LEIDEN UNIVERSITY MEDICAL CENTER

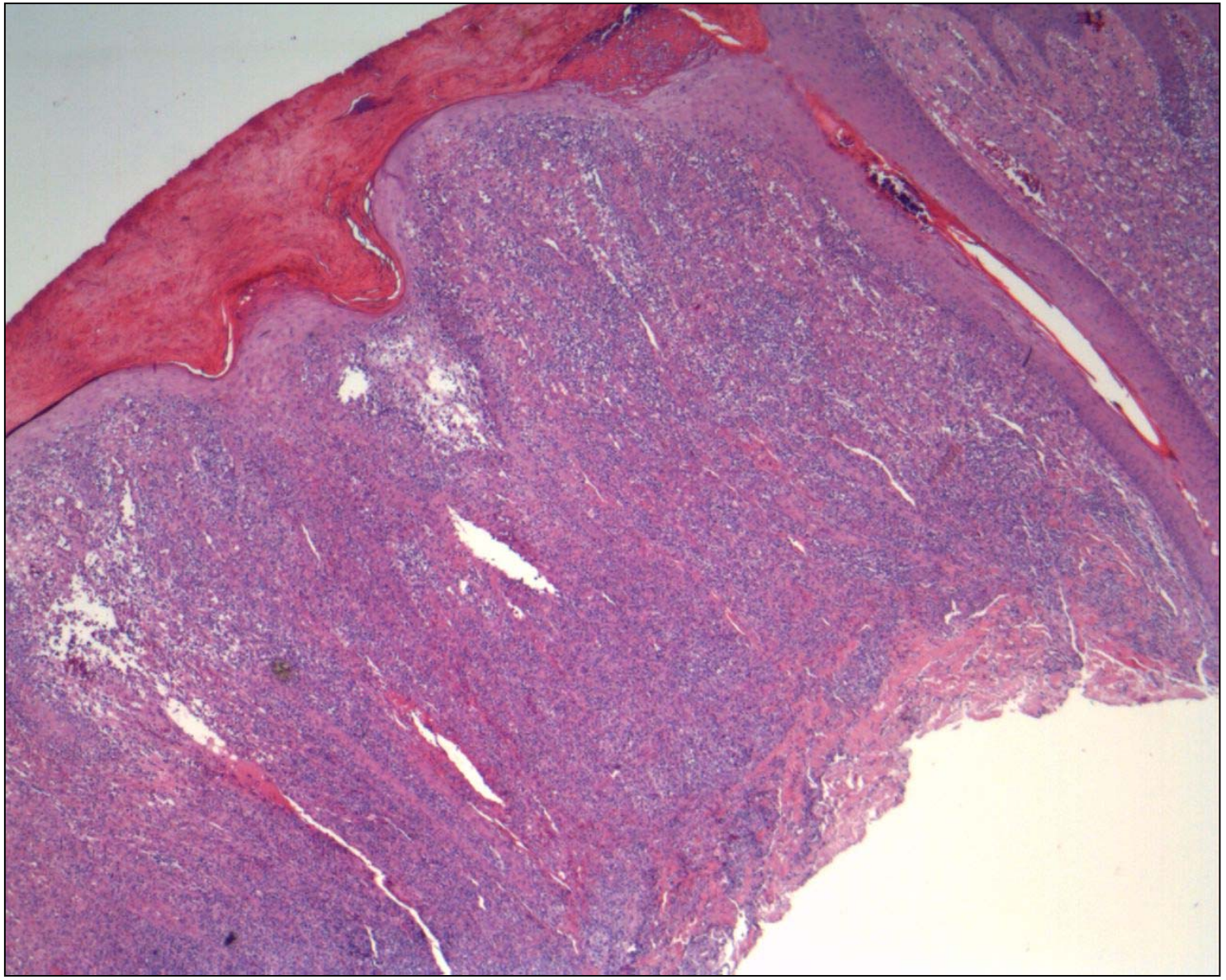
Differentiation between benign and malignant lymphoid infiltrates in the skin

Rein Willemze

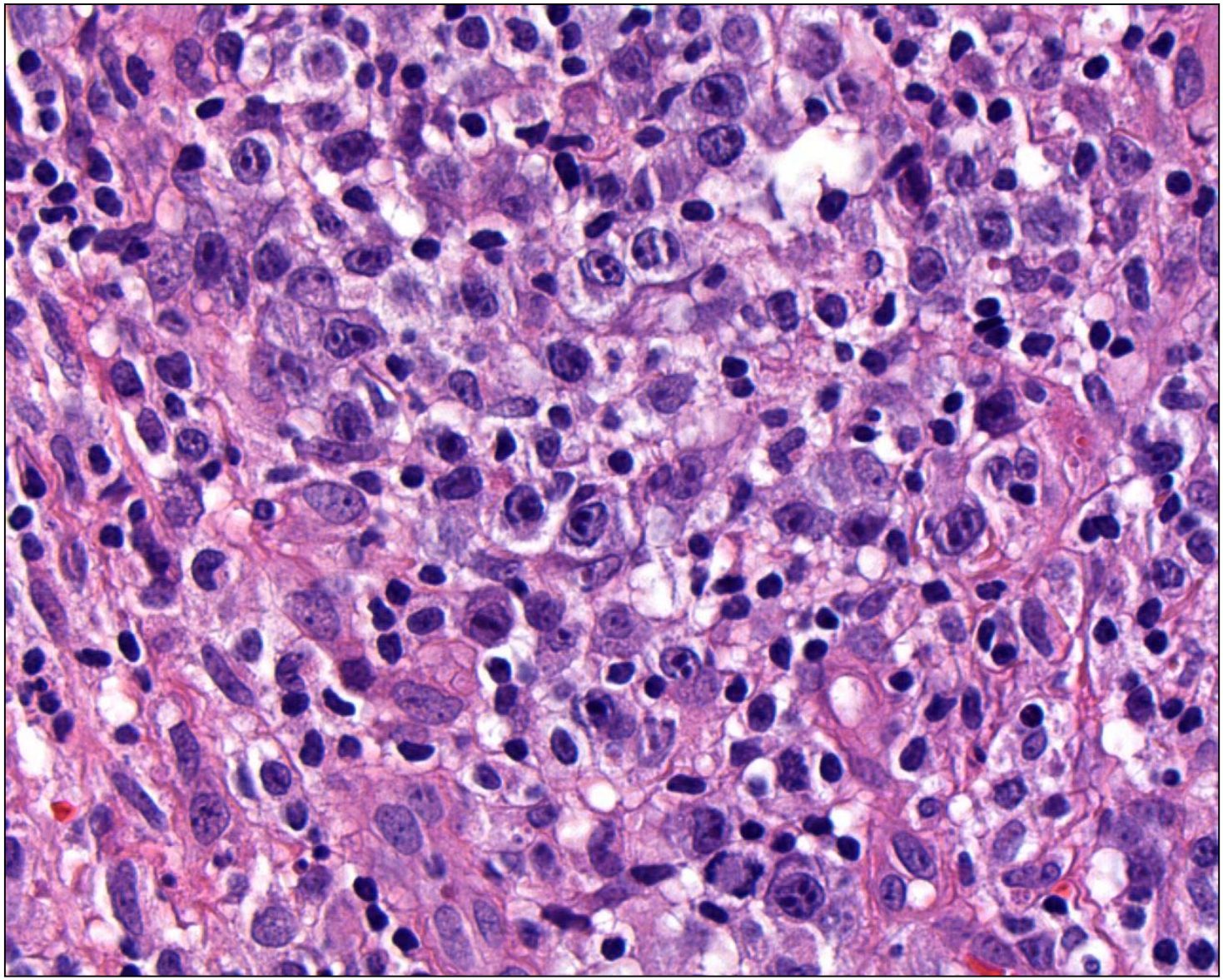
EAHP meeting, Uppsala, September 25-30, 2010


Benign?
Malignant?

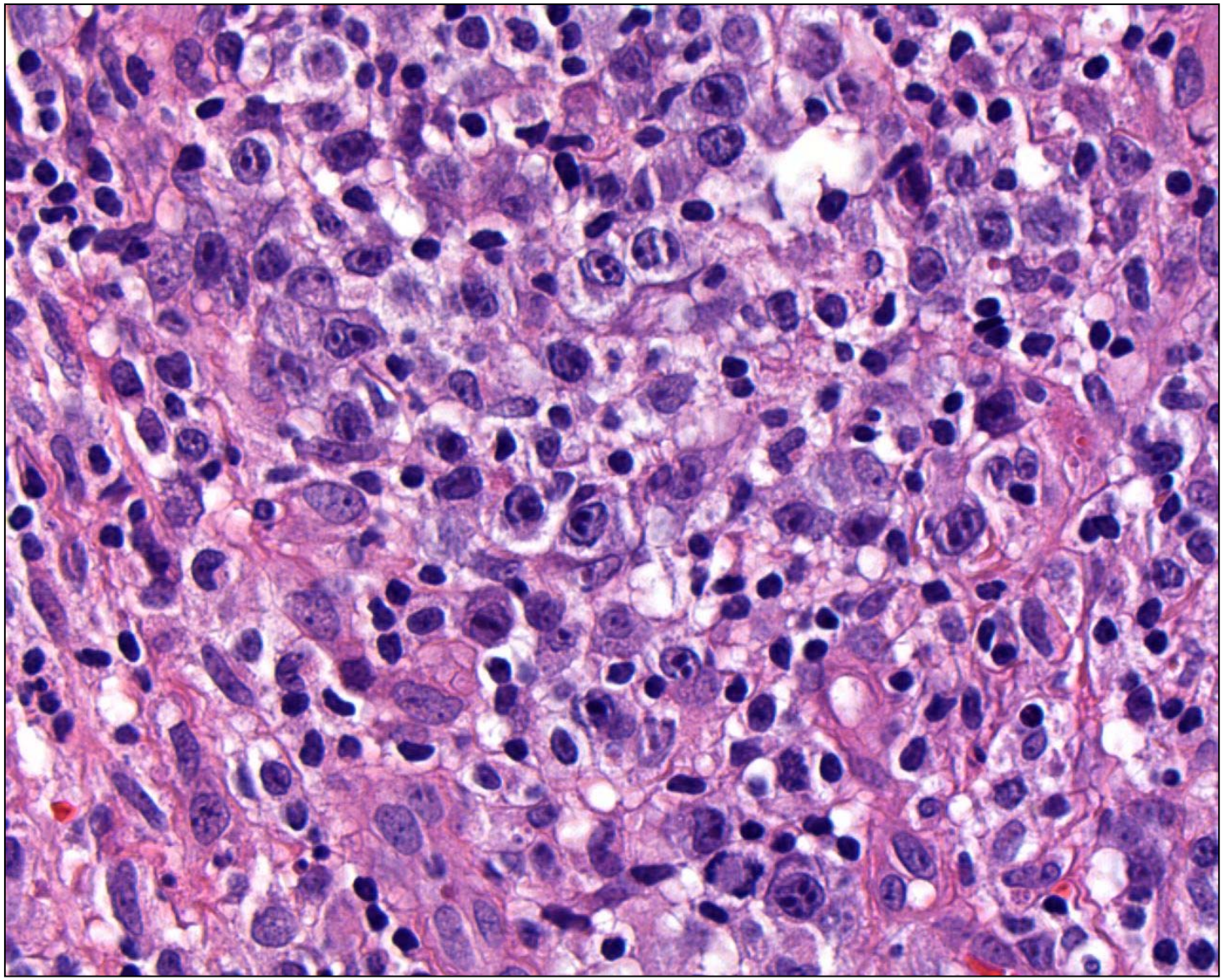
Casus 29 (PA: R04-81065)

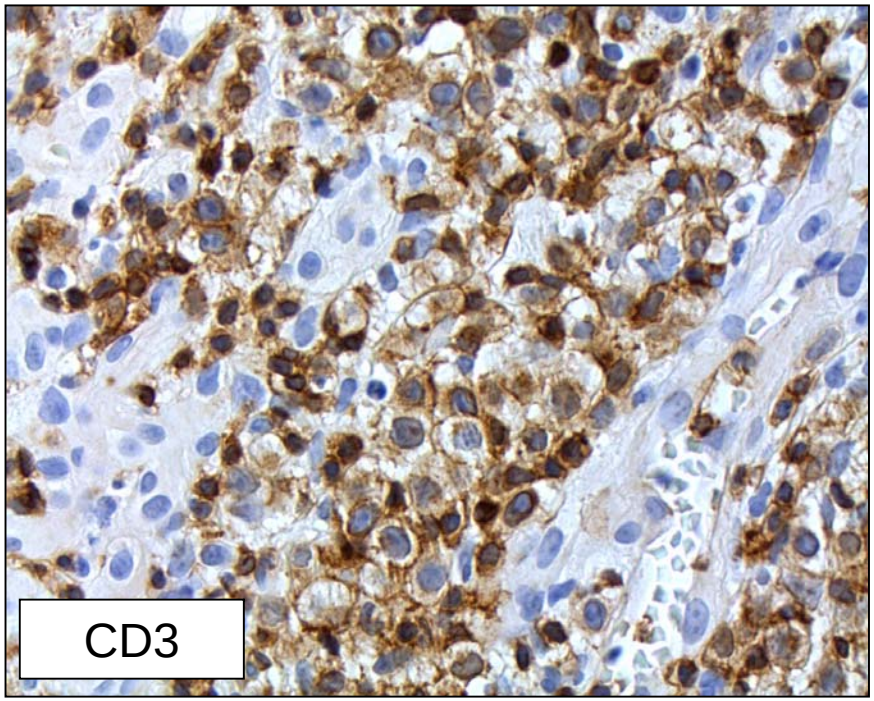


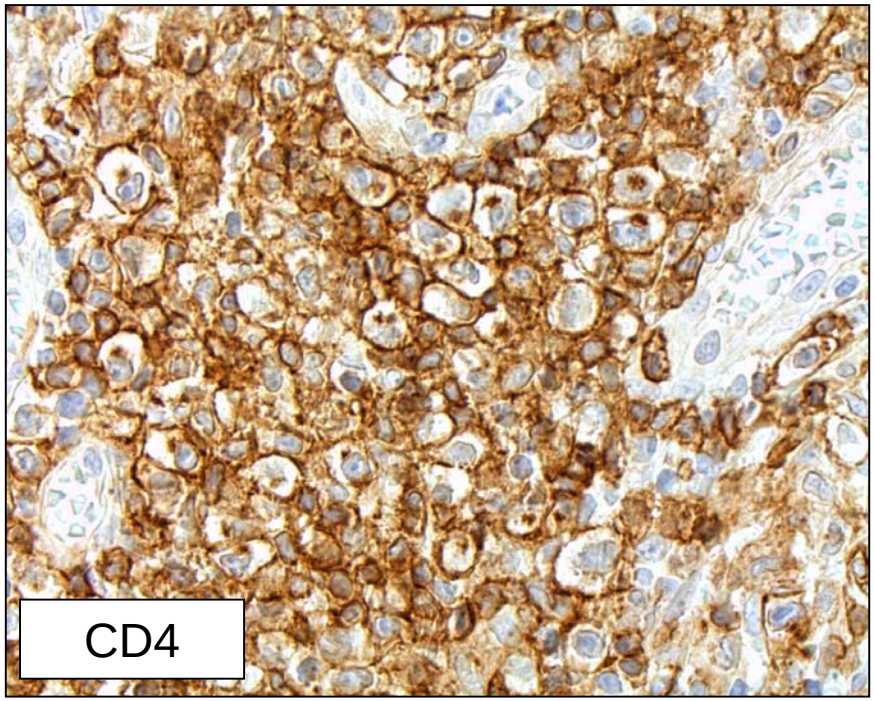
Atypical lymphoid infiltrate: benign or malignant ?



Atypical lymphoid infiltrate: CTCL or CBCL ?




CD3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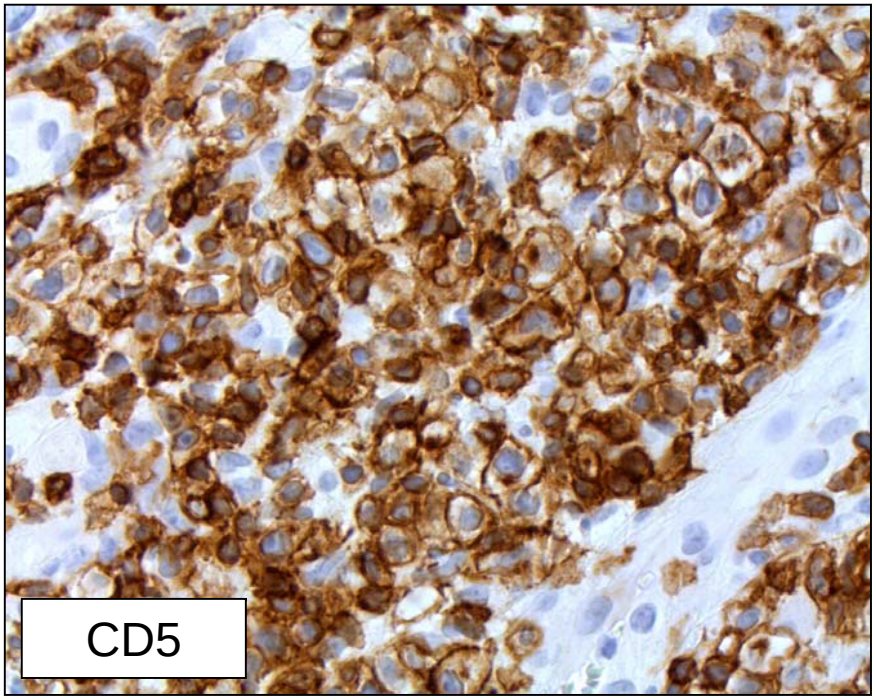
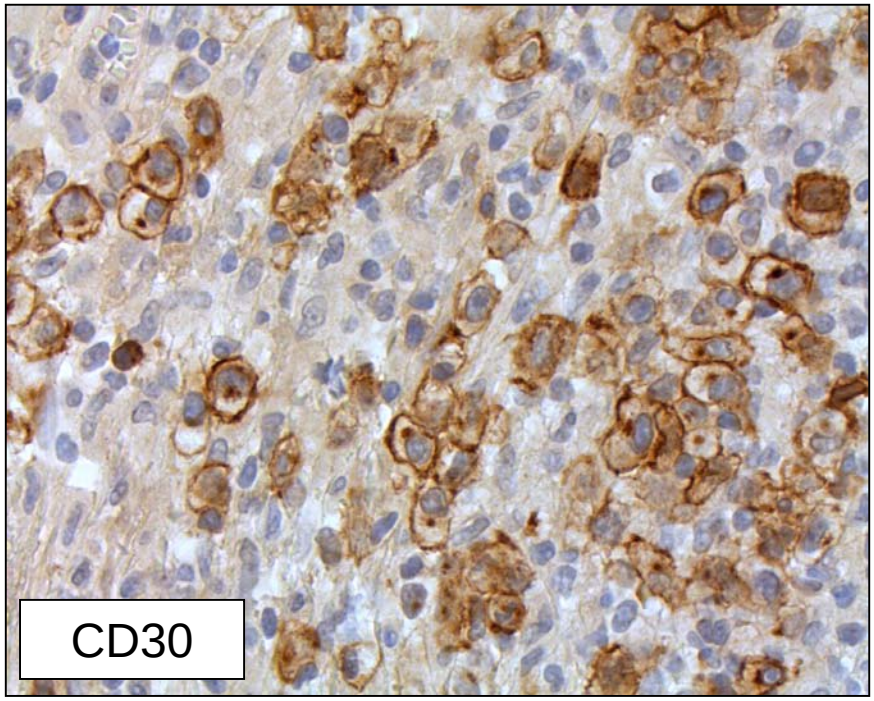
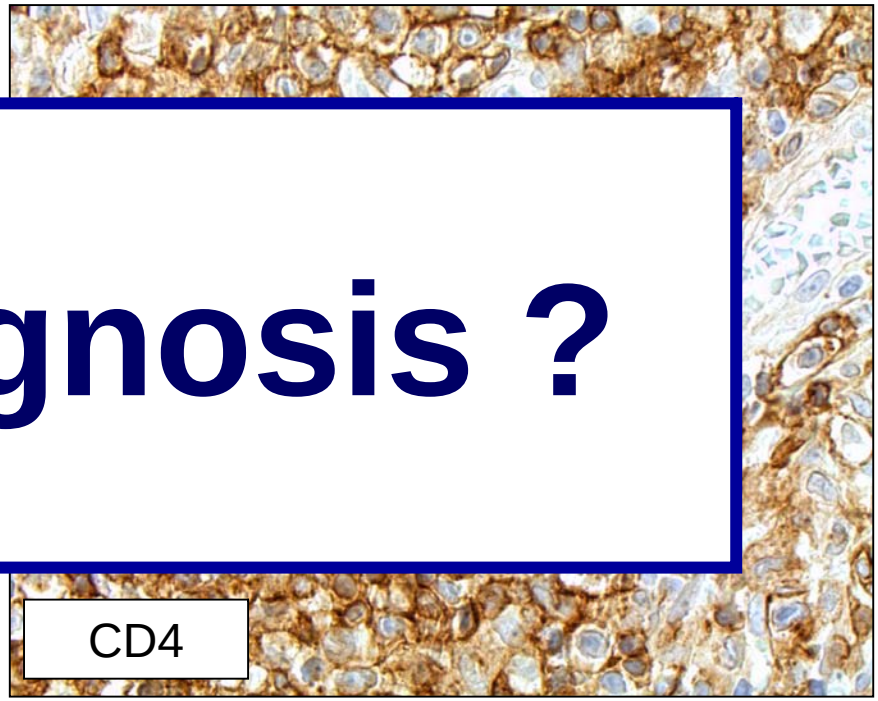
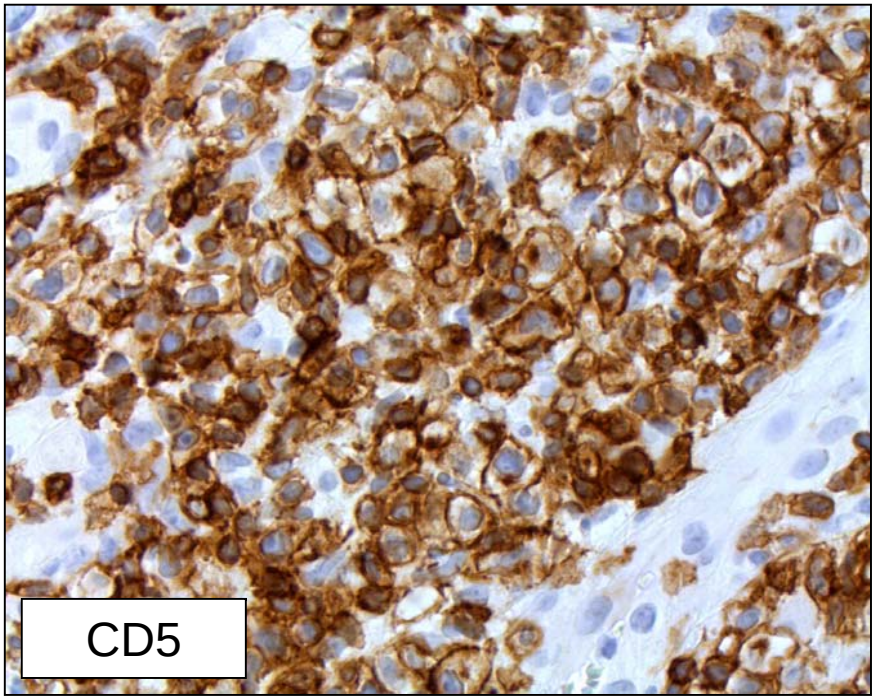
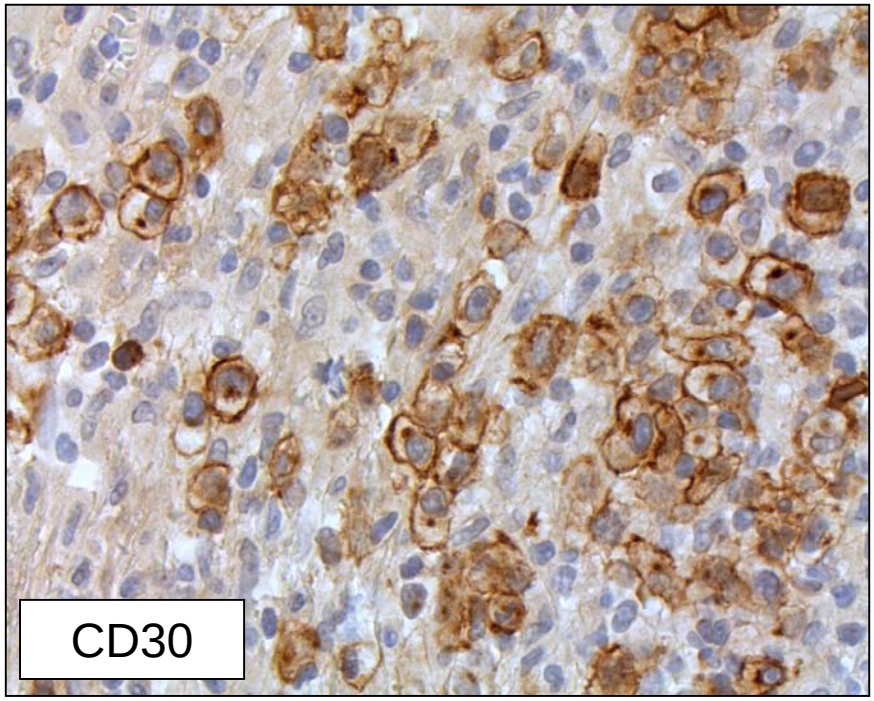

CD5


CD30

Your diagnosis ?







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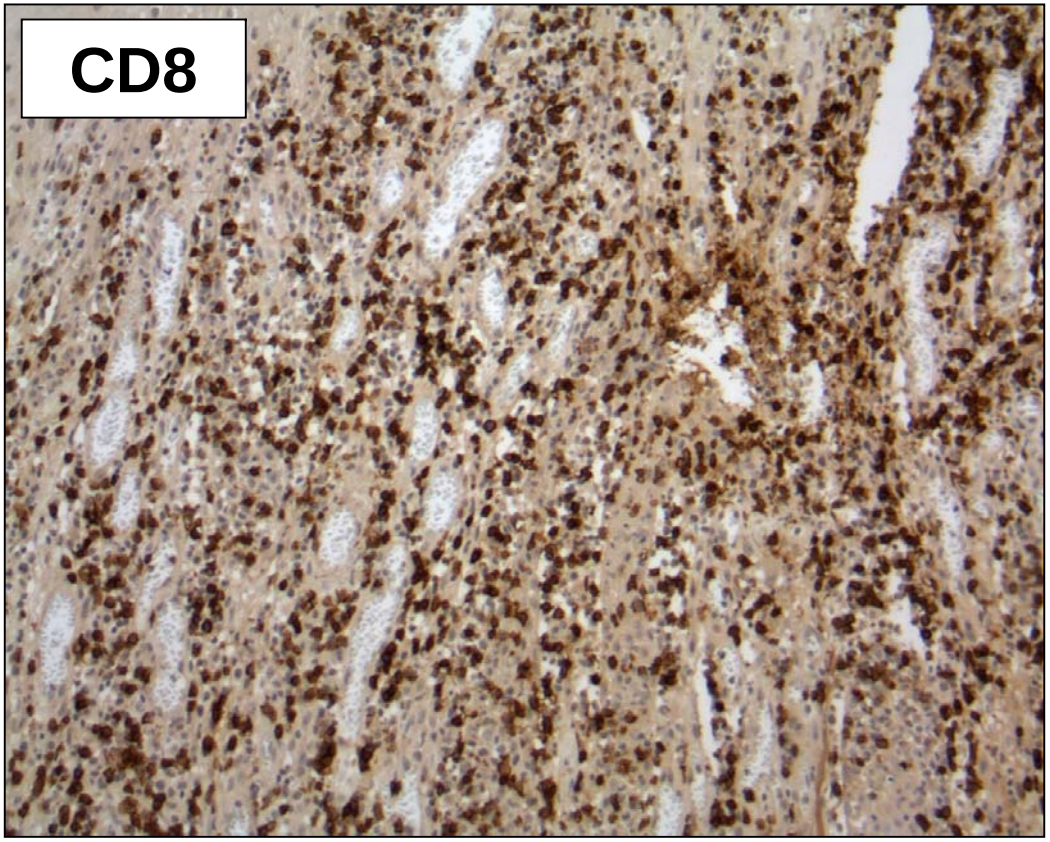

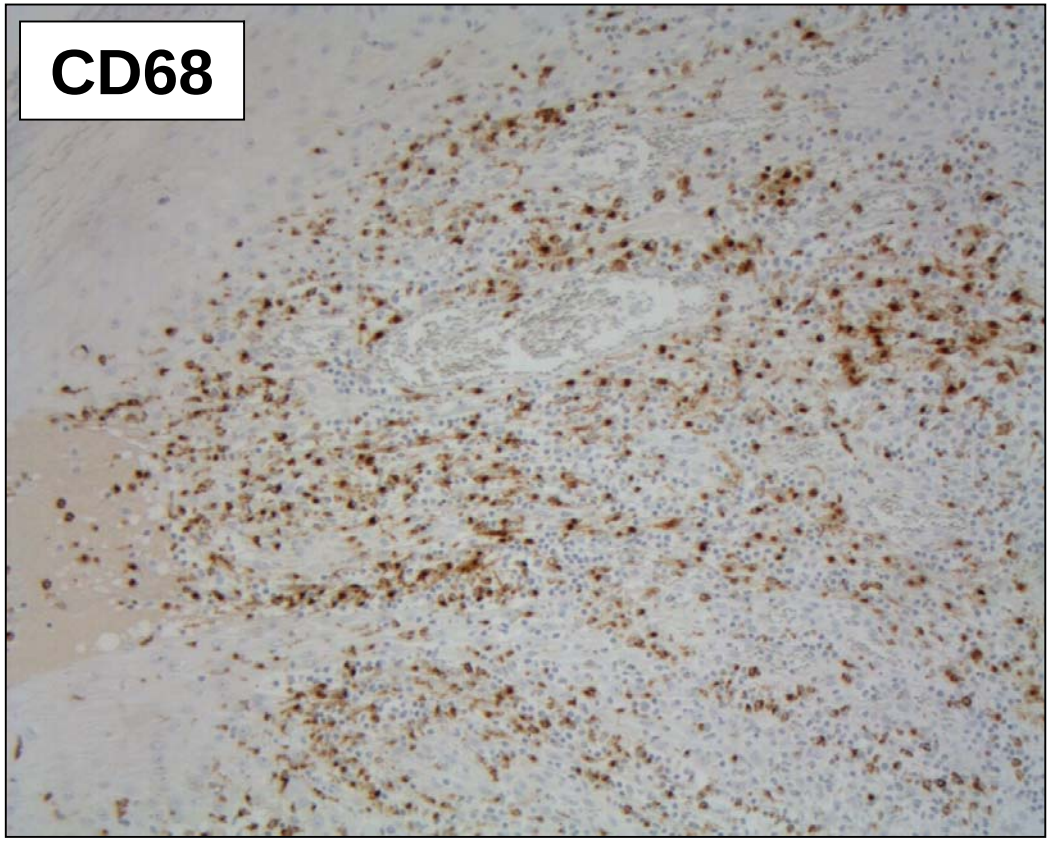

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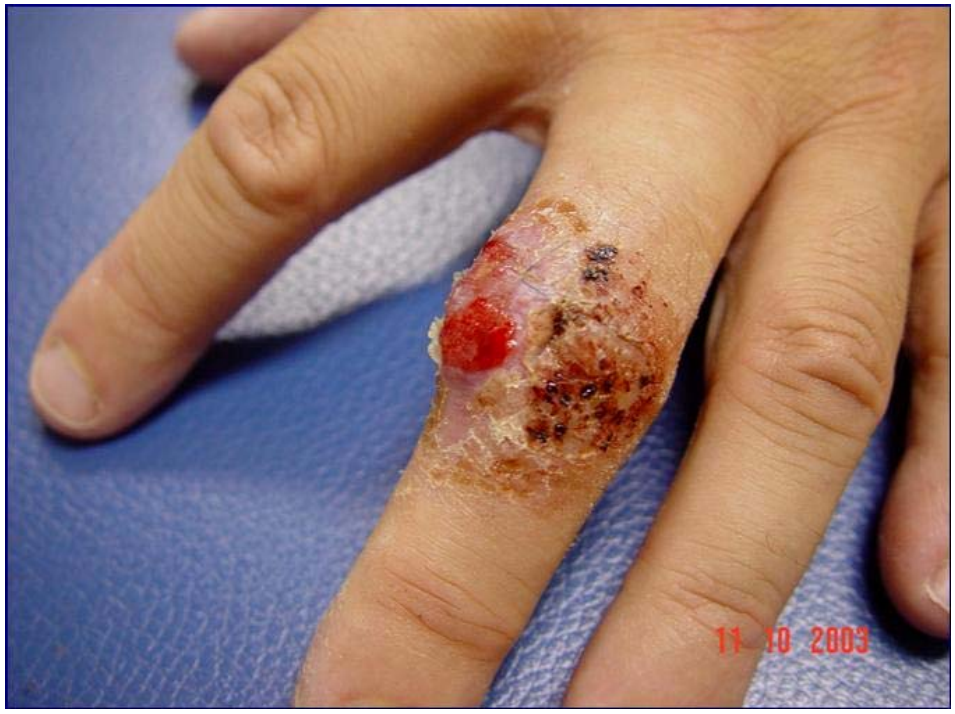
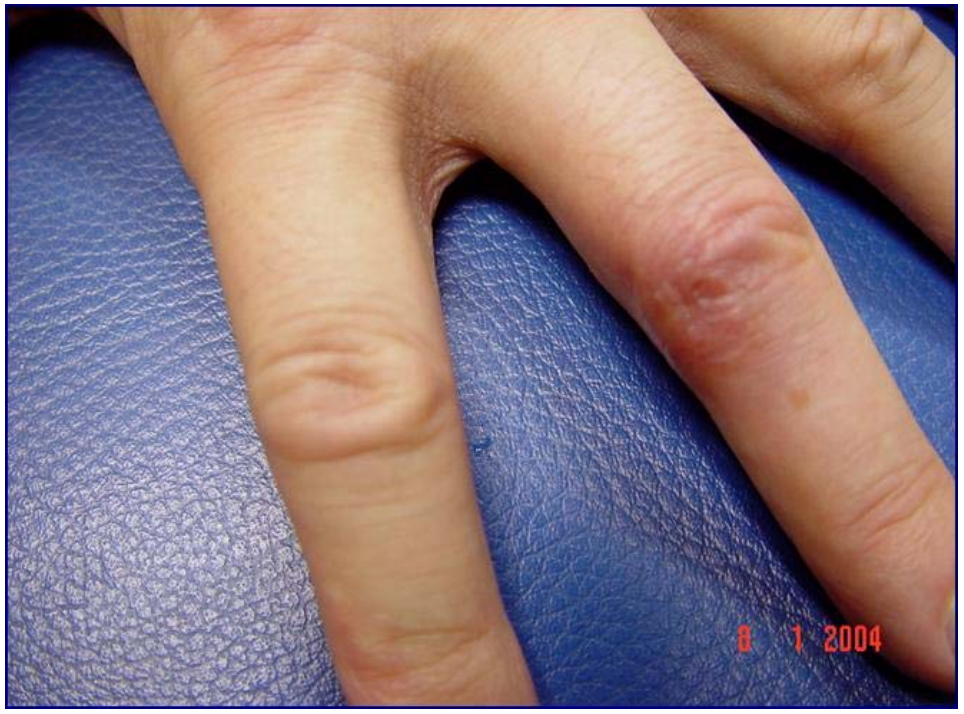




- Man, 35 years; farmer; contact with sheep.
- Solitary tumor middle finger. Disappeared within weeks.
- Diagnosis: Orff (milker’s nodule).

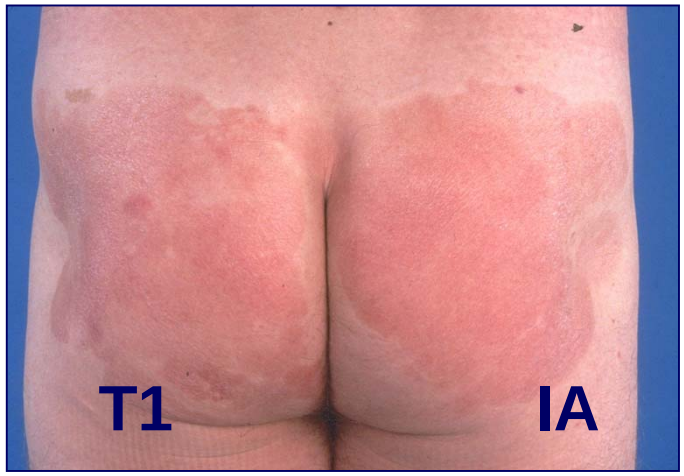
Differential atypical lymphoid infiltrate

- Should always be based on a combination of histology, immunohistrochemistry, (genotyping), **and clinical features.**
- Histological criteria alone often insufficient.
- Diagnostic immunohistochemical criteria:
  - **CTCL:** marker loss (CD2, CD3, CD4, CD5, CD8, but not CD7) aberrant phenotype (CD4+/8+; co-expression CD20)
  - **CBCL:** monotypic cIg or sIg expression
- Clonality analysis: be very careful !

