

# EPIDERMOTROPISM: A PRACTICAL APPROACH



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# Two main topics for discussion

- 1. Establishing a diagnosis of epidermotropic T-cell lymphoma**
  - Diagnosing mycosis fungoides in its early stage
- 2. Differential diagnosis of epidermotropic cutaneous T-cell lymphomas**



# DEFINITIONS

*J Cutan Pathol* 2010; 37: 525–529  
doi: 10.1111/j.1600-0560.2010.01515.x  
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Journal of  
Cutaneous Pathology

## ‘Epidermotropism’ vs. ‘exocytosis’ of lymphocytes 101: definition of terms

Maxell A Fung

- The terms **exocytosis** and **epidermotropism** are not clearly defined or consistently applied
- 19 responses from survey of 34 expert Dermatopathologists from Italy, US, UK and Australia

### Epidermotropism: some Dermatopathologists only use term if following present

- |   |             |
|---|-------------|
| • Diagnosis of lymphoma                       | 15/19 (79%) |
| • Basilar lentiginous pattern of infiltration | 5/19 (26%)  |

**For many, use of either term implies a diagnosis**  
**“.....one needs to know the diagnosis to describe the case!”**

### Exocytosis: some Dermatopathologists only use term if following present

- |                                    |            |
|------------------------------------|------------|
| • Diagnosis of reactive process    | 9/19 (47%) |
| • Spongiosis                       | 8/19 (42%) |
| • Pagetoid pattern of infiltration | 2/19 (10%) |



## ‘Epidermotropism’ vs. ‘exocytosis’ of lymphocytes 101: definition of terms

“In conclusion, ‘epidermotropism’ and ‘exocytosis’ (and ‘atypia’) can be defined in different ways that often telegraphically reveal the pathologist’s interpretation. As a listener, one is entitled, if not obligated, to request clarification whenever these words are used.”

## For the purposes of this talk.....

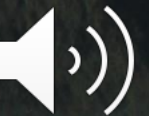
### “Epidermotropism”

- The movement of lymphocytes into the epidermis
- Should not be taken to infer a diagnosis of malignancy



# Establishing a diagnosis of epidermotropic T-cell lymphoma

- Diagnosing mycosis fungoides in its early stage



## MYCOSIS FUNGOIDES

**Commonest subtype of cutaneous lymphoma but still relatively rare**

- 0.29/100000/year (although 44% of primary cutaneous lymphoma)

**Prototypic epidermotropic T-cell lymphoma**

**Classical (Alibert) clinical presentation**

- Patches
- Plaques
- Tumours

**Early MF = patch/early plaque stage**



# Why is diagnosing early (patch/early plaque stage) mycosis fungoides difficult?

**Mycosis fungoides: Clinical features may only become distinctive as disease progresses**

Stage IA



Stage IB - IIA



IIB and above



**CLINICAL PRESENTATION: mycosis fungoides has many non-classical presentations; diagnosis may not be suspected at time of biopsy**

- Poikilodermatous mycosis fungoides
- MF in children and adolescents
- Hypopigmented mycosis fungoides
- Hyperpigmented mycosis fungoides
- Mycosis fungoides and ichthyosis
- Vesiculobullous mycosis fungoides
- Pustular mycosis fungoides
- Pigmented purpura-like mycosis fungoides
- Palmoplantar mycosis fungoides
- Verrucous/hyperkeratotic mycosis fungoides
- Unilesional mycosis fungoides
- 'Invisible' mycosis fungoides



# CLINICAL OVERLAPS: mycosis fungoides can clinically mimic many benign dermatoses

REVIEW ARTICLE

DOI 10.1111/j.1365-2133.2006.07526.x

## **Mycosis fungoides: a dermatological masquerader**

D. Nashan, D. Faulhaber,\* S. Ständer,\* T.A. Luger\* and R. Stadler†

Department of Dermatology, University of Freiburg, Hautstr. 7, 79104 Freiburg, Germany

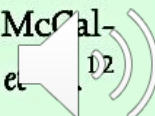
\*Department of Dermatology, University of Münster, Münster, Germany

†Department of Dermatology, Klinikum Minden, Minden, Germany

*Br J Dermatol 2007.156.1-10*

Clinical sign	Differential diagnosis	First author
Eczematous	Seborrhoeic eczema	Figure 1
	Perioral dermatitis	Wolf 1992 <sup>82</sup>
	Palmoplantar eczema	Spieth 2002 <sup>19</sup>
	Dyshidrotic eczema	Kempf 2005 <sup>80</sup>
	Contact dermatitis	Spieth 2002 <sup>19</sup>
	Atopic eczema	Kazakov 2004 <sup>12</sup>
	Scaling	Psoriasis
Psoriasis palmaris		Spieth 2002 <sup>19</sup>
Psoriasis plantaris		Figure 2
Parapsoriasis		Ackermann 1996 <sup>84</sup>
Tinea corporis		Chaves 2002 <sup>85</sup>
Tinea pedis		Resnik 1995 <sup>86</sup>
Erythematous	Erythema multiforme	Krebs 1978 <sup>87</sup> Kazakov 2004 <sup>12</sup>
	Annular erythema	Lim 2003 <sup>88</sup> Cogrel 2005 <sup>89</sup>
	Alopecia	Alopecia areata

For a further overview publications of Zackheim and McCallmont<sup>13</sup>—with 23 differential diagnoses—and Kazakov et al.<sup>12</sup> can be recommended.



## 2. HISTOLOGICAL OVERLAPS: broad spectrum of histological changes seen.

Many of the features present are also seen in benign dermatoses

ORIGINAL ARTICLE

### Histopathologic Features of Early (Patch) Lesions of Mycosis Fungoides

*A Morphologic Study on 745 Biopsy Specimens From 427 Patients*

*Cesare Massone, MD,\*† Kazuo Kodama, MD,\*‡ Helmut Kerl, MD,\* and Lorenzo Cerroni, MD\**

*Am J Surg Pathol 2005; 29: 550-60*

#### Some changes present in high percentage of cases

- Not specific for MF – also seen in, and sometimes more typical of benign dermatoses

#### Features which might be predictive of MF

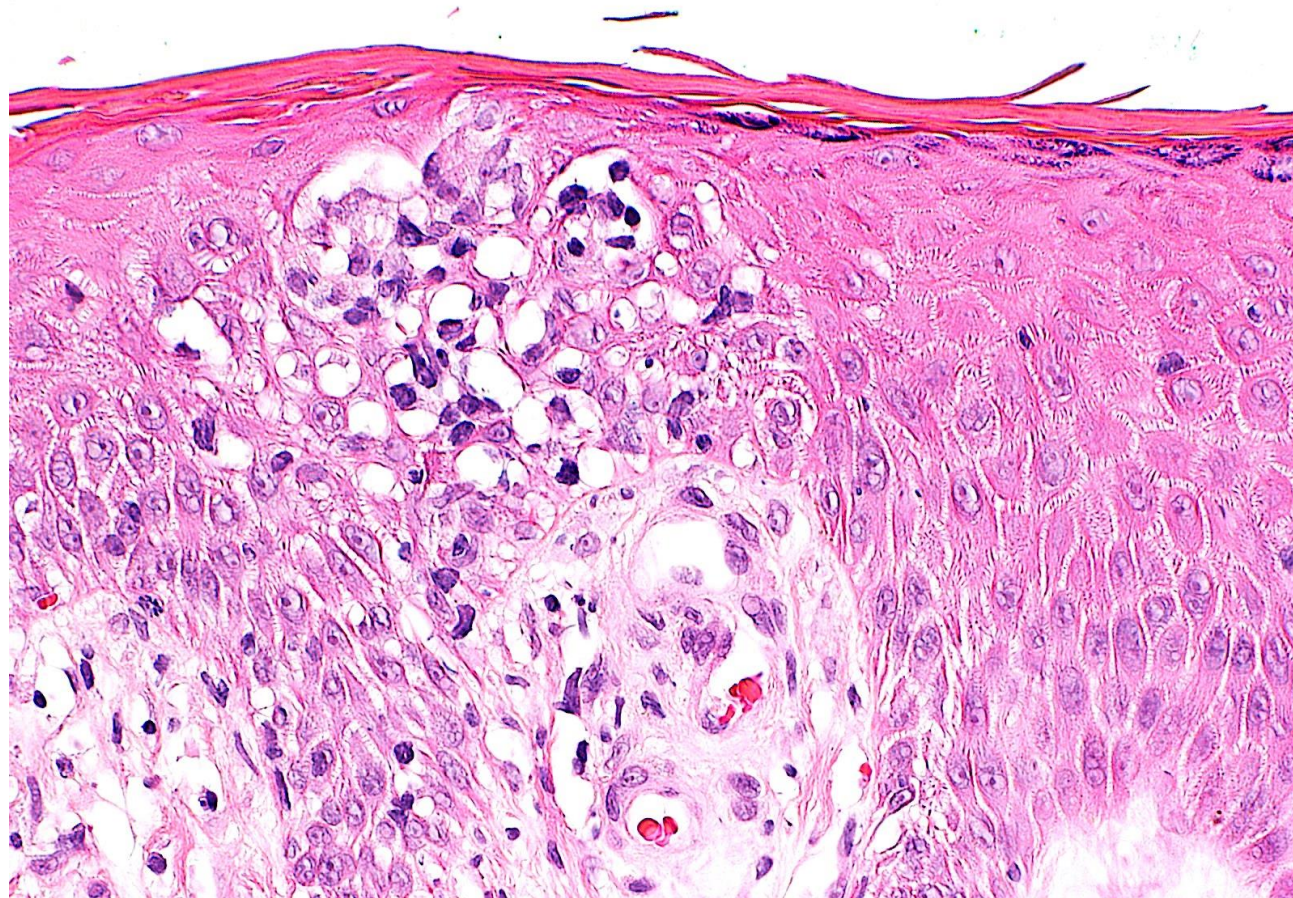
- Relatively infrequently seen
- Usually in association with non-specific changes or changes more frequently associated with dermatoses

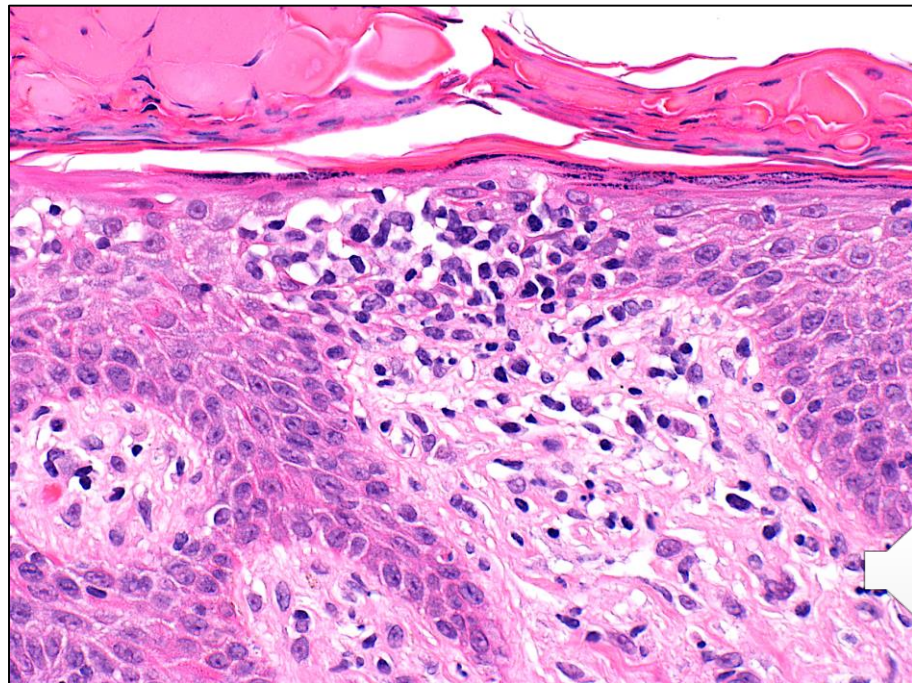
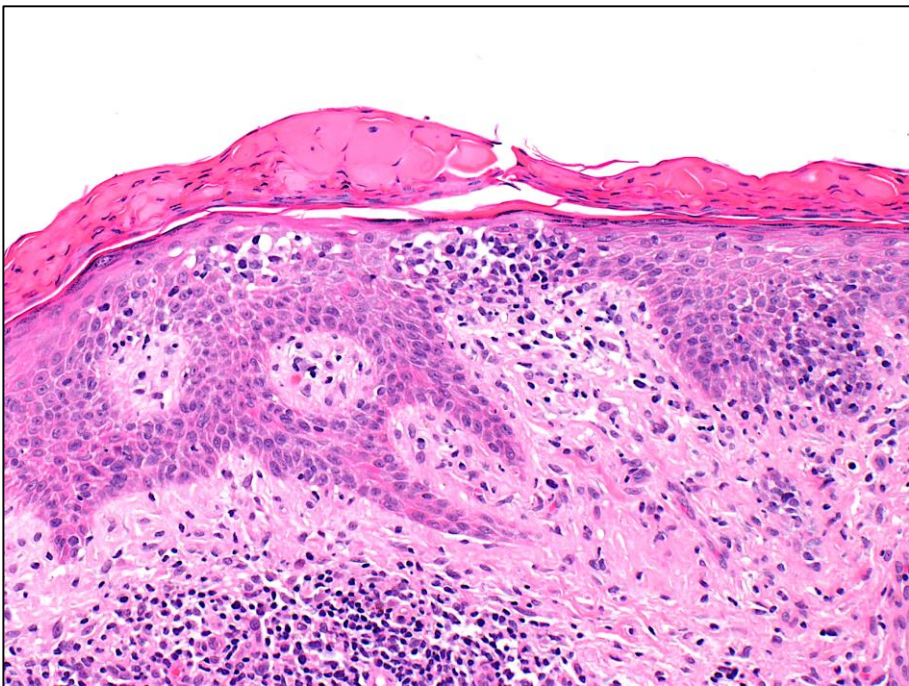
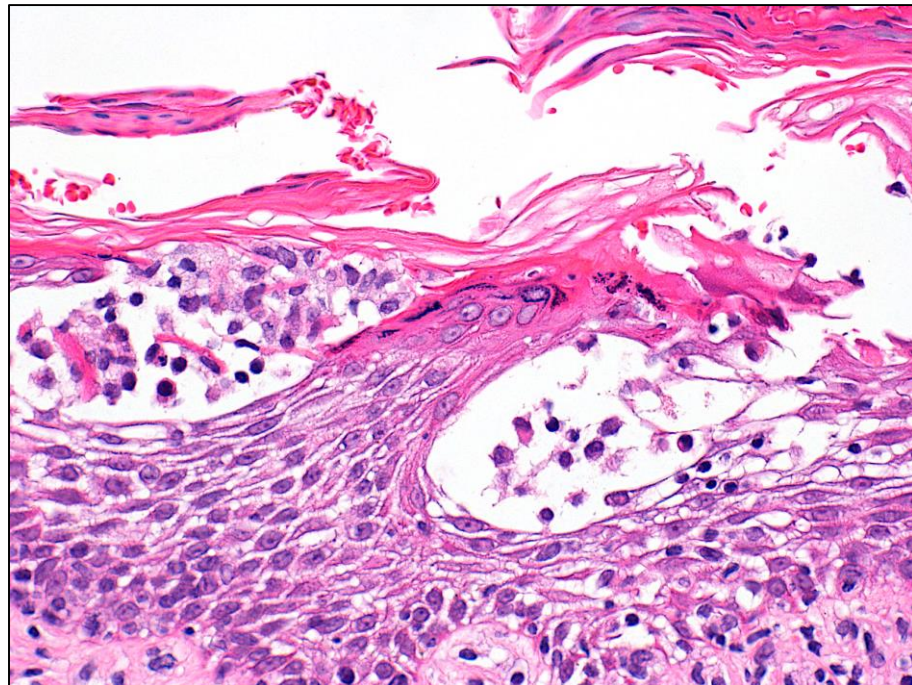
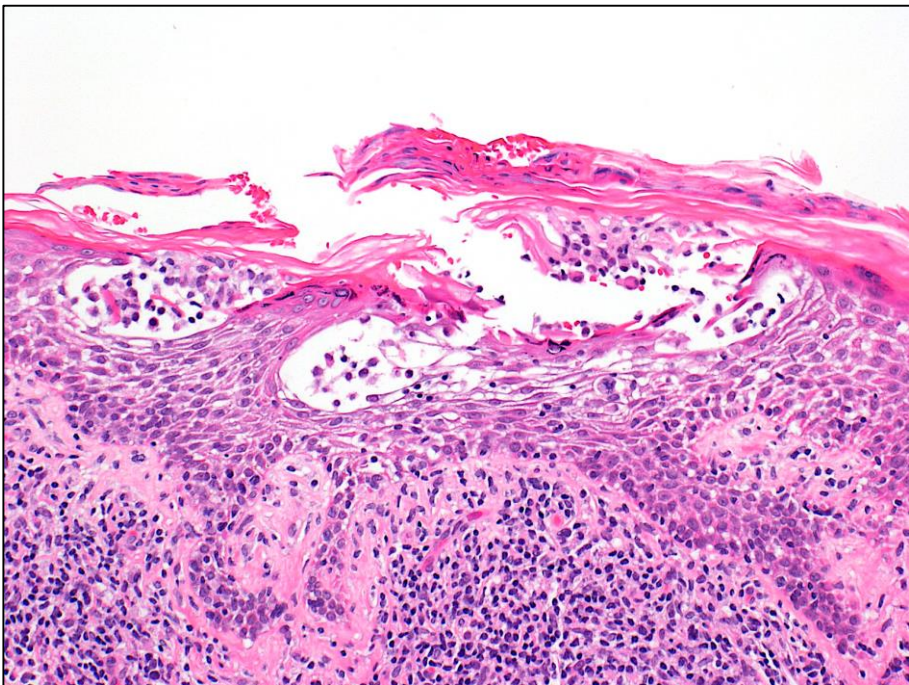
**TABLE 1.** Histologic Features of Early (Patch) Lesions of MF Observed in 745 Biopsy Specimens

Feature	No. (%)
Normal epidermis	356 (48)
Psoriasiform hyperplasia	258 (35)
Irregular hyperplasia	34 (4)
Flat and/or atrophic epidermis	97 (13)
Marked spongiosis	28 (4)
Necrotic keratinocytes	172 (23)
Changes at the dermoepidermal junction	
Focal interface dermatitis	438 (59)
Widespread interface dermatitis	30 (4)
Epidermotropism*	
Single lymphocyte epidermotropism	161 (22)
Basilar lymphocytes	170 (23)
Pautrier's microabscesses	140 (19)
"Haloed" lymphocytes	298 (40)
Disproportion exocytosis	124 (17)
Pagetoid epidermotropism	17 (3)
Absence of epidermotropism	32 (4)
Atypical lymphocytes	
Only in the epidermis	27 (4)
Both in epidermis and dermis	38 (5)
Only in the dermis	2 (0.3)
Dermal lymphocytic infiltrate	
Band-like	227 (30)
Patchy-lichenoid	492 (66)
Superficial perivascular	26 (3)
Dermal changes	
Papillary dermal fibrosis/coarse collagen bundles	725 (97)
Melanophages	56 (8)
Purpura	32 (4)
Edema of the papillary dermis	0

\*More than one feature was observed in some cases.

**HISTOLOGICAL OVERLAPS: presence of spongiosis is often a compounding feature**





# Topical therapies may modify histological picture.....

**Patients often treated with skin directed therapy prior to biopsy**

- Topical steroid
- UV light

**Alters histological picture towards an inflammatory process**

- Inflammatory cells/reactive lymphocytes often predominate in papillary dermis
- intra-epidermal lymphocytes disproportionately targeted by skin directed therapies

