

Primary Cutaneous  
CD30-Positive T-cell  
Lymphoproliferative Disorders

# Definition

- A spectrum of related conditions originating from transformed or activated CD30-positive T-lymphocytes
- May coexist in individual patients
  - Clonally related
  - Overlapping clinical and/or histological features
- Clinical, histologic, and phenotypic characteristics required for diagnosis

# Types

1. Primary cutaneous anaplastic large cell lymphoma (C-ALCL)
2. Lymphomatoid papulosis
3. Borderline lesions

# C-ALCL: Definition

- T-cell lymphoma, presenting in the skin and consisting of anaplastic lymphoid cells, the majority of which are CD30-positive
- Distinction from: (a) systemic ALCL with cutaneous involvement, and (b) secondary high-grade lymphomas with CD30 expression
- In nearly all patients disease is limited to the skin at the time of diagnosis
- Assessed by meticulous staging
- Patients should not have other subtypes of lymphoma

# C-ALCL: Synonyms

<i>Lukes-Collins:</i>	Not listed (T-immunoblastic)
<i>Kiel:</i>	Anaplastic large cell
<i>Working Formulation:</i>	Various categories (diffuse large cell; immunoblastic)
<i>REAL:</i>	Primary cutaneous anaplastic large cell (CD30+) lymphoma
<i>Related terms:</i>	Regressing atypical histiocytosis; Ki-1 lymphoma

# C-ALCL: Epidemiology

- 25% of the T-cell lymphomas arising primarily in the skin.
- Predominantly in adults/elderly and rare in children.
- The male to female ratio is 1.5-2.0:1.

# C-ALCL: Sites of Involvement

- The disease is nearly always limited to the skin at the time of diagnosis
- Extracutaneous dissemination may occur
  - Mainly regional lymph nodes
- Involvement of other organs is rare

# C-ALCL: Clinical Features

- Most present solitary or localized skin lesions which may be tumors, nodules or (more rarely) papules
- Multicentric cutaneous disease occurs in 20%
- Lesions may show partial or complete spontaneous regression (similar to lymphomatoid papulosis)
- Cutaneous relapses are frequent
- Extracutaneous dissemination occurs in approximately 10% of the patients. Mainly to regional lymph nodes and most frequently in patients with multicentric cutaneous disease



Ulcerated skin tumor

# C-ALCL: Etiology

Unknown.

