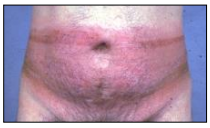
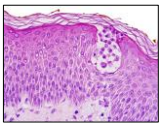
Selected Cases in Inflammatory Dermatopathology

Scott R. Florell, M.D.
Professor, Dermatology
10 February 2019

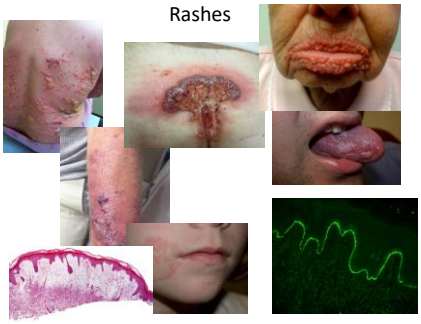




I have no relevant financial disclosures

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

Rashes



Garbage in, garbage out!

Ronald M Harris MD, MBA

Pathologists often get very limited clinical information

The Uninformed Dermatopathologist: An Occult Epidemic

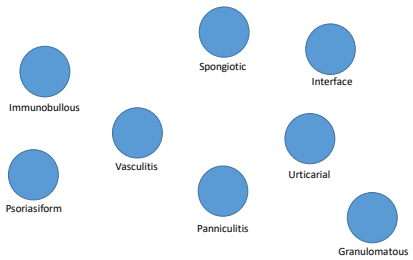
"We believe patient care can be rapidly and significantly improved by providing accurate history and physical examination findings, relevant clinical images, and a clinical differential diagnosis."


Keith L Duffy MD

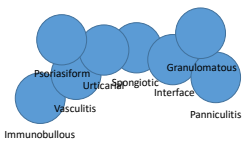

Anneli R Bowen MD


Scott R Florell MD

Common inflammatory patterns



Inflammatory patterns – they aren't specific

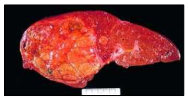


Although most cutaneous eruptions can be categorized into one of several inflammatory patterns, more specific diagnosis is only possible with careful clinical-histologic correlation

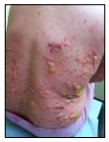
Objectives

- 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



Neoplastic liver disease



Blistering skin disease

Robert Flinner, MD
1930 – 2009
'Yoda'

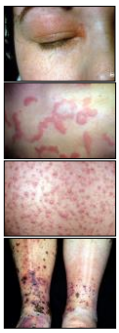
Proper diagnosis of inflammatory skin disease

- 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:

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

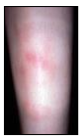


Epidermal

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

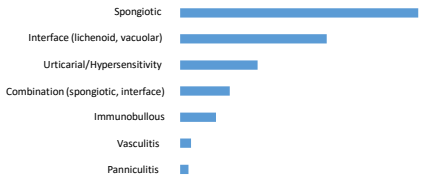
Dermatopathologist relies on . . .

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

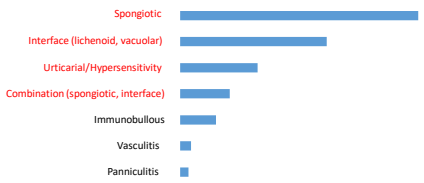
Dr. Anneli Bowen correlating clinical images and chart review with pathologic findings

Dermatopathology Consensus Conference

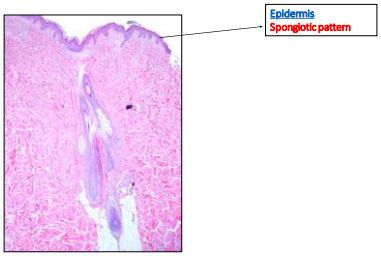
Inflammatory Patterns – University of Utah Dermpath



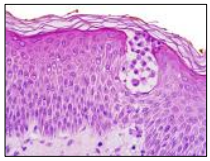
Inflammatory Patterns – University of Utah Dermpath



What Part of the Skin is Involved?

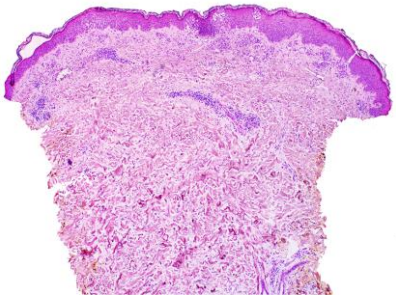


Spongiotic reaction pattern

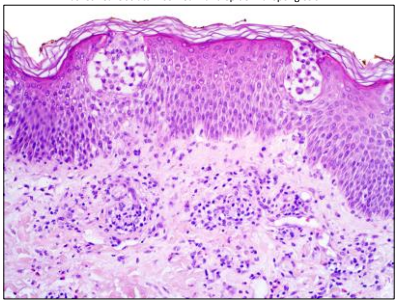


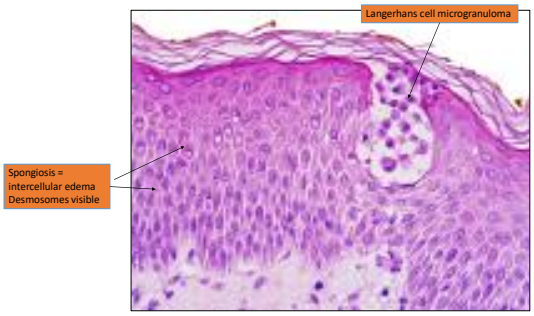
- Defined by intercellular edema:
  - Increased space between keratinocytes
  - 'Stretching' of desmosomal connections between keratinocytes
- Langerhans cell microgranulomas
- Lymphocyte exocytosis
- Parakeratosis variable, acute vs. chronic

