Inflammatory skin disease every pathologist should know

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General Concepts

• Pattern recognition
  – Epidermal predominant vs. dermal predominant
    • Epidermal changes trump dermal changes
  – Distribution of the inflammatory infiltrate
    • Superficial vs. superficial and deep
    • Location: perivascular, interstitial, nodular
  – Nature of inflammatory infiltrate
    • Mononuclear (lymphocytes and histiocytes)
    • Mixed (mononuclear and granulocytes)
    • Granulocytic

• Correlation with clinical presentation

• Never diagnose “chronic nonspecific dermatitis”
Principle Patterns: Epidermal Changes Predominant

- Spongiotic pattern
- Psoriasiform pattern
  - Spongiotic and psoriasiform often co-exist
- Interface pattern
  - Basal vacuolization
    - Perivascular infiltrate
    - or
    - Lichenoid infiltrate
Principle Patterns: Dermal Changes Predominant

- Superficial perivascular
- Superficial and deep perivascular
- Interstitial pattern
  - Palisading granulomatous
  - Nodular and diffuse
- Sclerosing pattern

- Panniculitis
- Bullous disease
- Miscellaneous
Spongiotic Dermatitis

- Three phases
  - Acute
  - Subacute
  - Chronic

- Different but overlapping histologic features
Spongiotic Dermatitis

• Acute spongiotic dermatitis
  – Normal “basket-weave” stratum corneum
  – Pale keratinocytes
  – Spongiosis
  – Spongiotic vesicles (variable)
  – Papillary dermal edema
  – Variable superficial perivascular infiltrate of lymphocytes often with some eosinophils
  – Rarely biopsied in acute phase
Spongiotic Dermatitis

• Subacute spongiotic dermatitis
  – Parakeratosis often with serum (wet scale)
  – Diminished granular layer
  – Spongiosis
  – Acanthosis (overlap with psoriasiform pattern)
  – Variable superficial perivascular infiltrate of lymphocytes often with some eosinophils
  – Less edema
Spongiotic Dermatitis

• Chronic spongiotic dermatitis
  – Hyperkeratosis
  – Parakeratosis
  – Irregular granular layer
  – Acanthosis (overlap with psoriasiform)
  – Minimal to mild spongiosis
  – Variable perivascular infiltrate, often with eosinophils
  – Dermis may be fibrotic
Common Clinical Types of Spongiotic Dermatitis

• Eczema Dermatitis Family
  – Atopic dermatitis
  – Contact dermatitis
  – Nummular dermatitis
  – Dyshidrotic dermatitis (hand/foot dermatitis)
  – Id reaction (autoeczematization)
  – Eczematous drug eruption
Eczema

- Clinical term
- Histologically spongiotic dermatitis
- Specific diagnosis dependent on correlation with clinical presentation

- CLINICAL SUBTYPES ARE HISTOLOGICALLY INDISTINGUISHABLE
Allergic Contact Dermatitis

- **Clinical**
  - Erythematous papules, plaques and sometimes vesicles
  - May have linear pattern
  - Secondary to type IV delayed hypersensitivity reaction
  - Examples: nickel allergy, poison ivy

- **Microscopic**
  - Typical spongiotic dermatitis
  - May have Langerhans cell microabscesses
Nummular Dermatitis

• Common form of eczema that is biopsied
• Clinical
  – Pruritic round to oval patches and plaques
  – Often on extremities
• Microscopic
  – Psoriasiform and spongiotic
  – Can be classified as psoriasiform dermatitis
• Differential diagnosis
  – Psoriasis
Practical Tips for Eczematous Dermatitis

• Dx: “spongiotic dermatitis, see note”
• (Dx in cases with acanthosis: “spongiotic psoriasiform dermatitis, see note”)
• Note: “The histologic features are compatible with an eczematous dermatitis. The DDx could include..... Clinicopathologic correlation is recommended.”
• Tips
  – Eliminate where possible more specific entities
  – Neutrophils in stratum corneum or epidermis: exclude dermatophytosis or psoriasis
  – Clinical history can be helpful
  – Langerhans cell microabscess: suggest contact dermatitis
Stasis Dermatitis