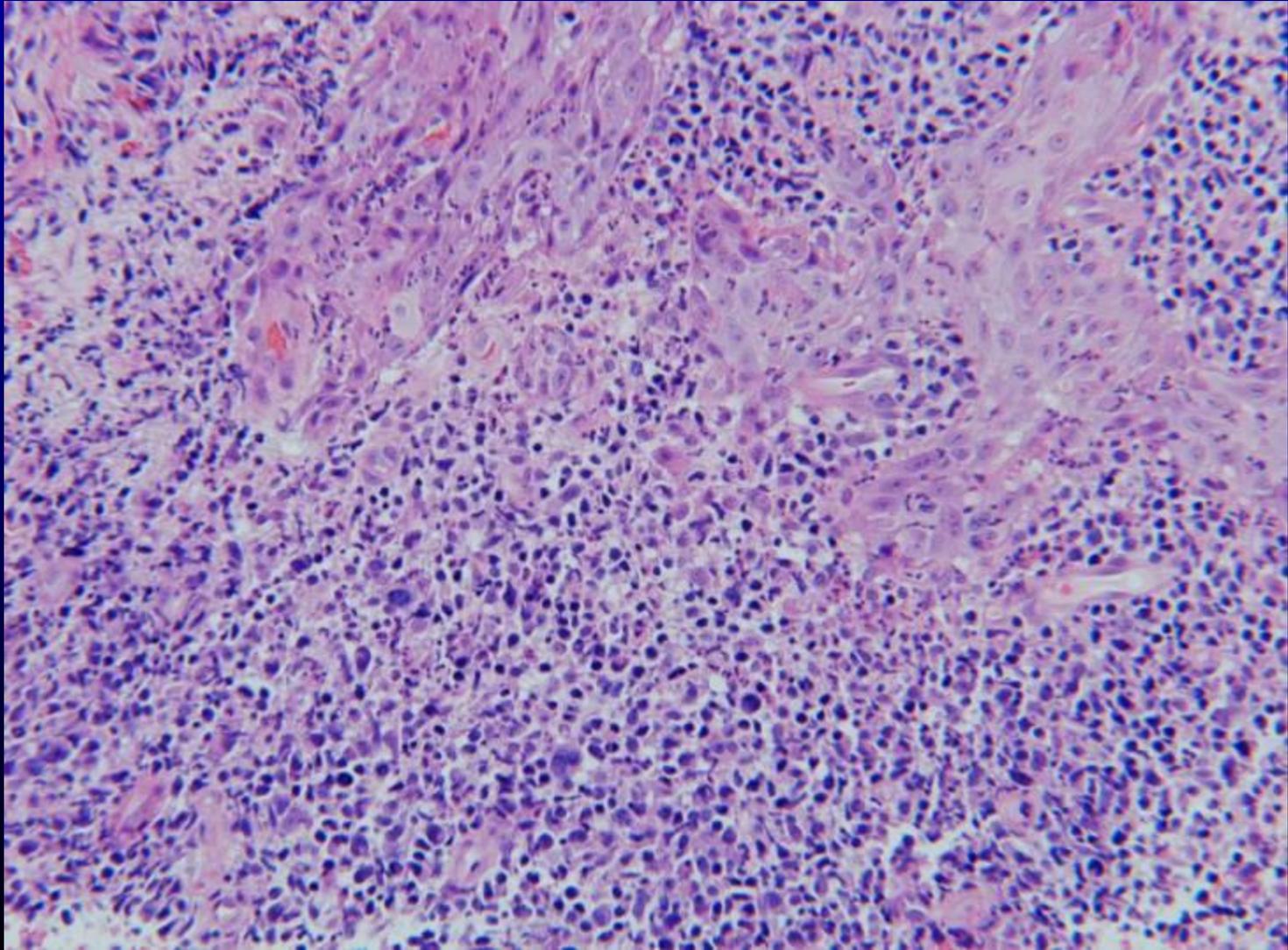
# C-ALCL: Morphology

- Similar to systemic ALCL
- Pleomorphic, multinucleated giant cells and Reed-Sternberg-like cells are often more numerous
  - Resemble the Hodgkin-like cells seen in Type A lesions of lymphomatoid papulosis
- Infiltrates are diffuse and usually involve upper and deep dermis and the subcutaneous tissue

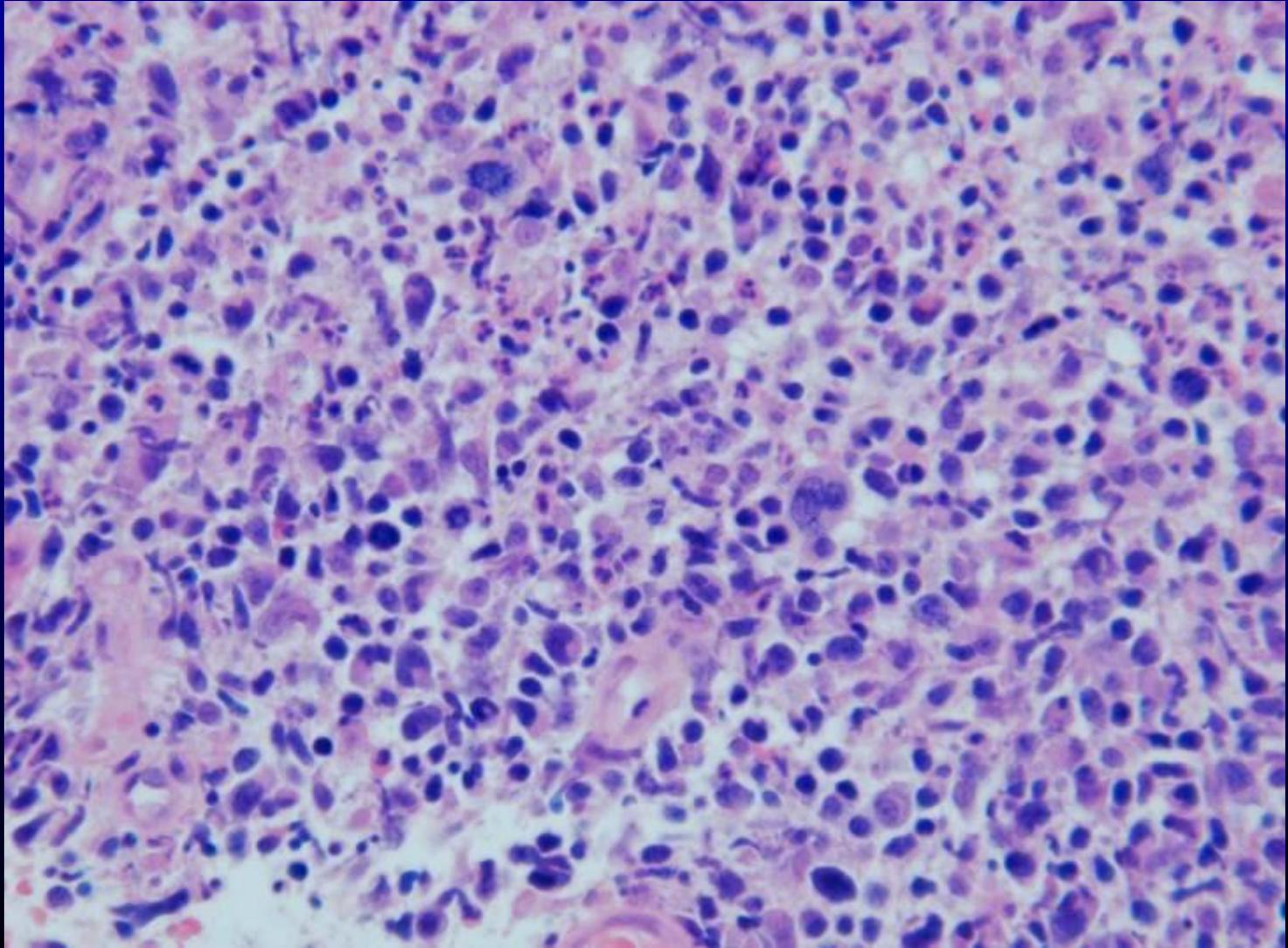
# C-ALCL: Morphology

- Epidermal invasion and ulceration may be present
- Epidermotropism less common
- A modest inflammatory background may be present. If abundant, lymphomatoid papulosis should be considered

