AAD Forum 009:

Skin and Systemic Malignancy: 
PARANEOPLASTIC DERMATOSES & 
CUTANEOUS METASTASES

Vincent Liu, MD
University of Iowa
Friday, March 3, 2017
9-11 am
Skin & Systemic Malignancy

- Medications
- Drug rash
- Melanoma
- Genodermatoses
- Paraneoplastic Dermatoses
- Cutaneous Metastases
Objectives

- To recognize the clinical and pathologic features of cutaneous metastases, their prognostic significance, and how their cutaneous manifestation is influenced by primary tumor, gender, and anatomic location
- To become familiar with the key clinical and pathologic features of the paraneoplastic dermatoses
- To understand the pathomechanism and classification of paraneoplastic dermatoses
- To identify the relationship between internal malignancies and cutaneous manifestations in paraneoplastic dermatoses
Malignant Melanoma
Metastatic to Skin

• Overview
  – Incidence: ~15-20% Stage I/II metastasize
  – Skin predilection: ~45% chance mets go to skin

• Clinical
  – Epidemiology:
    • #2-3 cutaneous met in Men (13-32% of all skin mets); #1 Men < 40 yo
    • #4 cutaneous met in Women (5-12% of all skin mets)
  – Morphology
    • Papulonodules (solitary, multiple)
    • Variably pigmented
  – Sites
    • Men: chest, arms, back
    • Women: lower extremities

• Pathologic
  – Epidermal sparing except in epidermotropic mets
  – Paucity of inflammation

• Prognosis
  – Distant skin metastasis => M1a
  – 5-y survival rate: 19%
Clinical Differential Diagnosis of Cutaneous Metastases

- **Primary Skin Tumor**
  - Keratinocytic
  - Melanocytic
  - Adnexal- follicular
  - Adnexal- eccrine
  - Merkel cell
  - Vascular
  - Smooth muscle
  - Neural

- **Lymphoma**
  - CTCL
  - CBCL

- **Histiocytic**
  - Histiocytoses
  - Granulomatous disorder

- **Dermatitis**
  - Hypersensitivity reaction
  - Eczema
  - Cellulitis
Breast Carcinoma Metastatic to Skin

- **Overview**
  - Skin predilection: Most common primary tumor

- **Clinical**
  - Epidemiology: ~70% skin mets in women
  - Morphology: papulonodules
    - Inflammatory (cellulitis-like)
    - Carcinoma erysipelatoides
    - Carcinoma telangiectoides
    - Carcinoma en cuirasse
    - Alopecia neoplastica
  - Sites: Anterior chest wall, abd, back

- **Pathologic**
  - Single filing
  - Ductular differentiation
  - Stromal sclerosis
  - Lymphovascular invasion

- **Prognosis**
  - Incurable
  - Skin-only mets => Mean survival of 57 months
Relative Incidence of Cutaneous Metastasis by Primary Tumor

- Incidence of primary tumor
- Rate of metastasis
- Likelihood metastasis involves skin

~10%
**Frequency of Metastatic Tumor to Involve Skin***

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>45%</td>
</tr>
<tr>
<td>Breast</td>
<td>30%</td>
</tr>
<tr>
<td>Nasal sinus</td>
<td>20%</td>
</tr>
<tr>
<td>Larynx</td>
<td>16%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Incidence data variable and evolving among different studies.
Cutaneous Metastases Ranked by Primary Tumor (% of skin mets)*

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Lung</td>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Colon</td>
<td>Colon</td>
<td></td>
</tr>
<tr>
<td>SCC head/neck</td>
<td>Melanoma</td>
<td>Melanoma</td>
<td>Ovary</td>
</tr>
<tr>
<td>Lung</td>
<td>SCC head/neck</td>
<td>Ovary</td>
<td></td>
</tr>
</tbody>
</table>

*Incidence data variable and evolving among different studies.

Metastatic Renal Cell Carcinoma

• Overview
  – Hi frequency of metasasis
  – Skin 7th site
• Clinical
  – Morphology: red papulonodules
  – Sites: Trunk, scars, scalp
• Pathologic
  – Vascularized tumor
  – Clear cell adenocarcinoma
  – Papillary, acinar
• Prognosis
  – Incurable
  – Death within 6-12 months
Anatomic Involvement of Cutaneous Metastases and Primary Tumor

<table>
<thead>
<tr>
<th></th>
<th>Head/neck</th>
<th>Chest</th>
<th>Abd</th>
<th>Umbilicus</th>
<th>Back</th>
<th>Arms</th>
<th>Legs</th>
<th>Perineum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Breast</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head/neck</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrocolic</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ovary</td>
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<td>+</td>
<td>+</td>
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<td></td>
<td></td>
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<tr>
<td>Kidney</td>
<td>++</td>
<td>+</td>
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</tbody>
</table>

Proximity of skin metastatic site to primary tumor
What’s in a zip code?

