



*Differential Diagnosis of Selected
Cutaneous Lymphoid Lesions*

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Potential Simulants of Mycosis Fungoides

- -Drug induced “pseudolymphomas”
- -Chronic lichenoid and spongiotic dermatitides
- -Actinic reticuloid
- -Pagetoid reticulosis

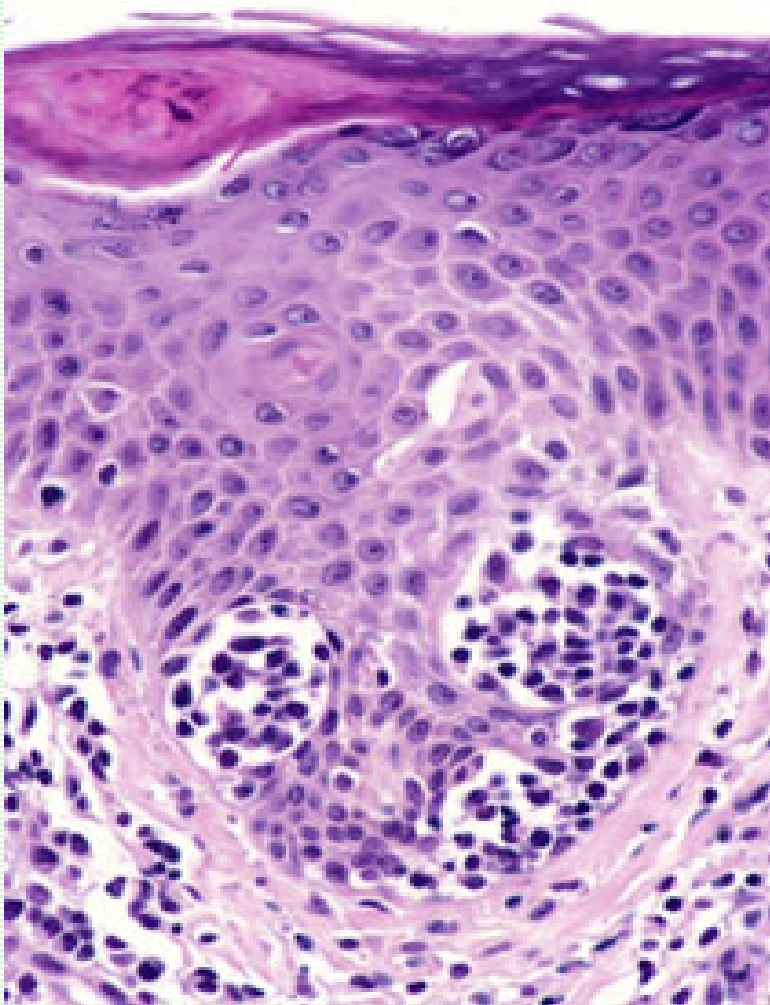
Because they share these features with MF:

-Grouped lymphocytes in the epidermis, and in the dermal interstitium

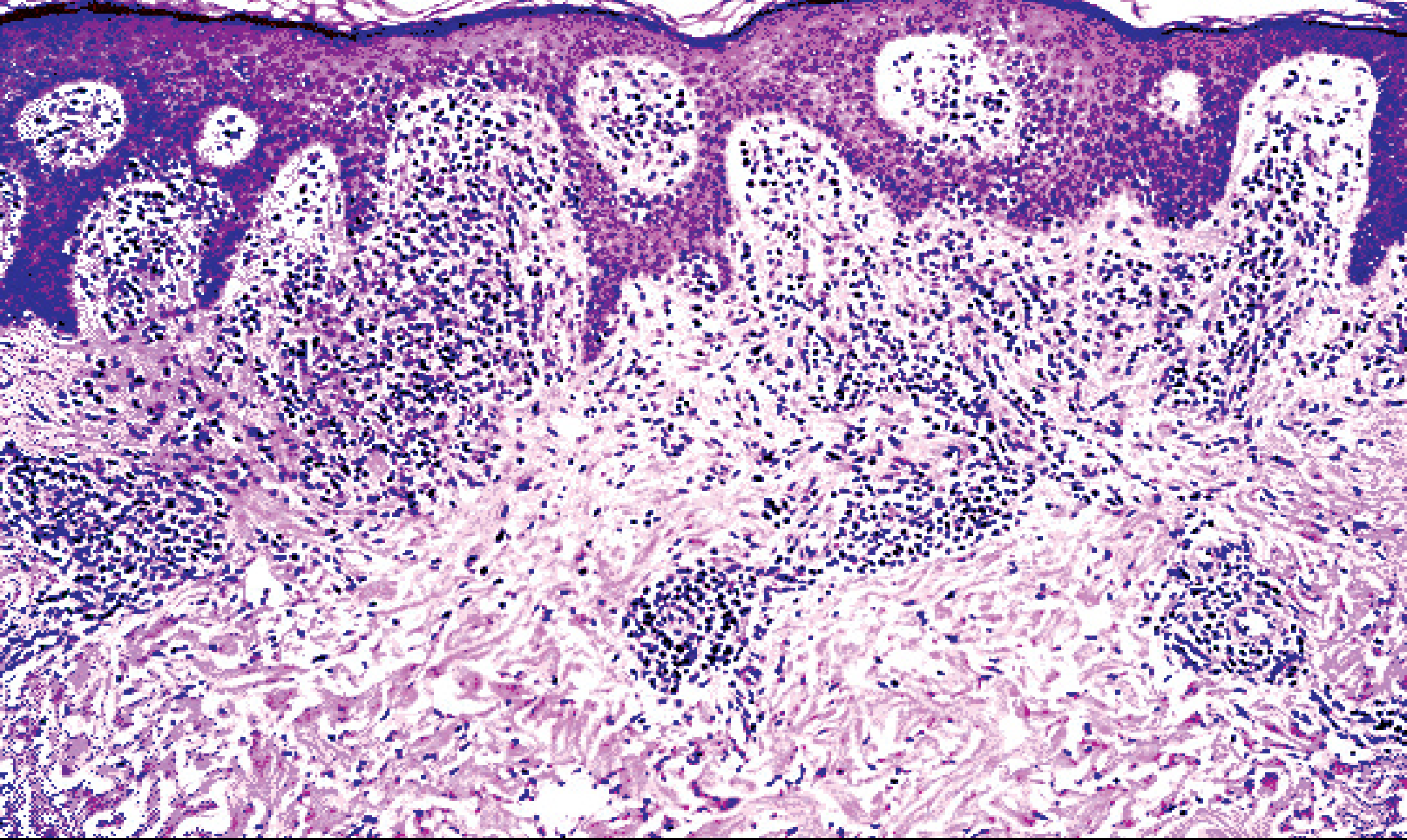
-Lymphocytes may be activated, and hence “atypical”

