Classification of Cutaneous T cell Lymphomas (CTCLs)

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CTCL, MF, and Sézary syndrome

- **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**
- **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 MF, occurring in about 5% of all cases of MF**


Baron Jean-Louis Alibert

[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 of MF

- **Frequency**

–US: approximately 1900 new cases of MF occur per year (ie, 0.64 cases per 100,000 population)*

* Weinstock MA et al. *Arch Dermatol.* 2007;143:1189-1190

•The continued rise in CTCL is substantial, and the cause of this increase is unknown

–More common in men and blacks (2:1 for both)

–Majority of patients are aged 45–65 years

•Mortality/morbidity

–The overall mortality rate is 0.064 per 100,000 persons; however, the mortality rate widely varies depending on stage of disease at diagnosis

New WHO-EORTC Classification

- **Facilitate more uniformity in diagnosis, management, and treatment of cutaneous lymphomas**
- **Provides a useful distinction between indolent and more aggressive types of primary cutaneous lymphoma**
- **This will prevent patients receiving high-grade treatment for low-grade biological disease**

Willemze R et al. *Blood.* 2005;105:3768-3785.
WHO = World Health Organization; EORTC = European Organisation for Research and Treatment of Cancer.

WHO/EORTC Classification of CTCL

CTCL, NK-cell Lymphomas
MF/MF variants and subtypes
Folliculotropic MF Pagetoid reticulosis Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders Primary cutaneous anaplastic large cell lymphoma Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified Primary cutaneous aggressive epidemiotropic CD8+ T-cell lymphoma (provisional) Cutaneous gamma/delta T-cell lymphoma (provisional) Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)

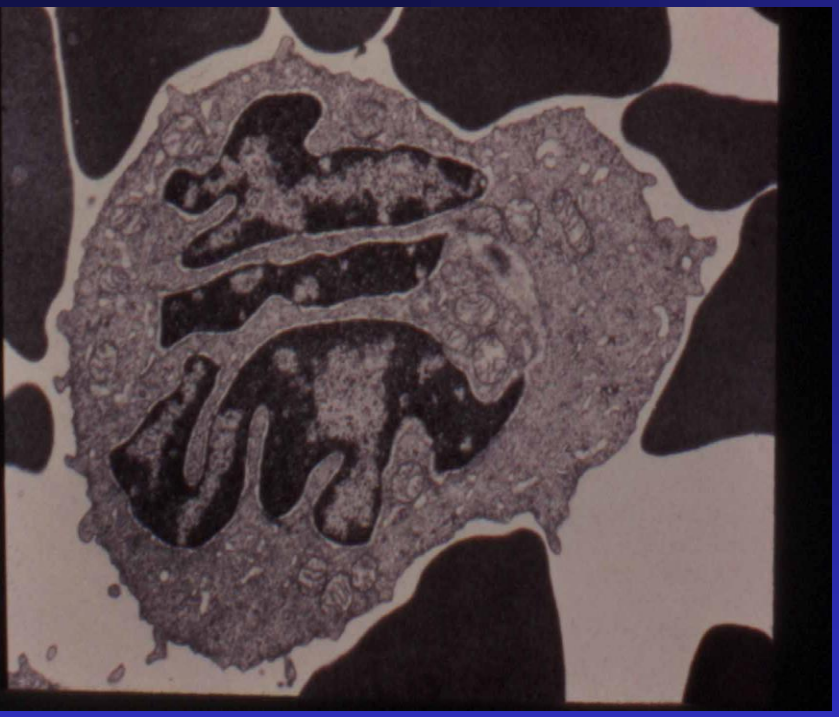
Precursor Neoplasm- "Blastic NK" or Plasmacytoid Dendritic Hematodermic Neoplasm

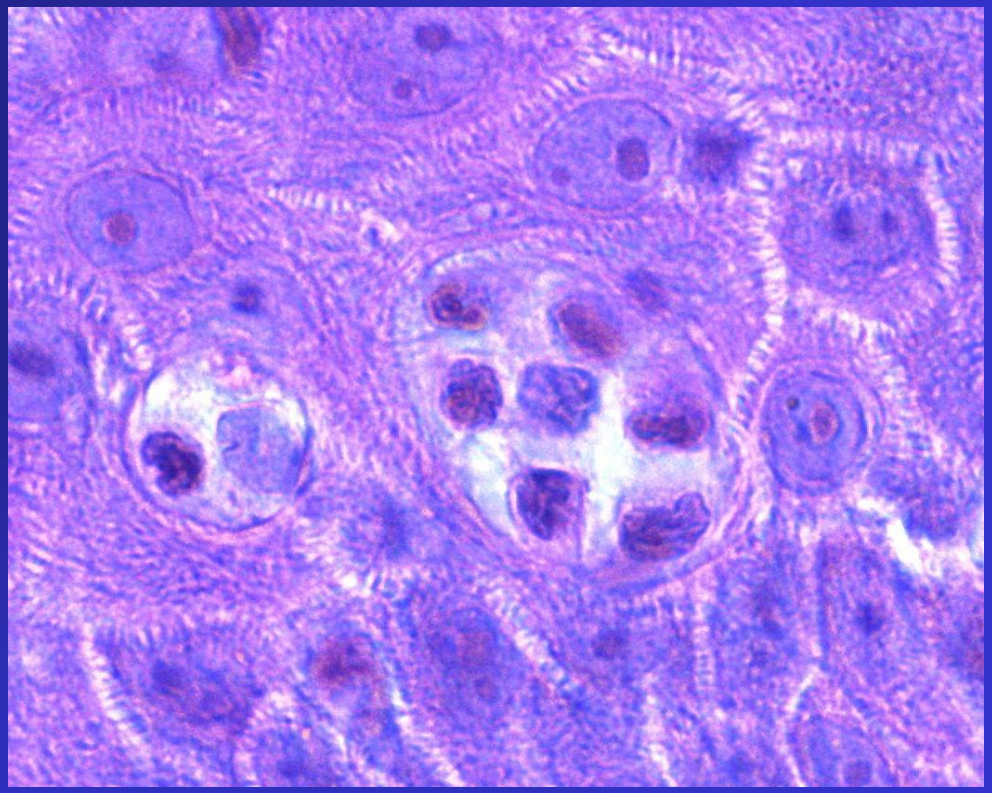
Willemze R, et al. *Blood*. 2005;105:3768-3785.

Cutaneous Lymphomas: Making the Diagnosis: Issues

1. Neoplastic vs atypical vs inflammatory
2. B-cell vs T-cell
3. Subtype
4. Primary cutaneous or systemic

Basis: accurate morphology

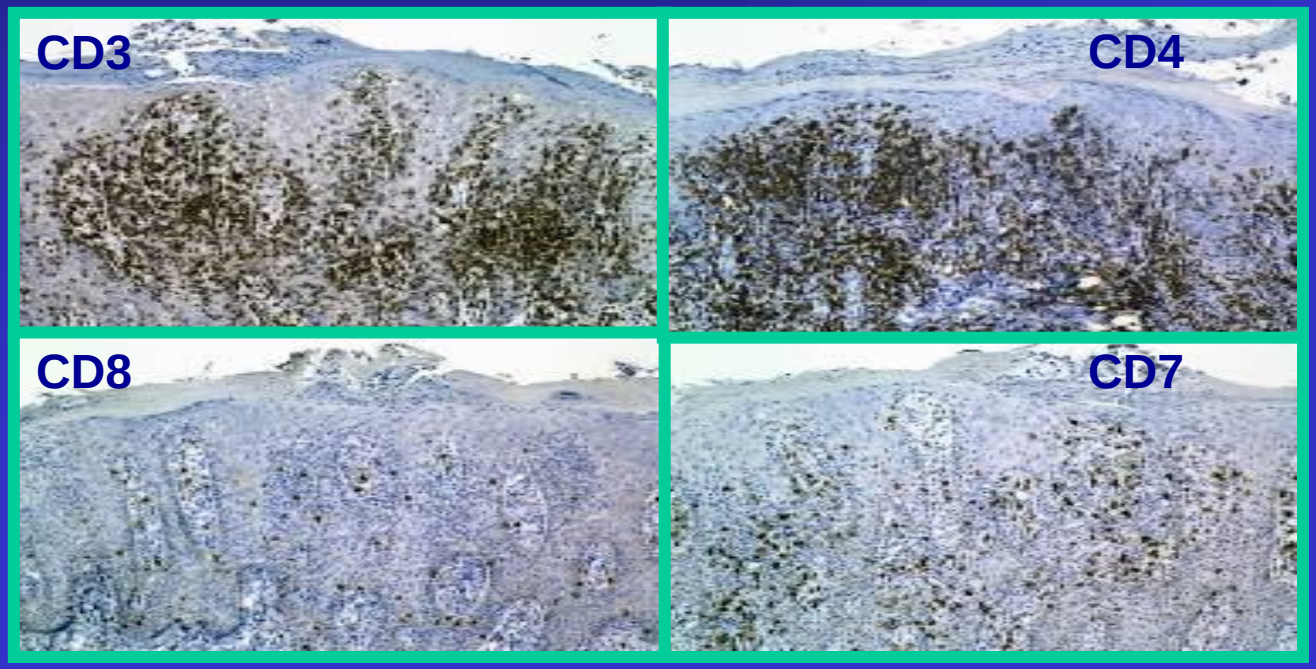




- Malignant cerebriform cell
  - Good Histology is key to classifying the “atypical cells”=
  - Cerebriform morphology shown by thin well stained section of epidermis

Immunophenotyping—Classic MF

- **Malignant skin-homing T-cells: $CD45RO^+$, CLA^+** $_{CLA = cutaneous\ lymphoid\ antigen.}$
- **$CD3^+$, $CD4^+$, $CD5^{+/-}$**
- **$CD7^{+/-}$, $CD26^{+/-}$**
- **Usually T-cell receptor (TCR) $\alpha\beta^+$**
- **Cytokine profile may change with disease progression (switch from Th1 to Th2 in advanced disease)**



