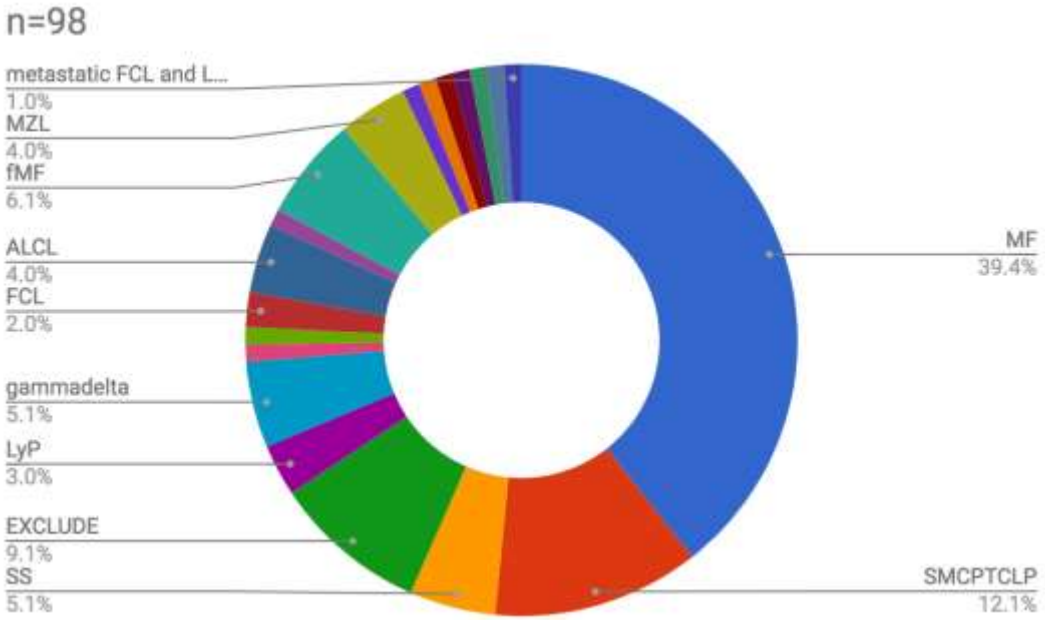
Challenges in cutaneous lymphomas

“Cutaneous lymphomas are only seen in hospital departments and are irrelevant for private practice”

- *Well-known and distinguished Danish dermatologist (1999)*

Changing landscape



Woman
D.O.B 1975
6 month history of asymptomatic nodule on the forehead
Clinical Dx: BCC??

Biopsy: dense lymphocytic infiltrate, no epidermotropism, mix B- and T- cells (CD4+ predominant), bcl-6+, slight atypia

Molecular: monoclonal TCR

DDx: Pseudolymphoma, CTCL, CBCL?

SMCPCD4LPD

Small- medium cell pleomorphic CD4+ lymphoproliferative disease (recognized in the WHO classification)

Probably clinically benign, but histologically and genetically malignant

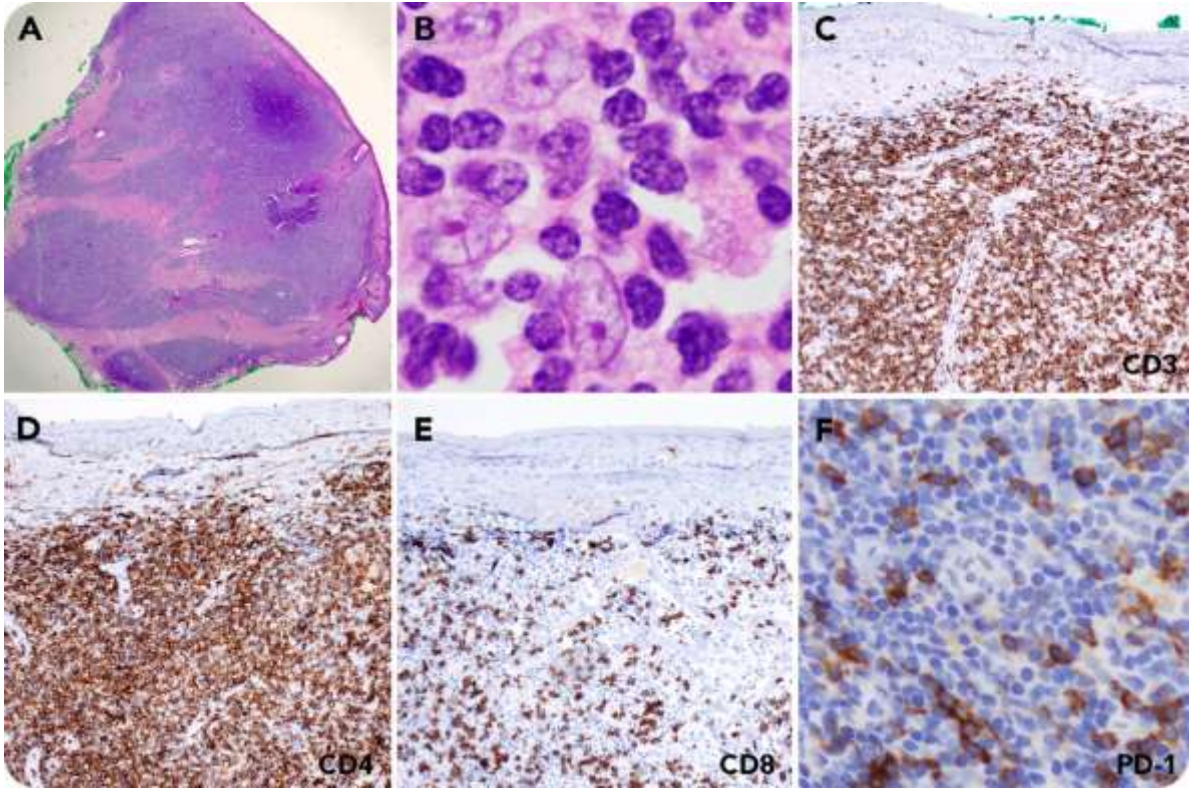
Dx: clinicopathological correlation (clinical features: single plaque or nodule, symmetric, not ulcerated)

Probably originates from T_{FH} cells (therefore rich B-cell component)

Can be difficult to differentiate from marginal zone B-cell lymphoma

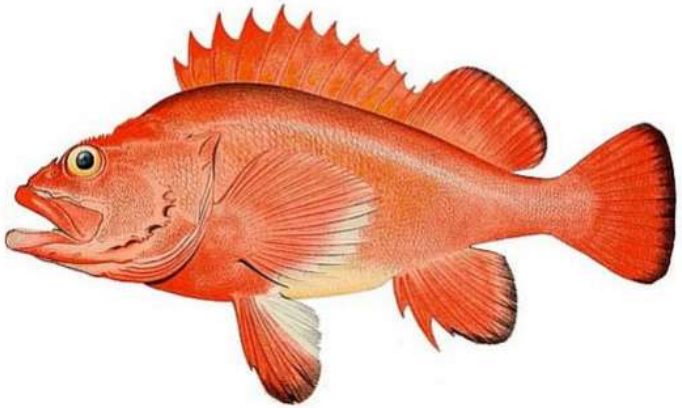
Earlier probably misdiagnosed as “pseudolymphoma”, atypical MZL, lymphoma NOS, LyP/Anaplastic lymphoma, cutaneous metastasis (depending on the imagination of the pathologist)

Pathology: mix T- and B- cell, CD4+ T-cells, bcl-6+, PD-1+ (rosettes), low proliferation rate, few mitoses, calls are small and medium sized and atypia is mild



Blood 2018 132:765; doi: https://doi.org/10.1182/blood-2018-05-850941

Red herring



A piece of information intended to be misleading

A red herring was a ploy in the 17th century used by criminals – just drag an old herring over the escape route through the woods and those durn huntin' dogs would lose their scent.

