Selective updates in dermatopathology of systemic disease
The Southeastern Dermpath Conference
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• I have no conflicts of interest to disclose
...I love dermpath
Outline

• Neutrophilic Dermatoses
• Connective tissue disease
• Granulomatous
• Bumps and syndromes
• Drugs
• Angiomatosis/Calciphylaxis

Neutrophils

Dr. Robert Douglas Sweet: First to detail syndrome of acute neutrophilic dermatosis
Sweet Syndrome: at least 2 major, 2 minor criteria

**Major Criteria:**
1. Abrupt onset of tender plaques, nodules, vesicles, pustules, bullae
2. Neutrophil-rich infiltrate w/o LCV

**Minor Criteria:**
1. Preceding respiratory/GI infection, vaccination or:
   - Inflammatory dermatosis/autoimmune
   - Hematologic or solid tumor
2. Fever >38, malaise
3. 3 of 4 of lab abnormality: ESR >20, C-reactive protein, leukocytosis >8000, shift >70%
4. Prompt response to steroids or potassium iodide

Sweet's interstitial neutrophils with leukocytoclasis
Sweet's Syndrome: Systemic Associations

- Malignancy (20%)
  - Hematologic (acute myelogenous leukemia)
  - Solid (GU, GI, Breast)
- Infections
  - URI, strep
  - GI: yersinia, salmonella
- IBD
- Pregnancy
- Rheumatoid arthritis
- Thyroid disease
Sweet’s Syndrome: Drug causes
- GCS-F
- All-trans retinoic acid
- Trimethoprim-sulfamethoxazole
- Minocycline
- Celecoxib
- Carbamazepine/diazepam
- Diclofenac
- Hydralazine
- Propylthiouracil
- Oral contraceptives

Sweet’s Syndrome: Extracutaneous manifestations
- Mucous membrane/ocular
- Pulmonary
- CNS
- Heart/aorta
- Bone
- Liver
- Kidney
- Muscle
- Spleen

Sweet’s with visceral disease
Sweet's Acute Neutrophilic Dermatosis

- Early lesions:
  - perivascular lymphos may predominate

- Established lesions:
  - neutrophil-rich interstitial infiltrate with leukocytoclasis, edema, and perivascular lymphocytes

- Older areas:
  - histiocyte-rich infiltrate, rare neuts
Sweet's Early Lesion

Sweet's Early Lesion: Perivascular lymphocytes

Sweet's Older lesion
Sweet's Older Lesion: Histiocyte-rich

Sweet's variants

- Neutrophilic dermatosis of the dorsal hands (pustular vasculitis of the hands)
- Subcutaneous
- Histiocytoid
- Eosinophil-rich
- Sweet's with vasculitis
Neutrophilic dermatosis of the dorsal hands

- Mostly lobular neutrophilic infiltrate
- Significant necrosis absent
- May see admixture of lymphocytes, histiocytes, multinucleated giant cells, eosinophils, reactive stromal cells
- May see abnormal segmentation of neuts
- Leukocytoclasis without vasculitis

Subcutaneous Sweet Neutrophilic Dermatosis

- Mostly lobular neutrophilic infiltrate
- Significant necrosis absent
- May see admixture of lymphocytes, histiocytes, multinucleated giant cells, eosinophils, reactive stromal cells
- May see abnormal segmentation of neuts
- Leukocytoclasis without vasculitis
Subcutaneous Sweet's

Myeloperoxidase

Pt with Hairy cell leukemia

Subcutaneous Sweet often with Leukemia
Subcutaneous Sweet’s: DDX

- Infection—deep fungal, bacterial
- Ruptured folliculitis/cyst
- Alpha-1 antitrypsin deficiency
- Vasculitis: Wegener’s, PAN
- Other neutrophil dermatoses
  - Rheumatoid neutrophilic dermatosis
- BRAF-inhibitor neutrophilic panniculitis

A 50 year old Female

Fevers, night sweats, bone pain, arthralgias, splenomegaly, MGUS

Recurrent blotchy rash and a few small subcutaneous nodules
Histiocytoid Sweet Syndrome

- Nuclear segmentation anomalies of neutrophils
  - Resemble histiocytes or bands
- May be evidence of dysgranulopoiesis, myeloproliferative disorders, leukemia
- Difficult to distinguish from leukemia cutis

“Pseudo-Pelgar-Huet” Sweet’s
Histocytoid Sweet Syndrome

A Dermal Infiltration of Immature Neutrophilic Granulocytes

Luis Requena, MD; Ester Kustner, MD; Gulderel Papic, MD; Marina Pascual, MD; Jordi Fernández-Herrero, MD
Javier Pizó, MD; Juan Antonio Ruiz Burgos, MD; David Chacón, MD; and Marinaldo Gómez, MD

Conclusions: This case series demonstrates that some fresh cutaneous lesions of Sweet syndrome are histopathologically characterized by an infiltrate mainly composed of cells that may be misinterpreted as histiocytes; when in fact they are immature myeloid cells. We named this histopathologic variant histiocytoid Sweet syndrome, which should not be mistaken with leukemia cutis or other inflammatory dermatoses that are histopathologically characterized by histiocytes interspersed between collagen bundles of the dermis.