# Primary Cutaneous Anaplastic Large Cell Lymphoma



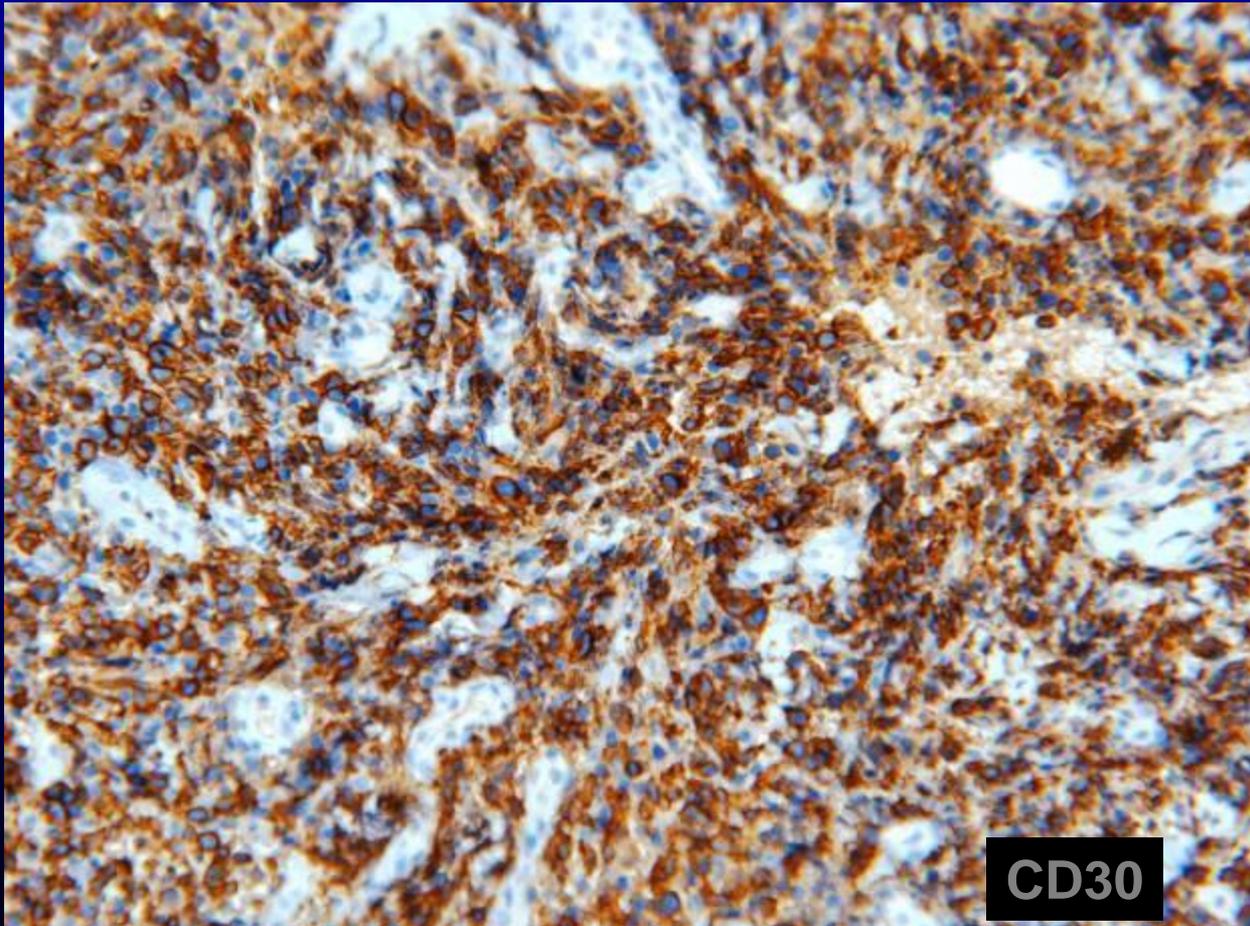
# Primary Cutaneous Anaplastic Large Cell Lymphoma

