What's new on the horizon in T-cell lymphoma

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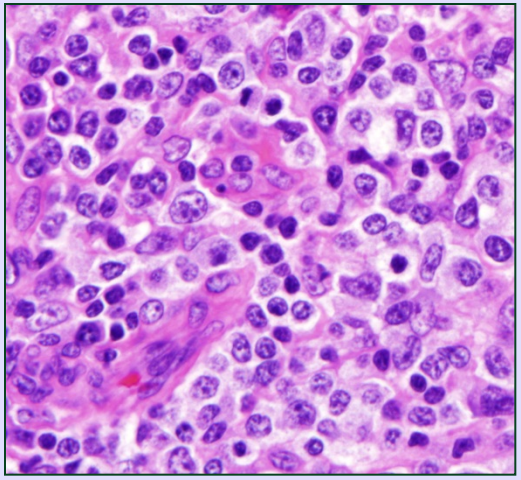
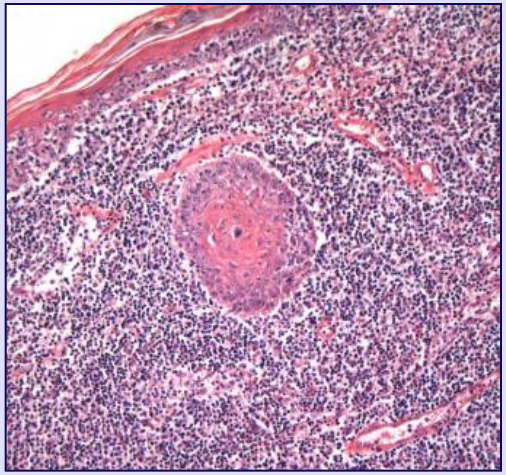
WHO classification: where are we today?

- Of 12 monographs planned for 4th Edition Bluebook series, only 7 are published
  - Series unlikely to be completed prior to 2017
- Appeal to Chris Wild, IARC Director
  - Need to update the classification, incorporate new data and concepts
- IARC authorized "Revised WHO classification" to be published in web-based format on *PUBCAN – target date 2016*
- Bluebook monograph and Ebook will be produced as well

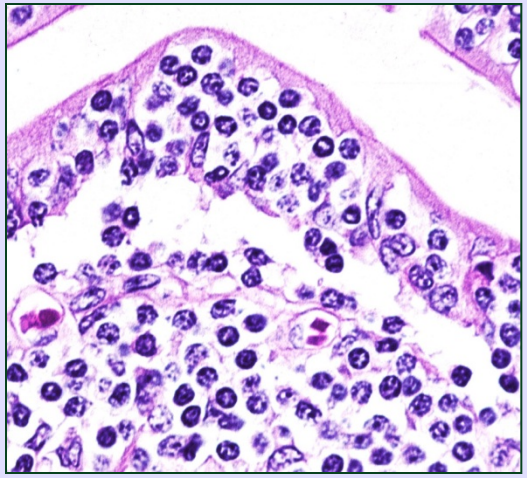
Clinical Advisory Meeting, March 31-April 1, 2014



