CTCL Management:

Lessons Learned

Youn H Kim, MD

Department of Dermatology

Multidisciplinary Cutaneous Lymphoma Program

Stanford Cancer Center & School of Medicine

Stanford, CA

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

- Lymphomatoid drug reaction (e.g., amlodipine, carbamazepine, cefuroxime, valsarten)
- 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

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

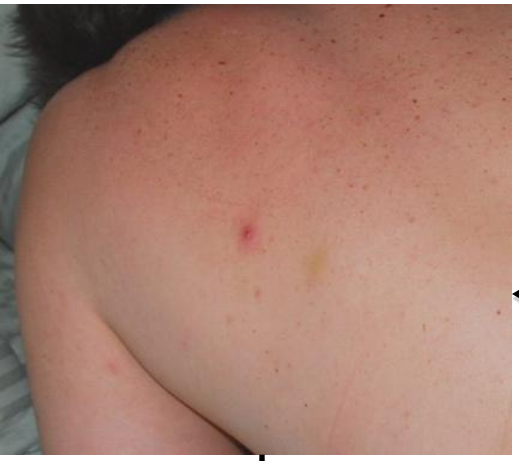
ESSENTIAL:[a]

- 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[b,c] on skin biopsy:
  - IHC: CD3, CD4, CD8, CD20, CD30, CD56, βF1, ALK1[e]

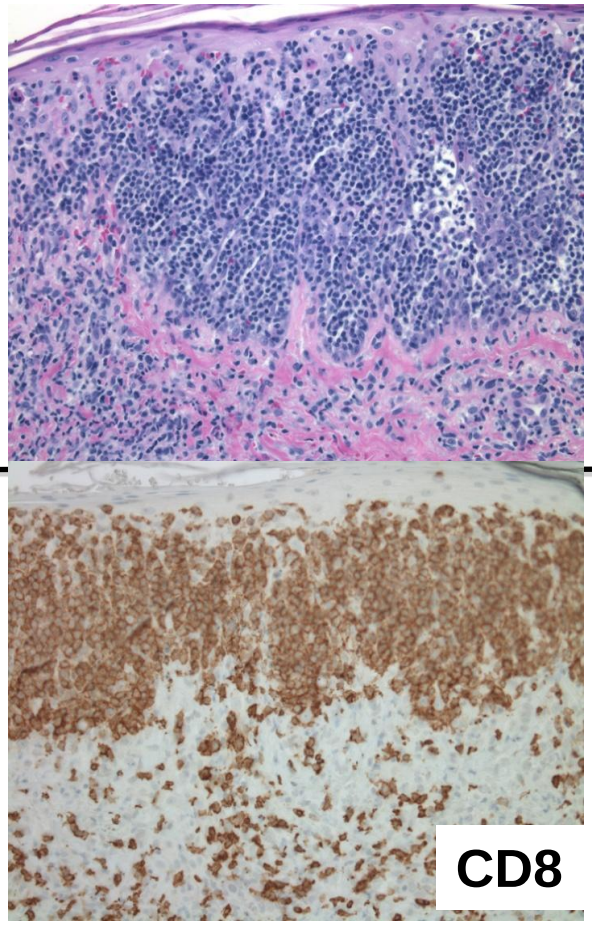
USEFUL UNDER CERTAIN CIRCUMSTANCES:

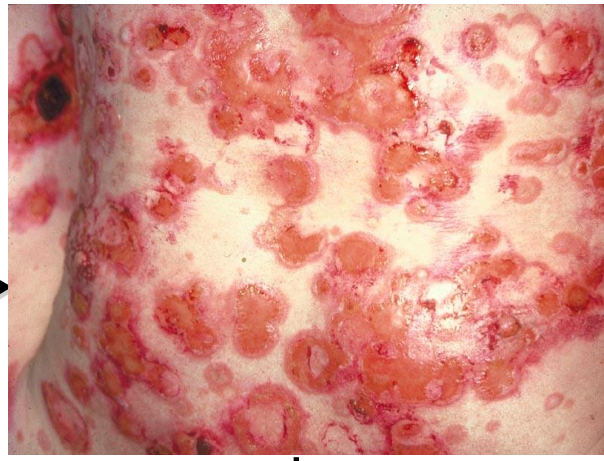
- On skin biopsy:
  - Expanded IHC: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, GM1, EBER-ISH
  - Molecular analysis to detect: gene rearrangements: TCR[d] (assessment of clonality)
- Excisional or incisional/core needle biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- 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+ 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

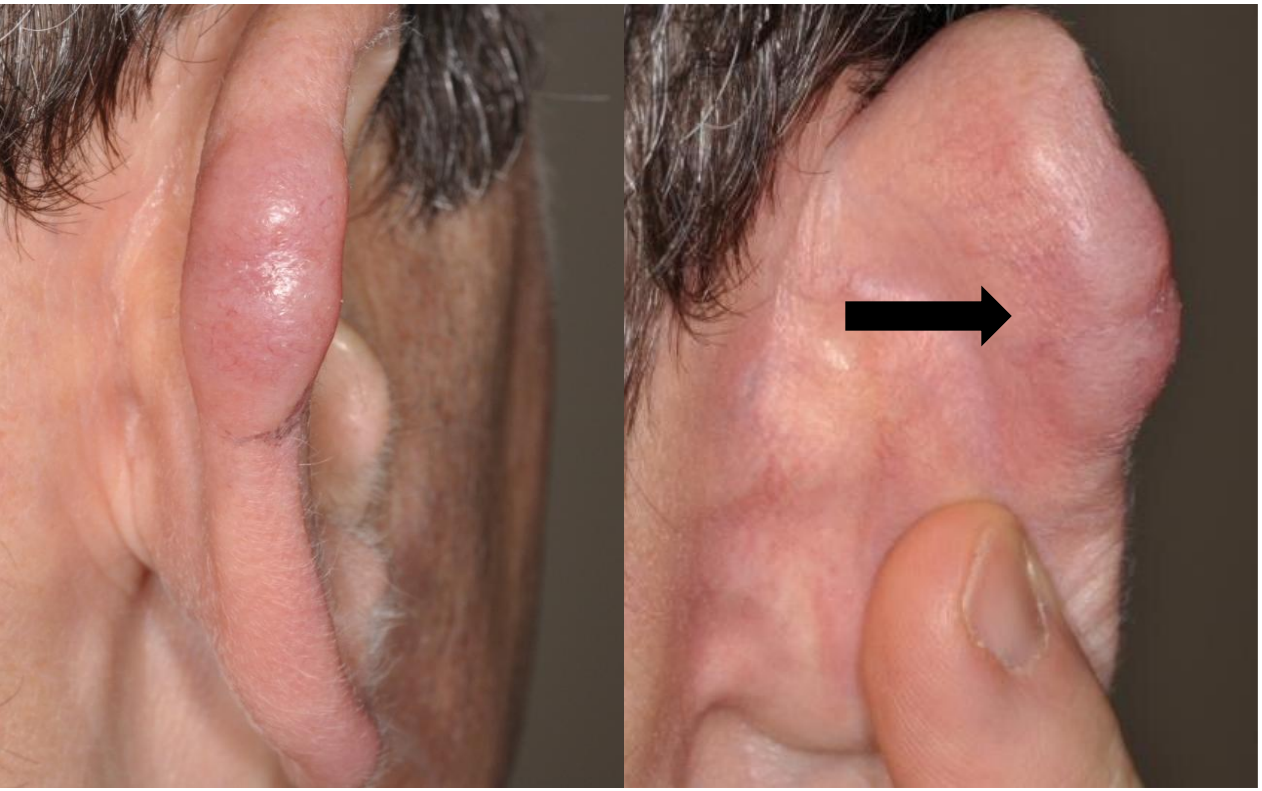
Janet Y. Li[1], Joan Guitart[2], Melissa P. Pulitzer[1], Antonio Subtil[3], Uma Sundram[4], Youn Kim[4], Janyana Deonizio[2], Patricia L. Myskowski[1] Alison Moskowitz[1], Steven Horwitz[1], Christiane Querfeld[1]

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

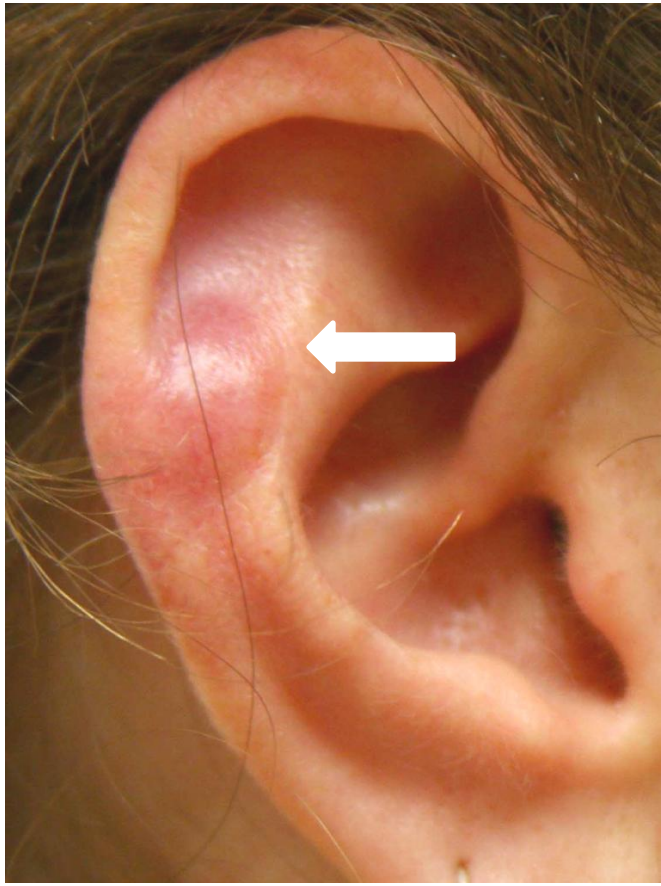
Am J Dermatopathol, in press 2013

Indolent Small/Med-sized CD8+ Lymphoid Proliferations with Predilection for the Ear and Face

Querfeld, MSKCC



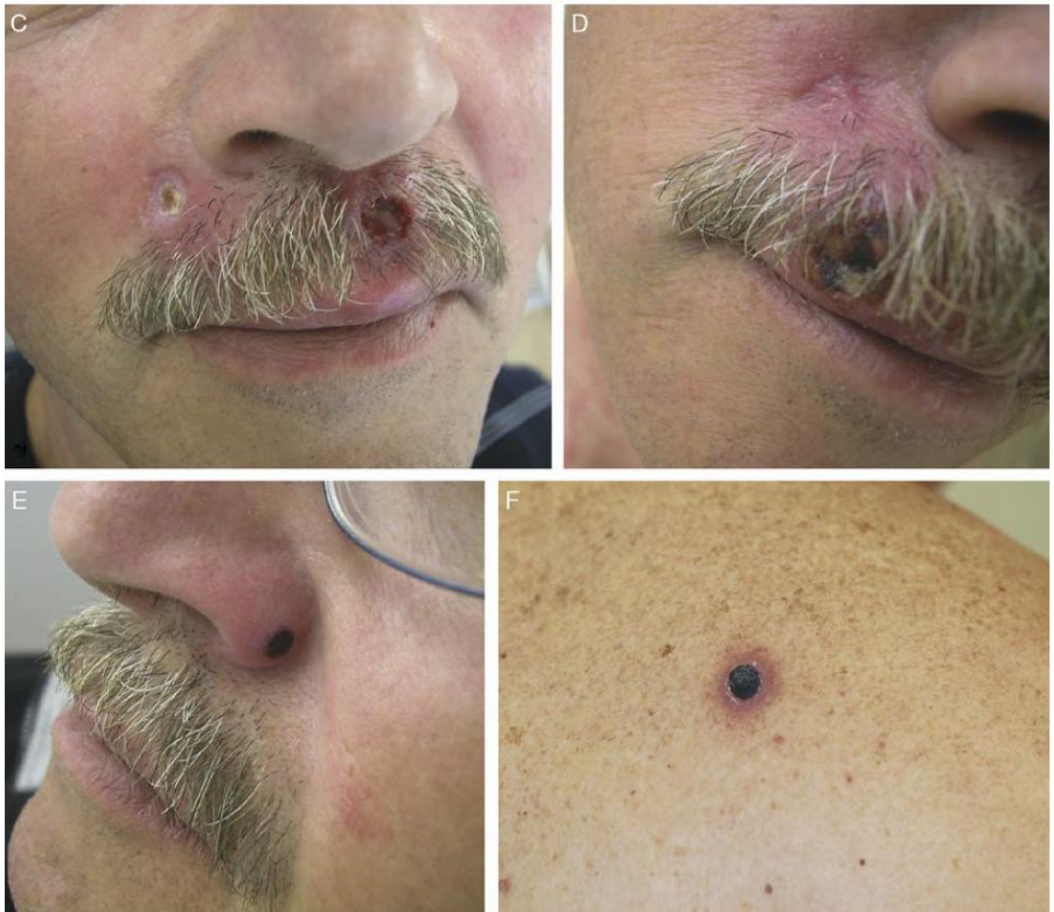
Stanford case



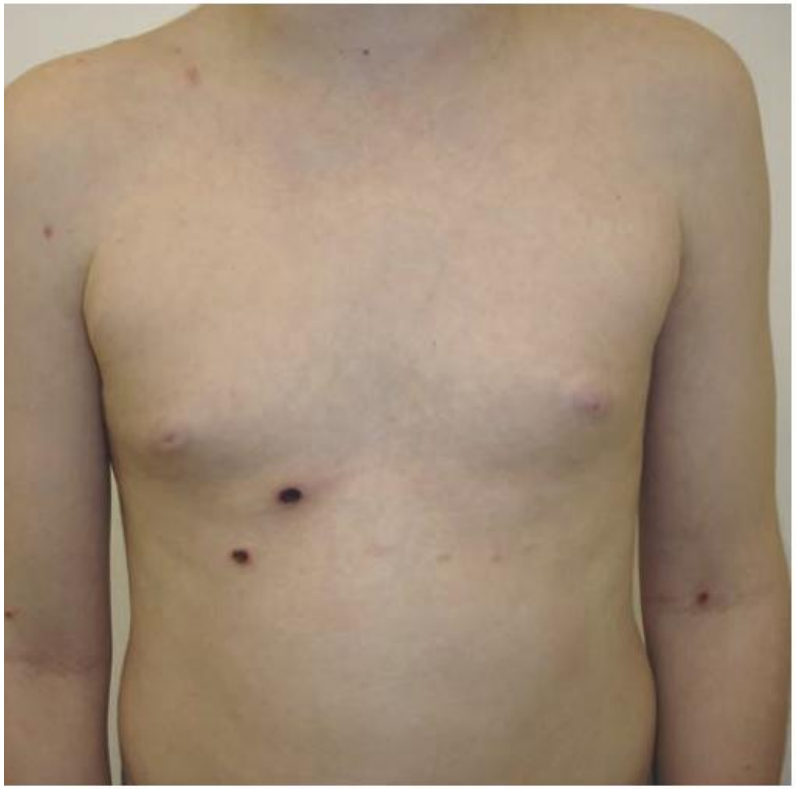
Angioinvasive Lymphomatoid Papulosis

A New Variant Simulating Aggressive Lymphomas

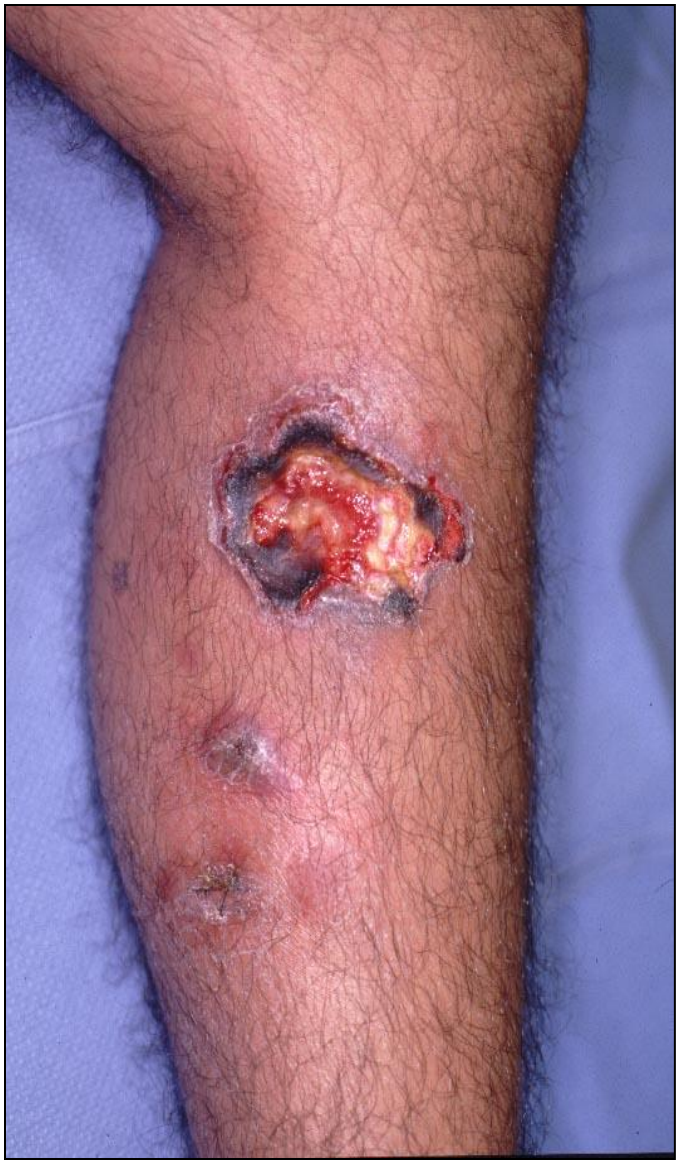
Werner Kempf, MD,† Dmitry V. Kazakov, MD, PhD,‡ Leo Schärer, MD,§*
Arno Rütten, MD,§ Thomas Mentzel, MD,§ Bruno E. Paredes, MD,§
Gabriele Palmedo, PhD,§ Renato G. Panizzon, MD,‖ and Heinz Kutzner, MD§

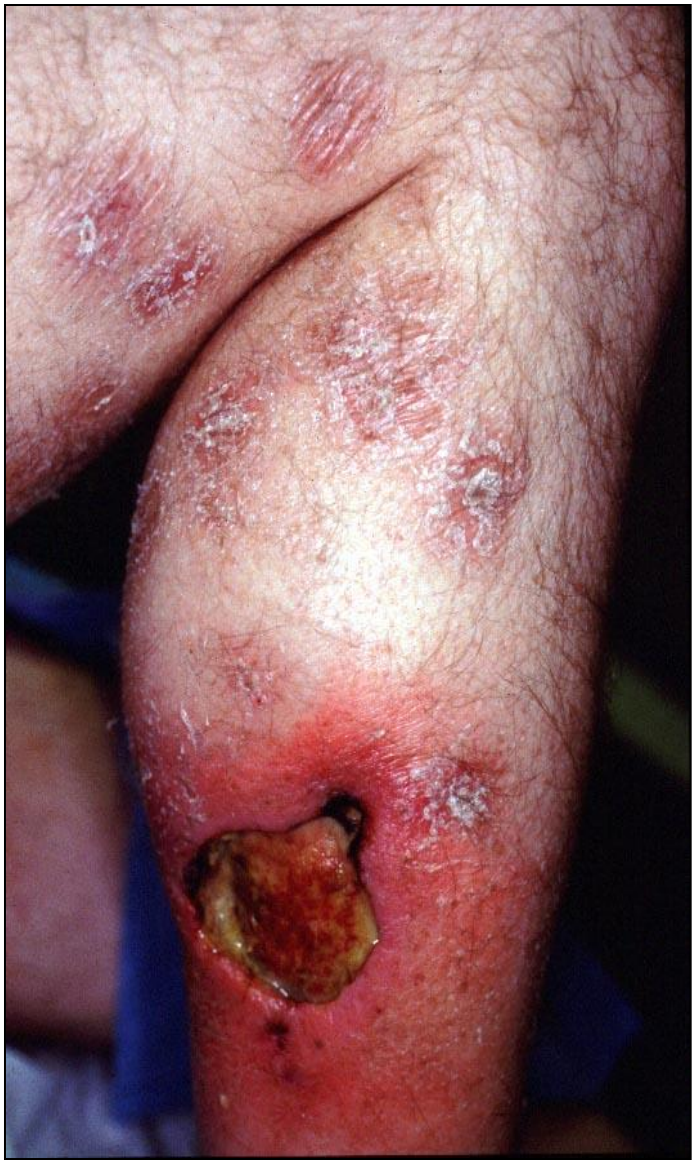


Am J Surg Pathol 2013;37:1-13



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



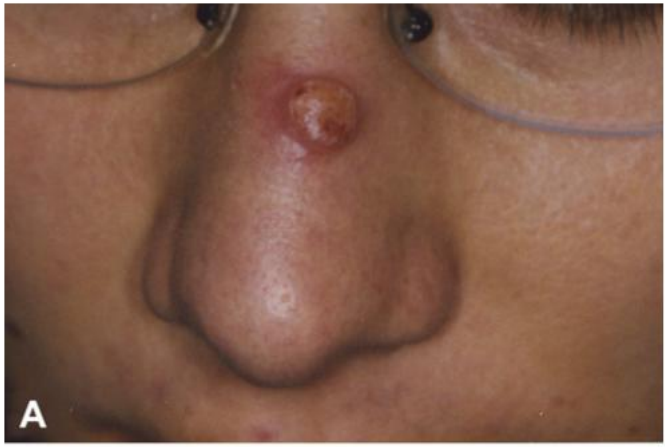


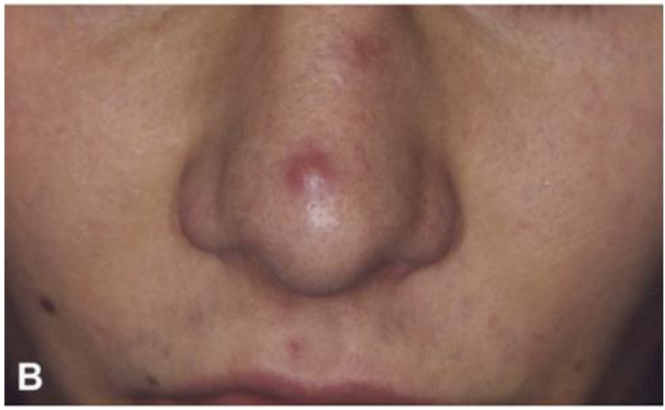
DERMATOPATHOLOGY

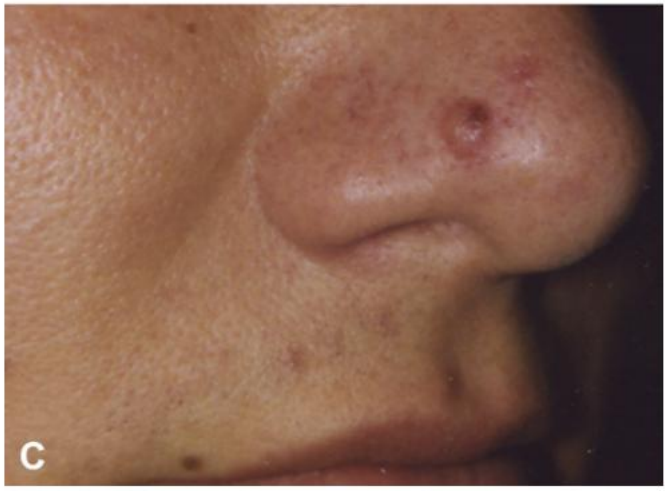
Follicular lymphomatoid papulosis of 11 cases, with new histopatho