- Mapped all cutaneous mets at UCSF (1991-2014); n=1984
- Head/neck > trunk > UEs > LEs
- Using control samples for sites (n=140), measured local immunologic factors:
  - T regulatory cells
  - CD4+ effector cells
  - CD8+ cells
- Favored metastatic sites:
  - Tregs
  - CD8+ cells
Pathologic Differential Diagnosis of Cutaneous Metastases

- Primary Skin Tumor
  - Keratinocytic
  - Melanocytic
  - Adnexal - follicular
  - Adnexal - sweat gland
  - Merkel cell
  - Vascular
  - Smooth muscle
  - Neural

- Lymphoma
  - CTCL
  - CBCL

- Histiocytic
  - Histiocytoses
  - Granulomatous disorder
### Immunohistochemical Distinction of Primary Tumors

<table>
<thead>
<tr>
<th>Primary</th>
<th>S100</th>
<th>CK5,6</th>
<th>CK7</th>
<th>CK20</th>
<th>ER, PR</th>
<th>EMA</th>
<th>PSA</th>
<th>CD45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Breast</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lung</td>
<td>-</td>
<td>+ (SCC)</td>
<td>+(aden)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colo-rectal</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prostate</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*Others: p63, TTF-1, CAM 5.2, MART-1, etc.*
Cutaneous Metastasis of Unknown Primary

• Incidence
  – All cancer risk of met to skin: ~0.7-9%
  – Metastatic cancer of unknown primary: ~5-10%
  – Fraction of cutaneous metastatic cancer with unknown primary: ~4.4%

• Significance
  – Unclear prognostic importance
  – Challenge of excluding primary skin source
Cutaneous Metastases: Conclusions

• Cutaneous metastases
  – Direct manifestations of internal malignancy
  – Usually papulonodular, but with a variety of skin variations => clinical ddx
  – Insight into pathogenesis, potential therapy

• Clinical clues to identifying primary:
  – Demographics: age, gender
  – Anatomic site: localize near primary
  – Statistical incidence: primary, likelihood of met to skin

• Pathologic differential diagnosis may be addressed with a battery of immunohistochemical studies
  – But thorough H&P and imaging frequently also required
  – Unknown primary

• Poor prognosis

• Hematolymphoid tumors special significance
  – Clinically resemble solid tumor malignancies
  – Distinction between primary or secondary cutaneous critical
  – Paraneoplastic dermatoses, pruritus common
Paraneoplastic Dermatoses: Classification

- Papulosquamous (epidermal proliferative) disorders
- Interface dermatitides
- Reactive erythemas
- Neutrophilic dermatoses
- Dermal proliferative disorders
- Deposition disorders
- Other dermatoses
# Paraneoplastic Dermatoses: Papulosquamous Disorders

<table>
<thead>
<tr>
<th>Dermatosis</th>
<th>Clinical</th>
<th>Histopathology</th>
<th>Systemic Neoplasm</th>
<th>Association</th>
<th>Epidemiology</th>
<th>Timing</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis Nigricans</td>
<td>Hyperpigmented, velvety papillomatosis: axillae</td>
<td>Hyperkeratosis, papillomatosis, acanthosis with elongated dermal projections</td>
<td>Most are Adeno CA: Intraabdominal:70-90%</td>
<td>Commonly with insulin resistance</td>
<td>Age: &gt; 40</td>
<td>Before: 20%</td>
<td>Closely parallel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastric: 50-60%</td>
<td></td>
<td>During: 60%</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Acquired Ichthyosis</td>
<td>Diffuse rhomboidal scales: trunk and extensor surfaces</td>
<td>Orthokeratosis, mild acanthosis, thin/absent granular layer</td>
<td>Hodgkin: 70-80%</td>
<td>NWE*</td>
<td>Gender: Both Age: Older</td>
<td>Usually after, but also before</td>
<td>Closely parallel</td>
</tr>
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<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripe Palms</td>
<td>Rugose, velvety palms. May be associated with AN</td>
<td>Hyperkeratosi s, acanthosis, papillomatosis</td>
<td>Lung CA #1, Gastric CA #2, esp. with AN</td>
<td>Over 90%</td>
<td>Gender: Both Age: Older</td>
<td>Before/During: 60%</td>
<td>NWE</td>
</tr>
<tr>
<td>Sign of Leser-Trelat</td>
<td>Increase in size and number of seborrheic keratoses. Pruritus. AN in 20% of cases.</td>
<td>Seborrheic keratoses. May resemble papilloma in AN</td>
<td>GI adeno CA: 1/3 Lymphoproliferative 1/5</td>
<td>NWE</td>
<td>Gender: Both Age: Older</td>
<td>Before and after</td>
<td>NWE</td>
</tr>
<tr>
<td>Bazex</td>
<td>Scaly erythematous plaques: acral areas</td>
<td>Hyperkeratosi s, parakeratosis, mononuclear perivascular infiltrate</td>
<td>SCC of oropharynx, larynx, esophagus, lungs</td>
<td>Nearly every case</td>
<td>Mostly males Age: 60-70</td>
<td>Before: 60% After: 15%</td>
<td>Closely parallel</td>
</tr>
</tbody>
</table>