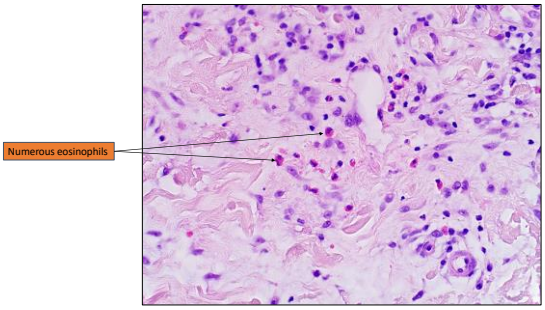
Smith EH, Chan MP. *Clin Lab Med* 2017;37:673-96



Basketweave stratum corneum and epidermal spongiosis

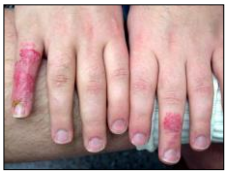




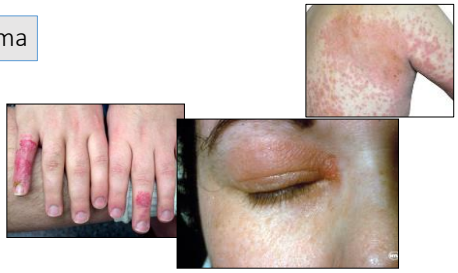


Spongiotic reaction pattern – eczematous eruptions

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

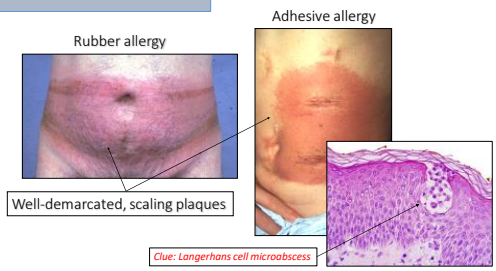


Eczema

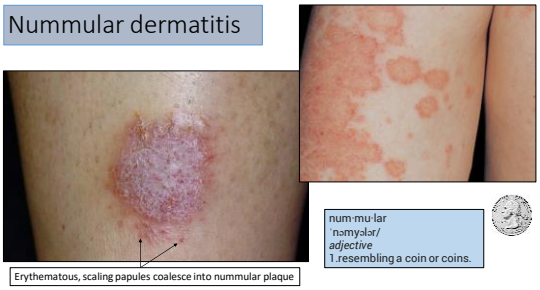


Red/weepy, red/scaly areas on skin

Contact dermatitis

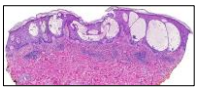


Nummular dermatitis



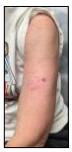
Id reaction

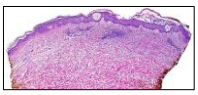
Vesicular contact dermatitis



- 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)

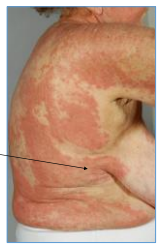
Comment: The overall pattern is that of dermatitis and eczema, including atopic dermatitis, contact dermatitis, nummular dermatitis, spongiotic drug reaction, or id reaction.

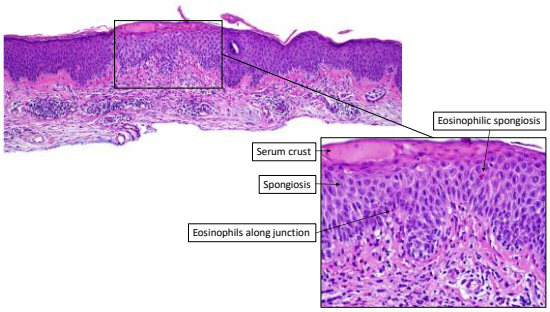
Clinical correlation is necessary.

Widespread itchy rash, 80 year old woman

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

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1. Contact dermatitis
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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 Y. Bakker, MD; Joint B. Ruiz, MD; Hendrik H. Pas, PhD; Marcel F. Jonkman, MD, PhD

JAMA Derm 2013

12 of 15 patients had spongiotic dermatitis

J Am Acad Dermatol 1994;30:973-6

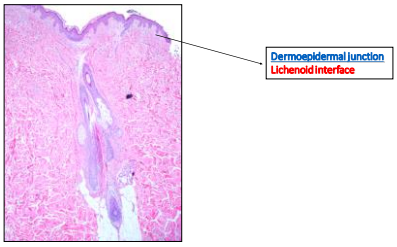
Diagnosis

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.