Arch Dermatol. 2005;141:834-842

Histopathologic Features of histiocytoid Sweet syndrome

Neutrophilic precursors: (ddx=leukemia cutis)
Strong (+) myeloperoxidase
Also (+) CD15, CD43, CD45 (LCA), CD68, MAC 386, HAM 56, and lysozome

Requena, L. et al., Arch Dermatol 2005;141:834-842

35-55% a/w myelogenous leukemia or MDS

Cutaneous histiocytoid Sweet syndrome and its relationship to hematological diseases

Sweet syndrome (SS) can present as a variant form of hematologic malignancy. A recent study has shown that cutaneous and hematologic malignancies may have overlapping features. The diagnosis of hematologic malignancy in a patient with SS can be challenging. The identification of cutaneous malignancies is important for the proper treatment of the underlying disease. The differential diagnosis of skin lesions, especially those that suggest hematologic malignancy, should be considered in the context of the patient's medical history and clinical presentation. The key points to consider include the duration of the skin lesions, the absence of constitutional symptoms, and the presence of other cutaneous manifestations.
Histiocytoid Sweet Syndrome Is More Frequently Associated With Myelodysplastic Syndromes Than the Classical Neutrophilic Variant
A Comparative Series of 52 Patients

Ghoufi L et al. Medicine Volume 95, Number 15, April 2016

- Hematological malignancies more often a/w H-SS than classic-SS (55.5% vs 25%)
  - Especially MDS
- Heme disease dx’d before, concomitant, or after skin
- Clinical presentation did not differ between H-SS and classic-SS
- Some with widespread annular lesions

MPO+ neutrophils and histiocytoid cells
- (-) CD117, CD34

Subcutaneous histiocytoid Sweet syndrome in a patient with myelodysplastic syndrome and acute myeloblastic leukemia

Ghoufi L et al. Medicine Volume 95, Number 15, April 2016
Controversies

Histiocytes or myeloid cells?
Truly associated with hematologic malignancies?

- Histiocytoid Sweet syndrome was not more frequently a/w hematologic malignancies than classic neutrophilic Sweet syndrome
- Results similar to classic SS:
  - ~11% with malignancy—85% hematological (AML)
Mainly composed of MPO (+) immature myelomonocytic cells with histiocytoid morphology
- MPO+ expression higher than 75% in almost all 6 samples
- MNDA+/MPO+ cells majority: not mature PMNs—also express mononuclear marker

Double stain:
- Black nuclear MNDA
- Cytoplasmic CD14 at the periphery
- No co-expression

Most of the cells coexpress MNDA (nuclei) and MPO (cytoplasm)
- Most cells are (+) MNDA in their nuclei, with only scattered (+) CD163
- Myeloid lineage

JAMA Dermatol. 2017;153(7):651
Lymphocytic Sweet Syndrome

- 2 patients reported with MDS + SS
- Initially solely lymphocytic
- Later lesion showed Sweet’s
Lymphocyte-rich Sweet's: not a/w MDS

- 9 biopsies, all with perivascular CD3+CD4+CD8- lymphs. No MDS

Neutrophils may not be readily apparent: fragmentation
Sweet Syndrome

- Variants including subcutaneous and histiocytoid
  - Debatable link with hematologic malignancy/MDS

- Lymphocyte rich may be a/w myelodysplastic syndrome
  (could this really be histiocytoid?)

- MPO helpful in interstitial and perivascular infiltrates
PNGD
Palisaded Neutrophilic and Granulomatous Dermatitis

- Overlap with: Churg-Strauss granuloma, cutaneous extravascular necrotizing granuloma, rheumatoid papules, superficial ulcerating rheumatoid necrobiosis, and interstitial granulomatous dermatitis with arthritis
- 6 patients: SLE, RA, undefined CVD
- Extremities, symmetric
- Few to many
- Skin colored to erythematous
- Smooth, ulcerated, or umbilicated surfaces

- Spectrum—reflects evolutionary stage
  - Early:
    - neutrophil-rich, LCV, degenerated collagen
  - Fully developed:
    - palisaded granulomas surrounding leukocytoclastic debris, fibrin, and altered collagen
  - Late:
    - palisaded granulomas with dermal fibrosis and scant neutrophilic debris
PNGD/Winkelmann Granuloma: Acral symmetric dermal papules

