Sezary Syndrome(SS) and other malignancies

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Disclosures

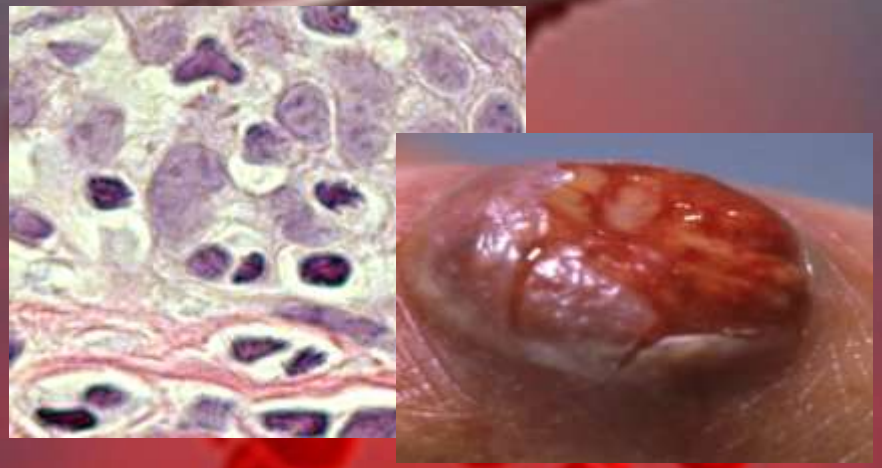
- IHCFLOW Laboratory:consultant and director
- NEOGENOMICS: contract consultant
- USF: contract reviewer
- Quest DermPath Dx: consultant
- Eisai: former Advisory Board, not active

New Book coming out

SPRINGER

CUTANEOUS HEMATOPATHOLOGY

CUALING ,HOANG, MORGAN, KADIN



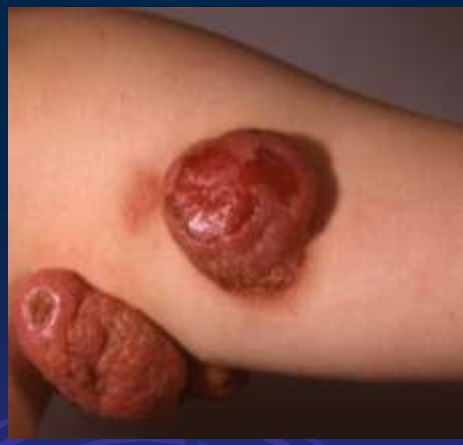
CTCL : Mf and SS

- Definition: Epidermotropic types of cutaneous T-cell lymphoma characterized by a distinct set of clinical, histologic and immunologic features
- All mycosis fungoides = CTCL, but not all CTCL = mycosis fungoides

- SS:It is a variant of CTCL. Aggressive, 5% of CTCL with generalized skin, blood, and lymph node dissemination. Like MF, arise from clonal T cells.
- Sezary syndrome may occur in 3 % of MF or present de novo without preceding MF.

All mycosis fungoides = CTCL, but not all CTCL = mycosis fungoides

- **In 1806, mycosis fungoides (MF) was first described[1]**
  - **Alibert, a French dermatologist, described a severe disorder in which large necrotic tumors resembling mushrooms presented on a patient's skin**
  - **Sezary , in 1938, described circulating" monstrous cells-cellules monstreuses" in blood**
- **In 1979, the term cutaneous T-cell lymphoma (CTCL) was proposed at an international workshop sponsored by the National Cancer Institute and as coined by the Lutzner group in 1975 [2,3]**
  - **CTCL was used to describe a heterogenous group of malignant T-cell lymphomas with primary manifestations in the skin**
  - **MF is the most common type of CTCL**
  - **Sézary syndrome (SS) is a variant of CTCL , 5% of all CTCL cases**



[1]Alibert JL. Description des Maladies de la Peau: Observees l'Hospital St. Louis et Exposition des Meilleurs Methods Suiview pour leur Traitement. Paris. In: Barrois l'aine et Fils, 1806.
[2]Lamberg SI, Bunn PA. *Cancer Treat Rep.* 1979;63:561 and Willemze R et al. *Blood* 1997:90:354-71.
[3]Lutzner, Edelson et al Cutaneous T cell lymphomas: The Sezary Syndrome, MF and related disorders, Ann Int Med 1975

Epidemiology

Frequency

- Mycosis Fungoides,early stage (< IIB)
- Mycosis Fungoides,late stage (> IIB)
- Sezary syndrome (5%)

NODULAR OR NON-EPIDERMOTROPIC

- cutaneous Peripheral T cell lymphoma:many subtypes
- CD30+ Lymphoproliferative Disorders

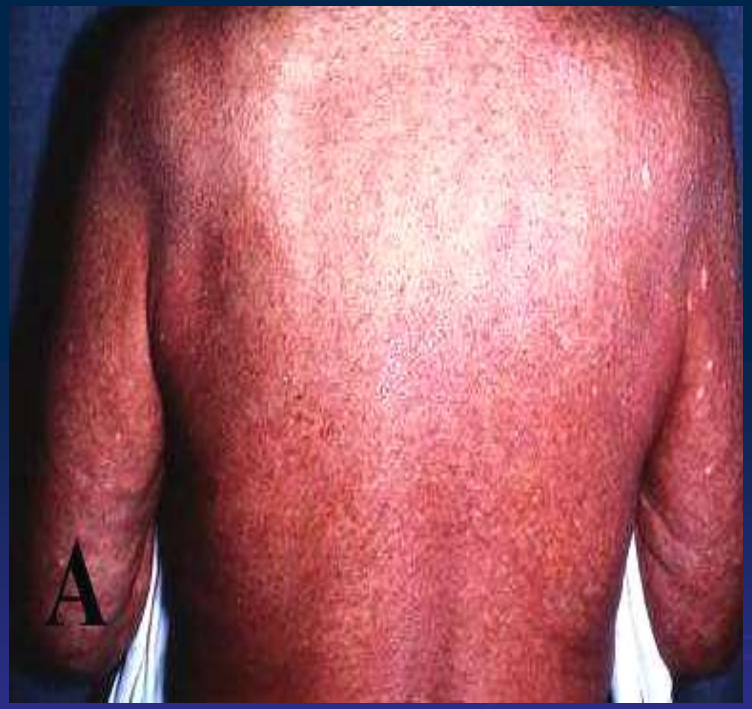
From Imam *al., Leuk. & Lymph. 2014*
and Bradford *et al., Blood 2009 (US SEER datasets*

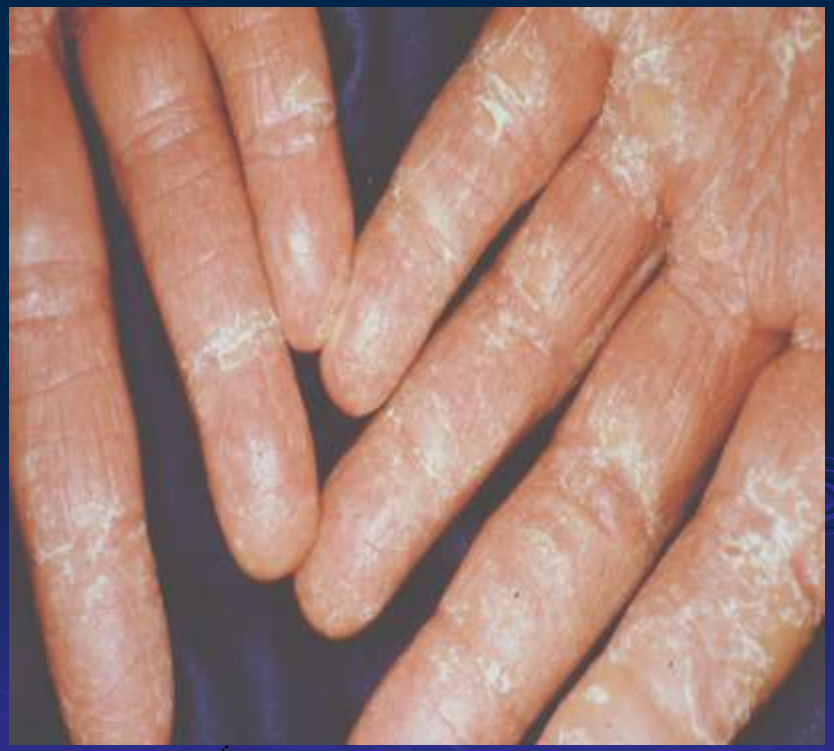
Sezary Syndrome and others

- Clinical
- Blood Findings=DX
- Skin histology
- DDX: tumor MF/ATL
- Biomarkers
- Lymph node dx
- Prognosis
- Others; CD30 + CTCL spectrum

SS Clinical- “red man syndrome”

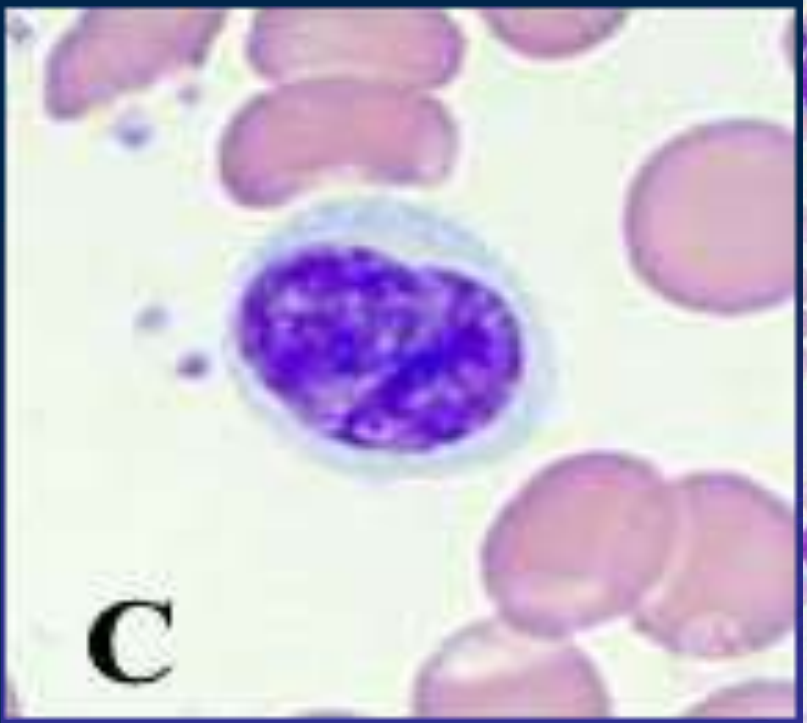
Older males, red skin, palmar hyperkeratosis
abrupt erythroderma, rarely with preceding MF;
T stage is T4 >80% of skin surface