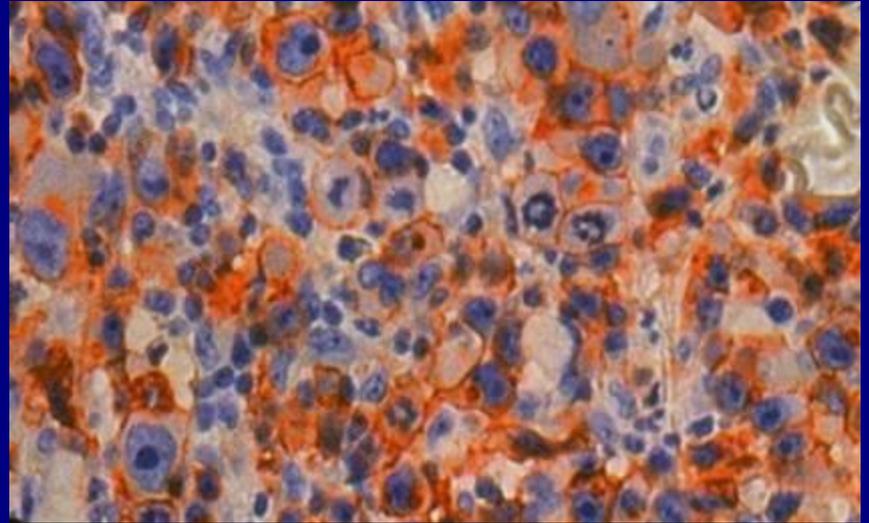
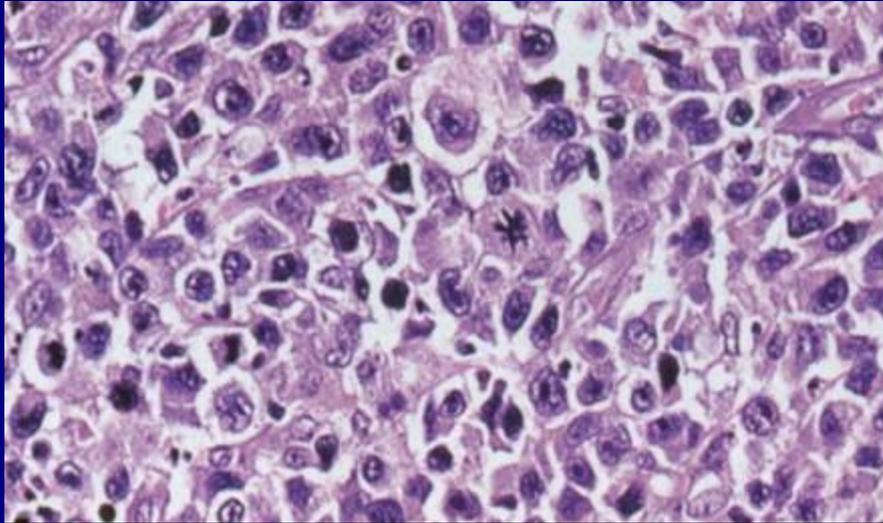


# C-ALCL: Immunophenotype

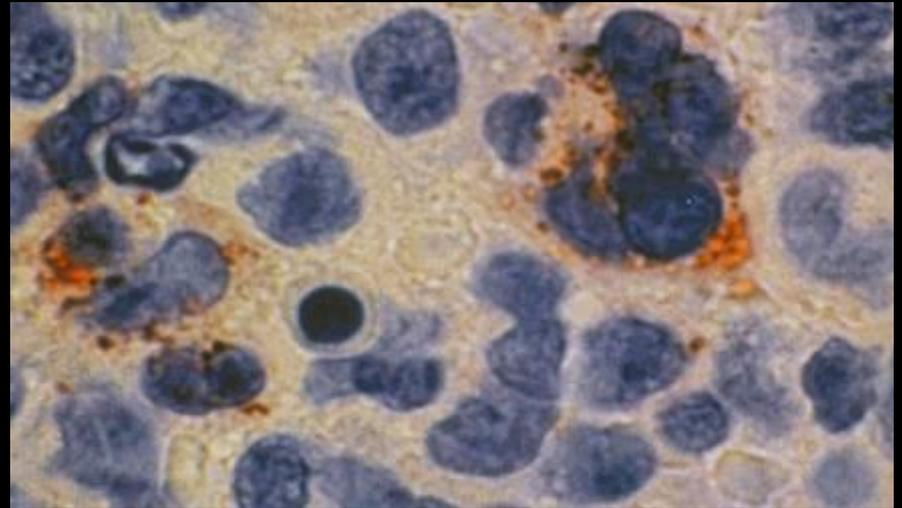
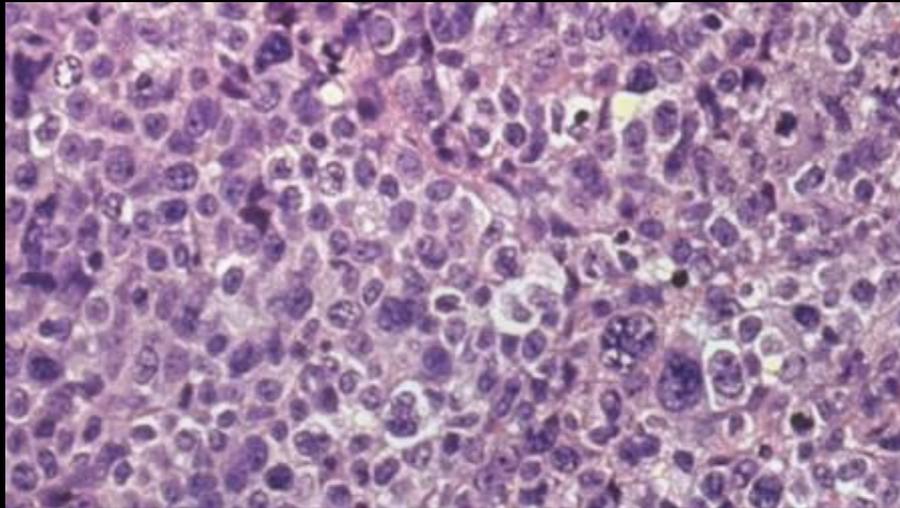
- Express T-cell antigens; Usually CD4+
- CD30: a majority (>75%) of the cells
- Cytotoxic granule associated proteins (granzyme B, perforin, TIA-1): 70% of the cases
- Loss of CD2, CD5 and/or CD3 are common, but null cell phenotypes are rare
- Cutaneous lymphocyte antigen (recognized by HECA-452): half of the cases
- Unlike systemic neoplasms, most cases are negative for EMA
- ALK: negative

