Primer of Immunohistochemistry (Leukocytic)

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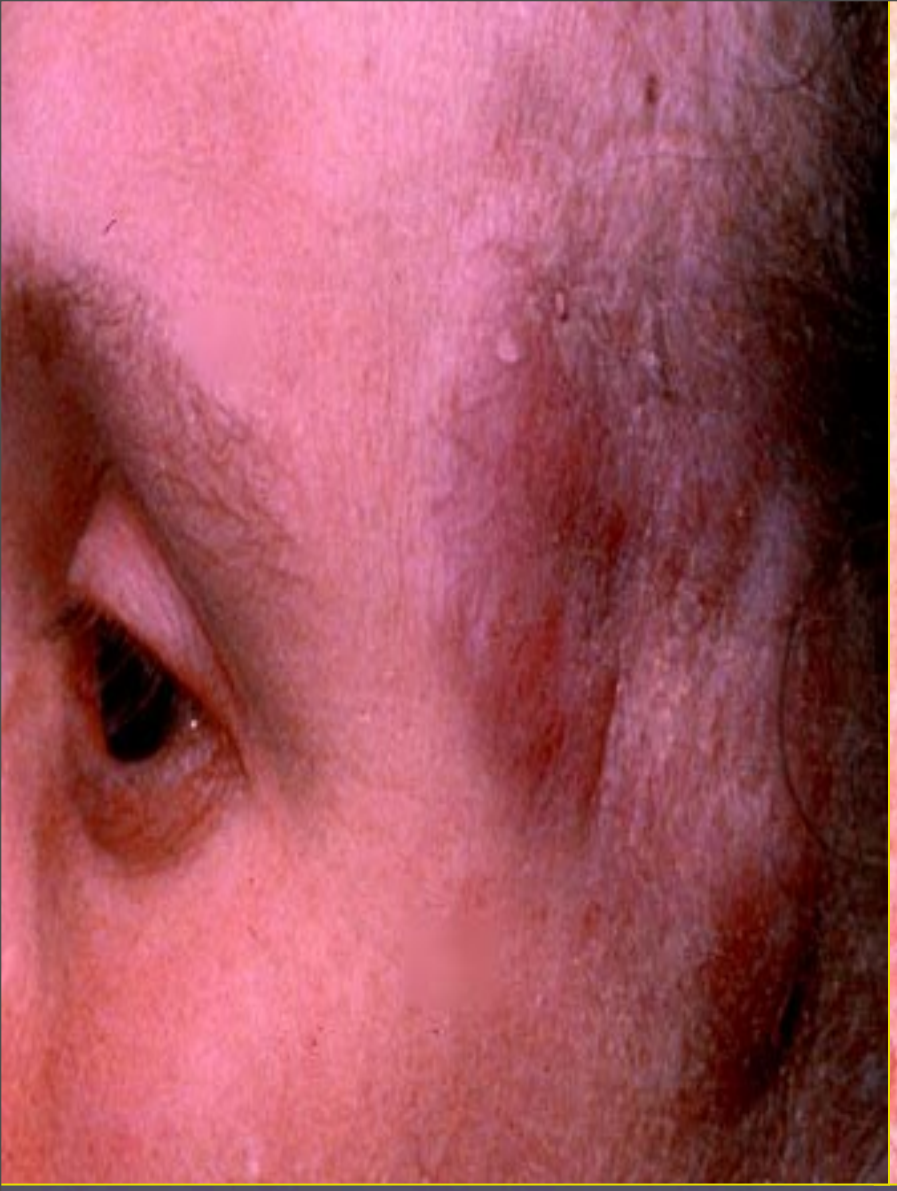
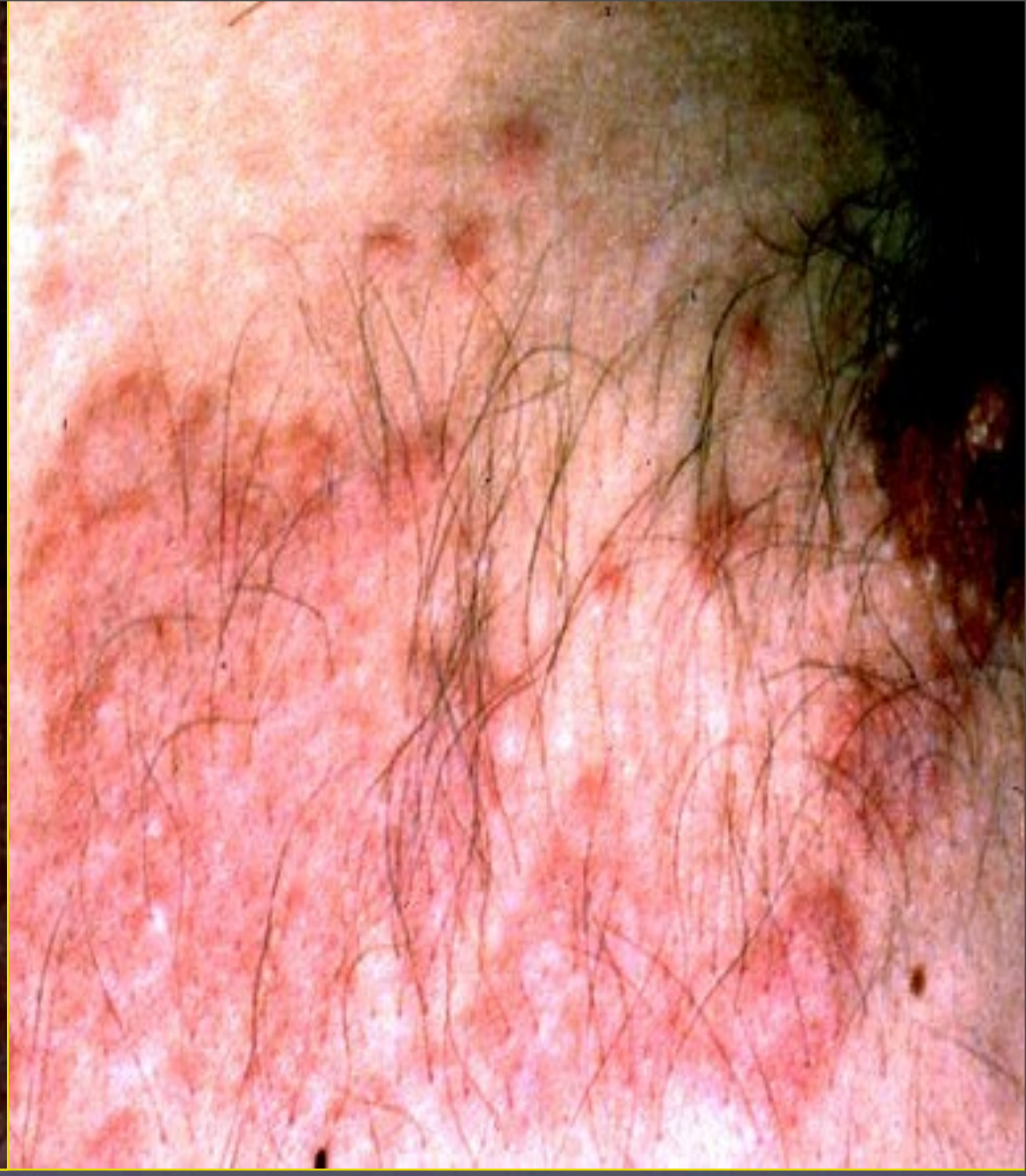
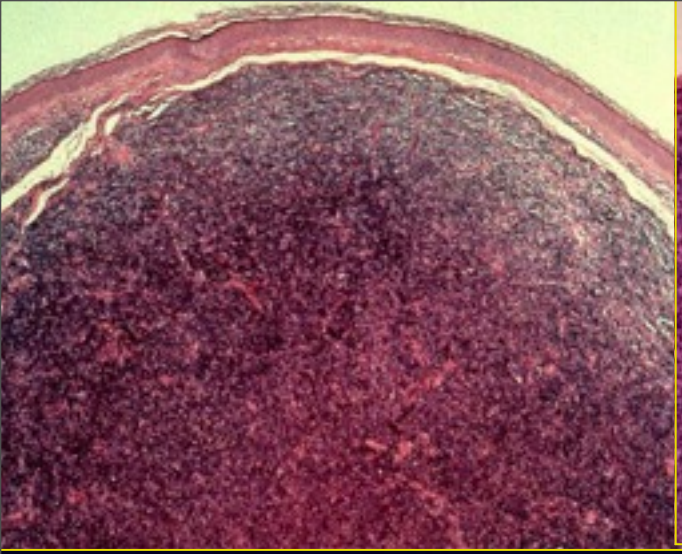
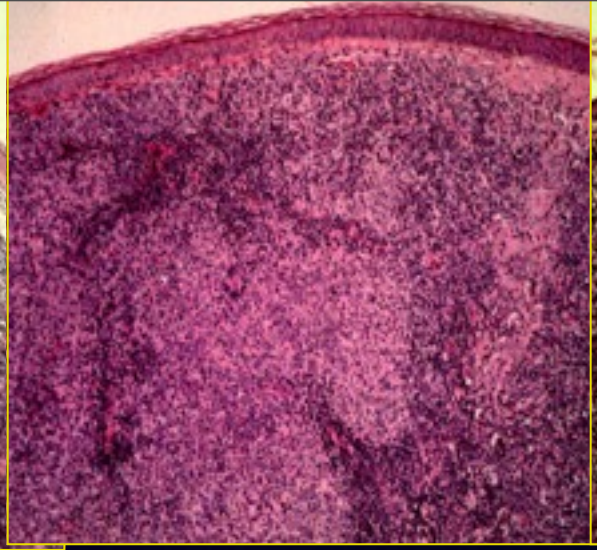
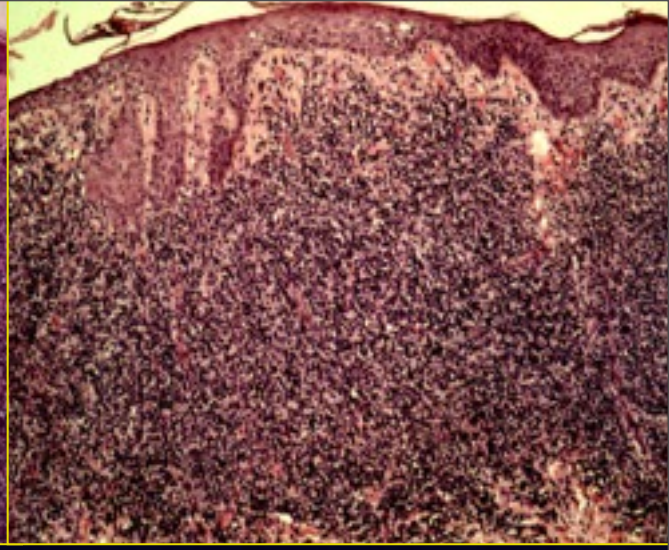
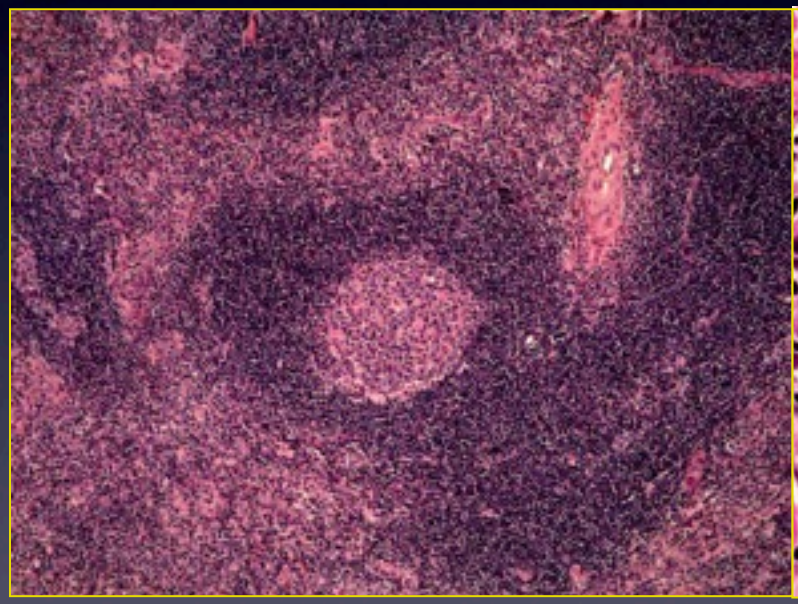
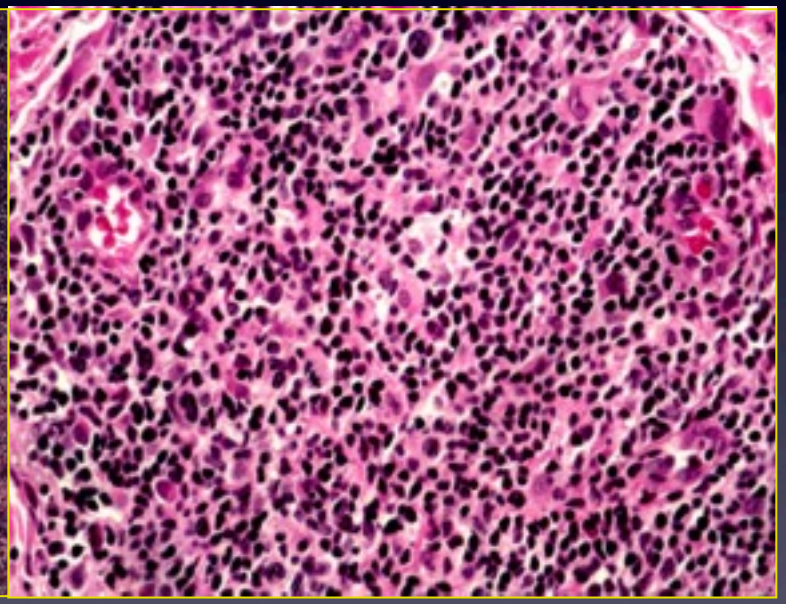
BENIGN LYMPHOID SKIN LESIONS CAPABLE OF SIMULATING LYMPHOMA

- -Jessner's lymphoid infiltrate
- -Dermal-subcutaneous lupus profunda
- -Lymphadenoma benigna cutis
- -Lymphocytoma cutis
- -Chronic lichenoid/spongiotic dermatitis
- -Drug-induced lymphoid pseudotumors
- -Actinic reticuloid
- -Inflammatory myofibroblastic pseudotumors
- -Kikuchi's disease
- -Cutaneous lymphoid hyperplasias, NOS





Cutaneous Lymphoid Hyperplasia: Clinical Images

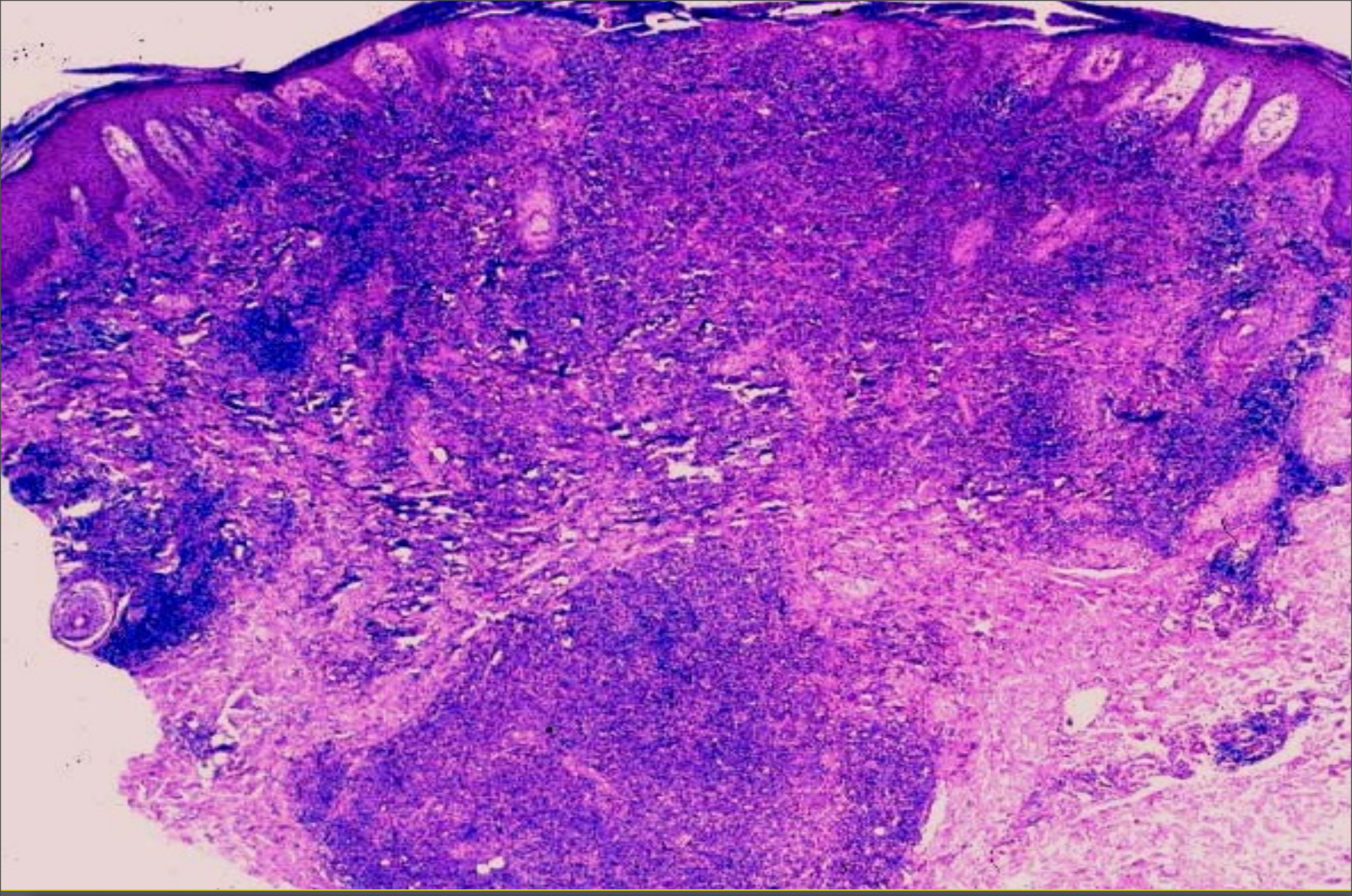






Cutaneous Lymphoid Hyperplasia: Microscopic Images

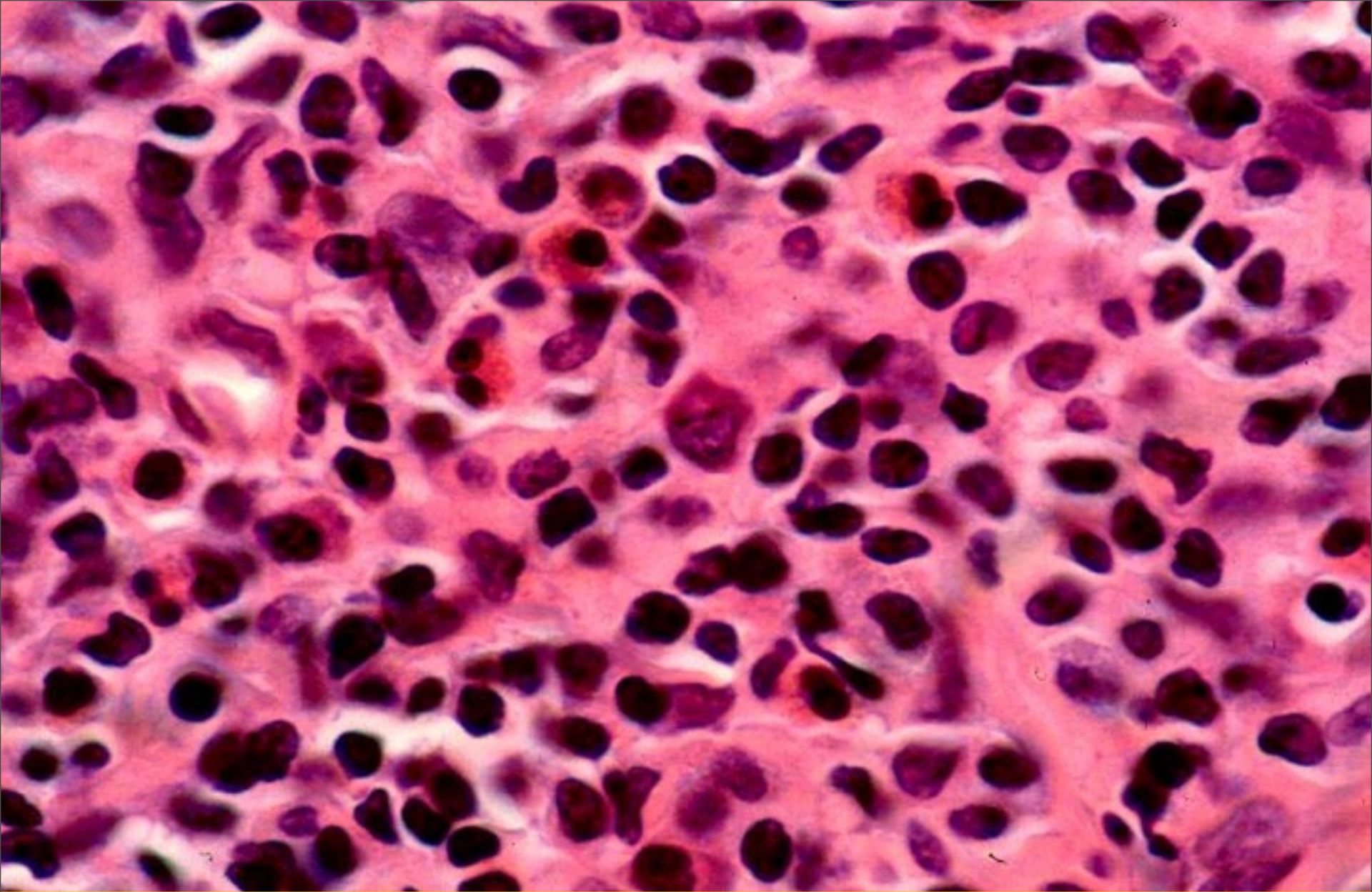
General Histologic Features for the Separation of Benign & Malignant Lymphoid Infiltrates of the Skin

Benign	Malignant
1. Recognizable as an organized immune response: follicles, plasma cells, granulocytes, mast cells, Langerhans cells, granulomas	1. No features of an organized immune response (not present as a mixture of cellular groupings)
2. Infiltrative pattern: predominantly superficial and perivascular, periadnexal	2. Infiltrative pattern: diffuse, full thickness or predominantly deep, without perivascular preference; expansive
3. Epidermal reaction: if involved, shows hyperkeratosis and/or dyskeratosis, spongiosis, acantholysis, liquefactive basal layer degeneration	3. No epidermal reaction: even if involved, generally shows little reaction to infiltration
4. Cellular composition: heterogeneous, with grouping or clustering of similar cells, such as plasma cells, small lymphocytes, or histiocytes	4. Cellular composition: uniform or if diverse a recognized selective combination of related cell types (for example, small lymphocytes and plasmacytoid lymphocytes or a mixture of follicular center cell types)
5. Cellular normalcy: although large and mitotically active cells may be present, these correspond to stimulated benign functional cell types (for example, immunoblasts, histiocytes)	5. Cellular anaplasia: bizarre forms not within the limits of stimulated reactive elements (for example, tumor giant cells, large [T] cells with smudgy hyperchromatic nuclei and extreme nuclear membrane complexity)

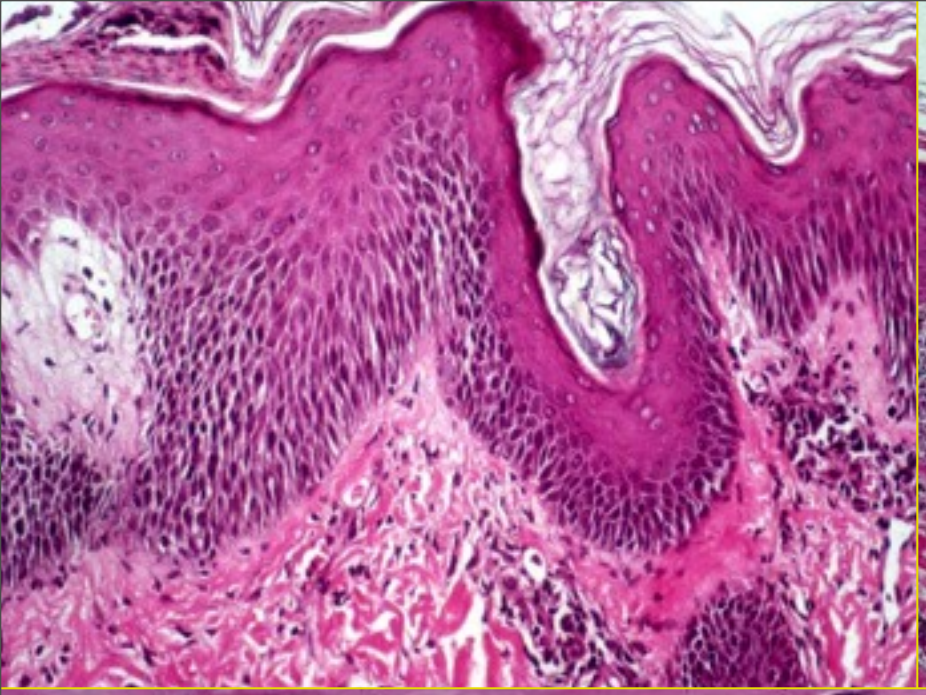
Banks PM: Lymphoid lesions. ***In: Pathology of Unusual Malignant Tumors***