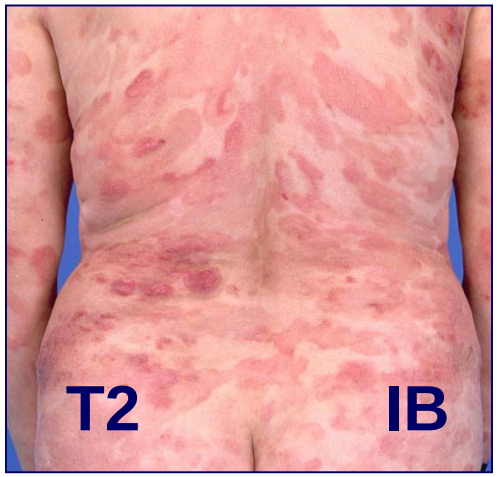
To be discussed

CTCL	Benign
Mycosis fungoides	BID; small/large plaque parapsoriasis
Folliculotropic MF	Alopecia mucinosa
Spectrum CD30+ LPD (C-ALCL; LyP)	Benign cutaneous CD30+ infiltrates
CD4+ S/M pleomorphic CTCL	Pseudo-T cell lymphoma
CBCL	**Benign**
pc marginal zone B-cell lymphoma	Cutaneous lymphoid hyperplasia (pseudo-B-cell lymphoma)
pc follicle center lymphoma	

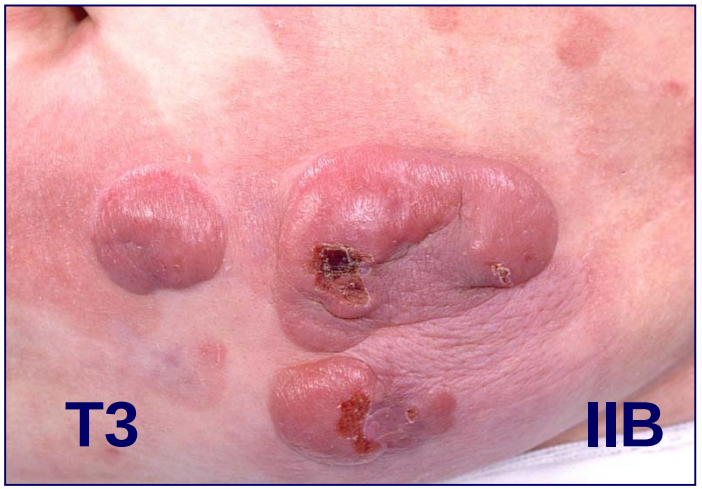
MF – skin stages



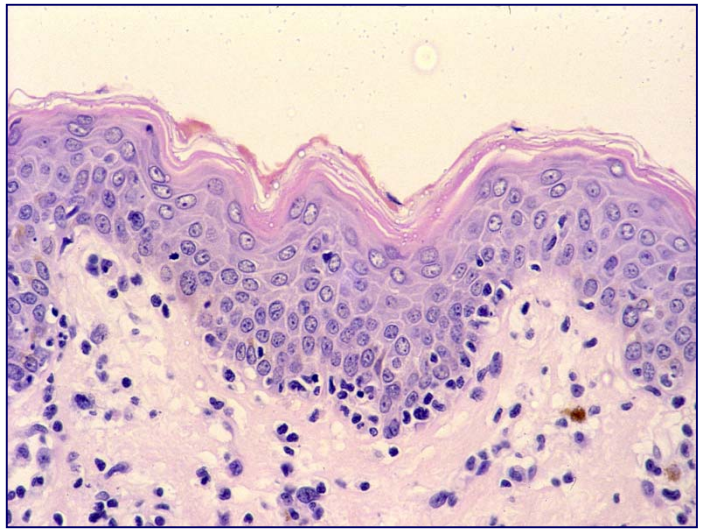
Patches

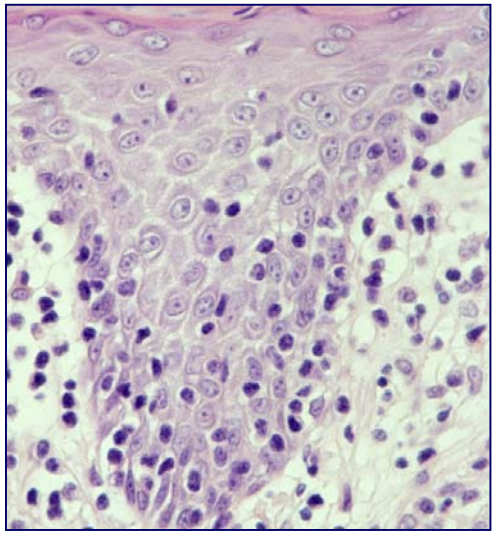


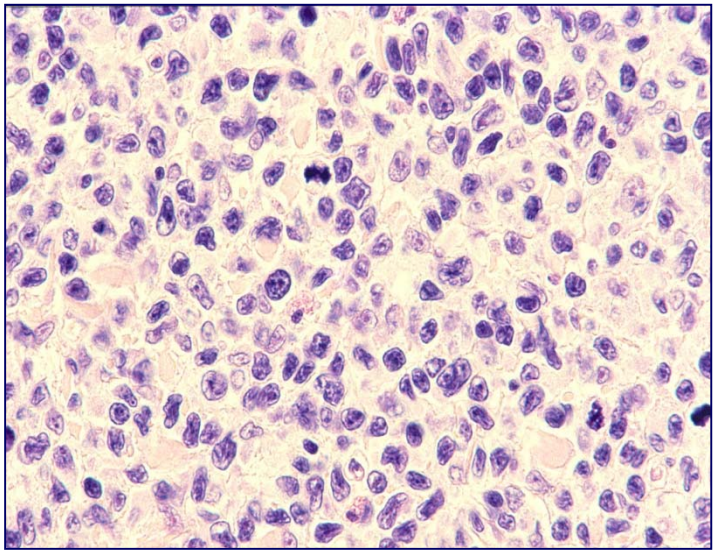
Plaques



Tumors







Problems and Controversies in MF

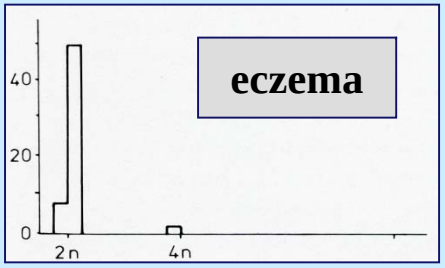
- **Differentiation between early patch/plaque stage MF and benign inflammatory dermatoses (histologic criteria for early MF).**

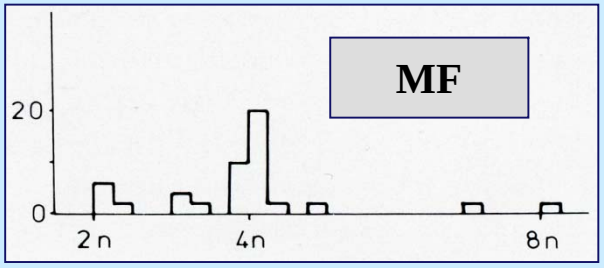
- **Should all cases of large plaque parapsoriasis or even small plaque parapsoriasis be considered as MF?**

Dutch approach 1975 - 1980

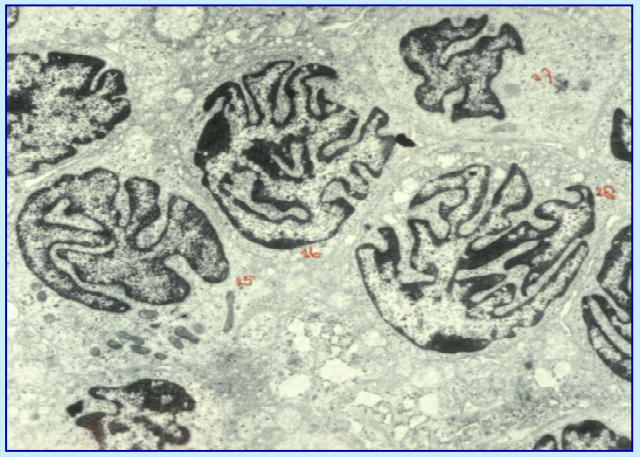
Differences between lymphocytes in MF and benign inflammatory dermatoses:

- DNA content
  (DNA-cytophotometry)





- nuclear shape
  (nuclear countour index
  morphometry)



Diagnosis MF: current Dutch approach

- Diagnosis of MF should always be based on a combination of clinical and histological criteria **(= golden standard).**

- **Additional** criteria:
  - Immunohistochemistry

    Loss of pan-T-cel markers (CD2,3,4,5, but not CD7 !!) is strongly suggestive/diagnostic of CTCL.
  - Gene rearrangement analysis: be critical !!

Histologic criteria early MF

Efficacy of histologic criteria for diagnosing early MF.
An EORTC Cutaneous Lymphoma group Investigation.

Santucci M. et al; Am J Surg Pathol 2000; 24: 40-50

“We conclude that the efficay of single histopathologic features in the diagnosis of early MF is generally poor. Only the presence of medium-large cerebriform cells in the epidermis or in clusters in the dermis proved to be a highly reliable feature”

ISCL algorithm for diagnosis of early MF

(Pimpinelli N. et al. J Am Acad Dermatol 2005)

Criteria	Scoring system
CLINICAL A: persistent and/or progressive patches B: additional criteria: 1) non-sun exposed site; 2) size/shape variation; 3) poikiloderma	2 points (A + 2 additional criteria) 1 point (A: + 1 additional criterion)
HISTOLOGY A: superficial lymphoid infiltrate B: additional criteria: 1. **epidermotropism** without spongiosis; 2) lymphoid **atypia**	2 points (A + 2 additional criteria) 1 point (A: + 1 additional criterion)
Clonal TCR gene rearrangement	1 point
IHC (marker loss using different criteria)	1 point

A total of 4 points is required for the diagnosis of MF

Evaluation ISCL algoritm

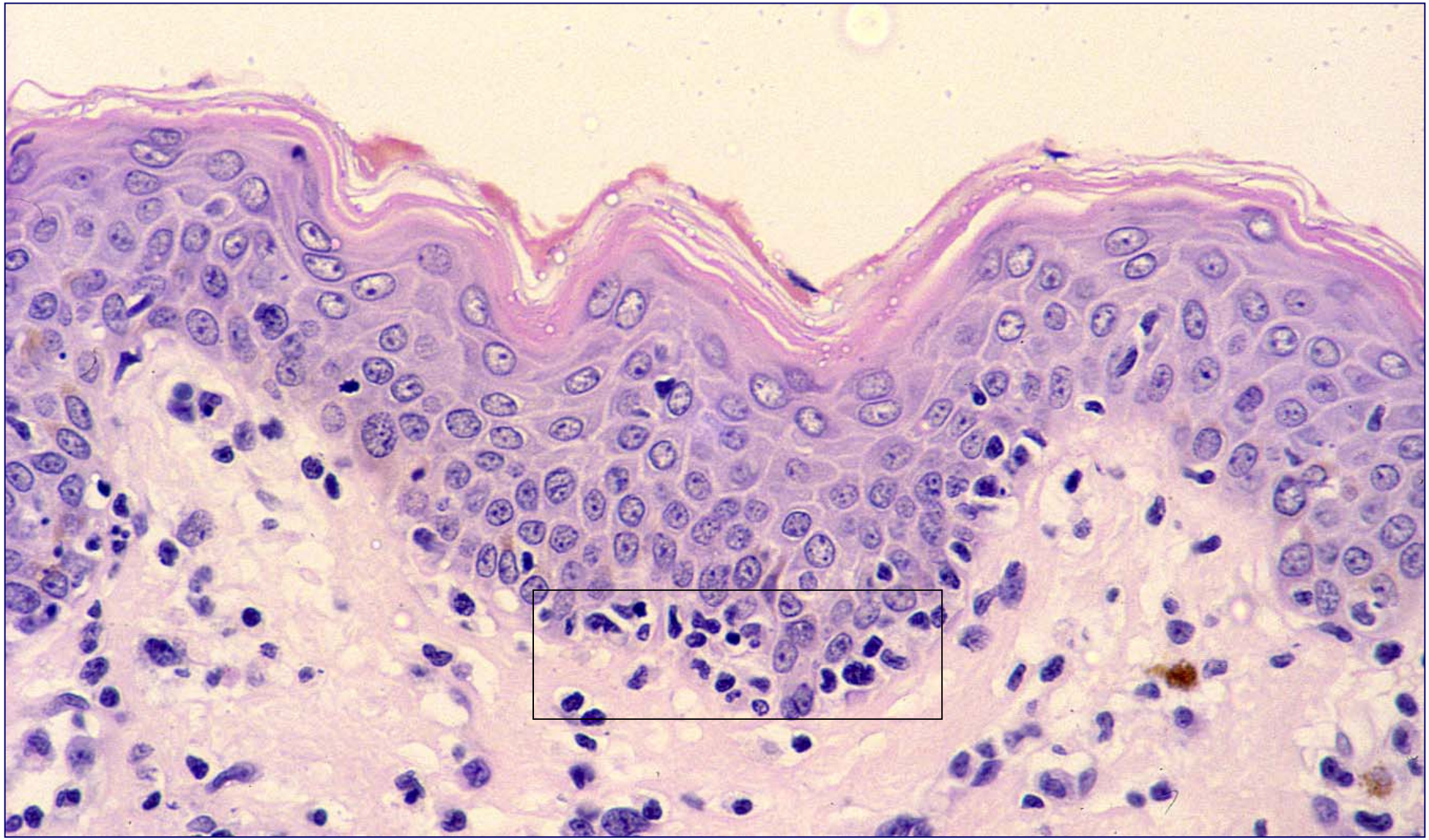
Ferrara G. et al; J Cutan Pathol, 2008

- 72 patients/biopsies with clinical features of parapsoriasis/ early MF (ISCL: 2 points)
- Histopathology:
  - 45/72 epidermotropism + atypia (ISCL: 2 points) → **MF**
  - 27/72 epidermotropism – or +, but no atypia (ISCL: 0 - 1 point)
- Genotyping: 4/12 clonal (3/4 had already ISCL 4)
- Aberrant phenotype: 8/72 (8/8 already ISCL score 4)

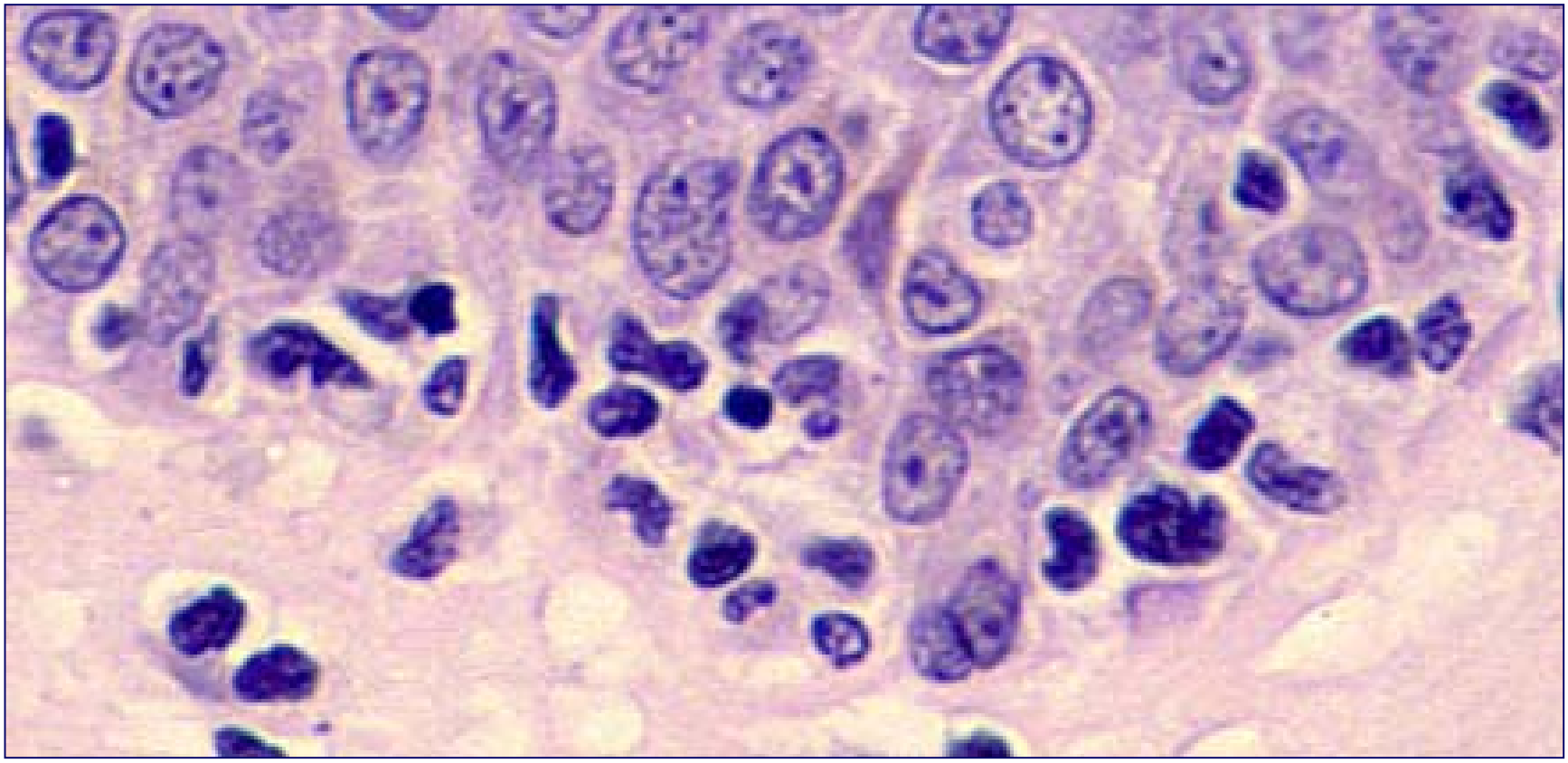
Conclusions:

- Diagnosis based on clinical and ghistological features
- Genotyping and phenotyping generally non-contributory.

Histology patch stage MF

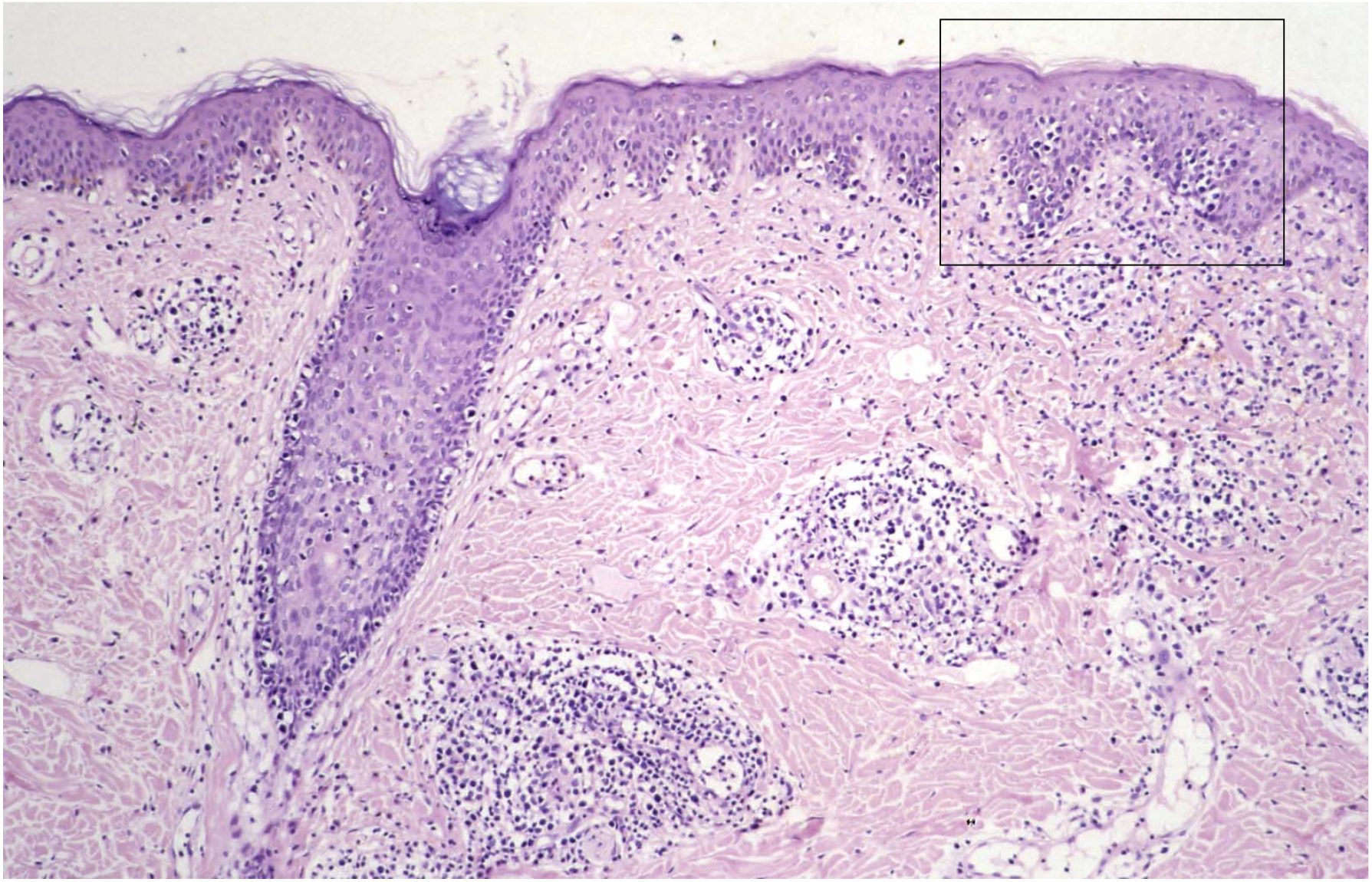


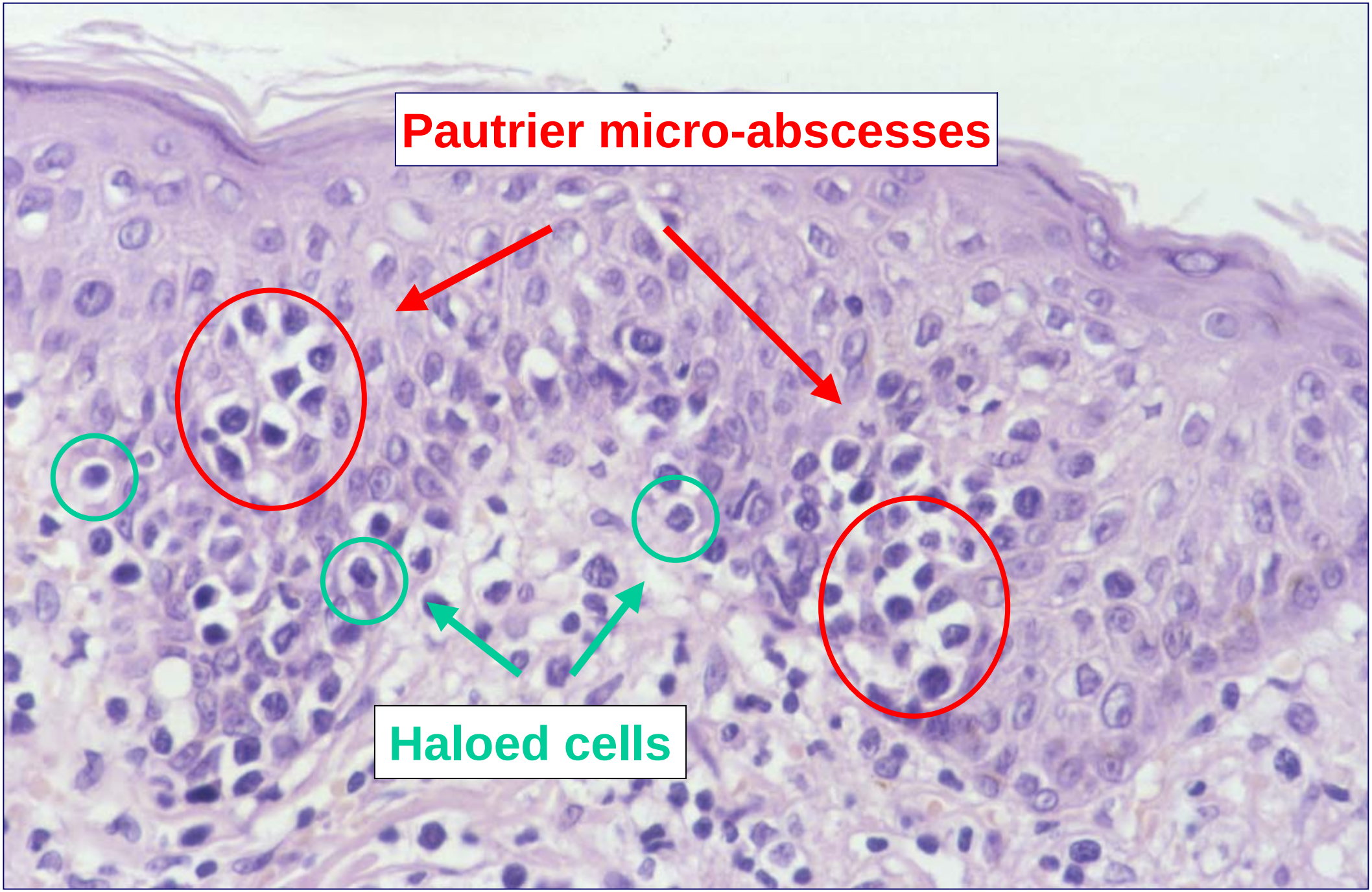
Histology patch stage MF



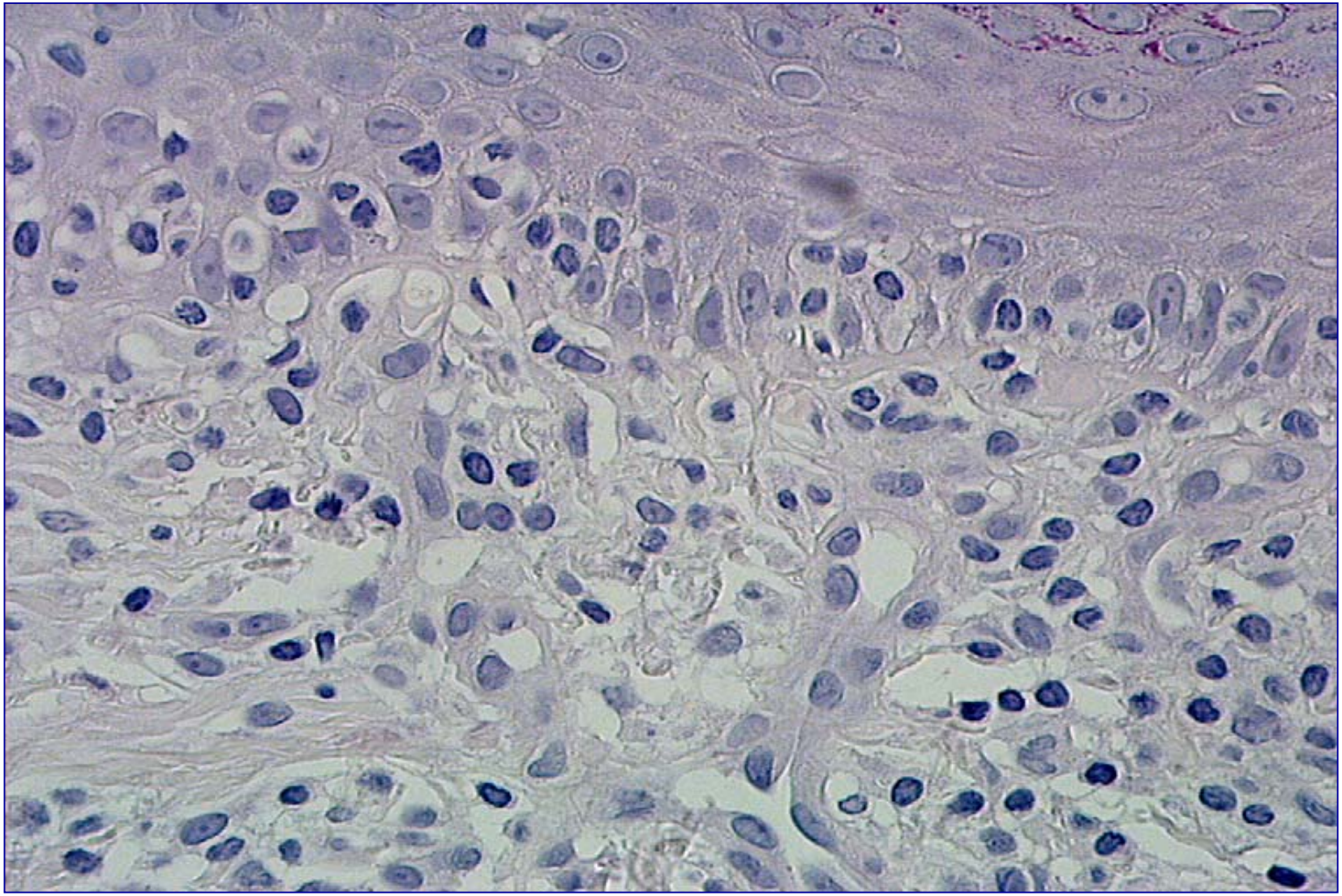
Atypical lymphocytes: hyperchromatic, partly haloed and too large, aligned along epidermal basal layer; no spongiosis

Histology patch stage MF

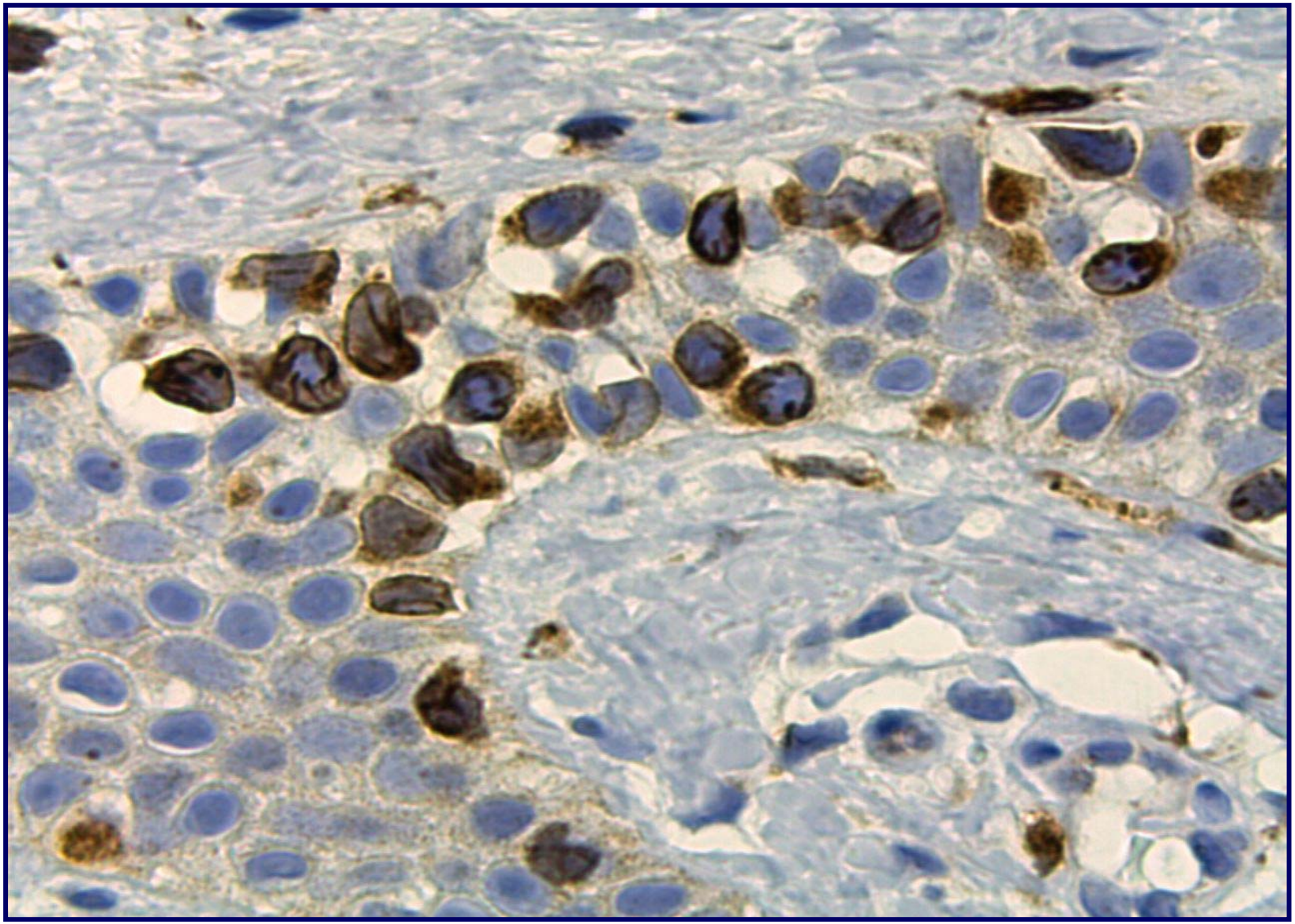



Pautrier micro-abscesses
Haloed cells

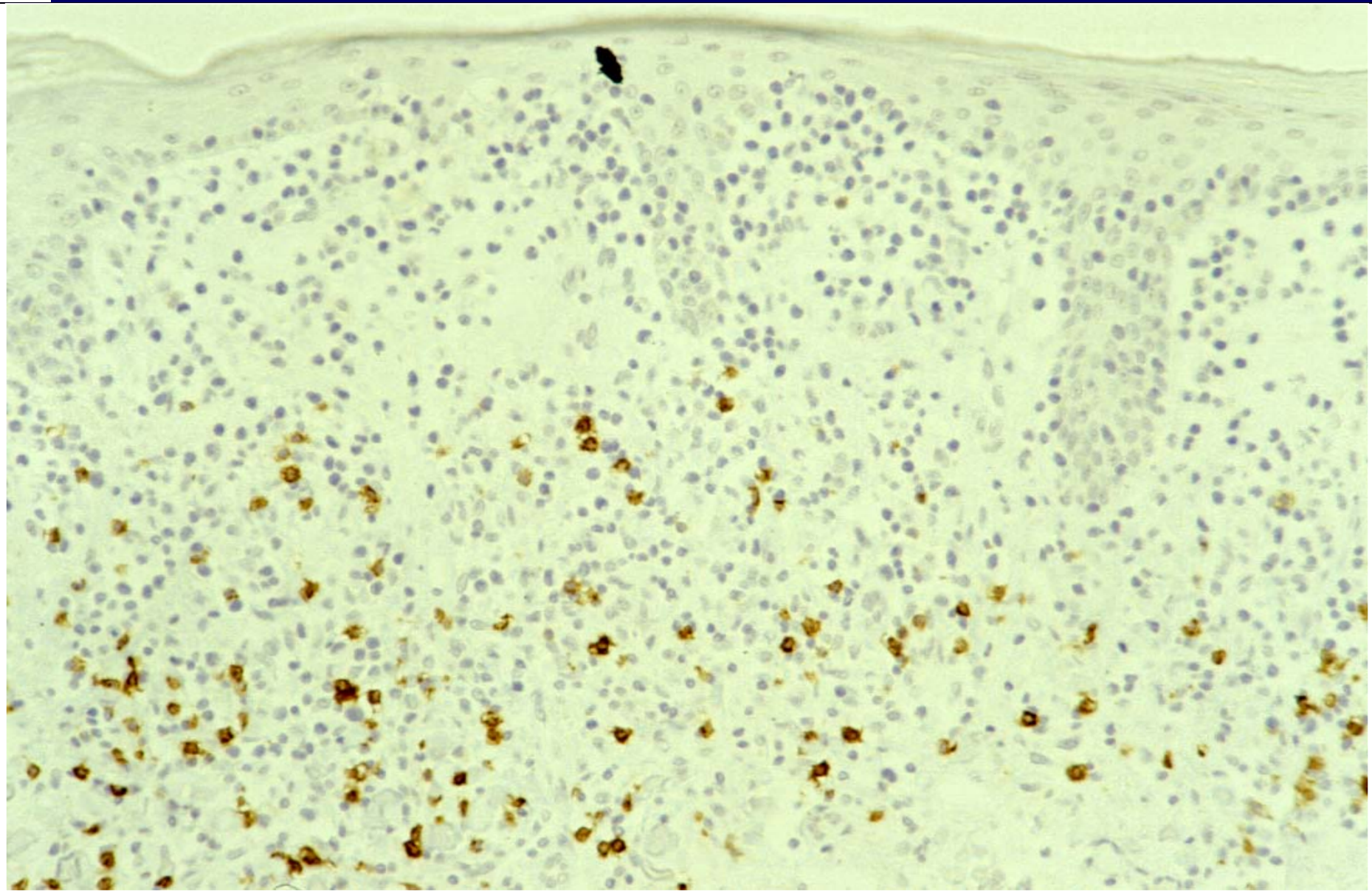
Mycosis fungoides ?



CD3 staining



Reactive CD8+ T-cells



Histologic criteria for early MF

- Band-like or lichenoid infiltrate in papillary dermis.
- Epidermotropic T-cells (without spongiosis):
  - With nuclei larger than those of dermal T-cells.
  - Aligned along the epidermal basal layer.
  - Haloed cells
  - Pautrier's microabscesses (rare).