**Should always recommend withdrawal of treatment for at least 2-4 weeks prior to biopsy**



# What features help establish a diagnosis?

- **Morphologic**
- **Phenotypic**
- **Molecular**
- **Clinical**

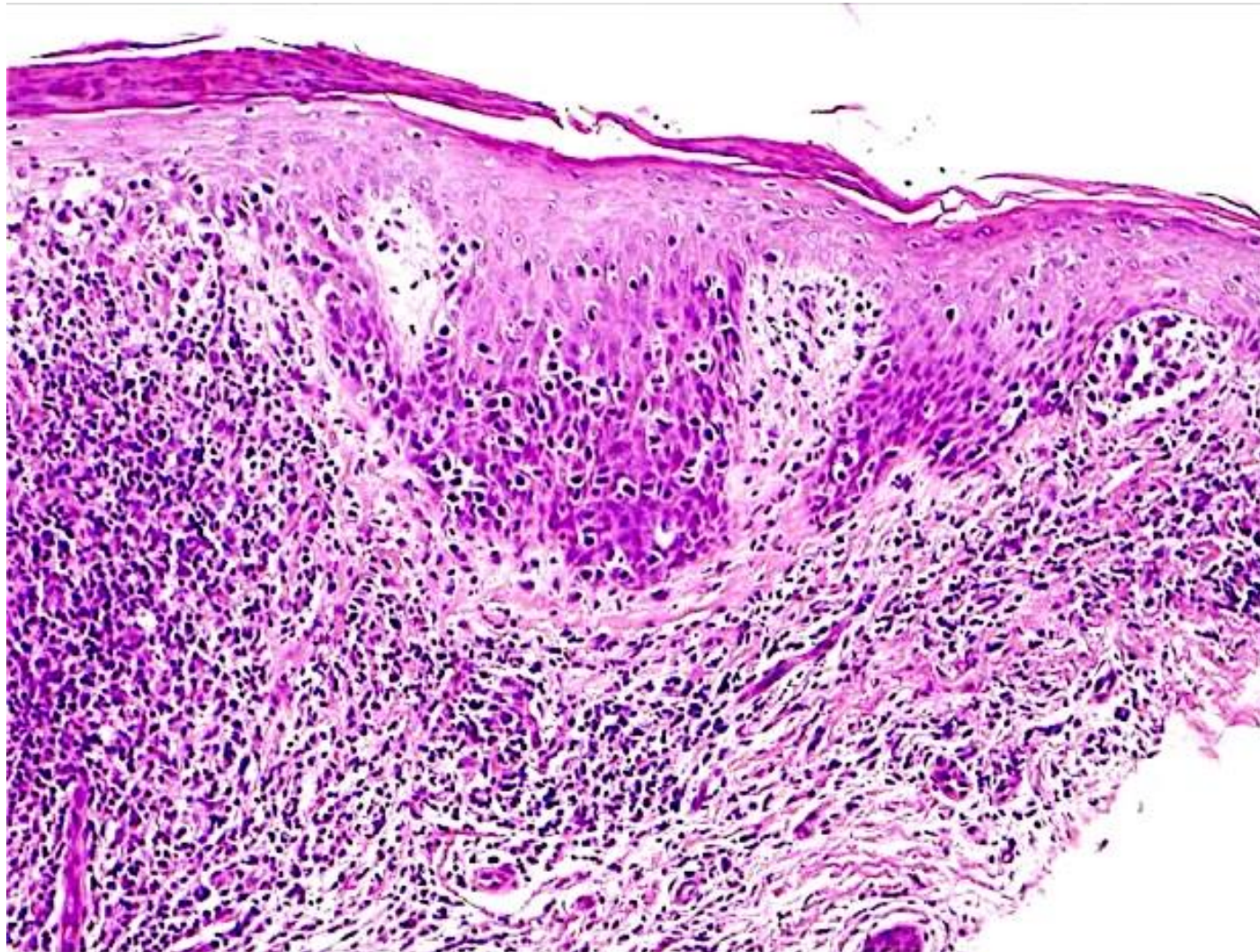


## MORPHOLOGIC FEATURES PREDICTIVE OF MF

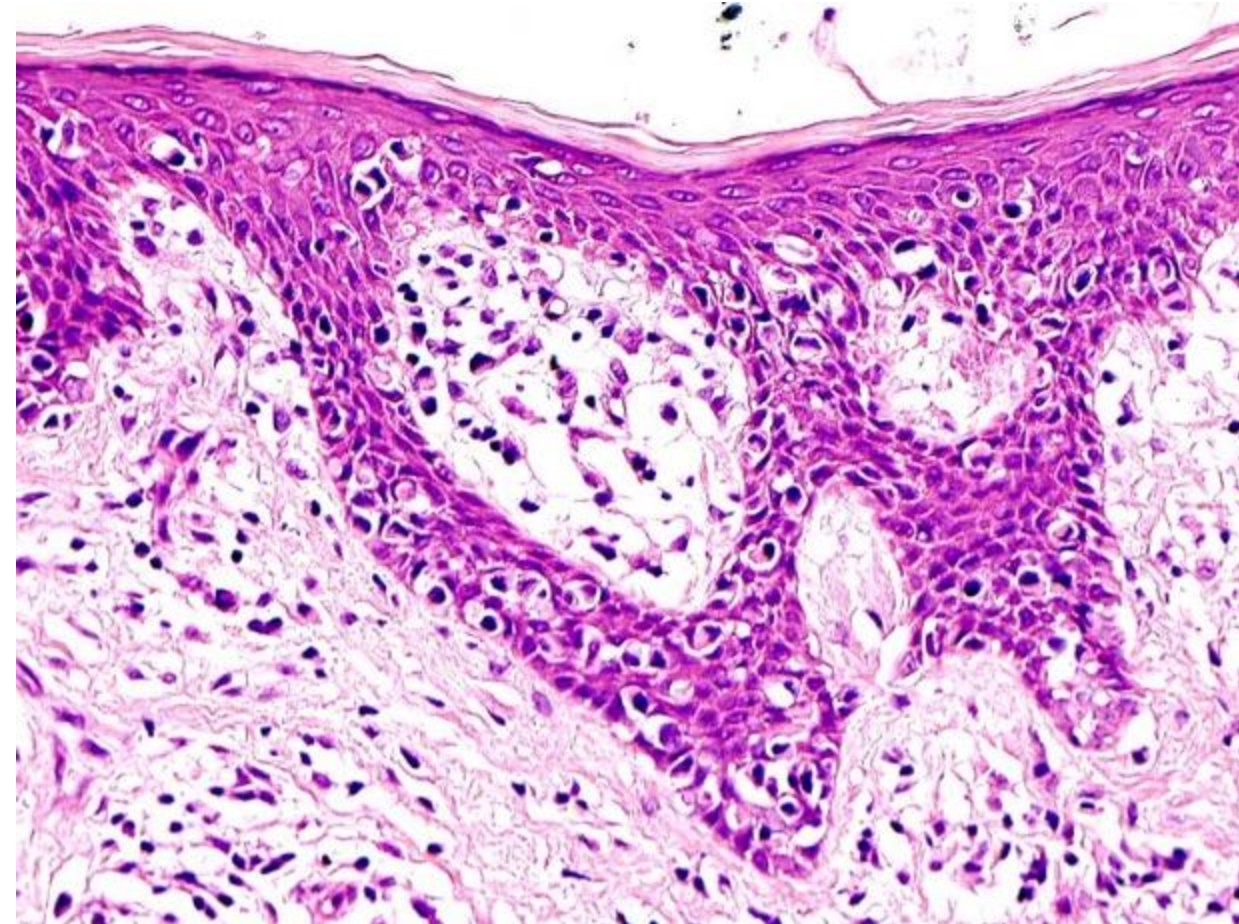
- Linear epidermotropism
- Disproportionate epidermotropism
- Medium/large cerebriform cells in epidermis
- Pautrier's microabscesses



**Disproportionate number of intraepidermal lymphocytes**  
(for degree of spongiosis/inflammatory features)



## “Medium/large cerebriform cells” and “haloed: lymphocytes”



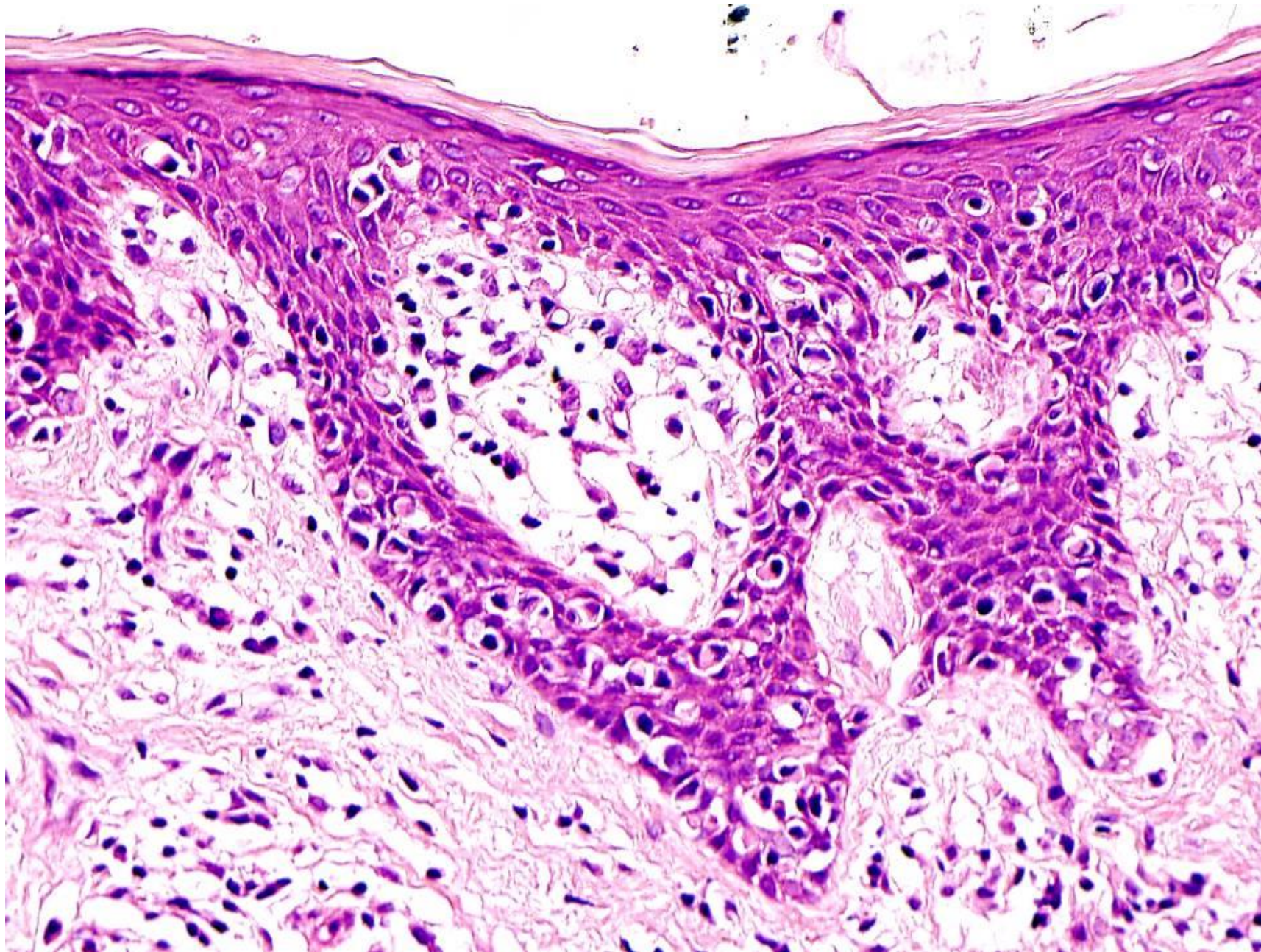
### **Medium/large cerebriform cells**

- Neoplastic lymphocytes in MF possess larger nuclei than present in concurrent dermal lymphocytes (the latter are often inflammatory in nature)
- The nuclei are usually hyperchromatic with irregular convoluted nuclear outlines.
- Same size or larger than adjacent keratinocytes
- Presence reported as relatively specific although possibly not sensitive for mycosis fungoides

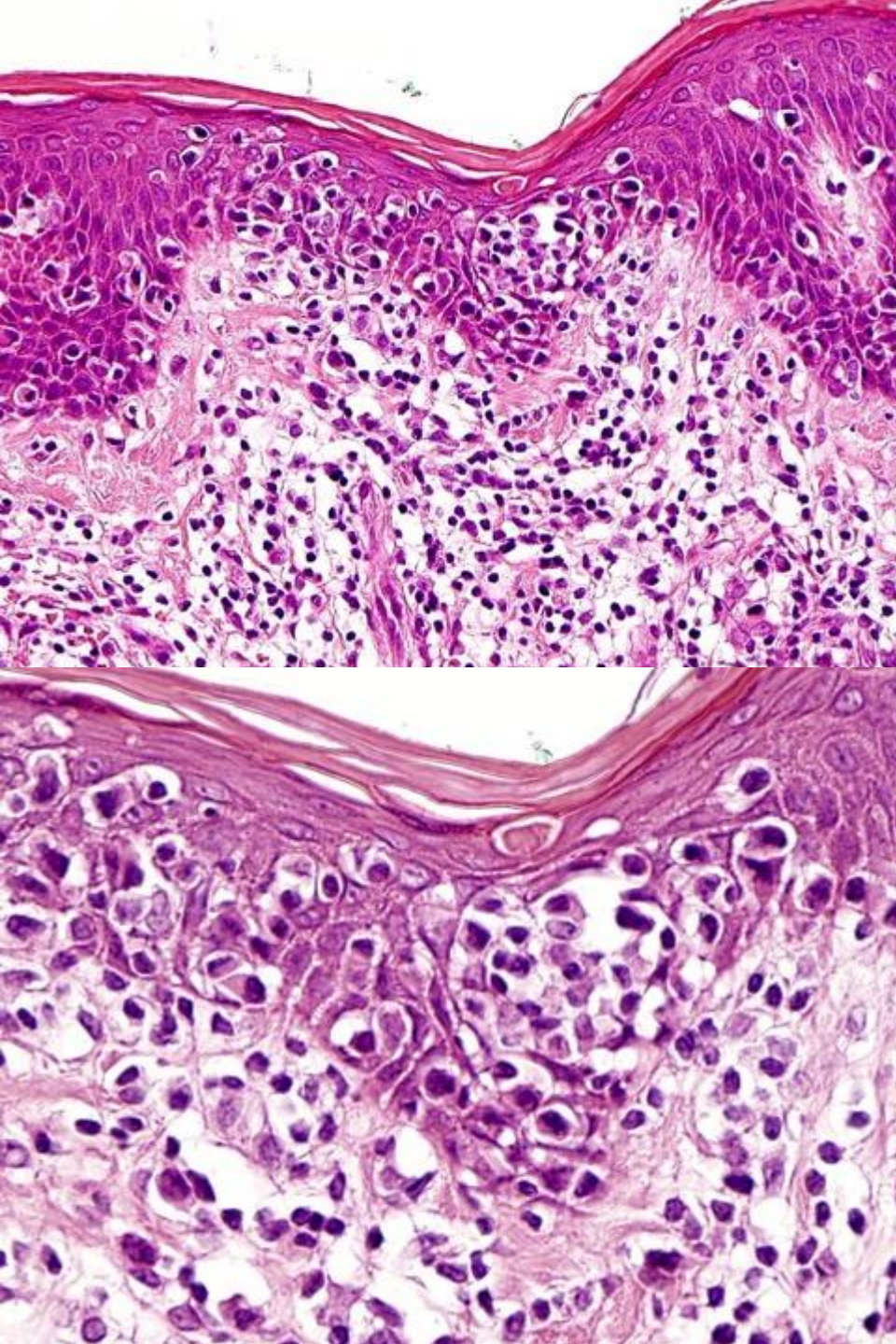
### **“Haloed lymphocytes”**

- Individually scattered intraepidermal lymphocytes
- Apparent perinuclear cytoplasmic clearing
- Results from artefactual cytoplasmic retraction





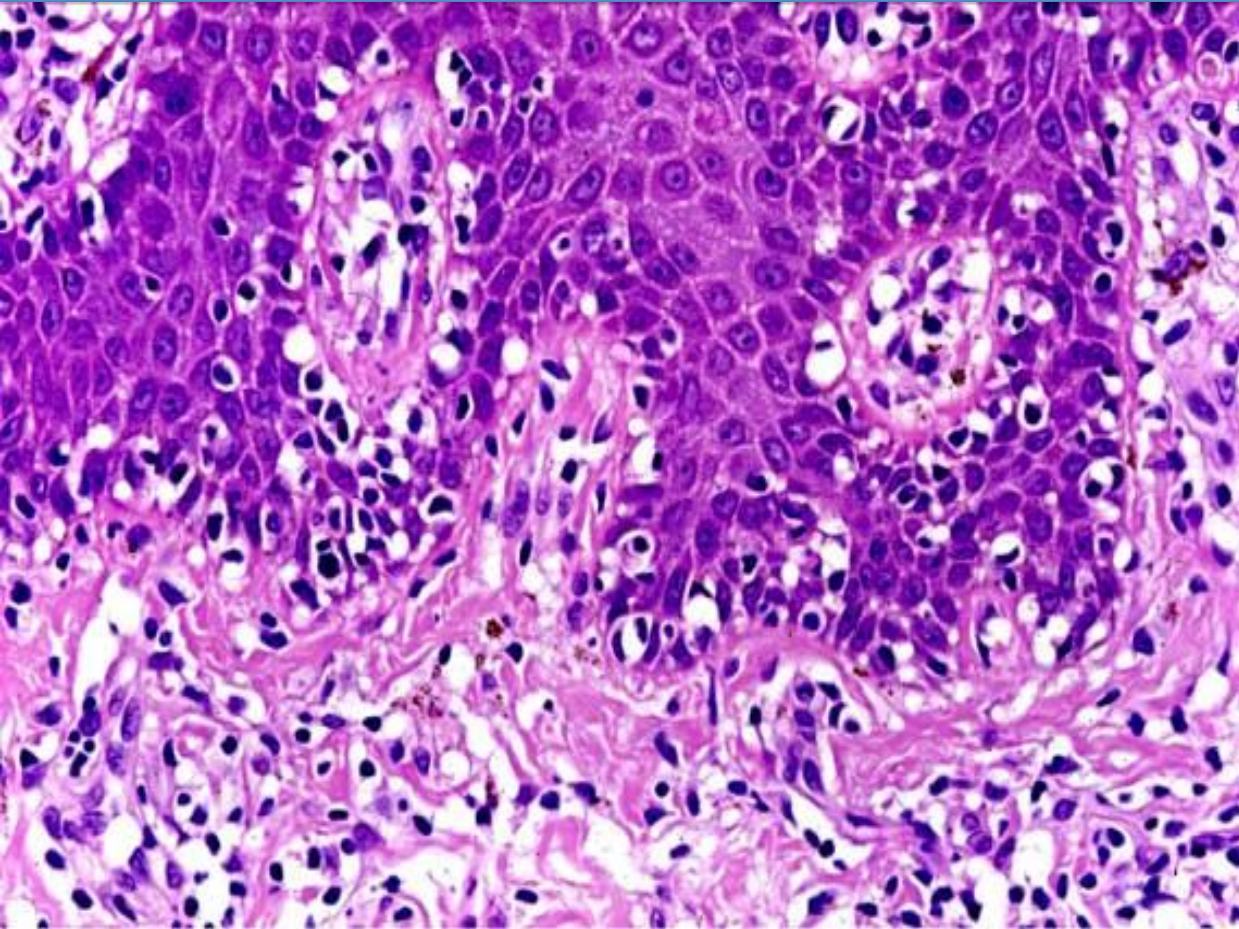
## Pautrier's microabscesses



- Well circumscribed, variably sized collections of closely apposed neoplastic T-cells within the epidermis
- Constituent lymphocytes are usually of similar size and irregularity
- Occasional dendritic cells may also be present
- Microabscesses lack features more commonly associated with spongiotic vesicles
  - Plasma and/or fibrin
  - Cytopathic changes in the adjacent epidermis.



## “Linear basilar epidermotropism”



**Formation of linear arrays of neoplastic lymphocytes in the basal layer epidermis**

- Span several rete ridges
- Pattern of epidermotropism that is thought to be sensitive although not entirely specific for mycosis fungoides



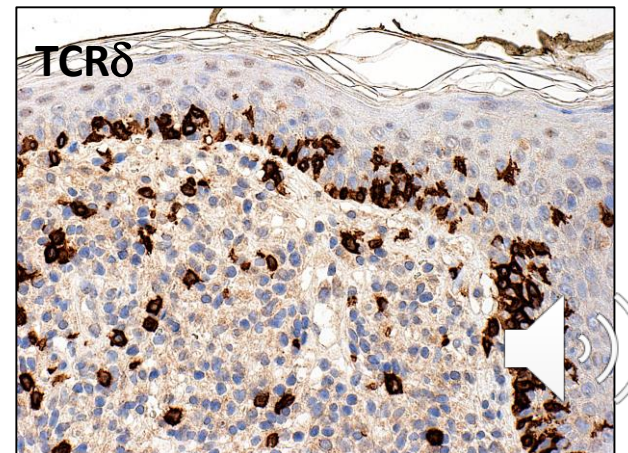
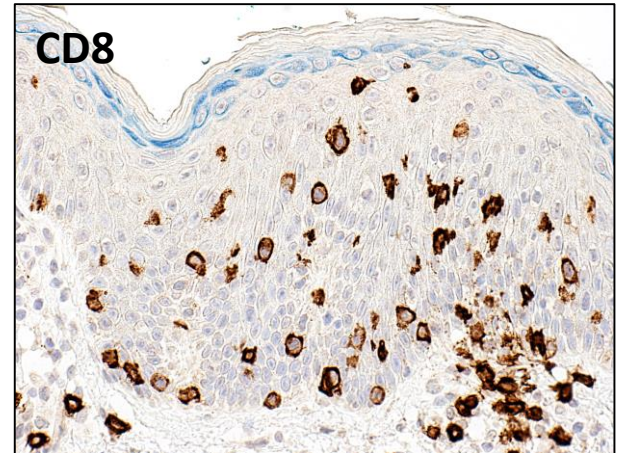
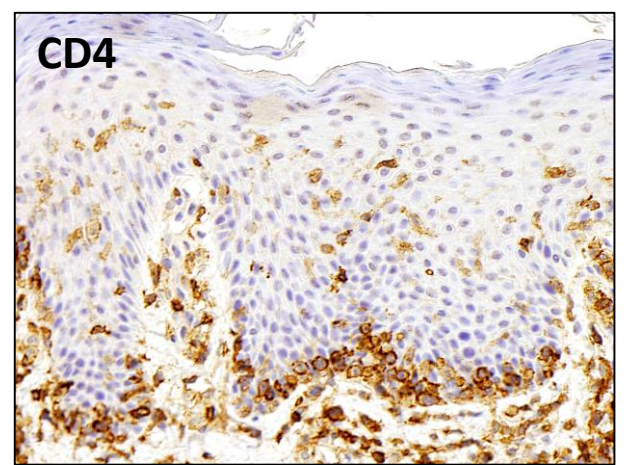
# PHENOTYPE

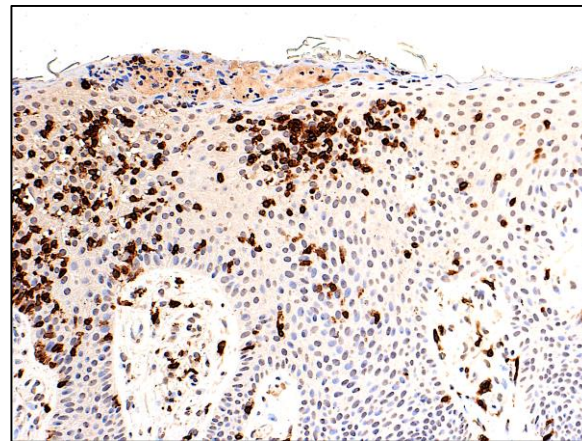
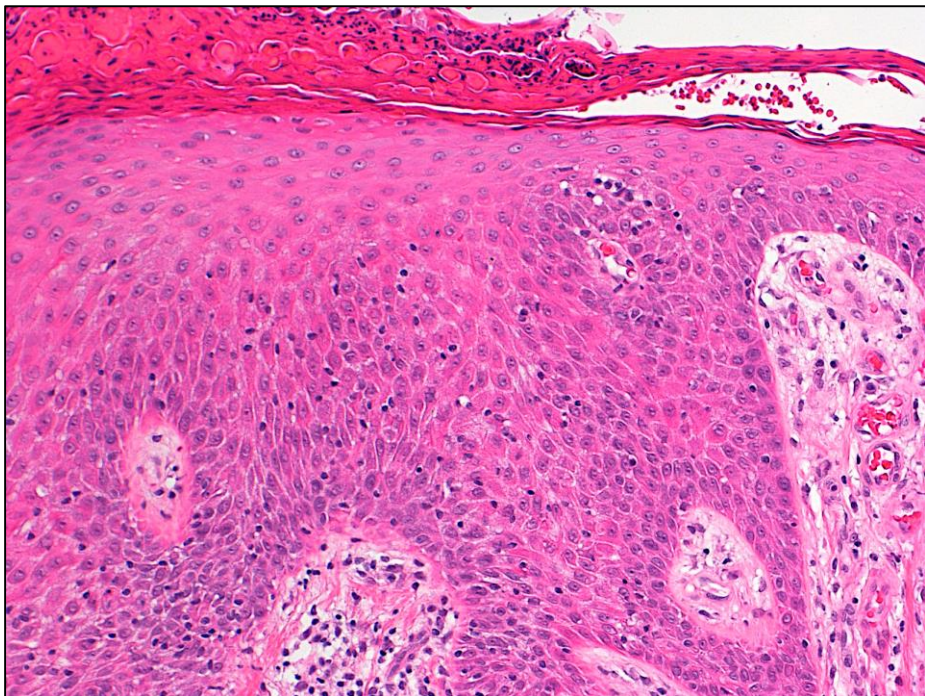
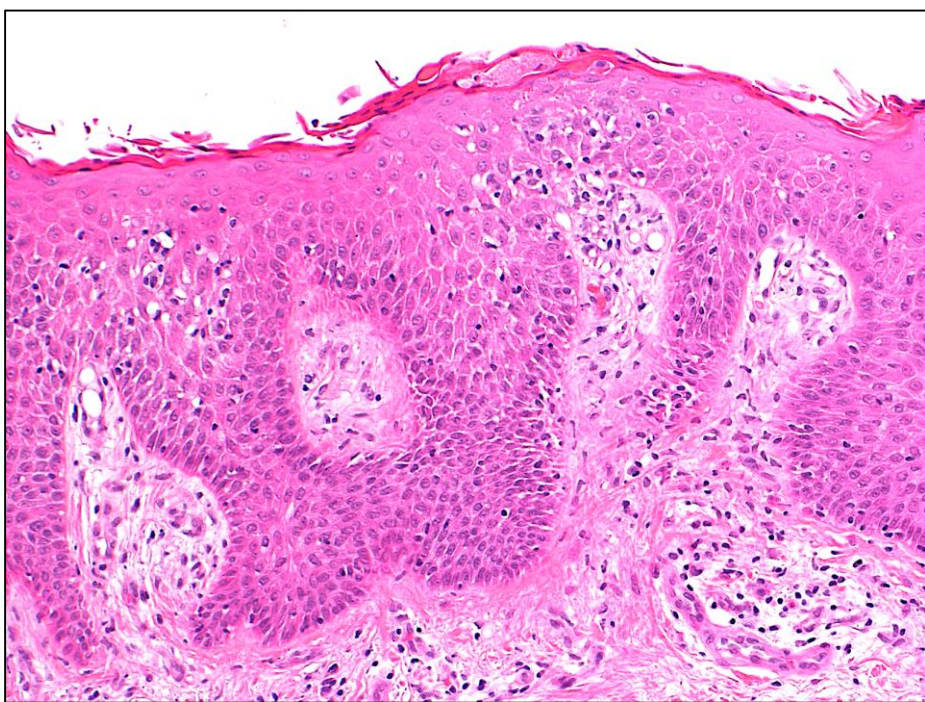
Mycosis fungoides typically a neoplasm of CD4+ T-cells, but variants described

