Paraneoplastic Skin Syndromes

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Internal Malignancy and the Skin

• 1868 - Hebra was the first to associate skin pigmentation with visceral cancer

• > 50 dermatological conditions reported as markers of malignancy

• Skin may be directly or indirectly affected
  • Direct - Tumor extension or metastasis
    • Eg: Sister Mary Joseph nodule
  • Indirect = “Paraneoplastic syndrome”
    • Variety of factors related to the neoplasia act as mediators in cell signaling
Paraneoplastic Dermatoses

• Heterogeneous group of clinical manifestations - often appear benign

• 2nd most common paraneoplastic site (#1 is endocrine syndromes)

• Commonly precede or follow visceral cancer

• Recognition may result in earlier diagnosis and better prognosis
Classification Criteria

• Tumor and skin findings develop simultaneously
• Follow a parallel course
• A specific type of neoplasia occurs with the paraneoplasia
• Dermatosis is rare in general population
• High frequency of association between skin reaction and tumor
Papulosquamous Disorders

- Acanthosis nigricans
- Acquired ichthyosis
- Acrokeratosis paraneoplasticca
- Extramammary Paget’s disease
- Pityriasis rotunda
- Florid cutaneous papillomatosis
- Acquired diffuse palmoplantar keratoderma
- Sign of Leser-Trelat
- Tripe palms
Acanthosis nigricans
Clinical Features

• Non-obese elderly person
• Velvety brown plaques
• Rapid extensive progression of florid skin lesions
• Unusual locations -> mucosa, palms, soles, elbows
Associated Cancers

• Adenocarcinoma:
  • Gastrointestinal -> stomach or liver, pancreas
  • Lungs
  • Uterus, Ovaries
  • Kidney
  • Breast
• Hematologic malignancies (AML, mycosis fungoides, lymphoma)
• Benign GI neoplasms
Pathogenesis

• Contrast other types of AN – normal insulin levels
• Transforming growth factor alpha elevated
Sign of Leser-Trelat

- Rapid increase in number and size of seborrheic keratosis
  - Ave. onset 15 weeks (days to a year)
- 50% pruritic
- Often associated with other paraneoplastic syndromes
  - AN 35%
  - Tripe palms
  - FCP
Associated Malignancies

• Adenocarcinoma
  • Stomach
  • Rectum
  • Breast
  • Lungs
  • Colon

• Variety of other tumors
Tripe Palms and Florid Cutaneous Papillomatosis

Tripe Palms

• Variant of acanthosis nigricans

• 75% of time occur with AN

• Often pre-date the diagnosis of cancer
  • Median 2 months before dx (range: 15 months before dx to 5 years after)

• Inconsistently respond to malignancy tx
  • May resolve with treatment or persist
Florid Cutaneous Papillomatosis

• Sudden eruption of pruritic papules
  • Indistinguishable from viral warts
• Dorsal aspect of hands/forearms -> trunk/face
• Much rarer than others with only 30 reports in the literature
Florid Cutaneous Papillomatosis

- Skin lesions coincide with presence of tumor
- Severity parallels course of malignancy

- Associated Tumors
  - Gastric Adenocarcinoma
  - Intra-abdominal cancers
  - Breast, lung, prostate
Acquired Diffuse Palmoplantar Keratoderma

- breast
- lung
- gastric cancers
- leukemia
- lymphomas
Acquired Ichthyosis
Acquired Ichthyosis

- Very rare
- Indistinguishable from ichthyosis vulgaris (autosomal dominant genodermatosis)
- Small, polygonal scales that lift up
- Widely distributed
- Spares palms and soles
Acquired Ichthyosis

• Associated cancers
  • Hodgkin lymphoma (70% of cases)
  • Kaposi sarcoma (also associated with HIV/AIDS)
  • Other lymphomas
  • Leukemia
• Solid tumors
  • Breast
  • Lung
  • Bladder
Bazex Syndrome (Acrokeratosis paraneoplastica)

- Rare acral psoriasiform dermatosis
- Internal malignancy -> squamous cell carcinoma of the upper aerodigestive tract
- Mild constitutional symptoms, weight loss, and other nonspecific findings of internal malignancy

- Dermatitis can precede malignancy in 2/3 of patients
  - 1 year on average, as long as 3 years
Pityriasis Rotunda

- Rare in N America and Europe
- Common among Japanese, S. African Bantu, West Indian blacks
- 5% of cases paraneoplastic
- Common: hepatocellular ca, gastric ca
- Reported: Leukemia, lymphoma, prostate ca
Pityriasis Rotunda