-Infiltrate is predominantly composed of T-cells

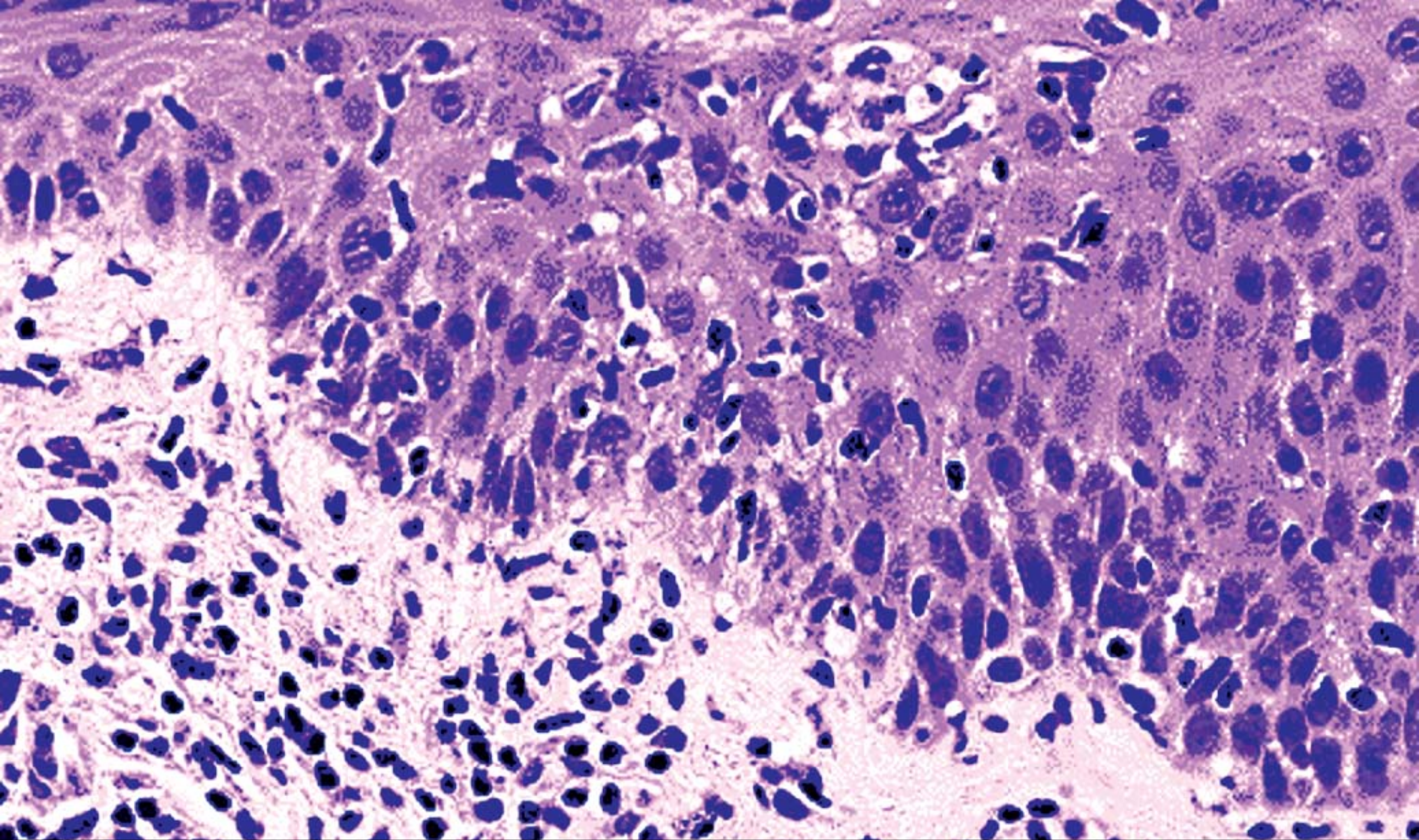
T-CELL "PSEUDOLYMPHOMA" VS. CUTANEOUS T-CELL LYMPHOMA



- It should be remembered that even after thorough morphologic and adjunctive analysis, it may be impossible to distinguish T-cell lymphomas from some "pseudolymphomatous" (lymphomatoid) T-cell infiltrates in the skin*
- This is especially true of selected drug eruptions (e.g., reactions to anticonvulsants, antipsychotics, antidepressants, antihistamines, and selected antibiotics)*