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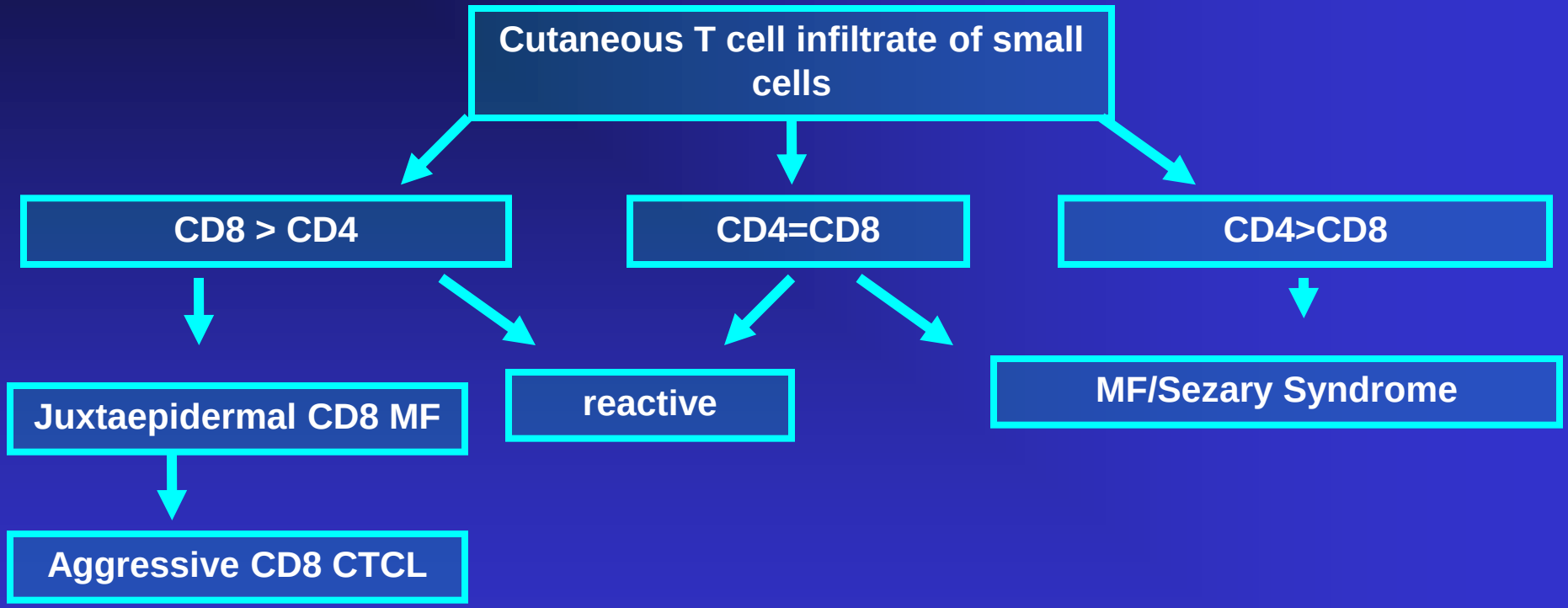
Immunophenotyping

- **CD4 and CD8 immunophenotypic can be very useful**



Flow Cytometry: Requires fresh tissue

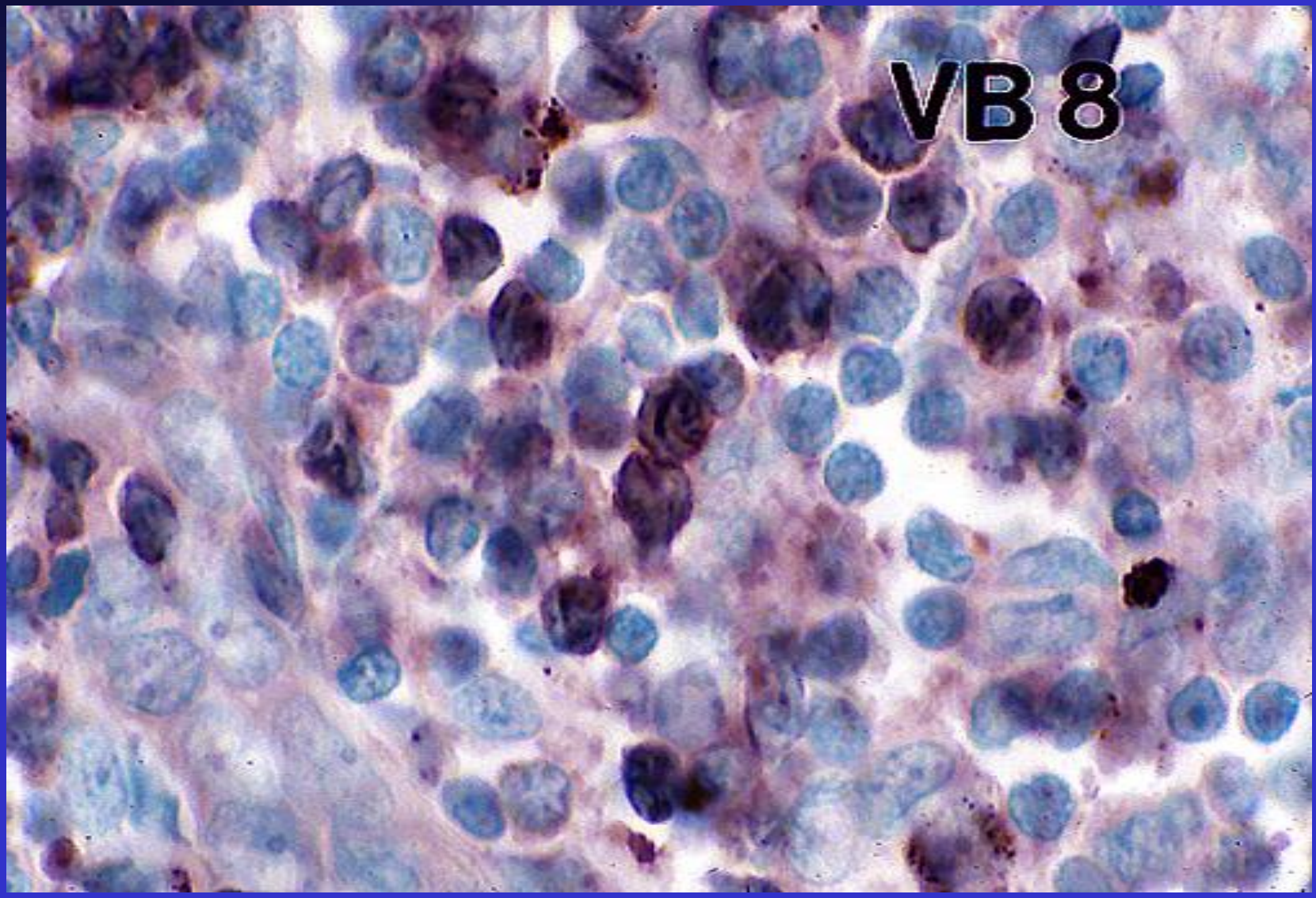
VIRTUAL FLOW CYTOMETRY does not require fresh tissue- formalin fixed tissue is ok

- **ROLE IN DIAGNOSIS, STAGING, AND TARGETED THERAPY**

ROLE IN DIAGNOSIS: SKIN BIOPSY MF

- **Determine markers: Immunopathologic Criteria**
- **1. CD2, 3 or 5 < 50% of T-cells**
- **2. CD7 < 10% of T-cells**
- **3. Epidermal discordance from expression of CD2,3,5, or 7 on dermal T-cells**
- **Pimpinelli N, et al. JAAD 2005:**

MF and transformation



Diagnostic Criteria: Blood

- **In Sézary Syndrome, flow cytometry and molecular evaluation of the blood are needed to establish the diagnosis:**

- **Demonstration of a T-cell gene rearrangement in the blood and *either* 1.0 K/µL or more Sézary cells OR one of the 2 criteria outlined by the International Cutaneous Lymphoma Society**

  - **–(1) increased $CD4^+$ or $CD3^+$ cells with CD4/CD8 of 10 or more by flow cytometery or**
  - **–(2) increase in $CD4^+$ cells with an abnormal phenotype (40% $CD4^+/CD7^-$ or 30% $CD4^+$/CD26]**

CAVEATS

- Peripheral blood flow cytometry
  - More objective than “Sézary prep”
  - May indicate abnormality (T cell antigen aberrancy) although
  - Molecular PCR test remain THE definitive test for clonality for T cells

ROLE IN STAGING MF

Table 6. Recommended evaluation/initial staging of the patient with mycosis fungoides/Sézary syndrome

- Complete physical examination including
  - Determination of type(s) of skin lesions
    - If only patch/plaque disease or erythroderma, then estimate percentage of body surface area involved and note any ulceration of lesions
    - If tumors are present, determine total number of lesions, aggregate volume, largest size lesion, and regions of the body involved
  - Identification of any palpable lymph node, especially those ≥ 1.5 cm in largest diameter or firm, irregular, clustered, or fixed
  - Identification of any organomegaly
- Skin biopsy
  - Most indurated area if only one biopsy
  - Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered.
  - Evaluation for clonality of TCR gene rearrangement
- Blood tests
  - CBC with manual differential, liver function tests, LDH, comprehensive chemistries
  - TCR gene rearrangement and relatedness to any clone in skin
  - Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including $CD4^+/CD7^-$ or $CD4^+/CD26^-$)
- Radiologic tests
  - In patients with $T_1N_0B_0$ stage disease who are otherwise healthy and without complaints directed to a specific organ system, and in selected patients with $T_2N_0B_0$ disease with limited skin involvement, radiologic studies may be limited to a chest X-ray or ultrasound of the peripheral nodal groups to corroborate absence of adenopathy
  - In all patients with other than presumed stage IA disease, or selected patients with limited T_2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted.
- Lymph node biopsy
  - Excisional biopsy is indicated in those patients with a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered, or fixed
  - Site of biopsy
    - Preference is given to the largest lymph node draining an involved area of the skin or if FDG-PET scan data are available, the node with highest standardized uptake value (SUV).
    - If there is no additional imaging information and multiple nodes are enlarged and otherwise equal in size or consistency, the order of preference is cervical, axillary, and inguinal areas.
  - Analysis: pathologic assessment by light microscopy, flow cytometry, and TCR gene rearrangement.

