Penn Medicine

SOUTH BEACH SYMPOSIUM

How to differentiate CTCL

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How to differentiate CTCL

Session goals

CLINICAL-PATH CORRELATION

TOOLS FOR DIAGNOSIS

CTCL & BIOLOGICS

Mycosis fungoides (most common CTCL subtype)

- Rare primary cutaneous T-cell lymphoma (NHL) of skin homing T-cells
- Sporadic
- Scaly patches, plaques in a “bathing trunk distribution”
  - —But many clinicopathologic variants
- Chronic, recurrent
- May progress: tumors, erythroderma
- De novo erythroderma, LAD, keratoderma = Sezary Syndrome
- Early stage indolent course with good prognosis
- Advanced stage worse prognosis, risk of infection/sepsis
- All stages - associated with increased risk of other cancers

MF/SS tumor cell characteristics

Mature T-cells (SALT)

- CD45RO+CD3+CD4+CD7-CD26-
- Can undergo large cell transformation: CD30+/-
- Skin homing chemokine receptors: CCR4 (vs CCR7 in SS)

Th2 skewed (advanced disease)

- IL-4, IL-5, IL-10
- Th1 suppression, eosinophilia, ↑IgE, itch

Th17: IL-17, IL-26

IL-13, IL-31 (itch)

Immunophenotype plasticity, with advanced disease

Acquire cytotoxic phenotype, express gamma/delta TCR

Guenova. Clin Cancer Res. 2013
Singer. J Invest Dermatol. 2013
Geskin. Blood 2015
Watanabe. Sci Transl Med 2015
Durgin. JAAD 2021
Dummer. Nat Rev Dis Primers 2021
Morgenroth. Curr Onc Rep 2023

Common Pathways Affected in CTCL

Cell cycle/apoptosis

- TP53, FAS, TAM, CDKN2A

TCR signalling

- CD28, PLCG1, ZEB1, CTLA4, PRKCQ

NF-kB

- NFkB, CARD 11, TNFRSF1B

JAK/STAT

- JAK1, JAK3, STAT3, STAT5

Epigenetic

- ARID1, DNMT3A, NCOR1, MLL21, KMF2C, SETD1A, MLL3

Current clinical panels not tailored to CTCL

Targetable mutations: no silver bullets

- JAK gain of function mutations < 1% of CTCL
  —Ruxolitinib ORR 20% (Moskowitz. Blood 2021)
- Response to anti-PD1 mAb (pembrolizumab)
  —CBLB deletion

CTCL dx = clinicopathologic correlation

BENIGN REACTIVE SKIN CONDITIONS CAN MIMIC CTCL

CTCL SUBTYPES CAN HAVE SIMILAR HISTOPATHOLOGY

Making a CTCL dx:

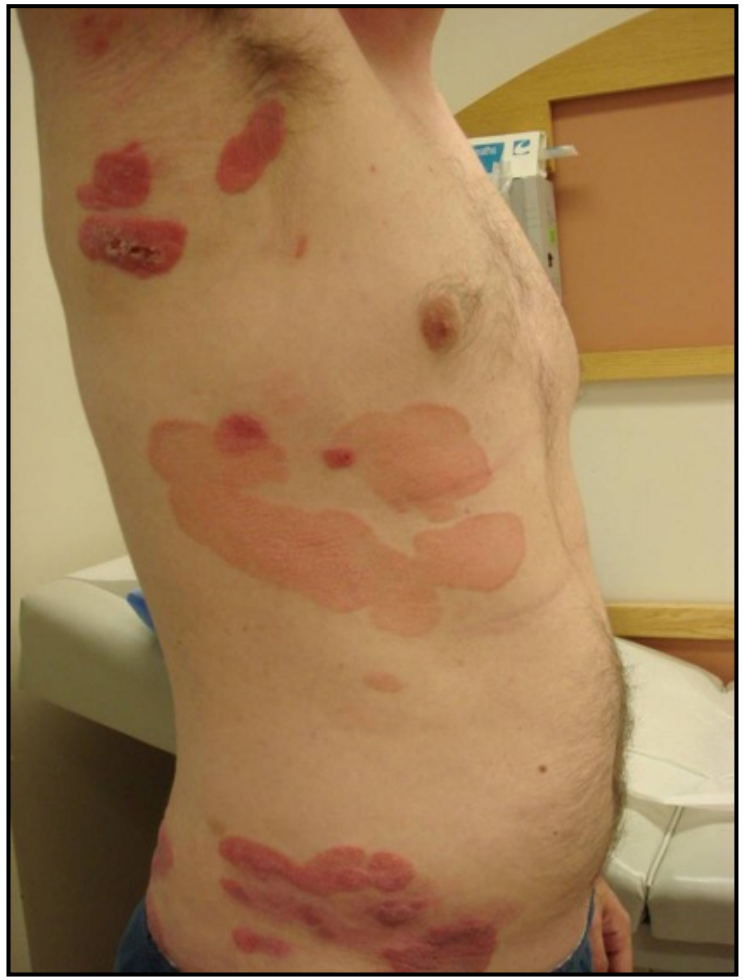
May take months/years/decades

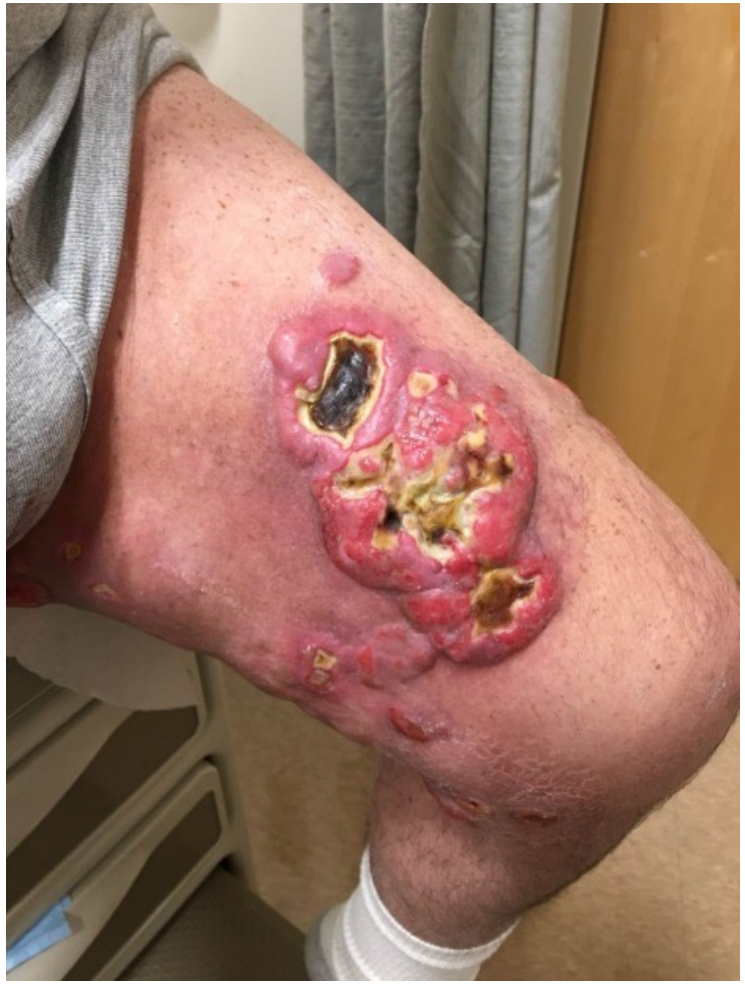
Possible benign chronic “precursors” or associated dx

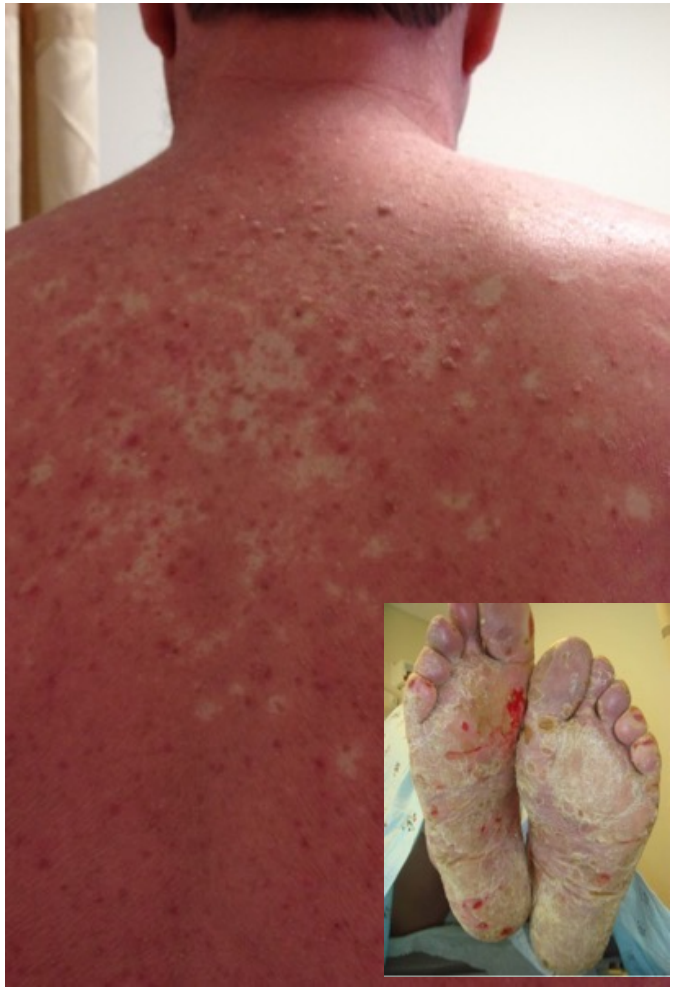
- Large plaque parapsoriasis, digitate dermatosis, PLC, follicular mucinosis, atypical pigmented purpura