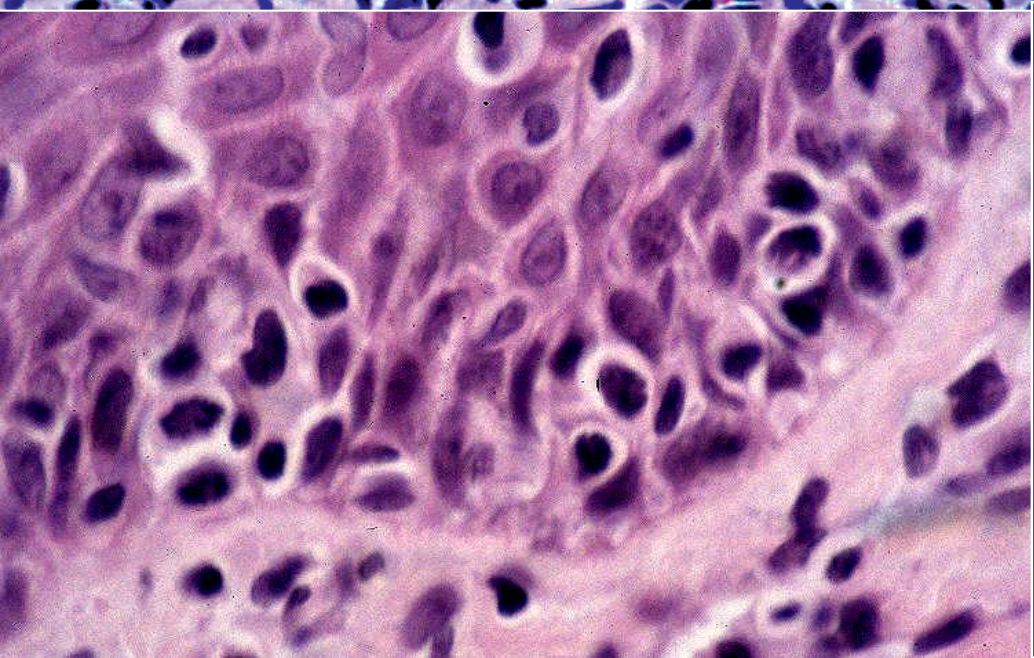
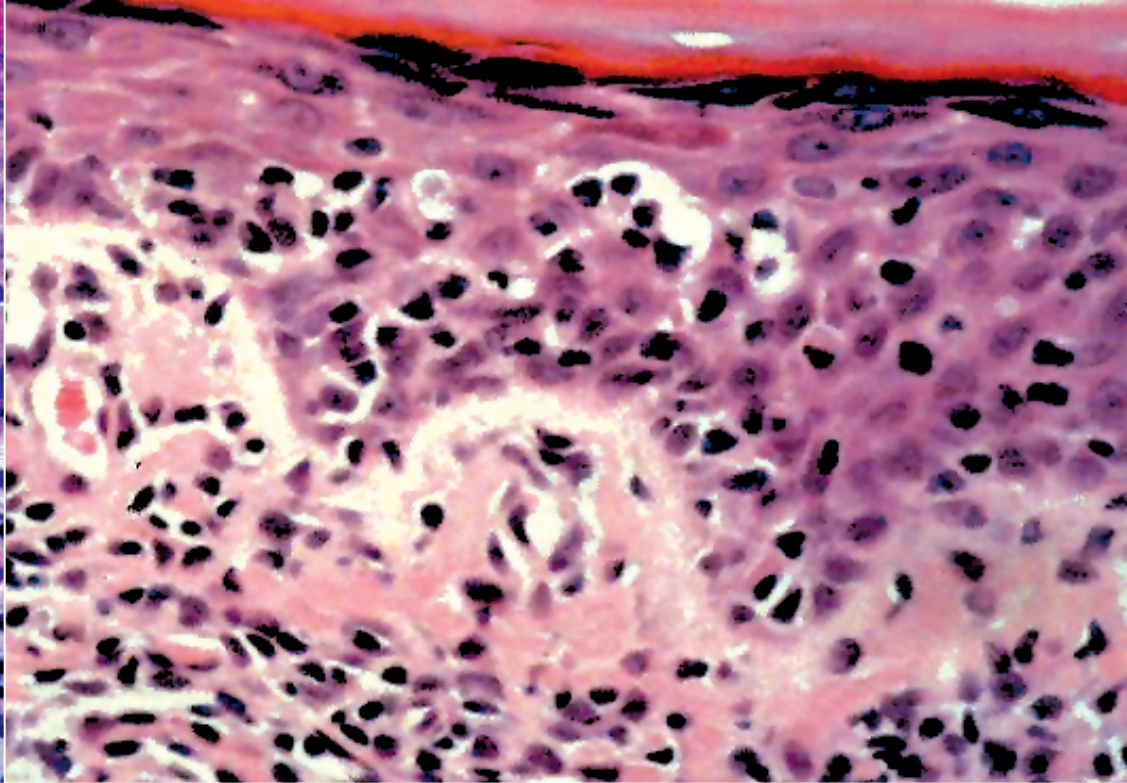
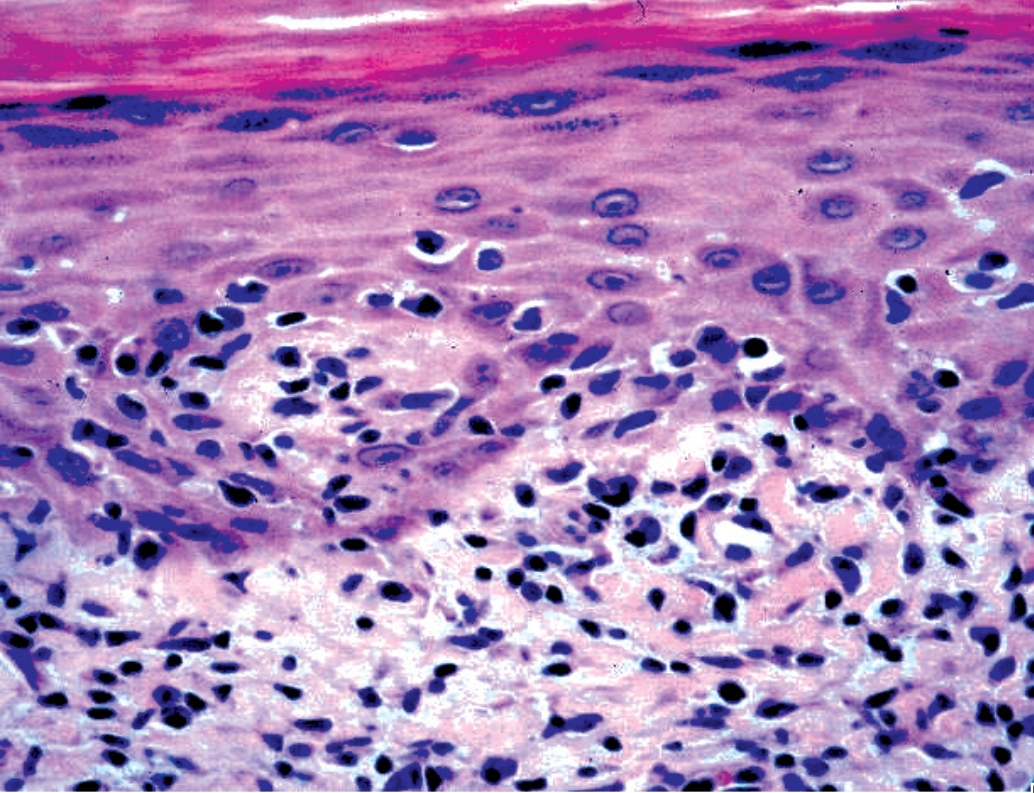
Mycosis Fungoides-Like Drug Eruption



