Involvement of Skin by Internal Malignancy

- Direct (non-paraneoplastic)
  - Presence of tumor cells within the skin
  - Direct tumor extension
  - Metastases
- Indirect (paraneoplastic)
  - No presence of tumor cells within the skin
  - Visceral tumors may secrete a variety of inflammatory, proliferative and/or metabolic factors that lead to cutaneous changes
  - Up to 20% of cancer patients experience paraneoplastic syndromes, but often unrecognized
  - Cutaneous manifestations may develop before a diagnosis of malignancy is determined; thus, these findings may aid the physician in the early identification of malignancy.

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  - Sources referenced on each slide and at end of presentation
- Few photos are personal clinical photos
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Cutaneous Manifestations of Internal Malignancy

POMA Winter Conference District 8
January 2018
Ashley Kittridge, DO, FAAD
No COI
**Paraneoplastic Syndrome**

- Curth’s Postulates: At least one of the following:
  - Malignancy & cutaneous disorder are of concurrent onset
  - Malignancy & cutaneous disorder should follow a parallel course
  - Successful treatment of the malignancy leads to regression of the skin disease
  - Recurrence of the malignancy leads to a return of the skin disease
  - A specific malignancy is associated with a specific cutaneous disorder
  - There is a statistically significant relationship between the malignancy & cutaneous disorder based on case-control studies
  - There is a genetic association between the malignancy & cutaneous disorder

**Paraneoplastic Syndromes**

- Strong correlation w/malignancy:
  - Acanthosis Nigricans Maligna (ANM)
  - Acquired pachydermatoglyphia (tripe palms)
  - Erythema gyratum repens (EGR)
  - Acrokeratosis paraneoplastica (Bazex Syndrome)
  - Acquired hypertrichosis lanuginosus (AHL)
  - Necrolytic migratory erythema (NME)
  - Leser-Trelat sign (LTS)
  - Paraneoplastic pemphigus (PNP)
  - Necrobiotic Xanthogranuloma (NXG)
  - Primary pappuus/Primary Systemic Amyloid

- Weaker correlation w/malignancy:
  - Dermatomyositis
  - Pyoderma gangrenosum
  - Sweet syndrome
  - Trousseau Syndrome
  - Extramammary Paget’s disease
  - Systemic itch
  - Acquired ichthyosis
  - Flashing

**Paraneoplastic Syndromes w/Strong Correlation with Malignancy**

- Acanthosis Nigricans Maligna (ANM)
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- Primary Systemic Amyloid

**Familial Cancer Syndromes**

- Autosomal Dominant:
  - Neurofibromatosis
  - Multiple Endocrine Neoplasia
  - Peutz Jeghers
  - Gardner’s
  - Cowden
  - Muir Torre

- Autosomal Recessive:
  - Ataxia Telangiectasia

- Weaker correlation:
  - Dermatomyositis
  - Pyoderma gangrenosum
  - Sweet syndrome
  - Trousseau Syndrome
  - Extramammary Paget’s disease
  - Systemic itch
  - Acquired ichthyosis
  - Flashing

**Paraneoplastic Syndromes with Strong Correlation with Malignancy**

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- Acquired pachydermatoglyphia (tripe palms)
- Erythema gyratum repens (EGR)
- Acrokeratosis paraneoplastica (Bazex Syndrome)
- Acquired hypertrichosis lanuginosus (AHL)
- Necrolytic migratory erythema (NME)
- Leser-Trelat sign (LTS)
- Paraneoplastic pemphigus (PNP)
- Necrobiotic Xanthogranuloma (NXG)
- Primary Systemic Amyloid
Acanthosis Nigricans Maligna

- Clinical:
  - Hyperkeratotic and velvety plaques
  - Involvement of oral/mucosal and acral sites
- Distinguish AN from ANM
- Suspect underlying malignancy when:
  - Older patient
  - Non-obese, non insulin resistant, non diabetic
  - cachectic appearance
  - sudden onset
  - Extensive/severe involvement
  - Unusual clinical distribution
    - Oral mucosa and axial sites
- Associated malignancies
  - Gastric adenocarcinoma
  - Bronchogenic carcinoma (Tripe palms only)
  - Gastric adenocarcinoma (Tripe palms + ANM)

Acquired Pachydermatoglyphia (Tripe Palms)