PNGD: Histology

**Early**
- Pandermal neutrophils, +/- eosinophils
- Leukocytoclasis
- Strands of basophilic material
- Granular collagen alteration/necrosis
- Papillary dermal edema
- Foci of LCV
Vasculitis and Eosinophils

PNGD: Histology

Later
- Less prominent neutrophils
- Palisading histiocytes/granulomas around
  - neutrophilic debris
  - degenerated collagen
- Broad collars of fibrin around vessels
- Resolves with fibrosis, NLD-like

Medicine, 1983; 62:142-58
RK Winkelmann and colleagues, Mayo:
credited for recognizing the association of cutaneous extravascular necrotizing granuloma and systemic disease
Associated diseases:
- RA, LE, vasculitis, lymphoma, leukemia, myeloma, SBE, IBD, CAH
• 9 cases of paraneoplastic PNGD
• Spectrum of paraneoplastic granulomatous dermatitides: PNGD/IGD (interstitial granulomatous dermatitis)
• 37 cases of paraneoplastic PNGD/IGD
• Most commonly associated neoplasic: hematologic (MDS 24%)
  - Prostate, esophageal, hypopharyngeal, breast, endometrial, and lung

Am J Dermatopathol 2019;41:835–845

Am J Dermatopathol 2019;41:835–845

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Am J Dermatopathol 2019;41:835–845
PNGD ? IGD? Winkelman? IGD-like drug?

- PNGD, interstitial granulomatous dermatitis (IGD), IGD-drug reaction represent cutaneous reaction patterns
- Systemic trigger:
  - Lupus, vasculitis, RA and other arthritides, malignancy (hematologic> solid), medications

  *"Reactive granulomatous dermatitis"

• Pale, flat/minimally raised, macules, papules, plaques
  - resolved within 24-48 hours
  - Nonpruritic—not urticaria

• Histology:
  - Neutrophilic dermal infiltrate, leukocytoclasis, no vasculitis
  - Sweet syndrome like but no edema
  - Basophilic collagen alteration

Schnitzler syndrome, Still disease, systemic lupus erythematosus, Sjögren syndrome, cryopyrin-associated periodic syndrome

Schnitzler's syndrome

- 47 lupus patients with neutrophilic dermatoses—lit review
- Presenting symptom in 32%
- Hydralazine LE, neonatal LE
- Paucicellular—papillary dermis (26%), cell-rich Sweet-like (52%), in between (22%)
- Insidiously distinguishable from bullous dx (DH, BLE, LIGA), Sweet
- Interface dermatitis/mucin not often present

SLE patients: skin biopsy with neutrophilic-rich infiltrate c/w SLND or NUD

- SLND: lesions lasted longer localized to sun-exposed areas; prednisone required
- NUD: resolved within one week (spontaneous or antihistamines), but
- NUD cases not a/w SLE flare-up
- 80% of SLND cases a/w flare-up of SLE
- 60%, SLND developed concomitantly with SLE as a presenting sign

Lupus (2018) 27, 628–636
Still's Disease:
Salmon-colored rash, evanescent with fever

Ferritin 13,028 (13-150)

Persistent papules and plaques in adult-onset Still's disease

• Nonevanescent lesions
• Pruritic persistent plaques of red-brown coalescent papules with adherent scales
• Bizarre linear pattern—Koebner-like
• Lichenoid papules and plaques
• Widely distributed
  • Trunk, neck, face, extensor sides of extremities

Persistent papules and plaques in adult-onset Still's disease

Multiple individual necrotic keratinocytes upper epidermis—singly or aggregates
Less common: basal vacuolar alteration, nuclear dust, and sub-/intracorneal pustules
Neutrophil-rich infiltrate in the dermis


Updates in adult-onset Still disease: Atypical cutaneous manifestations and associations with delayed malignancy

- Persistent and classic AOSD lesions
- a/w lymphoma (B,T) breast Ca over other types
- Malignancy dx after AOSD dx 13/31 (42%) after (-) initial workup


- Glycosylated ferritin level is relatively constant over time
- independent of fluctuations in disease activity
Rare specific dermatologic feature of IBD
- Necrotizing suppurative and/or granulomatous folliculitis
- Perifollicular vessels: leukocytoclastic or granulomatous vasculitis
- Bug stains negative

Sterile folliculitis with vasculitis in Crohn disease pt (PG/Sweet-like)

Dermatomyositis
228 adult dermatomyositis skin biopsies:

- Interface dermatitis in 91% of biopsies (lesional)
- 95% had at least 1 of: perivascular inflammation, mucin, basovacuolization
- 74% with vessel dilation / vessel damage
- Unlikely DMM if no vascular dilatation, mucin, or perivascular inflammation
- Prednisone decreases likelihood/severity of: perivascular inflammation, vessel damage and basal vacuolization