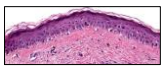
Immunofluorescence studies may be indicated if an autoimmune blistering disorder is a clinical possibility.

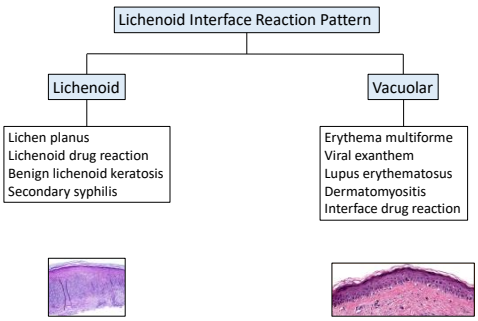
What Part of the Skin is Involved?



Lichenoid Interface Reaction Pattern

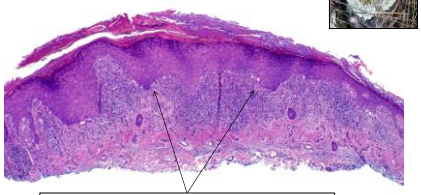
- Subdivided into:
  - Lichenoid interface dermatitis - band-like lymphocytic infiltrate
  - Vacuolar interface dermatitis -sparse lymphocytes tagging the dermal-epidermal junction
- Both are characterized by lymphocyte-mediated destruction of the basal layer
- Destruction of the basal layer results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



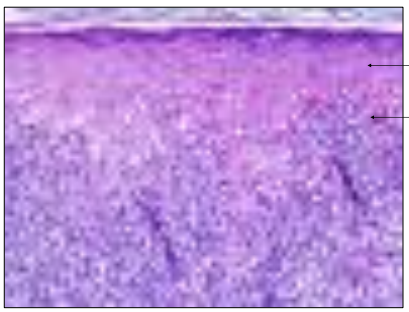


Lichenoid Reaction

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



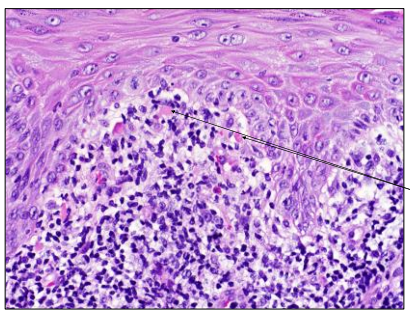
Inflammation hugging the dermoepidermal junction - lichenoid



Large, hypereosinophilic keratinocytes

Inflammation obscures dermal-epidermal junction

Infiltrate mostly lymphocytes

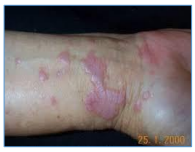


Apoptotic keratinocyte
Dyskeratotic keratinocyte
Civatte body

Eosinophilic globules at the dermal-epidermal junction

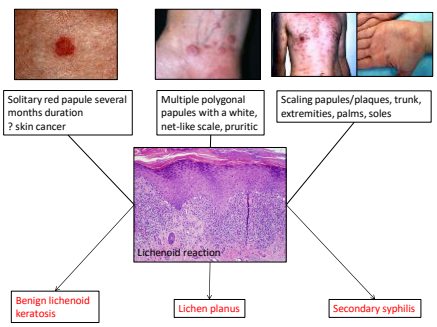
Lichenoid interface reaction pattern

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



Myth

A dermatopathologist doesn't need history to make a diagnosis.



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.

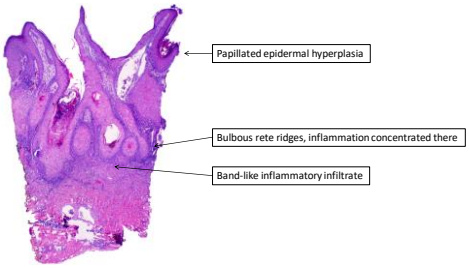
Important Point!

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

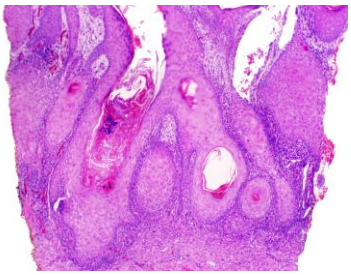
Recent Challenging Clinicopathologic Correlation

72 yo female with history of squamous cell carcinoma of the lower leg, recurrent x 2

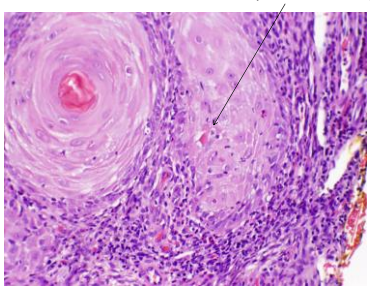
Right lower leg, punch biopsy



Well-differentiated keratinocytes



Band like, lichenoid inflammation and occasional dyskeratotic keratinocytes

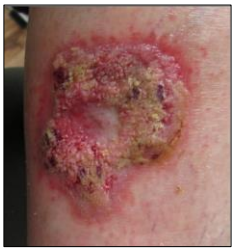


Diagnosis so far . . .