- CD8+ (younger patients)
- CD56+
- CD4-/CD8-
- $\gamma/\delta$  TCR
- In order to qualify as MF, these phenotypically unusual cases must present typically and run normal relatively indolent course

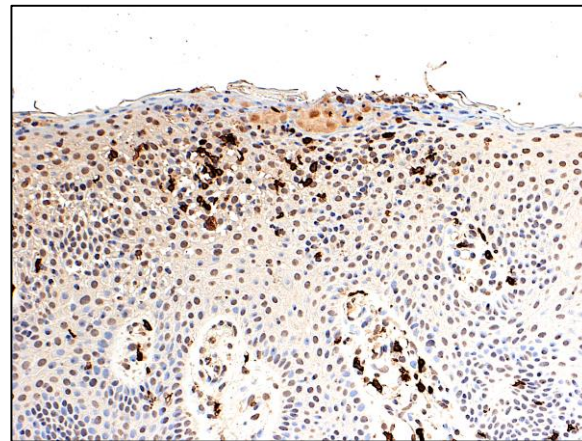
Pan-T-cell antigens may be lost but often not in early stages

- CD7 > CD2, CD3, CD5
- Partial loss of CD7 frequent in MF but limited value as similar in variety of benign dermatoses: complete/near complete loss perhaps more significant

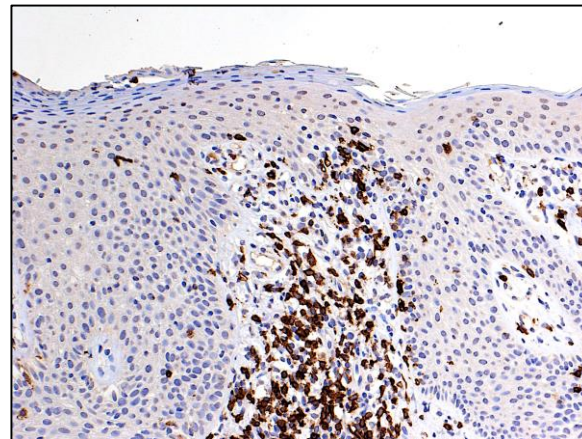




**CD3**

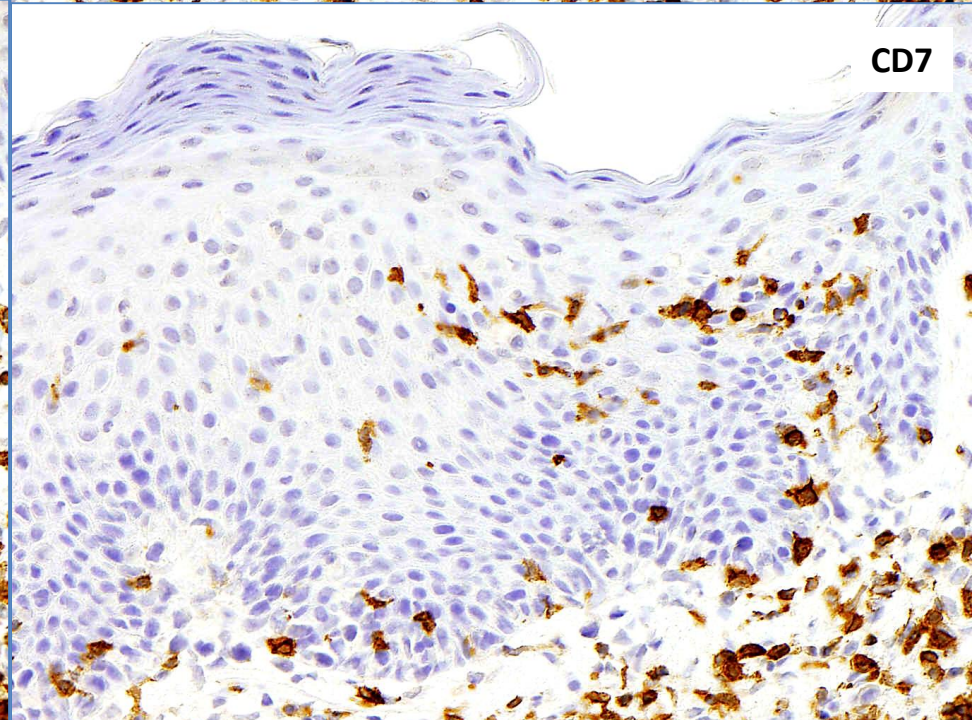
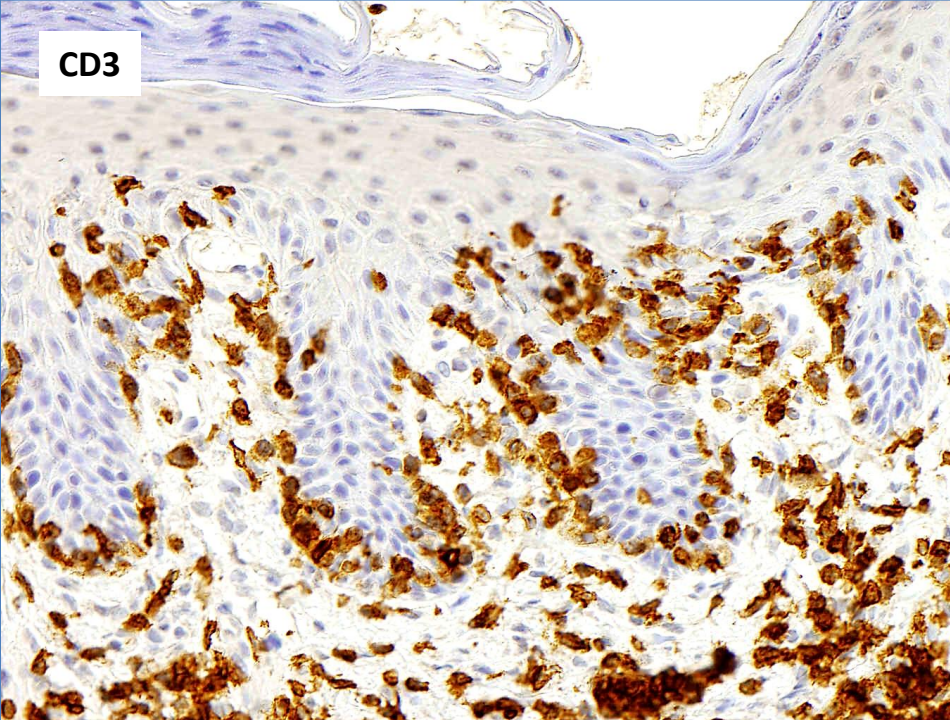
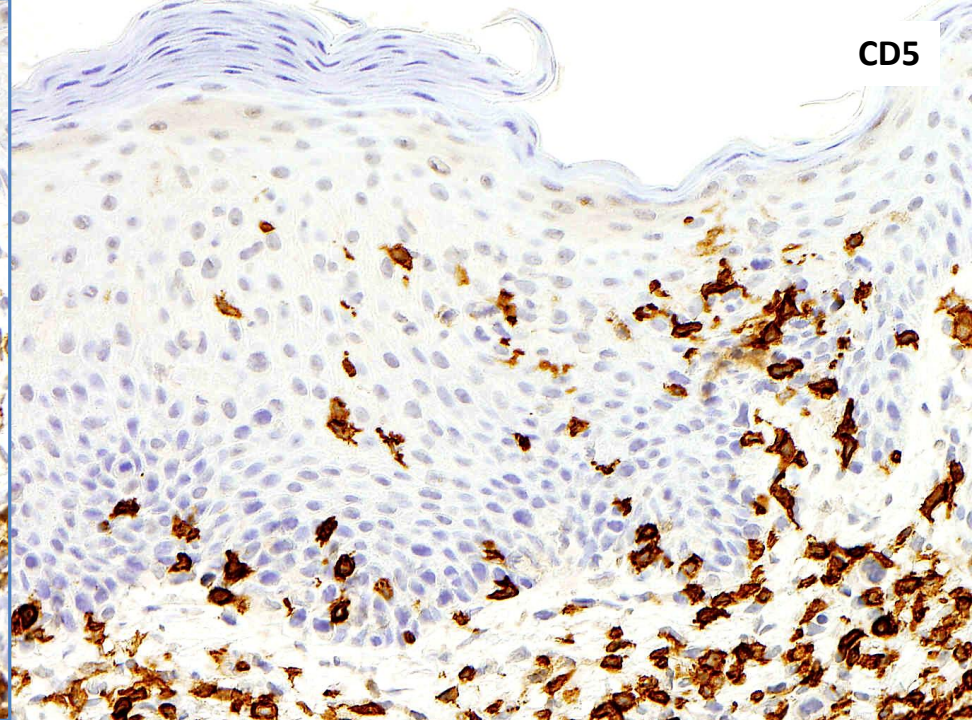
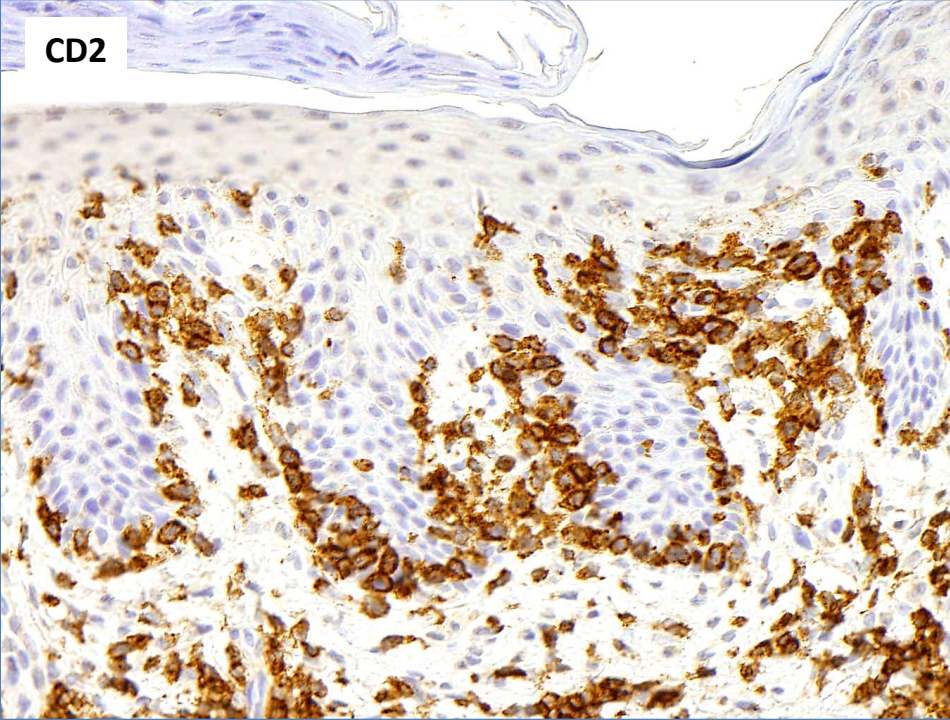


**CD5**



**CD7**





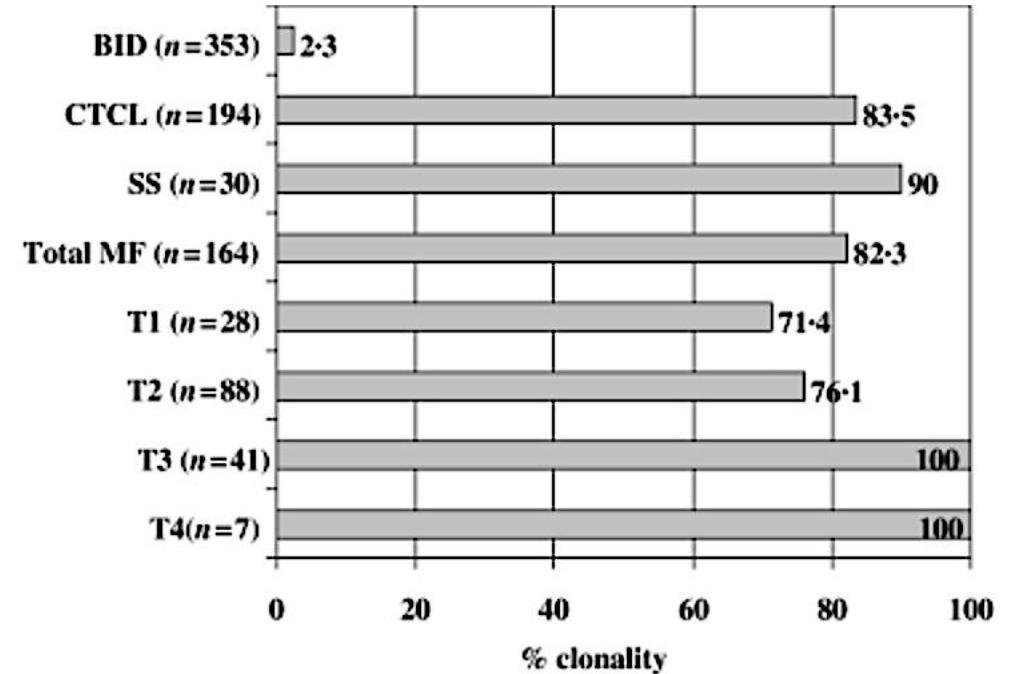
# CLONALITY:

**Demonstrating dominant T-cell clone is not specific and variably sensitive.....**

**Benign dermatoses may harbour dominant clones**

**Clonality less sensitive for early stages of disease**

Authors	Dermatosis	Tissue	Techniques	Number of cases clonal
Schiller et al. [49]	Lichen planus	FFPE	PCR-TCRG/DGGE and Genescan	9/36 <sup>a</sup>
Lukowsky et al. [50]	Lichen planus	FFPE	PCR-TCRG/HD and GeneScan	3/14
Lukowsky et al. [50]	Lichen sclerosis	FFPE	PCR-TCRG/HD and GeneScan	19/39
Shieh et al. [51]	PLC	Fresh/frozen	PCR-TCRG/DGGE	3/6 <sup>a</sup>
Plaza et al. [55]	PLC	FFPE	PCR-TCRB/GeneScan	2/9
Magro et al. [52]	PLC	FFPE	PCR-TCRB/GeneScan	24/46 <sup>a</sup>
Weis et al. [53]	PLEVA	Fresh/frozen	Southern blot	3/3 <sup>a</sup>
Dereure et al. [54]	PLEVA	FFPE	PCR-TCRG/HD	13/20 <sup>b</sup>
Plaza et al. [55]	PLEVA	FFPE	PCR-TCRB/GeneScan	2/4 <sup>a</sup>
Toro et al. [56]	PPD	FFPE	PCR-TCRG/PAGE	12/17 <sup>b</sup>
Plaza et al. [55]	PPD	FFPE	PCR-TCRB/GeneScan	3/11 <sup>a</sup>
Crowson et al. [57]	PPD	FFPE	PCR-TCRG/Agarose gels	4/12
Kreuter et al. [58]	Systemic sclerosis	Fresh/frozen	PCR-TCRG/GeneScan	20/44
Magro et al. [60]	Lupus profundus	FFPE	PCR-TCRG/PAGE	8/19
Plaza et al. [55]	DLE	FFPE	PCR-TCRG/GeneScan	1/2
Choi et al. [62]	Drug induced HSR	FFPE	PCR-TCRG/PAGE	1/8
Brady et al. [61]	Drug induced HSR	FFPE	PCR-TCRG/DGGE	2/14
Plaza et al. [55]	Drug induced HSR	FFPE	PCR-TCRG/GeneScan	5/15 <sup>a</sup>
Thurber et al. [59]	Erythema nodosum	Not stated	PCR-TCRG/GeneScan	1/1
Thurber et al. [59]	Psoriasis	Not stated	PCR-TCRG/GeneScan	1/8
Ponti et al. [15]	Chronic eczema	Fresh/frozen	PCR-TCRG/HD	3/8



**Demonstration of identical clone in more than one biopsy is much more predictive of MF**



# It is not just us that find it difficult!

## Diagnosing early (patch/early plaque stage) mycosis fungoides is difficult and can take a long time

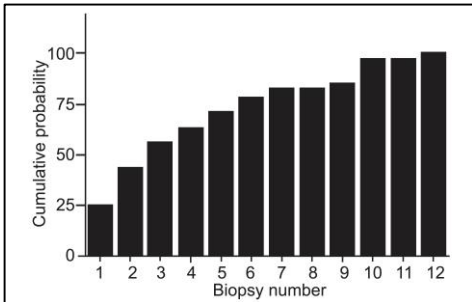
Acta Derm Venereol 2015; 95: 472–475

### CLINICAL REPORT

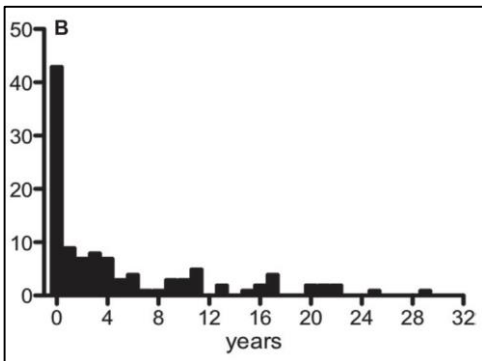
#### Delay in the Histopathologic Diagnosis of Mycosis Fungoides

Anne G. SKOV and Robert GNIADCKI

Department of Dermatology, University of Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark



Cumulative probability of a positive biopsy as a function of biopsy sequence number.



Onset of disease to diagnostic biopsy

Multiple biopsies often required and in some cases diagnosis based purely on clinical grounds

- Diagnosis on first Bx: 24%
- Diagnosis on subsequent Bx: 45.9%
- Diagnosis never made on Bx: 29.3%

Cumulative probability increases in line with number of biopsies

In cases where multiple biopsies required, median time from onset of skin symptoms to diagnosis = 4.3 years

(similar findings in Suzuki SY et al, J Dermatol Sci 2010; Kim YH et al, Arch Dermatol 2003; Quaglino P et al, Cancer 2012; van Doorn R et al, Arch Dermatol 2000



## 2. Differential diagnosis of epidermotropic cutaneous T-cell lymphomas

**IT'S NOT JUST MYCOSIS FUNGOIDES!**



# EPIDERMOTROPIC CUTANEOUS T-CELL LYMPHOMAS

**Epidermotropic cutaneous T-cell lymphoproliferative disorders and lymphomas exhibit a broad range of clinical behaviour**

- Lesions that spontaneously regress
- Rapidly progressing aggressive malignancies that are often fatal

**Accurate diagnosis essential for prognostication and to ensure appropriate treatment; not always straightforward**

- For some entities the pathological appearances do not accurately predict biology
- Certain disease subtypes show considerable overlap in the pathological features they display
- Clinical correlates are essential for establishing some diagnoses in many/most



## **Main problem lies with those displaying a cytotoxic phenotype**

- CD8+ mycosis fungoides
- Mycosis fungoides with  $\gamma/\delta$  phenotype
- Lymphomatoid papulosis variants (some)
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous  $\gamma/\delta$  T-cell lymphoma

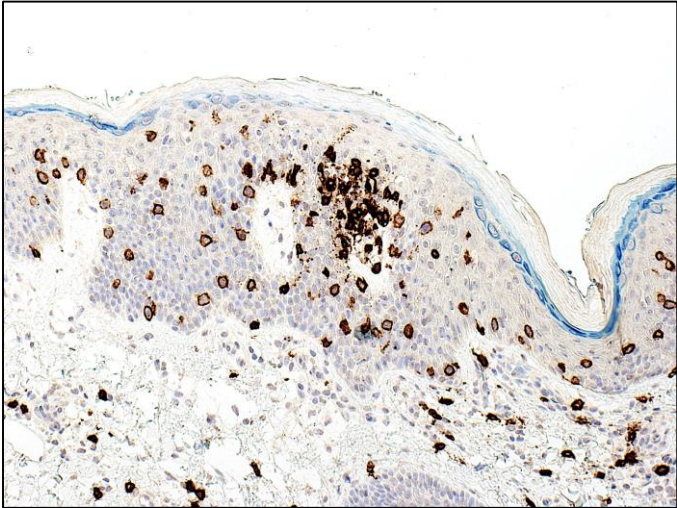
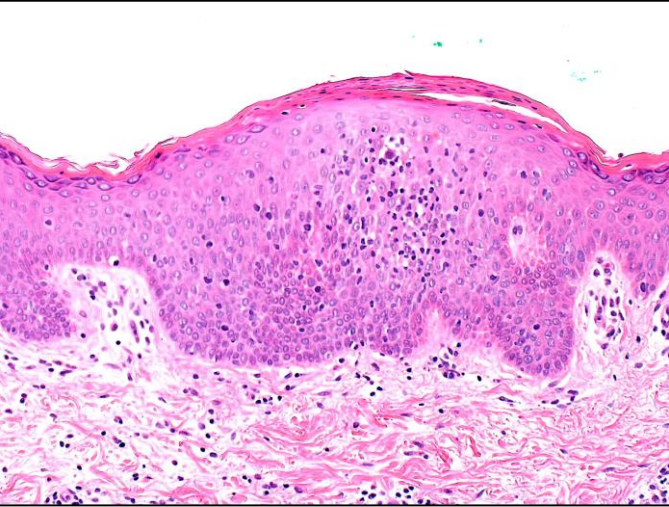
## **Narrower differential for CD4-positive cases**

- Typical mycosis fungoides
- Lymphomatoid papulosis variants (some)
- Some systemic lymphomas, e.g. adult T-cell leukaemia/lymphoma