• Clinical
  – Lower extremities associated with venous insufficiency
  – May develop ulcers

• Microscopic
  – Subacute to chronic spongiotic dermatitis
  – Variable acanthosis
  – Lobular proliferation of thick-walled dermal vessels
  – Extravasated erythrocytes, siderophages, perivascular lymphocytes
  – Variable dermal fibrosis
Initial presentation of stasis dermatitis mimicking solitary lesions: A previously unrecognized clinical scenario

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\begin{itemize}
  \item 37 cases of stasis dermatitis presenting as solitary lesion
  \item 33/37 no history of venous stasis
  \item 33\% mistaken for SCC; 24\% mistaken for BCC
\end{itemize}

Stasis Dermatitis

• Differential diagnosis
  – Eczematous dermatitis
  – Kaposi sarcoma (acroangiodermatitis)

• Tips
  – High index of suspicion
  – Vascular changes key feature
  – Sometimes clinically mimics neoplasm: consider deeper levels
  – Can have other form of eczematous dermatitis on stasis background (descriptive dx: spongiotic dermatitis and stasis change)
Psoriasis

Psoriasis vulgaris

- Clinical
  - Usually presents in 2nd-3rd decades
  - Erythematous plaques with silvery scale
  - Extensor surfaces, scalp, gluteal cleft, glans penis
  - Nail pitting and yellow discoloration
  - Arthritis 1-5%
Psoriasis Vulgaris

• Microscopic
  – Uniform acanthosis with elongated rete ridges
  – Absent (diminished) granular layer
  – Prominent parakeratosis (dry scale)
  – Neutrophils in stratum corneum (Munro’s microabscess) and/or epidermis (pustules of Kogoj)
  – Suprapapillary plate thinning
  – Dilated, tortuous papillary dermal vessels
  – No eosinophils
Partially treated psoriasis
Psoriasis Vulgaris

• Differential Diagnosis
  – Nummular dermatitis
    • Spongiosis, wet scale, often has eosinophils
  – Contact dermatitis
    • Spongiosis, wet scale, often has eosinophils,
      Langerhans cell microabscesses (+/-)
  – Dermatophytosis
  – Drug-induced psoriasis
Dermatophytosis

• Clinical
  – Annular scaly plaques with central clearing
  – Usually on trunk
Dermatophytosis

• Microscopic
  – Neutrophils in stratum corneum
  – Parakeratosis
  – Hyphae in stratum corneum (usually seen with PAS or GMS stain)
  – Acanthosis
  – Variable spongiosis
  – Superficial perivascular infiltrate often with some eosinophils
Dermatophytosis

• Tips:
  – Neutrophils may be absent in lesions treated with topical steroids
  – Always get PAS or GMS stains if clinical history is “rash not responsive to topical steroids”
  – Look for fungi adjacent to neutrophils
Drug-Induced Psoriasis

• Tumor necrosis factor-α (TNF-α) inhibitors can cause psoriasis-like rash
• Most commonly seen in patients with inflammatory bowel disease on TNF-α inhibitors
• Looks like psoriasis vulgaris except with eosinophils in the dermis
34-year-old woman with Crohn’s disease

Presented with erythematous plaques involving vulva

Clinical diagnosis: cutaneous Crohn’s disease
Psoriasis Vulgaris

• Practical tips
  – Eosinophils absent in psoriasis (except drug-induced; intravascular eosinophils don’t count)
  – Epidermal hyperplasia not always uniform
  – Impetiginization not seen
  – Some features may be absent in partially treated psoriasis
  – Descriptive dx: psoriasiform dermatitis
Guttate Psoriasis

- **Clinical**
  - Rapid onset
  - Widespread disease
  - Small scaly plaques
  - Antecedent streptococcal infection

- **Microscopic**
  - Minimal acanthosis
  - Diminished granular layer (variable)
  - Focal mounds of parakeratosis with neutrophils (sometimes neutrophils absent)

