Cutaneous Lymphoma: Diagnosis, Staging and Prognosis

Henry K. Wong, MD, PhD
Department of Dermatology
University of Arkansas

Cutaneous Lymphoma Foundation
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Conflict of Interests

- Actelion – Research, advisory board
- Novartis - research
- Elorac – research
- Regeneron - Advisory
Cutaneous T cell lymphoma, indolent but can be an aggressive cancer. Much like Dr. Jeckyll and Mr. Hyde, we need to better understand the cancer to find the right "potion" to treat CTCL (Mr Hyde).
Cutaneous Lymphoma

- Overview
- Clinical Presentation
- Diagnosis
- Staging
- Prognosis
Cells that become lymphoma

Immune cells protect the skin

T and B cell cells migrate to the skin to guard. T cells more often. Persistanace of abnormal cells is associated with skin disease.
Cutaneous Lymphoma: How common?

- Non-Hodgkin lymphoma (NHL) (71,850)
- Hodgkin lymphoma (HL) (9,290)

B-cell lymphoma (770 / yr -1%)

- T-cell lymphoma (70%)
- 15% T-cell lymphoma
- 85% B-cell lymphoma

Cutaneous lymphoma

30% B cell

References:

Note: B-cell and T-cell sub-classifications are illustrated on slides 10 and 11, respectively.
WHO/EORTC Lymphoma Classification

Skin Lymphomas

B cell

Primary cutaneous marginal zone B cell lymphoma

Primary cutaneous follicular center

Primary cutaneous diffuse large B cell – leg type

T cell

Primary cutaneous CD30+ T cell disorder

Mycosis fungoides

Sezary syndrome

Primary cutaneous γδ TCL

Peripheral TCL-NOS

Subcutaneous panniculitic-like TCL
Variable presentation of cutaneous lymphoma
CD30+ Lymphoproliferation

Lymphomatoid Papulosis

CD30+ Anaplastic large cell lymphoma (ALCL)
CTCL: Scaly patches
CTCL: Patches and plaques
Cutaneous T-Cell Lymphoma (MF/SS)
Common Mimickers

1. New Zealand Dermatological Society Incorporated. Published online at: http://www.dermnetnz.org
Mycosis Fungoides (MF)

Epidemiology

- Described in 1806 by Alibert
- 3% of non-Hodgkin’s lymphoma – etiology unclear
- Annual incidence: 0.36-0.90/100,000
- Median age 55 - 60 years
- 2:1 male predominance
- African americans affected greater than caucasian
- Leukemic phase - Sézary Syndrome
  - Atypical Sézary cells in the peripheral blood
MF Clinical History

- Indolent for many years, “premymotic stage”
- Minimal symptoms in early stage
- Bathing trunk distribution
- Thin patches with cigarette paper atrophy, ‘poikiolodermatous’ appearance
- Symptoms of itchiness with late disease
- Progresses on skin before internal involvement
- Fevers, chills, secondary infections with late stage disease
Diagnosis / Staging

- Complete physical exam
- Skin biopsy of suspicious lesion
  - Multiple biopsies may be necessary of early stage lesions
  - Immunohistochemistry – CD3, CD4, CD45, CD5, CD7
  - TCR gene clonality studies
- Blood count with differential, chemistry, liver function test, lactate dehydrogenase LDH, Sezary studies
- Imaging - CT or PET/CT if lymph node palpable
- Lymph node biopsy if palpable
Body surface area – T staging

<table>
<thead>
<tr>
<th>T1</th>
<th>&lt; 10% BSA</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>&gt;10%</td>
<td>IB</td>
</tr>
<tr>
<td>&lt; 80%BSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>tumor</td>
<td>IIB</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 80% BSA</td>
<td>III-IV</td>
</tr>
</tbody>
</table>
Diagnosis

Clinically suspicious skin lesion

Monitor

Not CTCL

Immune histo -
TCRGR (-)

Close follow-up
Repeat biopsy

Suspicious for CTCL

Immunehisto+
TCRGR (-)

Research

Diagnostic for CTCL

Immunehisto -
TCRGR (+)

+ Clinical morphology

Treat for CTCL
Histopathology

- Historically “classic” features
  - Epidermotropism without spongiosis
  - Atypical lymphocytes
  - Pautrier microabscesses

- Other features
  - Haloed lymphocytes
  - Solitary lymphocytes in the basal layer
  - Lymphocytes in epidermis larger than those in dermis
  - Dermal collagen fibrosis

Normal

Mycosis fungoides
Immune markers of CTCL

**Antigens expressed**
- CD3
- CD4
- CD7

**Antigens lost**
- TCR/CD3
- CD45RO+
- CD5/CD7
- CD26
- CD28
- CLA (PSGL-1) binds CD62E

Chrom 10, p15, p16, p53
Clonality and Molecular Analysis

- Dominant clone (Standard)
  - DNA analysis for clonality
    - PCR-based techniques
    - TCR-gamma gene
    - (threshold 1%; sensitivity 80%)

