Adventures In Inpatient Dermatology
Instructive Cases from University of Michigan...

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I have no relevant relationships with industry.
Clinical History

- 50-year-old male
- Hypertension, diabetes, hepatitis C
- Violaceous, scaly eruption
- Hands, arms, and legs
Clinical DDX:
Psoriasis
Dermatomyositis
Lichen Planus
A little psoriasiform, a little spongiotic, a bit lichenoid…….

Your diagnosis?
Necrolytic Acral Erythema

Clinical Features

- Rare cutaneous eruption associated with hepatitis C virus (HCV) infection
- 1st described in Egypt
- Distinctly acral with involvement of dorsal hands, dorsal feet and lower extremities
- Early lesions – dusky, erythematous plaques; often flaccid blisters and/or erosions
- Older lesions – lichenified, violaceous plaques with scale & hyperpigmentation
Histologic Features – Well-developed lesion

- Hyperkeratosis, variable parakeratosis
- Neutrophils in stratum corneum
- Psoriasiform dermatitis with variable spongiosis
- Scattered dyskeratotic keratinocytes
- Moderate superficial lymphocytic infiltrate
Necrolytic Acral Erythema

Pathogenesis

- **Hepatitis C virus** infection results in hepatocellular dysfunction
- Leads to elevated glucagon levels and/or decreased amino acid levels
- May also have hypoalbuminemia and/or zinc deficiency
- These deficiencies cause epidermal protein depletion and alter skin inflammatory cascades, resulting in.....
- Necrolytic cutaneous eruption
What is Necrolytic Acral Erythema?........
Just another name for a nutritional deficiency?

Probably, yes....!
Nutritional Deficiencies

Glucagonoma
Acrodermatitis Enteropathica

Necrolytic erythemas with overlapping histologic features....

Spectrum of nutritional deficiencies more similar than dissimilar....
Nutritional Deficiencies

- Acrodermatitis enteropathica
- Glucagonoma syndrome
- Pellagra
- Hepatitis C virus infection
- Biotin deficiency
- Cystic fibrosis
- Pancreatitis
- Anorexia nervosa
- Cirrhosis

“Deficiency Dermatitis”
Necrolytic Erythema/Nutritional Deficiency

Histologic Features – Variable Patterns

- Classic – “upper epidermal pallor”
- Parakeratosis and mild spongiosis
- Interface dermatitis with necrotic keratinocytes
- Epidermal necrosis
- Subcorneal pustules
- Psoriasiform hyperplasia

Need to correlate clinically!
Clinical History

- 78 year-old male
- History of abdominal colectomy and ileostomy for colon cancer
- Growing peristomal “mass”
Reactive vs. Neoplastic?
Pseudoverrucous Nodules

- Rare condition 1st described at urostomy sites
- Unique presentation of chronic irritant dermatitis
- Multiple smooth, moist, dome-shaped papules & nodules
- Perianal area secondary to urinary incontinence or encopresis
- Colostomy sites secondary to ill-fitting ostomy appliances
- Lesions regress once irritant removed
Clinical History

28-year-old female with painful, pruritic vulvar eruption
• Relief of symptoms from topical benzocaine (Vagisil®)
• Multiple moist, closely set, flesh-colored to erythematous papules
• Erosions, erythema and denudation
• Multiple “nonspecific” biopsies
Multiple biopsies interpreted as “non-specific”....
How do we make this make sense? ........
Clinically distinct irritant contact dermatitis in genitocrural area

Similar, if not identical, eruptions have been termed →
- Granuloma gluteale infantum/adultorum
- Perianal pseudoverrucous papules
- Jacquet’s erosive diaper dermatitis

Causative agents: Urine, feces, talc, Vagisil® (benzocaine), etc. plus occlusion/maceration

Near complete resolution
3 months after cessation of topical benzocaine
Nosology is a mess!