- Clinical:
  - Yellowish, velvety, diffuse palmar hyperkeratosis
  - accentuated dermatoglyphic patterns
  - resembles intestinal villosities \( \rightarrow \) Tripe palms
- 90% of cases associated with malignancy
  - Bronchogenic carcinoma (Tripe palms only)
  - Gastric adenocarcinoma (Tripe palms + ANM)

N Engl J Med 2007; 357:e10


Acquired Pachydermatoglyphia (Tripe Palms)
Erythema Gyratum Repens (EGR)

- Migratory polycyclic plaques with trailing scale
- Migrates 1cm/day
- Wood-grain appearance
- 80% with underlying malignancy
  - Lung/bronchogenic cancer > esophagus > breast
  - Most often precedes diagnosis of malignancy

http://stanfordmedicine25.stanford.edu/blog/archive/2014/Tripe-Palms.html

References:


An. Bras. Dermatol. 2012 Feb; 87(1)

N Engl J Med 2010; 362:1814
Acrokeratosis Paraneoplastic (Bazex’s Syndrome)

- Clinical:
  - Psoriasiform plaques at acral sites (fingertips, helices, nose, scalp)
  - May spread to involve more proximal areas
  - Nail dystrophy
- Distinguish from psoriasis/unusual distribution for psoriasis
- All cited cases associated with malignancy
- 60-70% of cases cutaneous findings precede malignancy
- 80% associated with SCC of upper aerodigestive tract
- Isolated cases of breast cancer, cholangiocarcinoma, colon adenocarcinoma and Hodgkin’s disease have been reported
- Treatment of underlying malignancy (as shown in pictures)

Acquired Hypertrichosis Lanuginosa (AHL)

- Clinical
  - Long, fine, thin, white hairs of face and ears → cranio-caudal spread to trunk
  - Sudden onset
  - NOT terminal hairs
- Distinguish from other causes of hypertrichosis (drug, porphyria, endocrine)
- Malignancy associations:
  - Women: colorectal > lung and breast cancer
  - Men: lung > colorectal cancer
  - Often appears late in cancer course → Poor prognosis

**References:**

- Acrokeratosis Paraneoplastica (Bazex’s Syndrome): [Link](http://www.dermis.net/dermisroot/en/34562/image.htm)
- Acquired Hypertrichosis Lanuginosa (AHL): [Link](https://www.dartmed.org/MED/2013/104_543-549/)

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**POMA District VIII 31st Annual Educational Winter Seminar**
January 25-28, 2018
Acquired Hypertrichosis Lanuginosa (AHL)

Necrolytic Migratory Erythema (NME)

- Clinical:
  - Irregularly shaped intensely erythematous patches
  - Expand resulting in circinate or polycyclic morphology
  - Superficial, flaccid vesicles rupture forming crust
  - May appear eczematous
  - Abdomen, perineum, thighs, buttocks
  - May be mistaken for intertrigo

- Glucagonoma syndrome:
  - NME + insulin resistance + hyperglucagonemia
  - Angular chelitis
  - Weight loss
  - Diarrhea

- Distinguish from disease with similar cutaneous findings:
  - Hepatic cirrhosis/hepatitis C infection
  - Celiac disease
  - Intestinal malabsorption
  - Nutritional deficiencies of amino acid, zinc, and essential fatty acids

- Associated malignancy:
  - Glucagon-secreting tumor of the pancreas (alpha cells)

- Rash may precede other findings of glucagonoma for years, but 50% have metastases at time of diagnosis.
Leser-Trelat Sign

- Clinical:
  -Abrupt onset of numerous seborrheic keratoses

- Entity is controversial
  -SKs usually seen in elderly when malignancy is more prevalent
  -Young individuals with Leser-Trelat associated with malignancy shows validity of sign

- Associated malignancy:
  -Gastric or colon adenocarcinoma
  -Lymphoproliferative malignancy
  -Other

- Associated malignancy:
  -Gastric or colon adenocarcinoma
  -Lymphoproliferative malignancy
  -Other

Paraneoplastic Pemphigus (PNP)

- Clinical:
  -Painful, persistent erosions of mucosal surfaces (tongue, nose, mucous of lips, etc.)
  -May spread to skin
  -Polymorphous crusted plaques
  -Fragile vesicles/bullae
  -Hemorrhagic stomatitis resembling SJS
  -Esophagus, stomach, duodenum, intestines and lung may be involved

