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
  - Folliculotropic MF
  - Pagetoid reticulosis
  - Granulomatous slack skin

Sézary syndrome

Primary cutaneous CD30+ lymphoproliferative disorders
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

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

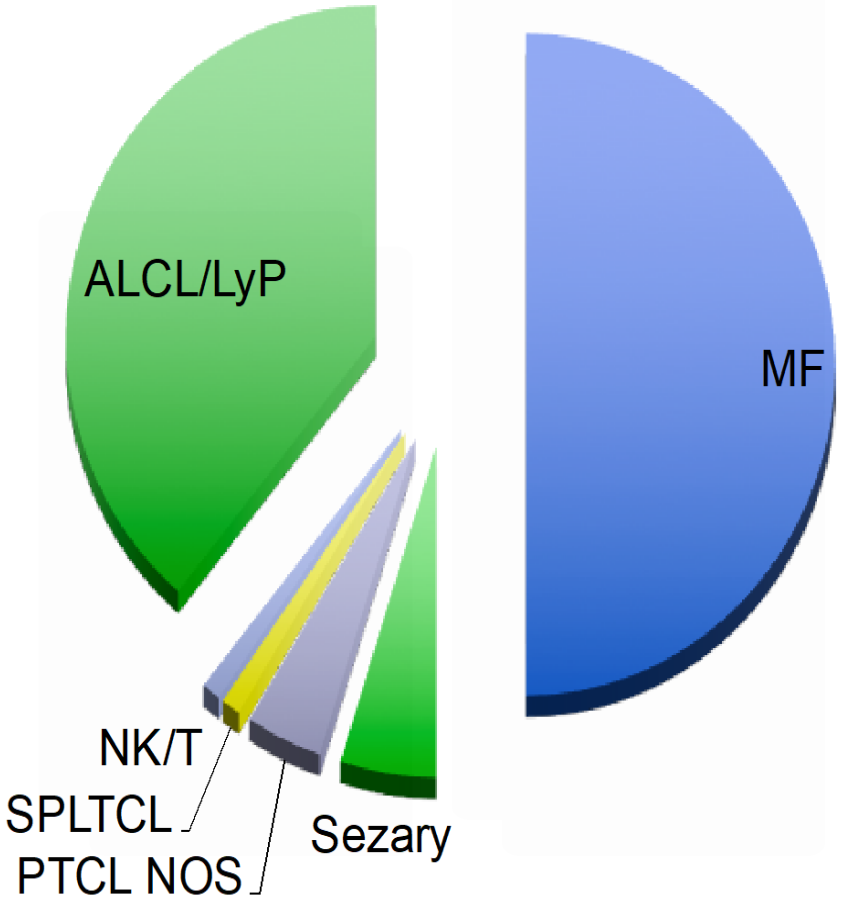
Cutaneous γ/δ T-cell lymphoma (provisional)

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma

Primary cutaneous peripheral T-cell lymphoma, unspecified

Swerdlow et al. Blood. 2016.

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, 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

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

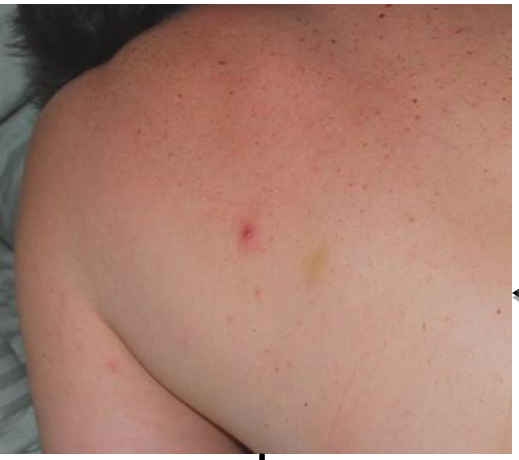
- Lymphomatoid drug reaction
- Misc. inflammatory dermatoses (esp. actinic reticuloid)
- Infections

Neoplastic

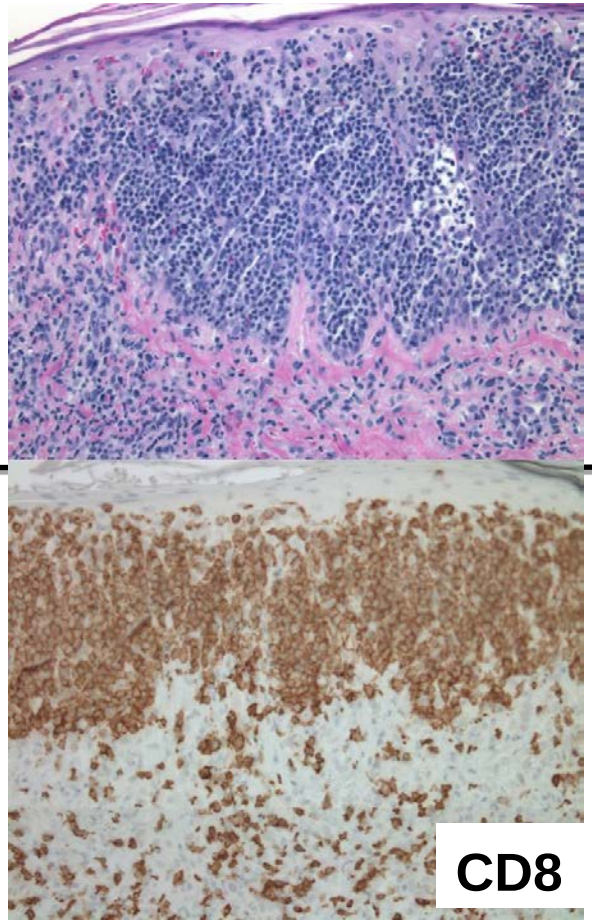
- CD8+ AETCL
- Lymphomatoid papulosis, type D
- CD8+ MF (hypopig variant)
- SubQ panniculitis-like TCL
- CD8+ LPD of ear/face
- PTCL NOS
- Secondary skin involvement of PTCL

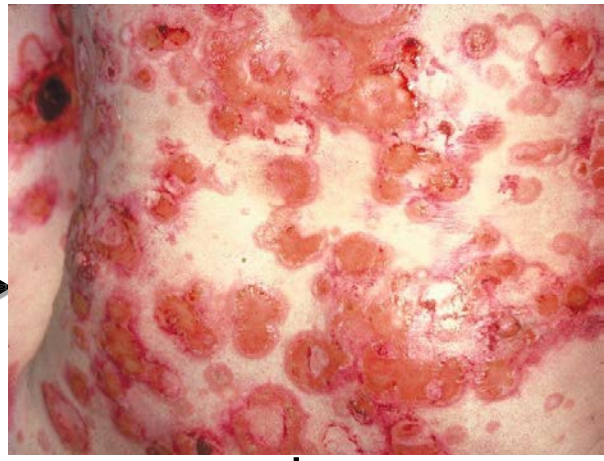
Clinico-pathologic correlation is essential

Type D CD8+ LyP vs. CD8+ aggressive epidermotropic cytotoxic TCL



LyP type D





CD8+ aggressive epidermotropic cytotoxic TCL

Courtesy T Subtil

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§§*

Am J Surg Pathol 2007;31:1887

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

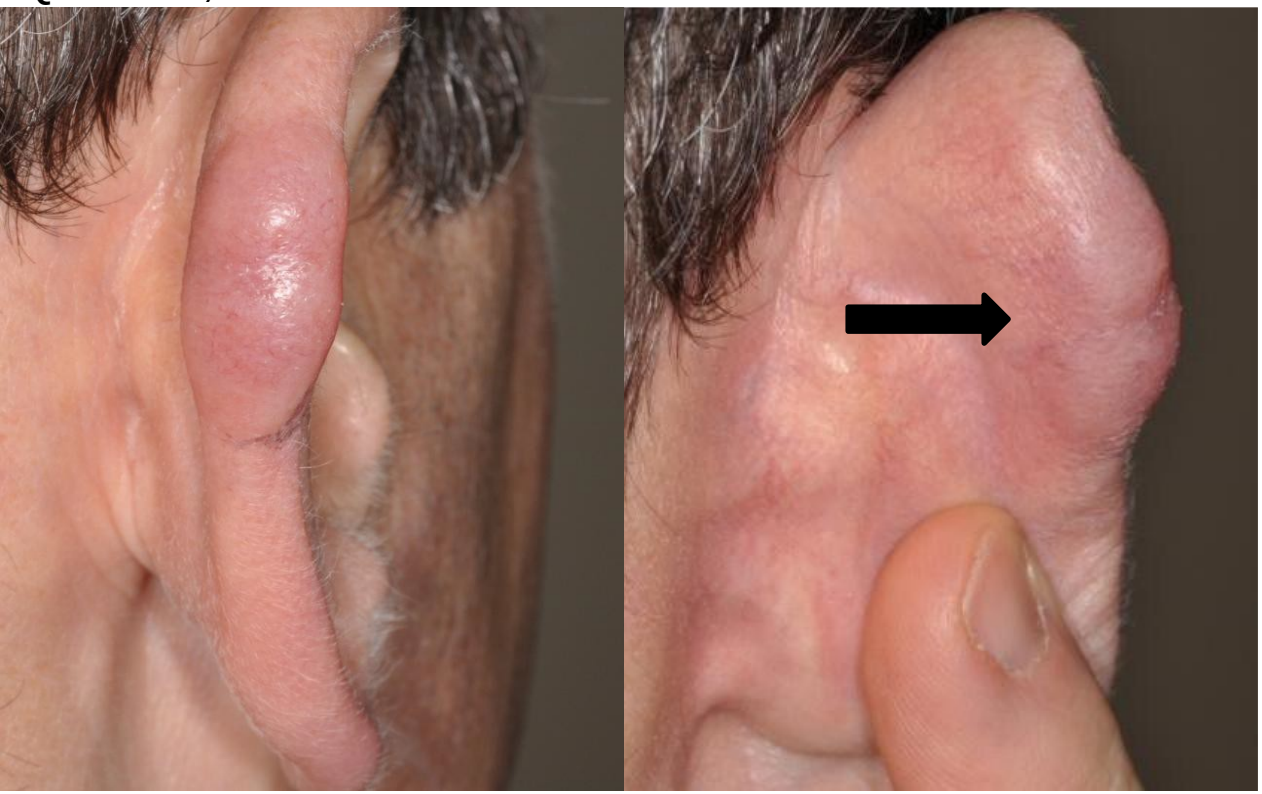
Janet Y. Li[1], Joan Guitart[2], Melissa P. Pulitzer[1], Antonio Subtil[3], Uma Sundram[4], Youn Kim[4], Janyana Deonizio[2], Patricia L. Myskowski[1] Alison Moskowitz[1], Steven Horwitz[1], Christiane Querfeld[1]