“Granuloma gluteale”.....lesions are not granulomatous

“Pseudoverrucous papules”....lesions are often not verrucous

“Jacquet’s diaper dermatitis”....often no diaper involved

“Erosive genitocrural papulonodular dermatosis”....lengthy but at least is appropriately descriptive!

**Key Points**

- A severe irritant contact dermatitis
- Distinctive, reproducible cutaneous eruption
- Often nonspecific histology
- Can simulate squamous neoplasia in some cases
- Chronic topical benzocaine use can be a causative agent
- Must correlate clinically!!
Clinical History

- 15 year-old female
- Fever, arthralgia, myalgia
- Fixed erythematous plaques with fine scale
- Laboratory evaluation
  - Elevated WBC with 85% neutrophils
  - Elevated serum ferritin
Diagnosis:
Fixed Eruption of Still’s Disease
(Systemic Juvenile Idiopathic Arthritis)
Still’s Disease

- Still’s disease ≈ Juvenile idiopathic arthritis (Juvenile rheumatoid arthritis)
- Idiopathic systemic inflammatory disorder
- Diagnosis of exclusion
- Polyarthritis and polyarthralgia
- Spiking fevers
- Leukocytosis with neutrophilia
- Elevated ferritin levels
- Evanescent, non-pruritic salmon-pink maculopapular eruption = *classic* rash of Still’s disease
- Less well-recognized, *fixed* cutaneous eruption
  - Pruritic, erythematous papules & plaques
  - Neck, trunk, extremities
Key Points

- Cutaneous manifestations occur in up to 85% patients
- Unique eruption of persistent, erythematous papules/plaques seen in subset of patients
- Distinctive upper epidermal dyskeratosis (verrucous incontinentia pigmenti-like)

Clinical History

- 45 year-old male
- HIV +
- Slowly expanding crusted red plaque on forearm
Do you want to get more immunostains or stain for microorganisms?
Mycobacterial Spindle Cell Pseudotumor

**Clinical Features**

- Rare mycobacterial infection
- Immunocompromised patients, especially HIV infection
- Lymph nodes, bone marrow, and **skin**
- *Mycobacterium avium intracellulare* most commonly
- Red-brown plaques or nodules
Mycobacterial Spindle Cell Pseudotumor

**Histologic Features**

- Diffuse dermal CD 68+ spindle cell proliferation
- Vaguely storiform
- Scattered mitotic figures
- Interspersed epithelioid histiocytes & neutrophils helpful clue
- Amphophilic granular collections of organisms (if lucky)
- Fite stain positive and GMS variably positive
In setting of immunosuppression and a fibrohistiocytic spindle cell proliferation, consider **mycobacterial spindle cell pseudotumor**.
Clinical History

- 53 year-old male with history of ALL
- Hematopoietic stem cell transplant
- Complicated by GVHD, pseudomonas pneumonia, altered mental status, and sepsis
- Rare scattered skin lesions
Your diagnosis?
Infection caused by free-living, ubiquitous amebae of soil and water
- Genera - *Acanthamoeba, Balamuthia, Naegleria*
- Amebic keratitis 2° contaminated contact lens solution
- Facultative parasite of immunosuppressed patients (AIDS, organ transplantation)
- Amebic meningoencephalitis most common
- 90% patients with disseminated disease have skin lesions – papules, pustules, nodules, ulcers
- Grave prognosis with CNS involvement
Histologic Features

- Variable tissue reaction in dermis and/or subcutis
- Granulomatous and/or suppurative
- Rare reports of vasculitis
- *Amebae*, 15-40 µm in width, present as cysts or trophozoites in tissue
Cutaneous Acanthamebiasis

**Trophozoites**
- Infectious & invasive form
- Single large nucleus
- Prominent nucleolus
- Basophilic cytoplasm
Cutaneous Acanthamebiasis

