CTCL Diagnosis and Staging

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WHO classification of primary cutaneous lymphomas

**Cutaneous T-cell and NK-cell lymphomas**

- Mycosis fungoides
  - MF variants and subtypes
- Folliculotrophic MF
- Pagetoid reticulosis
- Granulomatous slack skin
- Sézary syndrome
- Primary cutaneous CD30+ lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosus
- Subcutaneous panniculitis-like T-cell lymphoma*
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma
- Cutaneous γ/δ T-cell lymphoma (provisional)
- Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma
- Primary cutaneous peripheral T-cell lymphoma, unspecified

Cutaneous T cell lymphomas: Epidemiology

WHO data
Diagnosing Cutaneous T-cell Lymphomas
Lesson #1
Clinical-pathologic correlation is essential for optimal diagnosis & management

Take Home Message

- Numerous mimics of clinical OR path features exist
- Correlation of clinical AND pathologic information is essential for optimal diagnosis

=> appropriate work-up, prognostication, and management
Differential diagnosis of CD30+ atypical lymphoid infiltrates in the skin

Reactive

- Lymphomatoid drug reaction (e.g., amlodipine, carbamazepine, cefuroxime, valsartan)
- Arthropod reaction
- Infection (esp. viral)
- Misc. inflammatory dermatoses

Neoplastic

- pc CD30+ LPD
  - Lymphomatoid papulosis
  - pc CD30+ ALCL
- MF (esp. Large cell transformation, Woringer-Kolopp)
- Other CTCLs
- Secondary skin involvement of sALCL, HD or other sLPD

Clinico-pathologic correlation is essential
PC CD30+ lymphoproliferative disorder spectrum: LyP === borderline === pc CD30+ ALCL

<table>
<thead>
<tr>
<th>Lymphomatoid papulosis</th>
<th>pc CD30+ ALCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% spontaneous regression</td>
<td>&lt; 25% spontaneous regression</td>
</tr>
<tr>
<td>Papules &gt;&gt; nodules</td>
<td>Mostly nodules/tumors</td>
</tr>
<tr>
<td>Crops of lesions, +/- grouped</td>
<td>Single, grouped, multifocal</td>
</tr>
<tr>
<td>Multiple histologic subtypes (types A-D, other); type A most common, type B MF-like (low CD30), type C ALCL-like, type D mimics CD8+ AETCL</td>
<td>Usu. sheets of anaplastic large cells</td>
</tr>
</tbody>
</table>

**CLINICAL-PATHOLOGIC CORRELATION IS ESSENTIAL**
Primary Cutaneous ALCL

- Represents about 8% of cutaneous lymphoma cases.
- Unlike systemic ALCL, PC-ALCL typically follows an indolent course and although cutaneous relapses are common an excellent prognosis is usually maintained.
- Do not need treatment with CHOP/CHOP-like therapy, as used for systemic ALCL
- Treatment can be local tx but often require systemic tx (e.g. methotrexate, brentuximab)
Lymphomatoid Papulosis (LyP)

- Often spontaneously regressing process
- Treatment often is observation or local tx

- LyP has been reported to be associated with other lymphomas such as MF, PC-ALCL, systemic ALCL, or Hodgkin lymphoma
Differential diagnosis of epidermotropic process with CD8+ lymphoid infiltrates

Reactive
- Lymphomatoid drug reaction
- Misc. inflammatory dermatoses (esp. actinic reticuloid)
- Infections

Neoplastic
- CD8+ AETCL
- Lymphomatoid papulosis, type D
- CD8+ MF (hypopig variant)
- SubQ panniculitis-like TCL
- CD8+ LPD of ear/face
- PTCL NOS
- Secondary skin involvement of PTCL

Clinico-pathologic correlation is essential
Type D CD8+ LyP vs. CD8+ aggressive epidermotropic cytotoxic TCL

LyP type D

CD8

CD8+ aggressive epidermotropic cytotoxic TCL

Courtesy T Subtil
Multicenter Case Series of Indolent Small/Medium-sized CD8+ Lymphoid Proliferations with Predilection for the Ear and Face

