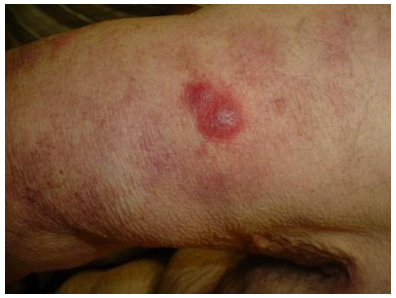
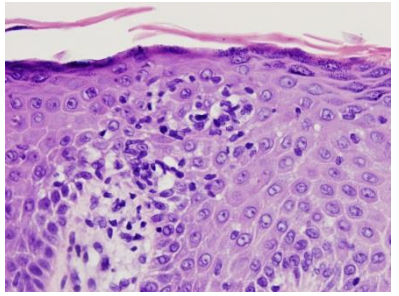
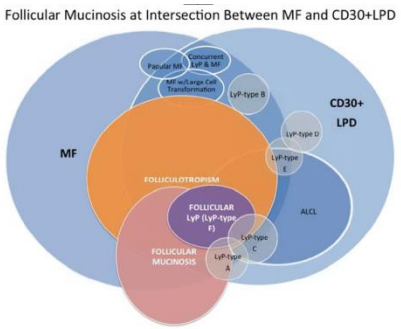




Lymphoma Research Foundation

Annual North American Educational Forum on Lymphoma

CUTANEOUS T-CELL LYMPHOMA



Vincent Liu, MD

University of Iowa

Saturday, October 19, 2019

Objectives

- To adopt the "Who-What-When-Where-How-Why?" format to better understand and manage cutaneous T-cell lymphoma (CTCL)
- To highlight the critical importance of clinicopathologic correlation for accurate diagnosis and optimal management
- To appreciate the value of multidisciplinary care
- To recognize that care must be patient-centered and address quality-of-life issues in decision-making

Alphabet Soup

- WHO-EORTC
  - World Health Organization-European Research Treatment of Cancer
- USCLC
  - United States Cutaneous Lymphoma Consortium
- ISCL
  - International Society for Cutaneous Lymphoma
- CLF
  - Cutaneous Lymphoma Foundation
- NCCN
  - National Comprehensive Cancer Network
- LRF
  - Lymphoma Research Foundation

Questions for Cutaneous Lymphoma Clinic

- Who
- What
- When
- Where
- How
- Why

Overview

- Who
  - Inform diagnosis
  - Guide treatment
- What
  - Clinicopathologic presentation lead to specific diagnosis (classification)
  - Diagnosis portends prognosis, management
- When
  - Evolution updates diagnosis(-es)
  - Progression dictates treatment
- Where
  - Staging component
  - Nuances of therapy
- How
  - How can we help-> management
- Why
  - Research into etiopathogenesis

WHO is the patient?

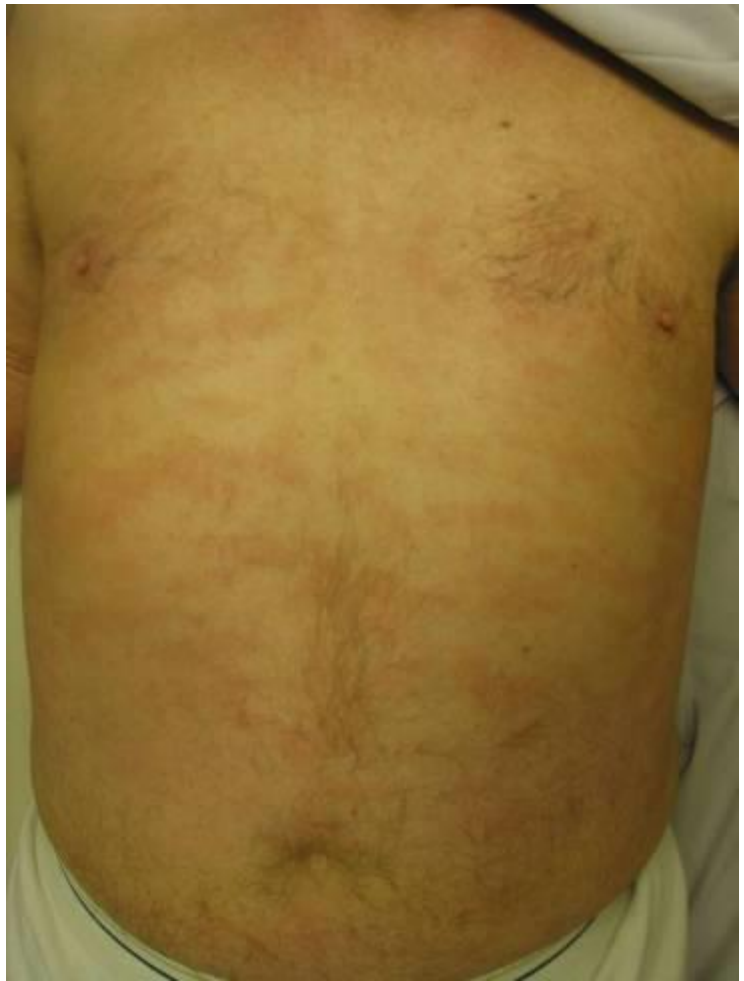
Overall story

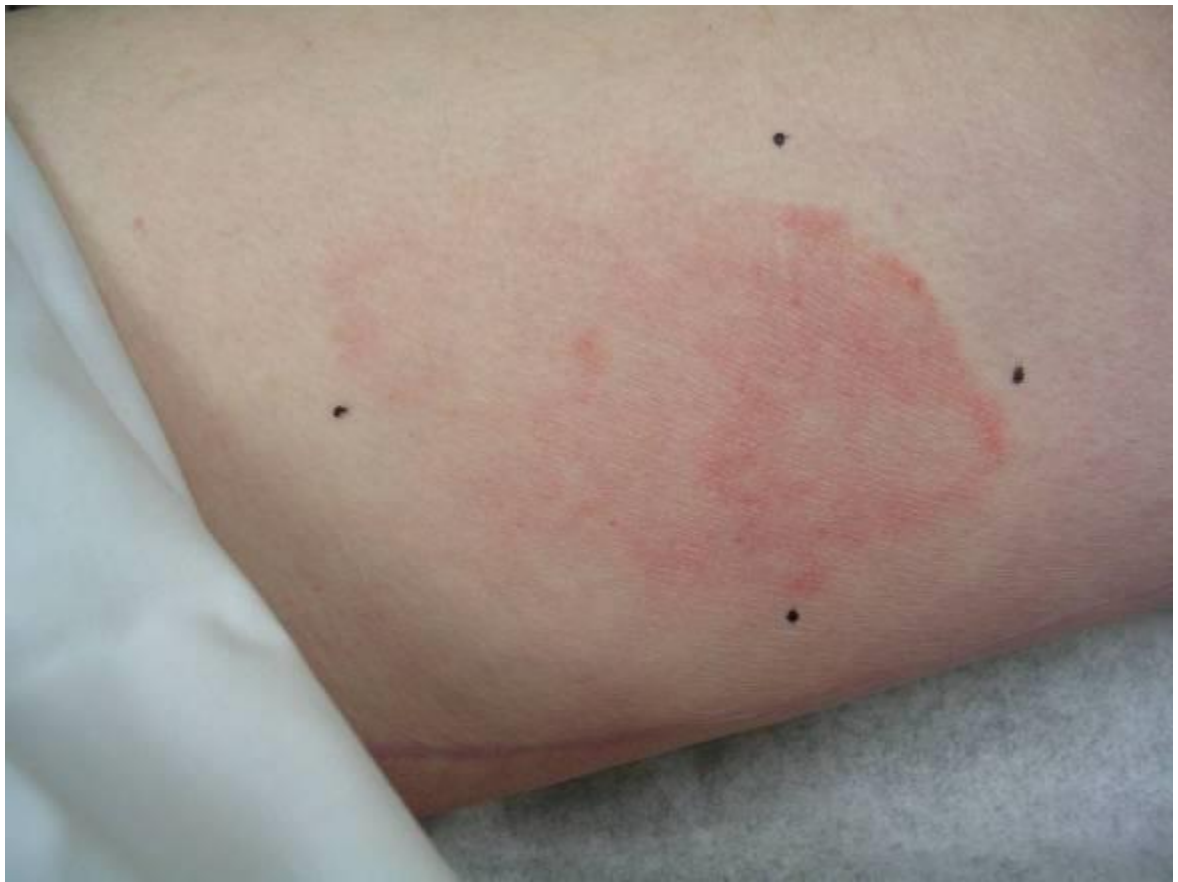
- HPI- esp pt concerns
- PMH
  - Implications for presentation
  - Implications for tx
- SH
  - Implications for tx
  - Pt concerns
- FH
  - Oncologic hx

Cutaneous lymphoma story

- How & when did it present?
- Work-up
  - Who evaluated pt?
  - Histopathology- skin bx, LN bx
  - Laboratory studies- bloodwork
  - Imaging
- Treatment
  - Skin-directed tx
  - Systemic tx

Patient #1





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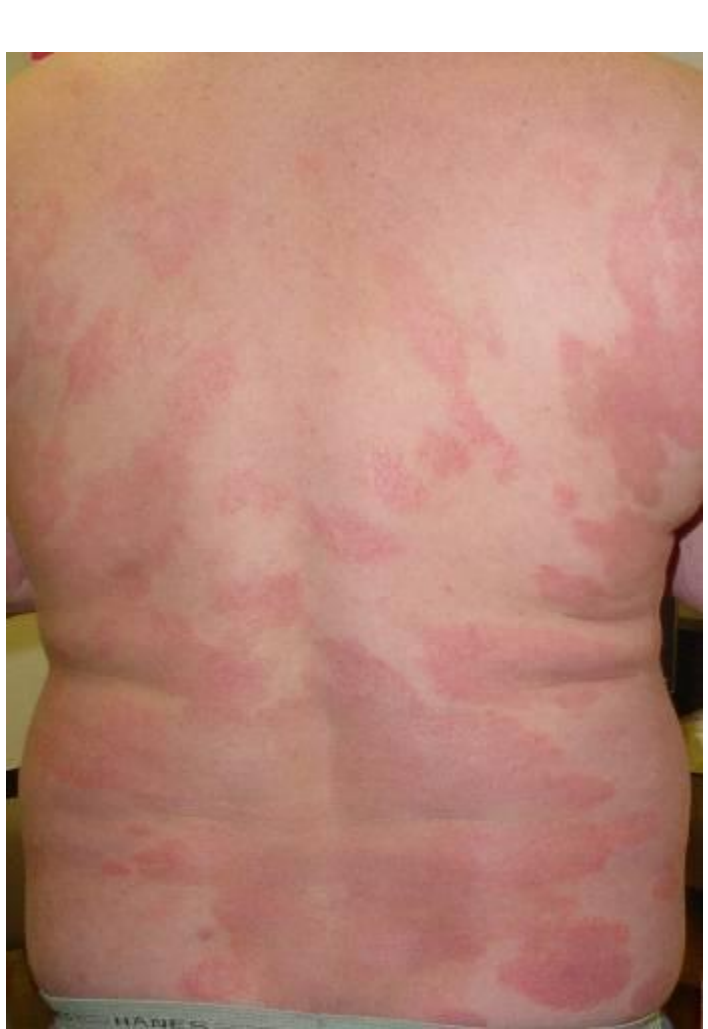
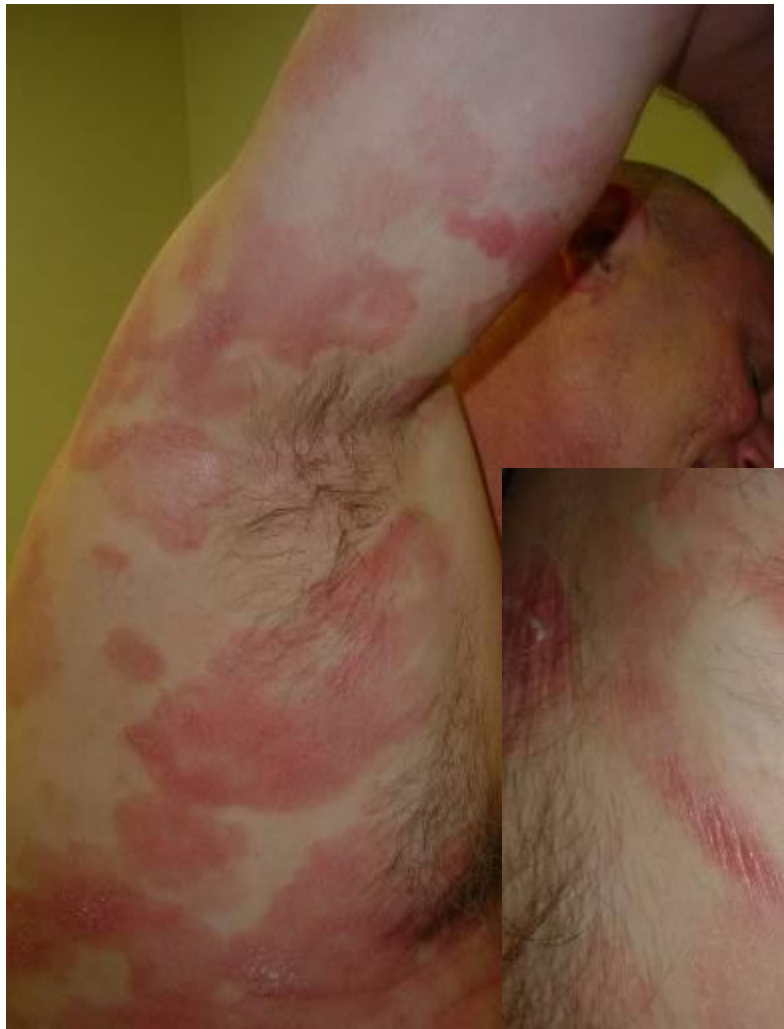
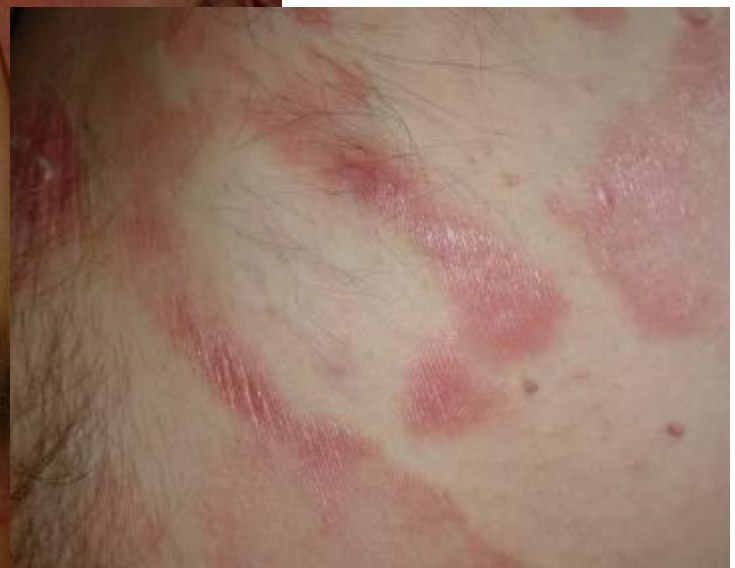
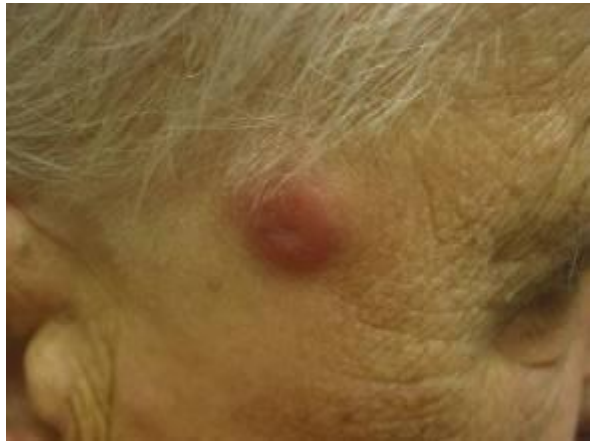
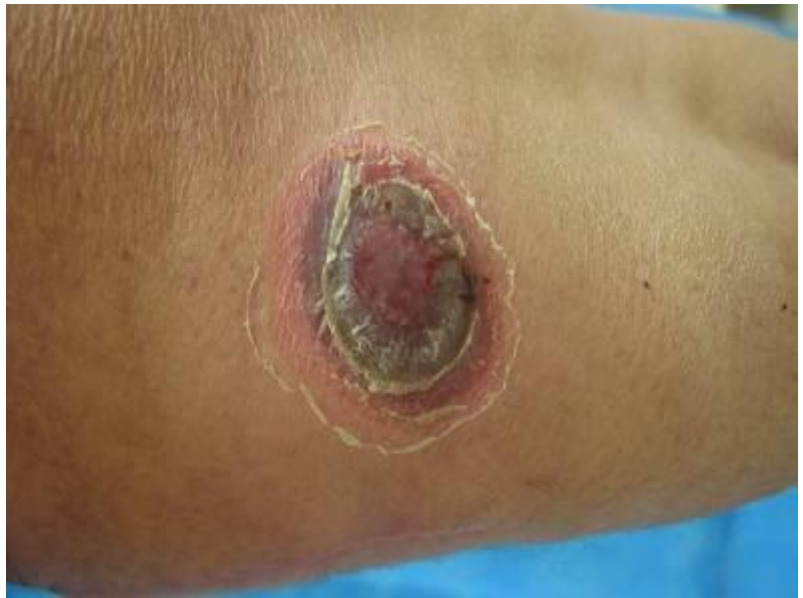


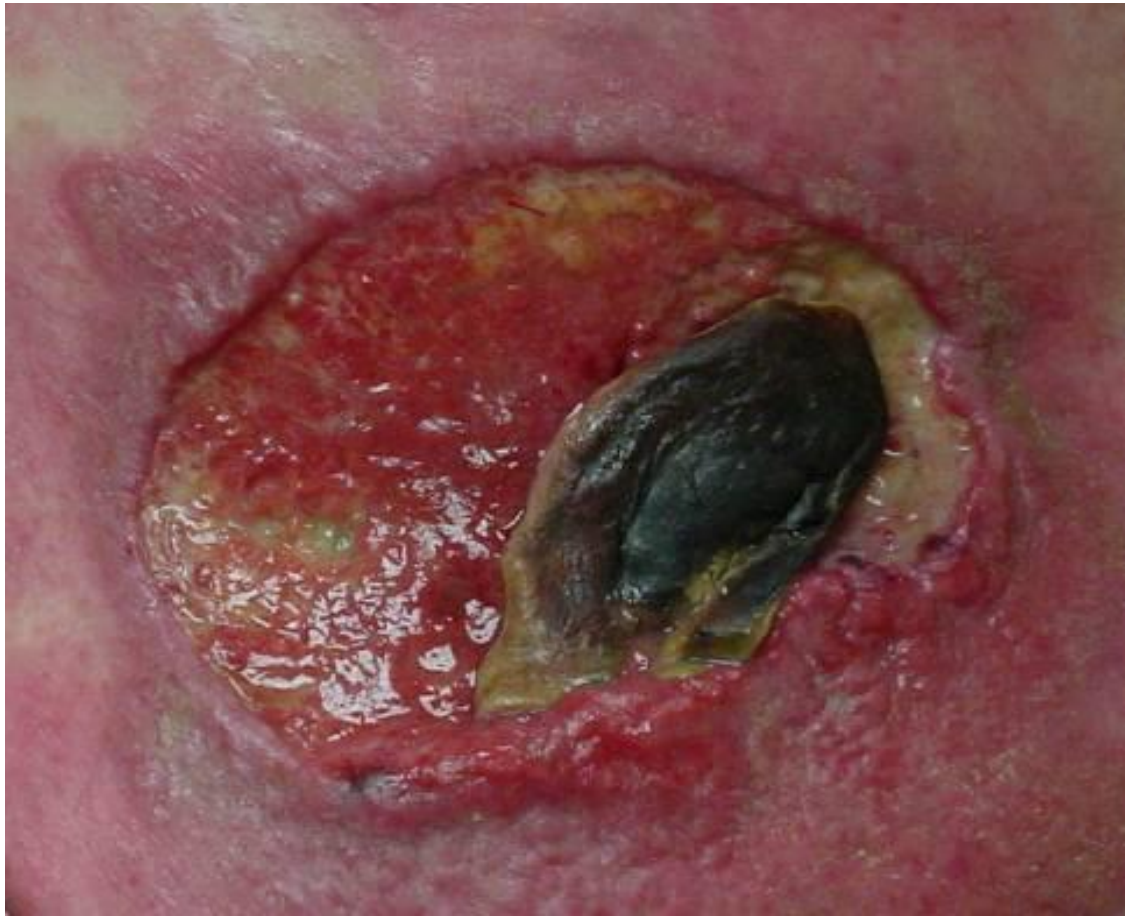




Patient #3







WHAT does the patient have?