Any refractory, worsening dermatitis (MF one of the great imitators)

MF patches, plaques, tumors, erythroderma







MF/CTCL clinical and histologic subtypes

Classic

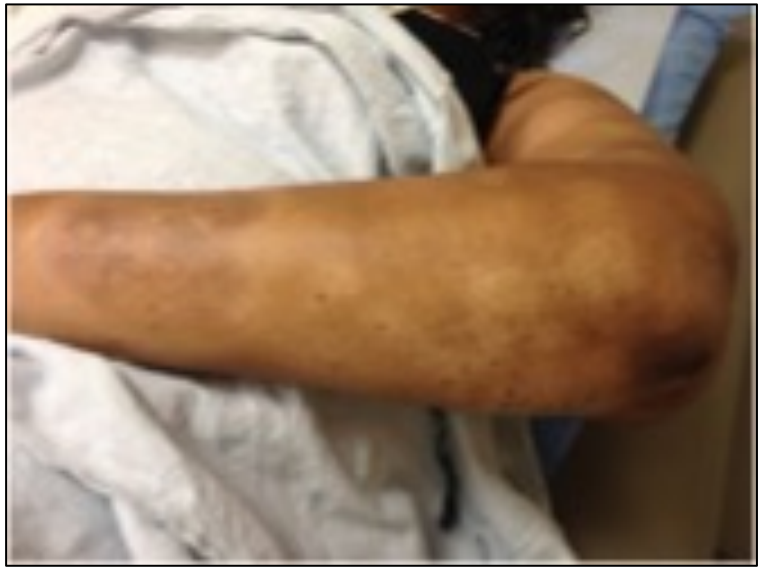
Indolent

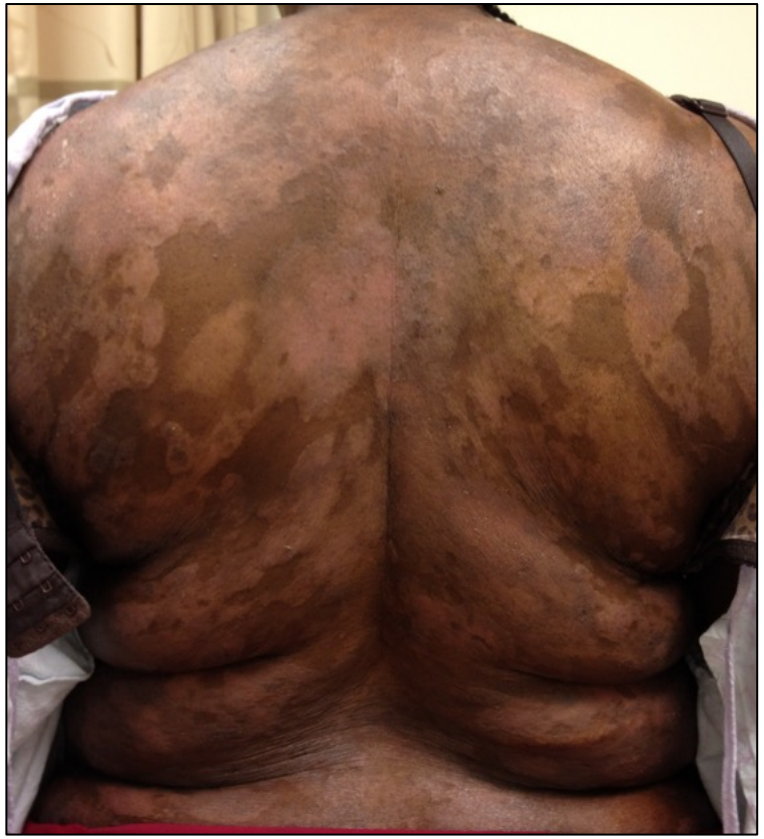
- Hypopigmented, hyperpigmented
- Pigmented purpuric dermatosis like
- Granulomatous, granulomatous slack skin
- Syringotropic, Pagetoid reticulosis, Ichthyosiform
- Palmoplantar, Digitate, Papular, Bullous, Dyshidrotic, Verrucous, Pustular, Poikilodermatous

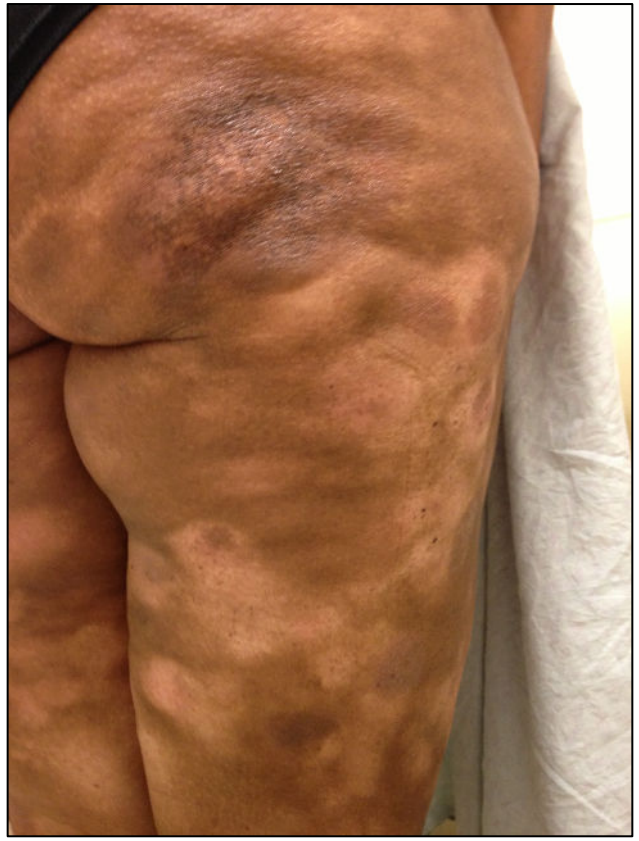
Aggressive

- Erythrodermic
- Folliculotropic (if plaques/tumors)
- Immunophenotype switched
- Large cell transformed (CD30 negative worse than CD30 positive)