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?

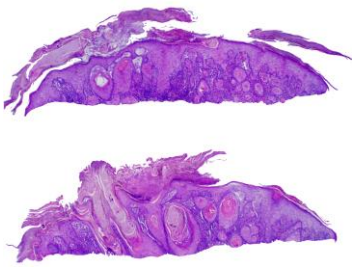
Right lower leg

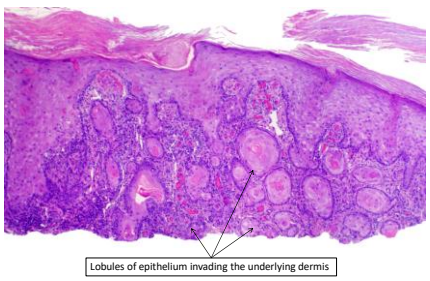


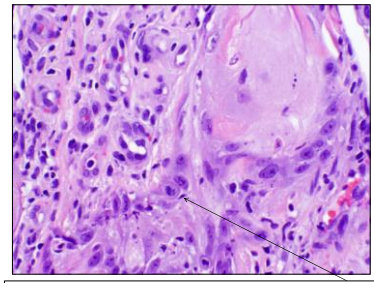
Large eroded plaque with velvety surface and yellow crust

Original Biopsy – two years prior

Shave biopsy, lower leg



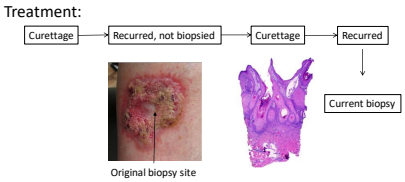




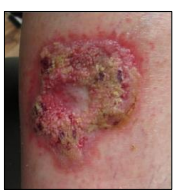
Diagnosis – biopsy two years prior

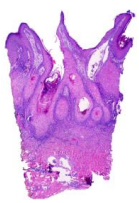
Invasive squamous cell carcinoma

Treatment:

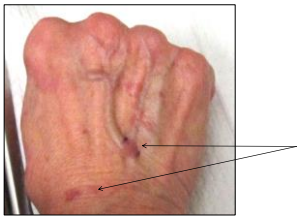


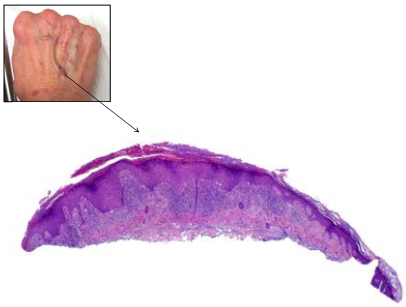
Back to Current Case . . .

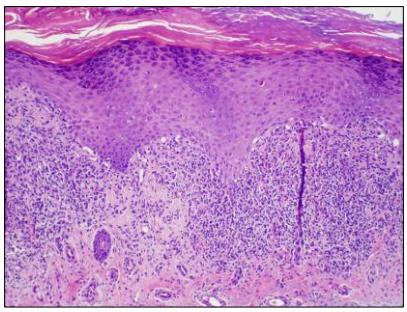


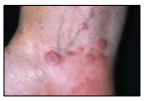


At follow-up, she was noted to have several itchy purplish papules



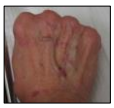






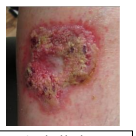
Flat-topped polygonal papules

Diagnosis



Lichen planus

Hypertrophic variant

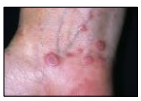


Our patient had both patterns

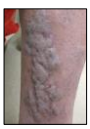
Lichen Planus

- 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



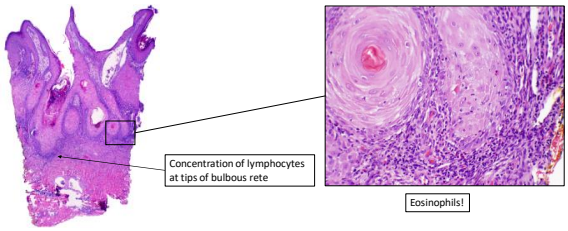
Hypertrophic lichen planus



- 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

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

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

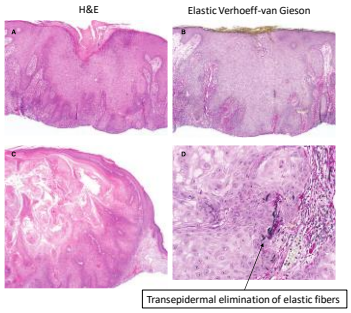
Background: Distinguishing keratoacanthoma (KA) and hypertrophic lichen planus (LP) histopathologically can be difficult, and the challenge is compounded by the tendency of KA to arise in association with hypertrophic LP.

