F024
Syndromes with Risk for Internal Malignancy

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DISCLOSURES
I do not have any relevant relationships with industry.

Objectives
• Diagnose cutaneous signs of internal malignancy more accurately
• Recognize benign skin findings that indicate an increased risk for cancer
• Obtain a targeted family history for genetic syndromes with skin features

Tumor Syndromes
Hair Follicle Related
• Birt-Hogg-Dubé
• PTEN hamartoma
  • Bannayan-Riley-Ruvalcaba
• Lynch: Muir-Torre Variant
Multiple Endocrine Neoplasias
• MEN1, MEN2B
• Carney Complex

Others
• Peutz- Jegher
• FAP: Gardner variant
• Leiomyomas and Renal Cell Cancer
• Dyskeratosis Congenita
• Li-Fraumeni
• Palmoplantar Keratoderma
Risk is increased for which of the following cancers?

A) Lung  
B) Gastric  
C) Renal  
D) Prostate  
E) Skin

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Fibrofolliculoma

- Small, firm, dome-shaped papules
- On face, neck, back, upper trunk
- Areas with sebaceous glands

Birt-Hogg-Dubé Syndrome

Fibrofolliculomas, Trichodiscomas, Acrochordons
I. Autosomal Dominant Inheritance

II. Birt-Hogg-Dubé Syndrome
- FLCN (Folliculin) mutation, 17p11.2
  - highly conserved protein
  - interacts with plakophilin in cell adhesion
  - role in ciliogenesis and cell polarity which leads to cysts
  - causes abnormal growth and differentiation of sebaceous glands
  - Renal cancer in 15-30%


III. Lung features
- Cysts (70%)
- Spontaneous pneumothorax (25%)

• visible on CT, not x-ray


Consultation Indications
- fibrofolliculomas
- perifollicular fibromas
- trichodiscomas/angiofibromas
- acrochordons > or = 5


Birt-Hogg-Dubé Surveillance Guidelines
- Periodic MRI of the kidneys (3 centimeters or rapidly growing of concern)
- Routine Full Skin Exam for melanoma
- High Resolution of the chest at baseline
  - Follow-up for respiratory symptoms

GeneReviews

Keratoacanthoma
Which inherited cancer syndrome is most likely?

A) Rombo  
B) Peutz-Jegher  
C) Cowden (PTEN hamartoma)  
D) Lynch syndrome (HNPCC)  
E) Gorlin syndrome

Lynch Syndrome: Muir-Torre Variant

A) Rombo  
B) Peutz-Jegher  
C) Cowden (PTEN hamartoma)  
D) Lynch syndrome (HNPCC)  
E) Gorlin syndrome

Muir-Torre Variant

Occur before internal malignancy or concurrently in about 30%  
> Sebaceous Adenoma  
> Sebaceous Epithelioma  
> Sebaceous Carcinoma  
> Keratoacanthoma
Of the following, which mutation is most closely associated with the Muir-Torre variant?

A) MLH1  
B) MSH2  
C) MSH6  
D) PMS2

Muir-Torre Variant

**Immunohistochemical Staining**

- MSH2 most common mutation
- Also MLH1 and MSH6
- Confirms *Somatic* Mutation in tumor
- Blood test needed to confirm germ-line mutation

Sebaceous Adenomas

Sebaceous Carcinoma in Muir-Torre Variant

May appear similar to epidermoid cyst

Genetics Referral

**Lynch Syndrome**

Skin sebaceous neoplasm and personal or family history of related cancer:

- Colorectal
- Endometrial
- Ureter or Bladder
- Gastric
- Ovarian
- Small bowel
- Glioblastoma
- Biliary tract
- Pancreatic

Multiple Mucosal Neuromas

**Multiple Endocrine Neoplasia Type 2B**
- Also called Mucosal Neuroma Syndrome
- Autosomal Dominant
- **RET** is the only gene; testing detects 98%
  - Most common mutation in exon 16 (M918T), less common exon 15 (A883F)
- Oral mucosal neuromas may be first to present

**MEN 2B**
- Medullary Thyroid Cancer (MTC) in virtually all (100%)
  - Early thyroidectomy (< age1)
- Pheochromocytoma (50%)
- Gastrointestinal symptoms from hamartomas (ganglioneuromas)
- Hyperparathyroidism (30%)

**MEN2B Oral Mucosal Neuromas**
- On tongue, pathognomonic for MTC
- “Blubbery” lips
- Oral findings benign

Which of the following diagnoses should be considered?
A) Multiple mucosal neuromas
B) Myxoid neurofibromas
C) Syringomas
D) Basal cell nevi
E) Mucous cysts
24-year-old; metastatic Medullary Thyroid Cancer

MEN2B
Characteristic appearance
• “blubbery” lips
• prominent jaw
• Elongated face
• “Lanky” build

With digital pigment and anemia, risk of which cancer is increased?
A) Gastrointestinal
B) Lung
C) Esophageal
D) Skin
E) Breast

- STK11 mutation, autosomal dominant
- 94% with clinical diagnosis have a mutation
- Association of gastrointestinal (P-J) polyps and mucocutaneous pigmentation
- Polyps most common in small intestine (jejenum > ileum > duodenum)
Peutz-Jeghers Syndrome

Associated Tumors

• Epithelial: colorectal, gastric, pancreatic, breast, ovarian cancer
• Females: Sex cord tumors with annular tubules (SCTAT), Adenoma malignum of the cervix
• Males: Sertoli cell tumors that secrete estrogen, gynecomastia
• Overall cancer relative risk up by 10%

Genetics Referral Indications

• Mucocutaneous Pigmentation and one or more P-J polyps
• Ovarian sex cord/ Sertoli cell tumor
• Adenoma malignum of the cervix
• Pancreatic or breast cancer


Risk of which cancer(s) is increased?