MF hypopigmented, hyperpigmented







MF: folliculotropic

5% of all MF cases

Classic: Follicular papules, alopecia mucinosa infiltrated plaques/nodules

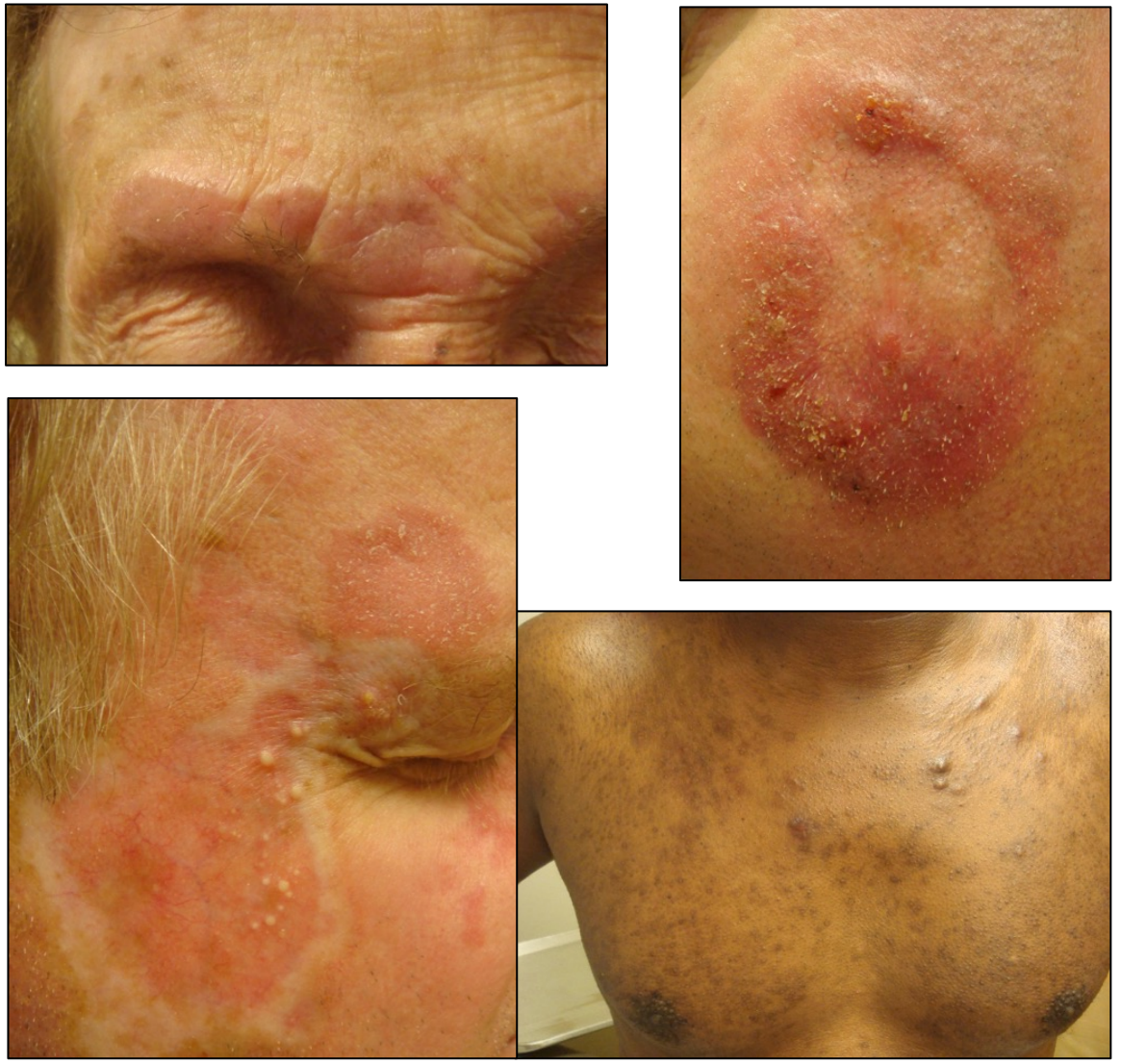
Less common

- Mimic alopecia areata, acneiform lesions, comedones, keratosis pilaris, lichen spinulosa, furunculosis

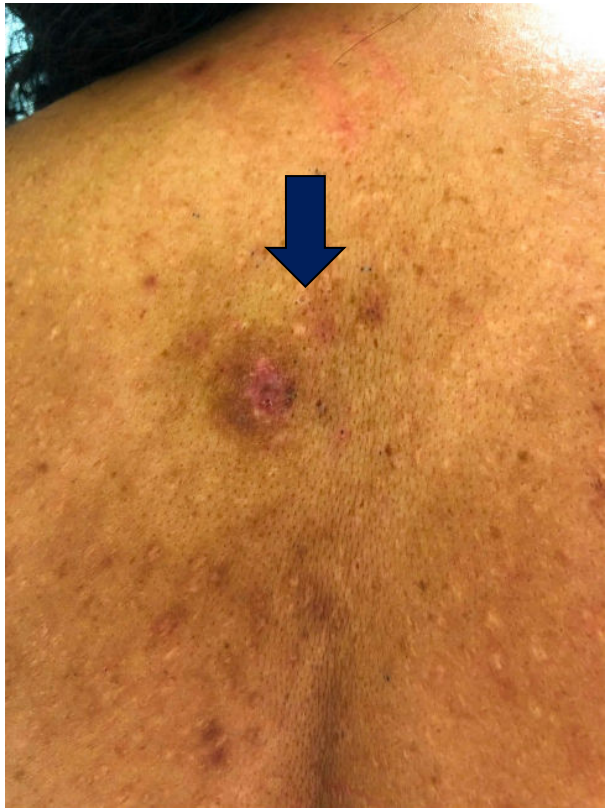
Difficult to treat - depth of infiltrate, pruritus

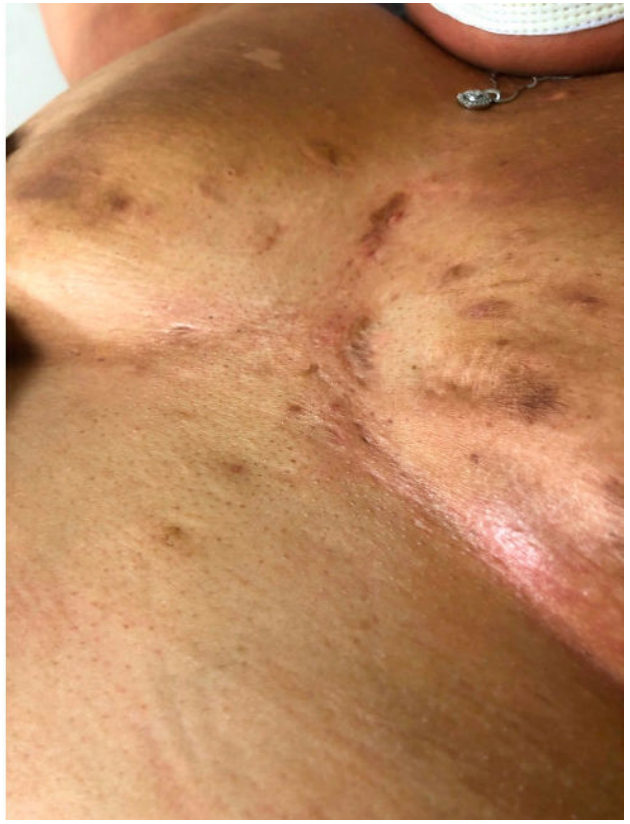
Prognosis = clinical presentation, infiltrate

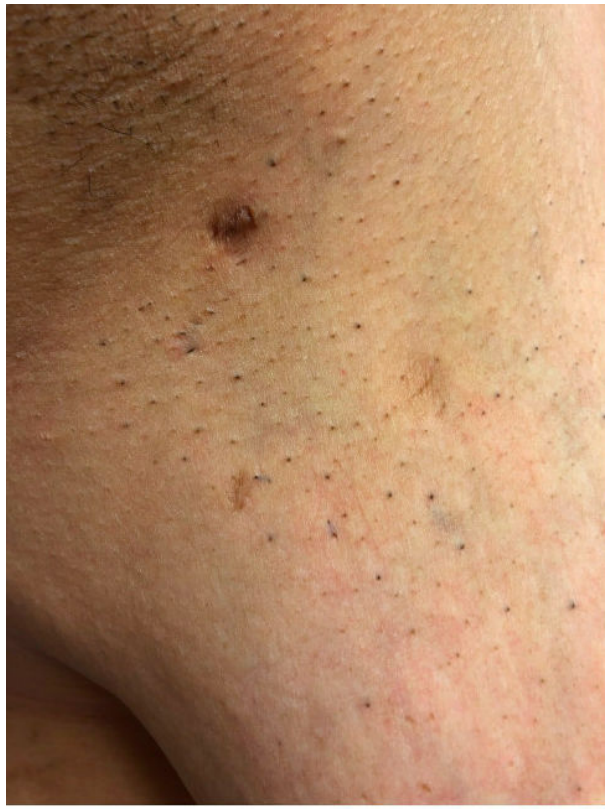
- Van Santen JAMA Dermatol 2016, BJD 2017
- Hodak JAAD 2016

