Overview of Cutaneous Lymphomas: Diagnosis and Staging

Lauren C. Pinter-Brown MD, FACP
Health Sciences Professor of Medicine and Dermatology
Definition of Lymphoma

- A cancer or malignancy that comes from a clonal expansion of one lymphocyte (B, T, or natural killer) in a lymph node, blood or other tissue such as skin.

- Lymphocytes are a part of our immune system.

- The skin is the second most common extranodal (outside of lymph nodes) site of involvement for lymphomas.
Cellular Origins of Lymphomas / Leukemias

PLURIPOTENT STEM CELL

LYMPHOID STEM CELL

PRECURSOR T - CELL

PRECURSOR B - CELL

MATURE T - CELL

MATURE B - CELL

ACUTE LEUKEMIAS

ACUTE LYMPHOBLASTIC LEUKEMIAS

LYMPHOBLASTIC LYMPHOMAS / LEUKEMIAS

NON-HODGKIN’S LYMPHOMAS

LYMPH NODES, EXTRANODAL TISSUES like marrow, blood and skin

S. J. Schuster, 2003
Cutaneous Lymphomas: Why are they different?

• T-cell lymphoma accounts for 60-80% of all primary (limited to the skin) cutaneous lymphomas; the reverse of lymphomas in general.

• The behavior and treatment for a skin lymphoma will often be radically different from a similar looking or named lymphoma that begins in the lymph node, so cutaneous lymphomas have their own classification and staging systems to help decide on treatment.
Cutaneous Lymphomas: Why are they different?

• Unlike the general group of lymphomas or other malignancies, the pathologists’ diagnosis in a case of cutaneous lymphoma may not be the final diagnosis, but rather, may suggest a group of conditions such that clinico-pathologic correlation (cooperation between the pathologist and clinician) will determine the final diagnosis.

• Patients with skin lymphomas may use a team of doctors for their care (pathologists, dermatologists, oncologists, radiologists and radiation therapists).
FIGURE 3. Skin Anatomy.
Monoclonal Antibodies

- Proteins that our bodies or a laboratory can make that bind (attach) to specific protein markers (called *antigens*) on lymphoma or other cells.

- They can be used to help make a diagnosis on slides or from blood.

- They can be used as a treatment of specific cancers.
## Types of Cutaneous B-cell Lymphomas (CBCLs)

<table>
<thead>
<tr>
<th>Indolent (slow) CBCL</th>
<th>Aggressive (faster) CBCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary cutaneous follicle center lymphoma (11%)</td>
<td>• Primary cutaneous diffuse large B-cell lymphoma, leg type (4%)</td>
</tr>
<tr>
<td>• Primary cutaneous marginal zone lymphoma (7%)</td>
<td>• Primary cutaneous diffuse large B-cell lymphoma, other, intravascular large B-cell (&lt;1%)</td>
</tr>
</tbody>
</table>
Indolent (slow) CBCLs

- Red nodules rarely ulcerating
- Primary cutaneous marginal zone lymphomas can present acutely or more slowly over months; primary cutaneous follicular center lymphomas over months to years
- Over 50% return in skin but patients continue to have an excellent outcome; less than 10% become extracutaneous (outside the skin) (especially marginal zone lymphomas)
Cutaneous T-Cell Lymphoma (CTCL)

• CTCL defines a heterogenous group of malignant lymphomas with primary manifestations in skin. The term was “coined” in 1979.

• Mycosis fungoides (MF) is the most common CTCL.

• Sezary’s Syndrome (SS) represents 5% of all cases of MF.
Types of Cutaneous T-Cell Lymphomas (CTCLs)

**Indolent CTCLs**
- Mycosis fungoides (MF) (44%)
- MF variants and subtypes
  - Folliculotropic MF (4%)
  - Pagetoid reticulosis (<1%)
  - Granulomatous slack skin (<1%)
- CD30+ lymphoproliferative disorders
  - Anaplastic large cell lymphoma (8%)
  - Lymphomatoid papulosis (12%)
- Subcutaneous panniculitis-like T-cell lymphoma (1%)
- CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder (2%)

**Aggressive CTCLs**
- Sézary syndrome (SS) (3%)
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (<1%)
- Primary cutaneous γ/δ T-cell lymphoma (<1%)
- Primary cutaneous acral CD8+ T-cell lymphoma (provisional)

CD-30 + Lymphoproliferative Disorder
“Clinico-pathologic correlation needed”

- Mycosis Fungoides (Transformed)
- Lymphomatoid Papulosis
- Primary Cutaneous ALCL
- Secondary Cutaneous ALCL
- Systemic ALCL
- Hodgkin Lymphoma
CD 30+ Lymphoproliferative disorders are a spectrum of conditions

• Primary cutaneous Anaplastic Large Cell Lymphoma (PC-ALCL)
• Lymphomatoid Papulosis (LyP)

• LyP and PC-ALCL can overlap clinically and histologically, so clinico-pathologic correlation is essential for correct diagnosis

• Transformed MF and MF are also in differential diagnosis of CD30+ skin lesions
• Different skin lesions can appear on the same person
Lymphomatoid Papulosis (LyP)

• “Clinically benign; histologically malignant”
• Recurrent crops of papules (like insect bites) <2 cm (smaller than an inch) which heal by themselves in 3-6 weeks sometimes leaving a dark area or a scar
• Lesions are red-brown, with central red or black appearing on the trunk or extremities
• As lesions evolve, they can have a blister or pus in the center
• Variable frequency and/or severity or outbreaks with different patients and in same patient over time
• Younger median age than primary cutaneous ALCL (45 vs. 60 yo)
• Increased chance of MF, ALCL and Hodgkin lymphoma
Primary Cutaneous ALCL (PC-ALCL)

- 25% of CTCL
- Presents as solitary or localized skin lesions (>2cm) that may be ulcerated tumors, nodules, or papules in patients without any other diagnosis of LyP, lymphoma or extracutaneous involvement
- 20% have more than one area of skin disease
- Characterized by partial or complete spontaneous regression (40%), but frequent skin relapses
- 10-25% develop extracutaneous dissemination, mainly to regional nodes, mostly those with many skin lesions at once
Mycosis Fungoides (MF)

- The term “MF” was first used in 1806 by Alibert, a French dermatologist because he though the lesions looked like a fungus (it’s not!)