J Cutan Pathol. 2019;46:401–410

Absence of interface dermatitis: DMM less likely but still c/w if clinical supports DMM

Basal vacuolization not required for dx of DMM: 25% absent

Eosinophils were seen but rare

J Cutan Pathol. 2019;46:401–410

A 67-year-old man pruritic eruption

- Interface dermatitis, dermal mucin, necrotic keratinocytes in acrosyringia
- Autoimmunity tests(+) anti-NXP2
- Lung Ca
- Resolution of rash with Rx Ca

Am J Dermatopathol 2017;39:e3–e7
Ab’s present in only 50% and 70% of pts
CPC needed for seronegative pts

Kurtzman DJB, Vleugels RA. J Am Acad Dermatol 2018;78:776-85

Anti-MDA5 Interstitial lung disease—higher risk of rapid progression
- High-resolution CT

- 21 year old with classic clinical DMM
- Antibody tests (-)
- “Non-specific” biopsy

• Perivascular lymphocytic infiltrate
• Increased mucin
• Dermal necrosis, vascular inflammation/damage
• Vascular injury a/w DM subtype (+) anti-MDA5
• Biopsy led to ILD dx


Clin-path features of pityriasis rubra pilaris + DMM – PRP before, simultaneous, after DMM.

Review of path
• Follicular hyperkeratosis
• Vascular interface dermatitis
• Alternating (vert/horiz) ortho/parahyperkeratosis
• Dermal mucin
• Arrector pili myositis

Dermatopathology 2015;2:1–8

Bumps and syndromes
Birt-Hogg-Dubé Syndrome

1. Fibrofolliculoma
2. Trichodiscoma
3. Acrochordons
   a/w renal tumors, pulmonary cysts, pneumothoraces, bullous emphysema

Multiple perifollicular fibromas: report of a case and analysis of the literature

Perifollicular fibroma in Birt–Hogg–Dubé syndrome: an association revisited

While perifollicular fibroma bears histopathologic resemblance to angiofibroma, the cases in this report illustrate the utility of placing perifollicular fibroma in the spectrum of fibrofolliculoma/trichodiscoma.
Genetic testing: (+) FLCN gene mutation
Renal cyst on MRI
"Felt "lung collapse"
A spectrum of histology in BHD

Trichodiscoma, perifollicular fibrous papule, perifollicular fibroma, fibrofolliculoma

Hamartomas of perifollicular or interfollicular connective tissue and hair follicle epithelial components related to BULGE

Birt-Hogg-Dubé Syndrome

• Genetic counseling
• Evaluate and monitor for renal cancer
• Occurs in 15% by age 70
• As young as 20 years
• Pneumothorax risk 50x higher

***Genetic counseling
• Evaluate and monitor for renal cancer
• Occurs in 15% by age 70
• As young as 20 years
• Pneumothorax risk 50x higher
Sebaceous Neoplasms of Muir-Torre Syndrome

- Sebaceous Adenoma
- Sebaceoma
- Sebaceous Carcinoma

Benign and malignant skin tumors and internal cancers show microsatellite instability (MSI) due to germline mutations in DNA mismatch repair (MMR) proteins, MLH1, MSH2, MSH6, PMS-2 (Lynch).

- 24 articles 2000-2016
- Sensitivity of MMR IHC in detecting germline MMR mutation ~81%
  - positive predictive value ~44%
- High false positivity rate
- Better if extracutaneous sebaceous tumors, multiple sebaceous neoplasms
- Lack of robust evidence to perform reflexive universal screening of MTS-associated cutaneous neoplasms
**Table 5: Multi-Tumor Syndrome Appropriate Use Scenarios**

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>1 A panel ratings</th>
<th>2 A panel ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>NC (75)</td>
<td>NC (66)</td>
</tr>
<tr>
<td>Age &gt; 60, 1 tumor</td>
<td>NC (75)</td>
<td>1.14 OUT</td>
</tr>
<tr>
<td>Age &gt; 60 tumor &gt; 1</td>
<td>NC (75)</td>
<td>1.14 OUT</td>
</tr>
<tr>
<td>Age &gt; 60, multiple tumors</td>
<td>UA (75)</td>
<td>UA (75)</td>
</tr>
<tr>
<td>Age &gt; 60, BCC w/ sub diff</td>
<td>UA (75)</td>
<td>UA (75)</td>
</tr>
<tr>
<td>Age &gt; 60, KA w/ sub diff</td>
<td>UA (75)</td>
<td>UA (75)</td>
</tr>
<tr>
<td>Age &gt; 60, cystic sub tumors</td>
<td>UA (75)</td>
<td>UA (75)</td>
</tr>
<tr>
<td>Age &gt; 60, MTS tumor, neuroendocrine or visceral malignancy</td>
<td>UA (75)</td>
<td>UA (75)</td>
</tr>
</tbody>
</table>