Mycosis Fungoides-Like Drug Eruption

HISTOLOGIC FEATURES FAVORING A DIAGNOSIS OF MYCOSIS FUNGOIDES

- **--/Relative lack of spongiosis and interface keratinocyte damage**
- **--Linear arrays of lymphocytes in the basal epidermis**
- **--Groups of atypical lymphocytes in the epidermis with minimal associated spongiosis**
 - **--“Basketweave” fibrosis in the upper dermis**
- **--Follicular lymphoid infiltrates and/or mucinosis**



**Mycosis Fungoides:
Microscopic Images**

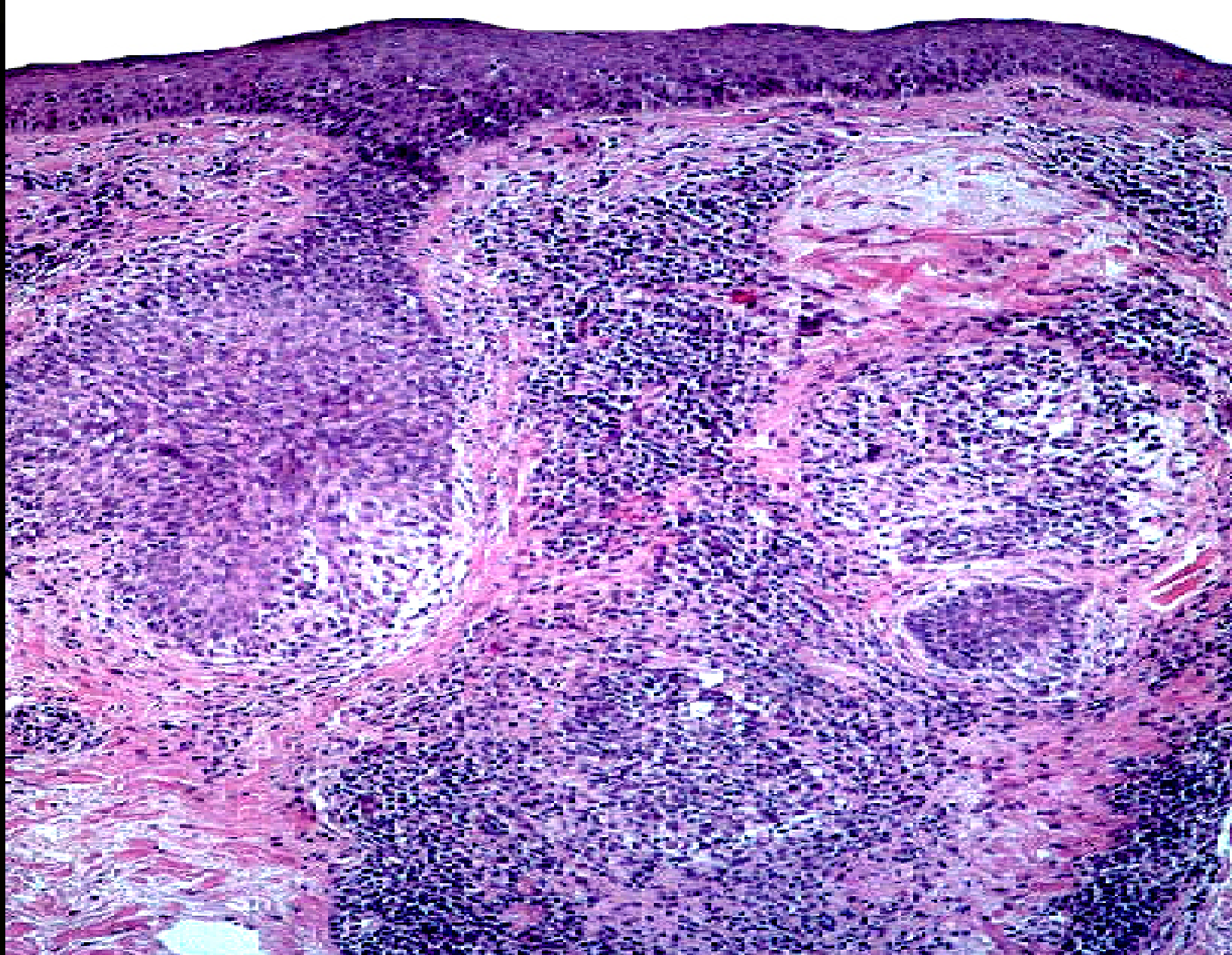
Histologic Criteria for the Diagnosis of Mycosis Fungoides
***Smoller BR, et al.: Reassessment of histologic parameters in the diagnosis
of mycosis fungoides.
Am J Surg Pathol 1995; 19: 1423-1430.***

“On univariate analysis, the following parameters were significant at beyond the $p = 0.01$ level: Pautrier's abscesses, haloed lymphocytes, exocytosis, disproportionate epidermotropism, epidermal lymphocytes larger than dermal lymphocytes, hyperconvoluted intraepidermal lymphocytes, and lymphocytes aligned within the basal layer.”