Acanthamoebic Cysts
- Hardier form
- Can survive adverse environmental conditions
Magnetic resonance imaging – 1.8 x 1.9 cm area of hyperintensity secondary to amebic encephalitis-associated hemorrhage
Gross autopsy of brain – confirmed amebic encephalitis-associated hemorrhage in the left frontal posterior periventricular white matter
On post-mortem, both lungs diffusely necrotic with numerous *Acanthamoeba* cysts and trophozoites
Case report

Acanthamoeba infection in a patient with chronic graft-versus-host disease occurring during treatment with voriconazole


Abstract: We report a case of disseminated infection with Acanthamoeba in a patient with graft-versus-host disease after hematopoietic stem cell transplant (HSCT) for acute lymphocytic leukemia. The infection involved the brain, skin, and lungs and occurred despite treatment with voriconazole for mold prophylaxis, and did not respond to treatment with multiple other agents reported to have activity against Acanthamoeba. To our knowledge, infection with Acanthamoeba has been reported in 4 other patients after HSCT or bone marrow transplant, and our case is the first to be diagnosed ante-mortem.

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Key words: Acanthamoeba; pretseps; graft-versus-host disease; voriconazole

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58 year-old male

Recent cardiac symptoms resulting in cardiac catheterization and stent placement

Firm white sclerotic and telangiectatic plaque with ulceration

Clinical impression: Morphea vs. Lichen sclerosus

Your diagnosis?
Increasing incidence due to expanded use of diagnostic & therapeutic fluoroscopic invasive procedures

- Cardiac catheterization and/or stent placement
- Cardiac radiofrequency ablation
- Abdominal angiography and/or stent placement

Increased risk if procedure was prolonged or difficult and/or repeated exposure

Radiation dosage of ≥10 Gy

Most frequently involves axilla, scapula, & mid-back

Latency period after exposure ranges from days to years

Geometric, often rectangular, plaque with variable sclerosis, atrophy, ulceration and/or telangiectasia

Histology

- Acute, subacute, or chronic radiation dermatitis
- Acute – Interface change with basal vacuolar alteration and epidermal necrosis
- Chronic – Epidermal hyperplasia or atrophy
  Dermal sclerosis/hyalanization
  Decreased or absent adnexae
  Vascular ectasia
  Variable ulceration
  Stellate “radiation” fibroblasts
Fluoroscopy-Induced Radiation Dermatitis

H/O bowel-associated AVM and >15 abdominal angiograms
Key Points

- Increasing in incidence so be advised!
- Patients often unaware that they had ionizing radiation or forgot that they even had a procedure!
- Clinical and histologic differential diagnosis:
  - Fixed drug eruption (acute)
  - Lichen sclerosus, morphea (chronic)
- Geometric plaque, biopsy changes of radiation dermatitis, and appropriate history allow for diagnosis
51 year-old female
10 month of arthralgias and worsening painful lower leg lesions
ANA 1:160
P-ANCA positive, >1:320 titer
WBC 2.8 x 10⁹/L
Clinical impression: Vasculitis vs. thrombotic vasculopathy
Vasculitis....?

Thrombotic vasculopathy....?
PMHx: Recreational drug use in remote past

Vasculitis....?
Thrombotic vasculopathy....?

Repeat biopsy?
Additional lab studies?

KEEP IT SIMPLE
More Information
It all makes sense now........

Urine toxicology: Positive for Cocaine
**Diagnosis:** Levamisole Toxicity

(Vasculitis and Neutropenia Associated with Levamisole-Adulterated Cocaine)
Purpura of the ears: a distinctive vasculopathy with circulating autoantibodies complicating long-term treatment with levamisole in children


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Accepted for publication: 4 December 1998