[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

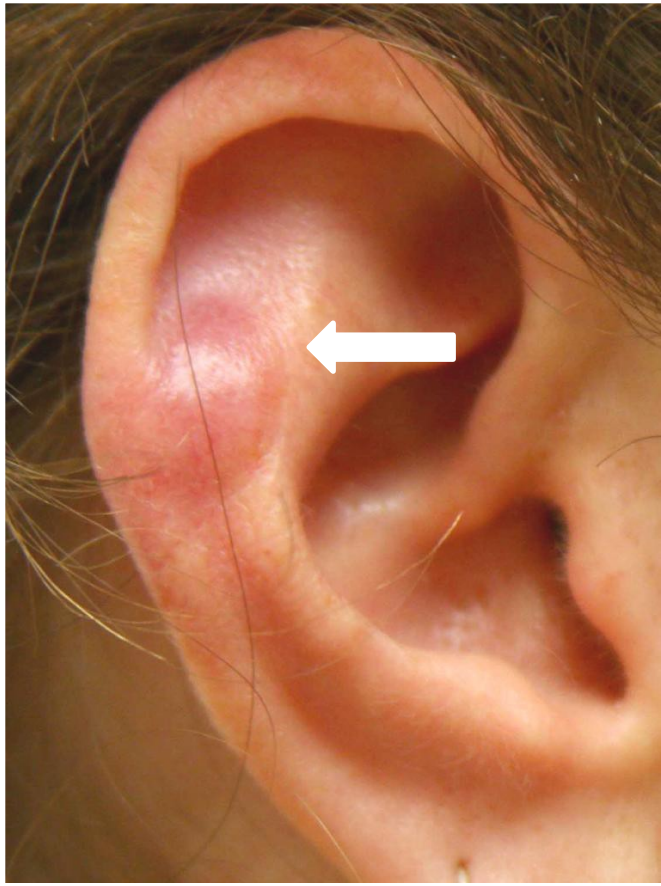
Am J Dermatopathol, in press 2013

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

Querfeld, MSKCC



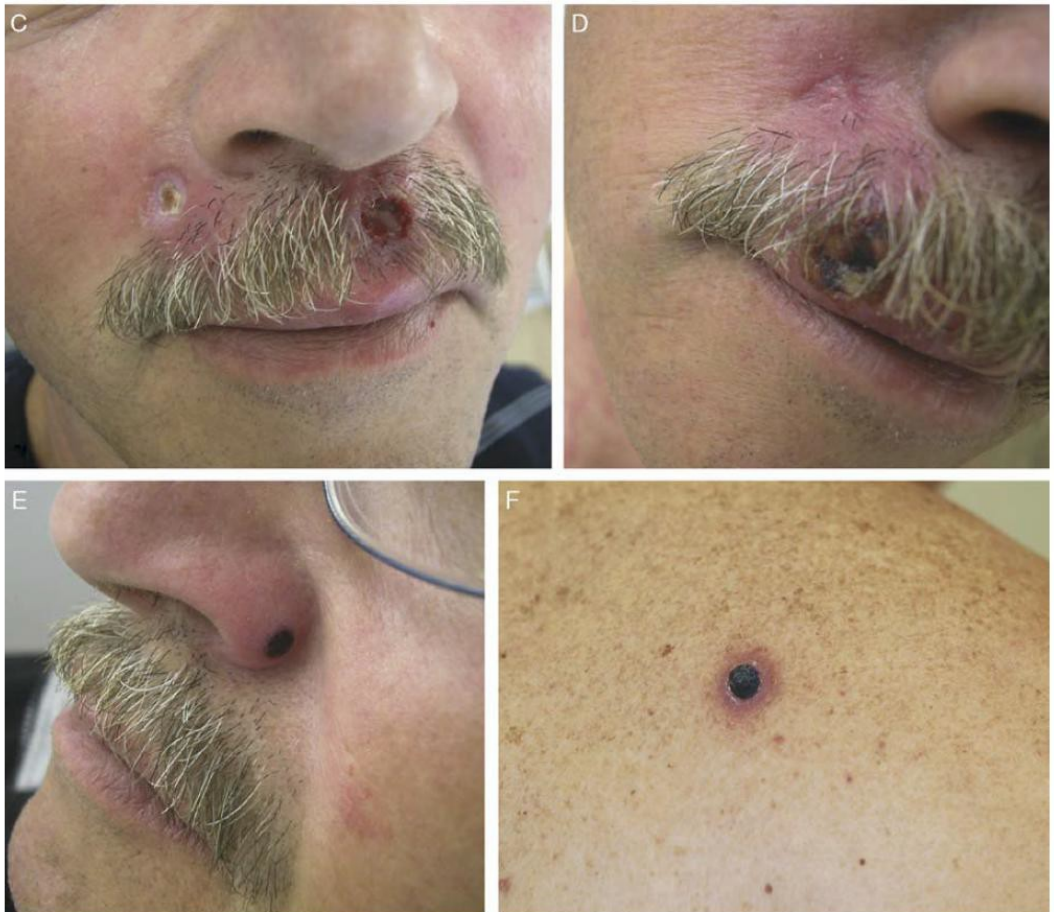
Stanford case



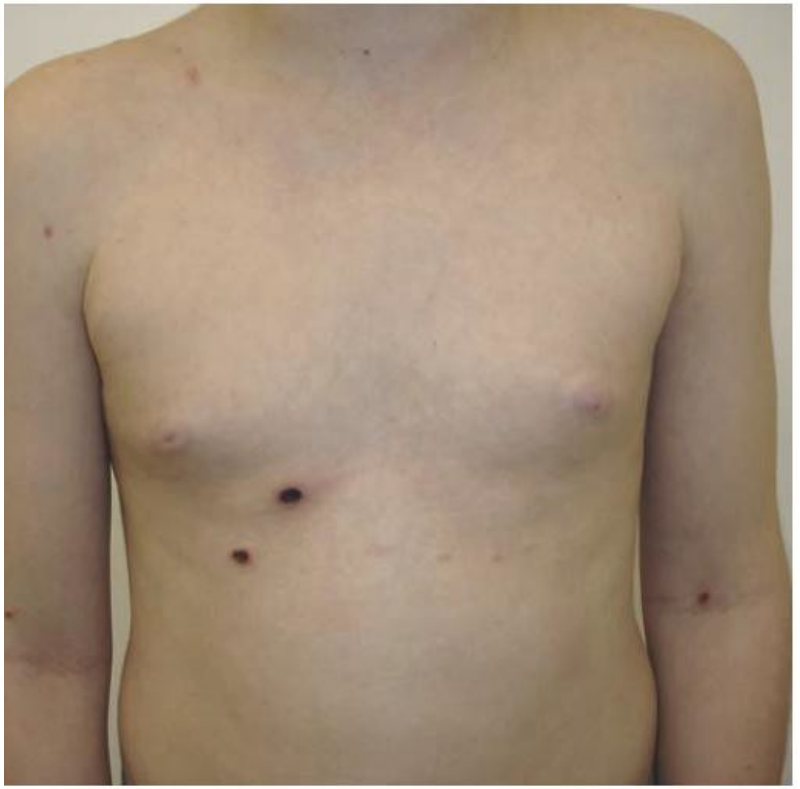
Angioinvasive Lymphomatoid Papulosis

A New Variant Simulating Aggressive Lymphomas

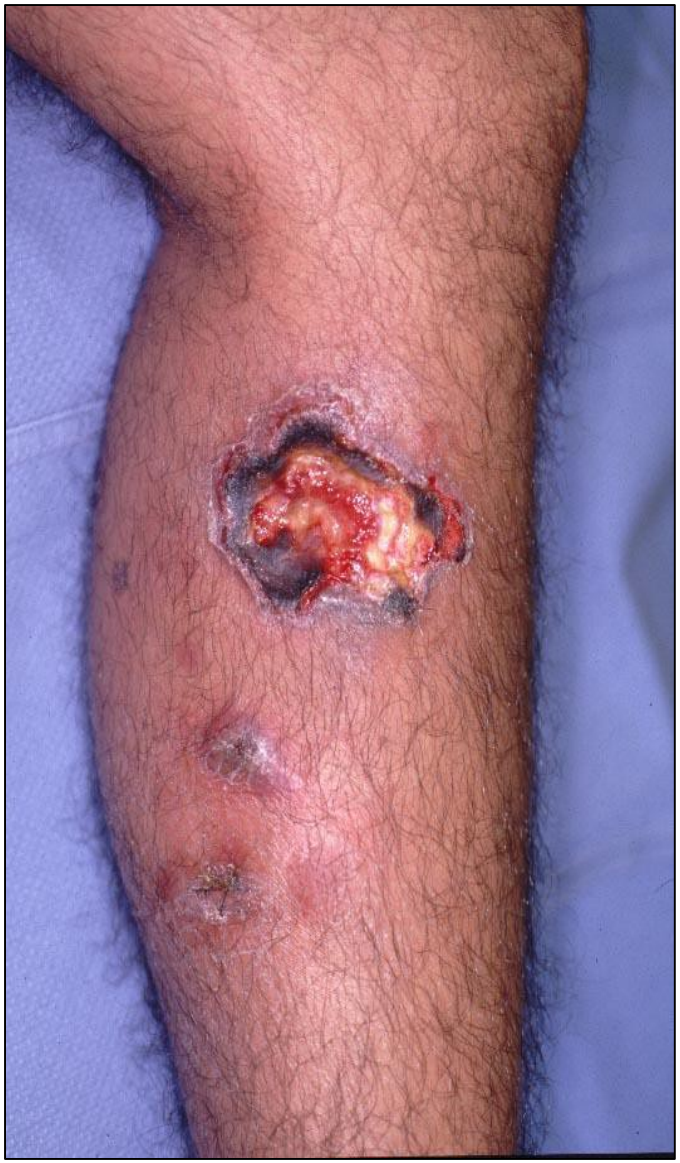
Werner Kempf, MD,† Dmitry V. Kazakov, MD, PhD,‡ Leo Schärer, MD,§ Arno Rütten, MD,§ Thomas Mentzel, MD,§ Bruno E. Paredes, MD,§ Gabriele Palmedo, PhD,§ Renato G. Panizzon, MD,‖ and Heinz Kutzner, MD§*

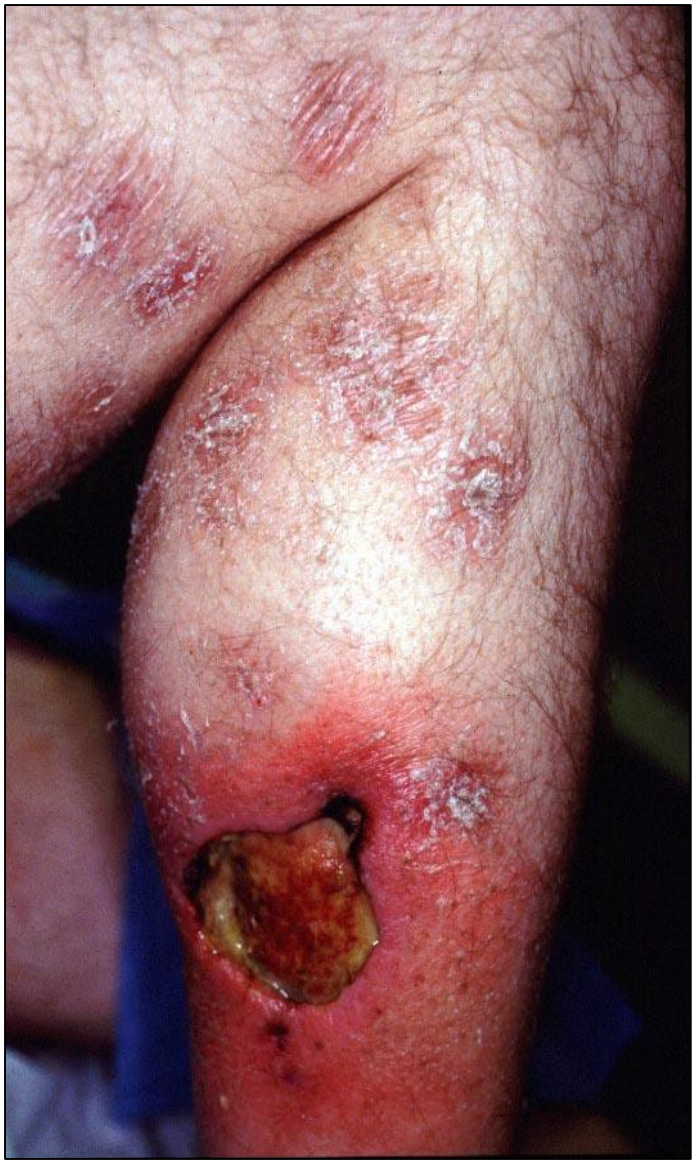


Am J Surg Pathol 2013;37:1-13



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



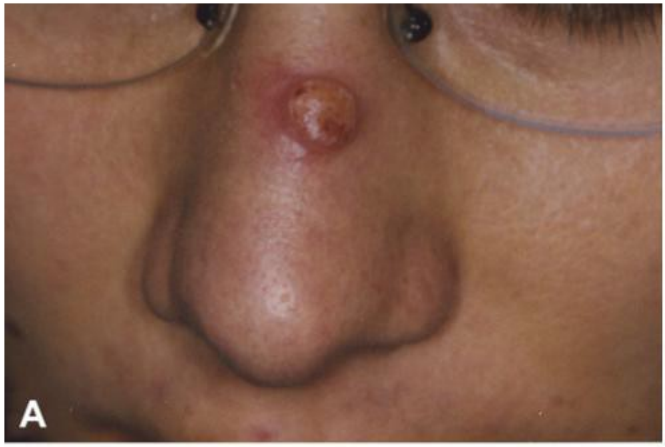


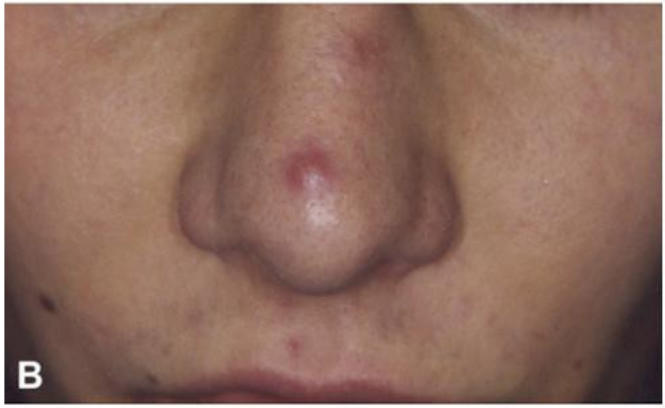
DERMATOPATHOLOGY

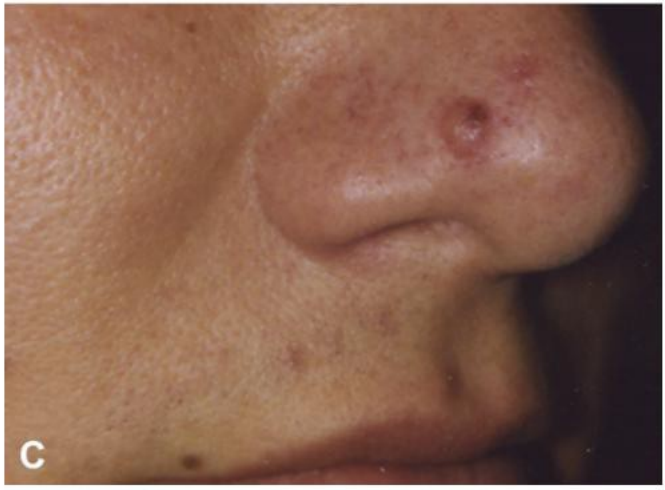
Follicular lymphomatoid papulosis of 11 cases, with new histopatho