Annell R. Bowen, Lindsay Burt, Kenneth Boucher, Payam Tehrani-Firouzi and Scott R. Florell

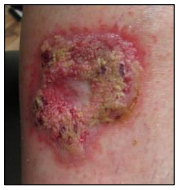
- Proliferation index similar between KA and hypertrophic LP
- p53 staining increased in KA > HLP (p = 0.024), but present in both
- Perforating elastic fibers seen in KA > HLP (p < 0.0001)

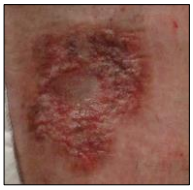
J Cutan Pathol 2012;39:243-50

J Cutan Pathol 2012;39:243-50

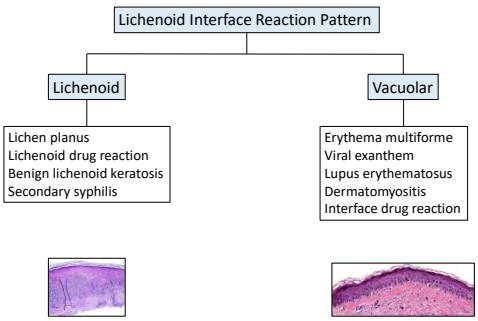


After 3 weeks topical steroid

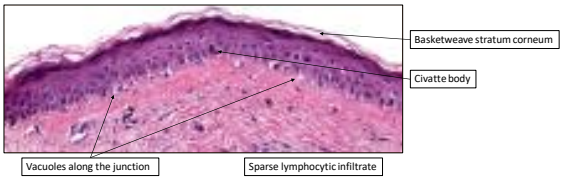




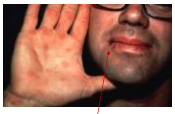
Lesion thinner



Vacuolar Interface Reaction Pattern

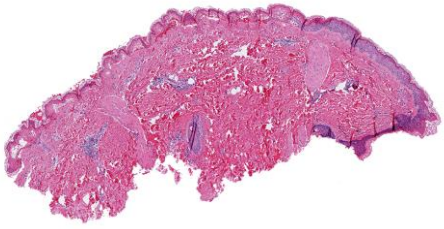


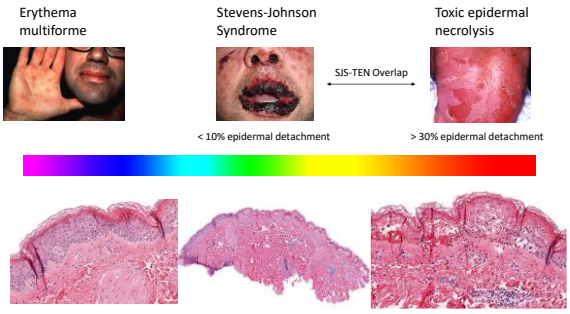
Erythema Multiforme



- 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





Diagnosis

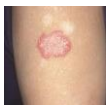
VACUOLAR INTERFACE DERMATITIS (SEE COMMENT)

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

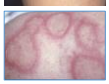
Connective tissue diseases

- 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

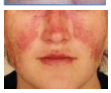
Lupus erythematosus



Discoid LE



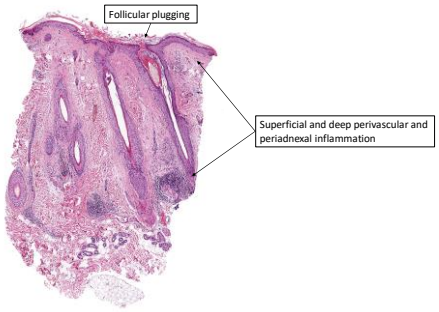
Subacute cutaneous LE

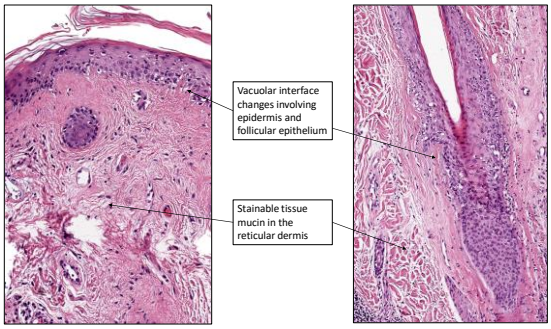


Systemic LE

- 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

Front Immunol 2016;7:35



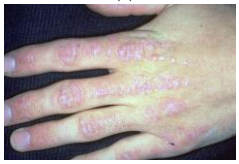


Dermatomyositis

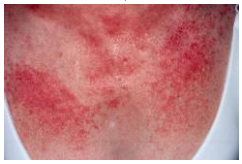
- Autoimmune disease affects skin and muscles
- Associated with increased risk of malignancy
- Complications include calcification

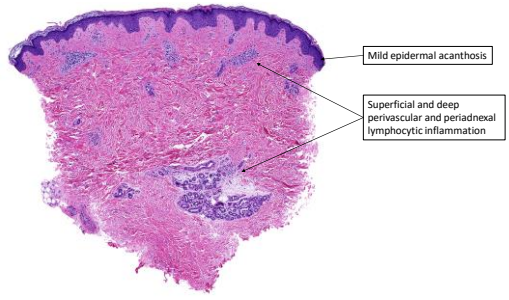
Violaceous erythema of eyelids - heliotrope