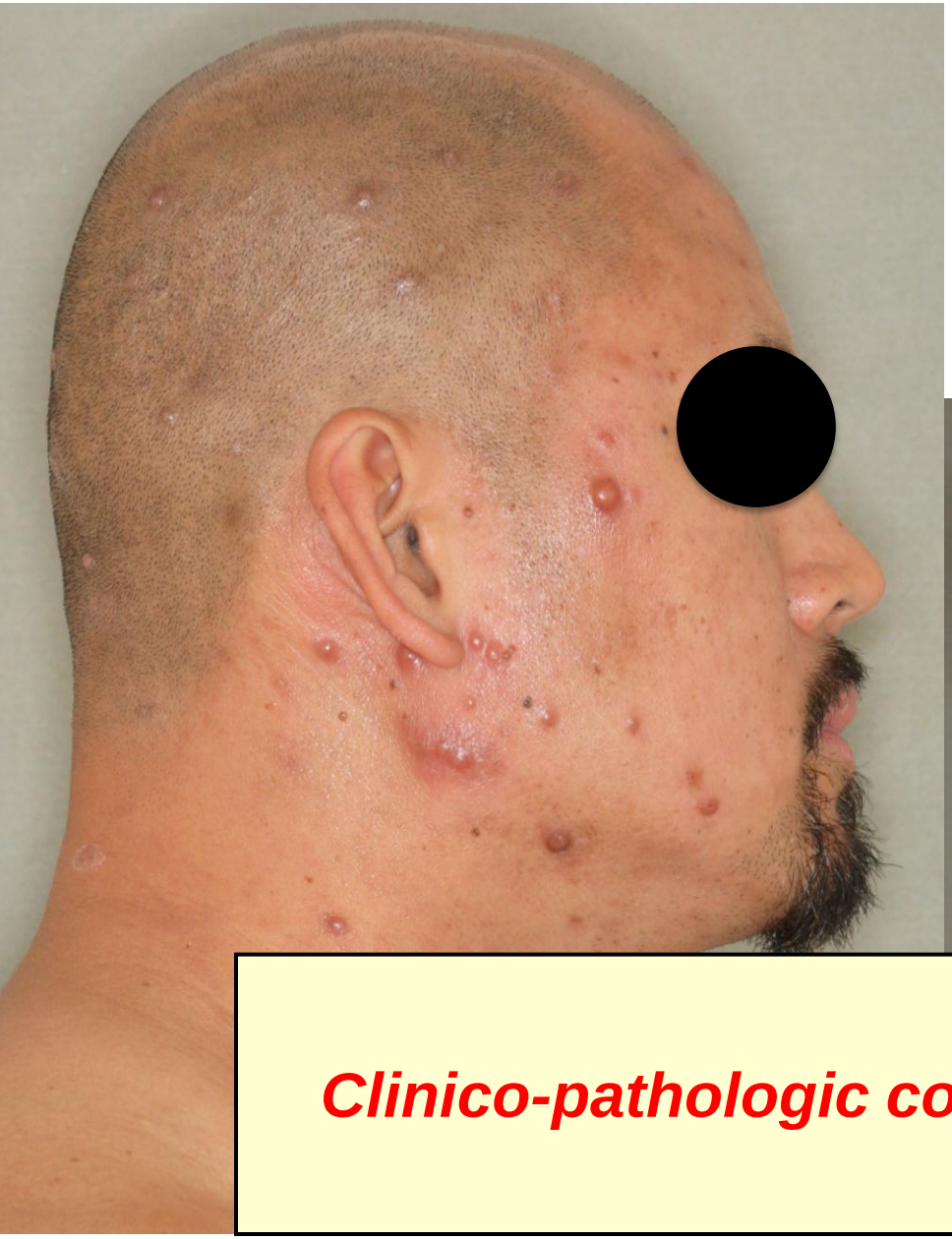
Werner Kempf, MD,[a] Dmitry V. Kazakov, MD, PhD,[b] Hans-Peter Baumga
Zürich and Zug, Switzerland; Pilsen and Prague, Czech Republic,

J Am Acad Dermatol 2013;68:809









Folliculotropic 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)?**

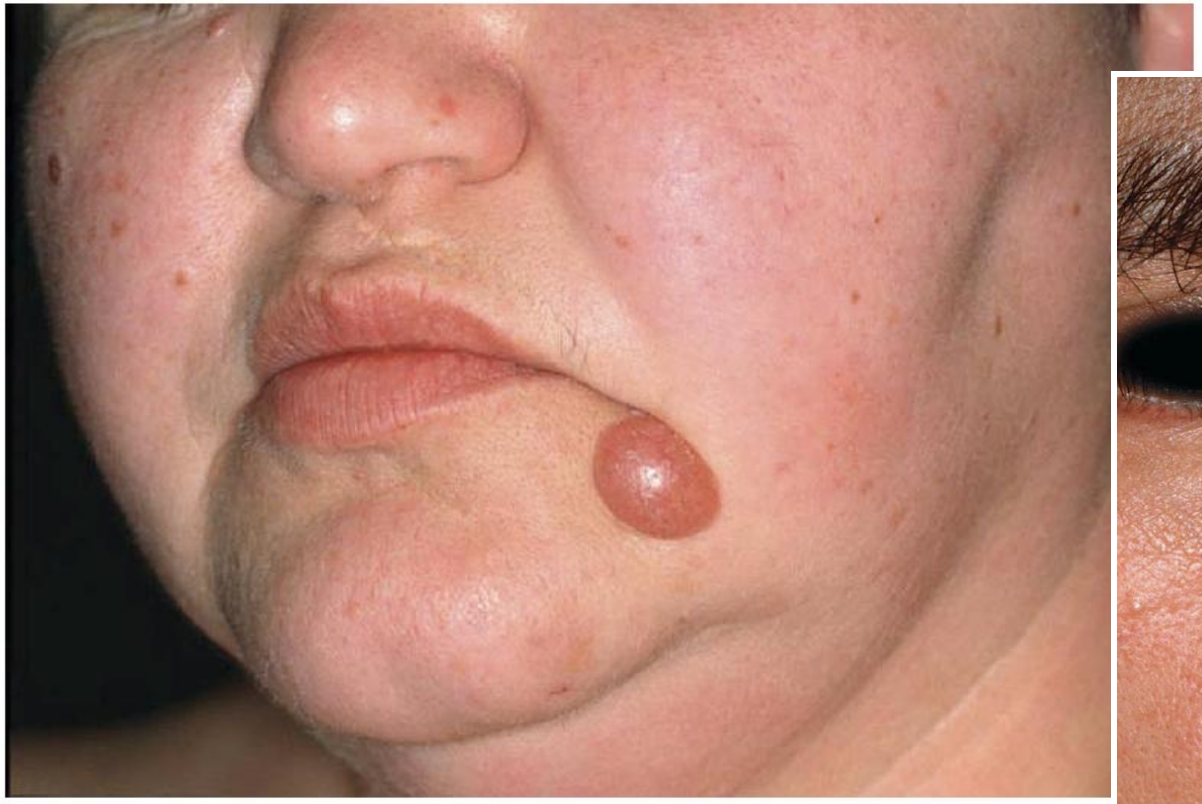
Primary Cutaneous CD4+ Small-/Medium-Sized Pleomorphic T-Cell Lymphoma: A Cutaneous Nodular Proliferation of Pleomorphic T Lymphocytes of Undetermined Significance? A Study of 136 Cases

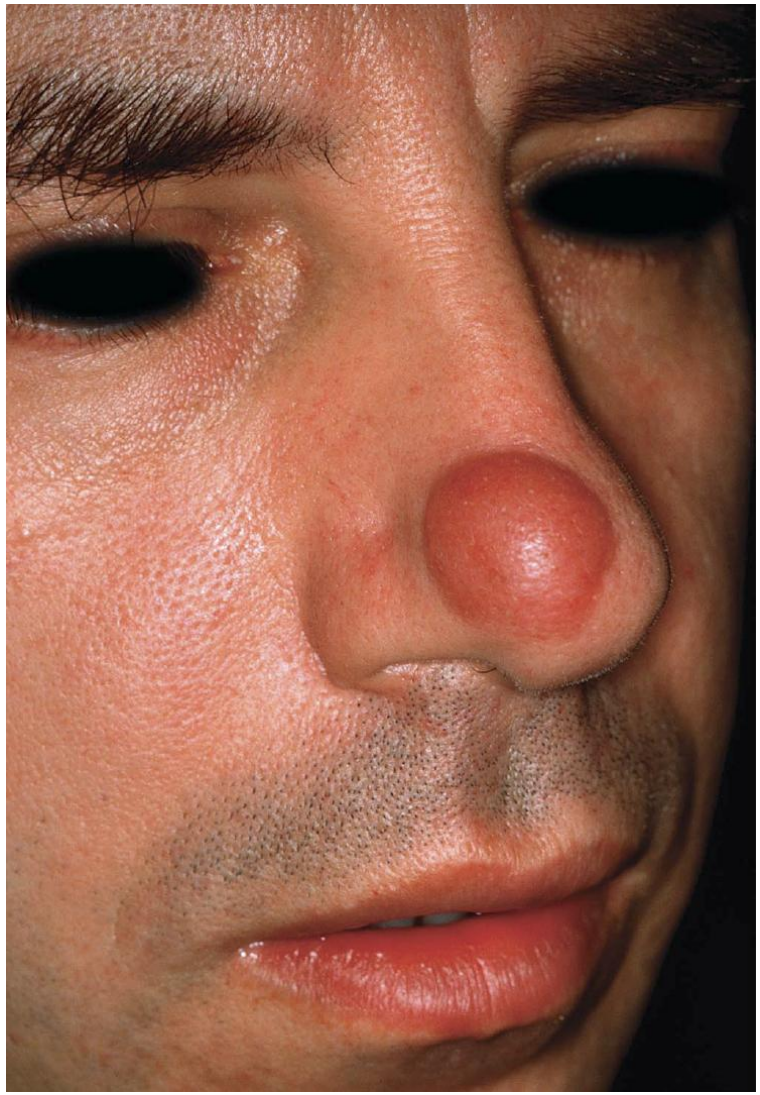
Helmut Beltraminelli, MD,† Bernd Leinweber, MD,* Helmut Kerl, MD,* and Lorenzo Cerroni, MD**

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”?

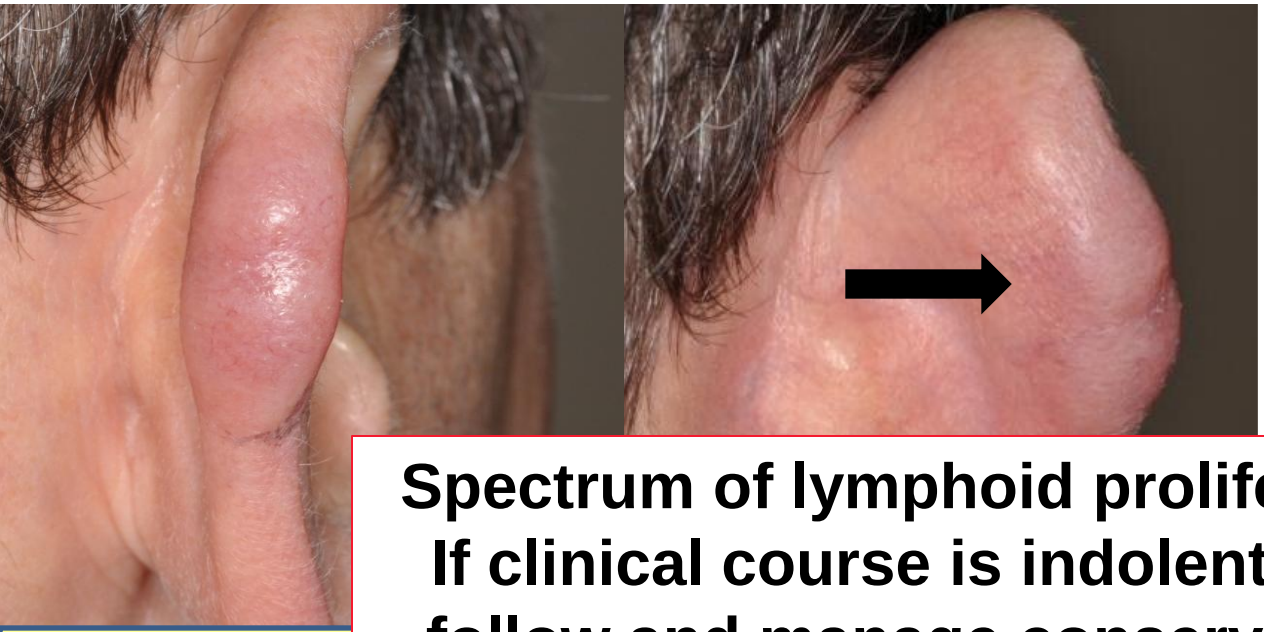




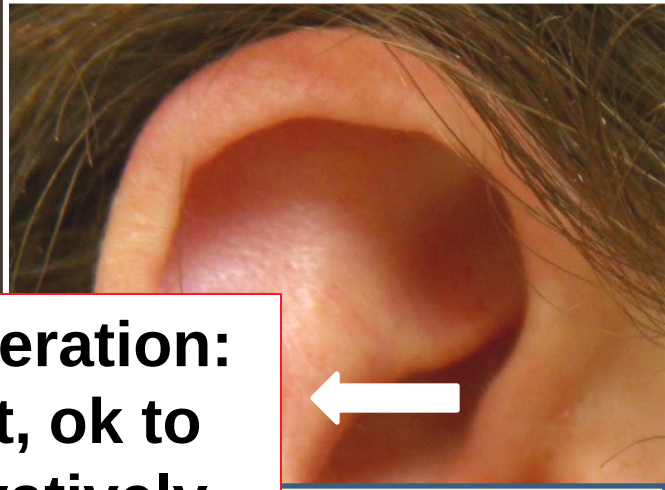
Am J Dermatopathol 2009;31:317-322

Indolent sm/med-sized CD8+ lymphoid proliferation of the ear/face

Querfeld, MSKCC



Stanford case



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?

Helmut Beltraminelli[1,2], Robert Müllegger[3] and Lorenzo Cerroni[1]

[1]Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria,
[2]Department of Dermatology, University Hospital of Basel, Switzerland and
[3]Department of Dermatology, Hospital of Wiener Neustadt, Austria

J Cutan Pathol 2010;37:81-84

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**

NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
NHL Table of Contents
Discussion

DIAGNOSIS

ESSENTIAL:

- Biopsy of suspicious skin sites
- Dermatopathology review of slides

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- IHC of skin biopsy[a,b,c] (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;[a] PCR methods[d]
- 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[e] serology in at-risk populations. HTLV-1 PCR if serology is indeterminate

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:[f]
  - 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
  - TCR gene rearrangement of peripheral blood lymphocytes if blood involvement suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies
  - Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT (≥T2, large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Pregnancy testing in women of child-bearing age[g]

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

STAGE

(MFSS-2 and MFSS-3)

Stage IA	See Primary Treatment (MFSS-4)
Stage IB-IIA	See Primary Treatment (MFSS-5)
Stage IIB	See Primary Treatment (MFSS-6)
Stage III	See Primary Treatment (MFSS-7)
Stage IV	See Primary Treatment (MFSS-8)

[a] Clinically or histologically non-diagnostic cases. Pimpinelli N, Olsen EA, Santucci M, et al., for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063.

[b] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[c] Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

[d] 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.

[e] See map for prevalence of HTLV-1 by geographic region.

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

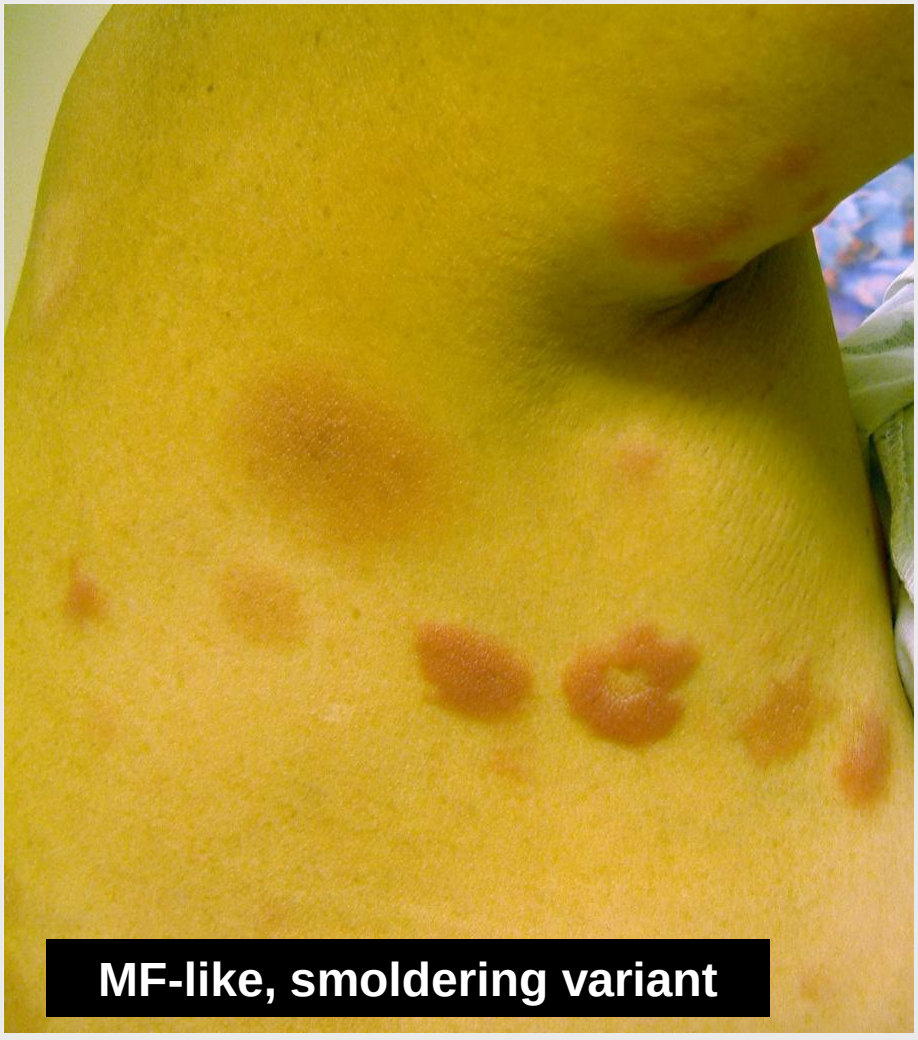
[g] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

DIAGNOSTIC CRITERIA AND CLASSIFICATION OF CLINICAL SUBTYPES OF ATLL[a]