Janet Y. Li¹, Joan Guitart², Melissa P. Pulitzer¹, Antonio Subtil³, Uma Sundram⁴, Youn Kim⁴, Janyana Deonizio², Patricia L. Myskowski¹
Alison Moskowitz¹, Steven Horwitz¹, Christiane Querfeld¹
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Am J Dermatopathol, in press 2013
Indolent Small/Med-sized CD8+ Lymphoid Proliferations with Predilection for the Ear and Face

Querfeld, MSKCC

Stanford case
Angioinvasive Lymphomatoid Papulosis
A New Variant Simulating Aggressive Lymphomas

Werner Kempf, MD,* † Dmitry V. Kazakov, MD, PhD,‡ Leo Schärer, MD,§
Arno Rütten, MD,§ Thomas Mentzel, MD,§ Bruno E. Paredes, MD,§
Gabriele Palmedo, PhD,§ Renato G. Panizzon, MD,|| and Heinz Kutzner, MD§

Angioinvasive, aggressive NK/T-cell lymphoma, nasal-type
Dermatopathology

Follicular lymphomatosid papulosis of 11 cases, with new histopatho

Werner Kempf, MD,a Dmitry V. Kazakov, MD, PhD,b Hans-Peter Baumga
Zürich and Zug, Switzerland; Pilsen and Prague, Czech Republic,

Mycosis Fungoides - the greatest masquerader

Clinical & Histologic Variants/Subtypes

- Hypopigmented/vitiligenous MF
  - Children, African American, Asian
- Pagetoid reticulosis (Woringer-Kolopp type only)
- Folliculotropic MF (+/- FM)
  - Head and neck
- Granulomatous MF
  - Granulomatous slack skin
- Bullous MF
- PPE-like MF
- Interstitial MF
- Icthyiosiform MF
- Palmar plantar MF
- Hyperkeratotic/verrucous MF
- Papular MF
- Invisible MF
- Spongiotic MF
- Lichenoid MF
- CD8+ MF
- Large cell (transformed) MF
Folliculotropic Mycosis Fungoides

Clinico-pathologic correlation is essential
Mycosis Fungoides Diagnosis and Staging Evaluation
Clinical Phases of CTCL – Mycosis Fungoides

Patch

Plaque

Tumor

Erythroderma
Mycosis Fungoides Clinical Presentation

Patches, Plaques

Hypopigmented Patches, Plaques
Mycosis Fungoides Clinical Presentation
Sezary Syndrome
Why is it so hard to diagnose early disease?
Tools to Diagnose Cutaneous Lymphoma

- History
- Physical exam
- Skin biopsy (often multiple!)
- Blood tests
- Imaging (CT scans or PET/CT)
- Bone marrow, lymph node biopsy
Routine histology is the most important tool

- Multiple biopsies over a period of time are often needed for diagnosis. Prior treatment may alter the biopsy appearance.
- Separation of MF from other inflammatory dermatoses can be difficult.
- Important histologic features include:
  - Pautrier microabscesses
  - Lymphocytes with a clear perinuclear halo
  - Lymphocytes aligned along the basal layer
  - Intraepidermal lymphocytes with hyperconvoluted nuclei
  - Epidermal lymphocytes and epidermotropism
MF histology varies by type/stage

• **Patch Stage**
  • Band-like infiltrate along the papillary dermis, DEJ, & basal layer
  • Pautrier microabscess are uncommon
  • Fibrosis of the papillary dermis may be present

• **Plaque Stage**
  • Increased dermal infiltrate
  • Nuclei are larger and indented “cerebriform”
  • Pautrier microabscess are more common

• **Tumor Stage**
  • Monomorphic infiltrate with atypical lymphocytes
  • Entire dermis and even subcutis may be involved
  • Epidermotropism and pautrier microabscess are uncommon
Special studies used to diagnosis cutaneous lymphoma