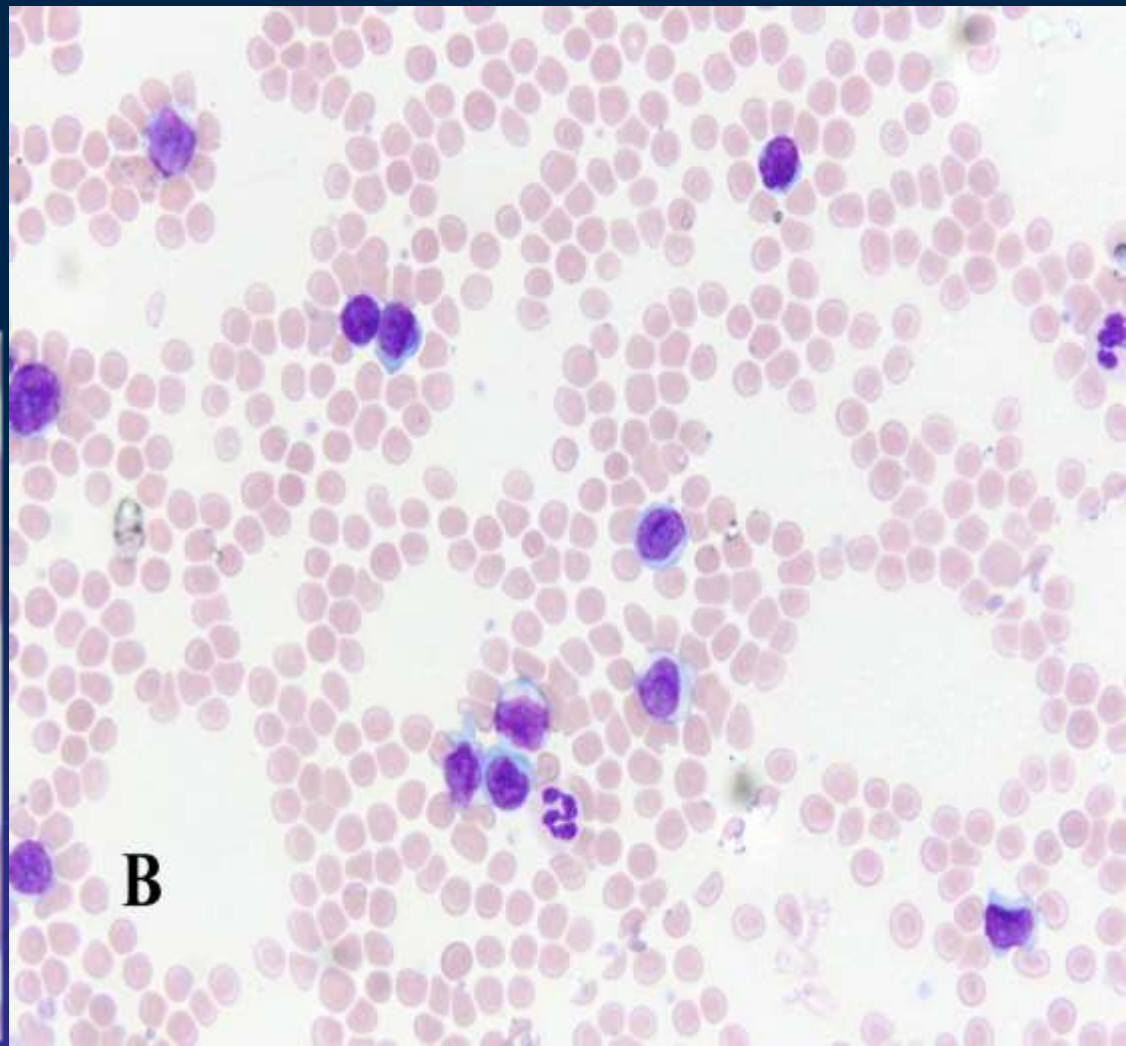




Blood

- Sezary cells
- grooved nuclei or cerebriform
  - “Monstrous cells”: 14-25 um in diameter





SS Blood Involvement

- B_0 remains 5% or less Sézary cells.
- B_1 is defined as more than 5% Sézary cells but either less than 1.0 K/µL absolute Sézary cells or absence of a clonal rearrangement of the TCR or both.
- B_2 is now defined as a clonal rearrangement of the TCR in the blood and either 1.0 K/µL or more Sézary cells or one of the following:
  - (1) increased $CD4^+$ or $CD3^+$ cells with CD4/CD8 of 10 or more or
  - (2) increase in $CD4^+$ cells with an abnormal phenotype (40% $CD4^+/CD7^-$ or 30% $CD4^+$/CD26.

Olsen et al 2007, ISCL/EORTC

SS Diagnosis- T4 + B2

- SS is thus defined as meeting T4 plus B2 criteria,

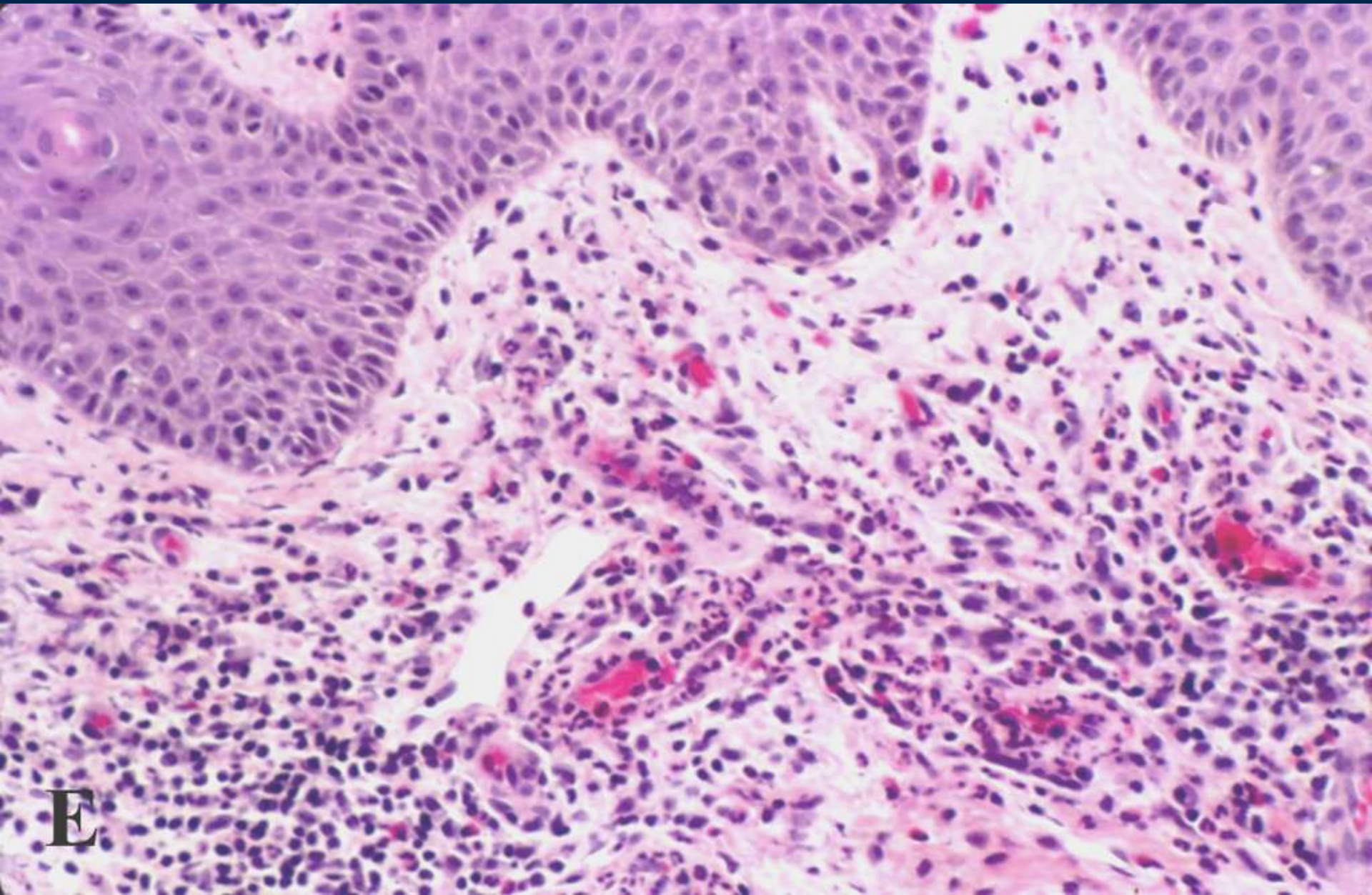
- T4 refers to a confluence of erythema covering at least 80% of the body surface
- B2 a high blood tumor burden.
- Caveat: ISCL recommends: Where the biopsy of erythrodermic skin may only reveal suggestive but not diagnostic histopathologic features, the diagnosis may be based on either a lymph node biopsy or fulfillment of B2 criteria including a clone in the blood that matches that of the skin.

Sezary Histology

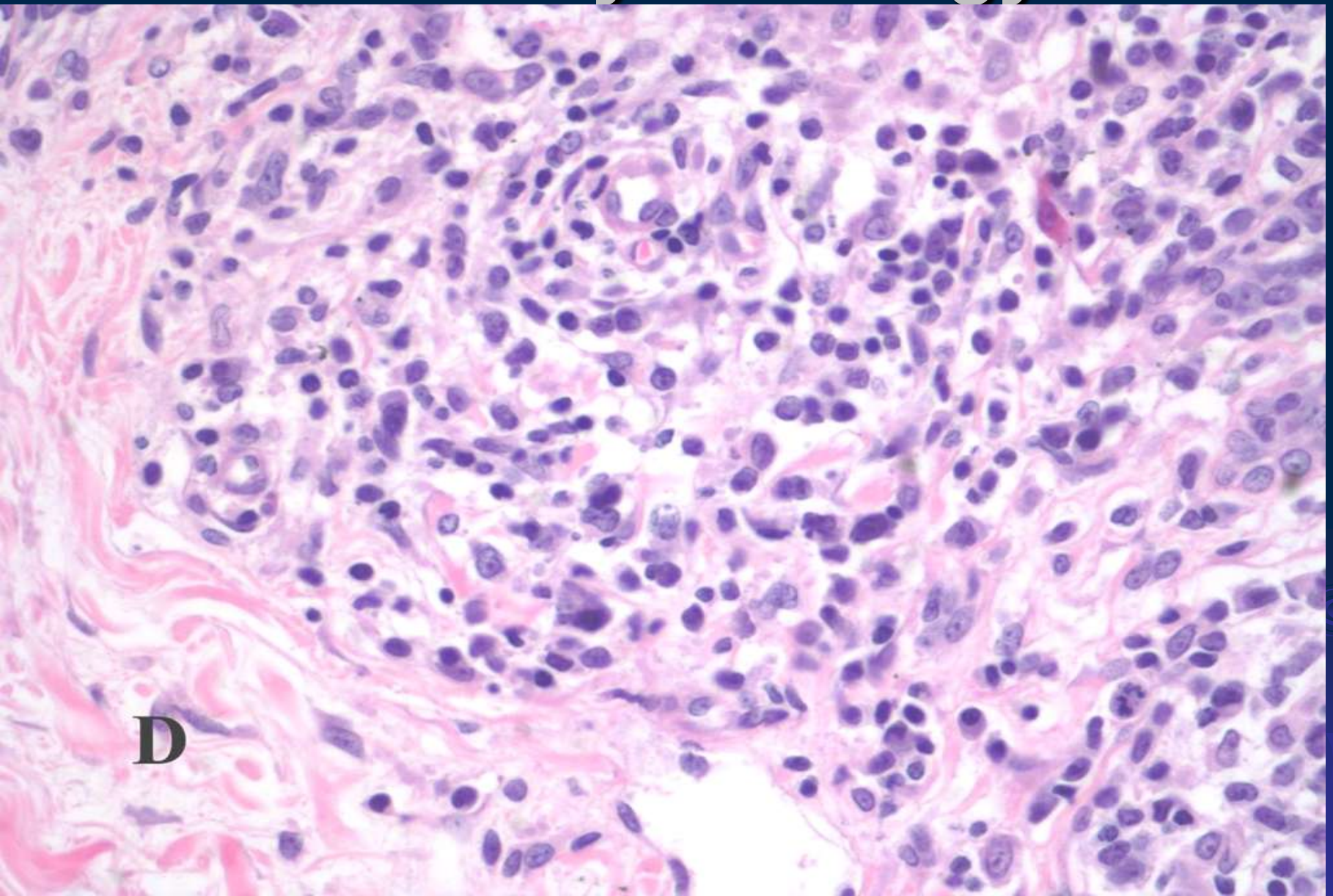
- Nonspecific epidermal changes akin to chronic dermatitis common. Epidermotropism is often minimal or absent, making the diagnosis in skin more challenging.
- Inflammatory histology common (33%): Lymphoid infiltrate ranges from sparse and perivascular , mild dermal fibrosis and occasional plasma cells and eosinophils
- Rarely : MF-like with lichenoid, follicular mucinosis or tumor nodules as in transformed MF

Trotter, M.J. et al. Cutaneous histopathology of Sezary syndrome: a study of 41 cases with a proven circulating T-cell clone. *J. Cutan. Pathol. 24, 286, 1997*.