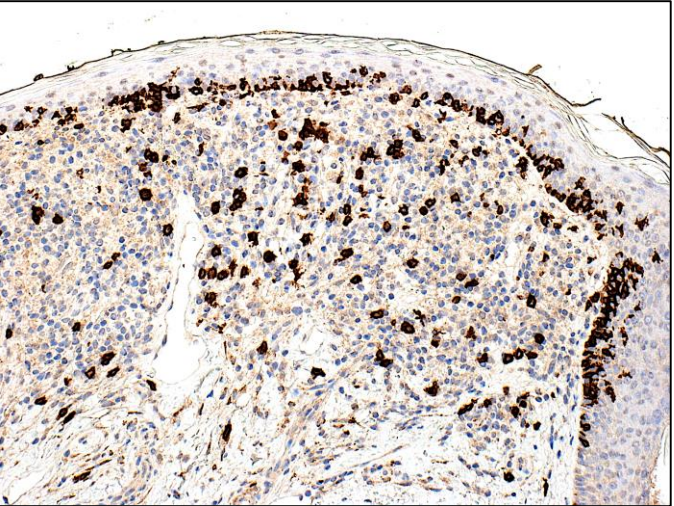
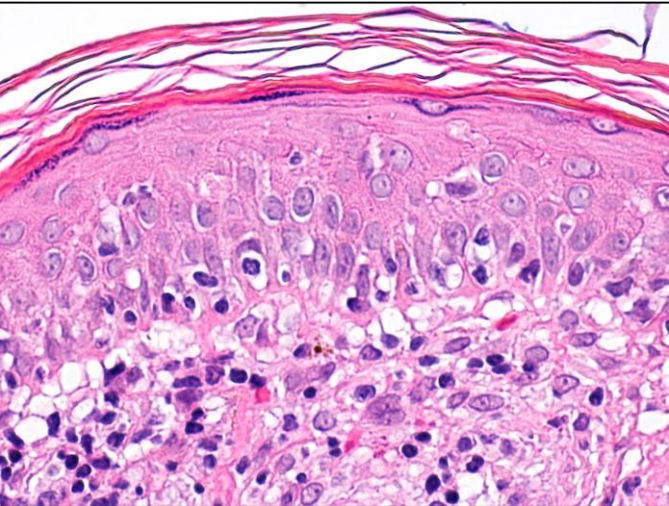


# Mycosis fungoides with unusual phenotype

**CD8+ MF:** young, early stage disease, hypopigmented patches, favourable prognosis (probably related to stage)



**MF with  $\gamma/\delta$  phenotype:** looks and behaves like typical MF



# LYMPHOMATOID PAPULOSIS: LARGELY A CLINICAL DIAGNOSIS

- Crops of papular, papulonecrotic, nodular skin lesions
- Grouped but may be in different stages of development
- Spontaneous regression of individual lesion; 3-6 weeks
- Chronic but benign course; months-years
- 5 year survival ~100%
- No treatment required or low dose methotrexate, PUVA or XRT for large, numerous or scarring lesions
- **Problems in diagnosis arise when histological variants encountered**

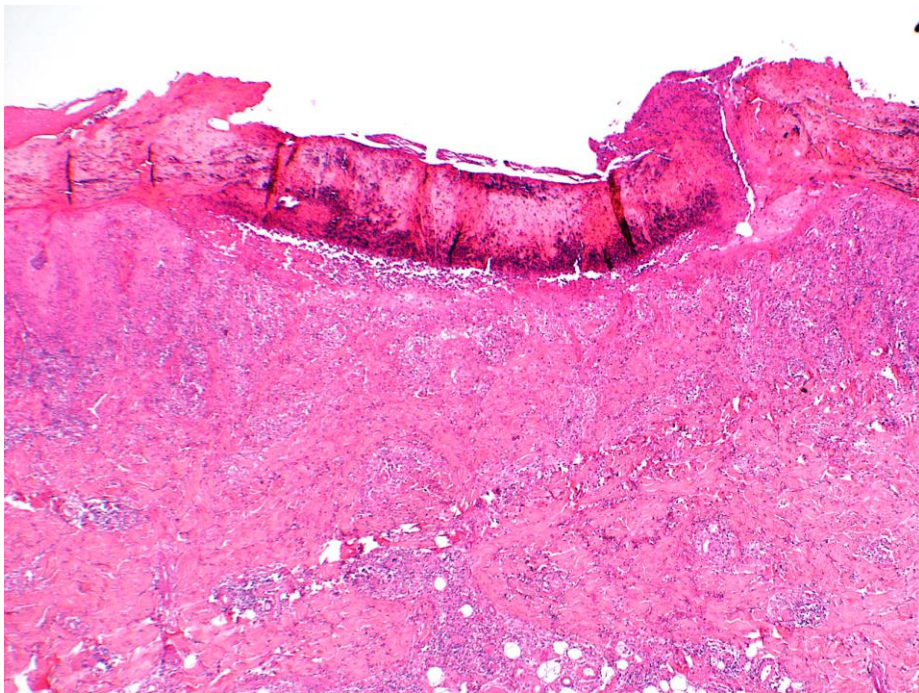


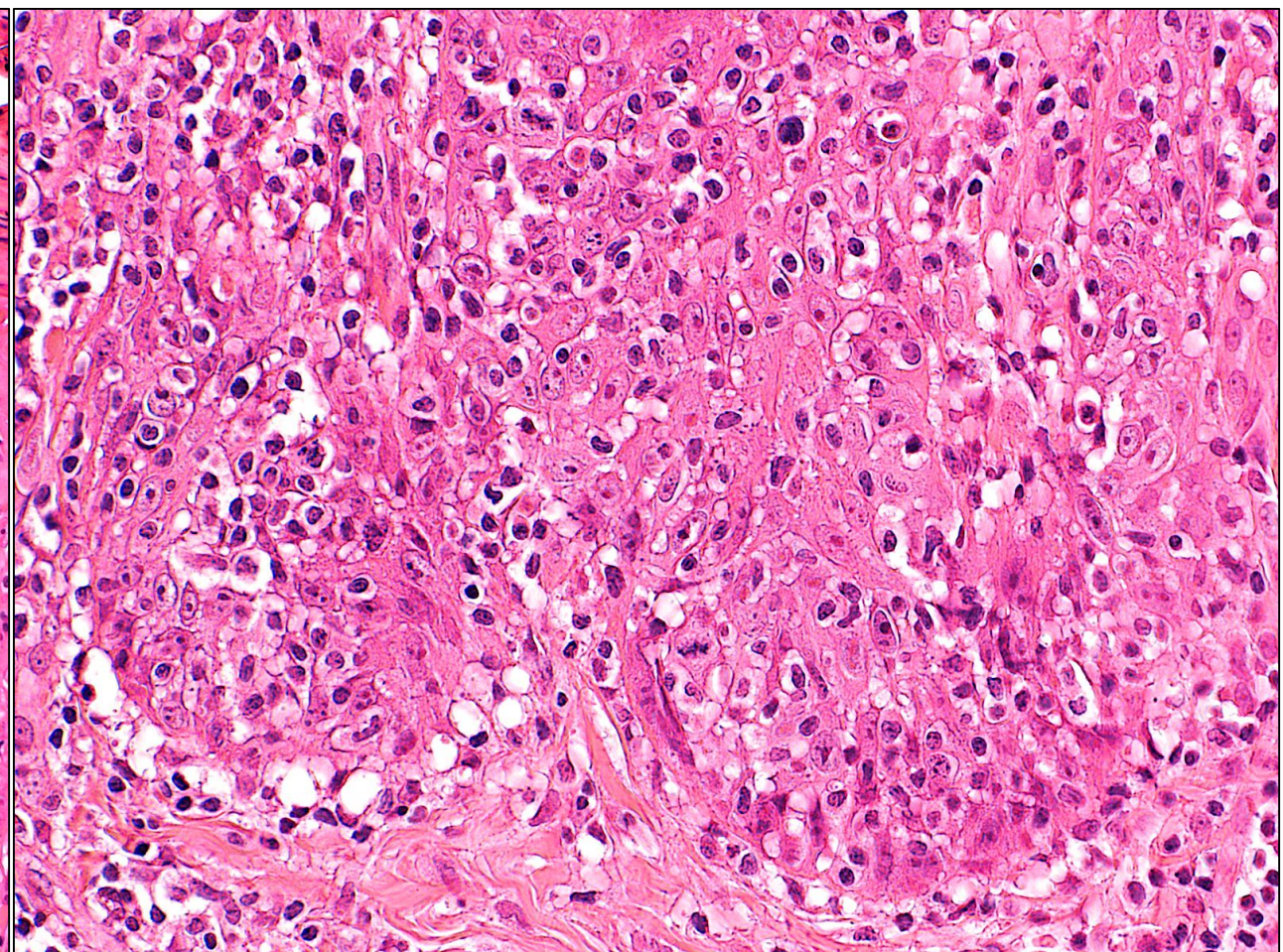
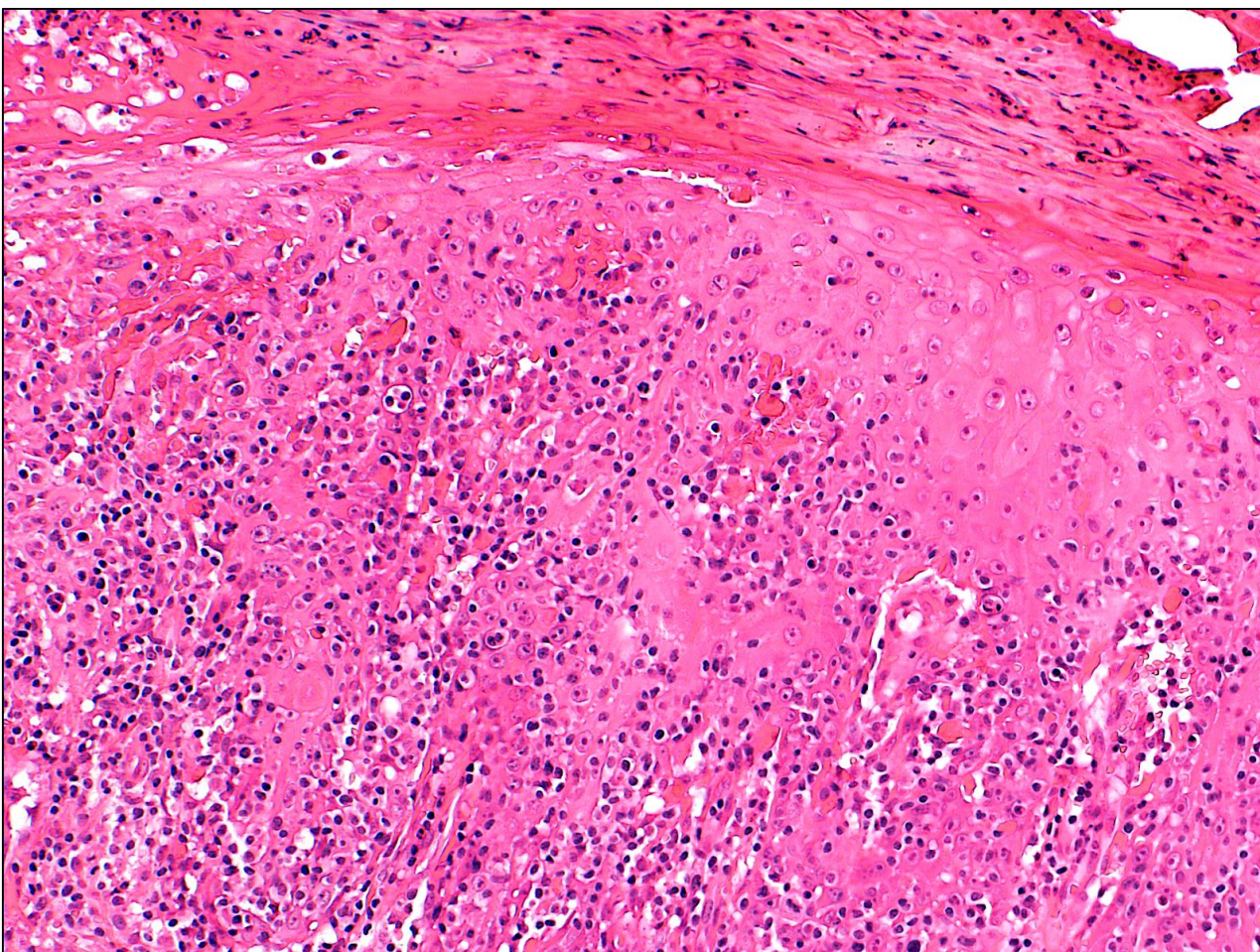
# Lymphomatoid papulosis type D: Saggini A et al, Am J Surg Path 2010;34:1168

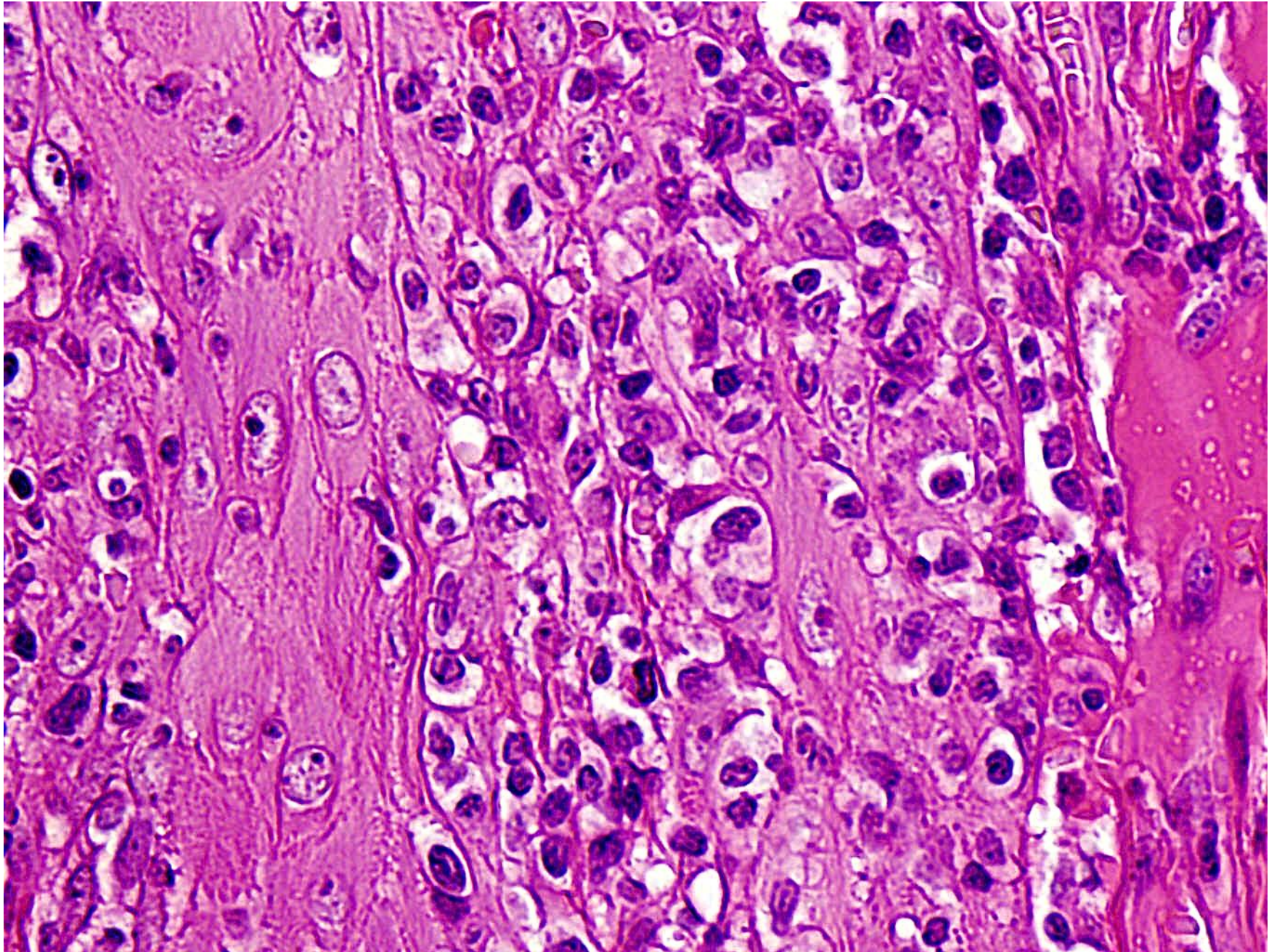
- LyP variant characterised by prominent epidermotropism and cytotoxic phenotype
- (LyP-B: similar morphology, CD4+)

## Clinical case

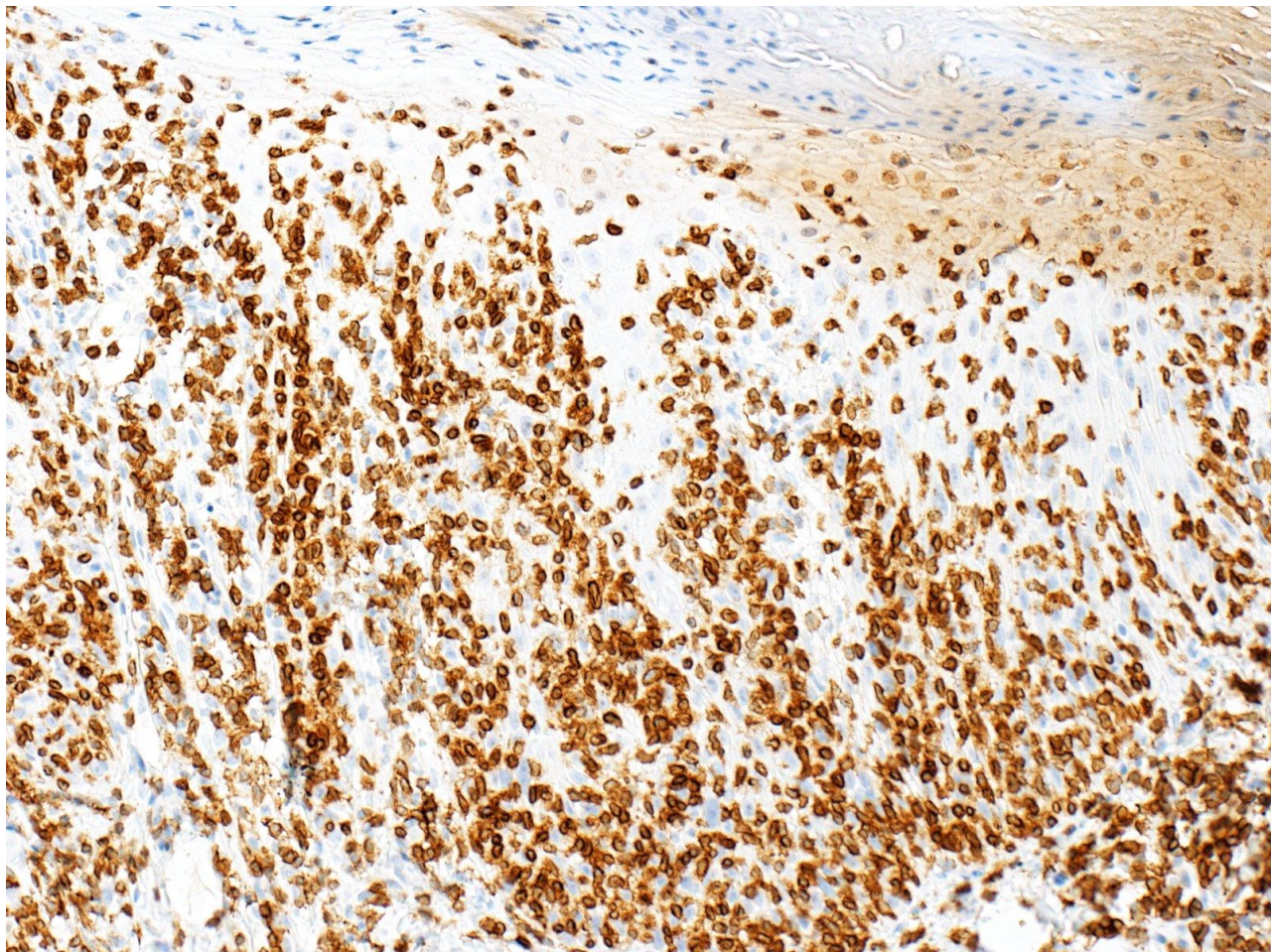
- 48 year old male with ulcerating papules on fingers and face
- Resolve spontaneously



