Inflammatory dermatopathology is probably the most difficult part of my job as a dermatopathologist.

I have no relevant financial disclosures.
Pathologists often get very limited clinical information
"We believe patient care can be rapidly and significantly improved by providing accurate history and physical examination findings, relevant clinical images, and a clinical differential diagnosis."

Common inflammatory patterns

- Spongiotic
- Interface
- Urticarial
- Panniculitis
- Immunobullous
- Vasculitis
- Psoriasiform
- Granulomatous

Inflammatory patterns – they aren’t specific

Although most cutaneous eruptions can be categorized into one of several inflammatory patterns, more specific diagnosis is only possible with careful clinical-histologic correlation.
Objectives

- Understand that:
  - There are hundreds of inflammatory skin disorders.
  - Gross/c clinical examination of the skin predicts histologic features.
  - Histology is a critical component in diagnosis of inflammatory disorders.
  - Clinician must provide an appropriate biopsy.
  - Clinical correlation is essential to narrowing the differential.
- Review four common inflammatory patterns.
- Provide a few tips on findings that can point to a specific diagnosis.

Flinner Conference – The importance of the gross examination

- Neoplastic liver disease
- Blistering skin disease

Proper diagnosis of inflammatory skin disease

- Gross / clinical examination findings are important.
- Clinician must recognize the part(s) of the skin involved.
Inflammatory Dermatoses

- Inflammatory processes can affect any part of the skin
- The level of inflammation within the skin or appendage involved has a clinical correlate:

<table>
<thead>
<tr>
<th>Level of skin</th>
<th>Example</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermis</td>
<td>Eczema</td>
<td>Redness, scale, itchy</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Vasculitis</td>
<td>Purpura</td>
</tr>
<tr>
<td>Dermis</td>
<td>Hives, urticaria</td>
<td>Welts, not scaly, itchy</td>
</tr>
<tr>
<td>Follicles</td>
<td>Folliculitis</td>
<td>Pustules</td>
</tr>
<tr>
<td>Fat</td>
<td>Panniculitis</td>
<td>Inflammatory nodules</td>
</tr>
</tbody>
</table>

Proper diagnosis of inflammatory skin disease

- Clinician must recognize the part(s) of the skin involved
- Appropriate biopsy to examine the area of inflammation:
  - Punch into the subcutaneous adipose tissue probably best
  - Shave biopsy ok for superficial inflammatory processes, not for panniculitis
Proper diagnosis of inflammatory skin disease

• Clinician must recognize the part(s) of the skin involved
• Appropriate biopsy to examine the area of inflammation:
  • Punch biopsy into the subcutaneous adipose tissue probably best
  • Shave biopsy ok for superficial inflammatory processes, not for panniculitis
• Sampling an appropriate lesion for histopathology:
  • New lesion if possible
  • Not traumatized – secondary changes of scratching can mask pathology
  • Not treated – topical corticosteroids can mask pathology

Dermatopathologist relies on . . .

• Clinical information provided on the requisition
• Relationship with the submitting provider
• Chart review
• Photography
• Collaboration with other dermatopathologists for challenging cases
• Medical literature
Dermatopathology Consensus Conference

Inflammatory Patterns – University of Utah Dermpath

- Spongiotic
- Interface (lichenoid, vacuolar)
- Urticarial/Hypersensitivity
- Combination (spongiotic, interface)
- Immunobullous
- Vasculitis
- Panniculitis
Inflammatory Patterns – University of Utah Dermpath

- Spongiotic
- Interface (lichenoid, vascular)
- Urticarial/hypersensitivity
- Combination (spongiotic, interface)
- Immunobullous
- Vasculitis
- Panniculitis

What Part of the Skin is Involved?
Spongiotic reaction pattern

- Defined by intercellular edema:
  - Increased space between keratinocytes
  - ‘Stretching’ of desmosomal connections between keratinocytes
- Langerhans cell microgranulomas
- Lymphocyte exocytosis
- Parakeratosis variable, acute vs. chronic

Smith EW, Chan MP. Clin Lab Med 2017;37:673-96

Basket weave stratum corneum and epidermal spongiosis
Spongiosis = intercellular edema, desmosomes visible

Spongiotic reaction pattern – eczematous eruptions

- Atopic dermatitis
- Nummular dermatitis
- Contact dermatitis
- Id reaction
- Eczematous drug eruption
- Seborrheic dermatitis
**Eczema**

Red/weepy, red/scaly areas on skin

**Contact dermatitis**

Rubber allergy

Well-demarcated, scaling plaques

Adhesive allergy

Clue: Langerhans cell microabscess

**Nummular dermatitis**

Nummular, resembling a coin or coins

Erythematous, scaling papules coalesce into nummular plaque
Id reaction

- Autoeczematization
- Widespread, quick dissemination of a previously localized eczematous process
- Changes mimic the initial lesion, often blunted

Vesicular contact dermatitis

Few days later

Requires several weeks of systemic corticosteroids to stop reaction

Diagnosis

SPONGIOTIC DERMATITIS WITH EOSINOPHILS (SEE COMMENT)

Comment: The overall pattern is that of dermatitis and eczema, including atopic dermatitis, contact dermatitis, nummular dermatitis, spongiotic drug reaction, or id reaction.