# Primary Cutaneous Anaplastic Large Cell Lymphoma

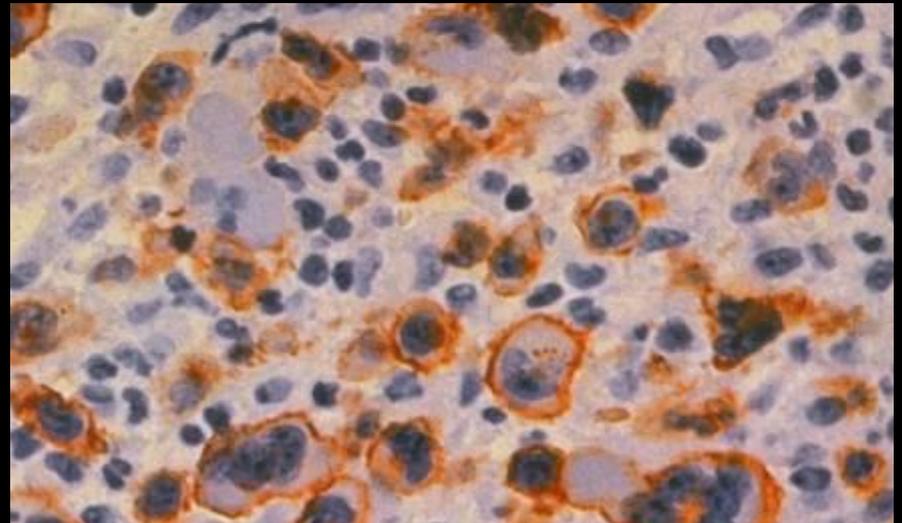
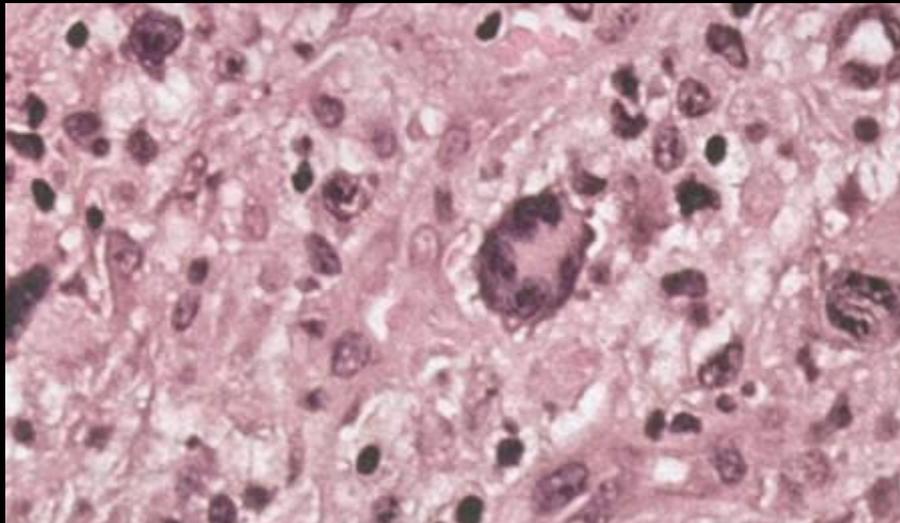




**CD30**



**TIA-1**



**CD30**

# C-ALCL: Genetics

- TCR genes are clonally rearranged in most cases
- t(2;5) translocation is not found in this disease
- *NPM-ALK* fusion transcripts have been reported in a few cases by sensitive, nested RT-PCR
  - Small minority
  - Most likely represent systemic ALCL presenting with cutaneous disease

# C-ALCL: Cell of Origin

Transformed or activated skin-homing T-lymphocyte

# C-ALCL: Prognosis and Predictive Features

- Favorable: 90% at 5 years
- Extracutaneous disease: unfavorable
- Spontaneous regression: favorable
- Limited disease: skin-directed therapies (radiotherapy or surgical excision)
- Overt/developing extracutaneous involvement: aggressive, multiagent chemotherapy
- Multifocal skin lesions, but no extracutaneous disease: multi-agent chemotherapy given (it does not prevent subsequent skin relapses)