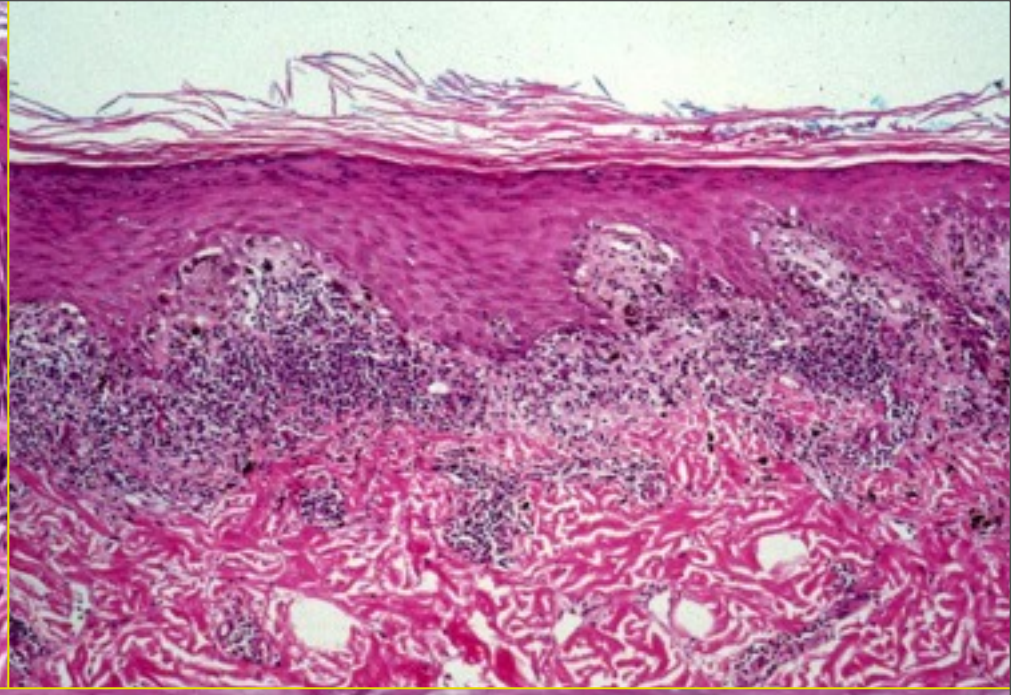


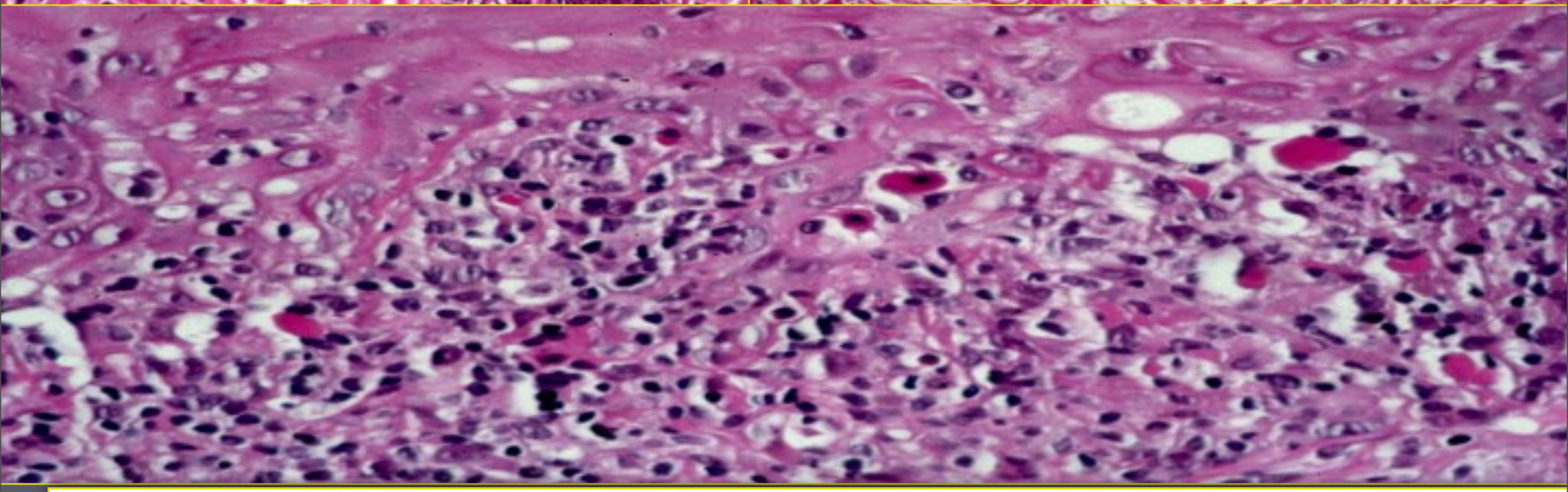
Lymphomatoid Papulosis-- An Exception to the "Top-Heavy = Benign" Rule



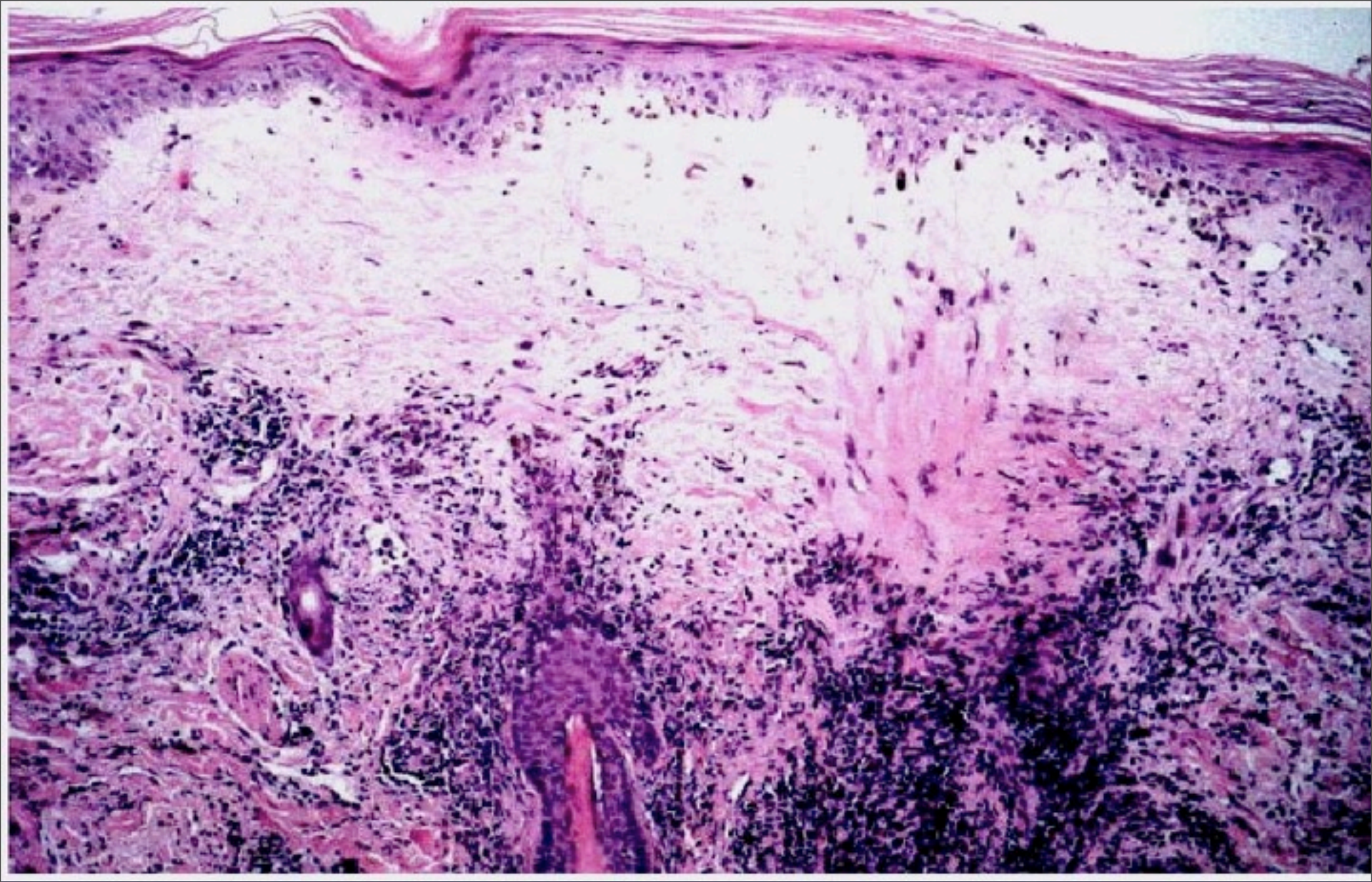
Pseudolymphomatous Arthropod Bite Reaction



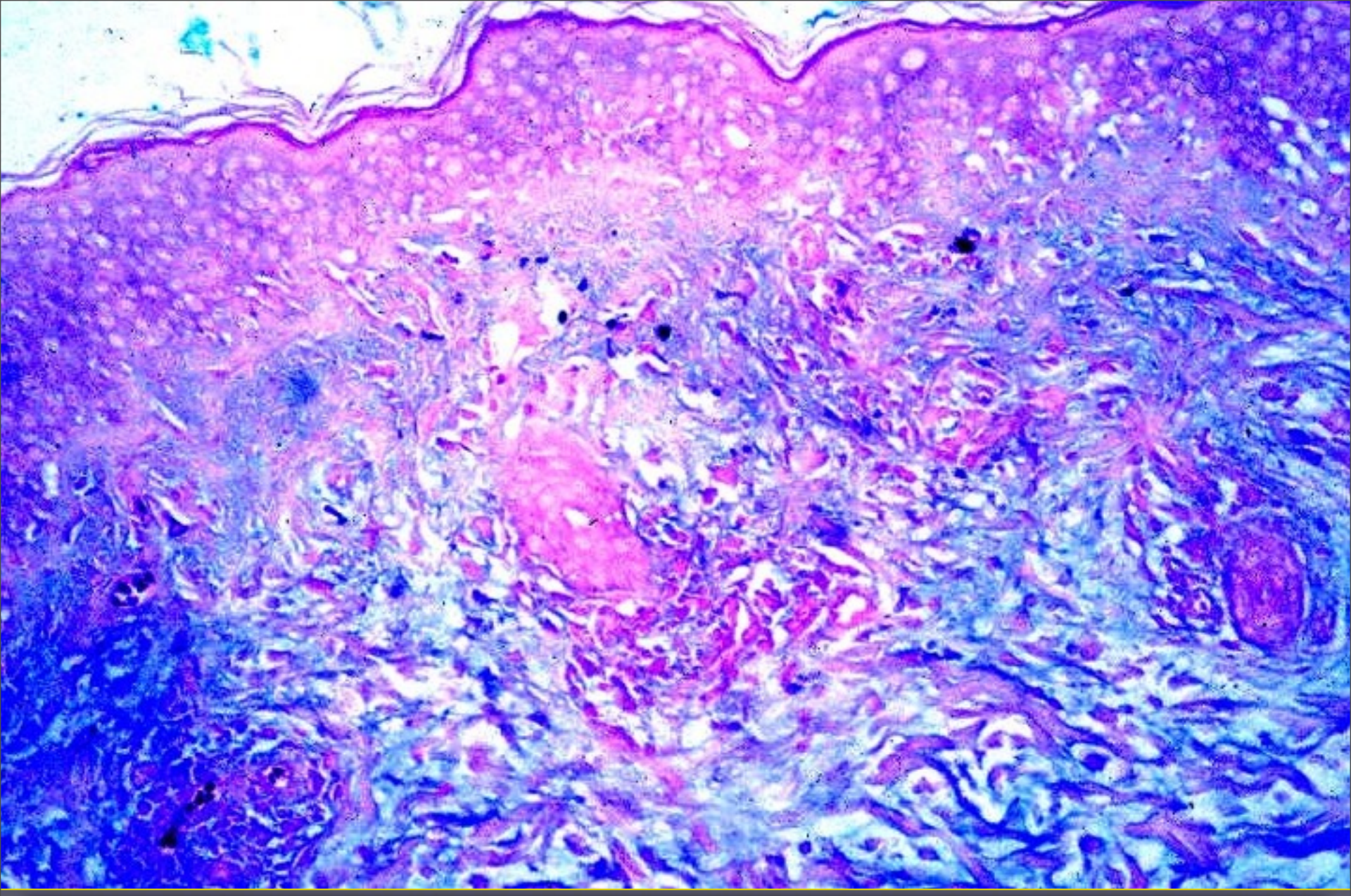




"Secondary" Epidermal Changes in Dermatitides Featuring Lymphoid Infiltrates



“Tumid” (Dermal) Lupus Erythematosus



Colloidal Iron-Positivity in "Tumid" (Dermal) Lupus Erythematosus

IIMMUNOHISTOLOGY IN DDx OF SMALL-CELL & MIXED DEEP DERMAL LYMPHOID INFILTRATES

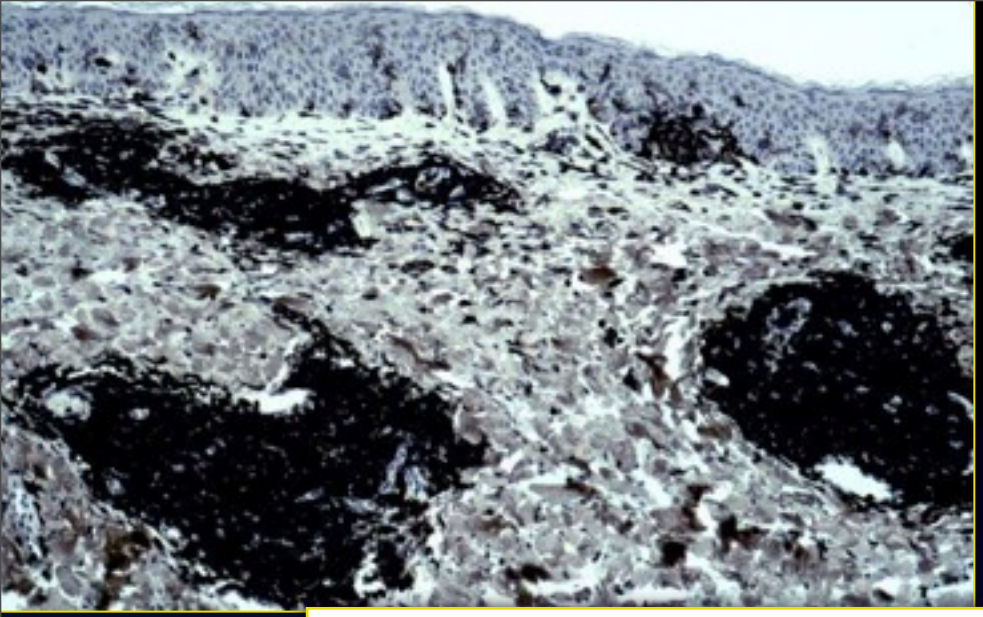
- ***Features Arguing for Malignancy***

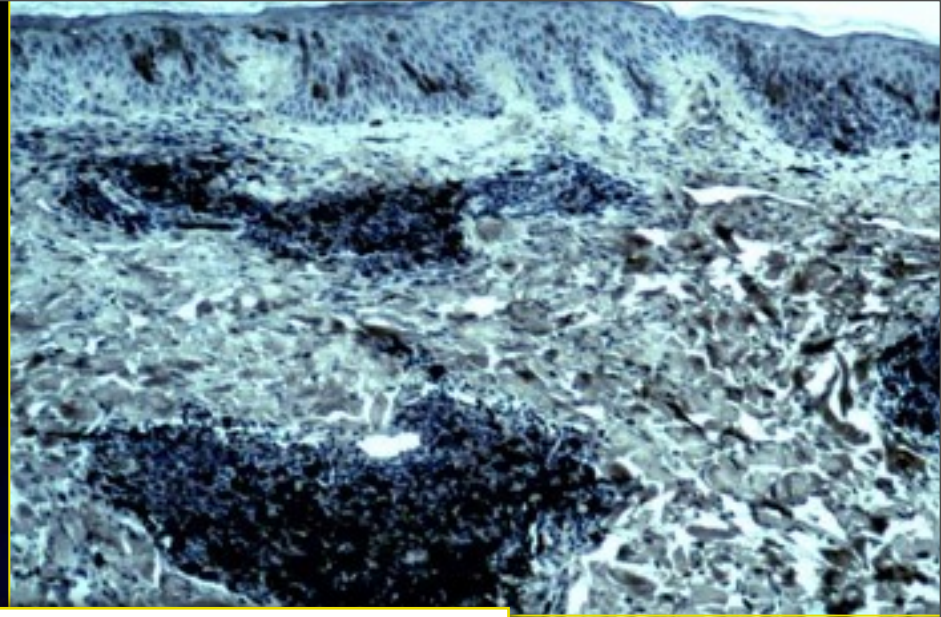
-- ≥75% B-cells; especially with few admixed T-lymphocytes

-- Ig light chain monotypism on B-cells in infiltrate (light chain ratio of ≥10:1)

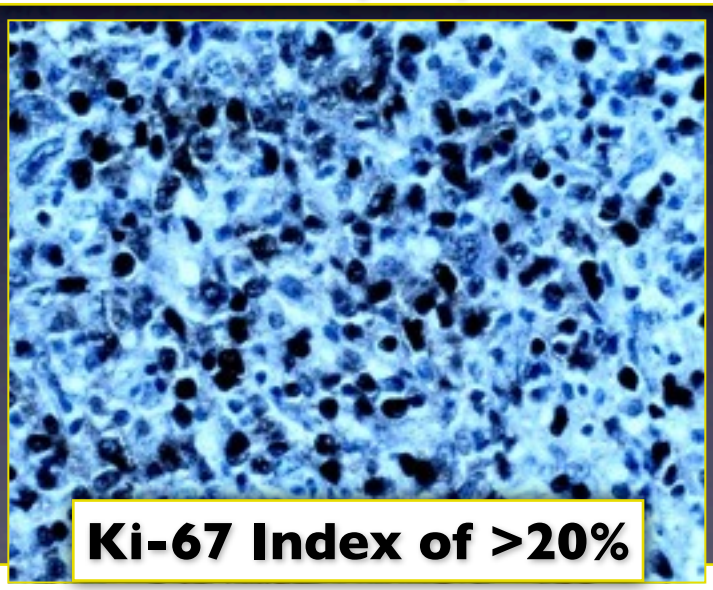
-- Proliferative index of >20% in atypical lymphoid cells

-- Coexpression of CD5/CD19 or CD20/CD43



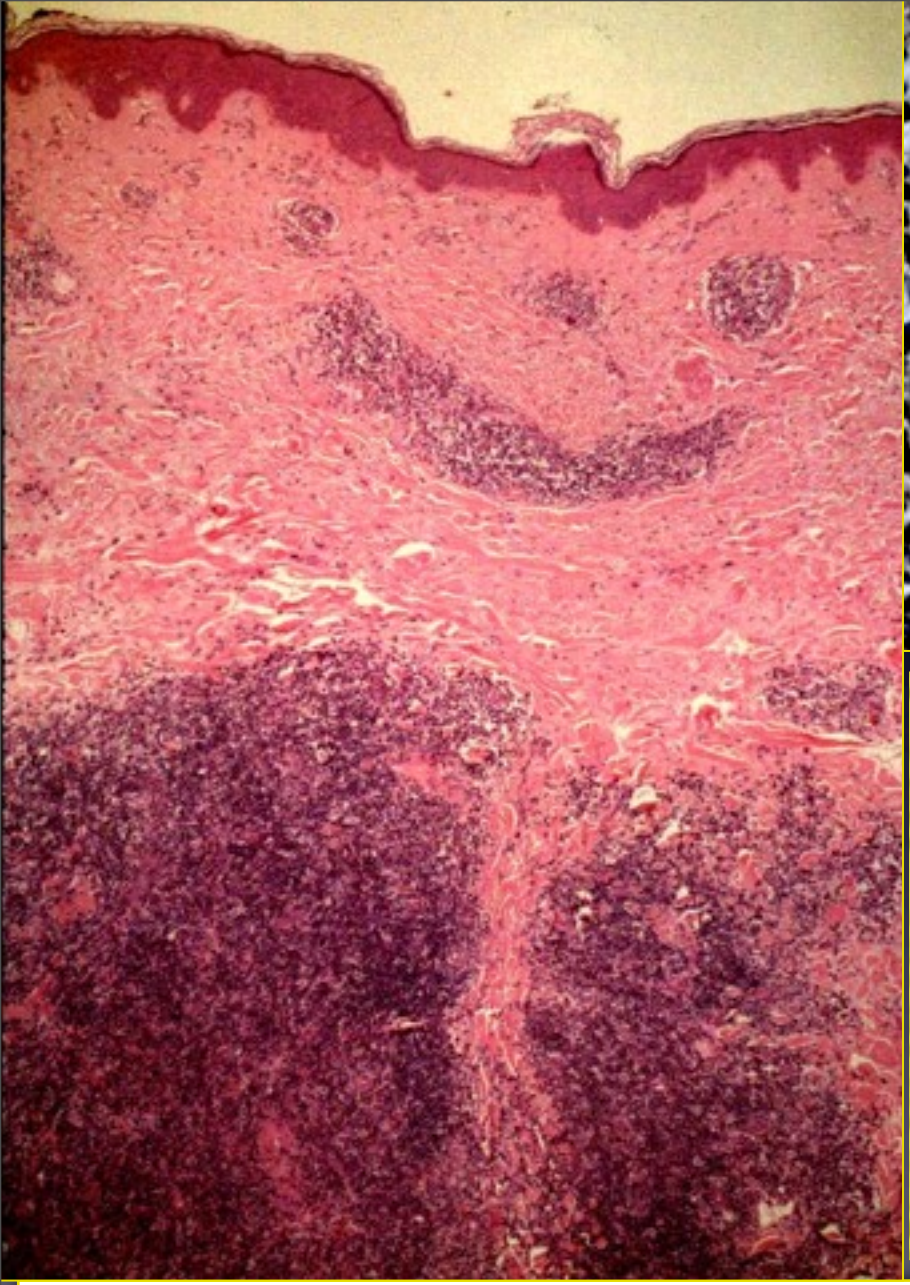


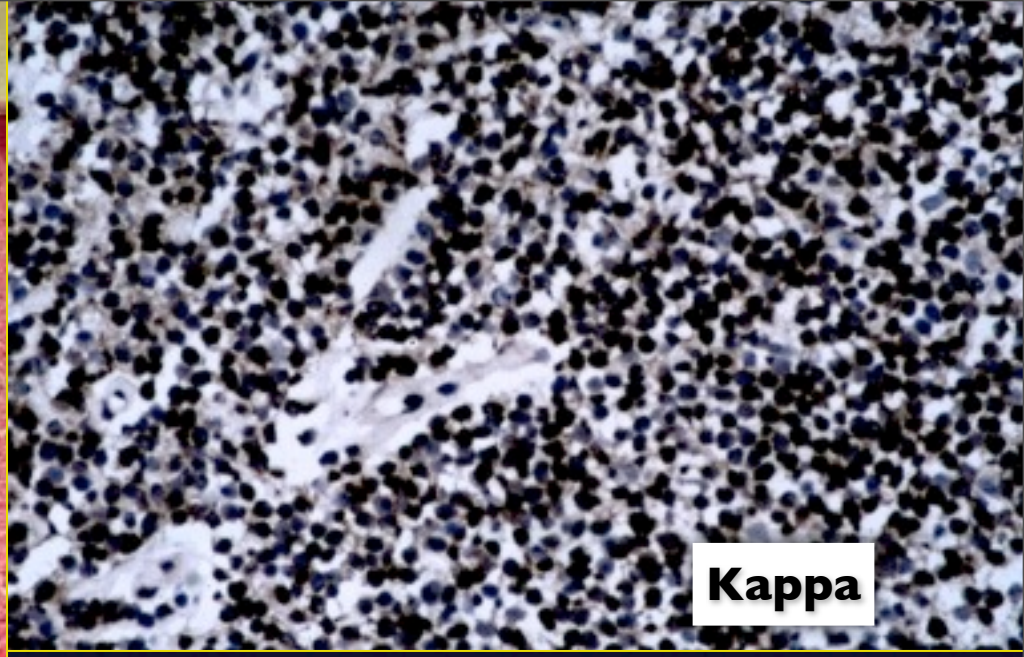
Coexpression of CD20 (left) & CD43 (right)