• *Olsen et al. Revision to the staging and classification.. Blood 2007 1713-1722.*

ROLE IN STAGING NON MF CUTANEOUS LYMPHOMAS

Table 3. ISCL/EORTC recommendations for staging evaluation in cutaneous lymphomas other than MF/SS

Complete history/review of systems and physical examination
Laboratory studies
Complete blood count, comprehensive serum chemistries, serum LDH
Whenever indicated, relevant flow cytometric studies of peripheral blood mononuclear cells
Imaging studies*
CT of chest, abdomen and pelvis with contrast alone or with whole-body PET (^{18}F-FDG); include CT or ultrasound of neck if clinically indicated
Whole-body integrated PET/CT (as alternative imaging study to the standard contrast-enhanced CT)
Bone marrow biopsy and aspirate†
Required in cutaneous lymphomas with intermediate to aggressive clinical behavior as categorized in the WHO-EORTC classification
Should be considered in cutaneous lymphomas with indolent clinical behavior, but not required unless indicated by other staging assessments
Additional studies as indicated clinically

*Lymph nodes that are >1.0 cm in short axis and/or have significantly increased PET activity should be sampled for tissue examination (an excisional biopsy is preferable whenever possible).

Youn H. Kim, Rein Willemze, Nicola Pimpinelli, Sean Whittaker, Elise A. Olsen, Annamari Ranki, Reinhard Dummer, and Richard T. Hoppe, for the ISCL and the EORTC

TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC)

Blood. Jul 2007; 110: 479 - 484

ROLE IN THERAPY

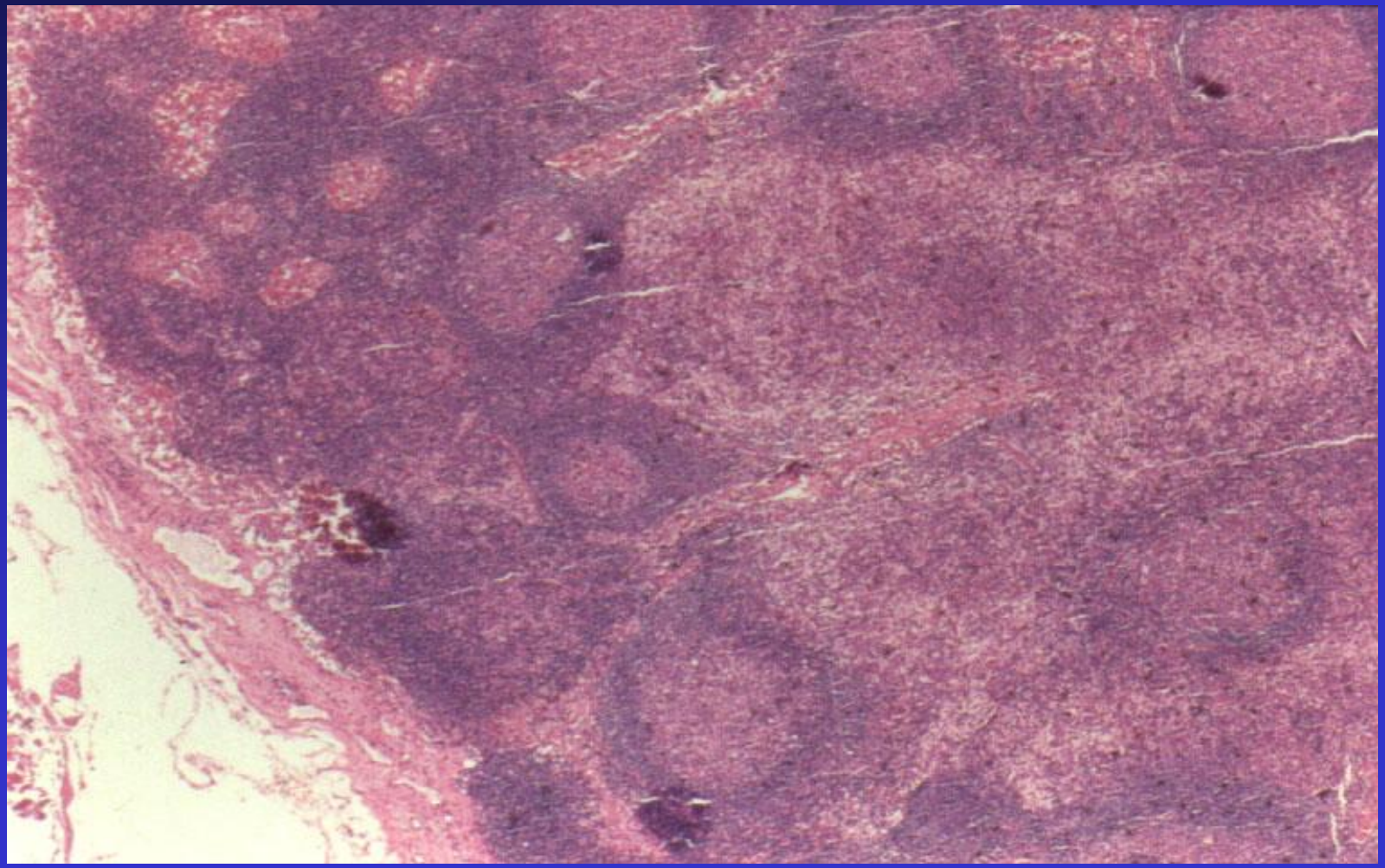
- **CYTOKINE PROFILE: Decreased cell-mediated immunity with a dominant Th2 cytokine profile is frequently observed in patients with advanced stages of mycosis fungoides or Sézary syndrome.**
- **TARGETED surface molecules**
  - **–CD52-Alemtuzumab(Campath)**
  - **–(IL-2R alpha chain, CD25 antigen)**
  - **–RITUXAN IN B CELL LYMPHOMAS**

Most Important Prognostic Factors

- In multivariate analyses, the most important prognostic factors are related to stage of disease:
  - Presence of visceral disease[1,2]
  - Type of skin involvement[1,2]
  - Lymph node involvement[3]
  - Blood involvement[3]

[1]Bunn PA, Lamberg SI. *Cancer Treatment Reports* 1979;63:725-728
[2]Schechter GP, et al. *Blood* 1987;69:841-849
[3]Klemke et al. *Br J Dermatol*. 2005;153:118-124

LYMPH NODE GRADING-LN GRADING AIDED BY FLOW CYTOMETRY



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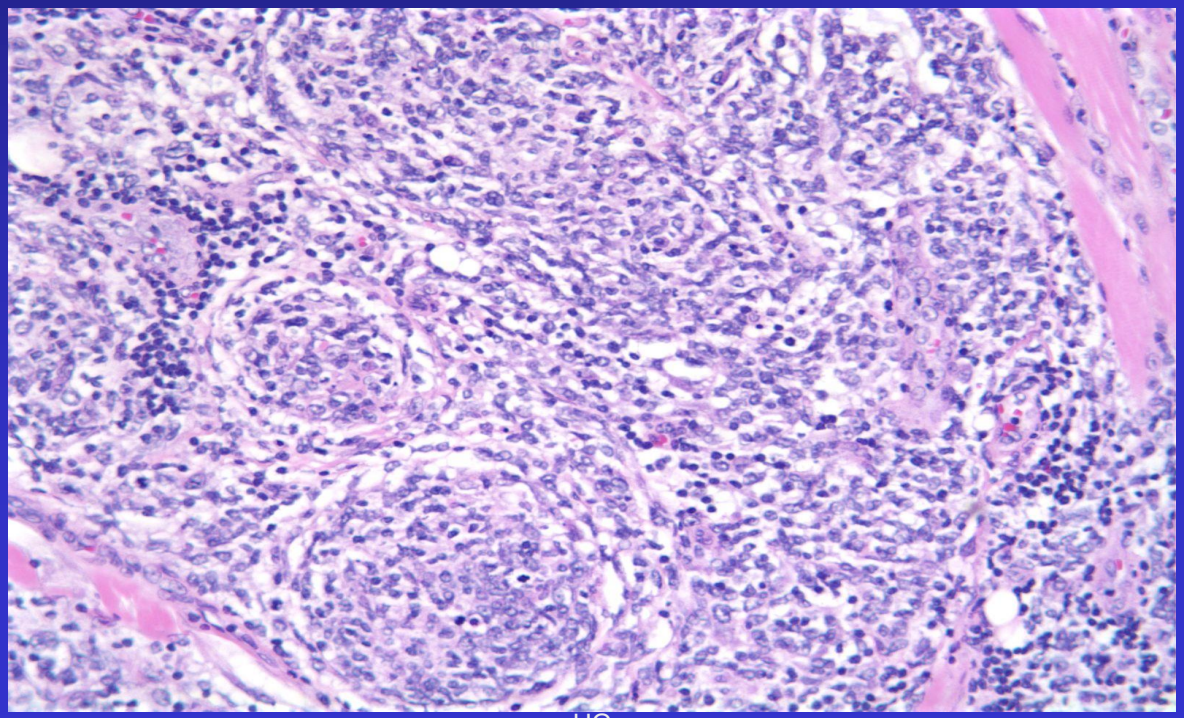
FOLLICULAR LYMPHOMA