- Associated malignancy:
  -84% hematological cancer/disease
  -16% non-heme malignancies

- Mortality 75-90%
  -Progressive respiratory failure most common cause of death

<table>
<thead>
<tr>
<th>Associated Malignancy</th>
<th>Occurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>39</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>18</td>
</tr>
<tr>
<td>Castleman disease</td>
<td>18</td>
</tr>
<tr>
<td>Epithelial origin carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>Thymoma</td>
<td>6</td>
</tr>
<tr>
<td>Sarcoma (intrathoracic)</td>
<td>6</td>
</tr>
<tr>
<td>Waldenstrom's macrogloublenia</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin lymphoma, melanoma</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Necrobiotic Xanthogranuloma

- Rare histiocytic disorder
- Clinical:
  - Indurated xanthomatous (yellow-colored) plaques with necrosis & ulceration
  - How to differentiate from xanthelasma?
  - More indurated
  - May have an active erythematous border
  - Ulceration
  - Dimpling
  - Sequestration
  - Periorbital location
  - May extend into the orbit—proptosis, decrease ocular movement, loss of vision
  - Can involve extracutaneous sites
- Malignancy associated:
  - >80% with monoclonal paraproteinemia, usually IgG kappa type
  - 10% Multiple myeloma
  - Lymphomas & leukemia less common

Primary Systemic Amyloidosis

- Clinical:
  - Waxy, translucent or purpuric papules
  - Periorbital and pinch purpura
  - Amyloid infiltration of blood vessels results in fragility
  - May appear after rubbing the eyes, coughing, or straining during defecation
  - Macroglossia
  - "Shoulder Pad" sign
  - Direct deposition of amyloid in the deltoid muscles
  - Follicular 'spicules' on the face (myeloma pts)
- Pathophysiology:
  - Deposition of protein AL (light chain)
- Association:
  - Almost always have an underlying plasma cell dyscrasia
  - Multiple myelomas in 15–16% of cases

Cutaneous Manifestations of Internal Malignancy
Ashley L. Kittridge, DO

POMA District VIII 31st Annual Educational Winter Seminar
January 25-28, 2018
Follicular Spicules of Myeloma

Paraneoplastic Syndromes w/Weaker Correlation with Malignancy
- Dermatomyositis
- Pyoderma gangrenosum
- Sweet syndrome
- Trousseau Syndrome
- Extramammary Paget’s Disease
- Systemic itch
- Acquired ichthyosis
- Flushing (Carcinoid Syndrome and others)
Dermatomyositis

- Clinical:
  - Heliotrope rash, scalp rash, severe pruritus, “shawl” and “V” signs, Gottron’s papules & sign, linear extensor erythema, “holster” sign, dilated periungual erythema/capillary loops and ragged cuticles
  - Myopathic, amyopathic, subclinical myopathy
- Incidence of cancer in DM increased 5-7x
- 10-20% of adult DM pts have malignancy
- No increased risk in juvenile DM
- Incidence of malignancy decreases in the 3 years after diagnosis
- Most commonly associated adenocarcinomas of:
  - Ovary, breast, cervix, lung, GI tract

Dermatomyositis
Heliotrope rash

Gottron’s papules
Dermatomyositis
Gottron’s rash

Dermatomyositis
Periungual erythema, dilated capillary loops and ragged cuticles

Dermatomyositis
Linear extensor erythema
Dermatomyositis
"Shawl sign"

Dermatomyositis
"V" sign

Dermatomyositis
"Holster" sign
Pyoderma Gangrenosum

- Tender, erythematous plaques, nodules, and occasionally pustules
- Acneiform Papules and pustules may be present on face, neck, trunk and extremities
- Fever, malaise, arthralgia
- Hemorrhagic necrosis of skin, tendons, muscles
- Pathergy: lesions induced or worsened by trauma/debridement to skin
- Anterior lower leg most common site
- Diagnosis of exclusion (exclude infection, malignancy, other inflammatory)
- 50% of cases of PG have an associated disease:
  - IBD (65%) > Rheumatologic conditions (16%) > Hematologic malignancy (13%)
- PG and malignancy
  - IgA gammopathy in 10% of PG cases
  - Other hematologic malignancies include AML and myelodysplasia
  - Solid organ malignancies reported much less commonly