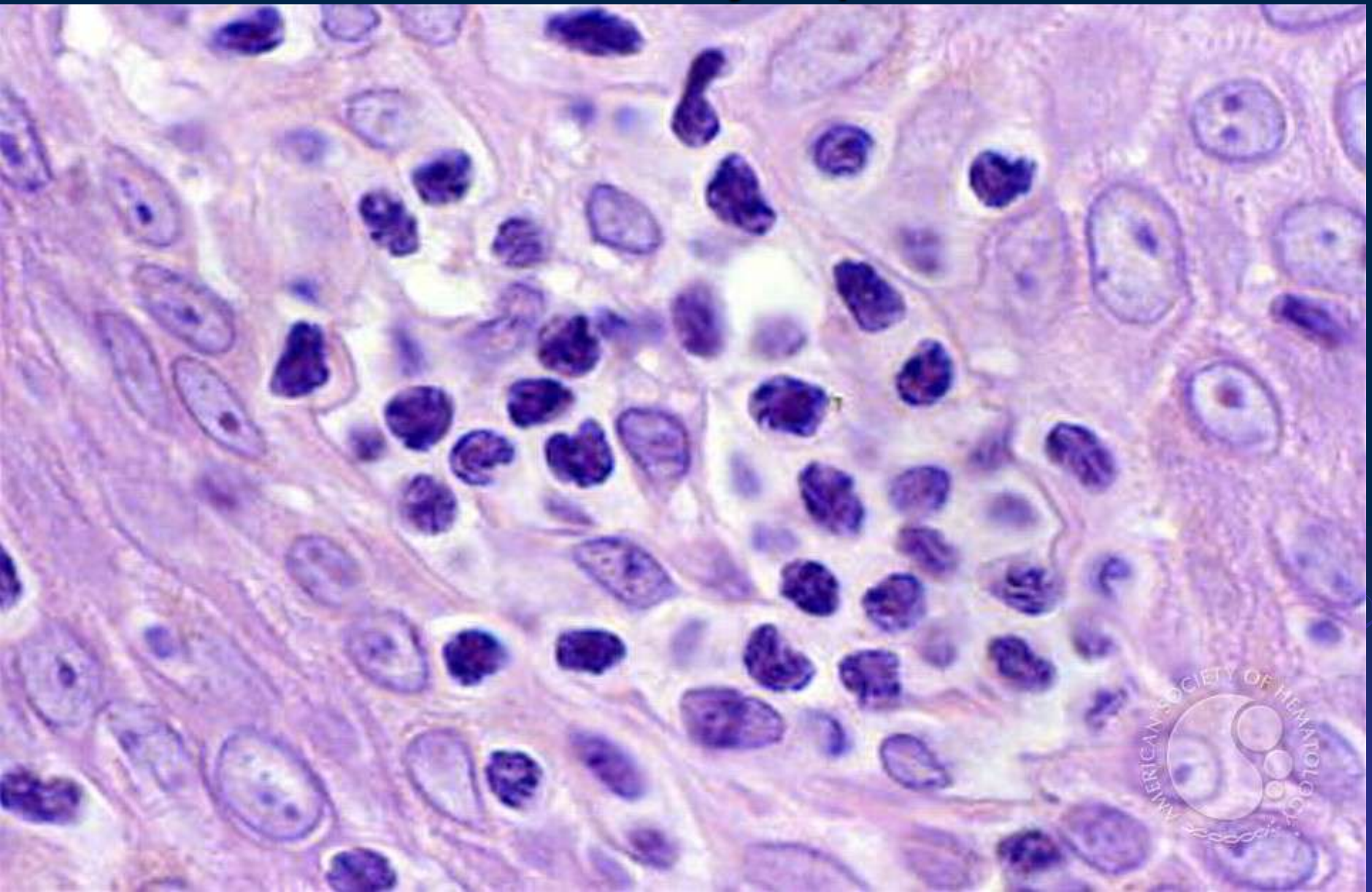
Sezary Syndrome-non specific inflammatory histology



Sezary histology

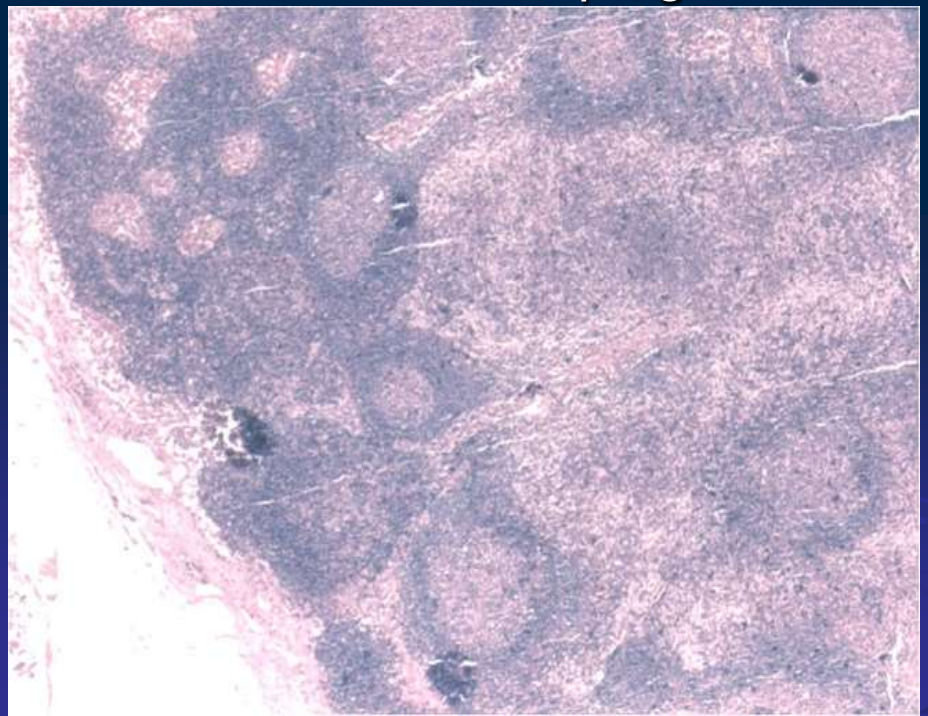


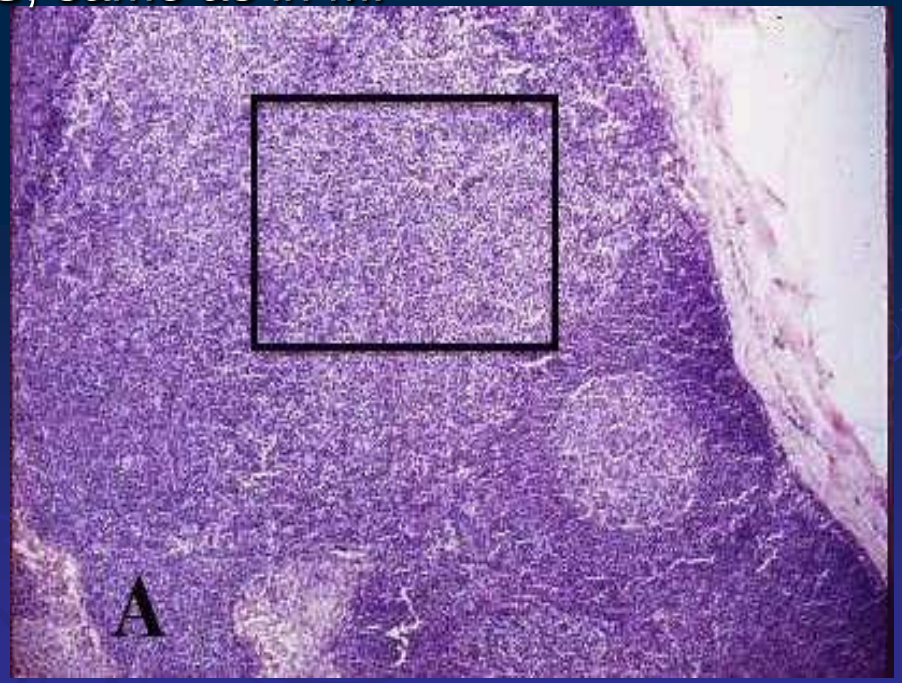
Darier's nests(seen below in… MF plaque) not as common in Sezary biopsied skin