***J Cutan Pathol* 2000; 27: 406-409.**

The histologic value of adnexal (eccrine gland & follicle) infiltration in mycosis fungoides.

Rongioletti F, Smoller BR

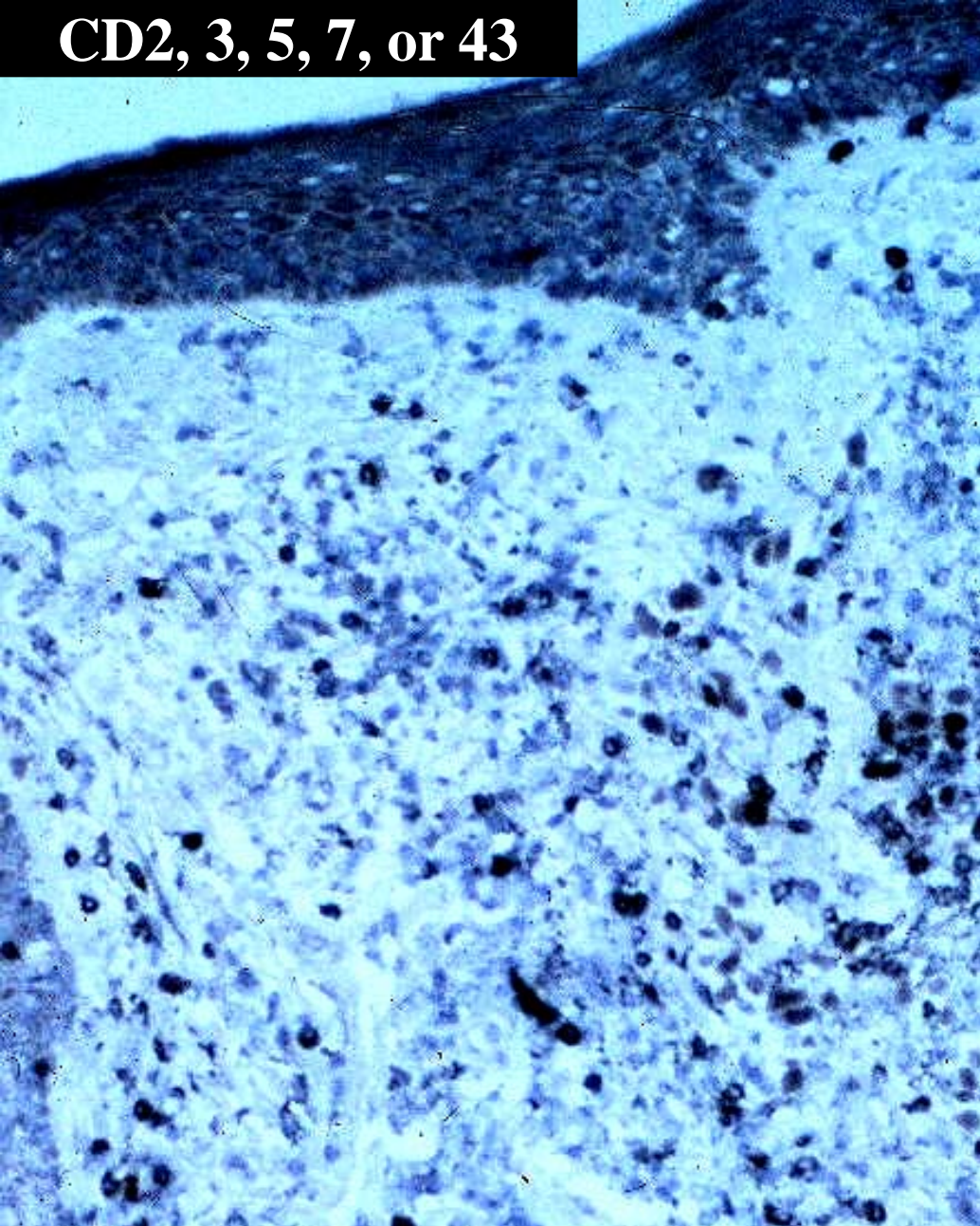


Mycosis Fungoides-- Follicular Involvement

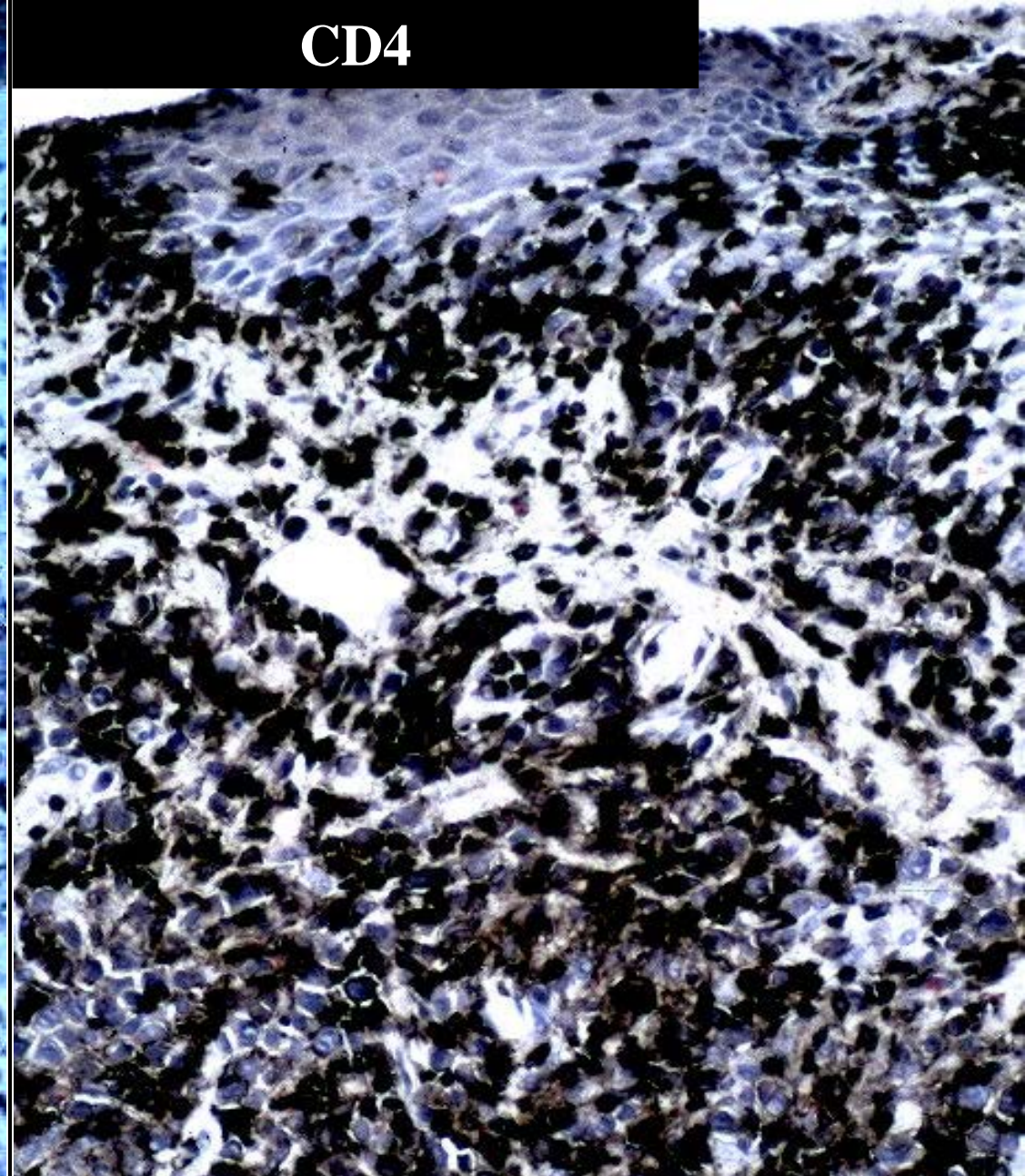
IMMUNOHISTOLOGY IN DDx OF CUTANEOUS T-CELL LYMPHOMAS

- Antibodies used to CD 2,3,4,5,7,8, 43, & 45R0**