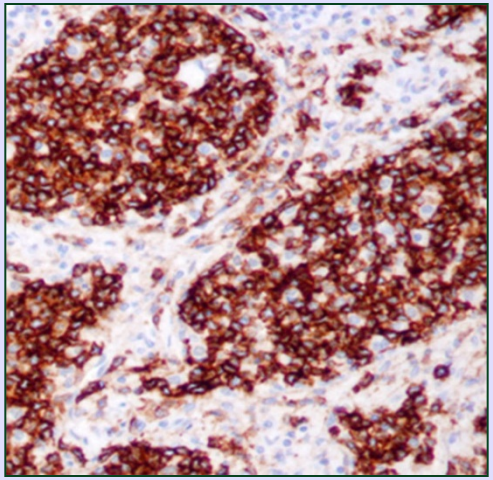
AITL & other nodal TFH lymphomas



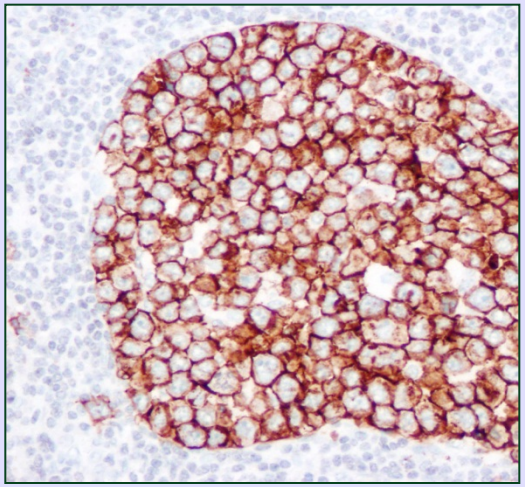
1°Cut CD4+ T-LPD



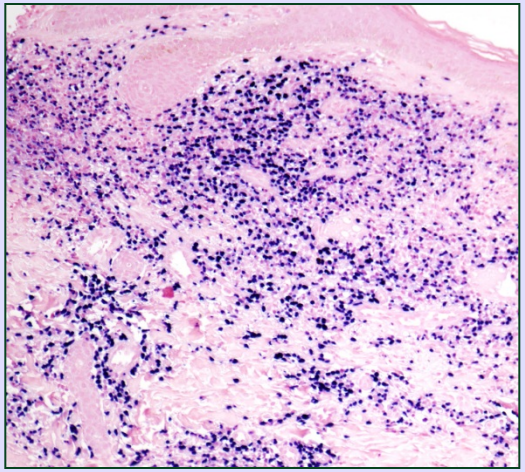
Intestinal T-cell lymphomas



HSTCL / γδ

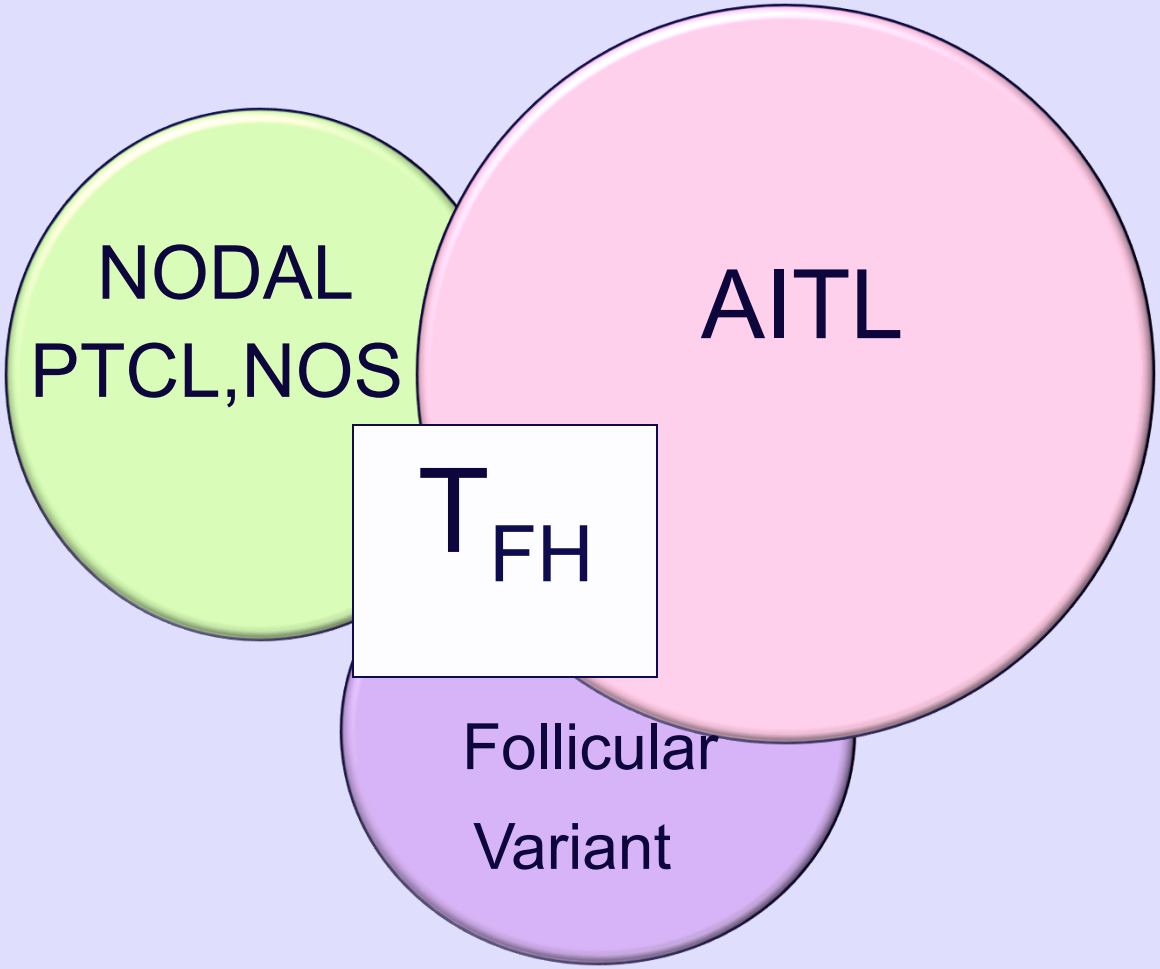


ALCL, ALK-negative



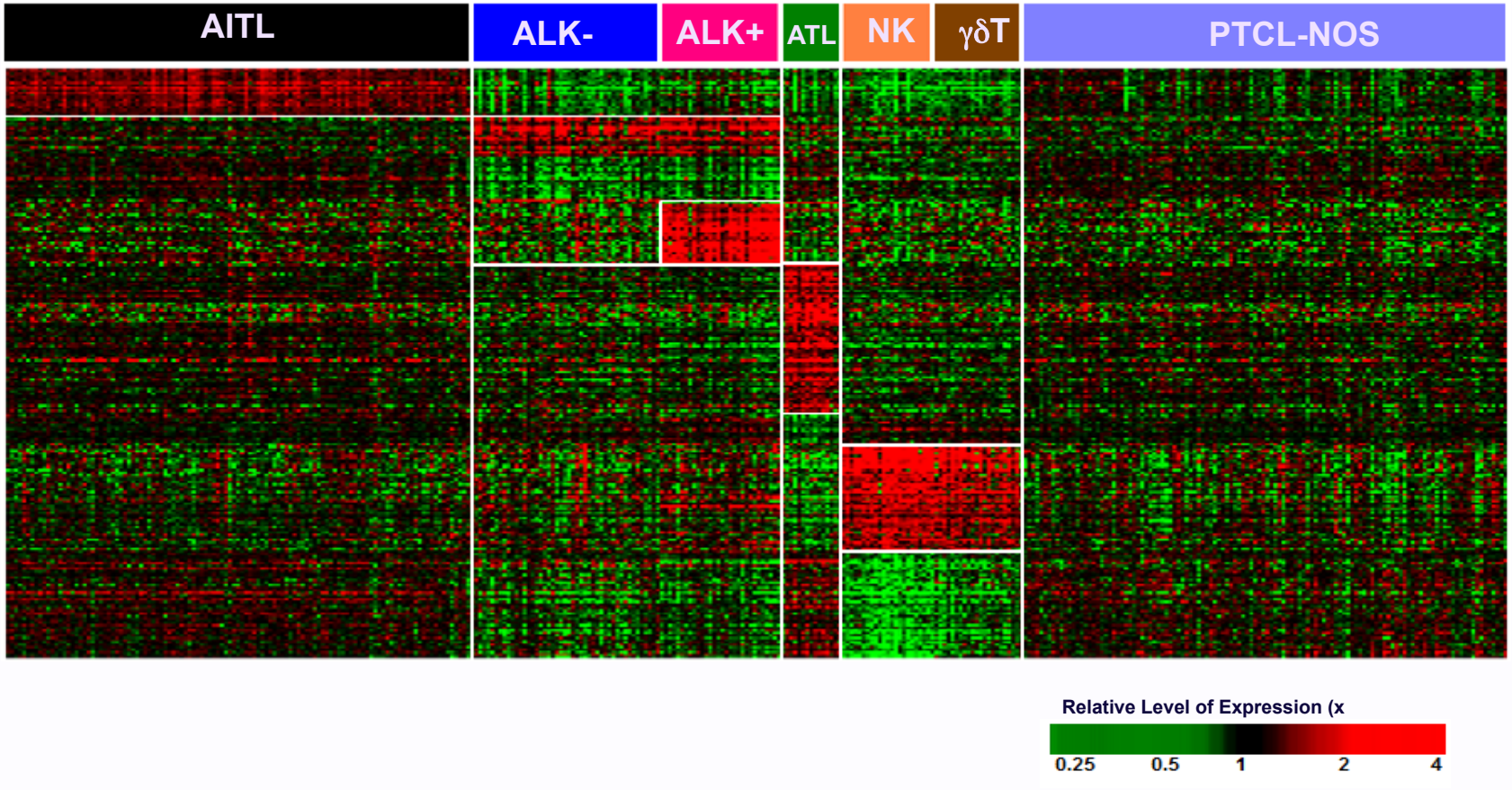
EBV+ T/NK disease

Nodal Peripheral T-cell Lymphomas of TFH Origin



- Gene expression profiling and mutation analysis has helped to clarify the interrelationship among nodal T-cell lymphomas of TFH origin

Gene expression profiling allowed reclassification of 14% of PTCL, NOS as AITL



Gene expression signatures of PTCL ; Iqbal et al. *Blood 2014*

Genomic Findings in AITL and TFH derived lymphomas

- 20-45% in *IDH2*, *DNMT3A* and *TET2 in AITL*
  - *Genes involved in pathogenesis of gliomas, AML*
- *TET2* mutations also seen in other PTCL of TFH origin (up to 60%)
- *RHOA* mutations in 60% of AITL and some PTCL, NOS, all with TET2

Lemonnier 2012, Cairns 2012; Couronne 2012, Sakata-Yanagimoto 2014, Palomero 2014

Nodal Peripheral T-cell Lymphomas (2008)

PTCL, NOS

T-zone variant

Lymphoepithelioid cell variant

Follicular variant

Angioimmunoblastic T-cell lymphoma

Nodal Peripheral T-cell Lymphomas (2015)