Is it "lymphoma"?

- Clinical differential diagnosis
  - Inflammatory
    - Erythema annulare centrifigum
  - "Pseudolymphomas"
  - T-cell dyscrasia
    - Parapsoriasis
    - Pigmented purpura
  - Drug-induced MF
  - Infectious
    - Syphilis
- Pathologic differential diagnosis
  - Langerhans cell histiocytosis
  - Other histiocytic disorders
  - Melanoma

What type?

- Primary vs Secondary
- T/NK vs B
- Specific diagnosis

Cutaneous T-Cell (and NK-Cell) Lymphomas: *WHO-EORTC Classification*

- Mycosis fungoides
- MF-variants
  - Pagetoid reticulosis
  - Folliculotropic, syringotropic, granulomatous variants
- Subtype of MF
  - Granulomatous slack skin
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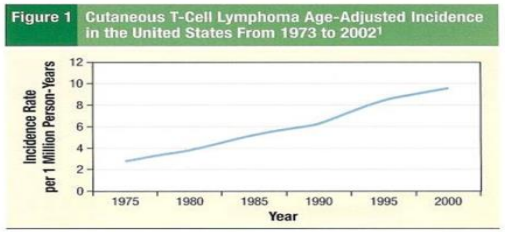
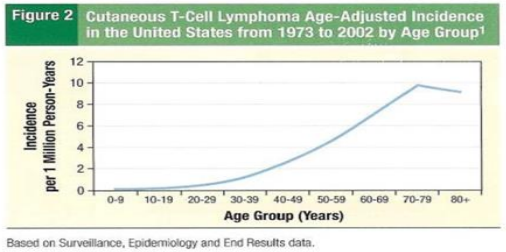
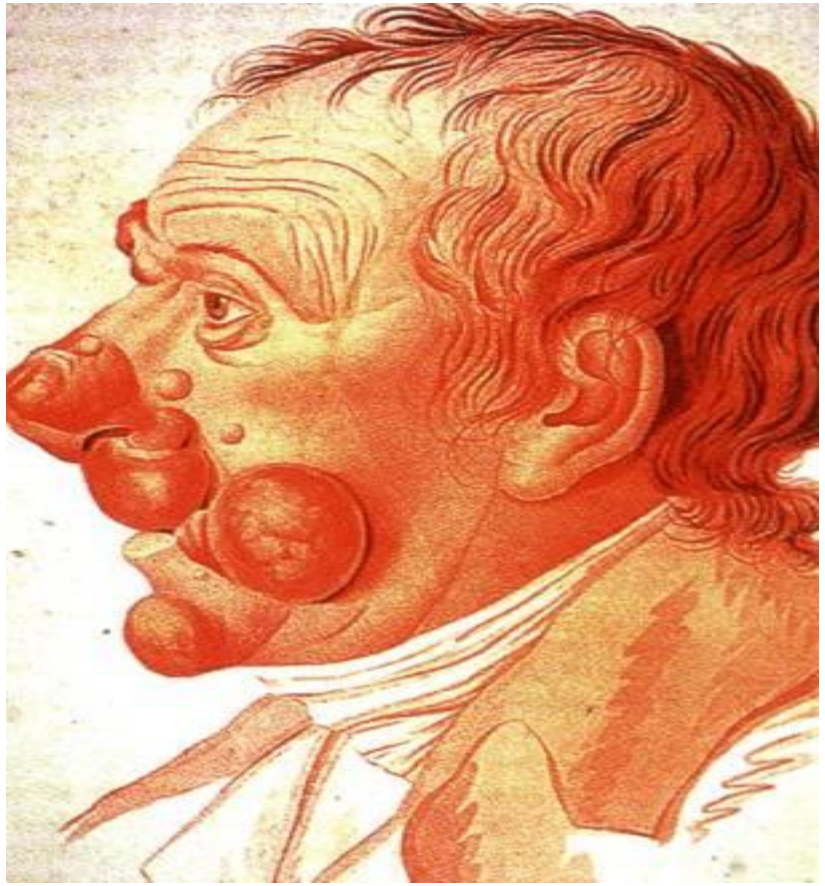
  - Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)
- Adult T-cell leukemia/lymphoma
- Angioimmunoblastic T-cell lymphoma

Mycosis Fungoides- *Background*

- History: Coined in 1806 by Alibert for resemblance to fungating tumors
- Epidemiology: Male:Female = 2:1; Black > White; Median age 55 yo
- Incidence: 0.29/100,000/yr
- Etiology: ?HTLV-1; ?ionizing radiation; ?chronic antigen stimulation (silicone breast implants)

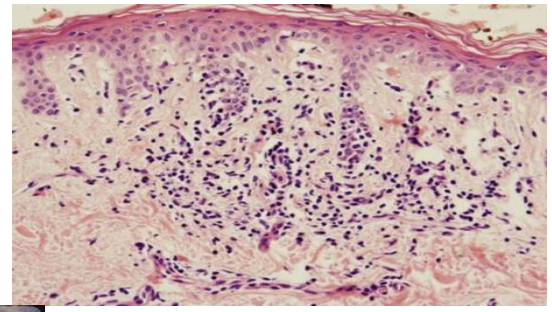


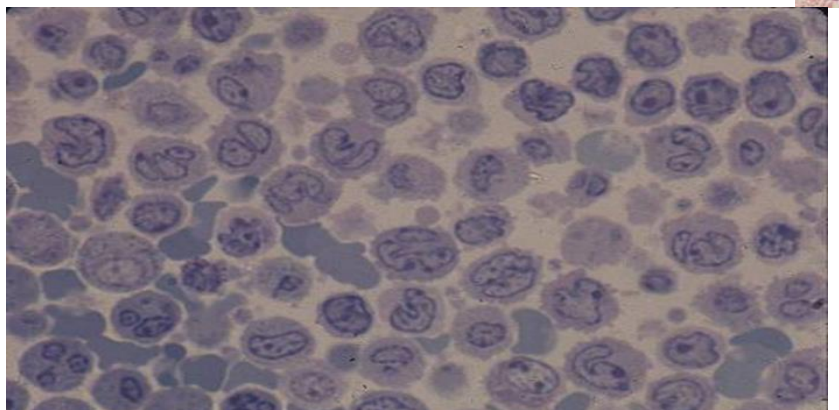




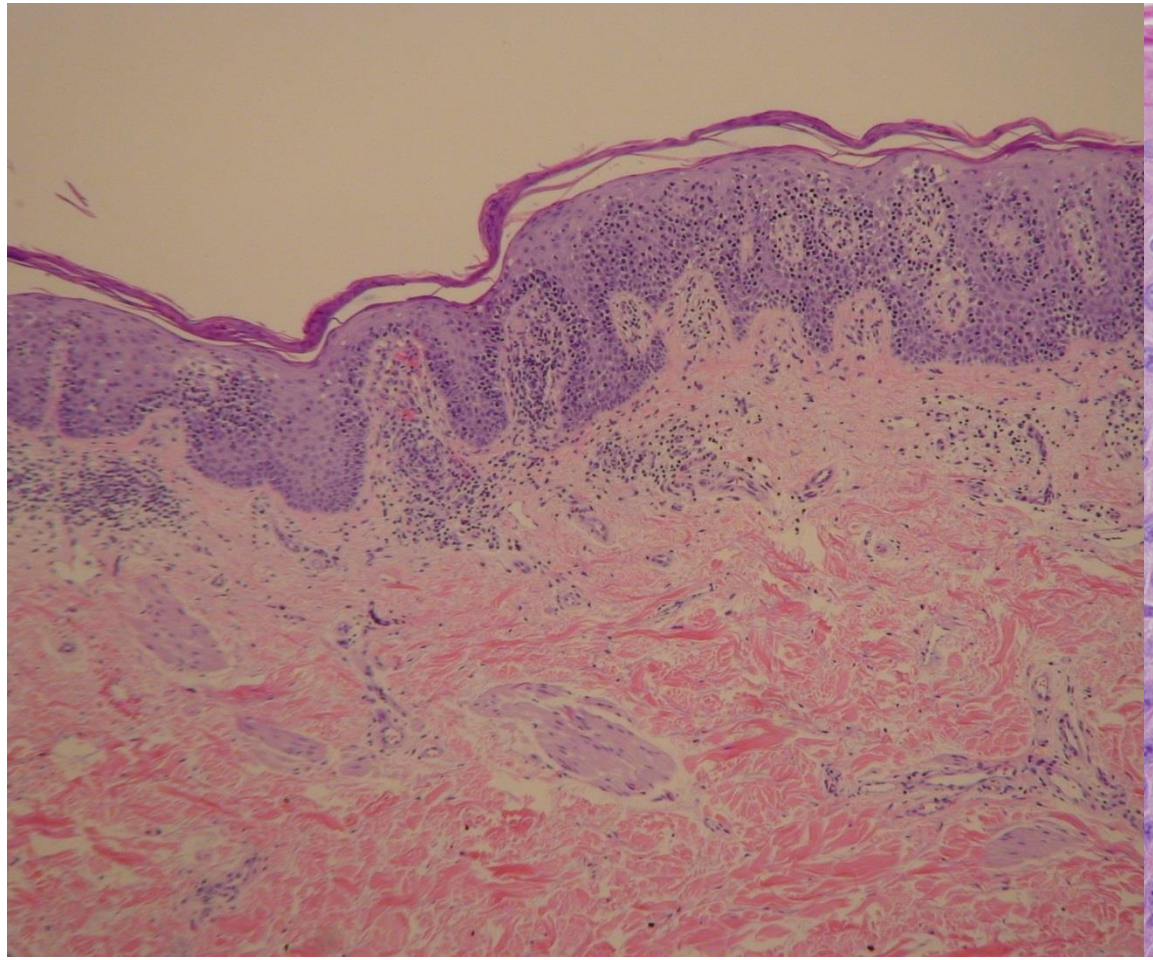
Mycosis Fungoides: *Pathology*

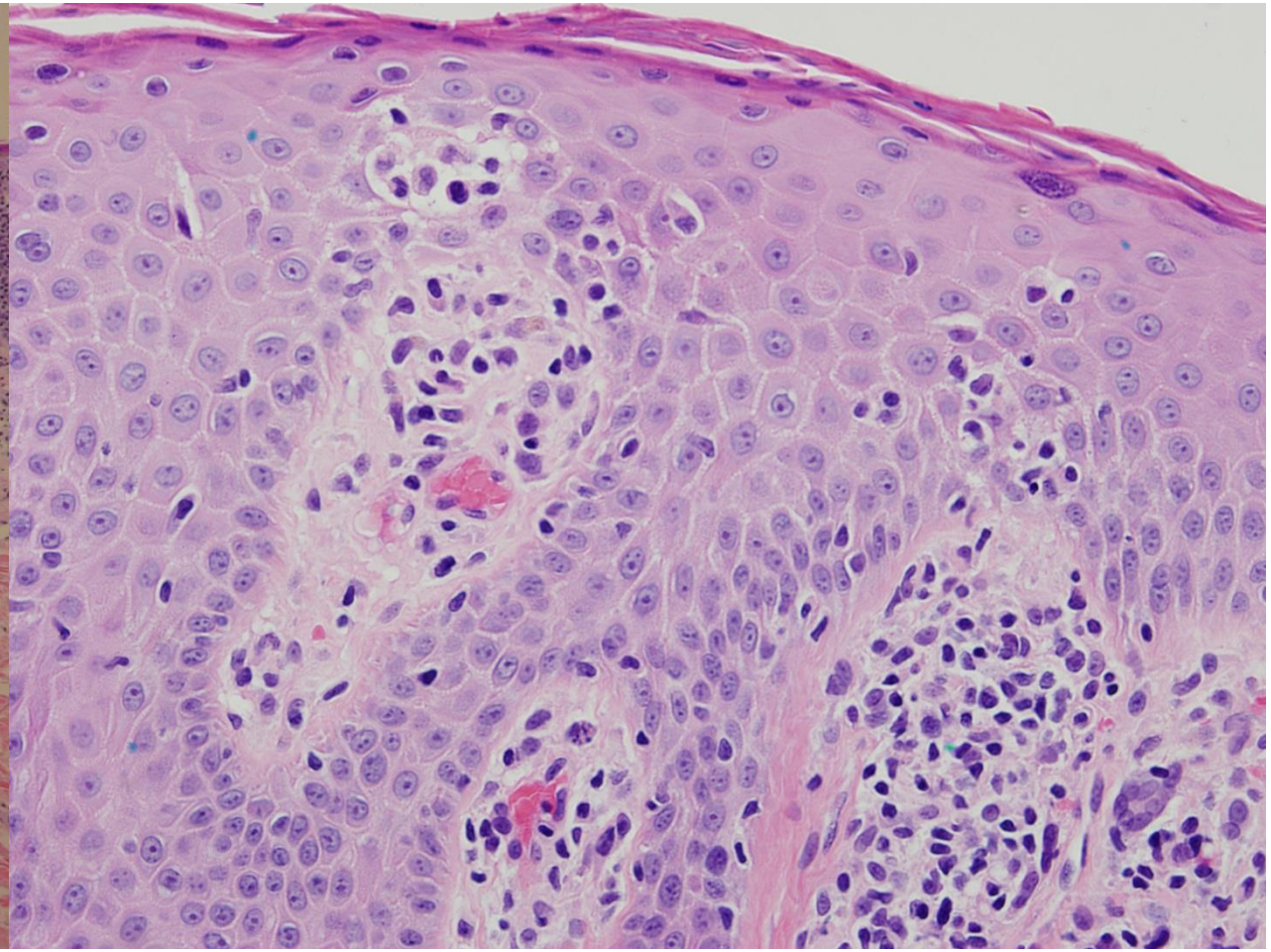
- Epidermis
  - Epidermotropism of atypical lymphocytes
    - Pautrier's microabscesses
    - Haloed lymphocytes along dermal-epidermal junction
  - Relative paucity of spongiosis
- Dermis
  - Papillary dermal sclerosis
  - Lymphocytic atypia