Clinical correlation is necessary.

Widespread itchy rash, 80 year old woman

Papules coalescing into plaques on trunk

Some with scale
The histologic differential should include which of the following?

1. Contact dermatitis
2. Drug reaction
3. Arthropod assault reaction
4. Autoimmune bullous dermatosis
5. All of the above
Eosinophilic spongiosis: A clinical, histologic, and immunopathologic study
Edward Ruiz, MD; Jeu-Shyong Deng, MD; and Edward A. Abell, MR, MRCP
Pittsburgh, Pennsylvania

- Autoimmune bullous disorders:
  - Bullous pemphigoid
  - Pemphigus
- Contact dermatitis
- Arthropod assault reaction and scabies
- Drug reactions

12 of 15 patients had spongiotic dermatitis

Immunofluorescence studies may be indicated if an autoimmune blistering disorder is a clinical possibility.

**EOSINOPHILIC SPONGIOSIS (SEE COMMENT)**

Comment: Eosinophilic spongiosis may be associated with contact dermatitis, autoimmune blistering diseases (pemphigoid or pemphigus), drug reactions, or arthropod assault reactions.

Immunofluorescence studies may be indicated if an autoimmune blistering disorder is a clinical possibility.
What Part of the Skin is Involved?

- Dermoepidermal junction: Lichenoid interface

Lichenoid Interface Reaction Pattern

- Subdivided into:
  - Lichenoid interface dermatitis: band-like lymphocytic infiltrate
  - Vacuolar interface dermatitis: sparse lymphocytes tagging the dermal-epidermal junction
- Both are characterized by lymphocyte-mediated destruction of the basal layer
- Destruction of the basal layer results in melanin incontinence

Lichenoid

- Lichen planus
- Lichenoid drug reaction
- Benign lichenoid keratosis
- Secondary syphilis

Vacuolar

- Erythema multiforme
- Viral exanthem
- Lupus erythematosus
- Dermatomyositis
- Interface drug reaction
Lichenoid Reaction

Lichen

A simple slow-growing plant that typically forms a low, crustlike, leaflike, or branching growth on rocks, walls, and trees.

Inflammation hugging the dermoepidermal junction - lichenoid

Large, hypereosinophilic keratinocytes

Inflammation obscures dermoepidermal junction

Infiltrate mostly lymphocytes

Apoptotic keratinocyte

Dyskeratotic keratinocyte

Civatte body

Eosinophilic globules at the dermoepidermal junction
Lichenoid interface reaction pattern

- Lichen planus
- Lichenoid drug reaction
- Benign lichenoid keratosis
- Secondary syphilis

Myth

A dermatopathologist doesn’t need history to make a diagnosis.
Diagnosis

**LICHENOID DERMATITIS (SEE COMMENT)**

Comment: If the lesion is solitary and of several months duration, this most likely represents a lichenoid keratosis. If multiple lesions are present, lichen planus or a lichenoid drug reaction would be in the differential diagnosis.

Clinical correlation is necessary.

**Important Point!**

Although most cutaneous eruptions can be categorized into one of several inflammatory patterns, more specific diagnosis is only possible with careful clinical-histologic correlation.

Recent Challenging Clinicopathologic Correlation
72 yo female with history of squamous cell carcinoma of the lower leg, recurrent x 2
Band like, lichenoid inflammation and occasional dyskeratotic keratinocytes

Diagnosis so far...

Epidermal hyperplasia and lichenoid tissue reaction, possible hypertrophic lichen planus

* Is this person known to have lichen planus?
* Could you send a clinical image of the lesion?
* May we review the previous biopsies?

Right lower leg

Large eroded plaque with velvety surface and yellow crust
Original Biopsy – two years prior

Shave biopsy, lower leg

[Image of histological sections showing lobules of epithelium invading the underlying dermis]
Keratinocytes are malignant appearing, poorly organized, and some are dividing.