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





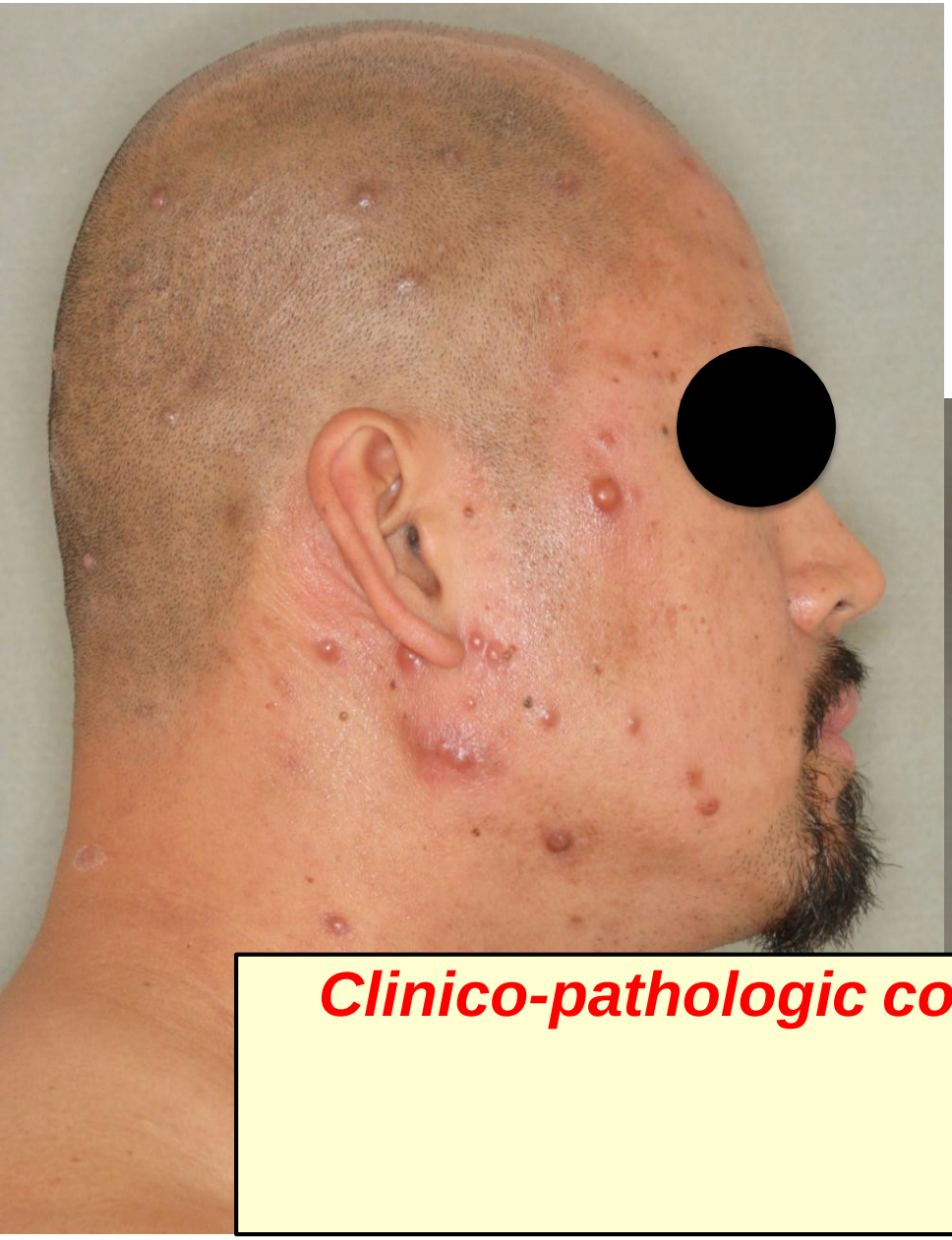


Mycosis Fungoides - the greatest masquerader
Clinical & Histologic Variants/Subtypes

- 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

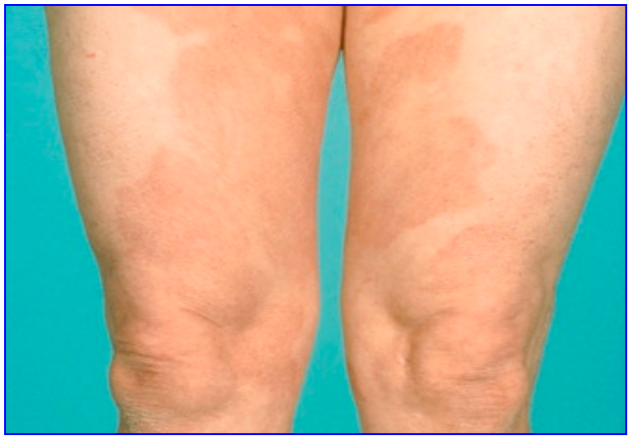


Folliculotropic Mycosis Fungoides

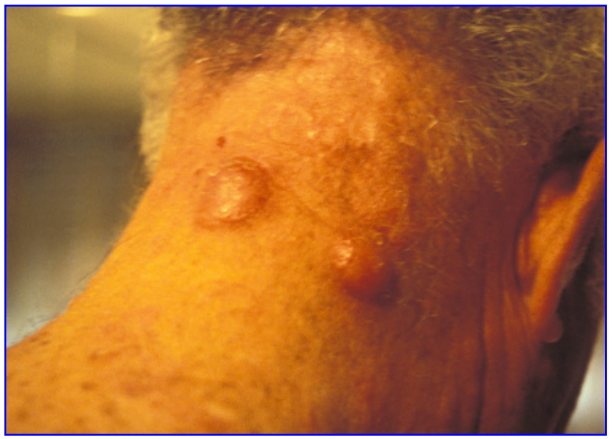
Clinico-pathologic correlation is essential

Mycosis Fungoides Diagnosis and Staging Evaluation

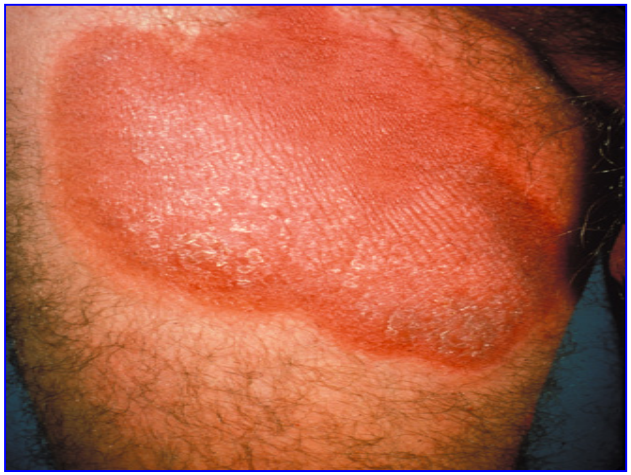
Clinical Phases of CTCL – Mycosis Fungoides