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# Paraneoplastic Dermatoses: Interface Dermatitides

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<th>Timing</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatomyositis</td>
<td>Heliotrope rash: periorbital. Flat topped papules over knuckles</td>
<td>Interface dermatitis with variable mucin deposition</td>
<td>Increased ovarian CA in females</td>
<td>25-30%</td>
<td>Gender: unclear&lt;br&gt;Age: 50’s, 60’s, Older than non-CA assoc DM</td>
<td>Before/during Most within 1 year.</td>
<td>Closely parallel</td>
</tr>
<tr>
<td>Paraneoplastic Pemphigus</td>
<td>Pruritic polymorphous lesions, bullae, papules/plaques: trunk, oral</td>
<td>Suprabasilar acantholysis, vacuolar interface degeneration&lt;br&gt;DIF: IgG linear at junction</td>
<td>¾ hematolymphoid: non-Hodgkin 42% CLL 29%</td>
<td>75%</td>
<td>Avg. age: 59&lt;br&gt;Before: 50%</td>
<td>Not parallel</td>
<td></td>
</tr>
</tbody>
</table>
## Paraneoplastic Dermatoses: Reactive Erythemas

<table>
<thead>
<tr>
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<th>Epidemiology</th>
<th>Timing</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythema Gyratum Repens</strong></td>
<td>Rapidly progressing erythematosous rings: trunk, proximal extremities</td>
<td>Hyperkeratosi s, superficial dermal perivascular lymphohistiocytic infiltrate</td>
<td>Bronchial CA #1 (32%)</td>
<td>82%</td>
<td>2 M: 1 F</td>
<td>Before: 80%</td>
<td>Closely parallel</td>
</tr>
<tr>
<td><strong>Necrolytic Migratory Erythema</strong></td>
<td>Erythematous macules/papules in annular configuration: face, abdomen, thighs, perianal/oral</td>
<td>Parakeratosis, keratinocytes with pyknotic nuclei</td>
<td>Pancreatic alpha cell tumor</td>
<td>Almost always</td>
<td>Gender: Both Age: 50’s, 60’s</td>
<td>Early or late</td>
<td>Not parallel</td>
</tr>
</tbody>
</table>
# Paraneoplastic Dermatoses: Neutrophilic Dermatoses

<table>
<thead>
<tr>
<th>Dermatosis</th>
<th>Clinical</th>
<th>Histopathology</th>
<th>Systemic Neoplasm</th>
<th>Association</th>
<th>Epidemiology</th>
<th>Timing</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sweet Syndrome</strong></td>
<td>Erythematous tender plaques/nodules in upper extremities. Fever, neutrophilia.</td>
<td>Dense and extensive neutrophilic infiltrate with vasculopathy</td>
<td>AML and Lymphoma: 85%</td>
<td>20%</td>
<td>Gender: NWE</td>
<td>Before: 2/3 Within 1 month: 40%</td>
<td>Closely parallel</td>
</tr>
<tr>
<td>Pyoderma Gangrenosum</td>
<td>Discrete ulcers with undermined borders. Pathergy.</td>
<td>Dense dermal neutrophilic infiltrate.</td>
<td>AML #1 Multiple Myeloma #2</td>
<td>7%</td>
<td>F &gt; M Avg. age: 45-52</td>
<td>NWE</td>
<td>NWE</td>
</tr>
</tbody>
</table>

