Selected Cases in Inflammatory Dermatopathology

Scott R. Florell, M.D.
Professor, Dermatology
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I have no relevant financial disclosures
Inflammatory dermatopathology is probably the most difficult part of my job as a dermatopathologist.
Rashes
"Mrs. Nortman just sent in this fax of a rash that she's got on her stomach."
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

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

Robert Flinner, MD
1930 – 2009
‘Yoda’
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>
Epidermal

Dermal

Folliculitis

Vasculitis - purpura

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 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
Dr. Anneli Bowen correlating clinical images and chart review with pathologic findings
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, vacuolar)
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- Immunobullous
- Vasculitis
- Panniculitis
What Part of the Skin is Involved?

Epidermis
Spongiotic pattern
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 EH, Chan MP. *Clin Lab Med* 2017;37:673-96
Basketweave stratum corneum and epidermal spongiosis
Spongiosis = intercellular edema
Desmosomes visible

Langerhans cell microgranuloma
Numerous eosinophils
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

Well-demarcated, scaling plaques

Clue: Langerhans cell microabscess

Rubber allergy

Adhesive allergy
Nummular dermatitis

Erythematous, scaling papules coalesce into nummular plaque

Nummular
ˈnəmyələr/
adjective
1. resembling a coin or coins.
Id reaction

Vesicular contact dermatitis

Few days later

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

Requires several weeks of systemic corticosteroids to stop reaction
Diagnosis

<table>
<thead>
<tr>
<th>SPONGIOTIC DERMATITIS WITH EOSINOPHILS (SEE COMMENT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment: The overall pattern is that of dermatitis and eczema, including atopic dermatitis, contact dermatitis, nummular dermatitis, spongiotic drug reaction, or id reaction.</td>
</tr>
<tr>
<td>Clinical correlation is necessary.</td>
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</table>
Widespread itchy rash, 80 year old woman

Papules coalescing into plaques on trunk

Some with scale
Serum crust
Spongiosis
Eosinophilic spongiosis
Eosinophils along junction
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
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,a Jau-Shyong Deng, MD,a,b and Edward A. Abell, MB, MRCP
Pittsburgh, Pennsylvania

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

Case Report/Case Series
Bullous Pemphigoid as Pruritus in the Elderly
A Common Presentation
Christiaan V. Bakker, MD; Jorrit B. Terra, MD; Hendri H. Pas, PhD; Marcel F. Jonkman, MD, PhD

12 of 15 patients had spongiotic dermatitis

JAMA Derm 2013

Diagnosis

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 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
Lichenoid Reaction

lichen
ˈlīkən/
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 dermal-epidermal junction

Infiltrate mostly lymphocytes
Apoptotic keratinocyte
Dyskeratotic keratinocyte
Civatte body

Eosinophilic globules at the dermal-epidermal 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.
Solitary red papule several months duration? skin cancer

Multiple polygonal papules with a white, net-like scale, pruritic

Scaling papules/plaques, trunk, extremities, palms, soles

Benign lichenoid keratosis

Lichenoid reaction

Lichen planus

Secondary syphilis
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.
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
Papillated epidermal hyperplasia

Bulbous rete ridges, inflammation concentrated there

Band-like inflammatory infiltrate
Well-differentiated keratinocytes
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
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

Original biopsy site

Current biopsy
Back to Current Case . . .

![Image of skin lesion]

![Histological image]
At follow-up, she was noted to have several itchy purplish papules
Diagnosis

Lichen planus

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

Eosinophils!

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

**Background:** Distinguishing keratoacanthoma (KA) and hypertrophic lichen planus (LP) histopathologically can be difficult, and the challenge is compounded by the tendency of KA to arise in association with hypertrophic LP.

- 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
Hypertrophic lichen planus

Keratoacanthoma

Transepidermal elimination of elastic fibers
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

Basketweave stratum corneum

Civatte body

Vacuoles along the junction

Sparse lymphocytic infiltrate
Erythema Multiforme

• Usually seen in young adults, 2\textsuperscript{nd} – 4\textsuperscript{th} 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

< 10% epidermal detachment

SJS-TEN Overlap

> 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.
• 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

Subacute cutaneous LE

Discoid LE

Systemic LE

*Front Immunol* 2016;7:35
Superficial and deep perivascular and perianexial inflammation

Follicular plugging
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

Violaceous erythema of eyelids - heliotrope

Poikiloderma, chest
Superficial and deep perivascular and periadnexal lymphocytic inflammation
Mild epidermal acanthosis
Subtle vacuolar interface changes

Mild keratinocyte enlargement and hypereosinophilia

Rare Civatte bodies

Findings can be quite subtle in dermatomyositis!