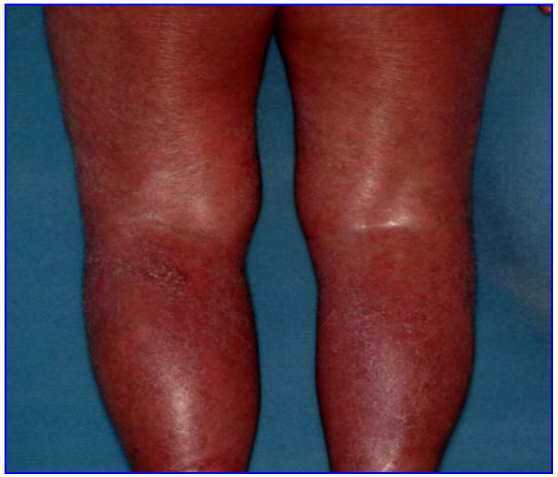
Patch



Tumor

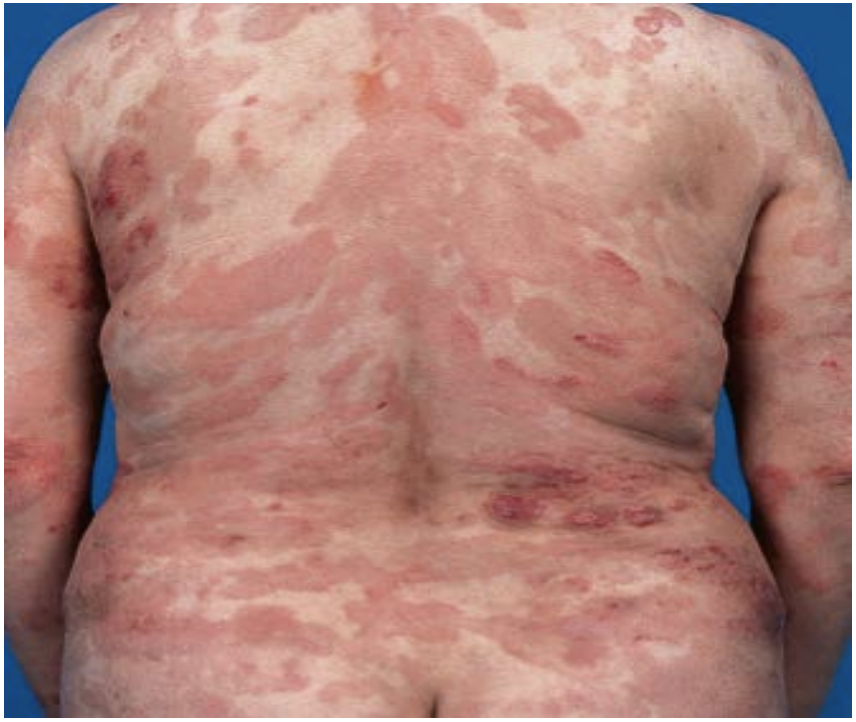


Plaque

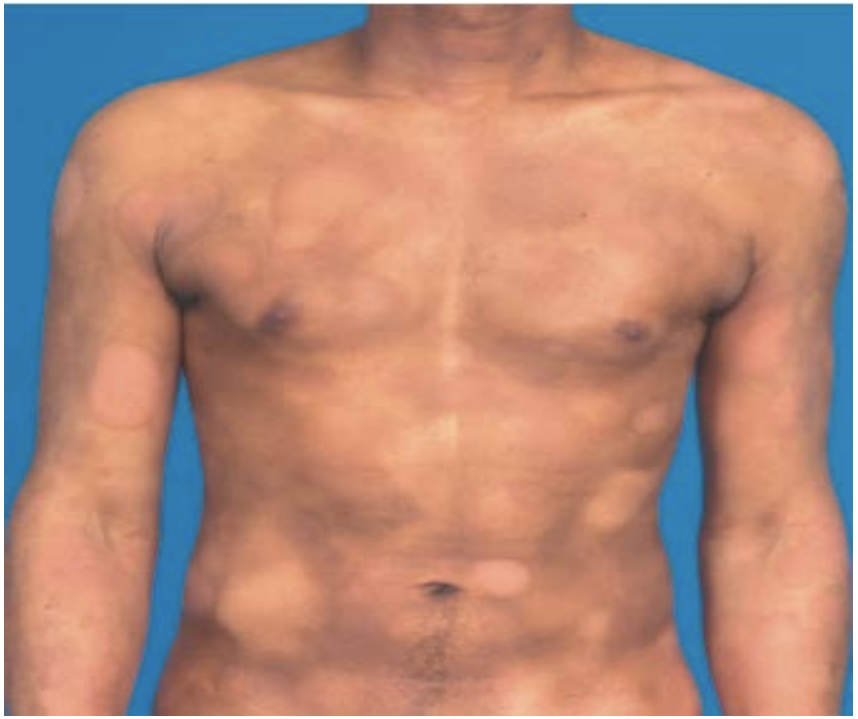


Erythroderma

Mycosis Fungoides Clinical Presentation

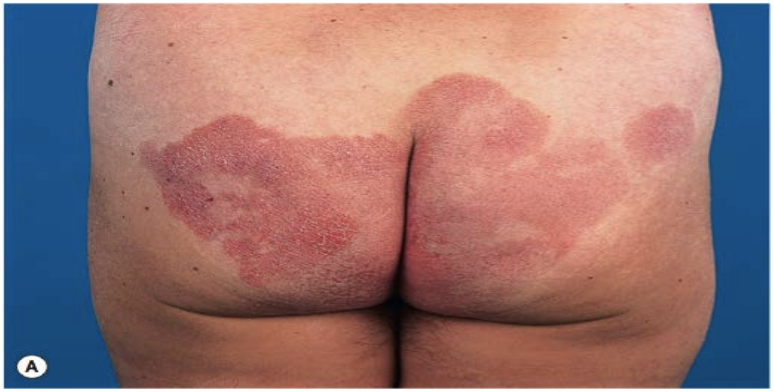


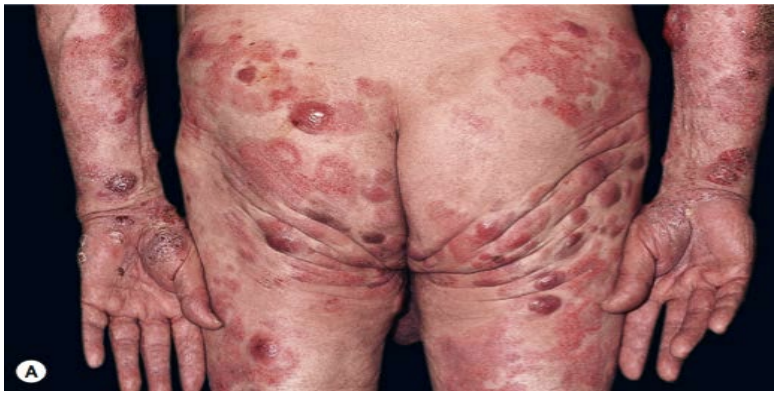
Patches, Plaques

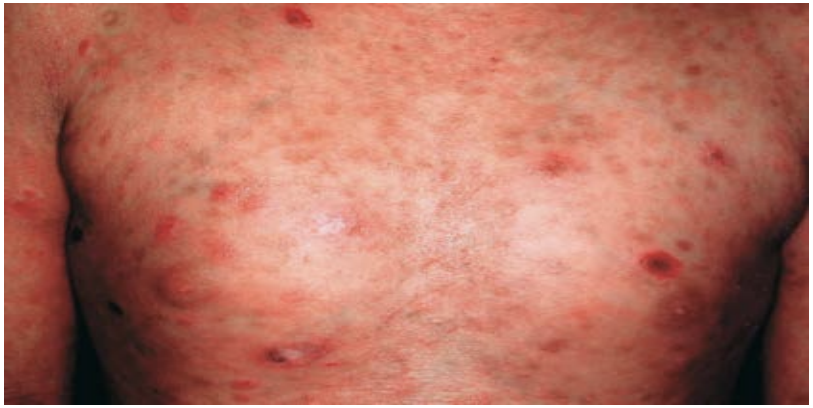


Hypopigmented Patches, Plaques

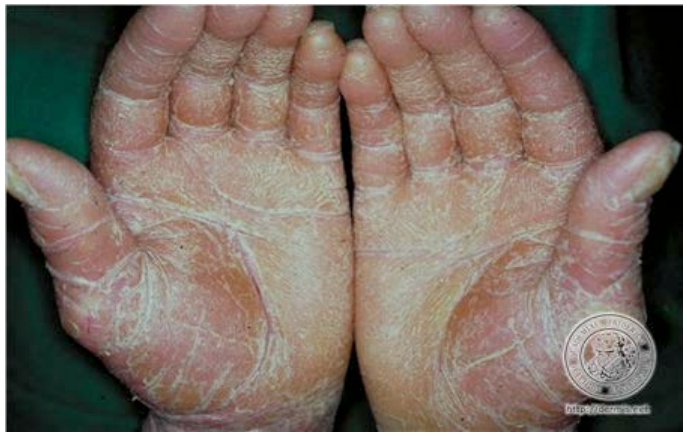
Mycosis Fungoides Clinical Presentation

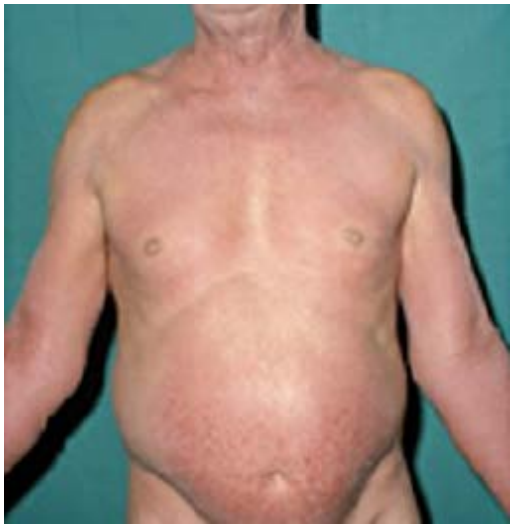


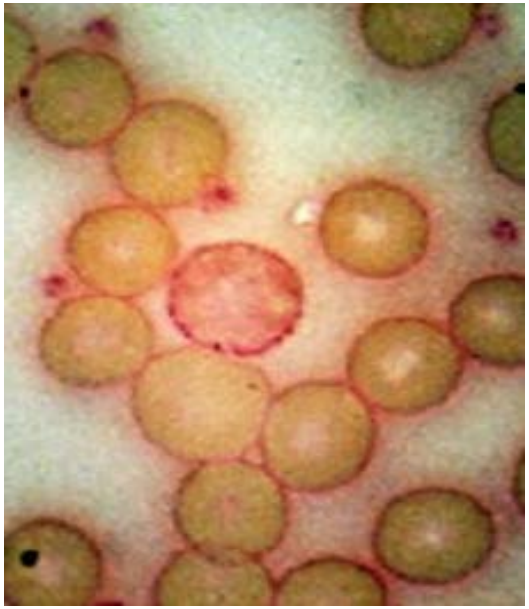


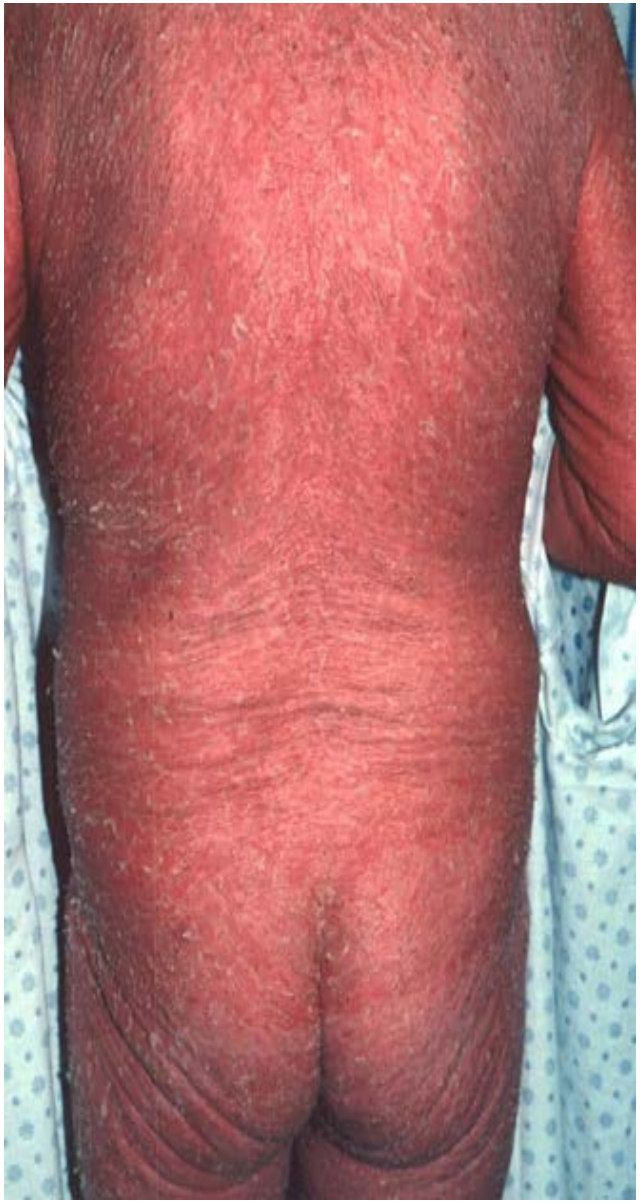


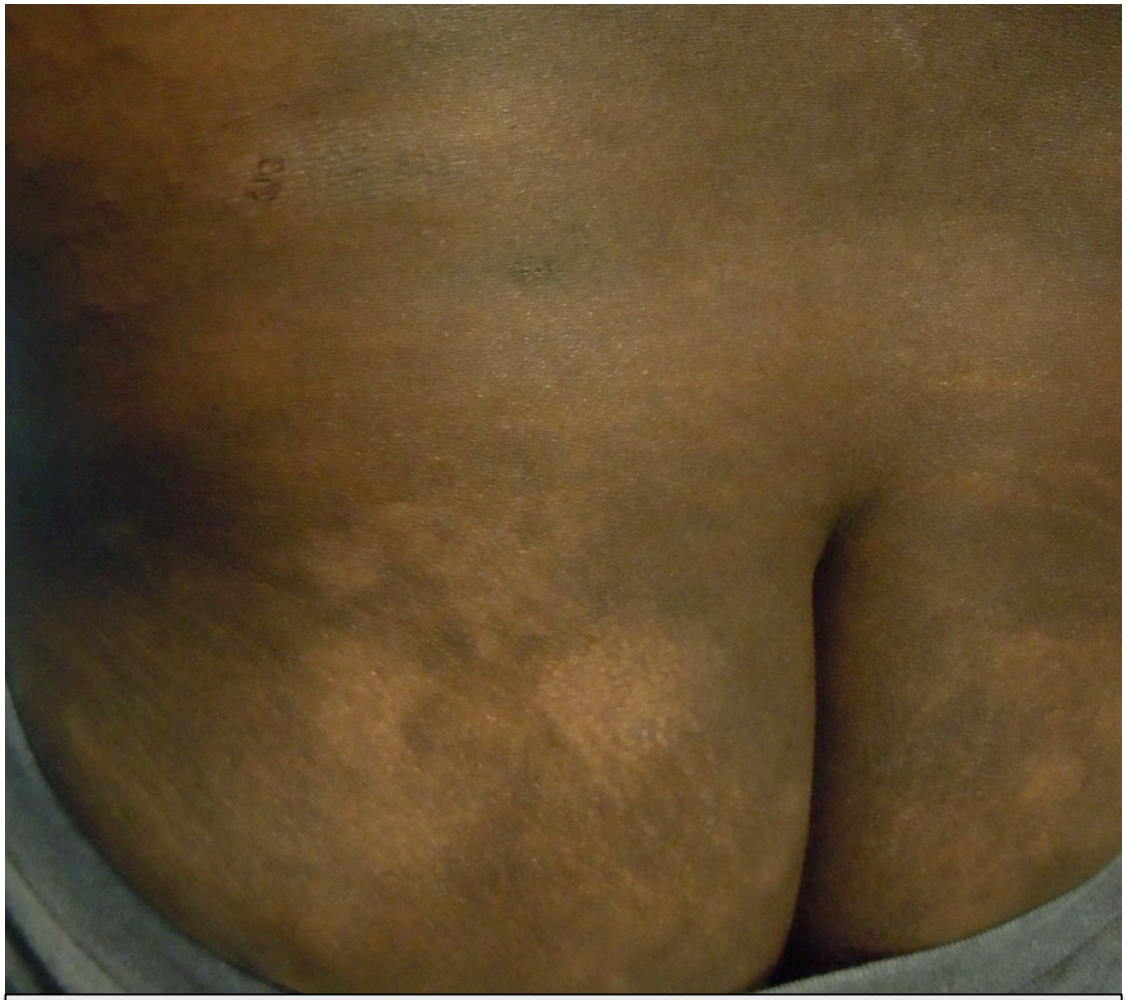
Sezary Syndrome











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

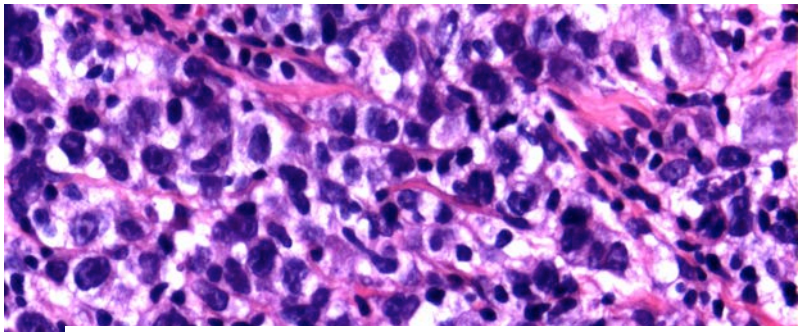
MF histology varies by type/stage

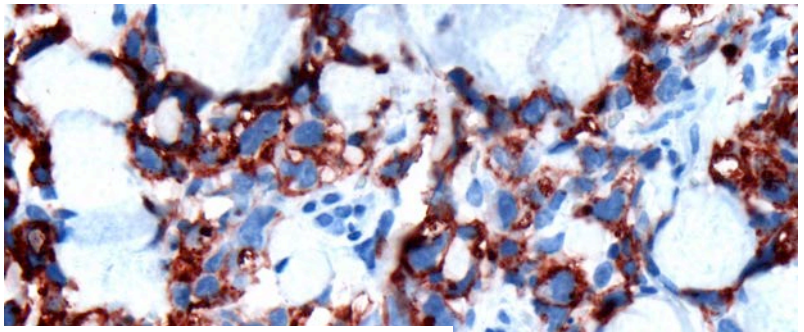
- Patch Stage
  - Band-like infiltrate along the papillary dermis, DEJ, & basal layer
  - Pautrier microabscess are uncommon
  - Fibrosis of the papillary dermis may be present
- Plaque Stage
  - Increased dermal infiltate
  - Nuclei are larger and indented "cerebriform"
  - Pautrier microabscess are 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

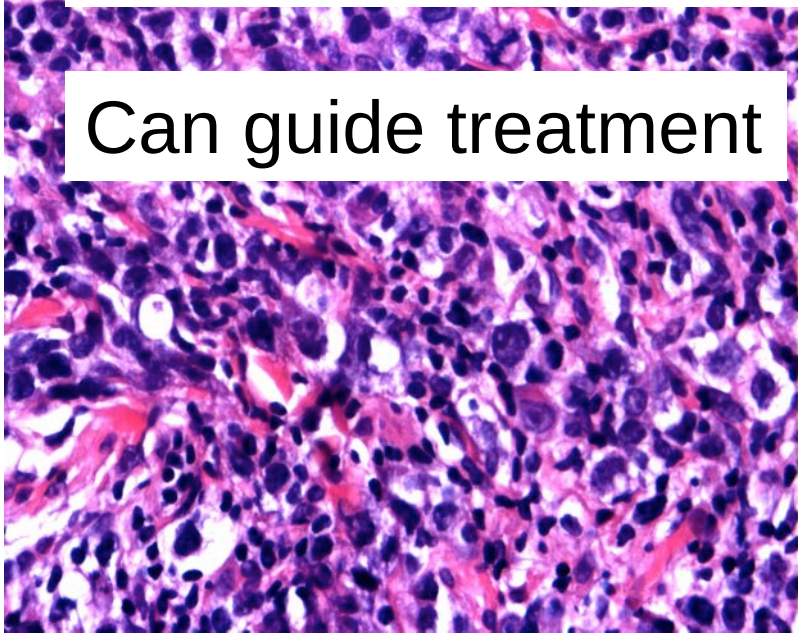
Immunohistochemical Stains - “Markers”