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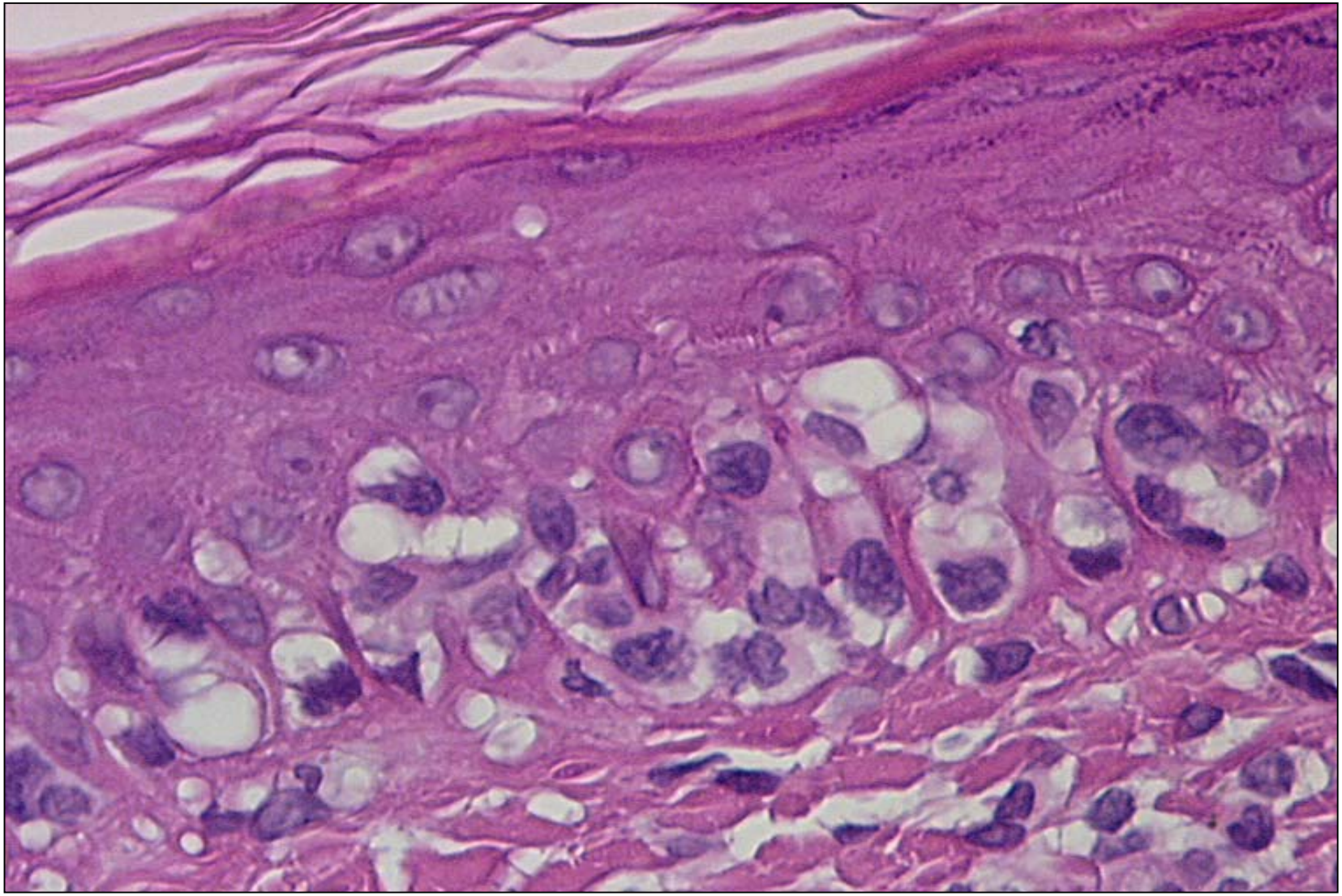
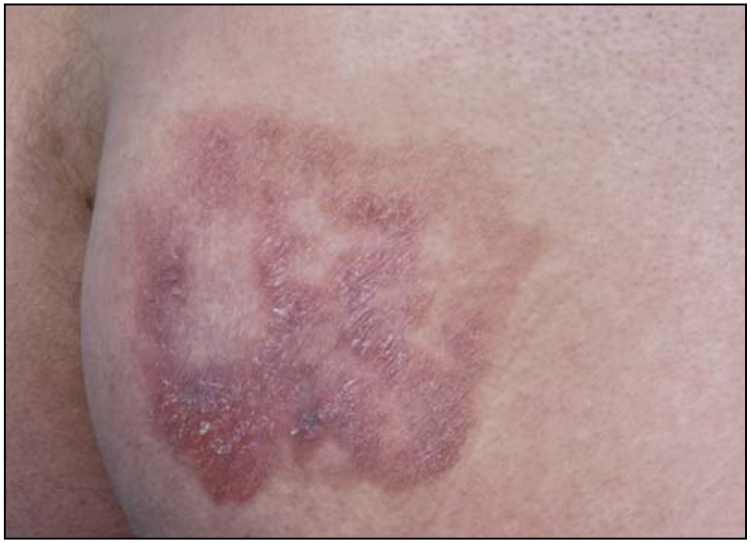
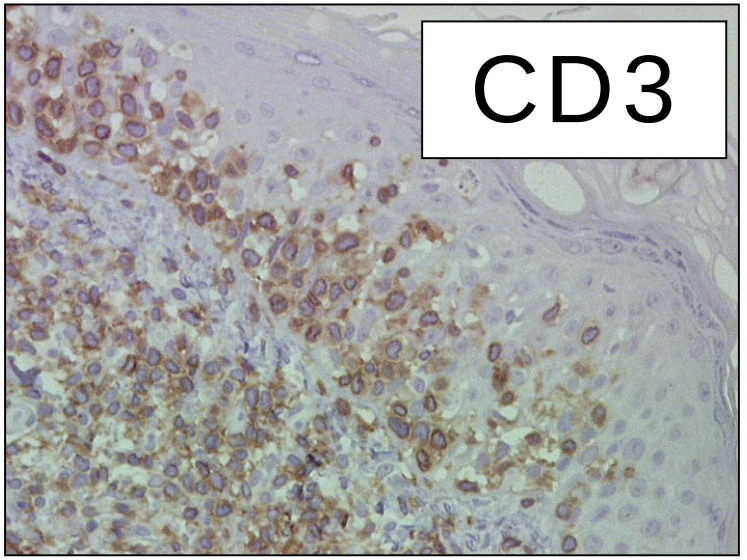
HOWEVER . . . . .

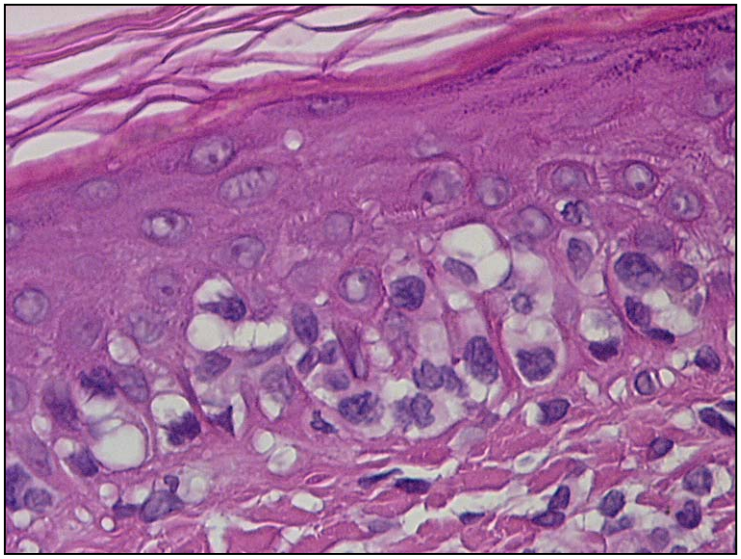
Epidermotropic CTCL ? MF?

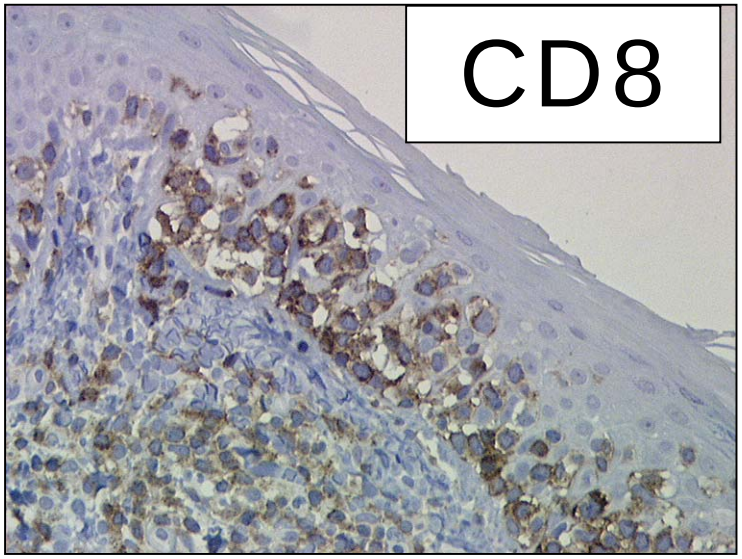


CD8+ MF: behaves as CD4+ MF

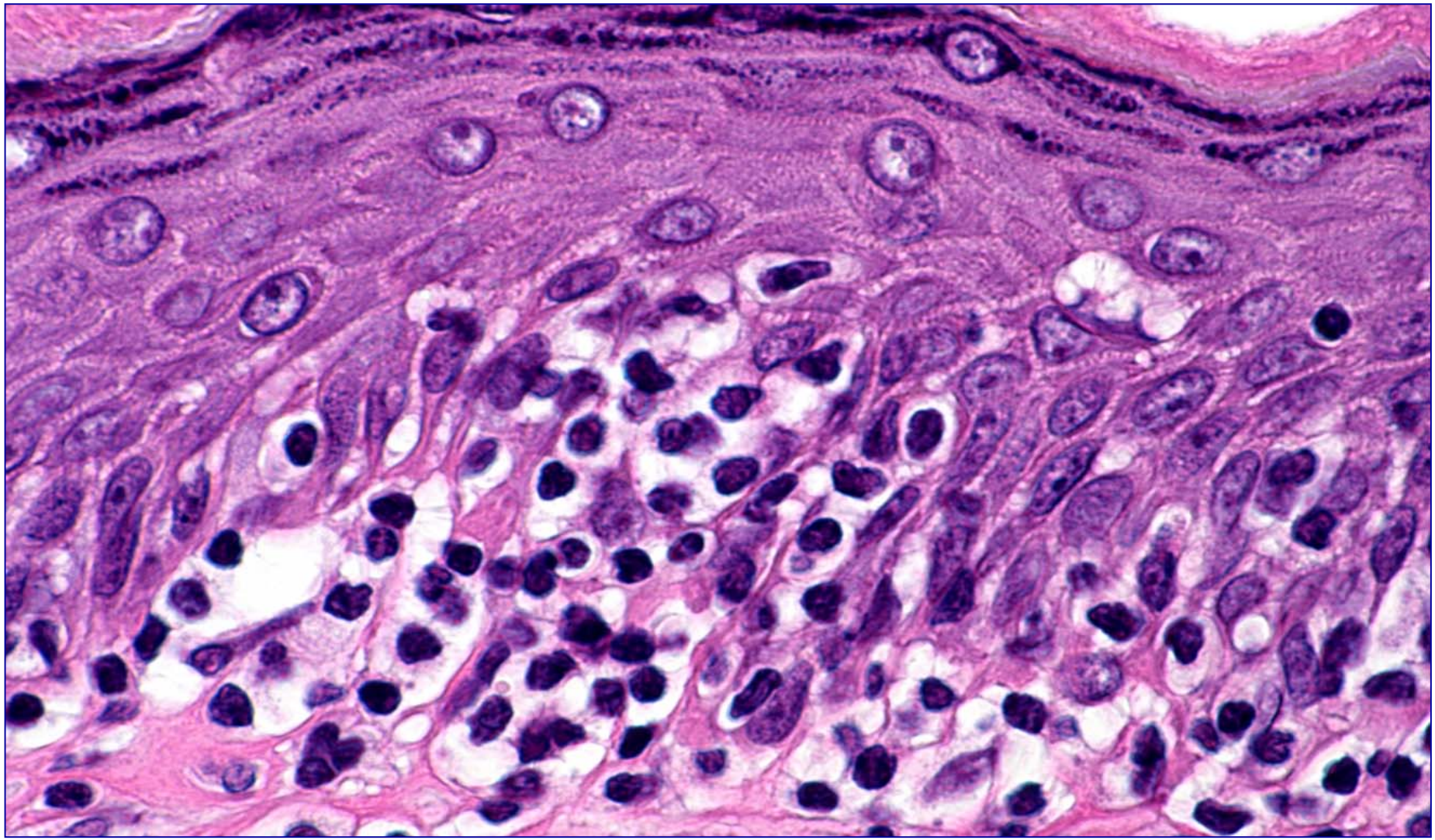








Epidermotropic CTCL ? MF?

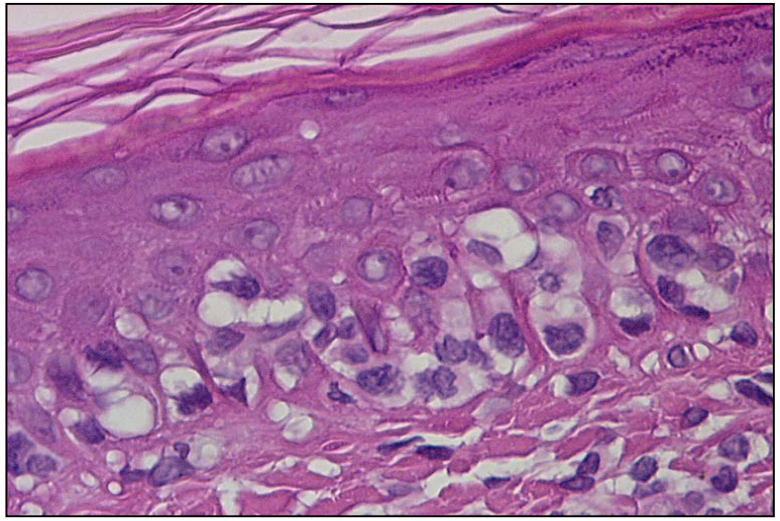


Diagnosis

Histologic features of mycosis fungoides in lichen sclerosis

Citarella L. Et al; Am J Dermatopathol 2003;25:463-465

Clinicopathologic correlation



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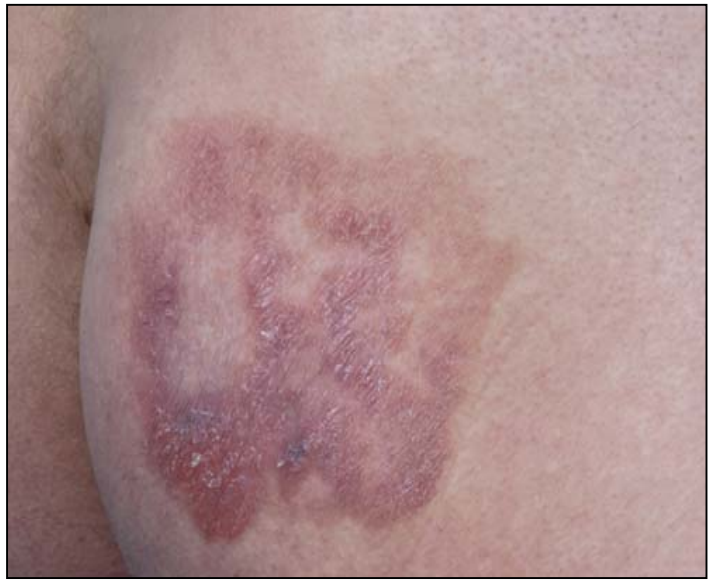
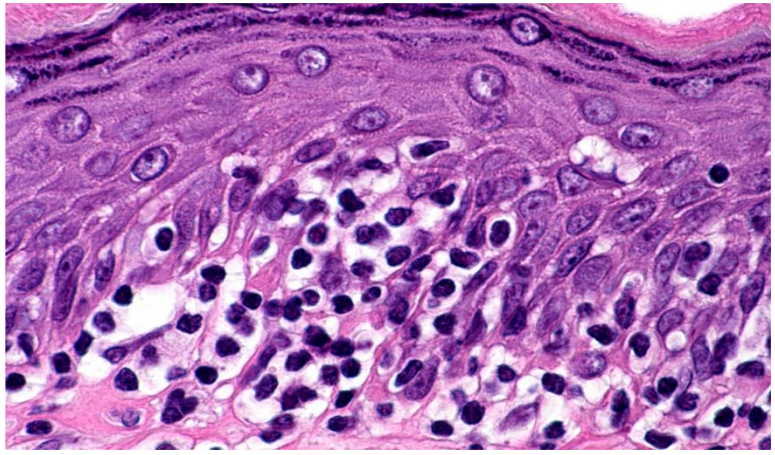


= MF



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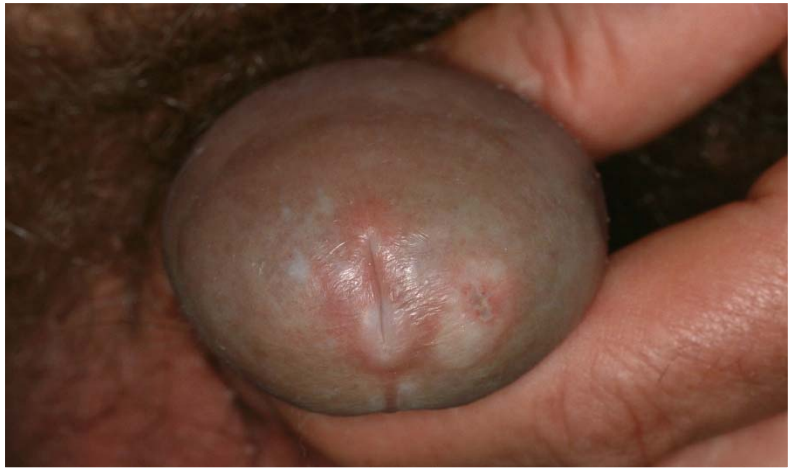


? MF

Controversies MF

- Differentiation between early patch/plaque stage MF and benign inflammatory dermatoses (histologic criteria for early MF).

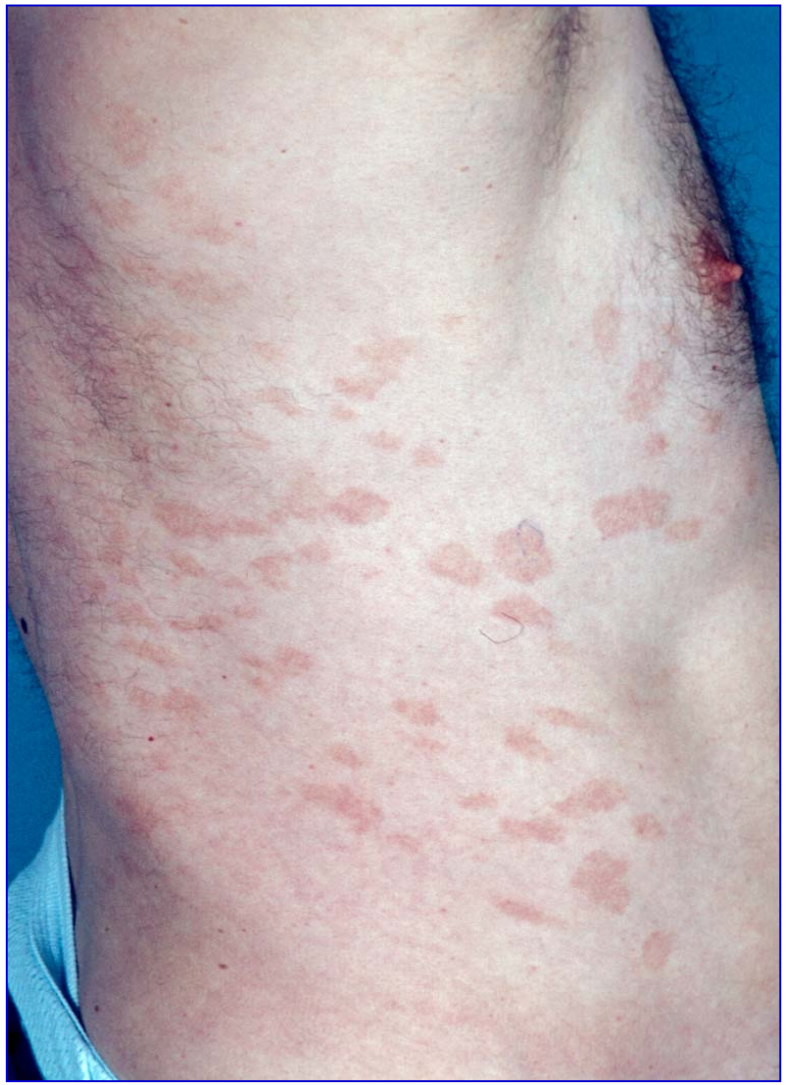
- **Should all cases of large plaque parapsoriasis or even small plaque parapsoriasis be considered as MF?**

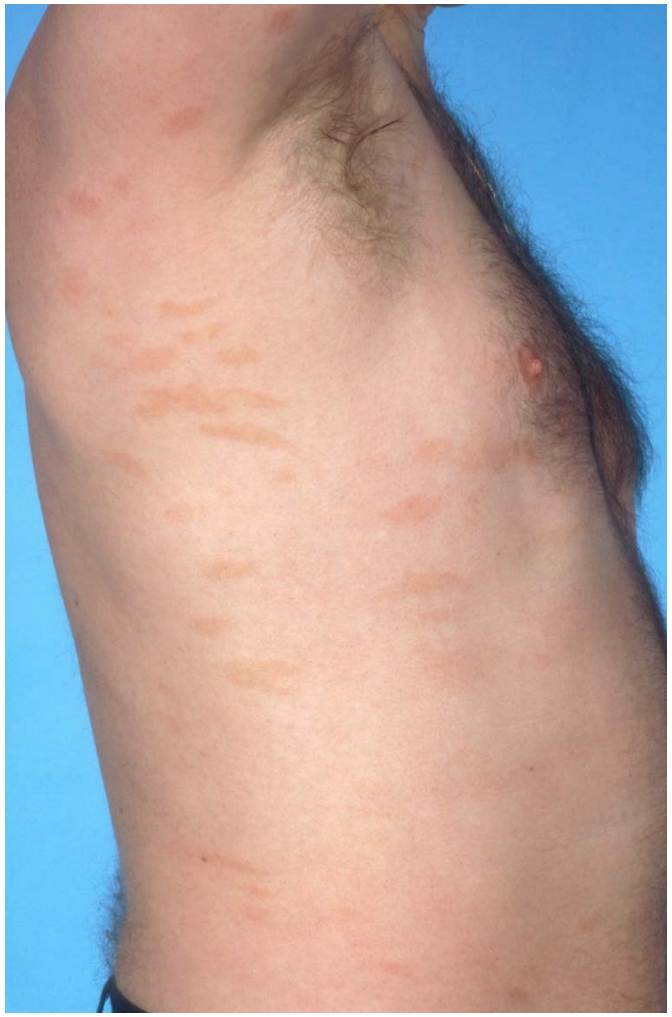
“Parapsoriasis en plaques”

- **Large plaque parapsoriasis (LPP)**
  - Subtype: poikiloderma vasculare atrophicans (= MF)
  - General view: LPP = MF

- **Small plaque parapsoriasis** (chronic superficial dermatitis)
  - Subtype: digitate dermatosis
  - Emerging view: SPP is an early phase of MF (controversial)
  - Based on the observation that some patients with a history of SPP developed decades later typical MF.

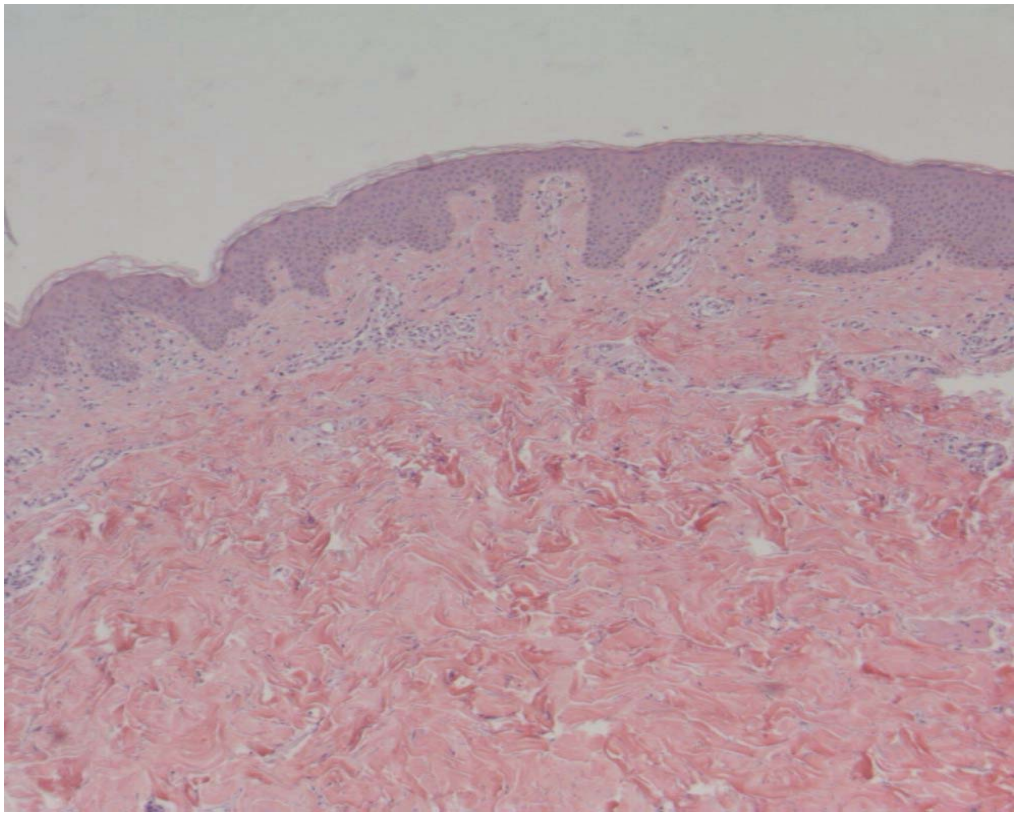
Small plaque parapsoriasis

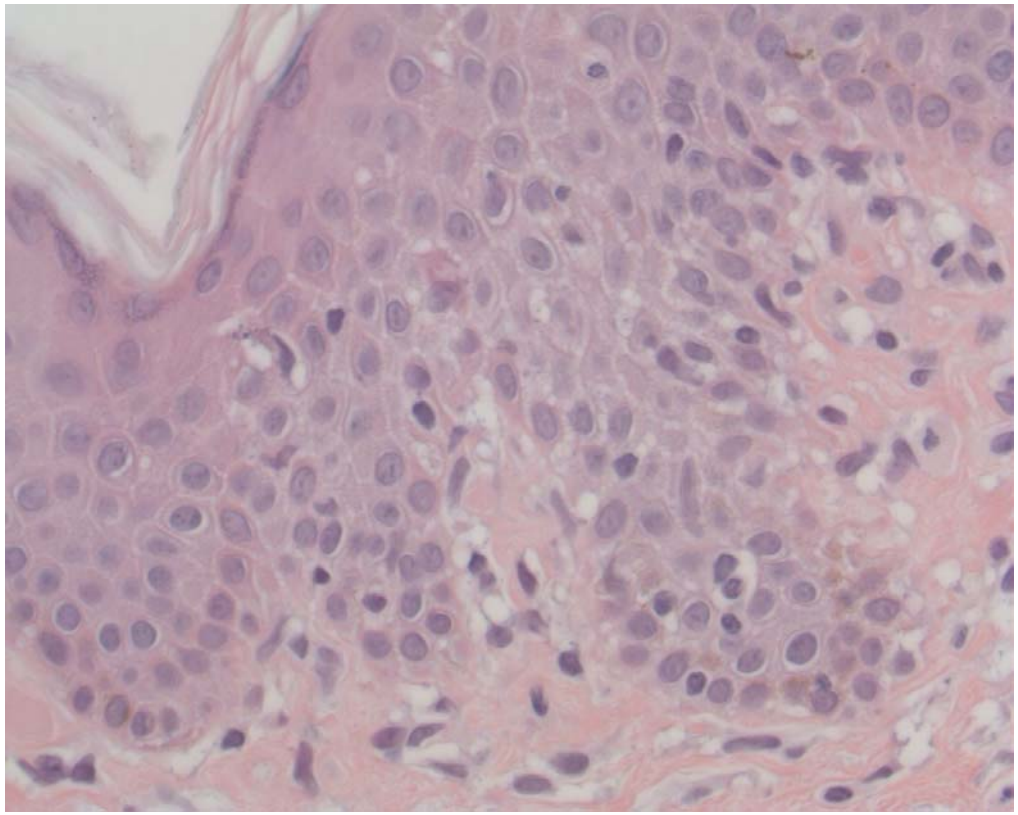




Digitate dermatosis

Mycosis fungoides ?





SPP/LPP vs MF: Dutch view

Histology in case of LPP/SPP or early MF:

- consistent with MF : MF
- not consistent with MF: LPP/SPP (or whatever, but not MF)
- suspicion, no definite MF: suspect MF (**repeat biopsies**)

- Phenotyping & genotyping: not or rarely contributory

IMPORTANT:

- No therapeutic consequences (both nbUVB; PUVA; steroids)
- Both LPP and patch stage MF have an excellent prognosis, with a life-expectancy similar to that of a healthy control population.

To be discussed

CTCL	Benign
Mycosis fungoides	BID; small/large plaque parapsoriasis
Folliculotropic MF	Alopecia mucinosa
Spectrum CD30+ LPD (C-ALCL; LyP)	Benign CD30+ infiltrates
CD4+ S/M pleomorphic CTCL	Pseudo-T cell lymphoma
CBCL	**Benign**
pc marginal zone B-cell lymphoma	Cutaneous lymphoid hyperplasia (pseudo-B-cell lymphoma)
pc follicle center lymphoma	

Alopecia mucinosa

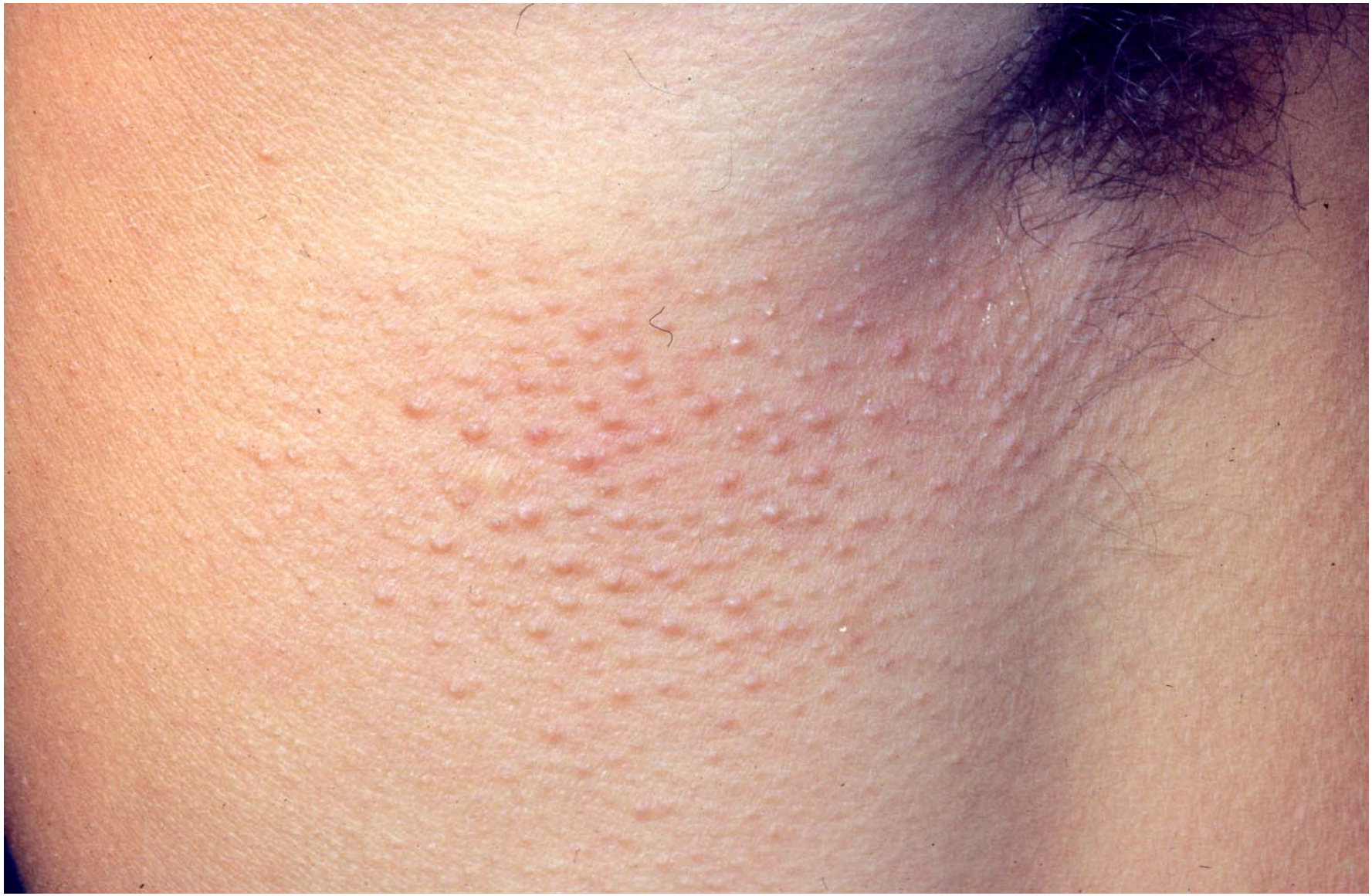
Syn: benign idiopathic follicular mucinosis

- Generally in children and young adults.
- Papular lesions, plaques, alopecia.
- Benign course.

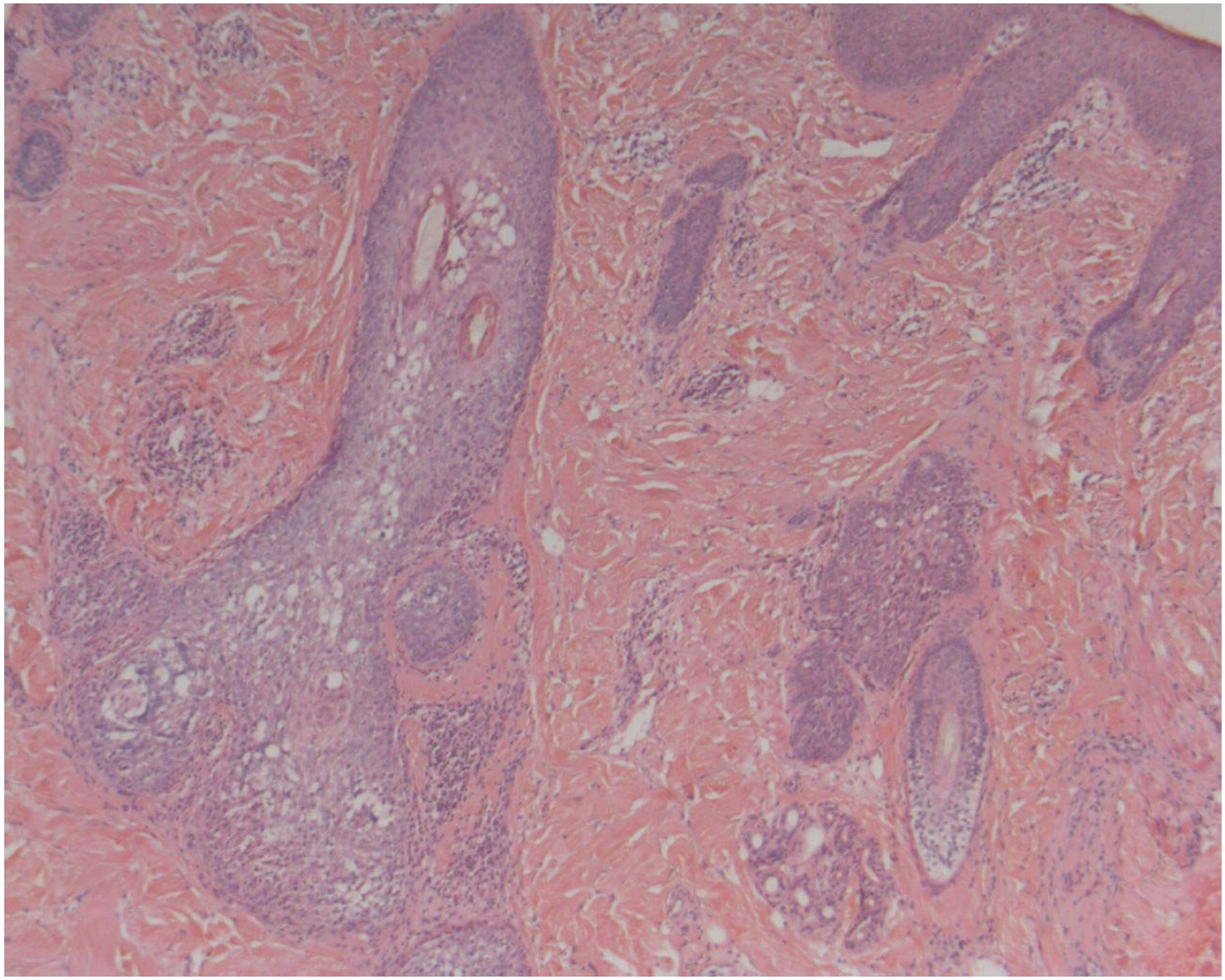
…….. alopecia mucinosa should be considered as early stage mycosis fungoides.