# Lymphomatoid Papulosis (LyP): Definition

- A chronic recurrent skin disease characterized by the appearance of spontaneously regressing papules and an atypical T-cell infiltrate which can mimic a T-cell lymphoma histologically
- The disease usually has a benign course
  - Not a lymphoma strictly speaking
  - Atypical lymphoproliferation which can be clonal and progress to lymphoma

# LyP: Synonyms

<i>Lukes-Collins:</i>	Not listed
<i>Kiel:</i>	Not listed
<i>Working Formulation:</i>	Not listed
<i>REAL</i>	Not listed

# LyP: Epidemiology

- A rare disease which predominantly affects adults/elderly
- Male to female ratio: 1.5:1

# LyP: Sites of Involvement

- Limited to the skin
- Extracutaneous dissemination only occurs in cases with progression to lymphoma

# LyP: Clinical Features

- Characteristic skin lesions are recurrent papules and/or nodules which regress spontaneously
  - Typically within 3 to 6 weeks
- Larger tumor lesions greater than 2.5 cm showing regression are rarely seen



# Lymphomatoid Papulosis



10 y/o girl with solitary enlarging nodule on the nose for 2 wks. Two weeks later, numerous papules developed. Complete durable remission of >16yrs after 9 weeks of oral methotrexate.



# LyP: Etiology

Unknown

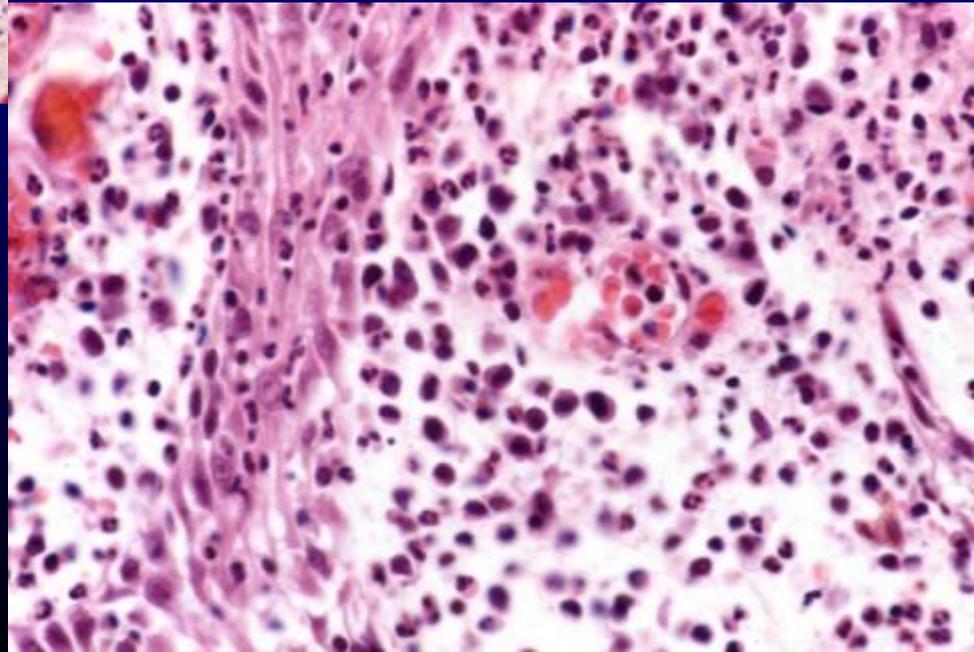
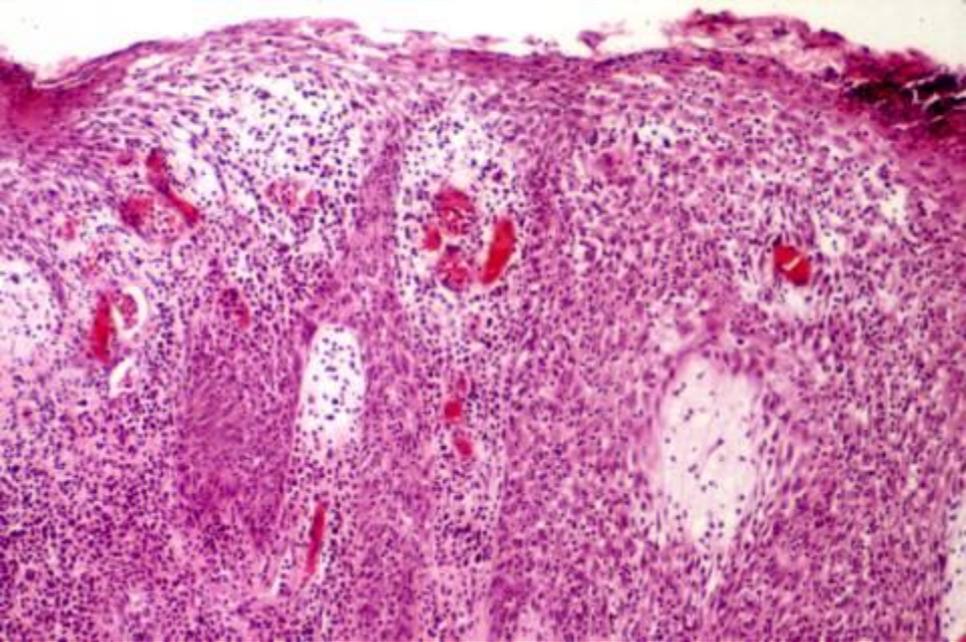
# LyP: Morphology