PTCL, NOS

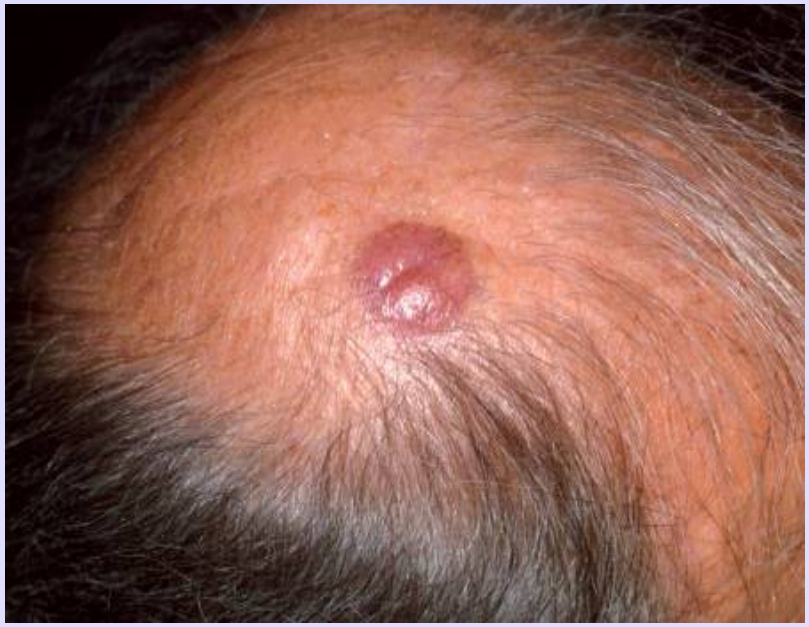
T-zone variant

Lymphoepithelioid cell variant

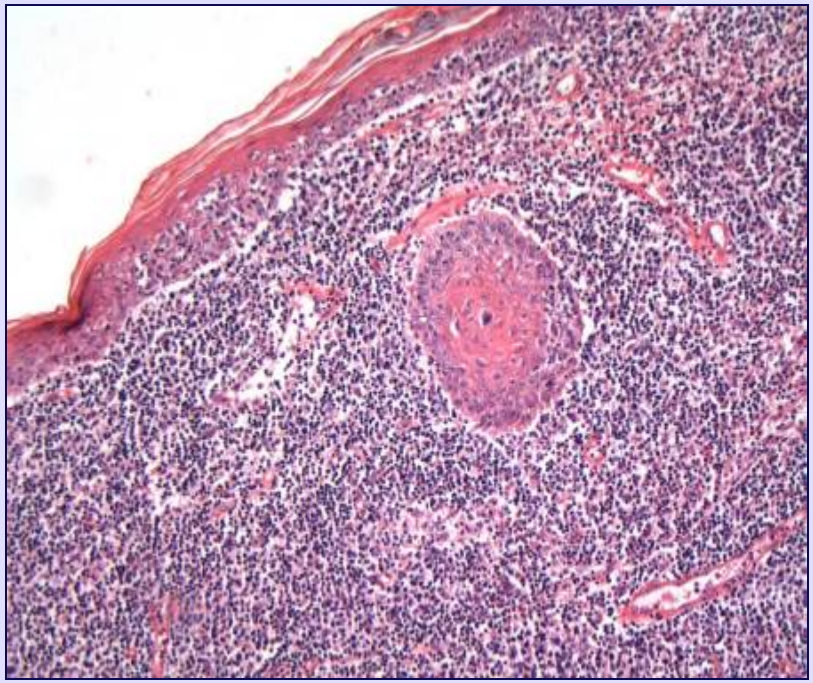
Angioimmunoblastic T-cell lymphoma