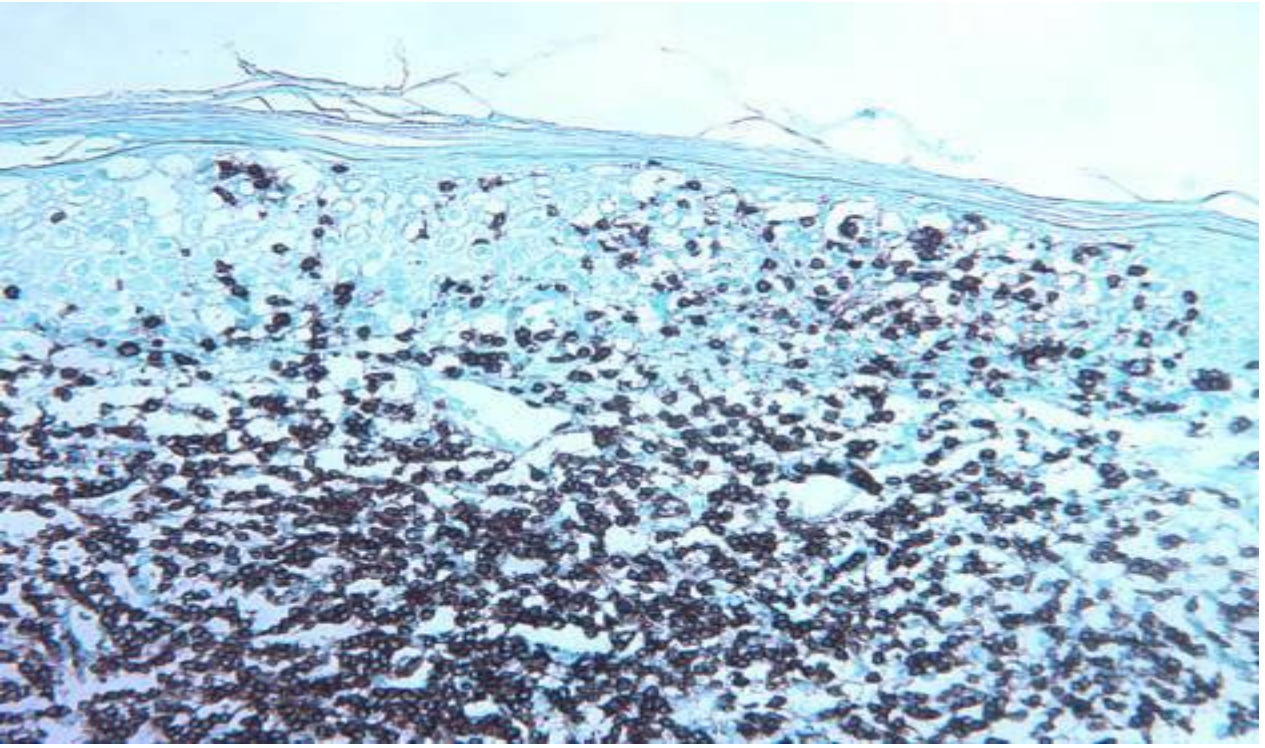
Mycosis Fungoides: *Pathology*



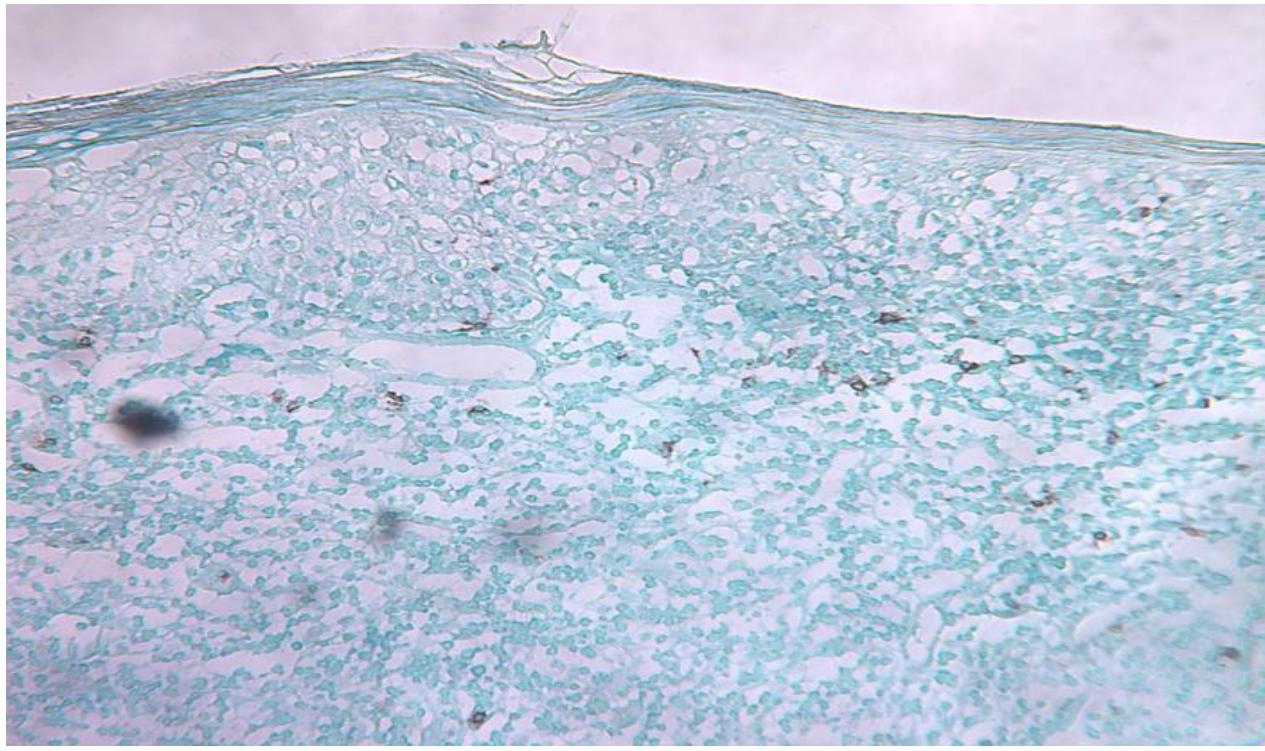


Mycosis Fungoides: Immunophenotype

- CD3

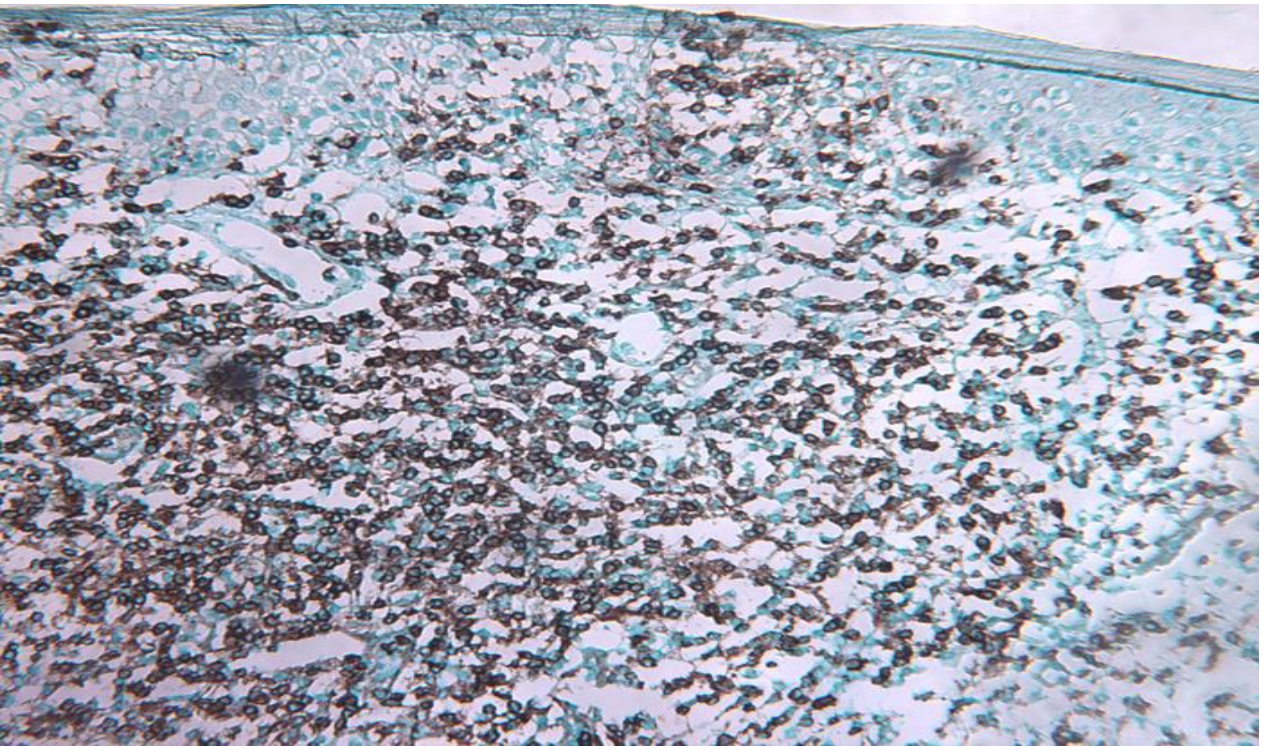


- CD20

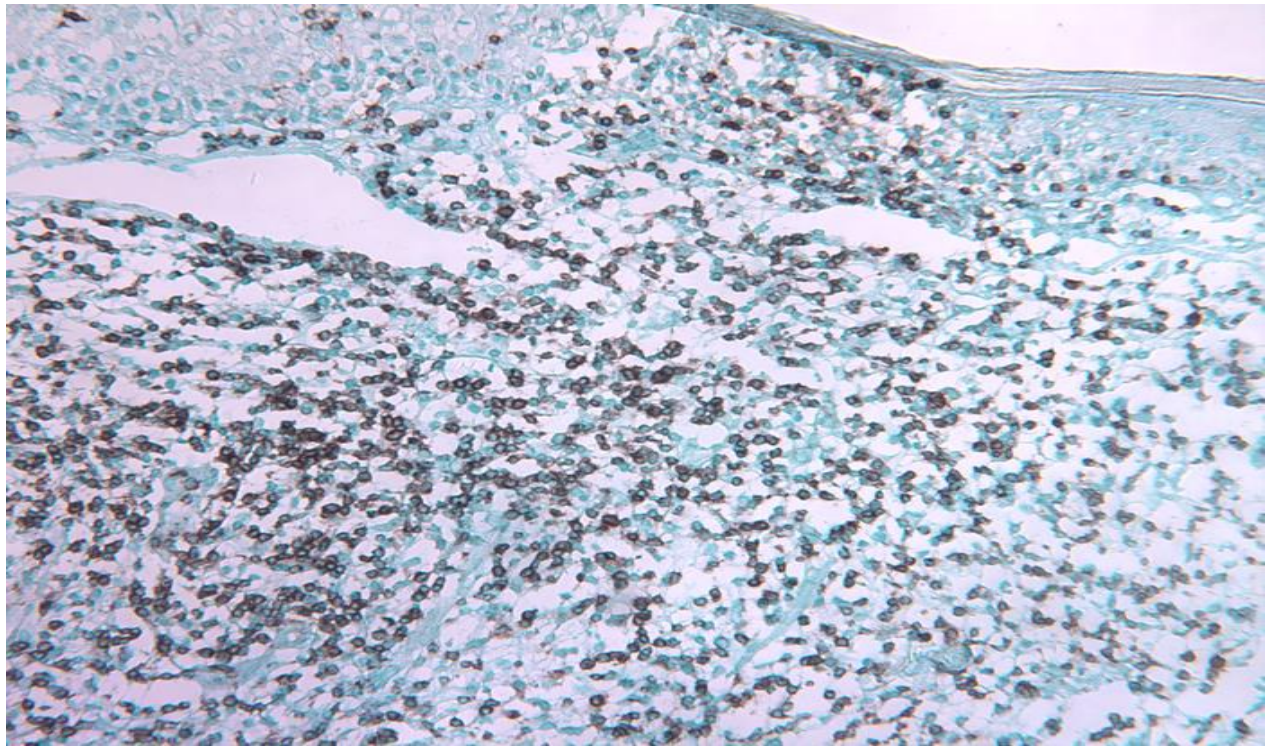


Mycosis Fungoides: Immunophenotype

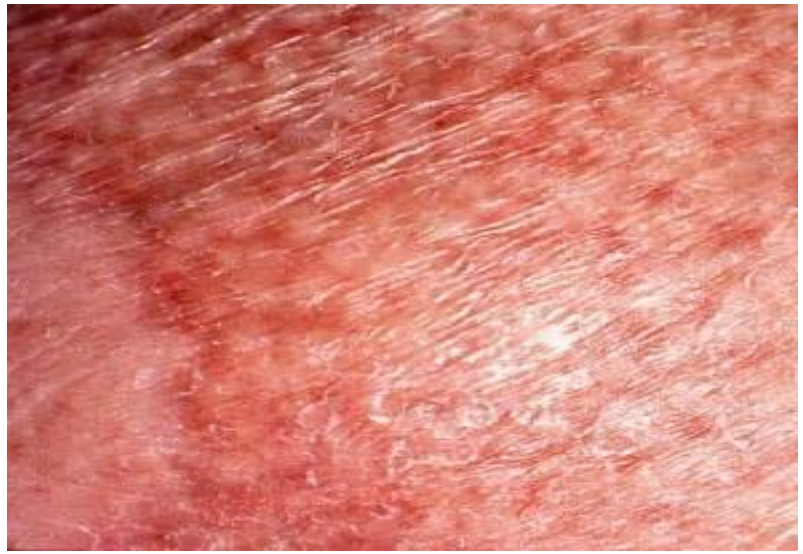
- CD4

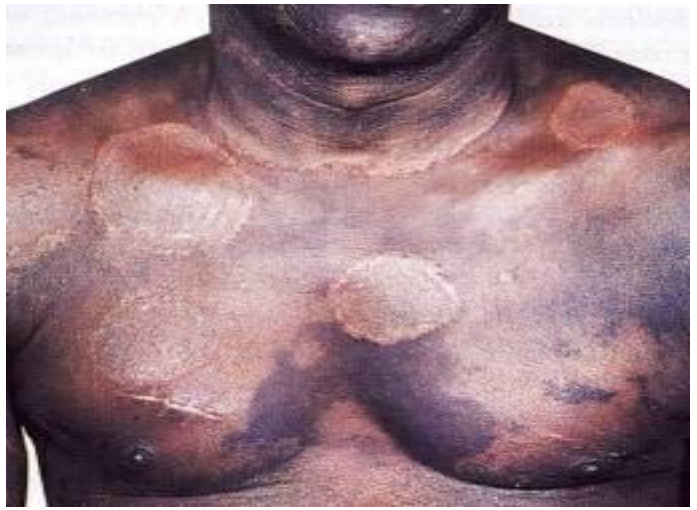


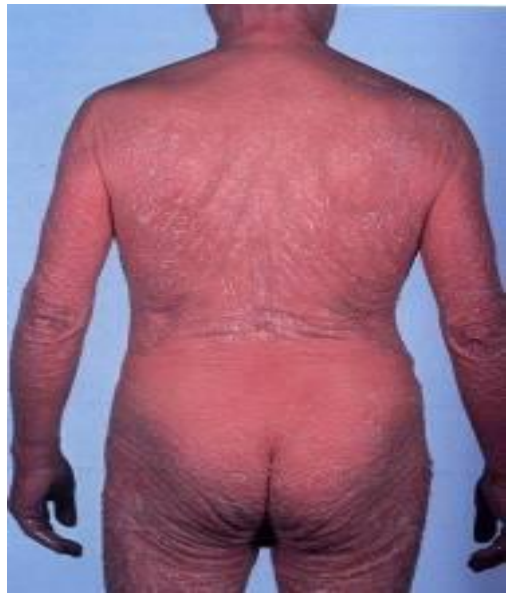
- CD7

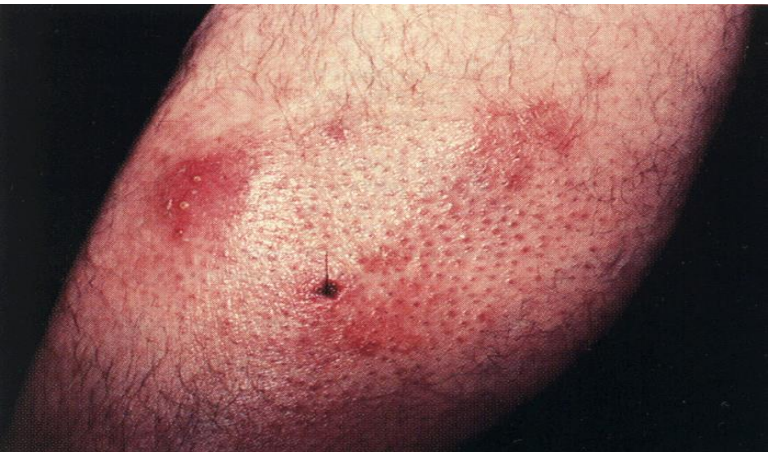


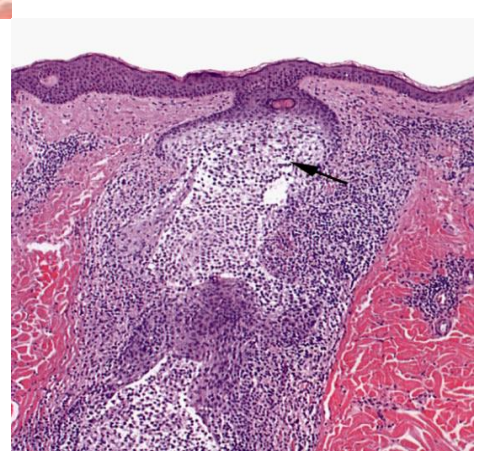
Mycosis Fungoides- *Variants*

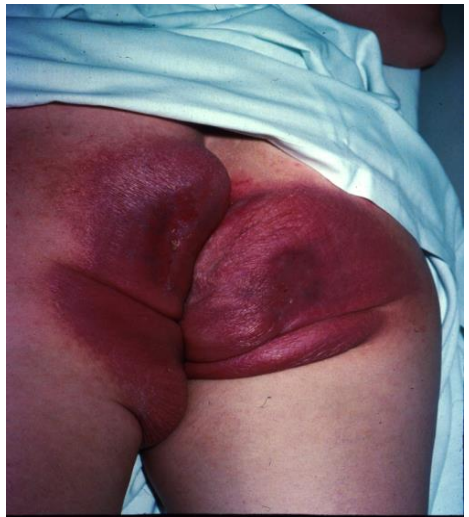


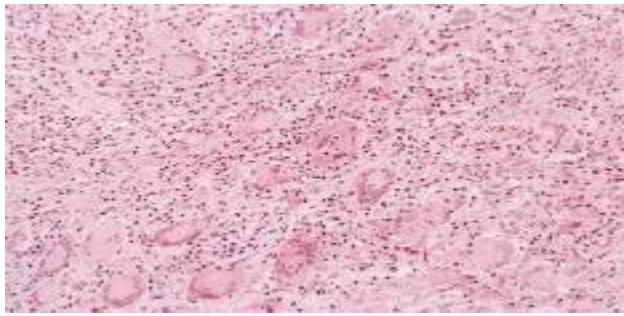












Mckee's Pathology of the Skin. Elsevier.