- Lesional skin
  - –Useful in cutaneous lymphomas other than MF (B cell)
    - **B cell lymphomas express monotypic light chains**
    - Punch Biopsy sensitivity: Flow cytometry detected clonality in 88% (15 of 17) of cutaneous primary or secondary B cell lymphomas, compared to 37% (three of eight) by immunohistochemistry - J Invest Dermatol 121:1522 1530, 2003



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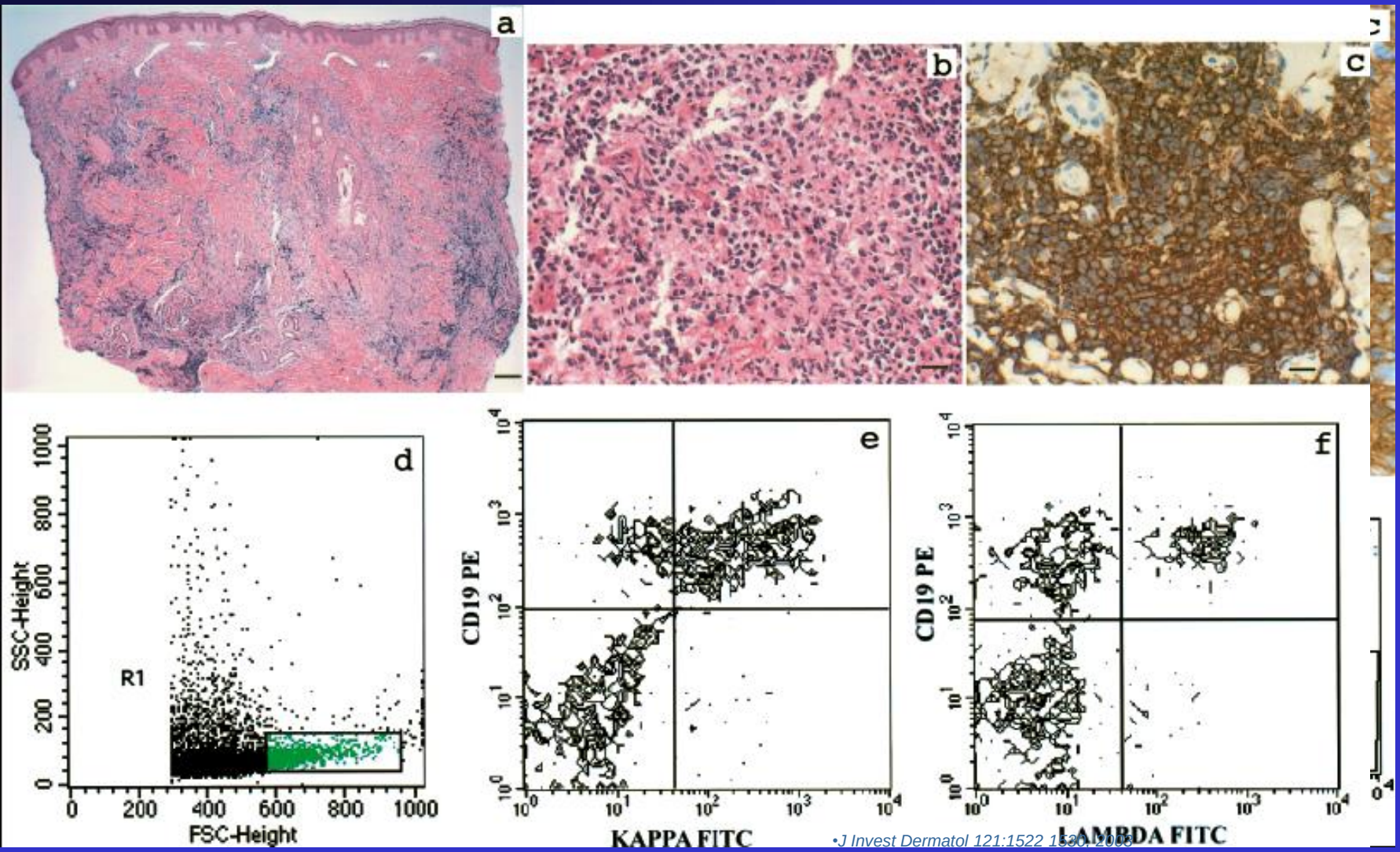
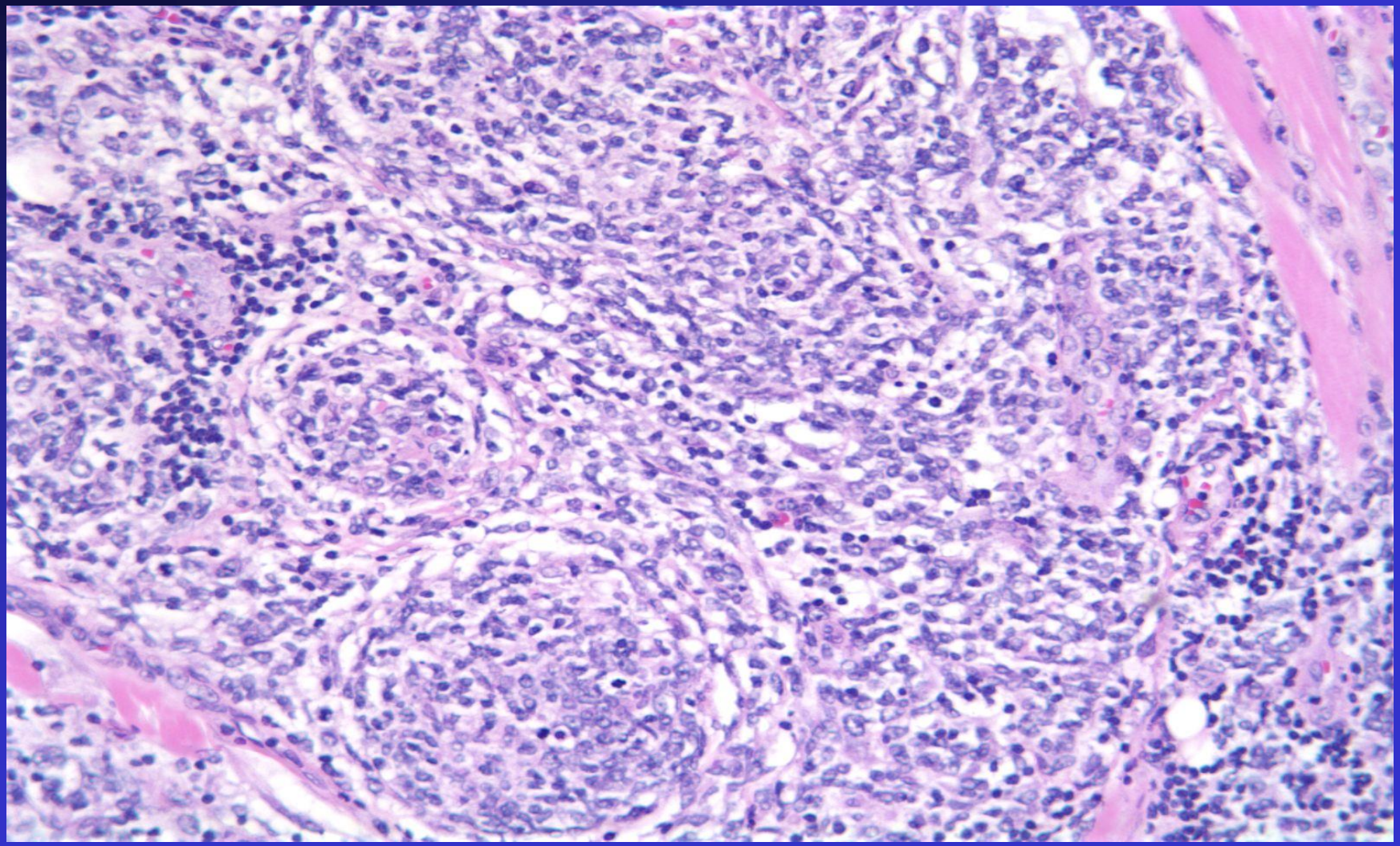
Flow cytometry and immunohistochemistry are complementary tools