- Novel markers (Research)
  - Surface markers – CD158, CD164
  - Molecular cellular markers - Tox
  - Epigenetic markers – TWIST1, PLS3
## Diagnosis of Early MF: 4 Points Required*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Major (2 Points)</th>
<th>Minor (1 Point)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent and/or progressive patches/thin plaques plus</td>
<td>Any 2</td>
<td>Any 1</td>
</tr>
<tr>
<td>1) Non–sun-exposed location</td>
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<tr>
<td>2) Size/shape variation</td>
<td></td>
<td></td>
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<tr>
<td>3) Poikiloderma</td>
<td></td>
<td></td>
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<tr>
<td><strong>Histopathological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial lymphoid infiltrate plus</td>
<td>Both</td>
<td>Either</td>
</tr>
<tr>
<td>1) Epidermotropism</td>
<td></td>
<td></td>
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<tr>
<td>2) Lymphoid atypia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Molecular</strong></td>
<td></td>
<td></td>
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<tr>
<td>Clonal TCR gene rearrangement</td>
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<td></td>
</tr>
<tr>
<td><strong>Immunopathological</strong></td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>1) CD2, 3, 5 &lt;50%</td>
<td></td>
<td></td>
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<tr>
<td>2) CD7 &lt;10%</td>
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<tr>
<td>3) Epidermal/dermal discordance</td>
<td></td>
<td>Any 1</td>
</tr>
</tbody>
</table>

# Mycosis Fungoides and Sézary Syndrome Clinical Staging System

<table>
<thead>
<tr>
<th>Stages</th>
<th>TNM Classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA Patches/plaques &lt; 10% BSA</td>
<td>T1 N0 M0 B0,1</td>
</tr>
<tr>
<td>IIB Patches/plaques &gt; 10% BSA</td>
<td>T2 N0 M0 B0,1</td>
</tr>
<tr>
<td>IIA Palpable nodes Tumors</td>
<td>T1-2 N1 M0 B0,1</td>
</tr>
<tr>
<td>IIB Erythroderma</td>
<td>T3 N0-1 M0 B0,1</td>
</tr>
<tr>
<td>IIA Nodes positive</td>
<td>T4 N0 M0 B0</td>
</tr>
<tr>
<td>IIB Visceral disease</td>
<td>T4 N1 M0 B1</td>
</tr>
</tbody>
</table>

B1 >5% Sézary cell; B2 Sézary cell >1000/mcl

Skin Lesions in Early Stage Mycosis Fungoides

- Patches: IA / T1 = <10%
- Plaques: IB / T2 = >10%
Advanced Stage Lesions in Mycosis Fungoides

Clinical CTCL Variants

Alibert-Bazin

Vitiligenous/hypopigmented
CTCL-Follicular MF
Variants of CTCL

• Small medium pleomorphic CD4+ TCL

Granulomatous slack skin
CTCL distribution by stage (n=3683)
Survival (%) at 5 years

<table>
<thead>
<tr>
<th>Stage</th>
<th>Series1</th>
<th>Series2</th>
<th>Series3</th>
<th>Series4</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB</td>
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</tr>
<tr>
<td>IIA</td>
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</tr>
<tr>
<td>IIB</td>
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</tr>
<tr>
<td>III</td>
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<tr>
<td>IV</td>
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</table>

<table>
<thead>
<tr>
<th>Studies</th>
<th>Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim (2003)</td>
<td>Arch Derm (US n=525)</td>
</tr>
<tr>
<td>Agar (2010)</td>
<td>J ClinOnc (Europe n=1502)</td>
</tr>
<tr>
<td>Desai (2015)</td>
<td>JAAD (US n=393)</td>
</tr>
</tbody>
</table>
Mycosis Fungoides and Sézary Syndrome: Survival by Clinical Stage

Time (years)

Probability (%)

IA (155) 29.5%
IB (133) 25.3%
IIA (60) 11.4%
III (59) 11.2%
IIB (84) 16%
IV (34) 6.5%

Mycosis fungoides statistics – US
Based on SEER database

Weinstock M 1999 Amer J Pub Health 89:1240-1244
Conservative or aggressive treatment?


Survival Among Patients Receiving Either Combined Therapy or Conservative Therapy

Topical RT+ Chemo

Survival (mo)

Percent Surviving

No. of Total Deaths

Combination 52 21
Conservative 51 19

All stages

P=0.72

Survival Among Patients Receiving Either Combined Therapy or Conservative Therapy
Summary

• Cutaneous lymphomas are B or T cell cancers infiltrating the skin
  – Most common variant is mycosis fungoides type
• Diagnosis can be challenging in the early stages
  – Skin biopsy is important for diagnosis
  – Repeat biopsy in early stage may be necessary
• Clinical staging depends mainly on extent of skin involvement
• Prognosis is dependent on clinical staging
Thank you