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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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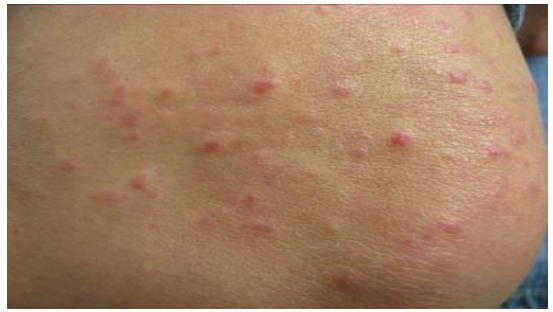
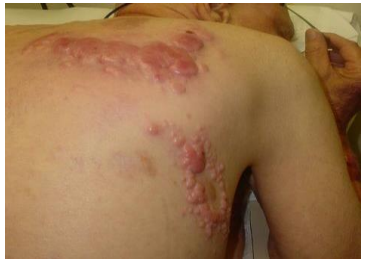
- Adult T-cell leukemia/lymphoma
- Angioimmunoblastic T-cell lymphoma

CD30+ Lymphoproliferative Disorders: *Lymphomatoid Papulosis*

- Demographics
  - Median age: 45
  - Male-to-female: 1.5:1
- ***Chronic, recurrent, asymptomatic, self-healing papulonodular/papulonecrotic eruption***
  - Trunk and limbs
  - Lesions and course similar to PLEVA
  - Hypopigmented scarring
- Course
  - Develops over days/weeks
  - Duration: months to >40 years

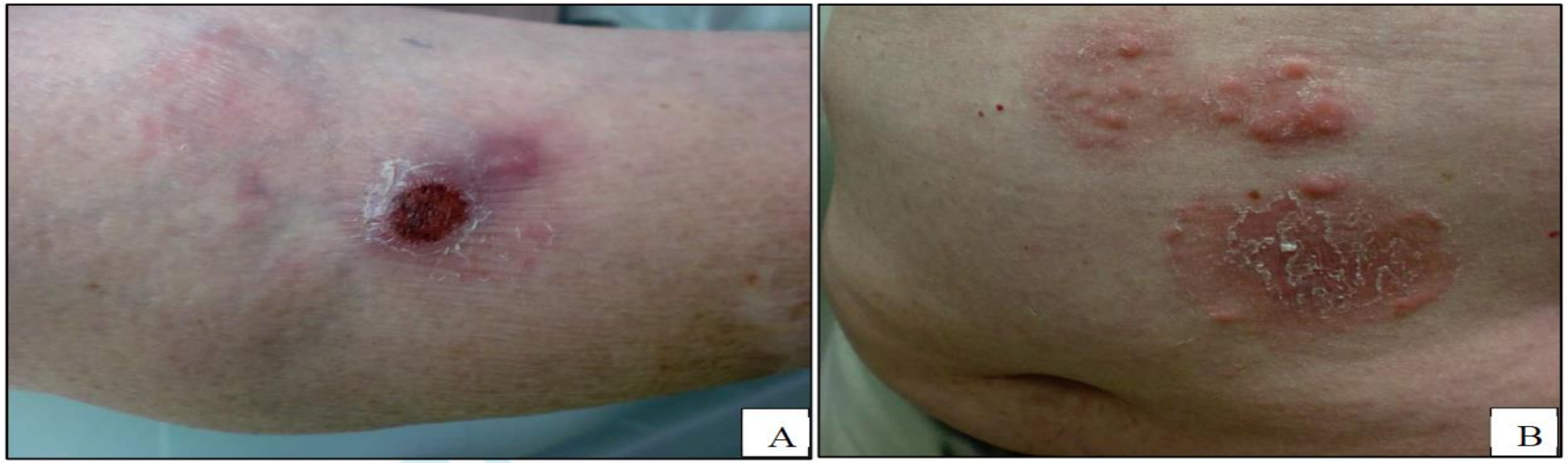


CD30+LPD:
Primary Cutaneous Anaplastic Large Cell Lymphoma



- Demographics
  - Older adults
  - Generally older than systemic ALCL with skin involvement
- ***Skin-colored to erythematous nodules, plaques, and tumors***
- Few to several centimeters in diameter
- Trunk, extremities, and occasionally face, affected
- Ulceration not uncommon

MF vs CD30+LPD?

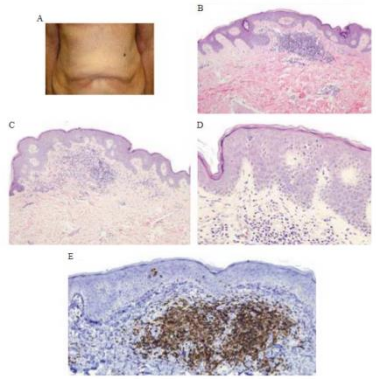


J Cutan Pathol. 2017 Aug;44(8):703-712.

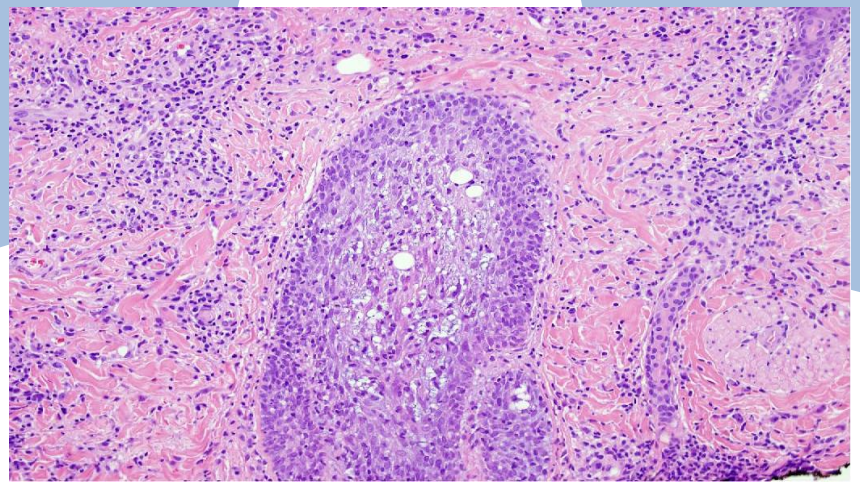
Integration

J Cutan Pathol. 2013 Aug;40(8):714-9.

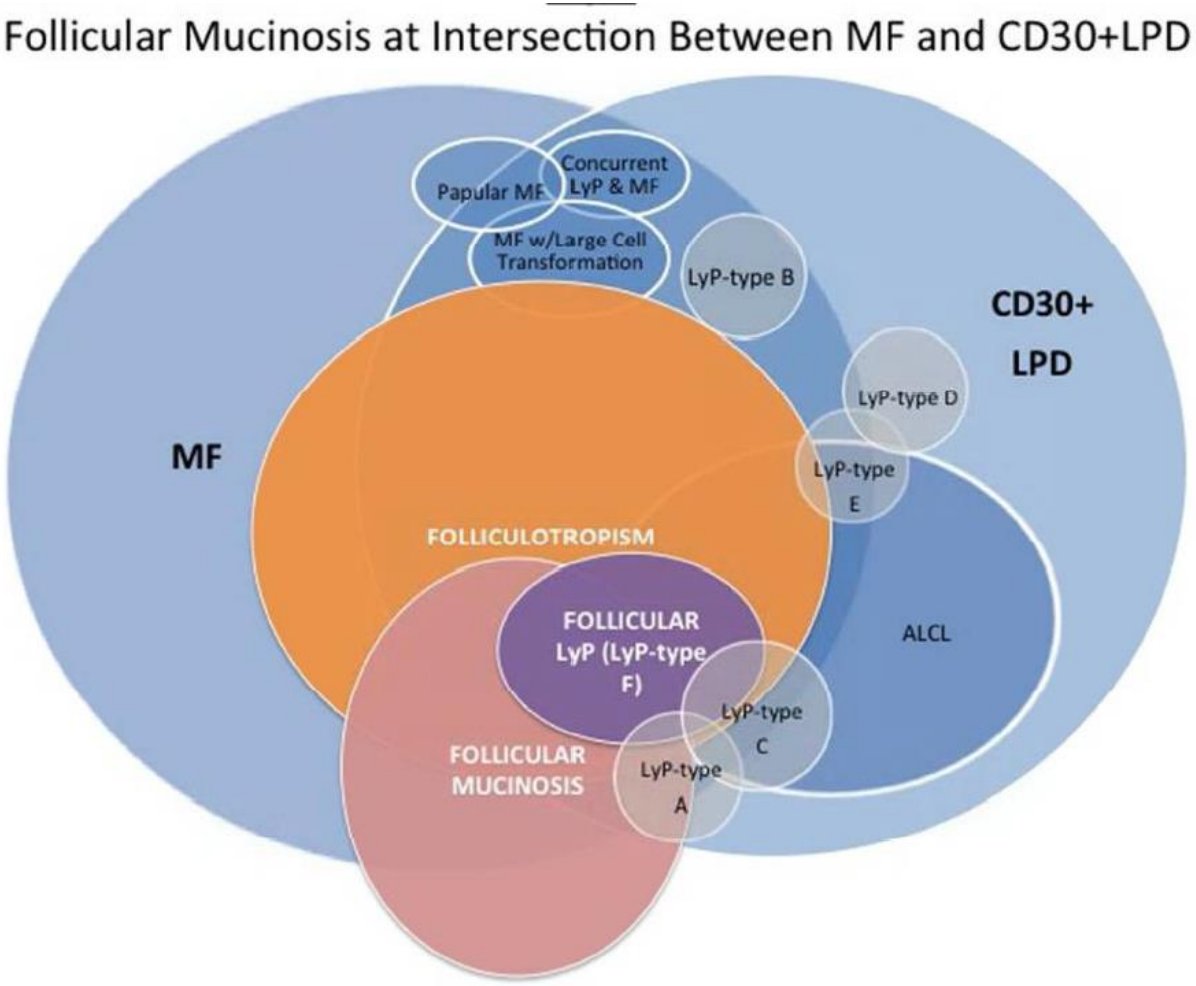
MF



CD30+ LPD

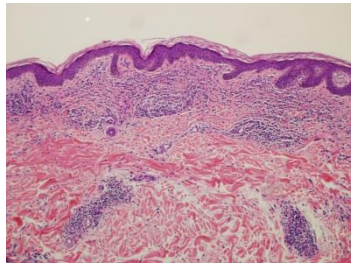


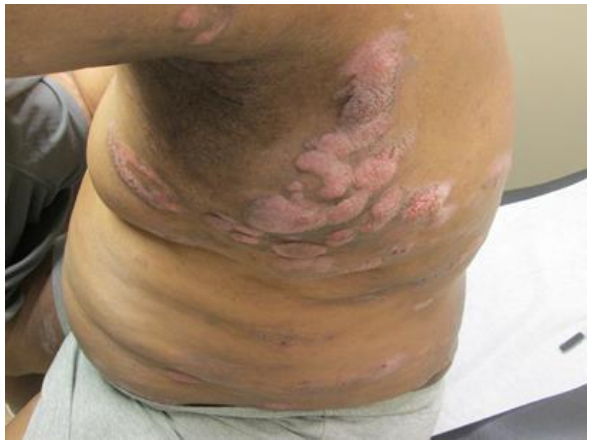
Integration



J Cutan Pathol. 2017 Apr;44(4):360-366.

Clinicopathologic Correlation





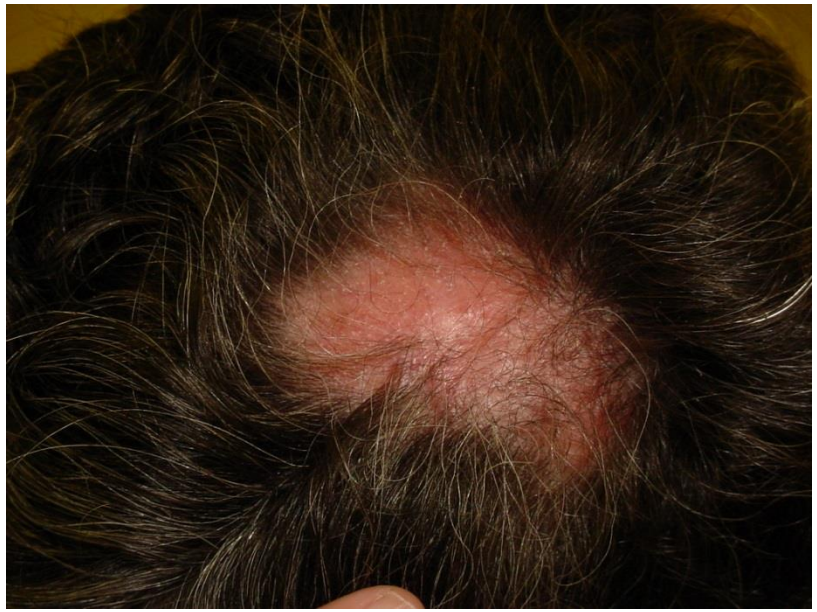
WHEN did this happen?

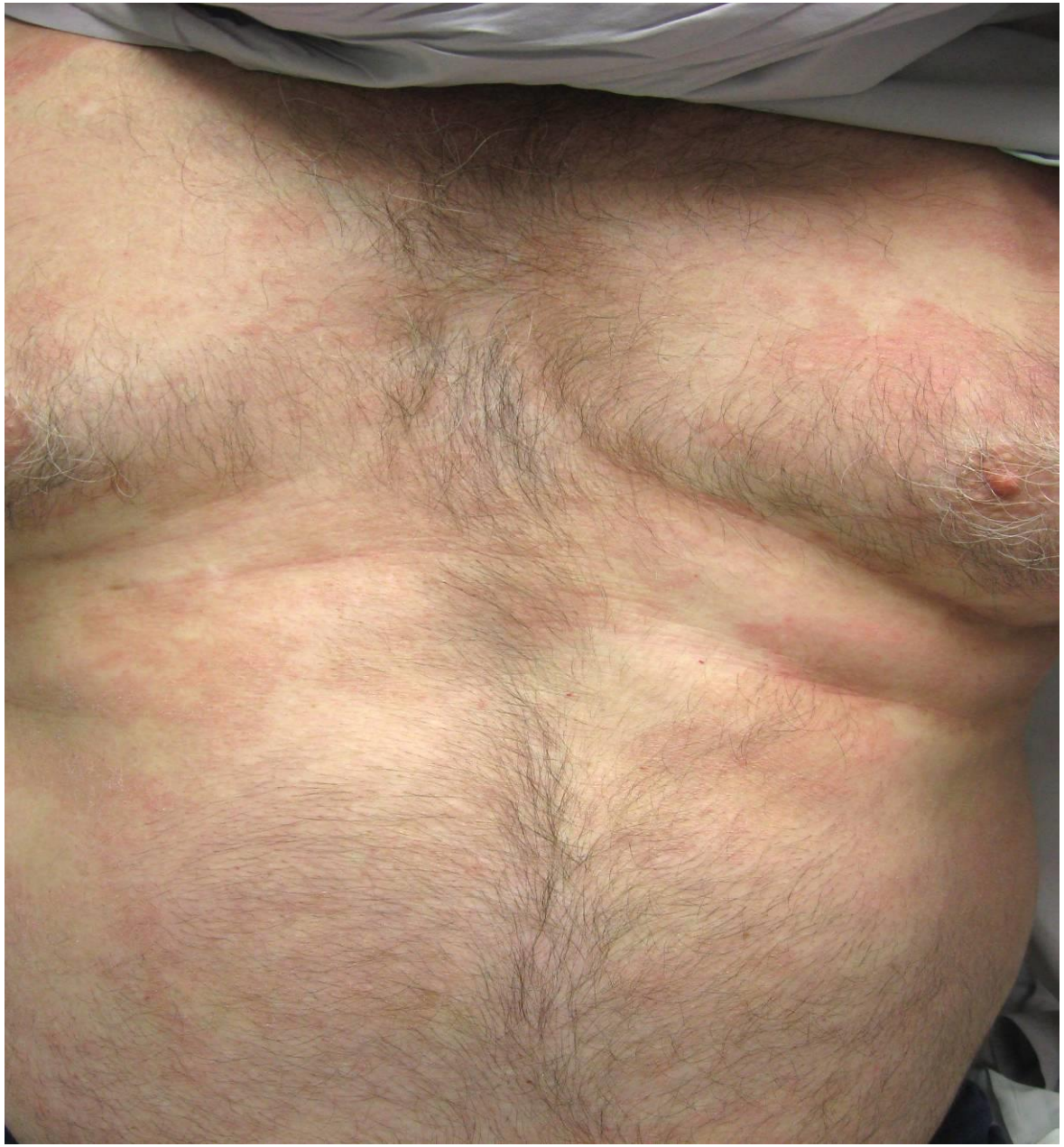
Evolution of features

- Progression assessment
- Transformation
  - MF large cell transformation
- Dual processes
  - MF & CD30+ LPD

Implications

- Prognosis
- Therapy
  - Aggressiveness
  - Tx of other malignancy
    - CLL
    - Plasma cell dyscrasia





WHERE is the disease?

Staging

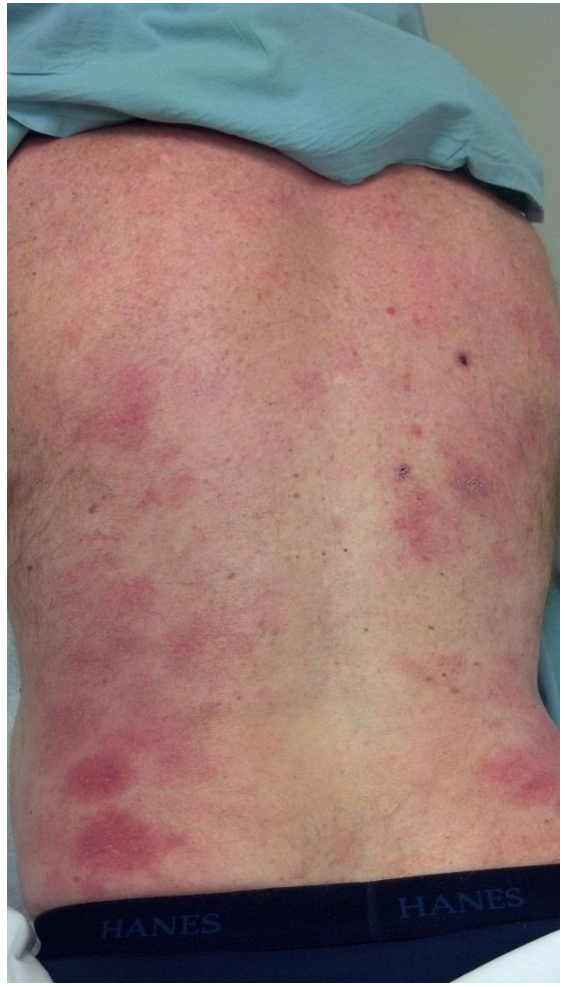
- Skin
  - Morphology
  - BSA
- Reticuloendothelial system
  - Lymph nodes
  - HSM
- Blood
  - B-symptoms

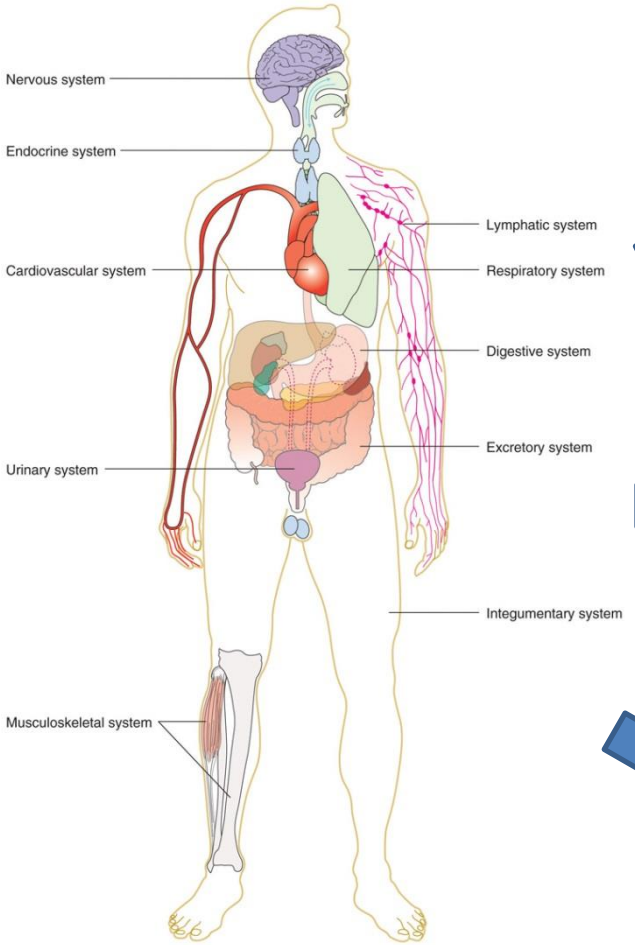
Testing

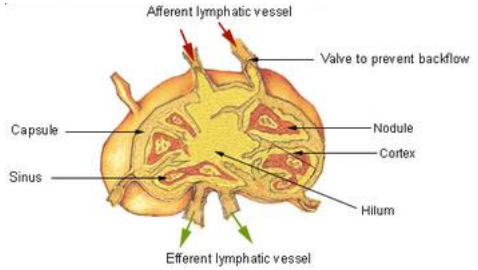
- Skin Biopsy
  - H&E
  - Immunohistochemistry
  - Clonality
- RES
  - ?CXR Stage IA/IB
  - CT(/PET) for >=Stage I
- Blood
  - Labs:
    - CBC
    - LDH
    - Chem-7
    - LFTs
    - Lipids
    - TSH
    - U/A
  - Flow cytometry of peripheral blood
  - Clonality studies of peripheral blood

WHERE is the disease?

