Important Decisions in Dermatopathology: The Clinico-Pathologic Correlation

Uma Sundram, MD, PhD
Departments of Pathology and Dermatology
Stanford University
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“Dermatopathology Specialists Needed”

- Skin and Allergy News Sep 2007: Interview of Dr. Clay Cockerell
- Changing trends in dermatopathology
  - Increasing numbers of primary care physicians evaluate skin disorders on a routine basis
  - Many of these biopsies are routed to general pathologists

Changing Trends

- Cockerell: Only 35% of skin biopsies come from dermatologists
- Economic pressures may also force PCP’s to keep and work up their difficult dermatology cases, rather than refer
- Dermatopathologists not being trained in numbers to meet demand
Diagnostic Errors

• Due to lack of understanding of the dermatologic clinical scenario, over-interpretation or under-interpretation of biopsies take place
• Purpose of this talk: To stress the importance of clinico-pathologic correlation and assessing the clinical scenario in conjunction with slide interpretation

Case I

• 45 year old female with persistent red patch on the left arm.
What is your diagnosis?

1. Mycosis fungoides
2. Drug eruption
3. Lichen planus
4. Lichenoid keratosis

What is your next step?

1. Call the clinician
2. Initiate immuno-histochemical studies
3. Initiate PCR analysis for TCR gene rearrangements

If you called the clinician, what would you ask about?

1. Size and number of lesions
2. Appearance of lesions (patches/plaques or papules)
3. Distribution of lesions (sun spared or sun exposed sites)
4. Duration of lesions
5. Drug history
6. All of the above
If ordering immunohistochemical studies, what would you order?

1. CD20 and CD3
2. CD3, CD4, and CD8
3. CD4 and CD8 only
4. CD20, CD3, and CD30
5. None

Would you order PCR analysis?

1. Yes
2. No

Clinical Clues

• Mycosis fungoides: Tend to be patches/plaques in sun protected sites, persistent, no temporal connection to drugs
• Lichenoid keratosis: Solitary small lesions
Clinical Clues

• Lichen planus: “Purple polygonal papules”, sometimes related to drugs
• Drug eruption: Have a temporal relationship to drug exposure

We called the clinician and…

• The lesion is solitary, limited to the arm, persistent patch, with no significant drug history

Our approach

• Given the solitary nature of the lesion and lack of clinical concern for mycosis fungoides, our final diagnosis was benign (so called “lymphomatoid”) lichenoid keratosis.
• The solitary nature of the lesion made the diagnoses of mycosis fungoides, lichen planus, and drug eruption less likely
Our approach

• We elected not to perform any further ancillary studies, knowing that reactive conditions can be CD4 predominant\(^1\) and can be clonal\(^2\)


Lichenoid Keratosis

• Common cutaneous entity, also known as lichen planus-like keratosis
• Clinically, these are solitary small lesions
• The clinical differential diagnosis usually includes basal cell carcinoma, squamous cell carcinoma, verruca, actinic keratosis, and atypical nevi

Lichenoid Keratosis

• On histology, typically characterized by a dense, relatively superficial lymphocytic infiltrate, numerous necrotic keratinocytes at the dermal-epidermal junction, and epidermal hyperplasia
• If the lesion is captured in its entirety, it is not unusual to see flanking areas of typical solar lentigo or seborrheic keratosis
Other Histologic Variants

- These include\textsuperscript{3,4}:
  - Lupus erythematosus-like
  - Bullous-type
  - Early/interface type
  - Late regressed/atrophic type
  - Mycosis fungoides-like (so called “lymphomatoid” lichenoid keratosis)


Lichenoid Keratosis and Mycosis Fungoides

- In a study of 15 cases of LK, these features, typical of MF, were found\textsuperscript{3}:
  - Pautrier's microabscesses (93%)
  - Epidermotropism (80%)
  - Lymphocytes populating the lower half of the epidermis (93%)
  - Cytologic atypia (47%)


Unilesional Mycosis Fungoides

- Separate from localized pagetoid reticulosis
- Rare and controversial\textsuperscript{5}
- Some documented association with drug exposure
- Truncal location, similar to lichenoid keratosis
- Ultimate separation from “lymphomatoid” lichenoid keratosis requires clinical correlation

What favors lichenoid keratosis?

- Histologic features that favor benign lichenoid keratosis, in the context of a small (<2 cm), solitary lesion:
  - Necrotic keratinocytes
  - Flanking findings of solar lentigo or seborrheic keratosis
  - Pointed rather than rounded rete pegs in areas of inflammation

Ancillary Studies: Are they needed?

- Specific comparative ancillary studies have not been done
- Positive clonality studies have been documented in benign lichenoid keratosis\(^5\)

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Case II

- 35 year old female with a few scattered itchy and tender papules that have developed a hemorrhagic crust.
What is your diagnosis?

1. Malignant lymphoma
2. Pityriasis lichenoides et varioliformis acuta (PLEVA)
3. Arthropod bite reaction
4. Herpetic dermatitis
5. Lupus erythematosus
6. Lymphomatoid papulosis

What would be your next step?