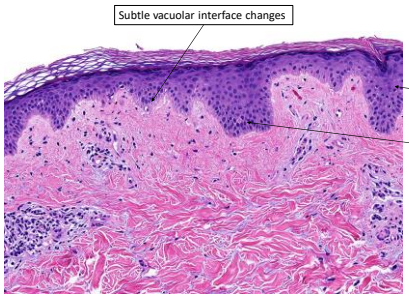
Gottron's papules



Poikiloderma, chest







Similar changes can be seen in drug reaction or viral exanthem

Findings can be quite subtle in dermatomyositis!

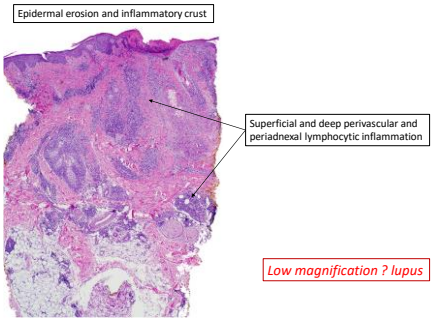
Diagnosis

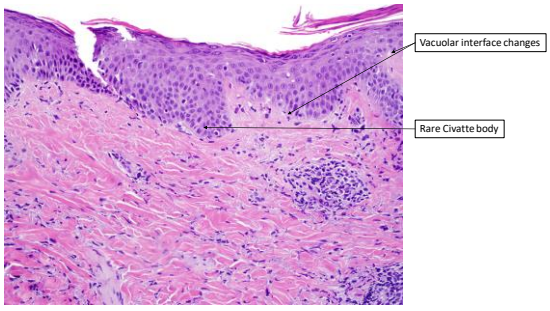
VACUOLAR INTERFACE DERMATITIS (SEE COMMENT)

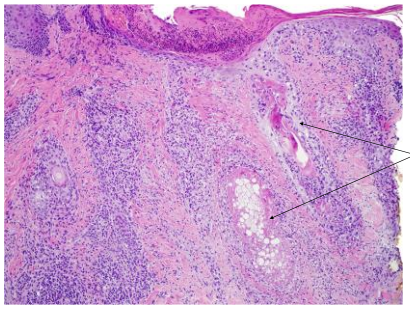
Comment: The histologic differential diagnosis includes a connective tissue disorder such as dermatomyositis or lupus erythematosus, or an interface drug reaction or viral exanthem.

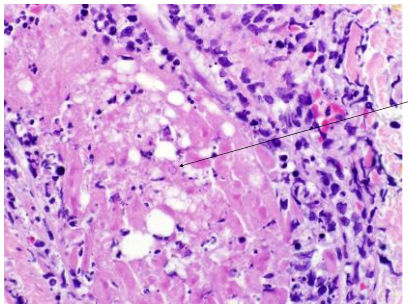
Venus Transit, June 6, 2012

Case 2 – tender scalp plaque

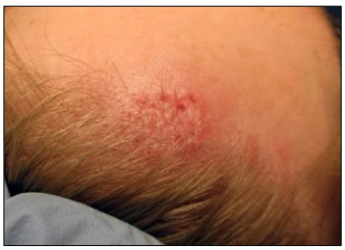








Scalp with tender erythematous plaque composed of coalescing papulovesicles, some crusted



60 year old man

Diagnosis?

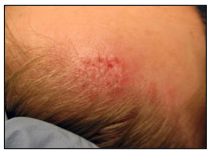
1. Lupus erythematosus
2. Interface drug reaction
3. Herpes zoster
4. Dermatomyositis
5. Syphilis

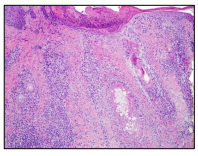
Diagnosis?

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

Important Point!

Necrotic pilosebaceous units are a clue to herpesvirus infection

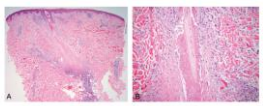




ORIGINAL STUDY

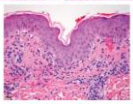
Folliculocentric Herpes: A Clinicopathological Study of 28 Patients

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



Perifollicular lymphocytic inflammation

Necrosis of follicular epithelium

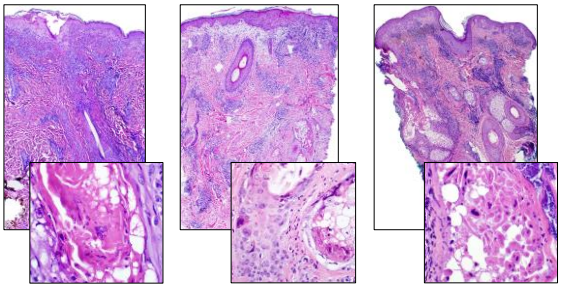


Vacuolar interface changes

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.