• Immunohistochemical stains or “markers”
  – Loss of markers associated with disease progression

• Molecular (DNA based) studies
  – Gene rearrangement or “clonality”
  – Flow cytometry
Immunohistochemical Stains - “Markers”

Help identify what type of lymphoma

Can guide treatment
Molecular studies in the diagnosis of cutaneous lymphoma

• Gene rearrangement or “clonality” studies
  – Varying techniques, some with higher sensitivity and specificity

• Flow cytometry
  – Phenotype of malignant T-cells can vary by type/stage
Lesson #2
Don’t forget to check the blood

Key diagnostic info may be in the blood compartment

- Sezary flow studies in the erythrodermic pt
- HTLV1 serology in ddx of MF/SS vs. ATLL
ATLL, spectrum of skin presentation

MF-like, smoldering variant

Acute, disseminated disease
ATL can mimic Sezary syndrome
Acute ATLL

Coutesy J Guitart
Clinical Case
Challenge of the red person
63 F with 4 yr h/o progressive erythroderma

- Itchy scalp and scaly red patches and plaques
  - Refractory to topical steroids; pred helps
  - Skin biopsy => spong derm
  - nbUVB, unable to tolerate
- Progressive erythroderma, keratoderma
  - Rebiopsy => psoriasiform derm
  - Soriatane => no response
- Immune suppressive therapies
  - Cyclosporin x 3 mo => PR
  - Humira added => no sig benefit, flares with CSA taper
  - Rebiopsy => psoriasiform derm with spong
- No drug etiology
Erythroderma with severe pruritus

DDx- eczematous derm, psoriasis, drug, PRP, MF/SS, other
Keratoderma of palms and soles
Differential diagnosis of erythrodermas

- Psoriasis
- PRP
- Eczematous dermatitis
- Drug reaction
- Sarcoidosis
- Scabies
- Autoimmune
  - DM
  - Overlap
  - CTCL (MF/SS)
  - Other hematolymphoid processes (e.g., ATLL, CLL, T-PLL)
  - Paraneoplastic
  - GVHD
  - Infectious (staph toxin)
  - Misc. inflammatory

Skin biopsies often non-diagnostic in erythrodermic skin of CTCL
When suspecting Sézary syndrome

- **Evaluation of blood compartment**
  - Flow cytometry c/w blood involvement
  - TCR PCR clone in blood identical to skin

- **Staging and other work-up**
  - CMP/LDH normal
  - Whole body PET/CT
    - 1-1.5 cm cm axillary/inguinal LNs, low SUVs

=> Sézary syndrome, stage IVA (T4NxM0B2)
Challenge of the red person

Take home message

Skin biopsies often non-diagnostic from erythrodermic skin of CTCL

MUST ASSESS BLOOD if suspect SS
Diagnostic Criteria for MF

- Algorithm for diagnosing early MF is based upon clinical, histopathologic, molecular, and immunopathologic criteria proposed by the ISCL/EORTC.

- The diagnosis of MF can be made using the point-based algorithm, which incorporates clinical, histopathologic, molecular, and immunopathologic criteria. A diagnosis of MF is made when a total of four points or more is determined.
• Clinical (max 2 points)
  – Persistant patches/plaques
    • Non sun-exposed sites, variably sized, poikiloderma
• Histopathologic (max 2 points)
  – Superficial lymphoid infiltrate
    • Epidermotropic and not spongiotic, atypia
• Molecular studies (1 point)
  – Clonal gene rearrangement study
• Immunopathology (1 point)
  – >50% T cells, loss of CD7, epidermal/dermal discordance
Staging of MF/CTCL involves the evaluation of skin, lymph nodes, viscera, and blood.