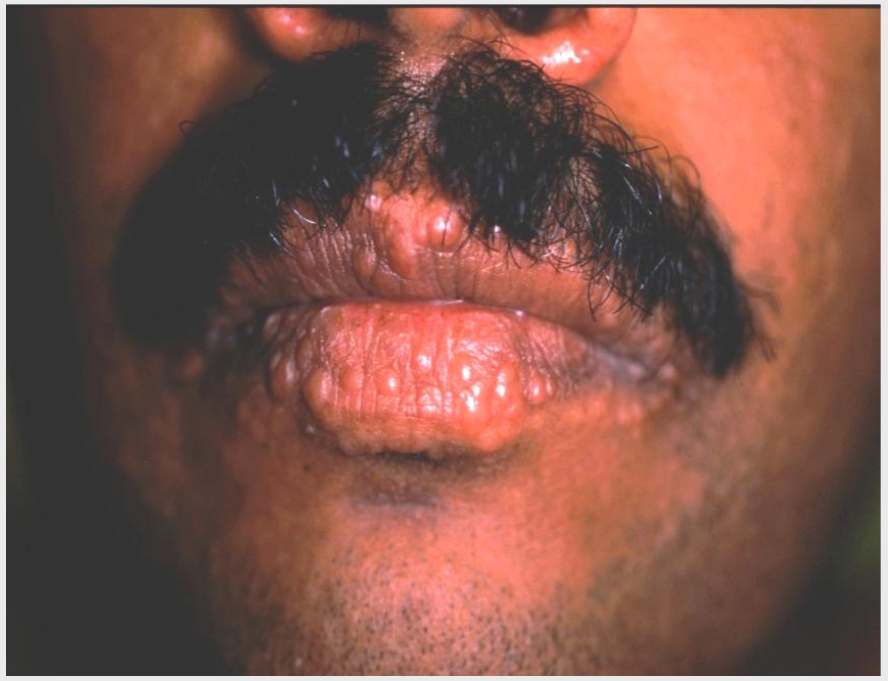
	Healthy Carrier	Smoldering ATL	Chronic ATL	Acute ATL	ATL Lymphoma
Anti-HTLV-1 serology	+	+	+	+	+
Clonal integration of provirus	- (blood)	+ (blood)	+ (blood)	+ (blood)	+ (lymph nodes)
Lymphocyte count	Normal	Normal	Elevated	Elevated	Elevated
Abnormal cells (%)	<5%	>5%	>5%	>5%	<1%
Hypercalcemia	-	-	-	+	+
LDH	Normal	≤1.5 N	≤2 N	>2 N	>2 N
Skin and lung involvement	-	+	+	+	+
Bone marrow or spleen involvement	-	-	+	+	+
Bone, GI, or CNS involvement	-	-	-	+	+

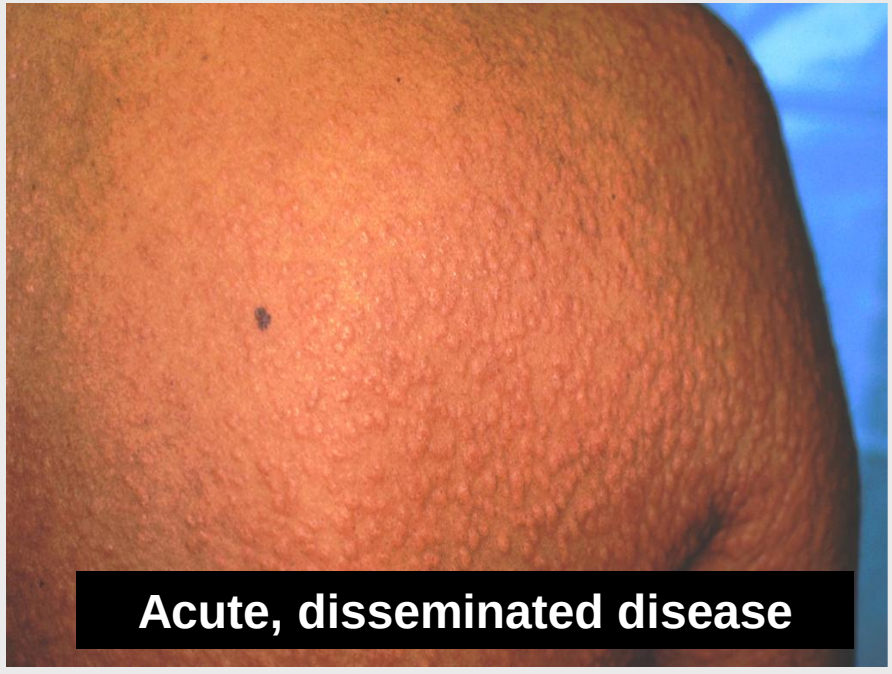
- **Neoplastic T-cells** are CD3+, **CD4+**, CD8-, CD25+; **epidermotropic**
- Endemic in Japan, the Caribbean, S Americas, Central Africa;
- Primarily transmitted by breast feeding