- NO: older, periocular Seb Ca
- YES: >60 multiple sub tumors, KA with sub diff, cystic sub tumor, MTS cancer


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**Table 6: MTS Appropriate Use Scenarios for the 1-Antibody Panel Grouped by Patient Age**

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Age &gt; 60 yrs</th>
<th>Age ≤ 60 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineural sebaceous carcinoma</td>
<td>UA (90)</td>
<td>UA (90)</td>
</tr>
<tr>
<td>One sebaceous tumor, head and neck location</td>
<td>UA (90)</td>
<td>UA (90)</td>
</tr>
<tr>
<td>Multiple sebaceous tumors</td>
<td>UA (90)</td>
<td>UA (90)</td>
</tr>
<tr>
<td>Basal cell carcinoma, subcutaneous differentiation</td>
<td>UA (90)</td>
<td>UA (90)</td>
</tr>
<tr>
<td>MTS tumor metastasis and/or visceral malignancy</td>
<td>UA (90)</td>
<td>UA (90)</td>
</tr>
</tbody>
</table>

- YES: any age if multiple sub tumors
- YES: any age if KA/cystic type or with MTS neoplasm or visceral cancer
- YES: one tumor non head/neck ≤ 60 years old
- NO: if periocular


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**Table 7: MTS Appropriate Use Scenarios for the 2-Antibody Panel Grouped by Patient Age**

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Age &gt; 60 yrs</th>
<th>Age ≤ 60 yrs</th>
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<td>MTS tumor metastasis and/or visceral malignancy</td>
<td>UA (90)</td>
<td>UA (90)</td>
</tr>
</tbody>
</table>

- YES: any age if multiple sub tumors
- YES: any age if KA/cystic type or with MTS neoplasm or visceral cancer
- YES: one tumor non head/neck ≤ 60 years old
- NO: if periocular

Mayo MTS risk score

- Scores for the four variables are summed to create a total score—possible range of 0–5
- Score of ≥2: sensitivity of 100% and specificity of 81% for predicting a germline mutation in a Lynch syndrome mismatch repair gene.

Lynch syndrome-related cancers include colorectal, endometrial, ovarian, small bowel, urinary tract (renal pelvis and ureter), and biliary tract cancers.

Table 2. The Mayo MTS syndrome risk score algorithm

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 40 years</td>
<td>1</td>
</tr>
<tr>
<td>Adult age (years)</td>
<td>0</td>
</tr>
<tr>
<td>Number of relatives with Lynch syndrome cancer</td>
<td>1</td>
</tr>
<tr>
<td>No family history of Lynch syndrome cancer</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Medication reactions

Gaps in Medical Dermatology

- Failure to recognize and treat patients with drug reaction eosinophilia and systemic symptoms (DRESS)
Drug rash with eosinophilia and systemic symptoms (DRESS)

Aka Drug-induced hypersensitivity syndrome (DIHS)
Multiorgan hypersensitivity reaction

Diagnostic criteria of DRESS
1. Cutaneous drug eruption
2. Lymphadenopathy ≥ 2 cm, hepatitis (liver enzymes ≥ 2x upper limit) or interstitial nephritis/interstitial lung/myocarditis
3. Hematologic abnormalities: eosinophilia ≥ 1.5 × 10⁹ L or atypical lymphocytes

Watanabe W. J Immunol research 2018;1-10

Drug rash with eosinophilia and systemic symptoms (DRESS)

• Delayed onset (vs other drug reactions)
  - ≥ 2-8 weeks after drug
• Typical drugs:
  - carbamazepine, phenytoin, phenobarbital, lamotrigine, dapsone, meclofenamate, salazosulfapyridine, allopurinol, NSAIDS, minocycline
• A/w reactivation of herpetic viruses (HHV6, CMV)

Watanabe W. J Immunol research 2018;1-10

Drug rash with eosinophilia and systemic symptoms (DRESS)

• Fever → pruritic maculopapular rash → generalizes
• Simulates EM, AGEP or exfoliative erythoderma
• Symptom onset → two or three sxs, stepwise progression of sxs
• Flare-ups weeks after drug stopped

Watanabe W. J Immunol research 2018;1-10
15 DRESS patients—biopsies reviewed

Histopathologic patterns

- Spongiotic
- Erythema multiforme-like
- Lichenoid
- No features confirmed DRESS or distinguish from other drug rash
Patient with DRESS due to antibiotic

Immune Checkpoint Inhibitors

- Anti-CTLA-4:
  - Ipilimumab, tremelimumab
- PD1 inhibitors:
  - Pembrolizumab and nivolumab, atezolizumab, durvalumab
- Cutaneous reactions common—simulate inflammatory dermatoses
- Inflammatory, immunobullous, alteration of epidermal keratinocytes or melanocytes
Checkpoint inhibitor immune-related adverse events