Discrete atypia overlooked - benign lymphoproliferation

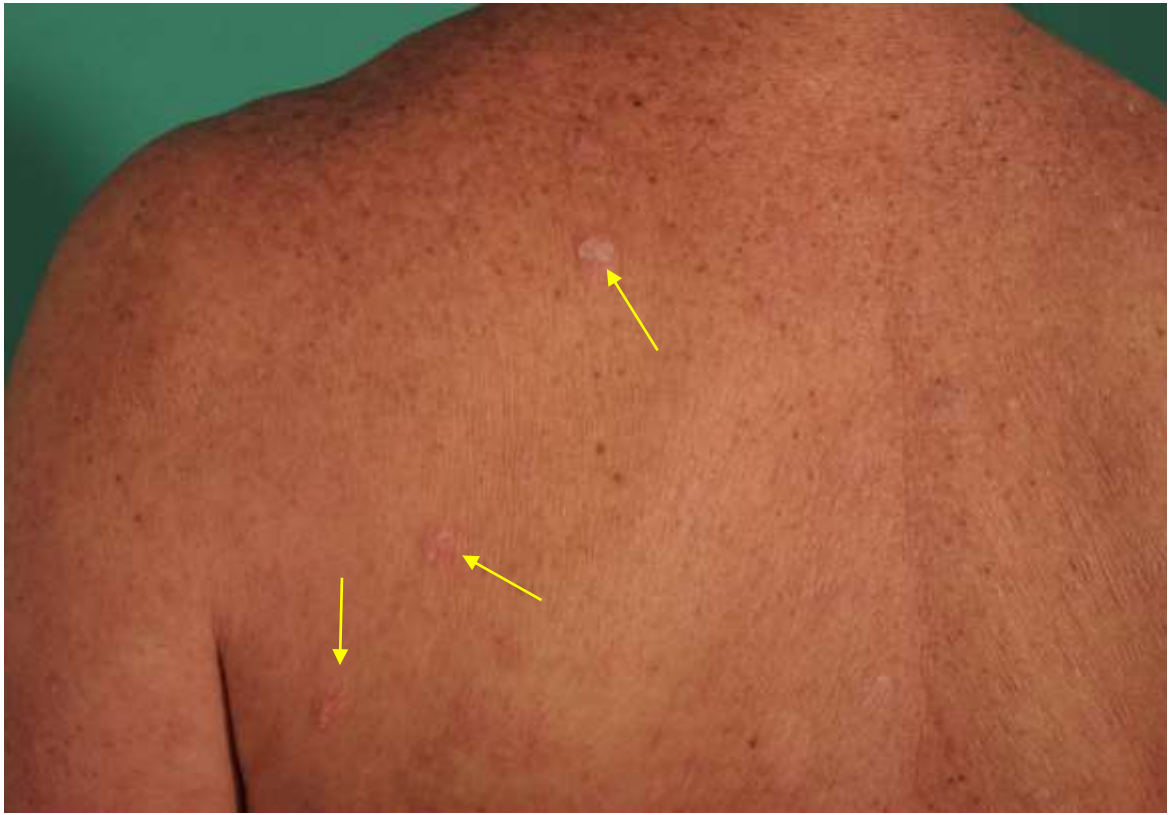
B-cell component - cutaneous B-cell lymphoma

Dense infiltrate - alarming for malignancy.

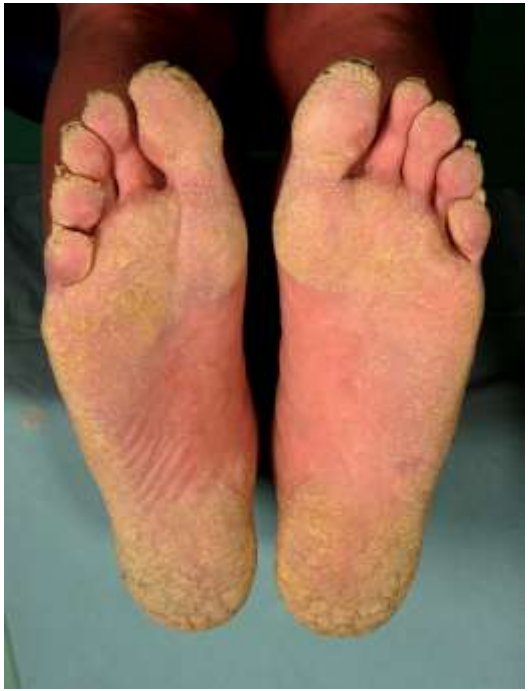
- 63-year-old male, previously healthy, no history of AD.
- 12 year history of eczema in head and neck area, controlled with topical steroids. Dx: AD
- Referred because of exacerbation and involvement of trunk and extremities and extreme itch
- Biopsy compatible with eczema
- Prick test positive to house dust mites (Dermatophagoides pteronyssinus), birch (Betula alba), grass mix (European standard mix)
- Patch test positive for Ni and formaldehyde (?relevance)
- Elevated IgE, allergic rhinitis, especially during pollen season
- Started on azathioprine and UVA1

Adult onset atopic dermatitis ?

- Minimal efficacy of Imuran and UVB (3 months)
- MTX 20 mg tried for another 3 months with negligible improvement
- Started on ciclosporin 3.5 mg/kg
- Rapid improvement within 1 month
- However, at the 4th month of treatment developed worrisome lesions on face and trunk
- Biopsy was taken and showed spongiosis and perivascular lymphocytic infiltrate compatible with eczema



infiltrative lesions



plantar hyperkeratosis

- CsA discontinued
- Started PUVA, Prednisone
- 3 biopsies obtained from infiltrative lesions: two showed eczema, one showed epidermotropic lymphocytic infiltrate, possible MF
- TCR was polyclonal
- Developed lymphadenopathy - biopsy from lymph node was unspecific
- Blood flow cytometry abnormal: CD4/CD8=18, loss of CD7 88% CD4+CD7- cells)
- Started on ECP

- Biopsies from the plaques finally established Dx of MF/SS
- Dx of SS was made
- Rx ECP / bexarotene / interferon / PUVA failed
- Further progression in lymph nodes and skin
- Decision of alloHSTC was made, but it was impossible to find a matching stem cell donor
- Hematologists decided to graft cord blood stem cells
- Post-transplant relapse and death 7 months after HSCT

True adult-onset AD (probably) does not exist. All cases I have seen (n=4) were (pre)-Sezary where disease exacerbated after immunosuppression

ciclosporin, 4 months

Imuran, 5 years

ciclosporin, 7 months

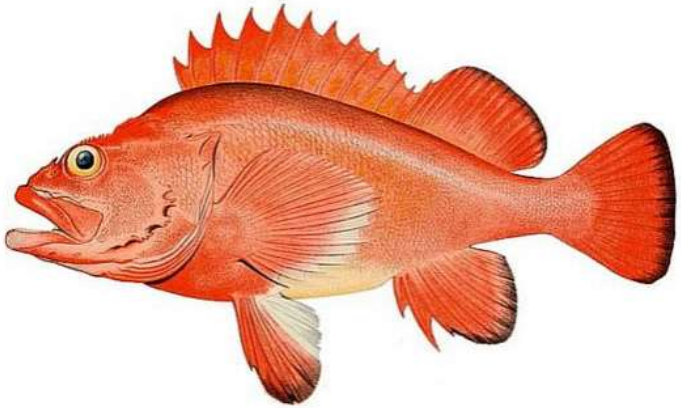
Early presentation of SS
n=263

Feature	Type 1 Erythroderma, n=67	Type 2 Dermatitis, n=129	Type 3 AD-like, n=13	Type 4 MF-like, n=28	Type 5 Leukemia without initial erythroderma, n=23
Essential clinical features	Erythroderma > 80% body	Pruritic, scaly, ill-demarcated lesions, hand eczema, neurodermatitis	Head and neck dermatitis, eczematous lesions on the trunk and flexural areas	Scaly patches and thin plaques, mostly on the trunk and gluteal area resembling early lesions of MF, parapsoriasis or psoriasis	Pruritus, sometimes with excoriations and eczematous lesions.
Skin biopsy prior to diagnosis	Spongiotic dermatitits (n=9), lymphocytic infiltrate (n=9), psoriasiform dermatitis (n=1)	Spongiotic dermatitis (n=17), lymphocytic infiltrate (n=16), psoriasiform dermatitis (n=1)	N=7: spongiotic dermatitis	N=7 spongiotic, lymphocytic infiltrate, N=8 lymphocytic infiltrate compatible with MF, n=1 psoriasiform dermatitis	Psoriasiform dermatitis (n=1), spongiotic dermatitis (n=2), psoriasiform dermatitis (n=1), lymphocytic infiltrate (n=3).
Age at diagnosis, mean (SD)	64.4 (16.0)	59.2 (16.3)*	60.2 (14.2)*	62.9 (16.8)	68.6 (14.8)
Male/female	42/25 (62.7%/37.3%)	78/51 (60.5%/39.5%)	5/8 (38.5%/61.5%)	17/11 (60.7%/39.3%)	12/11 (52.2%/47.8%)
Survival after diagnosis (mean (95% CI))	4.9 (3.7-6.2)	4.3 (3.7-5.0)	4.0 (2.1-5.9)	3.1 (2.0-4.1)	3.4 (2.3-4.4)
Survival after first sign, mean years (95% CI)	7.1 (5.5-8.7)	9.2 (8.1-10.3)*	11.5 (7.3-15.6)*	8.1 (5.8-10.3)	6.9 (4.9-8.9)
Diagnostic delay (years)	2.2 (2.4)	4.9 (4.4)	7.2 (4.4)	5.2 (4.1)	4.2 (4.4)

