An approach to the diagnosis of the common cutaneous lymphomas

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Cutaneous lymphoma prior to the 1980s was a black box

- Aside from MF and Sezary syndrome
- "Reticulum cell sarcoma"
- Little prognostic insight
- Low grade lymphomas not recognized

Primary v. secondary cutaneous lymphoma

- Primary cutaneous lymphoma
  - Presents in the skin
  - Staging workup negative
    - No palpable adenopathy
    - Negative chest X-ray or CT
    - Negative abdominal (+/- pelvic) CT
    - Negative bone marrow
  - No disease outside of skin 6 months later
- Secondary cutaneous lymphoma
  - Everything else

Secondary cutaneous lymphoma

- Systemic or nodal lymphoma that involves the skin
- Often has a different immunophenotype or genotype than primary cutaneous lymphoma of the same morphology
- Prognosis usually unfavorable
How progress occurred
• Delineation of B, T and NK/T cells
• Collaboration between Karl Lennert, a hematopathologist, and Gunter Burg, Helmut Kerl, Manfred Goos and others, dermatologists who were lymphoma clinicians and dermatopathologists

What makes a “type” of lymphoma?

Cutaneous B-cell lymphomas
• Marginal zone lymphoma
• Follicle center lymphoma
• Diffuse large B-cell lymphoma, leg type
• Diffuse large B-cell lymphoma, other
  – Intravascular large B-cell lymphoma
Cutaneous T-cell lymphomas

- Mycosis fungoides
  - Folliculotropic
  - Pagetoid reticulosis
  - Granulomatous slack skin
- Sezary syndrome
- Adult T-cell leukemia/lymphoma
- Primary CD30+ lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Anaplastic large cell lymphoma
- SQ panniculitis-like T cell lymphoma
- Extranodal NK/T
- Peripherial T-cell lymphoma, unspecified
  - Aggressive epidermotropic CD8+*
  - Gamma/delta T-cell lymphoma*
  - CD4+ small/medium T-cell lymphoma*

*= Provisional

To understand follicular lymphoma, you need to understand cutaneous lymphoid hyperplasia

Cutaneous lymphoid hyperplasia is a florid expression of skin-associated B-cell immunity

Cutaneous lymphoid hyperplasia—purported causes

- Arthropod assault
- Vaccination
- Medication
- Borreliosis
- …but most cases are “idiopathic”
Cutaneous lymphoid hyperplasia

Bcl-2

Cutaneous lymphoid hyperplasia

Ki67
Cutaneous follicle center lymphoma-
the neoplastic counterpart of lymphoid hyperplasia
**Cutaneous lymphoid hyperplasia v. follicular lymphoma**

<table>
<thead>
<tr>
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<th>Follicular hyperplasia</th>
<th>Follicular lymphoma</th>
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<tbody>
<tr>
<td>Bcl-2</td>
<td>negative</td>
<td>positive (30%)</td>
</tr>
<tr>
<td>Ki-67 high</td>
<td></td>
<td>Ki-67 moderate or low</td>
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<tr>
<td>CD10, bcl-6</td>
<td>CD10+, bcl-6+</td>
<td>CD10+ , bcl-6+</td>
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<tr>
<td>Light chain</td>
<td>polytypic (frozen)</td>
<td>restricted or absent (frozen)</td>
</tr>
<tr>
<td>only</td>
<td></td>
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**CD10**
Cutaneous lymphoid hyperplasia v. follicular lymphoma

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<th>Bcl-2</th>
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<td>moderate or low</td>
<td>CD10+, bcl-6+ interfollicular blasts</td>
<td>restricted</td>
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Primary cutaneous follicular lymphoma- clinical considerations

- Excellent prognosis (>95% 5 year survival)
- Local recurrences common
- Cytologic grading not important
- Local treatment adequate- no chemotherapy

Clonality in PCFCL

- Only 70% clonal by IgH
- Somatic hypermutation of variable region genes
- Deletions involving chr. 14
- Conventional K/l staining not helpful
- RNA amplification techniques possible in future
The other low grade B-cell lymphoma of note is marginal zone lymphoma.
Cutaneous marginal zone lymphoma