Literature:
Cerroni L, et al. Arch Dermatol 2002; 138; 182-189

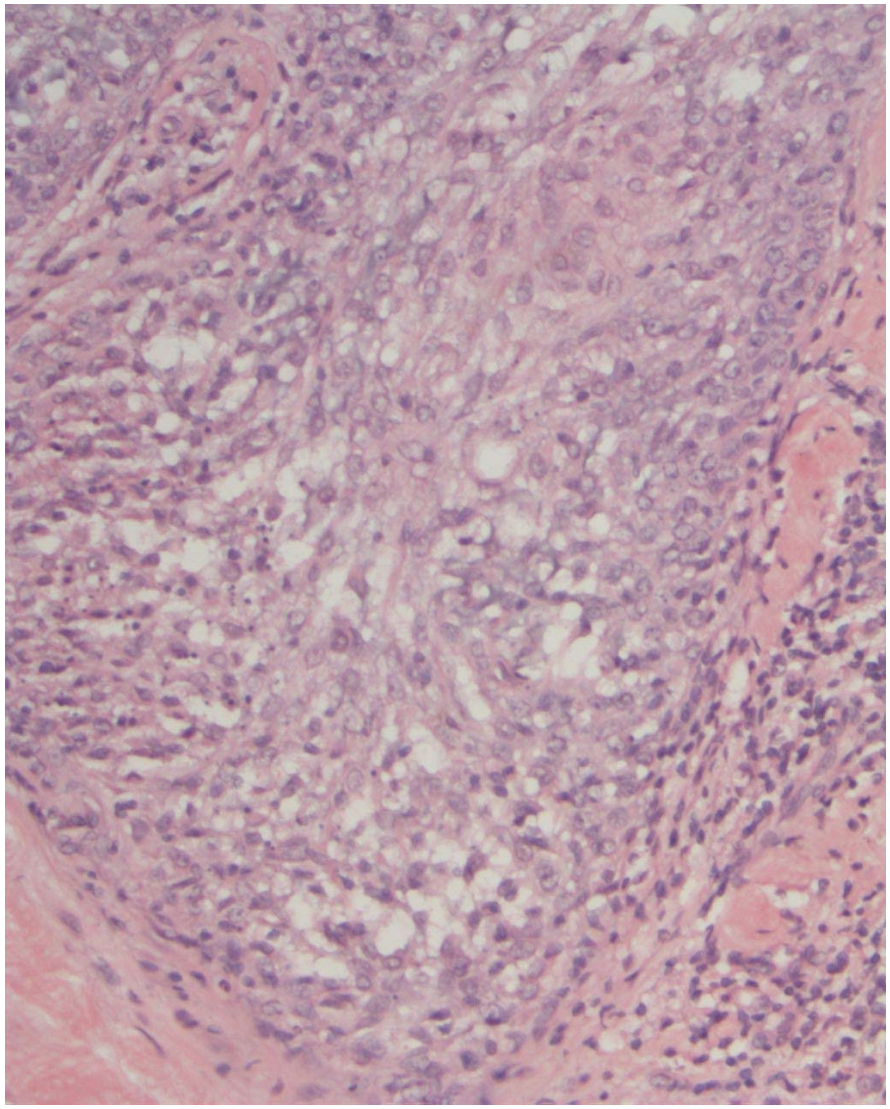
Alopecia mucinosa: MF?

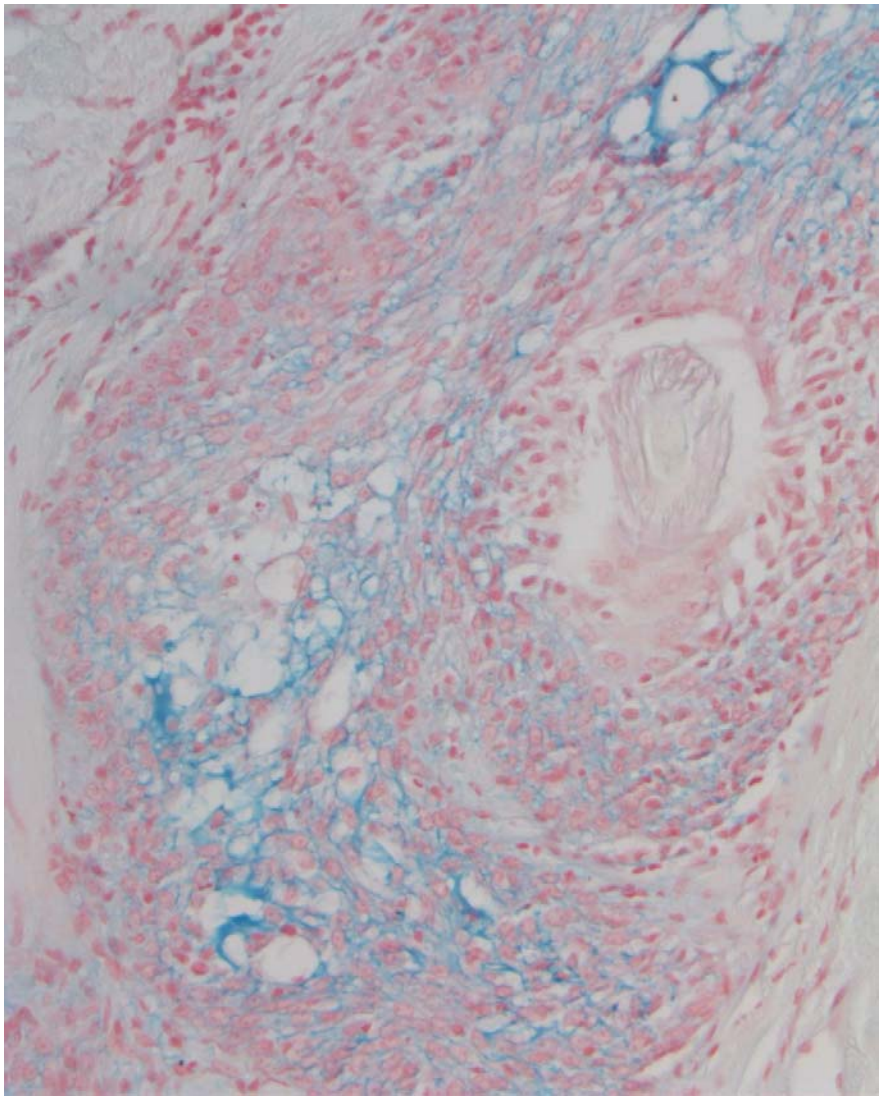


Alopecia mucinosa: MF?

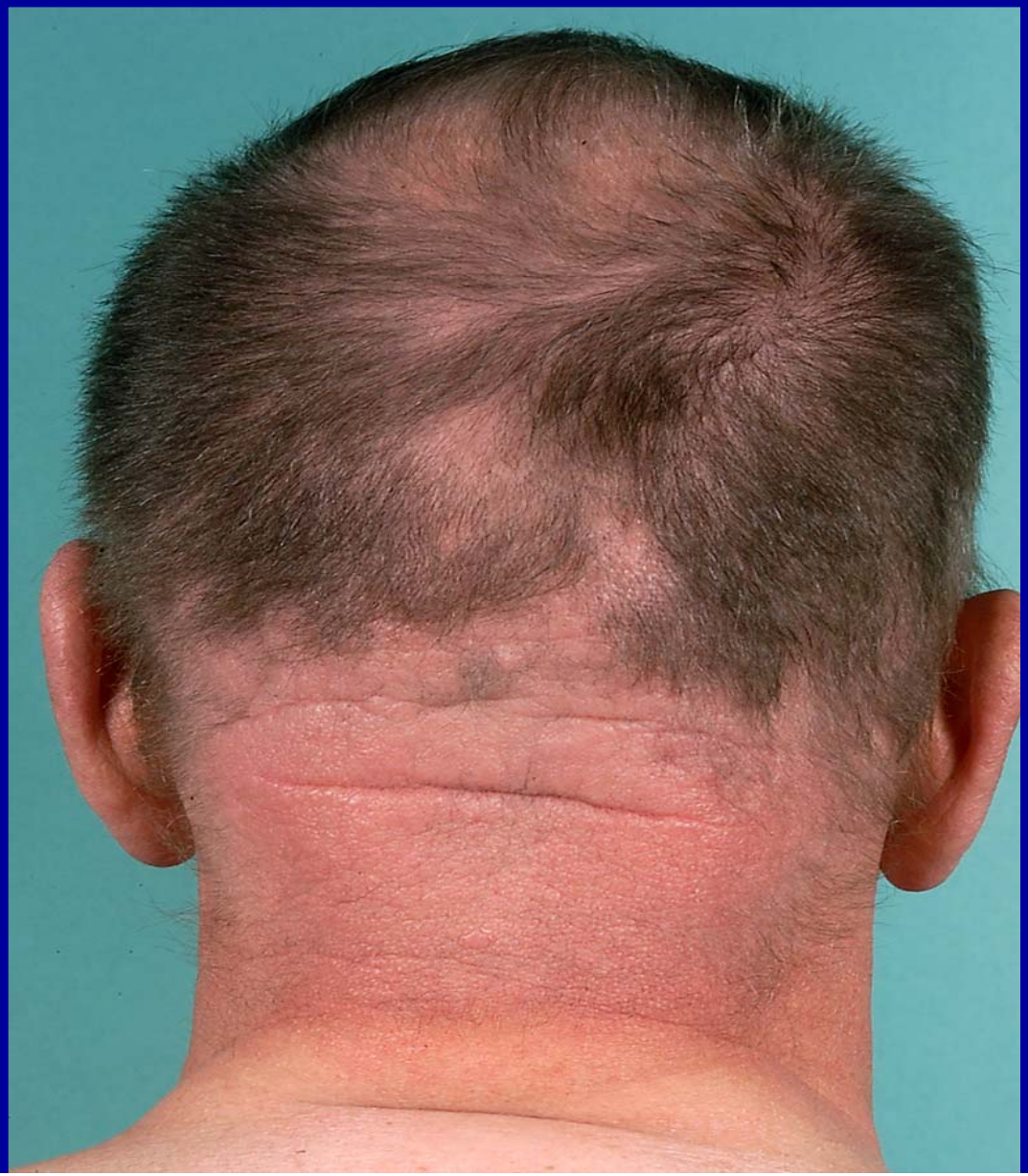


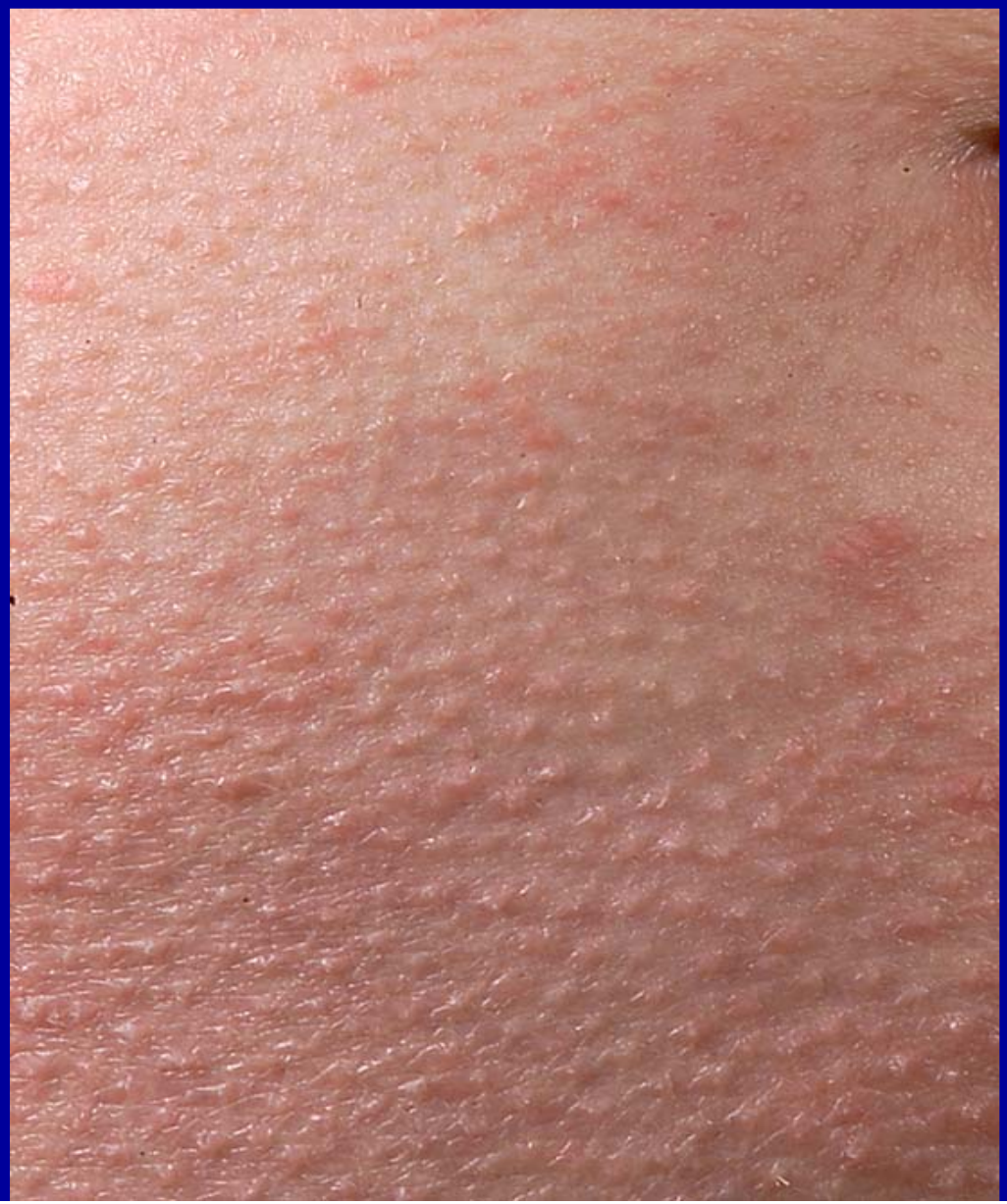
Alopecia mucinosa: MF?



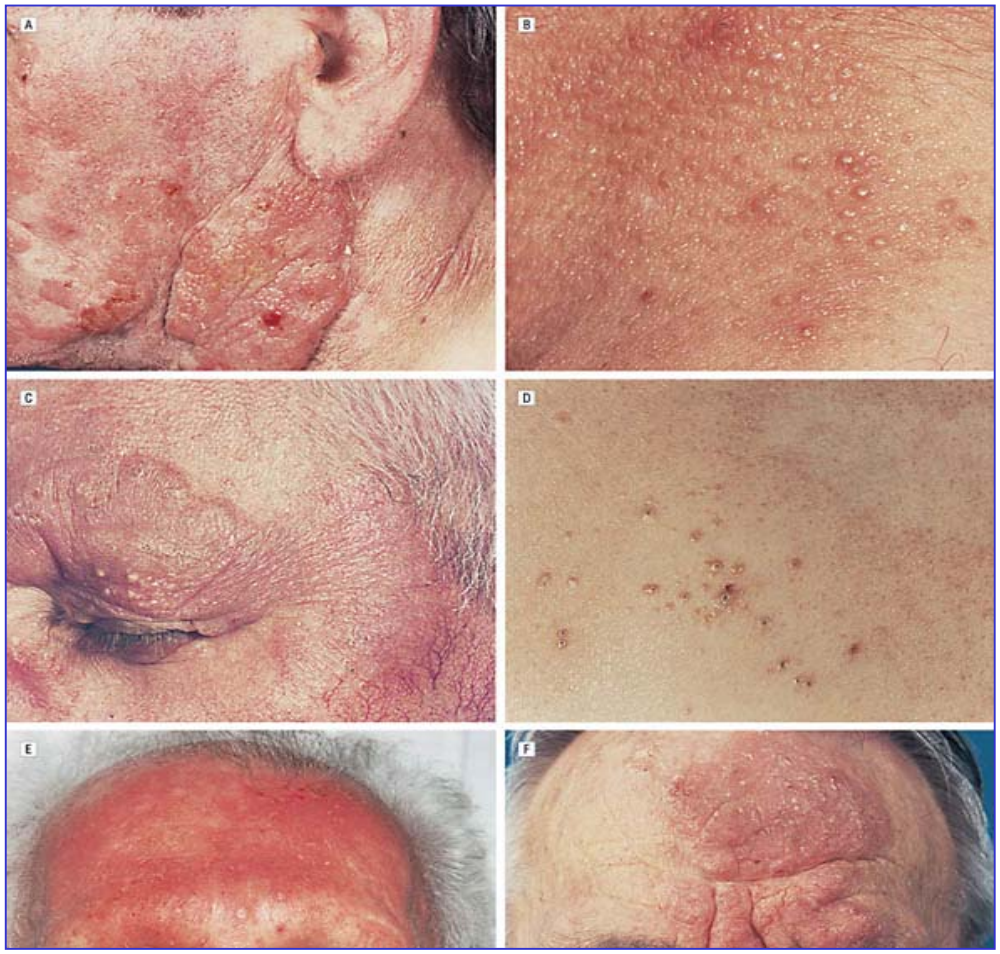


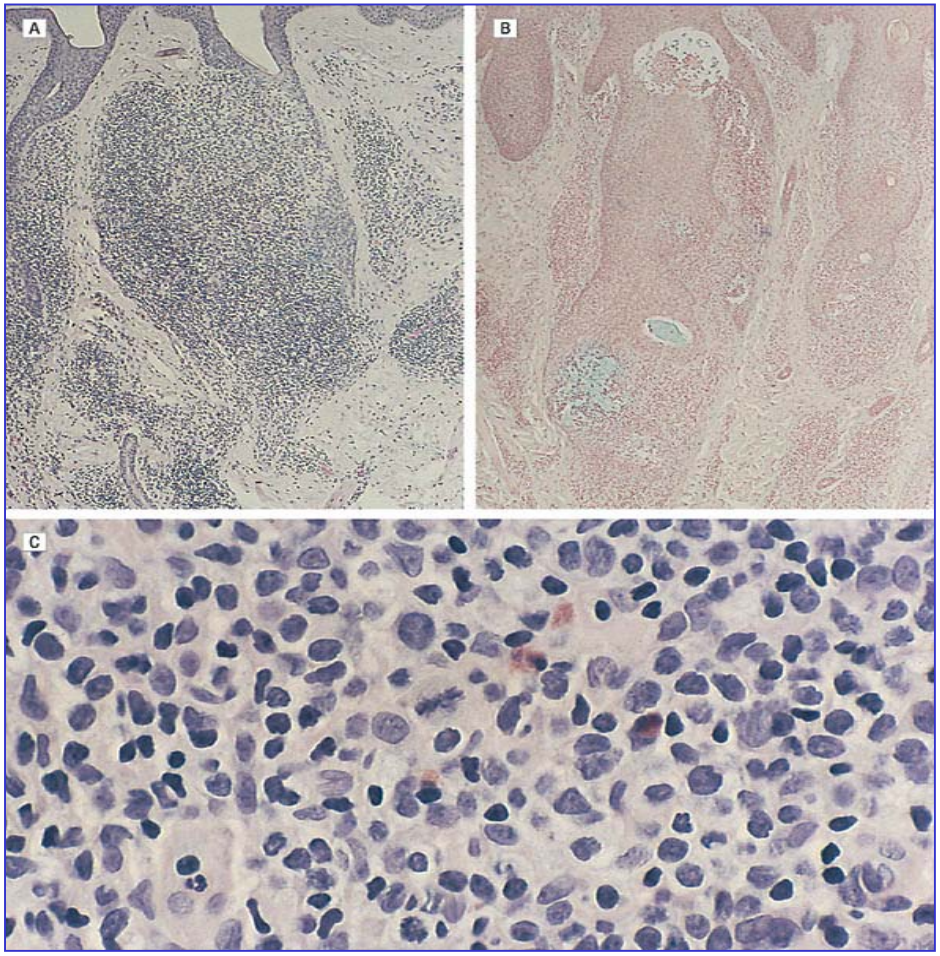
Folliculotropic Mycosis Fungoides





Folliculotropic MF





Van Doorn R. et al. Arch Dermatol 2002; 138; 191-198

Alopecia mucinosa vs folliculotropic MF

- Differentiation between alopecia mucinosa and early stage FMF may be difficult or even impossible.
- Progression from (so-called) AM to FMF has been reported.
- However, patients wits with localized follicular papules with or without alopecia without atypical (folliculotropic) T-cells should NOT be considered and labelled as a malignant lymphoma.
- Careful follow-up and in case of clinical suspicion additional biopsies are required.

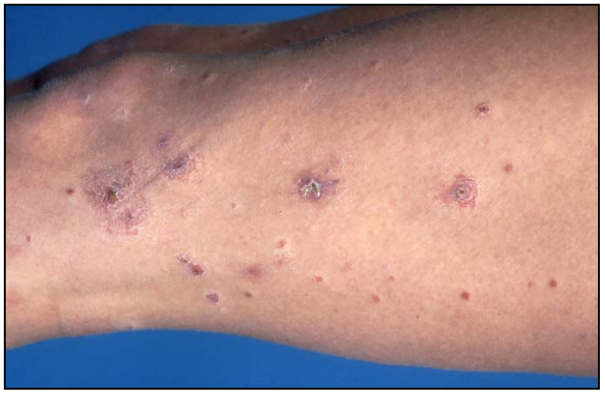
To be discussed

CTCL	Benign
Mycosis fungoides	BID; small/large plaque parapsoriasis
Folliculotropic MF	Alopecia mucinosa
Spectrum CD30+ LPD (C-ALCL; LyP)	Benign cutaneous CD30+ infiltrates
CD4+ S/M pleomorphic CTCL	Pseudo-T cell lymphoma
CBCL	**Benign**
pc marginal zone B-cell lymphoma	Cutaneous lymphoid hyperplasia (pseudo-B-cell lymphoma)
pc follicle center lymphoma	

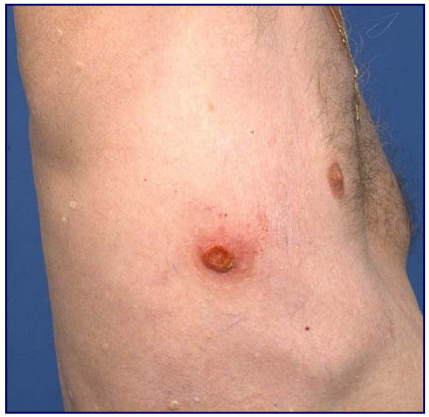
Primary cutaneous CD30+ LPD

Spectrum of primary cutaneous CD30+ LPD:

- **Lymphomatoid papulosis**
- **cutaneous anaplastic large cell lymphoma**
- **[borderline cases]**

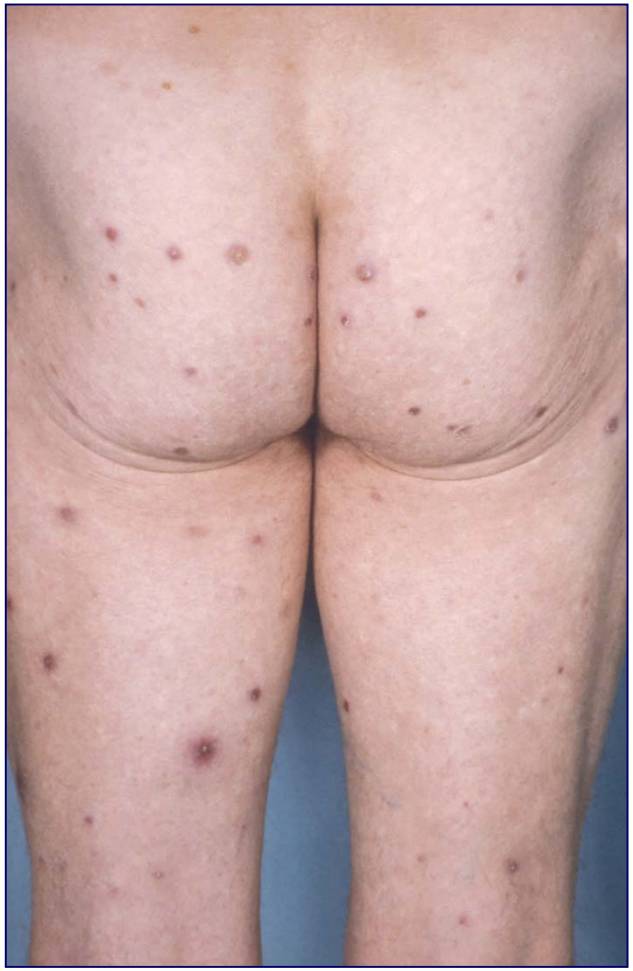


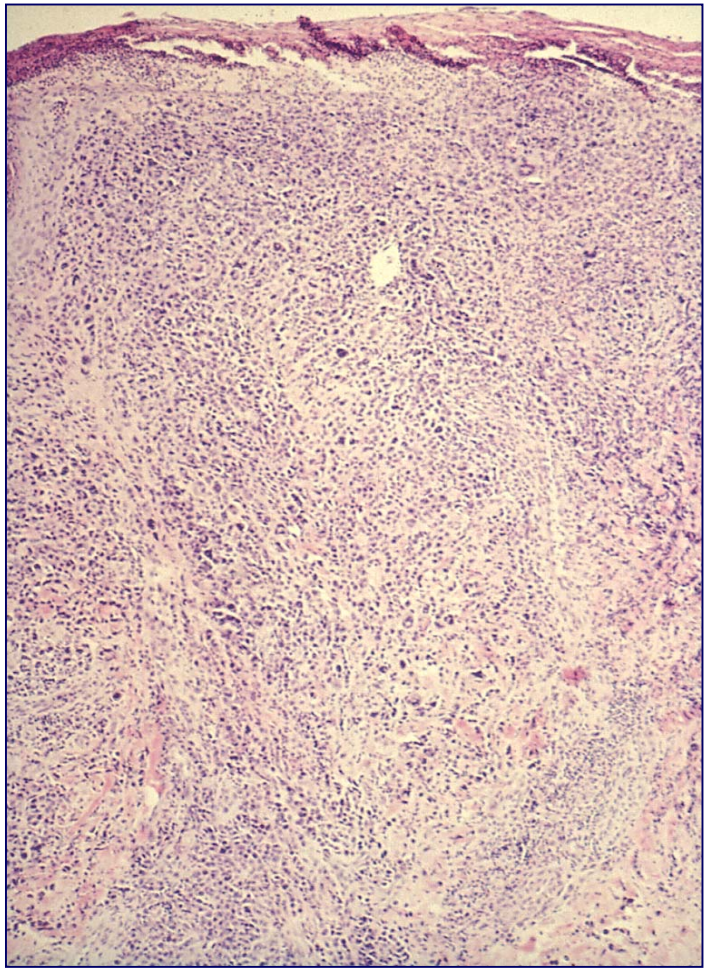
LyP

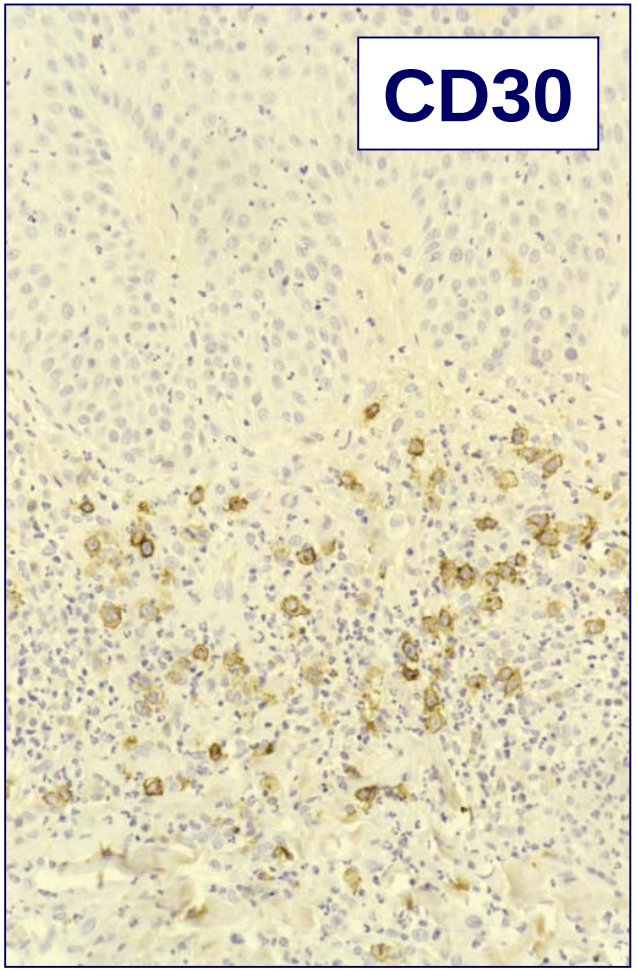


C-ALCL

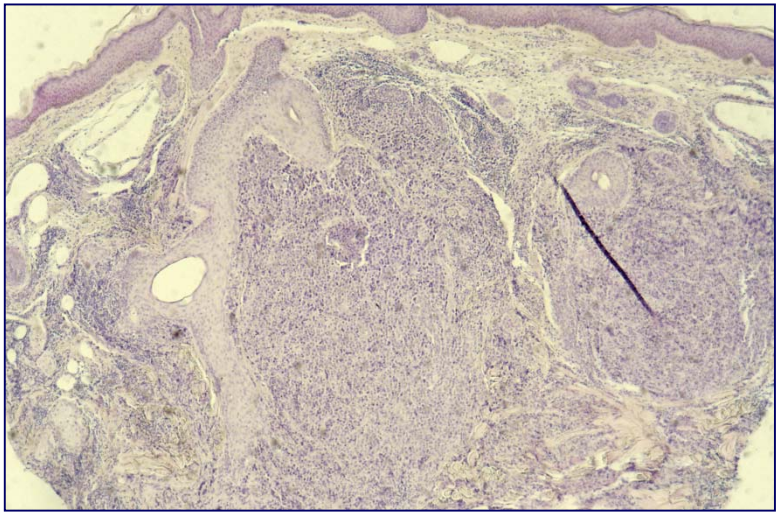
Lymphomatoid papulosis

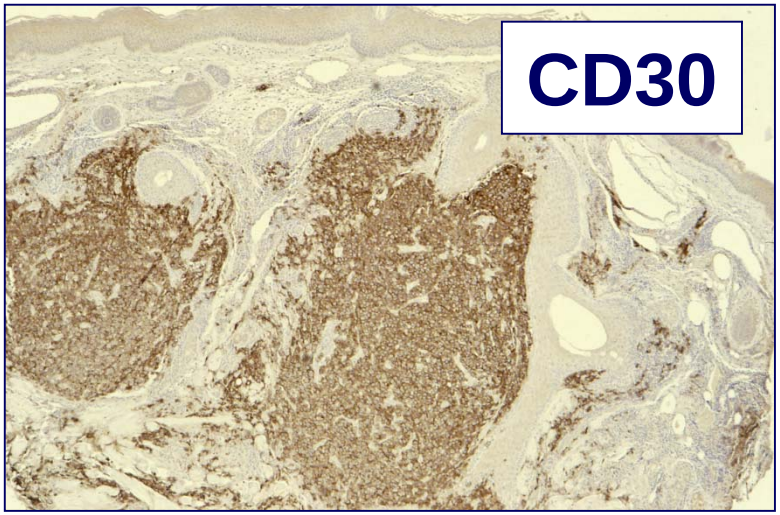


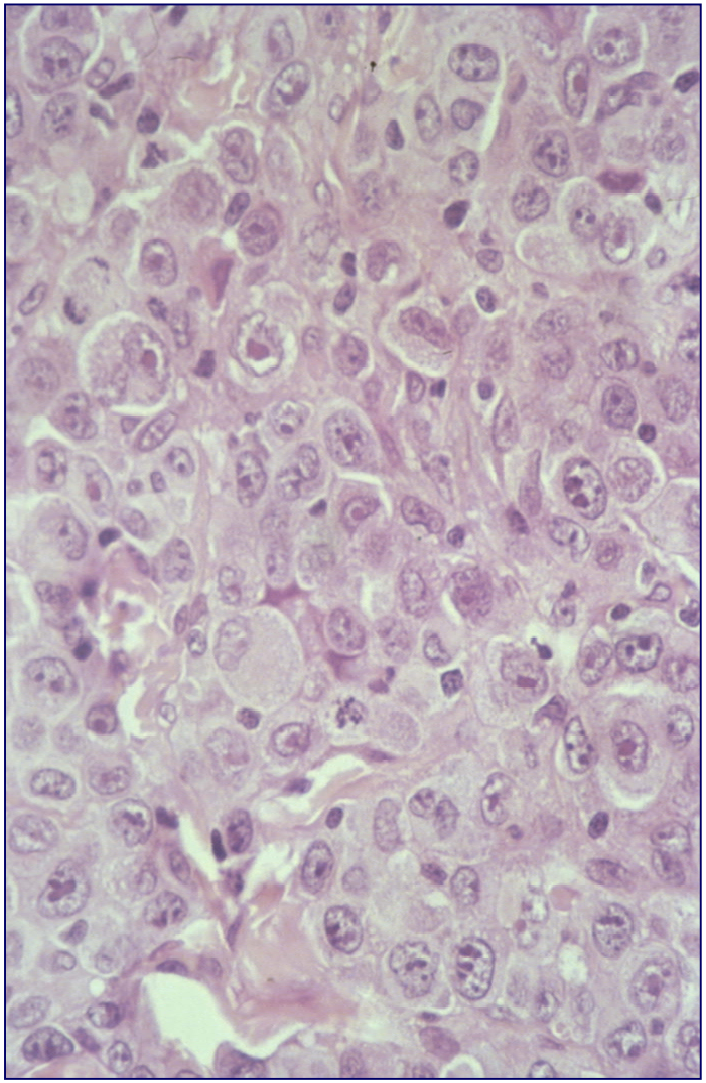


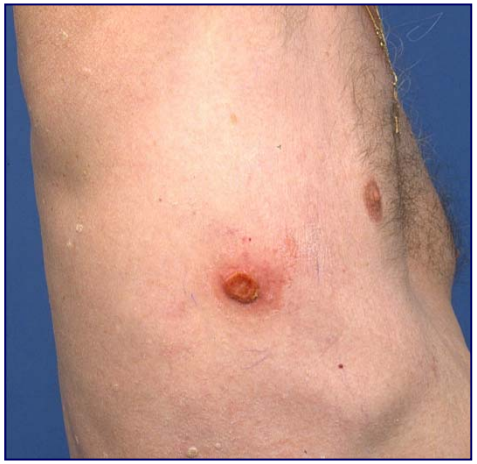


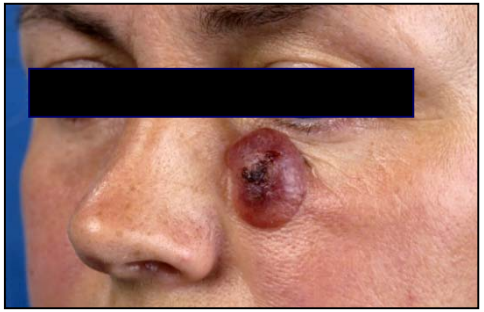
C-ALCL











DD. cutaneous CD30+ LPD

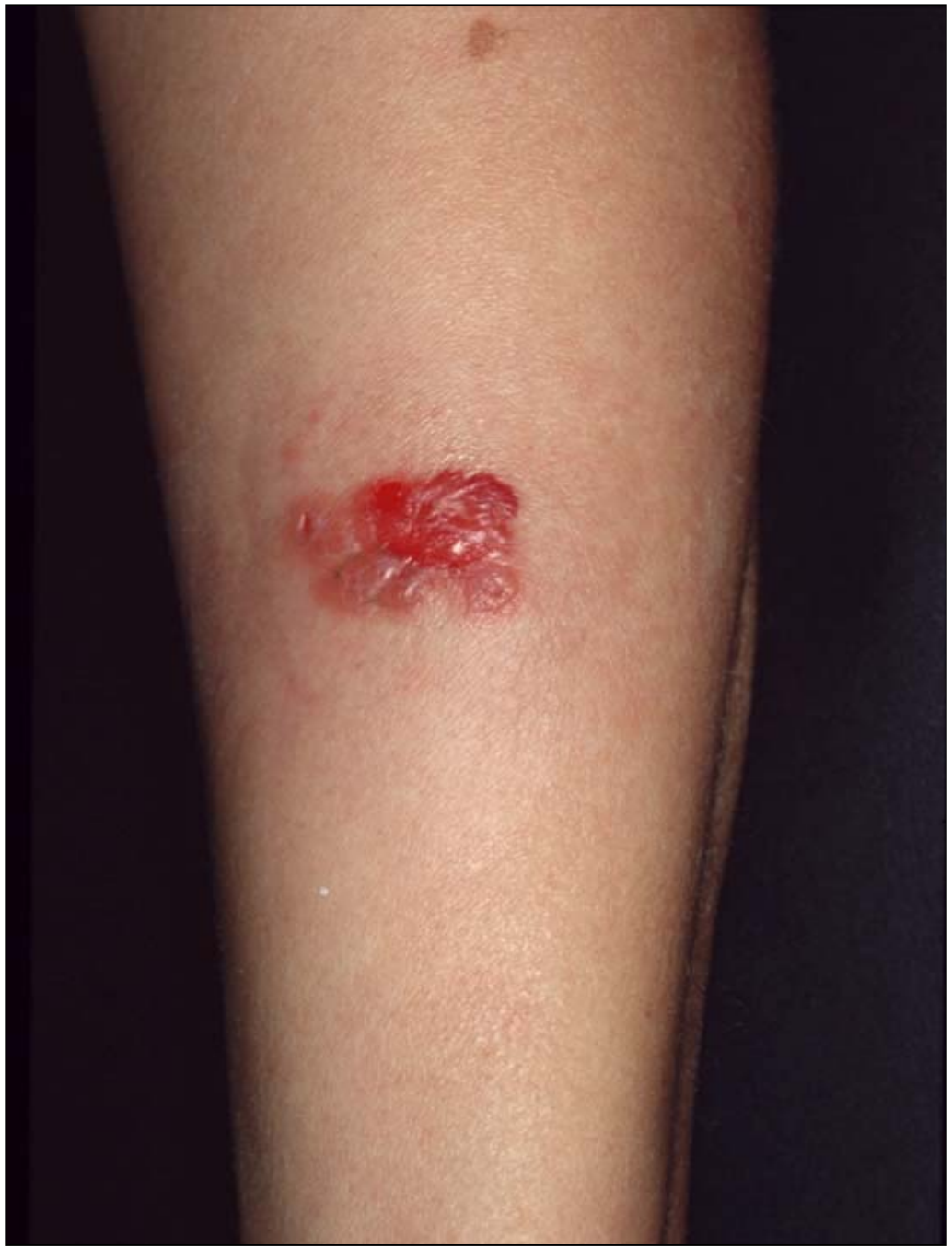
- Skin localizations of systemic ALCL (ALK + or -)
- MF with large cell transformation (CD30+)
- Other types of CTCL or T-NHL expressing CD30 (rare)
- Skin localizations of an EBV+ diffuse large B-cell lymphoma.
- **Reactive skin conditions with CD30 expression**