Mangold AR, Thompson AK, Davis MD, Saulite I, Cozzio A, Guenova E, Hodak E, Amitay-Laish I, Pujol RM, Pittelkow MR, Gniadecki R. Early clinical manifestations of Sézary syndrome: A multicenter retrospective cohort study. J Am Acad Dermatol. 2017 Oct;77(4):719-727

SS presenting as dermatitis (case of dr Pujol)

SS presenting as extensive ”psoriasiform dermatitis”

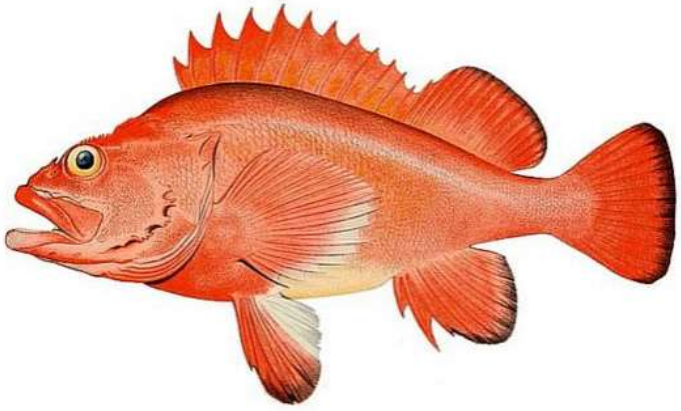


- Adult-onset AD is an established diagnosis (no, it is a problematic diagnosis in a patient without history of AD in the childhood)
- Lack of progression agrues against cancer (no, early SS can stay silent for years/decades, unless provoked by immunosuppression)
- Benign pathology (wrong, pathology and molecular will not help you much).
- Increased IgE, positive prick test, positive contact allergies indicate AD. Wrong again, these are normal findings in SS. Don’t rely on them.

- 58-year-old woman, previously healthy
- Referred with a single tumor on lower leg
- Biopsy showed T-cell lymphoma, NOS
- Referred for staging and radiotherapy but in the meanwhile developed infiltrative lesions on the leg
- New biopsy from the plaques: MF, epidermotropic, CD4+CD3+CD8-CD7-
- TCRgamma monoclonal
- Histology from the tumor had the same markers, but was not epidermotropic

Tumor d'emblee MF?

Electron beam radiation to the leg
Complete remission



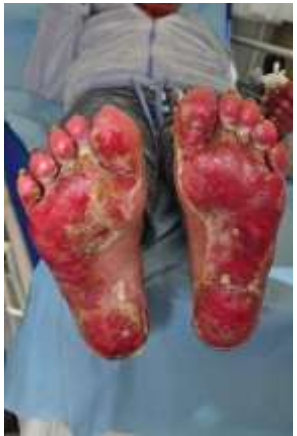
- I was fooled by pathology: epidermotropic CD4+ lymphoma with pathches and plaques is usually MF

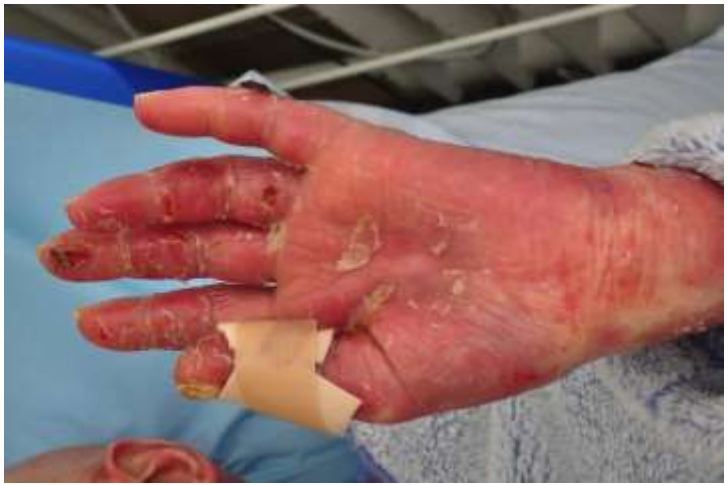
- However, early tumor formation is NOT a usual feature of MF

9 months later developed patches and plaques overall. PUVA/IFN no effect. Progressed rapidly, referred for TSEB

Relapse after TSEB

Re-biopsied: CD8- CD4- aggressive looking lymphoma betaF1 negative (!)





This is not MF

3 years

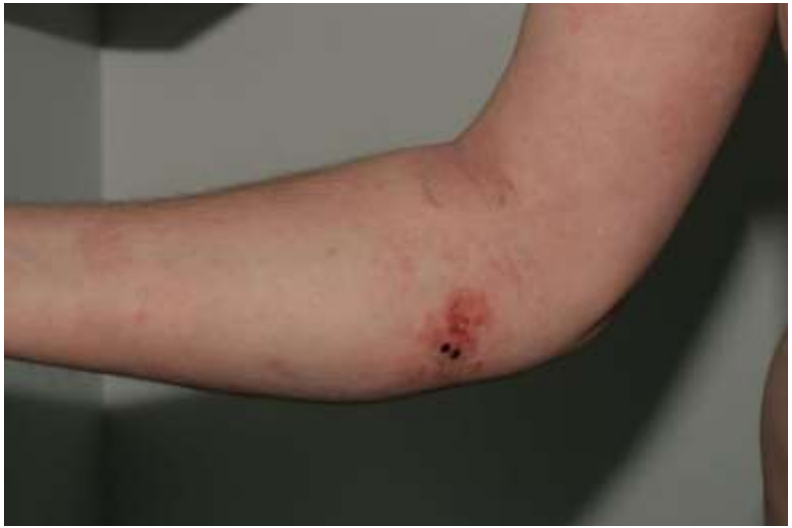
This is a gama-delta lymphoma

Gamma delta CTCL mimics MF in a number of cases

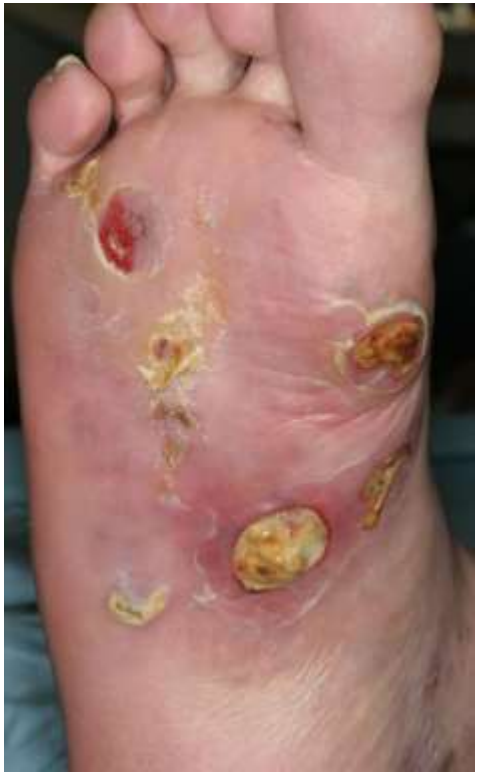
MF (good prognosis)	**MF like gamma delta lymphoma (warning signs)**
Evolution plaque → tumor, (almost) never debut with tumor	Tumors develop as an initial presentation
Lymph node involvement is late	Early lymph node involvement
Early lesions on sun-protected skin (except follicultotropic - scalp and face)	Random location from onset: distal limb, head and neck, widespread…
Pathology consistent in multiple lesions and during follow up	Surprising pathology findings, different biopsies give different results
TCR polyclonal or monoclonal	
CD3+ CD4+ CD8-	CD3+ CD4- CD8- (gamma delta) CD8+ with cytotoxic markers