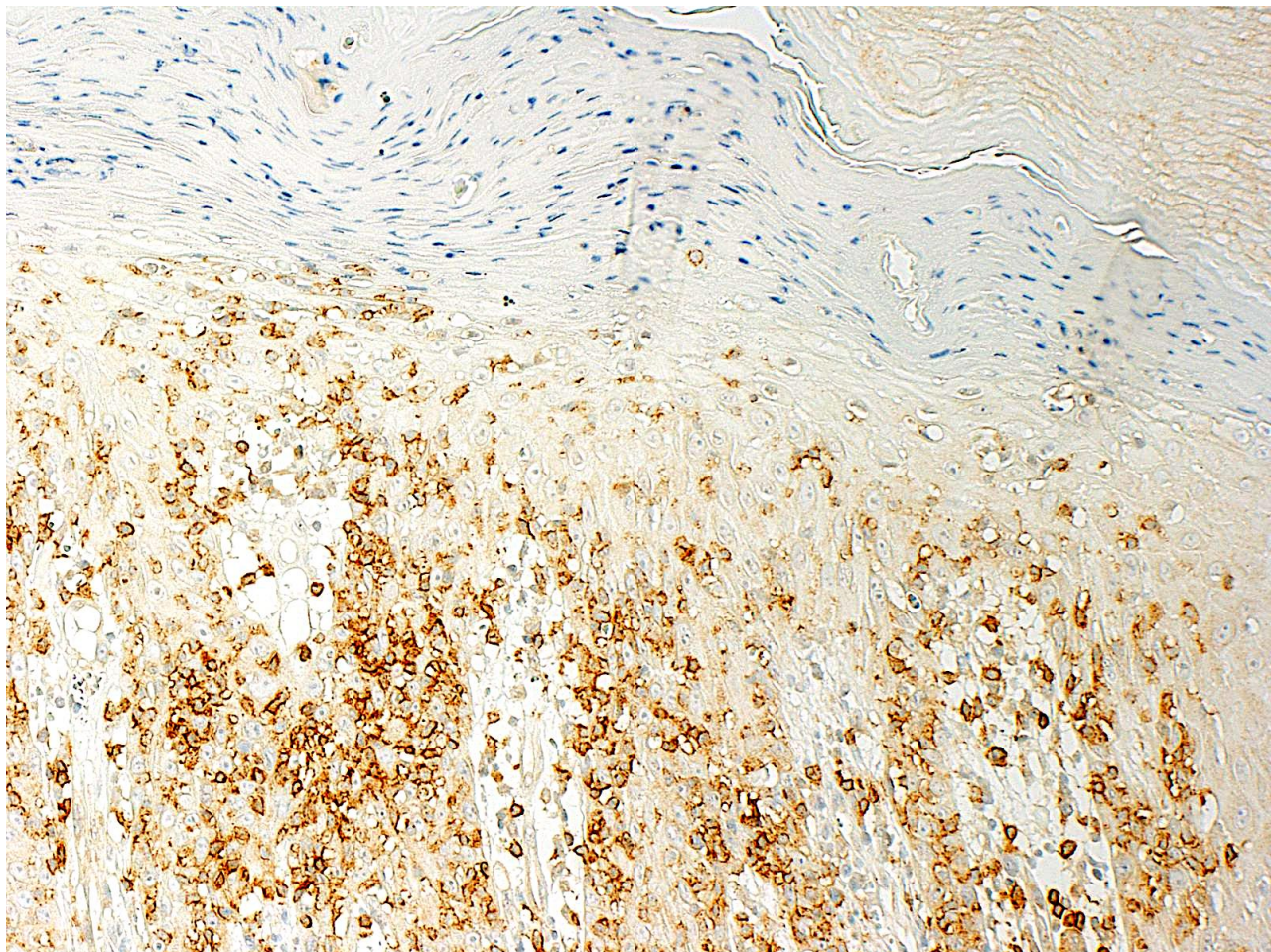




**CD3**

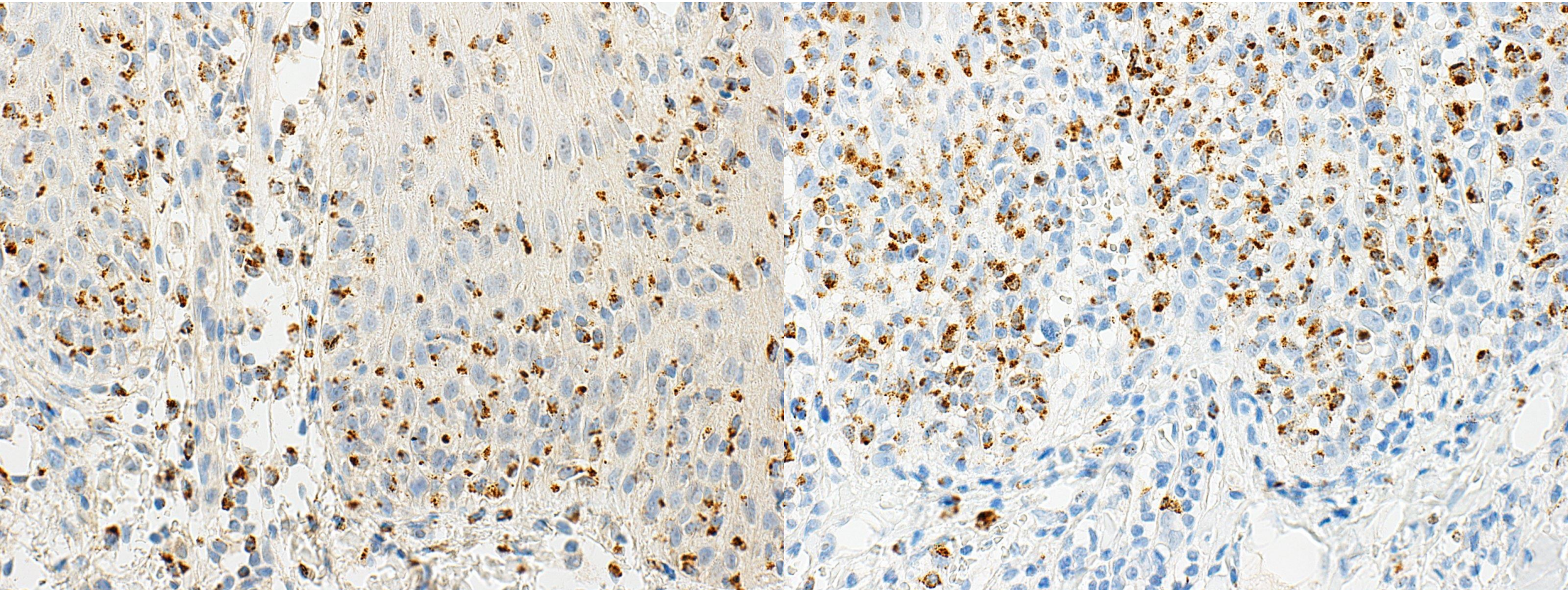


**CD8**



**TIA-1**

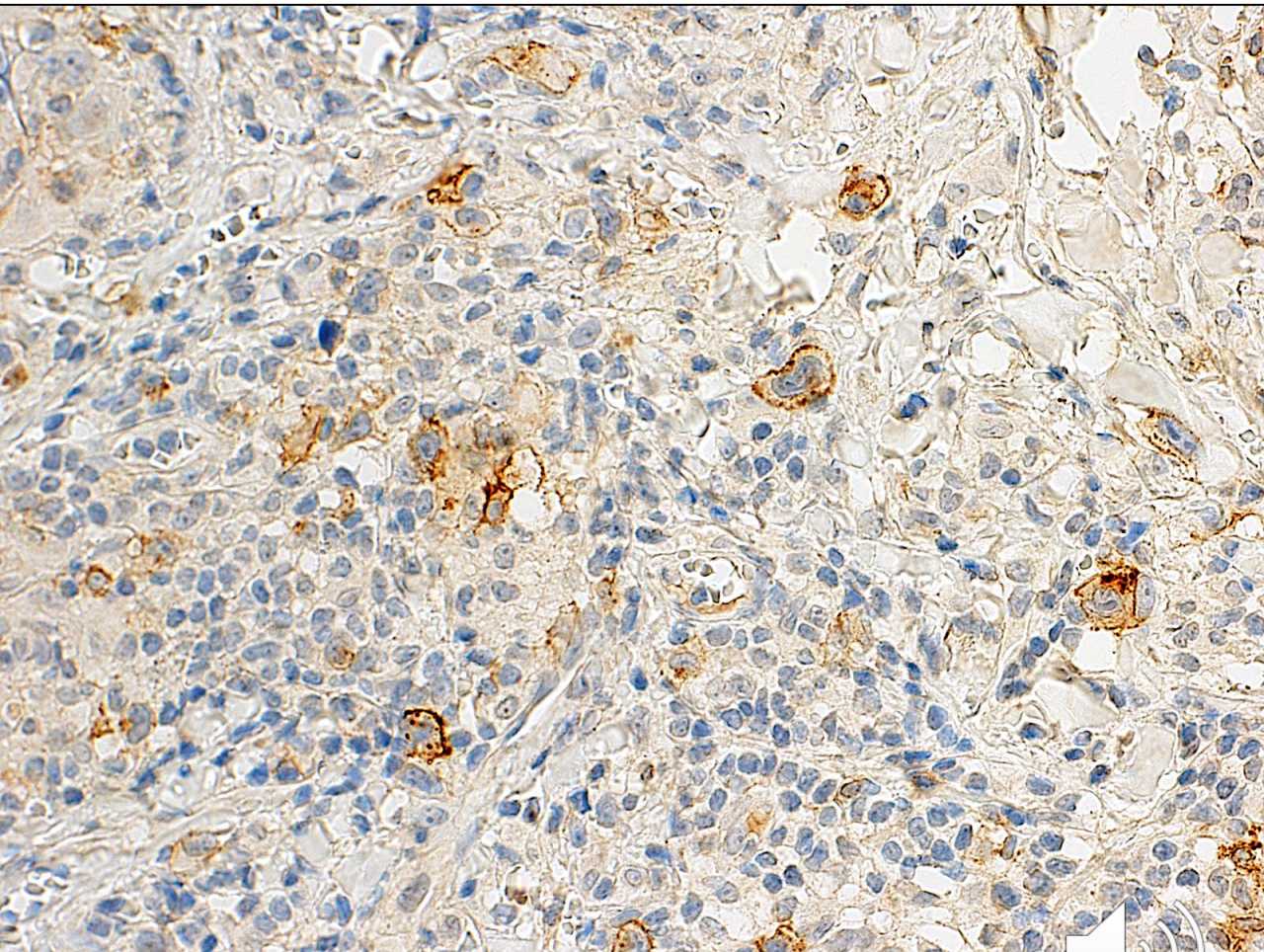
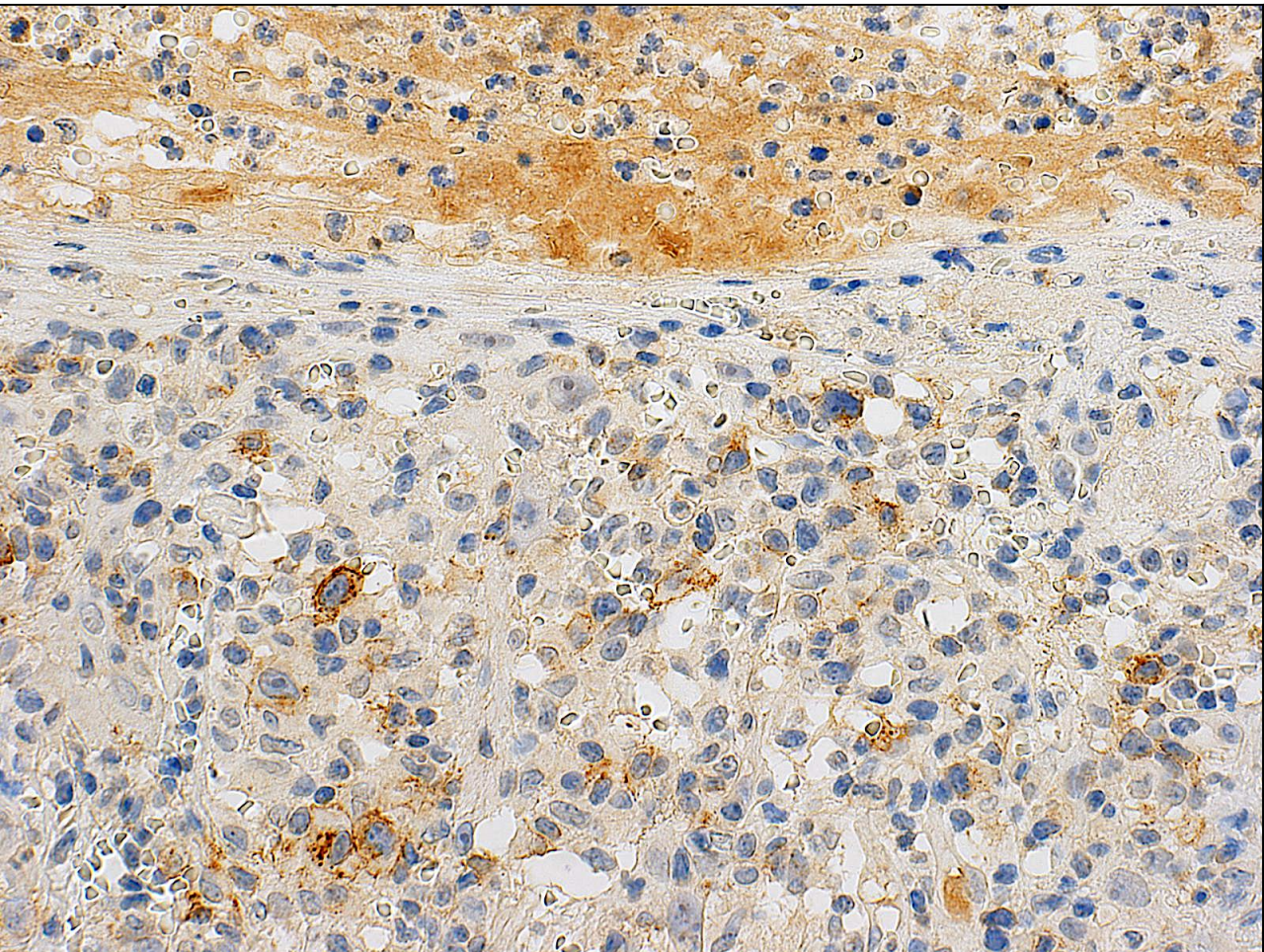
**GRANZYME B**



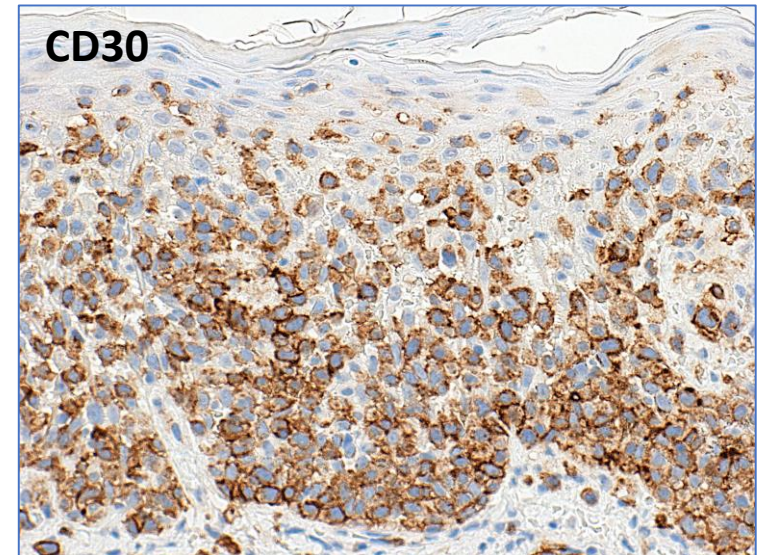
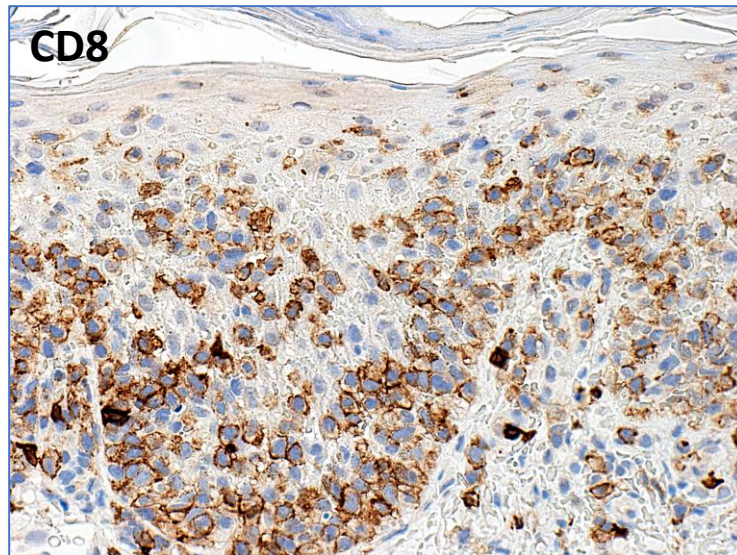
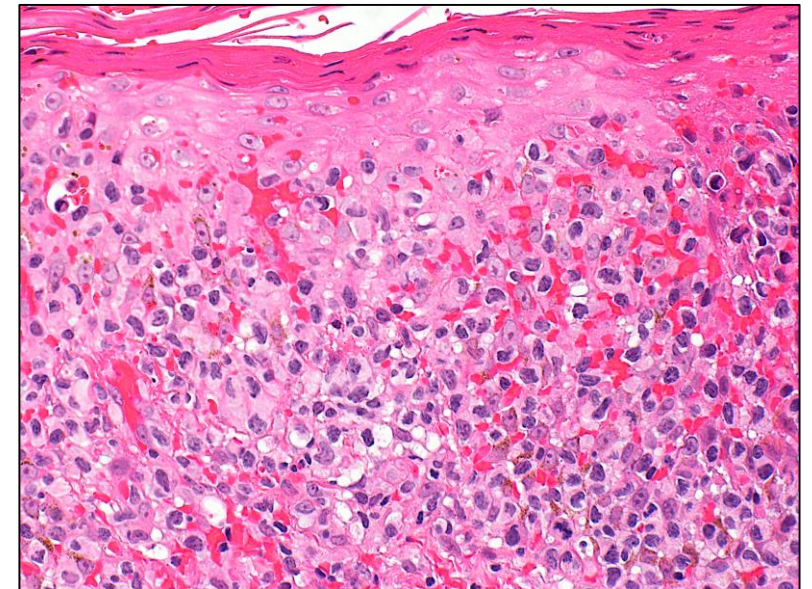
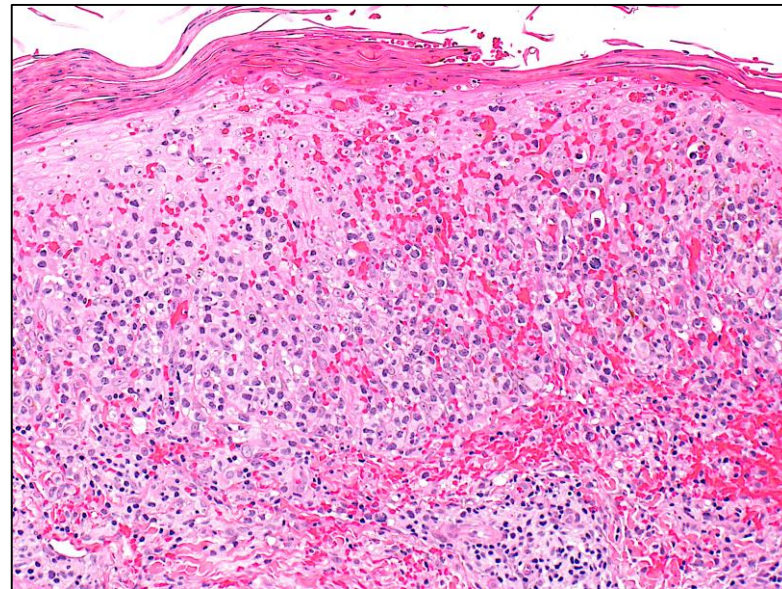
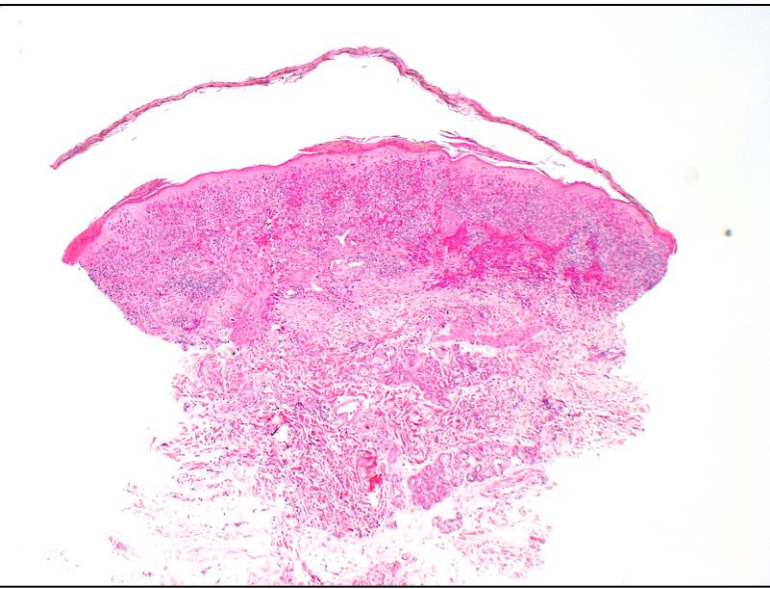
# CD30

Epidermis

Dermis



Some cases have bright CD30 expression.....



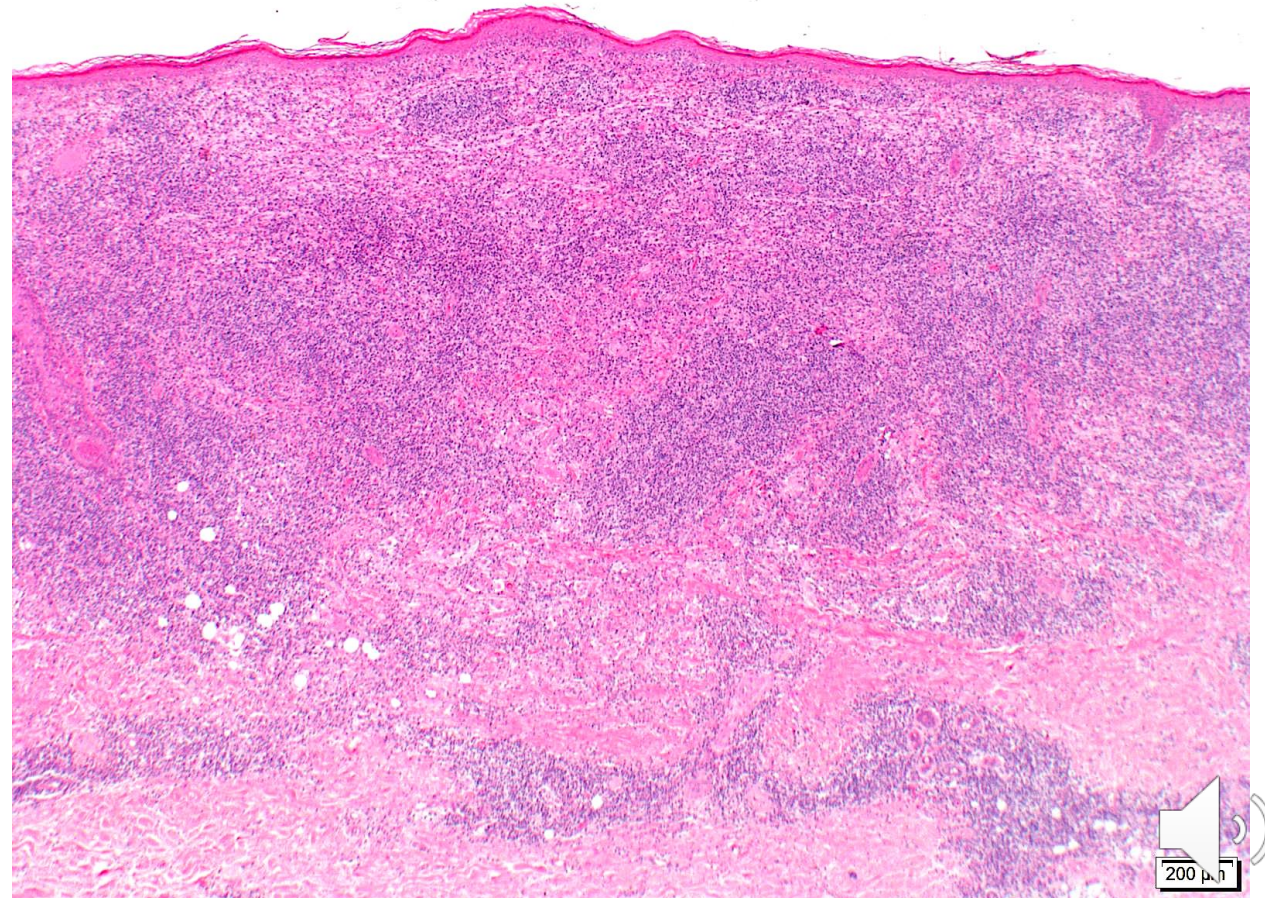
# Lymphomatoid papulosis with *DUSP22* rearrangement:

*Karai LJ et al, Am J Surg Pathol 2013.1173-81*

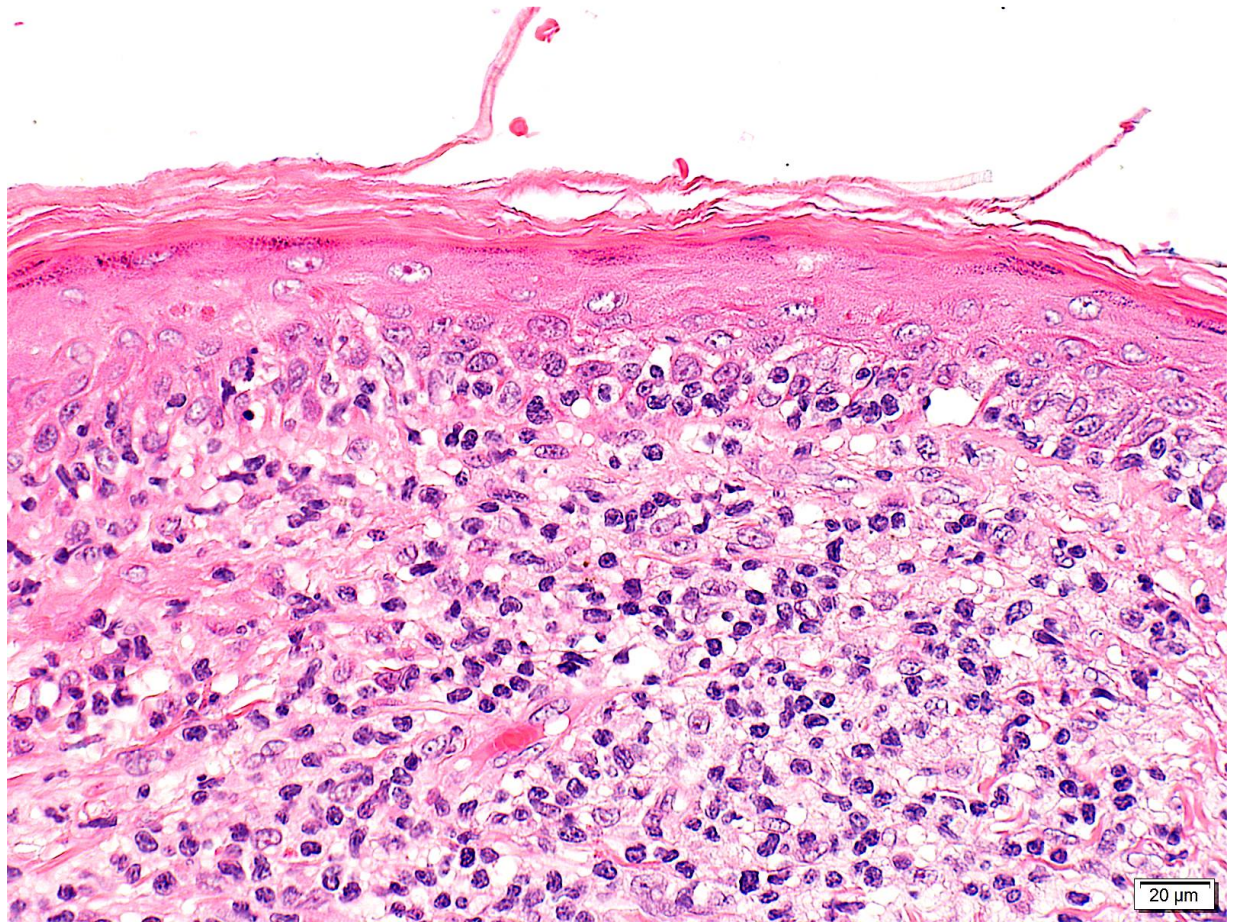
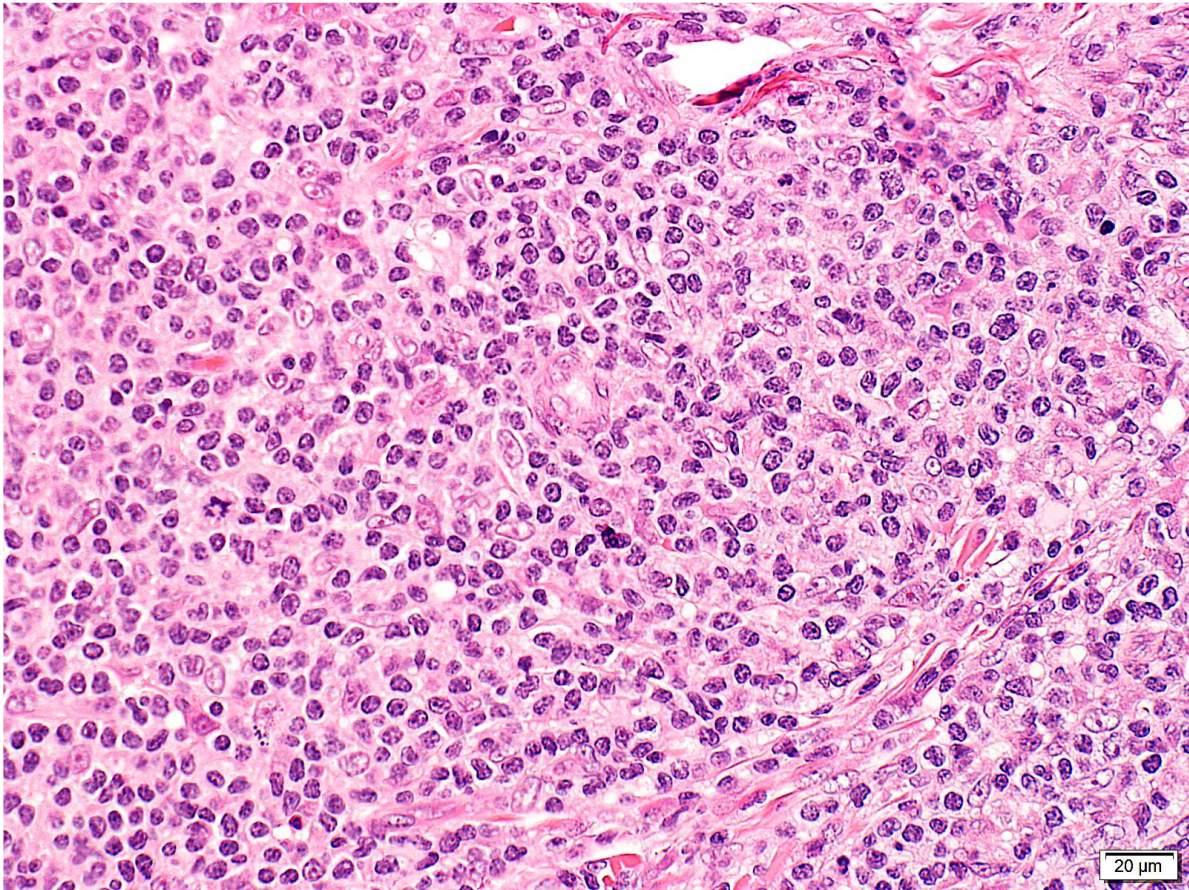
- Localised papules (oligolesional) that spontaneously regress
- Characterised by unusual biphasic morphology that includes an epidermotropic component
- Usually CD4-/CD8- or CD4-/CD8+

## **Clinical case:**

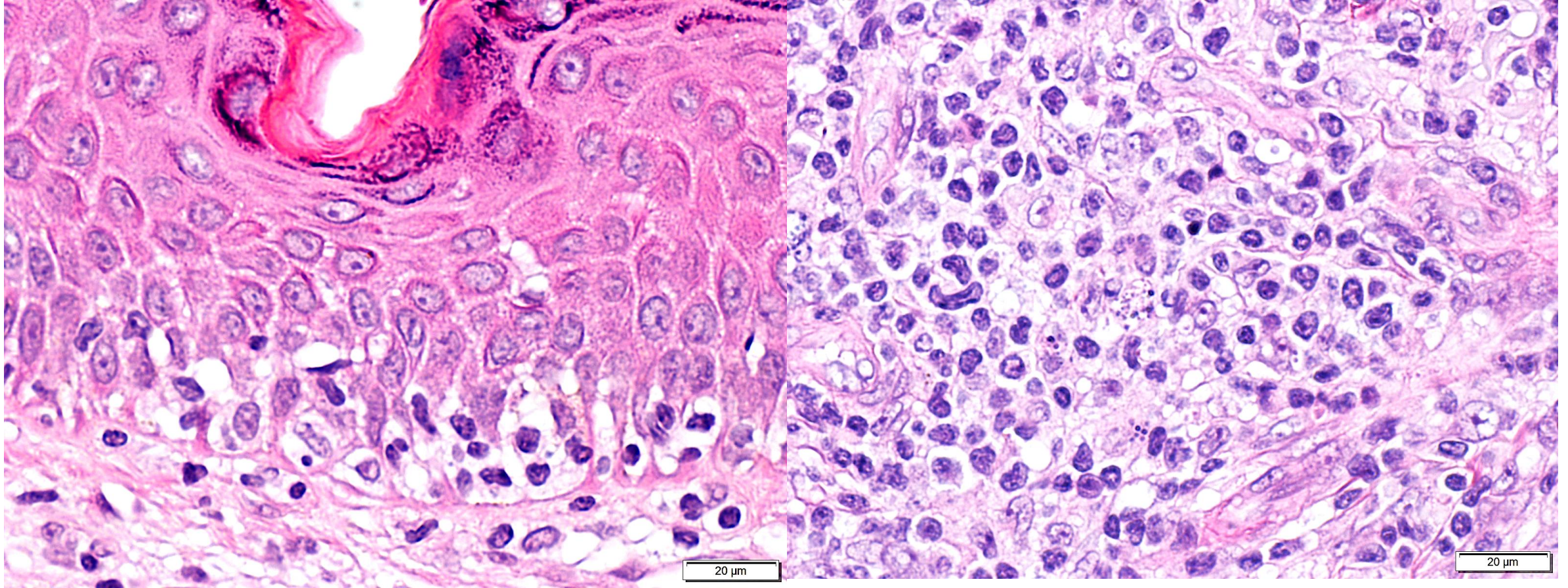
- 64-year-old male
- Spontaneously resolving nodules on arm
- Biopsy shows dense nodular infiltrate



- Ill-defined nodular lymphoid aggregates in dermis
- Linear basal epidermotropism in overlying and adjacent dermis

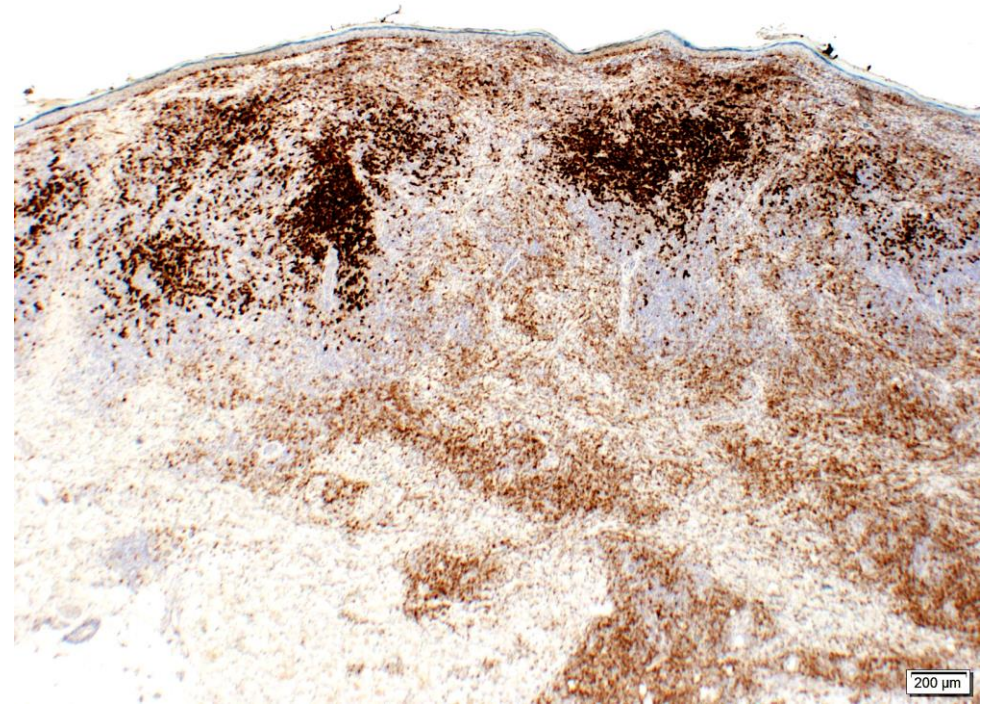


- **Epidermotropic lymphocytes generally small with irregular nuclei**
  - **Nodules of larger more blast-like lymphoid cells in dermis**

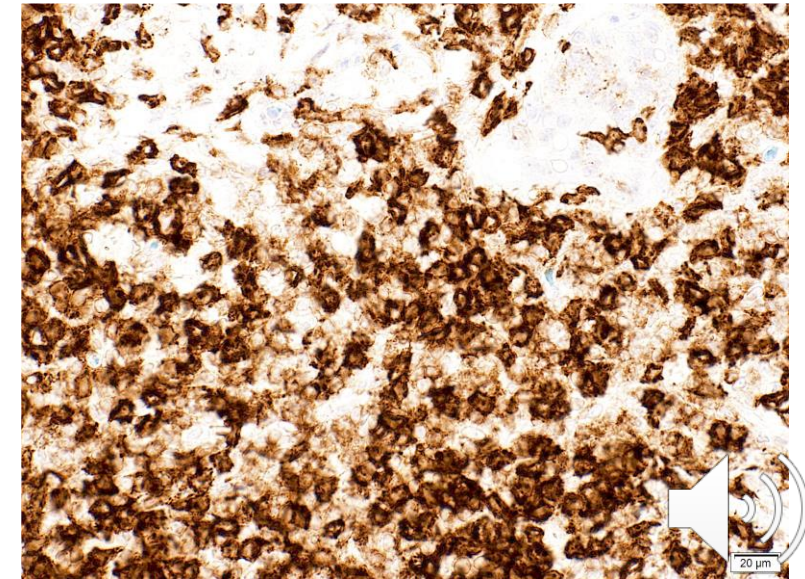
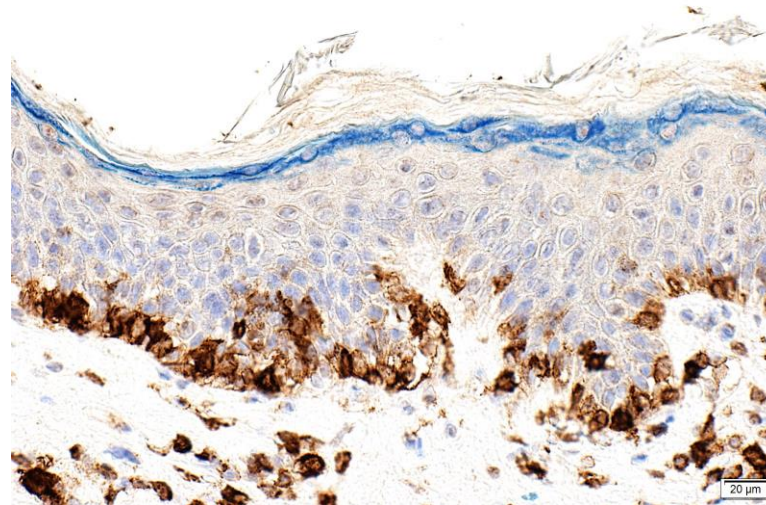


## Biphasic pattern of staining for CD30

- Large cells in dermal nodules strongly positive
- Smaller cells in dermis and epidermis weakly positive



## This case CD8+



# PRIMARY CUTANEOUS CD8+ AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMA

Rare: <1% of all CTCL

Most patients adult; typically present with generalized, rapidly progressing eruption

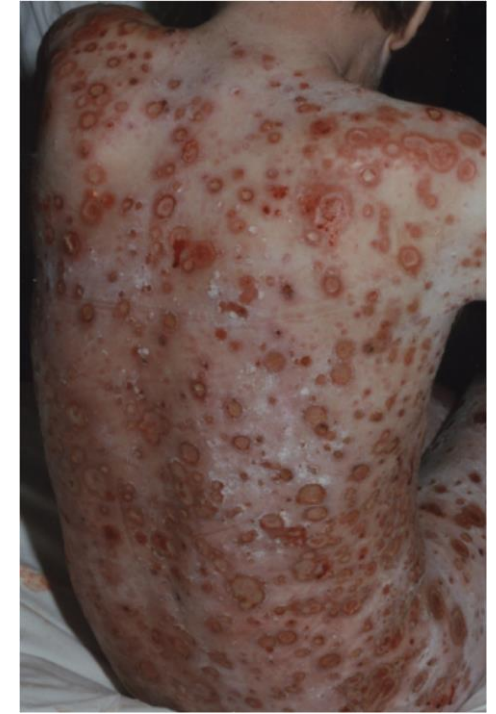
- Patches/plaques
- Nodules/tumours

Early, widespread visceral spread the norm; often unusual sites

- Testes, lungs, spleen, CNS

No standard treatment

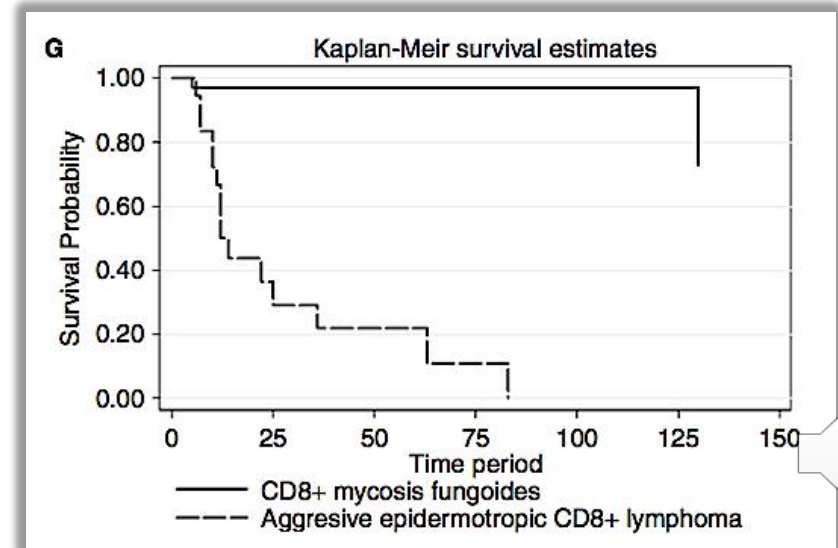
- Dismal outcome; median survival 12-32 months



*Berti et al. Am J Pathol 1999; 155: 483*

*Agnarsson et al. J Am Acad Dermatol 1990; 22: 569*

*Robson A et al. Histopathology: 2015;67:425-441*



# PATHOLOGICAL FEATURES

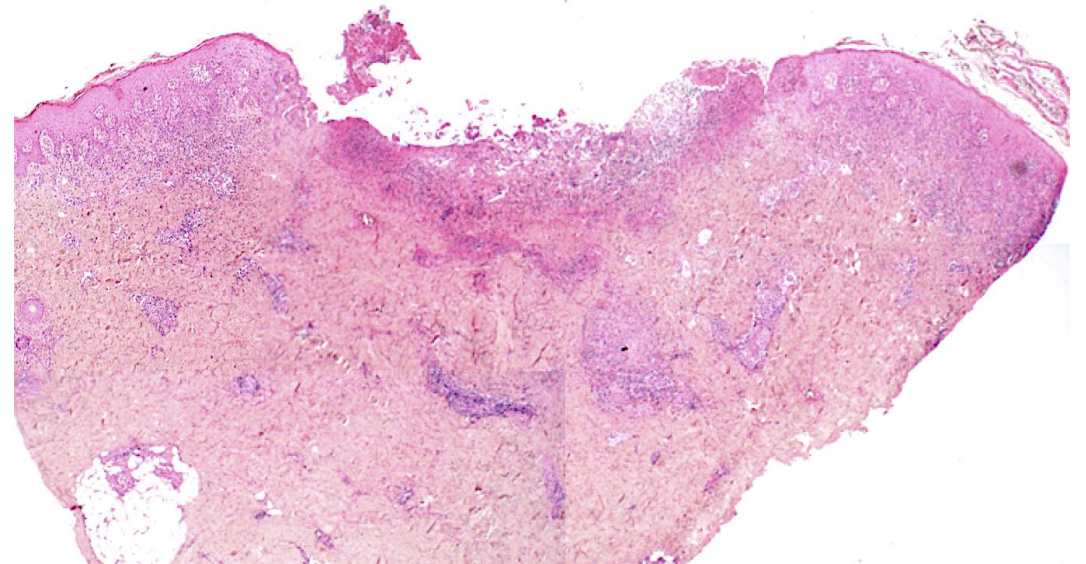
## Prominent epidermotropism the rule:

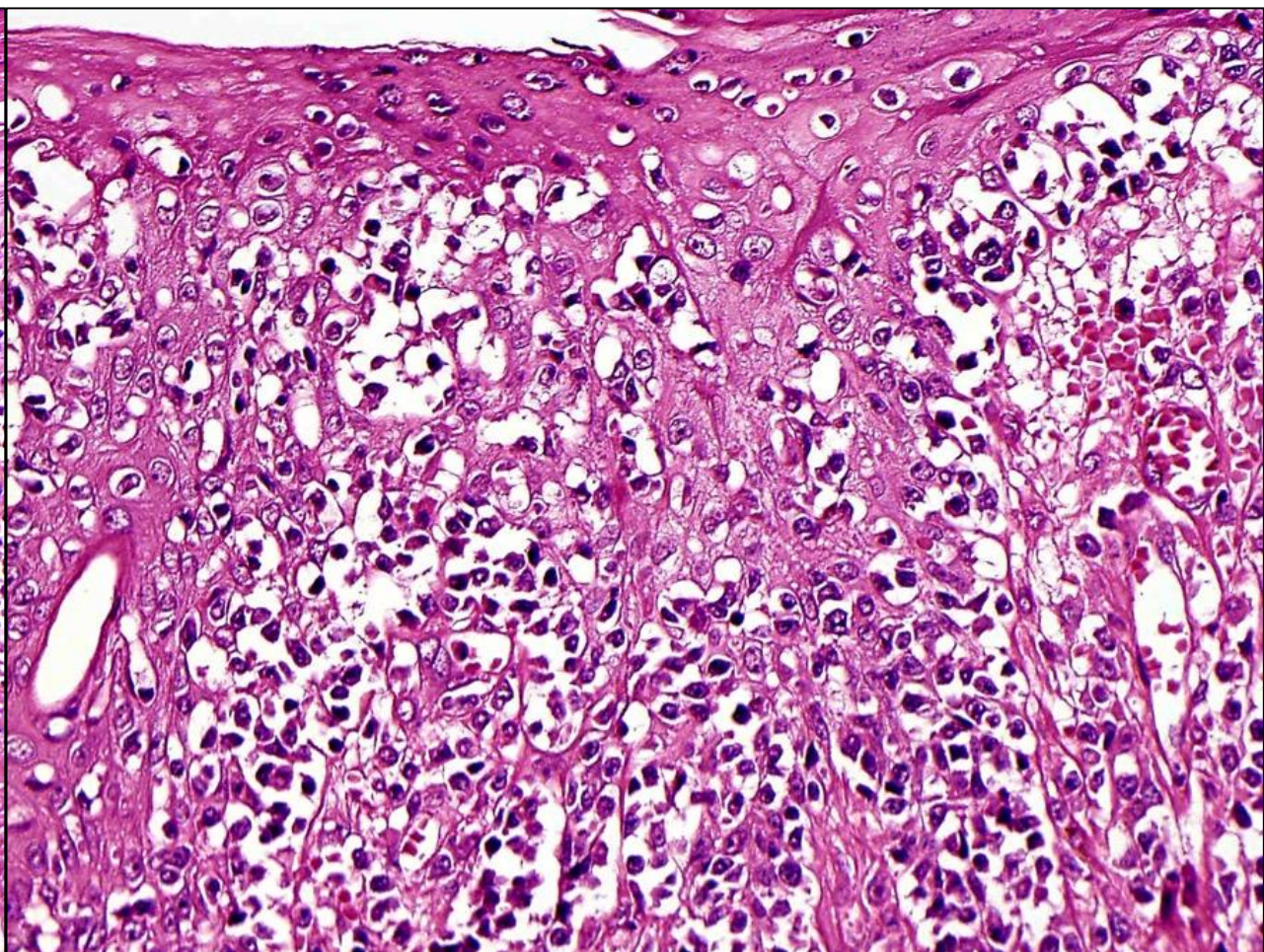
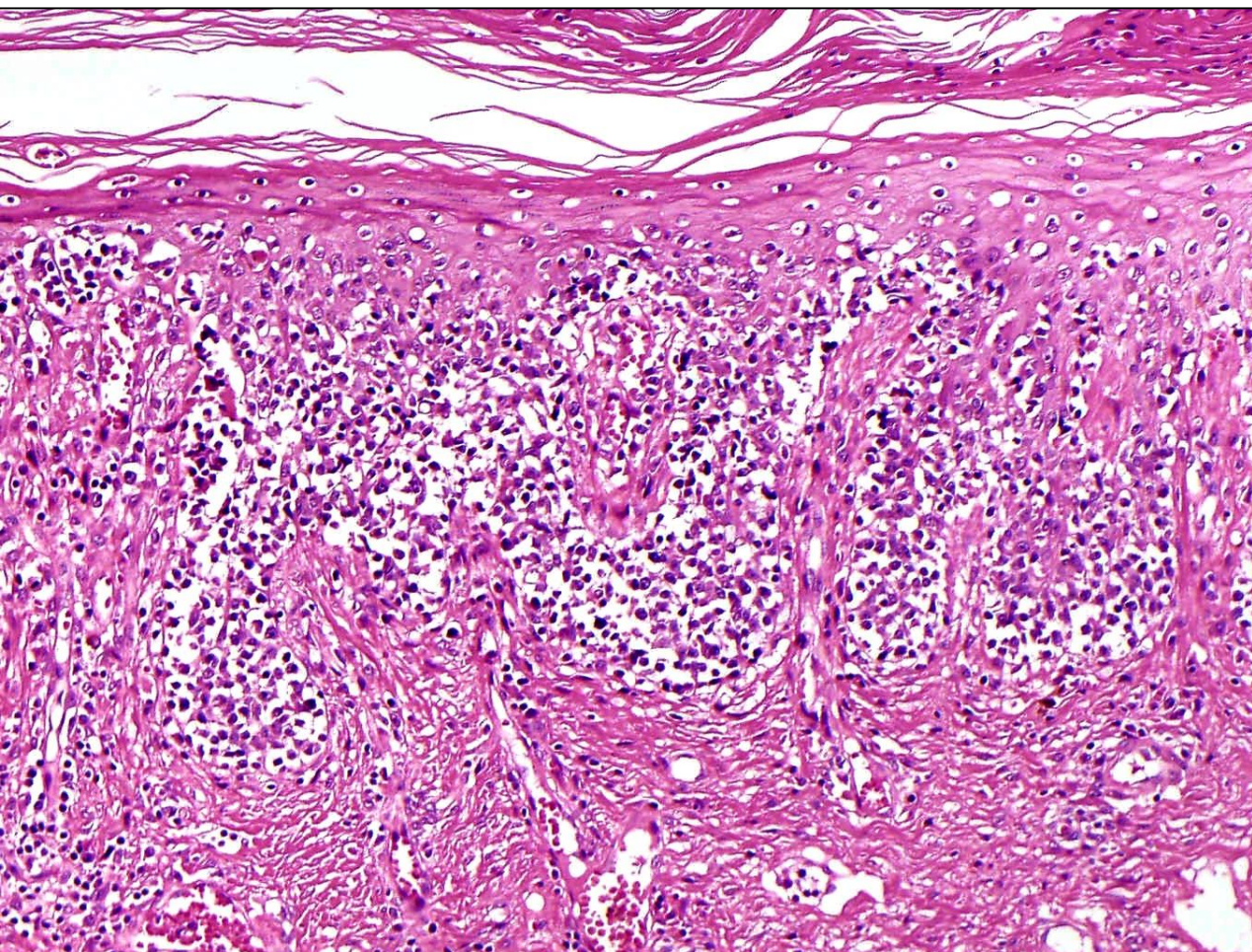
- Pagetoid appearance
- Epidermal necrosis and ulceration common

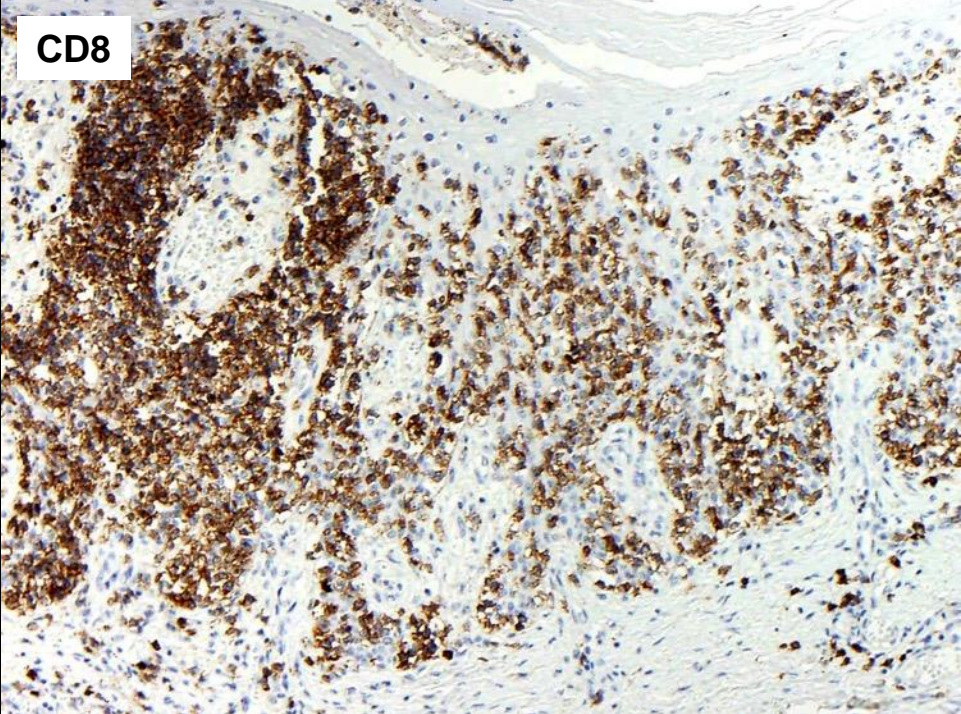
## Dermal component variable:

## Phenotype:

- CD8+/Cytotoxic molecule + T-cells
- $\beta$ F1+
- **CD7 often positive unlike other CTCL**

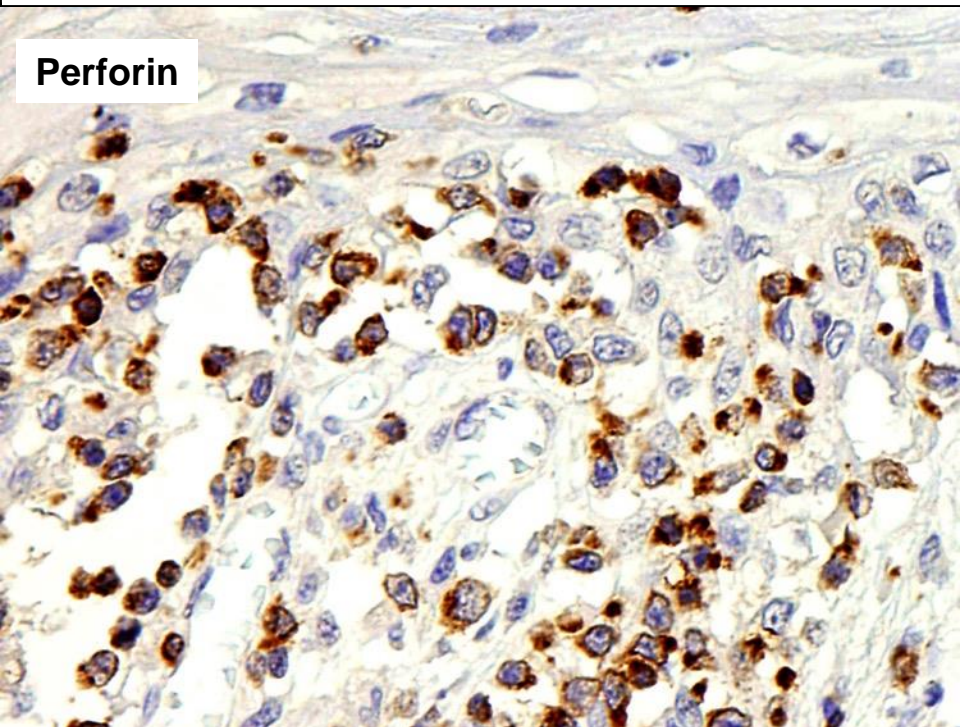
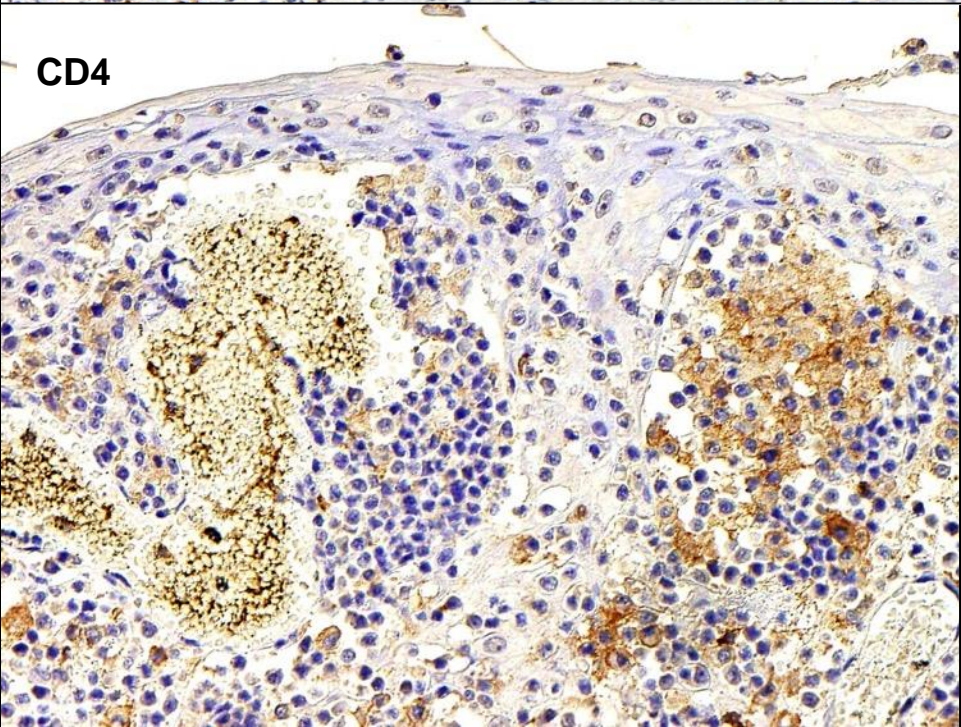






**Immunophenotype:**  
Cytotoxic phenotype

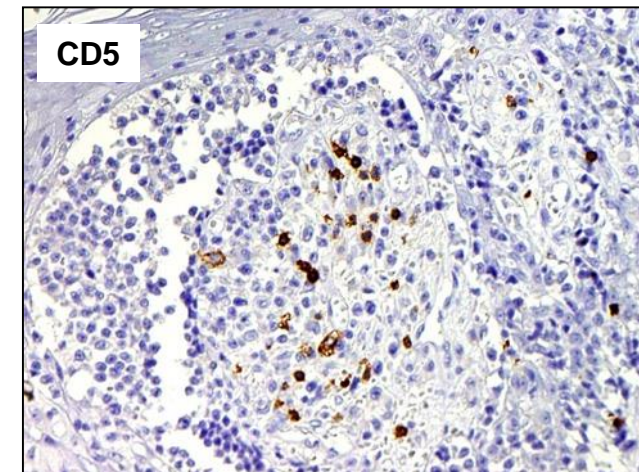
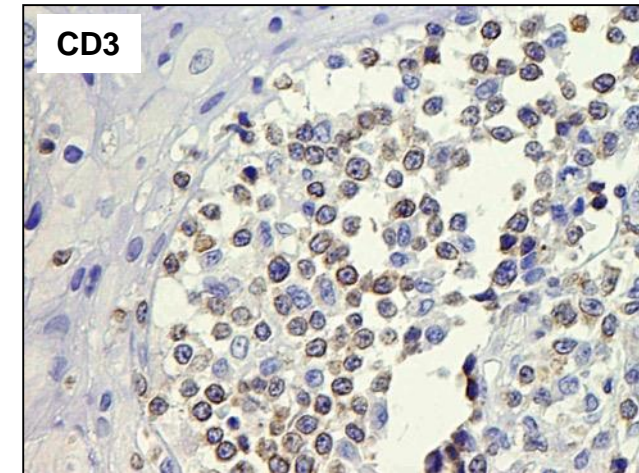
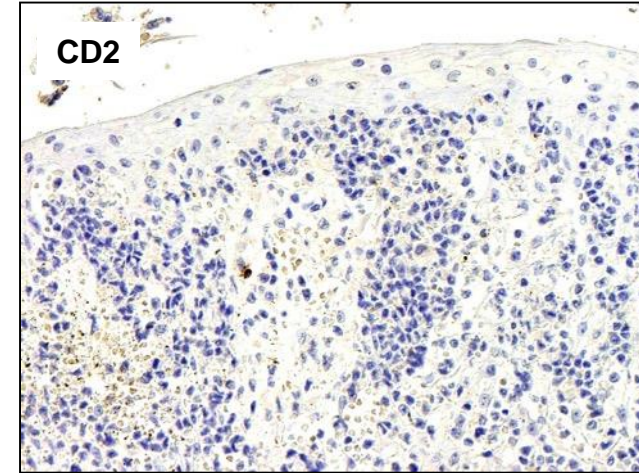
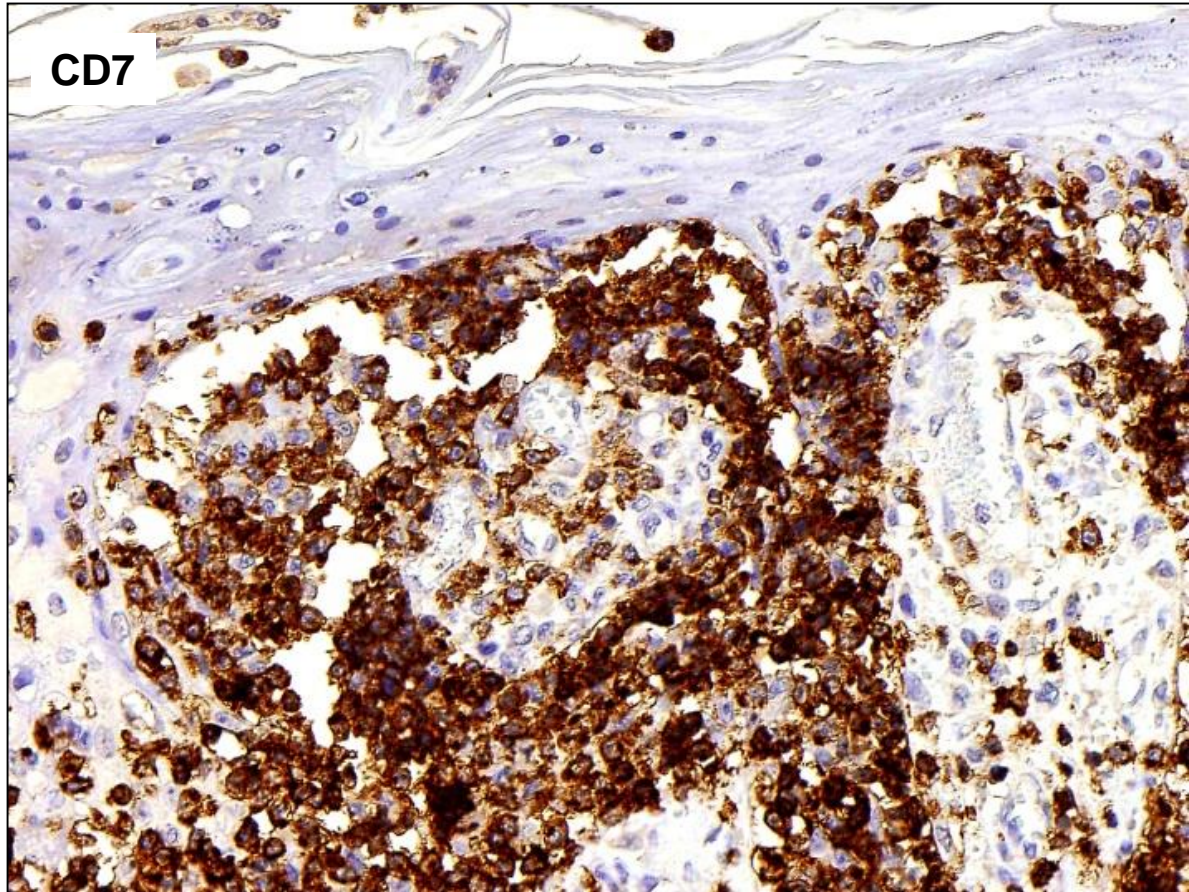
- CD8+
- Perforin+
- Granzyme B+
  
- CD4-



## Immunophenotype:

Loss of pan-T-cell antigens

- CD2/CD5-
- CD3 weakly +
- **CD7 strongly +**



# PRIMARY CUTANEOUS GAMMA DELTA T-CELL LYMPHOMA

## CLINICAL

- Neoplasm of adults (Median age = 61 years)
- Extremities frequently involved with rapid onset of
  - Patches and plaques
  - Necrotic nodules and tumours
- Usually localised to skin and extranodal sites - no involvement of:
  - Lymph nodes, spleen, bone marrow
- +/- haemophagocytic syndrome



*Guitart J et al, Am J Surg Pathol 2012*

## **No standard treatment**

- Systemic polychemotherapy the norm +/- stem cell transplant: responses poor
  - Median survival = 31 months
  - 5-year overall survival = 19.9%
- Presence of haemophagocytic syndrome associated with particularly poor outcome



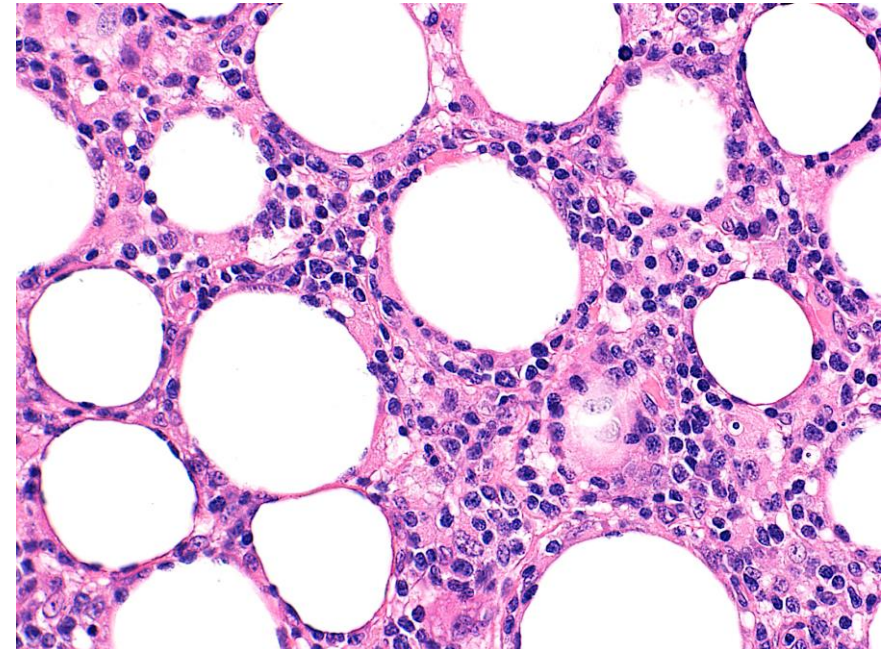
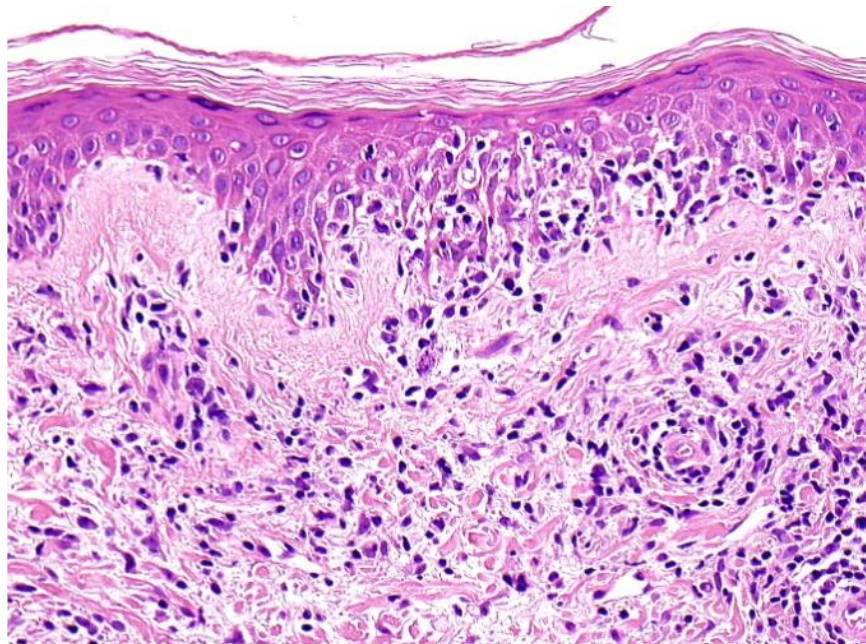
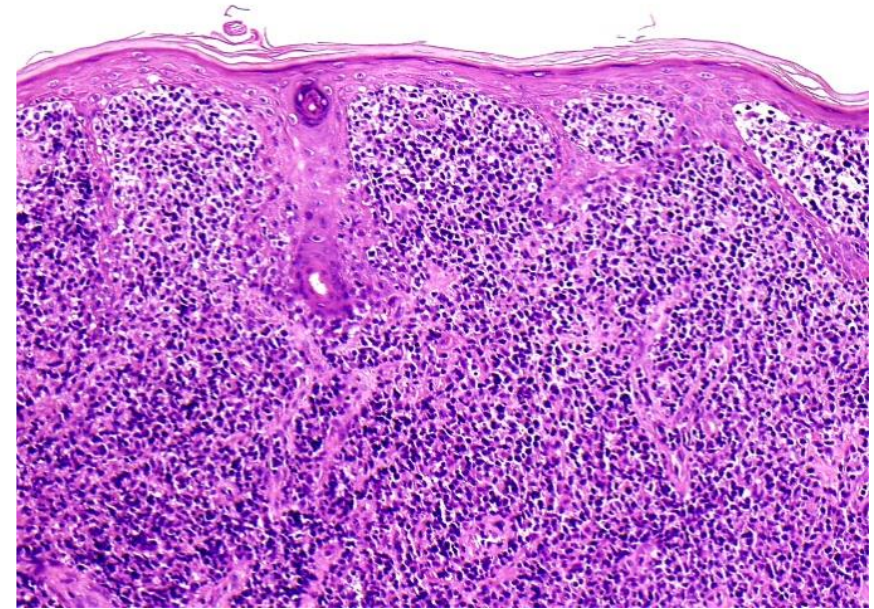
## PATHOLOGY