Similar changes can be seen in drug reaction 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.
Venus Transit, June 6, 2012
Case 2 – tender scalp plaque
Epidermal erosion and inflammatory crust

Superficial and deep perivascular and perianarial lymphocytic inflammation

Low magnification "lupus"
Necrotic pilosebaceous units
Peripheral marginization of chromatin
Scalp with tender erythematous plaque composed of coalescing papulovesicles, some crusted
Diagnosis?

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

1. Lupus erythematosus
2. Interface drug reaction
3. *Herpes zoster*
4. Dermatomyositis
5. Syphilis
Necrotic pilosebaceous units are a clue to herpesvirus infection
Folliculocentric Herpes: A Clinicopathological Study of 28 Patients

A. Neil Crowson, MD,* Jad Saab, MD,† and Cynthia M. Magro, MD‡

FIGURE 1. Dense lymphocytic infiltrate is found in close apposition to the hair follicles and blood vessels [A, hematoxylin and eosin (H&E), ×4]. The outer root sheath epithelium is necrotic (B, H&E, ×20) and there is a concomitant interfollicular interface dermatitis (C, H&E, ×40). The overall morphology would raise diagnostic consideration of discoid lupus erythematosus.

Perifollicular lymphocytic inflammation
Necrosis of follicular epithelium
Vacuolar interface changes
Herpes zoster
Pitfall! – something else to consider with lupus-like histology....
Late latent mucinous syphilis mimicking connective tissue disease

Silvija P. Gottesman | Yuliya S. Schoenling | Kelleigh S. Culpepper

J Cutan Pathol 2017;44:578-81

Flesh colored papules and nodules

Vacuolar interface, superficial and deep inflammation, mucin

FIGURE 5 Immunohistochemistry for Treponema pallidum highlights a single spirochete in the vicinity of a dermal capillary (T.pal IHC, ×600)
What Part of the Skin is Involved?

Dermis
Urticaria
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
Urticarial Hypersensitivity Reaction

- Urticaria
- Urticarial drug reaction
- Urticarial vasculitis
- Arthropod assault reaction
- Urticarial phase of bullous pemphigoid
Diagnosis

URTICARIAL HYPERSENSITIVITY REACTION (SEE COMMENT)

Comment: The features are compatible with urticaria, urticarial vasculitis, or an urticarial drug eruption.
Canyon Overlook, Zion National Park
Case 3 – punch biopsy from the lower leg
Superficial and deep perivascular and pannicular inflammation
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. Urticarial drug reaction
3. Urticarial vasculitis
4. Arthropod assault reaction
5. Urticarial phase of bullous pemphigoid
Diagnosis?

1. Urticaria
2. Urticarial drug reaction
3. Urticarial vasculitis
4. *Arthropod assault reaction*
5. Urticarial phase of bullous pemphigoid
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’
Annular Lunar Eclipse, June 2012
Case 4 – punch biopsy from the trunk
Subtle epidermal changes

Sparse perivascular inflammation
Spongiosis
Vacuolar interface change
Civatte bodies and lymphocyte exocytosis
Eosinophil
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 weeks after drug is first given

• Small foci of spongiosis
• Vacuolar change
• Rare dyskeratotic keratinocytes

MORBILLIFORM ERUPTIONS CAUSED BY PENICILLIN
A STUDY BY ELECTRON MICROSCOPY AND IMMUNOLOGIC TESTS*
MICHAEL J. FELDNER, M.D. AND LAWRENCE PRUTKIN, PH.D.

J Invest Dermatol 1970
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
Autoimmune blistering disorders, dermatitis, drug reaction, arthropod assault reaction

Eosinophilic spongiosis

Hypertrophic lichen planus
Lymphocytes concentrated at tips of bulbous rete, can mimic squamous cell carcinoma

Herpes zoster
Pathology may resemble lupus erythematosus, but necrotic pilosebaceous units are a clue to diagnosis

Arthropod assault reaction
Eosinophils in the fat is a clue to diagnosis, remember bite-like reaction in patients with hematologic malignancy

Spongiotic and interface dermatitis
Combinations of inflammatory patterns is a clue to a drug reaction