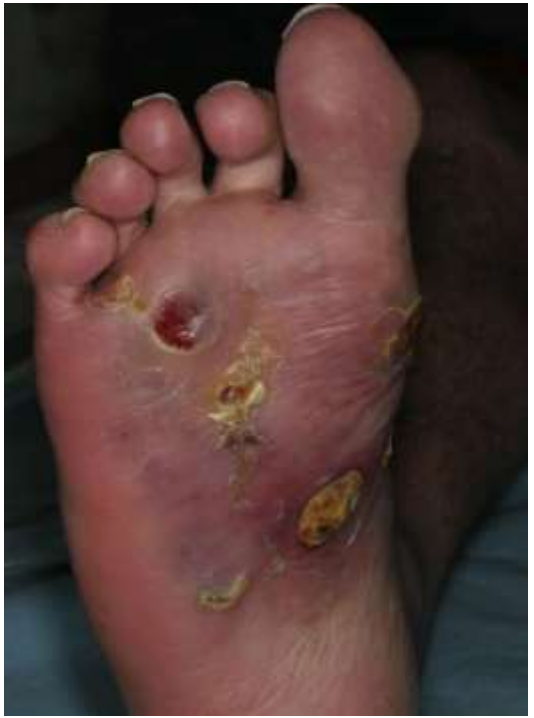
39-year-old man with thin patches

pathology: MF, CD3+CD4-CD8- betaF1 negative



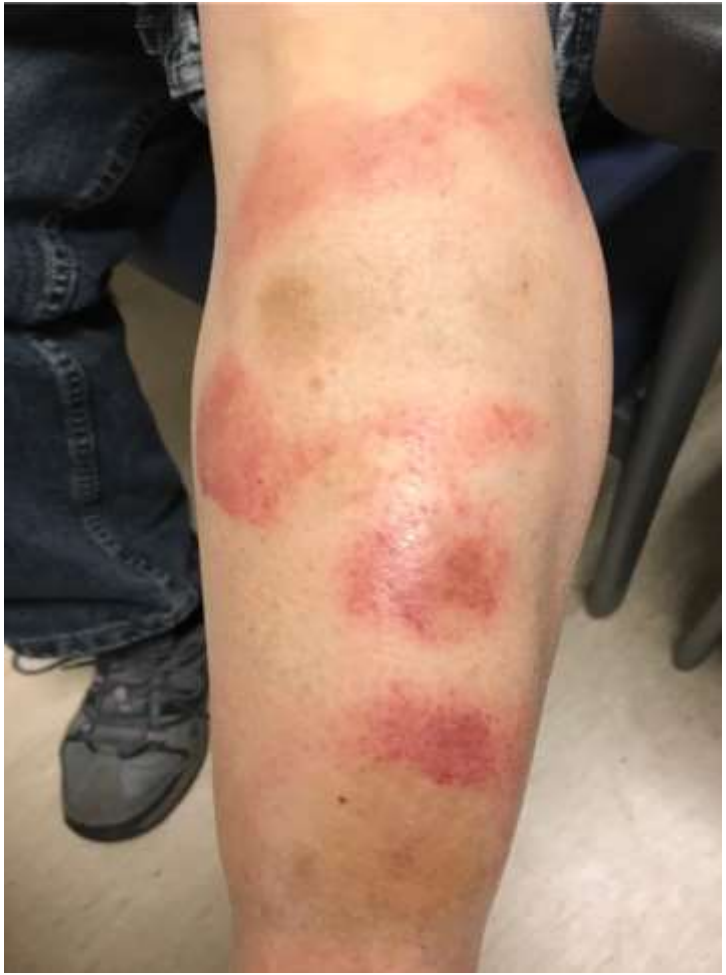
4 months later – lymph node involvement and tumors



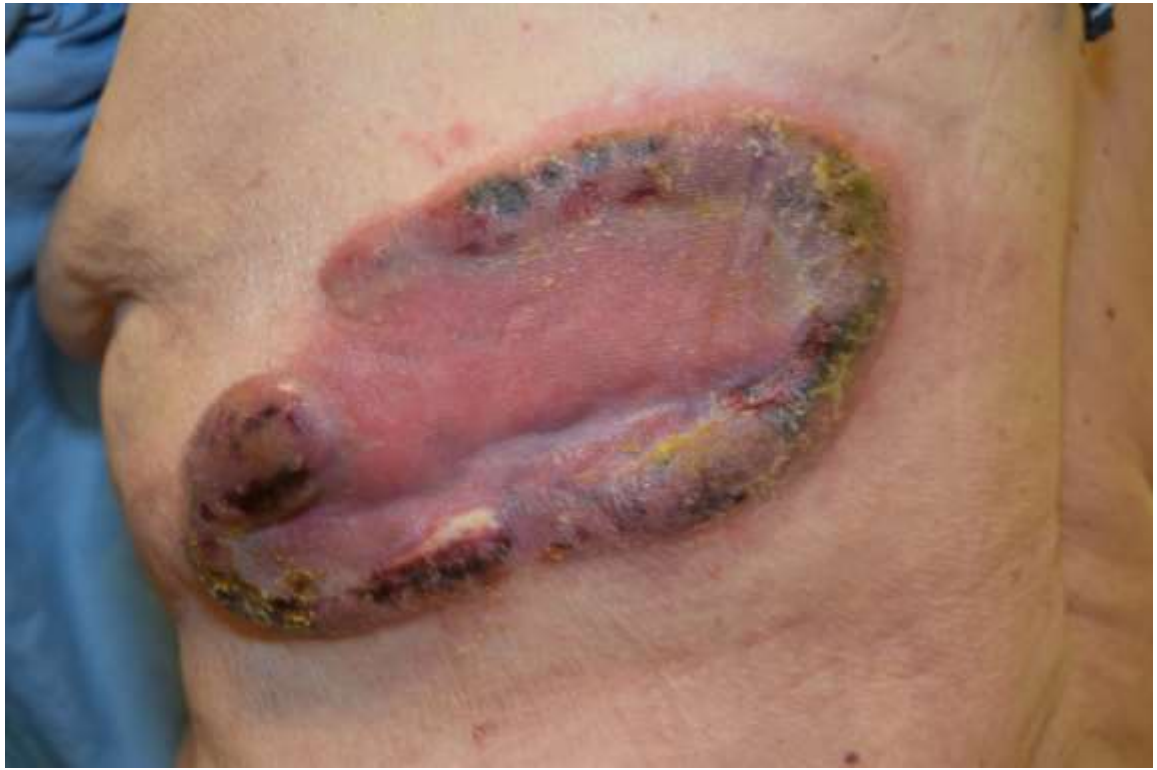


Did not respond to radiation or gemcitabine. Rx. Bone marrow transplant

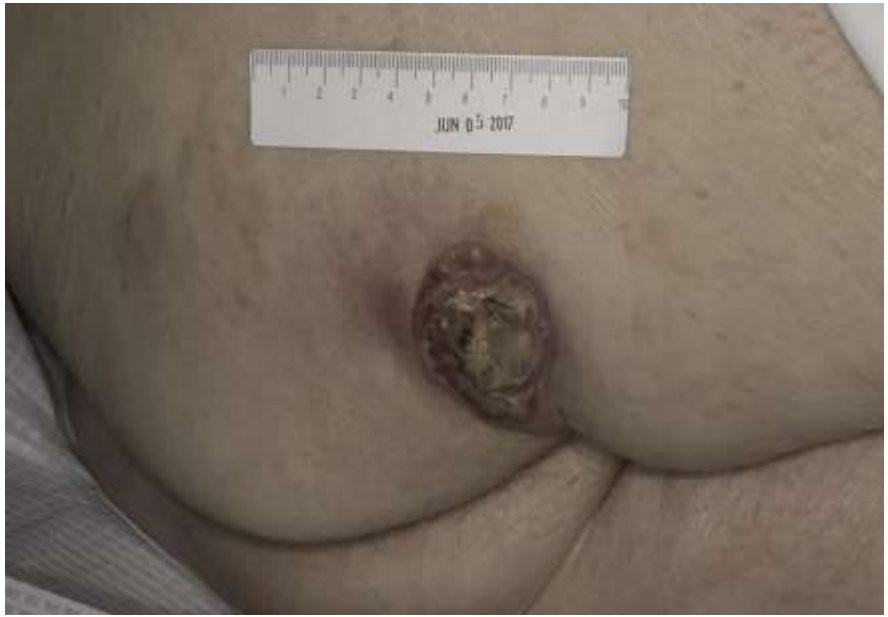
71-year-old man. 8 month history of eruption. Pathology: epidermotropic infiltrate, MF.

