CTCL Management: Lessons Learned

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Disclosure statement

Youn Kim, MD

• Steering Committee
  – Eisai, Millennium

• Consultant or Advisory Board
  – Kyowa, Celgene, Galderma, Medicis

• Investigator
  – Allos, Kyowa, Merck, Millennium, Seattle Genetics, Shape, Ceptaris/Yaupon, Eisai, Genentech
Clinical Issues in CTCL Management

• How can we optimize our diagnostic ability?
• How do we make optimal treatment decisions with available therapies?
• How can we improve therapeutics and outcome?
Lesson #1
Clinical-pathologic correlation is essential for optimal diagnosis & management

Challenge of so many histopath and clinical mimics
Differential diagnosis of CD30+ atypical lymphoid infiltrates in the skin

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

Neoplastic
- pc CD30+ LPD
  - Lymphomatomoid 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

**Lymphomatoid papulosis**
- 100% spontaneous regression
- Papules >> nodules
- Crops of lesions, +/- grouped
- 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

**pc CD30+ ALCL**
- < 25% spontaneous regression
- Mostly nodules/tumors
- Single, grouped, multifocal
- Usu. sheets of anaplastic large cells

**CLINICAL-PATHOLOGIC CORRELATION IS ESSENTIAL**
DIAGNOSIS

ESSENTIAL:
- Clinical presentation: see Overview and Definition
- Clinical pathologic correlation is essential
  - Biopsy of suspicious skin sites
    - Histopathology review of adequate biopsy (punch, incisional, excisional).
    - Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of cutaneous T-cell lymphoma. Rebiopsy if consult material is nondiagnostic.
  - Adequate immunophenotyping to establish diagnosis on skin biopsy:
    - IHC: CD3, CD4, CD8, CD20, CD30, CD56, βF1, ALK1

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- On skin biopsy:
  - Expanded IHC: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, GM1, EBER-ISH
  - Molecular analysis to detect: gene rearrangements: TCR (assessment of clonality)
- Excisional or incisional/core needle biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of HTLV-1 serology in at-risk populations to identify CD30+ ATLL
Type D CD8+ LyP vs. CD8+ aggressive epidermotropic cytotoxic TCL

LyP type D

CD8

CD8+ aggressive epidermotropic cytotoxic TCL

Courtesy T Subtil
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
Indolent CD8-positive Lymphoid Proliferation of the Ear
A Distinct Primary Cutaneous T-cell Lymphoma?

Tony Petrella, MD,* Eve Maubec, MD,† Pascale Cornillet-Lefebvre, MD,‡ Rein Willemze, MD,§
Michel Pluot, MD,‖ Anne Durlach, MD, PhD,¶ Eduardo Marinho, MD,#
Jean-Luc Benhamou, MD,** Patty Jansen, MD, PhD,†† Alistair Robson, MRCPath, DipRCPath,‡‡
and Florent Grange, MD, PhD§§

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
¹Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, ²Northwestern University, Chicago, IL, ³Yale University, New Haven, CT, ⁴Stanford University, Stanford, CA

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 lymphomatoid papulosis of 11 cases, with new histopatho

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

Folliculotrophic Mycosis Fungoides

Clinico-pathologic correlation is essential
Too many clinical, path variants & mimics leading to more confusion in diagnosis
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
Lesson #1: importance of clin-path correlation

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
Lesson #2
“OK” to be noncommittal with diagnosis
*Impact of a “lymphoma” label*
CD4+ sm/med-sized pleomorphic T-cell “lymphoma”

• Mostly benign/indolent course, especially in kids

• A lymphoid proliferation of undetermined significance vs. “lymphoma”

• CD4+ sm/med-sized pleomorphic T-cell lymphoproliferative disorder (LPD)?

Helmut Beltraminelli, MD, *† Bernd Leinweber, MD, * Helmut Kerl, MD, * and Lorenzo Cerroni, MD*

Am J Dermatopathol 2009;31:317-322

- Solitary/localized disease with benign outcome
- Majority of H/N
- Rare multifocal presentation with worse outcome
CD4+ sm/med pleomorphic T-cell “lymphoma” vs “LPD”?
Indolent sm/med-sized CD8+ lymphoid proliferation of the ear/face

Spectrum of lymphoid proliferation: If clinical course is indolent, ok to follow and manage conservatively

Indolent CD8⁺ lymphoid proliferation of the ear: A phenotypic variant of the small-medium pleomorphic cutaneous T-cell lymphoma?
Lesson #3
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
# Diagnosis