ATLL, spectrum of skin presentation

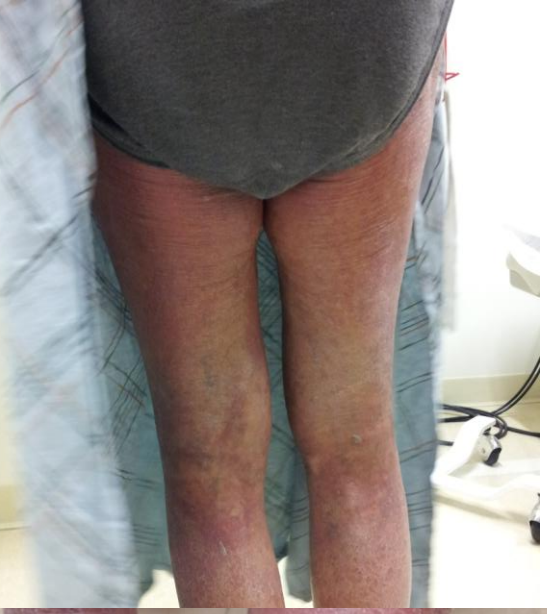


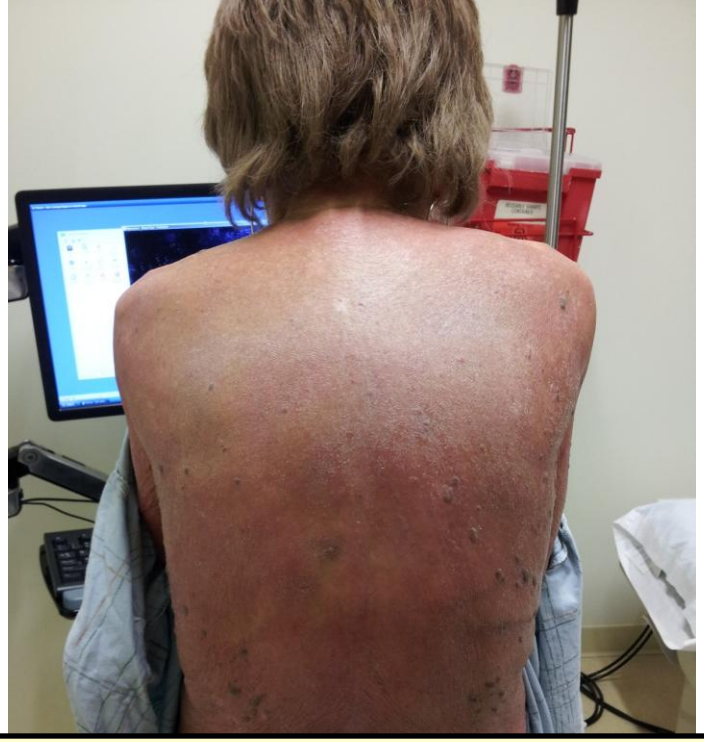
MF-like, smoldering variant

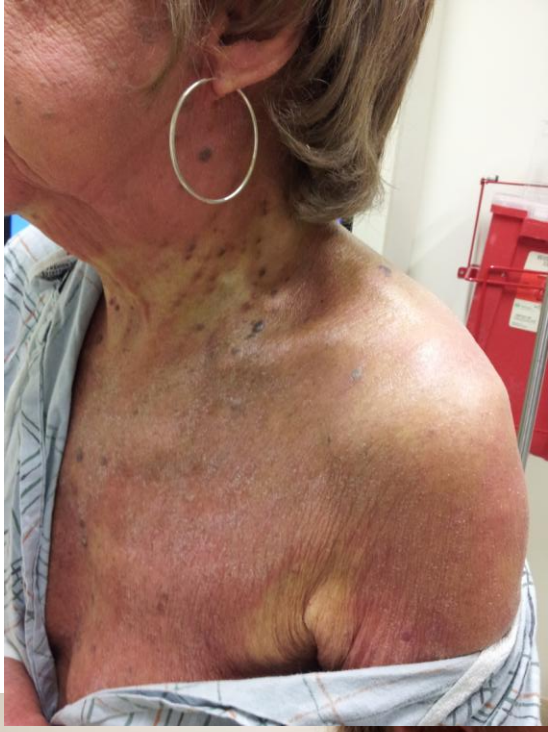


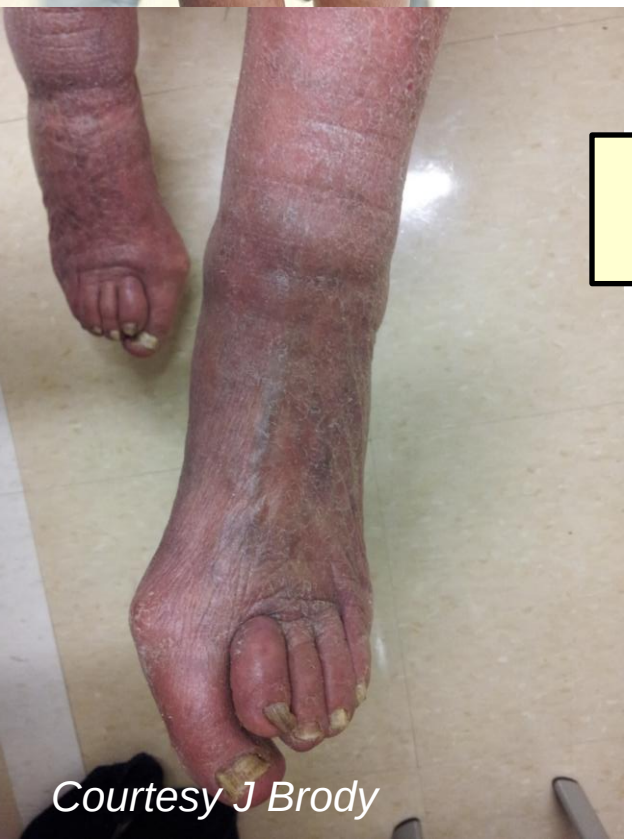


Acute, disseminated disease

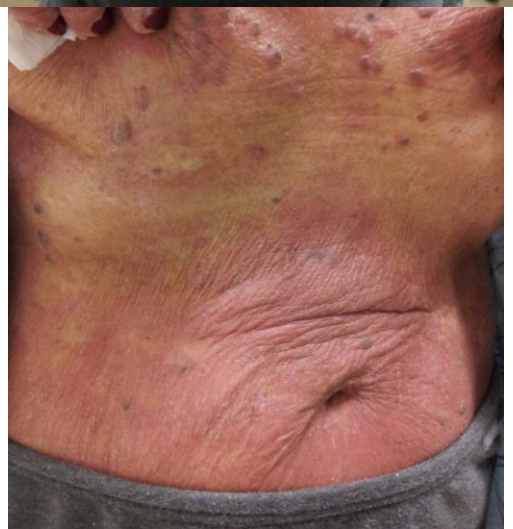


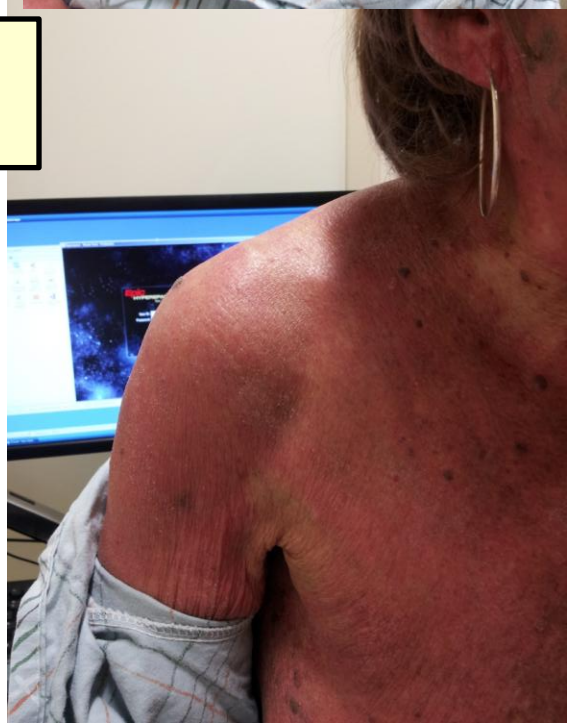




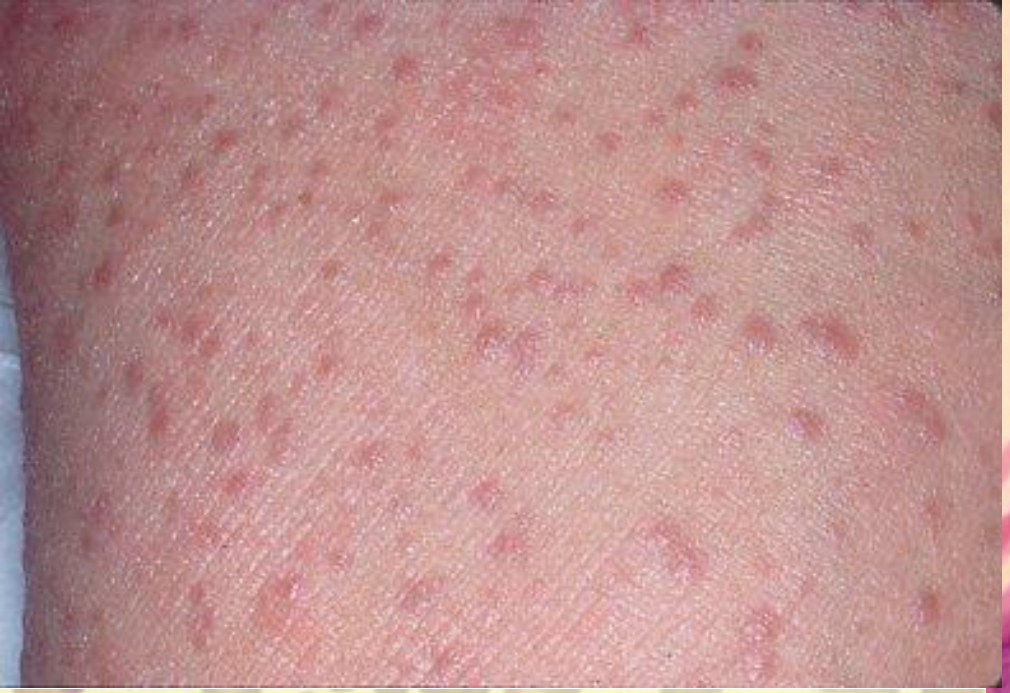


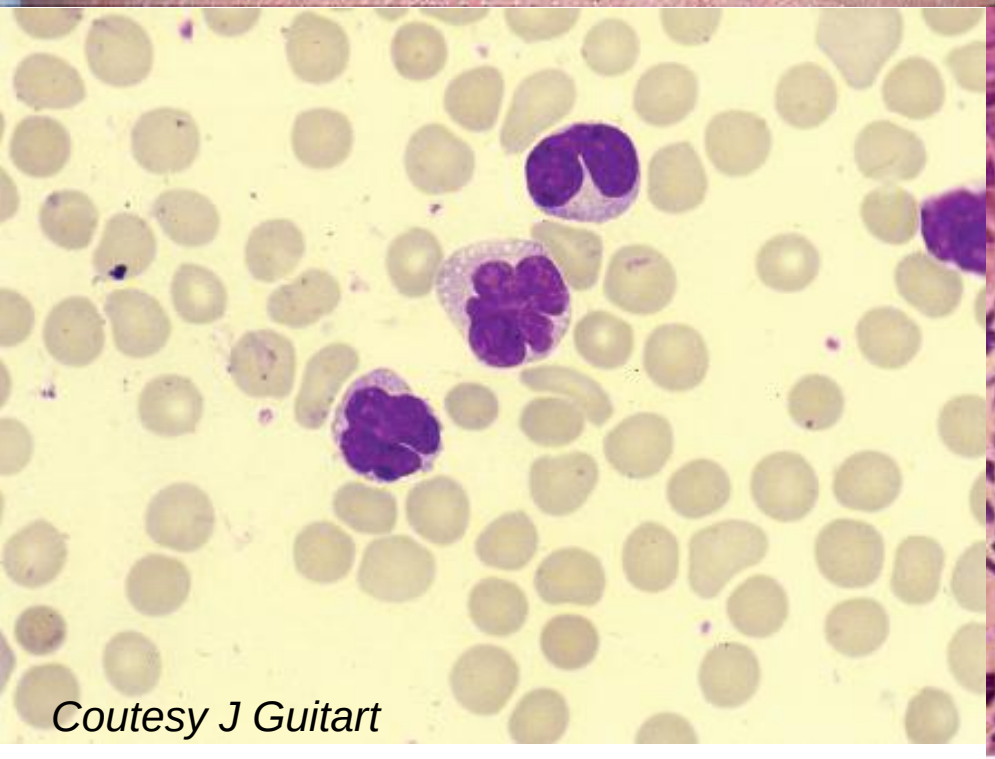
ATL can mimic
Sezary syndrome





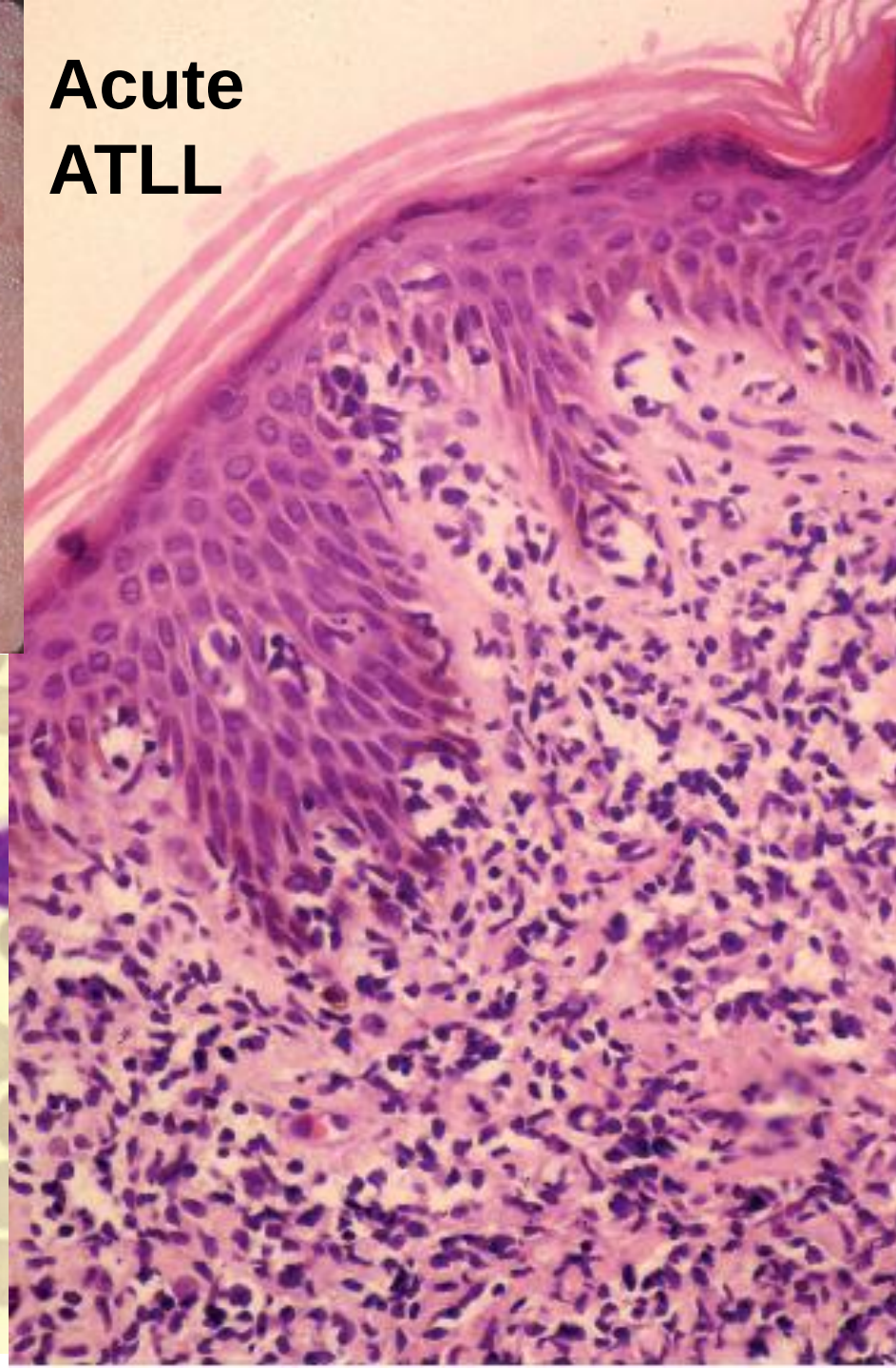
Courtesy J Brody



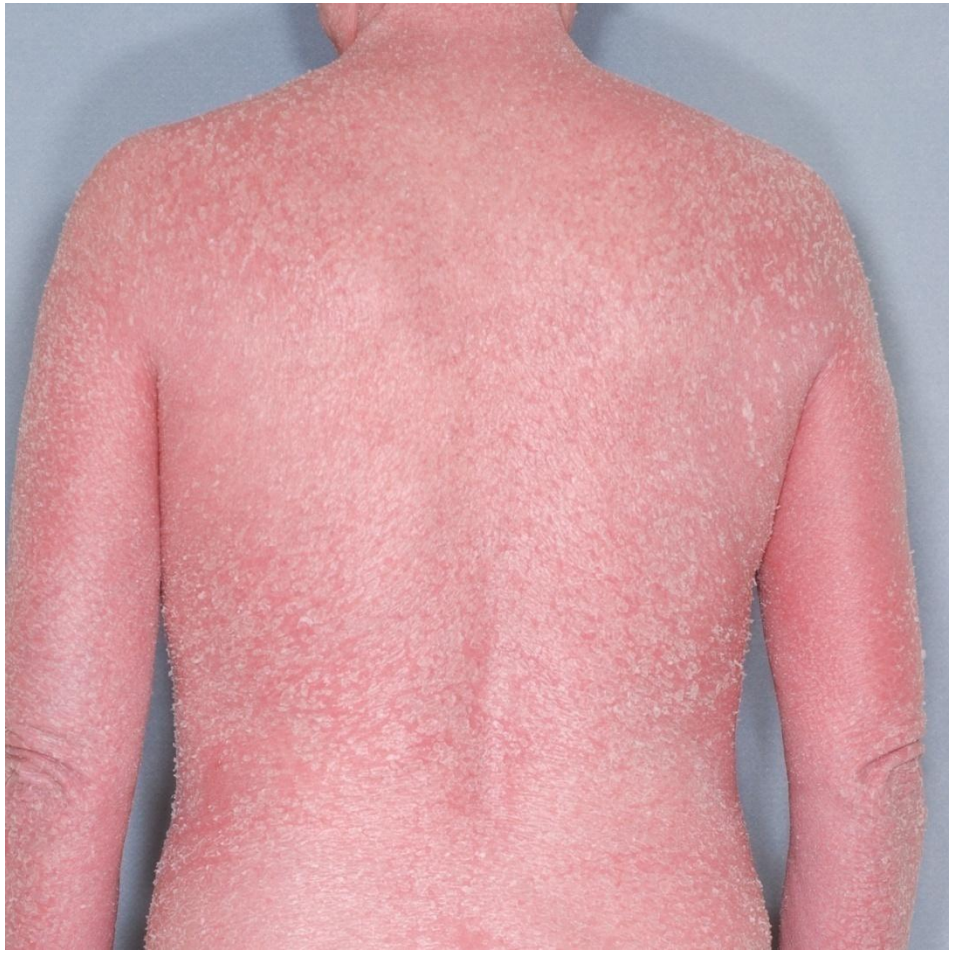


Coutesy J Guitart

Acute ATLL



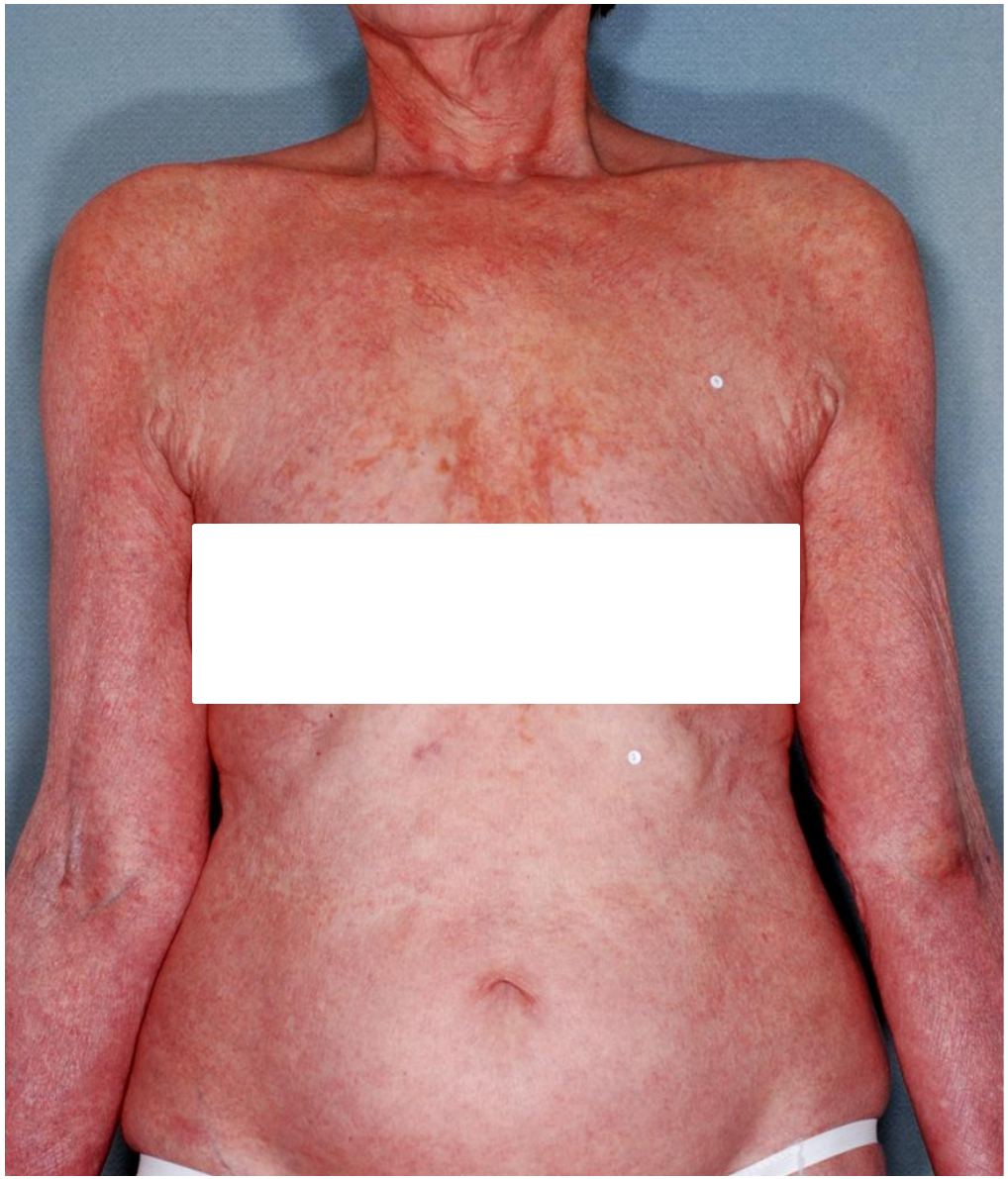
Challenge of the red person



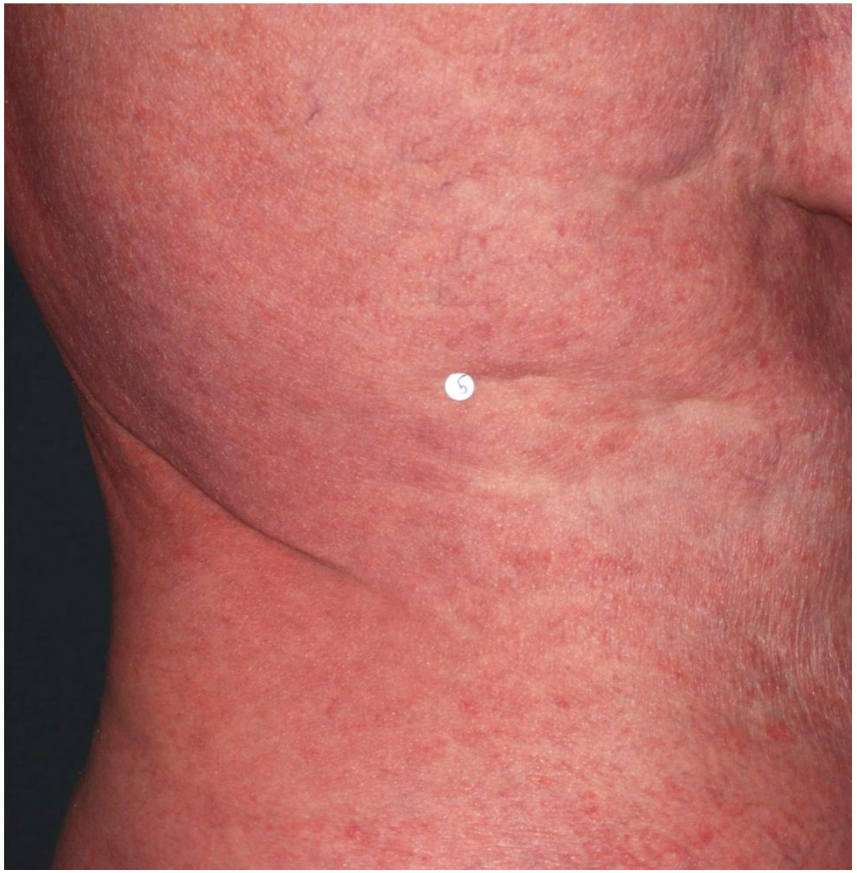
63 F with 4 yr h/o progressive erythroderma

- **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

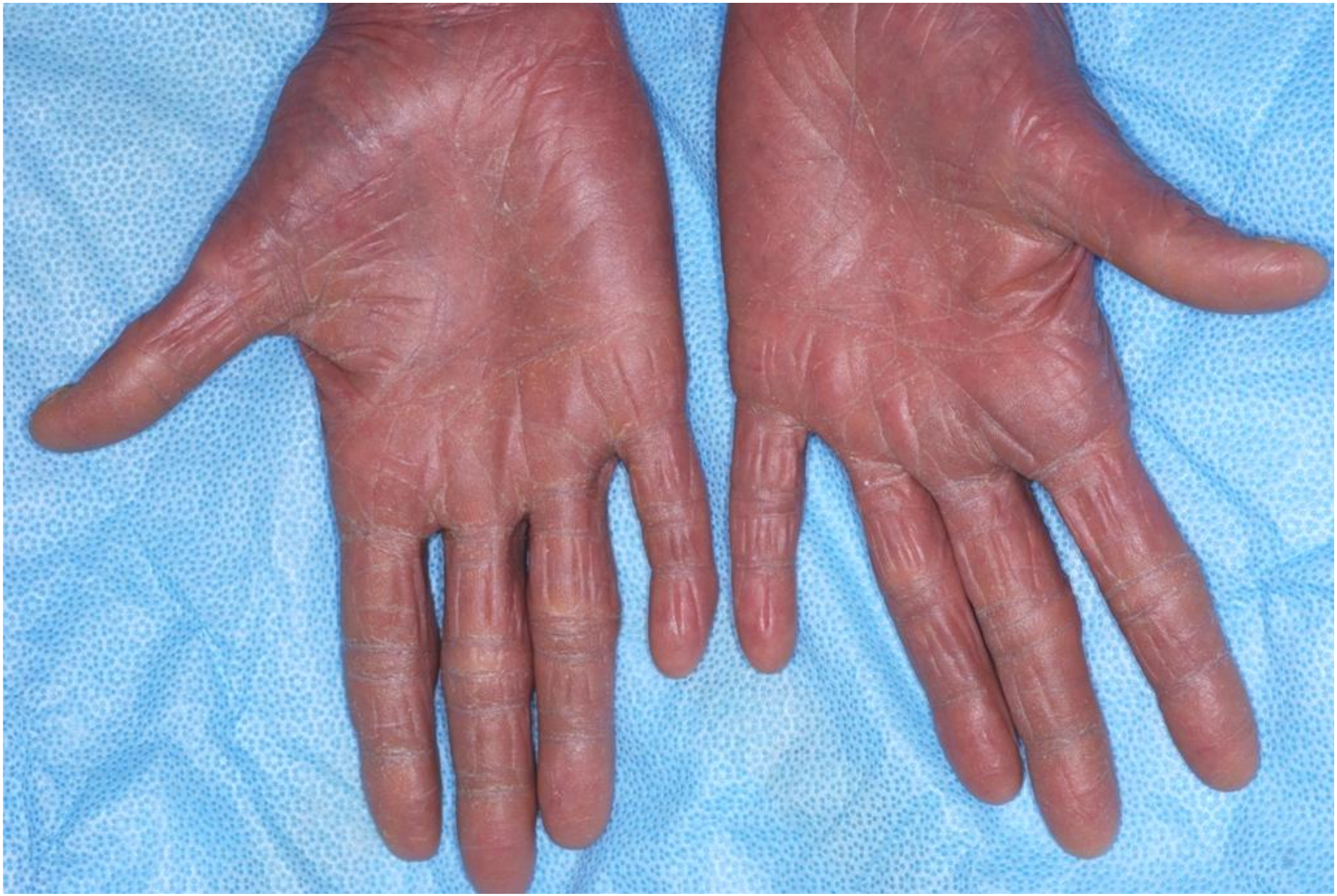
Erythroderma with severe pruritus

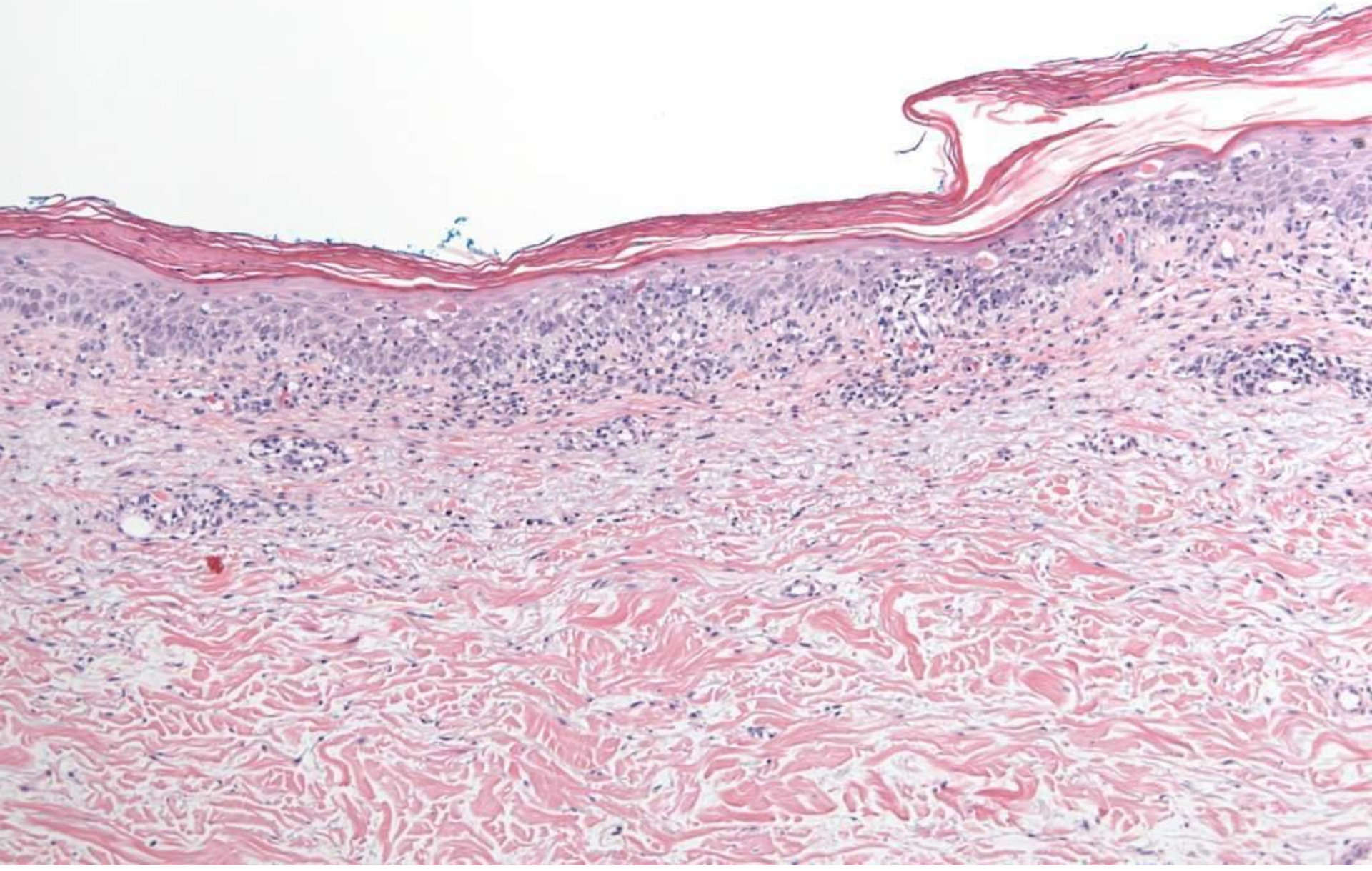


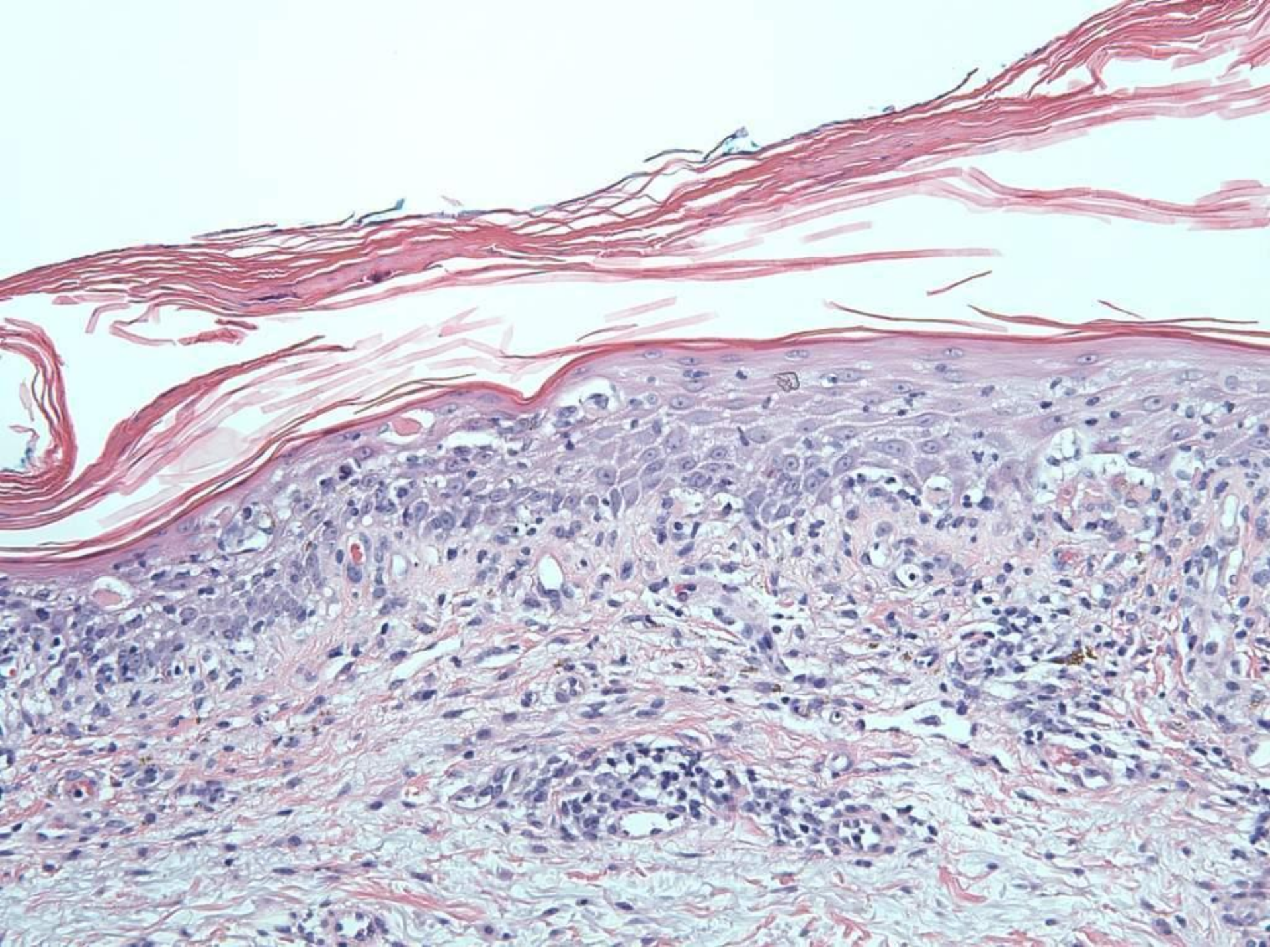
DDx- eczematous derm, psoriasis, drug, PRP, MF/SS, other



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)
- Paraneoplatic
- 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 Sezary 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