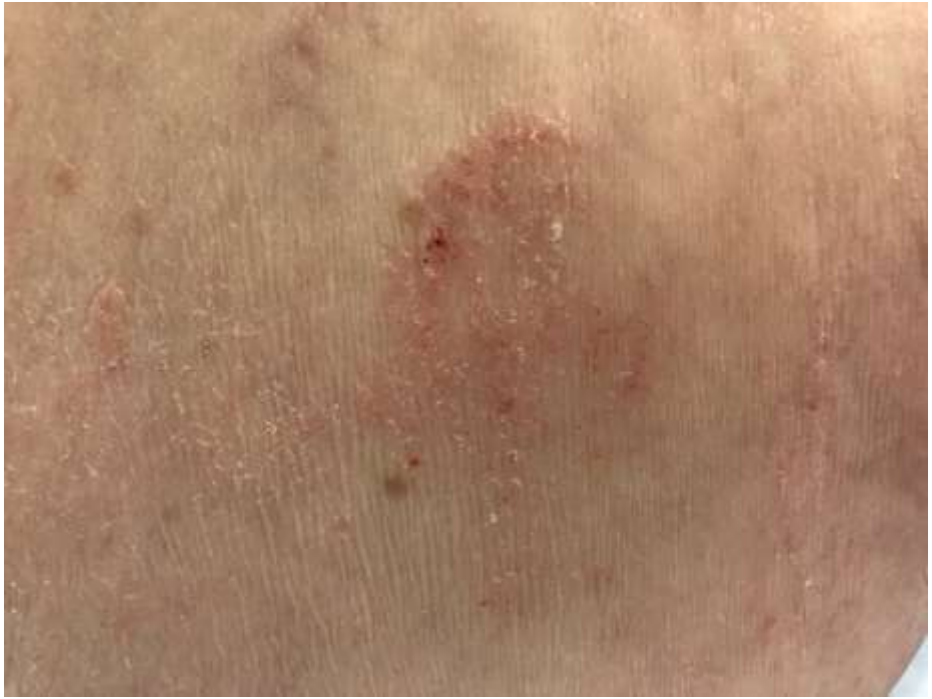


58 -year-old woman
Developed patches and plaques on left lower leg

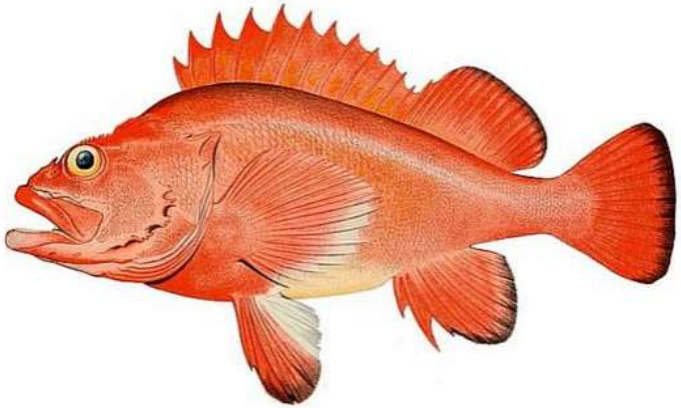


80 -year-old woman. Developed tumors, patches and plaques on the trunk





83 -year-old woman. Developed ulcerated tumor on the buttock and patches and plaques on the buttock and the trunk



- Don’t be fooled by pathology, if MF does not behave like it should reconsider the diagnosis

- Other agressive mimics of MF are: blastic lymphoma, NK-T lymphoma, CD8+ aggressive epidermtropic lymphoma … (they are rare, Dx is difficult and prognosis bad)

And now, 5 tips in 5 minutes

When I see grouped papules like this, the Dx is...

Edmonton

Copenhagen

Lymphomatoid papulosis (agminate type)

Heald, P., et al., *Persistent agmination of lymphomatoid papulosis: an equivalent of limited plaque mycosis fungoides type of cutaneous T-cell lymphoma.*J Am Acad Dermatol, 2007. **57**(6): p. 1005-11.

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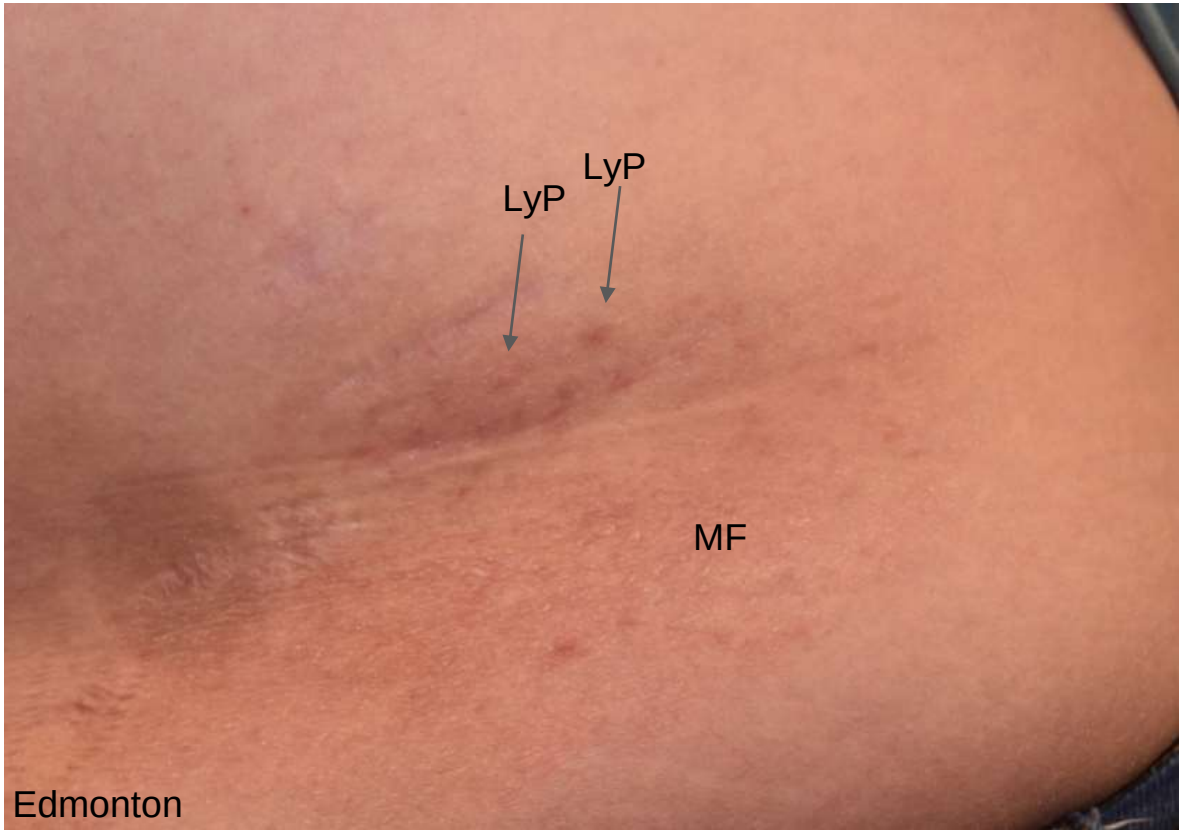
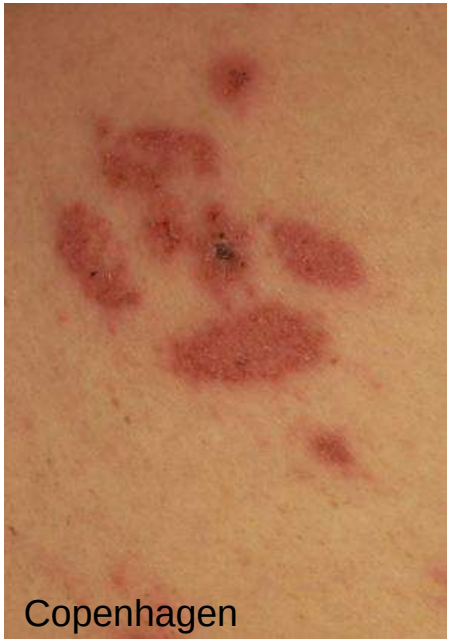