<table>
<thead>
<tr>
<th>Essential Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Exam</strong></td>
</tr>
<tr>
<td>Examination of entire skin</td>
</tr>
<tr>
<td>mSWAT</td>
</tr>
<tr>
<td>Palpation of peripheral lymph node regions</td>
</tr>
<tr>
<td>Palpation for organomegaly/masses</td>
</tr>
<tr>
<td>Rule out other - ANA</td>
</tr>
</tbody>
</table>

**CBC**: complete blood count; **CT**: computed tomography; **TCR**: t-cell receptor; **PET**: positron emission tomography; **LDH**: lactate dehydrogenase
%TSBA = (Total Body Surface Area)

- The body is divided into 12 regions with pre-assigned %TSBA based on methodology used to assess burns.
- The extent of skin disease is assessed for each region and quantified by using the patient’s palm as the ‘ruler’ to measure the %TBSA involvement with each region.
  - Patient’s palm with 4 fingers, excluding the thumb and measured from wrist to fingertips, is 1% of TBSA.
  - Patient’s palm without fingers is 0.05% of TBSA.
Staging of MF Involves Evaluation of Skin (T), Lymph Nodes (N), Viscera (M), and Blood (B)

<table>
<thead>
<tr>
<th>TNMB stages</th>
<th>Staging parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (T)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Patches and/or plaques covering &lt;10% BSA;</td>
</tr>
<tr>
<td></td>
<td>Further stratified into T1a (patch only) versus T1b (plaque ± patch)</td>
</tr>
<tr>
<td>T2</td>
<td>Patches and/or plaques covering ≥10% BSA;</td>
</tr>
<tr>
<td></td>
<td>Further stratified into T2a (patch only) versus T2b (plaque ± patch)</td>
</tr>
<tr>
<td>T3</td>
<td>One or more tumors (≥1 cm diameter)</td>
</tr>
<tr>
<td>T4</td>
<td>Coalescing erythema covering ≥80% of skin surface</td>
</tr>
<tr>
<td>LN (N)</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No clinically abnormal lymph nodes</td>
</tr>
<tr>
<td>N1</td>
<td>Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN0-2</td>
</tr>
<tr>
<td></td>
<td>Further stratified into N1a (TCR non clonal) versus N1b (TCR clonal)</td>
</tr>
<tr>
<td>N2</td>
<td>Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN3</td>
</tr>
<tr>
<td></td>
<td>Further stratified into N1a (TCR non clonal) versus N1b (TCR clonal)</td>
</tr>
<tr>
<td>N3</td>
<td>Clinically abnormal lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative</td>
</tr>
<tr>
<td>Nx</td>
<td>Clinically abnormal lymph nodes; no histologic confirmation</td>
</tr>
<tr>
<td>Visceral (M)</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No visceral organ involvement</td>
</tr>
<tr>
<td>M1</td>
<td>Visceral involvement, pathologically confirmed + organ involved specified</td>
</tr>
<tr>
<td>Blood (B)</td>
<td></td>
</tr>
<tr>
<td>B0</td>
<td>No significant blood involvement: &lt;5% Sézary cells. For clinical trials, B0 may also be defined as &lt;250/mL Sézary cells CD4+CD26- or CD4+CD7- cells or CD4+CD26- and CD4+CD7- cells &lt;15%</td>
</tr>
<tr>
<td>B0a</td>
<td>Clone negative</td>
</tr>
<tr>
<td>B0b</td>
<td>Clone positive</td>
</tr>
<tr>
<td>B1</td>
<td>Low tumor burden. Does not fit B0 or B2 criteria</td>
</tr>
<tr>
<td>B1a</td>
<td>Clone negative</td>
</tr>
<tr>
<td>B1b</td>
<td>Clone positive</td>
</tr>
<tr>
<td>B2</td>
<td>High blood tumor burden: Positive clone plus one of the following: &gt;1000/mL Sézary cells;</td>
</tr>
<tr>
<td></td>
<td>CD4/CD8 ≥10</td>
</tr>
<tr>
<td></td>
<td>CD4+CD7- cells ≥40 percent</td>
</tr>
<tr>
<td></td>
<td>CD4+CD26- cells ≥30 percent</td>
</tr>
<tr>
<td></td>
<td>For clinical trials, B2 may also be defined as &gt;1000/mL CD4+CD26- or CD4+CD7- cells.</td>
</tr>
</tbody>
</table>

For skin, plaque is any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiderma should be noted. Features such as folliculotropism (FT) or large-cell transformation (LCT; >25% large cells), CD30+, and ulceration are important to document. Tumor indicates at least one 1 cm solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, largest size lesion, region of body involved, and histologic features such as FT or LCT, CD30+.