 - Deletion of pan-T antigens and CD4-dominance suggests CTCL rather than dermatitis, but this feature is seen in only ~50% of cases of mycosis fungoides and Sezary's syndrome**

CD2, 3, 5, 7, or 43



CD4



Immunophenotype of Mycosis Fungoides in Paraffin Sections

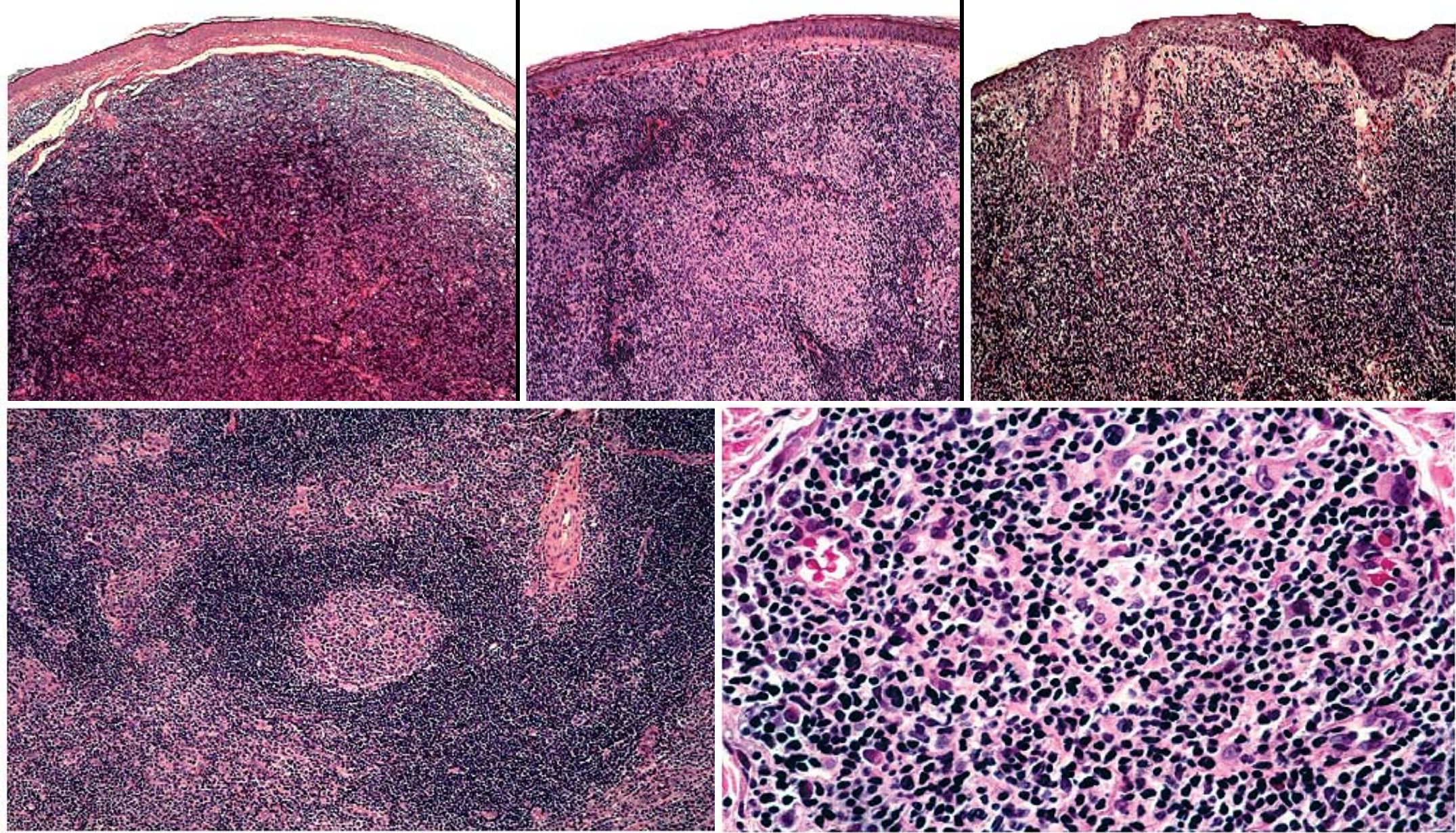
Prototypical Histologic Comparison of Benign & Malignant Lymphoid Infiltrates of the Skin