- **Differential Diagnosis**
  - Pityriasis rosea, dermatophyte infection
Guttate Psoriasis

- Practical tips
  - Clinical history
    - Rapid onset
    - Antecedent streptococcal infection 2/3
  - Neutrophils not always present
    - Descriptive diagnosis: Psoriasiform or spongiotic dermatitis, see note
    - Note: The mounds of parakeratosis suggest the possibilities of guttate psoriasis or pityriasis rosea
Lichen Simplex Chronicus and Prurigo Nodularis

• Clinical
  – Spectrum of same dermatologic disease
  – Secondary to persistent rubbing/scratching
  – Lichen simplex chronicus presents as pruritic indurated plaques
  – Prurigo nodularis presents as pruritic nodules
  – Lesions occur only where the skin can be reached: posterior scalp, ankle, shin, forearm, anterior thigh, genitalia
  – Can develop as a secondary change in underlying dermatitis
Lichen Simplex Chronicus and Prurigo Nodularis

• Microscopic:
  – Prominent compact hyperkeratosis
  – Variable parakeratosis
  – Thickened granular layer
  – Acanthosis, sometimes with pseudoepitheliomatosus pattern
  – Vertical fibrosis of papillary dermis
  – Mild perivascular lymphocytic infiltrate
  – Looks like acral skin (hairy palm sign)
Practical Tips

• Acral skin in non-acral location
• “Hairy palm” sign
• Clinical history: is it itchy?
• Descriptive diagnosis
  – Psoriasiform dermatitis with f/o LSC/PN
• May be superimposed on chronic spongiotic dermatitis
  – Spongiotic dermatitis with superimposed features of LSC
Lichen Planus

- Clinical
  - Pruritic violaceous, polygonal papules
  - Predilection for flexural surfaces of wrists and ankles
  - May be widespread
  - Oral: lace-like pattern
Lichen Planus

• Microscopic features
  – Hyperkeratosis without parakeratosis
  – Acanthosis with wedge-shaped hypergranulosis
  – Interface change with dense band-like lymphocytic infiltrate (rare eosinophils acceptable)
  – “Saw-tooth” rete pegs
  – Scattered dyskeratotic cells
Oral Lichen Planus

- Absent or subtle granular layer
- Parakeratosis
- Lichenoid infiltrate (sometimes less prominent)
- “Saw-toothing” not usually present
Lichen Planus

• Differential Diagnosis
  – Lichenoid benign keratosis
  – Lichenoid drug eruption
  – Lichenoid graft vs. host disease
  – Lupus erythematosus
  – Early lichen sclerosus
Lichenoid Benign Keratosis

- Solitary lesion
- Usually on trunk
- Middle-aged and older patients
- Clinically confused with basal cell carcinoma
- Looks like lichen planus or benign keratosis with lichenoid infiltrate
Lichenoid Drug Eruption

- Widespread violaceous papules
- May occur weeks to months after initiation of drug therapy
- May progress to exfoliative dermatitis
Lichenoid Drug Eruption

• Microscopic
  – Very similar to lichen planus
  – Occasional to frequent eosinophils
  – Often some parakeratosis

• Differential Diagnosis
  – Lichen planus, fixed drug eruption

• Practical tips
  – Look for eosinophils and parakeratosis
Lichen Sclerosis

- Early lesions:
  - Lichenoid infiltrate of lymphocytes and plasma cells with interface change
  - Psoriasiform epidermal hyperplasia may be present early
  - Basement membrane thickening may be present
  - Look for evidence of papillary dermal fibrosis
Lichen Sclerosus

- Established lesions
  - Homogenized or sclerotic papillary dermis
  - Scattered lymphocytes and plasma cells beneath altered collagen
  - Atrophic epidermis with compact hyperkeratosis and thickened granular layer
Practical Tips