- Immune-related adverse events with CPIs (70-85%):
  - liver, endocrine glands, gastrointestinal tract, and the skin (LEGS)
- Skin (up to 40%):
  - Lichenoid, BP-like, DH-like, granulomatous/sarcoidal disease-like,
    suprabasal acantholysis with lichenoid inflammation, paraneoplastic
    pemphigus-like with (+) DIF


Anti-CTLA-4 medication reactions (ipilimumab)

- 21 to 42 d following initiation, dose dependent
- Maculopapular drug: spongiosis + DHR with eos
- Vitiligo (months later, not dose dependent)
- Lichenoid dermatitis
- SJS/TEN, AGEP, DRESS-like, CD30+, Sweet/PG-like,
  granulomatous, Grover's, DH-like, alopecia areata, acneiform,
  dermatomyositis, regression of nevi, tumoral melanosis

Adv Anat Pathol 2019;26:40–55

PD1 inhibitors:

- Pembrolizumab and nivolumab, atezolizumab, and durvalumab
- Similar to but less common than anti-CTLA-4 eruptions, but
  delayed (weeks to months)
- Lichenoid mac/papular, pruritus, vitiligo
- Pemphigoid-like
- Vasculopathic, psoriasiform eruption
Suprabasal acantholytic dermatologic toxicities associated with checkpoint inhibitor therapy: A spectrum of immune reactions from paraneoplastic pemphigus-like to Grover-like lesions.

- PNP-like suprabasal blisters with linear IgG/IgA, cell surface IgG/C3, ELIZA 230kd
- Grover’s like

**Many months after 1st dose**

- Vs anti-CTLA-4 agent ipilimumab (3–4 weeks onset)
- Steroid responsive: no d/c of therapy (small sample)

**Pembrolizumab-induced sarcoidal infusion site reaction**

- PD-1 inhibitor for met. MM
- 3 months ➔ pulmonary/cutaneous sarcoid
- Pembrolizumab d/c’d, Sarcoid cleared
- Months later, sarcoid at infusion sites

**Cutaneous Reactions to Targeted Therapy**

**TABLE 1: Outline of Review**

<table>
<thead>
<tr>
<th>EGFR inhibitors</th>
<th>Kinase inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>v-ALK, BCR-ABL, JAK2,BRAF inhibitors</td>
<td>RAF/MEK inhibitor</td>
</tr>
<tr>
<td>MEK inhibitor</td>
<td>MEK inhibitor</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>cetuximab</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Ceritinib</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>dynemicin</td>
</tr>
<tr>
<td>Tivantinib</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>AZD6244</td>
<td>Trabectedin</td>
</tr>
<tr>
<td>OSI027</td>
<td>Tivantinib</td>
</tr>
<tr>
<td>VEGF inhibitor</td>
<td>growth factor inhibitor</td>
</tr>
<tr>
<td>Iressna (vemurafenib)</td>
<td>Stivarga (regorafenib)</td>
</tr>
</tbody>
</table>

**EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS**

- Cutaneous adverse events 50% to 90%, dose-dependent
- Acneiform, papulopustular eruption, xerosis, mucositis, hair/nail changes

**TABLE 2: Adverse Cutaneous Reactions Associated With EGFR, BRAF, and PDGFR Inhibitors**

<table>
<thead>
<tr>
<th>Kinase inhibitors may simulate other dermatoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- PR</td>
</tr>
<tr>
<td>- MF</td>
</tr>
<tr>
<td>- E nodosum</td>
</tr>
<tr>
<td>- PCT</td>
</tr>
<tr>
<td>- Sweet syndrome</td>
</tr>
<tr>
<td>- Drug eruptions</td>
</tr>
<tr>
<td>- EM, SJS, AGEP, lichenoid drug</td>
</tr>
</tbody>
</table>

**Am J Dermatopathol 2017;39:67–82**
Hand Foot Skin Reaction: Multikinase inhibitors

- Up to 80% with significant AE
- Sorafenib, sunitinib, and regorafenib
- Band-like necrosis—bulla
- Interface reaction
- Callus-like lesions

Most common cutaneous AE (48%) in sorafenib group
3–56 days after initiation of drug (median onset ~ 18 days)

<table>
<thead>
<tr>
<th>Drug reactions kinase inhibitors</th>
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</thead>
<tbody>
<tr>
<td><strong>TABLE 3. Drug Adverse Reactions Associated With Kinase Inhibitors</strong></td>
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<tr>
<td>MKP-4 (10)</td>
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<tr>
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<tr>
<td>Hand-foot skin reaction</td>
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<tr>
<td>Genital acne</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Anemia</td>
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<tr>
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<tr>
<td>Dermatitis</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Cutaneous mucositis</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Drug reactions kinase inhibitors</td>
</tr>
</tbody>
</table>
BRAFV600E INHIBITORS