Lymphadenopathy

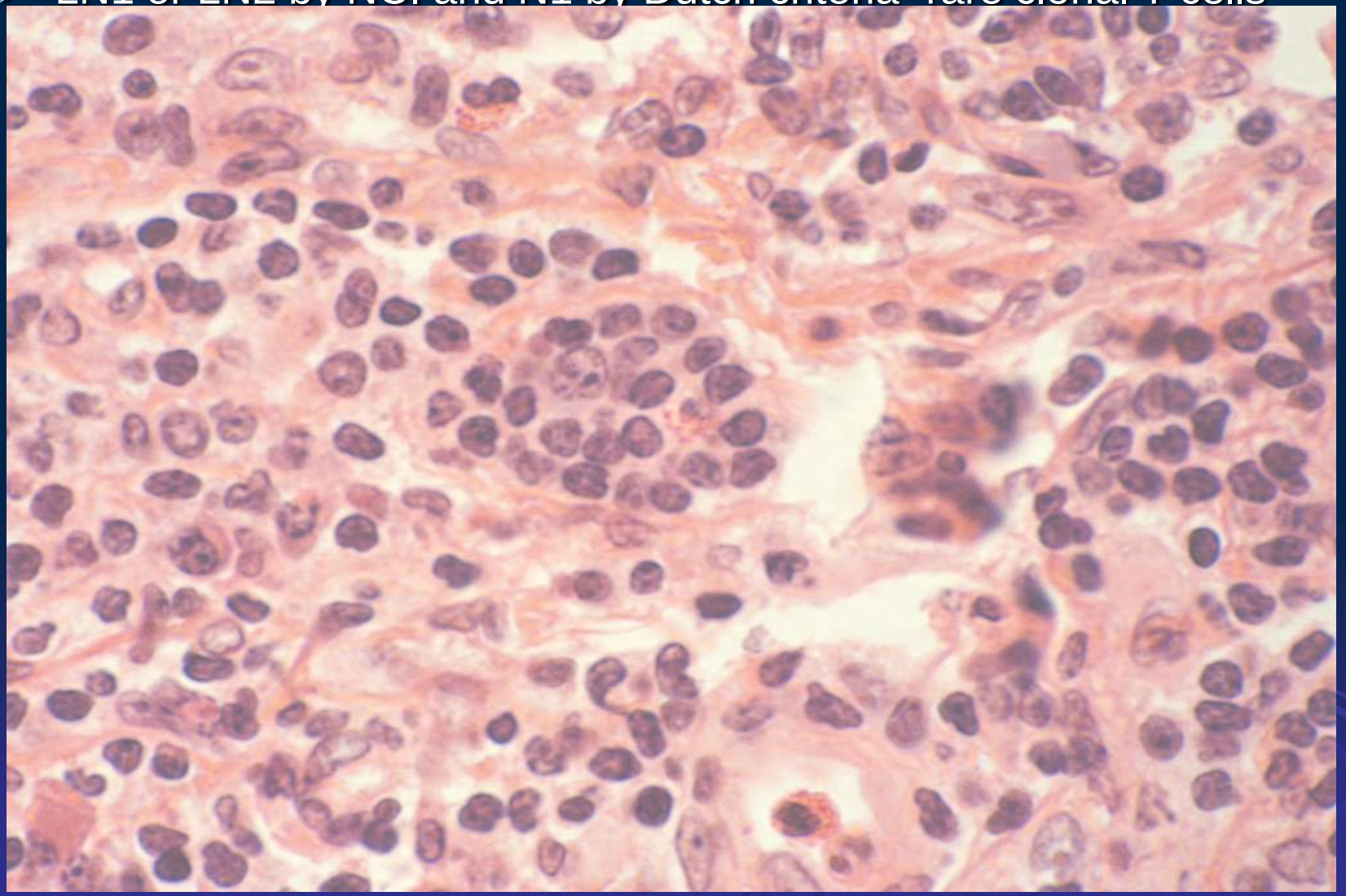
- > 1.5 cm, or any palpable node that is confluent, matted or fixed. Excisional bx needed,not needle or cytological.
- Histology a must: since involvement may be focal in MF/SS. SS often effaced lymph node, not like seen in MF
- Need to send for T cell clonality analysis
- LN involvement prognostic in SS, same as in MF



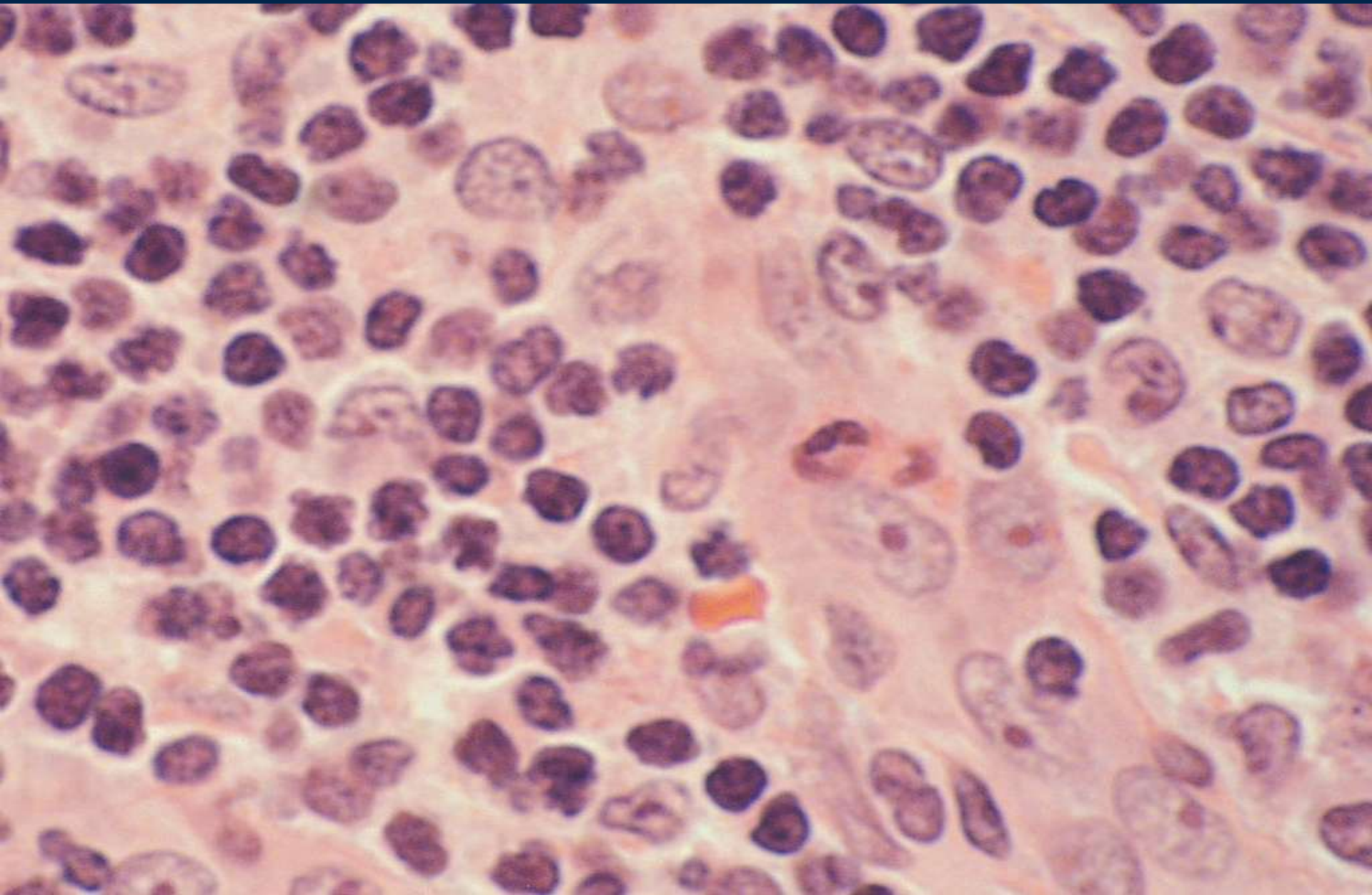


Uninvolved LNs

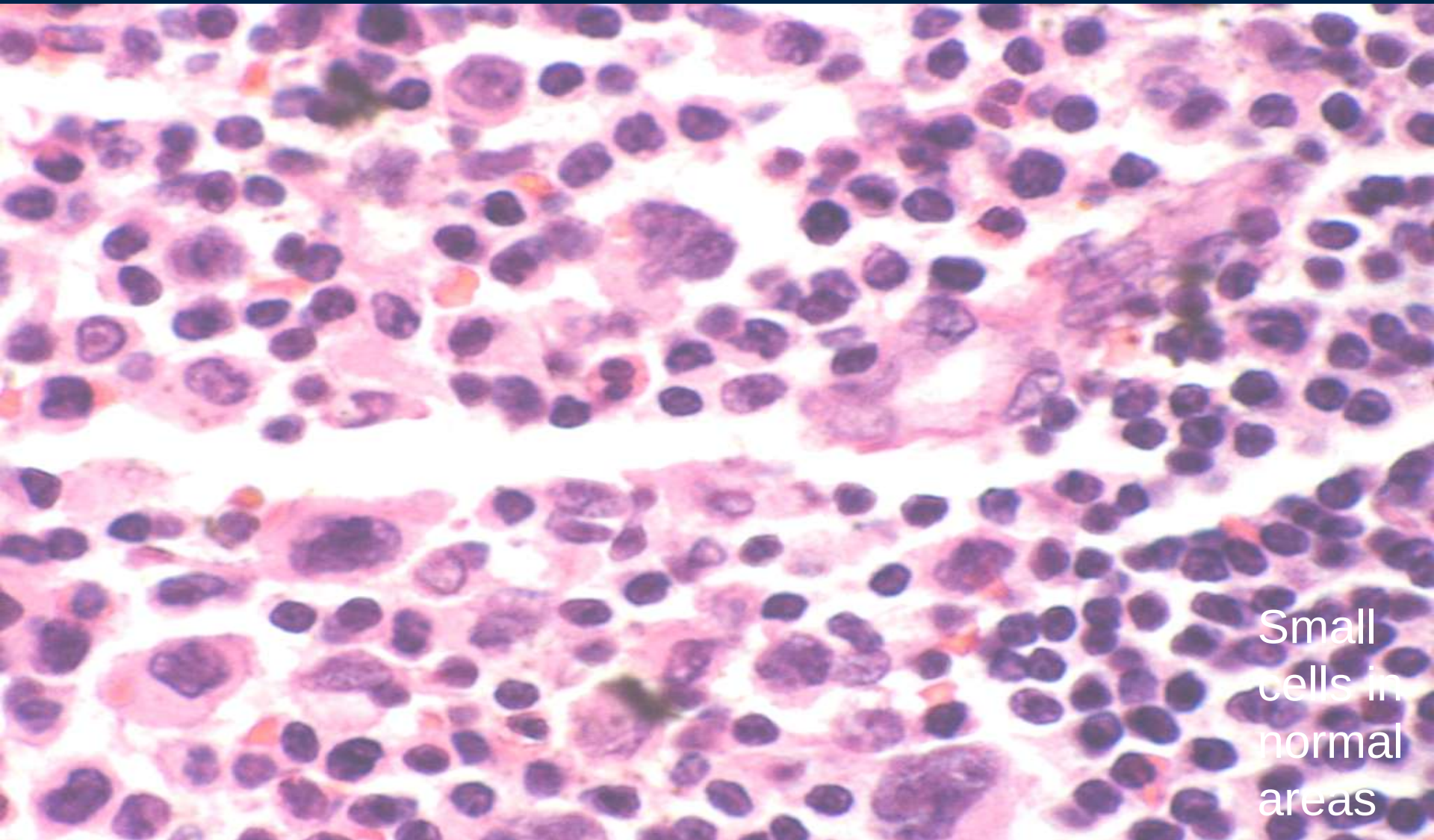
- LN1 or LN2 by NCI and N1 by Dutch criteria- rare clonal T cells



LN3- involved with tumor



LN4- effaced with monstrous tumor cells ,
seen in Sezary syndrome and advanced MF- Dutch N3 uses size in microns, in addition as cut off of atypical cells



Differential diagnosis of red skin from SS

- Erythrodermic MF(E MF)
  - “Absent” blood involvement(<5%)
  - T cell clonality found in both SS and E MF
- Reactive Erythroderma

  T cell clonality is also seen: 34% has T cell clone in benign inflammatory erythroderma