Coexistence of MF and LyP is a peculiar, but not uncommon type of agmination

DDx large cell transformation of MF



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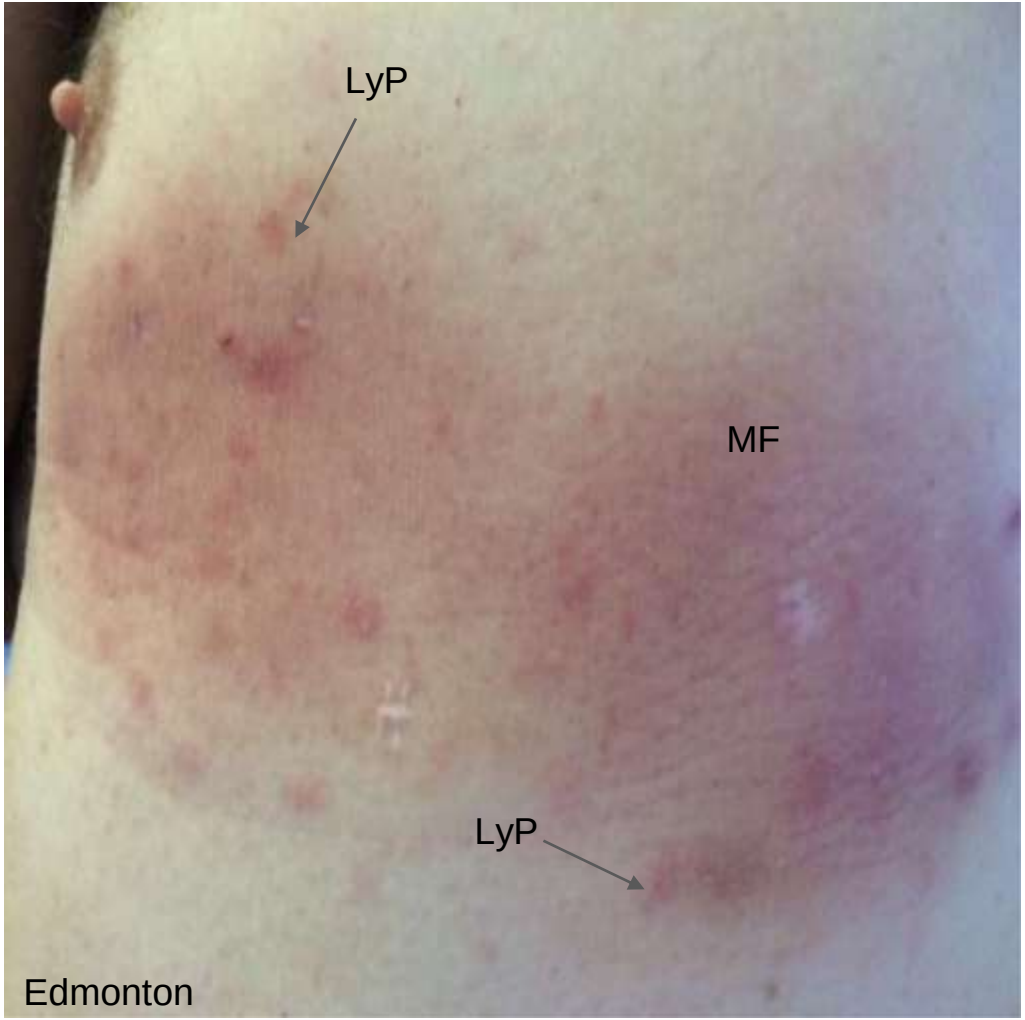
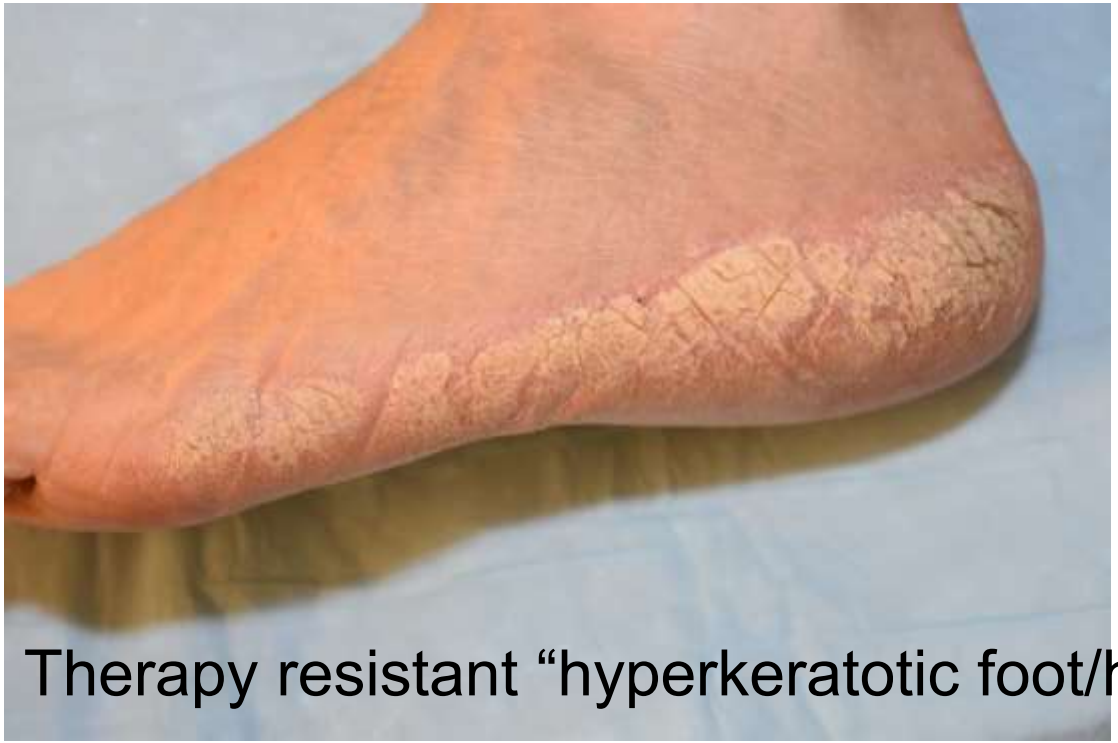


Coexistence of MF and LyP is a peculiar, but not uncommon type of agmination

Should we biopsy it?
YES, it might be a **mycosis fungoides**



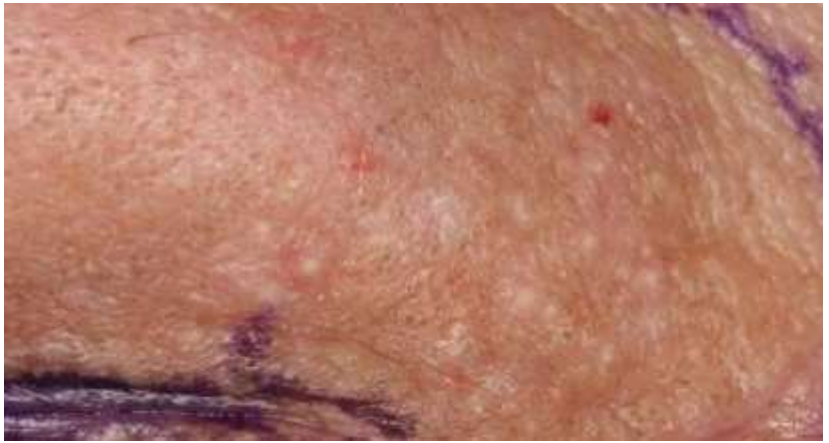
Therapy resistant “hyperkeratotic foot/hand eczema”

patient of Dr T Salopek

2

Case of dr E Guenova, Zurich

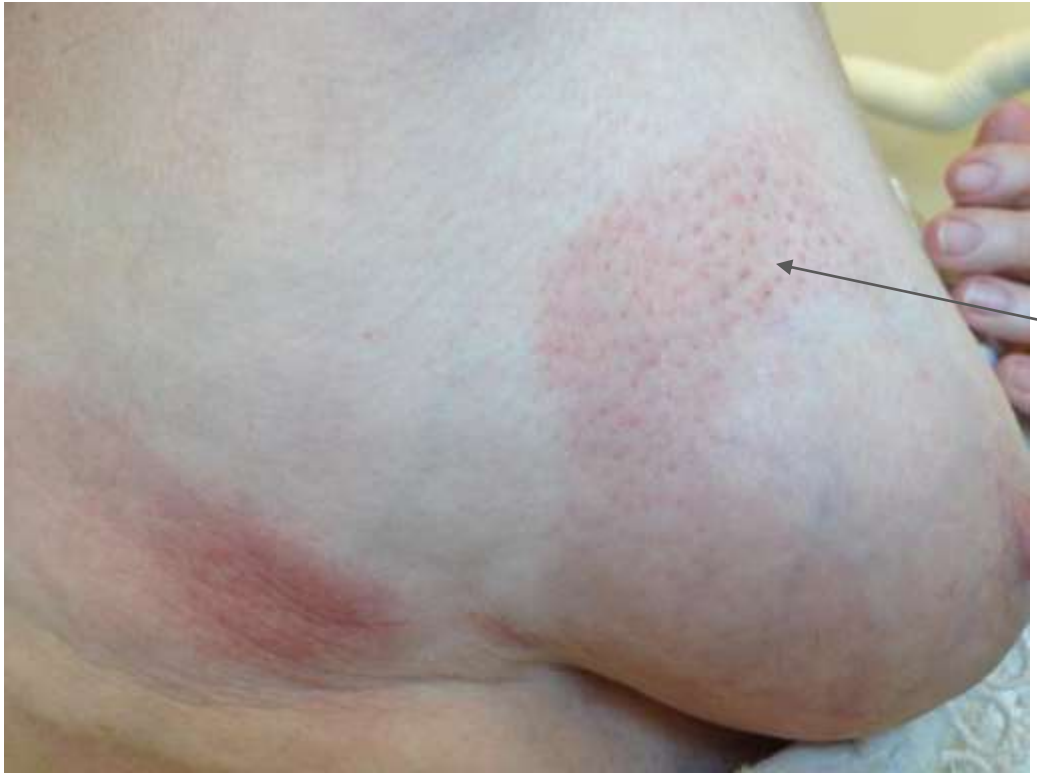
Typical folliculotropic MF is easy to recognize...