- Squamous proliferations:
  - SCC/KA/AK-like
  - Verrucous
  - Melanocytic proliferations
  - Inflammatory

Squamous proliferations arising in the setting of BRAF inhibition

- Vemurafenib and dabrafenib
- KA-like
- Verrucous keratosis
- Onset as 34 (VK) and 44 (KA) days
- No mets or recurrence
- Rare inv SCC, AK

Eruptive nevi—BRAF inhibitors
Neutrophilic Panniculitis
BRAF inhibitor therapy
• vemurafenib > dabrafenib
• ENodosum-like: lobular/septal, neuts, +/- granulomas, necrosis, vasculitis
• Fx=M lower-upper extremities, buttock
• Migratory arthralgias
• Days to weeks after initiating BRAF: median 21 days (3-195 days)
  **No need for D/C BRAF**
  • NSAID, oral/topical corticosteroids, spontaneous regression

Vemurafenib-Induced Neutrophilic Panniculitis: A New Case and Review of the Literature
Igor Vatexe-Otono, MD, Marta Díaz-Reyes, PhD, MD, PhD, Sara García-Beloso, MD, PhD, José M. Bautista-Pérez, MD, PhD
Am J Dermatopathol 2016;38:e93–e96

Pseudolymphoma due to anti-tumor necrosis factor agents—rare reports
• Adelimumab
• Infliximab
• Eternacept
• 48 cases viral and drug
  • Viral: lower median absolute eosinophil count and C reactive protein
  • Drug: lymphocytic exocytosis, dermal eosinophils, lymphocytes and histiocytes

J Cutan Pathol. 2017;44:1038 –1048

• Antibiotics, antiepileptics, NSAIDs most common
• Drug with denser lymphocytic infiltrate, more prominent spongiosis
• Overlap of features
  • Eosinophils (rare in viral)
  • Spongiosis

J Cutan Pathol. 2017;44:1038 –1048

Update on drugs summary

• Check point inhibitors/targeted therapy: frequent skin eruptions simulate known dermatologic conditions—weeks to months after onset
• Some are unique to the medication (KA-like, neut pannic, hand, foot skin reaction)
• Not necessary to stop the medication in some cases
• Pseudolymphomatous eruptions in DRESS and targeted Rx
• Drug and viral eruptions difficult to differentiate:
  • eos in both
  • Drug with more robust lymphocytes and eosinophils
Infectious/Granulomatous

- 16 year old
- Ulcer after vacation to Israel
- CD1a (+)

Histopathologic features of cutaneous leishmaniasis and use of CD1a staining for amastigotes in Old World and New World leishmaniasis

- Retrospective review
- Sarcoidal, diffuse, suppurative and granulomatous, palisaded, lichenoid
- CD1a (+) in amastigotes 9/16 (56%)
  - 5/7 (71%) Old World
  - 4/9 (44%) New World
• 3/4 (75%) cases CD1a (-); (25%) stained (+)
• CD1a (-) cases: Leishmania braziliensis, Leishmania peruviana, most common in Peru
• Not helpful in South America

• Amastigotes difficult to identify—PCR
• If eosinophils, amastigotes hard to find
• Clues: numerous plasma cells, "messy granuloma", PEH
• CD1a (+) in amastigotes—limitations:
  • Low sensitivity for New World species
  • MTB1 clone, not O10
  • Dendritic cell cytoplasmic prolongations mimics kinetoplast

J Cutan Pathol. 2017;44:1051–1052

• early erythema migrans—Steiner (-)
• Confirmed: B. burgdorferi 1:40 seropositivity and 1:8 seronegativity
• 7/8 agree: mild perivascular/interstitial mixed infiltrate: lymphocytes, eosinophils, neutrophils and plasma cells
• Spongiosis, interface change, perineural, periadnexal infiltrate
• 27-yr M with papules and burning
• Perineural granulomas in 18/29 (62%) patients, 22/40 (55%) biopsies
• Distribution similar to sarcoidosis small-fiber neuropathy (sensory disturbance w/o lesions)
• Face, proximal extremities, trunk

J Cutan Pathol 2015;42: 465–470

• Measles → fever, cough, conjunctivitis, nonvesicular skin rash
• Anti-MeV IgM (ELISA) → peak 7–10 days after onset of rash
• 13 biopsies and lit review confirmed helpful features
  • Syncytial epithelial giant cells (epidermis/acrosyringium)
  • Single and clustered necrotic keratinocytes
  • Pronounced folliculosebaceous and acrosyringeal involvement
• IHC: anti-measles virus (MeV) nucleoprotein and anti-MeV phosphoprotein
  Am J Dermatopathol 2019;00:1–10