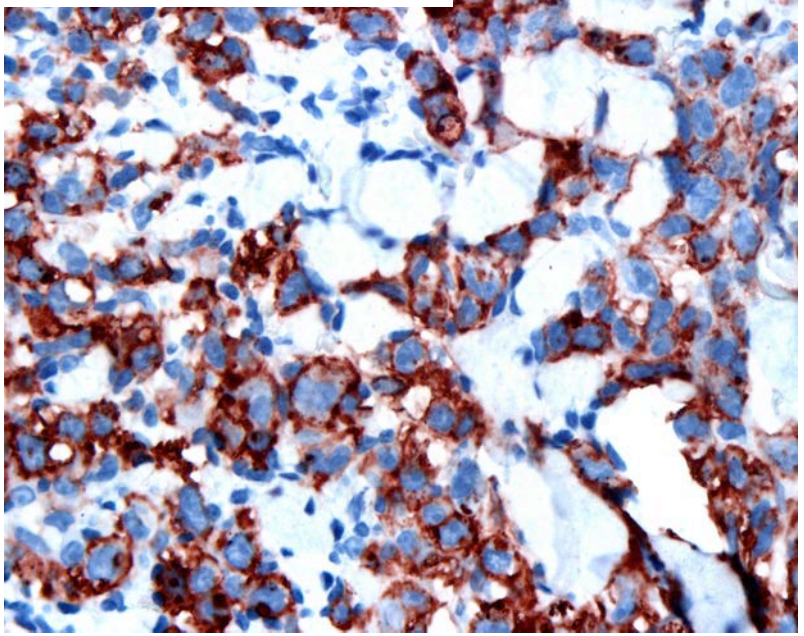




Help identify what type of lymphoma

Can guide treatment





Molecular studies in the diagnosis of cutaneous lymphoma

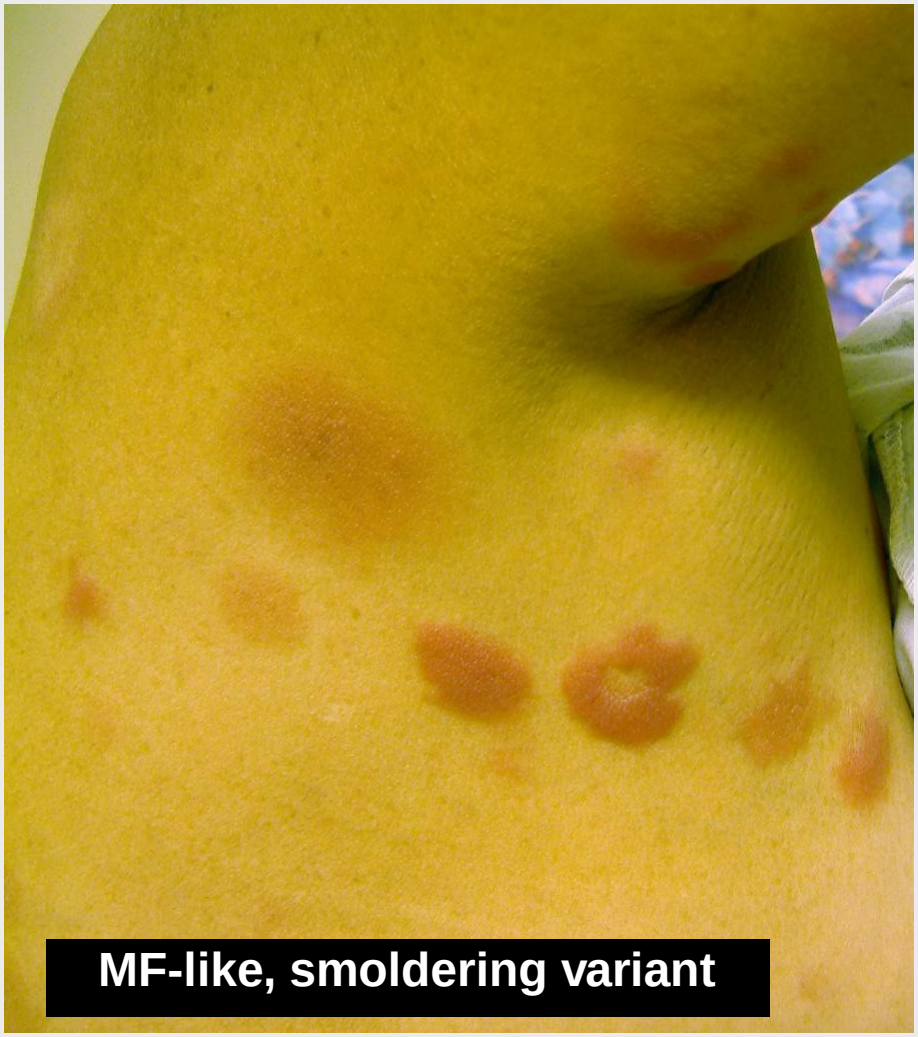
- Gene rearrangement or “clonality” studies
  - Varying techniques, some with higher sensitivity and specificty
- Flow cytometry
  - Phenotype of malignant T-cells can vary by type/stage

Lesson #2
Don’t forget to check the blood

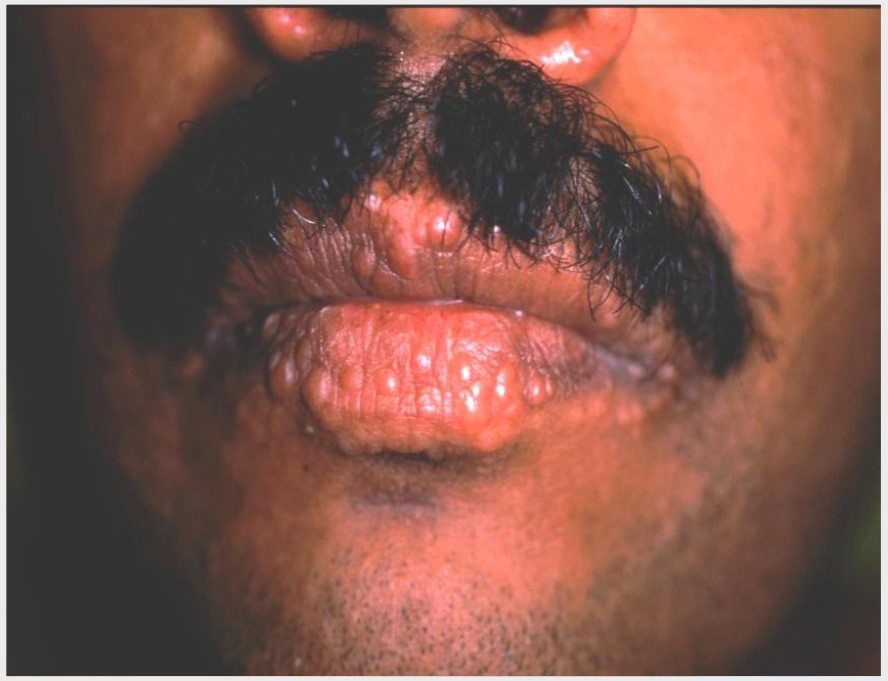
Key diagnostic info may be in the blood compartment

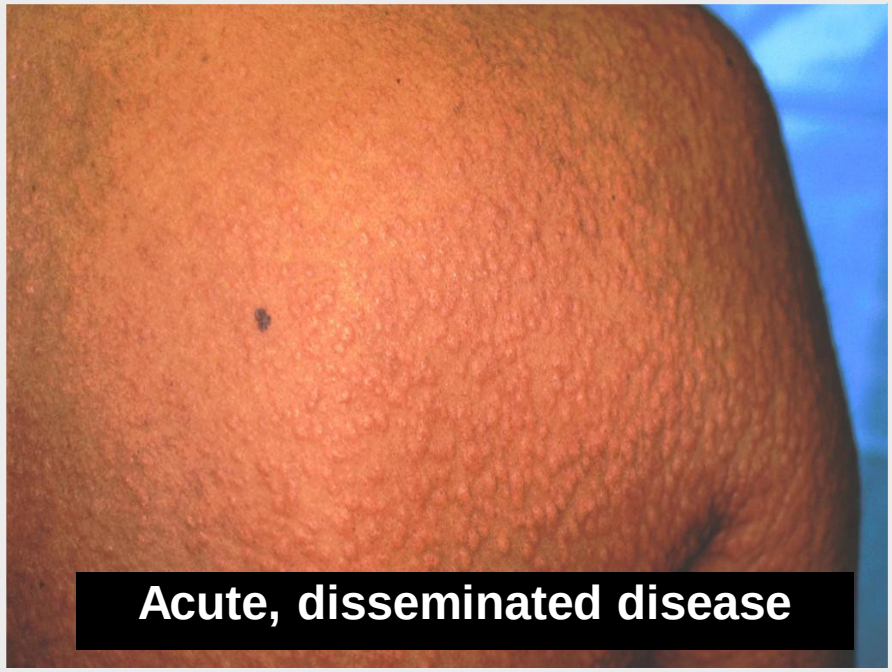
- **Sezary flow studies in the erythrodermic pt**
- **HTLV1 serology in ddx of MF/SS vs. ATLL**