Medium to large cells with coarsely clumped chromatin

- Apoptosis
- Necrosis
- Angioinvasion

Varied pattern of infiltration; often >1 present

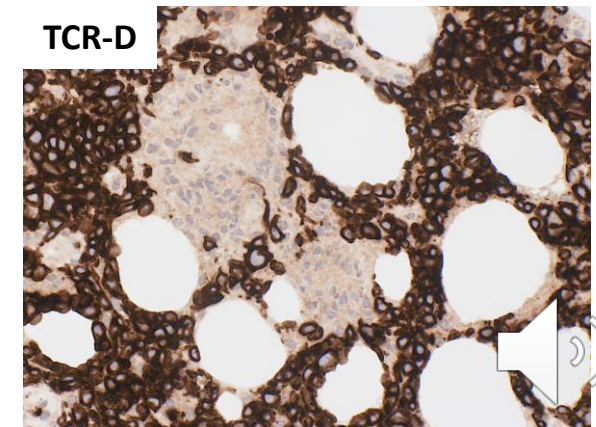
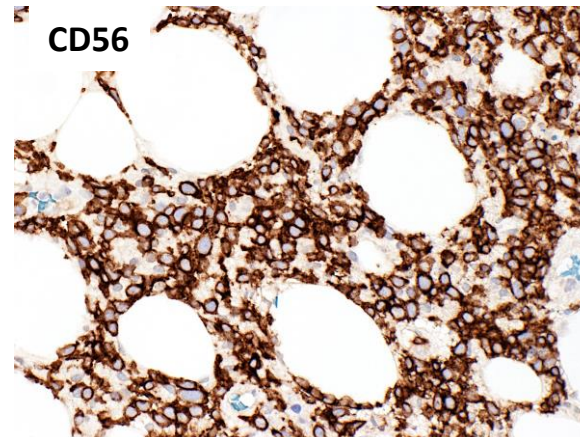
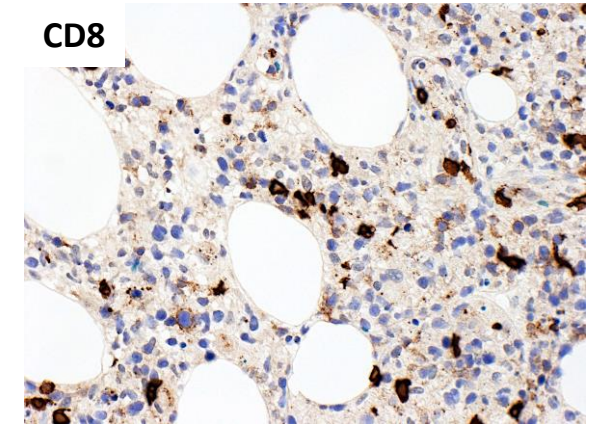
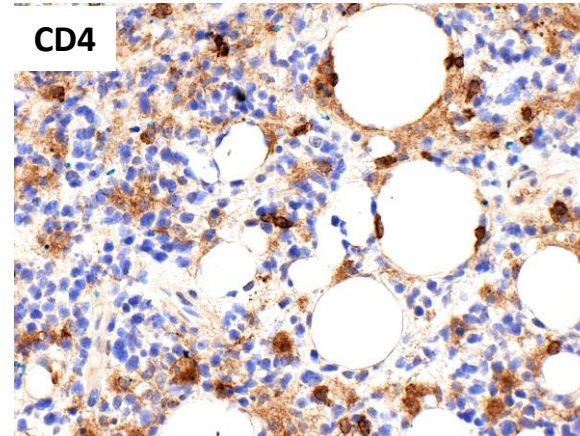
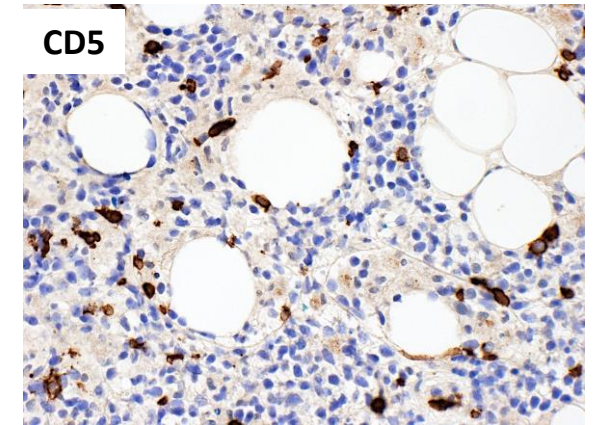
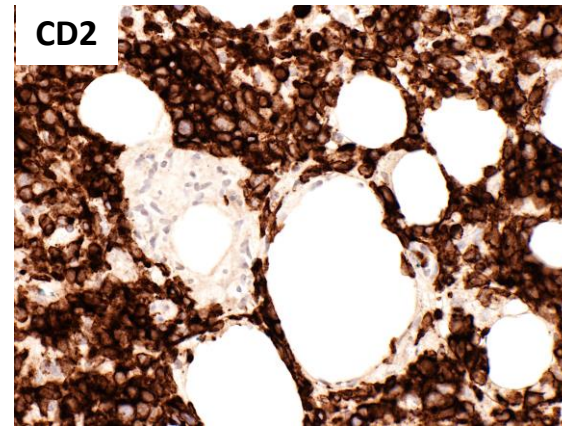
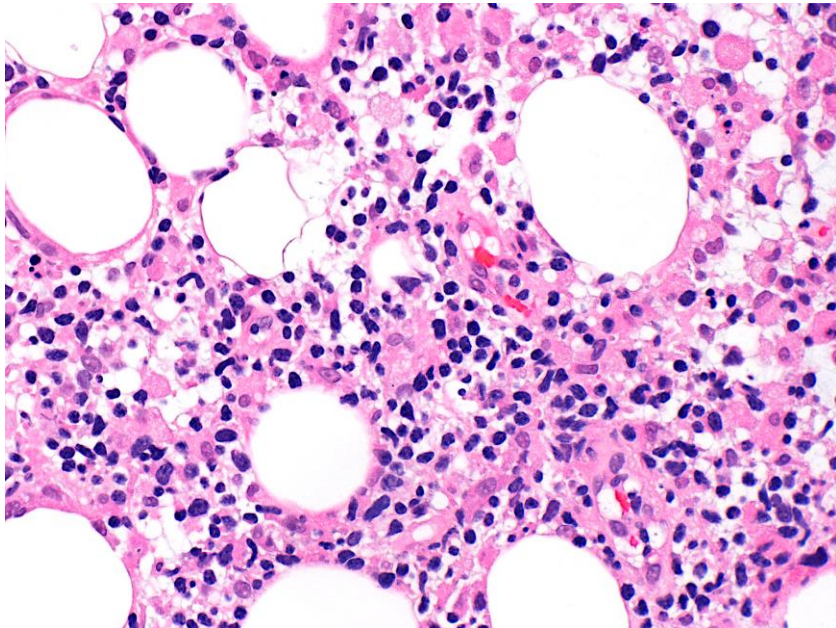
- Epidermotropic (but Pautrier's microabscess rare)
- Dermal
- Subcutaneous



## PHENOTYPE

### Neoplasm of mature activated $\gamma\delta$ T cells with cytotoxic phenotype

- Diagnostic clues
  - CD5 frequently negative
  - Often negative for CD4 and CD8
  - Positive for CD56
  - Cytotoxic molecule positive
- TCR- $\delta$ +



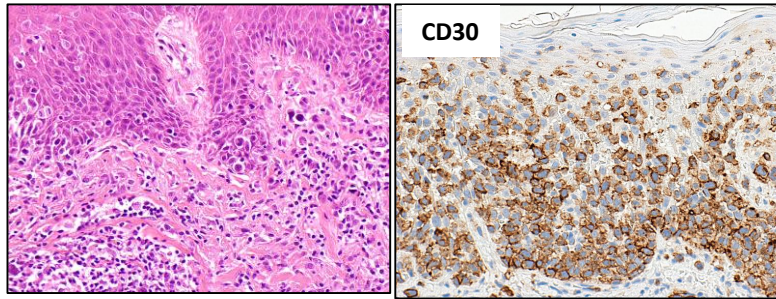
## D/Dx CUTANEOUS LYMPHOPROLIFERATIVE DISORDERS WITH EPIDERMOTROPISM

- Pathologies often overlapping and may be indistinguishable
  - Broad spectrum of clinical appearance and behaviour
    - Biopsy may provide some diagnostic clues but.....
      - .....**clinical correlation essential**



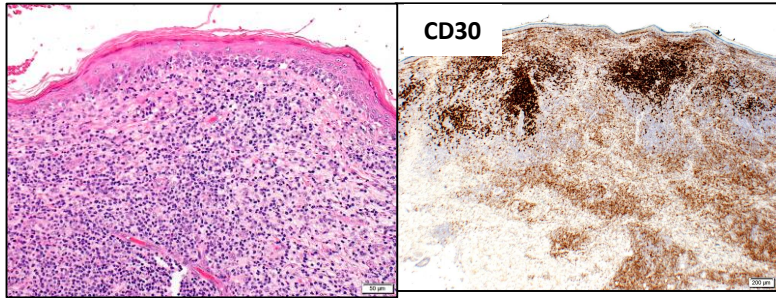
## Diagnostic clues

LyP-D



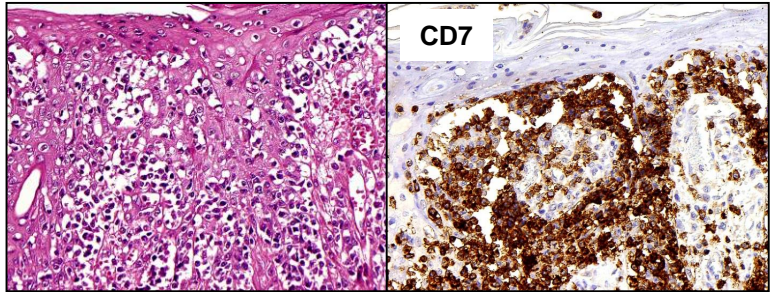
- CD30+ cells

LyP-*DUSP22r*



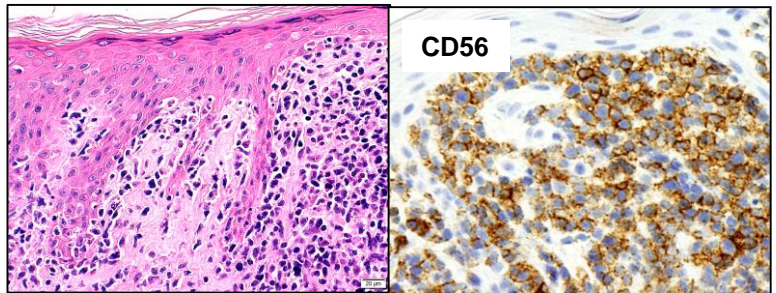
- Biphasic morphology and CD30

PC CD8+ AECTL



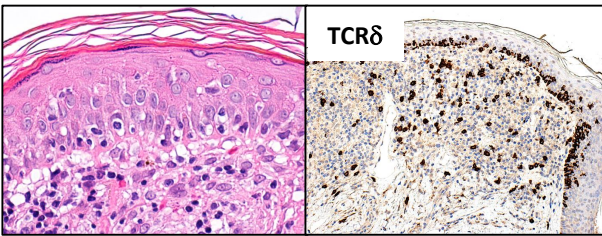
- CD7+ in absence of other pan-T-cell Ags
- CD30-

PGDTCL



- $\gamma\delta$  phenotype
- CD56+
- CD4-/CD8-
- CD5-





Various, e.g.

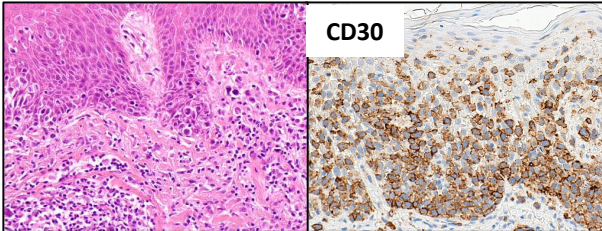
- $\gamma/\delta+$
- CD8+
- CD4+



Slowly evolving patches and plaques



**Mycosis fungoides**  
 Skin directed therapy incl. PUVA  
 Slowly progressive disease



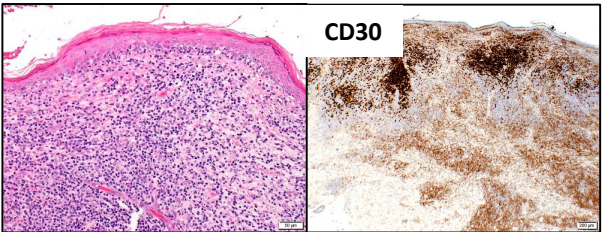
- CD30+ cells



Ulcerating papules, spontaneously resolve



**LyP-type D**  
 No treatment  
 Excellent prognosis



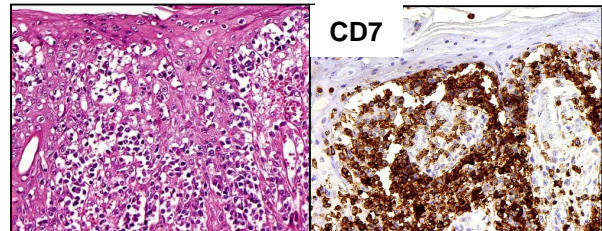
- Biphasic morphology and CD30



Grouped papules, spontaneous resolution (Karai et al, AJSP 2013)



**LyP-DUSP22r**  
 No treatment  
 Excellent prognosis



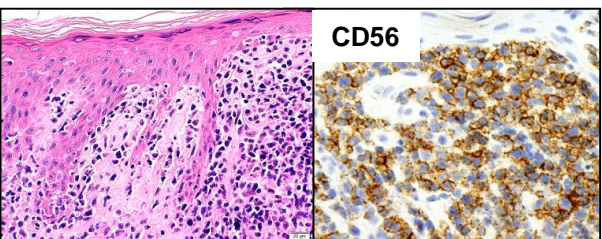
- CD7+ in absence of other pan-T-cell Ags
- CD30-



Multiple ulcers & tumours, rapid progression



**PC CD8+ AECL**  
 Polychemotherapy  
 Dismal prognosis



- $\gamma\delta$  phenotype
- CD56+
- CD4-/CD8-
- CD5-



Ulcerating nodules & tumours, plaques, rapid progression



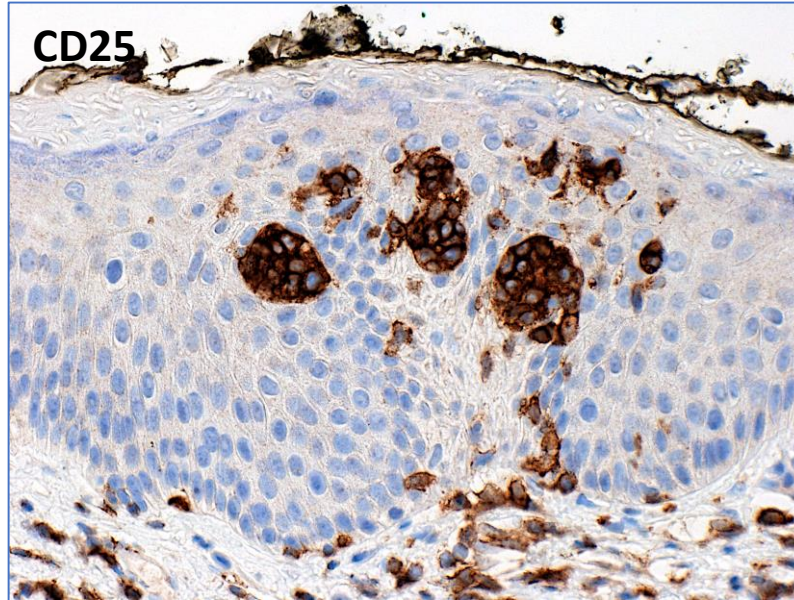
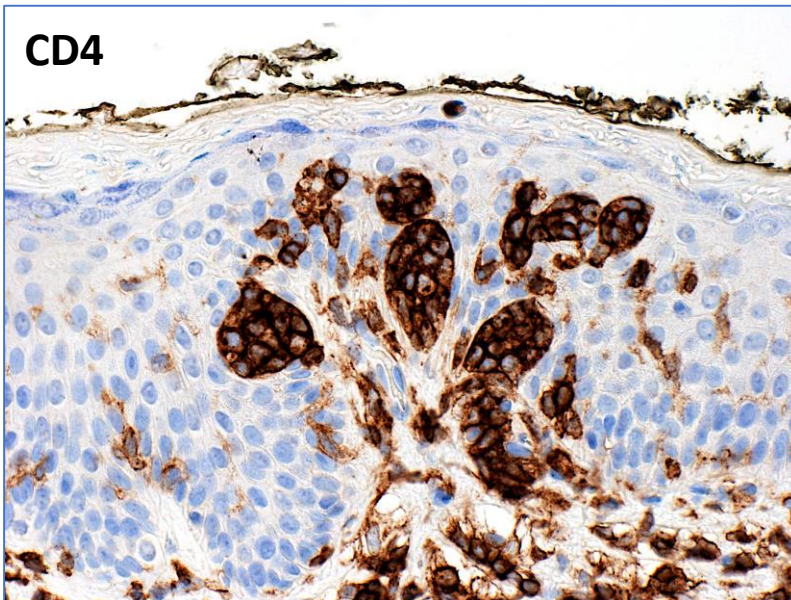
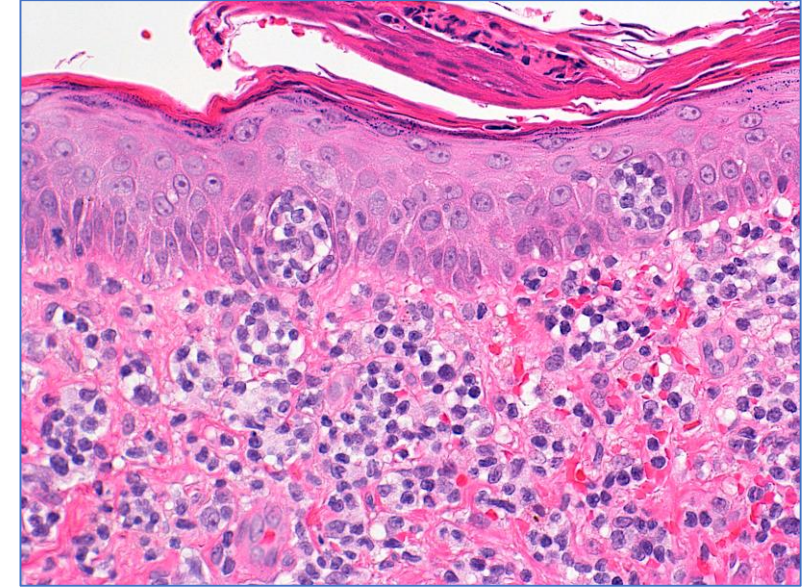
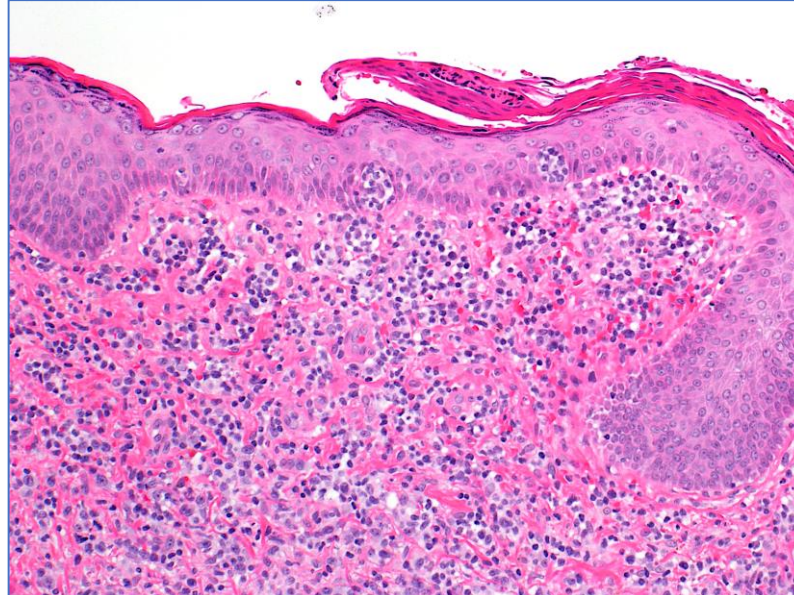
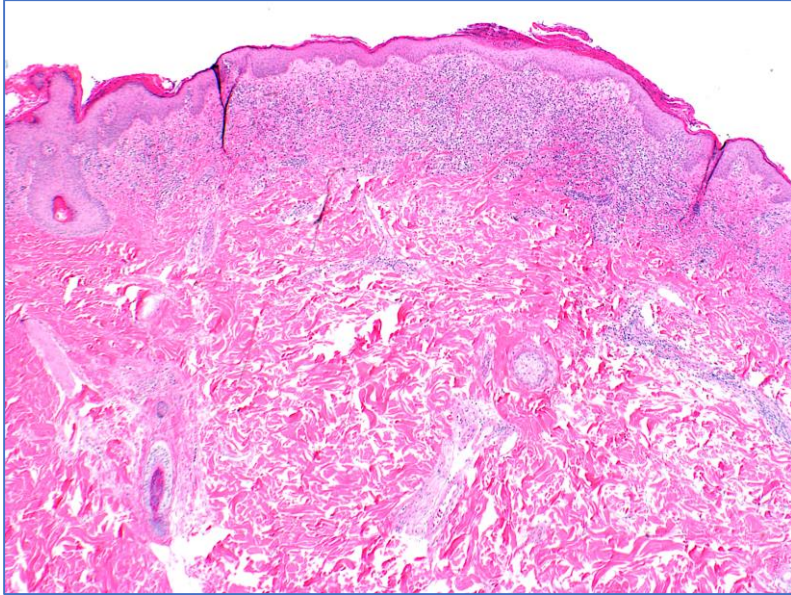
**PGDTCL**  
 Polychemotherapy  
 Dismal prognosis

Always expect the unexpected.....



# Systemic lymphomas rarely present as epidermotropic proliferations in skin, e.g.

## Adult T-cell leukaemia/lymphoma



- Positive staining for CD25 is a clue
- Serology FOR HTLV-1 to confirm



# Extranodal NK/T-cell lymphoma