**Essential:**
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

**Useful under certain circumstances:**
- IHC of skin biopsy (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1)
- Molecular analysis for TCR gene rearrangements (assessment of clonality) of skin biopsy
- PCR methods
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including Sezary cell prep, flow cytometry, and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of HTLV-1 serology in at-risk populations. HTLV-1 PCR if serology is indeterminate

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# Workup

**Essential:**
- Complete physical examination
- Examination of entire skin: assessment of %BSA (palm plus digits ≈1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
- Palpation of peripheral lymph node regions
- Palpation for organomegaly/masses
- Laboratory studies:
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1); CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26

**Useful in selected cases:**
- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)
- Biopsy of suspicious lymph nodes for identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites
- Rebiopsy if suspicious of large cell transformation
- Neck CT

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### Stage (MFSS-2 and MFSS-3)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>IA</td>
<td>See Primary Treatment (MFSS-4)</td>
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<tr>
<td>IB-IIA</td>
<td>See Primary Treatment (MFSS-5)</td>
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<tr>
<td>IIB</td>
<td>See Primary Treatment (MFSS-6)</td>
</tr>
<tr>
<td>III</td>
<td>See Primary Treatment (MFSS-7)</td>
</tr>
<tr>
<td>IV</td>
<td>See Primary Treatment (MFSS-8)</td>
</tr>
</tbody>
</table>

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TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.

See [map](#) for prevalence of HTLV-1 by geographic region.

Sezary syndrome (B2) is as defined on MFSS-2.

Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.
**Neoplastic T-cells** are CD3+, **CD4+**, CD8-, CD25+; epidermotropic
- Endemic in Japan, the Caribbean, S Americas, Central Africa;
- Primarily transmitted by breast feeding

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<table>
<thead>
<tr>
<th></th>
<th>Healthy Carrier</th>
<th>Smoldering ATL</th>
<th>Chronic ATL</th>
<th>Acute ATL</th>
<th>ATL Lymphoma</th>
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<tbody>
<tr>
<td>Anti-HTLV-1 serology</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>Clonal integration of provirus</td>
<td>- (blood)</td>
<td>+ (blood)</td>
<td>+ (blood)</td>
<td>+ (blood)</td>
<td>+ (lymph nodes)</td>
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<td>Lymphocyte count</td>
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<td>Normal</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
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<tr>
<td>Abnormal cells (%)</td>
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<td>&gt;5%</td>
<td>&gt;5%</td>
<td>&gt;5%</td>
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<td>Hypercalcemia</td>
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<td>LDH</td>
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<tr>
<td>Bone marrow or spleen involvement</td>
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<td>-</td>
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<td>Bone, GI, or CNS involvement</td>
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<td>-</td>
<td>+</td>
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</table>
ATLL, spectrum of skin presentation

MF-like, smoldering variant

Acute, disseminated disease
ATL can mimic Sezary syndrome
Acute ATLL

 Courtesy J Guitart
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 Sézary syndrome
    • Expanded CD4, H/S 16, CD4+/CD26- 80%, abs 2400
  – 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)
Clinical course and management of SS

- ECP + oral bexarotene => mild benefit
- Added IFN-alpha => no response, neutropenia
- MTX 35 mg => minimal benefit
- **Anti-CCR4 mab (mogmulizumab)**
  - Rapid reduction of SCs and pruritus
  - Near 3 yrs of great disease control
Case Study: Patient 03-Stanford
(SS; Stage IVA; 6 Prior Therapies; 0.3 mg/kg)

Pretreatment
Course 1 Day 1

Post treatment
Post Course 11
Response in Blood: Patient 01-Stanford (SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

Pre-treatment

CD3

CD4

CD26

CCR4 1G1

Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

Lymphoma cells
Response in Blood: Patient 01-Stanford Post-treatment

Lymphoma cells undetectable
Response >2 yrs

CD3+CD4neg
Normal CD3+CD4+

CD4
CD26
CCR4 1G1

% of Max

Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

Phase III RCT in CTCL ongoing for FDA approval
Challenge of the red person
Take home message

Skin biopsies often non-diagnostic from erythrodermic skin of CTCL

MUST ASSESS BLOOD if suspect SS
Lesson #4
Advanced MF/SS IS curative
Road to a CURE

Effective tumor killing => lasting responses by partnering with immune strategies

Diagram:
- **Tumor-directed killing**
- **Immunotherapy**

Graph:
- % Survival vs. Time

- The curve for Tumor-directed killing shows a sharp decline, indicating rapid tumor reduction.
- Immunotherapy shows a slower decline, suggesting sustained effectiveness.

