Genodermatoses with predisposition toward internal malignancy
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DISCLOSURES
Investigator: Scioderm; Allergan

Basal cell nevus (Gorlin’s) syndrome
• Autosomal dominant
  – 1:40,000 incidence
  – 20-30% de novo mutations
• Mutations in patched gene
  – Tumour suppressor gene
  – Receptor for signaling proteins in sonic hedgehog pathway
  – Suppressor of fused homolog (SUFU)
  • No jaw cysts; high medulloblastoma risk

Gorlin’s syndrome
Internal tumours
• Medulloblastoma
  – 2nd most common malignancy
  – Average onset - 2 years
  – Frequency up to 5%
  – if <3 and/or desmoplastic histology consider NBCCS
  – SUFU mutations
• Ovarian fibromas

Vismodegib
• Final results of trial
• Attrition noted
  – Hair loss; dysguesia; other SE
• Exploring intermittent dosing
• Rebound upon DC
Lancet Oncol 2016; 17: 1720–31
Risk Factors for Basal Cell Carcinoma Among Patients With Basal Cell Nevus Syndrome

- Age/number of sunburns significantly associated with BCC severity

JAMA Dermatol. 2017;153(2):189-192

Bazex-Christol-Dupre syndrome

- X-linked dominant – OMIM# 301845
- Basal cell carcinomas
  - Face
  - 15 to 26 years
- Follicular atrophoderma
  - Ice-pick marks
  - Dorsum of hands and elbows
- Hypotrichosis
- Twisted and flattened hairs on scanning electron microscopy

Bazex-Cristol-Dupre syndrome

- ACTRT1 mutations (2/6 families)
  - Actin-related protein T1 (ARP-T1)
    - Germline mutations in non-coding sequences around ACTRT1 in other families
      - In transcribed sequences encoding enhancer RNAs (eRNAs)
      - Impair enhancer activity and ACTRT1 expression
      - ARP-T1 binds GLI1 promoter – inhibiting GLI1 expression
      - Loss of ARP-T1 > activation of Hedgehog pathway

Nature Med 23(10):1226-33 OCT 2017

Muir-Torre syndrome

- Autosomal dominant; OMIM# 158320
- MSH1 or MSH2 (90%) genes
  - DNA mismatch repair defect, HNPCC/ Lynch syndrome variant
  - 9% of HNPCC
  - MSH6; PMS2 mutations
- Skin
  - Sebaceous neoplasms
  - Keratoacanthoma
- GI - Colon adenocarcinoma; proximal to splenic flexure
- Other GI, GU, breast, hematologic, lung CA

Gardner syndrome

- AD-APC gene; OMIM# 175100
- 1.8,300-16,000 incidence (FAP)
- Skin lesions: increased pigment
  - Epidermoid cysts: 50-65% of patients
  - Head, neck, and extremities; congenital
  - Multiple; pilomatrixoma-like
  - Increase in number/size then stabilize
- Bone – Osteomas (7%); before skin
  - Membranous bones: face/head
- Thyroid CA – females
- Desmoid tumours

Gardner syndrome

- Ophthalmologic
  - Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
  - Some kindreds; May be earliest finding
  - "Bear tracks" easily seen on ophthalmologic exam
- GI lesions – allelic to familial adenomatous polyposis
  - Premalignant adenomatous polyps – esp. colon
    - Rare before 10 yo; by 20 yo 50% of patients have polyps
    - High incidence of malignancy
Peutz-Jeghers syndrome

- AD - OMIM# 175200
- Serine-threonine kinase 11 (STK11)
  - ~40% spontaneous mutation
- Skin
  - Pigmented macules / lentigines
    - First yrs of life
    - Lips and buccal mucosa
    - Any mucosal surface
  - Digits, nails, palms, soles
  - All but buccal fade with time
- GI - Hamartomatous polyps
  - Small > large intestine
  - 30% with history of intussusception by 10
- Neoplasia
  - Increased breast, GI, ovarian, lung, endometrial, and pancreatic CA
  - Sex cord tumour with annular tubules
  - Calcifying Sertoli cell tumours of testes
  - Gynecomastia if estrogen secreting
  - Adenoma malignant
  - Rare aggressive cervical cancer