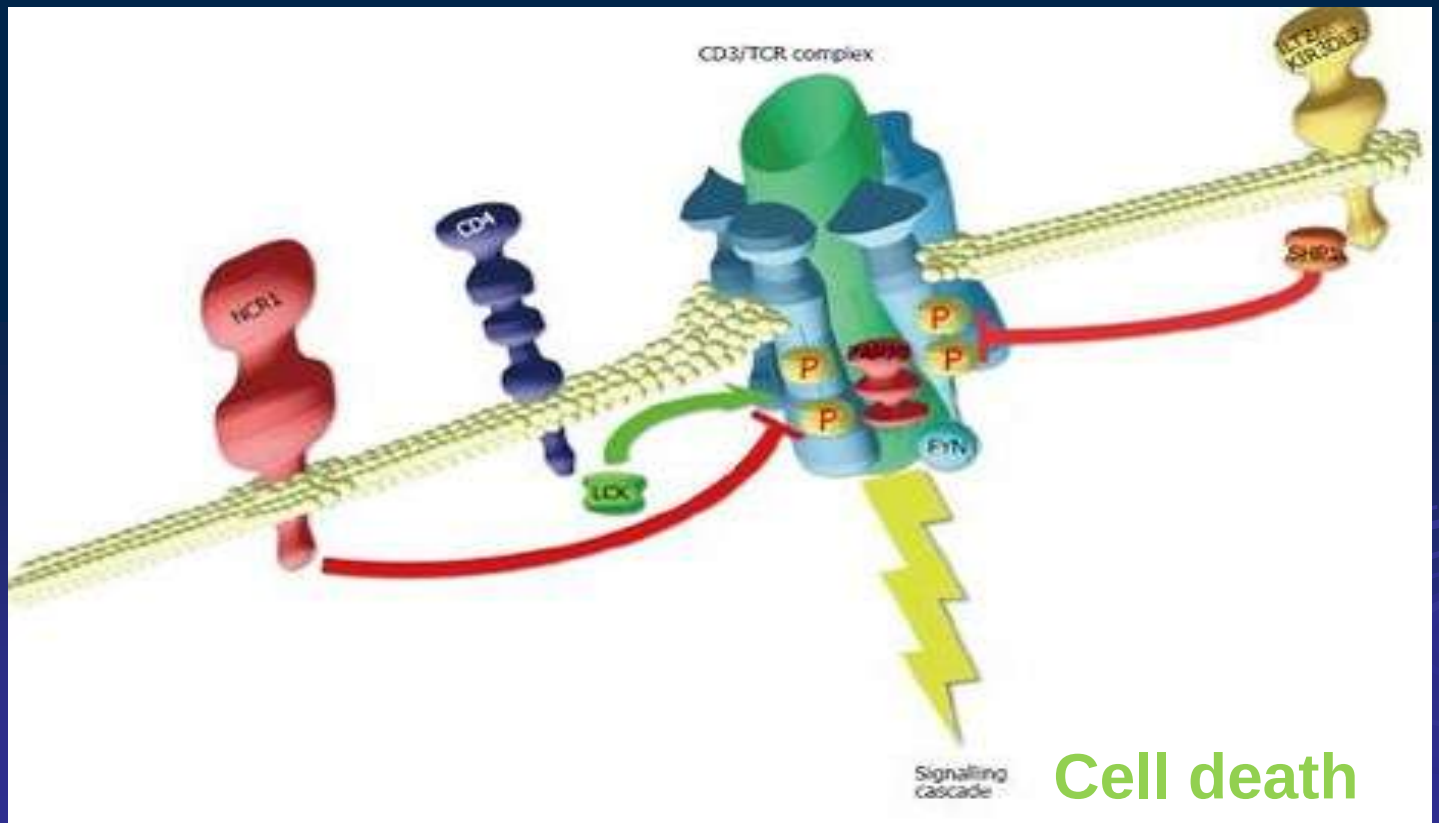
Delfau-Larue MH, Laroche L, Wechsler J, Lepage E, Lahet C, Asso-Bonnet M, Bagot M, Farcet JP. Diagnostic value of dominant T-cell clones in peripheral blood in 363 patients presenting consecutively with a clinical suspicion of cutaneous lymphoma. Blood. 2000;**96**:2987

Need for SS tumor marker, not just clonality

- Therefore the identification of a predominant T-cell clone might reflect a reactive rather than a neoplastic T-cell clone.
- The evaluation of other potential Sézary cell markers is consequently important for the diagnosis, prognosis and follow-up of SS. Among the proposed potential markers, several belong to the natural killer (NK) cell lineage

Killer Inhibitory Receptor(KIR)

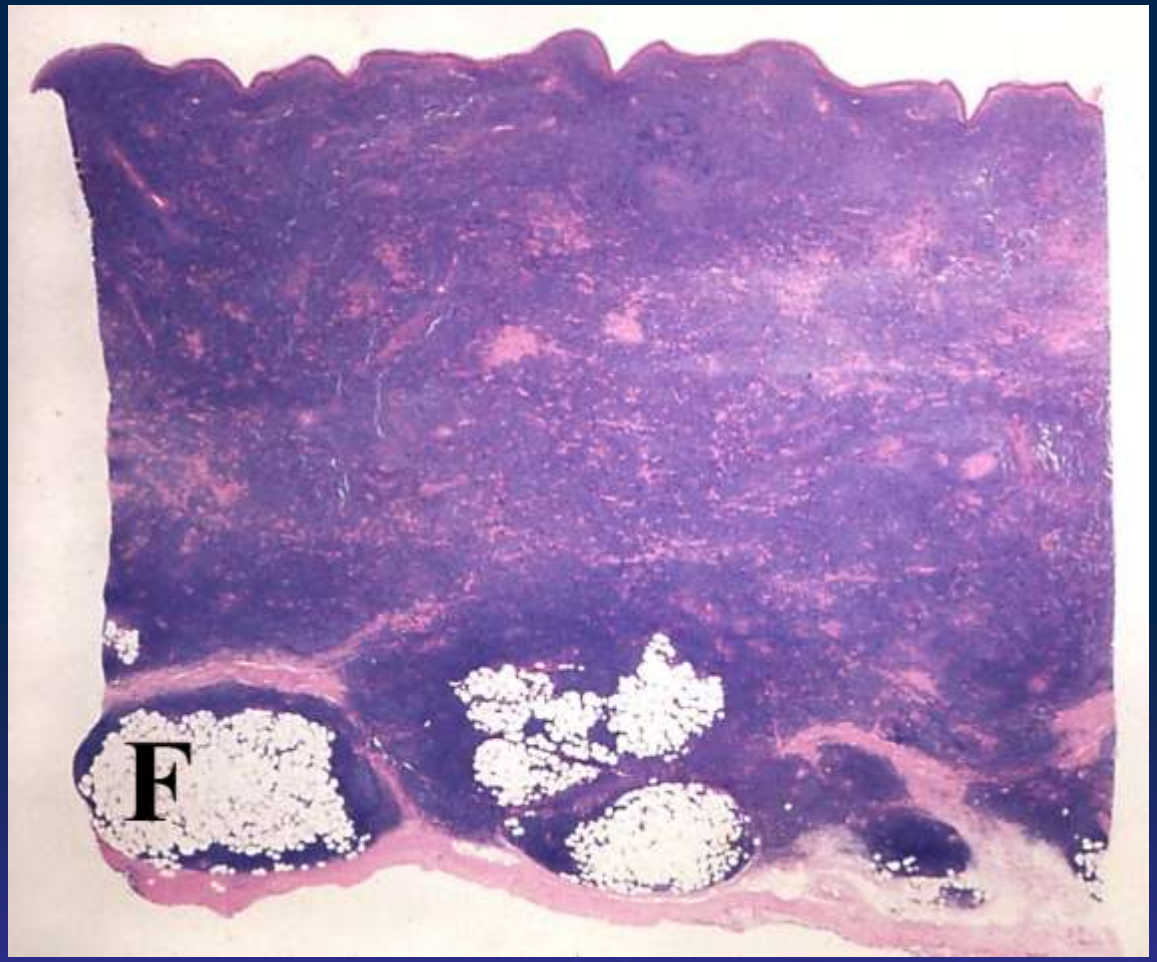
- KIR3DL2 is an inhibiting receptor of the KIR superfamily, normally expressed on a minor fraction of normal NK cells



KIR3DL2/CD158k molecule

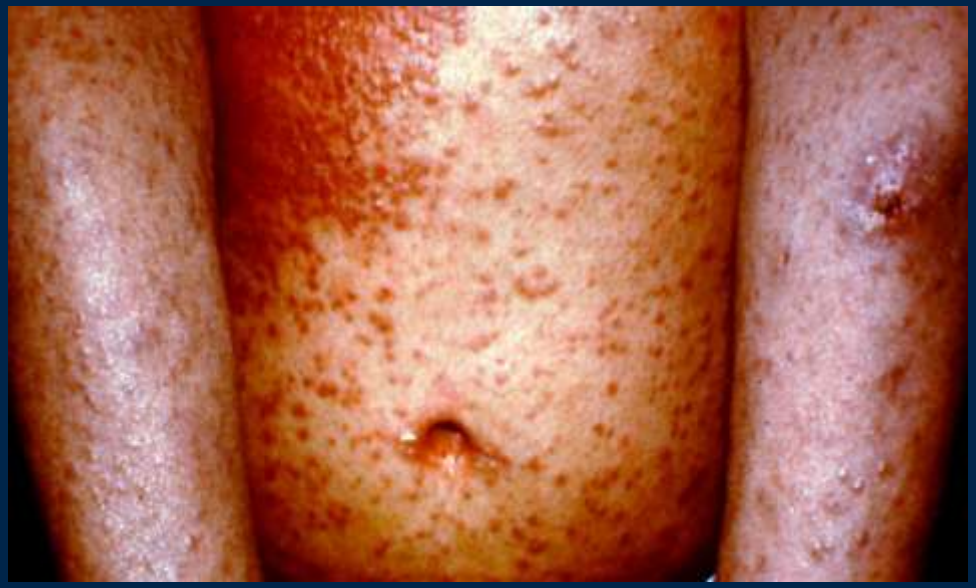
- **In the skin, KIR3DL2/CD158k significantly overexpressed in SS compared to erythrodermic inflammatory diseases.**
- The only occasional expression of KIR3DL2/CD158k on rare $CD4^+$ T-cells from healthy individuals makes it a valuable positive marker to identify malignant Sézary cells, when present at low levels, and to monitor the tumor cell load during therapy.
- **This unique molecule is also overexpressed in transformed MF(large T cell lymphoma) and HTLV-1+ Adult T cell lymphoma; a promising target of therapy**
- **Obama, Brit J of Hematology, 2007**