Am J Dermatopathol 2017;39:89-94

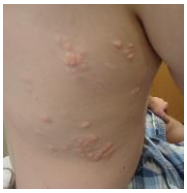
Herpes zoster



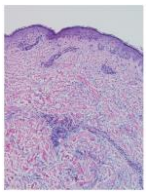
Pitfall! – something else to consider with lupus-like histology….

Late latent mucinous syphilis mimicking connective tissue disease

Silvija P. Gottesman[1] | Yuliya S. Schoenling[2] | Keliegh S. Culpepper[3,4]



Flesh colored papules and nodules



Vacuolar interface, superficial and deep inflammation, mucin

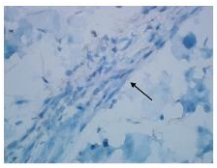
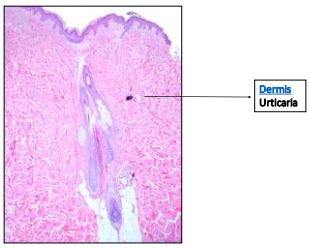


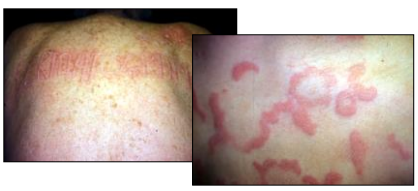
FIGURE 5 Immunohistochemistry for Treponema pallidum highlights a single spirochete in the vicinity of a dermal capillary (T.pal IHC, ×600)

J Cutan Pathol 2017;44:578-81

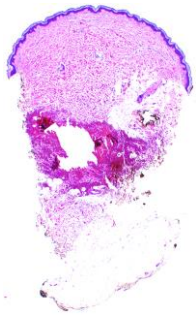
What Part of the Skin is Involved?



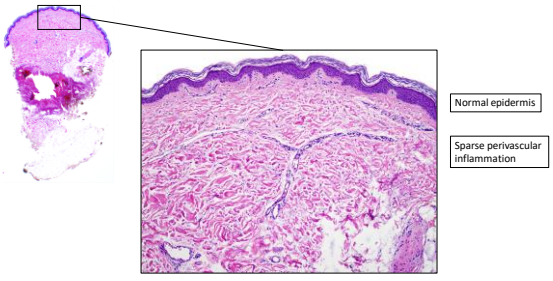
Dermis - Urticaria (Hives, Wheals)



Edematous papules and plaques *without* surface changes

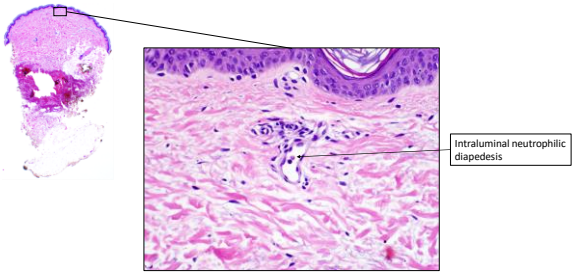


Relatively unremarkable low magnification

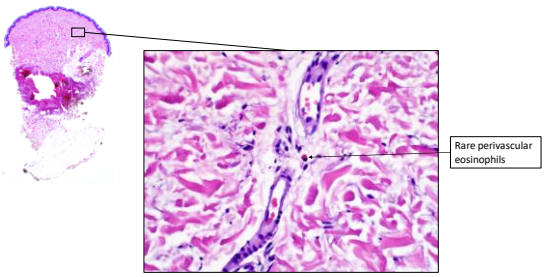


Normal epidermis

Sparse perivascular inflammation

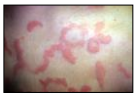


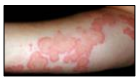
Intraluminal neutrophilic diapedesis



Urticarial Hypersensitivity Reaction

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





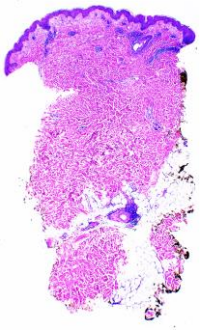
Diagnosis

URTICARIAL HYPERSENSITIVITY REACTION (SEE COMMENT)

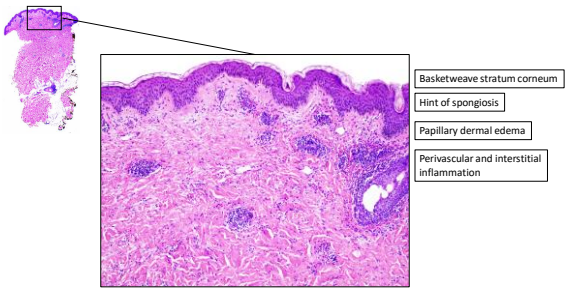
Comment: The features are compatible with urticaria, urticarial vasculitis, or an urticarial drug eruption.