Sweet’s Syndrome

- AKA acute febrile neutrophilic dermatosis
- Clinical:
  - Tender erythematous plaques, nodules and occasionally pustules
  - Acneiform papules on face, neck, trunk and extremities
  - Fever, malaise, arthralgia
  - Neutrophilic leukocytosis
  - Increased ESR
  - Anemia can be clinical indicator of underlying malignancy in these pts
- Three types:
  - Classic (1/3rd of cases) (most frequent presentation)
    - IBD, acute onset, bacterial, malignant
  - URI-related
    - URI, influenza, sinusitis
  - Drug-related
    - NSAID, oral contraceptives, thiazides, minocycline
- Treatment:
  - Treat any underlying malignancy
  - Systemic corticosteroids gold standard

Table I. Diagnosis of patients with Sweet syndrome (N = 87)

<table>
<thead>
<tr>
<th>Interval</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever onset of IBD:</td>
<td>80 (90%)</td>
</tr>
<tr>
<td>Malignancy associated with Sweet syndrome:</td>
<td>80 (90%)</td>
</tr>
<tr>
<td>IBD-related:</td>
<td>76 (88%)</td>
</tr>
<tr>
<td>URI-related:</td>
<td>71 (81%)</td>
</tr>
<tr>
<td>Drug-related:</td>
<td>22 (26%)</td>
</tr>
<tr>
<td>Systemic corticosteroids:</td>
<td>44 (51%)</td>
</tr>
</tbody>
</table>
Sweet’s Syndrome

- AKA superficial thrombophlebitis
- Superficial deep inflammation of veins due to blood clot formation or hypercoagulable state
- Clinical:
  - Palpable erythematous cords (representing inflamed vessels)
  - May appear at unusual sites
  - Ulcer
- Upper extremities
- Underlying malignancy 50%
- Often associated with neutropenia
- Pancreatic (22%)
- Lung (6%)

Treatment:
- Treat underlying cancer
- Heparin may help; warfarin has NO effect

Of note, Dr. Trousseau later himself developed this sign & predicted that he must have an underlying visceral malignancy; he subsequently died of gastric cancer several months later.

Trousseau Syndrome

- AKA migratory superficial thrombophlebitis
- Superficial or deep inflammation of veins due to blood clot formation/hypercoagulable state

Clinical:
- Palpable erythematous cords (representing inflamed vessels)
- May appear at unusual sites
- Ulcer
- Upper extremities
- Underlying malignancy 50%
- Often associated with neutropenia
- Pancreatic (22%)
- Lung (6%)

Treatment:
- Treat underlying cancer
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Of note, Dr. Trousseau later himself developed this sign & predicted that he must have an underlying visceral malignancy; he subsequently died of gastric cancer several months later.

Extramammary Paget’s Disease (EMPD)

- Clinical:
  - Non-inflammatory plaques occurring in apocrine gland-bearing areas
  - Vulva (60%)
  - Perianal region (20%)
  - Perineum (15%)
  - Anus (5%)

- Often mistaken for eczema, psoriasis, intertrigo or tinea
- Most commonly represents a primary intraepithelial adenocarcinoma arising locally from the epidermis or adnexal structure (75%)
- May also be secondary to an underlying visceral malignancy (25%)
  - Most common visceral tumors are anatomically unrelated to the involved skin (but not always)
  - Colon (15%)
  - Breast (10%)
  - Prostate (5%)

- Treatment:
  - Local excision
  - Cryotherapy
  - Radiofrequency ablation
  - Carboxytherapy
  - Chemotherapy
  - Immunotherapy

Of note, Dr. Trousseau later himself developed this sign & predicted that he must have an underlying visceral malignancy; he subsequently died of gastric cancer several months later.
Systemic/Paraneoplastic Itch

- Clinical:
  - Chronic pruritus (>6 weeks) and normal-appearing skin

- Workup:
  - First-line recommended workup:
    - Thorough history and examination (B symptoms, lymphadenopathy, jaundice)
    - Basic laboratory tests (CBC, CMP, TSH)
    - Chest x-ray
  - Second-line workup:
    - CT imaging (not generally recommended)
  - Has NOT been shown to decrease M&M other than those with high risk of lung CA