• Rare eosinophils acceptable in lichen planus
  – If numerous think lichenoid drug reaction
• Parakeratosis typically absent in lichen planus
  – Exception: oral lichen planus
• Solitary lesions that look like lichen planus:
  lichenoid benign keratosis
• Looks like lichen planus on genital skin:
  – Lichenoid interface dermatitis, see comment
  – Comment: the differential diagnosis includes lichen planus vs. early lichen sclerosus
Erythema multiforme spectrum

- Erythema multiforme
  - Self-limiting episodic eruptions
  - Erythematous macules, papules and targetoid lesions
  - Extensor surfaces, palms, soles, and oral mucosa
  - Associated with HSV, Mycoplasma, and drugs (sulfonamides)

- Stevens-Johnson syndrome: mucosal involvement <10% body surface area
Clinical Features

• Toxic epidermal necrolysis (TEN)
  – Widespread tender macular erythematous eruption with vesicles and bullae >30% body surface area
  – Associated with drugs
  – Mortality 25-50%

• Stevens Johnson-TEN overlap: 10-30% body surface area
Erythema Multiforme/TEN

• Microscopic
  – Normal basket-weave stratum corneum
  – Spongiosis
  – Dyskeratotic cells at all levels of epidermis
  – Basal vacuolization
  – Mild superficial perivascular lymphohistiocytic infiltrate (sometimes eosinophils)
  – Exocytosis of lymphocytes
  – Epidermal necrosis (seen in older lesions)
    • More common in TEN
Differential Diagnosis

- Lupus erythematosus/dermatomyositis
  - More epidermal change
- Morbilliform drug eruption
  - Less epidermal damage
- Graft versus host disease
  - Clinical history
Practical Tips: EM and TEN

- Necrotic keratinocytes, normal stratum corneum
- Disproportionate epidermal damage for amount of inflammation
- Histologic distinction between EM and TEN requires clinical information
- SJS and TEN: medical emergency
- TEN clinical ddx: Staph scalded skin syndrome
Staph scalded skin syndrome
Lupus Erythematosus

• Clinical
  – Chronic (discoid)
    • Well-demarcated scaly plaques
    • Erythematous to hyper or hypopigmented
    • Usually on head/neck (sun-exposed skin)
    • Most patients with skin only disease
  – Subacute
    • Scaly erythematous, often annular plaques
    • Upper trunk, extensor surfaces of arms
    • Positive ANA 75%
Lupus Erythematosus

• Clinical
  – Acute
    • Associated with systemic lupus erythematosus
    • Erythematous lesions
    • Malar rash
    • Positive ANA and anti-DNA antibodies
Lupus Erythematosus

• Microscopic
  – Histologic overlap between subtypes
  – Basal vacuolization
  – Perivascular and periadnexal mononuclear cell infiltrate
  – Epidermal atrophy (often)
  – Thickened basement membrane (often)
  – Increased dermal mucin
  – Follicular plugging (often)
  – May have reactive squamous atypia (AK clue)
Lupus Erythematosus

- Differential diagnosis
  - Dermatomyositis
  - Lichen planus
  - Actinic keratosis
    - Reactive atypia versus dysplasia
    - Lacks dermal mucin, follicular plugging, deep inflammation
Dermatomyositis

- Clinical
  - Systemic disease with muscle weakness (some patients have only cutaneous disease)
  - Heliotrope periorbital discoloration
  - Violaceous rash on face and neck
  - Periungual erythema
  - Gottron’s papules on hands
Dermatomyositis

• Microscopic
  – Basal vacuolization
  – Superficial perivascular mononuclear cell infiltrate, usually mild
  – Increased dermal mucin

• Differential diagnosis
  – Lupus erythematosus
Practical Tips LE/DM

- Eosinophils absent
- Mucin helpful but non-specific
- LE may have superficial or superficial and deep perivascular patterns
- ‘AK’ clue: reactive atypia in keratinocytes
- DM generally does not have deep infiltrate
- DM cannot be distinguished from LE
- Descriptive Dx: interface dermatitis
  - Note: The ddx would include connective tissue disease such as lupus erythematosus.
Graft vs. Host Disease