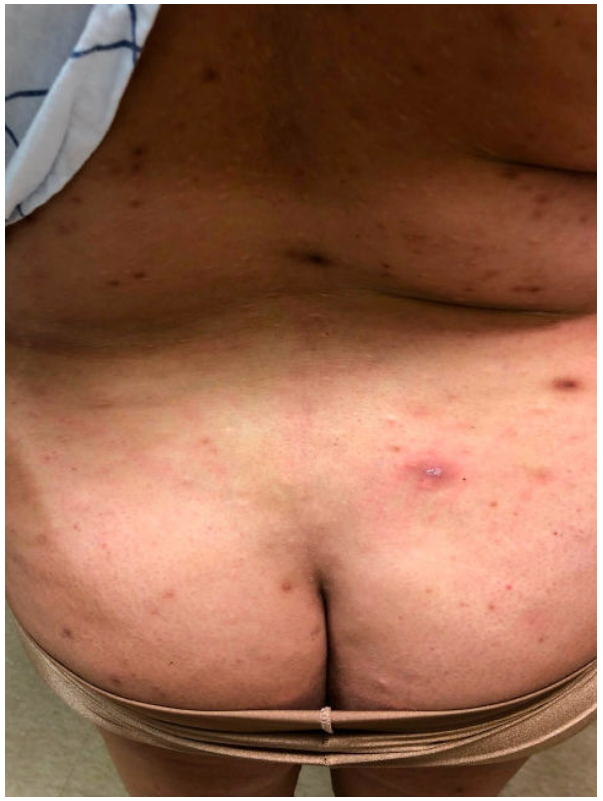


Furuncle, folliculitis, comedones, HS like lesions

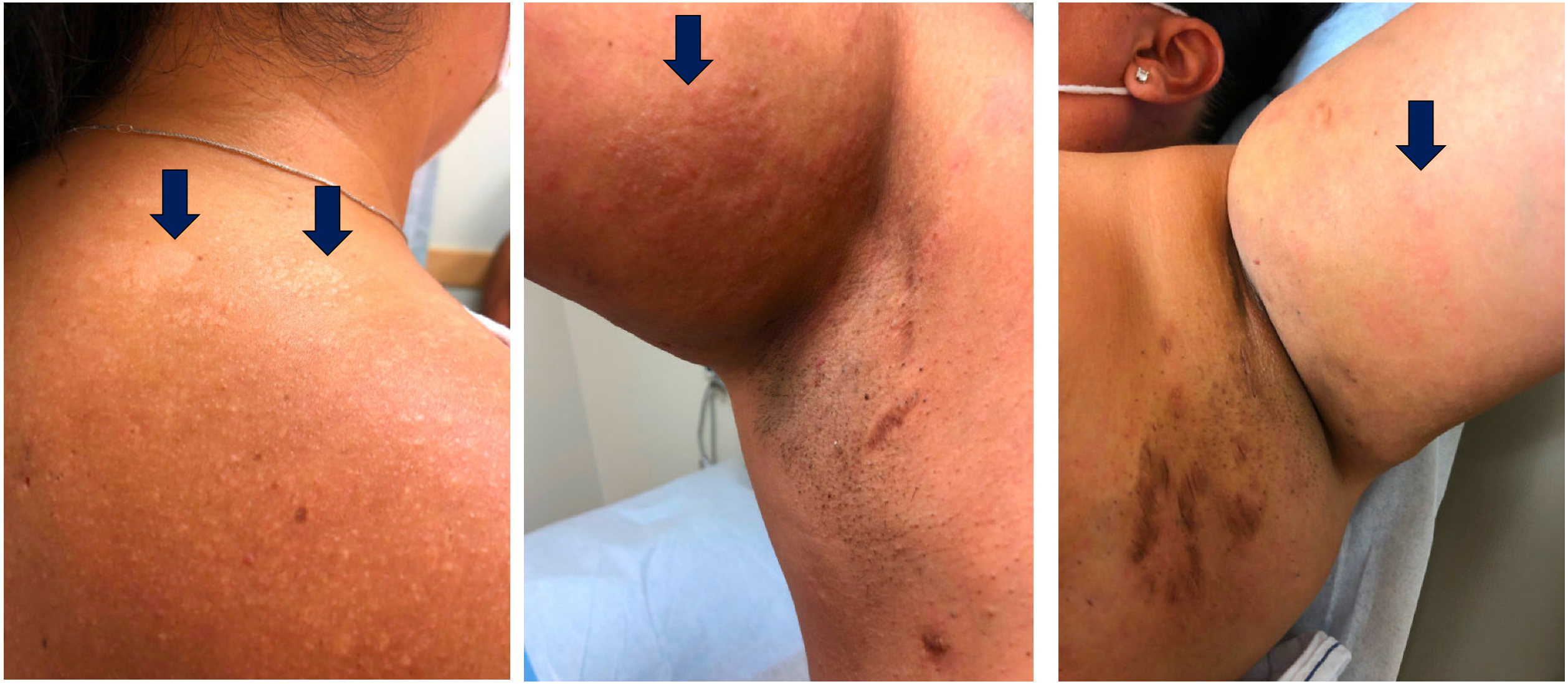






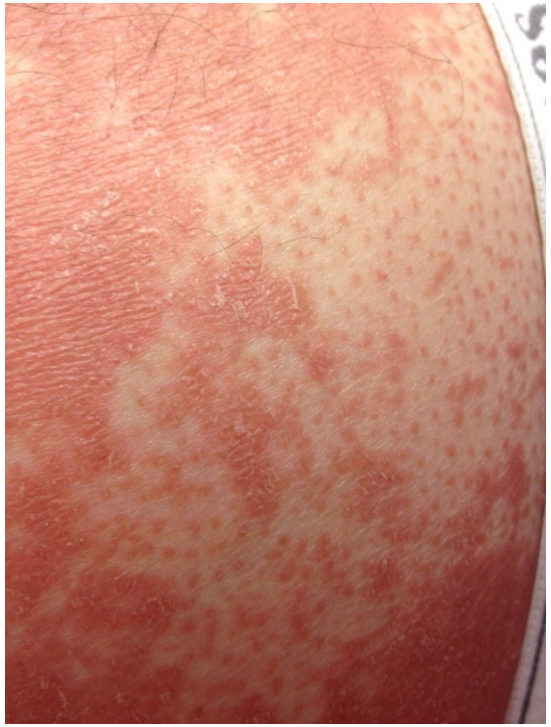


Severe itch “waking her up at night”

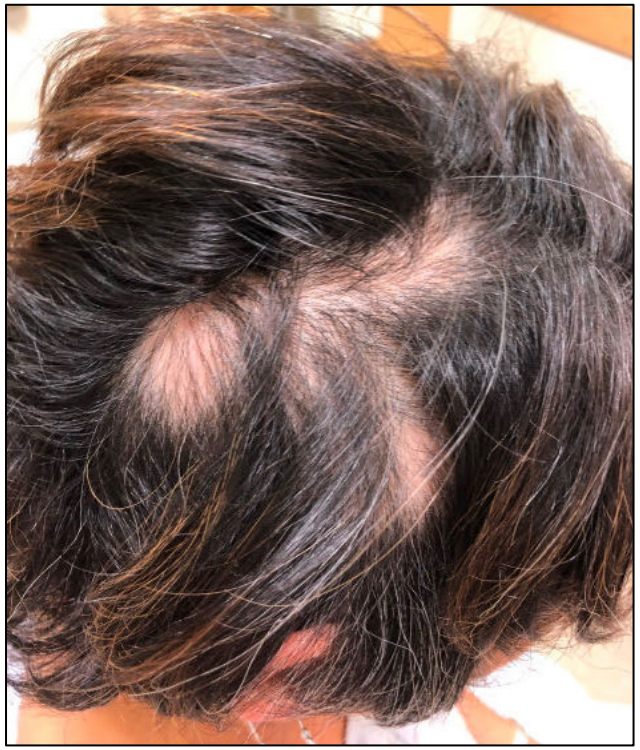


Follicular papules, annular patches → folliculotropic MF

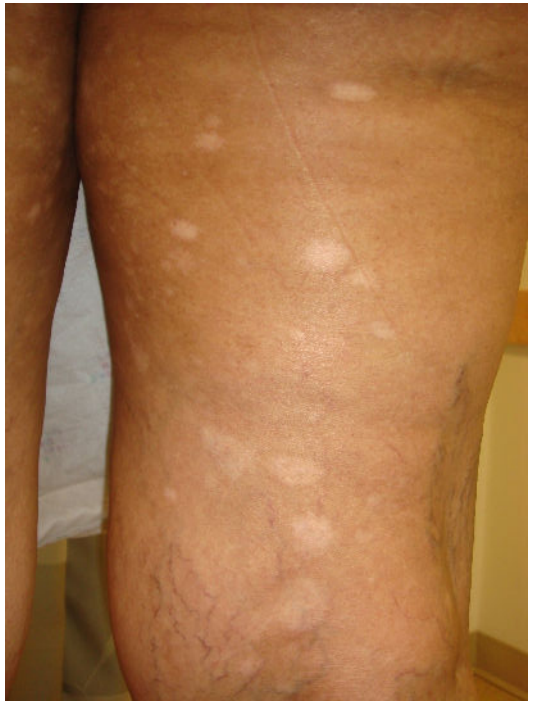
CTCL the great imitator



Pityriasis rubra pilaris



Alopecia areata



Tinea versicolor

Making a CTCL dx: biopsy tips

Biopsy often (off treatment x 2-3 wks)

Patches: broad shave biopsies (more epidermis), multiple lesions

Plaques/tumors/folliculotropic: punch biopsies (for depth)

Before starting systemic rx (anti-TNF, CSA, dupilumab)

Rebiopsy if nondiagnostic and discordant with clinical presentation

BUT early diagnosis of patch MF may not necessarily impact treatment, prognosis and may negatively impact disability/life insurance eligibility

Biopsy read/reviewed by a pathologist with expertise in CTCL dx

Making a CTCL dx: biopsy ancillary tests

Immunohistochemistry on biopsy

- Minimum: CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30
- Others: CD25, CD56, TIA1, granzyme B, TCRb, TCRd, CCR4, CSCL13, ICOS, PD-1

Molecular analysis of clonal TCR gene rearrangements (paraffin block or fresh tissue in Michel's)

- PCR based (TCR-PCR)
- High throughput sequencing of CDR3 region (TCR-HTS) (higher specificity)
- Clonal TCR GR can also be seen in non-malignant conditions

Other useful tests for diagnosis

- Peripheral blood flow cytometry in nondiagnostic extensive patch/erythrodermic pts
- 1/3 of Sezary Syndrome pts will have nondiagnostic skin biopsies.
- HTLV1, 2 Ab (to rule out adult T-cell leukemia/lymphoma which can mimic MF/SS histologically)
- HIV (HIV associated erythroderma can mimic MF/SS, usually CD8+)

Making a CTCL dx:

Clinicopathologic correlation essential

- Histologic overlap between CTCL subtypes
- Reactive inflammation can mimic CTCL
- TCR clonality (false neg/pos)

Beware of single lesion CTCL

- Need to follow patients over time – if they truly have CTCL, they will get other lesions
- Do a full body exam

”Atypical dermatitis” – what to do if CTCL work up negative but clinical suspicion high?