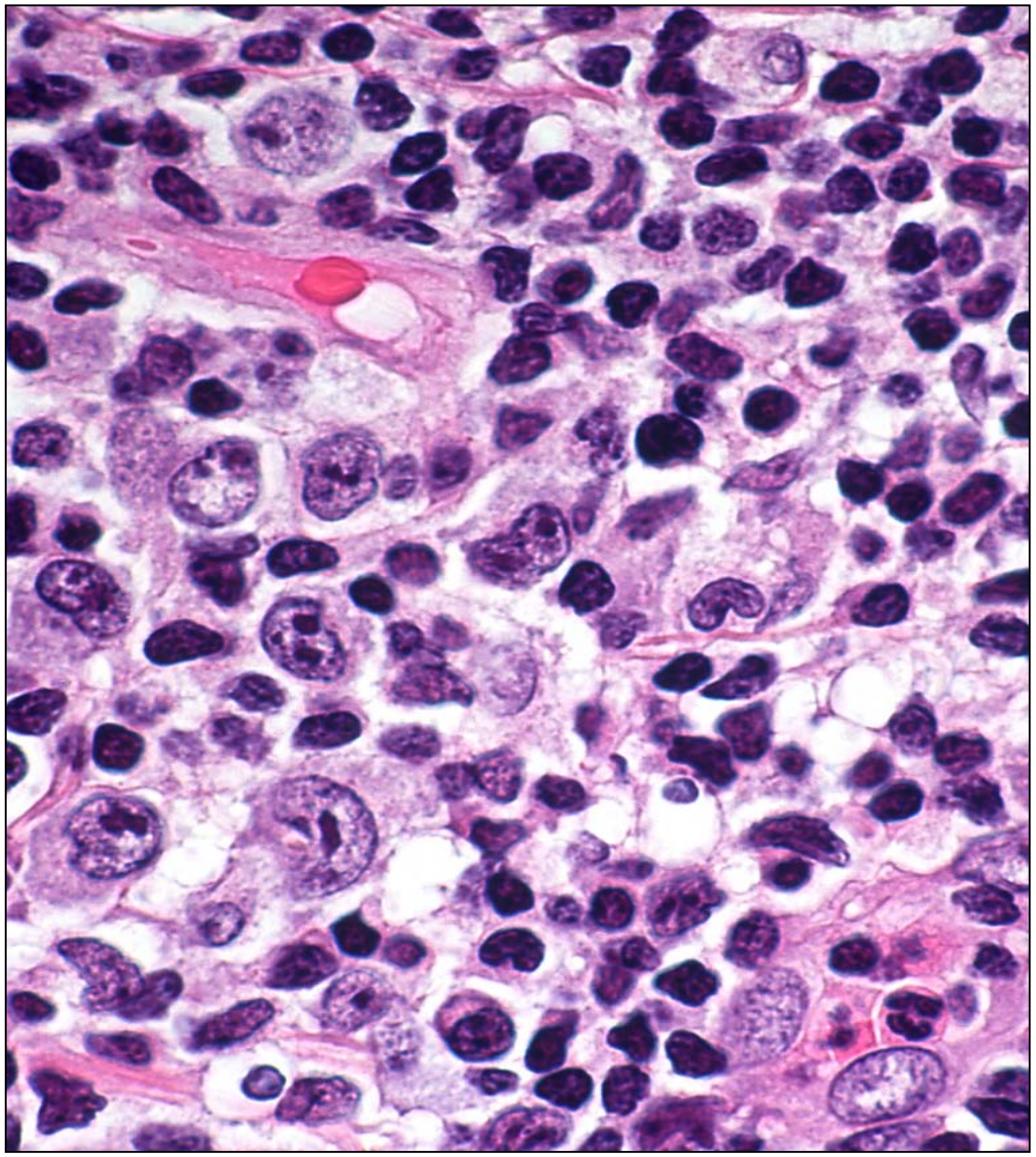
Benign cutaneous CD30+ conditions

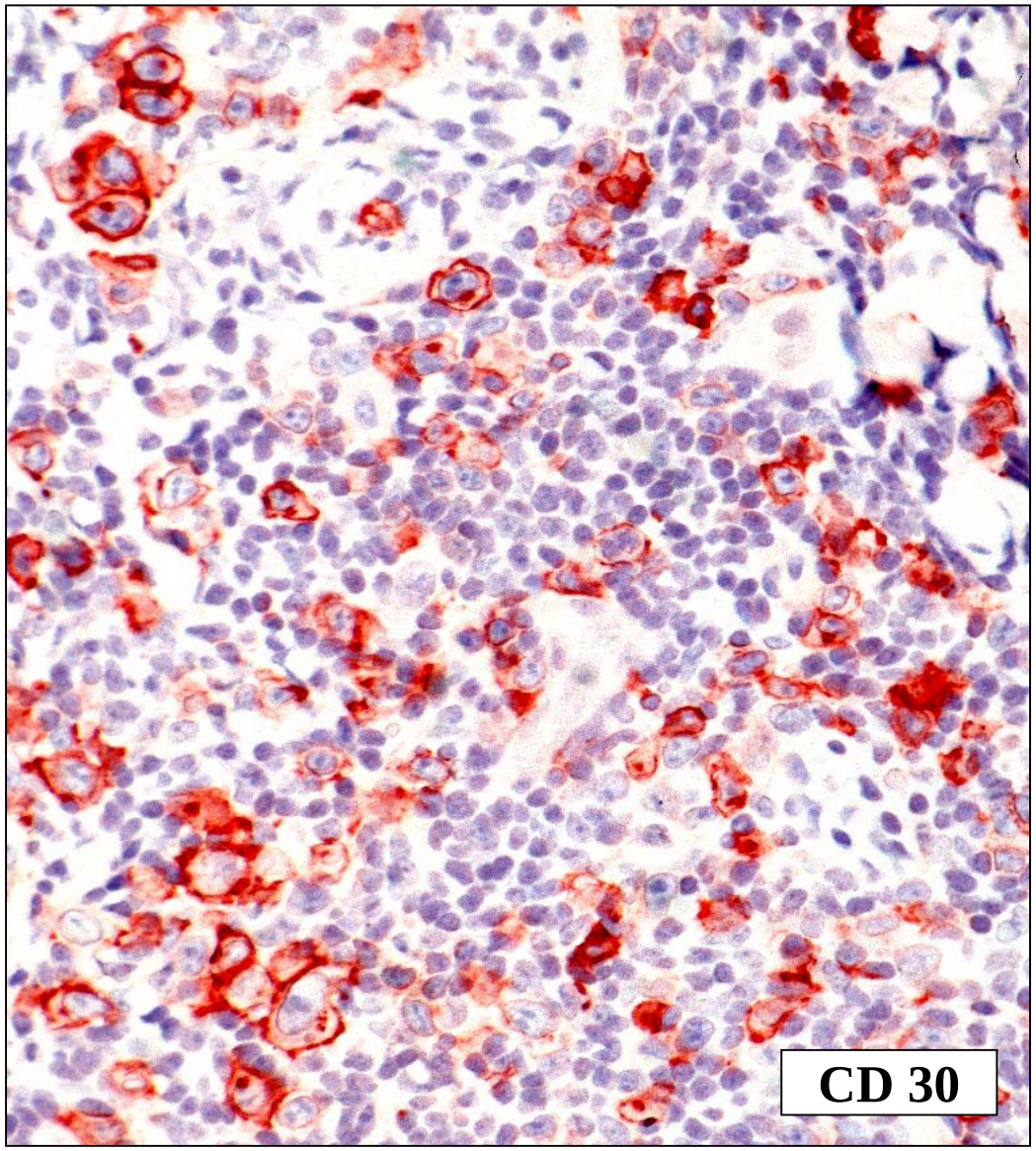
Viral infection:

- molluscum contagiosum
- Orf; milker's nodule
- Herpes virus infection
- HPV
- HIV

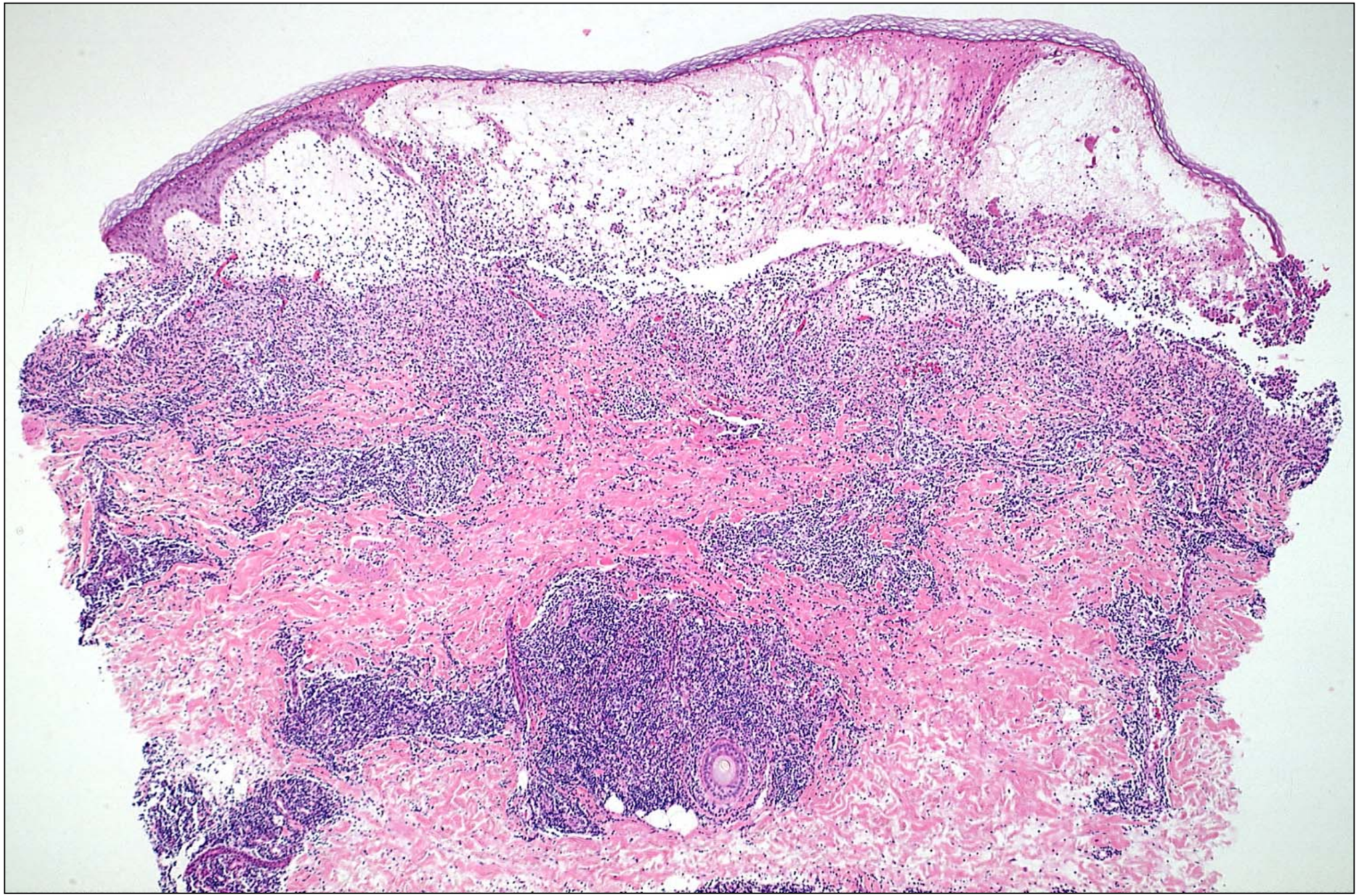
- Parasite infections (scabies)
- Atopic dermatitis
- Insect bites, patch tests, etc.
- Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE).

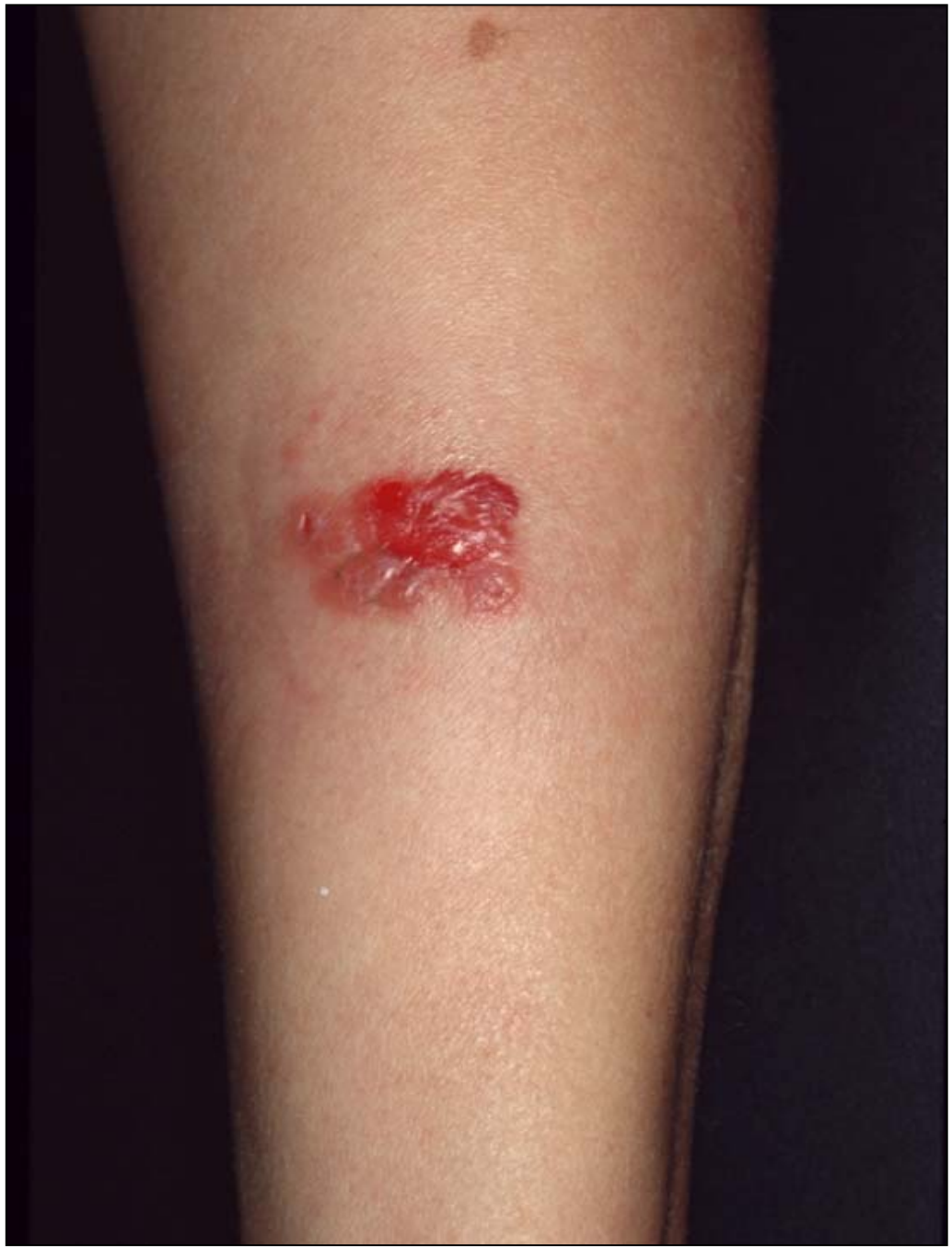






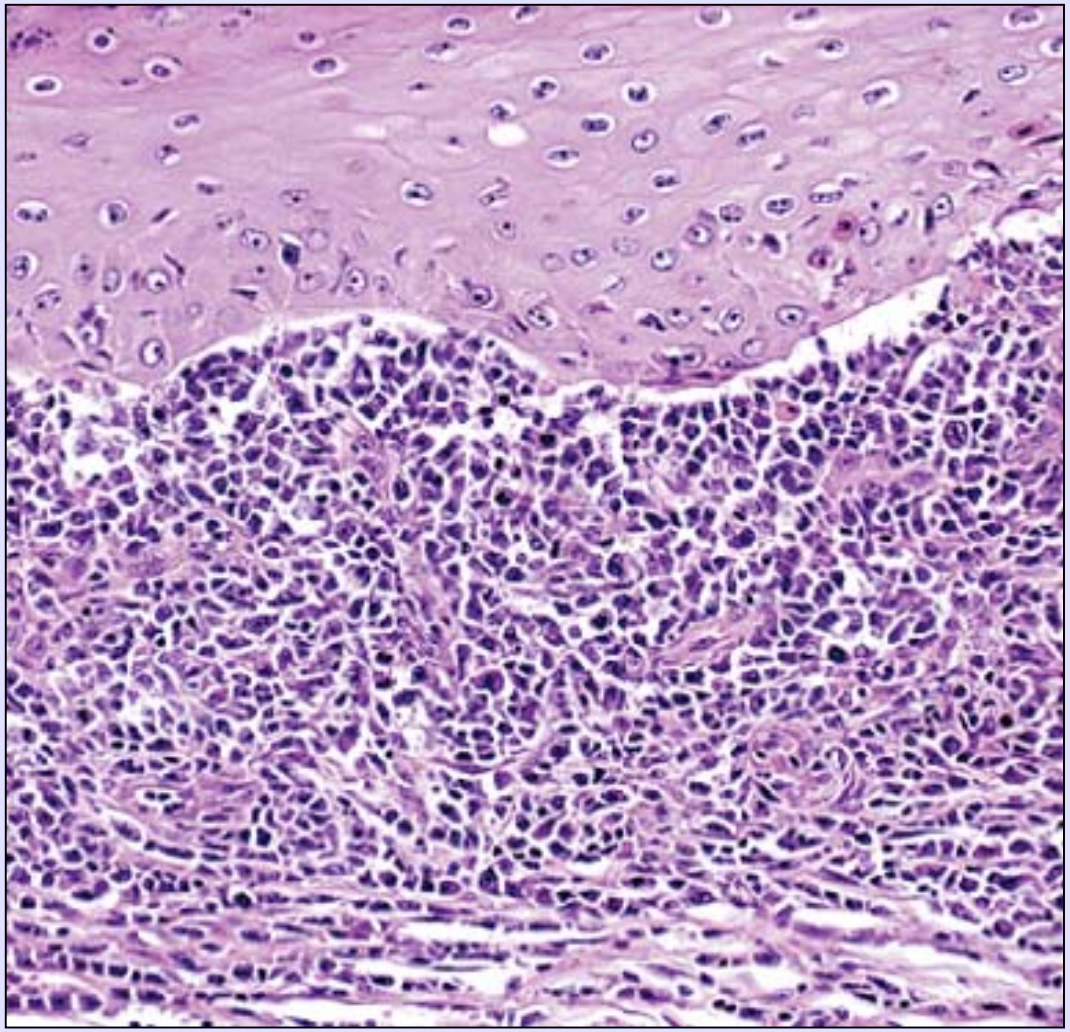
Primary cutaneous CD 30+ LPD?

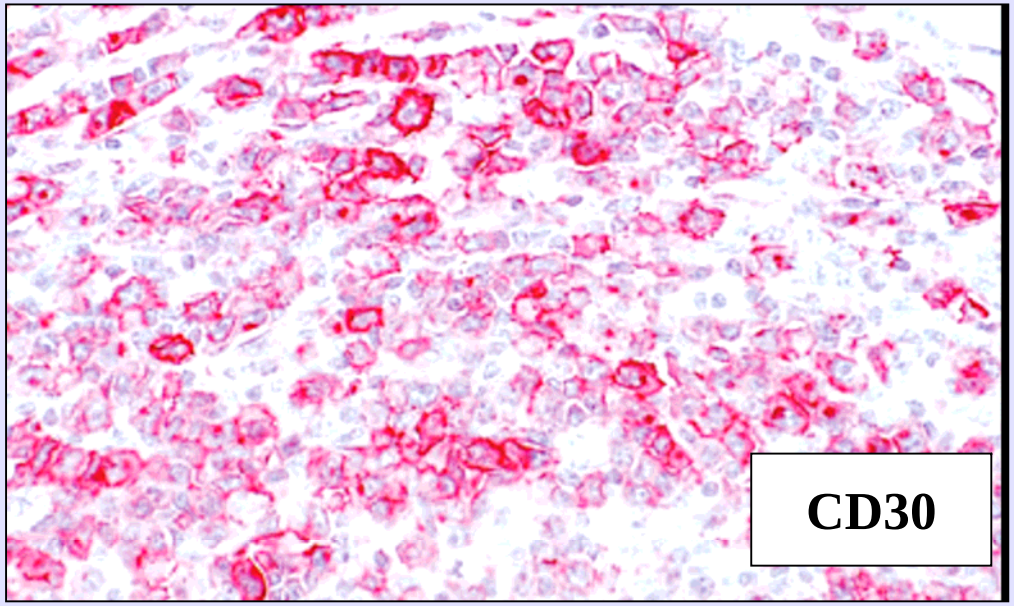




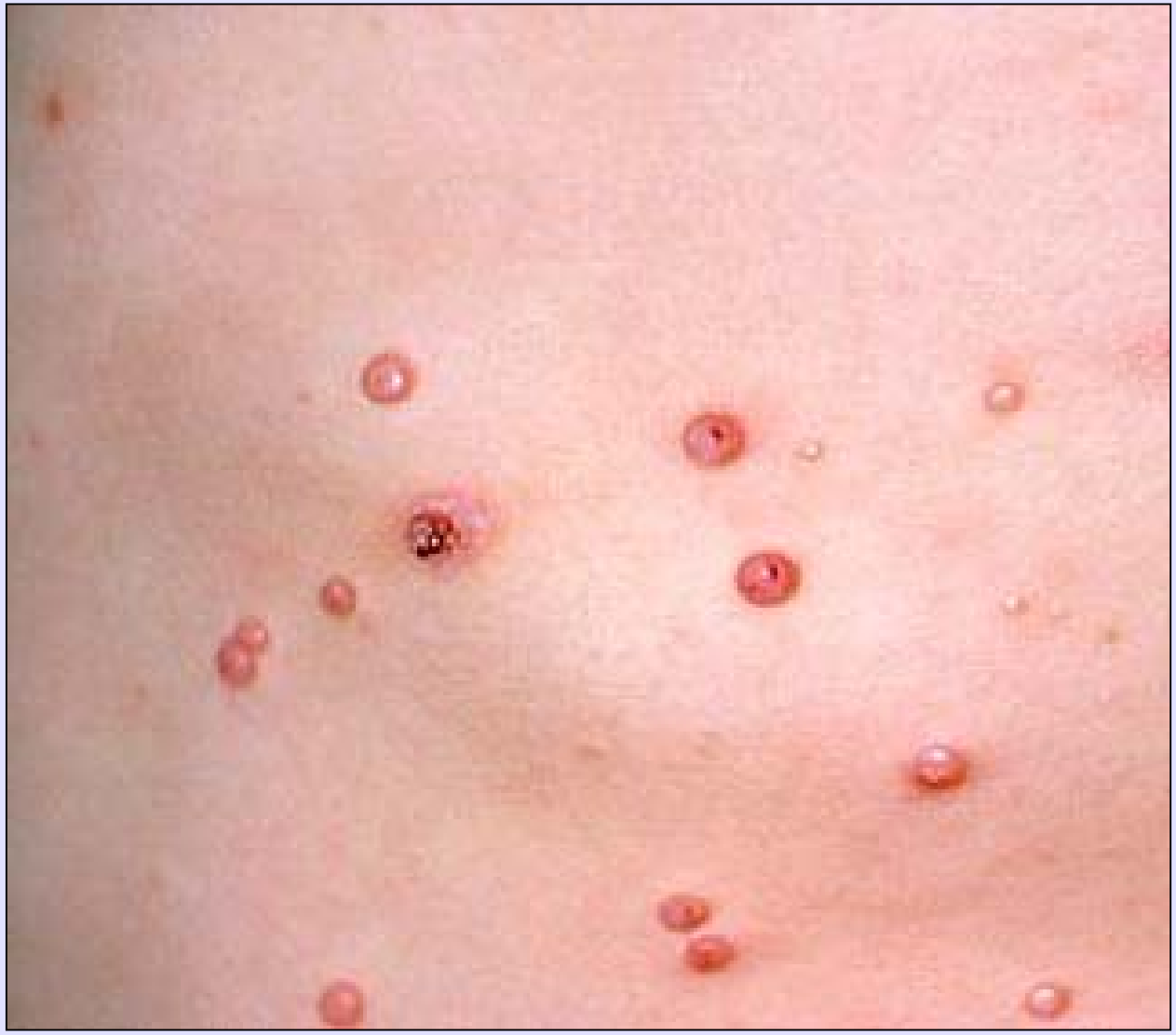
Diagnosis:

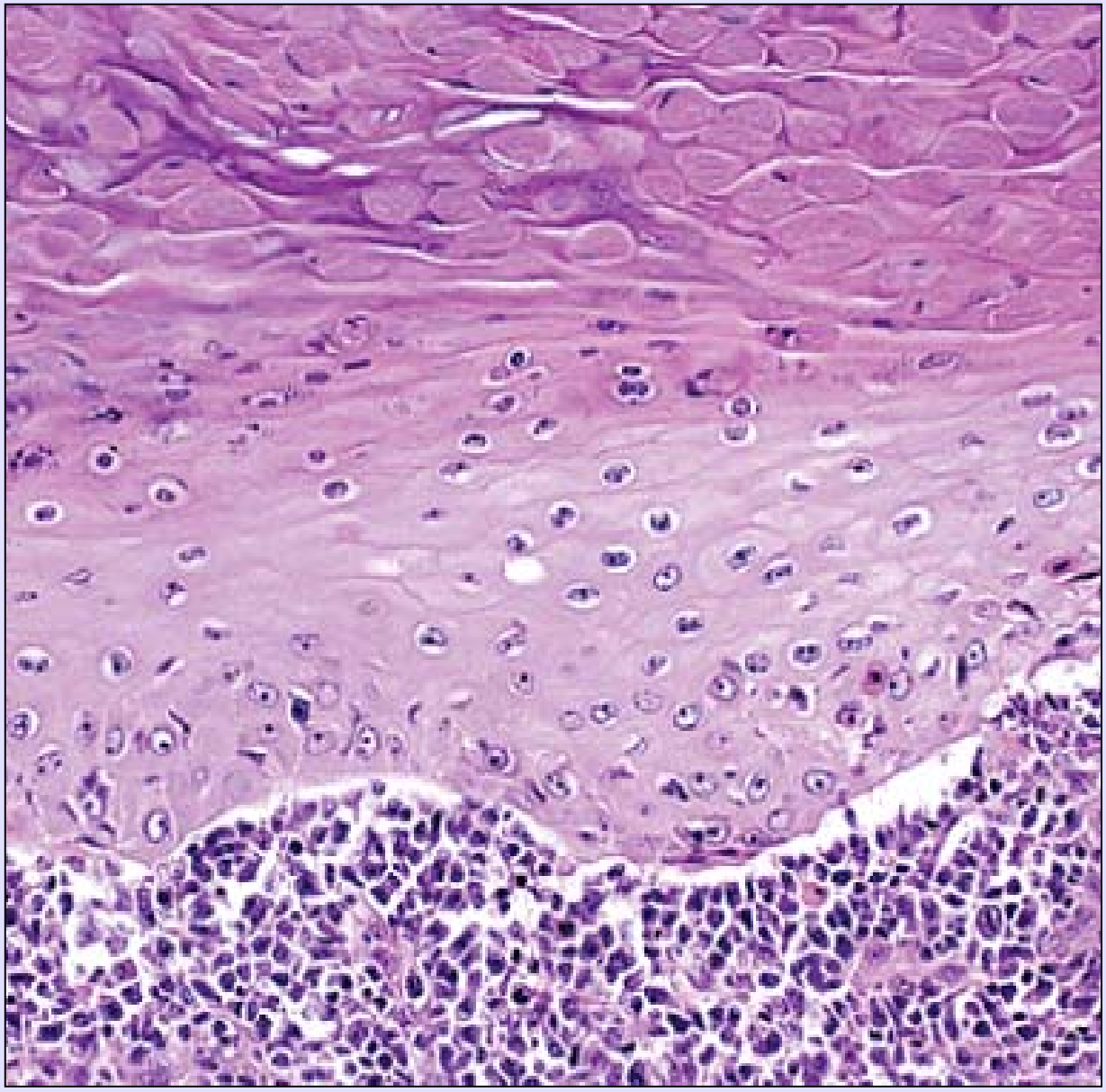
Herpesvirus infection





Primary cutaneous CD30+ LPD ?





Molluscum contagiosum!

Not every cutaneous infiltrate with large CD30+ T-cells belongs to the spectrum of primary cutaneous CD30+ LPD or is a CTCL.

To be discussed

CTCL	Benign
Mycosis fungoides	BID; small/large plaque parapsoriasis
Folliculotropic MF	Alopecia mucinosa
Spectrum CD30+ LPD (C-ALCL; LyP)	Benign cutaneous CD30+ infiltrates
CD4+ S/M pleomorphic CTCL	Pseudo-T cell lymphoma
CBCL	**Benign**
pc marginal zone B-cell lymphoma	Cutaneous lymphoid hyperplasia (pseudo-B-cell lymphoma)
pc follicle center lymphoma	

WHO-EORTC: PCSM-TCL (provisional)

- Originally defined as a subgroup of CD30- CTCL, non-MF/SS (nowadays PTCL, NOS) with <30% large neoplastic T-cells and a favorable prognosis.
- Clonal proliferation of small/medium-sized CD4+ pleomorphic T-cells; no signs or history of MF or SS.
- In most cases a solitary plaque or tumor.
- Nodular to diffuse dermal infiltrates.
- Phenotype: CD3+, CD4+, CD8-, CD30-, TIA-1-

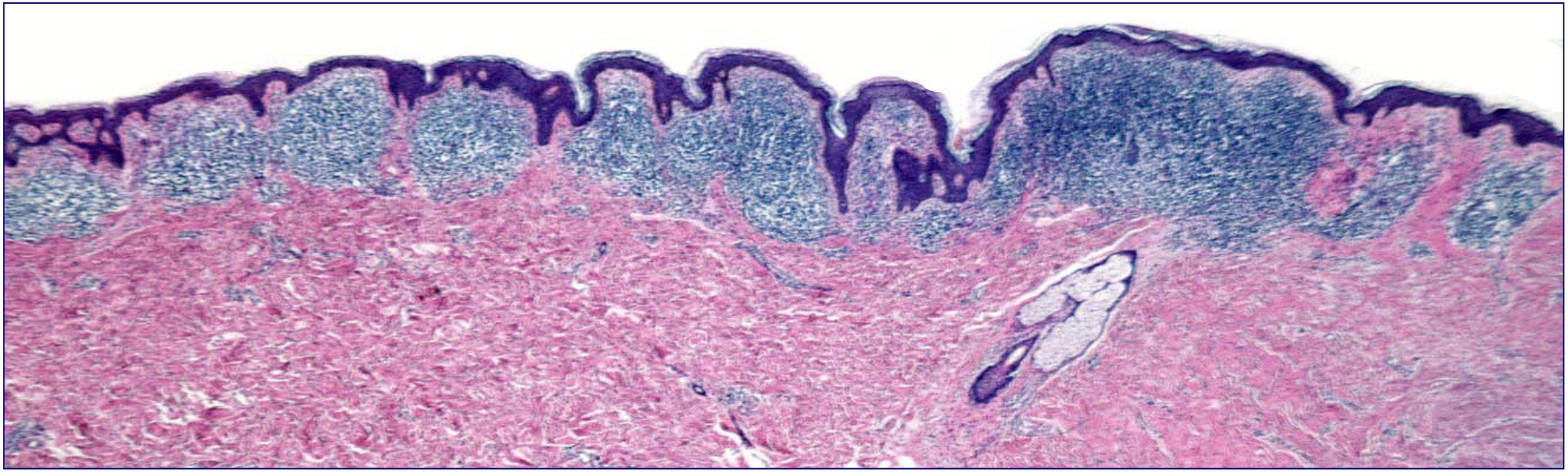
CTCL or pseudo-T cell lymphoma ?

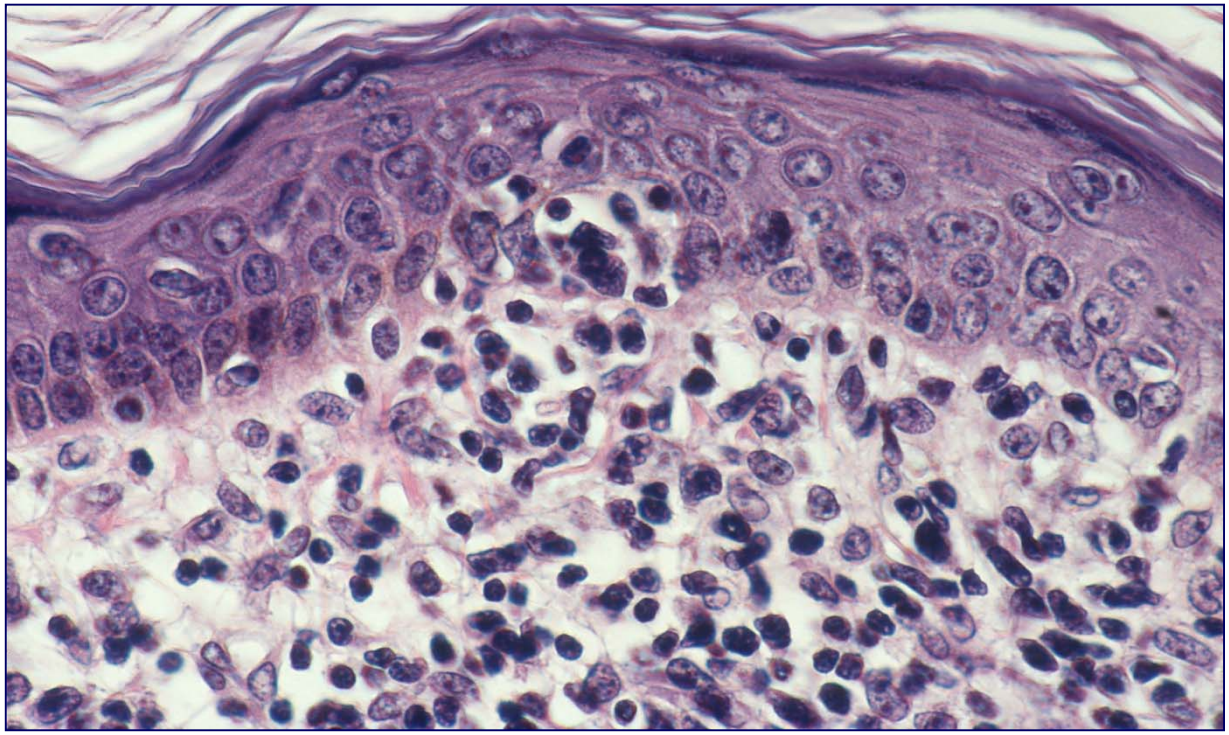
Lymphomatoid reactions (pseudo-T cell lymphoma)

- Histologic features suggestive of CTCL.
- Clinical features not consistent with CTCL.