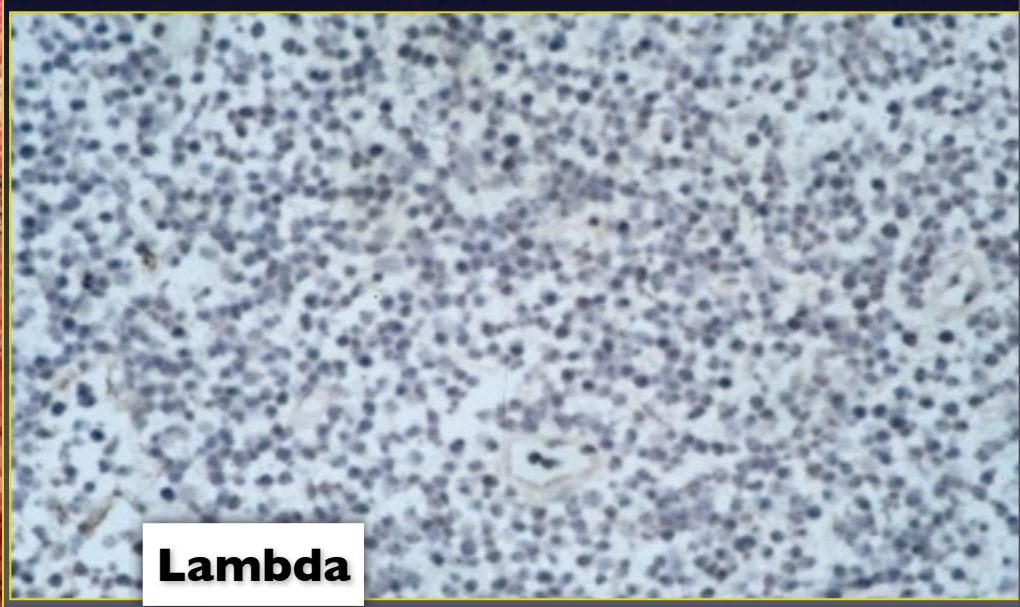


Ki-67 Index of >20%

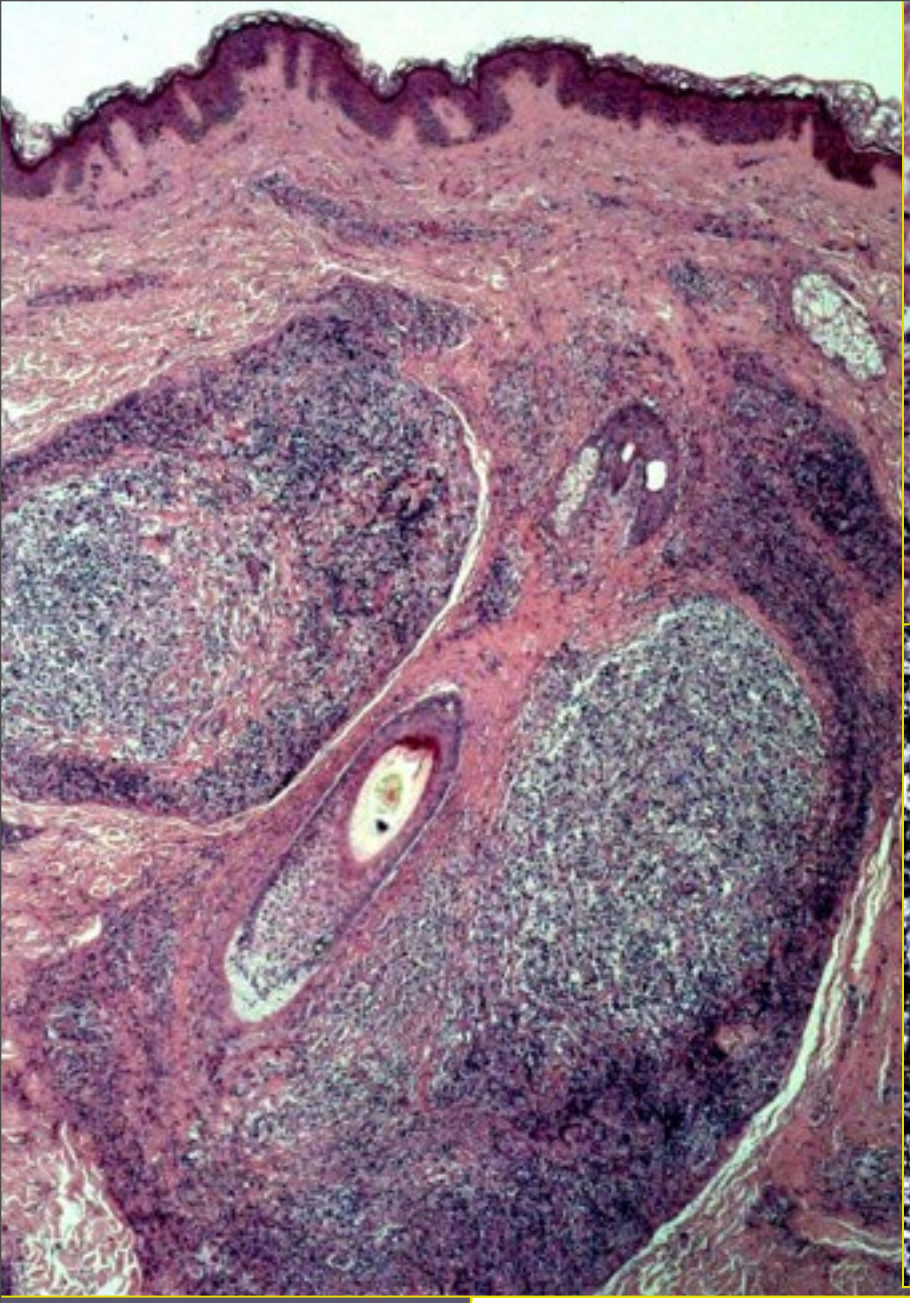
Immunohistological Findings Favoring Malignancy in Small-Cell & Mixed Large/Small Cell Lymphoid Infiltrates of the Skin

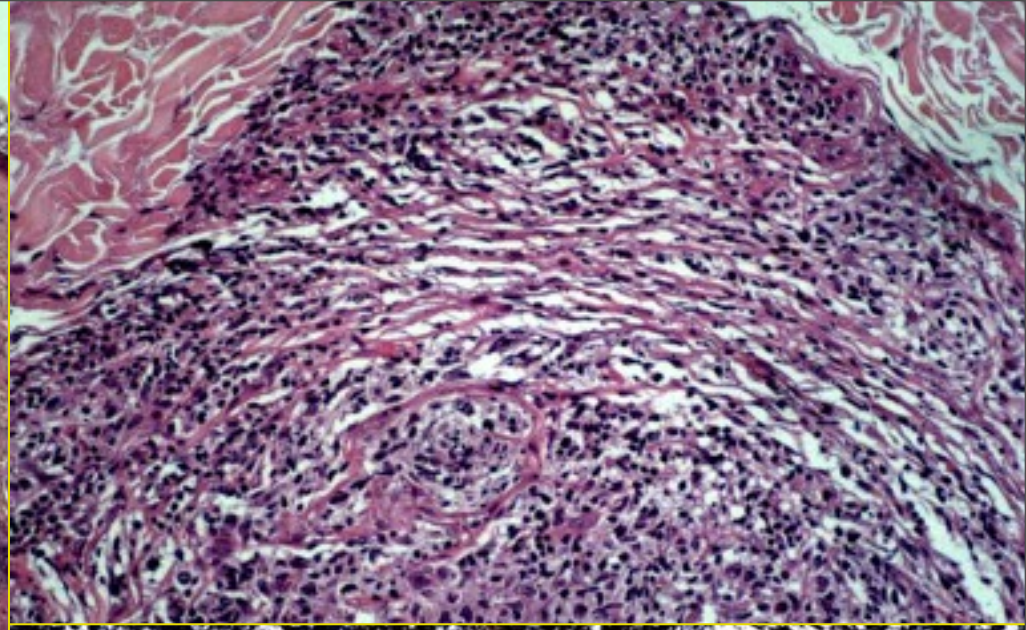


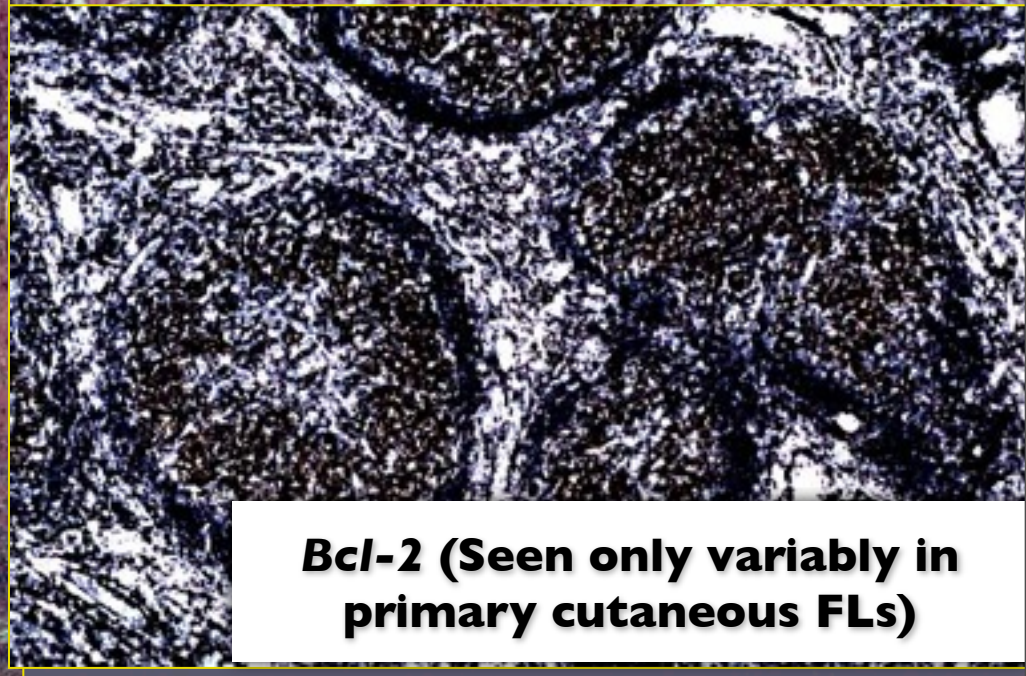




Small-Cell Lymphoma of the Skin: Light Chain Restriction in Frozen Sections







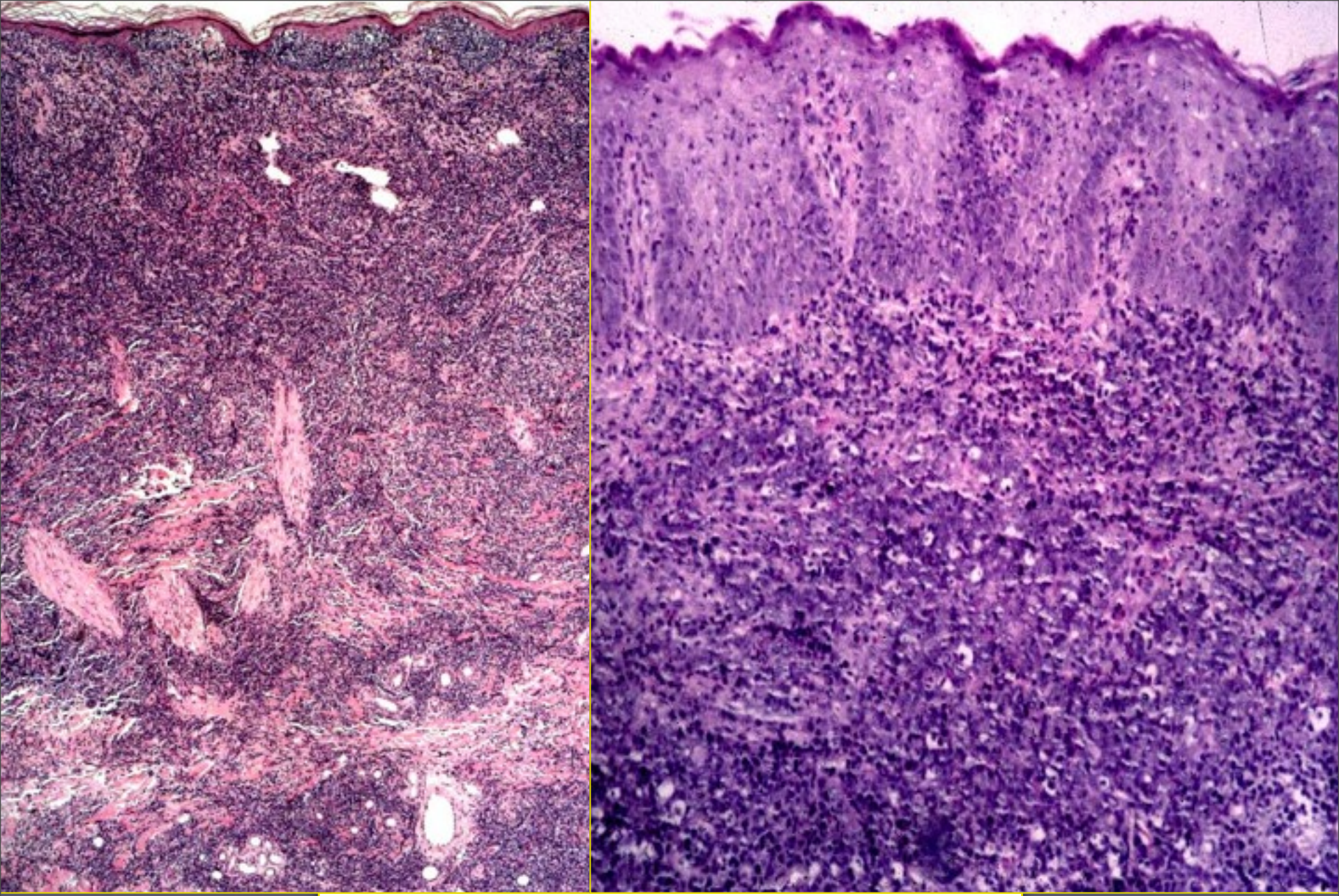
***Bcl-2* (Seen only variably in primary cutaneous FLs)**

Follicular B-Cell Lymphoma of the Skin

BCL-2 IN CUTANEOUS LYMPHOID LESIONS: Speaker's Series (Triscott J, et al., J Cutan Pathol, 1994)

LYMPHOID LESION	PRIMARY	SECONDARY
LARGE CELL FOLLICULAR ML	3/3	4/6
SMALL-CELL/MIXED FOLLICULAR ML	7/12	8/13
FOLLICULAR LYMPHOMA: TOTALS	10/15 (66%)	12/19 (60%)
BENIGN LYMPHOID LESIONS--	12/36 (33%)	

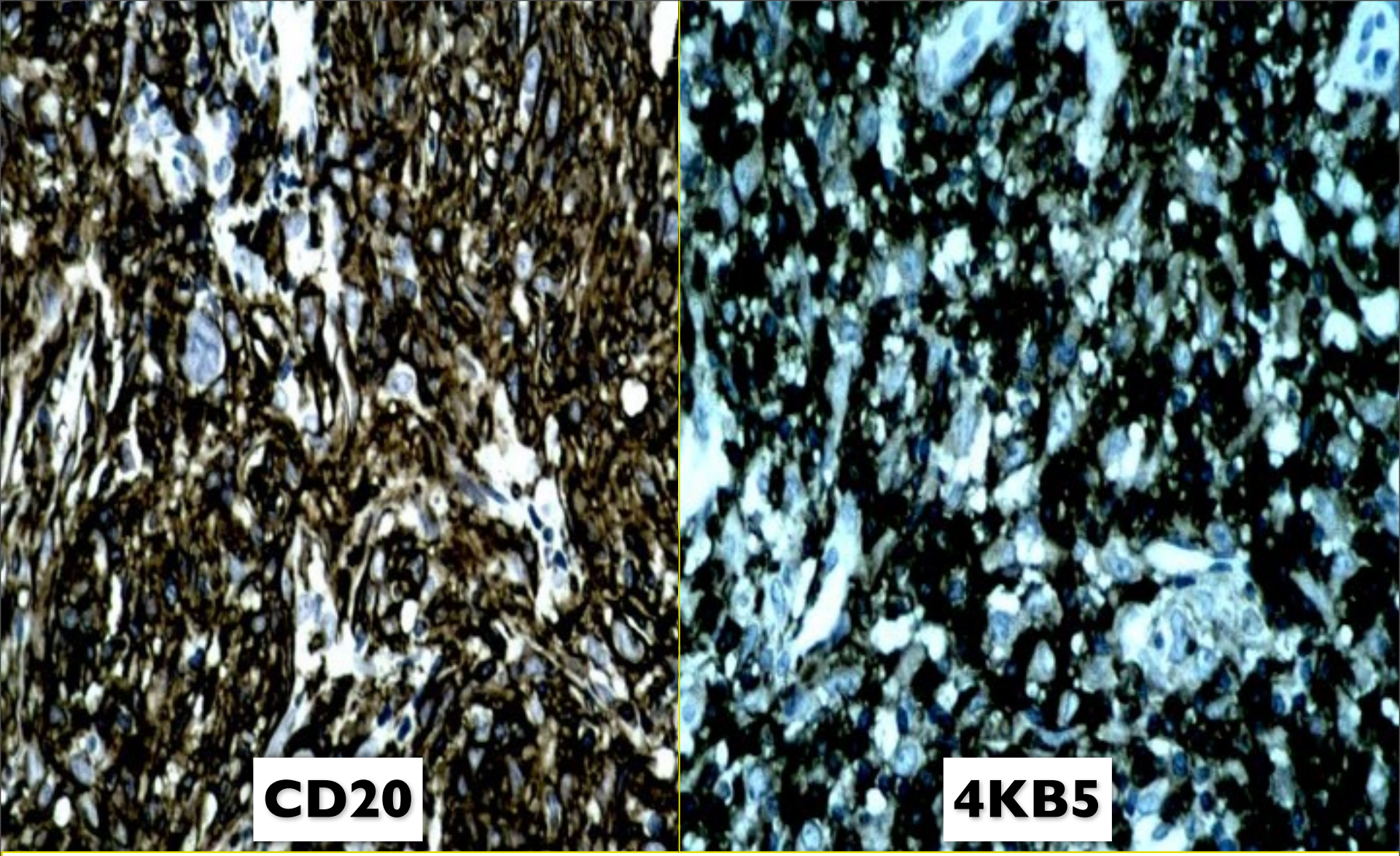
*MT-2 can be used in a similar fashion to bcl-2, but with similar reservations with regard to the distinction between benign & malignant follicular lymphoid lesions of the skin



Large-Cell B-Cell Lymphoma of the Skin

LARGE CELL B-CELL LYMPHOMA

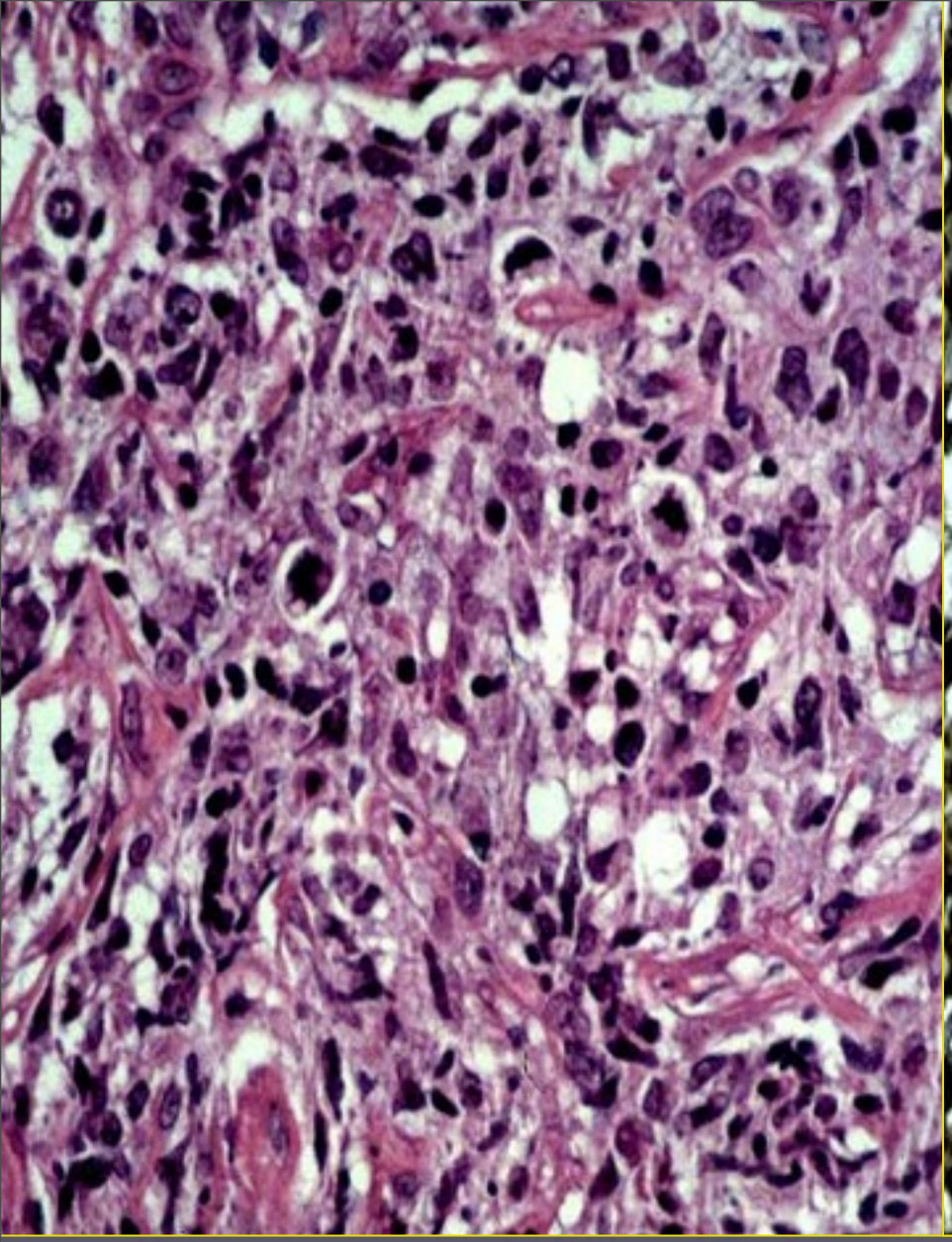
- -Paraffin sections: most useful and specific marker is still L26 (CD20); greater than 90% sensitive, and still very specific
- -Others include MB1, MB2, & 4KB5; as with other B-cell tumors, LCBCL may co-express CD43
- -We have little success in paraffin sections with kappa and lambda light chain immunoglobulin stains
- -Frozen section or flow cytometry: CD19, 20, 21, 22, and surface immunoglobulin restriction can be demonstrated in most cases. CD5+ in cases of transformed SLL
- -The latter studies and immunoglobulin gene rearrangement studies are rarely needed in most cases of B-cell *large cell* lymphomas

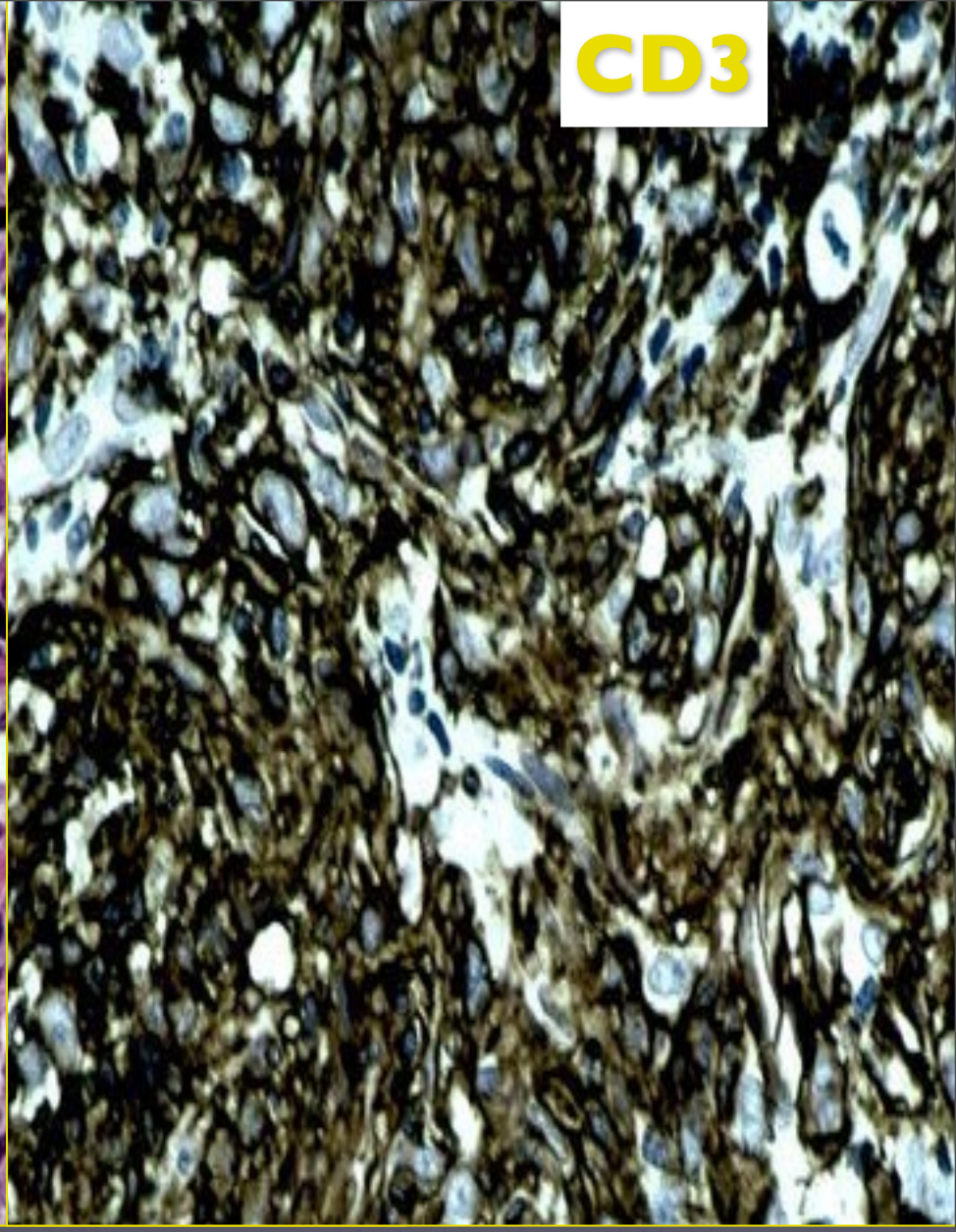


Immunophenotype of Large-Cell B-Cell Cutaneous Lymphoma

LARGE CELL T-CELL LYMPHOMA

- -After excluding mycosis fungoides, cutaneous T-cell cases are approximately equal in number to B-cell cases
- -Possible choices include peripheral T-cell lymphoma, NOS (PTCL); transformed mycosis fungoides (TMF), Lennert's lymphoma, and some cases of anaplastic large cell lymphoma
- -Most useful paraffin section markers include CD3, CD5, and CD43
- -Frozen/flow markers include CD2,3,4,5,7,8,9, 43, and 45RO; look for pan-antigen deletions