Choose rxs that bridge both dermatitis/psoriasis and CTCL

- Topical/oral steroids
- Phototherapy
- Retinoids
- Low dose oral methotrexate

Monitor closely and rebiopsy (especially if considering dupilumab, other biologics)

Checking blood flow cytometry

Depends on the assay and laboratory – lack of standardization

Minimum: CD3, CD4, CD7, CD8, CD26, TRBC 1

-CD4:CD8 ratio

-aberrant T-cell pop (% lymphocytes and absolute counts)

Commercial labs: standard lymphoma/leukemia panel lacks CD26

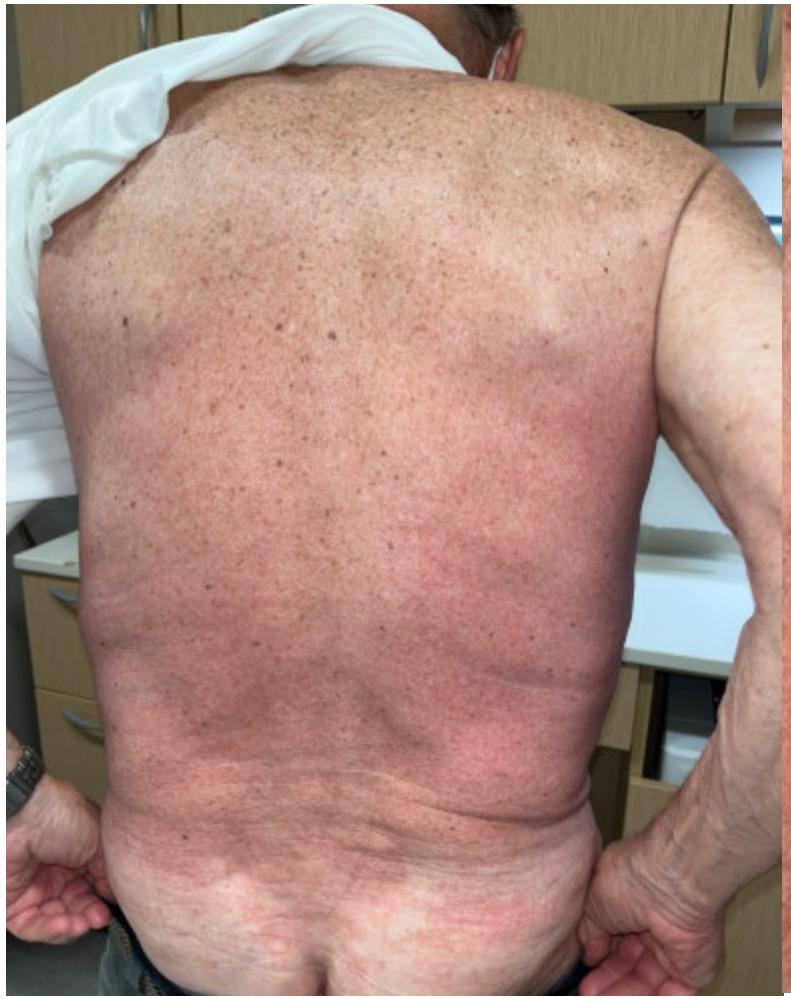
-20% of Sezary pts tumor cells CD7 is intact and only CD26 lost

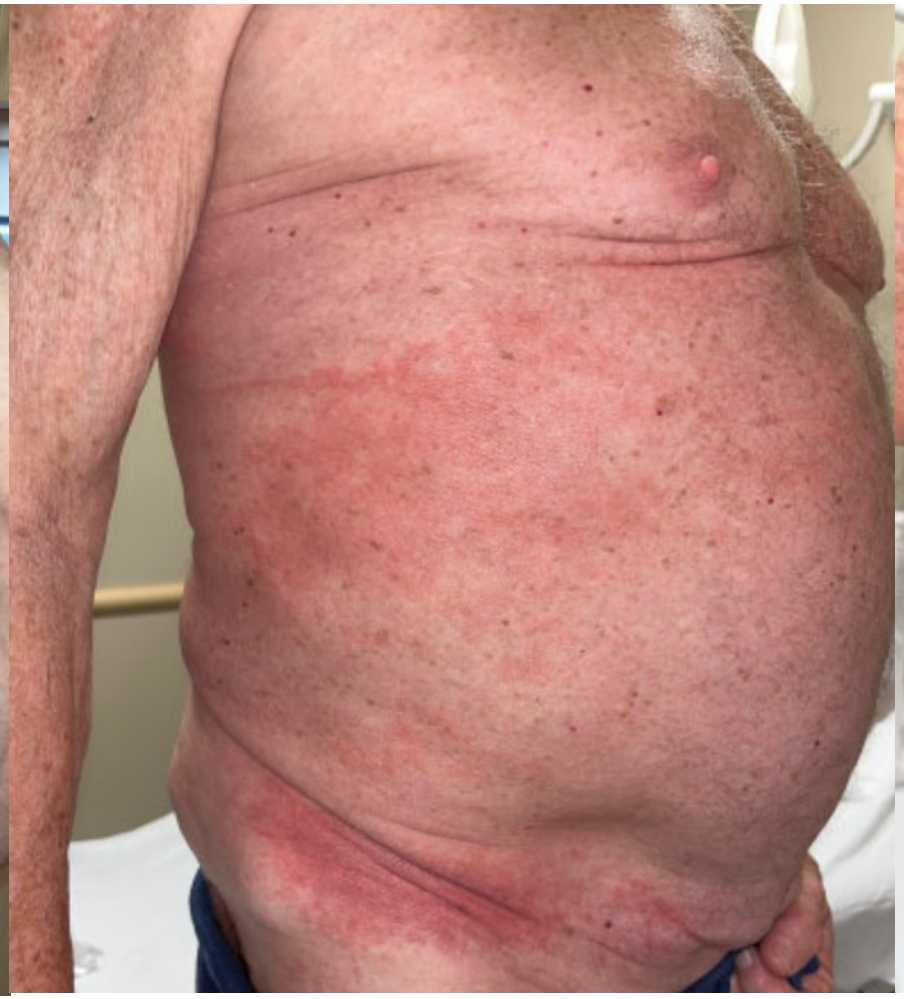
Specialty centers:

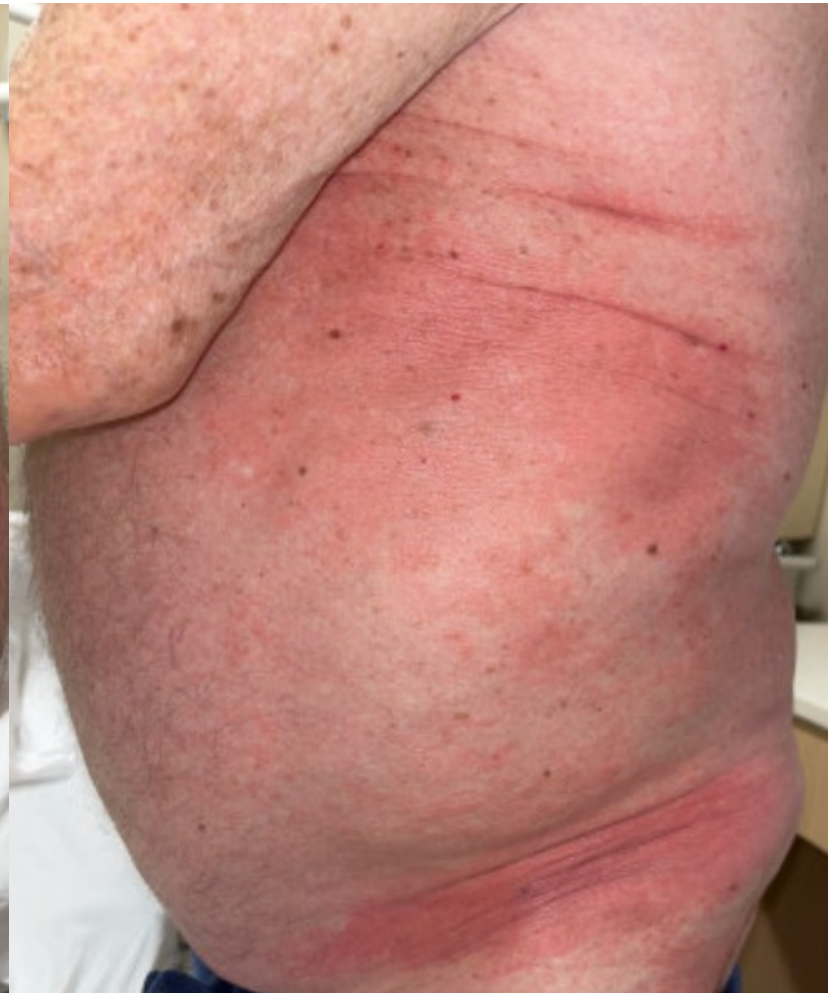
- Vbeta Ab panel (24 Ab covering 70% of T-cell repertoire)
- Higher specificity, labor intensive to run, expensive