facial localization

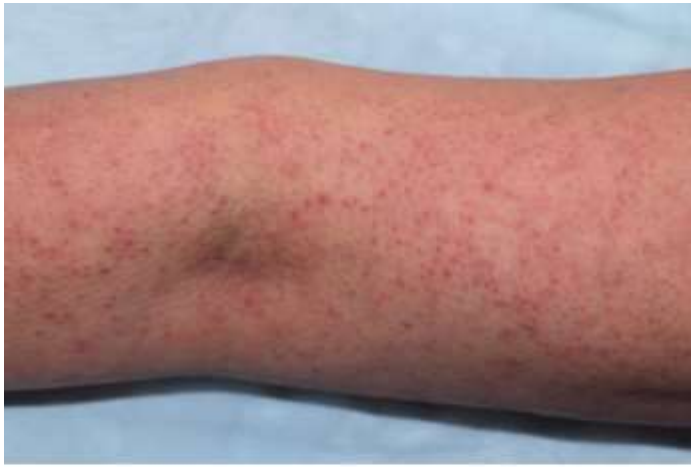
comedo-like lesions (folllicular mucinosis

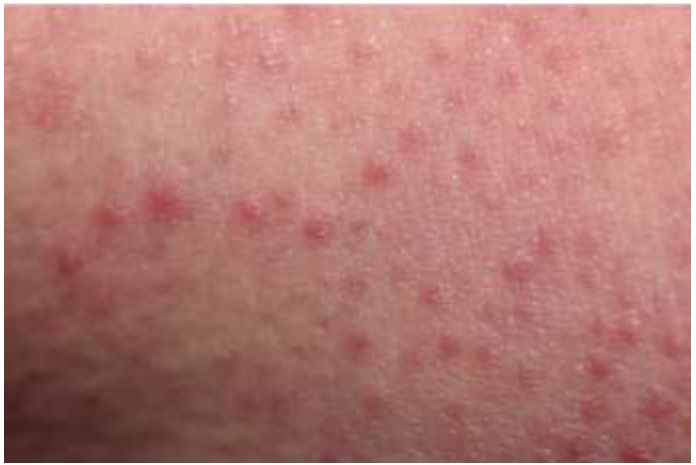
But less well known features are...