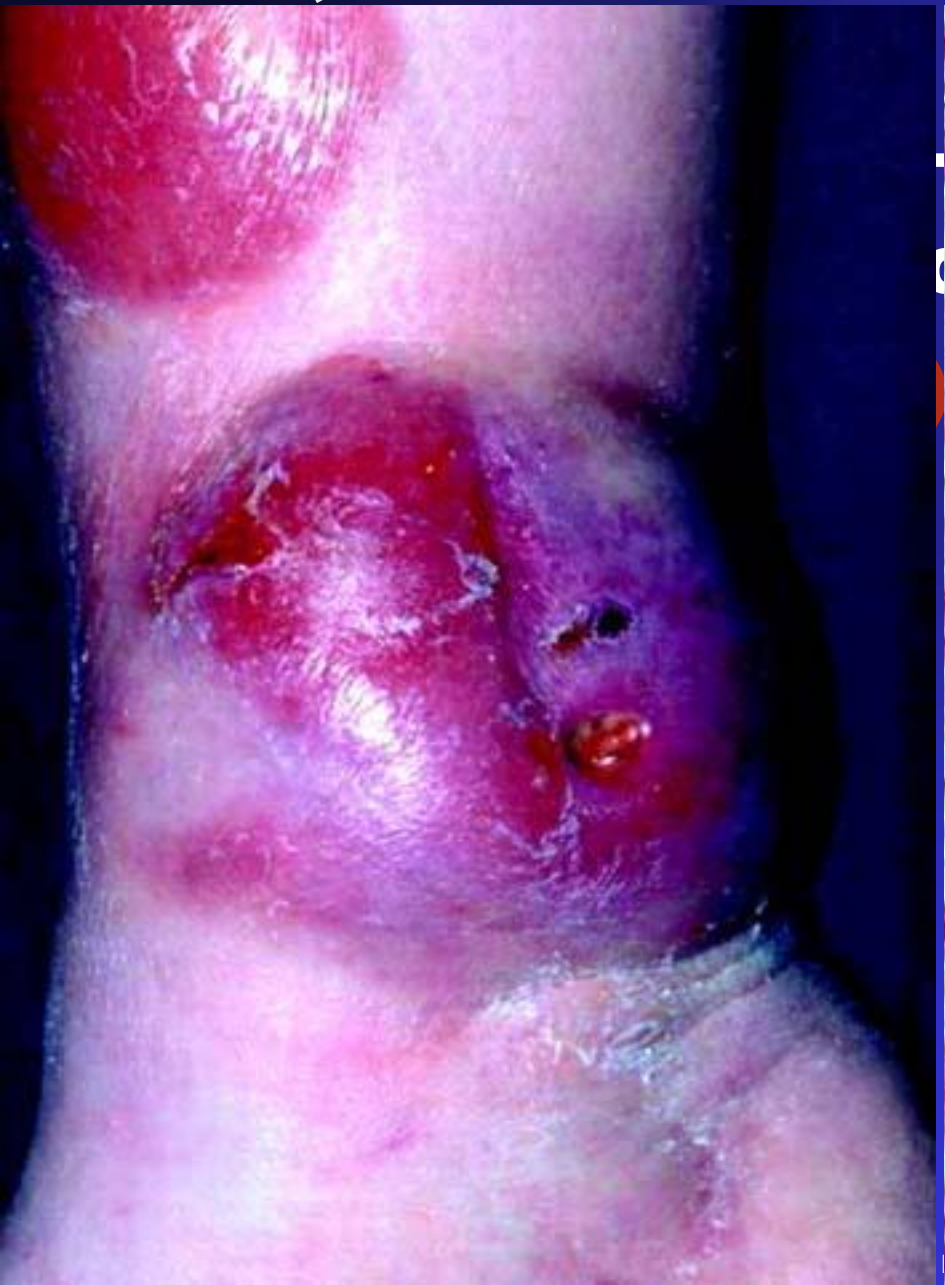


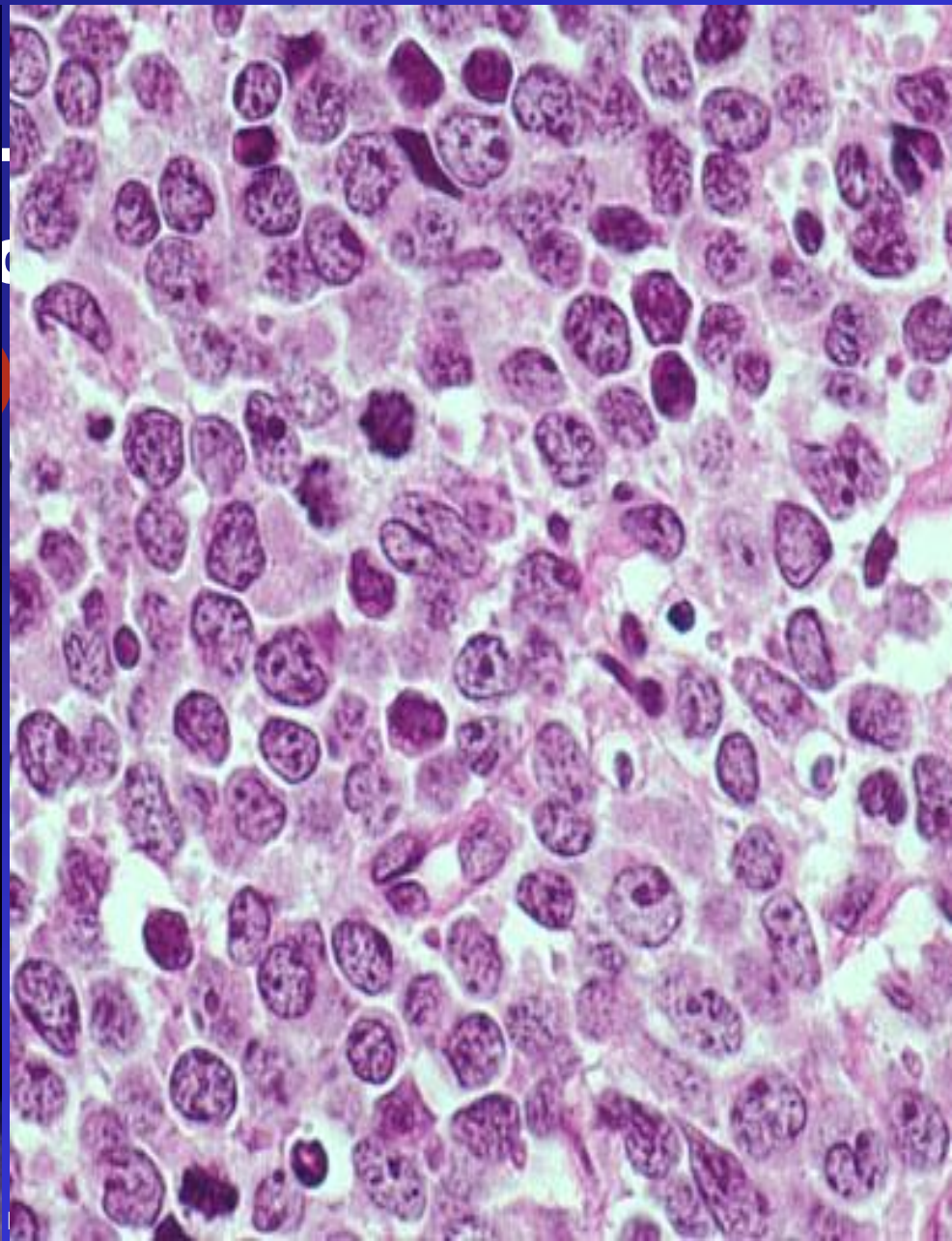
•J Invest Dermatol 121:1522 1530, 2003

FOLLICULAR LYMPHOMA

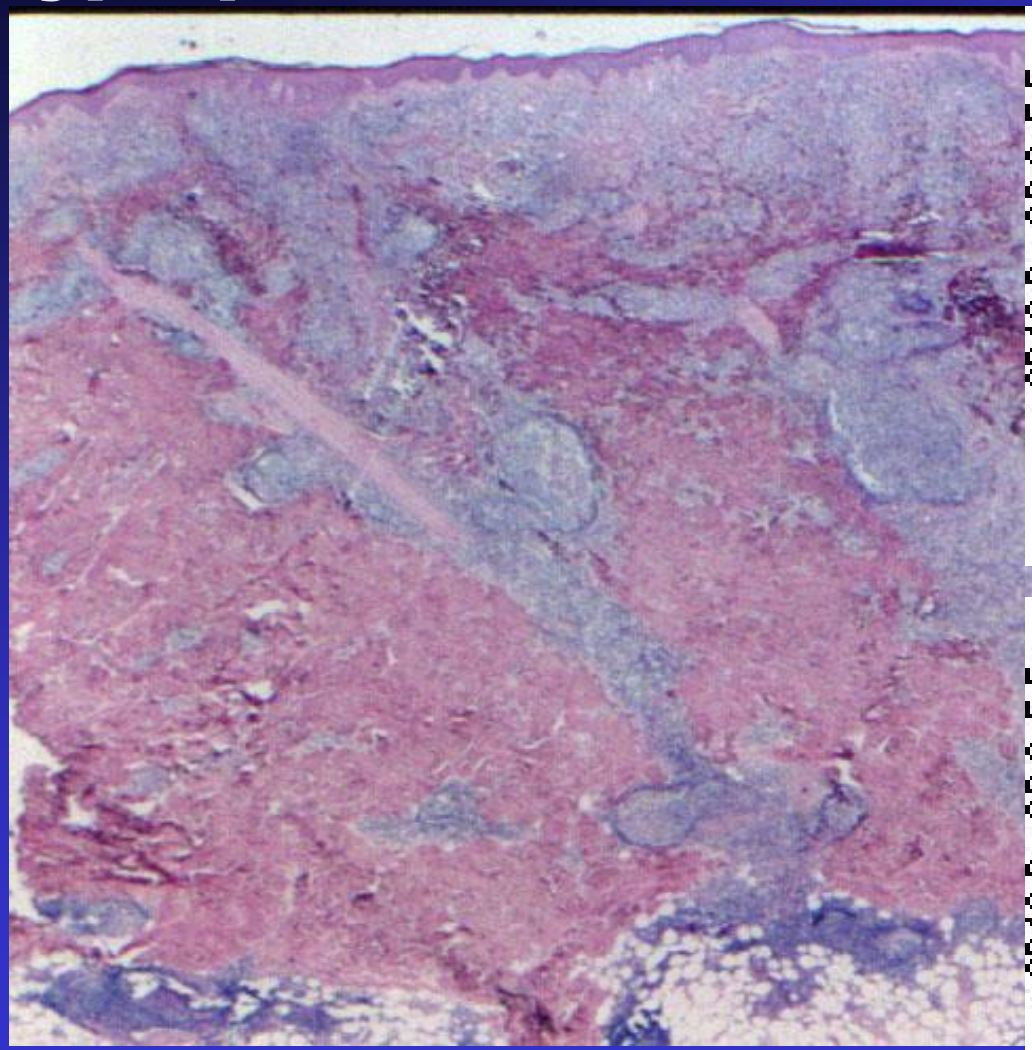


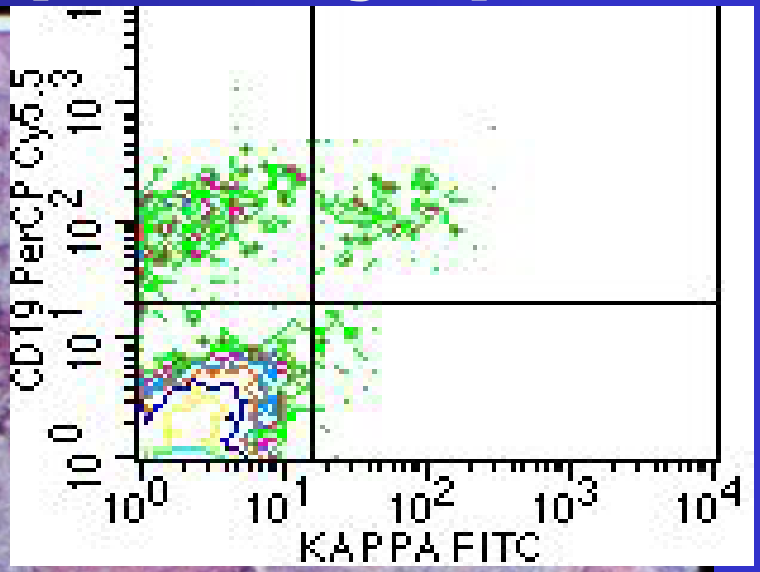
DLBC, LEG TYPE

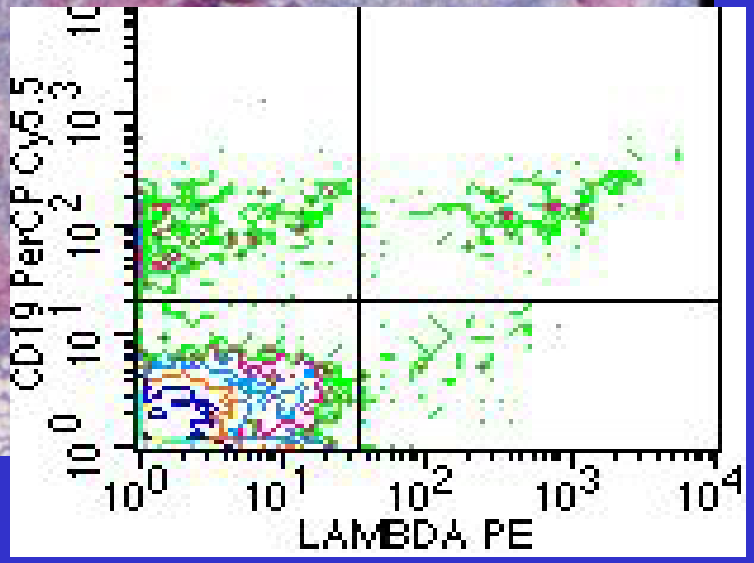




Differential DX : cutaneous lymphoid hyperplasia or cutaneous pseudolymphoma







Basic/Clinical Science

Progression of Cutaneous B-Cell Pseudolymphoma to Cutaneous B-Cell Lymphoma

Brittain F. Kulow,[1] Hernani Cualing,[2] Paul Steele,[2] Judi VanHorn,[1] John C. Breneman,[3] Diya F. Mutasim,[1] and Debra L. Breneman[1]

Journal of Cutaneous Medicine and Surgery