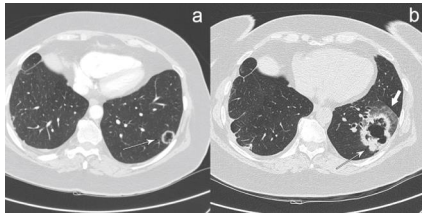
T
(Tumor):
Skin



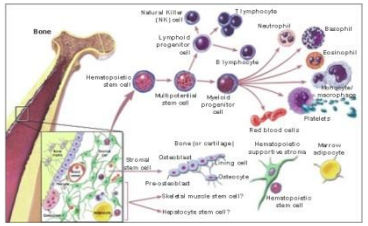




N
(Node):
Lymph
node

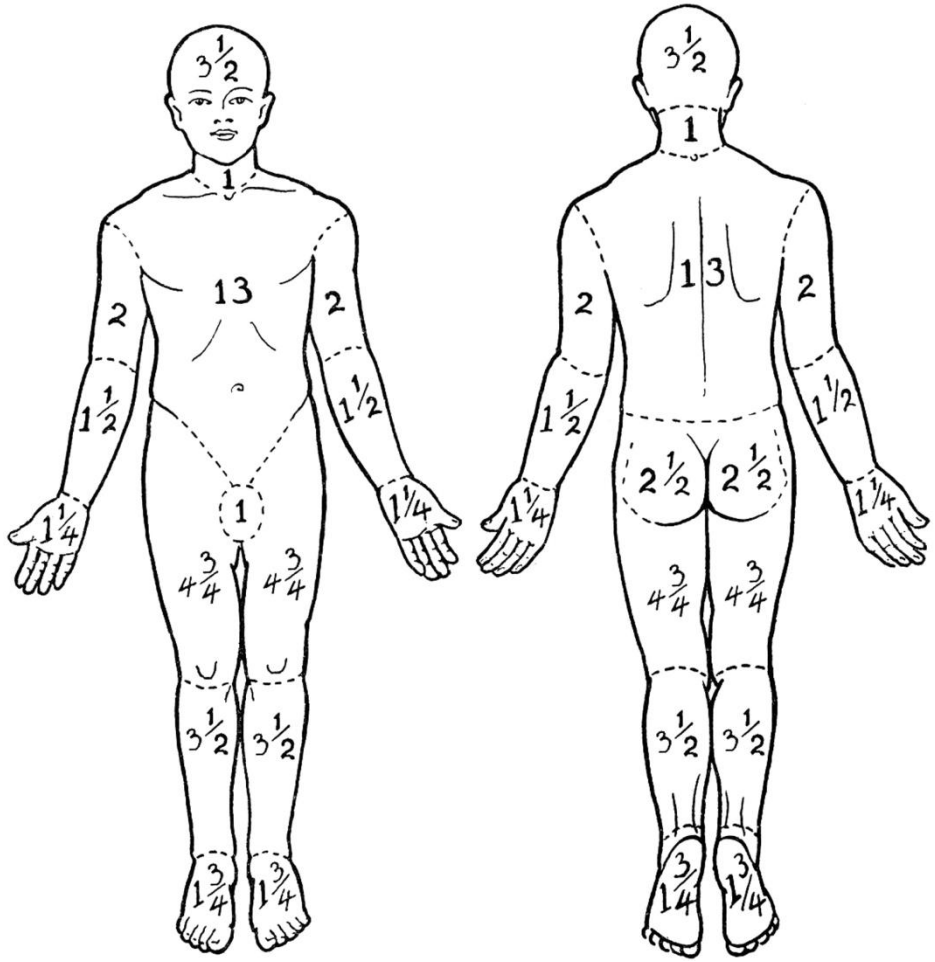


M
(Metastasis):
Internal
organs

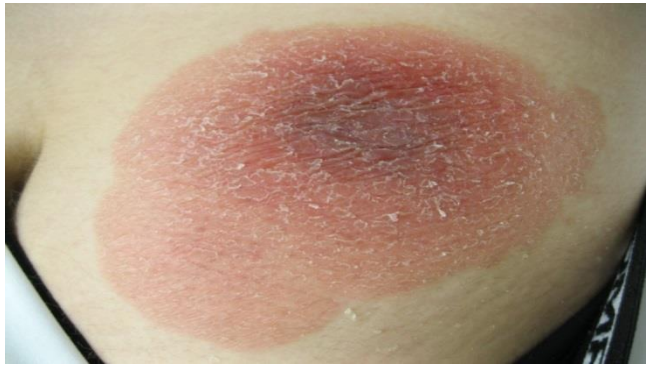


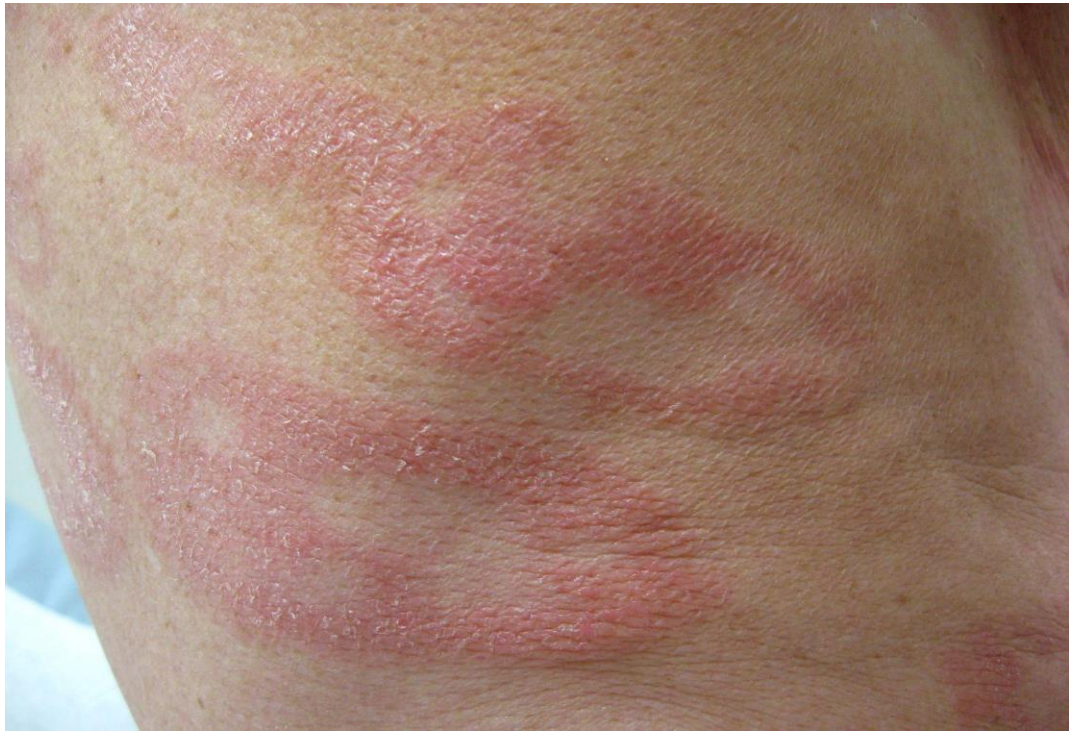
B
(Blood):
Blood &
Bone
marrow

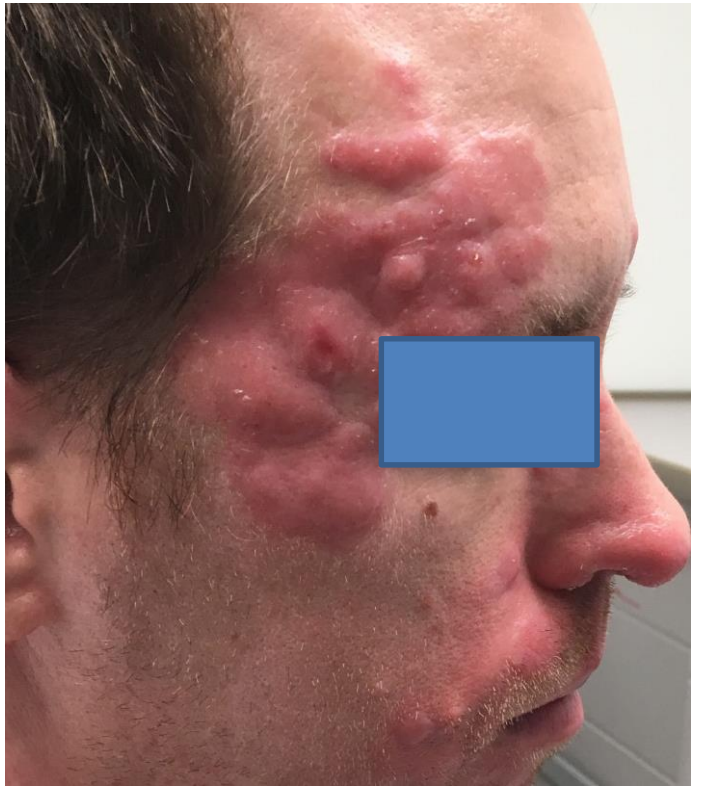
Body Surface Area



WHERE is the disease?







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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.

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- Neck CT

HOW can we help?

Prognosis

- Staging
- Counseling
  - Stage IA, most IB

Treatment

- Skin-directed therapy
  - Topical steroids
  - Nitrogen mustard (mechlorethamine)
- Phototherapy
  - PUVA
  - N-UVB
  - Extracorporeal photophoresis (ECP)
- Systemic therapy
  - MTX
  - Retinoids
    - Bexarotene
    - Acitretin
  - HDAC-I
    - Vorinostat
    - Romidepsin
  - IFN
  - Chemotx
  - ONTAK
  - BMT

TNMB		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[h,i]
Skin	T1	Limited patches,[j] papules, and/or plaques[k] covering <10% of the skin surface
	T2	Patches,[j] papules, and/or plaques[k] covering ≥10% of the skin surface
	T3	One or more tumors[l] (≥1 cm in diameter)
	T4	Confluence of erythema ≥80% body surface area
Node	N0	No abnormal lymph nodes; biopsy not required
	N1	Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Abnormal lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
	MX	Abnormal visceral site; no histologic confirmation
Blood	B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells[i]
	B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells but do not meet the criteria of B2
	B2	High blood tumor burden: ≥1000/mcL Sezary cells[i] or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells[i]

[h]Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722 and Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607.

[i]Sezary syndrome (B2) is defined as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either 1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of ≥10 or increase in CD4 cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD4+/CD26- of the total lymphocyte count).

[j]Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

[k]Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting and/or poikiloderma should be noted. Histologic features such as folliculotropism or large cell transformation (≥25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

[l]Tumor = at least one >1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

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Clinical Staging of MF and SS[h]

	T	N	M	B
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
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

[h]Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

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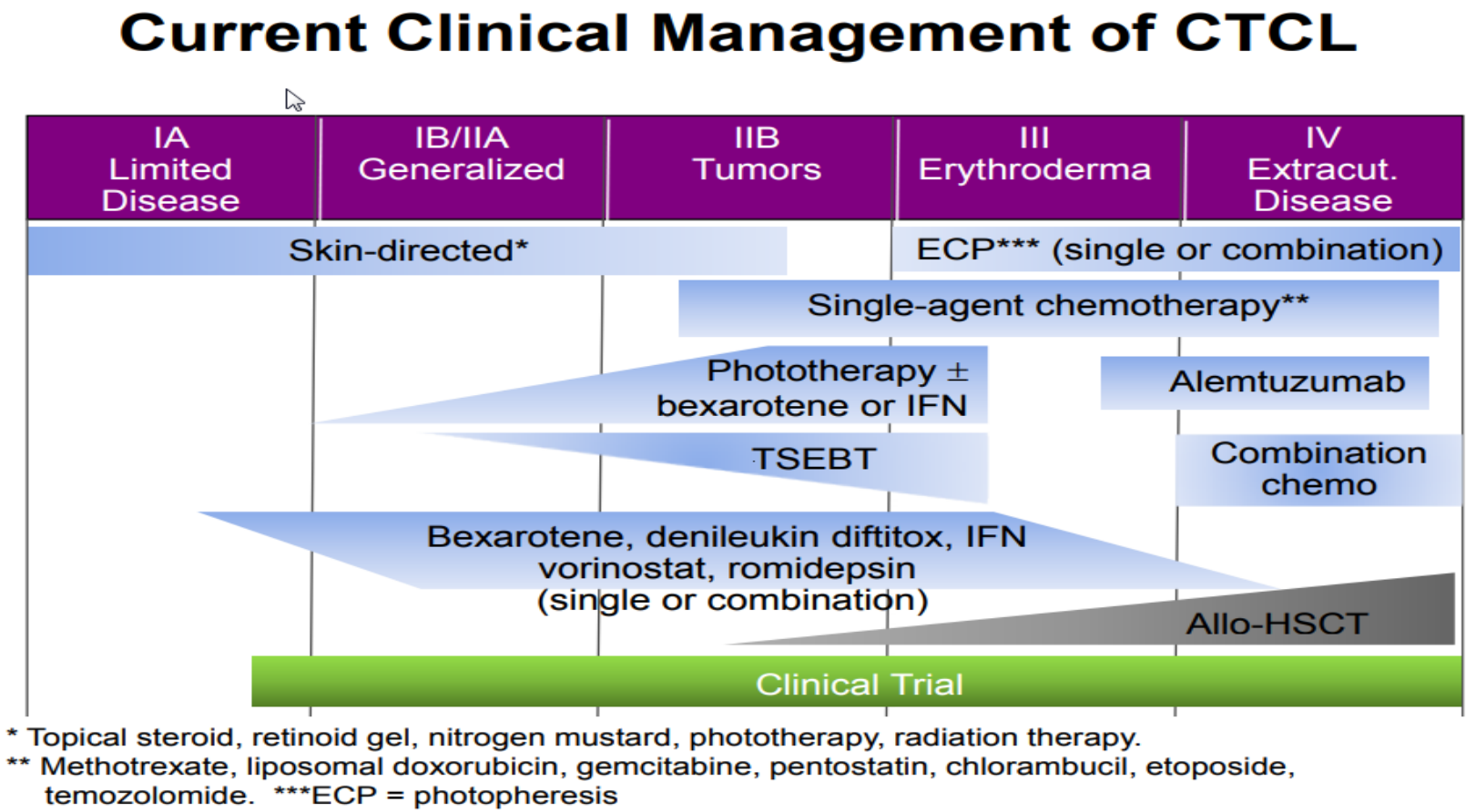
Stage-Directed Management



* Topical steroid, retinoid gel, nitrogen mustard, phototherapy, radiation therapy.
** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, temozolomide. ***ECP = photopheresis

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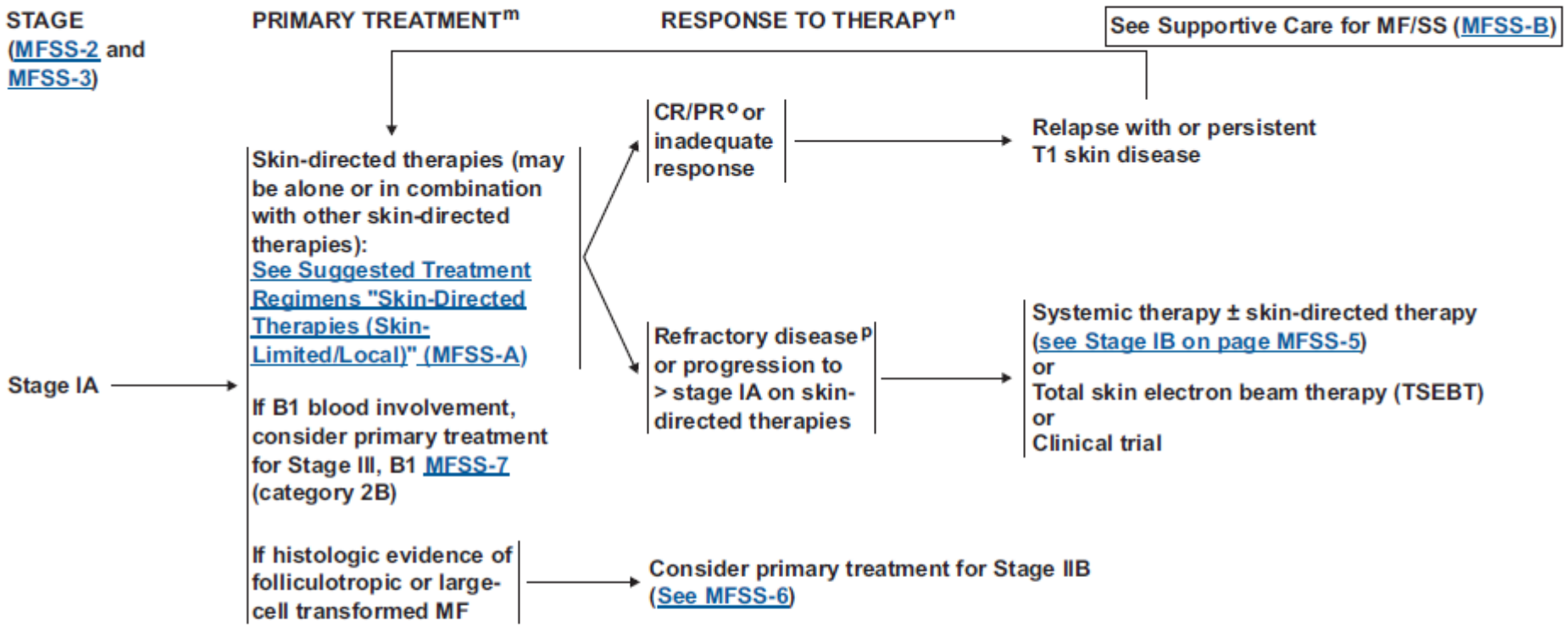

[m]It is preferred that treatment occur at centers with expertise in the management of the disease.

