910
Total US cancer deaths (#2 USA killer, 23%) 577,190 (>1500 per day)

Historic trends in cancer death rates

Still climbing: Lung
Leveled-off: Breast, prostate, leukemia
Falling: Colorectal, uterine, stomach
**Ocular Clues to Distant Cancers**

**Clue: Acute onset ptosis**

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>Preganglionic Horner's Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCULAR FINDINGS</td>
<td>Ptosis - Miosis - Anhydrosis</td>
</tr>
<tr>
<td></td>
<td>“Reverse” Horner's Syndrome?</td>
</tr>
<tr>
<td>CONFIRMATION</td>
<td>[−] Cocaine, [+] Hydroxyamphetamine testing</td>
</tr>
<tr>
<td>SYSTEMIC</td>
<td>Rule-out Pancoast’s tumor (apical lung mass situated at superior pulmonary sulcus)</td>
</tr>
</tbody>
</table>

**Remember Forever!**

Cocaine blocks norepinephrine uptake; Hydroxyamphetamine stimulates its release.
**Clue: Atypical xanthelasma**

**DIAGNOSIS**  
Necrobiotic xanthogranuloma  
(50% cases confined to periorbital skin!)

**OCULAR FINDINGS**  
Asymmetric, inflamed nodular periorbital masses exhibiting  
fibrinoid necrosis, Touton giant cells  
Frequently re-biopsied

**CONFIRMATION**  
Eyelid biopsy, hematologic evaluation

**SYSTEMIC**  
Plasma cell dyscrasia, Multiple myeloma  
NXG may precede hematologic abnormalities by years  
Requires lifetime follow-up  
*Other ocular myeloma clues:*  
- Band keratopathy, pars plana cysts  
- Kayser-Fleischer (copper) ring  
- Amyloid deposition  
- Orbital plasmcytoma  
- Lytic bone lesions

**Clue: Bilateral pigmented retinal patches**

**DIAGNOSIS**  
Gardner's Syndrome  
*Familial adenomatous polyposis with extracolonic manifestations*

**OCULAR FINDINGS**  
Multiple small, dark, RPE patches…  
POFL (Pigmented Ocular Fundus Lesions)

**CONFIRMATION**  
Ophthalmoscopy, examine family members (AD)  
Colonoscopy, lower GI imaging  
Gene locus 5q21

**SYSTEMIC**  
Hereditary familial polyposis  
100% inevitable colon cancer  
Desmoid tumors (fibromatosis), Osteomas
### Clue: Visible corneal nerves

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>Thickened corneal nerves</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCULAR FINDINGS</td>
<td>Thyroid evaluation</td>
</tr>
<tr>
<td></td>
<td>FNA, calcitonin</td>
</tr>
<tr>
<td></td>
<td>Urinary catecholamines</td>
</tr>
<tr>
<td></td>
<td>and VMA</td>
</tr>
<tr>
<td>CONFIRMATION</td>
<td>MEN Ila (5%): MEN IIb (100% cases)</td>
</tr>
<tr>
<td></td>
<td>Medullary carcinoma of thyroid (MCT)</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma, Parathyroid hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Mucosal neuromas</td>
</tr>
<tr>
<td></td>
<td>Marfanoid habitus</td>
</tr>
<tr>
<td>SYSTEMIC</td>
<td></td>
</tr>
</tbody>
</table>

#### DDx: Thickened Corneal Nerves

- Leprosy
- I.K.
- Fuch's
- Refsum's Icthyosis
- Keratoconus
- Lattice dystrophy
- MEN II
- Marijuana!

### Clue: Multiple facial papules

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>Cowden's disease (named after propositus!)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autosomal dominant inheritance</td>
</tr>
<tr>
<td>OCULAR FINDINGS</td>
<td>Multiple facial trichilemmomas</td>
</tr>
<tr>
<td></td>
<td>Keratotic papules resemble warts</td>
</tr>
<tr>
<td></td>
<td>Optic nerve drusen, retinal gliomas</td>
</tr>
<tr>
<td>CONFIRMATION</td>
<td>Skin biopsy, systemic workup</td>
</tr>
<tr>
<td>SYSTEMIC</td>
<td>Occult malignancies (especially thyroid, breast, and GI tract)</td>
</tr>
</tbody>
</table>

### MEN I [AD]

- **Werner**
  - Anterior pituitary neoplasms
  - Islet cell neoplasms
  - Parathyroid hyperplasia

- **Locus**
  - 11q13

- **Screening**
  - Ca⁺, Prolactin, GI hormones

### MEN Ila [AD]

- **Sipple**
  - MCT (100%)
  - Pheochromocytoma
  - Parathyroid hyperplasia

- **Locus**
  - 10 cen-10q11.2, *Ret* mutation

- **Screening**
  - Calcitonin, urine VMA and catecholamines

### MEN IIb (=III) [AD]

- **Sipple-Froboese**
  - MCT [100%]
  - Pheochromocytoma

- **Locus**
  - Mucosal neuromas, Marfanoid

- **Screening**
  - Calcitonin, urine VMA and catecholamines

### MEN IIa [AD]

- **Sipple**
  - MCT (100%)
  - Pheochromocytoma
  - Parathyroid hyperplasia

- **Locus**
  - 10 cen-10q11.2, *Ret* mutation

- **Screening**
  - Calcitonin, urine VMA and catecholamines

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**Screening**

- Ca⁺, Prolactin, GI hormones

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**Association of Technical Personnel in Ophthalmology**