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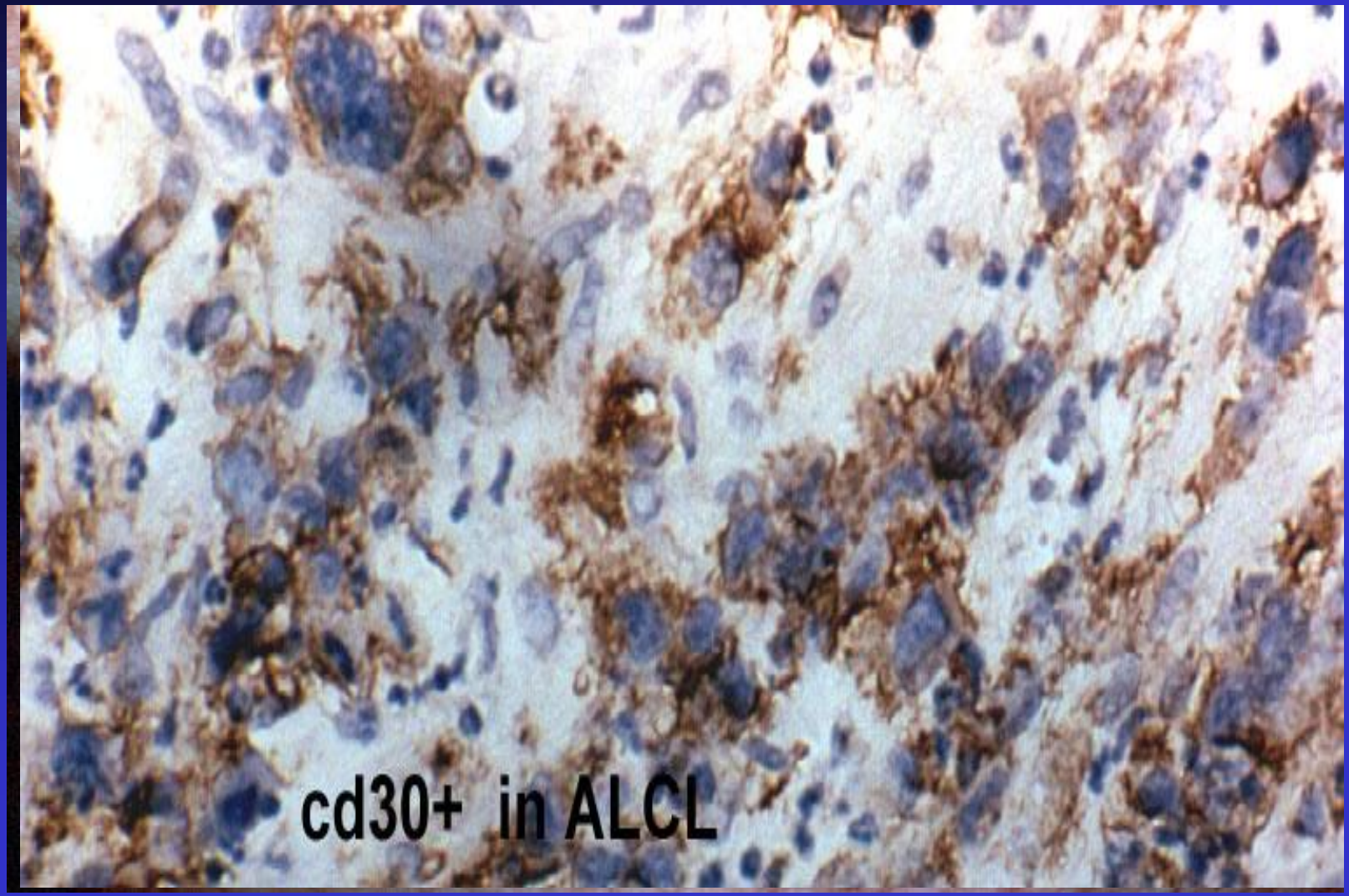
Cutaneous CD30+ LPD
May be useful in CD30 lymphomas

Represents a biologic and histologic spectrum with lymphomatoid papulosis (a benign disorder with spontaneous regression) at one end and primary cutaneous anaplastic large cell lymphoma (C-ALCL, an indolent CD30+ lymphoma usually treated with local therapy) at the other end.

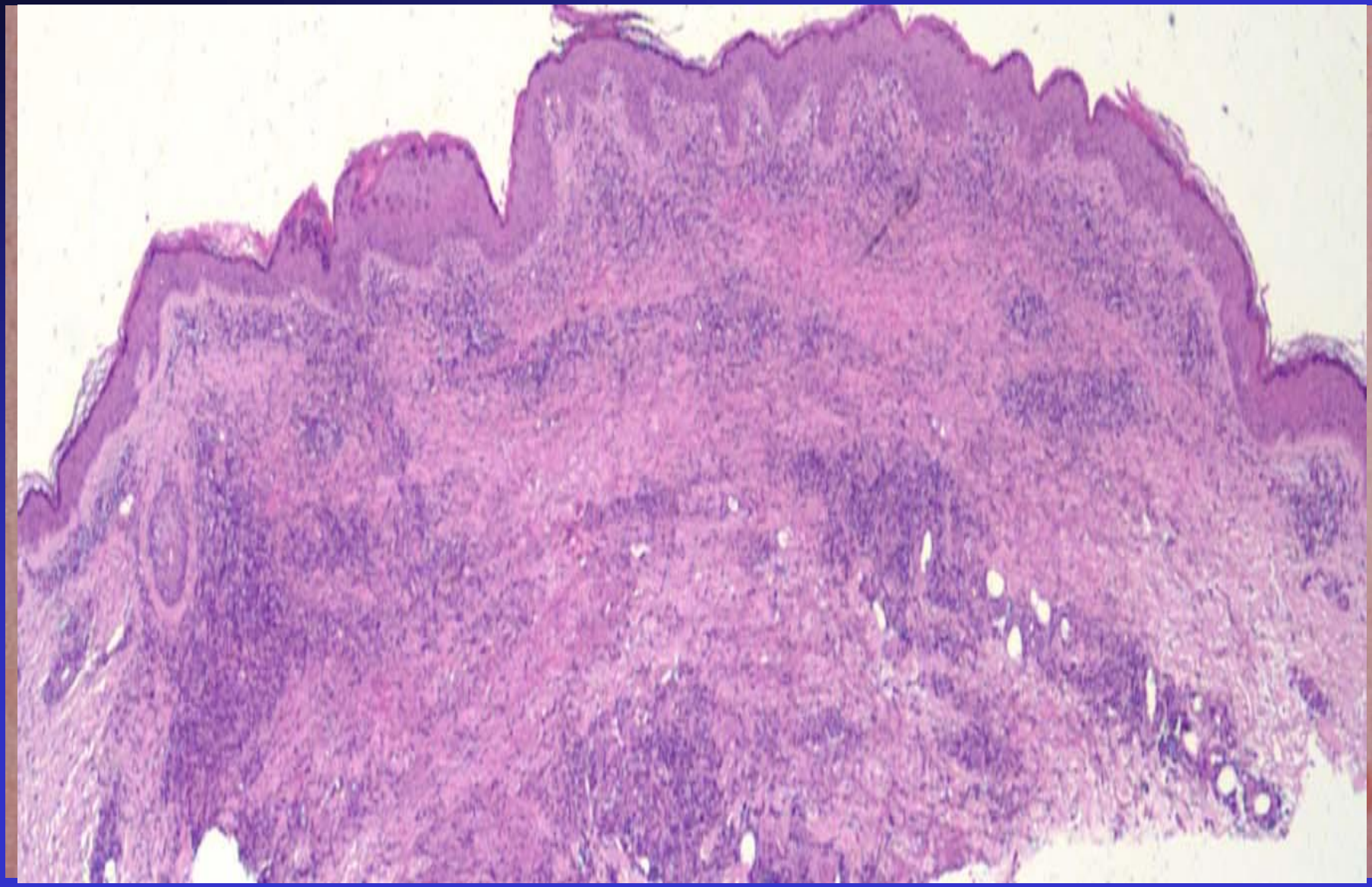
The classification of CD30+ LPD is predominantly based of the number and size of lesions, number of large CD30+ cells, and the clinical evolution of the lesion (progression versus regression).