[n]Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o]Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p]Refractory or intolerant to multiple previous therapies.

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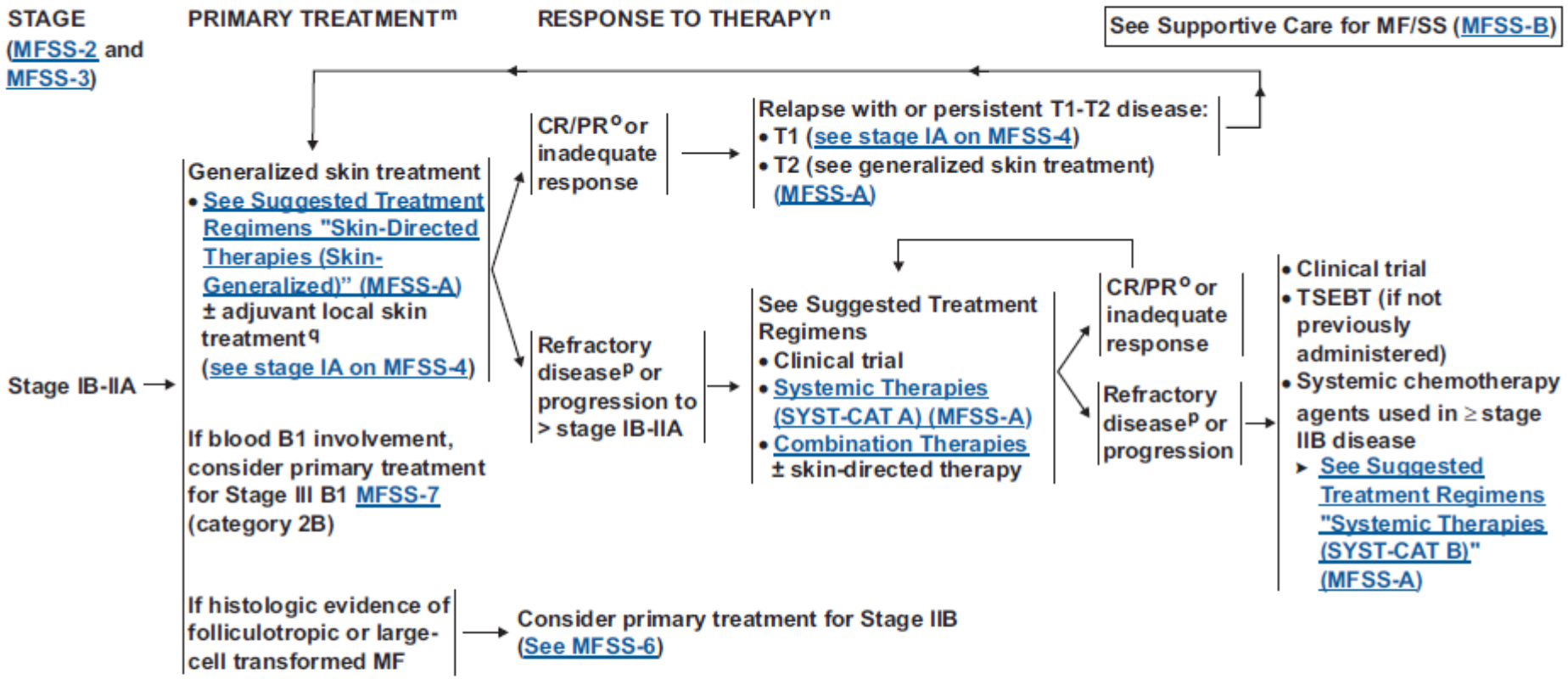

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[q]For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.

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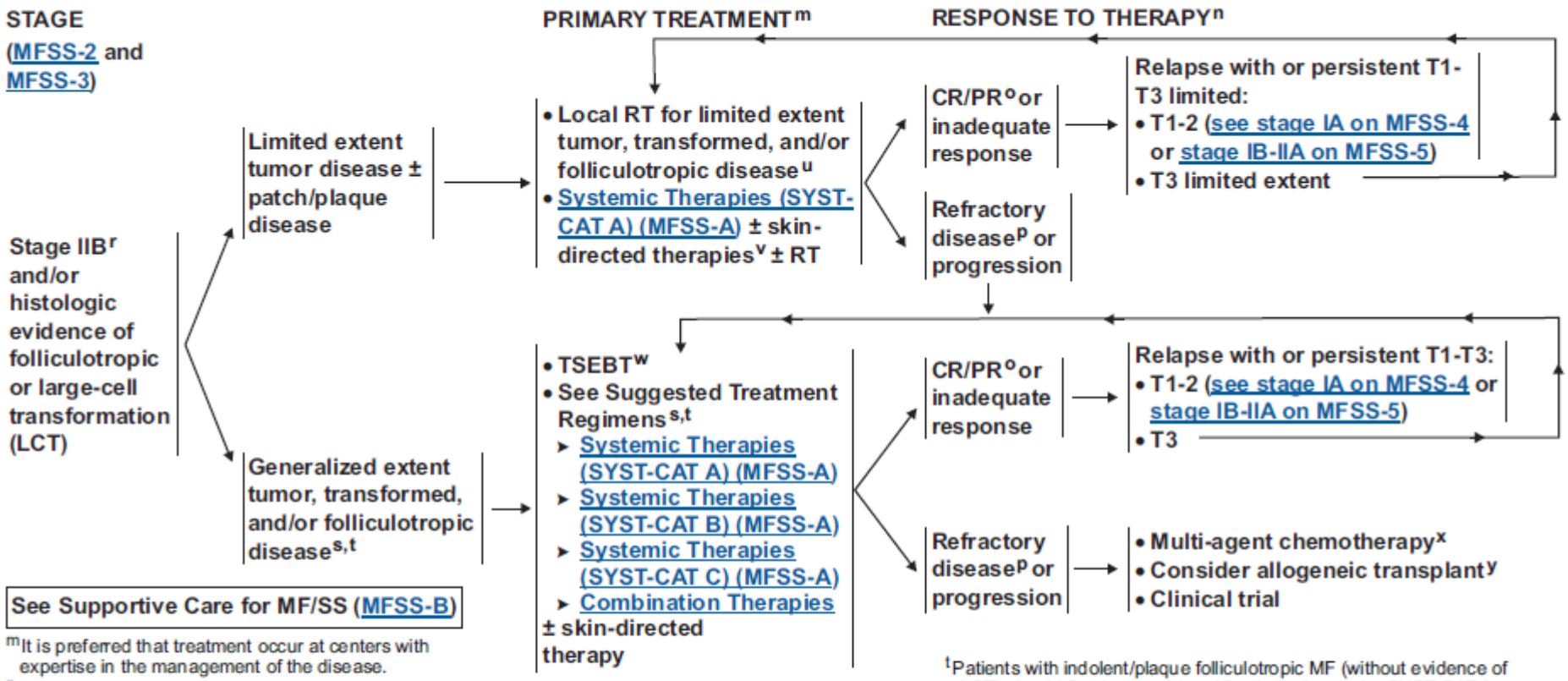

See Supportive Care for MF/SS (MFSS-B)

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[p] Refractory or intolerant to multiple previous therapies.

[r] Rebiopsy if suspect large cell transformation.

[s] Histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[t] Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST CAT B or SYST CAT C.

[u] For non-radiated sites, see Stage I-IIA. After patient is rendered disease free by RT, may consider adjuvant systemic biologic therapy (SYST-CAT A) after RT to improve response duration.

[v] Skin-directed therapies are for patch or plaque lesions and not for tumor lesions.

[w] May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

[x] Most patients are treated with multiple SYST-CAT A/B or combination therapies before receiving multiagent chemotherapy.

[y] The role of allogeneic HSCT is controversial. See Discussion for further details.

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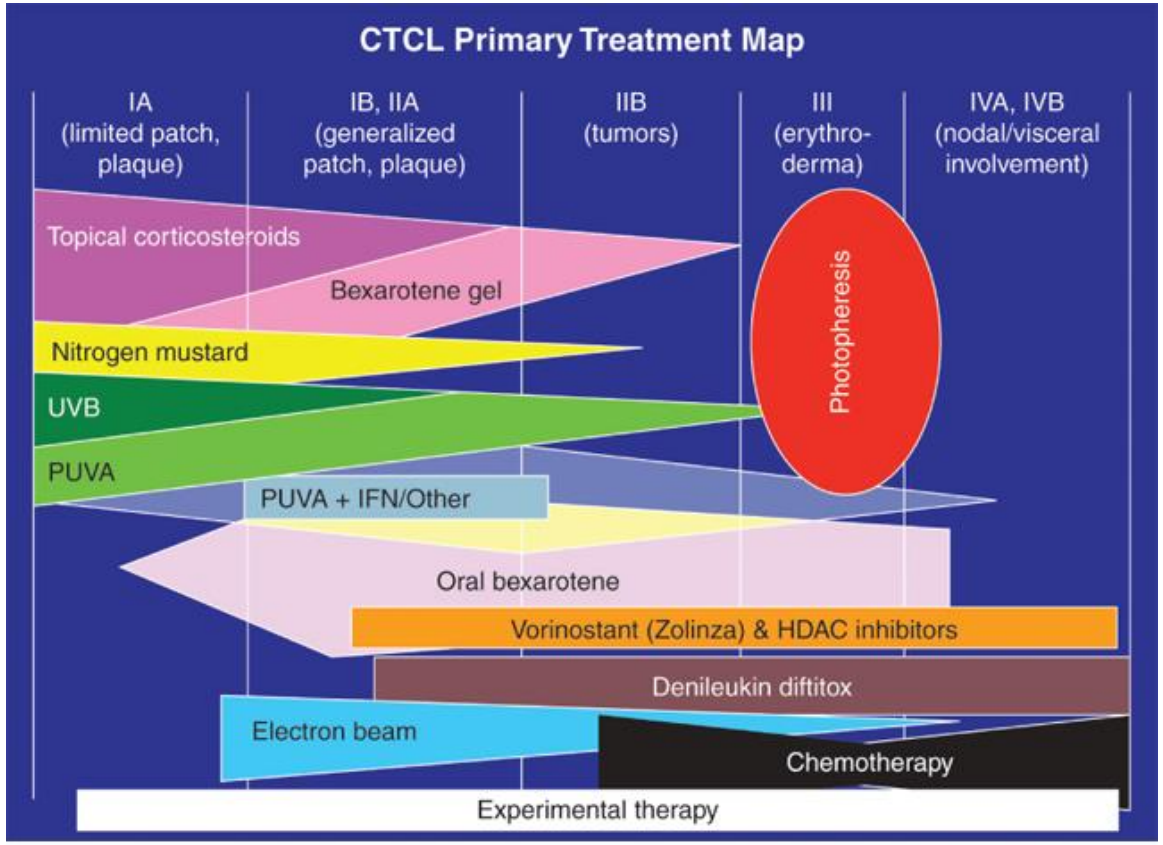

Source: Hagop M. Kantarjian, Robert A. Wolff: The MD Anderson Manual of Medical Oncology, 3rd Edition
www.accessmedicine.com

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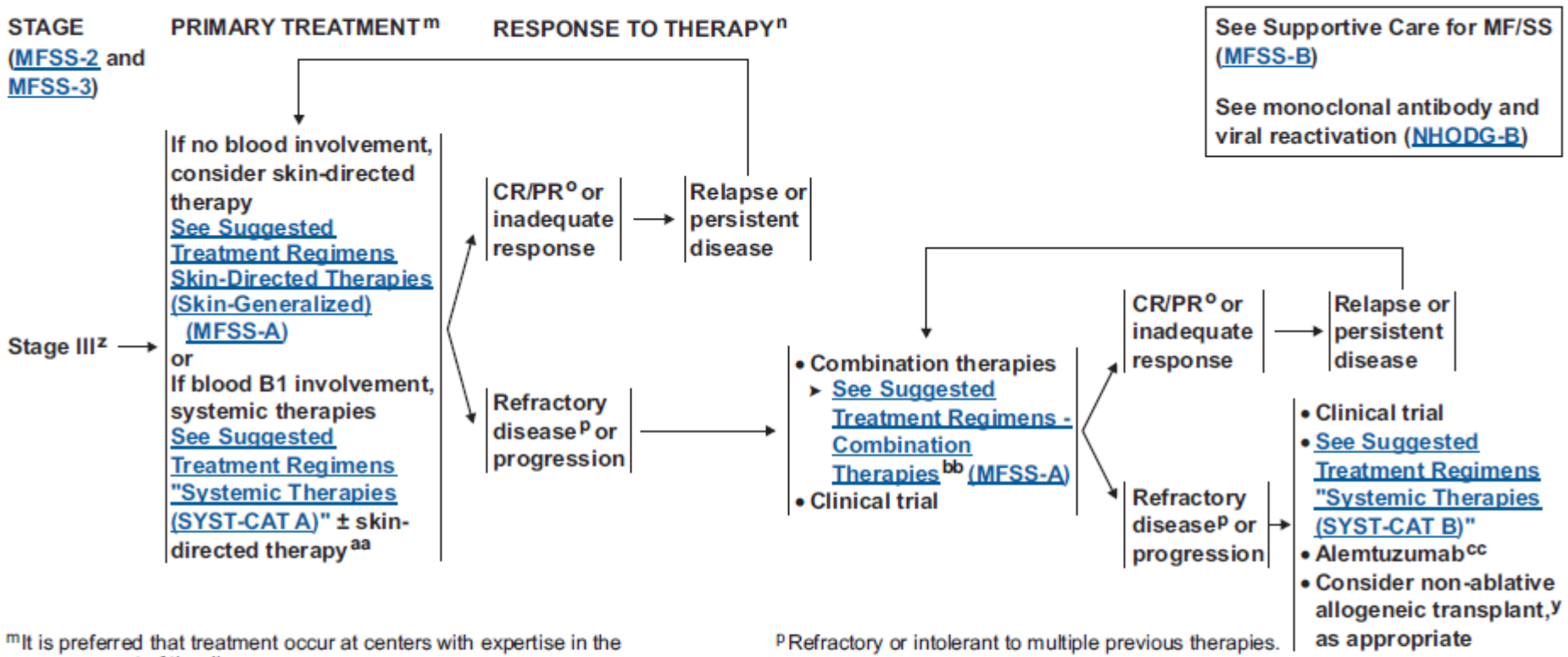

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[p] Refractory or intolerant to multiple previous therapies.

[y] The role of allogeneic HSCT is controversial. See discussion for further details.

[z] Generalized skin-directed therapies (other than topical steroids) may not be well-tolerated in stage III and should be used with caution. Phototherapy (PUVA or UVB) or TSEBT can be used successfully.

[aa] Mid-potency topical steroids should be included (± occlusive modality) with any of the primary treatment modalities to reduce skin symptoms. Erythrodermic patients are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.

[bb] Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

[cc] Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

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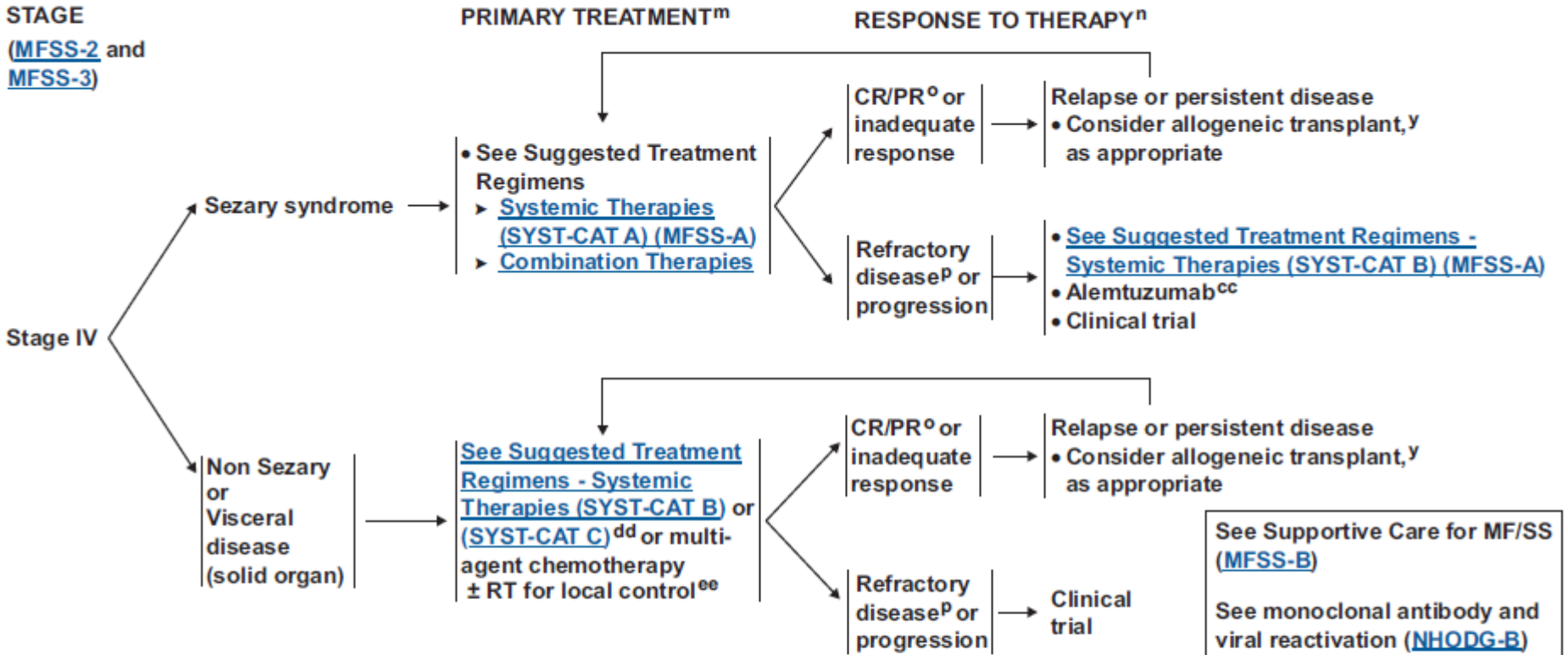

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[dd] Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[ee] Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.