Morgenroth. Curr Onc Rep 2023

MF mimicking drug eruption, eczematous



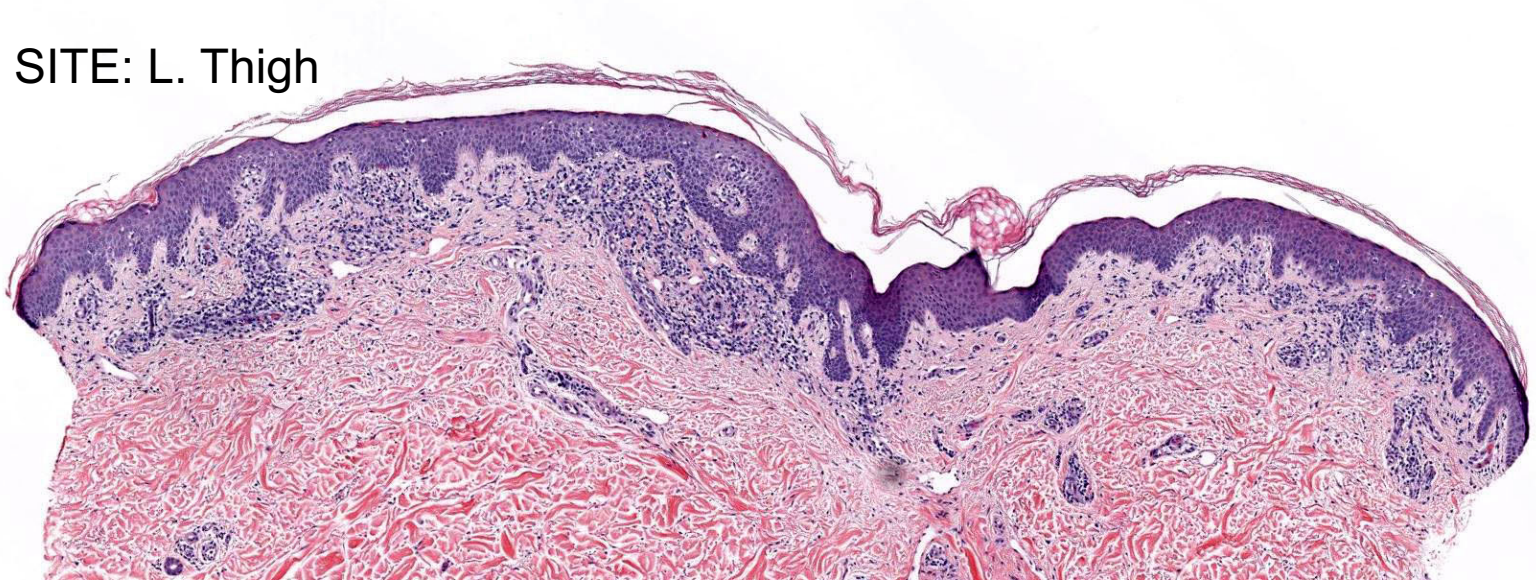


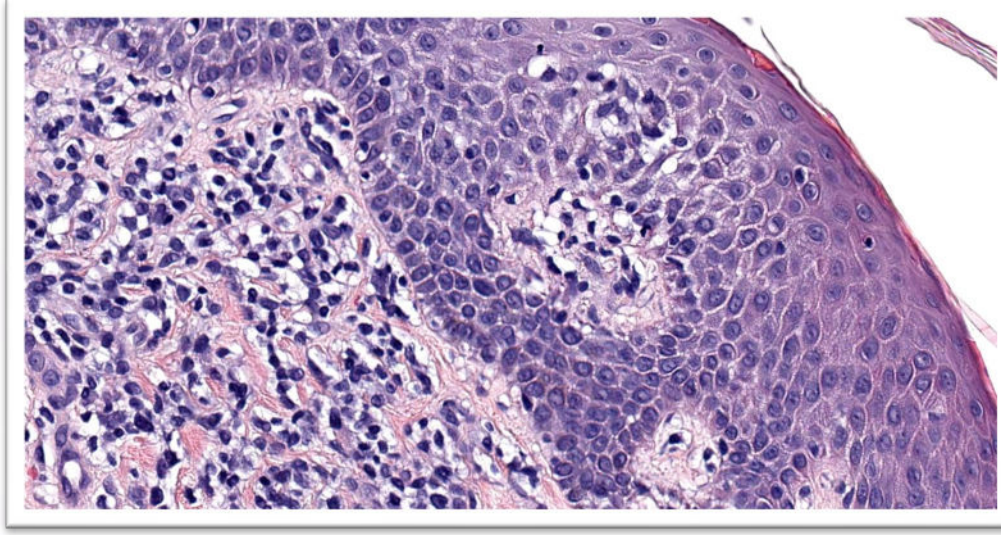


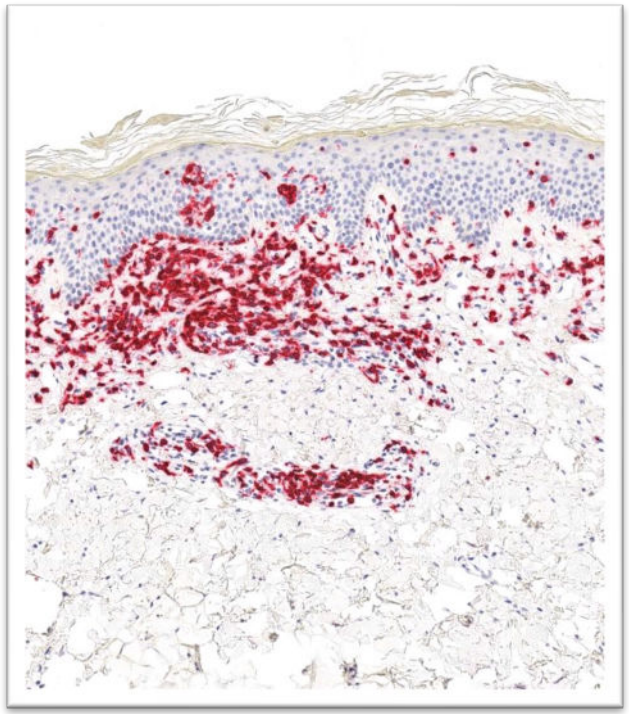
Itchy truncal rash x 4 yrs, skin biopsy “hypersensitivity reaction”

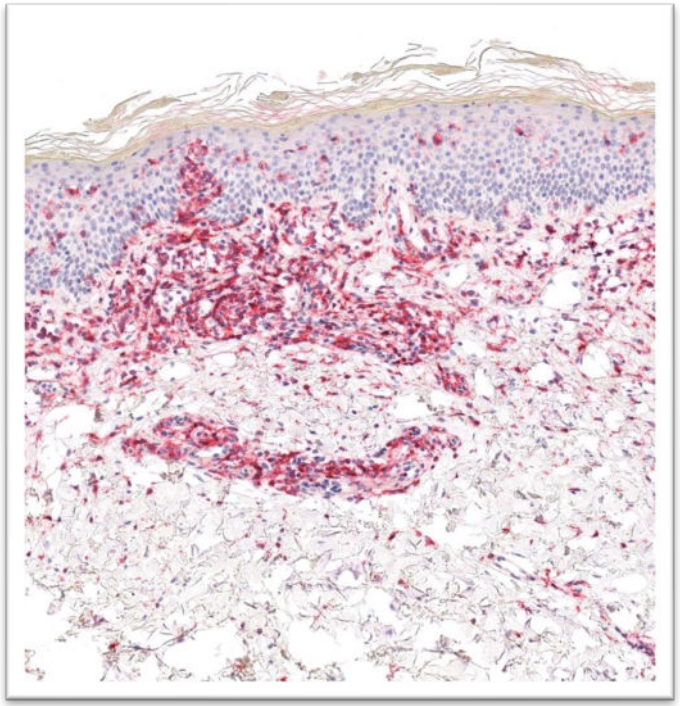
Allergy prick testing and blood tests negative. Started dupilumab – flared, rebx