It is extremely important to distinguish CALCL from secondary involvement of the skin by systemic ALCL, an aggressive disease that requires multiagent, systemic chemotherapy.

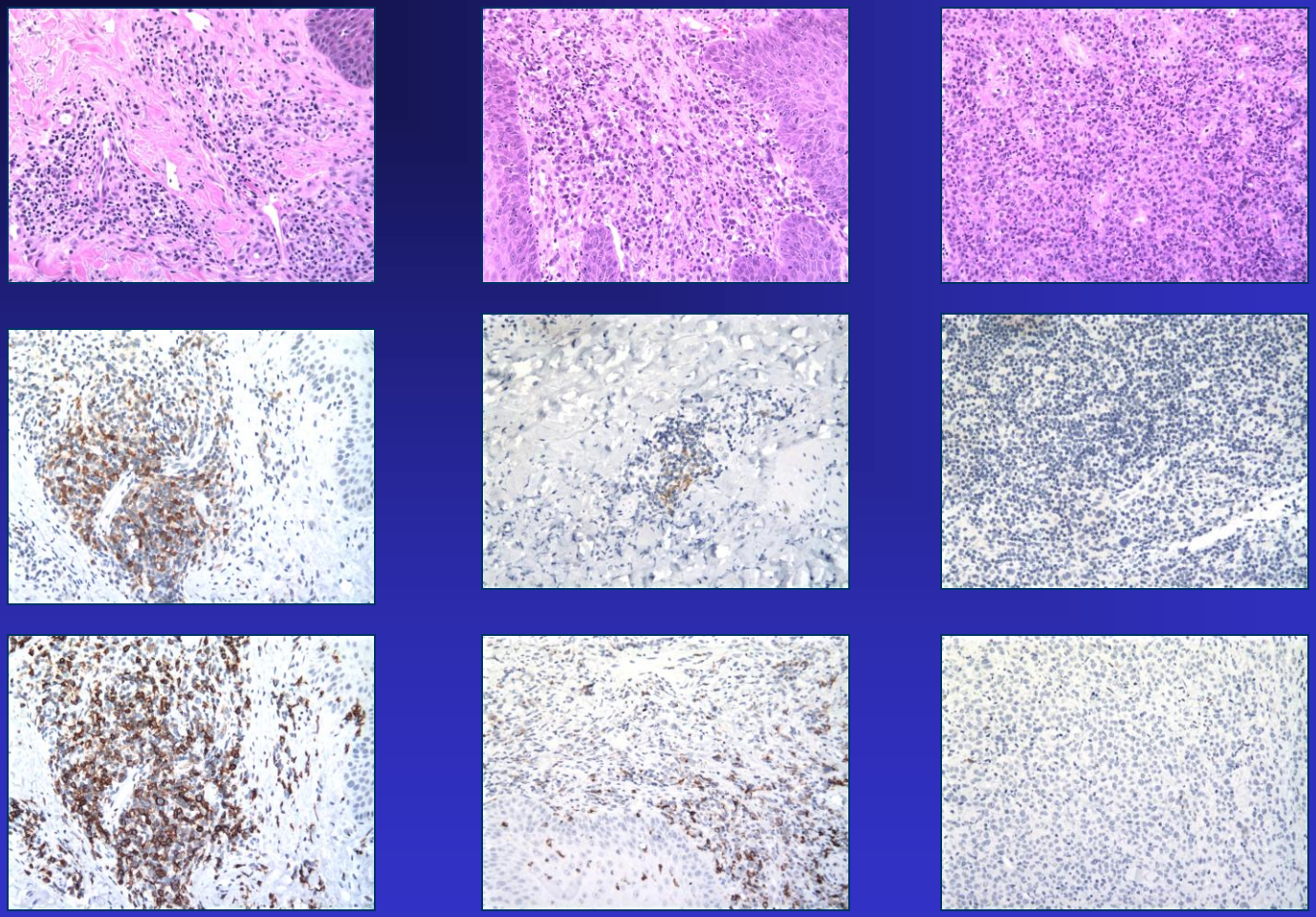
Ki-1+ Anaplastic LCL (ALCL)



Lymphomatoid Papulosis(LyP)



CLA and TRAF-1 are useful in differentiating Lymphomatoid Papulosis, cutaneous ALCL and systemic ALCL.



- H Lee Moffitt Cancer Center and Research Institute, Department Of Pathology and The University of South
- Florida, College of Medicine
- .Dorna Rezania, MD, Elizabeth Sagatys, MD, Marshall E. Kadin, M.D, Frank Glass, MD, Hernani Cualing MD.

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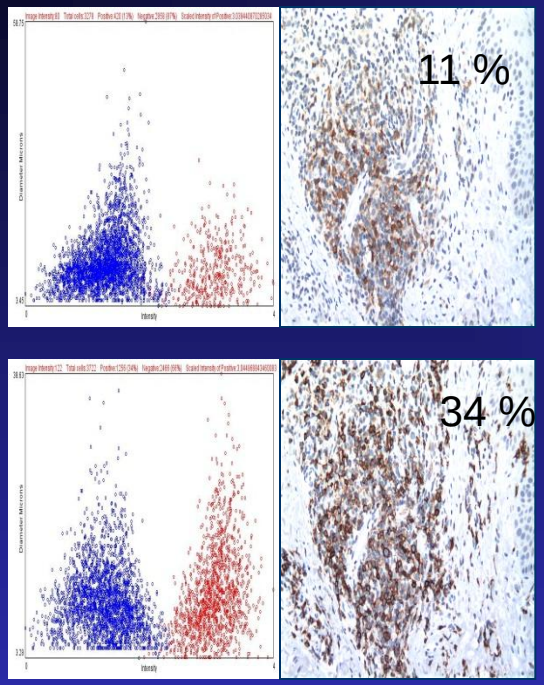
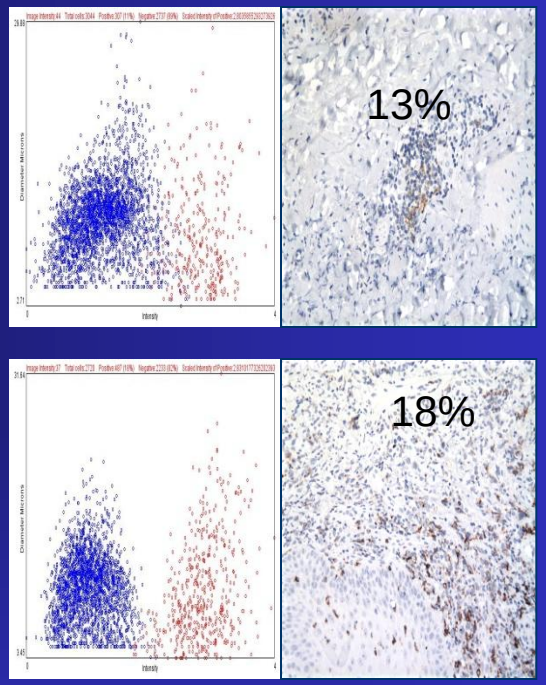
VIRTUAL FLOW CYTOMETRY OF IMMUNOSTAINED TISSUE IMAGES