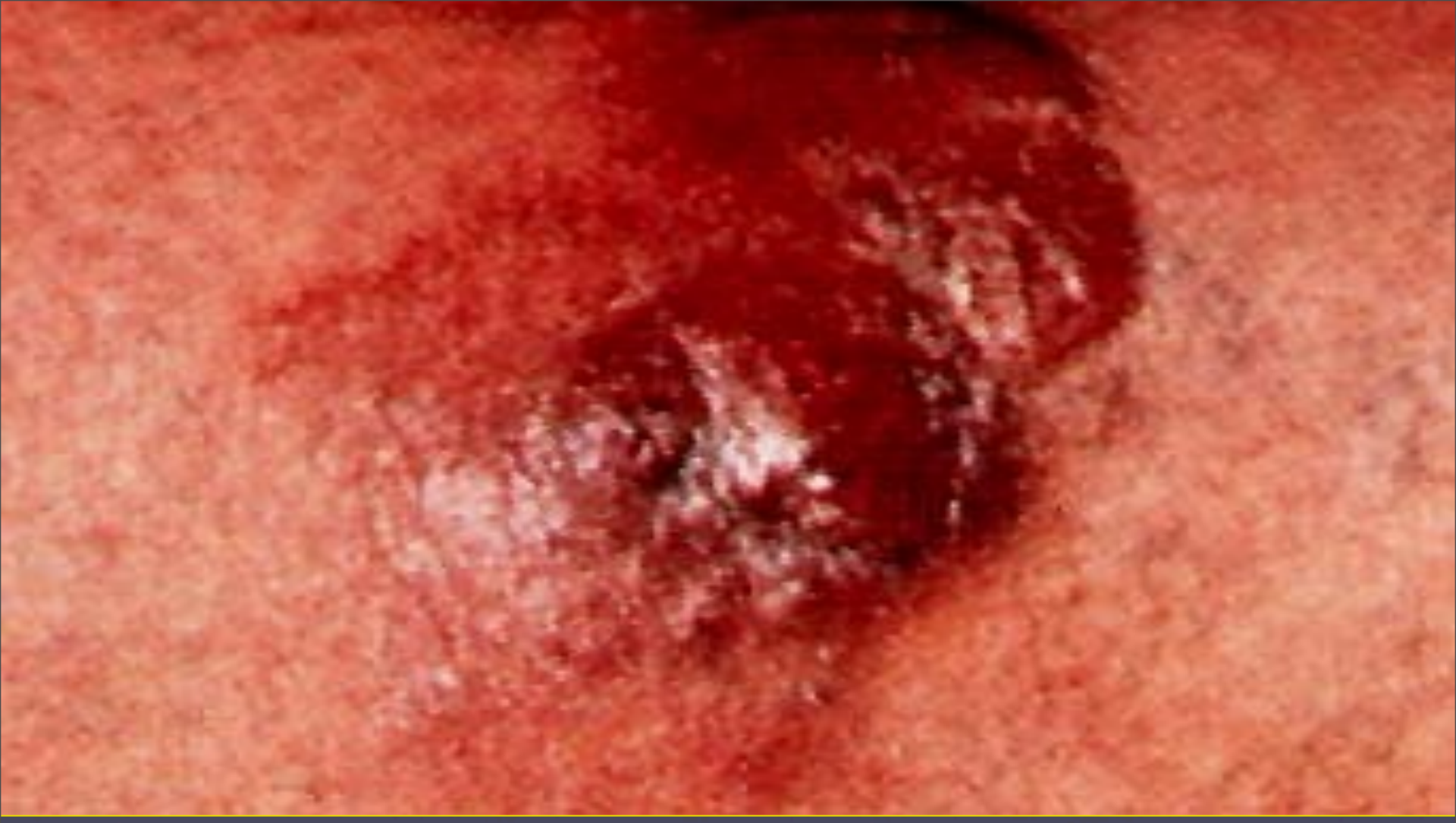




Large-Cell T-Cell Lymphoma of the Skin

PRIMARY CUTANEOUS CD30+ LARGE-CELL LYMPHOMA

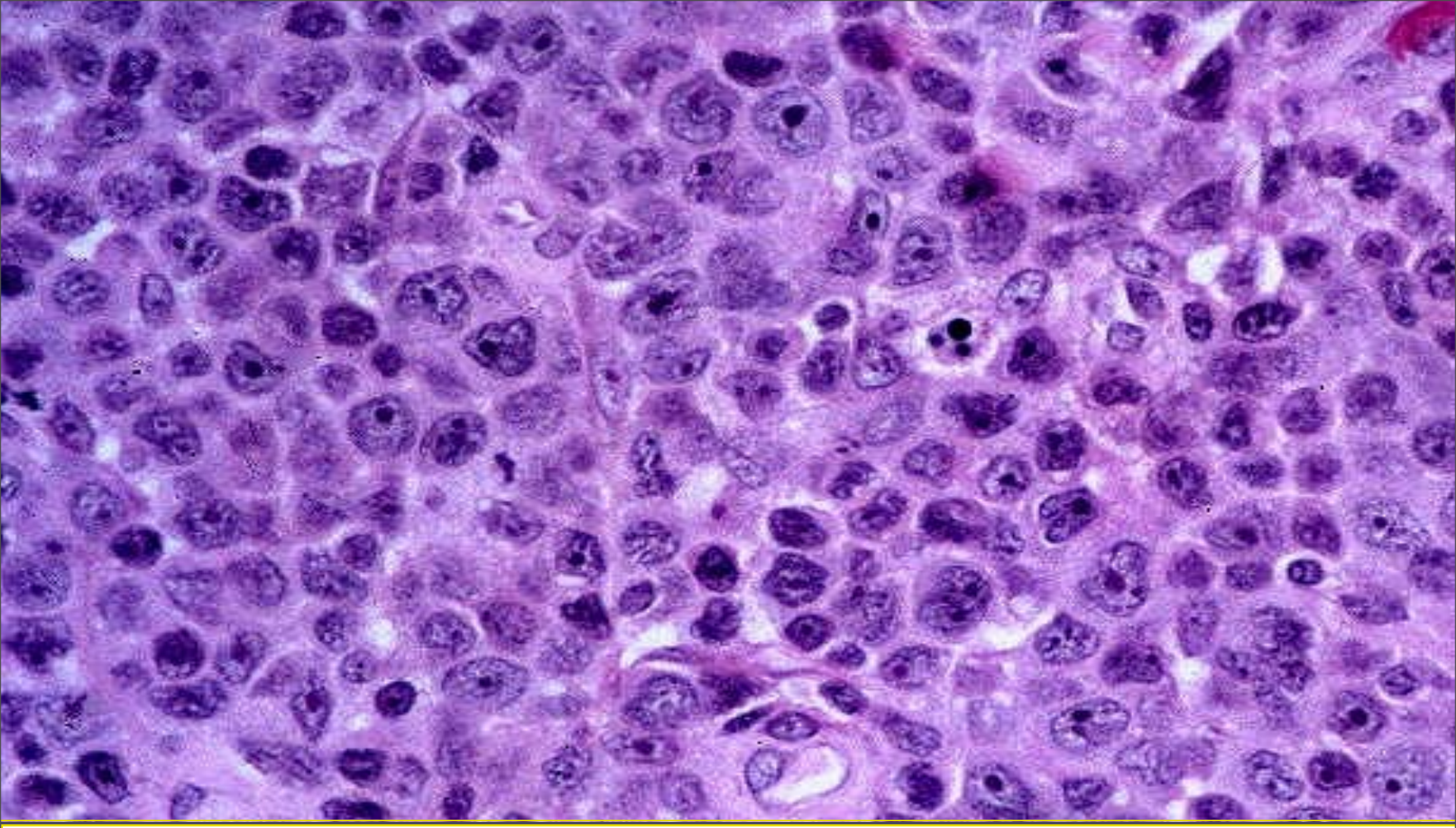
- --By definition, no nodal or visceral disease at presentation
- --Patients tend to be >60 yrs. of age
- --Relatively indolent behavior (90% at 4 yrs.)
- --Predominantly T-cell tumors
- --Reciprocal t(2;5) chromosomal translocation is often absent



CD30+ Anaplastic Large-Cell Lymphoma of the Skin: Clinical Image

ALCL: Histological Feaatures

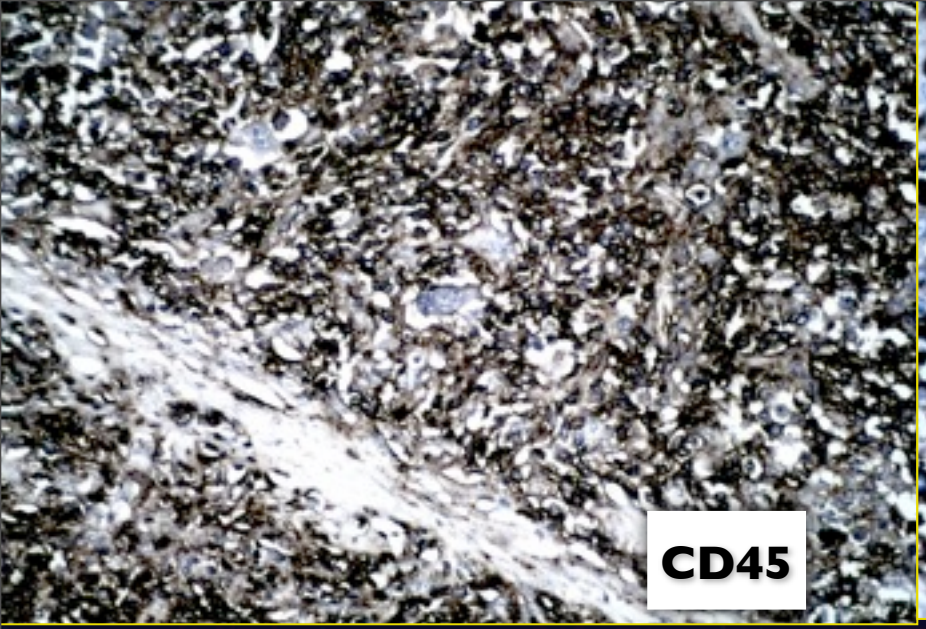
- --Heterogeneous population of large pleomorphic cells, usually closely apposed and interspersed with reactive leukocytes (including eosinophils, lymphocytes, neutrophils, macrophages, and plasma cells)
- --Multinucleated tumor cells common, including some with "wreath" forms and others resembling malignant "Touton" cells
- --Myxoid stroma and focal spindle-cell change may be evident, calling to mind the attributes of a sarcoma or sarcomatoid carcinoma or melanoma

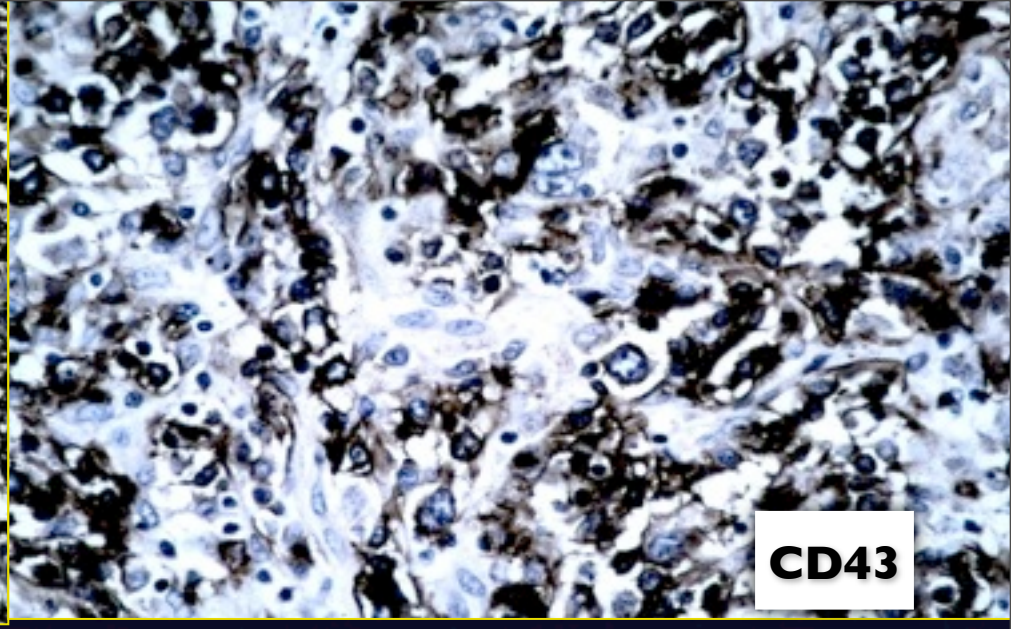


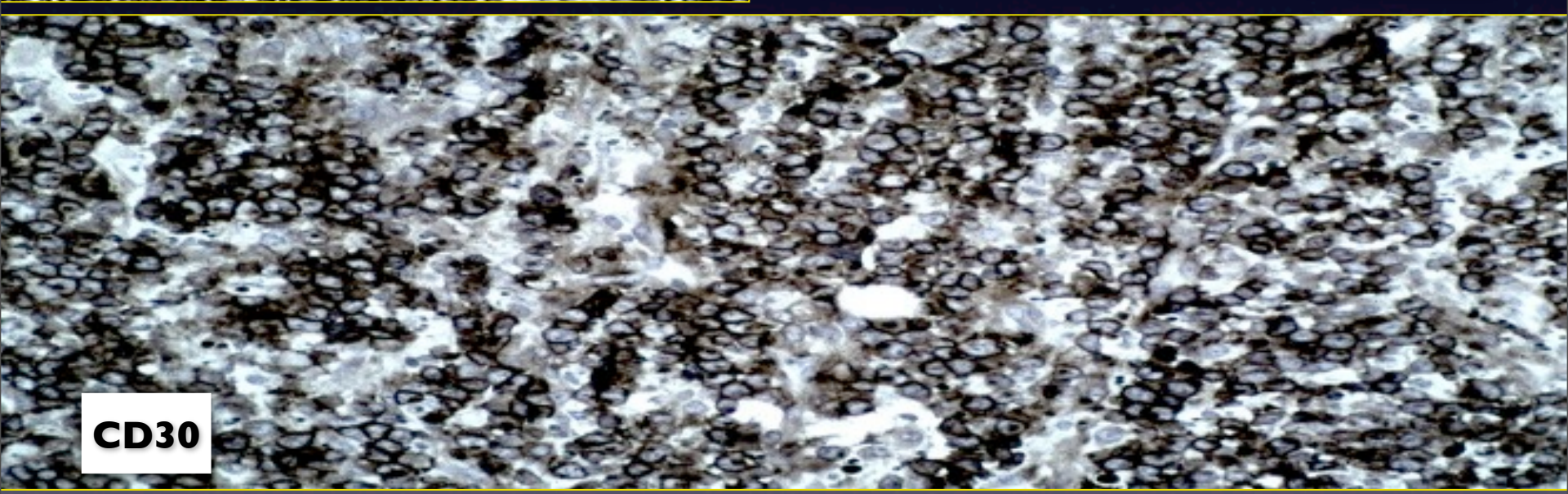
CD30+ Anaplastic Large-Cell Lymphoma of the Skin: Histology

IMMUNOLOGICAL PECULIARITIES OF ALCL

- --Approximately 15% of ALCLs lack CD45-immunoreactivity in paraffin sections
- --Roughly 75% of ALCLs are EMA-positive
- --70% are T-cell tumors, 20% are B-cell lesions, and 10% are "null-cell" lymphomas, using conventional immunohistologic reagents for typing
- --Rare examples may aberrantly express keratin polypeptides
- --May be HECA-452-positive



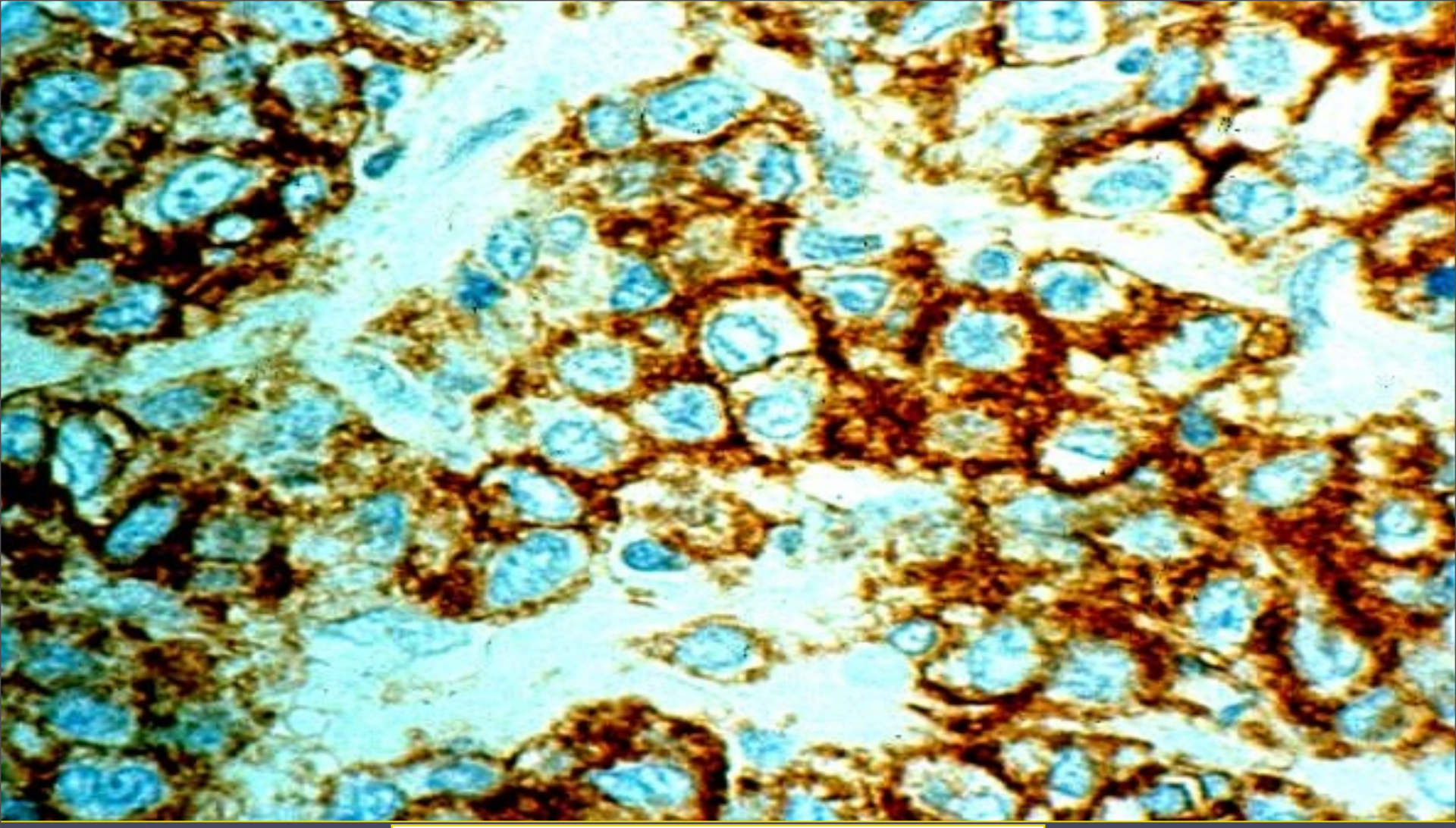




CD30+ Anaplastic Large-Cell Lymphoma of the Skin: Histology

CD30

- An activation marker that may be seen in florid reactive lymphoproliferations (e.g., mononucleosis), as well as Hodgkin's disease, non-Hodgkin's lymphomas, and embryonal carcinoma of gonads
- Recognized by Ki-1 and BER-H2, among other antibody reagents
- Should *never* be used as a marker of "malignancy"



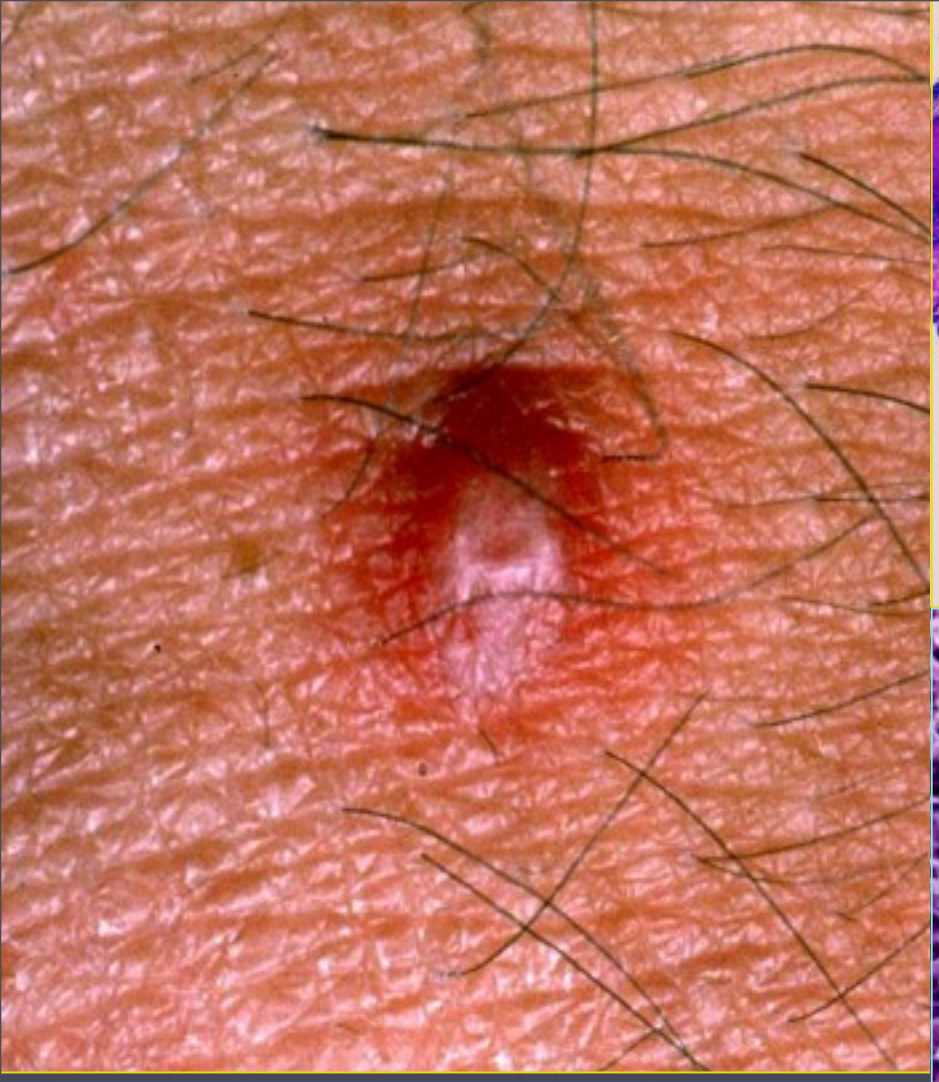
CD30+ Viral Exanthem of the Skin

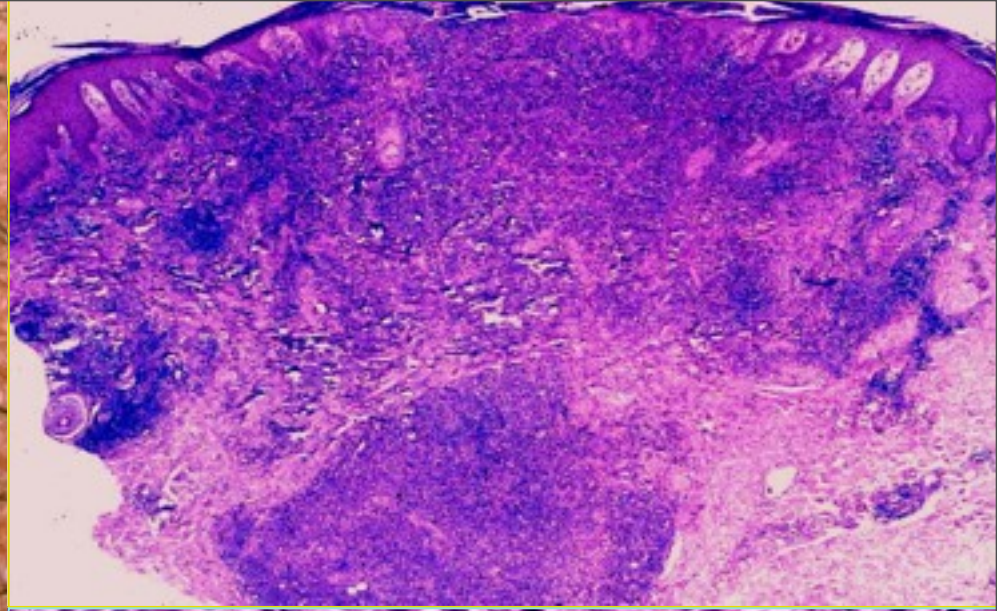
Does CD30-Negative ALCL Exist?