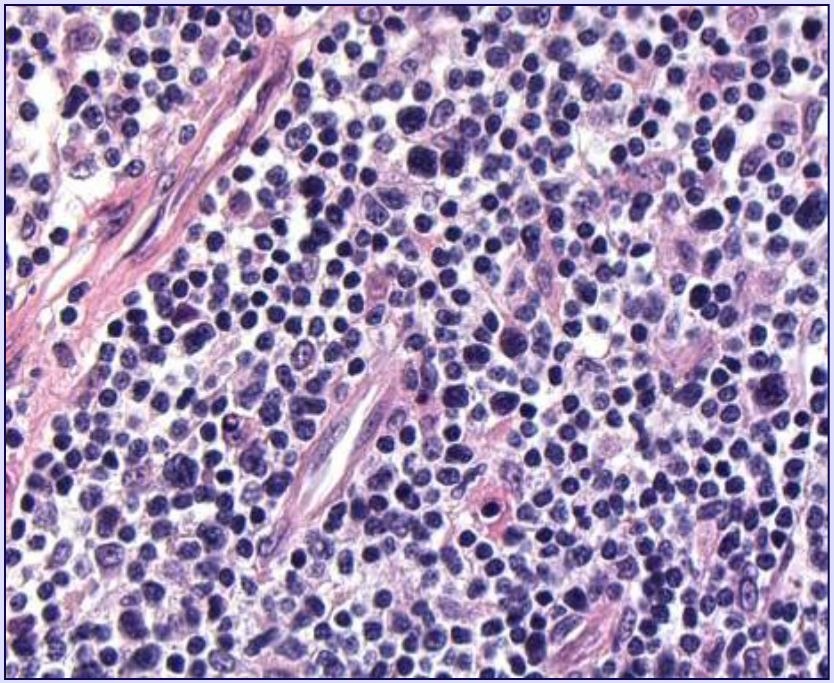
Nodal PTCL of TFH origin

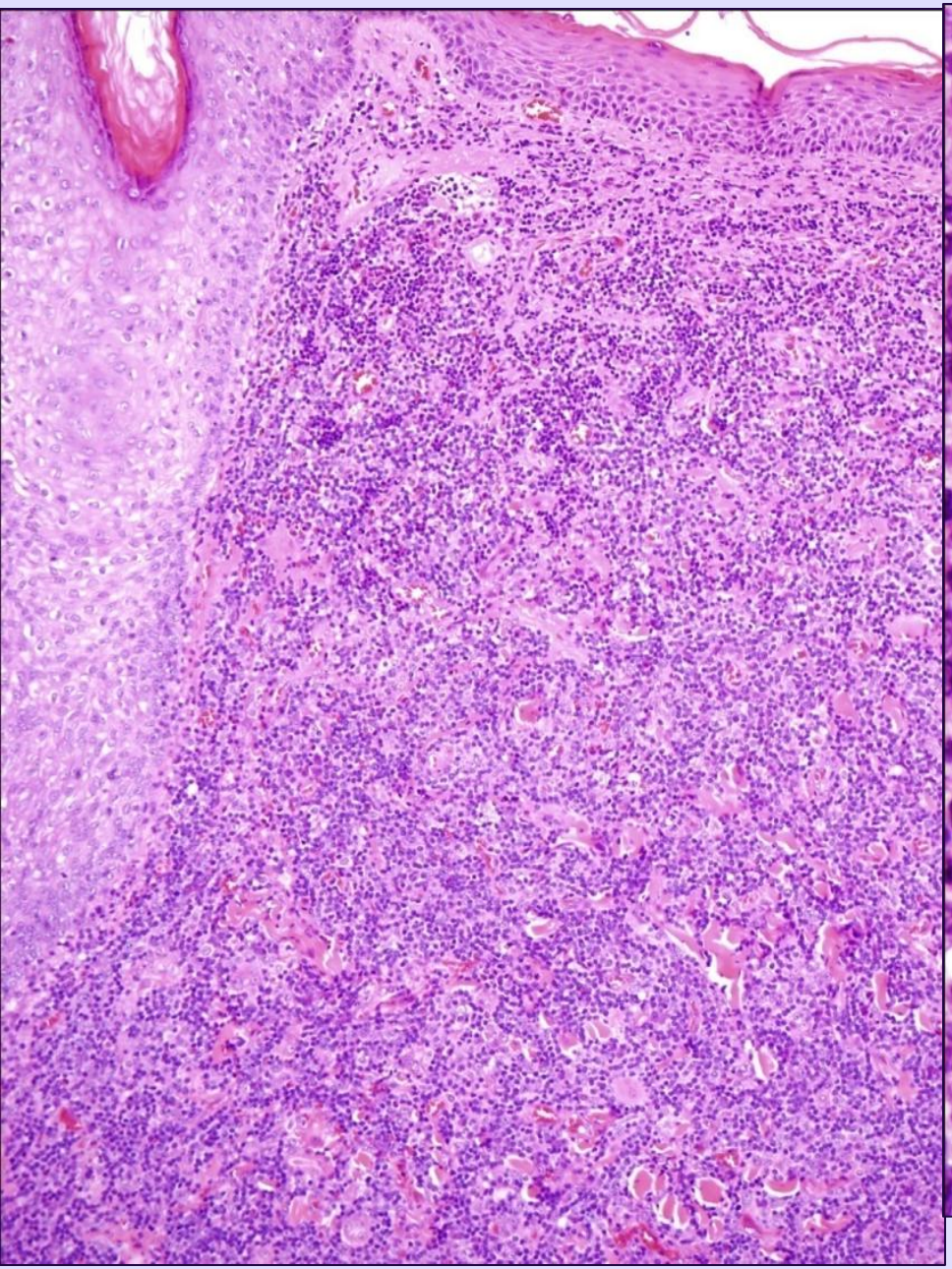
Follicular T-cell lymphoma (provisional)