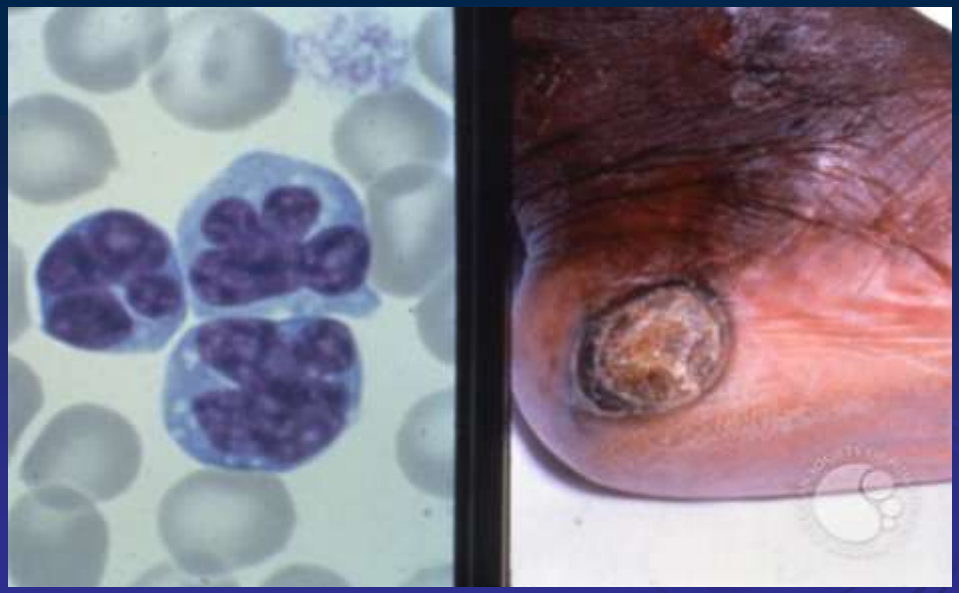
IIB or tumor histology

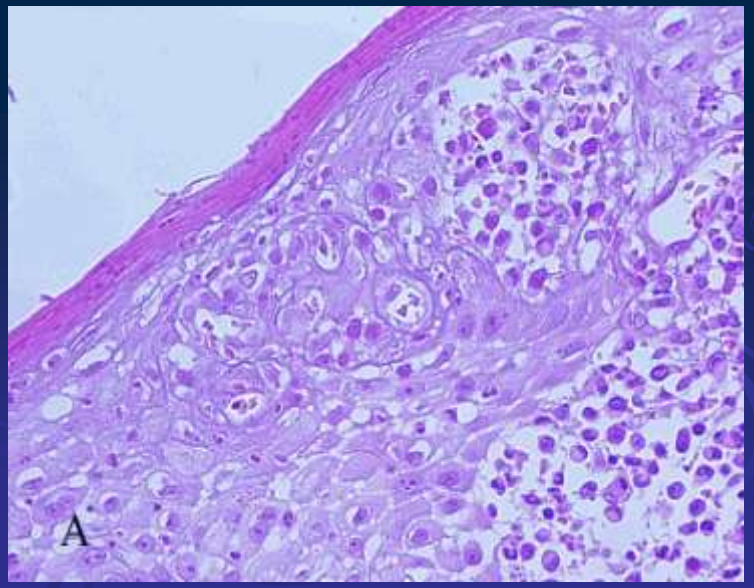


At least 25% of cells are large

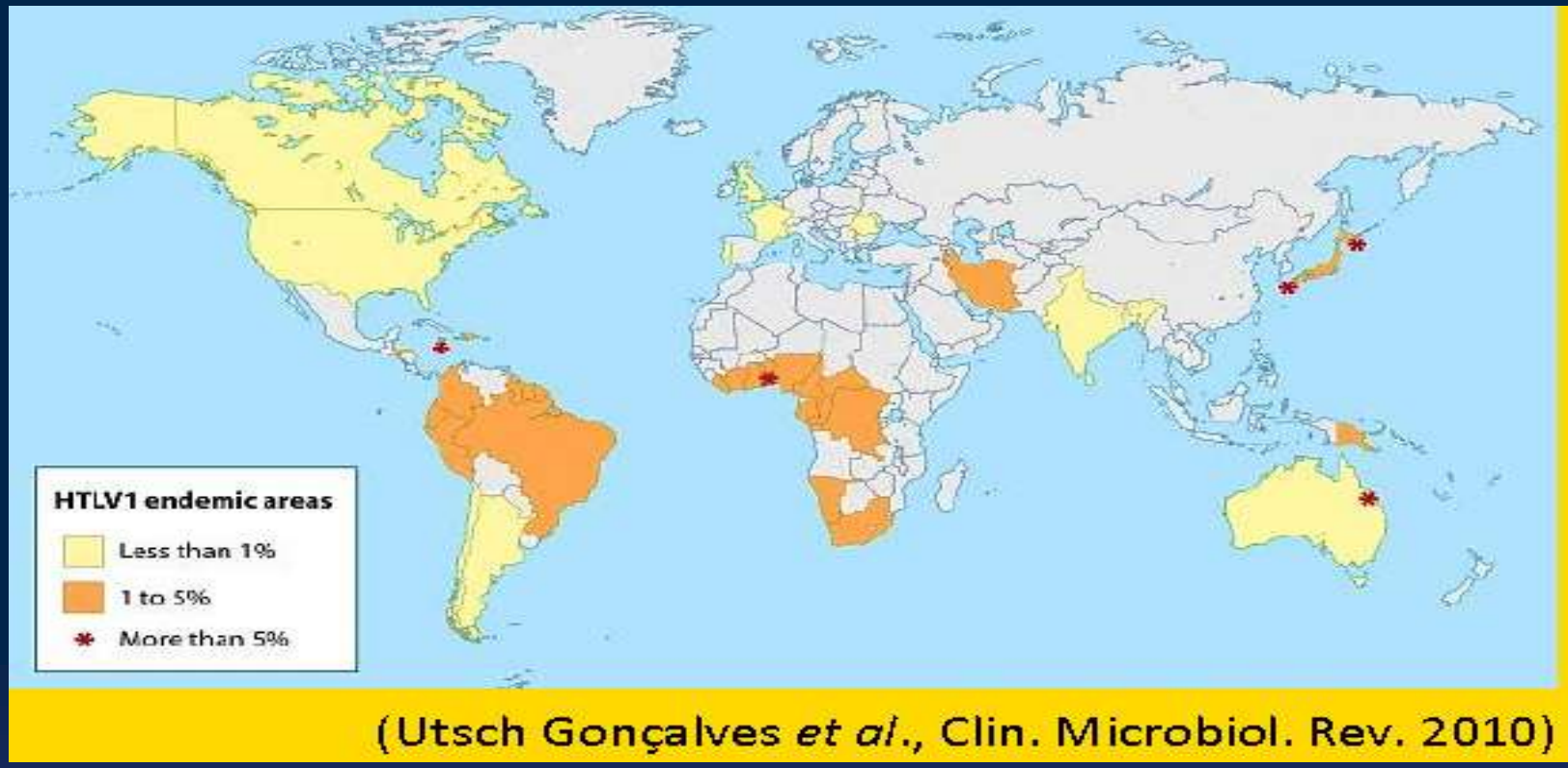
ATL-L can mimic MF/SS







Adult T cell lymphoma/leukemia

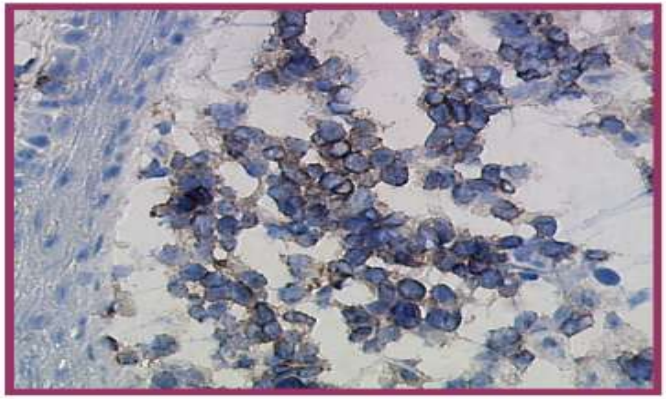


(Utsch Gonçalves *et al.*, Clin. Microbiol. Rev. 2010)

~20 million HTLV-1 infected people around the world, found in specific endemic areas. Highest prevalence in Japan, Africa, the Caribbean Islands,Central & South America:

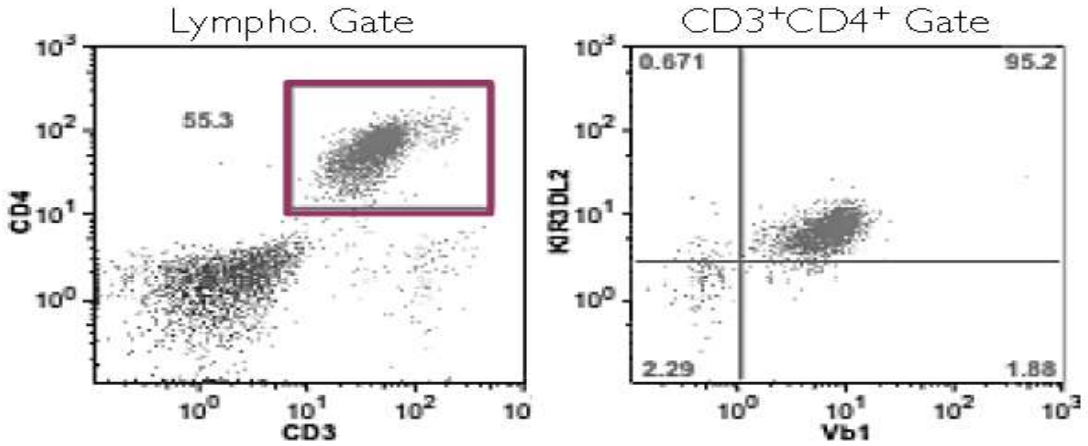
Biomarker and diagnostic tools

a- Sezary Syndrome



b- Transformed Mycosis Fungoides

Sezary Patient #4



N. Viaud[1], N. Granier[1], S. Zerbib[1], A. Dujardin[1], A. Marie-Cardine[2], C. Bonnafous[1], M. Bléry[1], C. Paturel[1], B. Rossi[1], A. Bensussan[2], M. Bagot[2] and H. Sicard[1]

[1]Innate Pharma, 117 Av. de Luminy, Marseille, France, [2]Hôpital Saint Louis, INSERM U976, Paris, France

AACR Annual Meeting 2013

Future Biomarker

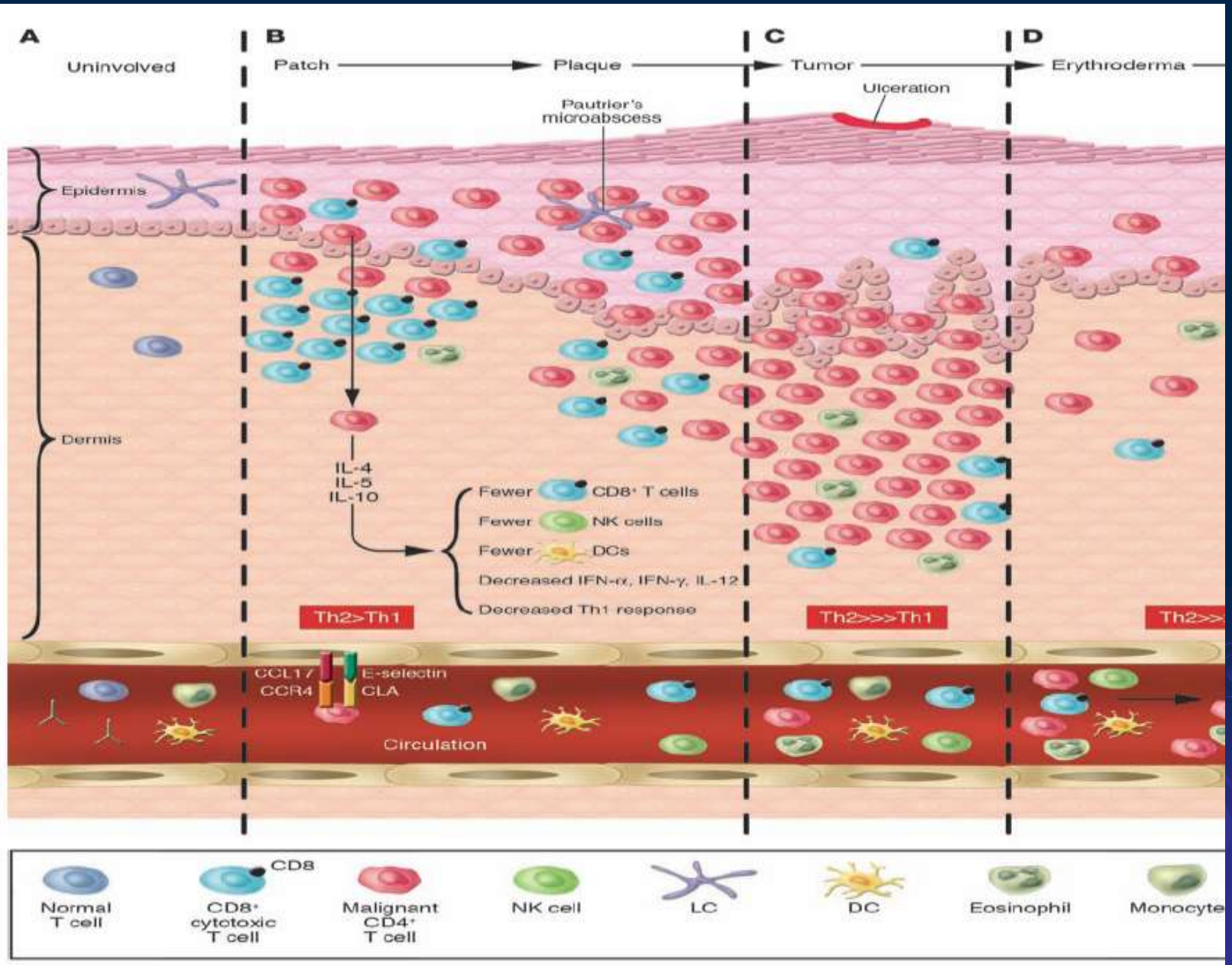
- IPH4102 is a humanized cytotoxic antibody which targets and destroys cells expressing KIR3DL2.
- Similar to Rituxan and other systemic therapy, targets tumor in Lymph nodes
- Early phases- by Innate Pharma