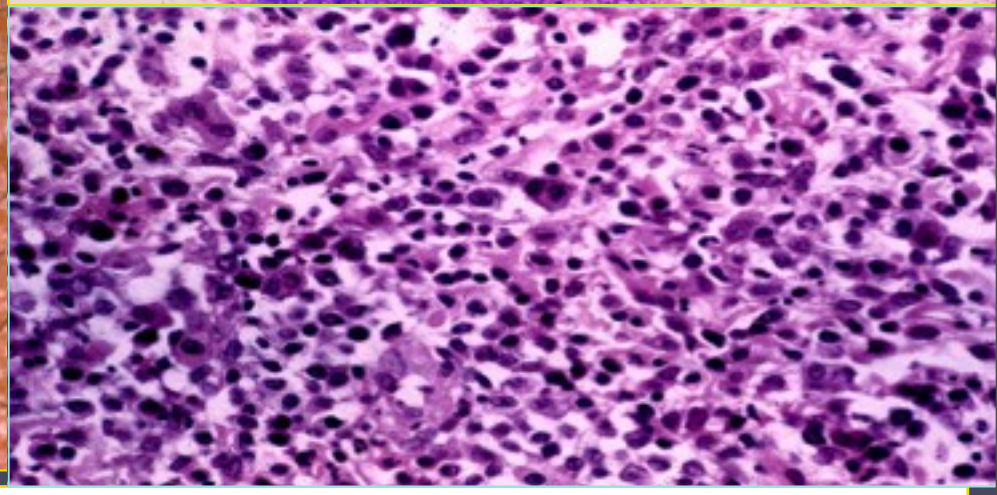
- In general, the diagnosis of ALCL is a morphological one rather than an interpretation mandating a particular immunophenotype

OTHER POTENTIALLY CD30+ LYMPHOPROLIFERATIONS OF THE SKIN

- *--Reactive lymphoproliferations (e.g., viral, drug-induced)*
- *--Lymphomatoid papulosis*
- *--Angiocentric immunoproliferative lesions ("lymphomatoid granulomatosis")*
- *--Transformed mycosis fungoides*
- --(Hodgkin's disease of the non-lymphocyte predominant types) (NOT SEEN IN SKIN)







Lymphomatoid Papulosis: A CD30+ Lymphoproliferation of the Skin That is Usually Self-Limited and Host-Confined: Progresses to Lymphoma in 20-30% of Cases

WHICH DISEASES HAVE BEEN RECLASSIFIED AS ALCL?

- -- Most examples of "malignant histiocytosis" in nodal and extranodal sites
- --"Regressing atypical histiocytosis" of the skin
- --It is likely that observed phagocytosis by intratumoral macrophages in these conditions is a *secondary epiphenomenon* due to cytokines released by the neoplastic cells

SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (SHML): General Features

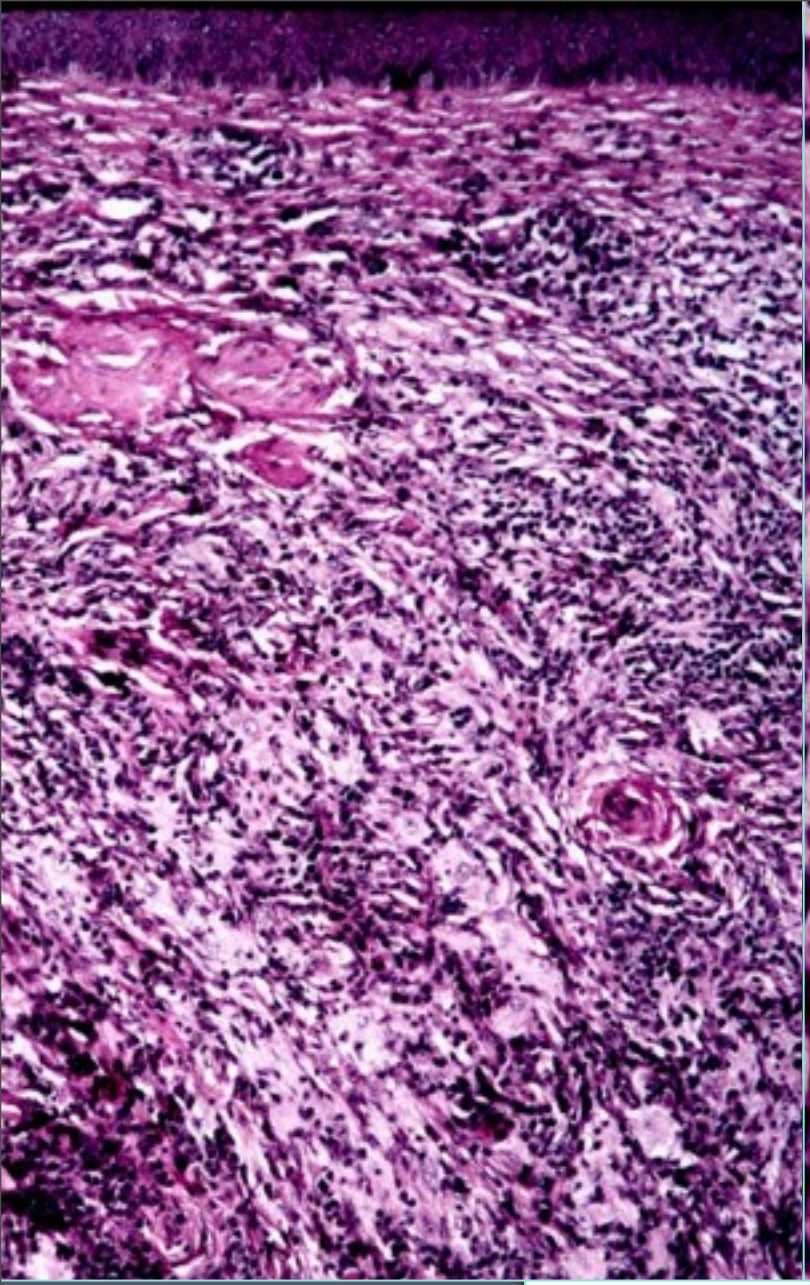
- --Described by Rosai & Dorfman in 1969
- --Initially thought to be more common in children than in adults, and to favor Black patients; these contentions have not survived as truths
- --Males slightly more often affected
- --Slow evolution over months
- --Systemic complaints may or not be present

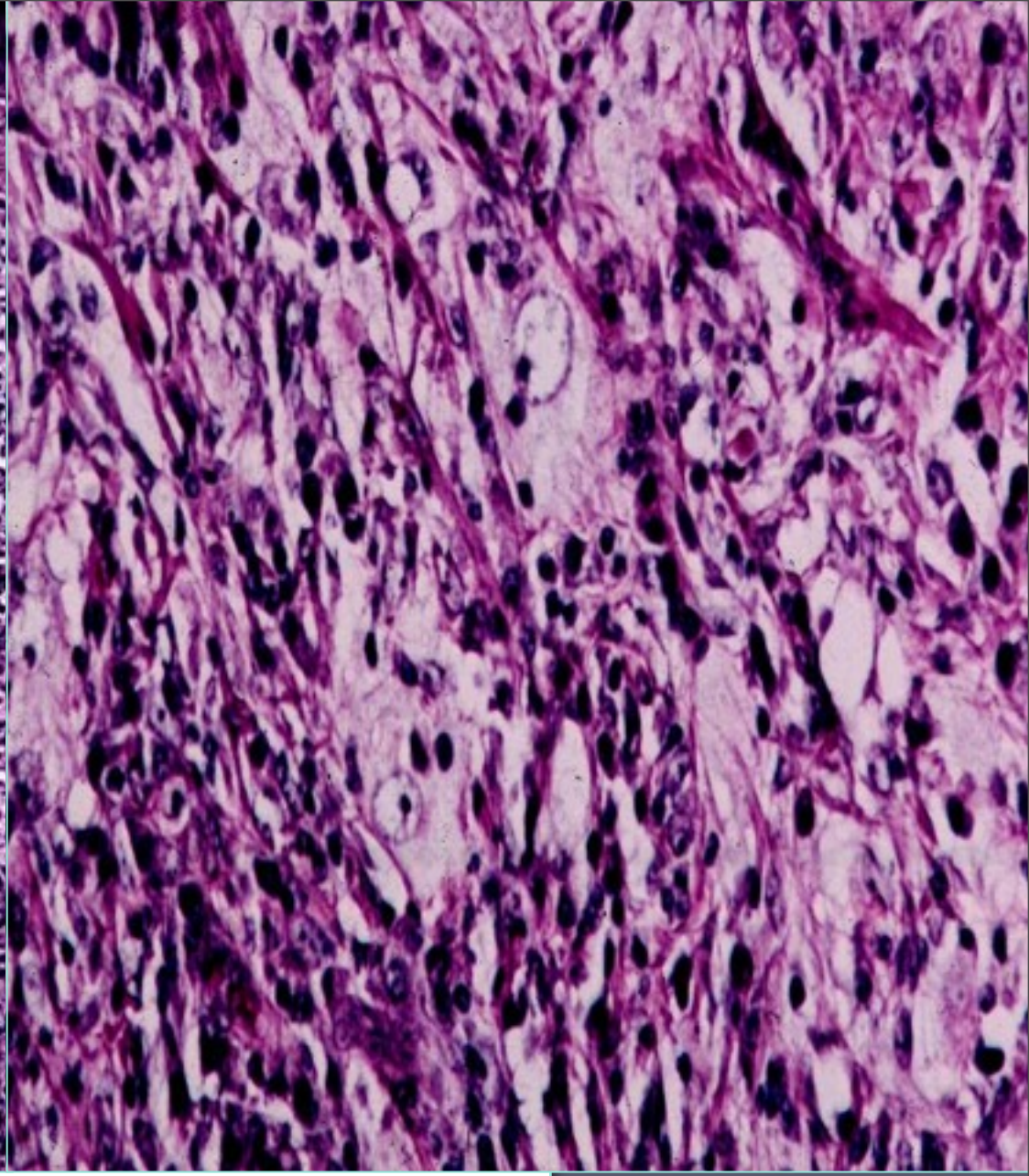
SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (SHML): Extranodal Disease: General Comments

- --Almost one-half of all patients with SHML have extranodal disease: skin is most commonly involved
- --Discovered because it usually produces an obvious clinical abnormality
- --Definite effect on prognosis by the *site* of extranodal disease; *e.g.*, laryngeal, renal, and pulmonary involvement by SHML was associated with potential mortality

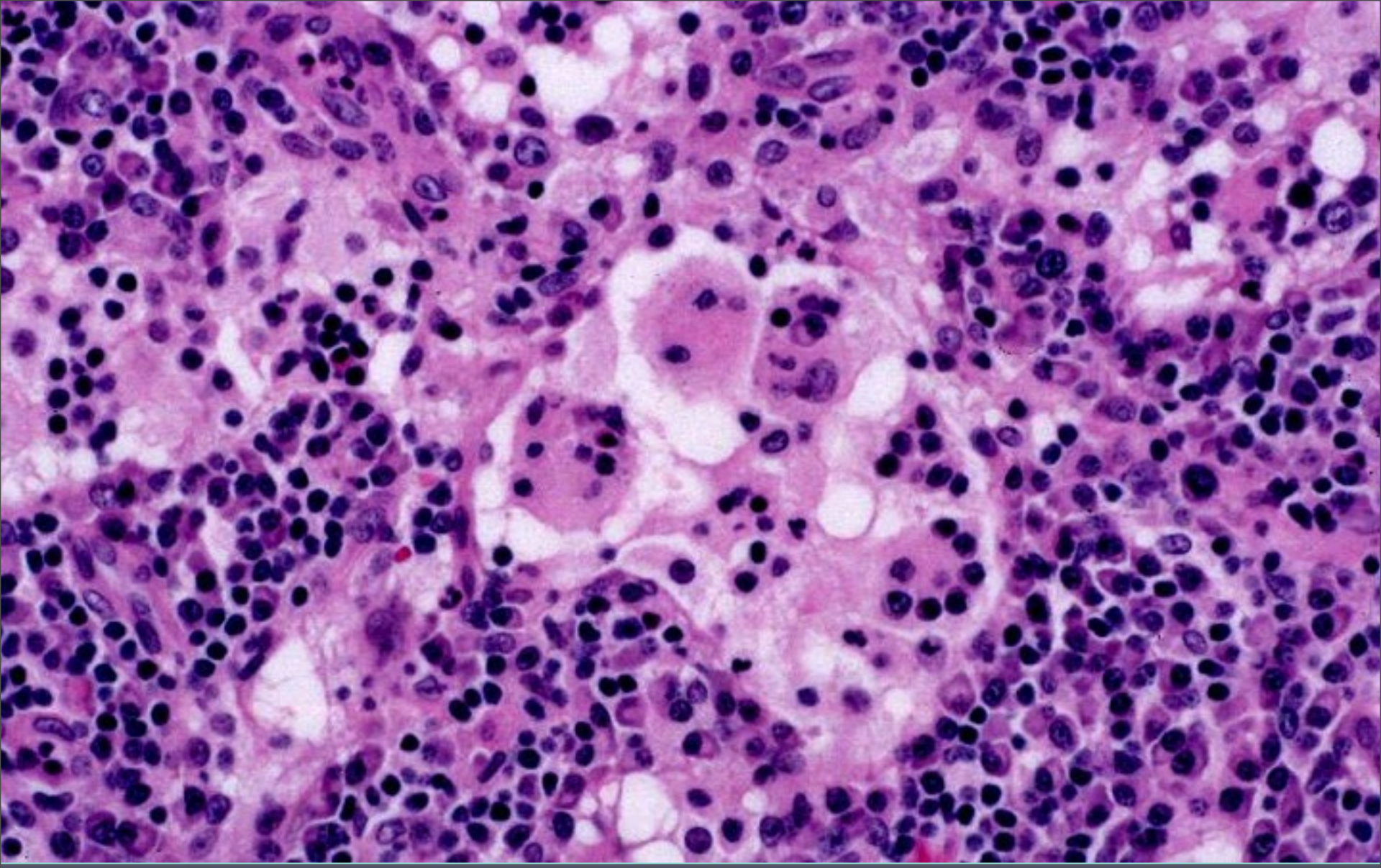
SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (SHML): Extranodal Disease: General Microscopic Findings

- --Histology of extranodal SHML is remarkably similar to that of nodal disease, complete with "sinuses," reactive germinal centres, and lymphemperipolesis
- *--HOWEVER*, extranodal lesions do show more fibrosis, fewer "classic" SHML histiocytes, and less lymphocytic phagocytosis
- --Criteria for "positivity" of extranodal sites may be *relaxed* if typical nodal disease





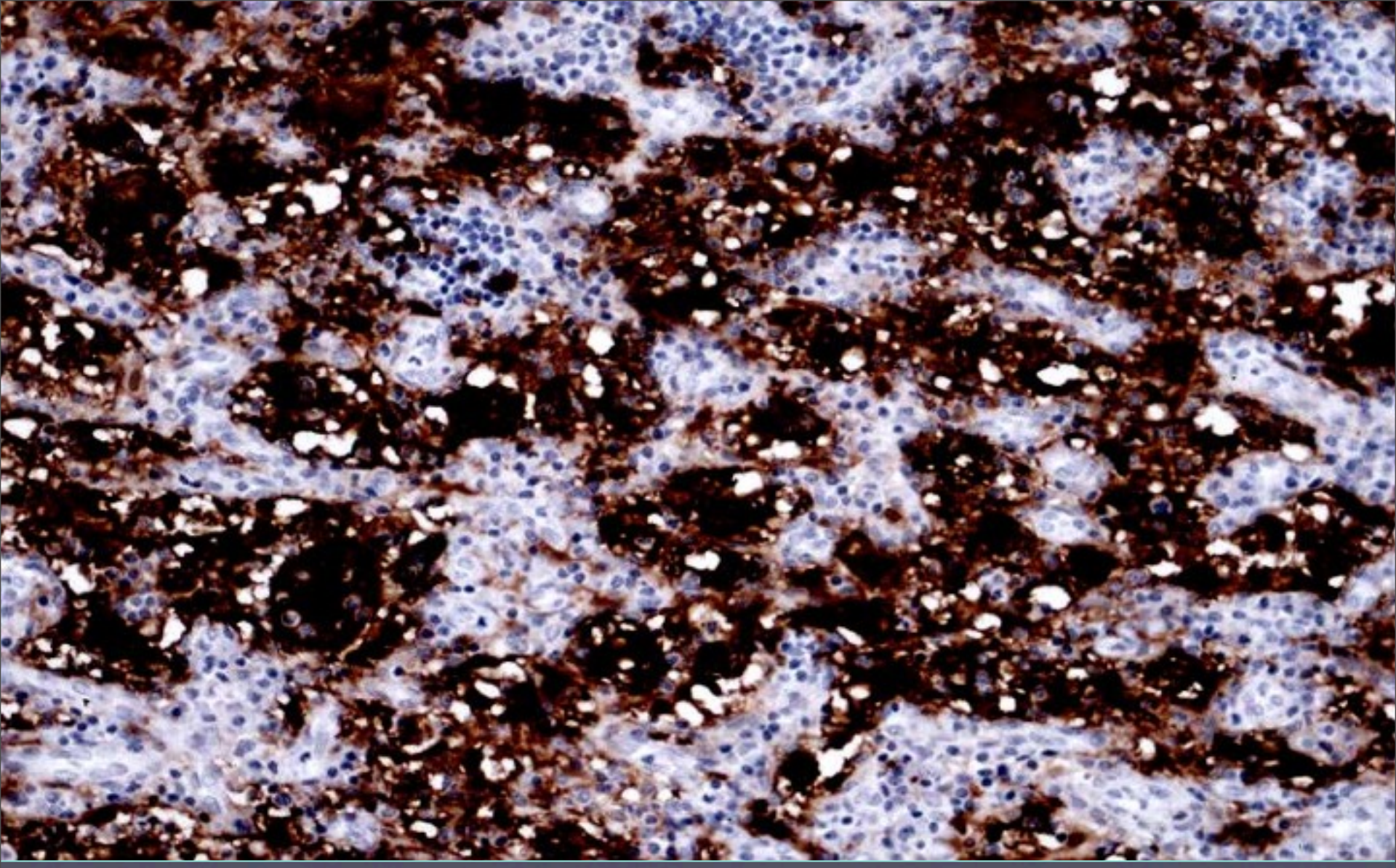
Cutaneous Rosai-Dorfman Disease



Lymphemperipolesis in the Histiocytes of Rosai-Dorfman Disease of the Skin

SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (SHML): Immunohistologic Findings

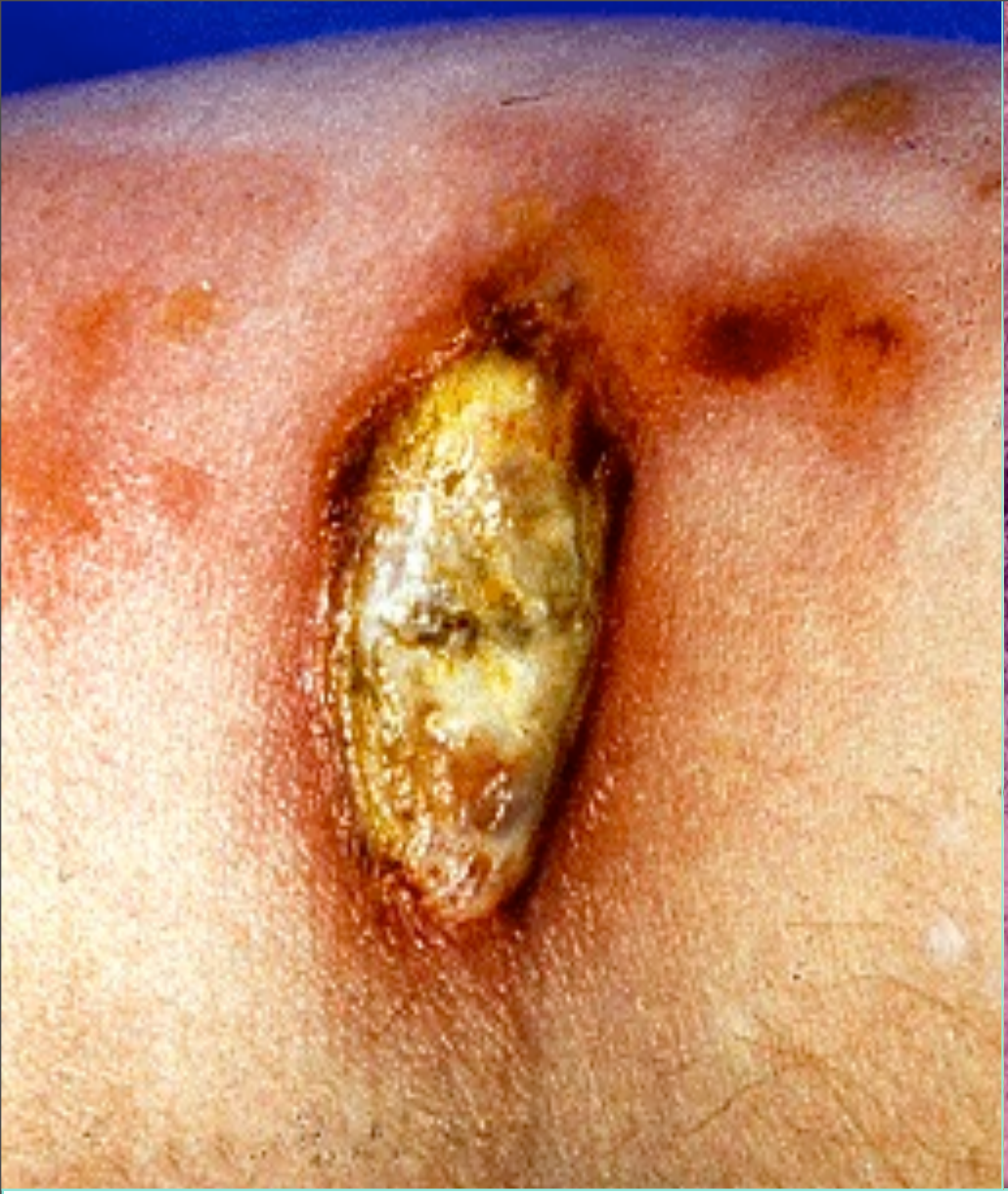
- --Positivity in typical SHML histiocytes for CD14, 15, and 45; variable reactivity for CD11b, 30, 43, 45R0, & 74
- --Uniform staining for S100 protein
- No labeling for CD1a
- --Immunoreactivity for CD30 is a potential trap, *vis-a-vis* a mistaken diagnosis of *anaplastic large cell (CD30+) lymphoma*