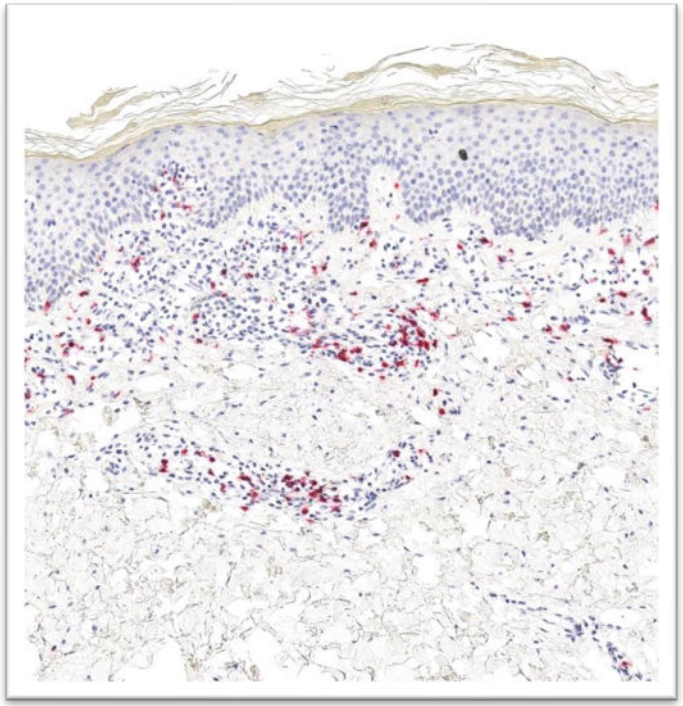
SITE: L. Thigh











FINAL PATH

MF/CTCL

CD3

CD4

CD8

Additional workup

CBC with diff, CMP, LDH, HIV, HTLVI/II Ab normal/negative

Rash BSA 80%, sent flow cytometry blood: Aberrant T cell immunophenotype detected

- CD4:CD8 ratio is 6.7
- Absolute abnormal T cell count: 839 /uL
- Absolute CD4+/7- count: 34/uL (2.2% of lymphs)
- Absolute CD4+/26- count: 859/uL (55.9% of lymphs)

TCR/PCR gene rearrangement studies showed matching clones in the blood, skin (244bp peak)

PET/CT showed mild prominent an FDG-avid right external iliac lymph node (possibly reactive)

MF/CTCL (T4NxM0B1) Stage IIIB

Dupilumab and CTCL

Initially the hope was that dupilumab may help CTCL, which also involves IL-4 pathway

—Some reports of benefit in CTCL pts with concomitant AD (Mollanazar *Cutis* 2020)

But multiple case reports of mycosis fungoides post-administration of dupilumab for presumed atopic dermatitis.

Unmasking of undiagnosed MF vs conversion of dermatitis to MF

Potential MOA: early MF (Th1) vs advanced MF (Th2) - selective Th2 inhibition by dupilumab may immunostimulate T_H1 or other cytokines and worsen MF

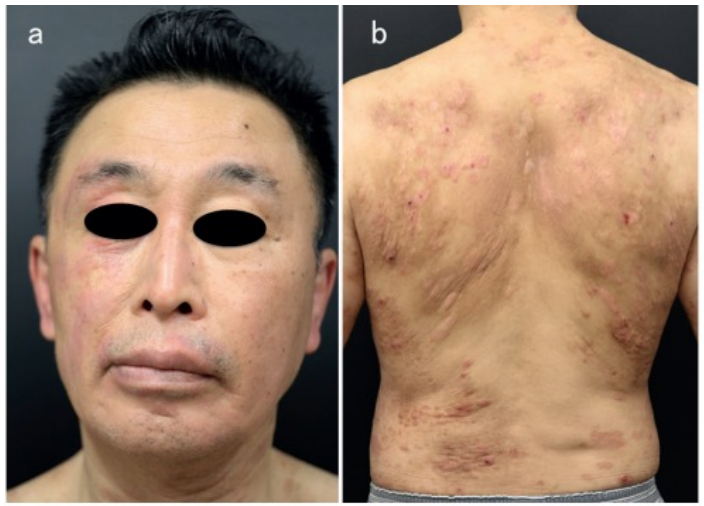


Fig. 1. (a) Erythematous lesions on the face. (b) Poikiloderma lesions accompanied by papules and nodules on the back. Written permission from the patient is given to publish these photos.

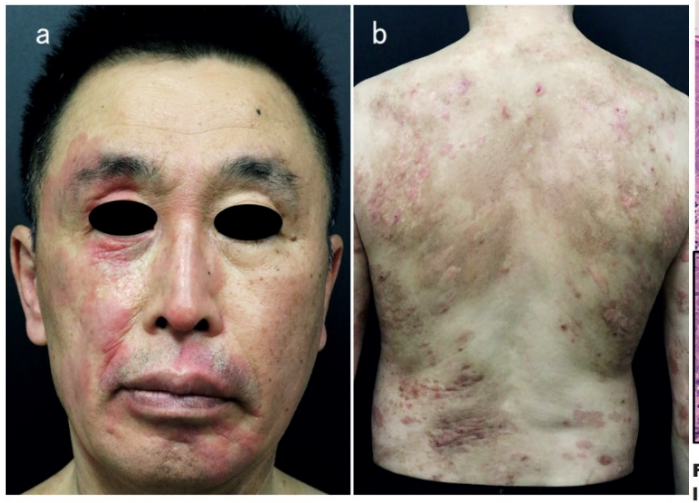


Fig. 2. (a) Face and (b) back after 1 month of treatment with dupilumab. Written permission from the patient is given to publish these photos.

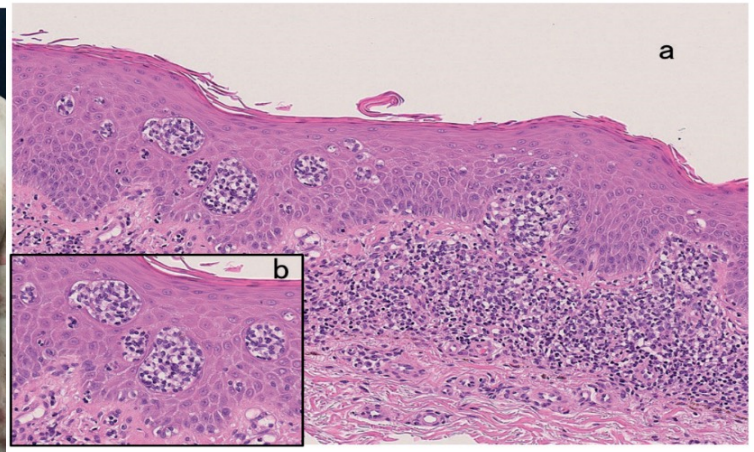


Fig. 3. Histopathology of the biopsy specimen from the erythematous lesion on the chest shows lymphocytic infiltrate in the dermis with prominent epidermotropism (a: haematoxylin and eosin; H&E ×100) and atypical lymphocytes into the epidermis (b: H&E ×400).

Chiba. Acta Derm Venereaol 2019
Russomano. JAAD Case Rep 2020

CTCLs

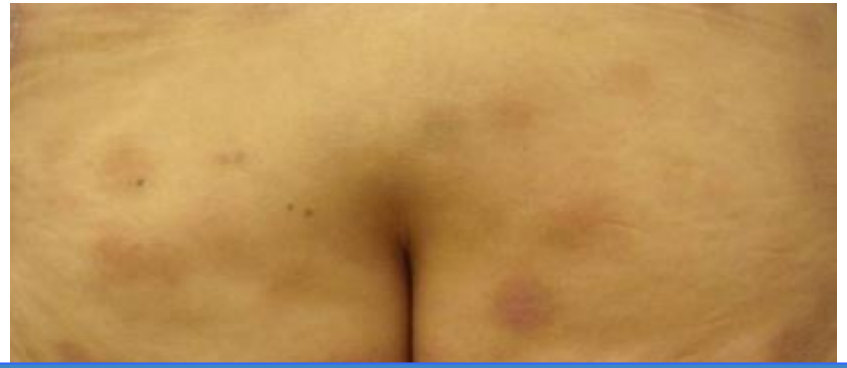
MF/Sezary (55%)

CD30 LyP/ALCL (25%)