- “MF” is the most common type of cutaneous lymphoma, and CTCL (40% of cases)

- Pathologically, MF affects the most superficial layer of the skin, the epidermis, and “epidermotropism” (with/without Pautrier’s microabscesses) distinguishes MF from other skin lymphomas.
Sezary’s syndrome (SS)

• Represents about 5% of all cases of MF

• Described by Sezary, another French dermatologist in 1938

• It is characterized by circulation of MF cells (or Sezary’s cells) in the blood

• Patients may have generalized redness and scaling of the skin, enlarged lymph nodes, scaling and slits in the palms and soles, changes in their nails, swelling of their legs and/or changes in their eyelids and itching
Mycosis Fungoides: Clinical and Histologic Variants/Subtypes

- Hypopigmented/vitiligenous MF
- Unilesional pagetoid reticulosis (Woringer-Kolopp type only)
- Follicular MF (+/- mucinosis)
- Granulomatous MF
  - Granulomatous slack skin
- Bullous MF
- PPE-like MF
- Interstitial MF
- Papular MF
Immunochemistry (proteins expressed by tumor cells): cells are typically CD3+, CD4+, CD8-, CD30-
Staging of Cutaneous Lymphomas

It’s different from other NHLs or HL!
Why do we have stages?

• To suggest an appropriate treatment
• To give an idea of what to expect
• To know what areas or test(s) to look at when we want to assess the effectiveness of a treatment in an individual
• To evaluate data from groups of participants in clinical trials and allow comparisons between trials
What don’t stages tell us?

• A disease may not and does not have to naturally progress from one stage to another

• Assignment of a stage does not tell us how an individual will do with their disease or a particular treatment
Staging of MF/SS
Staging involves assessment of tissues trafficked by T-cells

• Skin
• Nodes
• Blood
• Liver, spleen, and lung
Staging Evaluation for MF/SS

**Skin:**

- Do photography and/or document extent, type and distribution of skin lesions; may require additional biopsies

**Node:**

- Record size, numbers and locations on exam
- Consider node biopsy if large nodes are felt on physical examination
Staging Evaluation of MF/SS

Blood:

- Complete Blood Count/differential, liver function tests with LDH, sometimes HIV/HTLV I
- Flow cytometry, + T-cell gene rearrangement

Viscera:

- Chest Xray and physical exam
- Sometimes PET/CT and/or marrow examinations depending on findings on physical examination and blood
Positron Emission Tomography (PET)/Computerized Tomography (CT)
PET/CT
PET/CT
## Revised MF/SS staging

<table>
<thead>
<tr>
<th>TNMB</th>
<th>TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>T1: Limited patches, papules and/or plaques covering &lt; 10% of the skin surface</td>
</tr>
<tr>
<td></td>
<td>T2: Patches, papules and/or plaques covering ≥ 10% of the skin surface</td>
</tr>
<tr>
<td></td>
<td>T3: One or more tumors (≥ 1 cm in diameter)</td>
</tr>
<tr>
<td></td>
<td>T4: Confluence of erythema ≥ 80% body surface area</td>
</tr>
<tr>
<td>Node</td>
<td>N0: No clinically abnormal peripheral lymph nodes; biopsy not required</td>
</tr>
<tr>
<td></td>
<td>N1: Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2</td>
</tr>
<tr>
<td></td>
<td>N2: Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3</td>
</tr>
<tr>
<td></td>
<td>N3: Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4</td>
</tr>
<tr>
<td></td>
<td>NX: Clinically abnormal peripheral lymph nodes; no histologic confirmation</td>
</tr>
<tr>
<td>Visceral</td>
<td>M0: No visceral organ involvement</td>
</tr>
<tr>
<td></td>
<td>M1: Visceral involvement (must have pathology confirmation and organ involved should be specified)</td>
</tr>
<tr>
<td>Blood</td>
<td>B0: Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sezary) cells</td>
</tr>
<tr>
<td></td>
<td>B1: Low blood tumor burden: &gt; 5% of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2</td>
</tr>
<tr>
<td></td>
<td>B2: High blood tumor burden: ≥ 1000/mcL Sezary cells</td>
</tr>
</tbody>
</table>
Regional percent body surface area (BSA) in the adult.

## Revised MF/SS staging

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>IVA1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>IVA2</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Staging of other cutaneous lymphomas
Clinical Staging for other Lymphomas

• History: attention to “B” symptoms (fever, night sweats, weight loss)
• Physical exam: attention to LN areas, liver, spleen
• Complete blood count with evaluation of blood smear and differential
• Serum chemistries, including LDH
• Flow cytometry as indicated
• CT scans of neck, chest, abdomen and pelvis
• Additional radiological studies as indicated (e.g., PET scan, chest Xray, and/or MRI scan)
• Bone marrow biopsies as indicated
• In some cases, cerebrospinal fluid exam, bone or gastrointestinal exam
Proposed ISCL/EORTC TNM Staging System for Cutaneous Lymphomas other than MF/SS

• **Blood** 2007; 110(2): 479-484
• Complicated system of questionable utility