Cowden's syndrome

- OMIM# 158350: PTEN hamartoma syndrome
- Incidence 1:300,000
  - 1:2 – Male:female
- Present in second-third decade
- Skin
  - Trichilemmomas
- Mucosa
  - Papillomas
- Acral keratotic papules
  - Lipoma, angioma
  - Fibromas
  - Sclerotic fibromas
    - characteristic
- Breast
  - Virginal hypertrophy
  - Fibrocystic disease
  - Fibroadenoma
  - Adenocarcinoma
  - Gynecomastia (males)
- Thyroid
  - Goiter
  - Adenoma
  - Follicular adenoCA
- GI
  - Hamartomatous polyps
    - Colon / Usually benign
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)

- OMIM# 605839: AD
- Skin: Variable phenotype
  - Leiomyomas: Typically sensitive
  - Touch
  - Skull
- Utero leiomyomas
  - Female
  - Earlier presentation and more numerous than sporadic
- Renal cell carcinoma
  - Aggressive
  - Less penetrant
- All races
  - More common in eastern European
- Fumarate hydratase mutations
  - Krebs cycle enzyme
  - Converts fumarate to malate
  - No clear genotype/phenotype correlation

Birt-Hogg-Dube syndrome

- Autosomal dominant – OMIM# 135150
- Defect in folliculin
- Clinical
  - Fibrofolliculomas
  - Trichodiscomas
  - Acrocordons
  - Firm, dome shaped papules scattered predominantly on head and neck
  - Often surround central follicular os
  - Onset > 25 y/o
- Systemic
  - Renal cell carcinoma – less aggressive
  - Lung cysts
  - Pneumothorax
- Abdominal CT/ renal US to screen

Multiple endocrine neoplasia-Type 1

- Facial angiofibromas
  - Multiple
- Collagenomas
- Café-au-lait macules
- Lipomas
- Confetti-like hypopigmentation
- Gingival papules
  - Multiple

Multiple endocrine neoplasia-type IIb

- AD- RET proto-oncogene mutations
  - 50% spontaneous
  - First lesions noted from birth to first years of life
- Mucocutaneous
  - Mucosal neuromas
    - Tongue and lips
    - Thickened lips - Often earliest finding
      - Marfanoid habitus

Multiple endocrine neoplasia type IIb

- Endocrine
  - Medullary thyroid
  - Pheochromocytoma
- Management
  - Endocrine
    - Thyroid resection? (first 6 months of life)
  - Ophthalmology
  - Gastroenterology
  - Dermatology
Carney complex
- AD - Mutations in the cAMP-dependent protein kinase, regulatory, type I, alpha gene (PRKAR1A)

SKIN
- Profuse pigmented skin lesions
- Most common presenting feature
- Increase at puberty
- Nevi; Blue nevi
- Ephelides
- Centralfacial/mucosal lentigines
- Red Hair
- Myxoma – Cardiac
  - Skin; Breast; Oropharynx; Female genital tract

Endocrine
- Primary pigmented nodular adrenocortical disease (PPNAD)
  - Causes Cushing syndrome
  - Most frequent endocrine tumor
  - ~ 25% of patients
- Large-cell calcifying Sertoli cell tumors (LCCSCT)
  - 1/3 of affected males in 1st decade
  - Eventually almost all males
- Multiple thyroid nodules
  - Up to 75% of patients
  - Most are thyroid follicular adenomas
- Growth hormone-producing adenoma
  - Resulting in acromegaly
  - 10% of adults
- Other:
  - Mammary ductal fibroadenoma
  - Psammomatous melanotic schwannoma (PMS) - 50%
  - Rare nerve sheath tumor
  - ~10% of patients
  - Median age at diagnosis - 20yrs
  - Pheochromocytoma

Dyskeratosis congenita
- XLR
  - AD and AR forms
- Multisystem disorder of telomere maintenance
  - Reticulate skin pigmentation
  - Nail dystrophy
  - Leukoplakia
  - Hematologic abnormalities

Malignancy
- 10% of patients
- 3rd decade of life
- Squamous cell carcinoma
- Hodgkin’s disease; GI adenocarcinoma; bronchial or laryngeal carcinoma
- Leukoplakia is premalignant

Hematologic
- Bone marrow failure
- 50% of X-linked and AR patients develop marrow failure in 2nd decade
- Panocytes
- Bone in AR forms
- Infections
- Respiratory
- Main cause of death
- No reported endocrine abnormalities

Thank you for attending!
Please contact me should you have any questions.

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