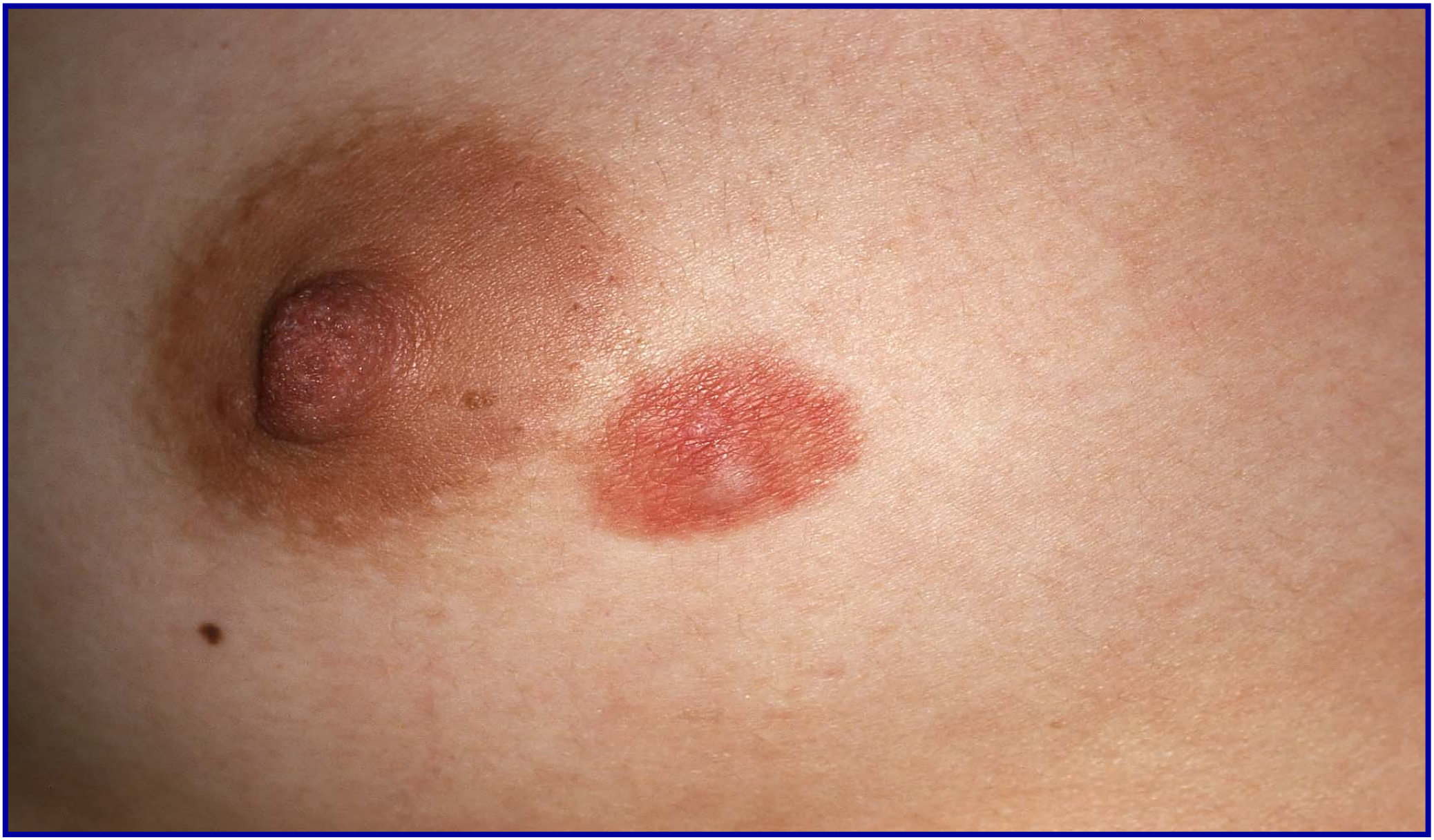
- Band-like pattern: resembles MF
- Nodular pattern: resembles PCTL, unspecified

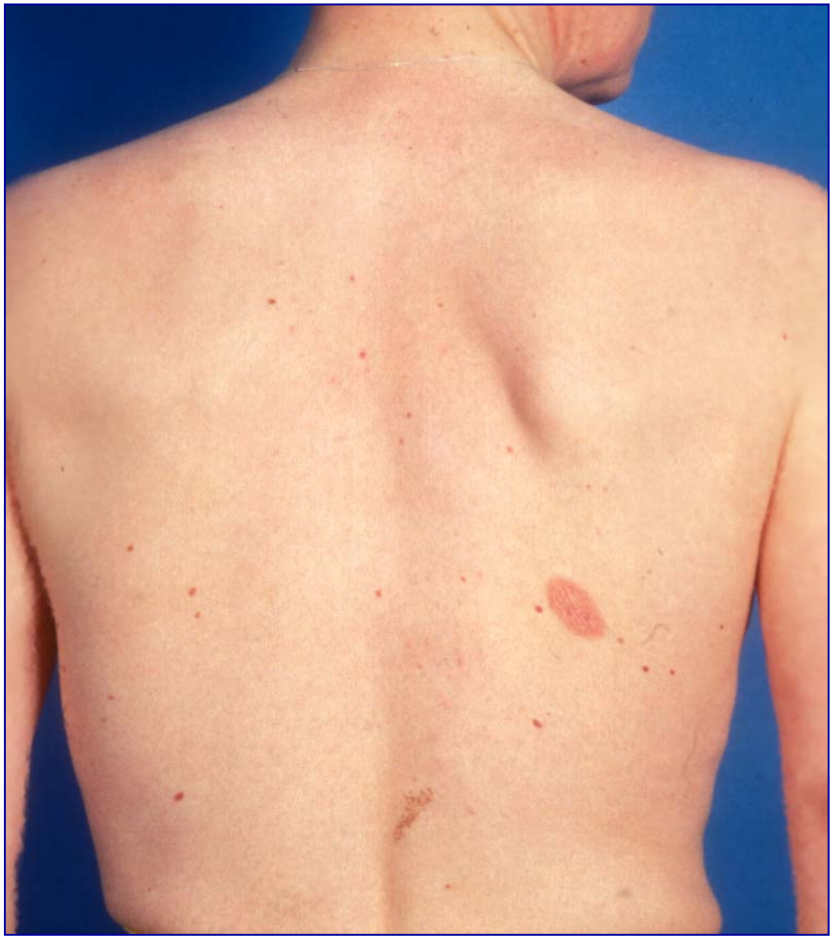
- Actinic reticuloid (CD8+ !!)
- Lymphomatoid drug reactions
- Lymphomatoid contact dermatitis
- Idiopathic pseudo-Tcell lymphoma

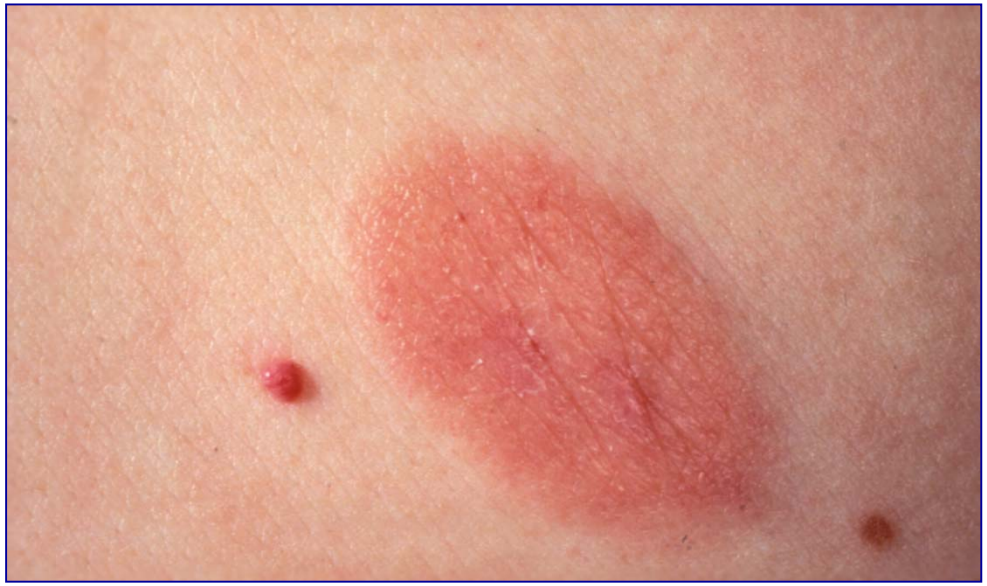




- Atypical T-cells →
- Sharply demarcated
- No of focal epidermotropism
- Considerbale admixture with
  - reactive CD8+ T-cells
  - CD20+ B-cells
  - CD68+ histiocytes
- Proliferation rate low (<10%)

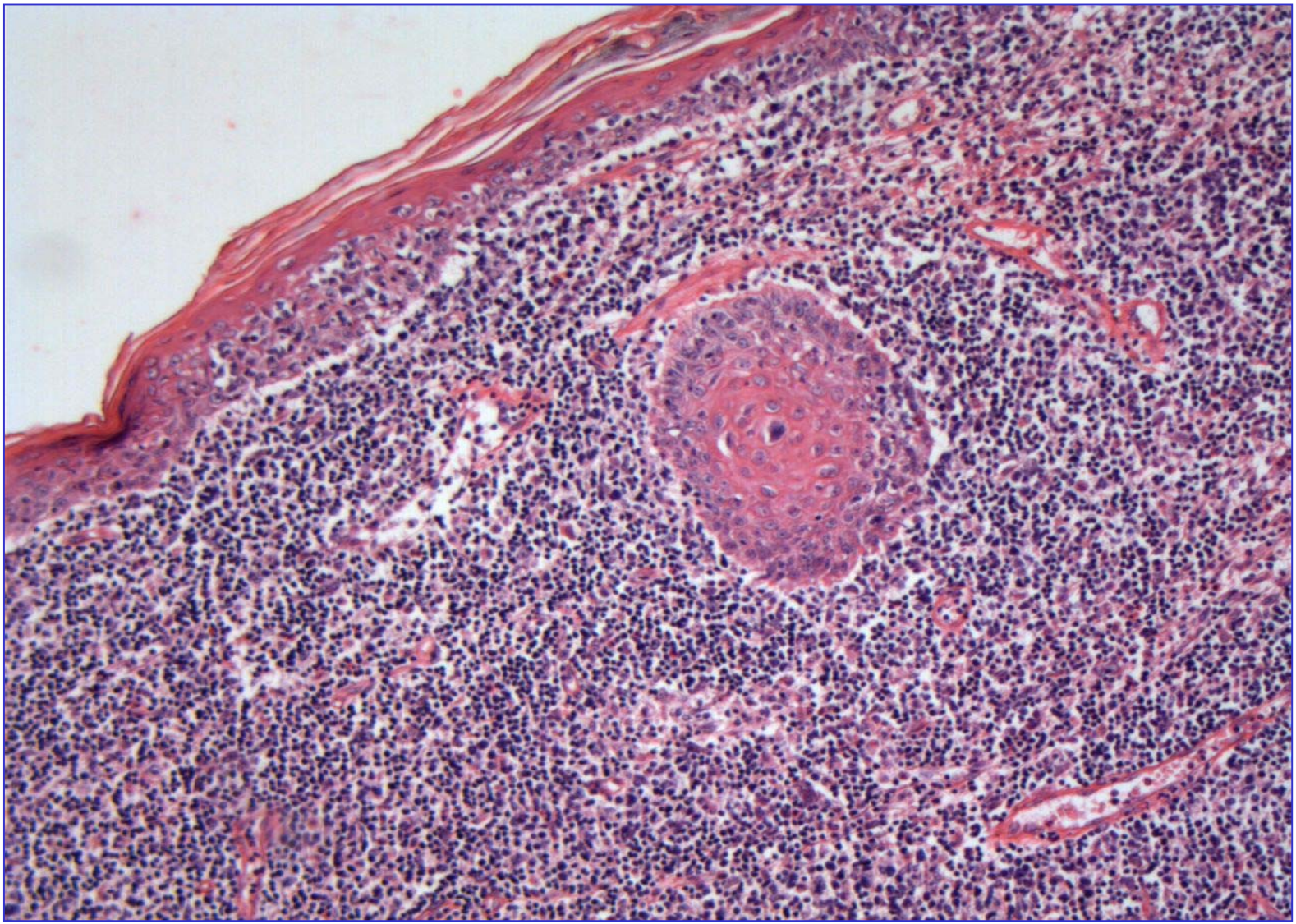




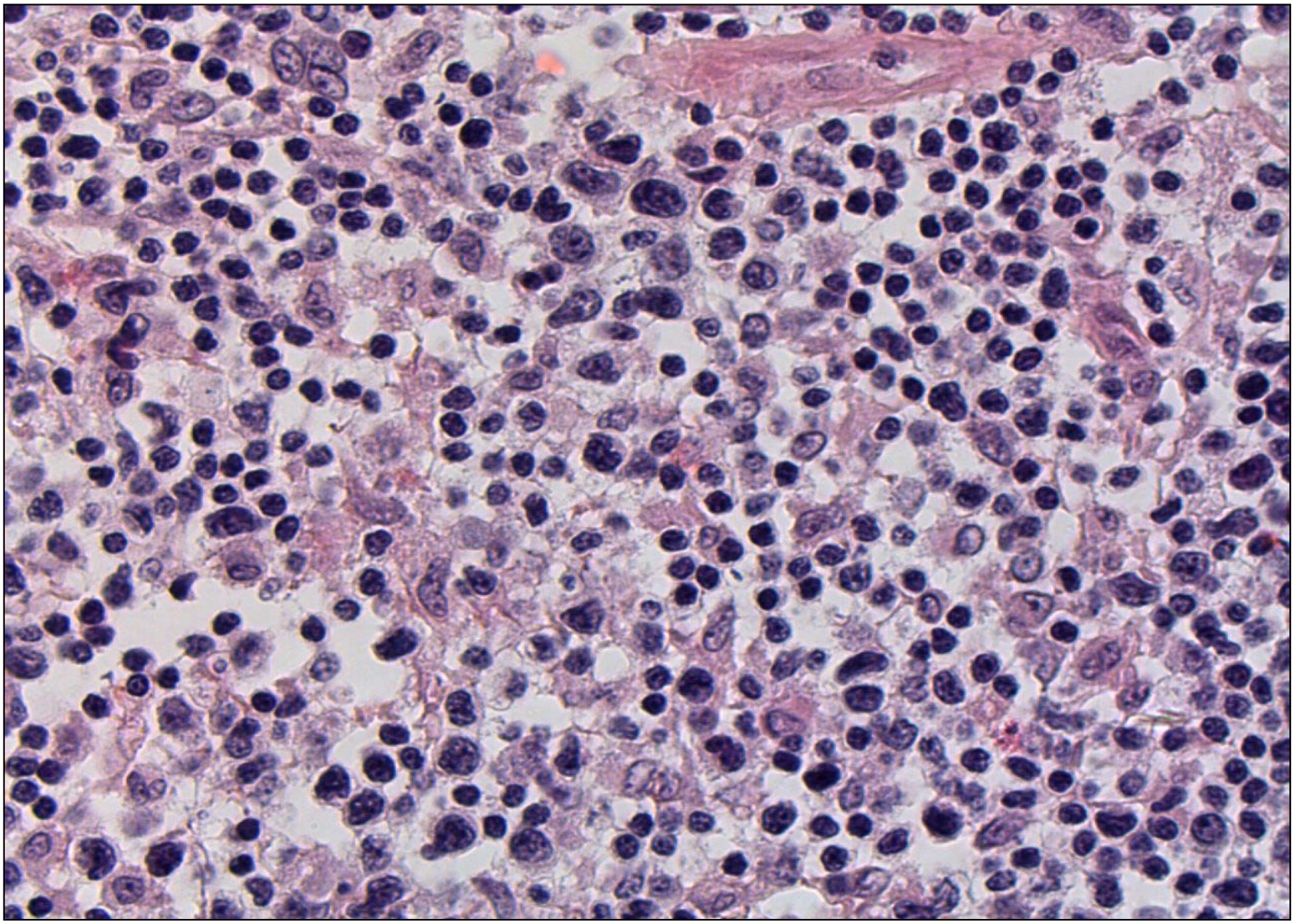


Lymphomatoid drug eruption
(pseudo-T-cell lymphoma)
due to anti-epileptics

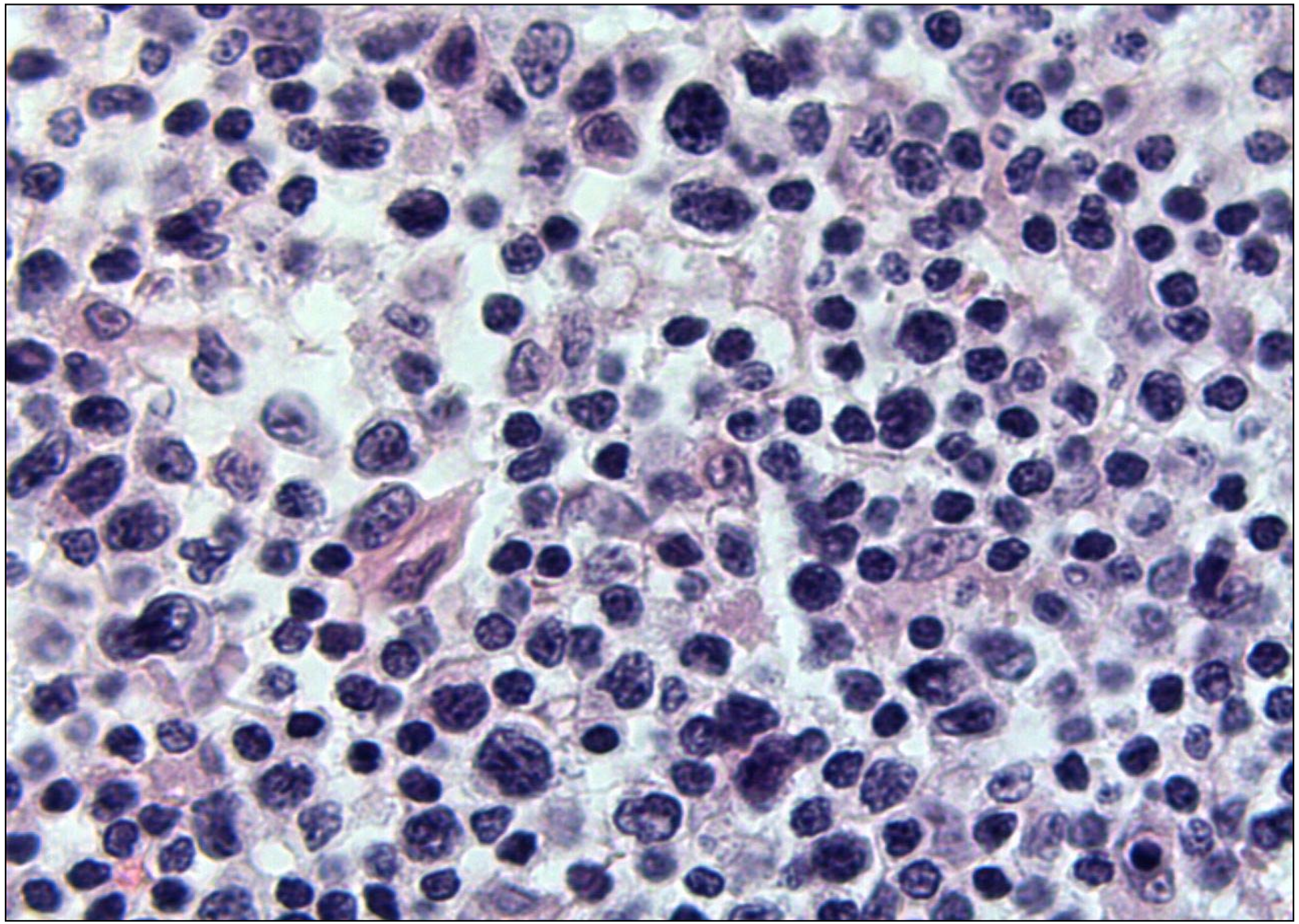
Patient 41 (PA: T94-13581)



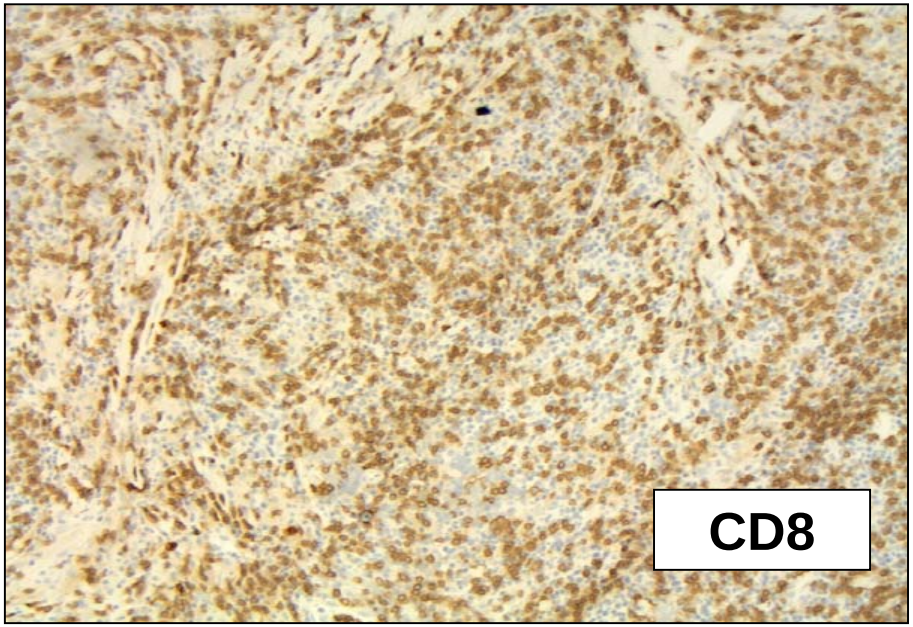
Patient 41 (PA: T94-13581)

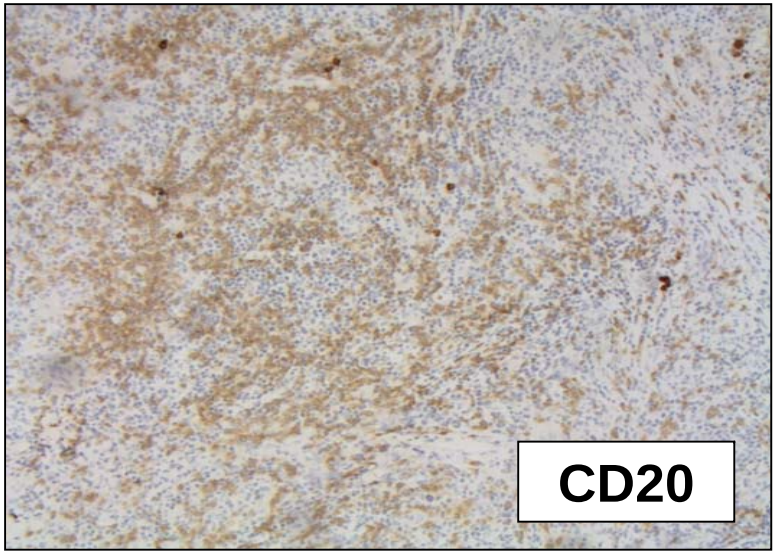


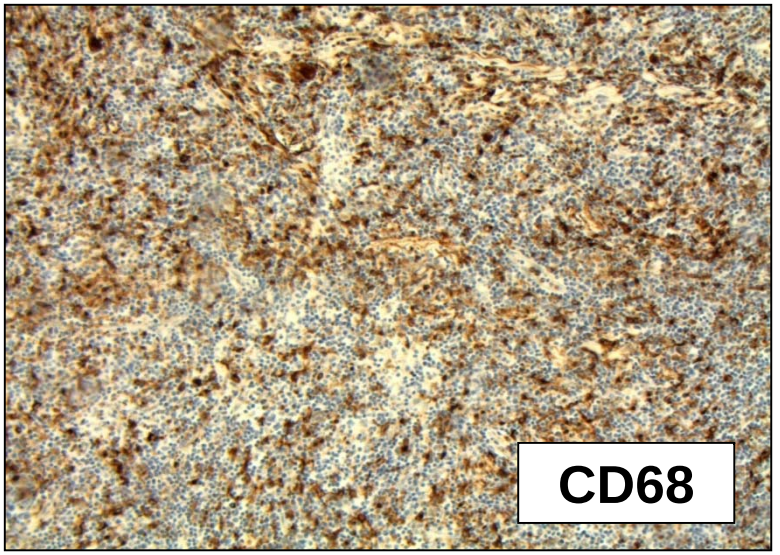
Patient 41 (PA: T94-13581)



Patient 41 (PA: T94-13581)







Histology highly suggestive of CTCL, but:

- Scattered blast cells (CD4+); predominantly small cells; no intermediate forms.
- No marker loss by atypical T-cells (CD2+, CD3+, CD4+, CD5+)
- Considerable admixture with CD8+ T-cells, CD20+ B-cells and CD68+ histiocyte.
- No clonal TCRß gene rearrangement.
- Clinical presentation suggestive of pseudo-T-cell lymphoma
  (Bakels V. et al; Am J Pathol 1997;150:1941-1949).

Diagnosis 1994: pseudo-T-cell lymphoma (nodular type)

Diagnosis 2005: CD4+ small/medium pleomorphic T-cell lymphoma

Summary CD4+ s/m pleomorphic CTCL

- Most cases show clinicopathologic features of the nodular pseudo-T-cell lymphomas from the past:
- Demonstration of clonality in such cases has been instrumental to consider these cases now as CD4+ pleomorphic s/m CTCL.
- Because of overlap: cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance.
- Recognition of these cases is important → no aggressive therapy
- CD4+ S/M pleomorphic CTCL that do not meet above criteria are rare.

Beltraminelli H. et al; Am J Dermatopathol 2009;31:317-322

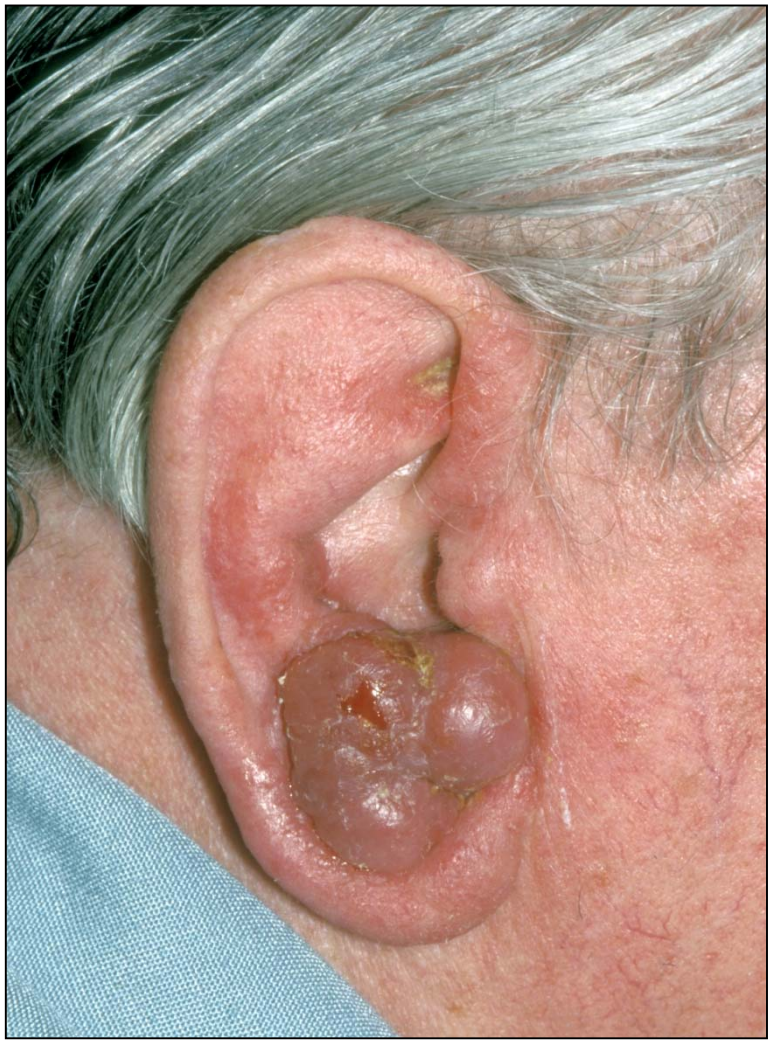
Results:

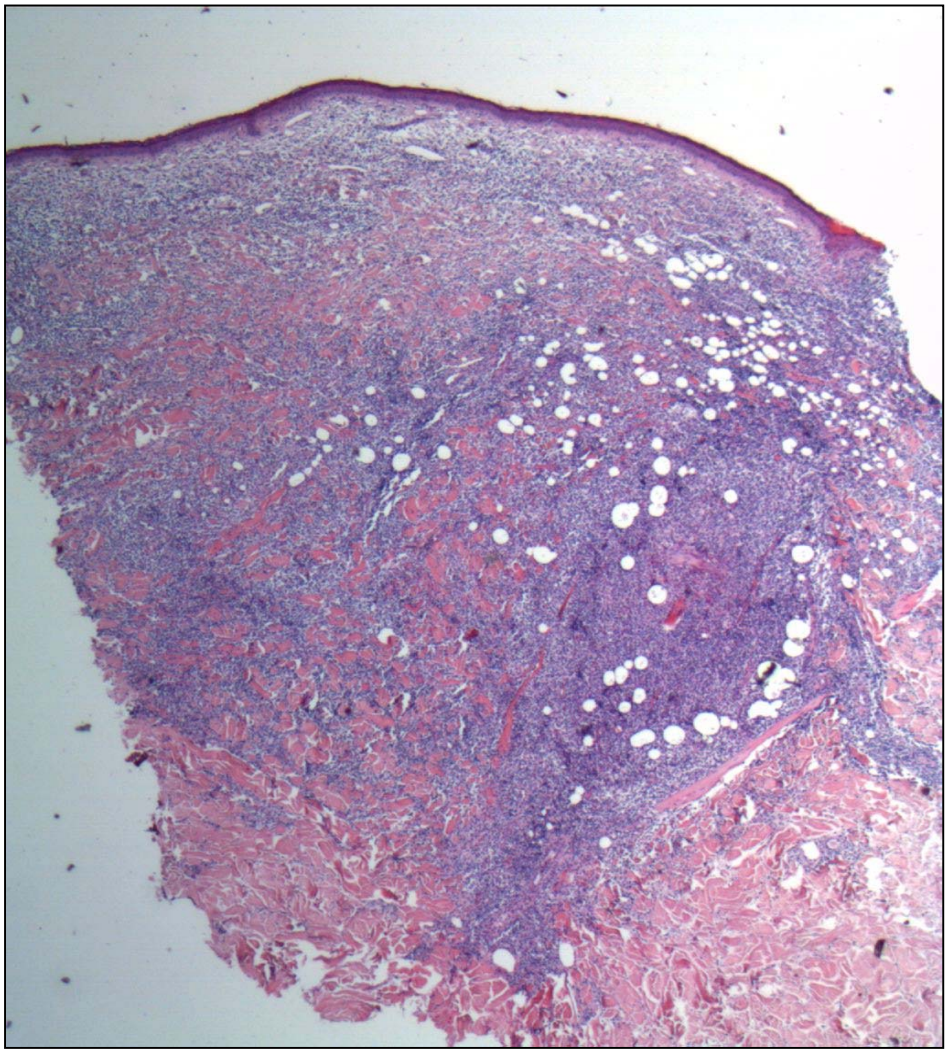
- 136 cases (Follow-up in 45 cases)
- 133/136 solitary lesion
- Follow-up: 41/45 Ao; 4/45 A+
- Clonal T-cells: 75/124 (60%)
- Partial marker loss CD5: 2/50

Conclusion:

- Cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance.

PCSM-TCL





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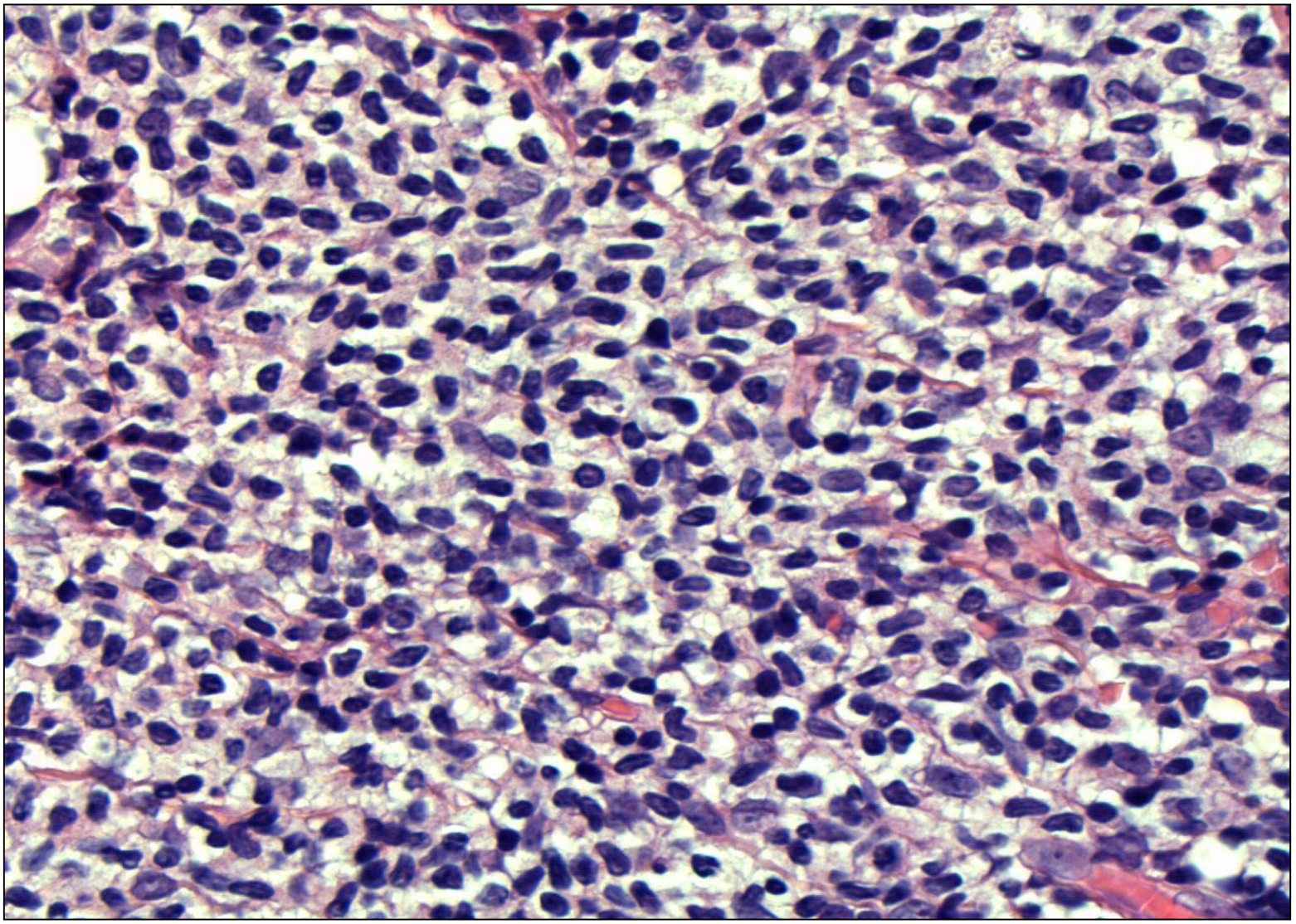
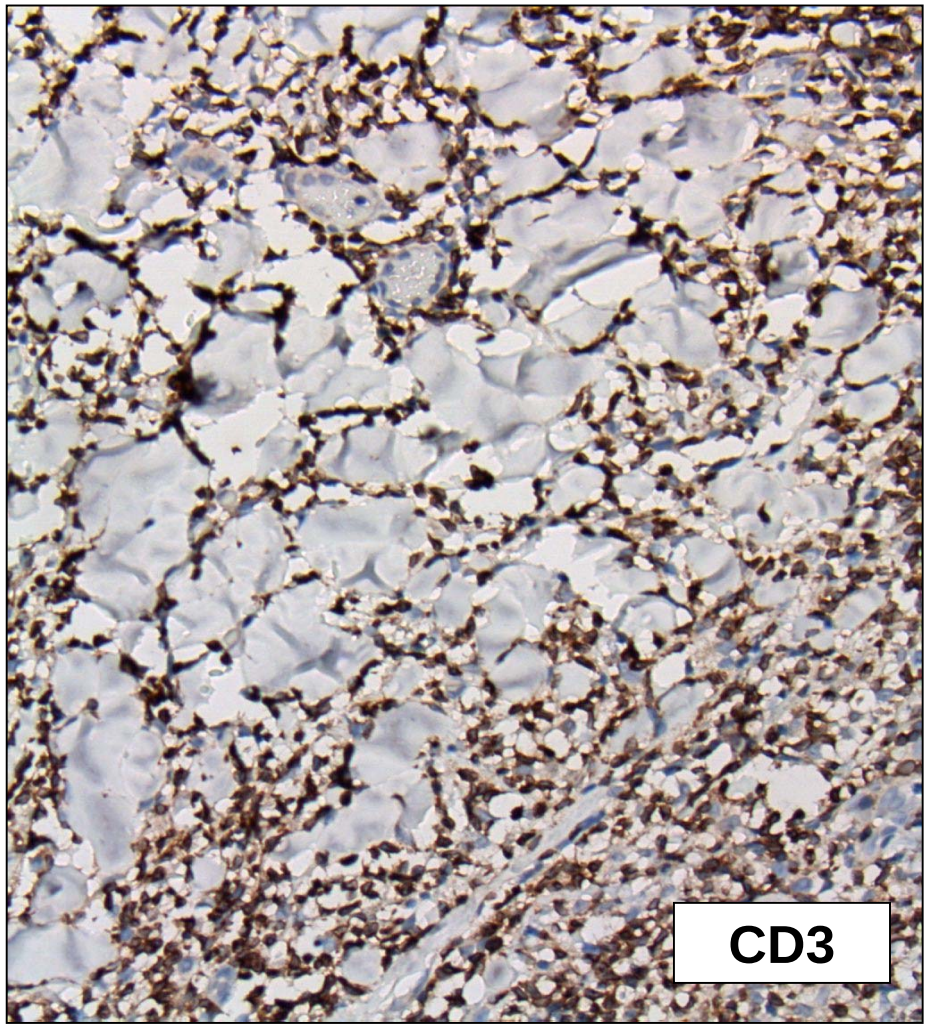
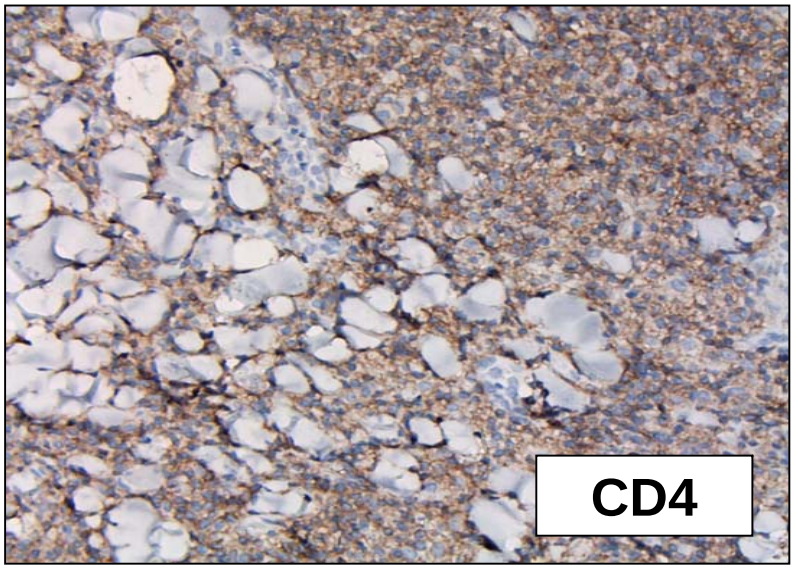
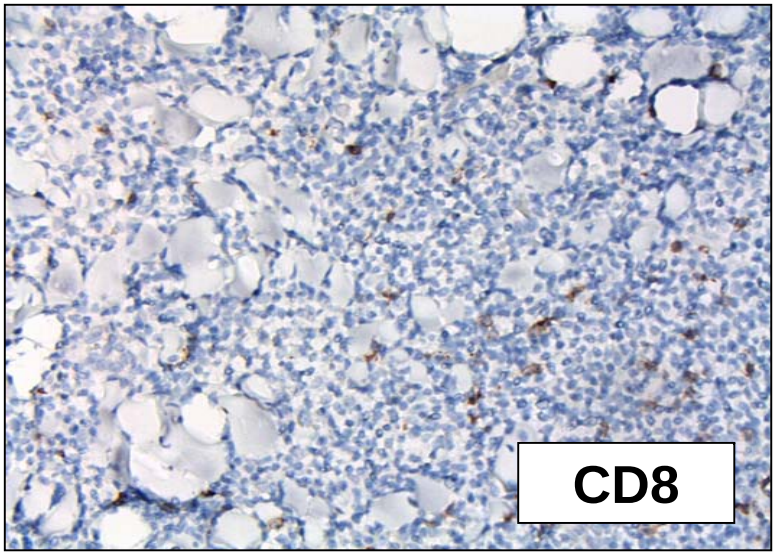


