### Selected Cases in Inflammatory Dermatopathology

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### I have no relevant financial disclosures



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





"Mrs. Nortman just sent in this fax of a rash that she's got on her stomach."

### Garbage in, garbage out!



Ronald M Harris MD, MBA

#### Pathologists often get very limited clinical information

### The Uninformed Dermatopathologist: An Occult Epidemic

"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."



Keith L Duffy MD



Anneli R Bowen MD



Scott R Florell MD

### Common inflammatory patterns



### 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/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







Robert Flinner, MD 1930 – 2009 'Yoda'

#### 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:

Level of skin	Example	Clinical
<ul> <li>Epidermis</li> </ul>	Eczema	Redness, scale, itchy
<ul> <li>Blood vessels</li> </ul>	Vasculitis	Purpura
<ul> <li>Dermis</li> </ul>	Hives, urticaria	Welts, not scaly, itchy
<ul> <li>Follicles</li> </ul>	Folliculitis	Pustules
• Fat	Panniculitis	Inflammatory nodules



#### 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



#### Inflammatory Patterns – University of Utah Dermpath





### 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





Basketweave stratum corneum and epidermal spongiosis







### Spongiotic reaction pattern – eczematous eruptions

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









Red/weepy, red/scaly areas on skin

### Contact dermatitis

#### Adhesive allergy



Clue: Langerhans cell microabscess

### Nummular dermatitis

Erythematous, scaling papules coalesce into nummular plaque

num·mu·lar 'nəmyələr/ adjective 1.resembling a coin or coins.





### Id reaction

Vesicular contact dermatitis





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

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




# 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?

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# Eosinophilic spongiosis: A clinical, histologic, and immunopathologic study

Edward Ruiz, MD,<sup>a</sup> Jau-Shyong Deng, MD,<sup>a,b</sup> 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 JAMA Derm 2013 12 of 15 patients had spongiotic dermatitis



#### **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?



## Lichenoid Interface Reaction Pattern

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











#### Lichenoid Reaction





Inflammation hugging the dermoepidermal junction - lichenoid

#### li∙chen

ˈlīkən/

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



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.





#### 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

#### Right lower leg, punch biopsy



#### 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







Keratinocytes are malignant appearing, poorly organized, and some are dividing

## Diagnosis – biopsy two years prior

#### Invasive squamous cell carcinoma



## Back to Current Case . . .





#### At follow-up, she was noted to have several itchy purplish papules









Flat-topped polygonal papules

## Diagnosis



## Lichen planus



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


# Helpful tips to diagnose hypertrophic LP



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.

Anneli R. Bowen, Lindsay Burt, Kenneth Boucher, Payam Tristani-Firouzi and Scott R. Florell

- 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)

## Hypertrophic lichen planus

## Keratoacanthoma



H&E

Transepidermal elimination of elastic fibers

# After 3 weeks topical steroid





Lesion thinner









## Vacuolar Interface Reaction Pattern



# Erythema Multiforme



Herpes labialis

- Usually seen in young adults, 2<sup>nd</sup> 4<sup>th</sup> 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



SJS-TEN Overlap

< 10% epidermal detachment

Toxic epidermal necrolysis



> 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)

Subacute cutaneous LE

eNA may play role in cutaneous LE inflammation

Systemic LE

Discoid 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

#### Violaceous erythema of eyelids - heliotrope



#### Poikiloderma, chest







Findings can be quite subtle in dermatomyositis!

# 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



Superficial and deep perivascular and periadnexal lymphocytic inflammation

## Low magnification ? lupus







Peripheral marginization of chromatin

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

# Diagnosis?

- 1. Lupus erythematosus
- 2. Interface drug reaction
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- 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,‡



Perifollicular lymphocytic inflammation

Necrosis of follicular epithelium

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



Am J Dermatopathol 2017;39:89-94

Vacuolar interface changes







# Pitfall! – something else to consider with lupus-like histology....

# Late latent mucinous syphilis mimicking connective tissue disease

Silvija P. Gottesman<sup>1</sup> | Yuliya S. Schoenling<sup>2</sup> | Keliegh S. Culpepper<sup>3,4</sup>



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





Sparse perivascular inflammation



Intraluminal neutrophilic diapedesis



## Urticarial Hypersensitivity Reaction

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







### 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





Basketweave stratum corneum

Hint of spongiosis

Papillary dermal edema

Perivascular and interstitial 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.



#### Insect Bite–like Reaction in Patients With Hematologic Malignant Neoplasms

Aviv Barzilai, MD, MSc; Dorit Shpiro, MD; Iris Goldberg, PhD; Yasmin Yacob-Hirsch, MSc; Carlos Diaz-Cascajo, MD; Dina Meytes, MD; Regina Schiby, MD; Ninette Amariglio, PhD; Henri Trau, MD



FIGURE 1 Typical clinical findings of ED with urticarial papules (A), bulla on urticarial ground (B) and eroded bulla (C). ED, eosinophilic dermatosis



Figure 3. Left, A biopsy specimen shows a superficial, deep, and interstitial perivascular infiltrate involving also the subcutaneous fat (original magnification ×20). Right, The infiltrate is composed of lymphocytes and eosinophils (original magnification ×200).

Eosinophilic dermatosis of hematologic malignancy: Correlation of molecular characteristics of skin lesions and extracutaneous manifestations of hematologic malignancy

Frank Meiss<sup>1</sup> | Kristin Technau-Hafsi<sup>1</sup> | Johannes S. Kern<sup>1,2</sup> | Annette M. May<sup>3</sup>

- 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

### Annular Lunar Eclipse, June 2012



### 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

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

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



#### Combinations of inflammatory patterns suggests a drug eruption







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





5. REQUESTED FOR PROPER EVALUATION History: Pertinent Clinical Findings and/or Diagram	Ins. Address		
45 year old Q with 2 weak history of itshy popular and plagnes with scale on the hilberal lower legis. ? Contact demonstrik, timen - please do PAS.	City  Policy #    BB Specimens/Sites/Type (P*1)  7    20		
Special Requests:	x	6. SIGNATURE	

### Summary





















#### Eosinophilic spongiosis

Autoimmune blistering disorders, dermatitis, drug reaction, arthropod assault reaction

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*