Diagnosis – biopsy two years prior

Invasive squamous cell carcinoma

Treatment:
- Curettage
- Recurred, not biopsied
- Curettage
- Recurred
- Current biopsy

Back to Current Case . . .
At follow-up, she was noted to have several itchy purplish papules
Diagnosis

Lichen planus

Flat-topped polygonal papules

Hypertrophic variant

Our patient had both patterns

Lichen Planus

• Cause unknown, some cases associated with hepatitis C
• Treatment topical corticosteroids, avoid injuring skin
• Skin injury (like surgery or biopsy) can cause outbreak of lichen planus – koebnerization

Koebnerization:
A process in which injury to the skin causes further formation of lichen planus

Hypertrophic lichen planus

• Lichen planus variant usually presenting on the shins
• Multiple erythematous to violaceous nodules or plaques
• Epidermal hyperplasia can be difficult to distinguish from SCC
• Complicating things – SCC can develop in setting of HLP

Smith EH, Chan MP. Clin Lab Med 2017;37:673-96
Helpful tips to diagnose hypertrophic LP

- Concentration of lymphocytes at tips of bulbous rete

Diagnosis of multiple SCCs/KAs on the legs should at least raise suspicion of HLP

Use of proliferation rate, p53 staining and perforating elastic fibers in distinguishing keratoacanthoma from hypertrophic lichen planus: a pilot study

- Proliferation index similar between KA and hypertrophic LP
- p53 staining increased in KA > HLP (p = 0.024), but present in both
- Perforating elastic fibers seen in KA > HLP (p < 0.0001)

J Cutan Pathol 2012;39:243-50
After 3 weeks topical steroid

Lesion thinner

Lichenoid Interface Reaction Pattern

Lichenoid
- Lichen planus
- Lichenoid drug reaction
- Benign lichenoid keratosis
- Secondary syphilis

Vacuolar
- Erythema multiforme
- Viral exanthem
- Lupus erythematosus
- Dermatomyositis
- Interface drug reaction
Vacuolar Interface Reaction Pattern

Vacuoles along the junction
Civatte body
Basketweave stratum corneum

Erythema Multiforme

• Usually seen in young adults, 2nd – 4th decade
• Males more often affected
• Eruption:
  • Asymptomatic
  • Erythematous, discrete macules, papules
  • Sometimes vesicles and bullae
  • Symmetrical distribution extremities, face, neck
• Most common cause - infectious agents, drugs
• Stevens-Johnson syndrome, toxic epidermal necrolysis with overlapping histology

Partial to full-thickness keratinocyte necrosis
Erythema multiforme  
Stevens-Johnson Syndrome  
Toxic epidermal necrolysis  
SJS-TEN Overlap  
< 10% epidermal detachment  
> 30% epidermal detachment

**Diagnosis**

**VACUOLAR INTERFACE DERMATITIS (SEE COMMENT)**

Comment: This histologic spectrum includes erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Clinicopathologic correlation is necessary.
Connective tissue diseases

- Lupus erythematosus, dermatomyositis
- Share vacuolar interface changes
- Varying degrees of dermal inflammation
- Dermal mucin
- Dermatomyositis and lupus erythematosus are variations on the same histologic spectrum

Lupus erythematosus

- Several clinical variants
- Skin may be only organ involved
- Type I inflammatory environment
- Accumulation of apoptotic cells, worsened by UV, leads to release of endogenous nucleic acids (eNA)
- eNA may play role in cutaneous LE inflammation

Discoid LE

Subacute cutaneous LE

Systemic LE

Front Immunol 2016:7:35
Vacuolar interface changes involving epidermis and follicular epithelium

Stainable tissue mucin in the reticular dermis

Dermatomyositis

• Autoimmune disease affects skin and muscles
• Associated with increased risk of malignancy
• Complications include calcification

Gottron's papules

Poikiloderma, chest

Violaceous erythema of eyelids - heliotrope

Gottron's papules

Mild epidermal acanthosis

Superficial and deep perivascular and periadnexal lymphocytic inflammation

AXR epidermal acanthosis
Findings can be quite subtle in dermatomyositis!

Similar changes can be seen in drug reactions or viral exanthem.

Diagnosis

VACUOLAR INTERFACE DERMATITIS (SEE COMMENT)

Comment: The histologic differential diagnosis includes a connective tissue disorder such as dermatomyositis or lupus erythematosus, or an interface drug reaction or viral exanthem.
Case 2 – tender scalp plaque

- Epidermal erosion and inflammatory crust
- Superficial and deep perivascular and peribulbar lymphocytic inflammation
- Low magnification Lupus
- Vacuolar interface changes
- Rare Civatte body
Scalp with tender erythematous plaque composed of coalescing papulovesicles, some crusted.

60 year old man.
Diagnosis?