• Clinical
  – Acute GVHD
    • Usually 2-4 weeks after bone marrow transplant
    • Late onset with lymphocyte reinfusion
    • Rarely solid organ transplants
    • Macular erythema on trunk, neck, hands, and feet
    • May form blisters
    • Systemic symptoms (e.g. diarrhea)
  – Chronic GVHD
    • Months to years after bone marrow transplant
    • Lichenoid: violaceous papules on extremities, palms, and soles
    • Sclerodermoid: presents as dermal sclerosis
Graft vs. Host Disease

- Microscopic
  - Acute GVHD
    - Grade 0: normal epidermis
    - Grade 1: Basal vacuolization, mild superficial perivascular lymphocytic infiltrate
    - Grade 2: Same as Grade 1 changes with dyskeratotic keratinocytes, satellite cell necrosis
    - Grade 3: Same as grade 2 but with cleft formation between dermis and epidermis
    - Grade 4: Same as Grade 3 but with complete separation of epidermis from dermis
Acute GVHD, grade II
Acute GVHD grade III
Lichenoid chronic GVHD
Sclerodermoid chronic GVHD
Practical Tips: Acute GVHD

- Rare to see GVHD earlier than 14 days
- May see late onset acute GVHD in some settings
- Eosinophils may be seen in GVHD
- Dx of drug eruption should be approached with caution
- Multiple levels may be needed
Dermal Hypersensitivity Reaction

- **Clinical:** Variable
  - Drug eruption
  - Urticaria
  - Arthropod bite reaction

- **Microscopic**
  - Superficial or superficial and deep perivascular infiltrate
  - Lymphocytes and some eosinophils, variable neutrophils
Morbilliform drug eruption

• Clinical
  – Blanchable, Symmetric, widespread macular or papular eruption

• Microscopic
  – Superficial perivascular infiltrate of lymphocytes and eosinophils
  – Mild vacuolar interface change sometimes present
Urticaria

• Clinical
  – Transient edematous pruritic plaques (hives)
  – Typically resolve in 24 hours

• Microscopic
  – Normal epidermis
  – Dermal edema
  – Superficial perivascular infiltrate of lymphocytes and eosinophils and sometimes a few neutrophils
  – Sometimes a deeper component present
Arthropod bite reaction

• Clinical
  – Solitary or grouped papules

• Microscopic
  – Superficial and deep infiltrate
  – Usually dense infiltrate
  – Lymphocytes and eosinophils
**Dermal hypersensitivity reaction**

- **Practical Tips:**
  - Descriptive dx: Dermal hypersensitivity reaction, see note
  - Note: The histologic features are consistent with a dermal hypersensitivity reaction such as a drug eruption. Clinicopathologic correlation is recommended.
  - Urticaria and drug eruption histologically indistinguishable but clinically different
  - If infiltrate is dense, consider arthropod bite reaction
Granuloma Annulare

• Clinical
  – Asymptomatic papules with annular configuration
  – Usually on extremities
Granuloma Annulare

• Microscopic
  – Most commonly involves upper and mid reticular dermis
  – Central zone of altered collagen fibers with associated dermal mucin surrounded by a palisade of histiocytes with some giant cells
  – Interstitial pattern common
  – Perivascular lymphocytic infiltrate with variable numbers of eosinophils
  – Neutrophils may be prominent early
  – Rarely may resemble sarcoidal granulomas
  – Rarely may be confined to the subcutis
Granuloma Annulare

• Differential Diagnosis
  – *Necrobiosis lipoidica*
  – *Rheumatoid nodule*
  – Granulomatous drug reaction
  – Sarcoidosis
  – Dermatofibroma
Practical Tips: Granuloma Annulare

- Palisade not always well developed
- Low power examination
- Altered collagen looks more ‘red’
- Interstitial pattern common
Necrobiosis Lipoidica

• Clinical
  – Yellow, indurated plaques on lower legs
  – Two-thirds of patients have underlying diabetes mellitus