* NWE = Not well established
## Paraneoplastic Dermatoses: Dermal Proliferative

<p>| Dermatosis                     | Clinical                                                                 | Histopathology                                                                 | Systemic Neoplasm                     | Association       | Epidemiology       | Timing         | Course         |
|--------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------|-------------------|-------------------|----------------|----------------|----------------|
| Multicentric Reticulohistiocytosis | Pink/brown papules/nodules: hands, face; symmetric athropathy             | Nodular infiltrate of histiocytes and multicellular giant cells with eosinophilic ground glass cytoplasm | No predominant cancer type            | 20-30%            | 1 M : 1.85 F Avg. age: 50 80% Caucasian | Unknown       | Not parallel  |</p>
<table>
<thead>
<tr>
<th>Dermatosis</th>
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<th>Epidemiology</th>
<th>Timing</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrobiotic Xanthogranuloma</td>
<td>Red orange dermal nodules/plaques that ulcerate: periorbital, trunk</td>
<td>Mid dermis to panniculus. Palisading xanthogranuloma, Touton giant cells, necrobiosis</td>
<td>Hematologic and lymphoproliferative</td>
<td>80% with benign IgG</td>
<td>Gender: Both Avg. age: 54-56</td>
<td>NWE</td>
<td>NWE</td>
</tr>
<tr>
<td>Scleromyxedema</td>
<td>2-4 mm waxy papules: symmetrically on arms, hands, face (leonine facies)</td>
<td>Fibroblast proliferation. Mild perivascular lymphoplasmacytic infiltrate with mucin</td>
<td>No clear specific malignancy: MM, Hodgkin, non-Hodg.</td>
<td>80% have monoclonal gammopathy IgG- lambda</td>
<td>Gender: Both Age 30-50</td>
<td>NWE</td>
<td>NWE</td>
</tr>
</tbody>
</table>

*NWE = Not well established*
## Paraneoplastic Dermatoses: Deposition Disorders

<table>
<thead>
<tr>
<th>Dermatosis</th>
<th>Clinical</th>
<th>Histopathology</th>
<th>Systemic Neoplasm</th>
<th>Association</th>
<th>Epidemiology</th>
<th>Timing</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous Amyloidosis</td>
<td>Smooth, waxy, nonpruritic papules/plaques: “pinch purpura” on eyelids</td>
<td>Apple-green birefringence with Congo red when stained with purple and crystal violet</td>
<td>Multiple myeloma, Thyroid or MEN</td>
<td>13-16% have Multiple Myeloma</td>
<td>Systemic: M &gt; F Avg. Age: 65</td>
<td>NWE</td>
<td>NWE</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Localized: NWE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NWE = Not well established*
## Paraneoplastic Dermatoses: Other

<table>
<thead>
<tr>
<th>Dermatosis</th>
<th>Clinical</th>
<th>Histopathology</th>
<th>Systemic Neoplasm</th>
<th>Association</th>
<th>Epidemiology</th>
<th>Timing</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertrichosis Lanuginosa Acquisita</strong></td>
<td>Soft, downy, nonpigmented lanugo hair: face, trunk, axillae</td>
<td>&quot;Mantle hair&quot; structures that extend parallel to epidermis</td>
<td>Men: Lung #1, Colorectal #2 Women: Colorectal #1, lung/breast #2</td>
<td>Nearly every case</td>
<td>3 F : 1 M Age: 40-70</td>
<td>Late in course of malignancy, but possible before</td>
<td>NWE</td>
</tr>
</tbody>
</table>

*NWE = Not well established*
**Paraneoplastic Dermatoses associated with Hematolymphoid Malignancies**

- **Lymphoid**
  - Paraneoplastic pemphigus
  - Exaggerated bite reactions

- **Myeloid**
  - Neutrophilic dermatoses

- **Plasmacytoid**
  - Necrobiotic xanthogranuloma
  - Scleromyxedema
  - Amyloidosis
  - Cryoglobulinemia
  - Subcorneal pustular dermatosis
Paraneoplastic Dermatoses: Conclusions

• Paraneoplastic dermatoses: heterogeneous group of dermatologic conditions associated with underlying internal neoplasms
• Paraneoplastic dermatoses useful
  – Allowing potential diagnosis of an underlying malignancy
  – Monitoring for tumor recurrence
  – Offering insight into pathogenesis.
• Association between internal malignancy and cutaneous manifestation vary
  – Strength
  – Timing
• Not always specific association, but clues for underlying malignancy
  – Sudden
  – Older
  – Rapid course
  – Atypical or more severe cutaneous lesions