1. Call the clinician
2. Order immunohistochemical studies
3. Perform PCR analysis
If you contact the clinician, what would you ask?
1. Distribution of lesions
2. Duration of lesions
3. Clinical course of the lesions (do they wax/wane or are they persistent)
4. Relationship to the sun
5. Systemic symptoms
6. All of the above

If you ordered immunohistochemical stains, what would they be?
1. None
2. CD20 and CD3
3. CD30
4. CD3, CD4, and CD8
5. CD56

Would you order PCR?
1. Yes, for IgH
2. Yes, for TCR
3. Yes, for both IgH and TCR
4. No
Clinical Clues

- If the lesions are grouped, the differential diagnosis would include arthropod bites and herpes
- If the lesions are in a sun-related distribution (i.e., face), lupus would enter into the differential
Clinical Clues

• If the lesions wax and wane, and resolve with scarring, the differential would include lymphomatoid papulosis
• If the lesions are persistent, and the patient has systemic symptoms, lymphoma is a consideration

We spoke to the clinician and...

• The lesions are on the back, somewhat grouped, and not in a sun-related distribution
• The patient does not have systemic symptoms
• The lesions are persistent and do not heal with scarring; there is no wax/wane course

Could this be malignant lymphoma?

1. Yes
2. No
Our approach

• Given the nature of the clinical lesions and the clinician’s lack of concern for a lymphoma, we favored a reactive process
• The papillary dermal edema, wedge shaped infiltrate and numerous deeply placed eosinophils suggested an arthropod bite reaction
• Clinical follow-up supported this diagnosis over lymphomatoid papulosis (the leading entity in the differential)

CD30+ Cells in Lymphocytic Infiltrates

• CD30 is a member of the TNF/NGFR superfamily
• Recognized by the monoclonal antibody Ki-1 raised on Hodgkin cells
• Known to be present on activated, but not resting, B and T cells

CD30+ Cells in Lymphomas

• CD30 is expressed in the following entities:
  – Reed Sternberg cells of Hodgkin lymphoma
  – Lymphomatoid papulosis
  – Anaplastic large cell lymphoma
  – Transformed mycosis fungoides
  – Pagetoid reticulosis
Inflammatory Diseases Can Also Have CD30+ Cells

- Herpetic dermatitis
- Arthropod bite reaction (scabies, spider bites, tick bites, other insect bites)

- Tuberculosis
- Atopic dermatitis
- Drug eruption (carbamazepine, cefuroxime)

CD30 Expression in Scabies

- Gallardo et al. described 11 skin biopsies of patients with known active lesions or persistent nodules post treatment
- All had dense lymphocytic/eosinophilic infiltrates with varying degrees of CD30 expression
- Some active lesions had Sarcoptes scabiei mites
- All lesions were CD4 predominant
- Lesions of less than 2 month duration were less likely to have CD30+ cells

References:
CD30 Expression in Other Arthropod Bite Reactions

- Cepeda et al. documented CD30 expression in 7 cases of arthropod bites, including 2 spider bite cases.
- CD30 expression was common in neutrophil-rich and eosinophil-rich inflammatory conditions.
- Gene rearrangement studies were negative for a T cell clone, but some showed B cell oligoclonality.


CD30 Expression in Herpes

- Leinweber et al. examined biopsies from 65 patients with known diagnoses of HSV1/2 and VZV.
- Nearly all demonstrated viropathic changes on histology, some subtle.
- Atypical lymphocytes were present in a majority of cases (67%).
- CD30 expression also present in a majority (80%).


CD30 Expression in Herpes

- About 5 cases had dense lymphocytic infiltrates and numerous atypical cells with CD30 expression.
- Two of these had clusters of atypical CD30+ cells; these were also positive for a T cell clone.
- BUT: classic histologic findings of herpes were present and PCR confirmed presence of herpetic DNA.
Dr. Cockerell’s Cases

• 65 year old woman sees a primary care physician with a solitary lesion
• Clinical diagnosis: basal cell carcinoma
• The pathologist notes epidermotropism of atypical lymphocytes and renders diagnosis of probable mycosis fungoides
• The patient seeks a second opinion from Dr. Cockerell
• His diagnosis: benign lichenoid keratosis

Dr. Cockerell’s Cases

• 36 year old woman who visits her PCP with complaints of a chronic rash
• The pathologist notes numerous atypical cells, and renders a diagnosis of “T cell lymphoma”
• The patient gets two cycles of chemotherapy which resolve the lesions but they reappear after the therapy has concluded

Dr. Cockerell’s Cases

• The oncologist asks for a second opinion
• Dr. Cockerell’s diagnosis: lymphomatoid papulosis, which does not require conventional chemotherapy for treatment
Summary

- Benign dermatologic entities can mimic malignant ones on histopathology ("clinically benign, histologically malignant")
- Conversation with the clinician is very important in arriving at an appropriate diagnosis
- Proper clinicopathologic correlation can avoid inaccurate diagnosis, avoid delay in correct diagnosis, and save money