Diagnosis of the Early Lesions of Mycosis Fungoides

Bruce R. Smoller, MD
Professor and Chair
Hough Endowed Chair in Pathology
Department of Pathology
University of Arkansas for Medical Sciences

Context
• Early diagnosis is a clinical-pathologic correlation that often requires immunologic and molecular data to establish the diagnosis
• Reliance of purely histologic features raises a differential diagnosis (to be discussed in a later presentation)

Usual clinical context is that of long-standing erythematous patches with slight scale
Often on buttocks and flanks but can be any site
Most common in middle-aged to elderly patients
Most common type of CTCL; accounts for about 50% of all cutaneous lymphomas

Histologic features
• Architectural
• Cytologic

Architectural features
• Cited in literature:
  - Psoriasiform epidermal hyperplasia or atrophy
  - Epidermotropism
  - Single lymphocytes along the DEJ
  - Collections of atypical lymphocytes within the epidermis (Pautrier’s microabscesses)
  - Papillary dermal fibrosis
  - Superficial bandlike or patchy infiltrate of lymphocytes
  - “Naked underbelly” sign
Architectural features

- Statistically good discriminators:
  - Halos around nuclei
  - Pautrier’s microabscesses
  - Large single lymphocytes within epidermis
  - Single lymphocytes along dermal epidermal junction
  - Excess numbers of lymphocytes in epidermis compared with amount of spongiosis (epidermotropism)
Architectural features

- Parameters that are not good discriminators:
  - Papillary dermal fibrosis
  - Acanthosis or atrophy
  - Dying keratinocytes
  - Dermal lymphocyte “atypia”
  - Presence of eosinophils and/or plasma cells
  - Mitotic activity - minimal in early stage lesions

Cytologic features

- Description in literature:
  - Small to medium-sized lymphocytes with indented, cerebriform nuclei (sometimes hyperchromatic)
  - Transformation to larger cells with vesicular nuclei and visible nucleoli occurs later in course of disease and is outside realm of this presentation

Cytologic features

- Study results:
  - Intraepidermal lymphocytes - several studies confirm this as reproducible
    - Size - about size of keratinocyte nuclei
    - Shape - markedly convoluted as at low magnification
  - Dermal lymphocytes - not as useful - difficult to tell reactive dermal T cell from scattered atypical cells
    - Size
    - Shape
Histologic features and prognosis

- Most patients with early patch/plaque stage MF have essentially normal life expectancy.
- Small subset have rapidly progressive disease.
- Not possible to discriminate these patients based upon histologic features of early biopsies - likely molecular fingerprint will provide the answers.

Overall prognosis

- Stage 1a (patches and plaques < 10% of body surface area): 97%-98% 10 year survival.
- Stage 1b (patches and plaques > 10% of body surface area): 83% 10 year survival.
- Tumors: 42% 10 year survival.
- Lymph node involvement: 20% 10 year survival.

Ancillary techniques

- Immunostains
- T-cell gene rearrangement studies

Useful Immunostains in Mycosis Fungoides

- CD2
- CD3
- CD4
- CD5
- CD8
- CD7
- CD30
Immunostains in MF

- Some disagreement about diagnostic criteria
  - Most authors include CD4+ and CD8+ epidermotropic T cell lymphomas into category of MF (WHO)
  - Minority prefer to separate CD8+ epidermotropic T cell lymphomas from the vast majority of CD4+ cases traditionally considered to be MF
  - Recent WHO Classification suggests same clinical course and prognosis and no reason to separate

Immunostains in early lesions of MF

- Study results:
  - CD4+, CD8-, CD7- is most commonly observed phenotype
  - Loss of pan T-cell antigens CD2, CD3, CD5 also seen in minority of early cases
  - 75% of cases, immunostains served only to confirm H and E diagnosis
  - In series of 250 cases, immunostains based upon loss of pan T-cell surface antigens revealed an earlier diagnosis than H and E in 4% of cases - but remember the life expectancy data!

CD3

CD4

CD8

Double-labeling of lymphocytes in the skin does not provide useful information

CD4/CD8 double labeling
T-cell gene rearrangements in Mycosis Fungoides

- Sensitivity
- Specificity

> 80% of patch-stage lesions of MF will demonstrate a clonal rearrangement using PCR technology.

Useful to confirm diagnosis if clinically suspicious and routine histology is less than fully diagnostic.

“Negative” result does not rule out MF diagnosis.

Close to 100% of later stage lesions demonstrate clonality, but not often needed in these cases.

T-cell gene rearrangements

- Specificity
  - Clonality has been demonstrated in lymphomatoid papulosis, “parapsoriasis” (small and large plaque), PLEVA, PLC - still controversial how these entities related to T cell lymphoproliferative disorders.
  - Also demonstrated in disease with no known potential for malignant transformation:
    - Lichen planus
    - Pigmented purpuric eruption
  - Important to have high index of suspicion when ordering test and to interpret findings in context to avoid over diagnosis.

- “Positive” result does not necessarily imply MF diagnosis.

Genetic aberrations in MF

- Chromosomal loss at 10q and abnormalities in p15, p16 and p53 tumor suppressor genes commonly seen in patients with MF - not specific.

- No specific chromosomal translocations associated with MF.

Differential diagnosis

- Pityriasis lichenoides chronica
- Digitate dermatosis (small plaque parapsoriasis, guttate parapsoriasis)
- Pityriasis rubra pilaris
- Lymphomatoid papulosis

Pityriasis lichenoides chronica

- Smaller, more discrete lesions
- Less intense infiltrate
- Scattered dying keratinocytes (unusual finding in MF)
- Slight hemorrhage
- Lack of Pautrier’s microabscesses, single atypical lymphocytes within epidermis and along DEJ
Digitate dermatosis

- Characteristic clinical appearance
- Small foci of epidermotropism, often with mild spongiosis
- Lymphocyte “atypia” not present
- No Pautrier’s microabscesses

Pityriasis rubra pilaris

- Clinical “skip areas” helpful if present
- Psoriasiform hyperplasia with scattered dying keratinocytes
- Pattern of alternating ortho- and parakeratosis
- Folliculo-centric process
- Minimal lymphoid infiltrate

Lymphomatoid papulosis

- Often multiple small papules/nodules without plaques
- Deeper infiltrate than MF
- Often many eosinophils
- Cytologic atypia in most cases more dramatic than in early MF

Arriving at a final diagnosis

- In most cases, patients must have an appropriate clinical presentation and course
- Histologic findings should demonstrate many, if not all, of the established criteria
- In cases with some uncertainty, confirming the T cell nature (often with loss of surface antigens) can increase certainty
- Given a high index of suspicion, a positive gene rearrangement results in a high likelihood of a correct diagnosis

Diagnostic possibilities

- Atypical lymphoid infiltrate
- Suggestive of mycosis fungoides
- Strongly suggestive of mycosis fungoides
- Consistent with mycosis fungoides
- Mycosis fungoides