TRAF-1

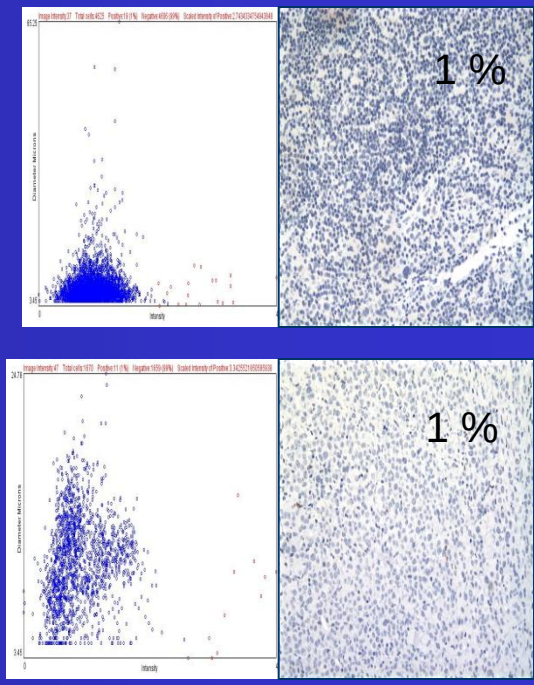
CLA



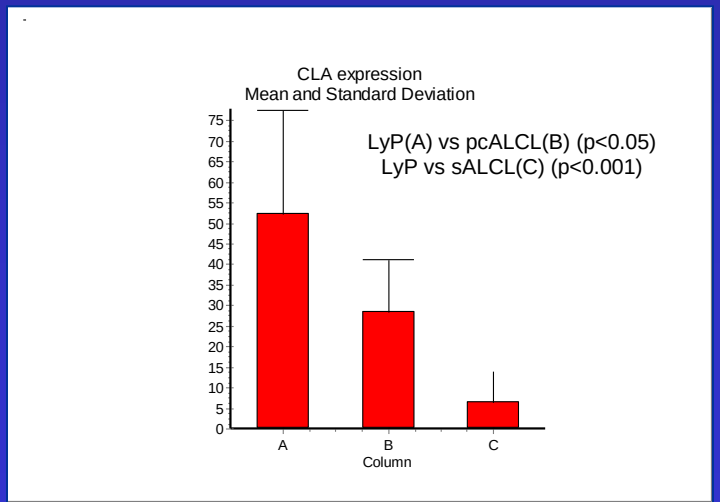
LyP

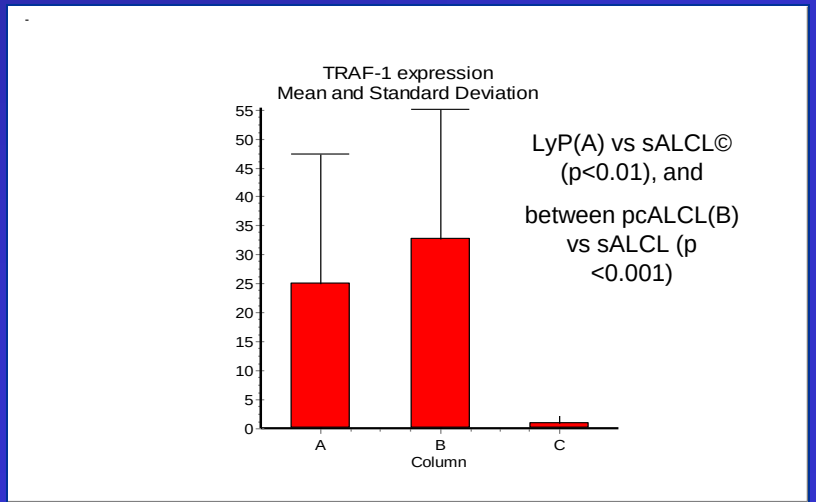


cutaneousALCL



Systemic ALCL





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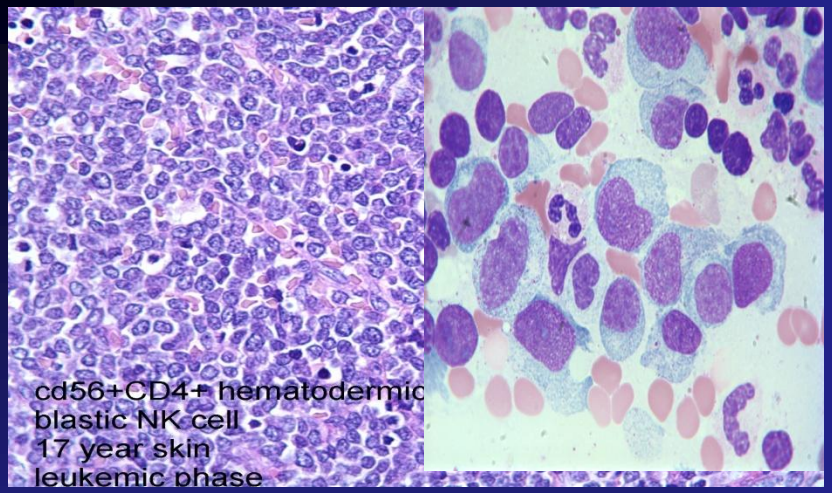

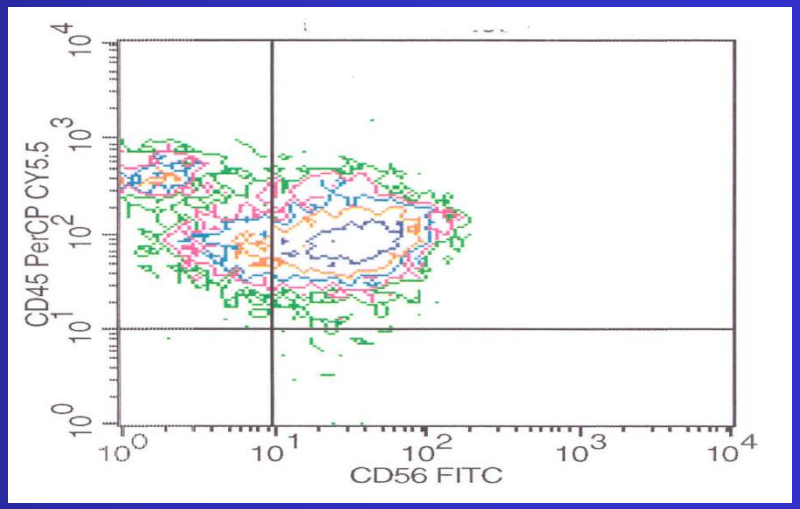

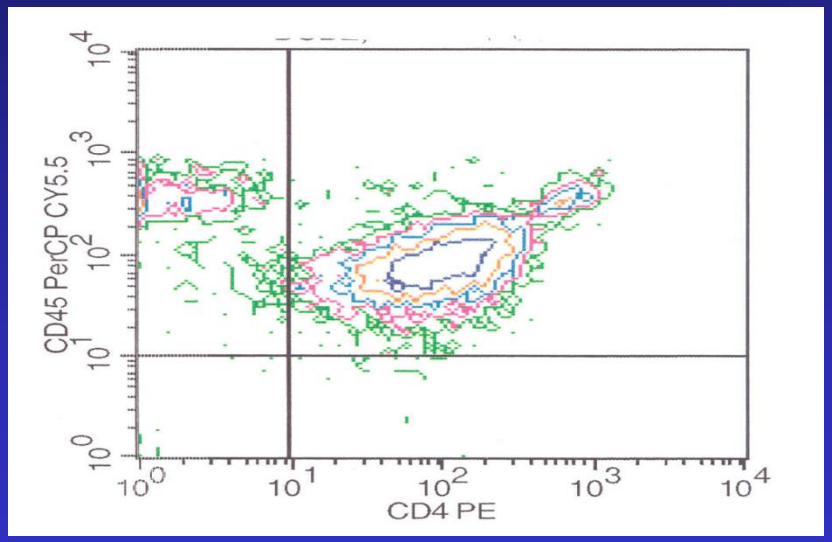

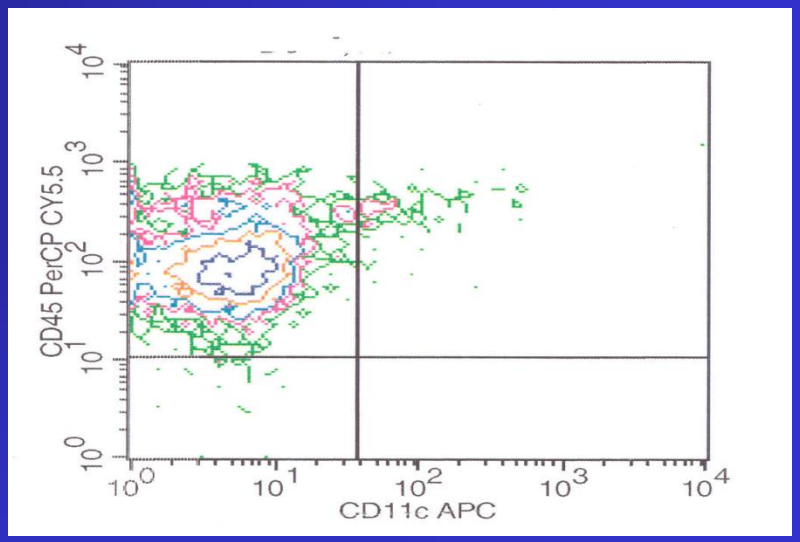

- **Flow cytometry results may be helpful in differentiating from the similar monocytic leukemia**

"DIFFERENTIATING CD4+/CD56+ HEMATODERMIC NEOPLASM FROM CD4+/CD56+ ACUTE MONOBLASTIC LEUKEMIA". USCAP Denver, 2008, *IT Yu, D Rezania, LC Moscinski, JD Messina, Sokol L, Morgan M, HD Cualing*, Moffitt Cancer Cancer & University of South Florida, Florida, USA

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Summary

- **Flow cytometry/immunohistochemistry have important roles in diagnosis, staging and targeted therapy of Cutaneous Lymphomas including MF.**
- **Non MF peripheral T cell lymphomas and B cell lymphomas of the skin and CD30 lymphomas workup should include immunophenotyping modalities**
- **Fresh tissue is amenable to flow cytometry and paraffin embedded tissue may benefit from quantitative tissue virtual flow cytometry**
- **non MF PTCL, CD30 lymphomas and CBCL are unique lymphoproliferative process with clinical course and outcome very different from histopathologically similar nodal lymphomas**
- **Cutaneous lymphoproliferative tumors: regard as lymphomas and send fresh tissue enabling use of ancillary tests**