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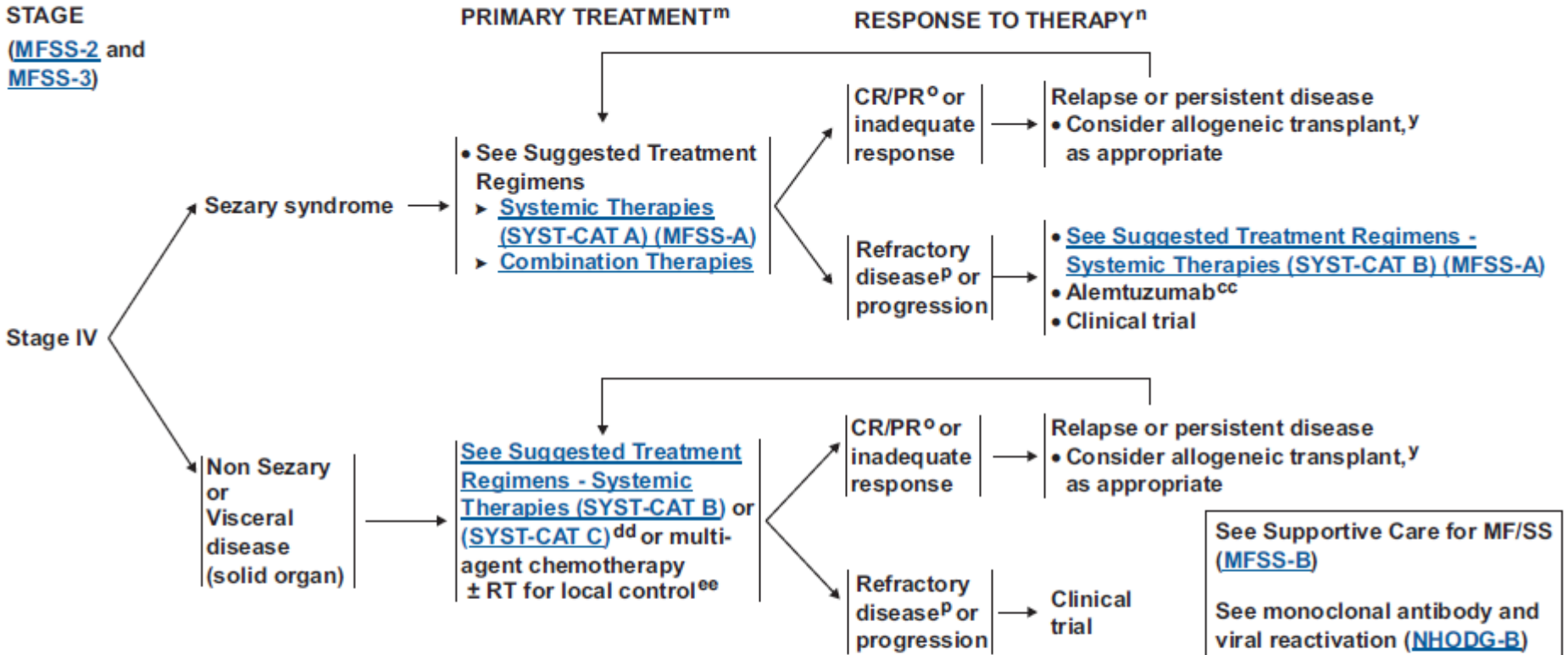

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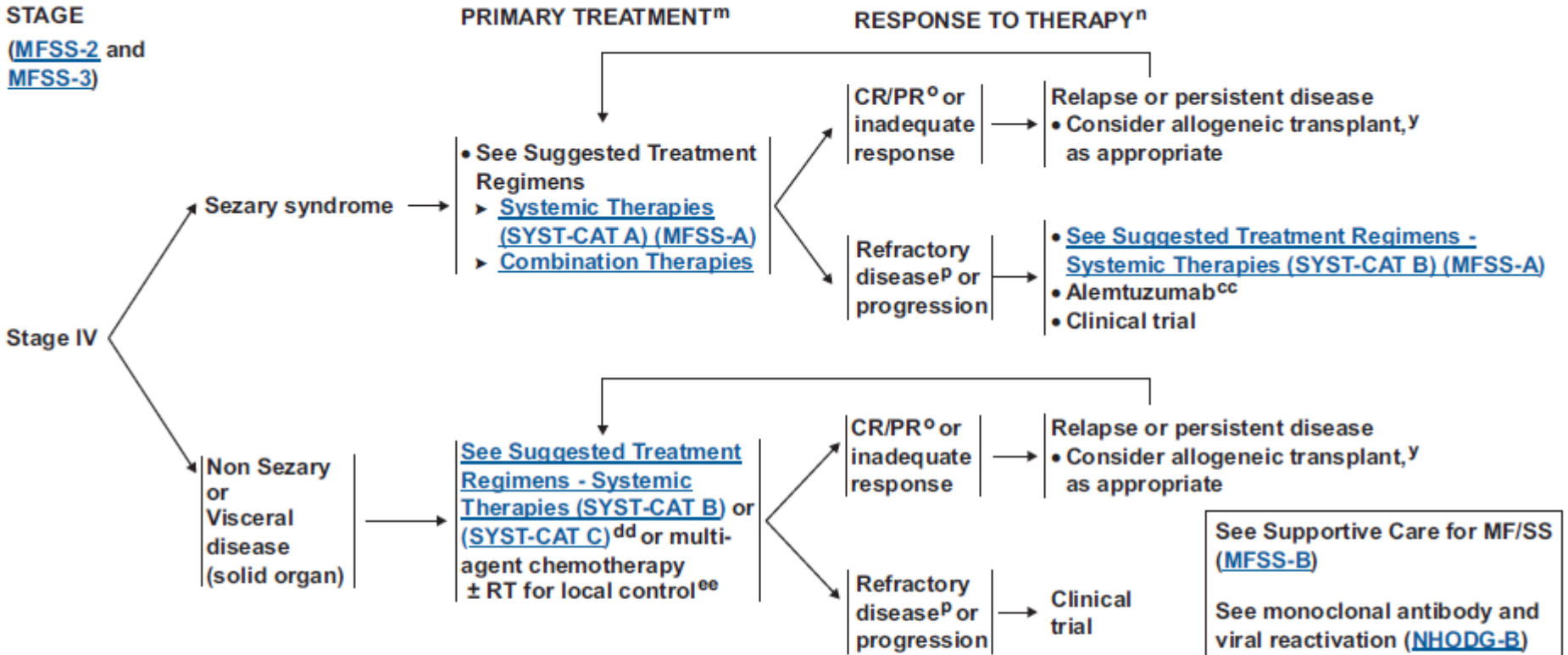
Discussion



[m] It is preferred that treatment occur at centers with expertise in the management of the disease.

[n] Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

[y] The role of allogeneic HSCT is controversial. See discussion for further details.

[cc] Lower doses of alemtuzumab administered subcutaneously has shown lower incidence of infectious complications.

[dd] Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[ee] Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

Systemic Therapies Continued

Vorinostat
Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39.
Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115.
Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416.

Romidepsin
Piekarz RL, Frye R, Turner M, et al. Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma. J Clin Oncol 2009;27:5410-5417.
Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010; 28:4485-4491.

Extracorporeal photopheresis (ECP)
Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med 1987;316:297-303.
Zic JA, Stricklin GP, Greer JP, et al. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. J Am Acad Dermatol 1996;35:935-945.

Methotrexate
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Liposomal doxorubicin
Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer 2003;98:993-1001.
Quereux G, Marques S, Nguyen J-M, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol 2008;144:727-733.

Gemcitabine
Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2006;7(1):51-58.
Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. Cancer 2005;104:2437-2441.
Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol 2000;18:2603-2606.
Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2010;21:860-863.
Awar O, Duvic M. Treatment of transformed mycosis fungoides with intermittent low-dose gemcitabine. Oncology 2007;73:130-135.

Pentostatin
Cummings FJ, Kim K, Neiman RS, et al. Phase II trial of pentostatin in refractory lymphomas and cutaneous T-cell disease. J Clin Oncol 1991;9:565-571.

Temozolomide
Tani M, Fina M, Alinari L, Stefoni V, Baccarani M, Zinzani PL. Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma. Haematologica 2005;90(9):1283-1284.
Querfeld C, Rosen ST, Guitart J, et al. Multicenter phase II trial of temozolomide in mycosis fungoides/sezary syndrome: correlation with O^6-methylguanine-DNA methyltransferase and mismatch repair proteins. Clin Cancer Res 2011;17:5748-5754.

Bortezomib
Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297.

Low-dose Pralatrexate
Horwitz SM, Duvic M, Kim Y, et al. Pralatrexate is active in cutaneous T-cell lymphoma (CTCL): Results of a multicenter, dose-finding trial [abstract]. Blood 2009;114:Abstract 910.

Pralatrexate
O'Connor O, Pro B, Pinter-Brown L, et al. PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) [abstract]. J Clin Oncol 2009;27:Abstract 8561.

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SUGGESTED TREATMENT REGIMENS
References

Combination Therapies

Skin-directed + Systemic

Rupoli S, Goteri G, Pulini S, et al. Long term experience with low dose interferon alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol 2005;75:136-145.

Kuzel TM, Roenigk HH Jr, Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. J Clin Oncol 1995;13:257-263.

McGinnis KS, Shapiro M, Vittorio CC, et al. Psoralen plus long wave UV A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T cell lymphoma. Arch Dermatol 2003;139:771-775.

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Stadler R, Otte H-G, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon alpha -2a plus acitretin versus interferon alpha -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998;92:3578-3581.

Systemic + Systemic

Foss F, Demierre MF, DiVenuti G. A phase 1 trial of bexarotene and denileukin diftitox in patients with relapsed or refractory cutaneous T cell lymphoma. Blood 2005;106:454-457.

Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa 2b (Intron A) for patients with cutaneous T cell lymphoma. Cancer 2007;109:1799-1803.

Talpur R, Ward S, Apisarnthanarax N, Breuer Mcham J, Duvic M. Optimizing bexarotene therapy for cutaneous T cell lymphoma. J Am Acad Dermatol 2002;47:672-684.

Suchin KR, Cucchiara AJ, Gottleib SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol. 2002;138:1054-1060.

Richardson SK, Lin JH, Vittorio CC, et al. High clinical response rate with multimodality immunomodulatory therapy for Sezary syndrome. Clin Lymphoma Myeloma 2006;7:226-232.

Allogeneic stem cell transplant

Duarte RF, Canals C, Onida F, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: A retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010;28:4492-4499.

Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant 2008;41:597-604.

Duvic M, Donato M, Dabaja B, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol 2010;28:2365-2372.

Molina A, Zain J, Arber DA, et al. Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. J Clin Oncol 2005;23:6163-6171.

Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant 2009;15:982-990.

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SUPPORTIVE CARE FOR MF/SS

Pruritus

- Assessment
  - Pruritus should be assessed at each visit using consistent measurements
  - Generalized pruritus and localized pruritus should be distinguished
  - Correlation between sites of disease and localization of pruritus should be noted
  - Other potential causes for pruritus should be ruled out

- Treatment
  - Moisturizers, emollients, and barrier protection
  - Topical steroid (appropriate strength for body region) ± occlusion
  - Optimize skin-directed and systemic therapy
  - Topical preparations - camphor/menthol formulations, pramoxine formulations
  - Systemic agents
    - First-line
      - Antihistamines
      - Doxepin
      - Gabapentin
    - Second-line
      - Aprepitant
      - Mirtazapine
      - Selective serotonin reuptake inhibitors
    - Third-line
      - Naltrexone

Infections

- Active or Suspected Infections
  - Erythroderma:
    - Skin swab and nares cultures for Staphylococcus aureus (S. aureus) infection or colonization
    - Intranasal mupirocin
    - Oral dicloxacillin or cephalexin
    - Sulfamethoxazole/trimethoprim, doxycycline if suspect MRSA
    - Vancomycin if no improvement or bacteremia
    - Bleach baths or soaks (if limited area)
  - Ulcerated and necrotic tumors:
    - Gram-negative rods (GNR) common in necrotic tumors may lead to bacteremia and sepsis
    - If high suspicion for infection, obtain blood cultures, start antibiotics even if fever absent
    - Role of wound cultures not clear due to colonization
    - Empirical therapy for both GNR and gram-positive coccal infections is necessary initially
- Prophylaxis
  - Optimize skin barrier protection
  - Mupirocin for S. aureus colonization
  - Bleach baths or soaks (if limited area)
  - Avoid central lines (especially in erythrodermic patients)
  - For patients receiving alemtuzumab, see NHODG-B.

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Patient Centered:
Quality of Life

International Journal of Dermatology

Report

Health-related quality of life in patients with cutaneous T-cell lymphoma?

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Abstract

Background Little is currently known about health-related quality of life (HRQoL) of patients with cutaneous T-cell lymphoma (CTCL), a condition characterized by chronic, pruritic, visible lesions, features which may be uniquely influential.

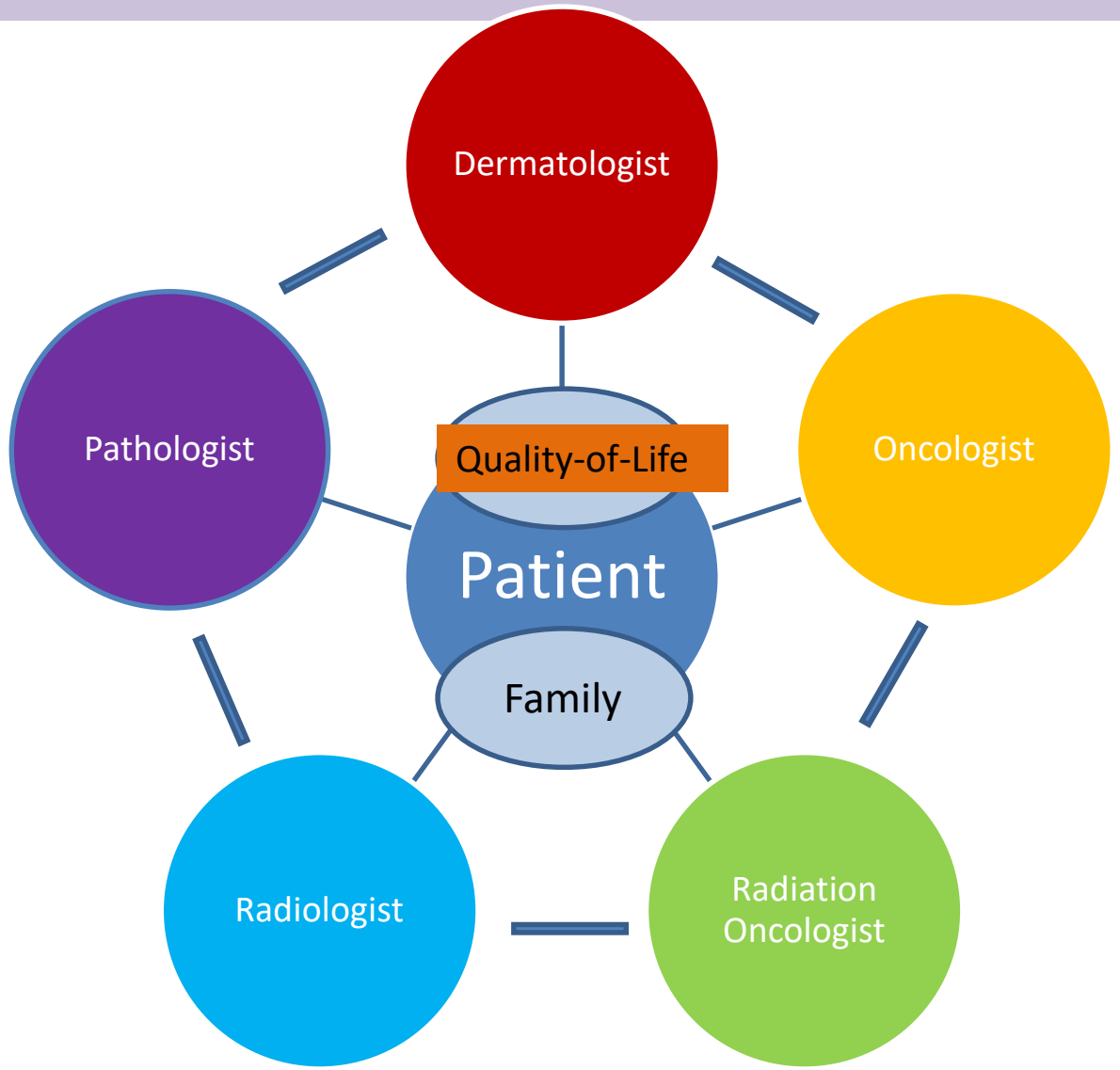
Objective The aim of this study was to establish baseline HRQoL data for patients with CTCL and identify its influencing factors.

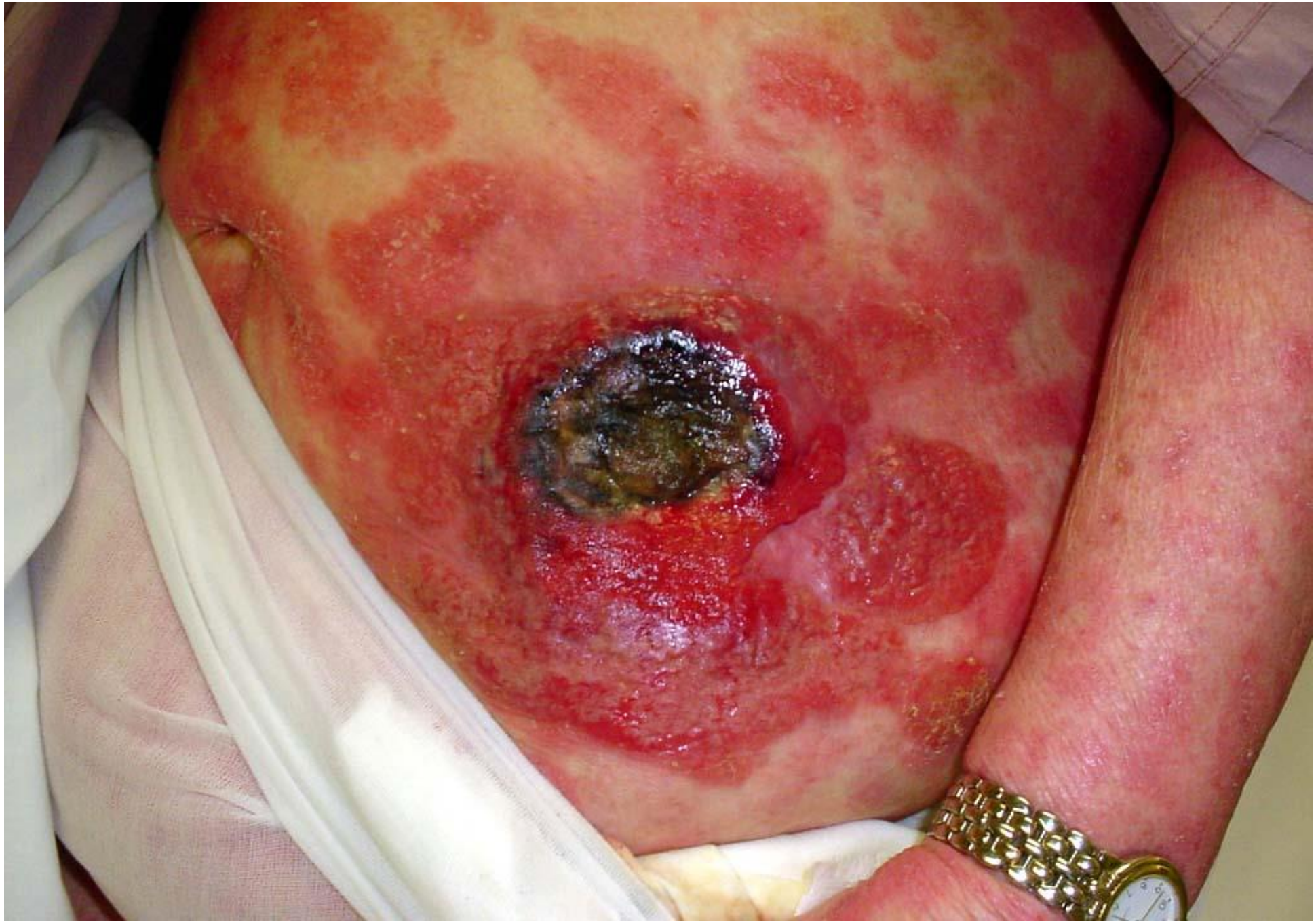
Methods Prospective, nonblinded survey design utilizing questionnaires including panels of QoL indices obtained from 105 patients with mycosis fungoides, Sezary syndrome, and CD30+ lymphoproliferative disorder. Chart review correlated QoL with year of disease onset/diagnosis, type/stage of disease, current/past therapies, and medical/psychiatric diagnoses.