1. Lupus erythematosus
2. Interface drug reaction
3. Herpes zoster
4. Dermatomyositis
5. Syphilis

**Important Point!**

*Necrotic pilosebaceous units are a clue to herpesvirus infection*
Perifollicular lymphocytic inflammation

Necrosis of follicular epithelium

Vacuolar interface changes

Herpes zoster

Pitfall! – something else to consider with lupus-like histology....
Late latent mucous syphilis mimicking connective tissue disease
Silvia P. Gottlieb, MD | Yukiko S. Schoening, MD | Kelleigh S. Culpepper, MD

Flesh colored papules and nodules
Vacuolar interface, superficial and deep inflammation, mucin
J Cutan Pathol 2017;44:578-81

What Part of the Skin is Involved?

Dermis - Urticaria (Hives, Wheals)

Edematous papules and plaques without surface changes
Relatively unremarkable low magnification

Normal epidermis

Sparse perivascular inflammation

Intraluminal neutrophilic diapedesis
Rare perivascular eosinophils

Diagnosis

**URTICARIAL HYPERSENSITIVITY REACTION (SEE COMMENT)**

Comment: The features are compatible with urticaria, urticarial vasculitis, or an urticarial drug eruption.
Case 3 – punch biopsy from the lower leg

Superficial and deep perivascular and panniculitis inflammation

Canyon Overlook, Zion National Park
Basketweave stratum corneum
Slight of spongiosis
Epidermal dermal edema
Perivascular and interstitial inflammation
Papillary dermal edema
Intraluminal neutrophilic diapedesis
Lymphocytes and lots of eosinophils
Numerous eosinophils in the subcutaneous adipose tissue
Case 3

18 year old female with pruritic, scattered and grouped erythematous papules on extremities

Diagnosis?

1. Urticaria
2. Acute urticaria drug reaction
3. Acute urticaria vasculitis
4. Arthropod urticaria reaction
5. Acute urticaria phase of bullous pemphigoid
Important Point!

Subcutaneous eosinophils are a clue to arthropod assault reaction

Diagnosis

**CONSISTENT WITH ARTHROPOD ASSAULT REACTION (SEE COMMENT)**

Comment: The differential diagnosis could include a drug reaction but that is favored less than an arthropod assault. Neither scabetic mite parts nor products are identified within the stratum corneum.

- Clinical and histologic features mimic arthropod assault, refractory to standard therapies – impaired quality of life
- Most in B-cell neoplasms:
  - Chronic lymphocytic leukemia (most common)
  - Mantle-cell lymphoma
  - Large-cell lymphomas
- May precede the diagnosis of the hematologic disorder
- No seasonal occurrence pattern
- T-cell infiltrate with eosinophils – ‘T-cell papulosis associated with B-cell malignancy’

Arch Dermatol 1999;135:1503-7; J Cutan Pathol 2018 epub ahead of print
Case 4 – punch biopsy from the trunk

- Subtle epidermal changes
- Sparse perivascular inflammation
35 year old female with pruritic erythematous macules and papules on trunk and extremities.

**Exanthematous drug reaction**

- Morbilliform or maculopapular
- Most common type of drug reaction, ~40% of all reactions
- Almost any drug can cause this pattern, usually 2–3 week after drug is first given

Small foci of spongiosis
- Vacular change
- Rare dyskeratotic keratinocytes

Important Point!

Combinations of inflammatory patterns suggests a drug eruption

**Diagnosis**

**Spongiotic and Interface Dermatitis with Eosinophils (See Comment)**

Comment: The combination of spongiotic and interface changes with eosinophils suggests a drug reaction.
Conclusions

• There are many skin rashes

• Important things to a dermatopathologist:
  • Relationship with healthcare provider
  • Clinical information
  • Photographs
  • Colleagues

• We reviewed four common inflammatory patterns – spongiotic, lichenoid, urticarial, and combination

Summary

<table>
<thead>
<tr>
<th>Image</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="spongiotic-spongiosis.png" alt="Image" /></td>
<td>Spongiotic spongiosis: An autoimmune blistering disorders, dermatitis, drug reaction, arthropod assault reaction</td>
</tr>
<tr>
<td><img src="lichenoid-lichen-planus.png" alt="Image" /></td>
<td>Lichenoid lichen planus: Symptomatic concentrated tips of bulbous rete, mimics squamous cell carcinoma</td>
</tr>
<tr>
<td><img src="urticarial-urticaria.png" alt="Image" /></td>
<td>Urticarial urticaria: Eosinophilic spongiosis, but necrotic pilosebaceous units are a clue to diagnosis</td>
</tr>
<tr>
<td><img src="combination-combination.png" alt="Image" /></td>
<td>Combination: Arthropod assault reaction, eosinophils in the fat is a clue to diagnosis, remember bite-like reaction in patients with hematologic malignancy</td>
</tr>
<tr>
<td><img src="interface-interface.png" alt="Image" /></td>
<td>Interface: Spongiotic and interface dermatitis: Combination of inflammatory patterns is a clue to a drug reaction</td>
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