- 5 children with pediatric nephrotic syndrome treated with adjuvant levamisole
- Sudden onset of purpuric necrotic plaques and hemorrhagic bullae with distinctive involvement of external ears (5/5)
- Histology – vasculopathic reaction ranging from leukocytoclastic vasculitis to occlusive thrombotic vasculopathy
- 4/5 patients developed circulating autoantibodies (ANA, lupus anticoagulant, pANCA and/or dsDNA)
- Cutaneous eruption resolved after discontinuation of levamisole
- Serum autoantibodies persisted for 2-14 months
Levamisole

- Anithelminthic and immunomodulatory agent
- Withdrawn from U.S. market in 2000 because serious side effects
- Key toxic effect – *agranulocytosis*
- Veterinary medicine – antihelminthic for livestock
- Increasingly used as cutting agent for cocaine
- Adds bulk and weight to cocaine
- Relatively undetectable when testing cocaine for purity
- Possible additive stimulant/psychoactive effect
- In 2011, DEA found it in *82%* seizures
- Potential public health epidemic
Durvet 698902 Levamed Soluble Drench Powder Dewormer, White, 52g
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Overshadowed by the Opioid Crisis: A Comeback by Cocaine

It’s the No. 2 killer among illicit drugs in the U.S. and kills more African-Americans than heroin does.

Anti-narcotic police in Peru dynamited a landing strip last month, saying it was used to ship cocaine.

In the United States, however, the war on drugs is focused on its own domestic front.
Cocaine use in Britain so high it has contaminated drinking water, report shows

Traces of illegal drug appear even after intensive treatment processes

Adam Withnall | @adamwithnall | Sunday 11 May 2014 10:37 | 74 comments
Levamisole Toxicity

- Secondary to use of adulterated *cocaine*
- Vasculopathy/vasculitis
  - Characteristic skin lesions
  - Purpuric necrosis of *ears/cheeks* pathognomonic
  - "Retiform purpura" on trunk/extremities
  - Skin biopsy – leukocytoclastic vasculitis, thrombotic vasculopathy, or combination
- Often other rheumatologic abnormalities
  - *pANCA* antibodies positive in majority
  - Lupus anticoagulant, ANA, MPO, Antiproteinase 3 (PR3)
- Bone marrow suppression
  - Neutropenia
  - Agranulocytosis

Levamisole Toxicity 2º Adulterated Cocaine

Muirhead TT, Eide MJ. N Engl J Med 2011; 364:e52
Levamisole Toxicity 2° Adulterated Cocaine

Retiform Purpura: Levamisole-adulterated Cocaine

Key Points

- Maintain high index of suspicion
- Purpuric necrosis of ears/cheeks and/or retiform purpura of trunk/extremities
- Serology suggesting connective tissue disease-associated vasculopathic process (pANCA, lupus anticoagulant, etc.)
- Vasculitis and/or thrombotic vasculopathy on biopsy
- Order urine toxicology to screen for cocaine use
- Potential for agranulocytosis
79 year-old female with history of CLL, “psoriasis,” and antecedent URI

3-week history of worsening skin eruption

Trunk, extremities, oral mucosa

Confluent, tender, dusky, erythematous to purpuric papules/plaques

Denudation and intact bullae

Transferred to our institution

Working diagnosis

- Stevens Johnson Syndrome
- R/O paraneoplastic pemphigus
**Diagnosis:** Dermal-epidermal separation with variable epidermal necrosis. Favor Stevens-Johnson syndrome.

**Comment:** Paraneoplastic pemphigus remains in the histologic differential diagnosis.
Direct Immunofluorescence

“Speckled” DIF Pattern
Lupus Erythematosus
Sjogren’s Syndrome
Mixed Connective Tissue Disease

Granular cytoplasmic IgG in keratinocytes
“Speckled” keratinocyte pattern
Ancillary Laboratory Tests
- ANA 1:2560, speckled pattern
- Anti-Ro (SSA) positive
- Anti-La (SSB) positive
- Rheumatoid factor positive

Better Diagnosis: Rowell Syndrome (Erythema Multiforme-like Lupus Erythematosus)
Major diagnostic criteria (all 3 needed)
- Any type of LE (SLE, SCLE, DLE)
- Erythema multiforme-like eruption
- Speckled ANA