Folliculocentric accentuation on the trunk

3

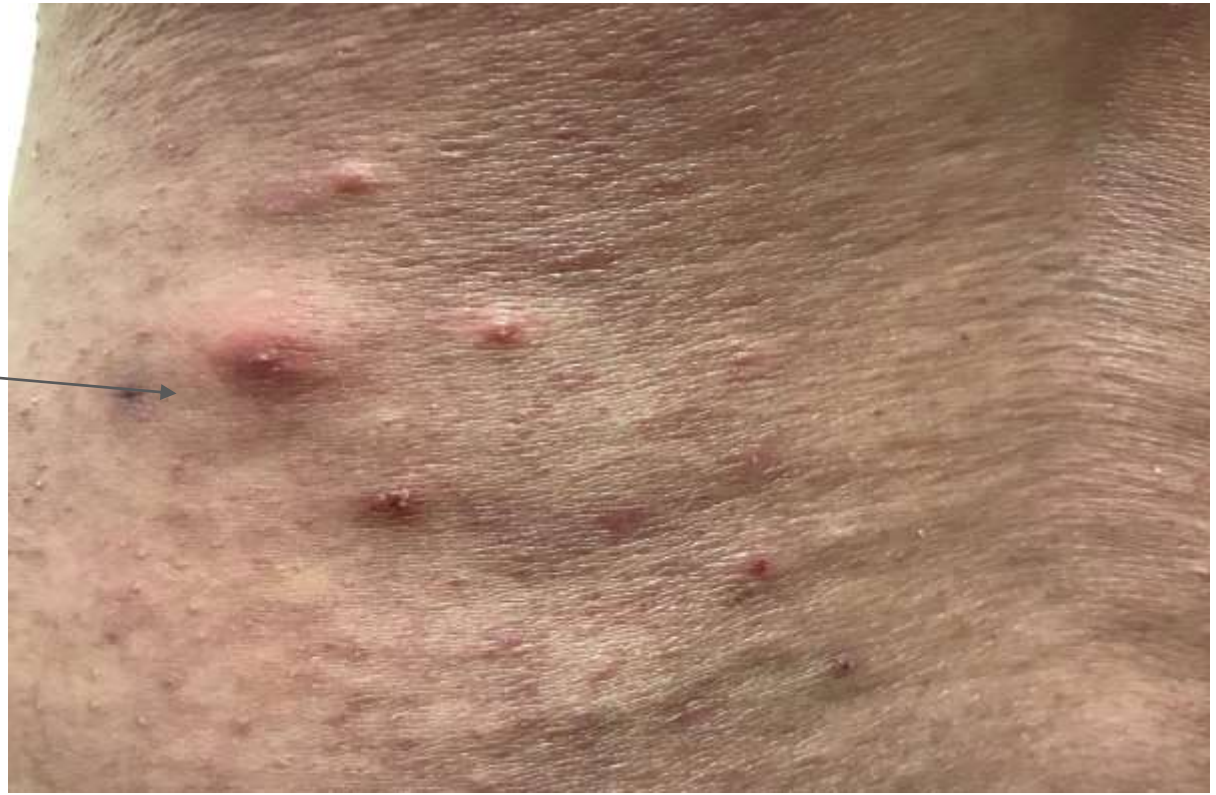




alopecia areata, even totalis

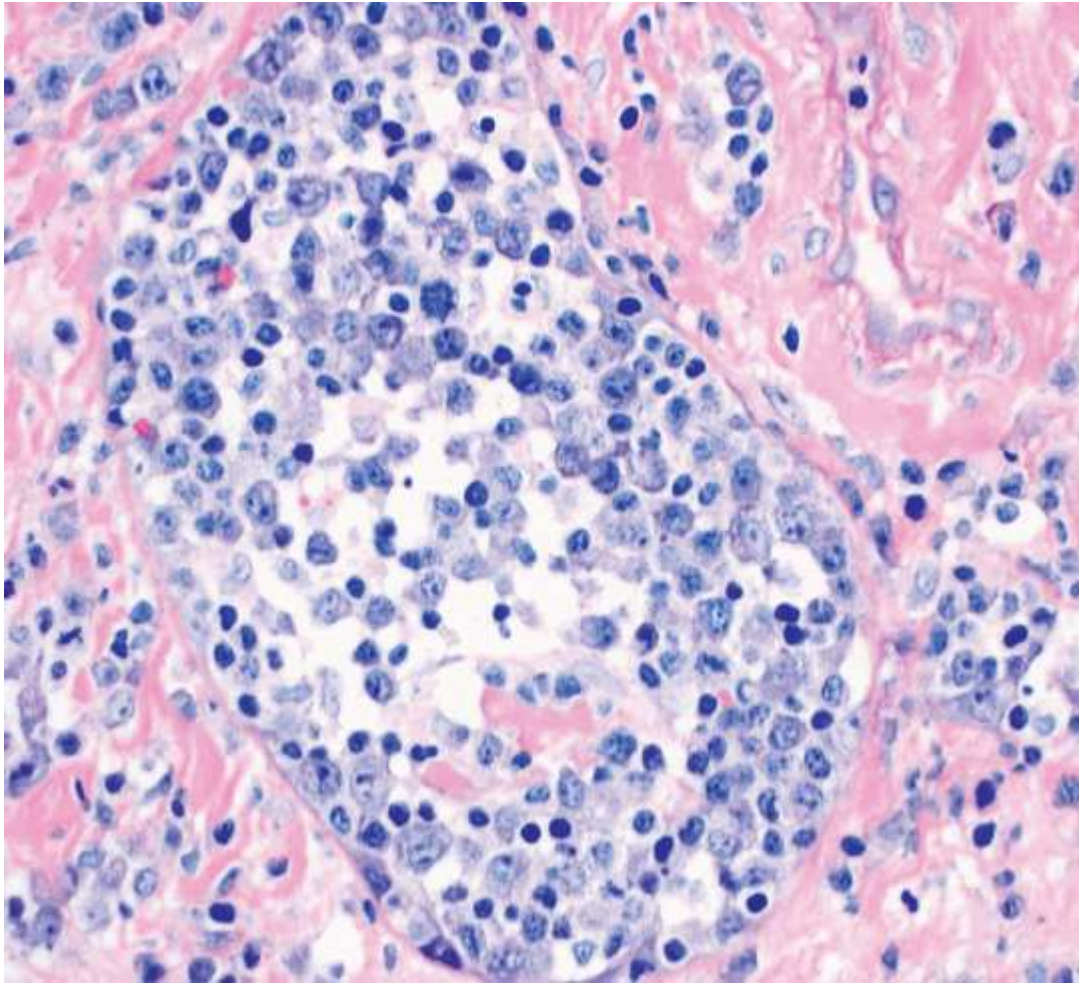
keratosis pilaris

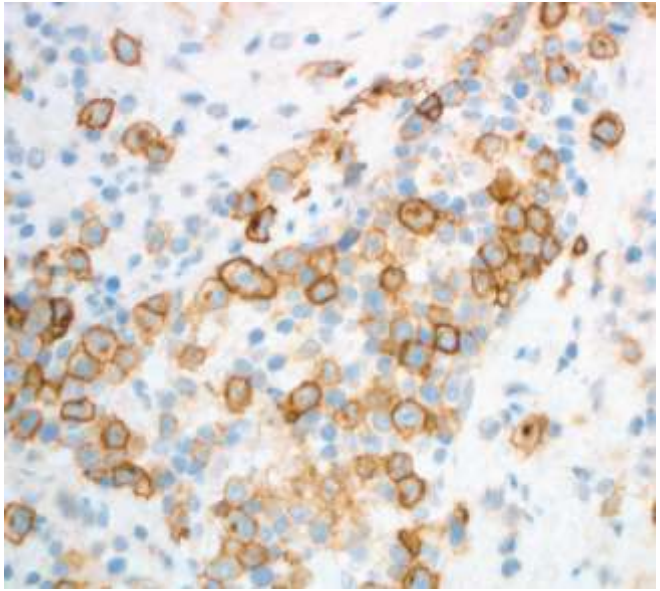
Acne- or HS- like lesions



In CTCL clinics usually trumps pathology

- 39-year-old male, diabetes II, obese
- Tx: metformin
- Consulted his family physician because of an ”irritated” skin tag in right groin
- The lesion was removed
- Histology was alarming: intravascular T-cell lymphoma, CD30+ CD4+ ALK-, CD15-, CD20-





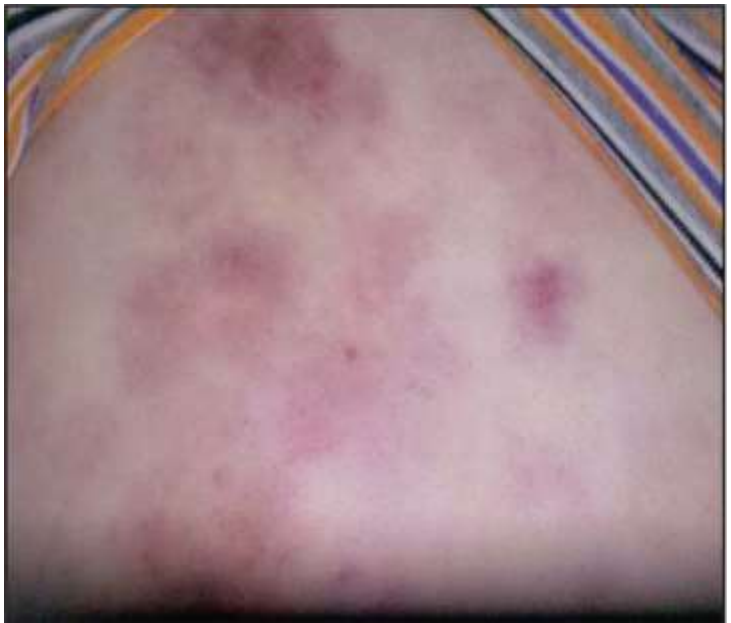
Intravascular accumulation of CD30+ lymphocytes CD4+, ALKnegative

Tentative diagnosis: intravascular lymphoma or leukemia.

- Referred to haematology. Kr. 100,000 worth imaging and staging: Bone marrow, PET/CT, blood tests all normal
- There was a small, palpable cervical lymph node which was removed. Pat: reactive changes. New derm-pat: increased number of plasma cell. Malignant lymphoma is a possibility. TCR rearrangement inconclusive
- Followed in hematology for 6 months – no signs of lymphoma but chemotherapy is considered. Patient was scared and asked for second opinion.

This is intravascular lymphoma

- 90% - B-cell
- 10% - T-cell, NK-T or large cell CD30+ALK+
- Aggressive
- Multiple skin lesions
- Death within months



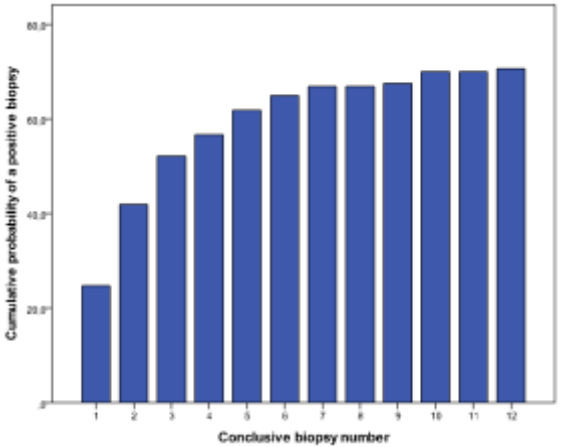
He has a benign atypical intravascular CD30+ T-cell proliferation

Diagnostic Criteria for Atypical Intravascular CD30+ T-Cell Proliferation

1. Association with trauma, ulceration, and/or inflammatory processes
2. Intralymphatic accumulation of medium- to large-sized activated lymphocytes
3. Expression of T-cell markers and CD30 and lack of B-cell marker expression by the medium- and large-sized intravascular lymphocytes
4. No loss of T-cell markers (eg, CD3; except for CD7) and absence of Epstein-Barr virus (EBV) RNA or EBV-associated proteins in the atypically appearing CD30+ lymphocytes
5. Absence of monoclonal rearrangement of T-cell receptor β or γ genes
6. No indication for cutaneous or systemic lymphoma by staging examinations
7. Indolent course with complete resolution after regression of ulceration or inflammatory process; no development of lymphoma during follow-up

Kempf et al. Am J Clin Path 2014;142:694-9

Keep on taking biopsies in difficult cases.



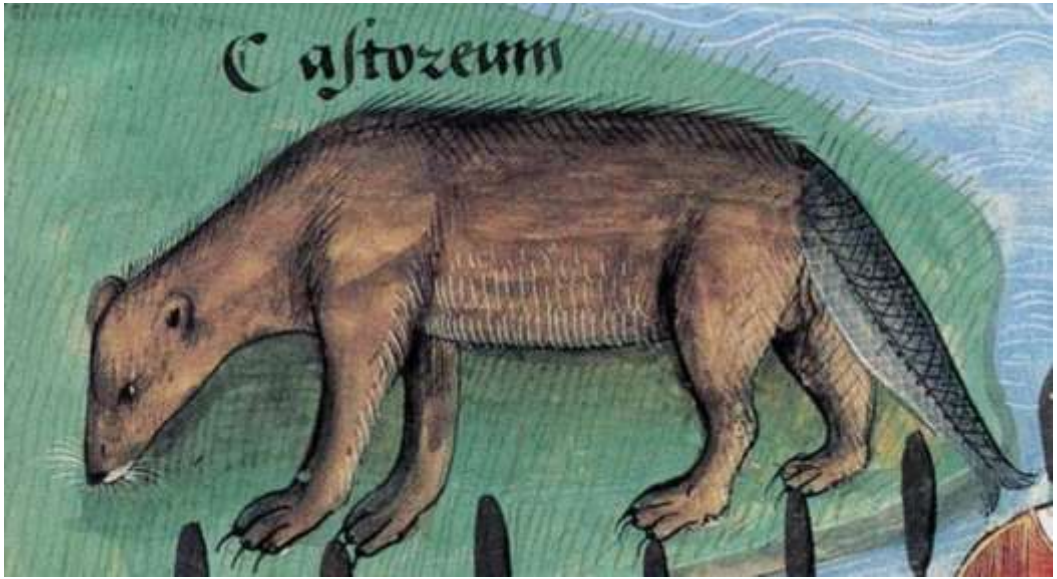
Each consecutive biopsy increases the diagnostic success by approximately 25%

5-10 biopsies may be needed to secure histopathological diagnosis

In up to 25% histopathology will not be specific

Skov A, Gniadecki R. Acta Derm Venereol 2015

Neither Fish Nor Flesh Nor Good Red Herring



Summa Theologica of Thomas Aquinas, which ***bases animal classification as much on habit as anatomy****.Therefore, Bishop of Quebec ruled that the beaver was a fish for purposes of dietary law.*

- AD vs Sezary
- γ δ lymphoma vs MF
- Red herrings distracting from MF diagnosis (alopecia, folliculitic lesions, KP)
- Trust your eyes, distrust your pathology (SMCPCD4LPD, “intravascular lymphoma”)-