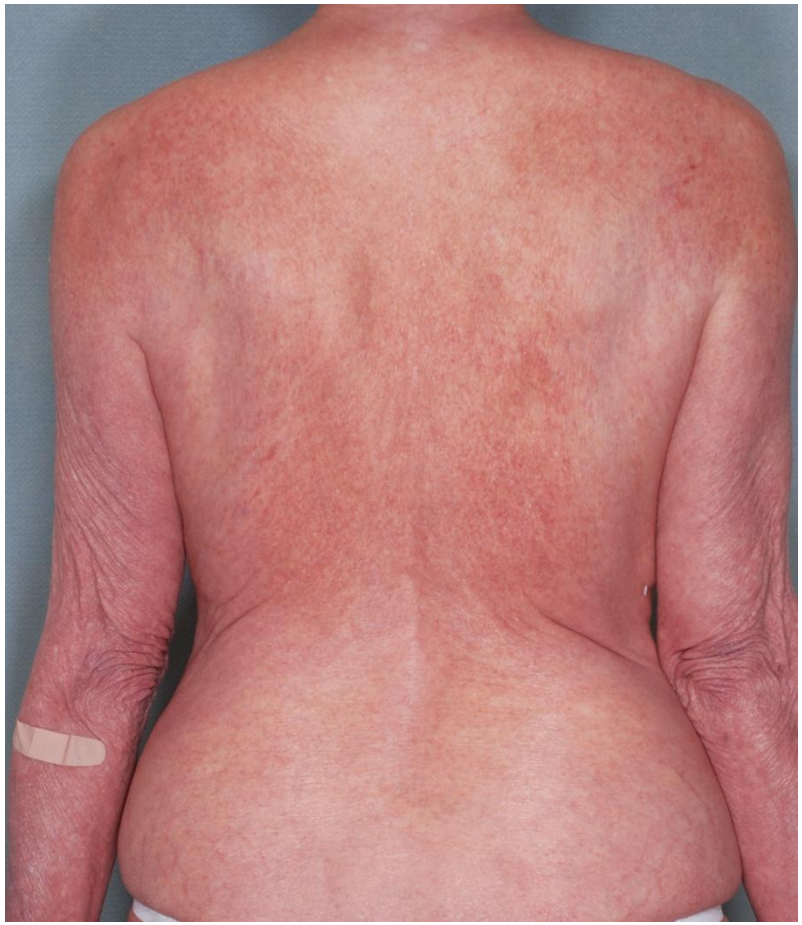
=> Sezary syndrome, stage IVA (T4NxM0B2)

Clinical course and management of SS

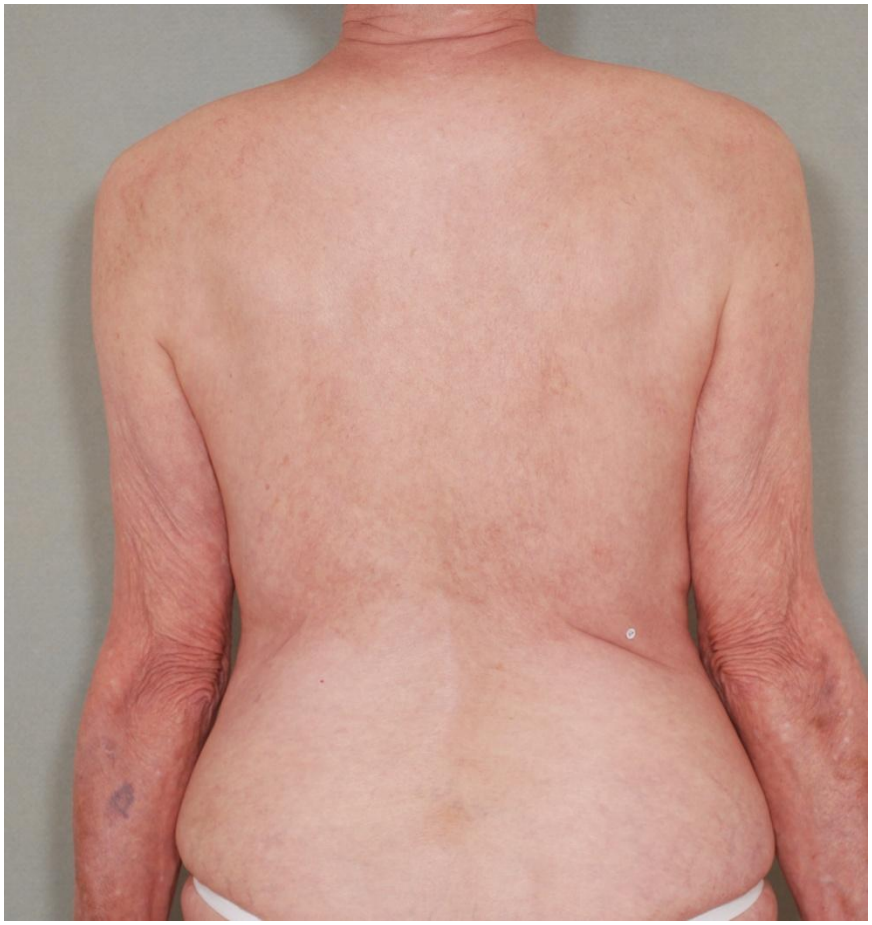
- ECP + oral bexarotene => mild benefit
- Added IFN-alpha => no response, neutropenia
- MTX 35 mg => minimal benefit
- **Anti-CCR4 mab (mogmulizumab)**
  - Rapid reduction of SCs and pruritus
  - Near 3 yrs of great disease control

Case Study: Patient 03-Stanford

(SS; Stage IVA; 6 Prior Therapies; 0.3 mg/kg)



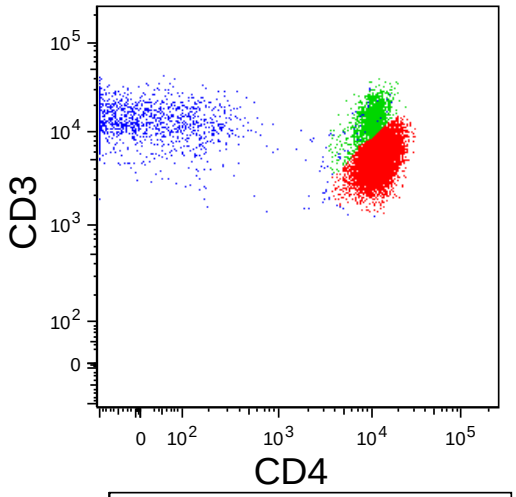
Pretreatment
Course 1 Day 1

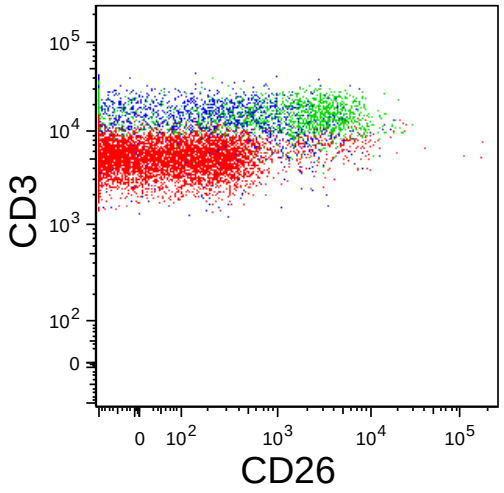


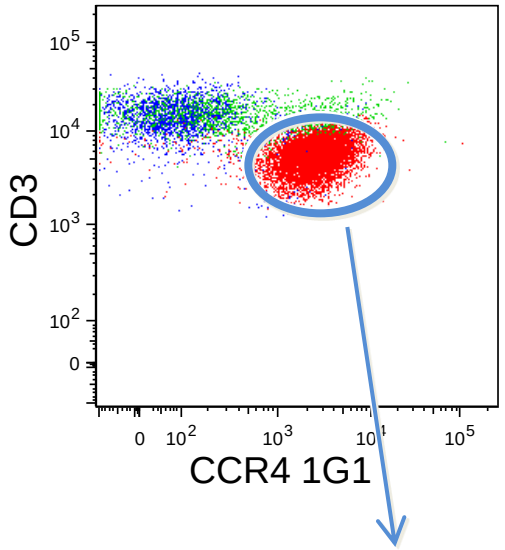
Post treatment
Post Course 11

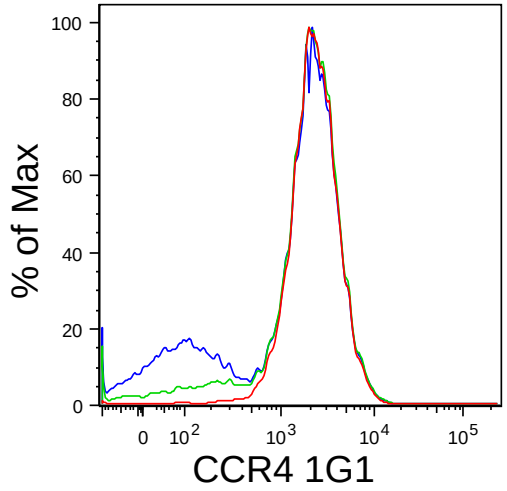
Response in Blood: Patient 01-Stanford (SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

Pre-treatment





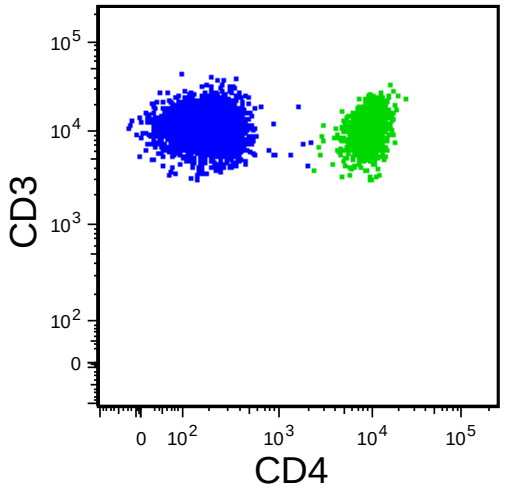


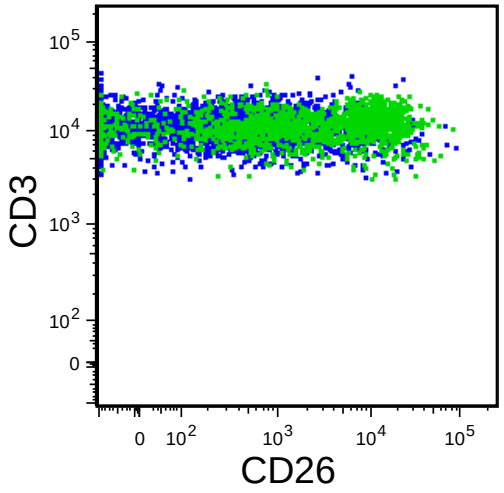


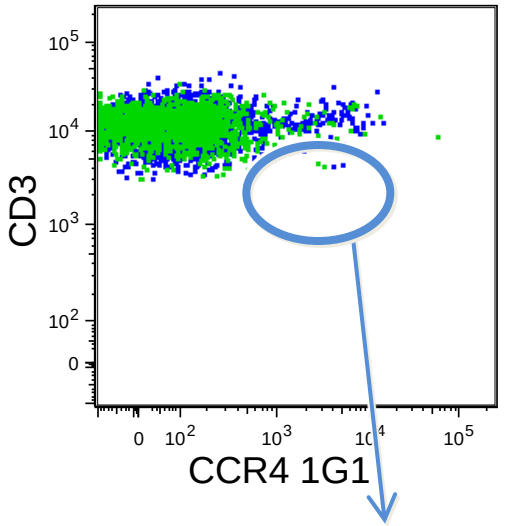
Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

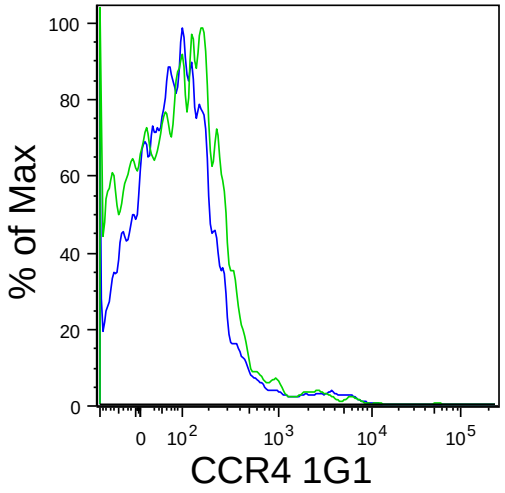
Lymphoma cells

Response in Blood: Patient 01-Stanford
Post-treatment







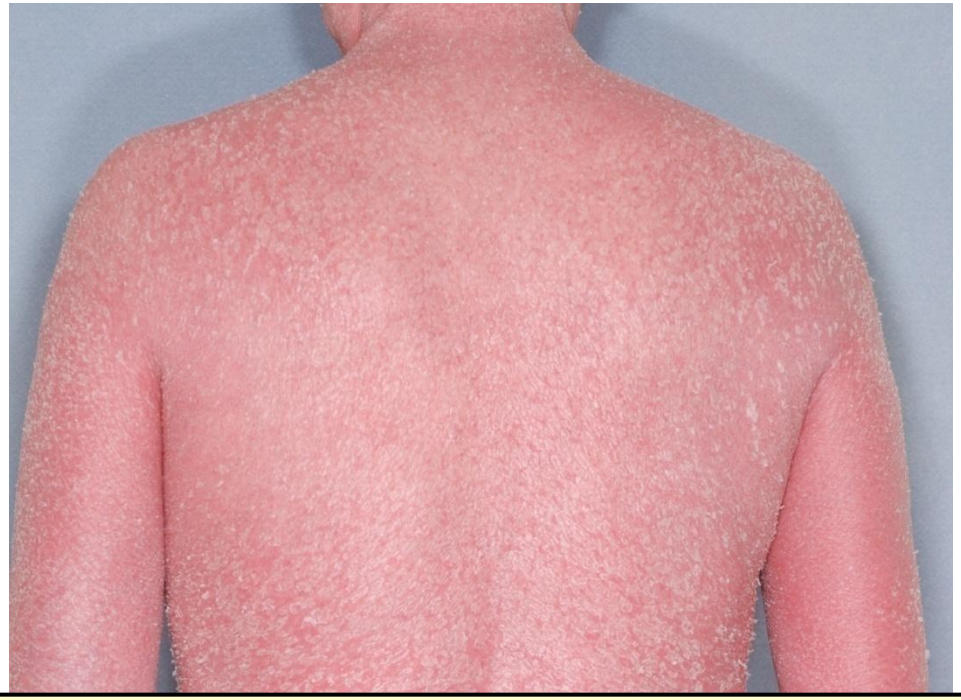


Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

Lymphoma cells undetectable
Response >2 yrs

Phase III RCT in CTCL ongoing for FDA approval

Challenge of the red person
Take home message



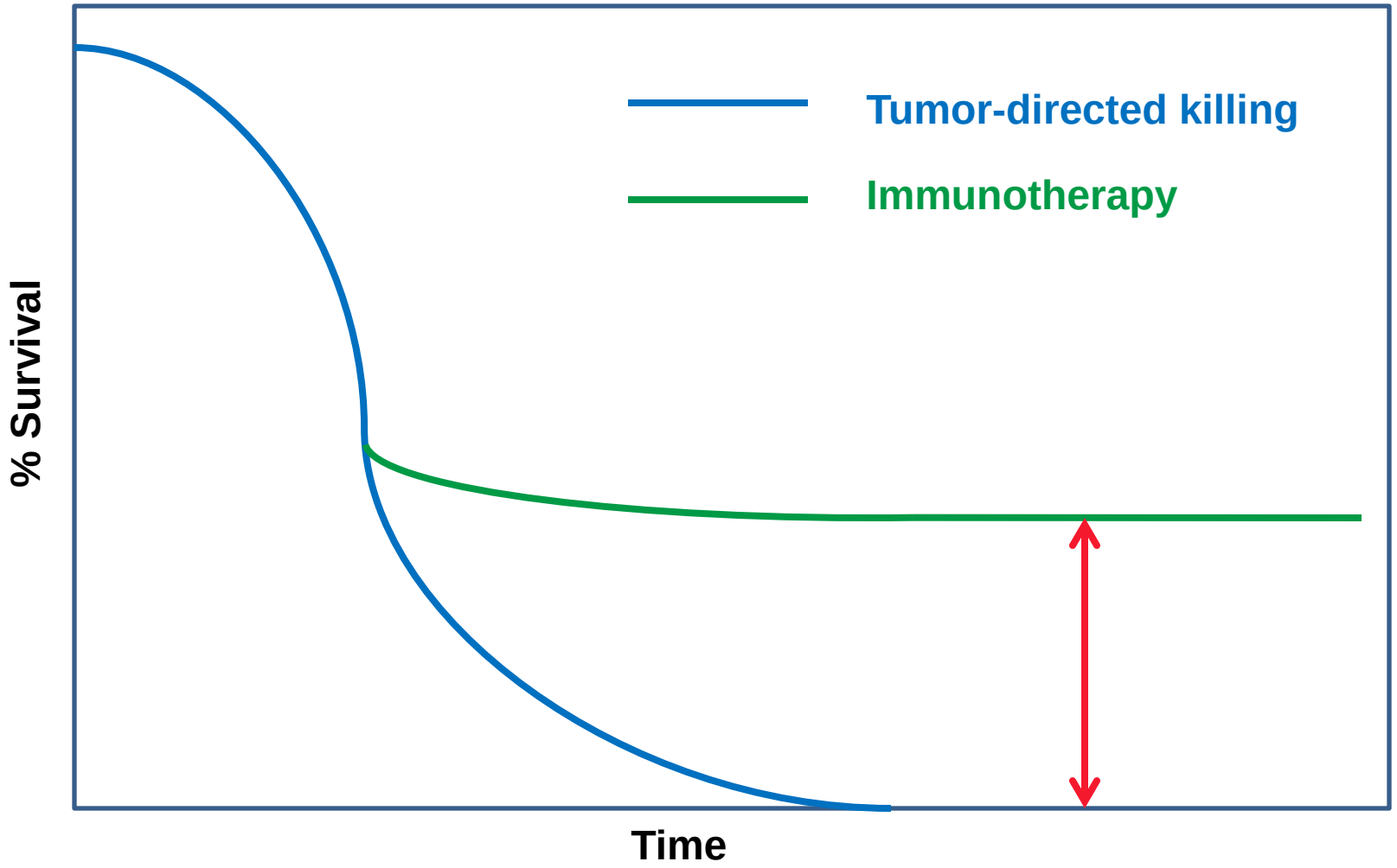
Skin biopsies often non-diagnostic from erythrodermic skin of CTCL