**2012 Scientific Session • Chicago**
### Acquired Skin Disorders Associated with Internal Neoplasia
*(adapted from Callen)*

<table>
<thead>
<tr>
<th>Dermatoses</th>
<th>Cancer / Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans</td>
<td>GI tract</td>
</tr>
<tr>
<td>Acquired ichthyosis</td>
<td>Lymphoproliferative (late)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Lymphoma of GI tract</td>
</tr>
<tr>
<td>Multiple seborrheic keratoses</td>
<td>Various sites (Lèser-Trelat)</td>
</tr>
<tr>
<td>Necrobiotic xanthogranuloma</td>
<td>Myeloma, paraproteinemia</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>Thymoma</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Liver</td>
</tr>
<tr>
<td>Pruritis</td>
<td>Hodgkin’s lymphoma, other malignancies</td>
</tr>
<tr>
<td>Systemic amyloidosis</td>
<td>Multiple myeloma, renal cell carcinoma</td>
</tr>
</tbody>
</table>

### Inherited Skin Disorders Associated with Internal Neoplasia
*(adapted from Callen)*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Skin lesion</th>
<th>Cancer / Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardner’s syndrome</td>
<td>Epidermal cysts</td>
<td>Colon</td>
</tr>
<tr>
<td>Cowden’s multiple hamartoma syndrome</td>
<td>Trichilemmoma</td>
<td>Breast, thyroid, colon</td>
</tr>
<tr>
<td>Peutz-Jeghers (19p)</td>
<td>Melanotic macules</td>
<td>GI, breast, ovary</td>
</tr>
<tr>
<td>Muir-Torre</td>
<td>Sebaceous growths</td>
<td>Colon</td>
</tr>
</tbody>
</table>
**Clue: Retinal vascular mass**

**DIAGNOSIS**
- von Hippel-Lindau syndrome (AD)

**OCULAR FINDINGS**
- Retinal hemangioblastoma (von Hippel)
- Cerebellar hemangioblastoma (Lindau)

**CONFIRMATION**
- Ophthalmoscopy, Fluorescein angiography
- Head CT or MRI

**SYSTEMIC**
- Renal cell carcinoma
- Pheochromocytoma

**COMMENT**
- von Hippel-Lindau syndrome now known to be a familial cancer syndrome. Tumor suppressor gene (VHL gene locus 3p25-26) has been identified.

**Familial cancer syndrome should be considered** whenever one or more of the following criteria are satisfied:
1. Clustering of cancers within families
2. Onset of adult-type cancers at early ages
3. Multiple different cancers arising within the same individual

**Familial Cancer Syndromes in Ophthalmic Practice**

- Heritable retinoblastoma
- WAGR
- MEN I
- MEN II
- Xeroderma pigmentosum
- Ataxia telangiectasia
- Gardner’s Syndrome
- NFT 1
- NFT 2
- von Hippel-Lindau

- Retinoblastoma
- Wilms nephroblastoma, aniridia
- Islet cell, anterior pituitary neoplasms
- Medullary carcinoma of thyroid, pheochromocytoma
- Cutaneous SCCa, BBCa, malignant melanoma
- Lymphoma
- Colorectal cancer
- Neurofibroma, optic nerve glioma
- Meningioma, glioma, schwannoma
- Hemangioblastoma, renal cell, pheochromocytoma

**Clue: Eyelid mass**

**DIAGNOSIS**
- Carney's complex (2p16, 17q2)

**OCULAR FINDINGS**
- Eyelid myxomas

**CONFIRMATION**
- Eyelid biopsy
- Cardiac/Pulmonary/GI evaluations
- Gene locus 2p16

**SYSTEMIC**
- Cardiac myxoma (#1 cardiac neoplasm)
- Pulmonary chondroma, epithelioid leiomyoma/leiomyosarcoma
- Extra-adrenal paraganglioma
**Clue: Real bad ptosis**

| DIAGNOSIS | Myasthenia gravis (autoantibodies to AChR, HLA-DR2) |
| OCULAR FINDINGS | (All may appear intermittent, highly variable) |
| | Diplopia (often early clinical feature) |
| | Ptosis, Lid twitch, Gaze limitation |
| CONFIRMATION | Tensilon test, serology |
| SYSTEMIC | Thymus abnormalities (up to 85%) |
| | Cortical thymoma |
| | Well-differentiated thymic carcinoma |
| COMMENT | Relationship between MG and thymus still a puzzle |
| | – Intrathymic autoregulatory disturbance? |
| | – 2’ thymic involvement in systemic disorder? |
| | – Above tumors express 153kD antigen which shares an immunogenic epitope with AChR subunit to activate AChR T-lymphocytes. |

**References**