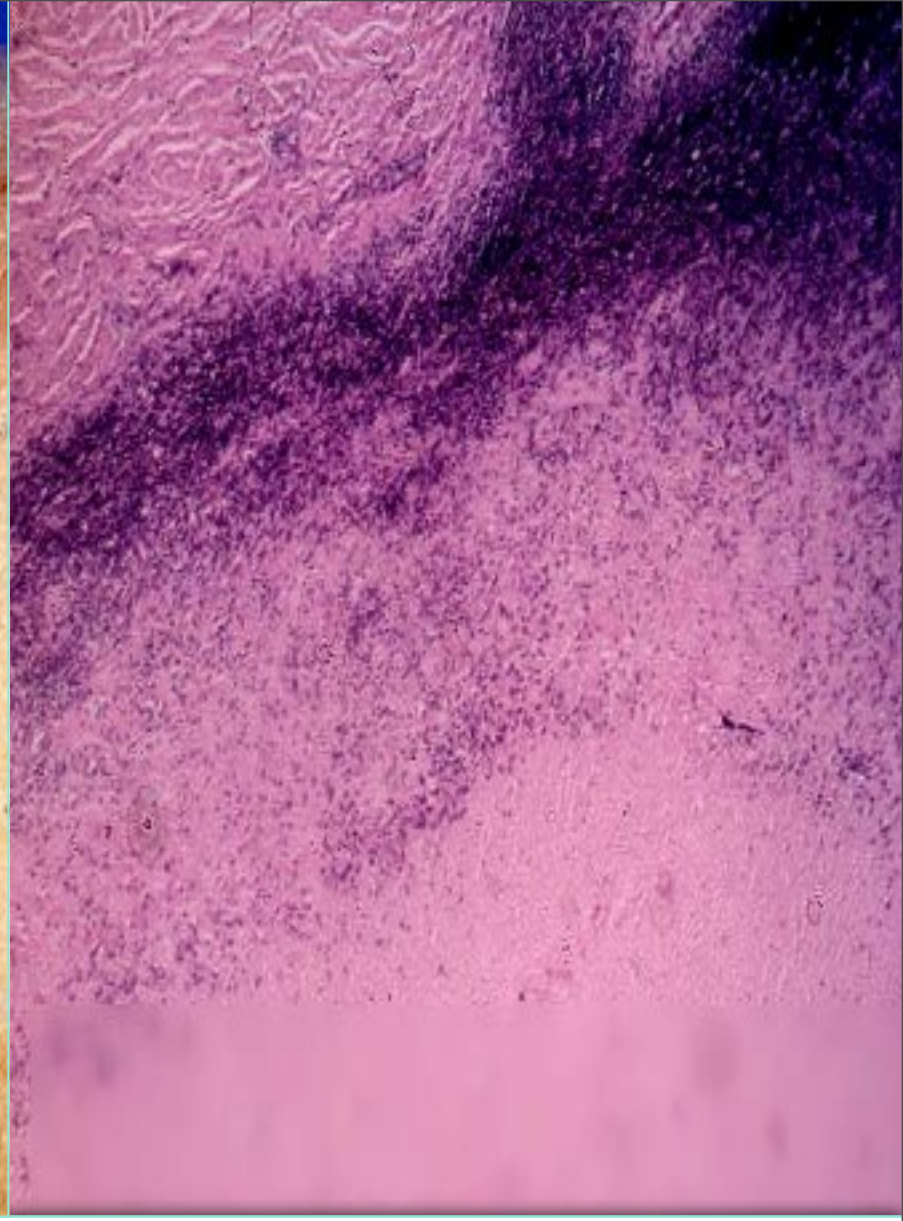


S100 Protein-Positivity in Rosai-Dorfman Disease of the Skin

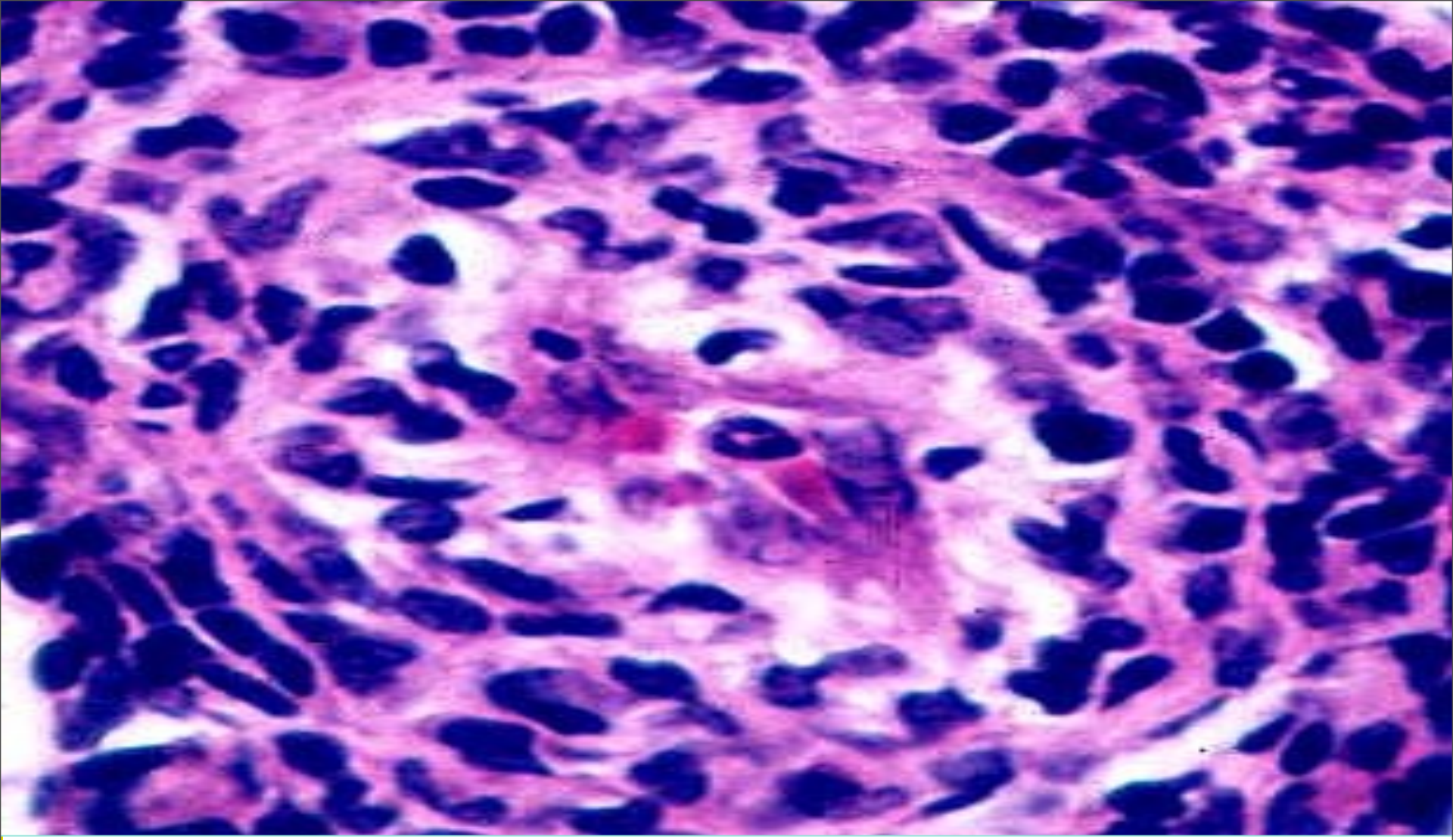
SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (SHML): Differential Diagnosis

- *--In Lymph Nodes--*
  - Metastatic carcinoma
  - Metastatic melanoma
  - Sinusoidal anaplastic large-cell lymphoma
- *--In Extranodal Sites, Including Skin--*
  - Anaplastic large cell lymphoma

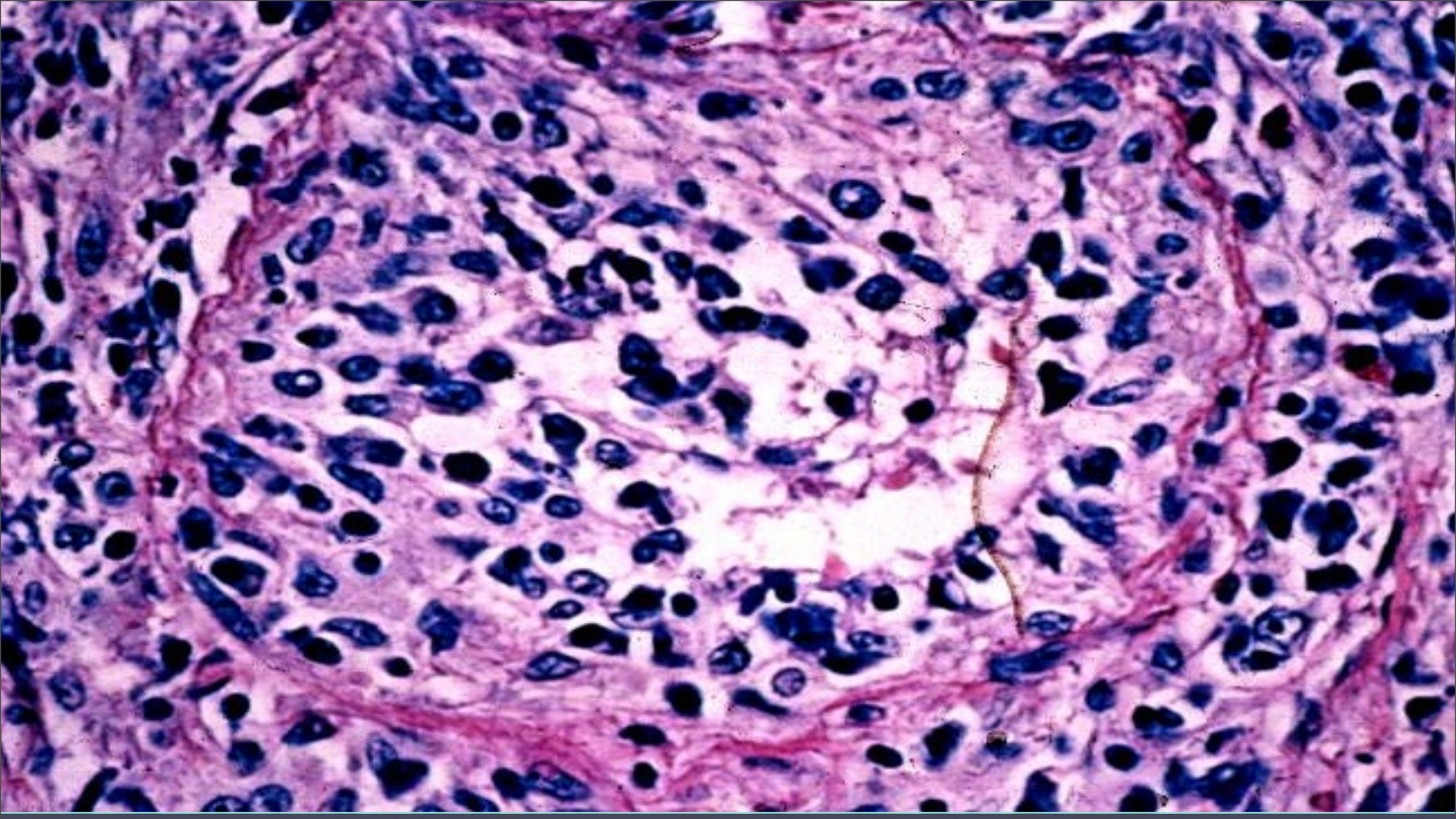




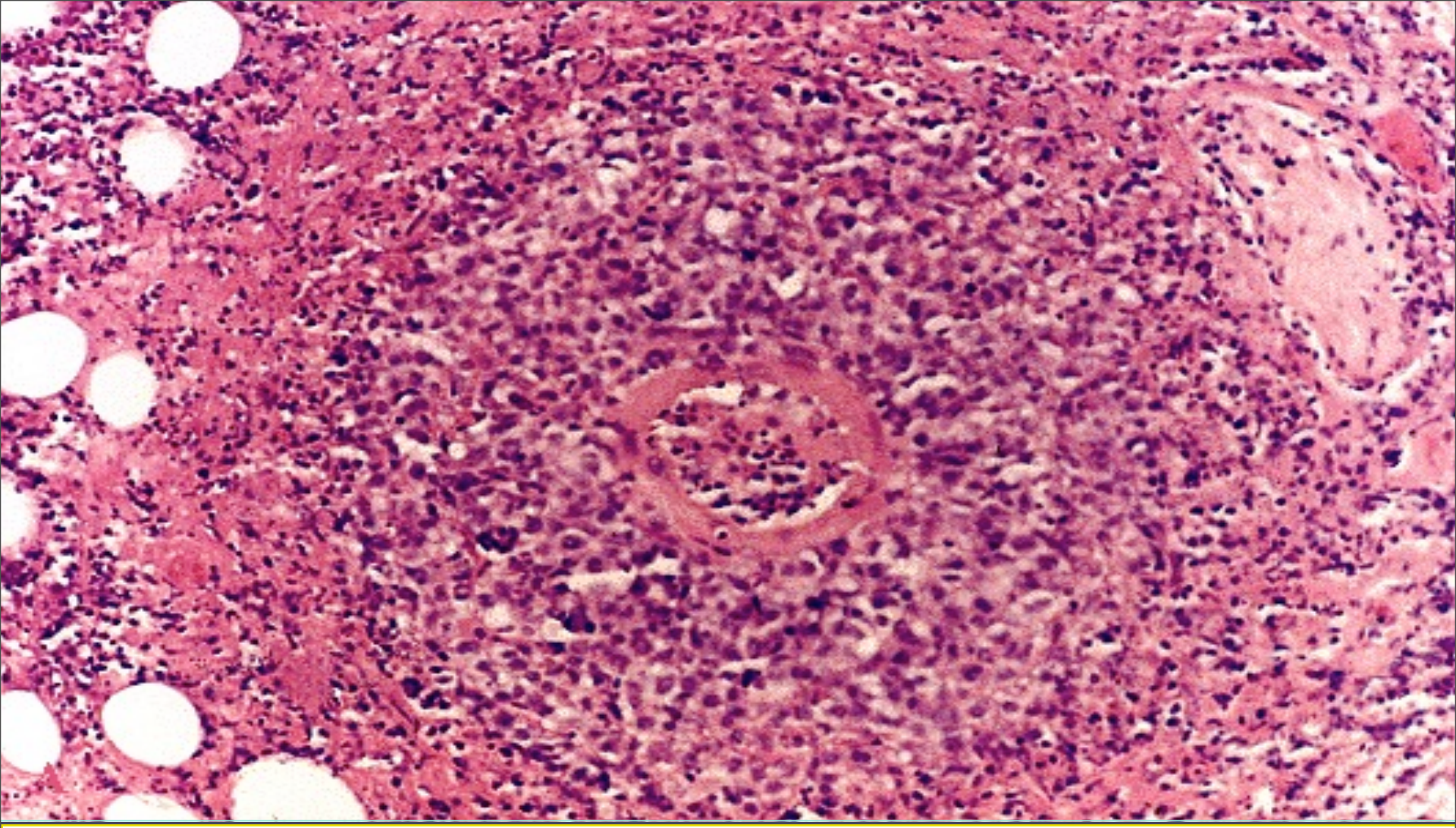
Geographic Necrosis of the Dermis & Subcutis, Caused by Vascular Involvement by Angiocentric Immunoproliferative Lesion of the Skin



Grade I Cutaneous Angiocentric Immunoproliferative Lesion



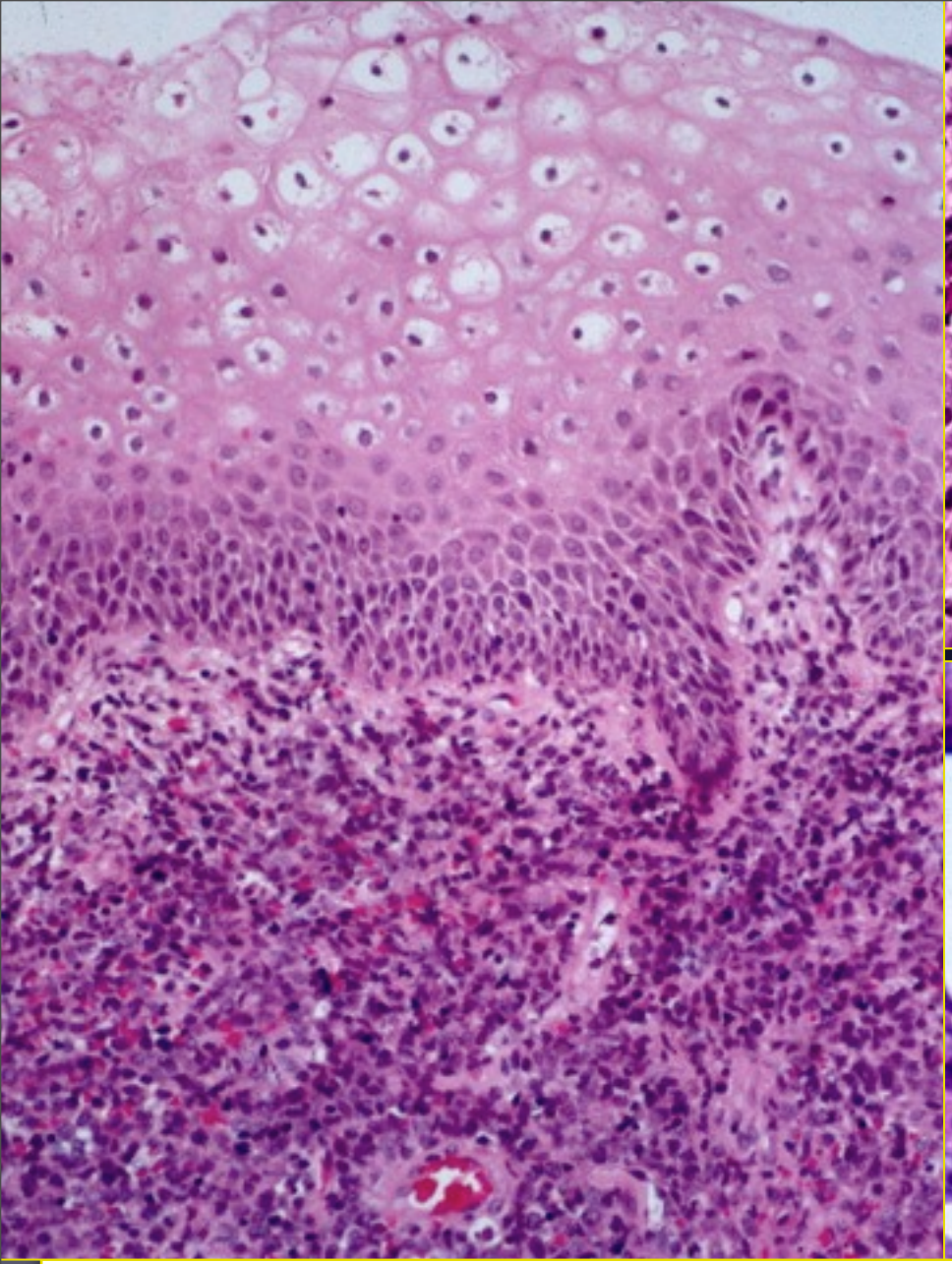
Grade II Cutaneous Angiocentric Immunoproliferative Lesion

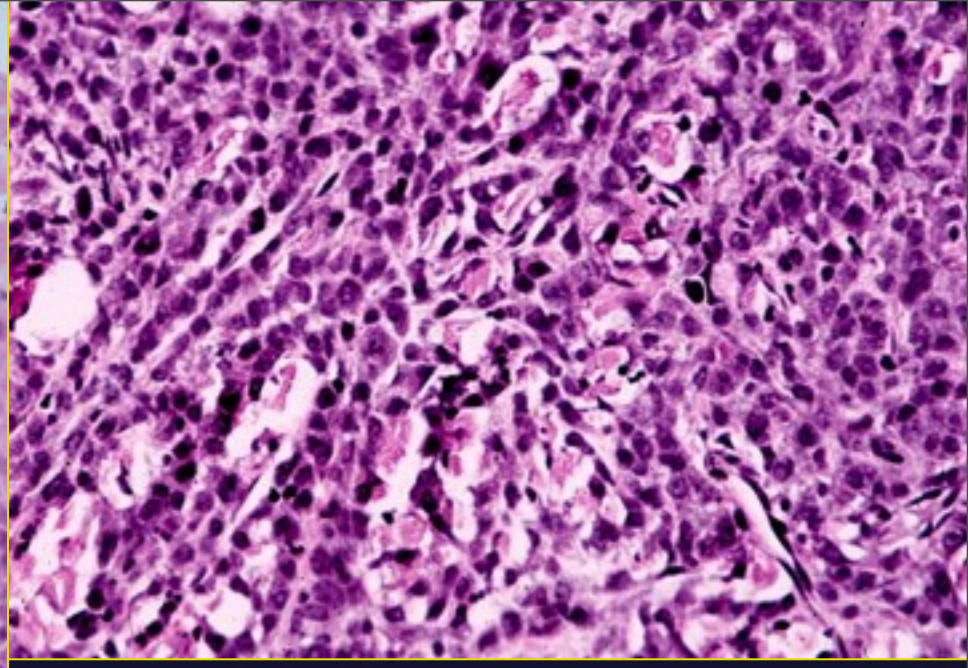


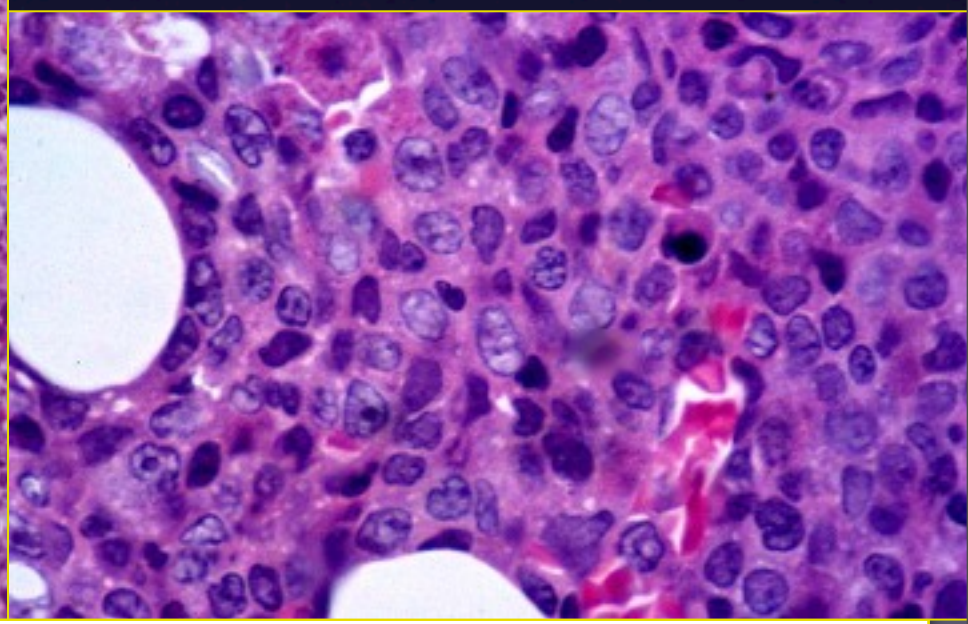
Grade III Cutaneous Angiocentric Immunoproliferative Lesion

GRANULOCYTIC SARCOMA: POTENTIAL

- -Similar distribution: confluent infiltrates, periadnexal or perivascular, or dissecting cords
- -Tend to be lower dermal or pan-dermal
- -Usually no epidermal involvement
- -Both may recruit other cell types: small lymphocytes, eosinophils, and neutrophils
- -Both may have angulated or irregular







Granulocytic Sarcoma (Extramedullary Myeloid Tumor) of the Skin

GRANULOCYTIC SARCOMA: POTENTIAL OVERLAP WITH CUTANEOUS LYMPHOMAS

- -Leder stain-- actually positive in only a minority of cutaneous GS cases; negative in lymphomas
- -GS may or may not be preceded by a history of known leukemia
- -In addition, both GS & lymphoma may produce erythematous or pruritic dermal nodules or papules

PATTERNS WITH "LYMPHOID" ANTIBODIES

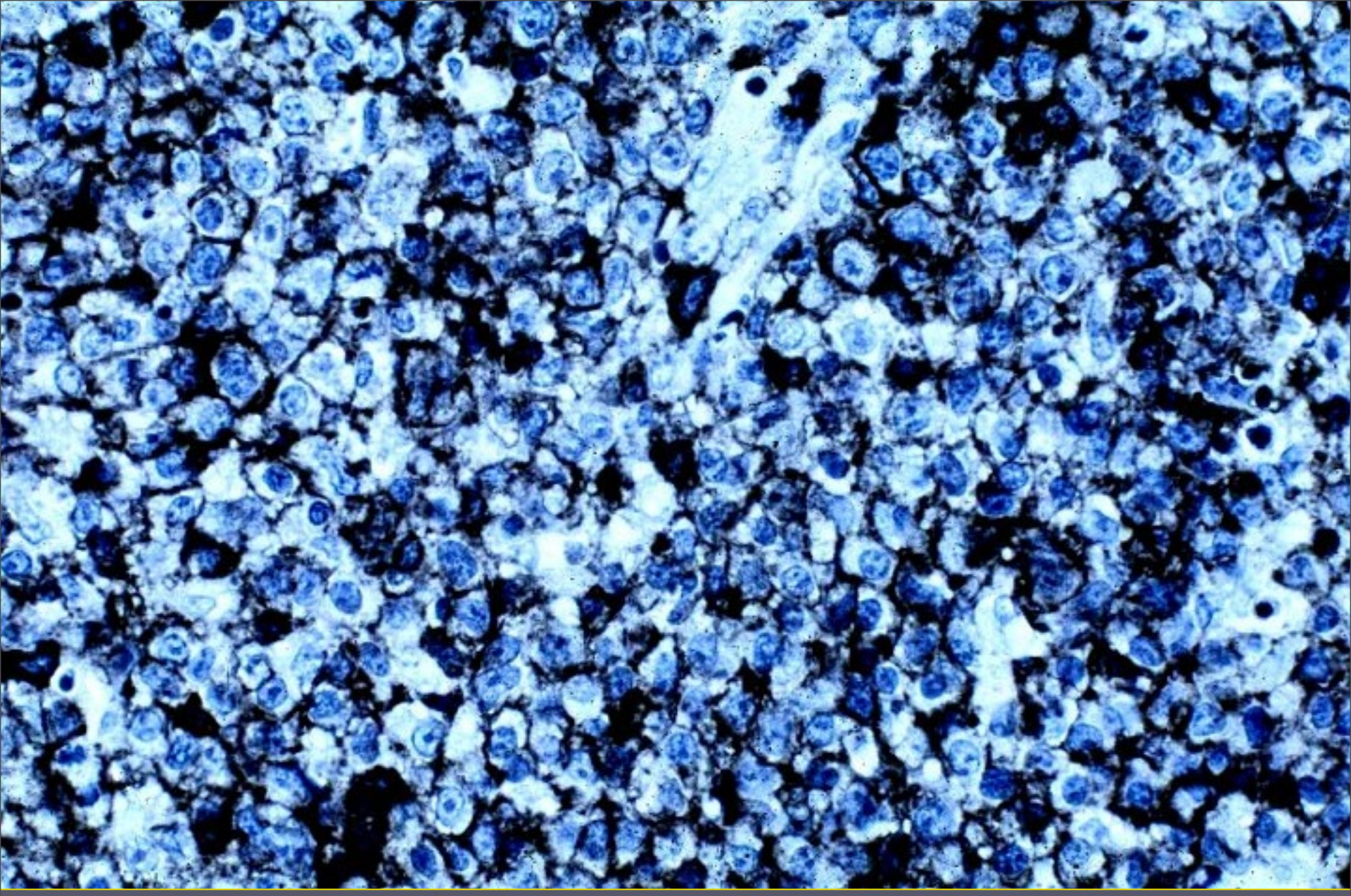
-Patterns from "standard" paraffin IP panel:

-CD45, CD20, CD45RO, CD3, CD43, +/-MB2

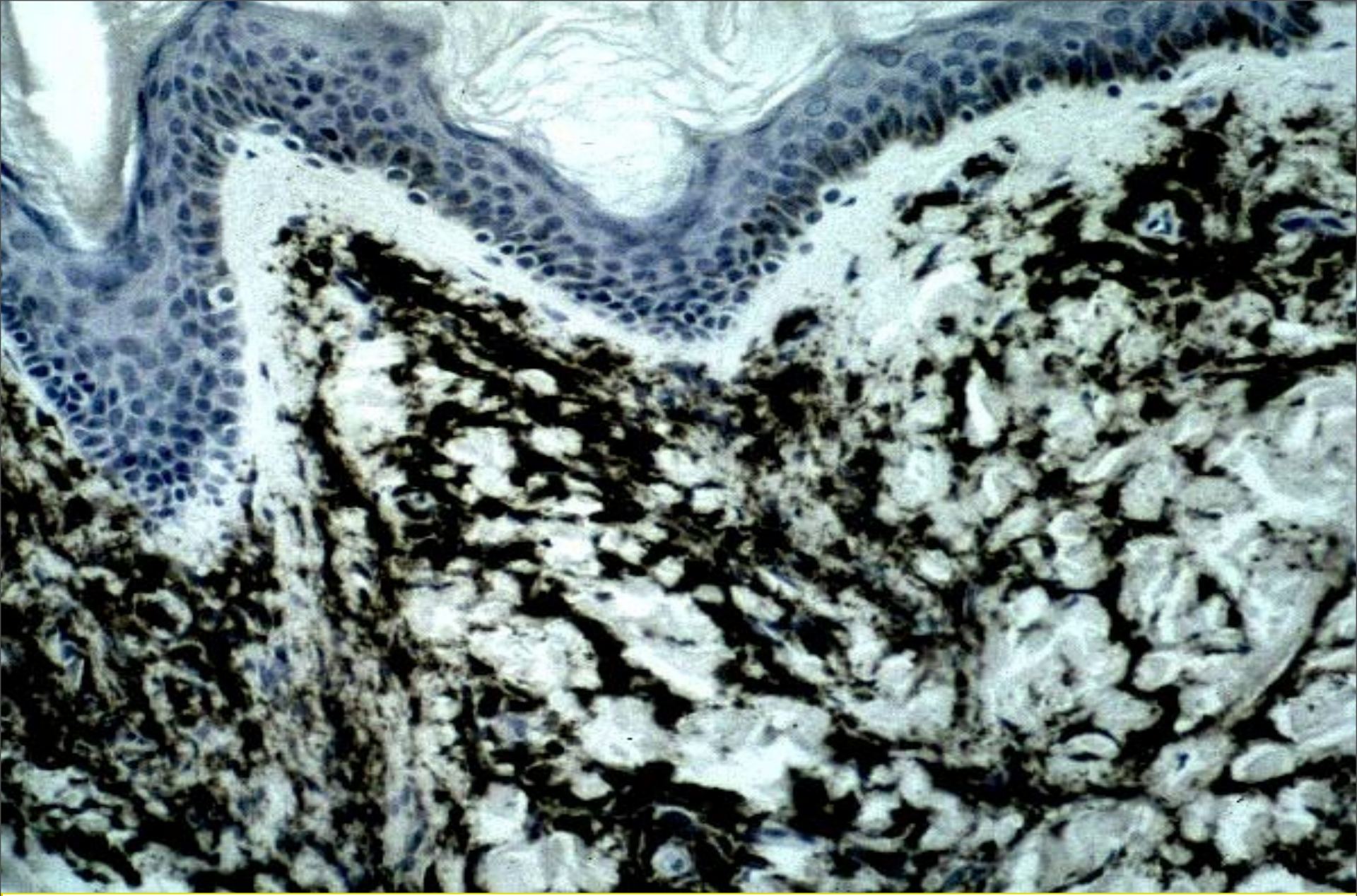
-B-cell: CD45+, CD20+, MB2+/-, CD45RO-, CD43+/-, CD3-

-T-cell: CD45+, CD45RO, CD3, and/or CD43+, CD20-, MB2-

-Cases that differ-- uncertain lineage, possibly granulocytic



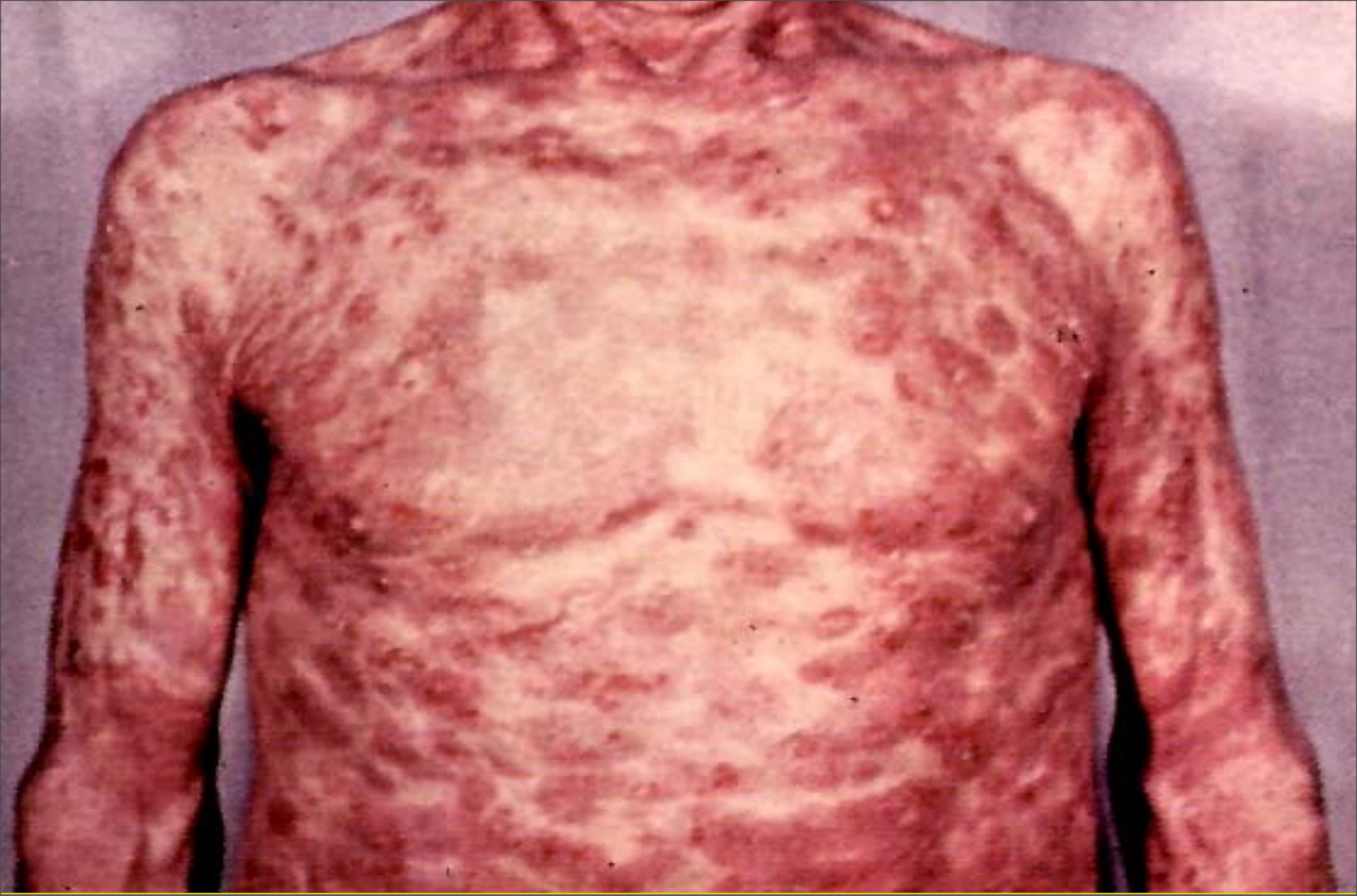
CD43 in Granulocytic Sarcoma of the Skin



Myeloperoxidase-Reactivity in Granulocytic Sarcoma of the Skin

LESSONS REGARDING GRANULOCYTIC SARCOMA

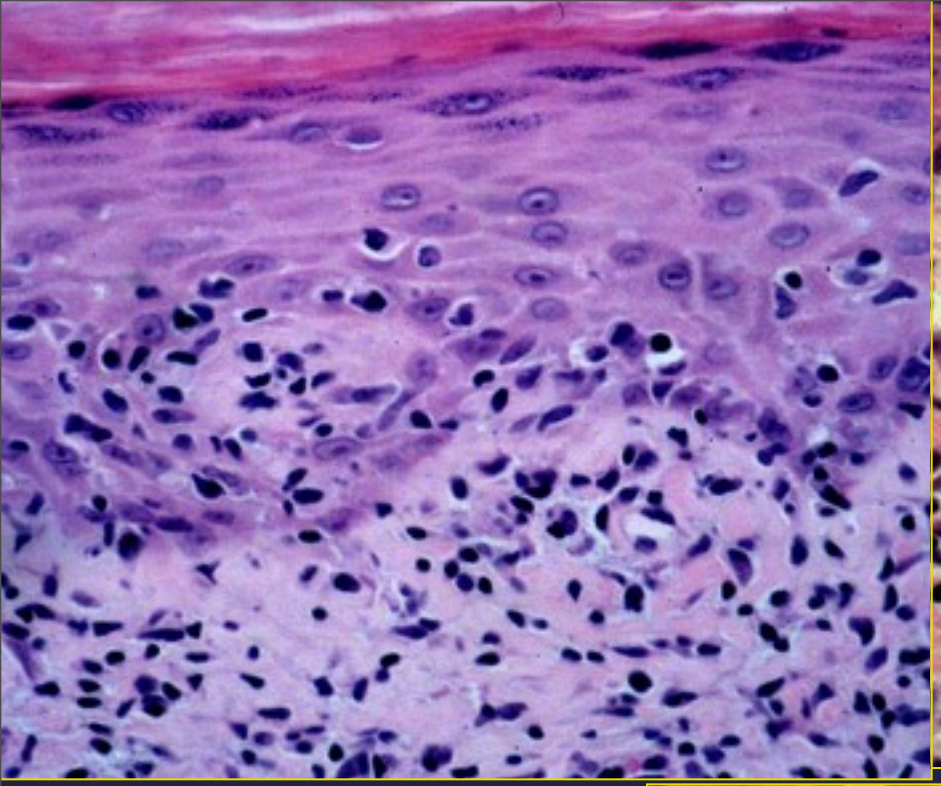
- -Shares many markers with lymphomas: CD45, CD43, MB2, and potentially, at least in some series, CD45RO, CD20, and CD15
- -In our cases, GS failed to express either CD45RO or CD20; thus, cases that are felt to be lymphoid but fail to express CD20 or CD45RO need further investigation
- -GS will reliably express such markers as lysozyme, myeloperoxidase, or CD15; these markers can be used in a second tier of antibodies
- -CD34, CD68, MAC387: relatively insensitive

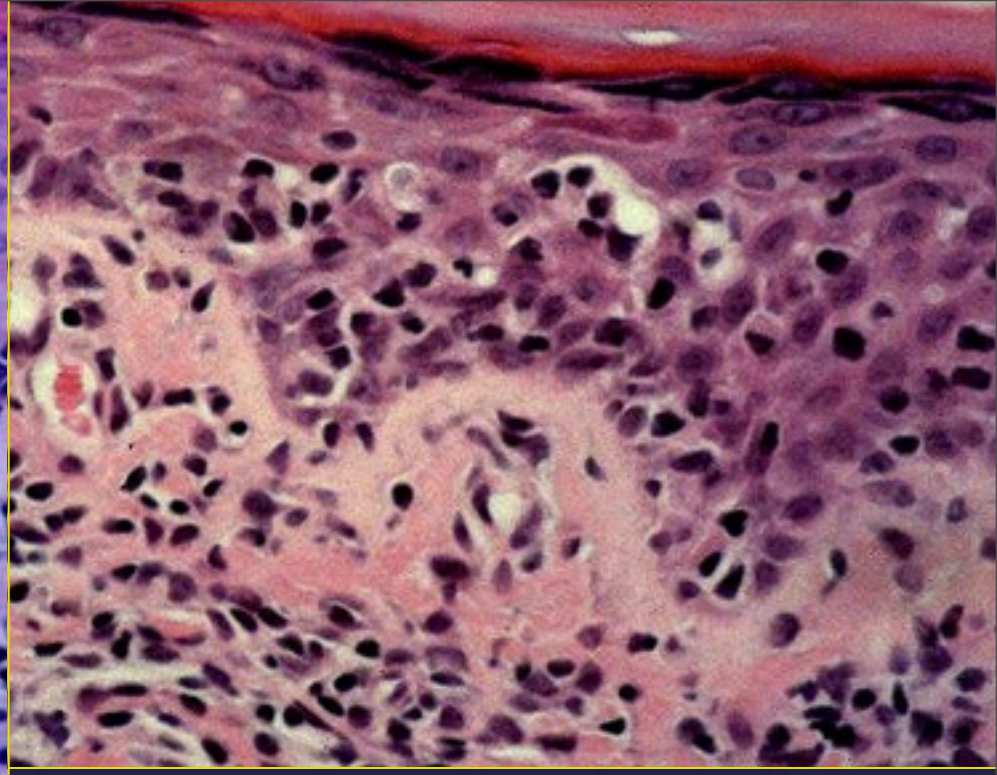


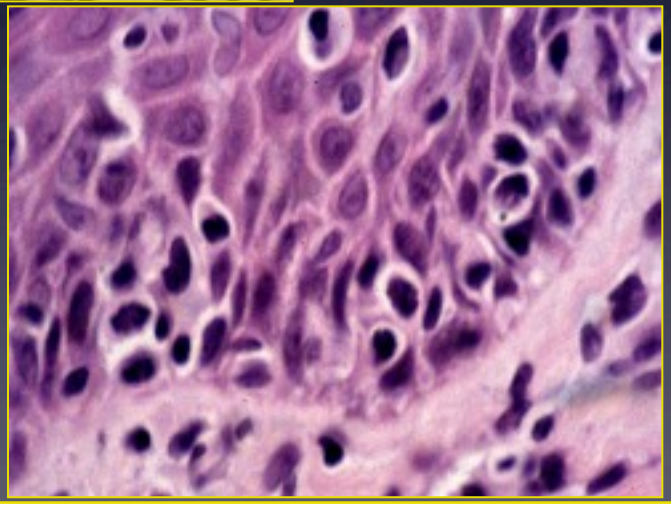
Mycosis Fungoides-- Clinical Image

HISTOLOGIC FEATURES FAVORING A DIAGNOSIS OF MYCOSIS FUNGOIDES

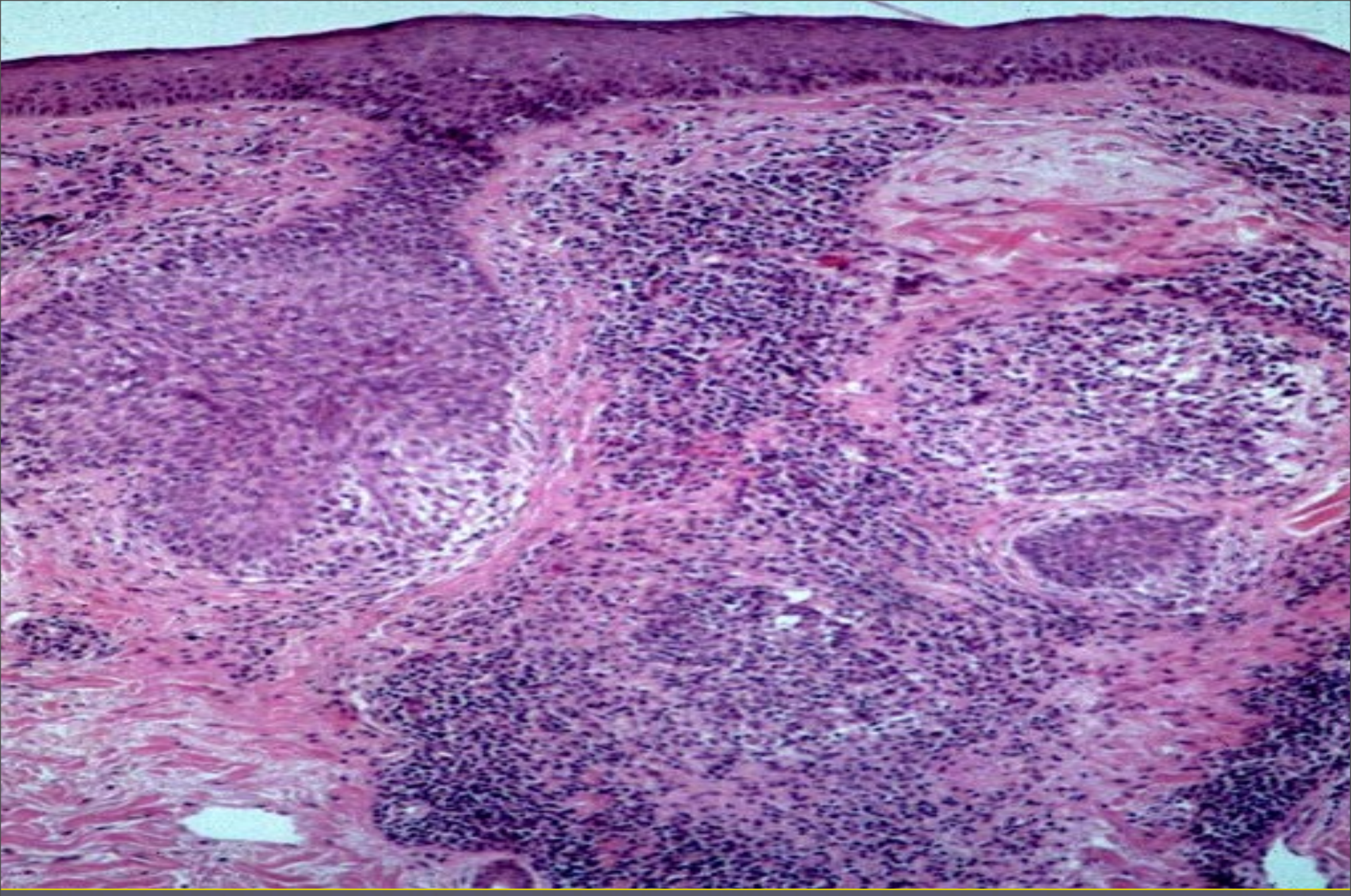
- –/Relative lack of spongiosis and interface keratinocyte damage
- --Linear arrays of lymphocytes in the basal epidermis
- --Groups of atypical lymphocytes in the epidermis with minimal associated spongiosis
- --"Basketweave" fibrosis in the upper dermis
- --Follicular lymphoid infiltrates and/or mucinosis







Mycosis Fungoides: Microscopic Images



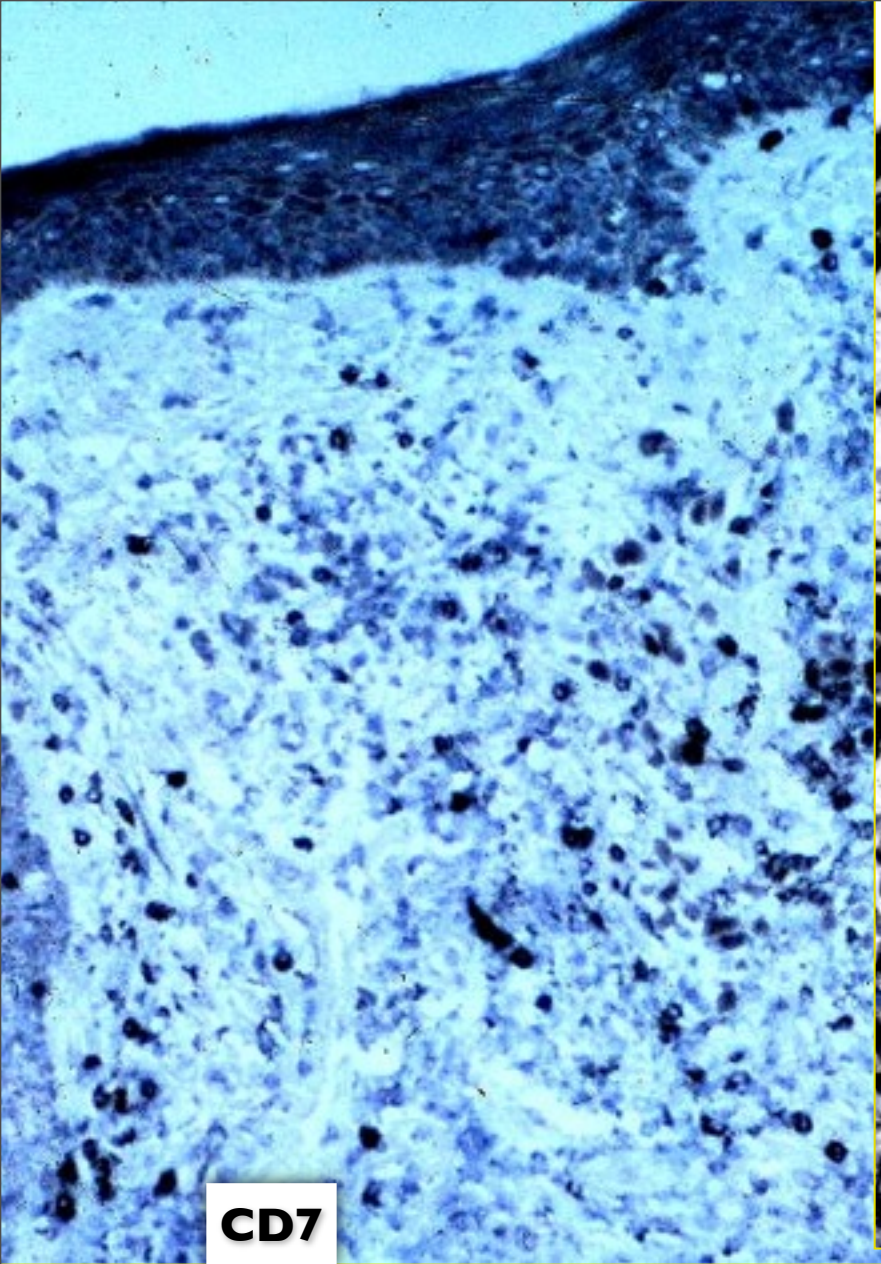
Mycosis Fungoides-- Follicular Involvement