Results Psychiatric condition was significantly associated with symptoms ($P < 0.01$), emotions ($P < 0.01$), and functioning ($P < 0.03$) subscales along with overall composite measure ($P < 0.01$). High-grade systemic therapy (OR = 5.28) showed greater increase in odds of a lower health state than low grade (OR = 1.54). The number of medical comorbidities was significantly related to itching ($P < 0.01$). Increased age was a protective factor with respect to the emotions ($P < 0.01$), functioning ($P < 0.01$), and overall composite ($P < 0.01$) but not predictive of symptoms. Lower income was associated with higher bother on the symptoms subscale.

Conclusions HRQoL in CTCL appears related to a number of factors, including presence of a psychiatric condition, use of systemic (particularly high grade) therapy, number of medical comorbidities, and income.

Patient-Centered, Multidisciplinary Care





Medical Documentation

- 1) ***MYCOSIS FUNGOIDES***
- **Stage**:

- **History**:

- **Work-up**:
- Consultations:

- Bloodwork:
-
- Histopathology:
-
- Radiographic Imaging:

-

- **Treatment**:
- Topical/Intralesional Therapy:
-
- Photo(chemo)therapy/Radiation therapy:
-
- Systemic therapy:
- - Antihistamines:
-
- - Systemic steroids
-
- - Methotrexate

- - Retinoids
-
- - Interferon
-
- - Vorinostat
-
- - Doxil

- - Gemcitabine
-
- - Pentostatin

- - Mogamulizumab

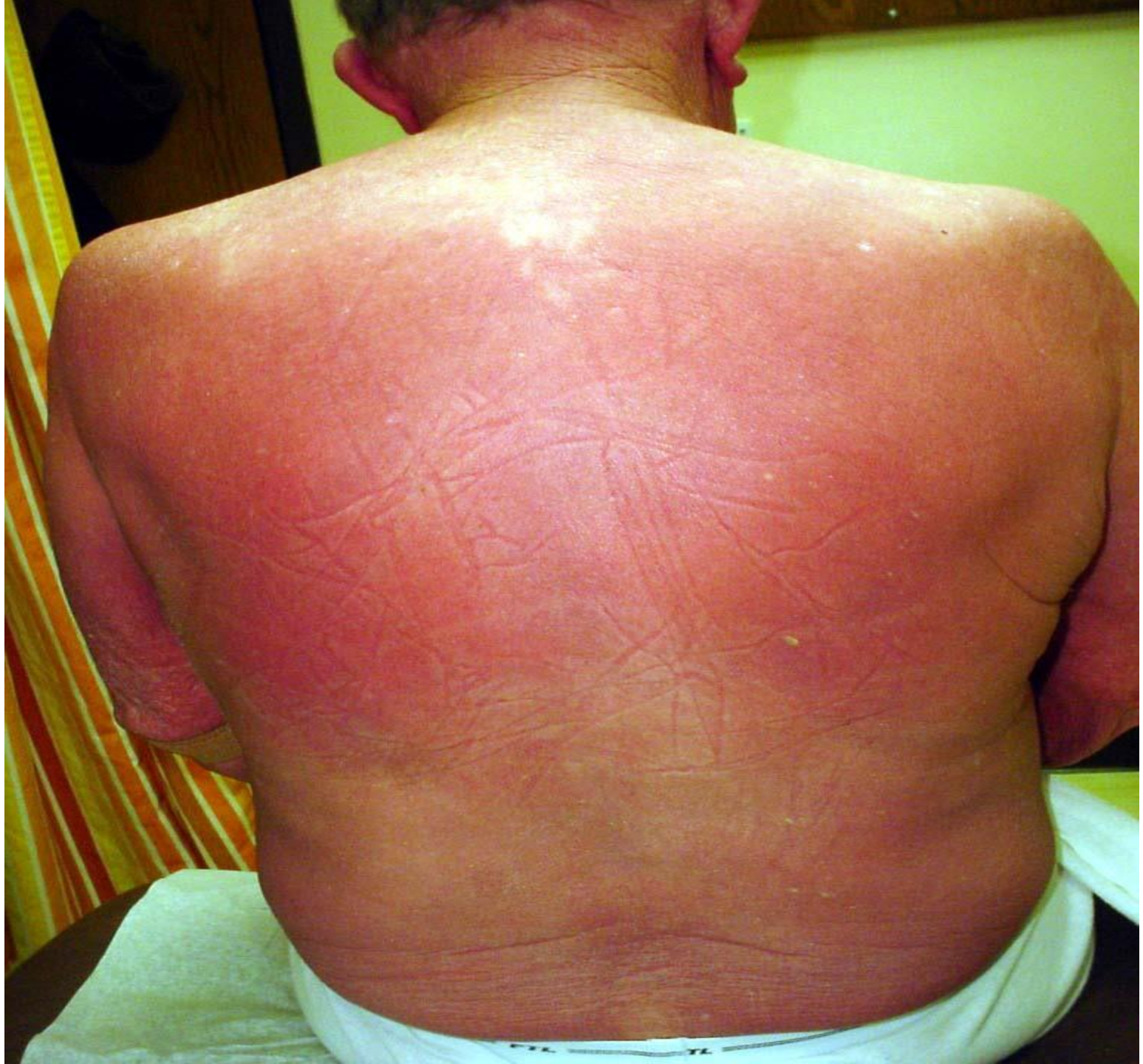
WHY did this happen?

Case observations

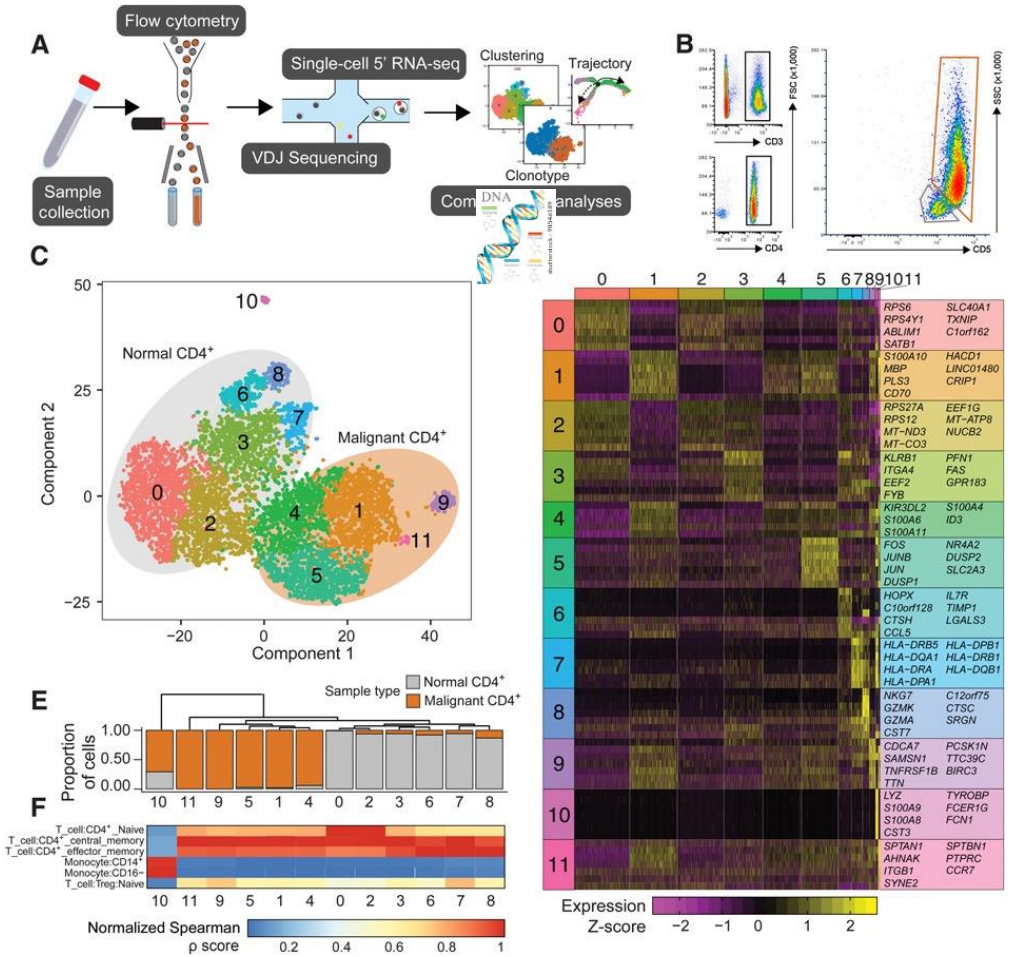
- Presentation
  - Unusual hx?
  - PE?
  - Work-up?
- Therapy

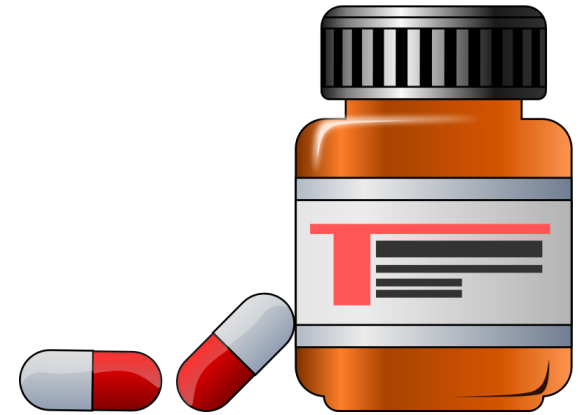
Research questions

- Clinical
- Pathologic
- Therapy



Research Into What Lies Beneath?





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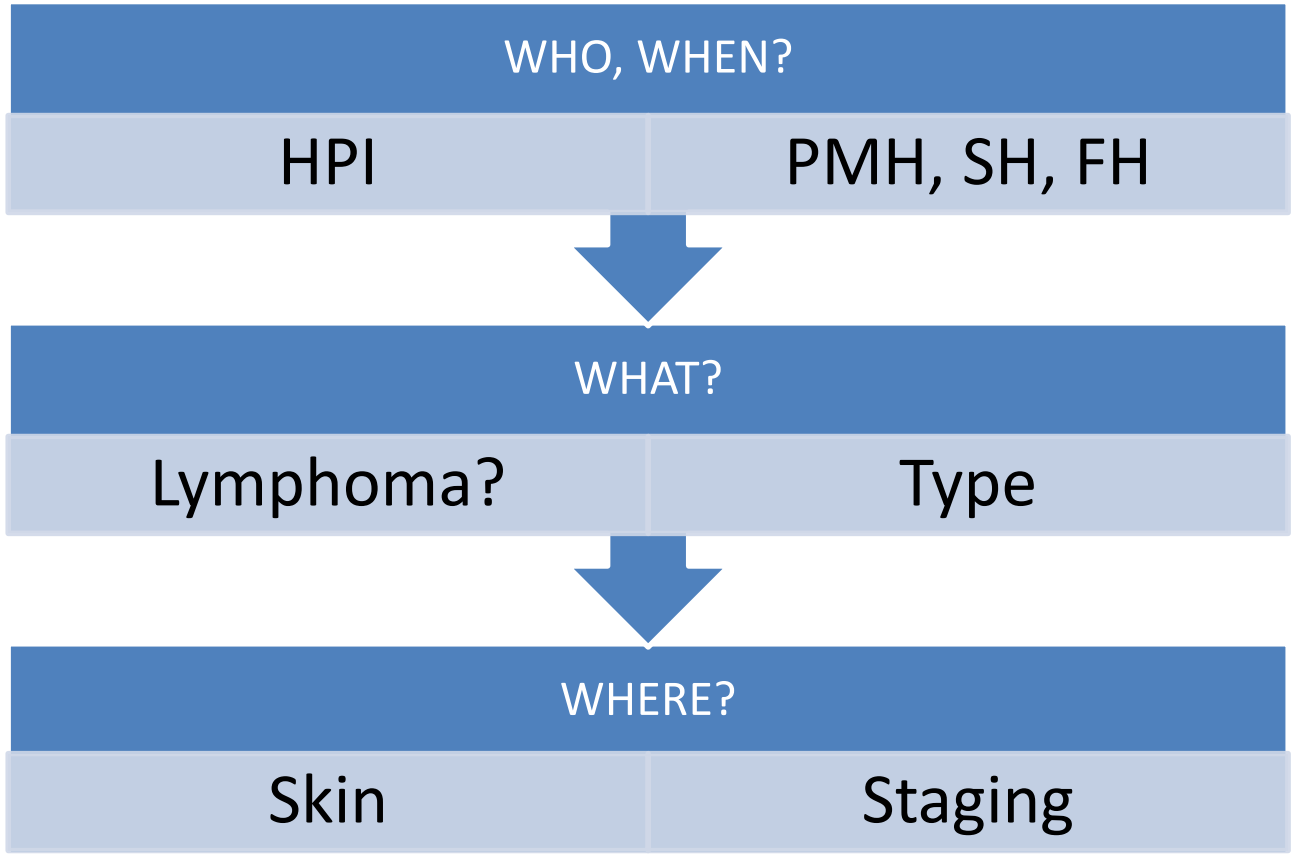
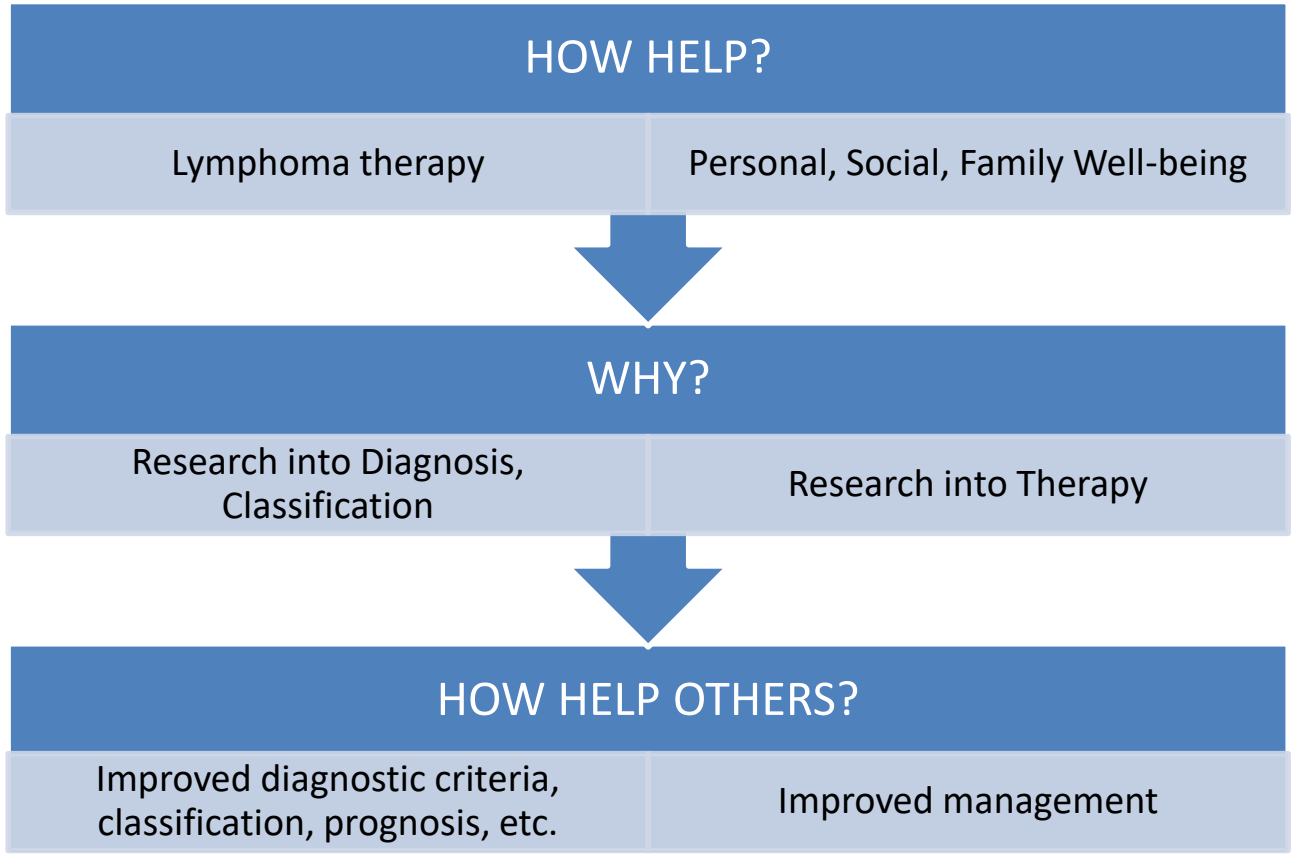

WHO, WHEN?
HPI
PMH, SH, FH
WHAT?
Lymphoma?
Type
WHERE?
Skin
Staging


HOW HELP?
Lymphoma therapy
Personal, Social, Family Well-being
WHY?
Research into Diagnosis, Classification
Research into Therapy
HOW HELP OTHERS?
Improved diagnostic criteria, classification, prognosis, etc.
Improved management

Conclusions

- "Who-What-When-Where-How-Why?" offers a framework to understanding cutaneous T-cell lymphoma (CTCL)
- Clinicopathologic correlation is key to accurate diagnosis and optimal management
- Multidisciplinary care coordination is critical
- Optimal care is patient-centered and addresses quality-of-life issues in decision-making