A) Gastrointestinal
B) Thyroid
C) Testicular
D) Pancreatic
E) Breast

Risk of which cancer(s) is increased?

A) Gastrointestinal
B) Thyroid
C) Testicular
D) Pancreatic
E) Breast

Carney Complex

• Pale at birth
• Brown to black
  • “ink spot” lentigines
• Increased at puberty
• Face, lips, mucosa
• Inner or outer canthi, vaginal or penile mucosa
**Carney syndrome:**

*A Multiple Endocrine Neoplasia*

- Embolic stroke secondary to cardiac myxomas
- Endocrine abnormalities: Cushing’s syndrome caused by PPNAD (pigmented nodular adrenocortical disease)
- Acromegaly due to growth hormone/ pituitary adenomas
- Prolactinemia

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**Carney Complex**

*Primary Pigmented Nodular Adrenocortical Disease (PPNAD)*

- Causes Cushing syndrome
- 75% of females, 100% have PPNAD at autopsy
- Weight gain
- Growth cessation
- “Moon facies”
- Hirsutism
- Striae
- Hypertension
- Buffalo hump
- Weakness
- Easy bruising
- Psychological disturbance

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**Carney Complex**

- Also known as
  - NAME (nevi, atrial myxoma, ephelides)
  - LAMB (lentigines, atrial myxoma, blue nevi)
- **PRKAR1A, Autosomal Dominant**
- Myxomas: skin, breast, oropharynx, female genital tract
- Large-cell calcifying Sertoli cell tumors (LCCSCT) in almost all by adult →

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**Risk of which cancer(s) is increased?**

- A) Gastrointestinal
- B) Uterine
- C) Esophageal
- D) Skin
- E) Renal
Risk of which cancer(s) is increased?
A) Gastrointestinal
B) Uterine
C) Esophageal
D) Skin
E) Renal

Cutaneous Leiomyomatosis
- Discrete, firm, papules fixed to overlying epidermis
- Birth to childhood; increase with age
- Lesions are spontaneously painful or painful with cold
- Contain smooth muscle cells

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)
- Also called Reed syndrome
- Autosomal dominant, \( FH \) mutation, 1q43
- **Diagnosis by fumarate hydratase activity in skin fibroblasts or lymphoblastoid cells**
- Fumarase activity < 60% in all affected
- **Test not available clinically in US; Study at NIH**

Hereditary Leiomyomatosis and RCC
- Uterine leiomyoma (fibroids) almost all women
  - Numerous, large
  - Irregular, heavy menstruation, pelvic pain
- Renal Cancer in 10% to 16%
  - Hematuria, low back pain
  - Aggressive
  - May be solitary

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)
Disruption of Fumarate Hydratase (FH) blocks fumarate to malate in Krebs cycle; leads to hypoxia and free radicals

Hereditary Leiomyomatosis and RCC Management
- Surgical excision, cryoablation or laser for painful lesions
- Medication: calcium channel blockers, alpha blockers, nitroglycerin, antidepressants, antiepileptic drugs
### Hereditary Leiomyomatosis and RCC Surveillance
- Full skin exam every 1 to 2 years for leiomyosarcoma
- Annual gynecology exam for women
- Biennial abdominal MRI (to avoid CT radiation) with contrast
  - Urologic oncologist referral when needed

### Genetics Referral Indications
**Cutaneous Leiomyomas**
Detectable Mutation in 85%

### Cowden syndrome
- Macrocephaly
- “Overgrowth” syndrome

### PTEN Hamartoma
**Cowden syndrome**
- Cancers of the thyroid (35%), breast (up to 67%), colon (9%), renal (35%), melanoma (5%) and endometrium (30%)
- Thyroid cancer: follicular or papillary, not medullary
- Numerous benign hamartomas
PTEN Hamartoma: Cowden Syndrome

**Criteria**

- **Pathognomonic**
  - Adult Lhermitte-Duclos disease
  - Mucocutaneous
    - Facial trichilemmomas
    - Acral keratoses
    - Papillomas

- **Major**
  - Breast cancer
  - Thyroid cancer
  - Macrocephaly
  - Endometrial cancer

*Operational diagnosis if:

- 6 or more facial papules—at least 3 trichilemmoma
- Cutaneous papules and oral papules
- 6 or more palmo/plantar keratoses

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**What is Lhermitte–Duclos disease?**

- Adult onset in Cowden
- Hamartomatous overgrowth of the cerebellum
- Gangliocytoma

**PTEN Hamartoma: Cowden Syndrome**

**Cowden syndrome**

- Acral papules

**Facial Tricholemmomas**

**Oral Papillomas**
PTEN Hamartoma
Banayan-Riley Ruvalcaba
• Allelic to Cowden (PTEN), autosomal dominant

Penile Hyperpigmented Macules

PTEN Hamartoma Syndrome Surveillance
• Age < 18: annual thyroid ultrasound, skin check, physical exam
• Adults: annual thyroid ultrasound, dermatology exam, colonoscopy, renal imaging. For family cancer hx, begin screening 5-10 years prior to youngest diagnosis
• For women: mammogram, breast MRI, transvaginal ultrasound or endometrial biopsy

Cutaneous leiomyosarcoma
• P53 mutation
• Li-Fraumeni syndrome

In Summary....
• Multiple primary cancers suggest a single gene cancer predisposition might be present
• A pedigree is a visual tool to recognize a genetic disorder
• Certain benign pathology diagnoses warrant further consideration
  > e.g. Sebaceous neoplasms, Fibrofolliculoma, Cutaneous leiomyoma, multiple mucosal neuroma
Thank You!