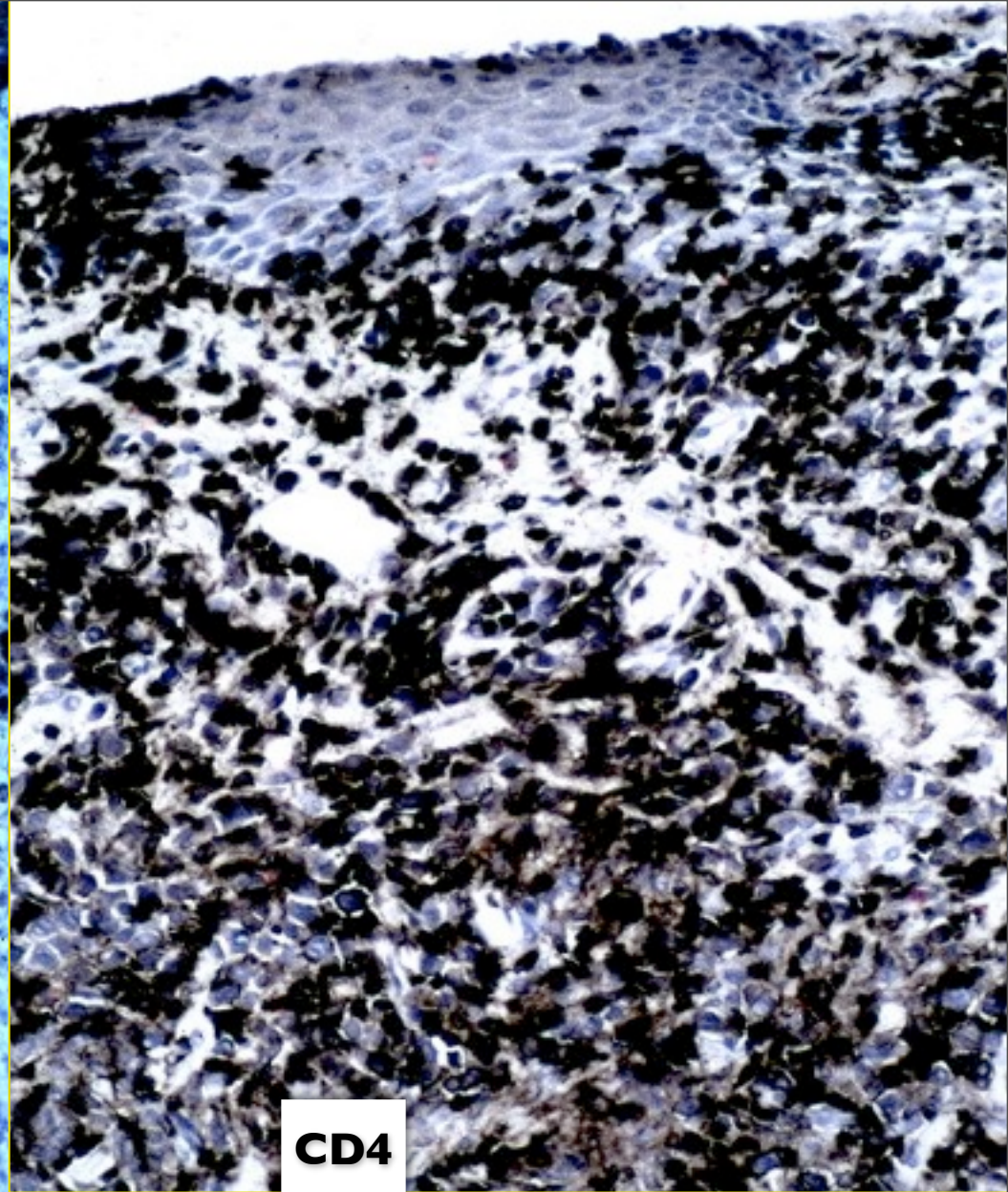
IMMUNOHISTOLOGY IN DDx OF CUTANEOUS T-CELL LYMPHOMAS

- *Paraffin Sections*

-- Antibodies used to CD3,4,5,7,8, 20,43, & 45R0

-- Deletion of pan-T antigens and CD4-positivity again suggests CTCL rather than dermatitis

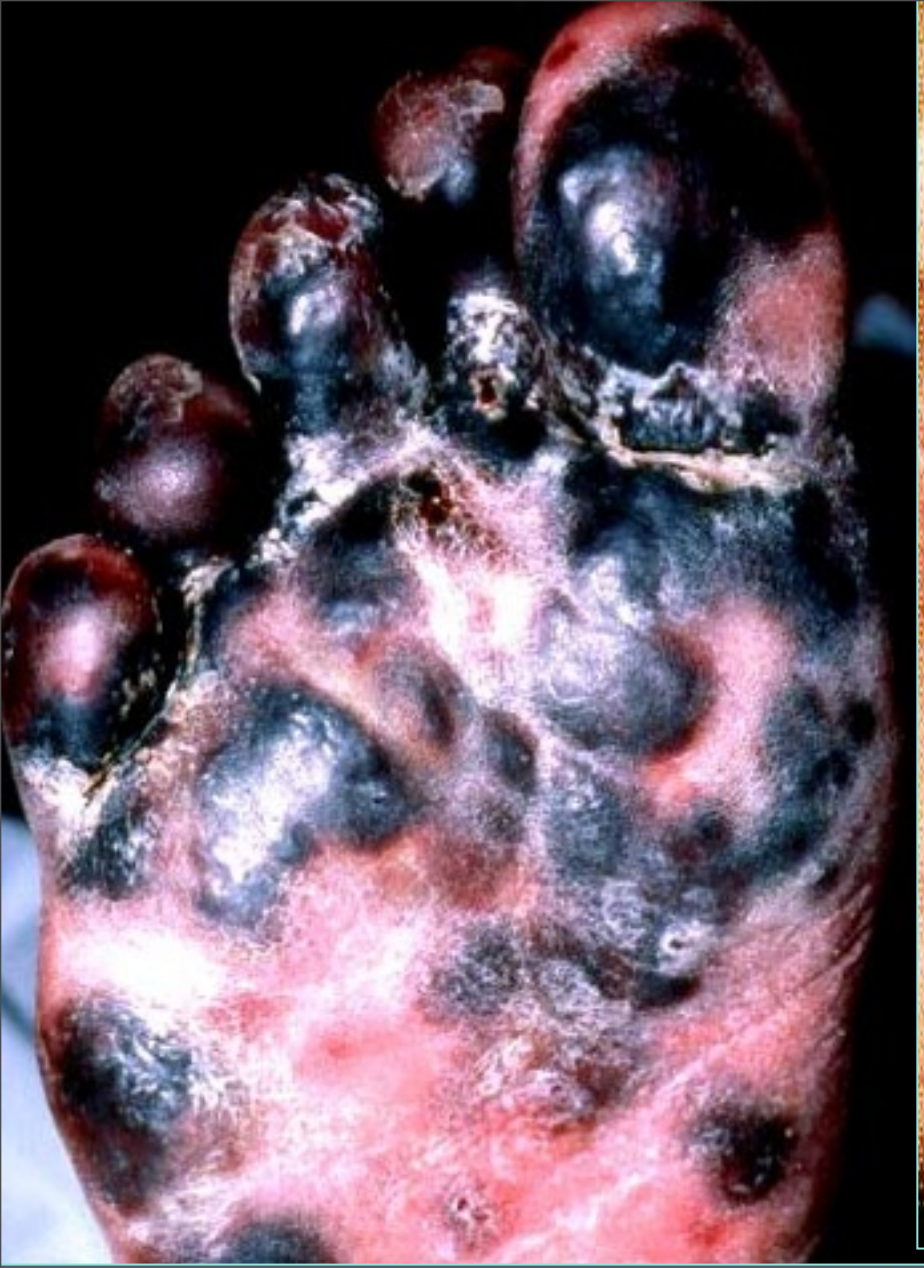


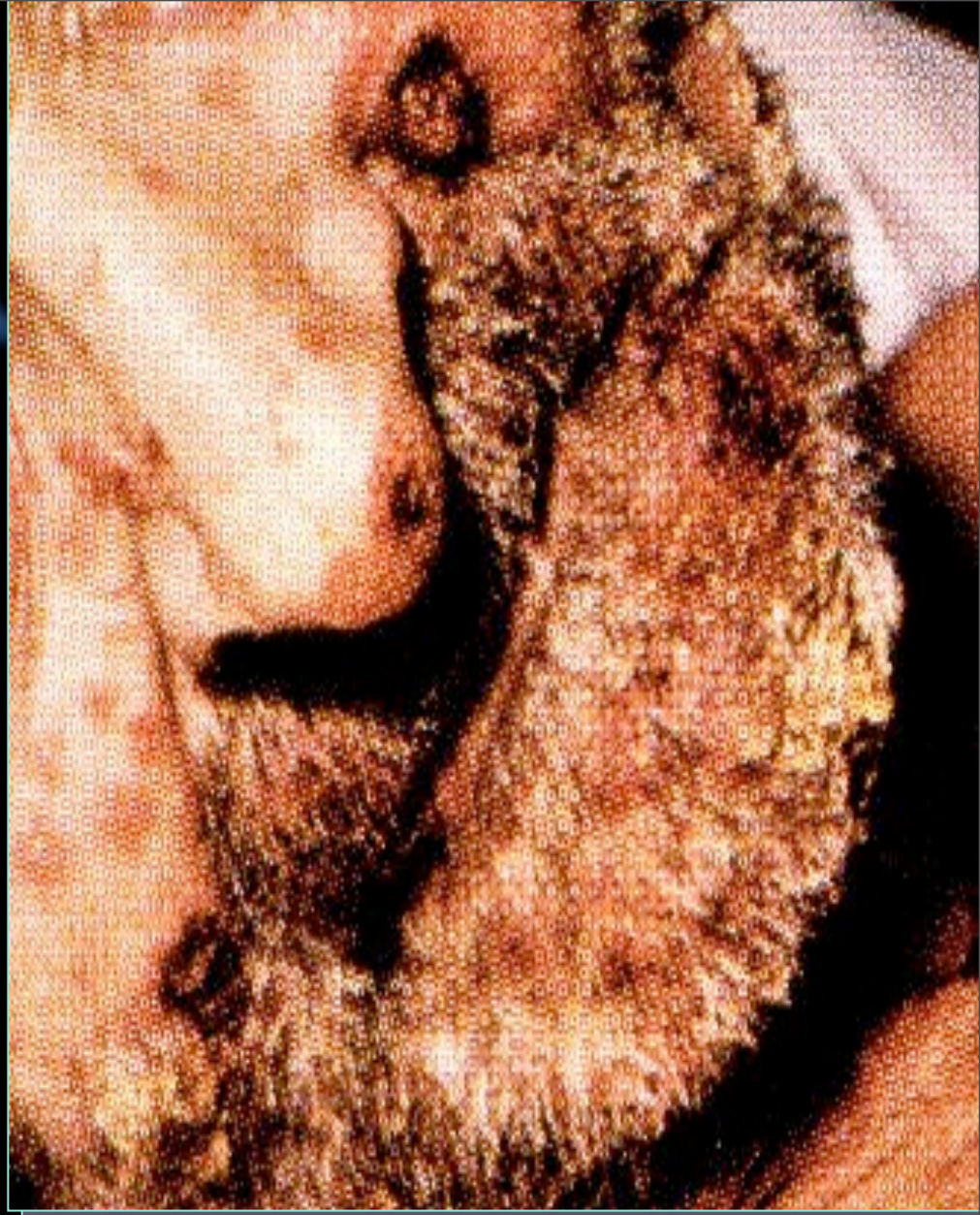


Immunophenotype of Mycosis Fungoides in Paraffin Sections

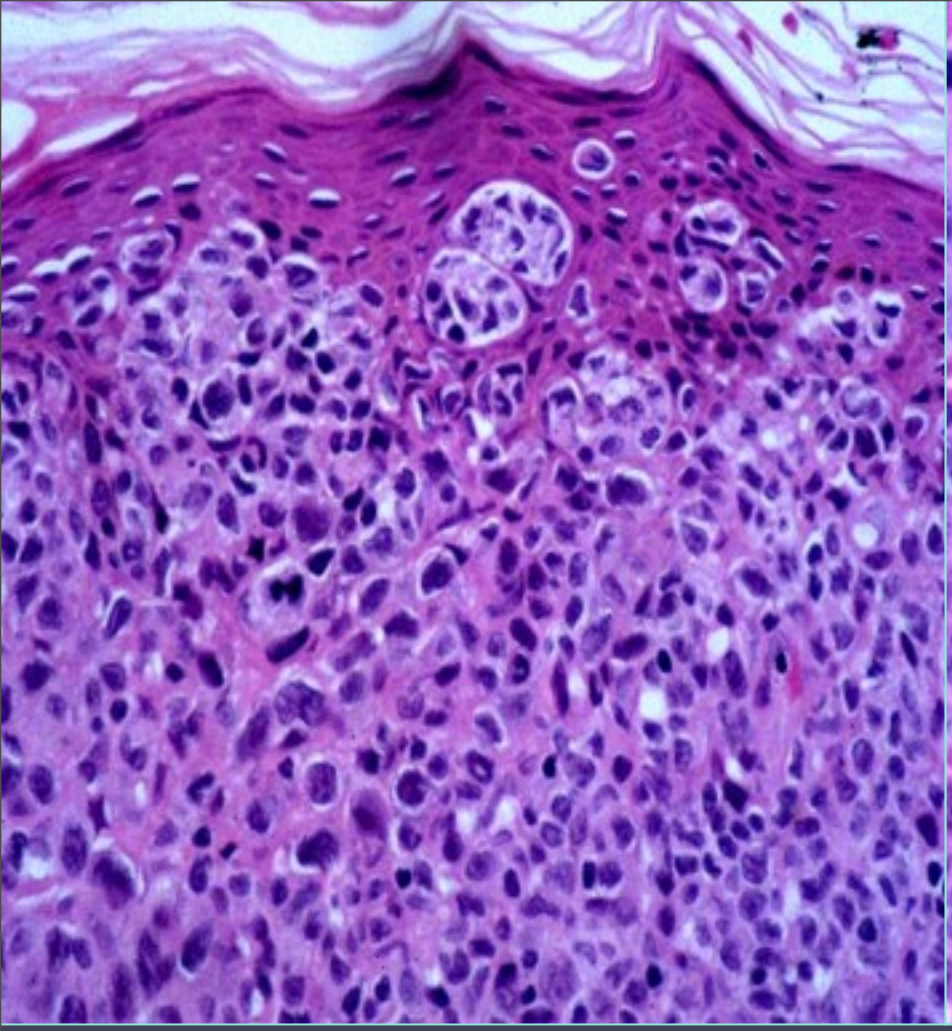
"Transformed" Mycosis Fungoides

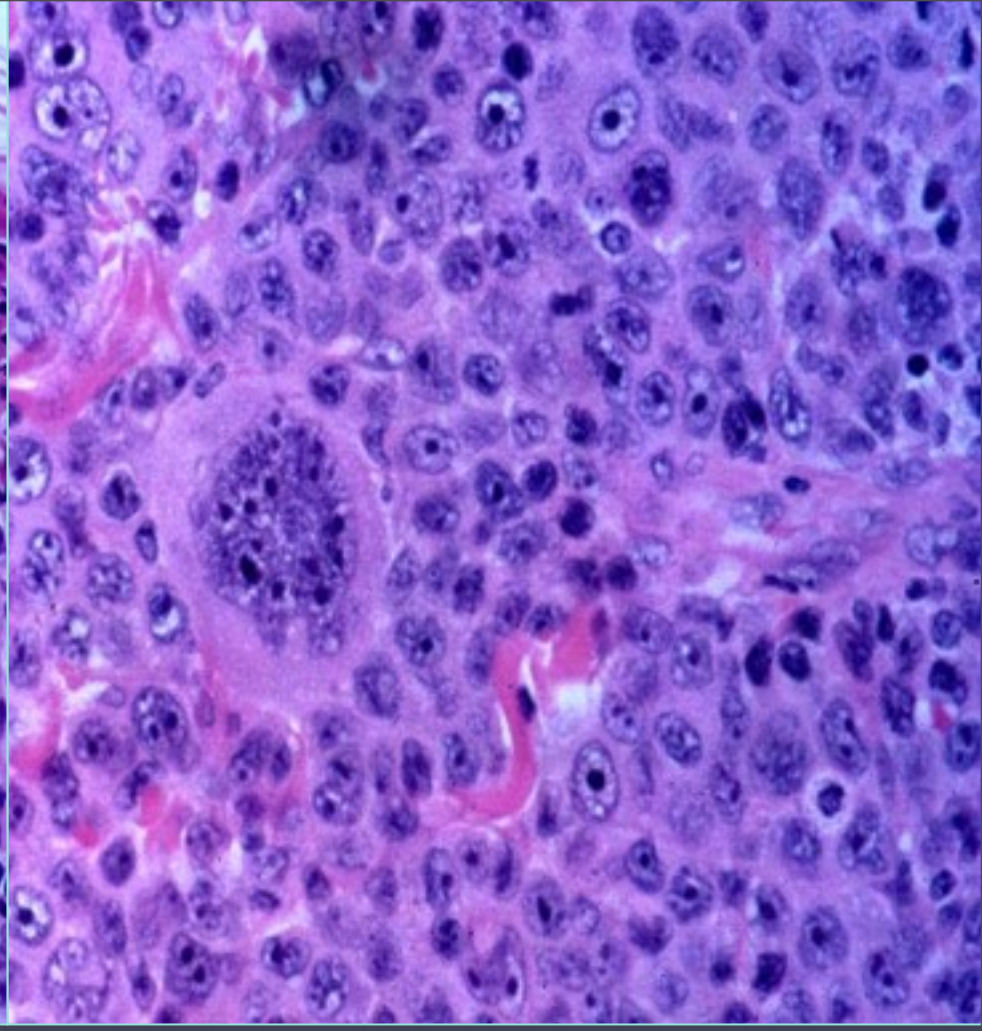
- --This term refers to selected cases in the "tumor phase" of MF, wherein nodular skin masses arise and grow rapidly
- --Microscopic image is virtually identical to that of ALCL, except that vestiges of the original MF may also be observed
- --The tumor cells in transformed MF are CD30+
- --Biological evolution of TMF is aggressive



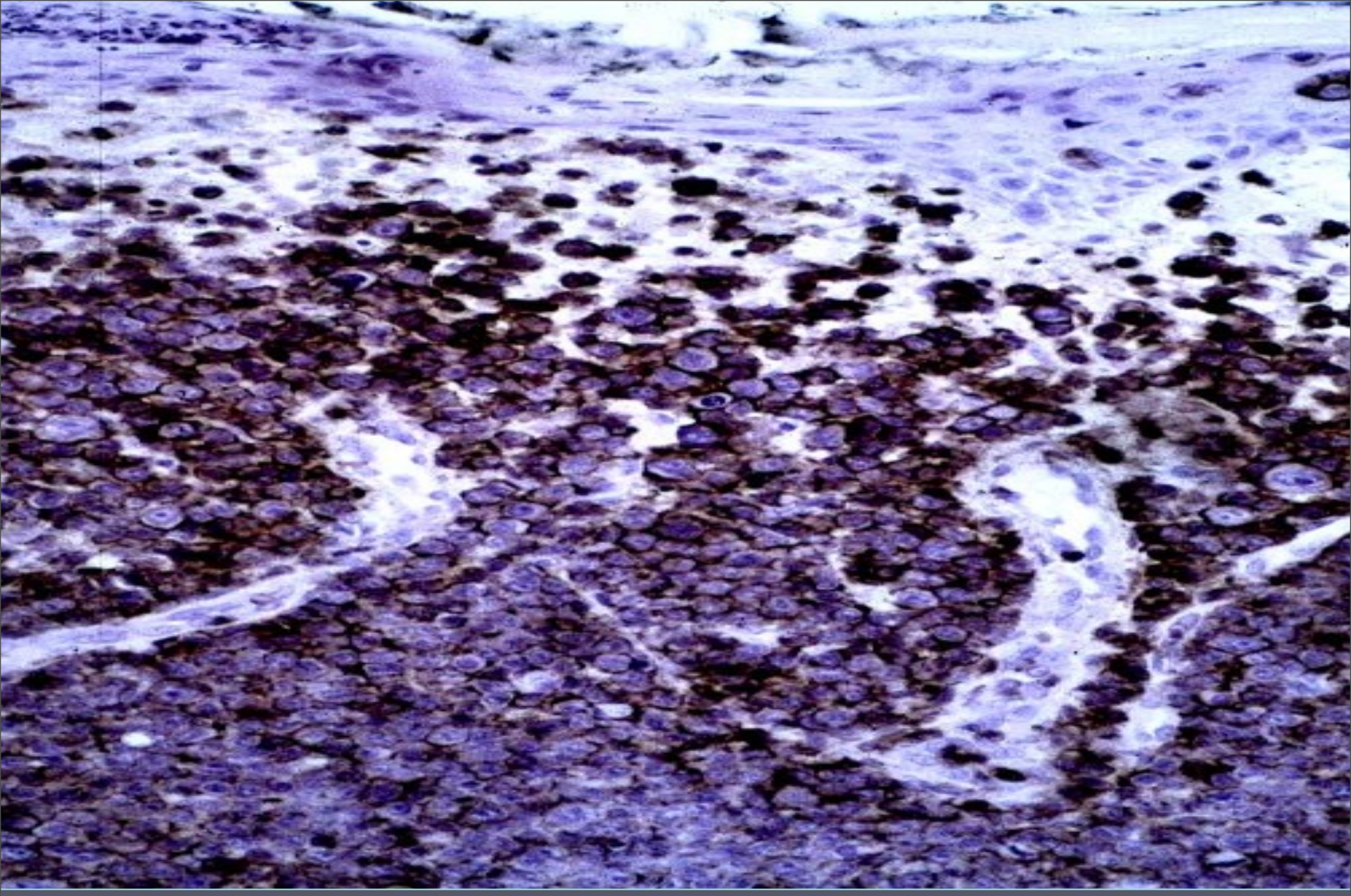


Transformed Mycosis Fungoides-- Clinical Images





Transformed Mycosis Fungoides--Histology



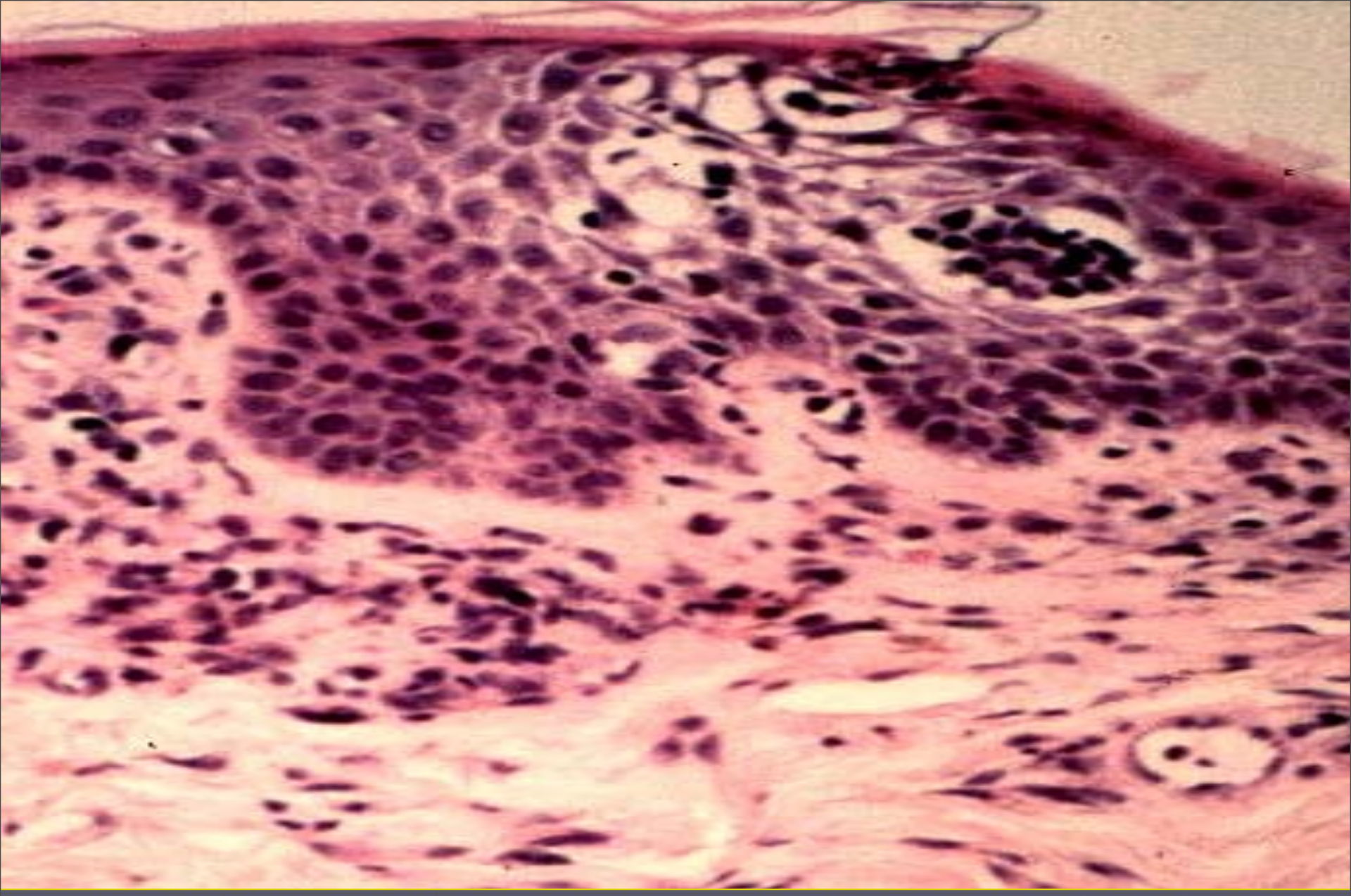
CD30 Positivity in Transformed Mycosis Fungoides

Potential Simulants of Mycosis Fungoides

- -Drug induced "pseudolymphomas"
- -Chronic lichenoid and spongiotic dermatitides
- -Actinic reticuloid

Because they share these features with MF:

- Grouped lymphocytes in the epidermis, and in the dermal interstitium
- May be activated, and hence "atypical"
- Predominantly composed of T-cells



Mycosis Fungoides-Like Drug Eruption

The Approach to Cutaneous Lymphoid Infiltrates

- --Make certain that the patient has had a thorough dermatological examination
- --Many difficult-to-diagnose 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 declare itself in time
- --Liberal use of special studies (immunohistology, genotyping, flow cytometry, etc.) is a necessity

Primer of Immunohistochemistry (Leukocytic)

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