ATLL, spectrum of skin presentation

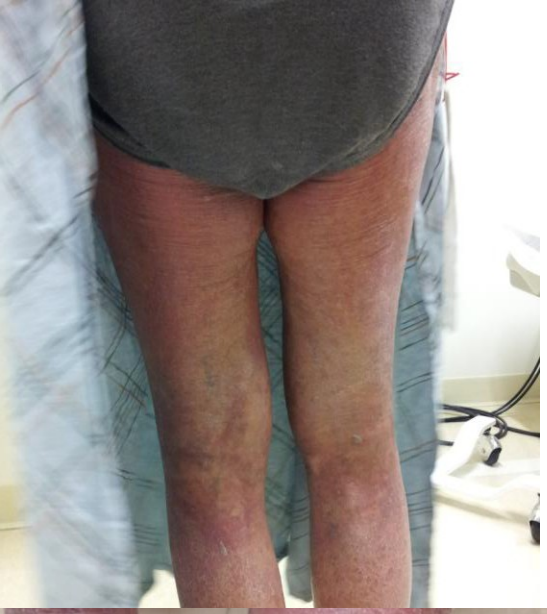


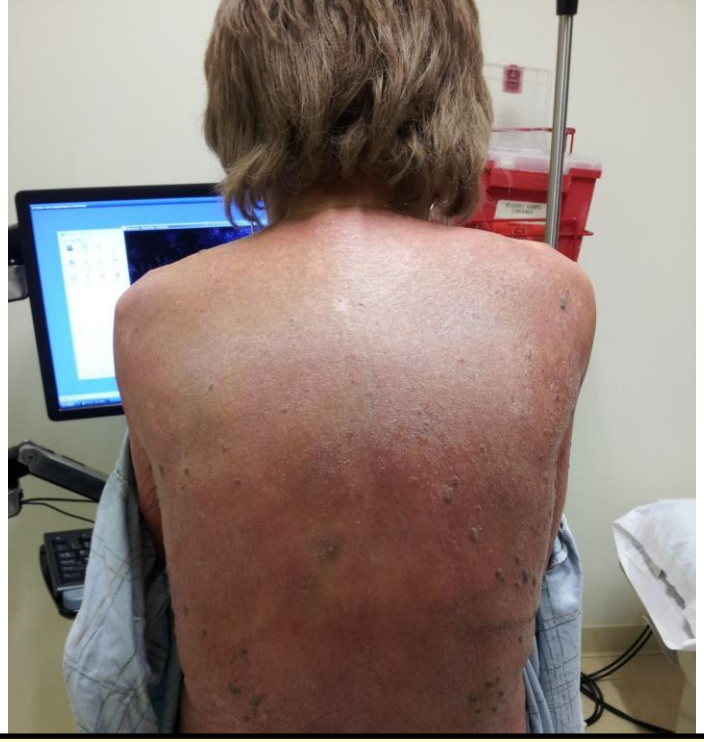
MF-like, smoldering variant

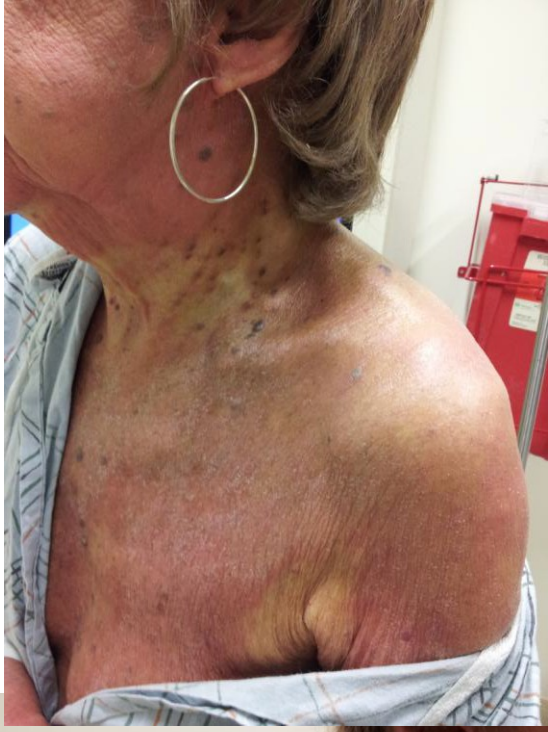


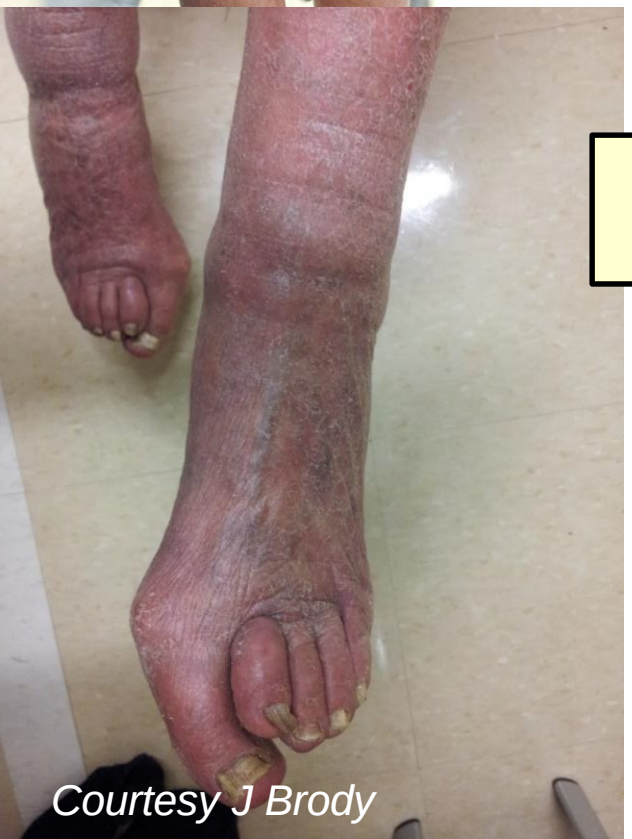


Acute, disseminated disease

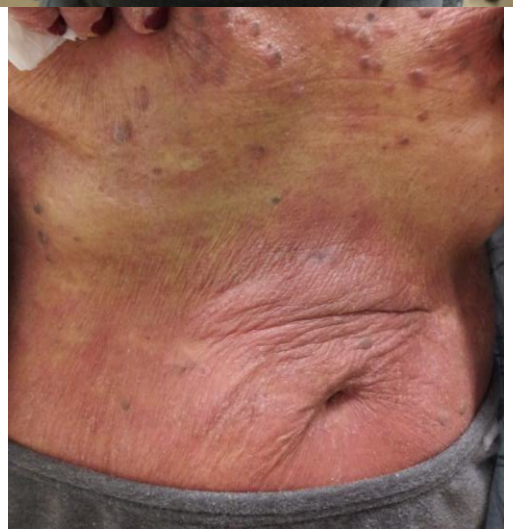


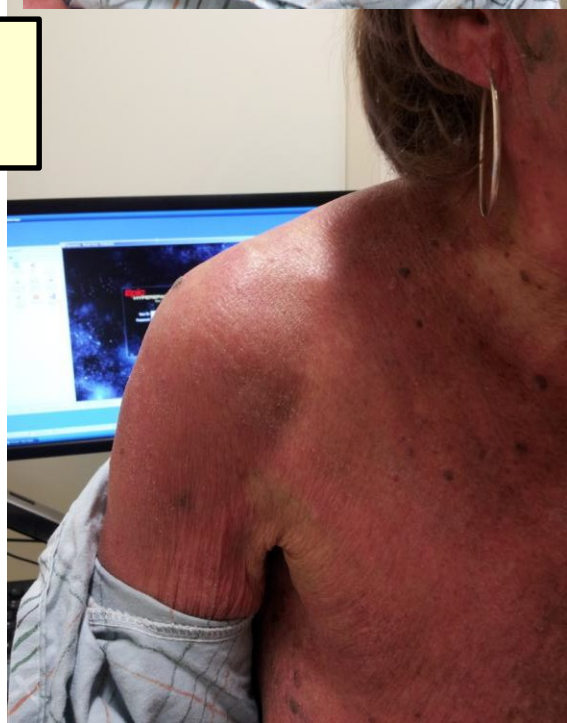




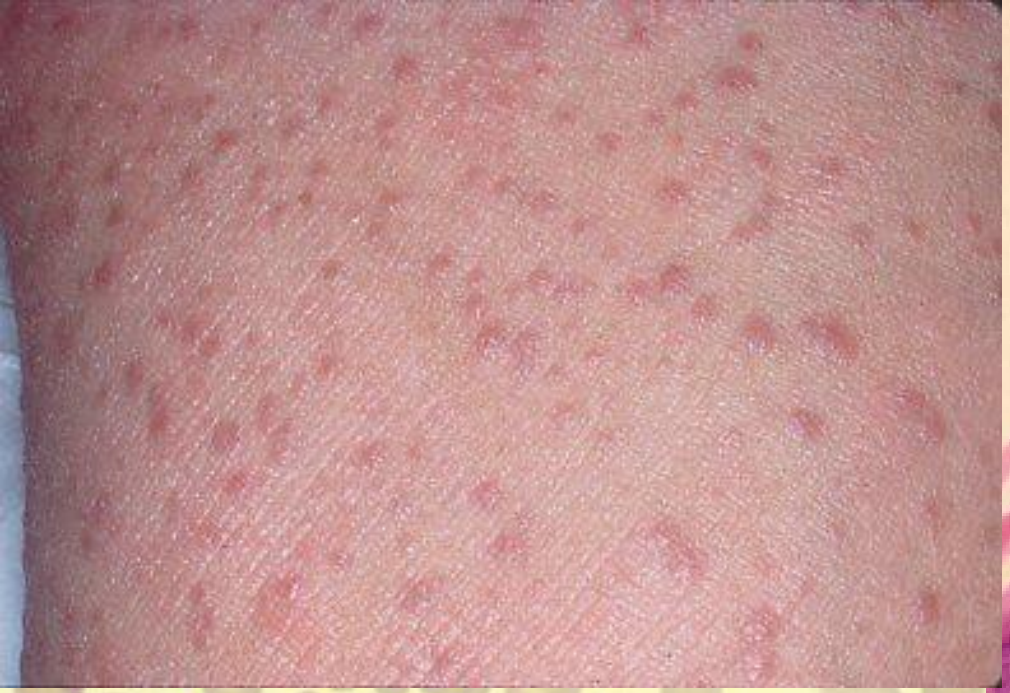


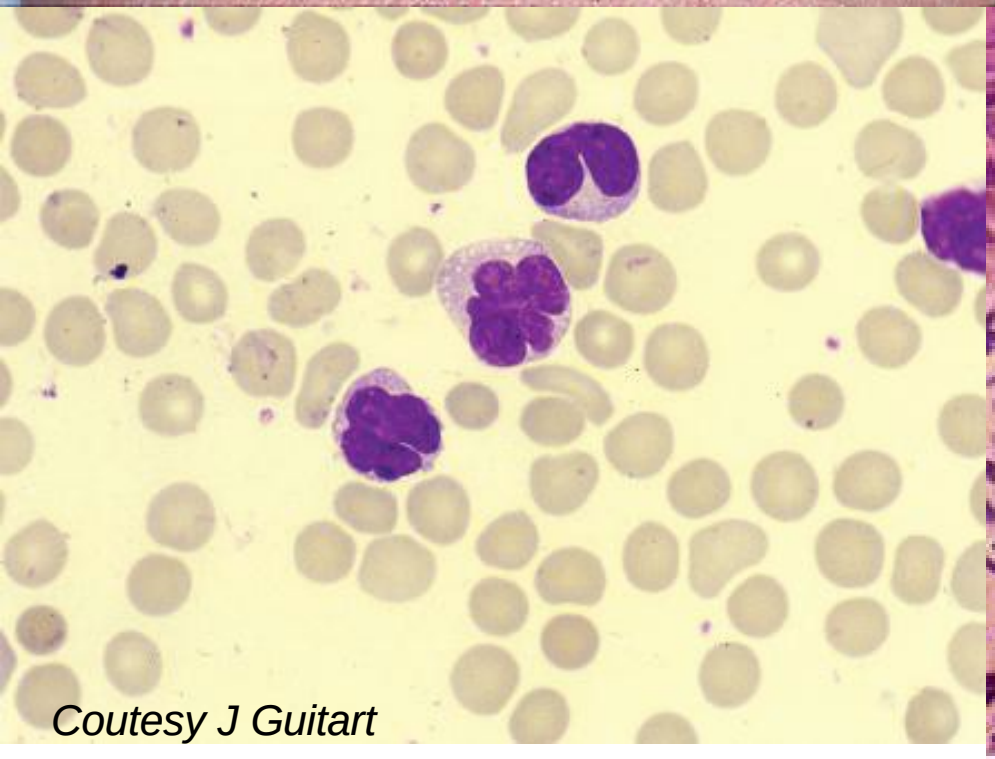
ATL can mimic
Sezary syndrome





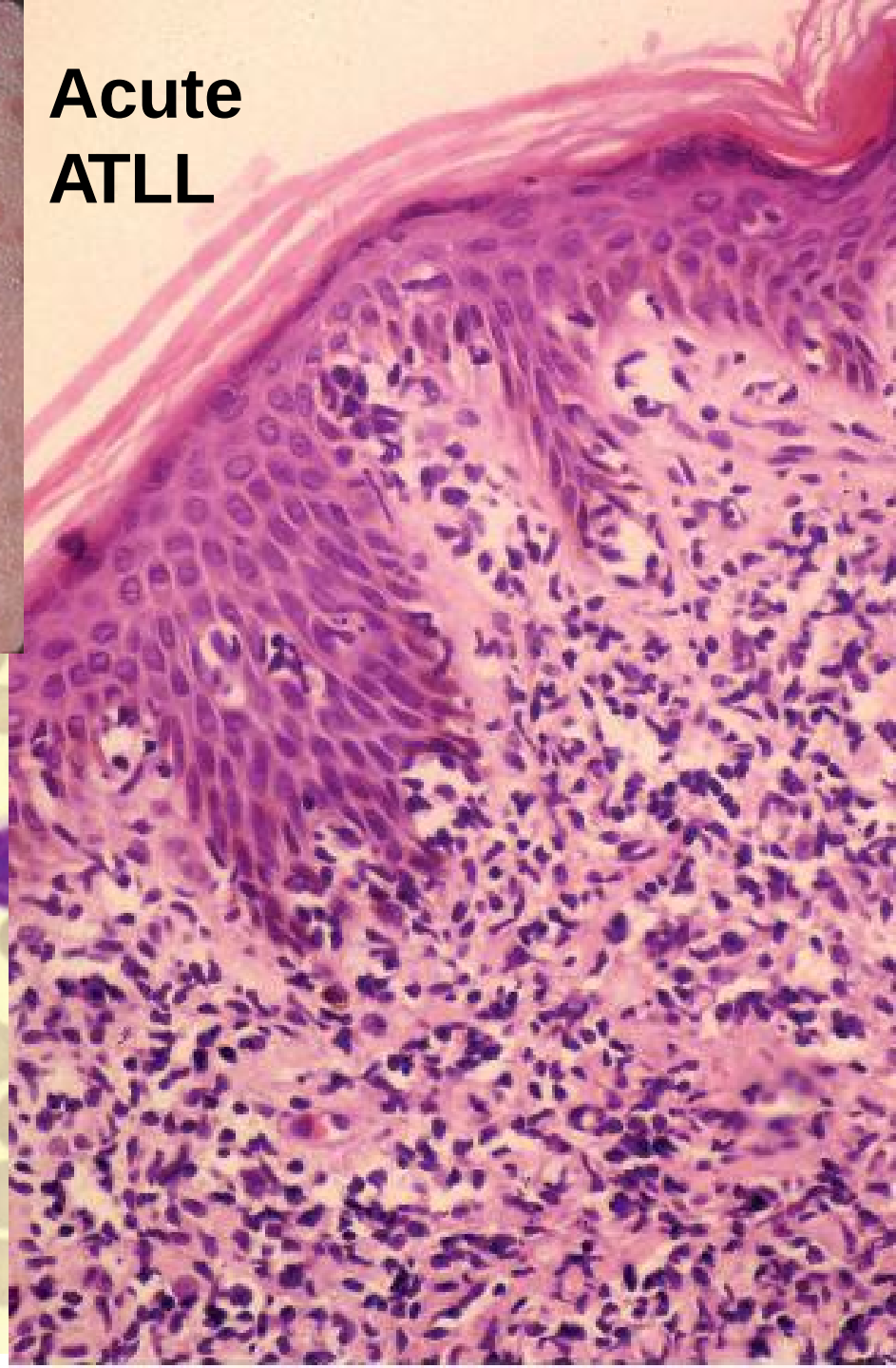
Courtesy J Brody





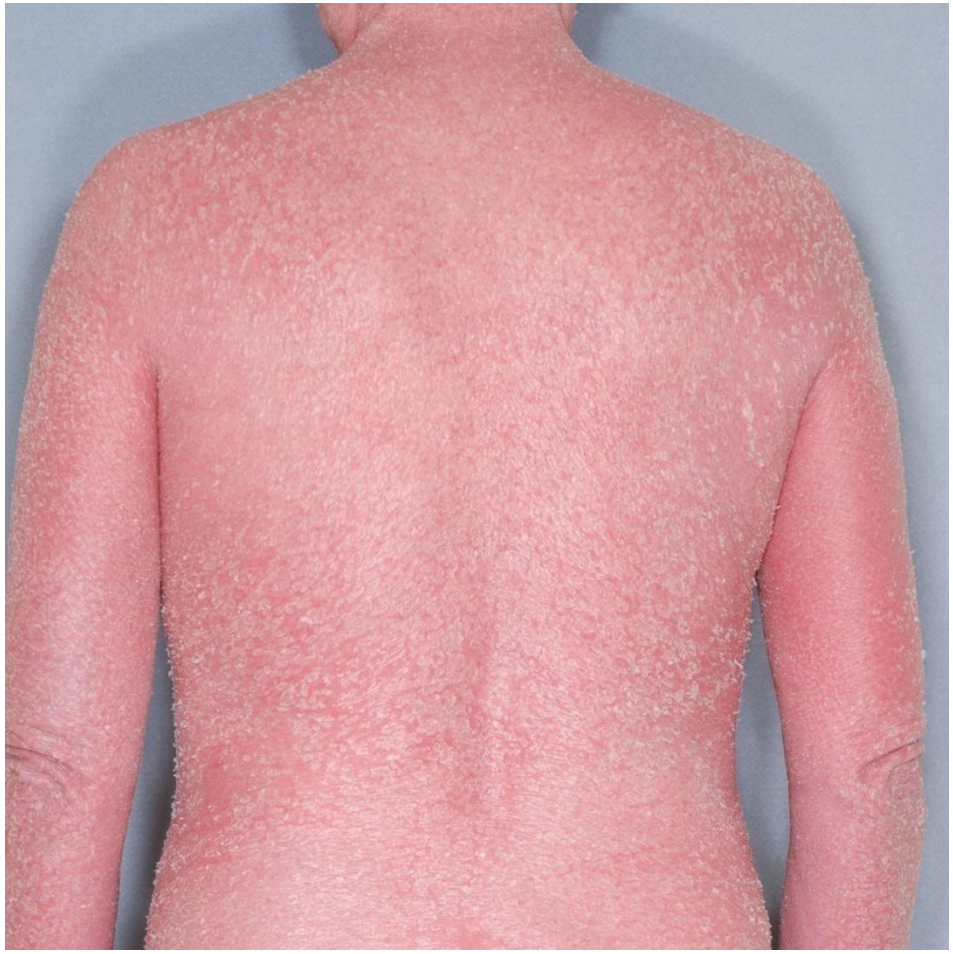
Coutesy J Guitart

Acute ATLL



Clinical Case

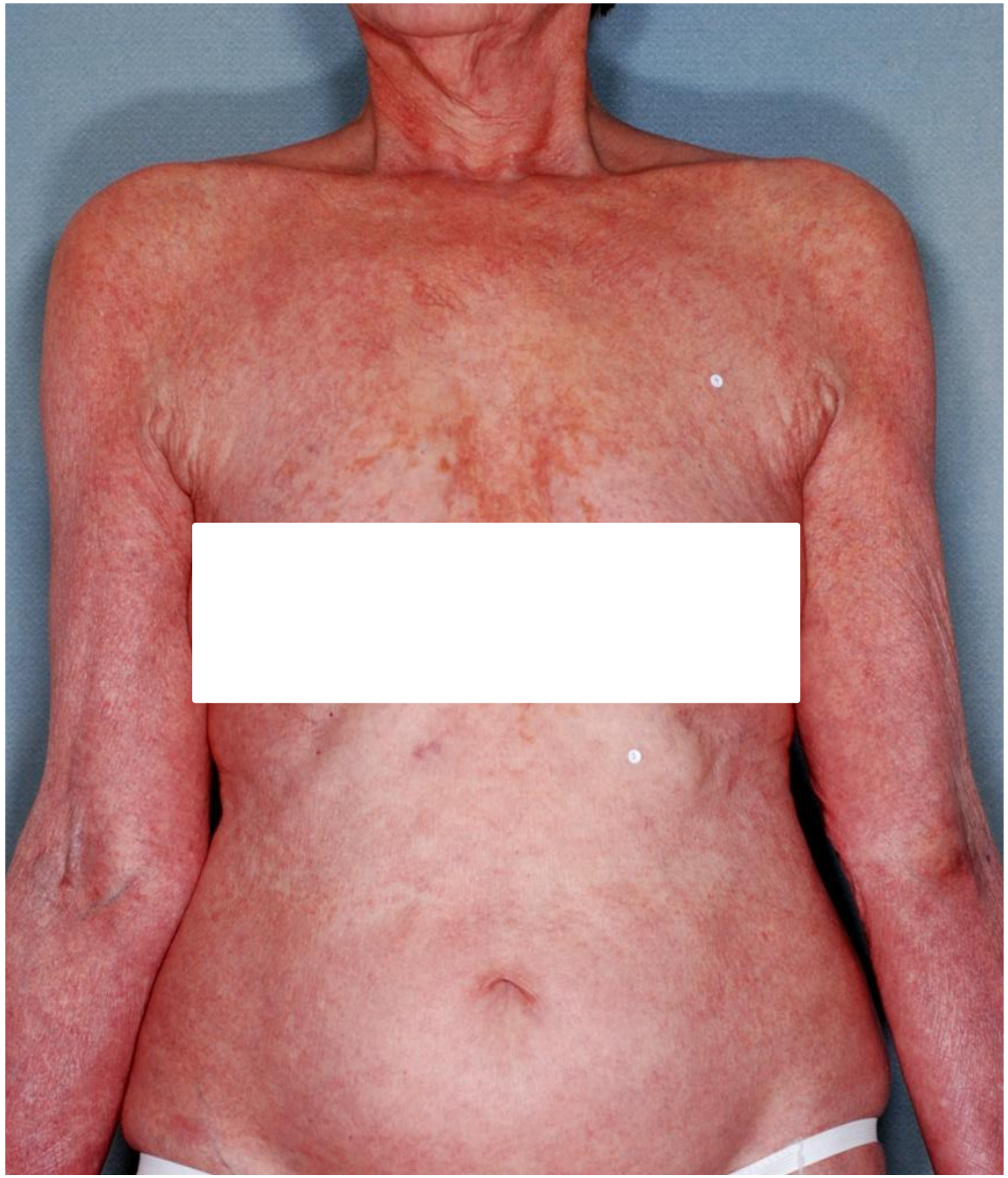
Challenge of the red person



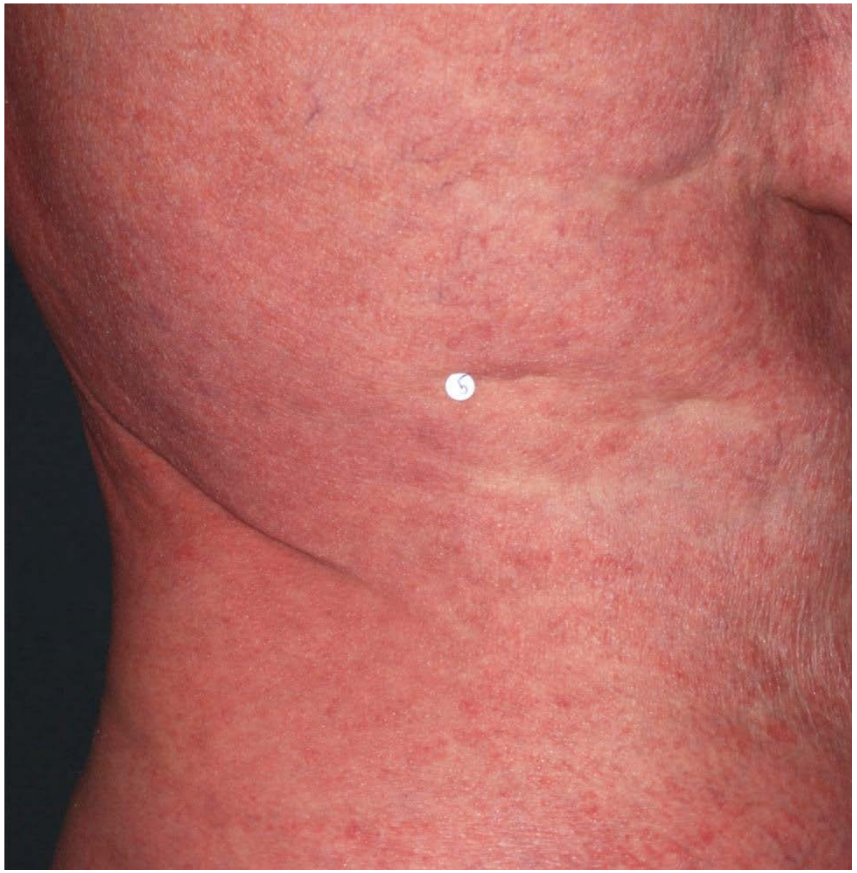
63 F with 4 yr h/o progressive erythroderma

- **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

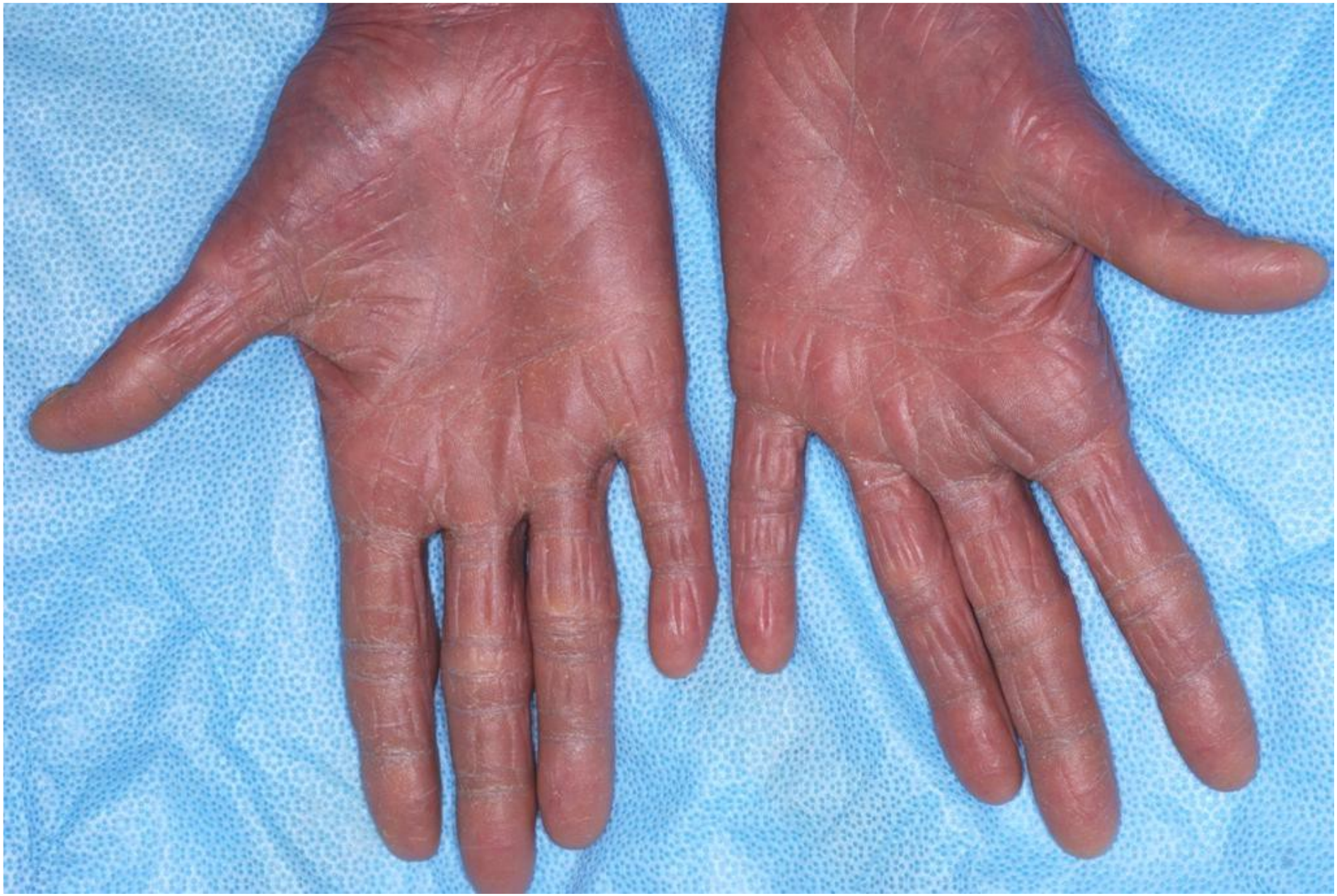
Erythroderma with severe pruritus



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)
- Paraneoplatic
- GVHD
- Infectious (staph toxin)
- Misc. inflammatory

Skin biopsies often non-diagnostic in erythrodermic skin of CTCL

When suspecting Sézary syndrome

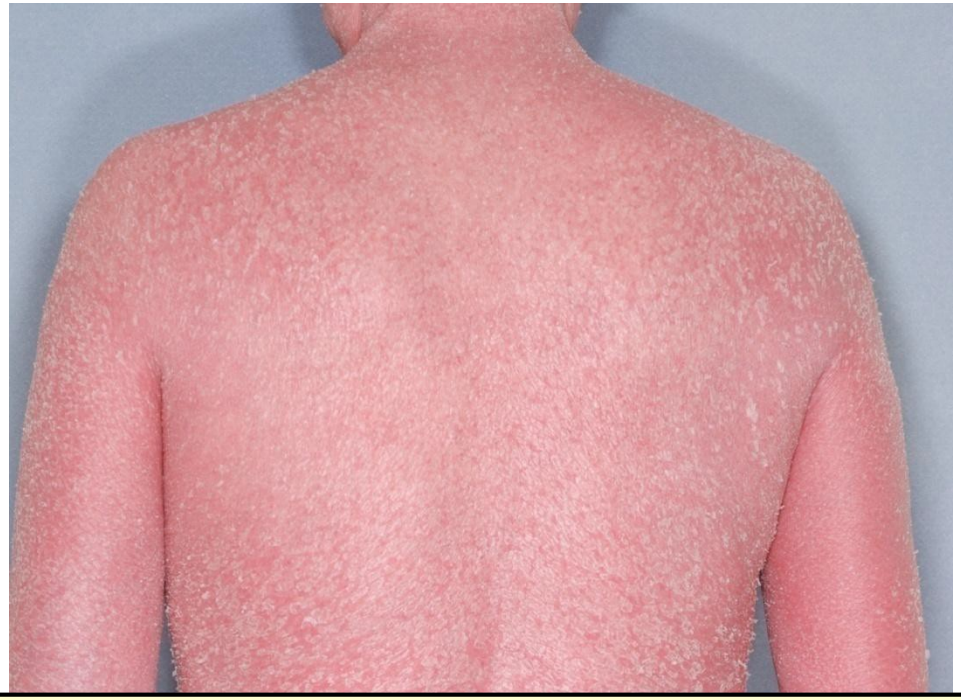
- **Evaluation of blood compartment**
  - **Flow cytometry c/w blood involvement**
  - **TCR PCR clone in blood identical to skin**

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

=> Sezary 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

J Am Acad Dermatol 2005 53:1053

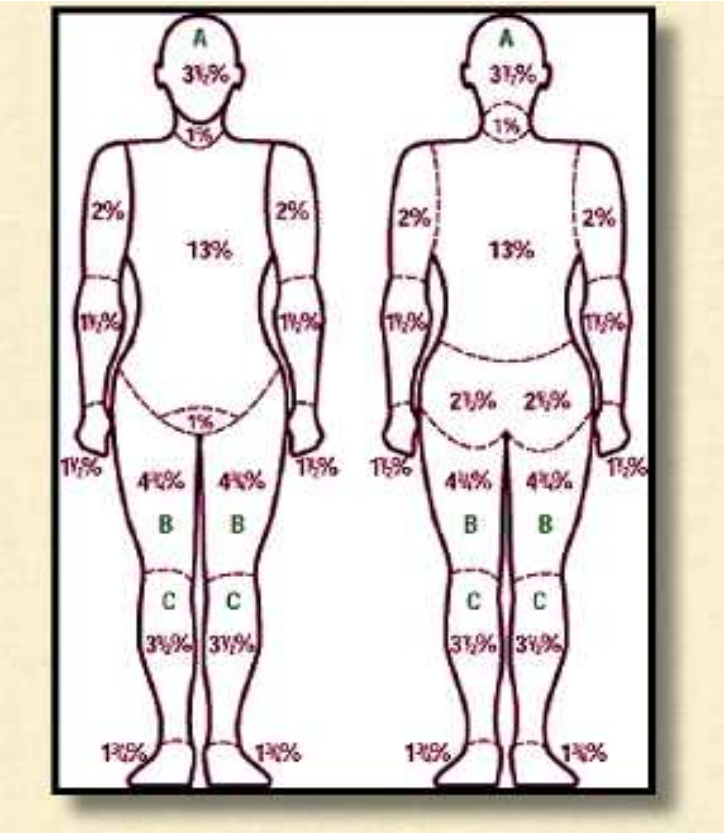
Staging of MF/CTCL involves the evaluation of skin, lymph nodes, viscera, and blood

Essential Workup				
Physical Exam	Labs	Imaging	Biopsy	Other