For node, abnormal lymph node (LN) indicates any LN ≥1.5 cm.

For viscera, spleen and liver may be diagnosed by imaging criteria alone.

## COMPOSITE ISCL/EORTC STAGING

### 2007 ISCL/EORTC Revision to the Staging System of MF and SS

<table>
<thead>
<tr>
<th>Stage</th>
<th>T (Skin)</th>
<th>N (Lymph Node)</th>
<th>M (Viscera)</th>
<th>B (Blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIA</td>
<td>1,2</td>
<td>1,2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>0-2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IVA₁</td>
<td>1-4</td>
<td>0-2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>IVA₂</td>
<td>1-4</td>
<td>3</td>
<td>0</td>
<td>0-2</td>
</tr>
<tr>
<td>IVB</td>
<td>1-4</td>
<td>0-3</td>
<td>1</td>
<td>0-2</td>
</tr>
</tbody>
</table>

**B0** Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL Sezary cells or <15% CD4+CD26- or CD4+CD7-

**B1** Low blood tumor burden: >5% of peripheral blood lymphocytes are Sezary cells but not meet criteria for B2

**B2** High blood tumor burden: ≥1000/mcL Sezary cells or CD4/CD8 ≥10 or ≥40% CD4+CD7- or ≥CD4+CD26- cells
Prognosis in MF best predicted by TNMB staging.

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>35.5</td>
</tr>
<tr>
<td>IB</td>
<td>21.5</td>
</tr>
<tr>
<td>IIA</td>
<td>15.9</td>
</tr>
<tr>
<td>IIB</td>
<td>4.7</td>
</tr>
<tr>
<td>IIIA</td>
<td>4.7</td>
</tr>
<tr>
<td>IIIIB</td>
<td>3.4</td>
</tr>
<tr>
<td>IVA1</td>
<td>3.9</td>
</tr>
<tr>
<td>IVA2</td>
<td>2.1</td>
</tr>
<tr>
<td>IVB</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Agar et al. JCO. 2010
Challenges of CTCL

- Rare heterogeneous group of lymphoproliferative disorders
- Need more translational research
- Management is complicated by involvement of multiple specialists with differing scope of practice and protocols:
  - Dermatologists, Oncologists/Hematologists, Pathologists (heme and derm), Radiation oncologists, & Clinical Investigation Core (Research)
- Diagnosis, staging, and management plan should be collaborative
- Requires adequate biopsy, laboratory analysis, history & physical exam, and imaging
- Standard of care is unclear
- Clinical Trials are key
- Emphasizes importance of multidisciplinary approach
Teamwork & Synergy in Clinical Care

Dermatology
(Cutaneous Oncology)

Medicine
(Medical Oncology,
BMT)

Radiation
Oncology

Pathology
(Dermpath/Hemepath)

Cutaneous Lymphoma
Clinical Care Providers
Support Staff

Courtesy Youn Kim MD
Separate physical space (separate clinics)
Path joins clinicians (ideal clinical-path correlation)

Derm
Rad Onc
Med Onc
Path
Derm
Rad Onc

Patient

Eczema? PRP? Sezary? Drug rash?

Sezary syndrome!
The importance of a team approach

- All patients with a new diagnosis of CTCL should be reviewed initially by a multidisciplinary team
- The diagnosis, staging and management plan should be collaborative
- Central review of pathology and the use of accredited laboratories for immunophenotypic and molecular studies is desirable
- Patient management should be shared between dermatologists and oncologists, or specialists, for all patients with stage IB disease and onwards
Questions