- Analogous to mucosal lymphomas
- Antigenic stimulation posited in etiology of mucosal lymphoma, MZL in Europe (borreliosis)
- Many cases previously called cutaneous lymphoid hyperplasia
- Immunocytoma is monomorphous plasma cell predominant type of MZL
PCMZL has two major histopathologic presentations

- Follicles, with interfollicular plasmacytoid lymphocytes and plasma cells
- Monomorphous infiltrates of plasmacytoid lymphocytes and plasma cells
Dutcher body

Kappa light chain
Lambda light chain

Diffuse large B-cell lymphoma

- Leg type (recognized in WHO-EORTC) is rare in U.S. vs. Europe
- T-cell rich B-cell lymphoma
- Bcl-2+ (but not t(14;18) due to gene amplification
- bcl-6, CD10 and MUM1 are variable; follicular center profile may be more favorable
Spindle cell lymphoma in the skin

- Most are B cell
- Originally described as diffuse LBCL, but now thought to be of follicular center origin
- A handful are T NOS or T=ALCL
Pax-5/CD3 double stain

Bcl-6 CD21 double stain
Angiotropic lymphomas
(malignant angioendotheliomatosis, intravascular lymphoma)

- B cell, usually, but some T or NK cell cases
- Bruise like lesions
- No adenopathy
- Sometimes present in normal appearing skin

- Simulant- intravascular histiocytosis, reactive angioendotheliomatosis

Cutaneous Spindle-Cell B-Cell Lymphoma
A Morphologic Variant of Cutaneous Large B-Cell Lymphoma:

Lorenzo Cerami, M.D., Laila El-Shabrawi-Cafarri, M.D.; Regina Fain-Pacheco, M.D., Philip E. LeBoit, M.D., and Helmut Keri, M.D.
Intravascular or intralymphatic histiocytosis

A simulator of intravascular lymphoma
Mycosis fungoides

- Recognition of patch stage disease (1979-)
- Progression to plaques, tumors in small minority
- Death from immune collapse
- Tremendous variability in clinical and histopathologic features
- Diagnosis of early disease not very important

The diagnosis of mycosis fungoides is clinicopathological-
Most important for early disease
Patch stage of mycosis fungoides

- Parapsoriasis en plaque, large plaque parapsoriasis are terms used by those who do not think it can be recognized or is lymphoma.
- Psoriasiform lichenoid, psoriasiform spongiotic lichenoid, and atrophic lichenoid are most important histopathologic patterns.
Histopathologic patterns of patch stage MF

- Superficial perivascular, slight epidermal hyperplasia*
- Psoriasiform lichenoid
- Psoriasiform spongiotic lichenoid
- Atrophic lichenoid
- Vacuolar*
- Lichenoid*

*most often non-diagnostic
Immunophenotype - patch stage MF

- Classic: CD3+, CD2+, CD5+, CD4+, CD7-, CD8-, TCR beta+, CD30-
- Variants: loss of CD2, CD5; “double negative” CD4-, CD8-
- Transformed: Cytotoxic markers+, CD30+
  - CD8+: CD4-, CD8+, TIA-1+
  - CD56+, either with CD4+ or CD8+

MF is phenotypically heterogeneous

- 15% of MF is CD8+ (Massone et al.)
- Sometimes, CD8+ cells predominate in blood while CD4+ are in skin
- CD56+ cases may be more common than previously realized
Immunophenotypic discrepancy between tissue and blood

- 20 patients with MF with blood involvement
- Immunophenotype discrepant in 11 (55%). Compared with FC findings in blood, immunohistochemical analysis of skin samples failed to detect partial deletion of CD2 (5/11 [45%]), CD3 (3/11 [27%]), and CD5 (3/11 [27%]) and overrepresented deletion of CD7 in 2 (18%) of 11 patients.
- CD8+ MF was missed by immunohistochemical analysis in 2 (18%) of 11 patients
- Identical T-cell populations were demonstrated by T-cell gene polymerase chain reaction in skin and blood in 8 of the 11 patients who had a discrepant immunophenotype.