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

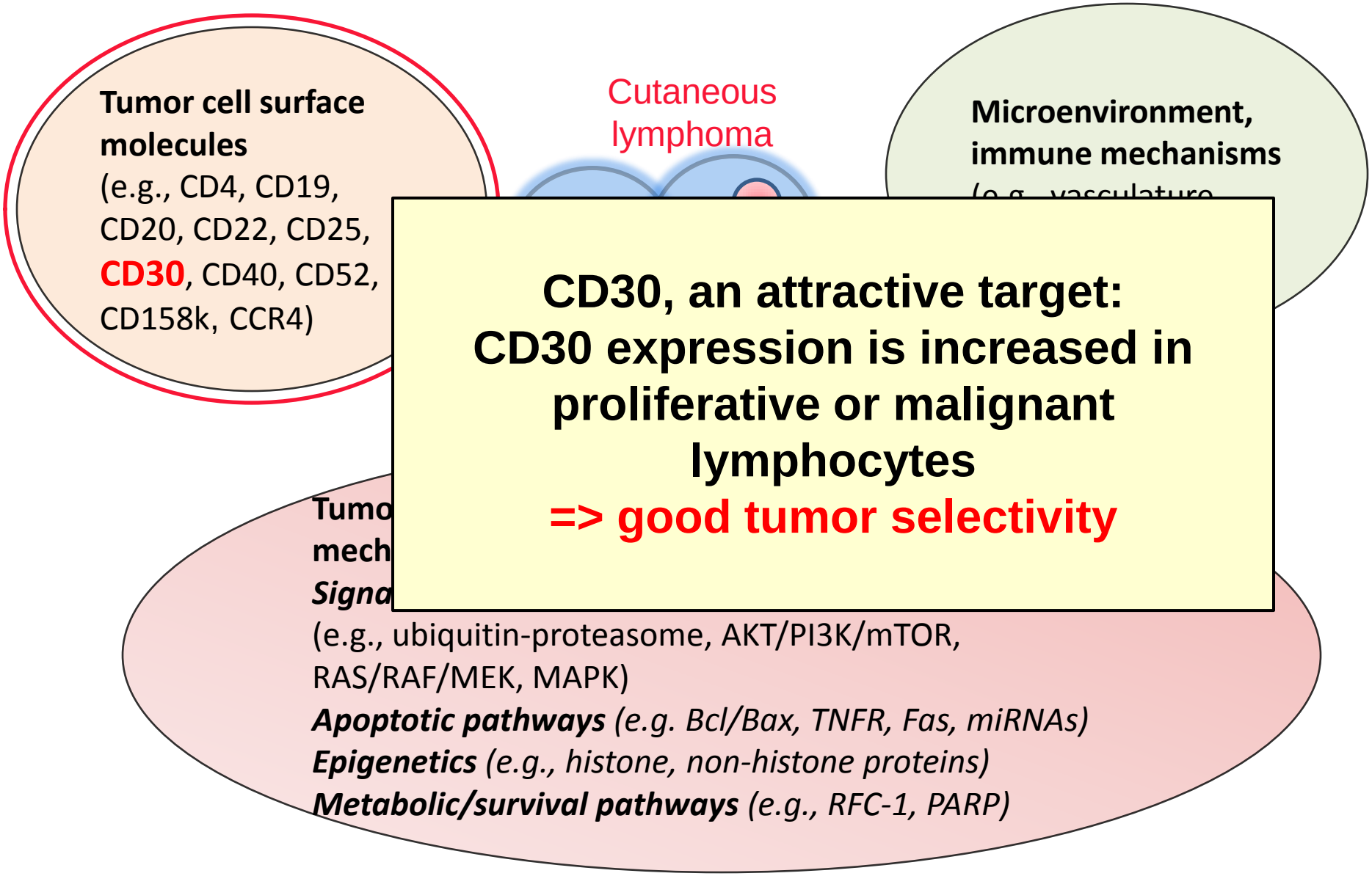


Era of Targeted Therapy

Newer agents for tumor-directed killing

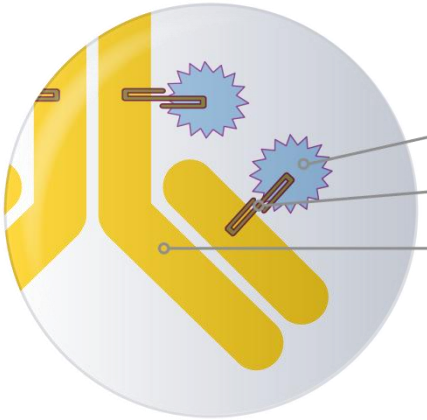
Kill the bad, spare the good cells

Targets for Therapy in Cutaneous Lymphoma



Brentuximab Vedotin Mechanism of Action

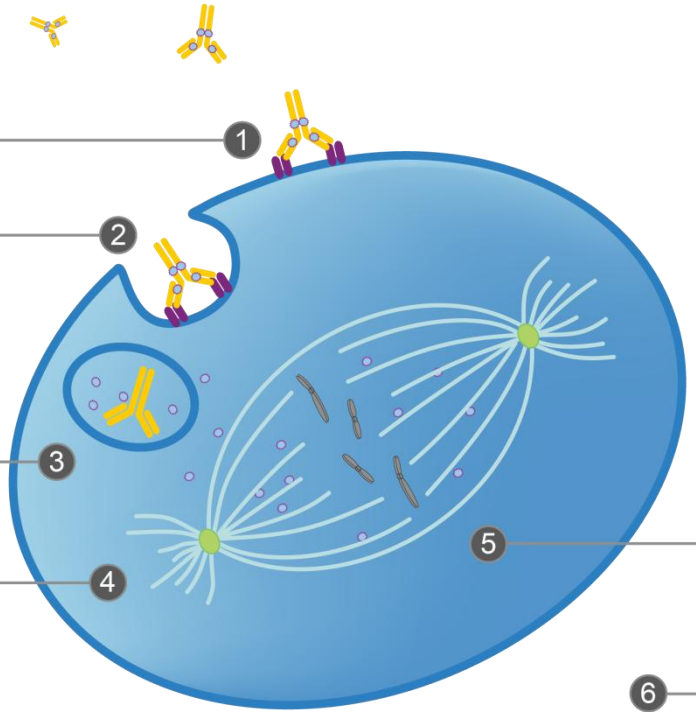
Antibody Drug Conjugate



Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

Anti-CD30 monoclonal antibody



ADC binds to CD30 — 1

ADC-CD30 complex is internalized and traffics to lysosome — 2

MMAE is released — 3

MMAE disrupts microtubule network — 4

5 — G2/M cell cycle arrest

6 — Apoptosis

Given IV every 3 wks

ASH abstract #797,
presented 12/10/2012

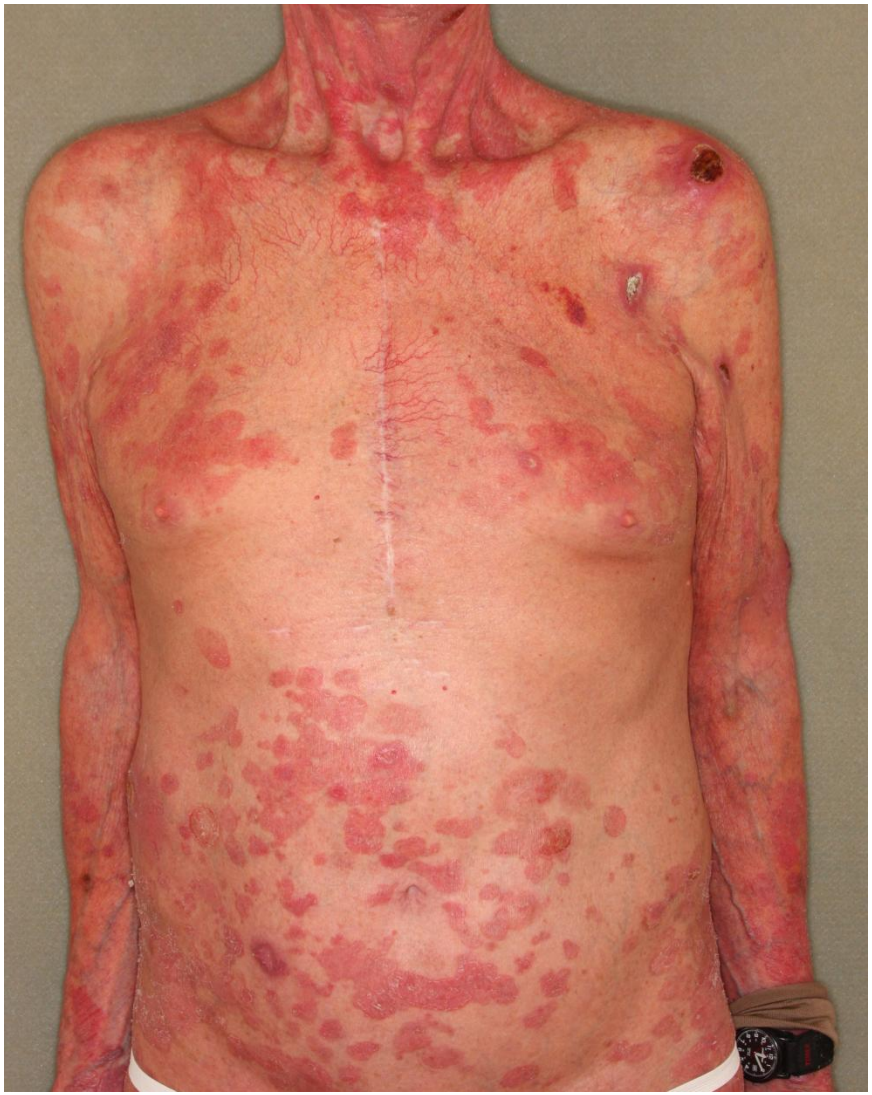
Brentuximab vedotin demonstrates clinical activity in mycosis fungoides / Sézary syndrome

Krathen M[1], Bashey S[1], Sutherland K[1], Sundram U[1], Nagpal S[1], Salva K[3], Wood G[3], Advani R[1], Hoppe RH[1], Reddy S[1], Pulitzer M[2], Horwitz S[2], Kim YH[1]

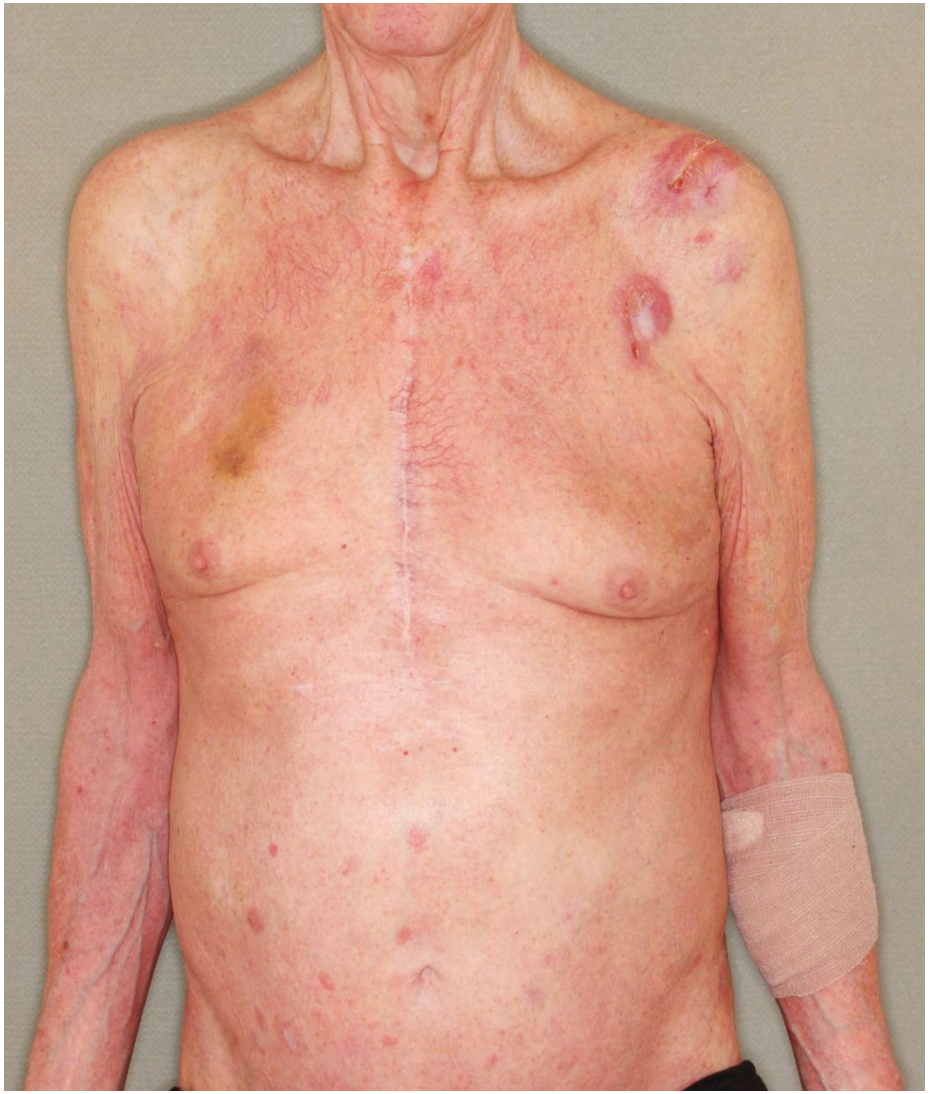
[1]Stanford Cancer Institute, Stanford, CA, USA
[2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[3]University of Wisconsin, Madison, WI, USA