Pathogenesis: Sezary syndrome =CD4 T cells

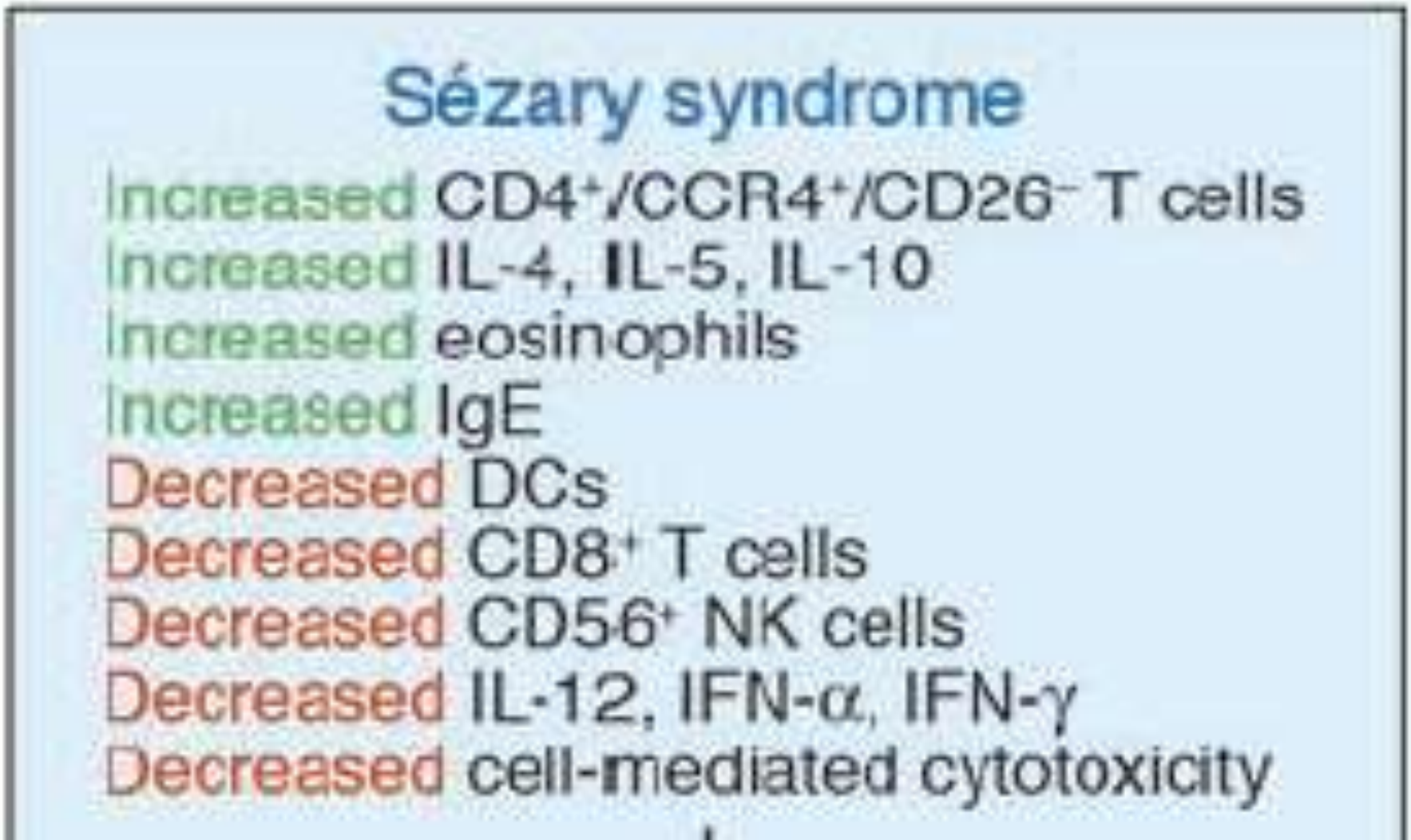
- The specific white blood cell here is called a CD4 memory cell.
- CD4 memory lymphocytes are regulators (brakes or accelerator) of the immune system in the skin.
- If these become cancerous, their messages becoming increasingly confusing (too many shouting; nobody being heard properly).
- If disease progresses, the ability to fight infection or cancer becomes more and more confused.

Other players: CD8 T cells or suppressors and Dendritic cells or antigen processing cells

Pathogenesis: Cutaneous T cell lymphoma, MF/SS



Sezary Syndrome pathogenesis is similar to tranformed or advanced MF= deregulation of normal immune response



Summary: Sezary Syndrome

- Circulating T-cells with large cerebriform nuclei : Dx needs blood smear evaluation+ TNM stage
- Lesions in skin are nonspecific or MF-like; Loss of epidermotropism=seldom bx
- LN effaced architecture: need bx, molecular clonality assay
- Clonal TCR rearrangement in

peripheral blood is useful but may benefit from tumor specific markers

Prognosis

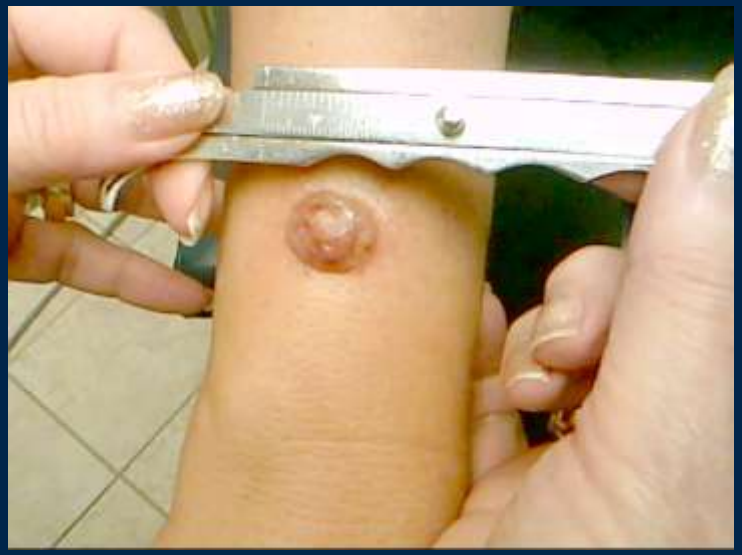
- Poor !

  20-27 % 5-year survival

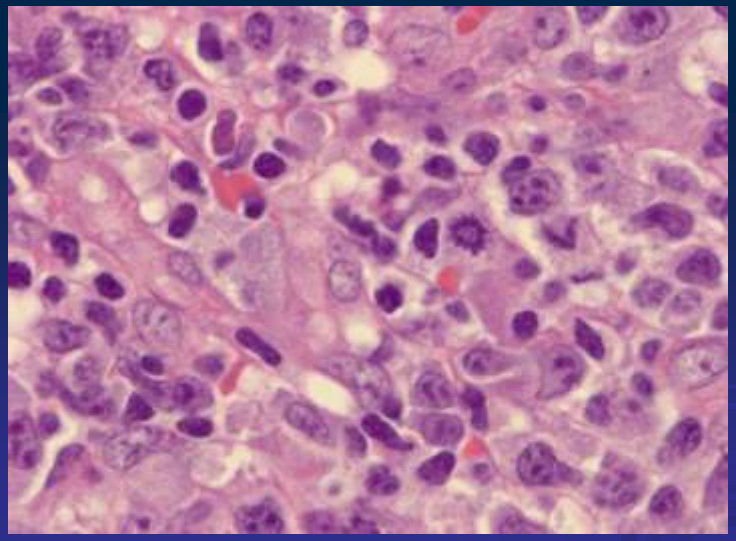
- Prognosis depends whether there is LN and/or blood involvement

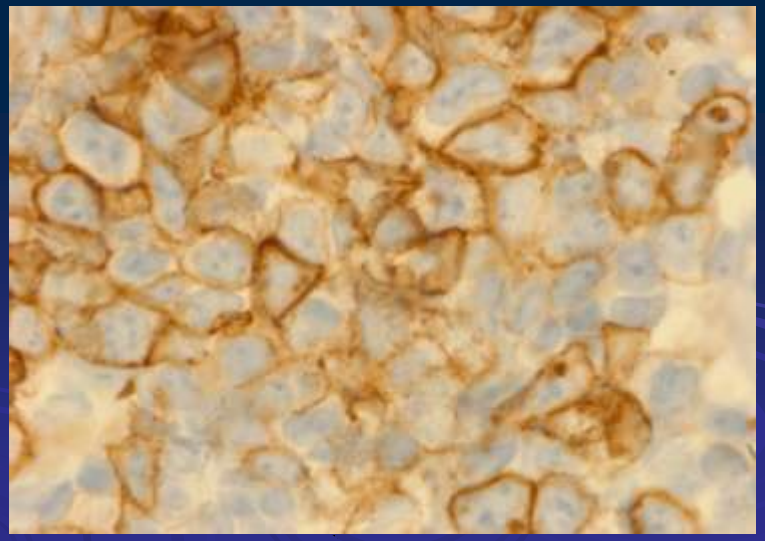
  Death from infection secondary to profound immunosuppression

Unlike: CD30 + CTCLs(LyP,cALCL)



“REGRESSING ATYPICAL HISTIOCYTOSIS”
LESIONS REGRESS AND RECUR IN THE PRIMARY CUTANEOUS
good prognosis!