- Papular lesions
  - Wedge-shaped, dermal infiltrates of atypical T-cells
  - Varying proportions of inflammatory cell
    - Neutrophils, eosinophils, macrophages and small lymphocytes
- The atypical T-lymphocytes may resemble the cerebriform cells seen in mycosis fungoides or have Reed-Sternberg (RS)-like features

# LyP: Morphology

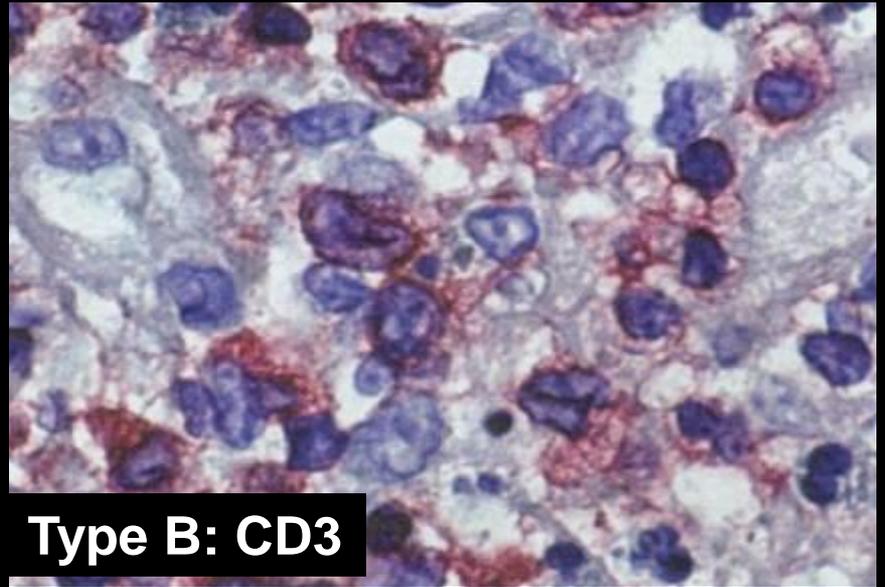
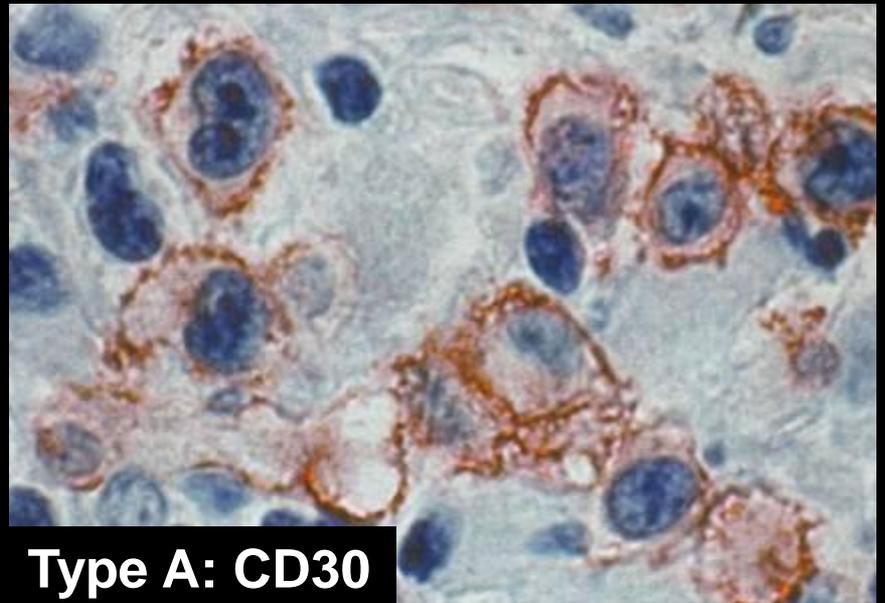
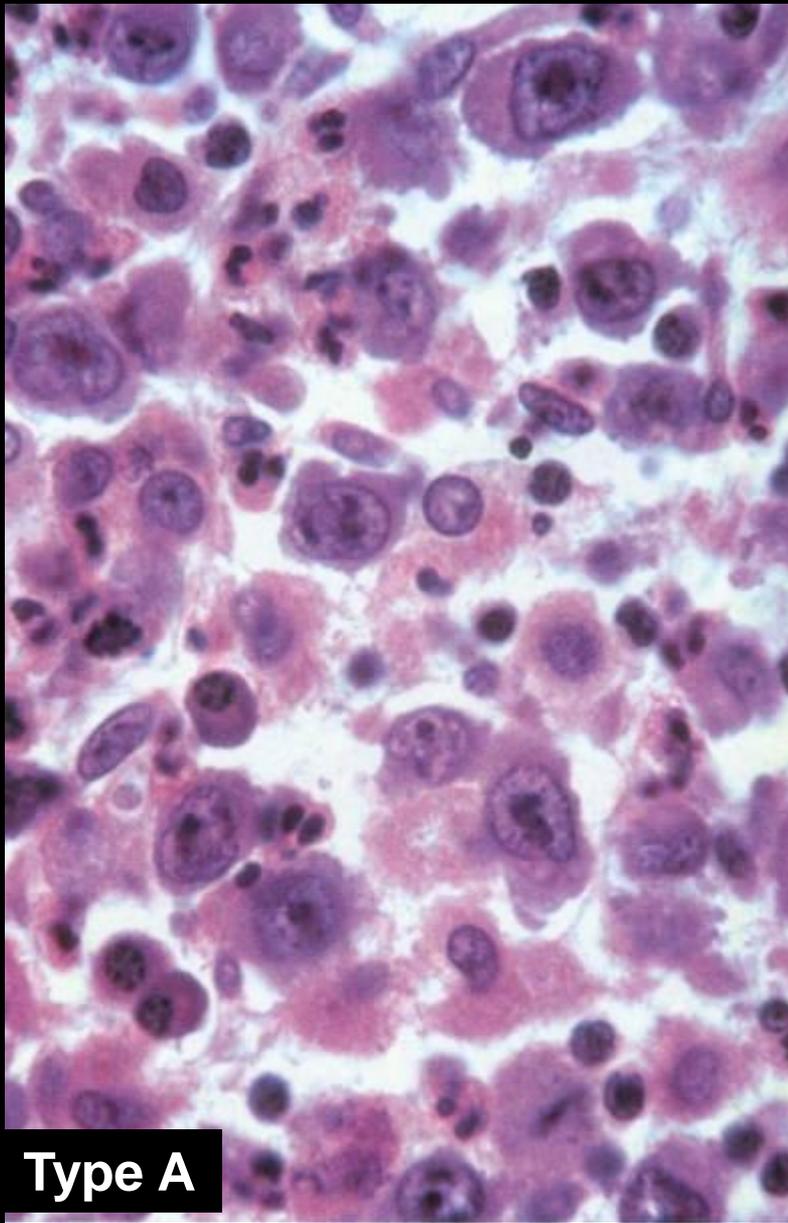
- A distinction is made between type A and type B lesions
- In type A lesions many RS-like cells are present together with numerous inflammatory cells
- Type B lesions show a predominance of cells with cerebriform nuclei and contain only few inflammatory cells
- In individual patients both types of lesions may exist