Benign

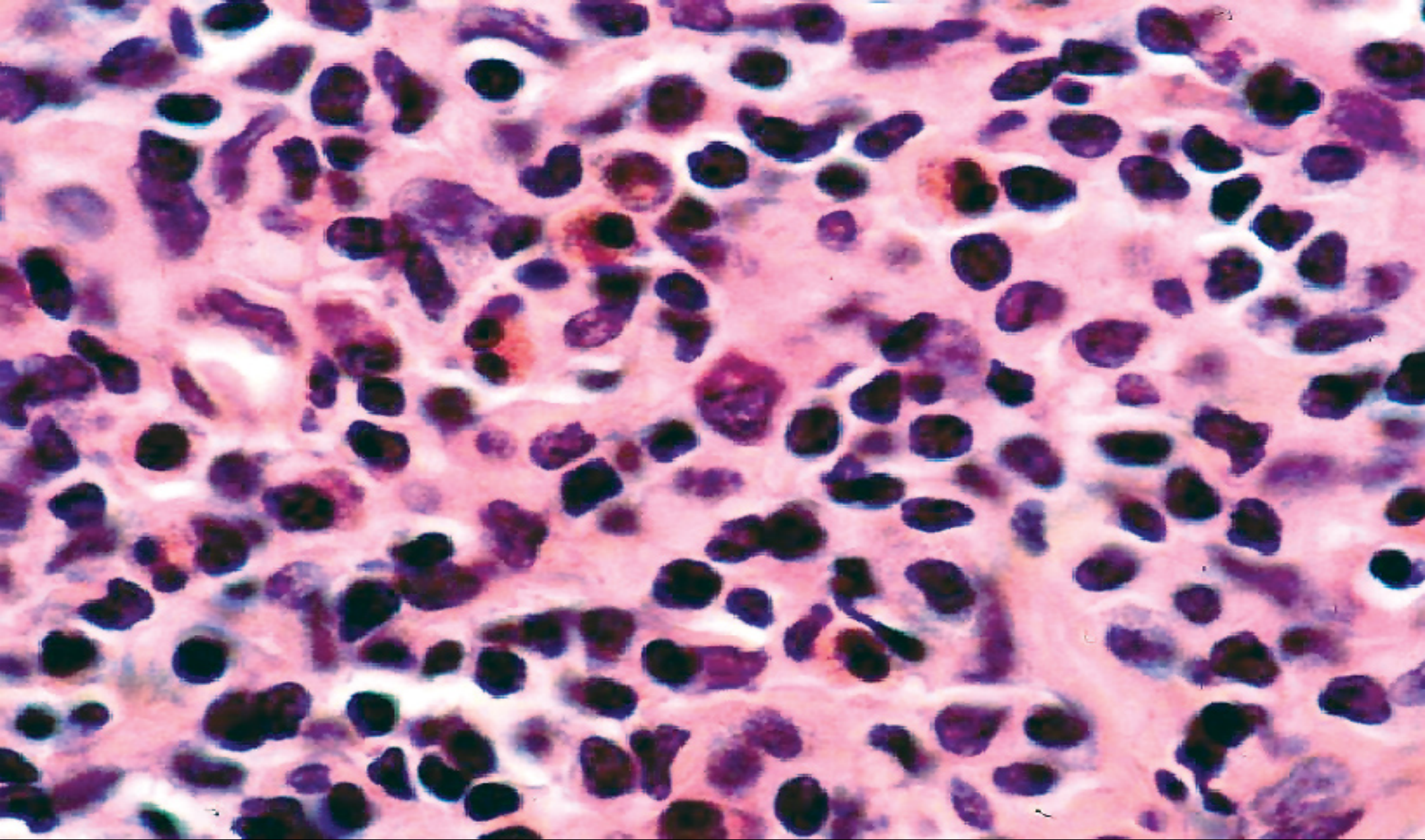
- Organized immune response (e.g., follicles with germinal centers, etc.); heterogeneous cellular constituency
- "Top-heavy" dermal infiltrate with perivascular & periappendageal preference
- Epidermal reaction often present (dyskeratosis, spongiosis, basal vacuolization, etc.)
- Cellular (nuclear) atypia is usually modest if present at all

Malignant

- No organized immune response; cellular monomorphism often present
- "Bottom-heavy" or diffuse infiltrate that dissects collagen & may involve the subcutis
- Inconspicuous or absent epidermal reaction
- Cellular (nuclear) atypia may be seen and can be extreme