PCSM-TCL

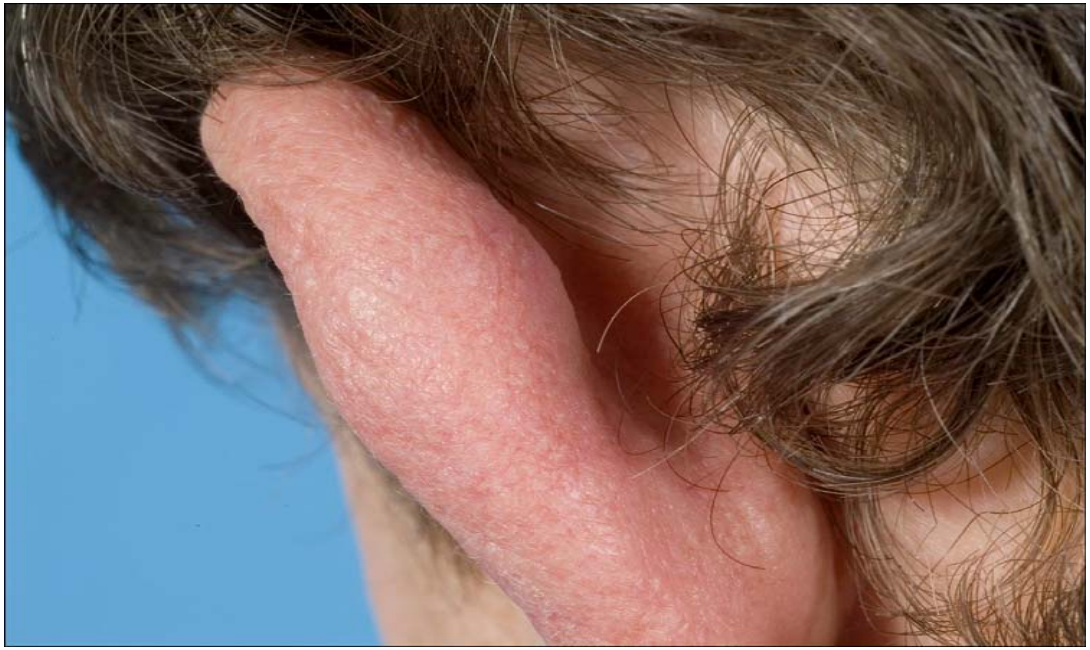






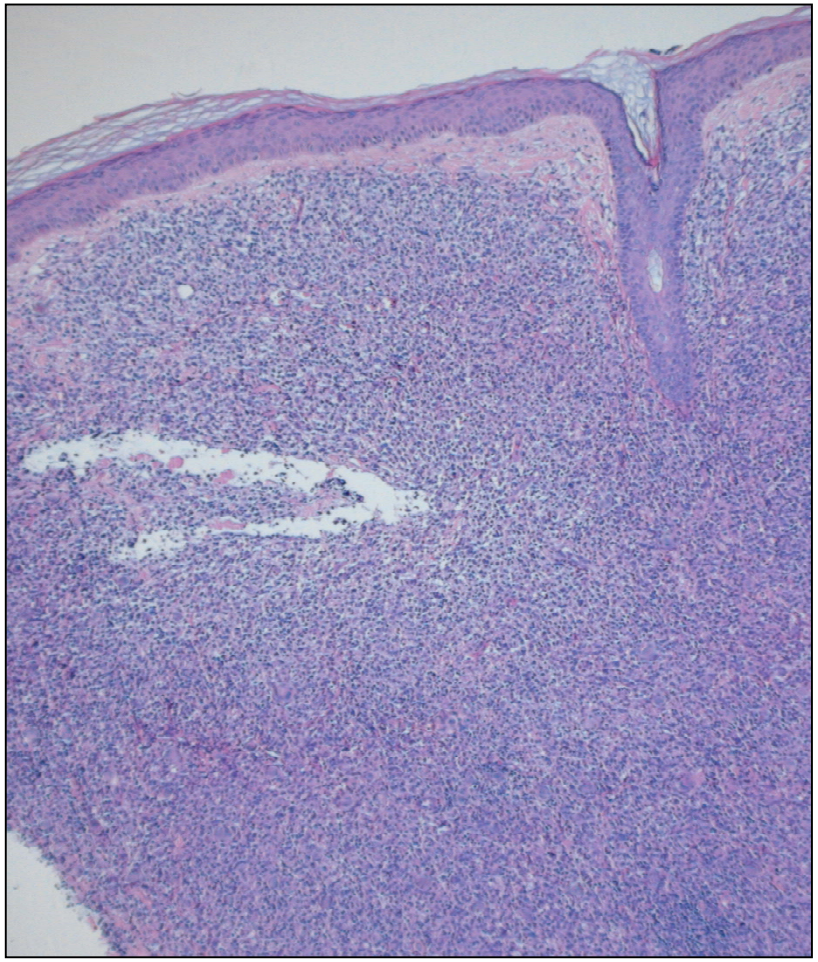
Patient 38 (PA: R05-82255)

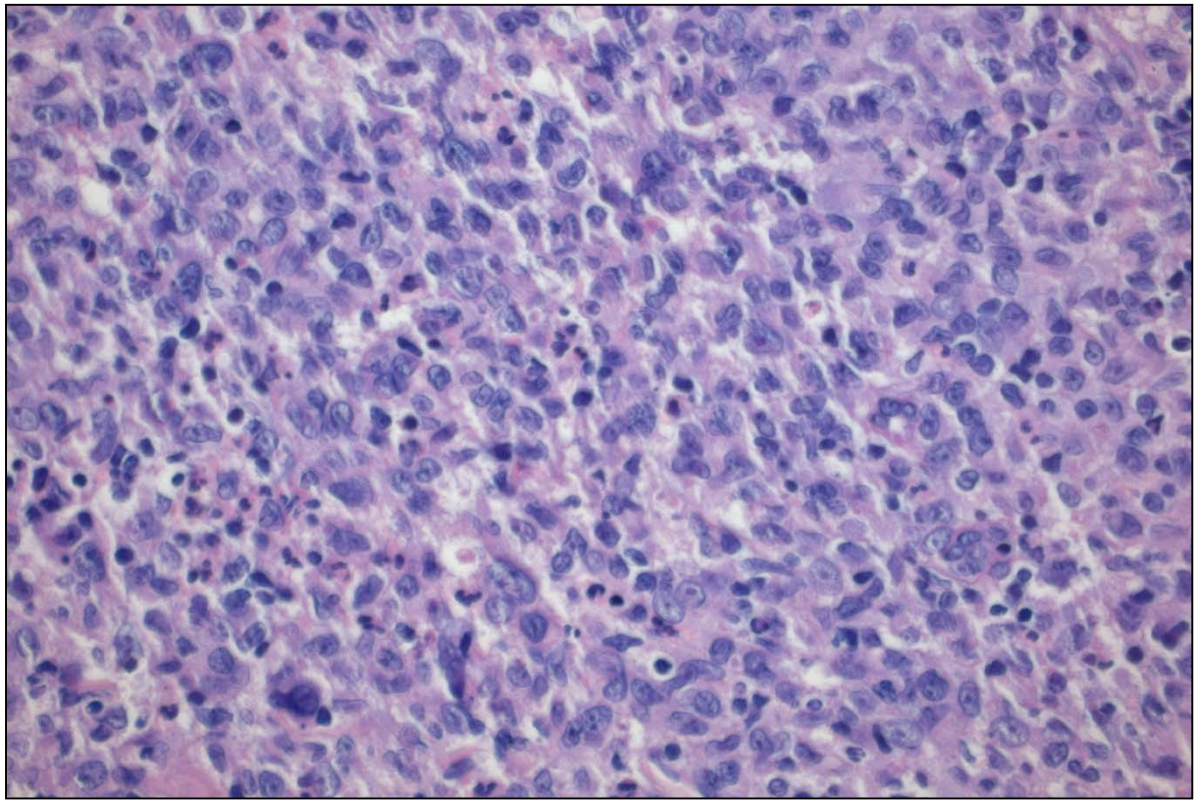
- Male, 51 years
- Infiltrated plaque on left ear for six month.
- No other skin lesions
- No further signs or symptoms



Benign or malignant ?

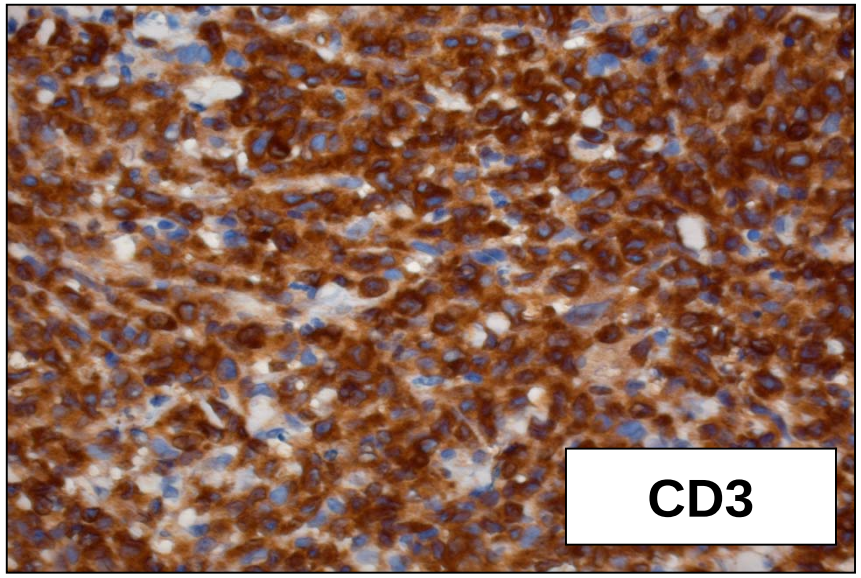
Patient 38 (PA: R05-82255)

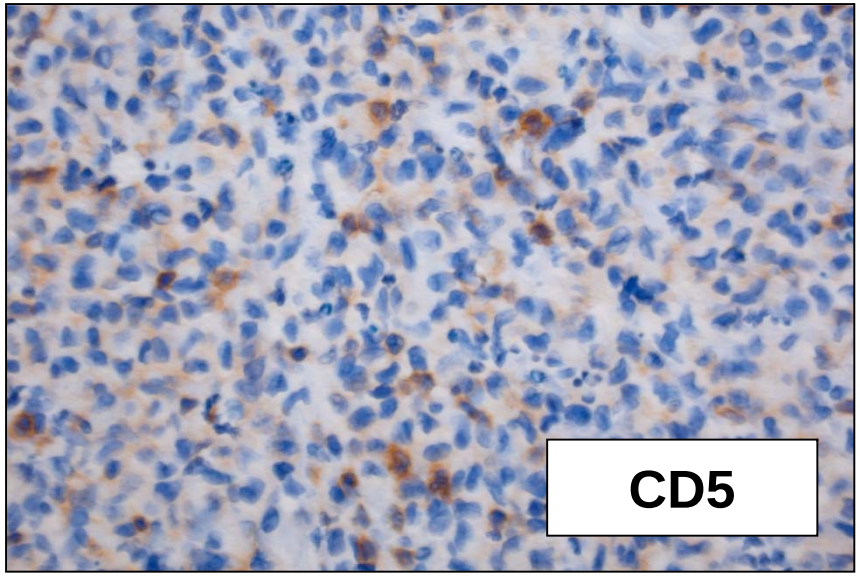


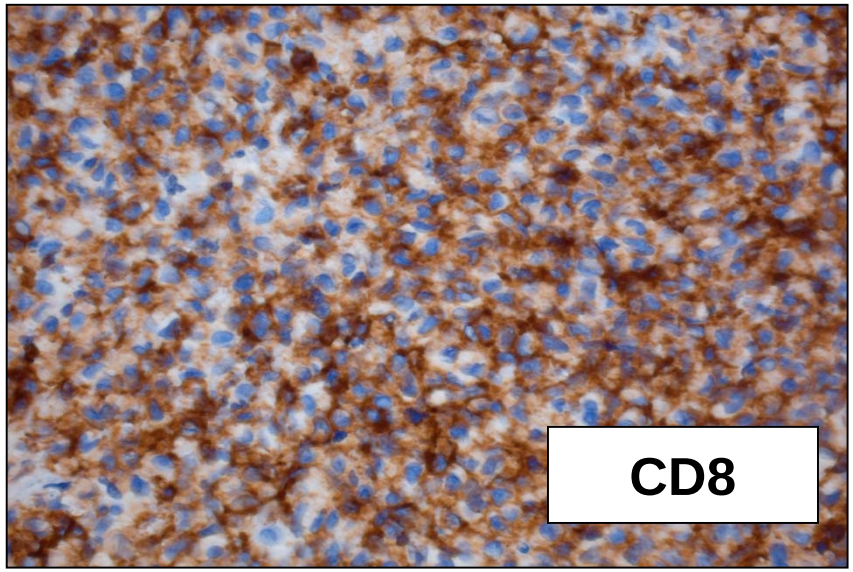


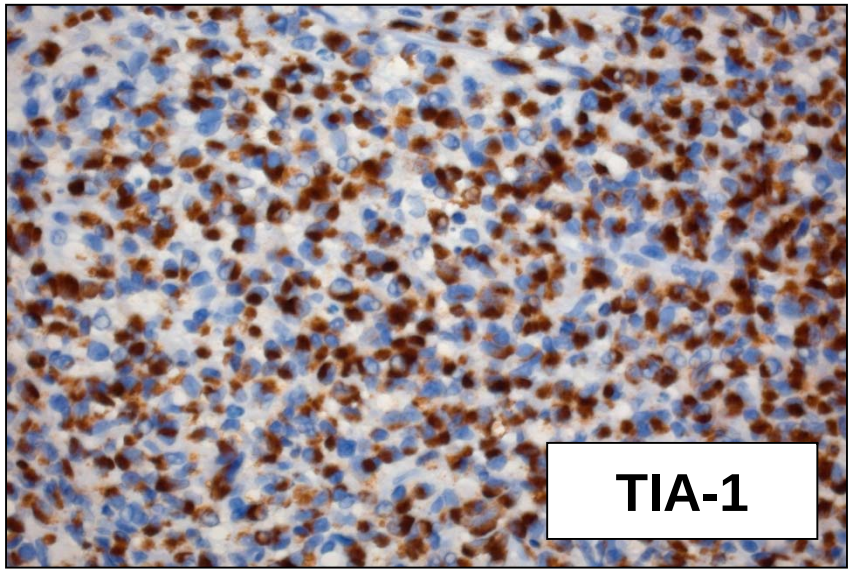
Benign or malignant ?

Patient 38 (PA: R05-82255)

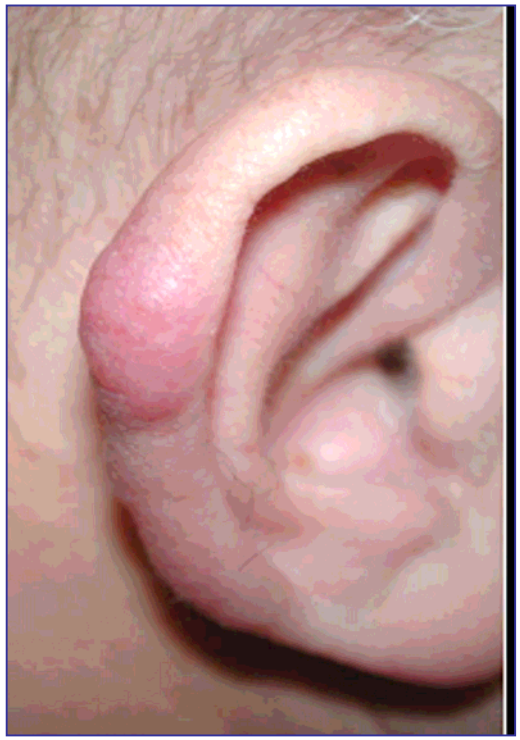


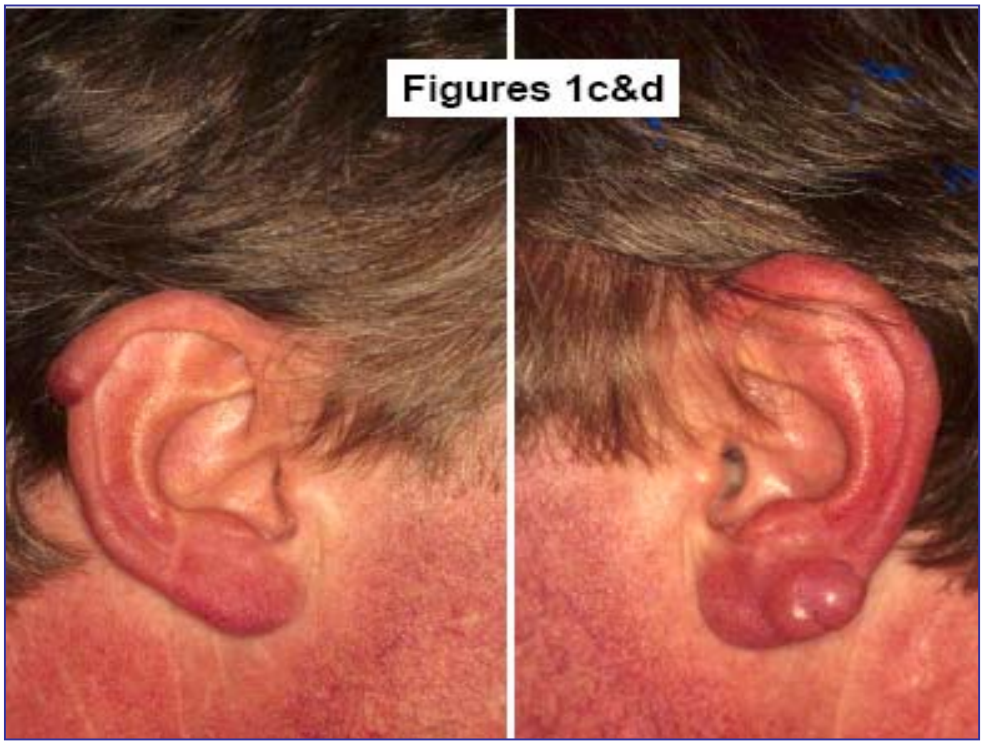


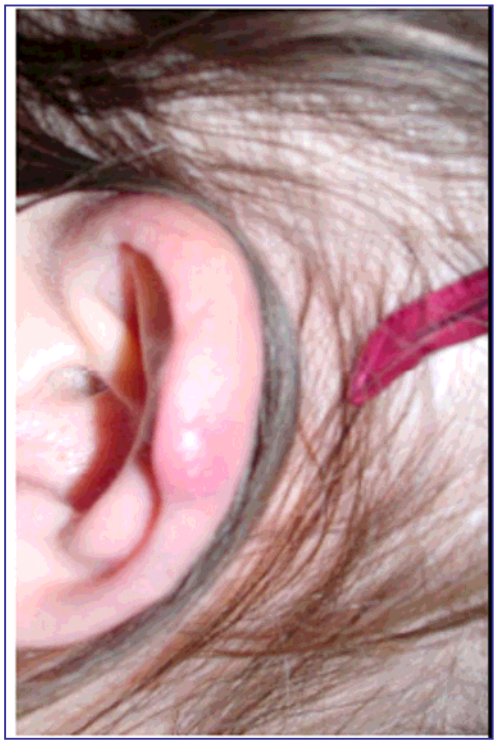




Similar cases from France







Clinical features:

- Slowly progressive nodules on the ear (or nose).
- Indolent clinical course.

Histology:

- Suggestive of high-grade malignant lymphoma.
- Diffuse; non-epidermotropic; medium-sized blast cells.
- Phenotype: CD3+, CD4-, CD8+, CD30-, TIA-1+, GrB-; loss panT-ag.
- Clonal TCR gene rearrangements.
- Low proliferation rate.

Indolent CD8- positive lymphoid proliferation of the ear.
A distinct primary cutaneous T-cell lymphoma?

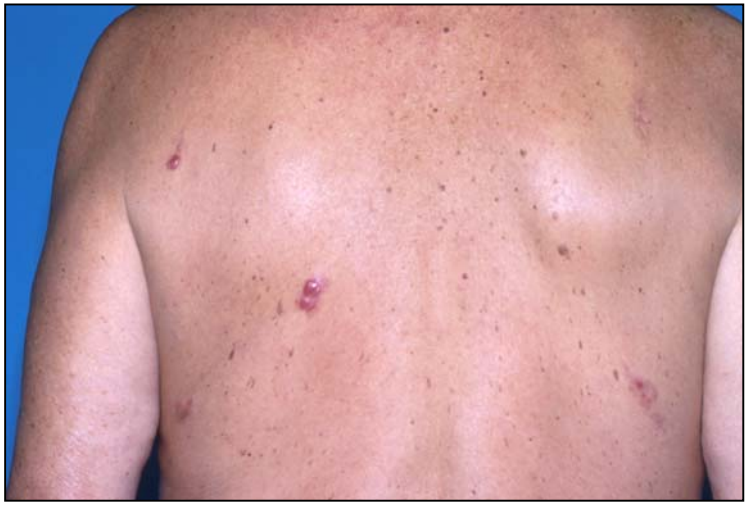
Petrella T. et al; Am J Surg Pathol 2007;31:1887-1892

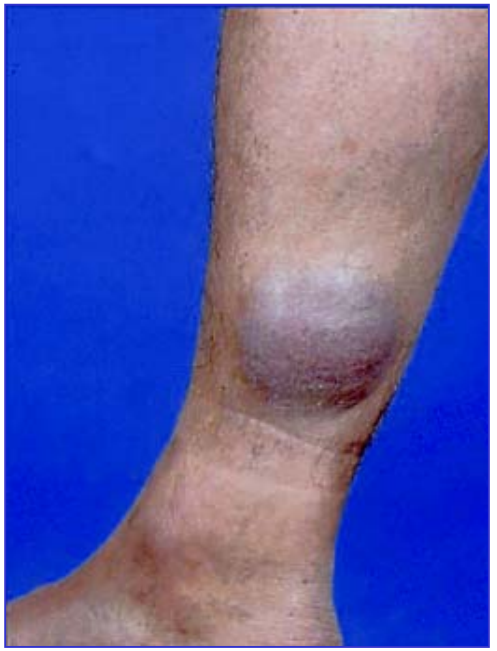
To be discussed

CTCL	Benign
Mycosis fungoides	BID; small/large plaque parapsoriasis
Folliculotropic MF	Alopecia mucinosa
Spectrum CD30+ LPD (C-ALCL; LyP)	Benign cutaneous CD30+ infiltrates
CD4+ S/M pleomorphic CTCL	Pseudo-T cell lymphoma
CBCL	**Benign**
pc marginal zone B-cell lymphoma	Cutaneous lymphoid hyperplasia (pseudo-B-cell lymphoma)
pc follicle center lymphoma	

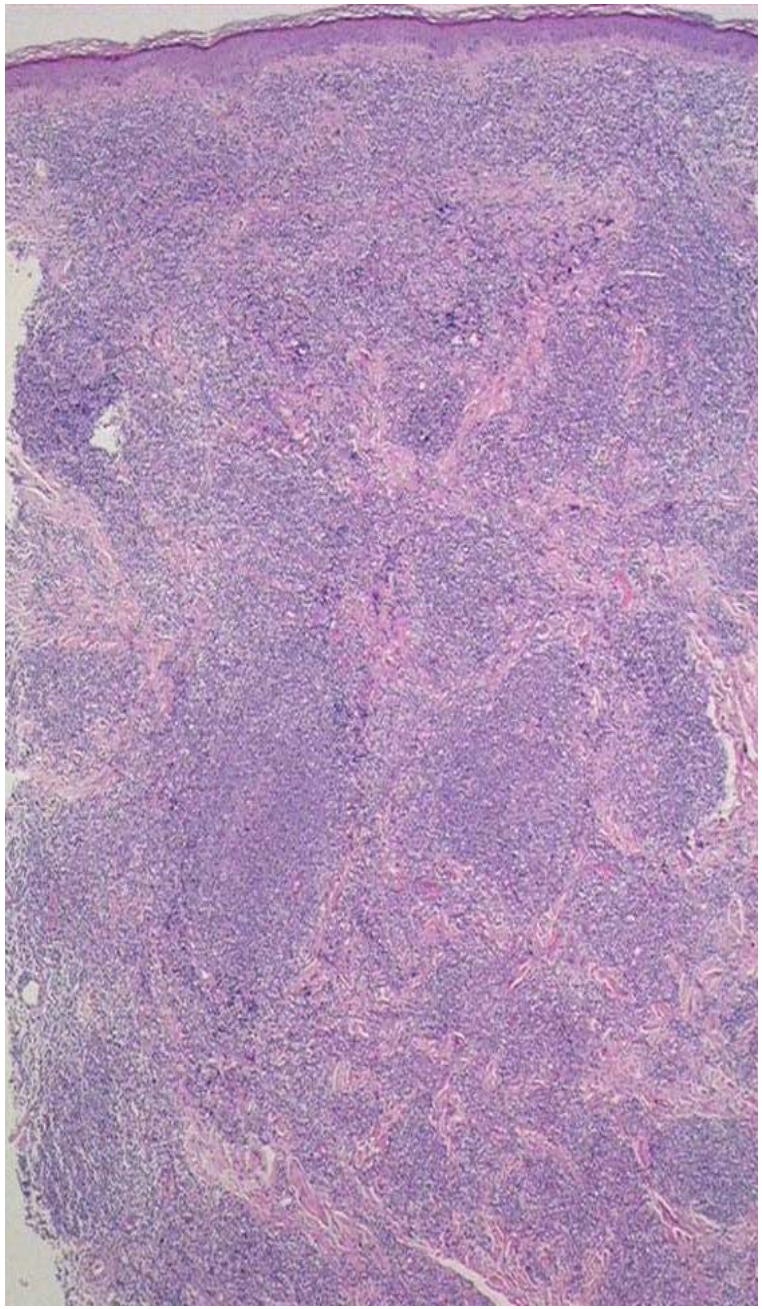
PCMZL: clinical features

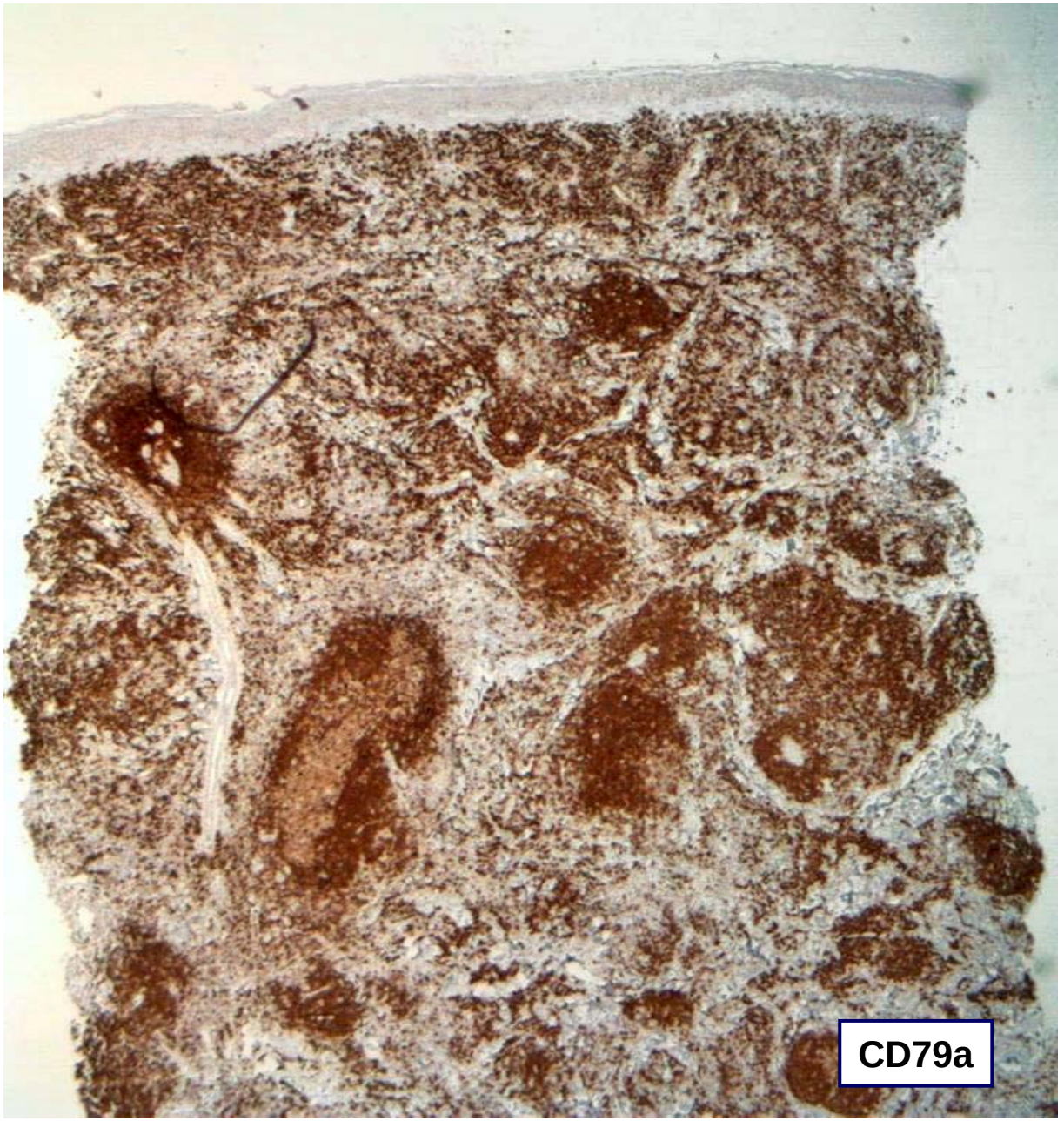
- Solitary, localized or multifocal.
- Skin relapses common (65%).
- Extracutaneous dissemination rare
- Excellent prognosis.
- Association with B.burgdorferi (Europe+; US and Asia: -)
- Nonaggressive therapy



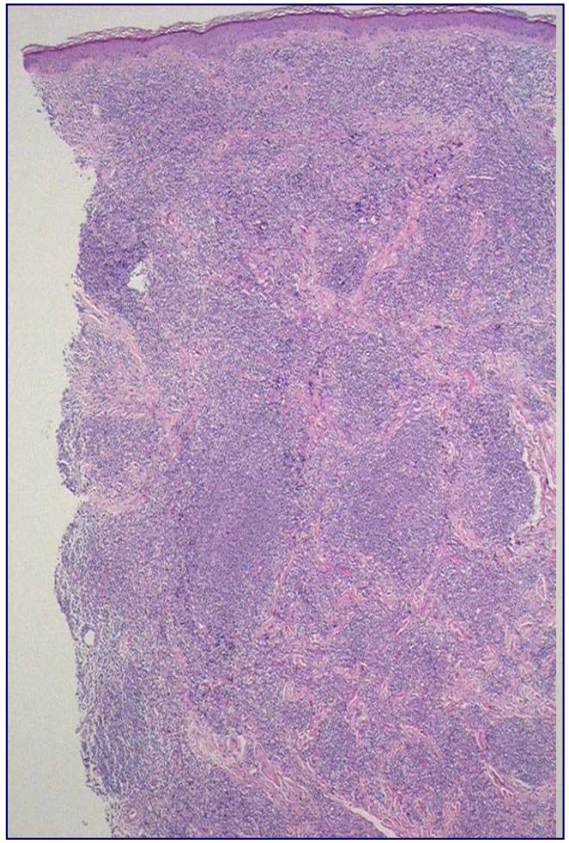


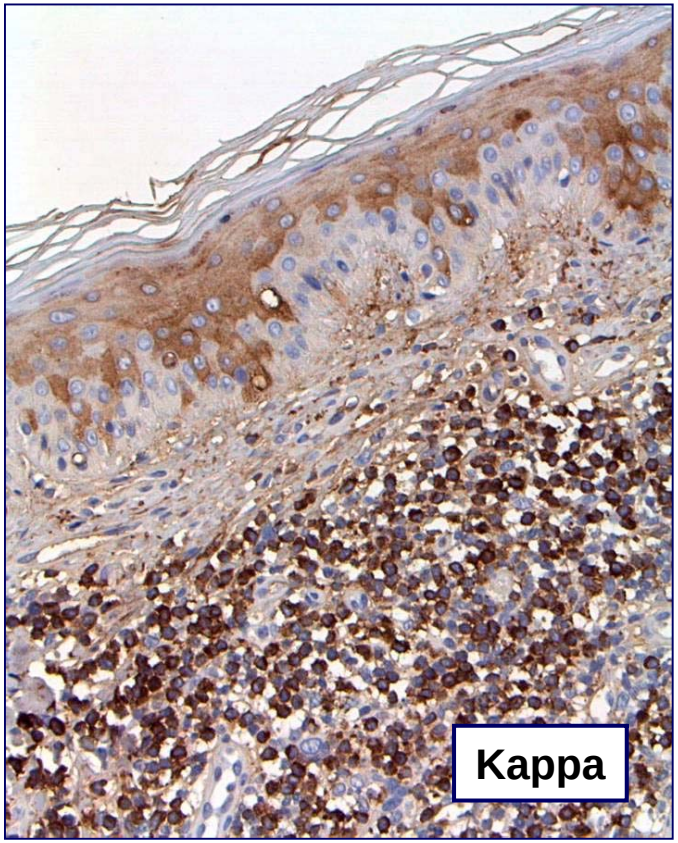
Senff NJ et al; J Clin Oncol 2007;25:1581-1587