87 yo M with MF IIB, LCT

Screening

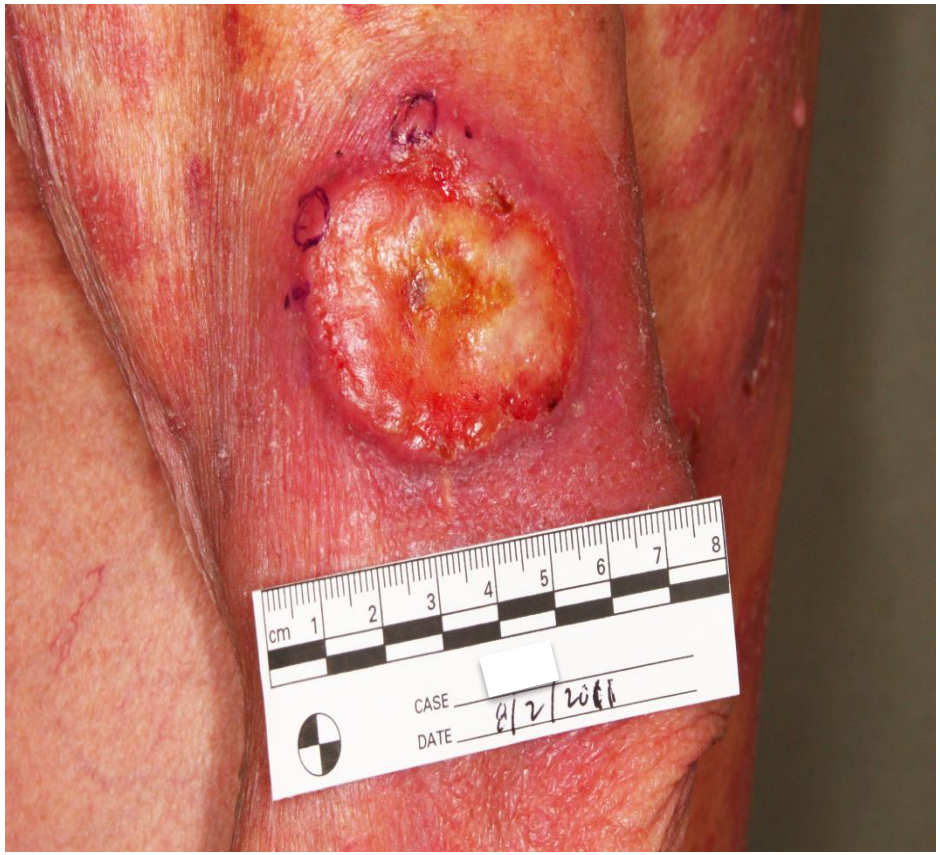


Cycle 6

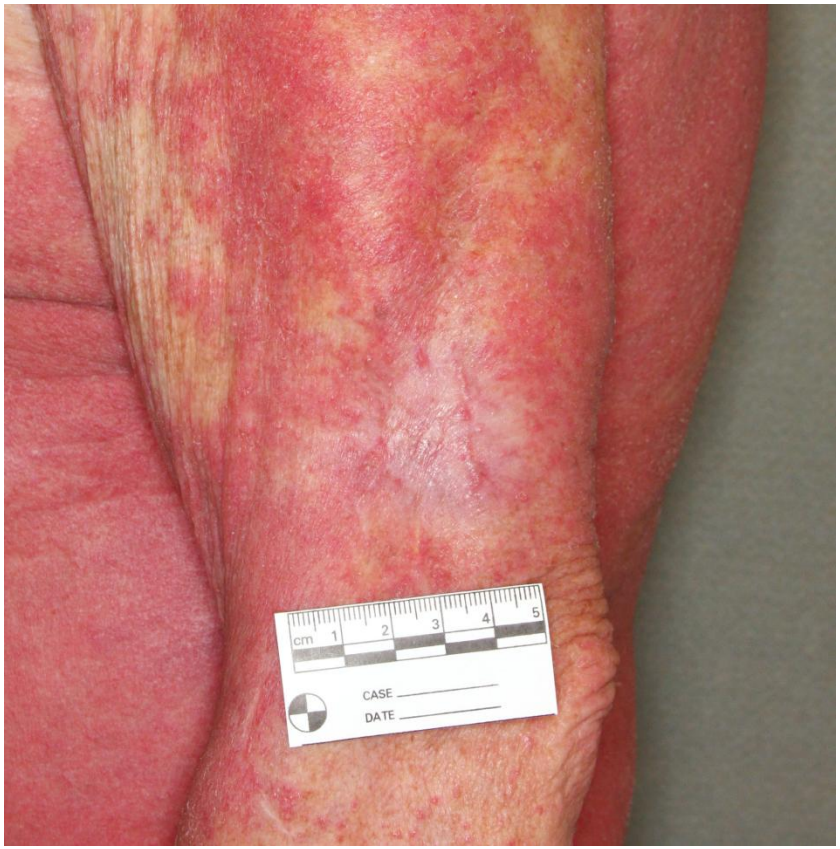


87 yo M with MF IIB, LCT

Screening

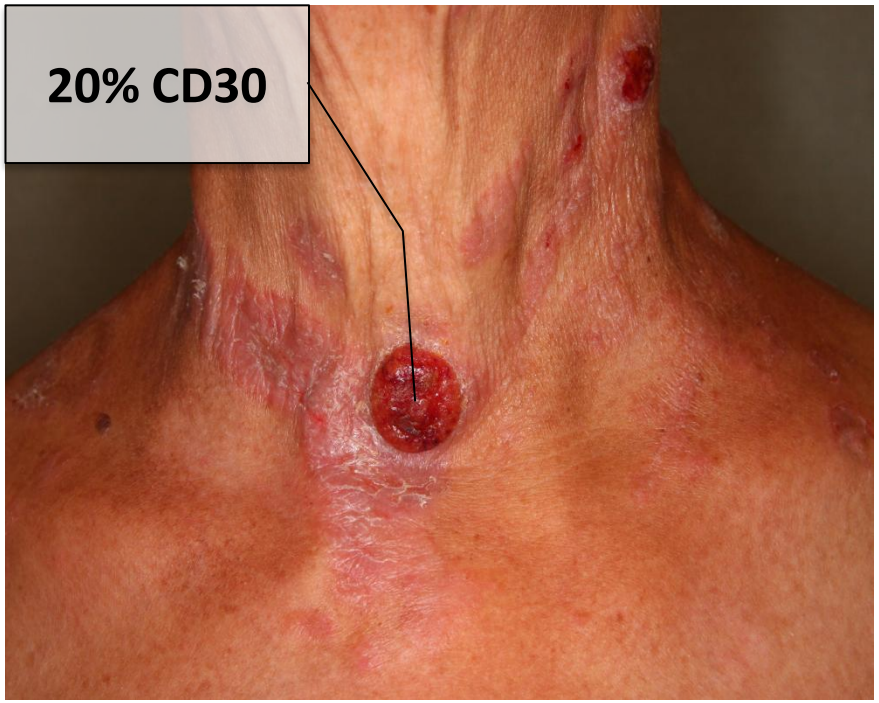


Cycle 6

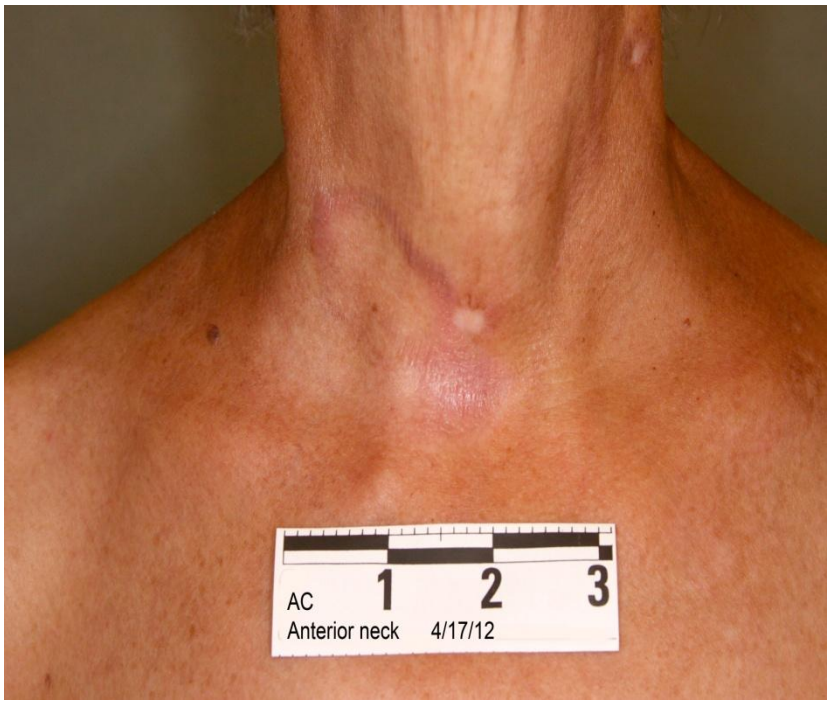


Subject 12: 66 yo F with MF IVB, LCT w/ oropharyngeal involvement

Screening

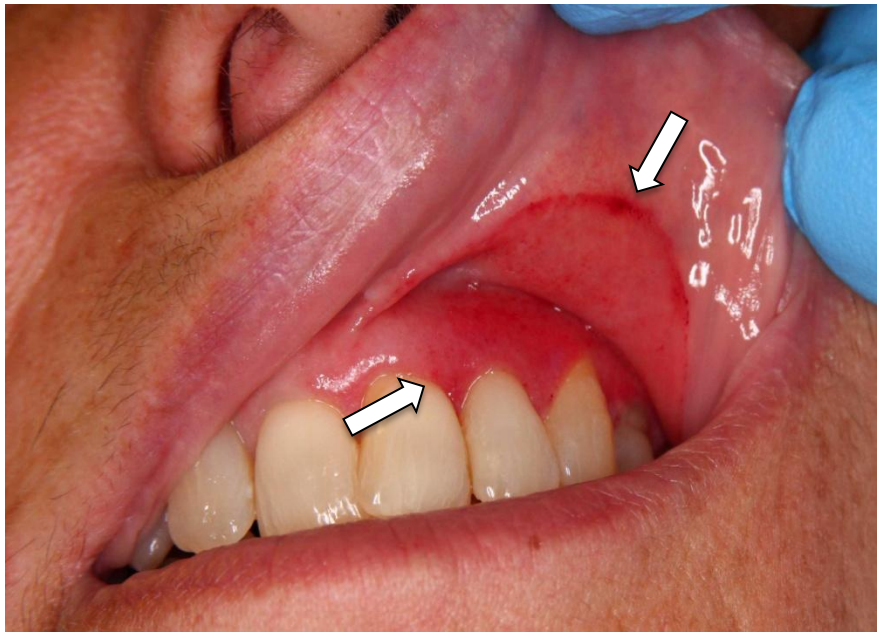


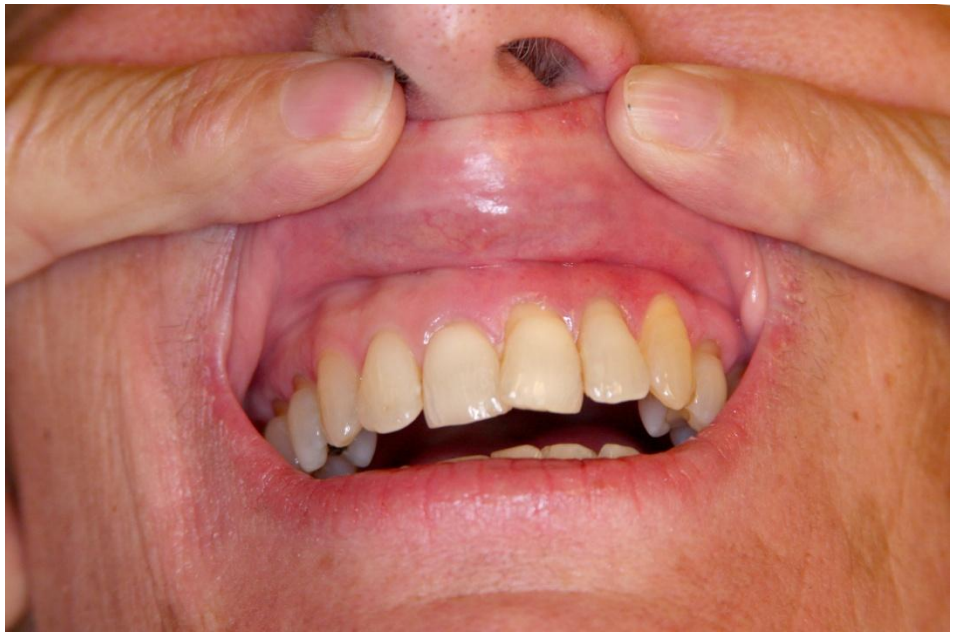
Cycle 10

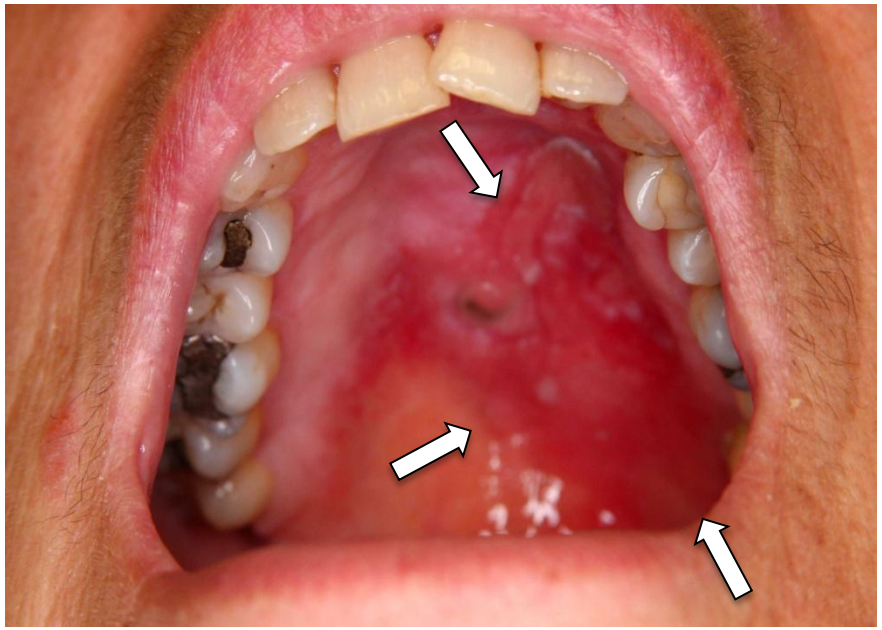


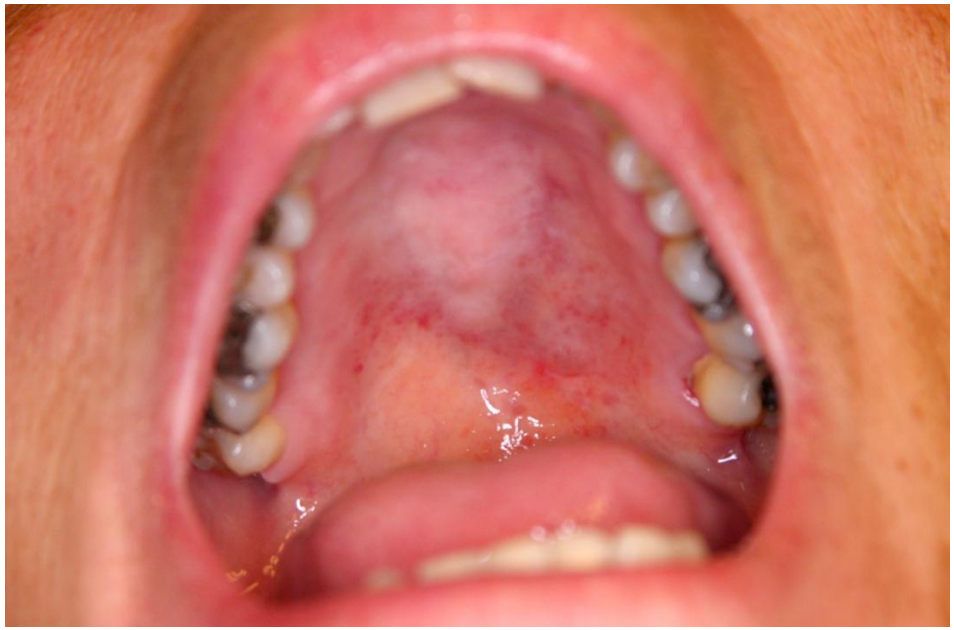
Screening

Cycle 10



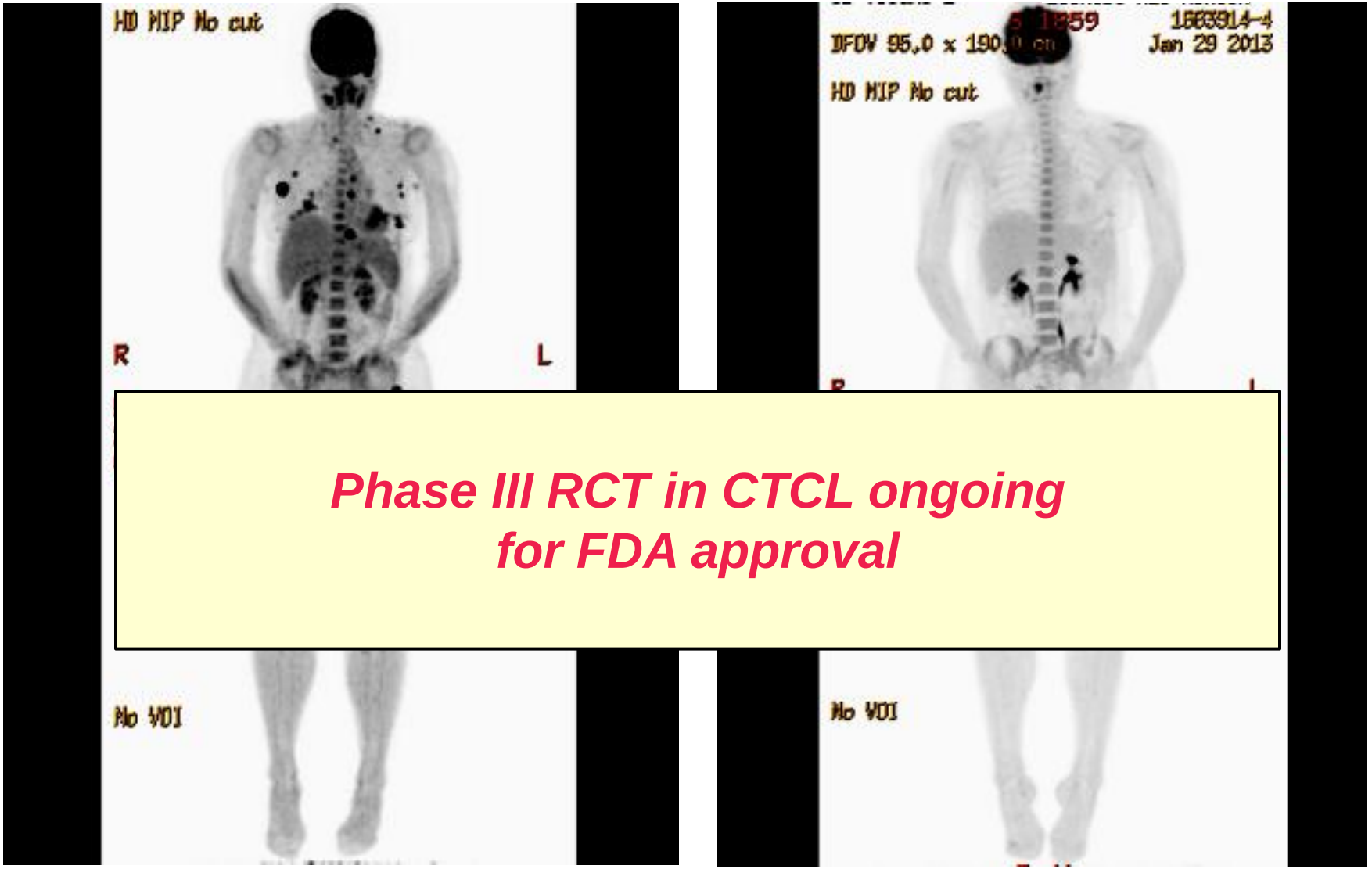






51 yo F stage IVA2 MF with LCT in skin/LNs: response to brentuximab vedotin

Pre-treatment 12/20/2012 **Post 2 cycles 1/29/2013**

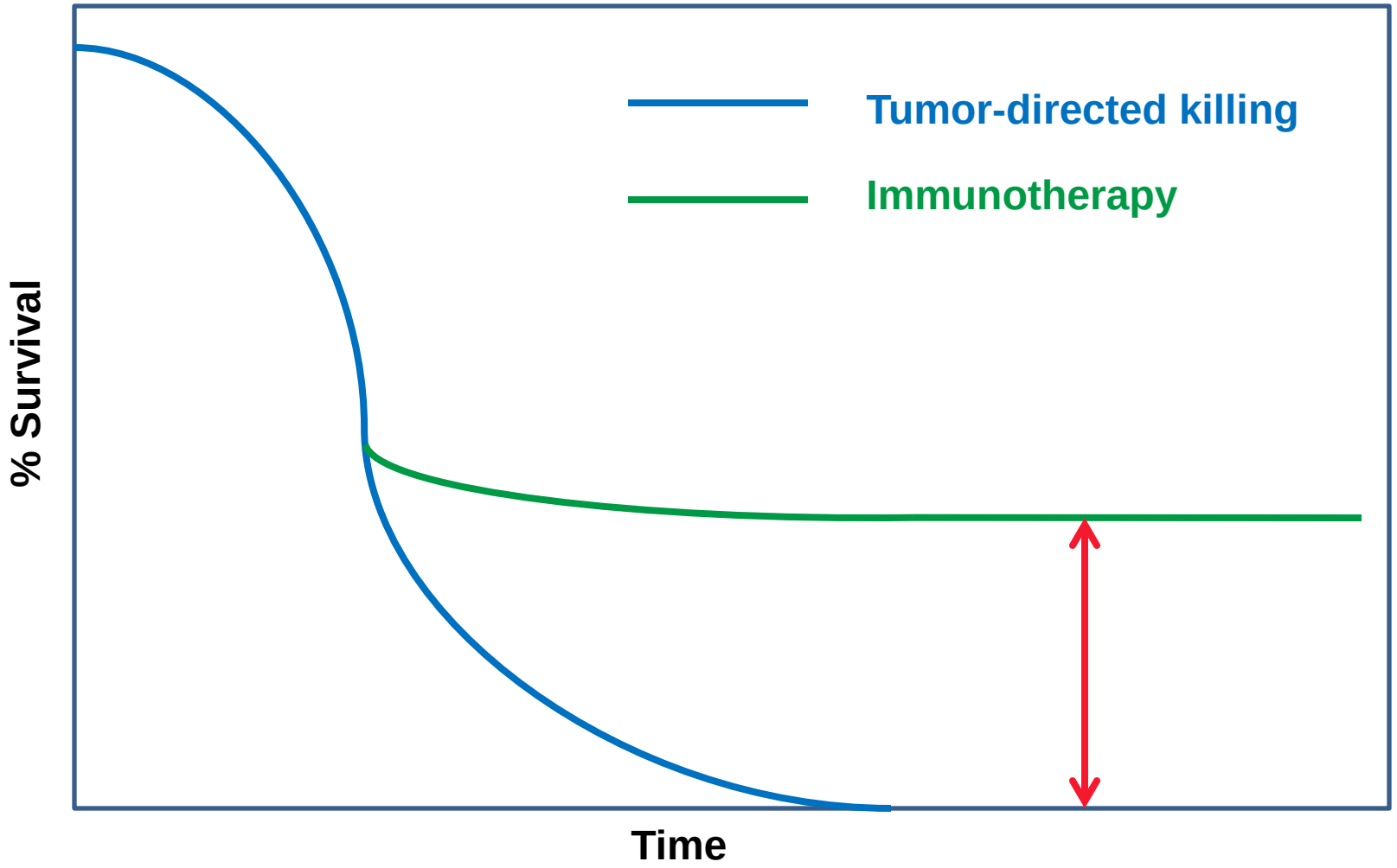


Phase III RCT in CTCL ongoing for FDA approval

Road to a CURE

How do we make the nice responses last?

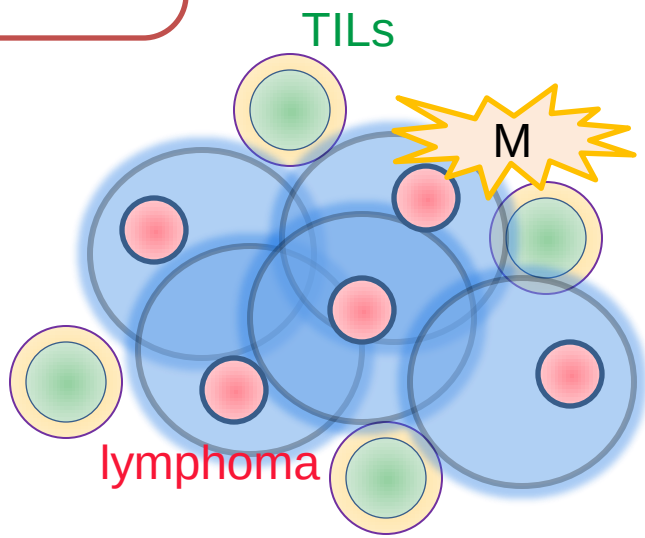
Partnering with immunotherapy



Immunotherapy strategies in cancer

Tumor-specific monoclonal antibodies

Cytokine therapy



Adoptive T-cell transfer

Immune-modulating agents or antibodies

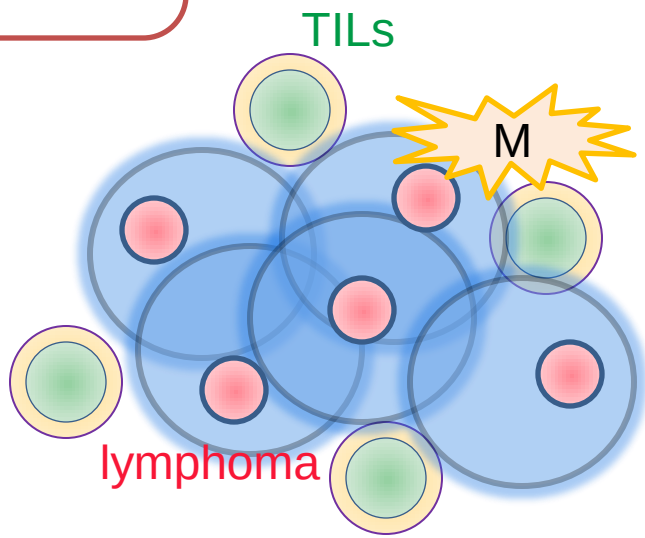
Allogeneic HSCT

Vaccine-based approaches

Immunotherapy strategies in cancer

Tumor-specific monoclonal antibodies

Cytokine therapy



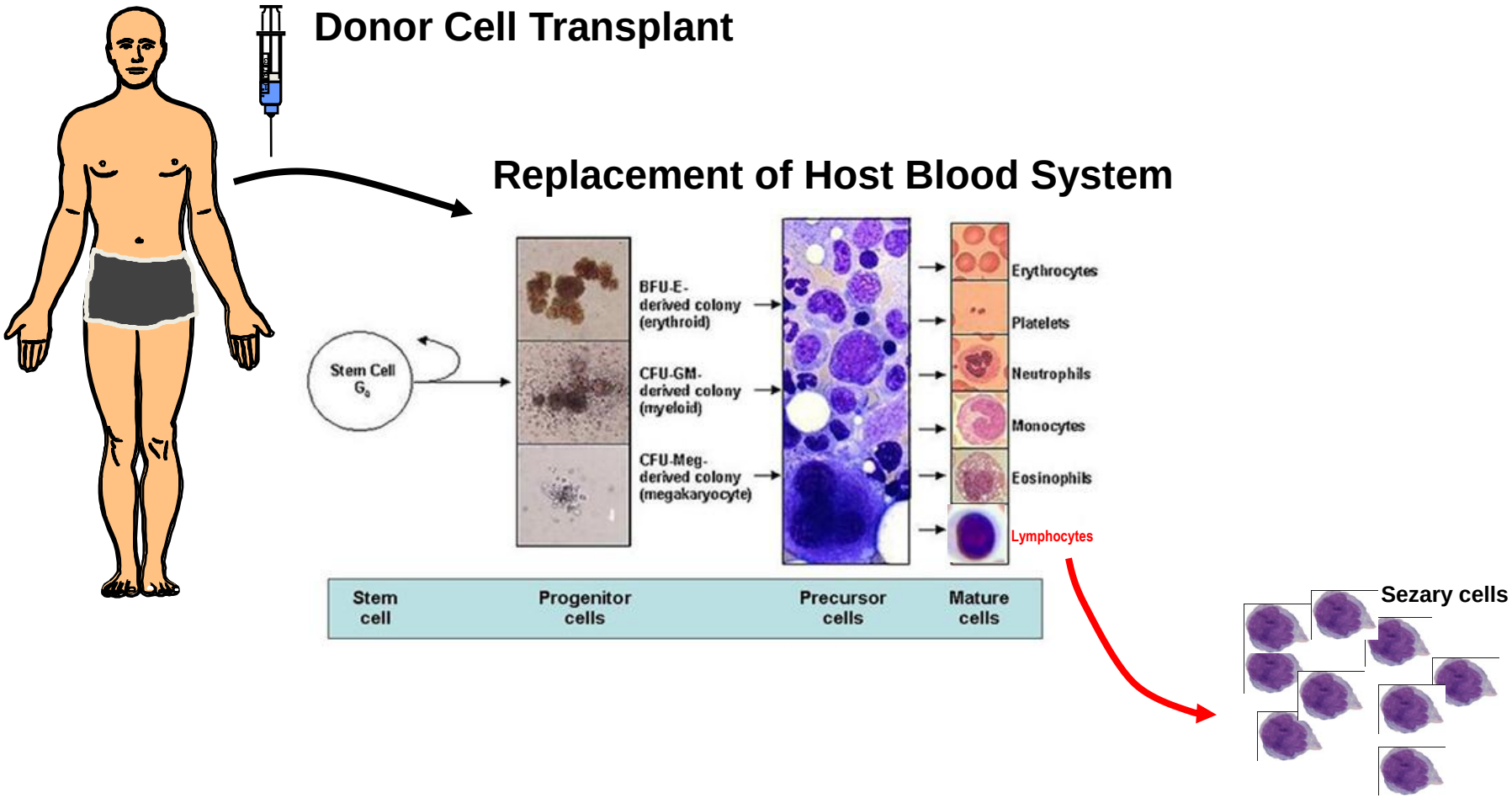
Adoptive T-cell transfer

Immune-modulating agents or antibodies

Allogeneic HSCT

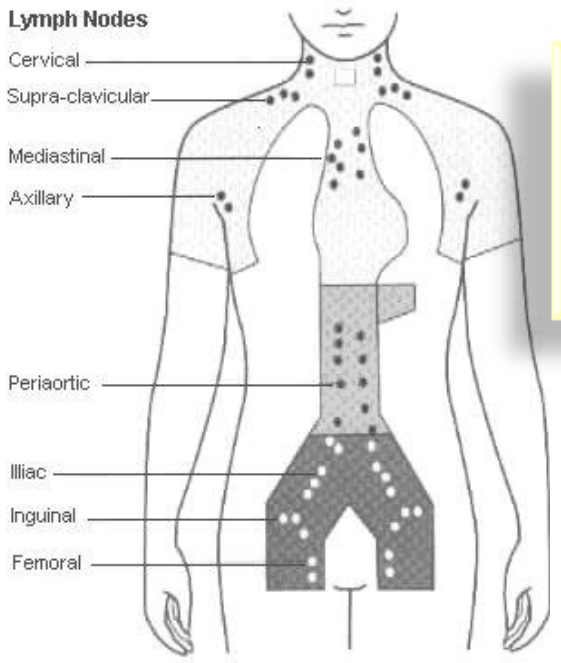
Vaccine-based approaches

Harnessing the graft-versus-lymphoma effect in allo HSCT as the ultimate cellular immune therapy