Cutaneous Lymphoid Hyperplasia: Microscopic Images



Pseudolymphomatous Arthropod Bite Reaction

IMMUNOHISTOLOGY IN DD_x OF SMALL-LYMPHOCYtic & MIXED DEEP DERMAL LYMPHOID INFILTRATES

Features Arguing for Malignancy

- $\geq 75\%$ B-cells; especially with few admixed T-lymphocytes**
- Ig light chain monotypism on B-cells in infiltrate (light chain ratio of $\geq 10:1$)**
- Proliferative index of $>20\%$ in atypical lymphoid cells**
 - Coexpression of CD20/CD43**

Paraffin section immunohistochemistry as an adjunct to morphologic analysis in the diagnosis of cutaneous lymphoid infiltrates

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In the skin, separation of selected lymphomas from lymph hyperplasia can be challenging. The authors examined 4 cutaneous lymphomas, excluding mycosis fungoides (26: lymphocytic or mixed tumors; 19 large cell lymphomas), "atypical" lesions, and 40 lesions of presumed lymphoid hyperplasia, comparing morphologic attributes of such proliferations with their immunophenotypes in paraffin sections. The object of this study was to determine whether immunologic data obtained from routinely-processed specimens could be used to further objectify morphologic interpretations. Features favoring lymphoma included a lesional epicenter in the dermis or subcutis; poor circumscription of lymphoid aggregates; and dissection of lymphoid cells between collagen bundles. Immunostains included antibodies to CD20, CD43, CD45RO, CD45RA, CD68, proliferating cell nuclear antigen (PCNA), and MB2. Eleven of 26 small lymphocytic or mixed cell lymphomas and 3 of 10 "atypical" cases demonstrated abnormal immunophenotype, including co-expression of CD43 and CD20 or non-physiological CD45RA distribution. In contrast, none of 40 cases with benign features manifested aberrant antigen expression. Thirty-one of 37 cases in which 2 of the cells typed as B lymphocytes showed malignant morphologic features, 5 were "atypical" and possibly lymphomatous and only one had benign features. PCNA stains showed greater positivity of the lymphoid nuclei in lymphomas, and a labeling index of >50% was correlated with malignancy in this context. These observations indicate that immunostaining provides useful adjunctive information in distinguishing benign from malignant cutaneous lymphoid proliferations in paraffin sections.

CLH vs. B-CELL LYMPHOMA & NON-MYCOSIS T-CELL LYMPHOMA

- --Immunohistology, ISH, & flow cytometry are much more effective in evaluating B-cell-rich lesions of the skin than they are in assessing dense dermal T-cell infiltrates
- -- Immunohistochemical documentation of a deletion of pan-T-cell antigens in a T-cell-dominated dermal lesion can be used as presumptive evidence for a diagnosis of non-mycosis-type T-cell lymphoma
- --*HOWEVER*, genotypic studies are much more important in the latter situation than in reference to B-cell-preponderant proliferations

CD30

- --An activation marker that may be seen in florid reactive lymphoproliferations as well as lymphomas
- --In the skin, CD30 may be seen in arthropod bite reactions, drug eruptions, and some viral exanthems
- --Should never be used as a marker of "malignancy"

Key Questions:

- Are histology & immunohistology uniformly effective in the differential diagnosis of cutaneous lymphoproliferations?*
- Are cutaneous lymphoid hyperplasia and malignant lymphoma of the skin truly mutually-exclusive?*

Nihal M, Mikkola D, Horvath N, Gilliam AC, Stevens SR, Spiro TP, Cooper KD, Wood GS: Cutaneous lymphoid hyperplasia: a lymphoproliferative continuum with lymphomatous potential. Hum Pathol 2003; 34: 617-622.

Cutaneous lymphoid hyperplasia (CLH) has been proposed to be the benign end of a continuum of lymphoproliferative disorders with cutaneous lymphoma at its malignant extreme.

An intermediate condition, known as "clonal CLH," was first recognized by us and shown to be a transitional state capable of eventuating in overt lymphoma. To better determine the prevalence of dominant clonality and risk of lymphoma among CLH cases, we studied the immunohistology and clonality of fresh-frozen samples from 44 CLH patients referred to a multidisciplinary cutaneous lymphoproliferative disorders program. Using a large panel of lymphoid markers, the cases were divided into 38 typical mixed B-cell/T-cell type CLH and 6 T-cell-rich type (T-CLH), the latter containing > 90% T cells.

Of the 44 patients, 38 had solitary or localized lesions (4 cases of T-CLH), and 6 had regional/generalized lesions (2 cases of T-CLH). Forty cases were of idiopathic etiology. Suspected etiologies among 4 other cases included mercuric tattoo pigment, doxepin, clozapine, and bacterial infection. Immunoglobulin heavy chain (IgH) and T-cell receptor (TCR)-gamma gene rearrangements (GR) were studied using polymerase chain reaction assays, which are approximately 80% sensitive. Overall, 27 cases (61%) showed clonal CLH: 12 IgH+ (27%; 3 cases of T-CLH); 13 TCR+ (30%; 1 case of T-CLH); and 2 IgH+/TCR+ (4%; neither case was T-CLH). Two cases (4%; 1 case of T-CLH) progressed to cutaneous B-cell lymphoma. Both of these patients presented with regional lesions. Our findings indicate that clonal overgrowth is common in CLH, links CLH to lymphoma, and probably involves both B- and T-cell lineages (although TCR GR by B cells and vice versa could not be ruled out). The high prevalence of dominant clonality in our series may have resulted from the sensitivity of our PCR assays as well as patient selection.

General Approach to Cutaneous Lymphoid Infiltrates

- --Make certain that the patient has had a thorough clinical examination
- --Many difficult-to-diagnose cutaneous lymphoid lesions are relatively indolent, and available therapies are not able to dramatically alter the natural history of the disease. Thus, there is no particular “penalty” in most cases for a conservative approach, and the disease will typically declare itself in time
- --Liberal use of special studies (immunohistology, in-situ hybridization, genotyping, flow cytometry, etc.) is a necessity
- --*Clinicians should be cautioned that CLH and lymphoma of the skin likely exist in a continuum, making close followup of the patient desirable*