- Associated malignancy:
  - Increased incidence hematological (5-10% Hodgkin’s) and bile duct carcinomas, but not other malignancies
  - Overall incidence of these malignancies in patients with chronic pruritus is very low
  - Other diseases associated with chronic pruritus:
    - Renal disease, liver disease, thyroid disease, diabetes, depression, and anxiety
    - Alcohol and tobacco use/abuse, higher BMI, and lower socioeconomic status

Acquired Ichthyosis

- Ichthyosis – dry, thick, & scaly skin
- Resembles fish scales

- Clinical:
  - Similar in appearance to ichthyosis vulgaris, which is an inherited ichthyosis
  - In contrast to congenital ichthyosis, the acquired form may also be present on the palms, soles, & skin flexures
  - When associated with malignancy, Hodgkin lymphoma is most common (70% of cases)
  - In most cases, it appears AFTER the diagnosis of malignancy
  - Malignancy workup is still prudent

Reference: https://www.aad.org/public/diseases/scaly-skin/ichthyosis-vulgaris
Flushing of Malignancy

- Consider malignancy in patients presenting with non-physiologic causes of flushing:
  - Episodes associated with concurrent systemic symptoms
  - Flushing involving extensive portions of the body
  - Episodes that do not resolve within minutes

Fig. 1: A thorough review of systems can aid the practitioner in determining which of the many causes of flushing may be affecting a patient.

DermNetNZ.org

Cutaneous Manifestations of Internal Malignancy
Ashley L. Kittridge, DO

Carcinoid Syndrome

- Only occurs in 5-10% of patients with carcinoid tumors
- 95% of carcinoid tumors found in appendix, rectum, and small intestine
- 40-50% of patients with tumors of small intestine or proximal colon present with Carcinoid
- LIVER metastases REQUIRED for Carcinoid Syndrome (alternative mechanism is bypass of first pass effect)
- Exception for gastric and bronchial carcinoid tumors - associated with flushing but liver metastases NOT required with these tumors
- Mediators released from tumor directly into circulation and bypass metabolism by liver

Clinical:
- Early
  - Episodes of flushing would be difficult to diagnose in this stage
  - Last 30 minutes & only for face, neck, & upper trunk
- Late
  - Pernicious dermatitis, atrophic hyperpigmentation & liver failure

Other symptoms:
- Spontaneous flushing
- Diarrhea
- Wheezing

Diagnosis:
- Elevated 24-hour urine 5-HIAA (degradation product of serotonin excreted in urine)

Familial Cancer Syndromes with Cutaneous Manifestations

- Autosomal Dominant:
  - Neurofibromatosis
  - Multiple Endocrine Neoplasia
  - Peutz-Jeghers
  - Gardner’s
  - Cowden
  - Muir-Torre
- Autosomal Recessive
  - Ataxia Telangiectasia
  - Bloom’s
  - Dyskeratosis Congenita
Autosomal Dominant Disorders Associated with Malignancy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Affected Gene</th>
<th>Malignancy</th>
<th>Clinical Manifestations</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Endocrine Neoplasia</td>
<td>MEN1</td>
<td>Pheochromocytoma, Parathyroid hyperplasia, Islet cell tumors</td>
<td>Hypertension, Hyperparathyroidism, Diabetes</td>
<td>Pancreatic Cancer</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia Type 2B</td>
<td>MEN2B</td>
<td>Medullary thyroid cancer, Parathyroid hyperplasia, Pheochromocytoma</td>
<td>Hyperparathyroidism, Hypertension</td>
<td>Medullary Thyroid Cancer</td>
</tr>
</tbody>
</table>

Autosomal Recessive Disorders Associated with Malignancy

<table>
<thead>
<tr>
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<th>Malignancy</th>
<th>Clinical Manifestations</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Hippel-Lindau disease</td>
<td>VHL</td>
<td>Renal cell carcinoma, Retinal angiomas, Pheochromocytomas</td>
<td>Retinal nevi, Hemangiomas, Hypertension</td>
<td>Renal Cell Carcinoma</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>Breast, prostate, brain, soft tissue sarcomas</td>
<td>High incidence of cancer across multiple organs</td>
<td>Breast Cancer</td>
</tr>
</tbody>
</table>

References:

- N Engl J Med. 2007; 357:e10
- An Bras Dermatol. 2012 Feb; 87(1)
- JAMA Dermatol. 2015;151(12):1381-1383
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