• Folliculotropism of infiltrate, necrosis of sebaceous gland, vacuolar change
  Am J Dermatopathol 2019;00:1–10
• Pyknotic keratinocytes epidermis and follicle
• Multinucleated keratinocytes
• Mild vascular change, pyknotic keratinocytes
• Parakeratosis and pyknotic spongiotic vesicle in acrosyringium
• Adnexal involvement with necrosis of sebaceous gland
• Pyknotic-spongiotic vesicles in acrosyringium and hair follicle

Antibodies for MeV nucleoprotein
• (+) single and clustered keratinocytes in epidermis, adnexae, dermis
• (+) Dermal spindle cells and lymphocytes
• (-) in pyknotic-spongiotic vesicle

Calciphylaxis
• Calcification of small and medium-sized vessels: subcutis
• Vascular occlusion-skin necrosis
• Hyperparathyroidism from renal disease
• Non-uremic
• Protein S or C deficiency
• Histology: mural or soft tissue calcification, fibrosis, intravascular thrombi, necrosis
• 24 calciphylaxis patients
  • 7/24 (29%) inadequate (no fat)
  • Especially noted in thigh samples
  • 8/17 (47%) adequate specimens but false-negative Dx
  • Ca+ stains correlated with true positive Dx (93% vs 55%)
  **Dermatopathology fellowship training correlated with true-positive diagnosis (82% vs 38%)**
  **Calcium stains (von Kossa or Alizarin red) good Dx adjunct
  • 8 changed from false-negative to true positive
  • Special stains for infection were (+) bacteria +/- fungus
  9/7 cases (53%)
  • One with (+) stain and culture
  • 21% in nonuremic patients:
  • warfarin use, diabetes mellitus, obesity, glucocorticoids, SLE, RA, Sjogren’s syndrome, prior malignancy
Peri-eccrine Ca++

Calcification of dermal vessels and diffuse dermal thrombi

Frequent dermal angioplasia

Perineural Ca++ noted

Perieccrine Ca++ not seen

Histopathology of Calciphylaxis: Cohort Study With Clinical Correlations

Calcification of dermal vessels and diffuse dermal thrombi

Frequent dermal angioplasia

Perineural Ca++ noted

Perieccrine Ca++ not seen

Pseudoxanthoma elasticum-like changes in nonuremic calciphylaxis: Case series and brief review of a helpful diagnostic clue

Initial bx of ulcer (-)

Bx clinically nl skin next to ulcer: dx
Diffuse dermal angiomasis: "Of the Breast"
Evaluate for peripheral vascular disease or coagulopathy
Diffuse Dermal Angiomatosis

- First described 1994 (Krell, et al)
- Variant of reactive angioendotheliomatosis
- Lesions variable:
  - Violaceous, reticulated, patch or plaques
  - Often with ulceration or surrounding dusky erythema
  - Often on extremities (thigh)

- Cases reported with pendulous breasts
  - Yang et al. Arch Dermatol 2006; 142:343-47

Diffuse Dermal Angiomatosis

- Co-Morbidities:
  - HTN, cardiovascular disease, peripheral vascular disease, smoking
  - May herald vaso-occlusion or compromising peripheral vascular disease
Angiogram showing severe stenosis of proximal left subclavian artery; B, with percutaneous stent placement, normal flow was restored.


DDA associated with calciphylaxis


Diffuse dermal angiomatosis associated with calciphylaxis: A 5-year retrospective institutional review

Hoothe M. O’Gorman1,2,3 | Qiang Wu1,4 | Steven B. Lackenby1 | Jessica A. Fasson1

- 24 cases of calciphylaxis
- African American race and comorbid congestive heart failure—only significant associations
- DDA not a/w disease severity or prognosis

Cutaneous reactive angiomatosis associated with cholesterol embolism

46 yo M h/I HIV, treated KS
• 2 new skin nodules
• Biopsies =KS, HHV8 (-) x2
• HHV-8 PCR (primers specific for the ORF26 gene) (+) both

(-)HHV-8 IHC does not exclude KS
**If histological/clinical suspicious for KS, with (-) HHV8 PCR to look for HHV-8 transcripts**

Neutrophilic dermatoses:
- think systemic/hematologic
- DM: interface dermatitis not required, eos rare
- Vasculopathy in DM clue for MDA5
- Calciphylaxis: Ca++ in eccrine, nerve, angiomatosis
- Neutrophilic urticarial dermatosis: adnexotropic
- AUC for Muir-Torre IHC: not for all Seb neoplasms
- Fibrous papules in BHD
- Targeted agents: skin SE common, mimic inflammatory dermatoses
- CD1a for leishmaniasis, sometimes