Minor diagnostic criteria (1 needed)
- Chilblain-like lesions
- Anti-Ro or anti-La antibody
- Positive rheumatoid factor
Acute Syndrome of Apoptotic Pan-epidermolysis (ASAP)

- Umbrella term for acute and widespread epidermal cleavage 2° apoptotic injury (TEN, GVHD, TEN-like LE)
- Rowell syndrome and TEN-like ACLE along same continuum
- May occur *de novo* or within setting of rebound ACLE or SCLE
Clinical History

- 78 year-old man
- H/O idiopathic hypereosinophilic syndrome & multiple comorbidities (CHF, CAD, s/p CABG, DVTs)
- 2 year history of painful, progressive, crateriform plaque with ulceration on forearm
- Extensive purulent drainage past 3 months
Initially biopsied at outside hospital

Diagnosis: “Ulceration with underlying dense superficial and deep perivascular and interstitial lymphoid infiltrate rich in eosinophils”

Comment: “Findings could represent ulcerated hypersensitivity reaction or infection”

Referred to UM, repeat biopsy performed

Clinical DDX:
- Infection
- SCC
- Pyoderma gangrenosum
- ?Vasculopathic/infarctive
- Other neoplasia?
CD30

CD3 +, Beta F1+, CD8 +/-
CD2, CD7, CD56, ALK, EBER negative, CD4 -/+
Original biopsy

CD 68
**Impression**

- CD30 + lymphoma, cytotoxic phenotype, distinctly angiocentric
- Paraffin tissue blocks from both biopsies sent for T-cell receptor gamma (TRG) and beta (TRB) gene rearrangement studies
- Clonal rearrangements identified in both TRG and TRB
6 patients, 27-70 years old, with solitary necrotic lesions
3/6 located on upper extremity
Angiocentric and angiodestructive, CD30 and CD8 positive, lymphoid infiltrate of medium to large pleomorphic/anaplastic cells
2/6 TIA1 positive (cytotoxic phenotype)
4/6 conspicuous eosinophils
3/5 cases positive TCR-gamma gene rearrangement
5 patients treated with surgical excision; 1 with XRT
All alive with no evidence of disease at 31 months (median follow up)
Clinical Course

- Initial staging (PET-CT):
  - Metabolic evidence for active malignancy
  - Bilateral neck/axillary lymph nodes
  - Lungs, spleen
  - Soft tissues of left arm and right gluteus musculature
- Classified as ALK-negative anaplastic large cell lymphoma, Stage IVA
- Palliative XRT given to arm
- DOD 3 months after diagnosis
Systemic Anaplastic Large Cell Lymphoma

- Primarily involves lymph nodes and extranodal sites (60%)
- Skin #1 extranodal site (21%)
- ~60% ALK + and t(2;5)(p23;q35) (ALK-NPM1) translocation
- ALK + and ALK – cases different clinical presentations and response to treatment
- ALK-positive systemic ALCL
  - Age onset 30’s
  - Male predominant (3:1)
  - Better prognosis and response to treatment
ALK-negative systemic ALCL

- Minority of cases
- Older age of onset
- Male:female roughly equal (0.9:1)
- 30% with \textit{DUSP22} [t(6;7)(p25.3;q32.3)] rearrangement
  - \textit{DUSP22} – Phosphatase that inhibits T-cell antigen receptor signaling
    - Tumor suppressor
  - Better prognosis ≈ sALK+ ALCL
- Remaining 70% genetically heterogenous – worse prognosis with more aggressive behavior

\textit{Feldman AL, et al. Blood. 2011; 117(3); 915-919.}
Histologic features

- Large, pleomorphic cells with prominent nucleoli
- Variable numbers of “hallmark” cells – eccentric horseshoe or kidney-shaped nuclei
- Variable patterns – sheet-like, lymphohistiocytic, angiocentric