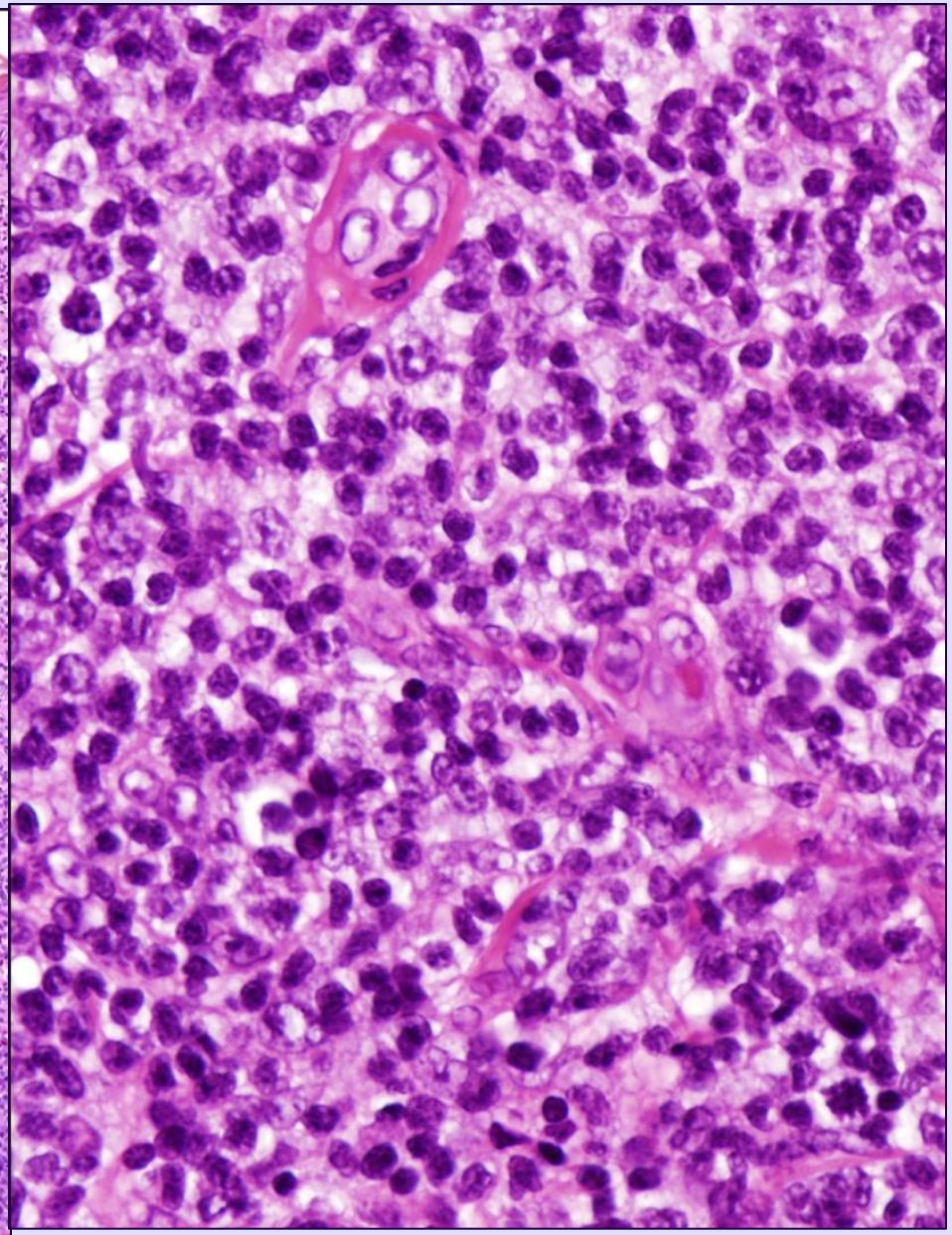


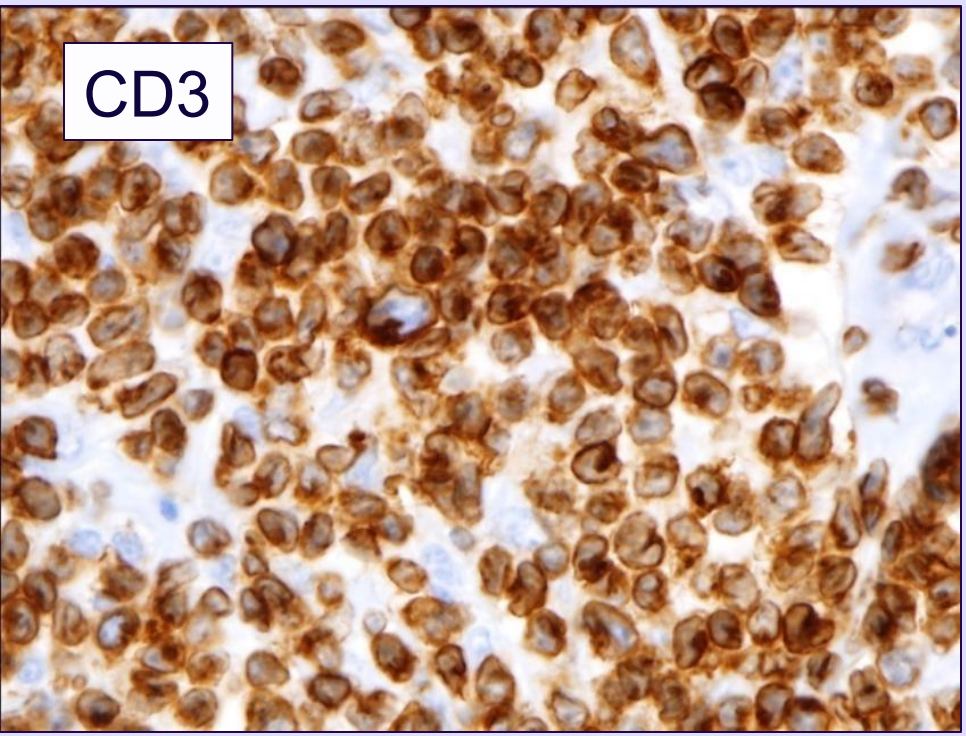
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*