The diagram highlights the importance of immunotherapy in achieving a longer survival rate, as indicated by the red arrow pointing upwards.
Era of Targeted Therapy

Newer agents for tumor-directed killing

*Kill the bad, spare the good cells*
Targets for Therapy in Cutaneous Lymphoma

Tumor cell surface molecules (e.g., CD4, CD19, CD20, CD22, CD25, CD30, CD40, CD52, CD158k, CCR4)

Cutaneous lymphoma

Microenvironment, immune mechanisms (e.g., vasculature)

CD30, an attractive target: CD30 expression is increased in proliferative or malignant lymphocytes => good tumor selectivity

Signal transduction/transcription activation pathways
(e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)

Apoptotic pathways (e.g. Bcl/Bax, TNFR, Fas, miRNAs)

Epigenetics (e.g., histone, non-histone proteins)

Metabolic/survival pathways (e.g., RFC-1, PARP)
Brentuximab Vedotin Mechanism of Action
Antibody Drug Conjugate

Monomethyl auristatin E (MMAE), microtubule-disrupting agent
Protease-cleavable linker
Anti-CD30 monoclonal antibody

ADC binds to CD30
ADC-CD30 complex is internalized and traffics to lysosome
MMAE is released
MMAE disrupts microtubule network
G2/M cell cycle arrest
Apoptosis

Given IV every 3 wks
Brentuximab vedotin demonstrates clinical activity in mycosis fungoides / Sézary syndrome


1Stanford Cancer Institute, Stanford, CA, USA
2Memorial Sloan-Kettering Cancer Center, New York, NY, USA
3University of Wisconsin, Madison, WI, USA
87 yo M with MF IIB, LCT
87 yo M with MF IIB, LCT

Screening

Cycle 6
Subject 12: 66 yo F with MF IVB, LCT w/ oropharyngeal involvement

Screening

Cycle 10

20% CD30
51 yo F stage IVA2 MF with LCT in skin/LNs: response to brentuximab vedotin

Pre-treatment 12/20/2012

Post 2 cycles 1/29/2013

Phase III RCT in CTCL ongoing for FDA approval
Road to a CURE
How do we make the nice responses last?

*Partnering with immunotherapy*
Immunotherapy strategies in cancer

- Tumor-specific monoclonal antibodies
- Cytokine therapy
- Immune-modulating agents or antibodies
- Adoptive T-cell transfer
- Vaccine-based approaches
- Allogeneic HSCT
- Lymphoma
- TILs
- M
Immunotherapy strategies in cancer

- Tumor-specific monoclonal antibodies
- Immune-modulating agents or antibodies
- Vaccine-based approaches
- Cytokine therapy
- Adoptive T-cell transfer
- Allogeneic HSCT

TILs

lymphoma

M
Harnessing the graft-versus-lymphoma effect in allo HSCT as the ultimate cellular immune therapy
A New Approach in Donor Cell Transplant
Non-Myeloablative Regimen with TLI/ATG
“Protective conditioning”

NEJM 353:1321, 2005
Stanford study on going

Enable Donor Cells to Engraft
aGVHD reduced to 2-5% (vs. 20-65%)
Mycosis fungoides, stage IVA w/ LCT in skin/LNs: **CR**

Pre-TSEBT

3.0+ yr (NED, no GVHD)
**Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR**

**Pre-TSEBT**  
CD4+/CD26-: 99%, abs 19,780

**2.0+ yr (NED, no GVHD)**  
CD4+/CD26-: normalized
Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-transplant

2.0+ yr (NED, no GVHD)
Immunotherapy strategies in cutaneous lymphoma

- Combination with newer targeted therapies, chemotherapies, radiation therapy
- Adoptive cell transfer
- Immune-modulating agents or antibodies
- Vaccine-based approaches
- Allogeneic HSCT

Cutaneous lymphoma

long-lasting, curative outcome
CTCL Management: Lessons Learned
Take home summary

• **Clinical-pathologic correlation** is **ESSENTIAL** for diagnosis

• “**OK**” to be noncommittal of the diagnosis
  – Follow and reassess; manage according to biologic behavior

• **Check the blood compartment** for diagnostic data
  – HTLV1 serology for ATLL
  – Sezary flow when suspecting SS

• **Advanced/refractory MF or SS IS curative**
  – Must balance risks and benefits of allo HSCT