• Examination of entire skin • mSWAT • Palpation of peripheral lymph node regions • Palpation for organomegaly/ masses	• CBC with Sézary cell count • Flow cytometric analysis (CD4, CD8, CD7, CD26) • TCR gene rearrangement of peripheral blood • Comprehensive metabolic panel & LDH • Rule out other - ANA	• Contrast-enhanced CT scan of the neck/chest/ abdomen and pelvis **or** • Whole-body PET/CT scan	• Biopsy of suspicious skin sites • Dermatopathology/ Hematopathology review of biopsy	• For treatment consideration, women of childbearing age should be tested for pregnancy • Test Lipids & TSH/T4 if considering targretin

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



TNMB stages	Staging parameters
Skin (T)	
T_1	Patches and/or plaques covering <10% BSA; Further stratified into $T1_a$ (patch only) versus $T1_b$ (plaque ± patch)
T_2	Patches and/or plaques covering ≥10% BSA: Further stratified into $T2_a$ (patch only) versus $T2_b$ (plaque ± patch)
T_3	One or more tumors (≥1 cm diameter)
T_4	Coalescing erythema covering ≥80% of skin surface
LN (N)	
N_0	No clinically abnormal lymph nodes
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN0-2 Further stratified into N1a (TCR non clonal) versus N1b (TCR clonal)
N_2	Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN3 Further stratified into N1a (TCR non clonal) versus N1b (TCR clonal)
N_3	Clinically abnormal lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative
N_x	Clinically abnormal lymph nodes; no histologic confirmation
Visceral (M)	
M_0	No visceral organ involvement
M_1	Visceral involvement, pathologically confirmed + organ involved specified)
Blood (B)	
B_0	No significant blood involvement: <5% Sézary cells. For clinical trials, B0 may also be defined as <250/mL Sézary cells CD4+CD26- or CD4+CD7- cells or CD4+CD26- and CD4+CD7- cells <15%
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low tumor burden. Does not fit B_0 or B_2 criteria
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: Positive clone plus one of the following: >1000/mL Sézary cells; CD4/CD8 ≥10 CD4+CD7- cells ≥40 percent CD4+CD26- cells ≥30 percent For clinical trials, B_2 may also be defined as >1000/mL CD4+CD26- or CD4+CD7- cells.