# Lymphomatoid Papulosis



# LyP: Immunophenotype

- The atypical T cells are CD4+, CD8-
- They often express aberrant phenotypes with variable loss of pan-T-cell antigens, e.g. CD2, CD5
- CD30 is positive in type A lesions, but often negative in type B lesions
- Cytotoxic granule associated proteins are expressed in most cases
- The ALK protein is consistently absent



# LyP: Genetics

- TCR gene rearrangement: majority of type B lesions and occasionally in type A lesions
  - Overall, 50% of the patients
- Identical patterns of rearrangement have been demonstrated in lymphomatoid papulosis and associated lymphoma lesions in some patients
- The t(2;5) translocation does not occur

# LyP: Possibly Normal Counterpart

Activated skin-homing T-lymphocytes

# LyP: Prognosis and Predictive Features

- Benign course, often of long duration (years)
- Low-dose methotrexate and psoralen/UVA (PUVA) therapy reduce the number of skin lesions and recurrences
- After discontinuation of therapy, the disease continues its natural course
- Treatment should be reserved for patients with large, numerous and/or scarring skin lesions

# LyP: Prognosis and Predictive Features

- Association with lymphoma is seen in 10-20%
  - Various lymphomas have been described, including mycosis fungoides, C-ALCL, and Hodgkin lymphoma
- No known criteria which can predict progression to lymphoma
  - Long term follow-up recommended

# Borderline Lesions

## Related term:

Lymphomatoid papulosis, diffuse large cell type (type C)

Anaplastic large cell lymphoma,  
lymphomatoid papulosis-like histology.

# Borderline Lesions

- Discrepancy between clinical features and histological appearance
  - Difficult to classify as either "classical" lymphomatoid papulosis or frank C-ALCL.
- Cases that mimic a lymphoma histologically (confluent sheets of CD30-positive atypical/anaplastic lymphoid cells), but resemble lymphomatoid papulosis clinically (regressing papules) have been referred to as lymphomatoid papulosis, type C
- The opposite situation (solitary skin tumours resembling lymphomatoid papulosis histologically) has been termed anaplastic lymphoma, lymphomatoid papulosis-like

# Borderline Lesions

- Reports of borderline lesions of primary cutaneous CD30-positive T-cell lymphoproliferative disorders are few
- The prognosis seems to be favorable, but long term follow-up is required