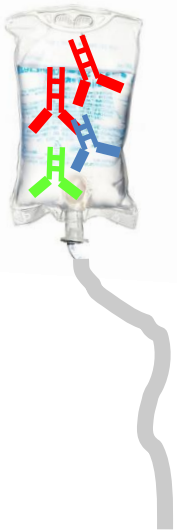
A New Approach in Donor Cell Transplant
Non-Myeloablative Regimen with TLI/ATG
"Protective conditioning"

NEJM 353:1321, 2005
Stanford study on going



TSEBT

+



Inverted Y field

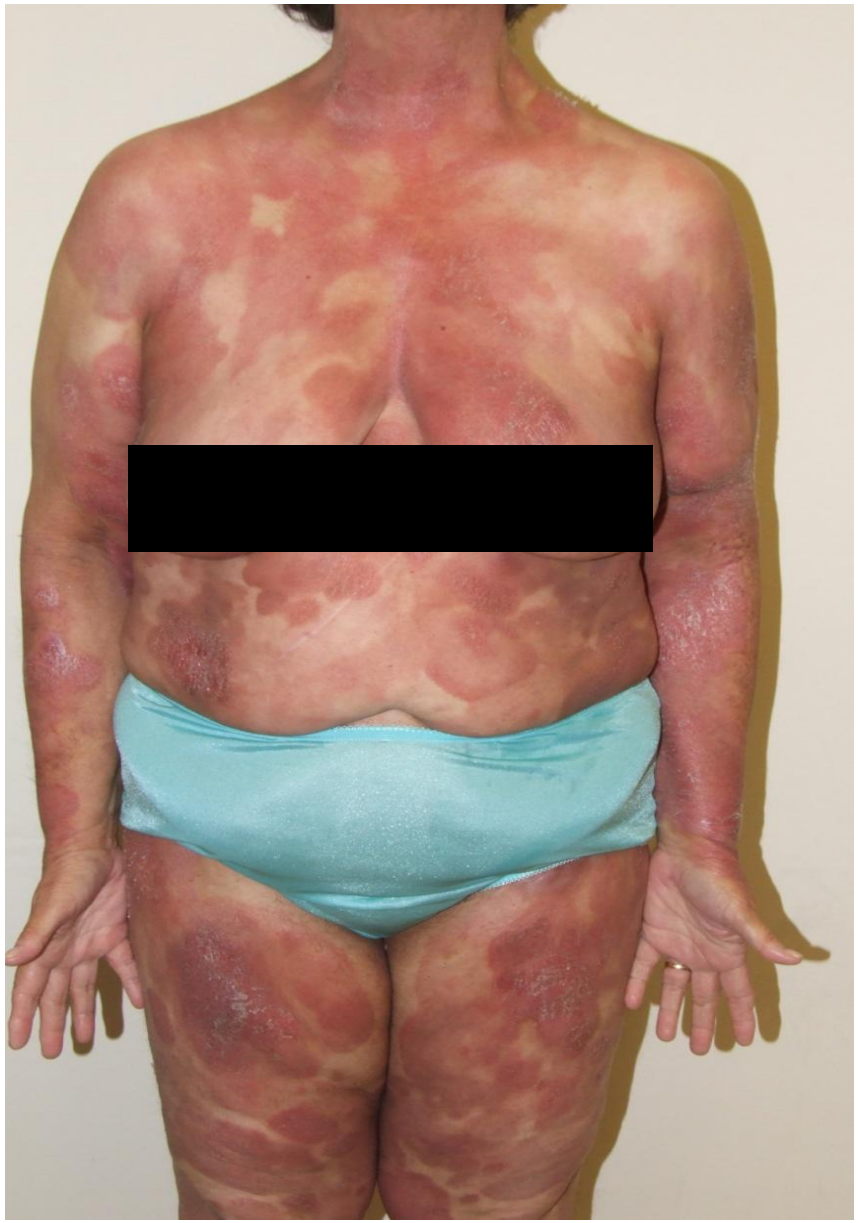
Total Lymphoid Irradiation (TLI)

Anti-Thymocyte Globulin (ATG, Rabbit anti-T cell antibodies)

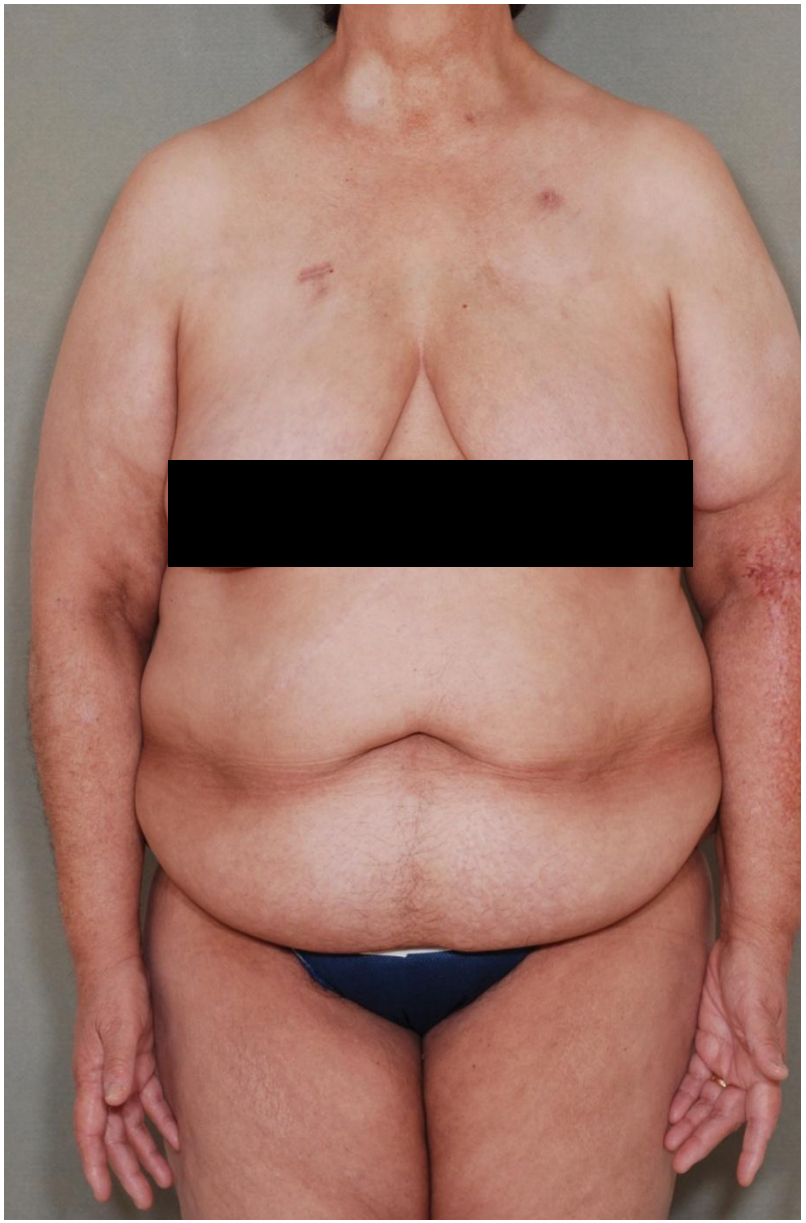
Enable Donor Cells to Engraft
aGVHD reduced to 2-5% (vs. 20-65%)

Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT



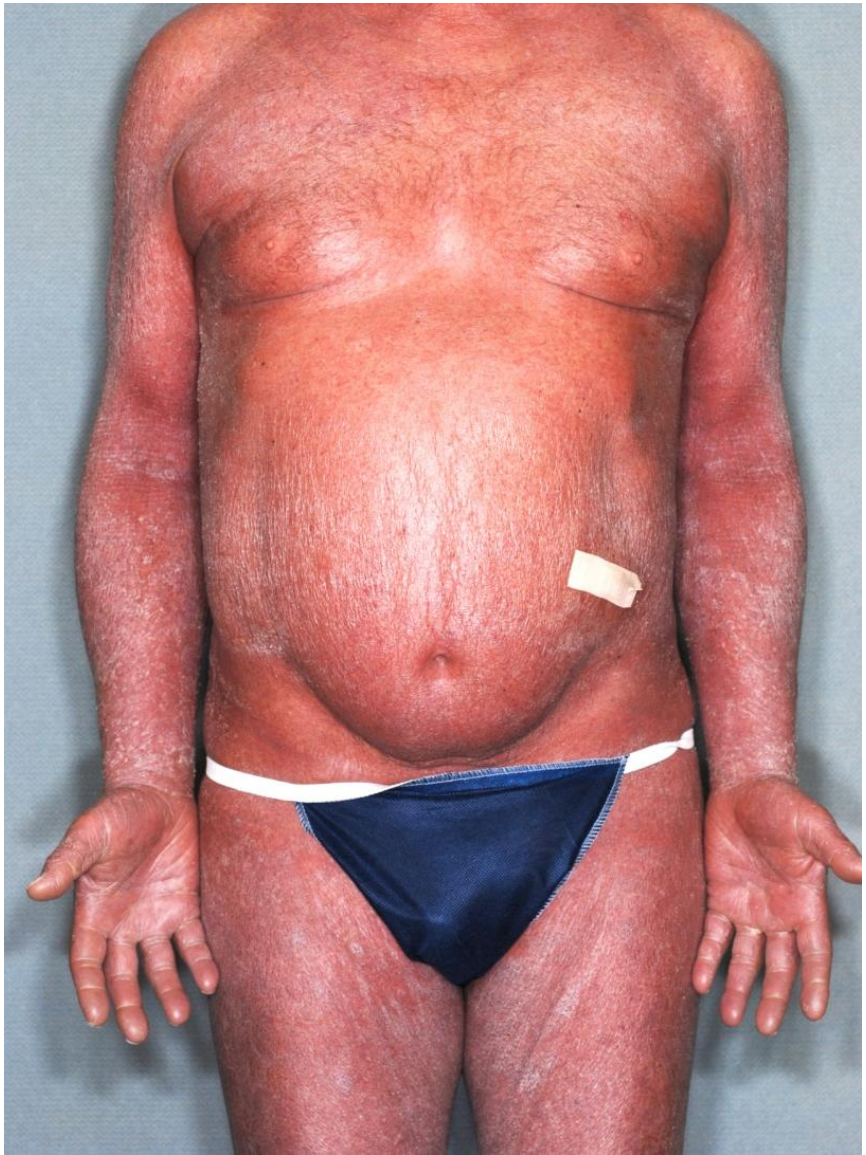
3.0+ yr (NED, no GVHD)



Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

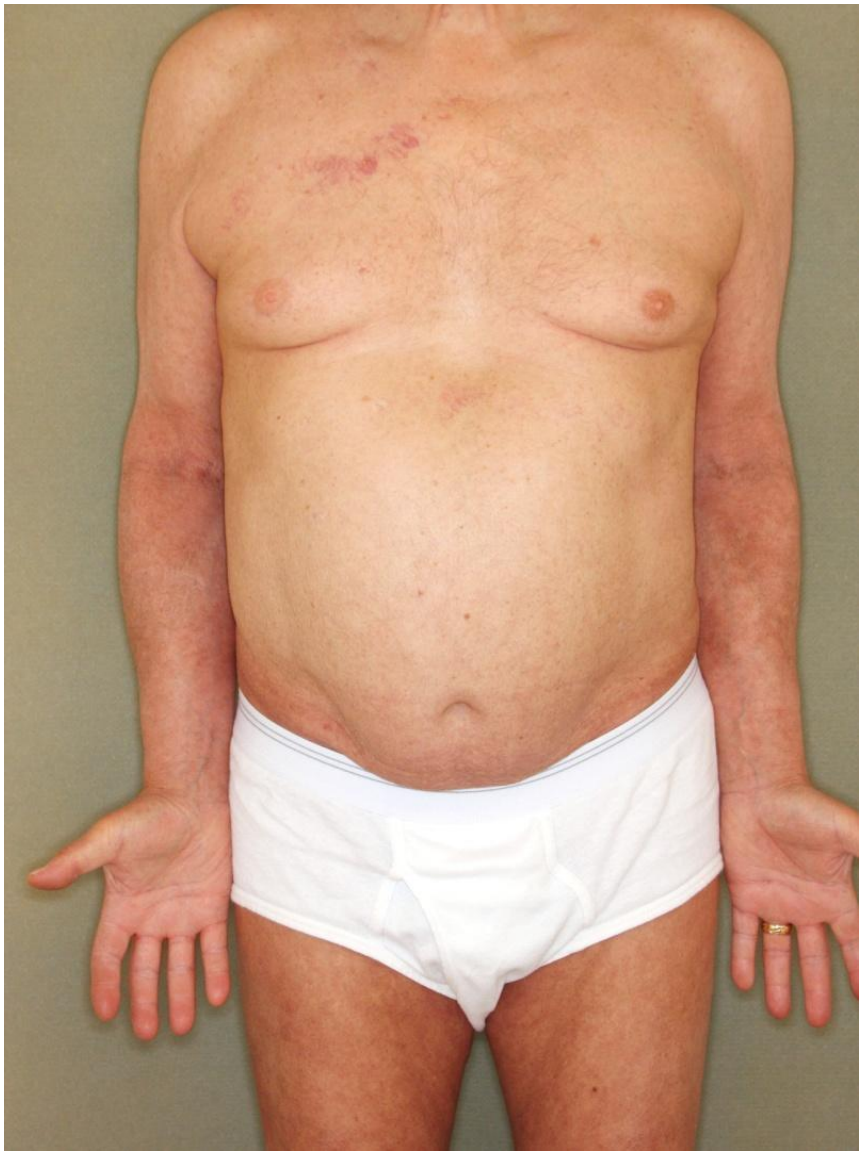
Pre-TSEBT

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



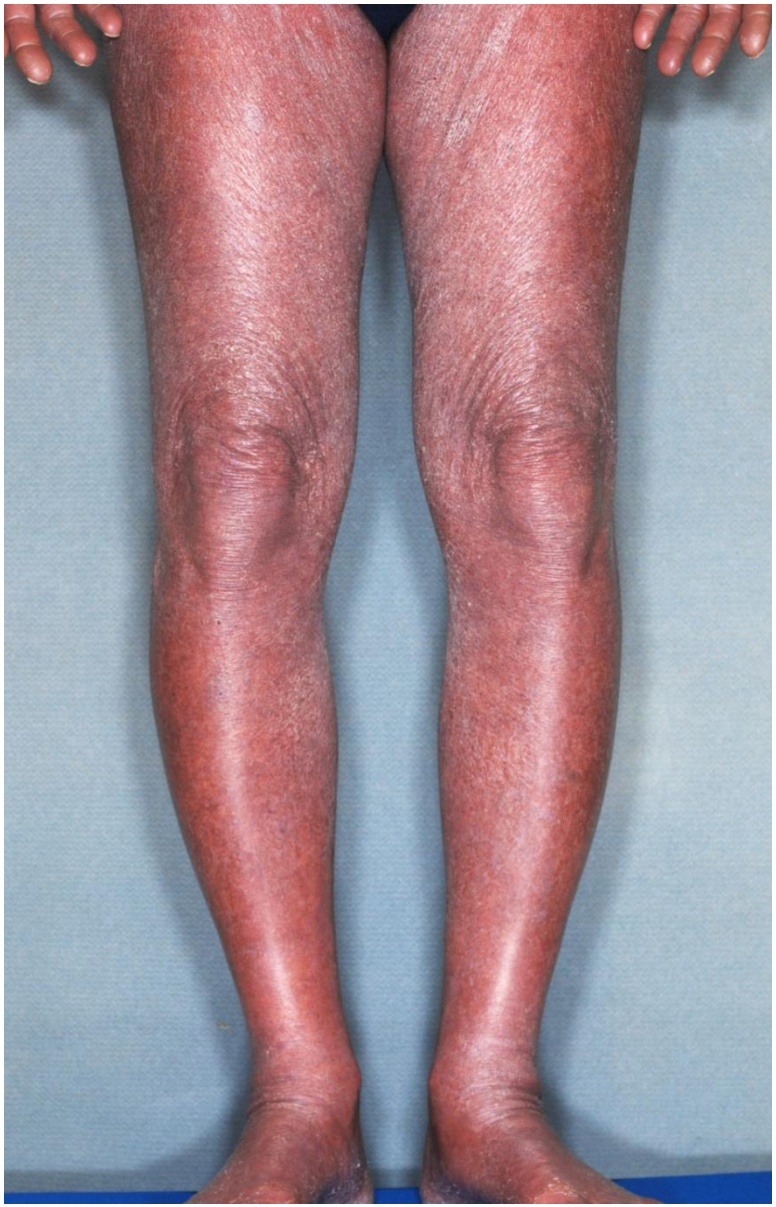
2.0+ yr (NED, no GVHD)

CD4+/CD26-: normalized

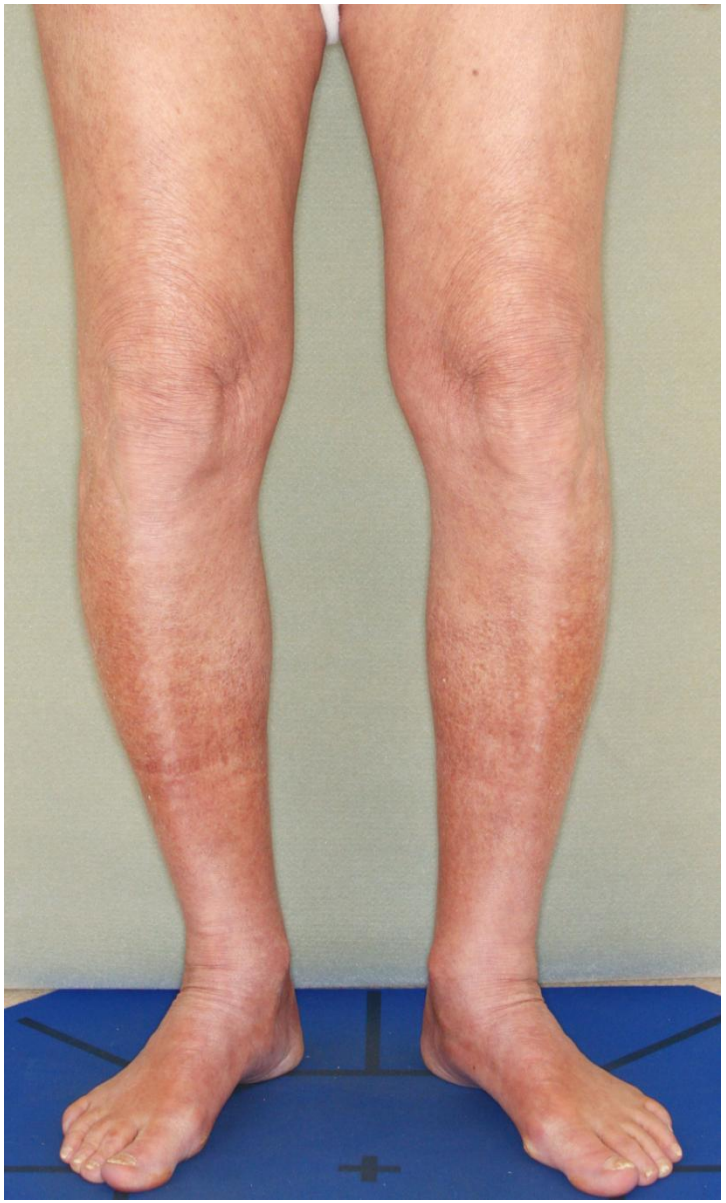


Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-transplant



2.0+ yr (NED, no GVHD)



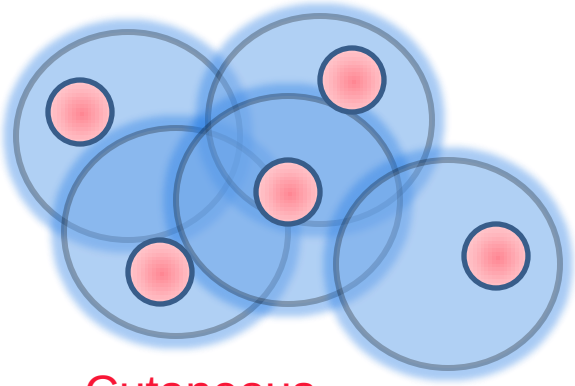
Immunotherapy strategies in cutaneous lymphoma

Combination with newer targeted therapies, chemotherapies, radiation therapy

long-lasting, curative outcome

Adoptive cell transfer

Immune-modulating agents or antibodies



Cutaneous lymphoma

Vaccine-based approaches

Allogeneic HSCT

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

Stanford Multidisciplinary Cutaneous Lymphoma Group

Ranjana Advani

Med Onc partners

Holbrook Kohrt
Sunil Reddy
Ron Levy

Wen-Kai Weng
Sally Arai
Katherine Wolpin
BMT partners