Staging of MF Involves Evaluation of Skin (T), Lymph Nodes (N), Viscera (M), and Blood (B)

For skin, plaque is any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikilderma 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.

A T cell clone is defined by PCR or Southern blot analysis. For B_2 the clone in the blood should match that of the skin.

Modified from: Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007; 110:1713; and, Olsen EA, Whittaker S, Kim YH, et al. J Clin Oncol 2011; 29:2598.

COMPOSITE ISCL/EORTC STAGING

2007 ISCL/EORTC Revision to the Staging System of MF and SS				
Stage	T (Skin)	N (Lymph Node)	M (Viscera)	B (Blood)
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

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

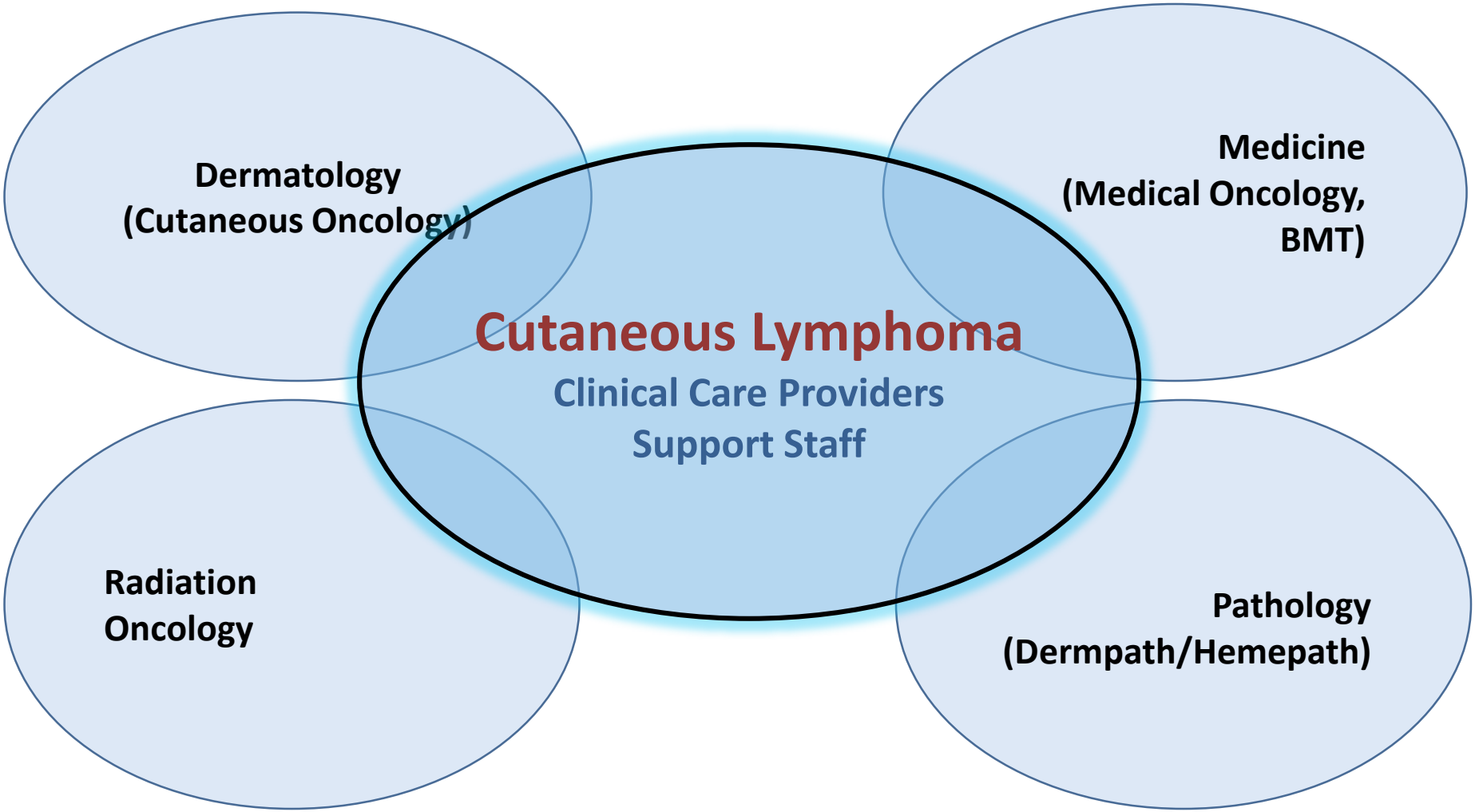
Clinical Stage	Median Survival (years)
IA	35.5
IB	21.5
IIA	15.9
IIB	4.7
IIIA	4.7
IIIB	3.4
IVA1	3.9
IVA2	2.1
IVB	1.4

Agar et al. JCO. 2010

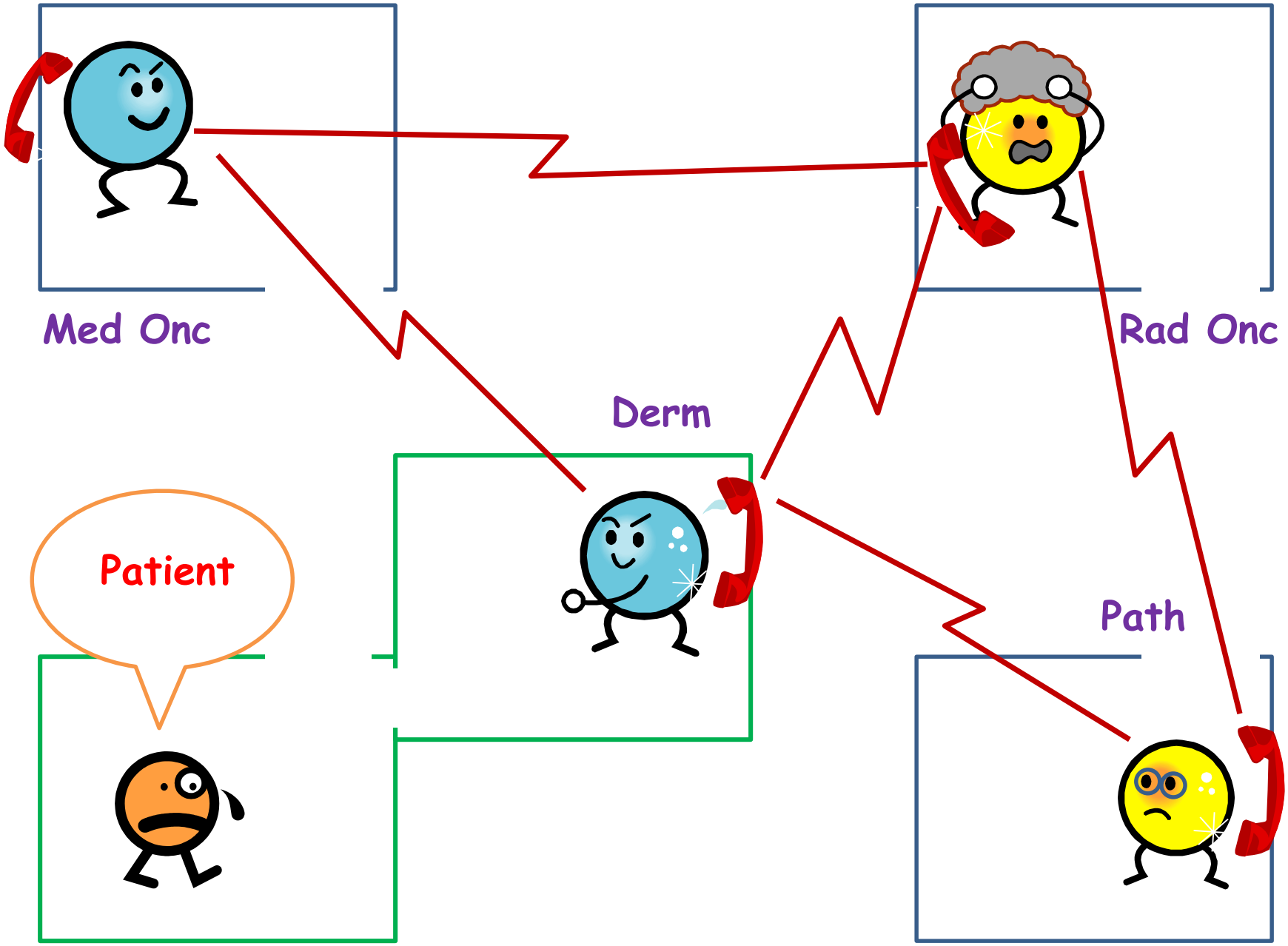
Challenges of CTCL

- 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

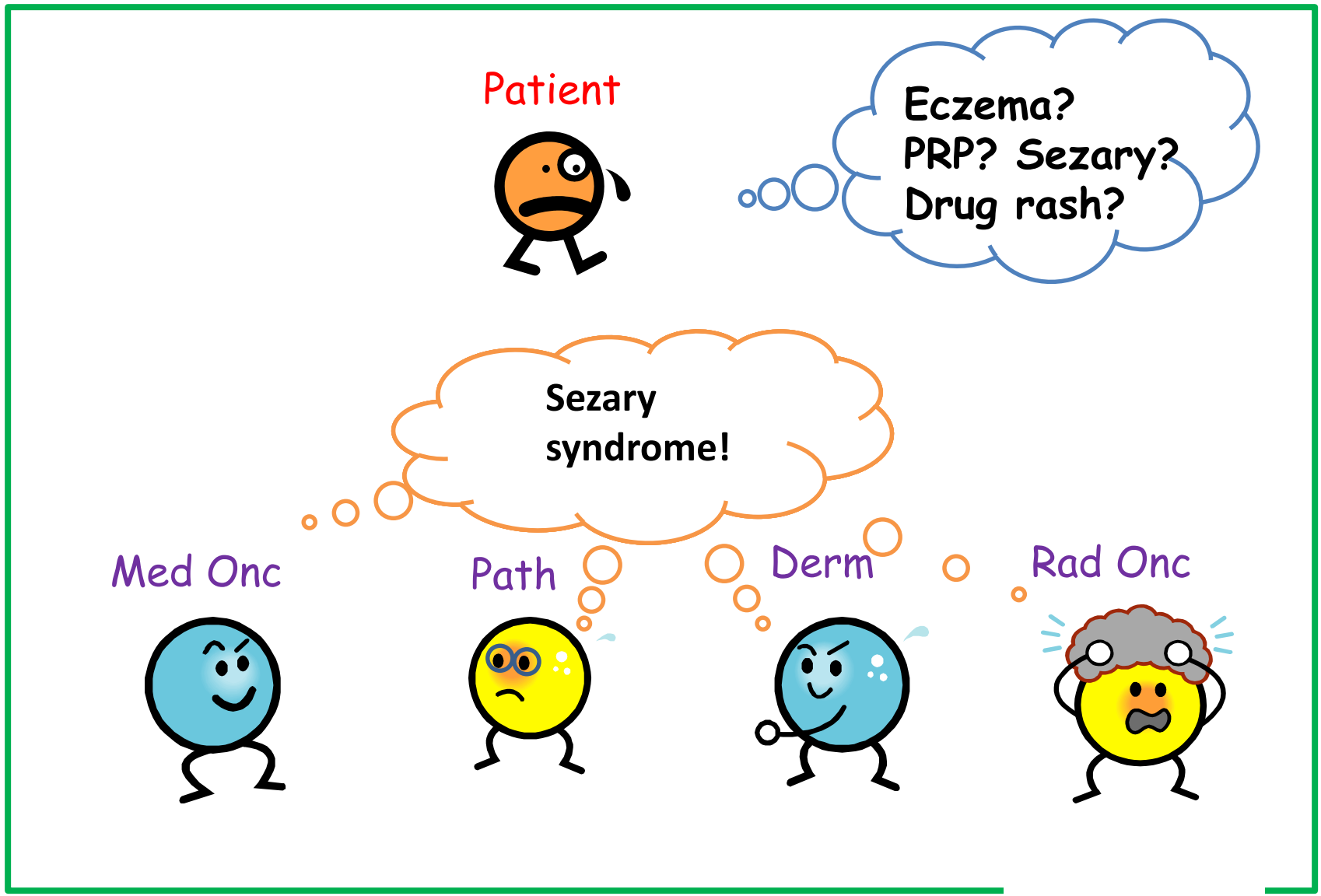


Courtesy Youn Kim MD



Separate physical space (separate clinics)

Courtesy Youn Kim MD



Path joins clinicians (ideal clinical-path correlation)

Courtesy Youn Kim MD

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 patient with stage IB disease and onwards

Questions