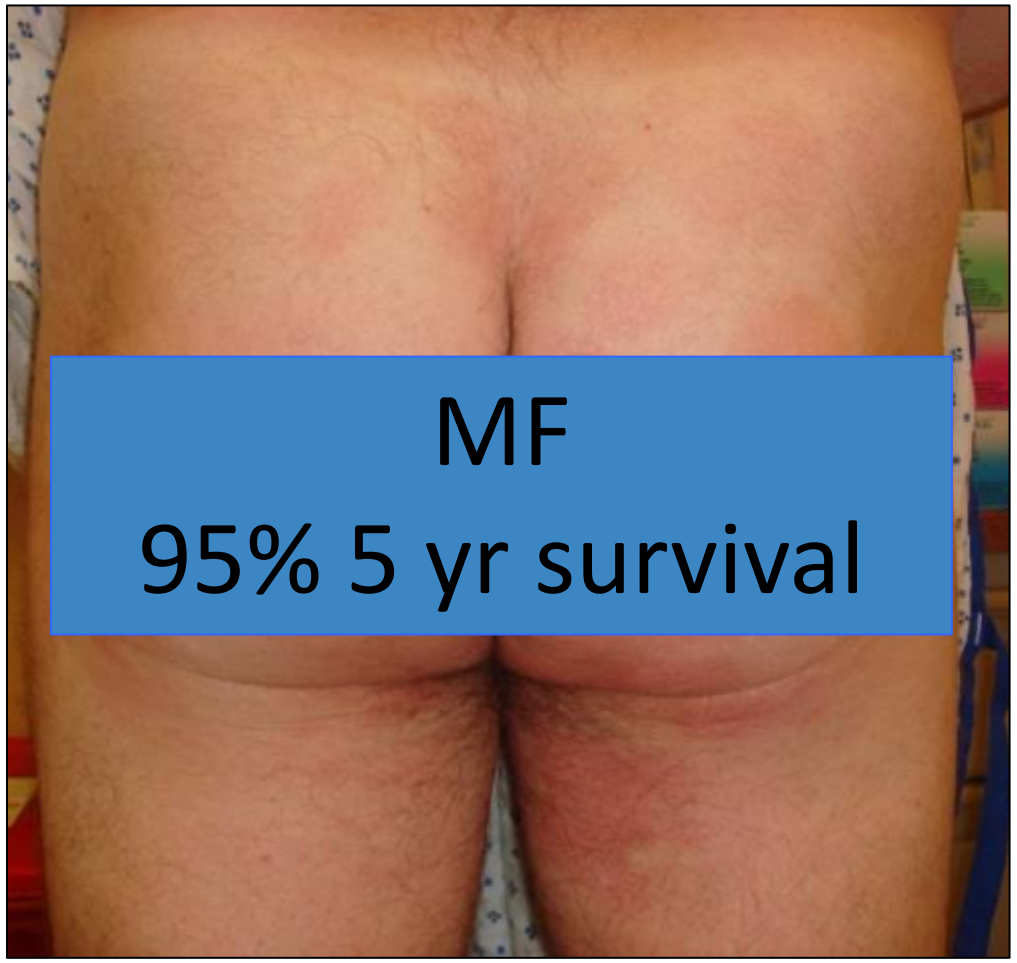
Other (20%)

Subcutaneous panniculitis like T-cell lymphoma
CD4+ small-medium pleomorphic T-cell LPD
Acral CD8+ small medium pleomorphic T-cell LPD
Extranodal NK/T
Aggressive epidermotropic CD8+ CTCL
PC Gamma delta TCL
Peripheral T-cell lymphoma NOS

Pink patches on buttocks



Gamma Delta CTCL
11% 5 yr survival

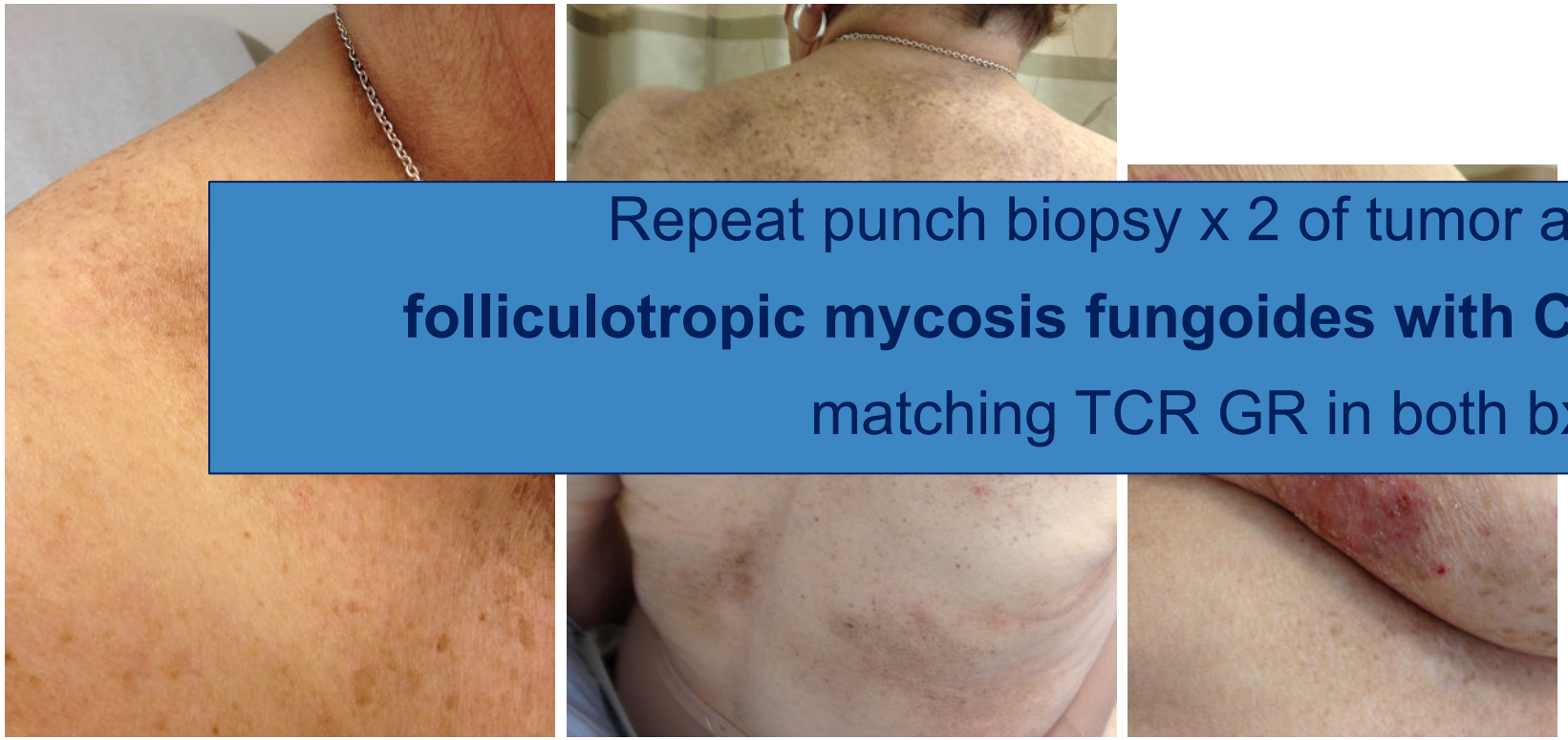


MF
95% 5 yr survival

Solitary tumor L cheek

Outside biopsy:

"atypical CD30+ T-cell lymphocytic infiltrate c/w **anaplastic large cell lymphoma**."



Repeat punch biopsy x 2 of tumor and patch:

folliculotropic mycosis fungoides with CD30 expression

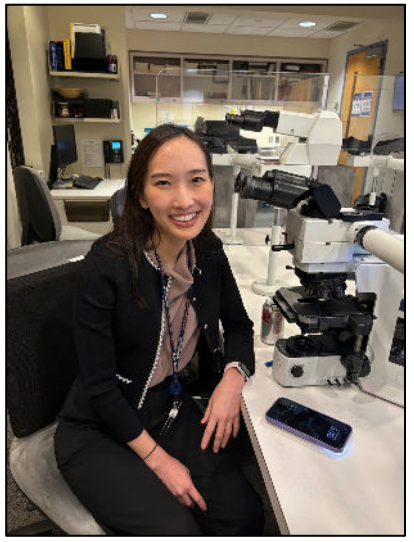
matching TCR GR in both bxs

Summary

MF/CTCL diagnosis is challenging

- Takes time to evolve, multiple biopsies
- One of the great imitators – multiple subtypes
- Mimic other dermatoses
- Overlap with other subtypes of CTCL
- Biopsy any refractory dermatitis prior to initiating dupilumab, TNFi, most biologics
- Do a full skin exam, remember clinicopathologic/molecular correlation for dx

#Team Penn CTCL



Alain Rook
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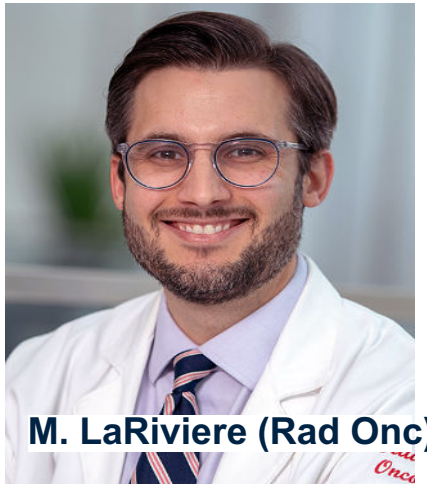
S. Barta (Med Onc)

J. Plastaras (Rad Onc)



M. LaRiviere (Rad Onc)