What to do when a biopsy is not diagnostic of MF

- The best way to “rule out” mycosis fungoides is to establish another condition
- Multiple biopsies and clinical correlation are better than TCR
- TCR is best on several specimens
Regarding the algorithm for the diagnosis of early mycosis fungoides proposed by the International Society for Cutaneous Lymphomas: suggestions from routine histopathology practice

Should early MF be worked up with IHC and PCR?

Patch stage MF- what to do when you’re stuck:

- Let the clinician know it is *not* an emergency
- Get clinical photos, or a detailed description
- Get multiple biopsies, especially broad shaves
- Ask the clinician to think about what it could be if it isn’t MF, and to biopsy a lesion that most resembles that condition (the best way to rule out the diagnosis of MF is to establish that of another disease)
- There is nothing lost by treating with conservative modalities (topical corticosteroids, UV) in uncertain cases, and a lot to be lost by being railroaded into an incorrect diagnosis of MF
- If you do get genotypic studies, biopsy several lesions, submit them for separate analyses, and ask for the sizes of the amplicons (if positive) to be compared. Amplicons of similar size imply common clonality, and seem more specific.

The critical point in neoplastic progression in MF is when lesions become plaques

- Markedly increased cytologic atypia
- Ability of neoplastic cells to grow outside an epithelial environment
- Ability of neoplastic cells to grow outside the skin
- Deleterious effects on host immunity
### CD30+ cutaneous infiltrates

- Inflammatory skin diseases, esp. infections
- Lymphomatoid papulosis
- Anaplastic large T cell lymphoma
- Tumors of mycosis fungoides
- Some DLBCLs

### CD30 and inflammatory skin diseases

- Infections
- Scattered single cells in many inflammatory skin diseases
- CD30 upregulated in HIV disease, in general, and pos. cells in man inflammatory diseases in this population
- Neutrophilic infiltrates in particular associated with CD30+ cells
- Pityriasis lichenoides with CD30+ cells
Lymphomatoid papulosis

- **Recurring relapsing disease**
- Spectrum of histopathologic patterns, Wilhemze types A-E
- Usually CD4+ CD30+ T-cell proliferation
- Variable clonality (PCR often neg.)
- **Diagnosis requires observation of behavior in many cases**

Lymphomatoid papulosis and lymphoma

- Can occur without other lymphoma, precede, or follow MF, ALCL or Hodgkin’s disease
- When associated with MF, clonally identical in many cases
- Particularly associated with atrophic patch stage MF
- Estimates of associated lymphoma from academic centers too high
Wilemze types of LYP

- Type A: Large cells, vesicular nuclei, wedge shape, admixed eos and neuts
- Type B: Bandlike, some epidermotropism, CD30 not consistent as in other types
- Type C: Sheets of large, atypical lymphocytes
- Type D: Pagetoid epidermotropism, CD8+
- Type E: Lymphomatoid vasculitis
Type A

CD30
CD30

Type A, follicular variant
A Variant of Lymphomatoid Papulosis Simulating Primary Cutaneous Aggressive Epidermotropic CD8+ Cytotoxic T-cell Lymphoma. Description of 9 Cases

Andresa Soggetti, MD,†‡ Andrea Gailis, MD,‡ Zsolt Argovyi, MD § Regina Farka· Pacher,* Atanisa Lixita, MD § Mario Magatia, MD * Lali Requena, MD § Inezid Simonitoc, MD ‡ and Lorenzo Corvini, MD *
Anaplastic large T cell lymphoma, CD30+

- Primary cutaneous vs. systemic, with large difference in clinical behavior
- Usually CD4+
- Systemic cases often have t(2;5), resulting in ALK/npm transcript
- MUM-1 and traf-1 more often pos. in systemic ALCL than in LYP
- Without clinical info, cannot tell ALCL from LYP type C, or some tumors of MF
Neutrophil-rich ALCL

- 5-50% of the cells in a high power field are neutrophils
- Neutrophils can occur in LYP and Hodgkin’s, so perhaps a link between these
- “Pyogenic” variant
- ?More common in HIV disease?
Small cell variant of ALCL

- Small cells often lack CD30
- Large cells are CD30+
- Both populations ALK positive