Strikingly circular, hyperpigmented scaly patches
Buttocks, thighs, trunk
Scale is uniform
Paget’s Disease

• Unilateral areolar dermatitis
  • Eczematous, sharply demarcated
  • Itch or burn, not painful

• Underlying breast cancer
  • 1-4% of all breast cancers
  • Ductal carcinoma in situ (DCIS)
  • Invasive breast carcinoma
Paget’s Disease
Extramammary Paget disease

- Eczematous dermatitis of groin or anogenital skin
- Slow growing
- About 1/3 associated with internal malignancy (2/3 de novo in skin)
- Internal malignancy portends a worse prognosis (median survival 1.5 years)
EMPD

- Most internal tumors are anatomically related and extend directly to involved skin
- Most common:
  - Rectal adenocarcinoma
  - Endocervical carcinoma
  - Transitional cell carcinomas of the bladder
  - Prostate
Extra-mammary Paget’s Disease

Ca link approx 50%
Erythematous Lesions

- Dermatomyositis
- Hypertrophic osteoarthropathy and digital clubbing
- Multicentric reticulohistiocytosis
- Necrolytic migratory erythema
- Sweet syndrome
Erythema Gyratum Repens

- Dramatic erythematous concentric scaly rings
- Wood-grain appearance
- Pruritic
- Rings **spread radially at a rapid rate** (1cm daily)
- Trunk and proximal extremities
- Elderly white men
- >80% have underlying malignancy
Erythema Gyratum Repens
Erythema Gyratum Repens

• Associated malignancy (>80%):
  • Transitional carcinoma of the kidney
  • Lung adenocarcinoma
  • Breast adenocarcinoma
  • Esophageal adenocarcinoma
Sweet Syndrome

• Tender, erythematous nodule or plaques
  • Vesicles, bullae, pustules
• Fever, neutrophilia, elevated ESR
• Responds rapidly to steroids

https://escholarship.org/uc/item/1zm2m110
Sweet’s Syndrome

Associated diseases:
• Malignancy (leukemia)
• Occasionally IBD, pregnancy, bypass syndrome, sarcoid, RA
• Idiopathic
Sweet Syndrome

- Underlying malignancy 20% of cases
  - Hematologic malignancy (80%)
    - AML most common
  - Solid tumors (20%)
    - Breast
    - GI
    - GU
Pyoderma Gangrenosum
Pyoderma Ganagrenosum

- Up to 50% underlying condition such as:
  - Inflammatory bowel disease
  - Diverticulosis
  - Arthritis
  - Chronic hepatitis
  - Behçet's syndrome
  - Malignancy
Pyoderma Gangrenosum

- Paraneoplastic - 4.5%-7%
- Atypical or bullous PG -> AML
- Hematologic tumors:
  - Chronic myeloid leukemia
  - Myeloma (usually IgA type)
  - Waldenström macroglobulinemia
  - Lymphomas
- Solid tumors: carcinoid, colon, breast, and bladder carcinoma
2° Hypertrophic Osteoarthropathy and Digital Clubbing
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• Clubbing:
  • Asymptomatic swelling of distal fingers
  • Nails convex, loss of angle at proximal nail fold

• Periostitis and arthralgias

• 90% -> underlying malignancy

• HOA – Peripheral non-small cell lung ca

• Clubbing – Small cell lung ca and mesothelioma
• Necrolytic migratory erythema

• Alpha-cell tumor of the pancreas (glucagonoma)
  • Low amino acid levels
  • Elevated glucagon

• Widespread
  • Erythematous papules and plaques
  • Evolve to vesicobullae
  • Then erosions and crust
Necrolytic Migratory Erythema

• Classic: middle-aged diabetic with characteristic rash
• Diagnosis often overlooked for years
• Debilitated at time of diagnosis
• Clue: Family history of endocrine neoplasms (glucagonoma with MEN)
Confirmation

• Labs:
  • Elevated glucagon
  • Abnormal glucagon response to arginine infusion
  • Glucose intolerance
  • Hypoaminoacidemia

• Imaging:
  • Celiac arteriography highlights hypervascularity of tumor more sensitive than CT scan
Multicentric Reticulohistiocytosis

- Reddish brown papules and nodules
- Hands, face, scalp, ears
- Oral lesions - 50%
- Destructive arthritis (mimics RA)
- Female:male = 3:1
Multicentric Reticulohistiocytosis