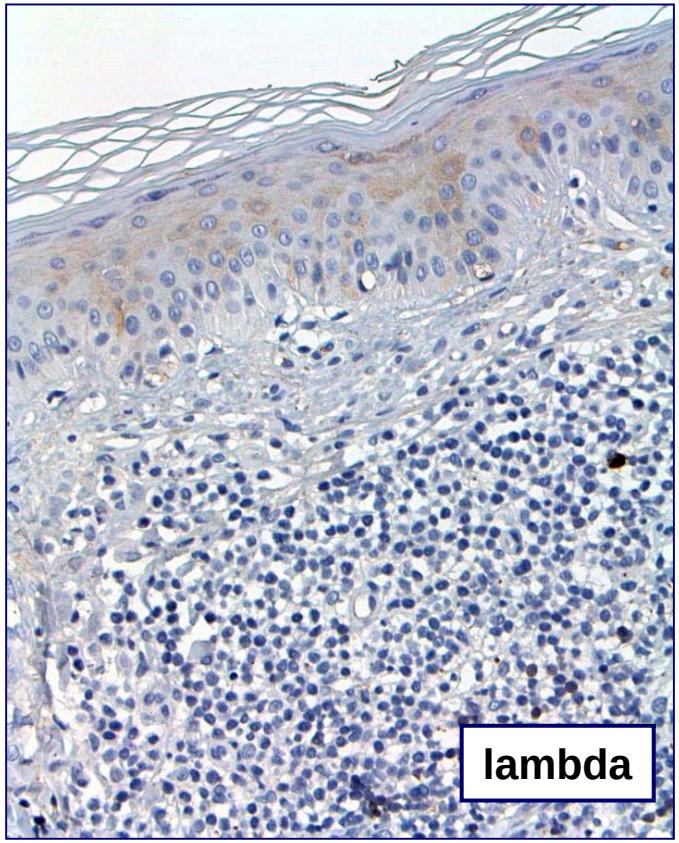



CD79a

PCMZL: phenotype

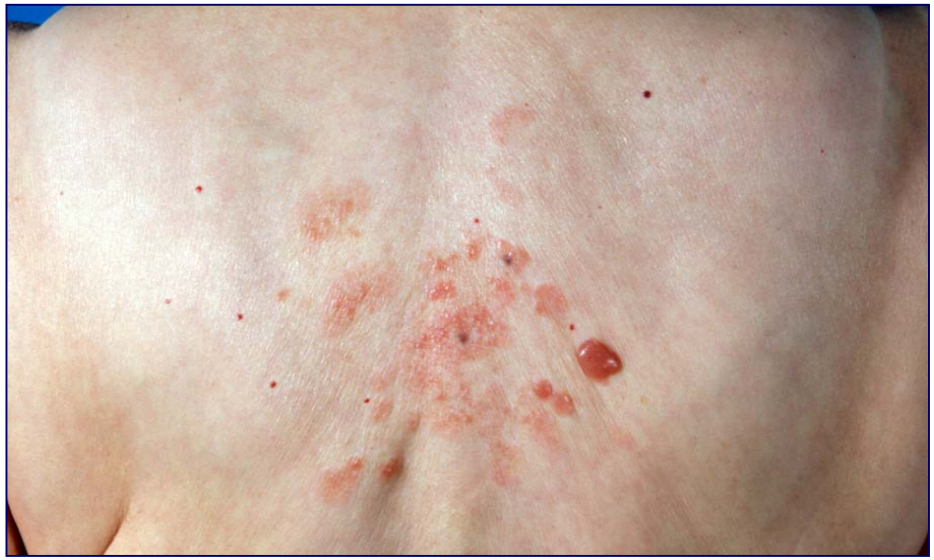


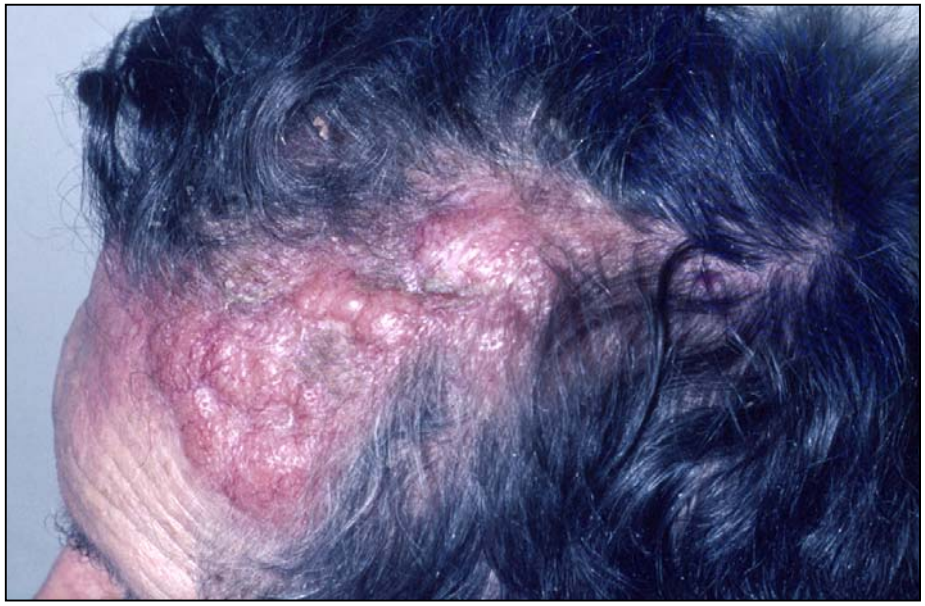


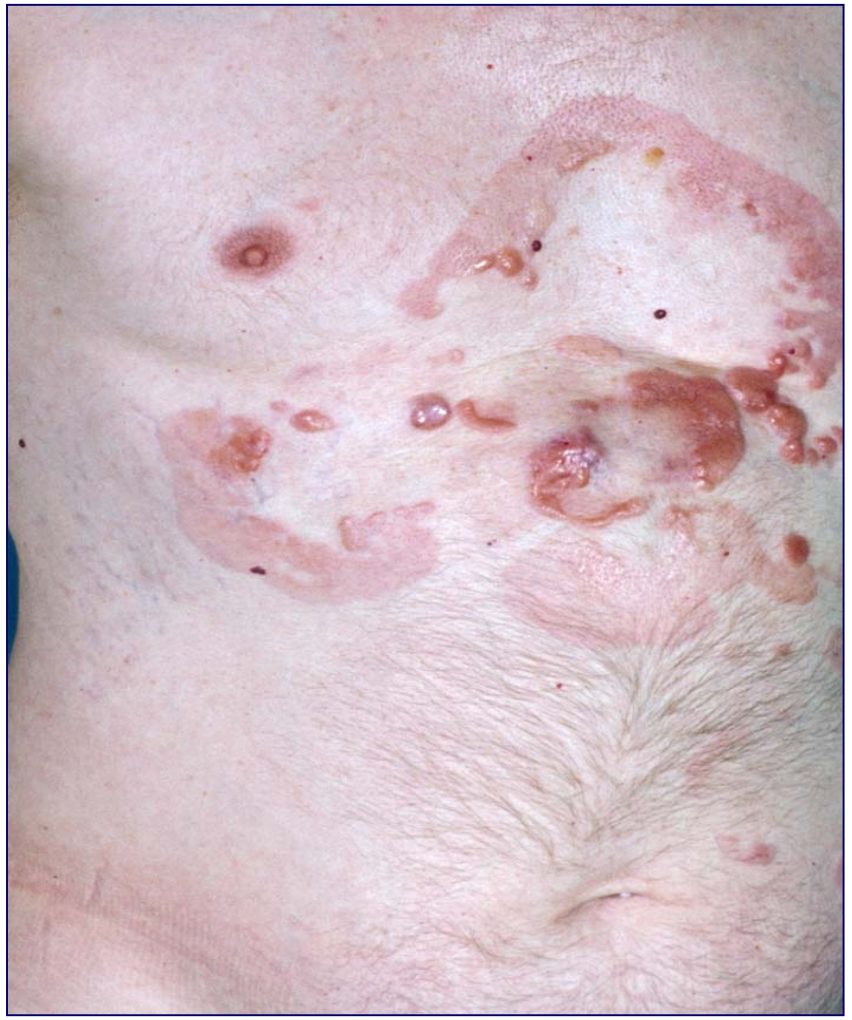


- Monotypic light chain expression plasma cells/ plasmacytoid cells (periphery; subepidermal area).
- CD79a+, CD20+/-, CD5-, **bcl-2+, bcl-6-, CD10-.**

PCFCL

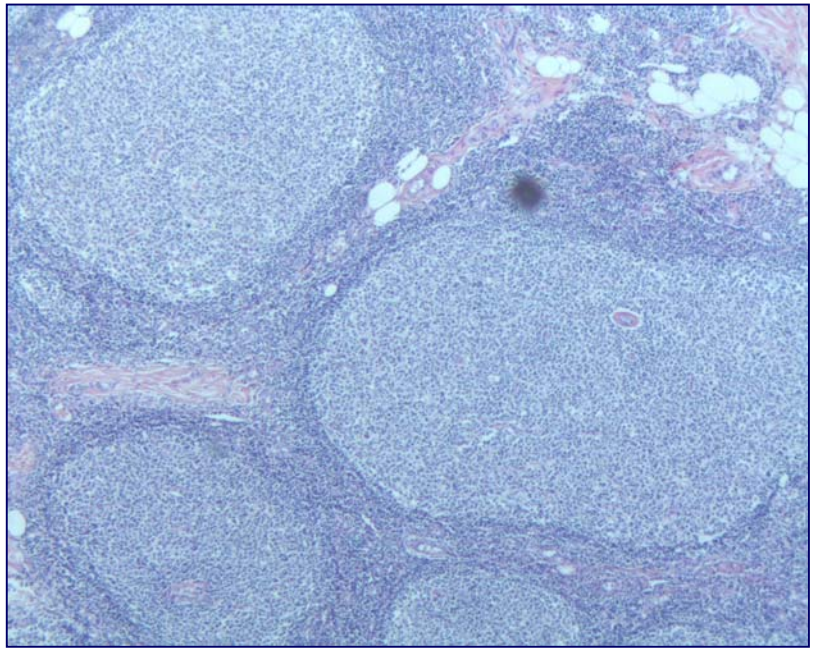




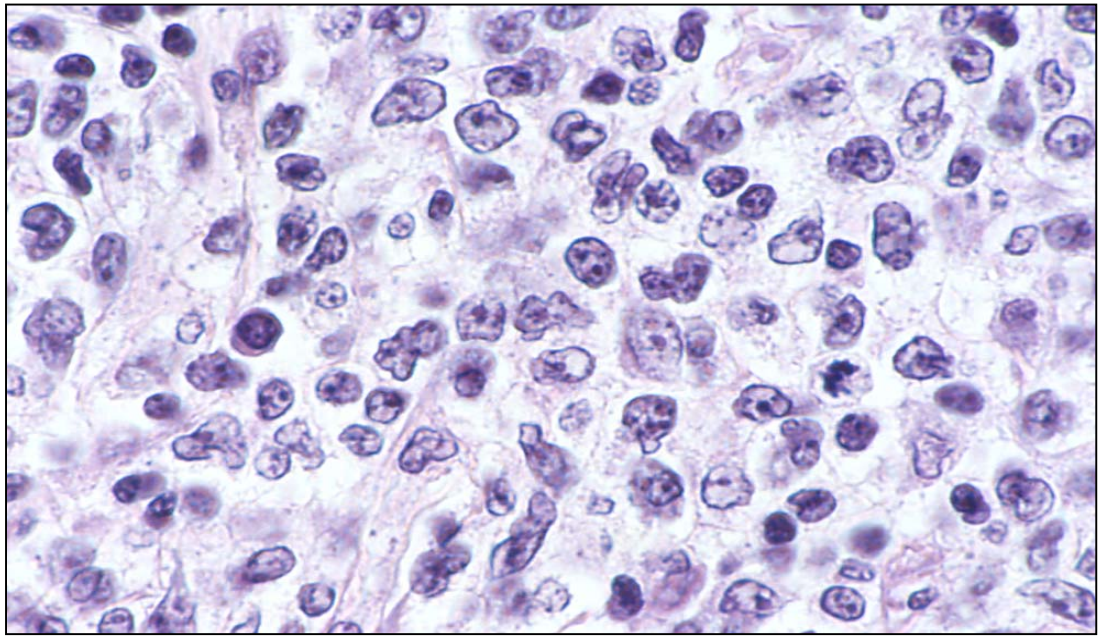


PCFCL: histology and phenotype

Follicular: <5%
Follicular & diffuse: 25%



diffuse large cell: >70%

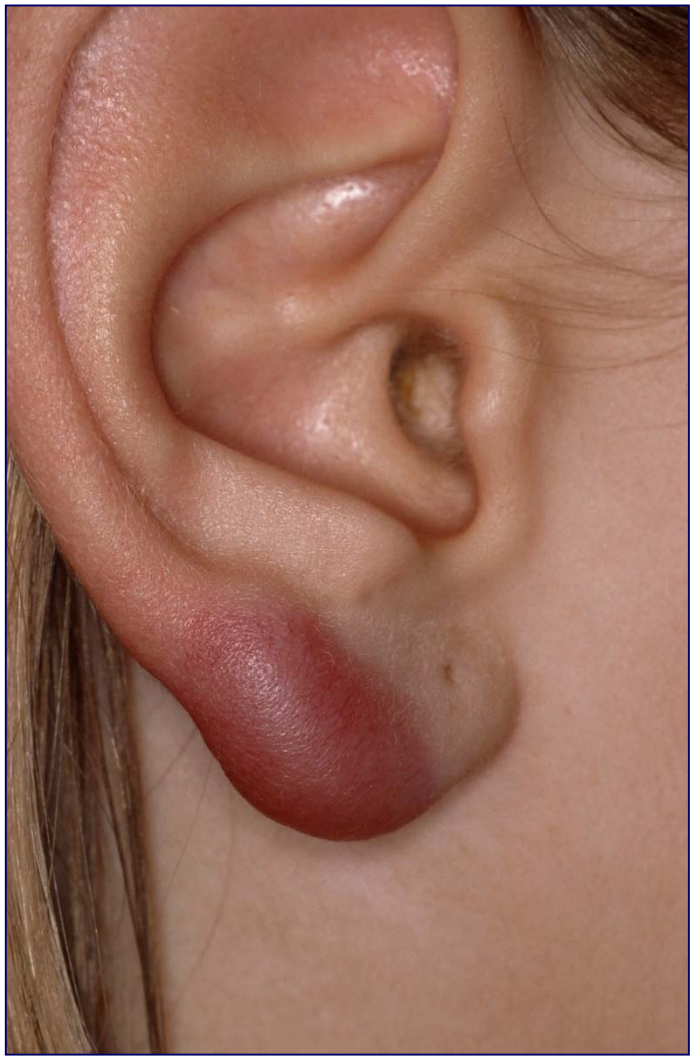


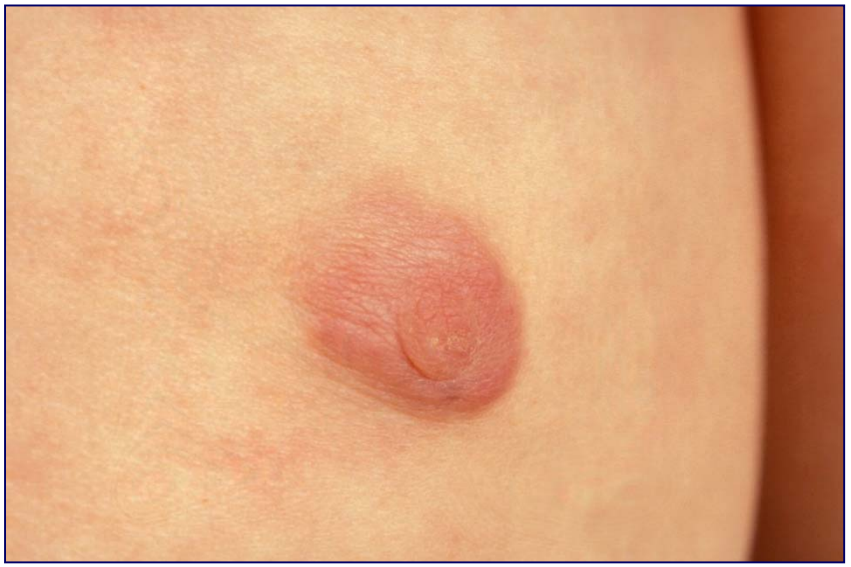
Phenotype: CD20+, bcl-6+, bcl-2-, CD10 -/+, Mum-1-, Fox-P1-

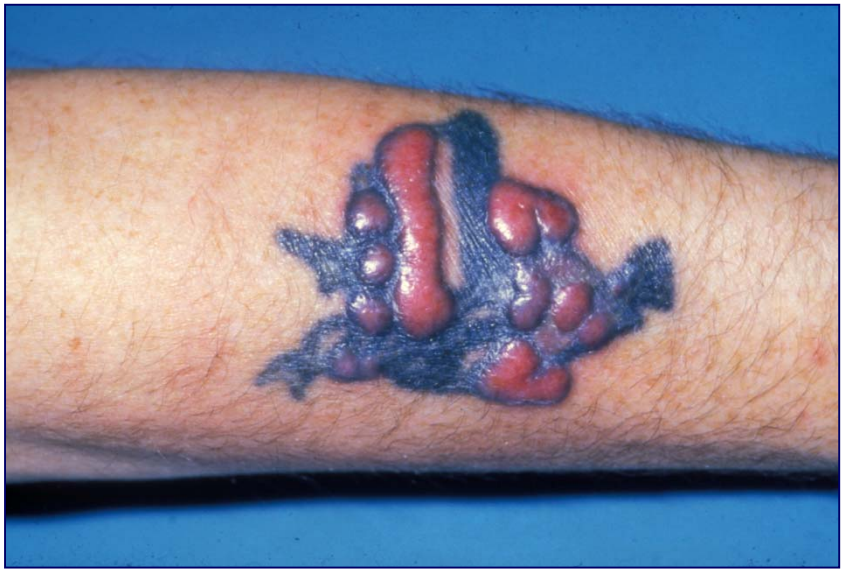
Cutaneous Lymphoid Hyperplasia

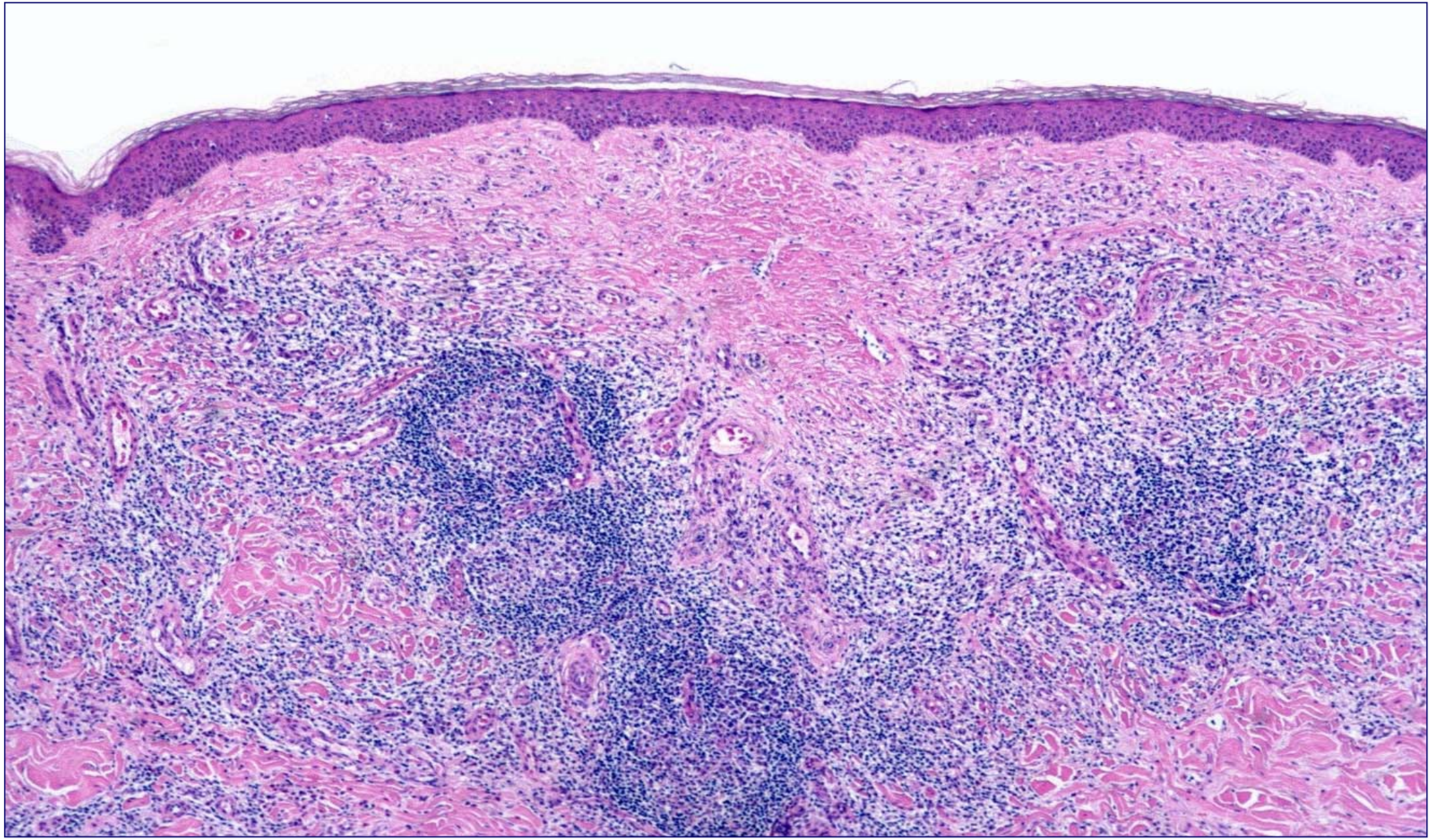
- **Presence of polyclonal B-cell proliferation (IHC)**
- **Etiology:**
  - Tick bites (Borrelia burgdorferi infection)
  - Tattoo pigments
  - Antigen injections; piercings; golden earrings, etc.
  - unknown
- **Synonyms:**
  - Pseudo-B-cell lymphoma
  - Lymphadenosis benigna cutis
  - Lymphocytoma cutis
  - Sarcoid of Spiegler-Fendt

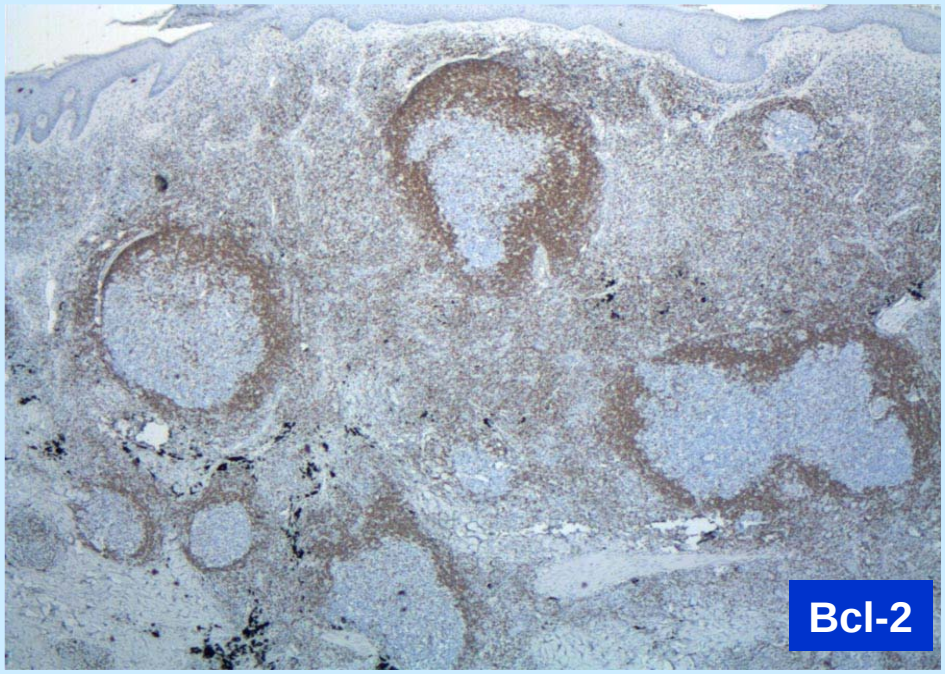
CLH – tick bite - tattoo

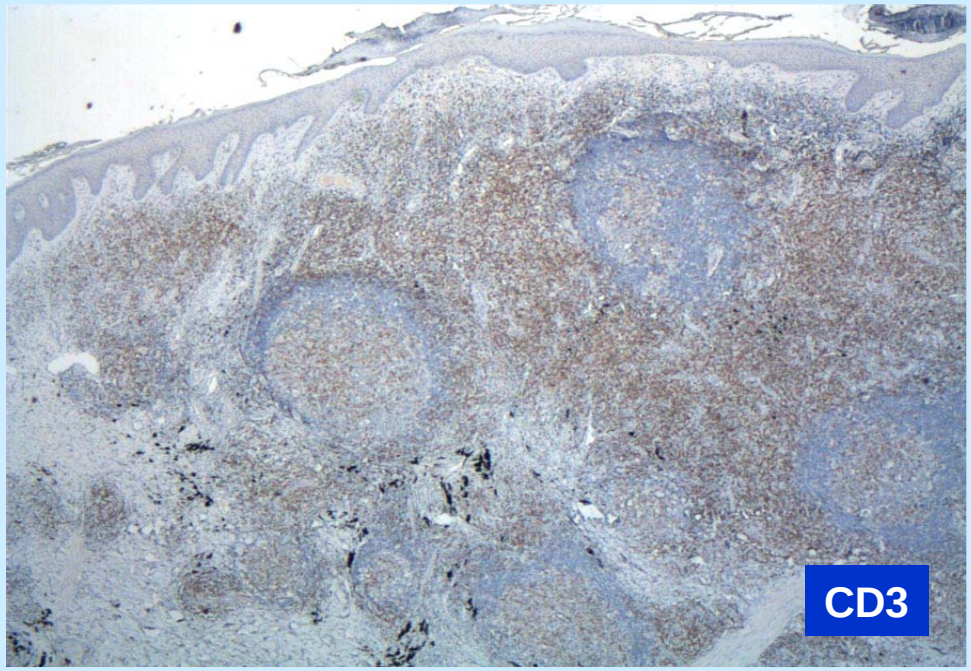


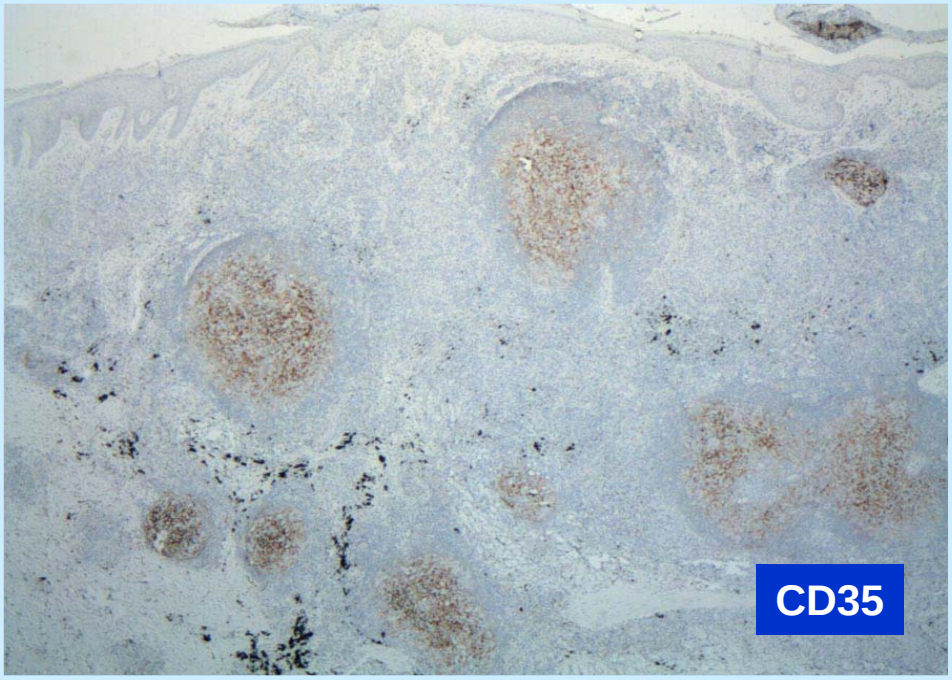


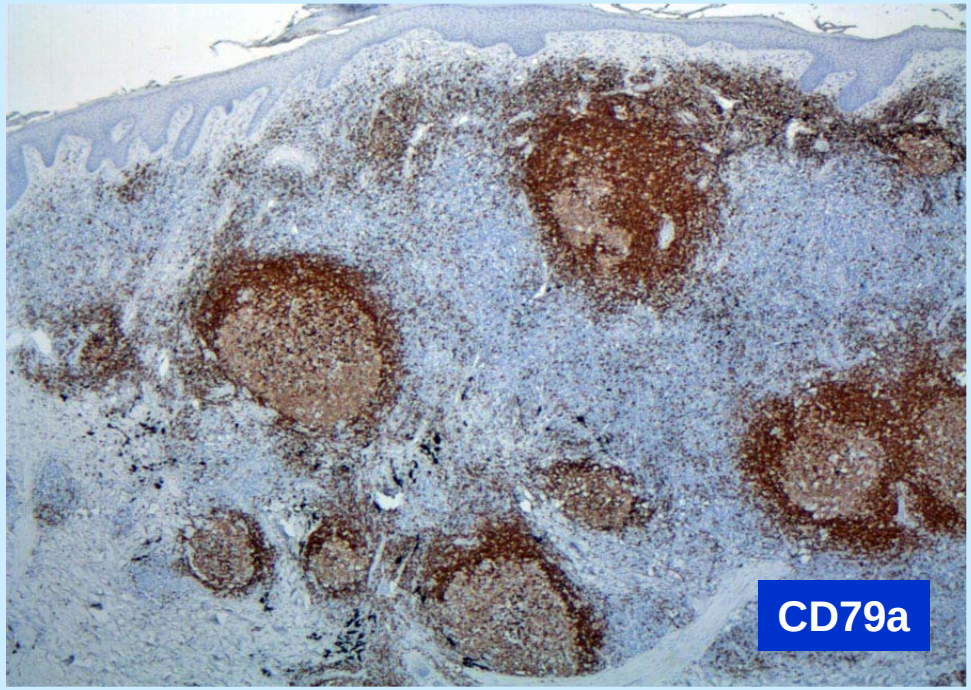





Bcl-2


CD3


CD35


CD79a

PCMZL and CLH

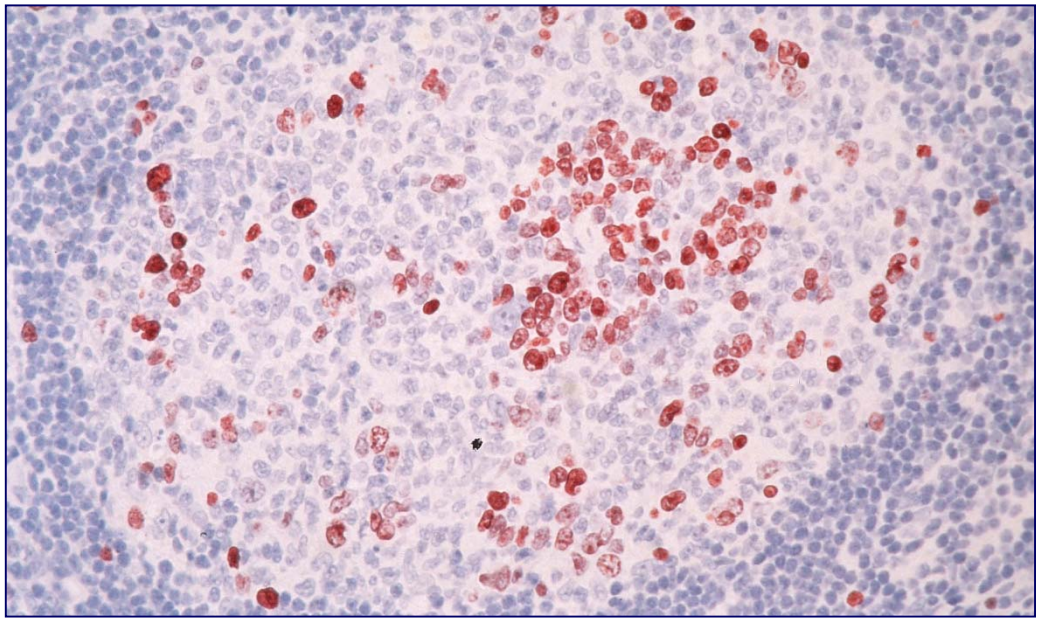
- Shared etiology: B. burgdorferi, antigen injections, tattoo (intradermal antigens).
- Numerous T-cells; reactive germinal centers -/+
- PCMZL: monotypic plasma cells/lymphoplasmacytoid cells may be few or sometimes lacking.
- CLH: may be clonal (10-20%)
- PCMZL and CLH: spectrum of disease ?

DD. PCMZL - CLH

- Characteristic clinical presentation.
- monotypic cIg expression by plasma cells/lymphoplasma-cytoid cells (subepidermal; periphery infiltrates)
- IgH gene rearrangement analysis non-contributory
- Definite diagnosis not possible:
  - atypical lymphoid proliferation or suspicion PCMZL.
  - No aggressive therapy; short-term control; biopsy of new skin lesions.

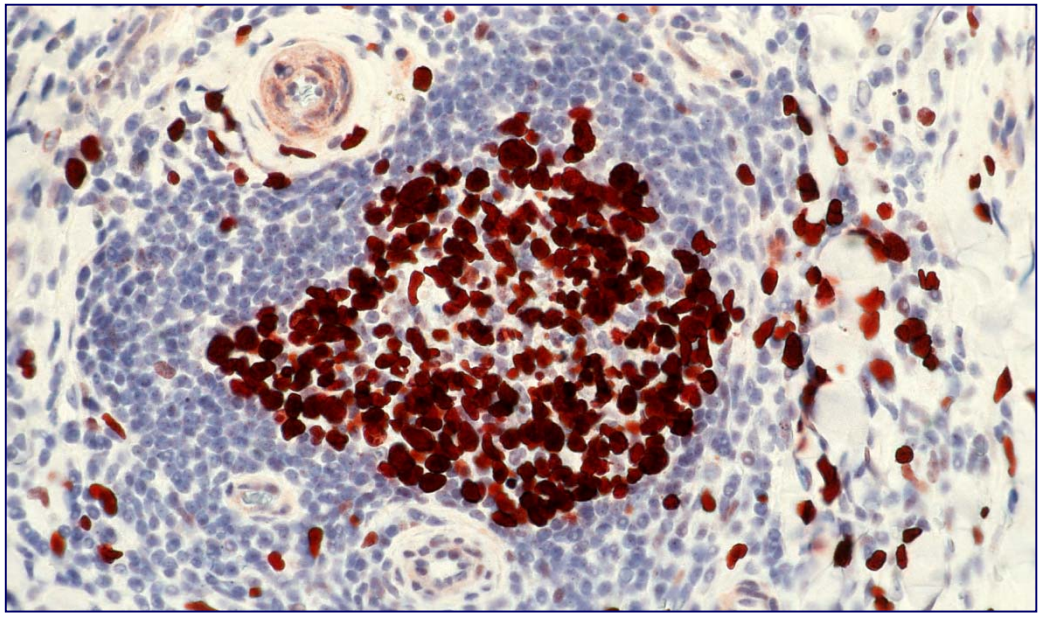
DD. PCFCL - CLH

- Characteristic clinical presentation.
- PCFCL with diffuse growth pattern: generally no problem.
- PCFCL with a follicular growth pattern:
  - Morphologic distinction between benign and malignant follicles.
  - Immunohistochemistry generally non contributory (bcl-6+, bcl-2-, CD10+/-). Proliferation rate ?
  - IgH gene rearrangement analysis non-contributory
- Definite diagnosis not possible:
  - atypical lymphoid proliferation or suspicion PCMZL.
  - No aggressive therapy; short-term control; biopsy of new skin lesions.



Follicular lymphoma

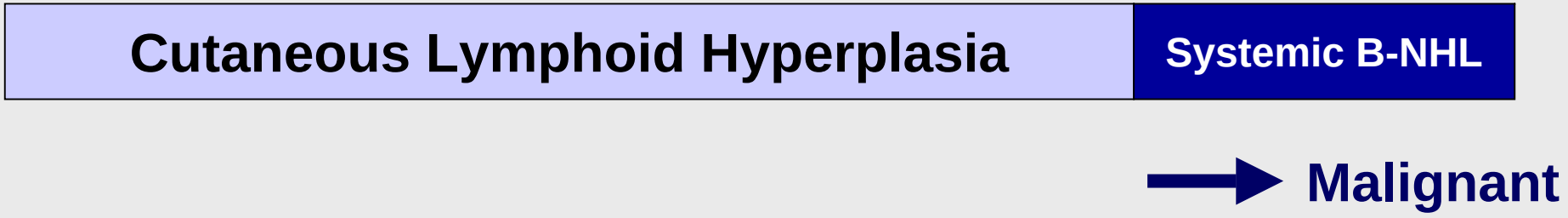
MIB-1 (Ki-67) staining



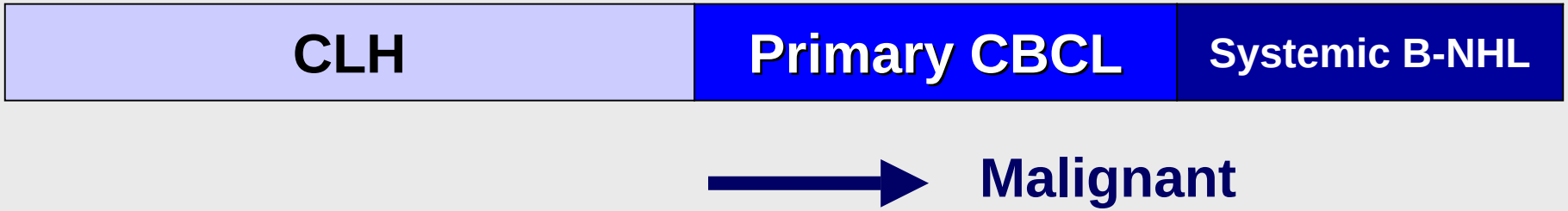
CLH (pseudolymphoma)

DD. CBCL – CLH: changing concepts

< **1980** (morphologic criteria)



> **1980** (immunophenotype)



> **1988** (gene rearrangement analysis)

Conclusions

- DD. benign and malignant lymphoid infiltrates in the skin: consider histopathology, phenotype, genotype **and clinical features.**
- Clinicopathologic correlation extremely important.
- Decisive criteria:
  - CBCL: monotypic Ig light chain expression.
  - CTCL: marker loss; aberrant phenotype
- Clonality analysis supportive in some cases, but not decisive.