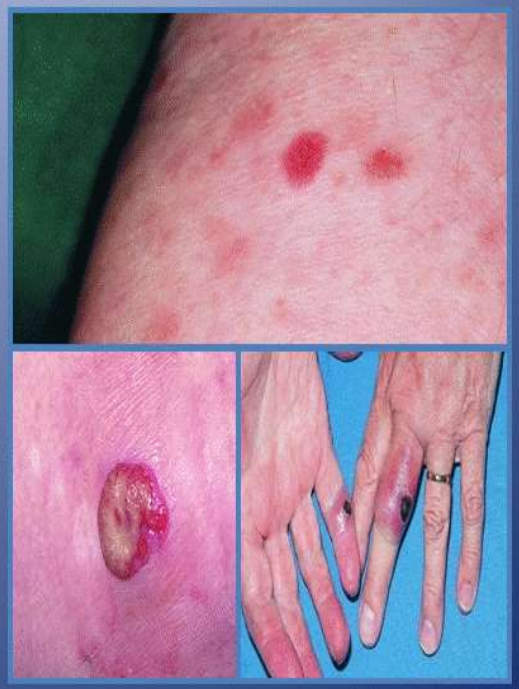




CD30 + CTCL spectrum: exception to the rule

Lymphomatoid Papulosis (LyP)

- Chronic, self-healing recurrent disorder
- Primarily adults
- M:F 2-3:1
- Trunk and extremities
  - Generalized eruption
- Five types
  - A, B, C,D, and E



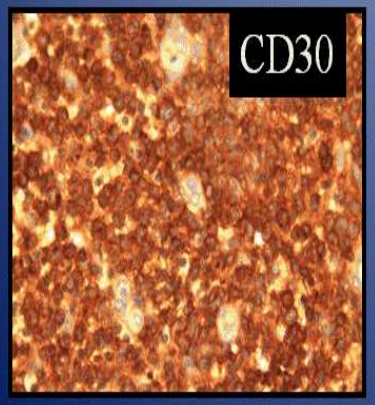
http://www.merckmedicus.com/ppdocs/us/hcp/content/white/chapters/white-ch-033-s002.htm

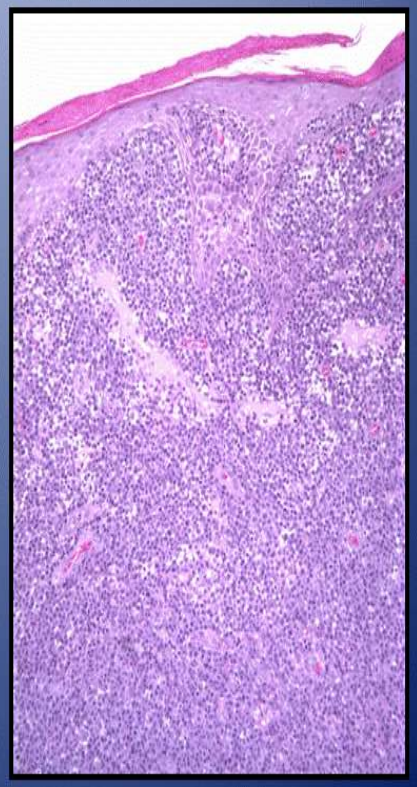
TYPE A.
Most remain LyP but about 10-20% of LyP progress to other malignancies: MF, Hodgkin lymphoma or tumor of cutaneous Anaplastic Large cell lymphoma

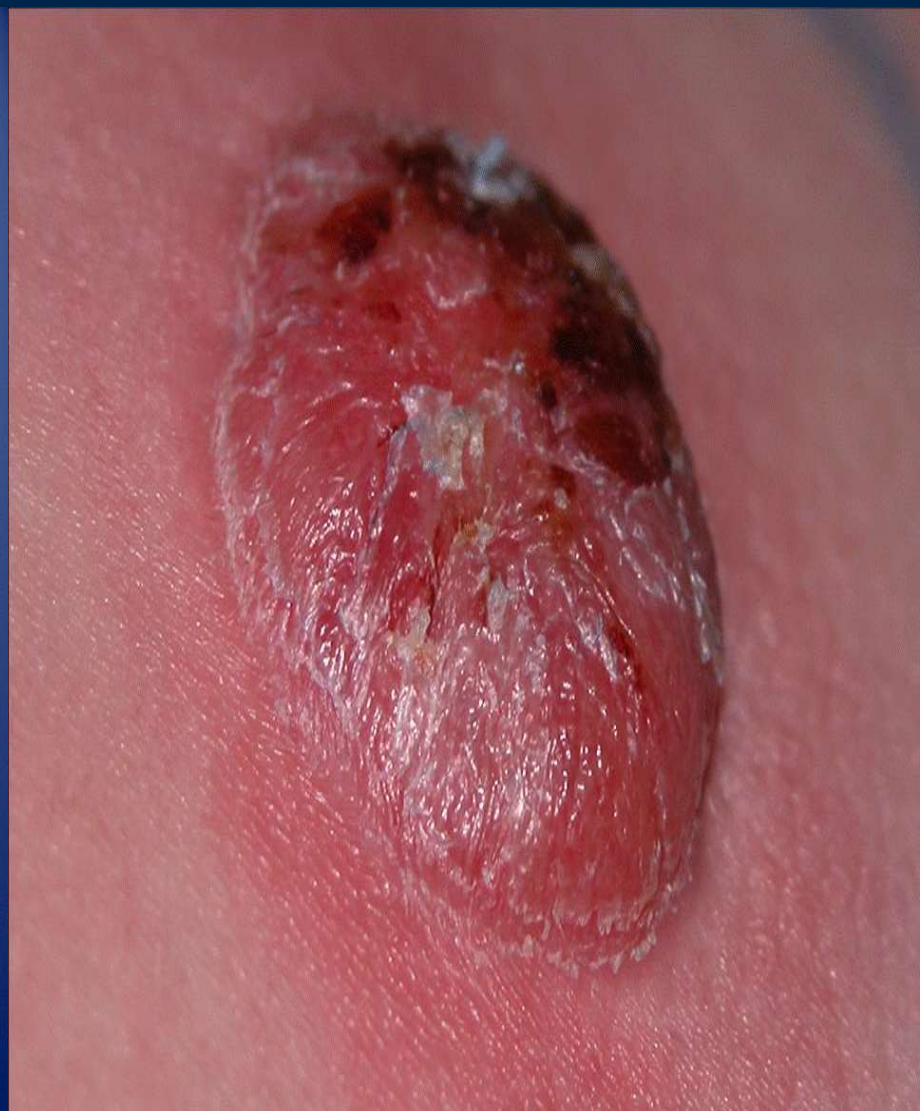
LyP to cALCL=same patient over 10 yrs

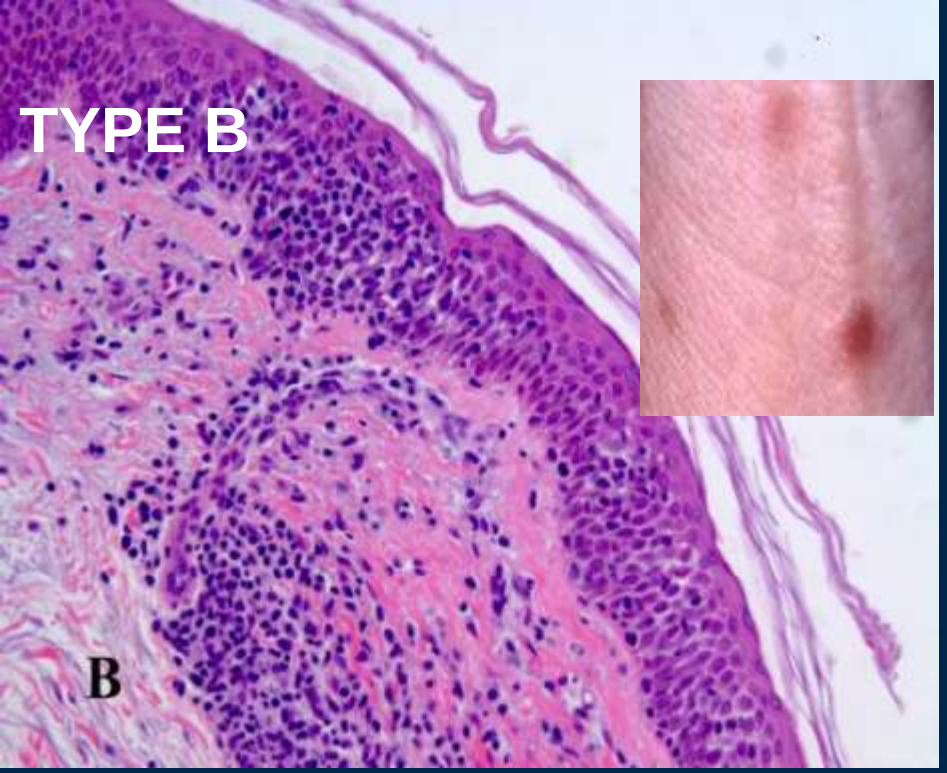
Right Flank Biopsy 1/05

- Primary cutaneous Anaplastic large cell (CD30 positive) lymphoma,ALK -

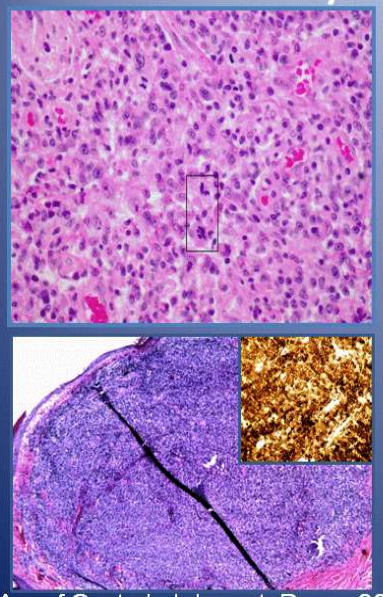






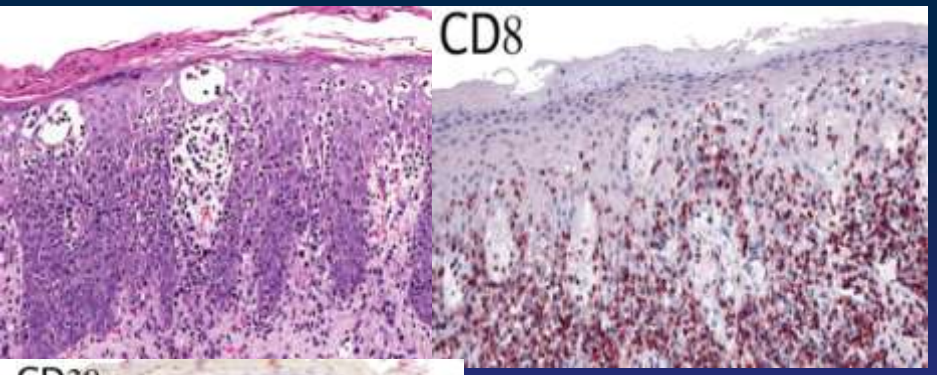


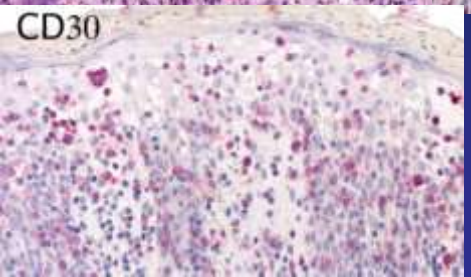
LyP Type C



- ALCL like
- Nodular infiltrates
  - Cohesive large sheets of atypical cells
- Minimal inflammation
- HISTORY!!!

Assaf C, et al. J. Invest. Derm. 2007. **127,** 1898–1904





TYPE D