• Paraneoplastic – 30%
  • No specific tumor
  • Breast, lung, muscle, GI, GU, hematologic
  • Age-appropriate cancer screening

• Other systemic diseases
  • Thyroid disease
  • Tuberculosis
  • Diabetes
  • Primary biliary cirrhosis
Dermatomyositis

• Increased risk of malignancy
  • Normal CK level
  • Disease refractory to treatment
  • Absence of myositis Ab
  • Overlap of autoimmune and lung disease
  • Cutaneous necrosis
  • Increased age (>65 years)
  • Leukocytoclastic vasculitis
  • Capillary damage in muscle biopsy
Dermatomyositis
Dermatomyositis

- Association with internal malignancy: 25% (reports vary 6-60%)
- Most malignancies detected within 24 months of diagnosis
  - Up to 5 years for ovarian
- Tumors are those common for patient’s age, race, sex
- Most common: ovarian, cervical, lung, pancreatic, gastric, non-Hodgkin lymphoma
Dermatomyositis

• Screening
  • Thorough history and physical exam
  • Sex and age-appropriate cancer screening

• Additionally for women:
  • CT chest, abdomen, pelvis
  • CA-125
Paraneoplastic Pemphigus

http://www.nature.com/jidsp/journal/v9/n1/full/5640129a.html
Paraneoplastic Pemphigus

- Heterogeneous group of autoimmune bullous disorders
- Painful intractable erosive stomatitis
- Polymorphous cutaneous eruption
  - Erythema
  - Papulo-vesicles
  - Bullae
  - Erosions
Paraneoplastic Pemphigus

• 2/3 cases
  • Known, pre-existing neoplasm
• 1/3 cases
  • Mucocutaneous symptoms before neoplasm detected
• Grim prognosis -> 10% 2 year survival
• Adults and elderly – rare in children
Associated Malignancy

• Hematologic malignancy
  • B-cell lymphoproliferative disorders -> 80%
  • CLL
  • Castleman disease
  • Thymoma
  • Walderstrom macroglobulinemia

• Solid tumors (rare)
  • Uterine ca
  • Melanoma
  • Primary liver tumors
  • Spindle cell sarcoma
  • Renal cell carcinoma
Carcinoid Syndrome

- Neuroendocrine tumor
- Occur anywhere in body
- Carcinoid syndrome rare – tumor has metastasized
  - Flushing – 75%
  - Diarrhea
  - Bronchospasm
  - Cardiac valve dysfunction
  - Pellagra-like skin rash

http://dermaamin.com/site/atlas-of-dermatology/3-c/227-carcinoid.html
Carcinoid

• Pellagra-like rash
• Erythematous phototoxic eruption
• Bullae form, heal with hyperpigmentation
  • ‘Peeling-paint’
• Casal’s necklace

Carcinoid Syndrome

• Diagnosis:
  • 5-hydroxyindole acetic acid (5-HIAA) elevated in urine
  • Abdominal CT scan shows metastases
  • PET to localize tumor
Hypertrichosis Lanuginosa Acquisita

- Increased white hair (lanugo type)
- May grow quite long
- Head and neck
  - Widespread
- 2 yrs before - 5 yrs after malignancy diagnosis
- Solid and heme malignancies
  - Lung
  - Colorectal
  - Breast
Cutaneous Metastases

4-5% pts
Gardner’s Syndrome

Familial Adenomatous Polyposis

• Autosomal dominant disease
  • Adenomatous polyps (colon)
  • Osteomas; scoliosis
  • Soft tissue tumors
    • Dermoids, lipomas, fibromas
  • Epidermoid/sebaceous cysts
  • Ocular changes

• Turcott’s syndrome
  • Familial adenomatous polyps
  • CNS tumors
Muir-Torre Syndrome

- Sebaceous skin tumors
  - Adenoma; epithelioma; carcinoma
- Visceral carcinoma
  - $1^0$ colon
  - Also bladder, uterine, prostate, small intestine

Cowden’s Syndrome

- Trichilemmomas
- Verrucous (warty) growths
- Oral fibromas
- Thyroid carcinoma
- Breast carcinoma
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Summary

- Heterogeneous group of skin reactions
- Recognition may allow detection of occult tumors
- Approximately 70% of cancers can be detected with:
  - Thorough history
  - Physical exam
  - Sex- and age appropriate cancer screenings
  - Targeted labs/screening
"If it doesn't itch, don't worry about it."
Thank You