Immunophenotype

- By definition, CD30 positive (strong) and ALK negative
- T-cell markers typically positive [CD43, CD2, CD3, +/-CD5, usually CD4, rarely CD8]
- Cytotoxic markers (TIA-1, granzyme, +/- perforin) often +
- Rarely EMA + (usually associated with sALCL, ALK+)
Lymphoid Infiltrates with Angiocentrism/Angiodestruction

- Anaplastic large cell lymphoma (EBV-)
  - Primary cutaneous
  - Systemic
- Cutaneous gamma/delta T-cell lymphoma (EBV-)
- Lymphomatomatoid papulosis, type E (EBV-)
- Extranodal NK/T-cell lymphoma, nasal type (EBV+)
- Lymphomatomatoid granulomatosis (EBV+)
- Hydroa vacciniforme-like lymphoproliferative disease (EBV+)
- EBV+ mucocutaneous ulcer (EBV+)
Clinical History

- 1 day old, 36 weeks gestation, female infant
- Diffuse scaly rash present at birth
- No collodion membrane
- Apgar scores 7 and 8
- No history of consanguinity
- Remote maternal history of dwarfism
- Dermatology consult requested because of skin “rash”
Diffuse feather-like, yellow to white, hyperkeratotic scale

Linear, shiny, smooth, erythematous thin streaks dorsum foot, lower leg, and hands
Von Kossa
Skeletal Survey

- Stippling of humeral and femoral epiphyses
- Butterfly deformities of multiple thoracic vertebrae
- Deficient ossification in T10, T11, and L1 vertebrae
- Hypoplastic first metacarpals and great toe proximal phalanges

Your diagnosis?
Clinical Features

- Rare X-linked dominant disorder of cholesterol biosynthesis
- Mutation in *EBP* gene (*emopamil binding protein*)
- Clinical phenotype due to functional mosaicism of EBP gene
- Results in the accumulation of 8-dehydrocholesterol and other cholesterol precursors
- Cutaneous, skeletal, & ocular abnormalities
- Lifespan and congnitive function generally unaffected
Conradi-Hünermann-Happle Syndrome
(Chondrodysplasia Punctata 2)

Extra-Cutaneous Features

Skeletal findings
- Short stature
- Rhizomelic shortening of the limbs
- Hip dysplasia
- Joint contractures
- Scoliosis

Craniofacial defects
- Broad nasal bridge
- Hypertelorism
- Cranial asymmetry
- Frontal bossing
- High arched palate

Cataracts

Chondrodysplasia Punctata (Cdp)
Conradi-Hünermann-Happle Type (CdpX2). In: Ruggieri M, Pascual-Castroviejo I, Di Rocco C (eds)
Neurocutaneous Disorders Phakomatoses and Hamartoneoplastic Syndromes. Springer, Vienna

Conradi-Hünermann-Happle Syndrome (Chondrodysplasia Punctata 2)

**Cutaneous Findings**

- Congenital ichthyosiform erythroderma with feather-like hyperkeratotic scale – resolves in months
- Blashko-linear follicular atrophoderma
- Whorled hypopigmentation may develop later
Conradi-Hünermann-Happle Syndrome
(Chondrodysplasia Punctata 2)

**Ichthyosiform erythroderma H&E**
- Infundibular follicular plugging
- Intracorneal and infundibular calcification

**Chondrodysplasia Punctata**
- Epiphyseal stippling
- Deposits of amorphous calcified material

- Both present at birth
- Both regress

Congenital Ichthyoses/
Congenital Ichthyosiform Erythroderma
Nonbullous Congenital Ichthyosiform Erythroderma

Bullous Congenital Ichthyosiform Erythroderma

Netherton’s Syndrome
Trichorrhexis invaginata

Conradi-Hünermann-Happle Syndrome
Infundibular keratotic cysts with Ca++