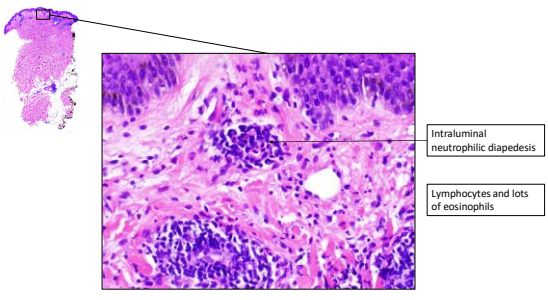
Canyon Overlook, Zion National Park

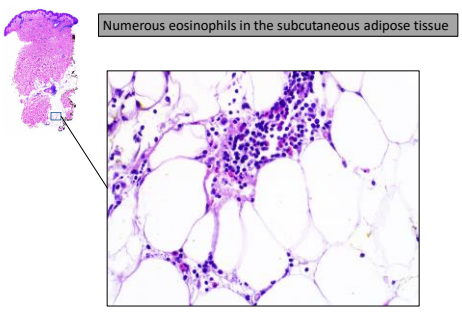
Case 3 – punch biopsy from the lower leg



Superficial and deep perivascular and pannicular inflammation

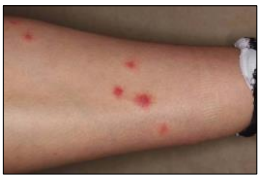

Basketweave stratum corneum
Hint of spongiosis
Papillary dermal edema
Perivascular and interstitial inflammation


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?

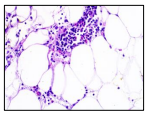
1. Urticaria
2. Urticarial drug reaction
3. Urticarial vasculitis
4. Arthropod assault reaction
5. Urticarial phase of bullous pemphigoid

Diagnosis?

1. Urticaria
2. Urticarial drug reaction
3. Urticarial vasculitis
4. *Arthropod assault reaction*
5. Urticarial phase of bullous pemphigoid

Important Point!

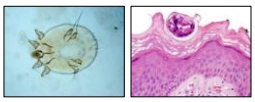
Subcutaneous eosinophils are a clue to arthropod assault reaction



Diagnosis

CONSISTENT WITH ARTHROPOD ASSAULT REACTION (SEE COMMENT)

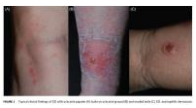
Comment: The differential diagnosis could include a drug reaction but that is favored less than an arthropod assault. Neither scabetic mite parts nor products are identified within the stratum corneum.

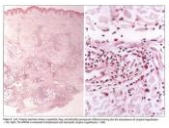


Insect Bite–like Reaction in Patients With Hematologic Malignant Neoplasms

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

Frank Meiss[1] | Kristin Technau-Hafsi[1] | Johannes S. Kern[1,2] | Annette M. May[3]



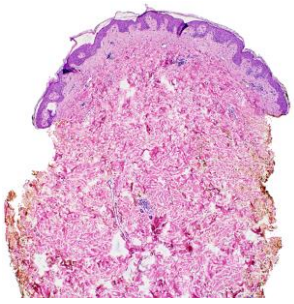


- *Clinical and histologic features mimic arthropod assault, refractory to standard therapies – impaired quality of life*
- Most in B-cell neoplasms:
  - Chronic lymphocytic leukemia (most common)
  - Mantle-cell lymphoma
  - Large-cell lymphomas
- May precede the diagnosis of the hematologic disorder
- 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

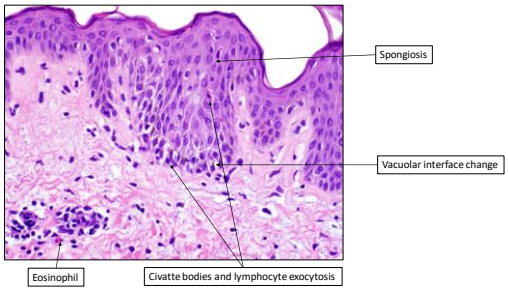
Annular Lunar Eclipse, June 2012

Case 4 – punch biopsy from the trunk

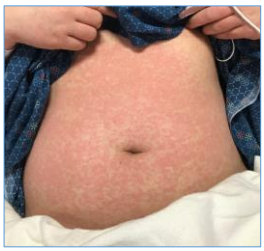


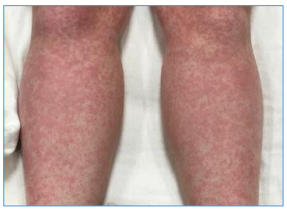
Subtle epidermal changes

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

Apaydin R, et al. *J Eur Acad Dermatol Venereol* 2000;14:518-20

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MORBILLIFORM ERUPTIONS CAUSED BY PENICILLIN

A STUDY BY ELECTRON MICROSCOPY AND IMMUNOLOGIC TESTS*

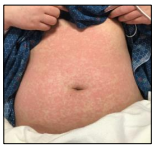
MICHAEL J. FELLNER, M.D. AND LAWRENCE PRUTKIN, PHD.

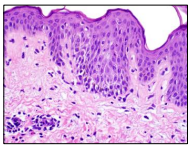
- Small foci of spongiosis
- Vacuolar change
- Rare dyskeratotic keratinocytes

J Invest Dermatol 1970

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

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