• Microscopic
  – Affects entire dermis
  – Tiered arrangement of elongated zones of altered collagen (necrobiosis) separated by an interstitial infiltrate of histiocytes
  – Multinucleated histiocytes common
  – Aggregates of lymphocytes and plasma cells
Practical Tips

• Low power examination
• Tiers of altered collagen and histiocytes create layer cake or bacon look
• Plasma cells favor necrobiosis lipoidica over GA
• Most cases on legs
• Ambiguous cases
  • Dx: palisading granulomatous dermatitis
  • Note: what you favor
Rheumatoid Nodule
Rheumatoid Nodule

• Microscopic
  – Lesions are located in the deep dermis, subcutaneous fat or soft tissue
  – Central areas of acellular fibrin surrounded by histiocytes and giant cells in a palisaded pattern
  – Lymphocytes, plasma cells and eosinophils may be present
Erythema Nodosum

- Most common form of panniculitis (>80%)
- Acute onset of tender, erythematous nodules
- Shins most common site, often bilateral
- Subcutaneous hypersensitivity reaction
  - Idiopathic
  - Associated with infection (e.g. group A β-hemolytic streptococcus)
  - Drugs (e.g. sulfa drugs, oral contraceptives)
Erythema Nodosum

• Microscopic
  – Widened septae with edema, inflammation, and later fibrosis
  – Lymphocytes, histiocytes, eosinophils and some neutrophils
  – Small granulomas
  – Lobular inflammation at periphery of subcutaneous fat lobule
Erythema Nodosum

• Differential Diagnosis
  – Infection
  – Trauma
  – Erythema induratum
  – Lipodermatosclerosis
Nodular Vasculitis (Erythema Induratum)

- **Clinical**
  - Chronic, recurring tender nodules on lower legs, especially calves
  - Subcutaneous hypersensitivity
    - Subset: reaction to underlying infection with *M. tuberculosis*

- **Microscopic**
  - Acute vasculitis in septae affecting artery and/or veins
  - Adjacent lobular panniculitis with granulomas and fat necrosis
  - Septae may be widened in older lesions
Lipodermatosclerosis

• Clinical
  – Usually bilateral indurated plaques on medial aspects of lower legs
  – Associated with stasis changes secondary to venous insufficiency and obesity
Lipodermatosclerosis

- Microscopic
  - Widened septae
  - Membranocystic fat necrosis
    - Cystic cavities lined by a crenulated, hyaline membrane
  - Mild perivascular lymphocytic infiltrate
  - Overlying features of stasis change in dermis and epidermis
Panniculitis practical tips

• Look for predominant pattern at low power
• Most cases are erythema nodosum
• Absence of inflammation: think lipodermatosclerosis
Bonus Diagnosis: Chondrodermatitis Nodularis Helicis
Chondrodermatitis Nodularis Helicis (CNCH)

• Clinical
  – Older patients
  – Crusted to ulcerated lesion on helix
  – On “sleeping side”
  – Essentially a small pressure ulcer
  – Clinically mimics squamous cell carcinoma or basal cell carcinoma
CNCH

- Microscopic
  - Ulcer
  - Reactive epidermal hyperplasia
  - Fibrinoid degeneration of dermis
  - Proliferation of perichondrial fibroblasts
CNCH

• Tips
  – High index of suspicion from ear lesions
  – Fibrinoid change
  – Absence of atypia
Bonus Diagnosis: Rosacea

• Clinical features
  – Predominantly involves central face
  – Erythema, telangiectasia early
  – Acneiform lesions, pustules, papules later
  – Can mimic basal cell carcinoma

• Microscopic features
  – Perivascular and perifollicular infiltrate
  – Lymphocytes, histiocytes, sometimes granulomas
Rosacea Practical Tips

- If BCC suspected clinically, get deeper levels
- Diagnosis: Perivascular and perifollicular lymphohistiocytic infiltrate, see comment
- Comment: The histologic features are consistent with rosacea in the right clinical context. CPC recommended.