- *Was provisional in 2008*
- *Another TFH derived neoplasm*

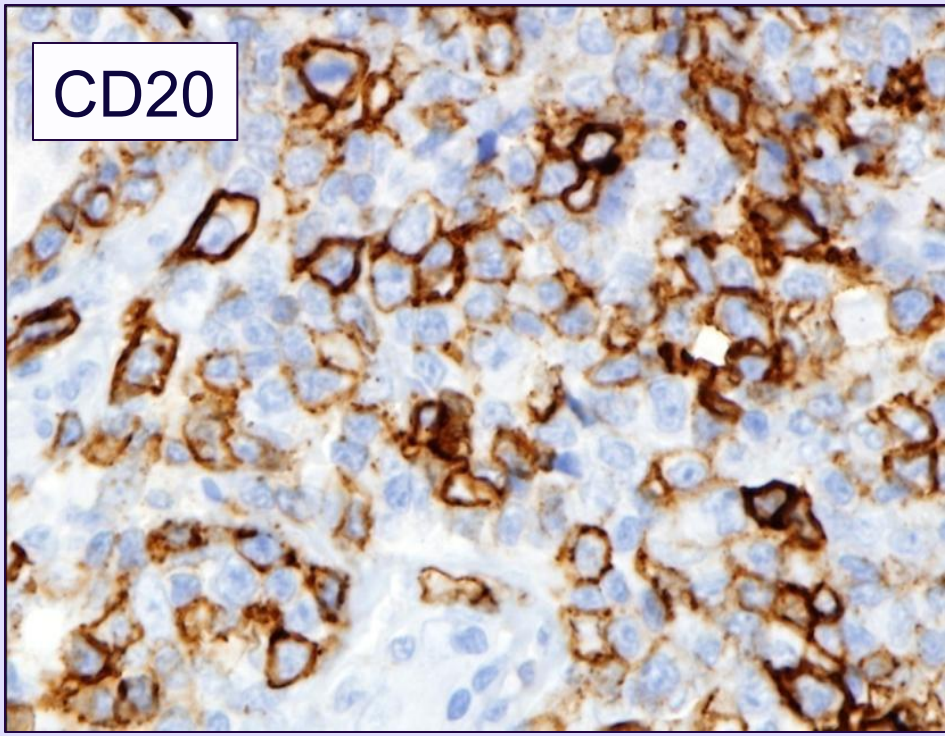








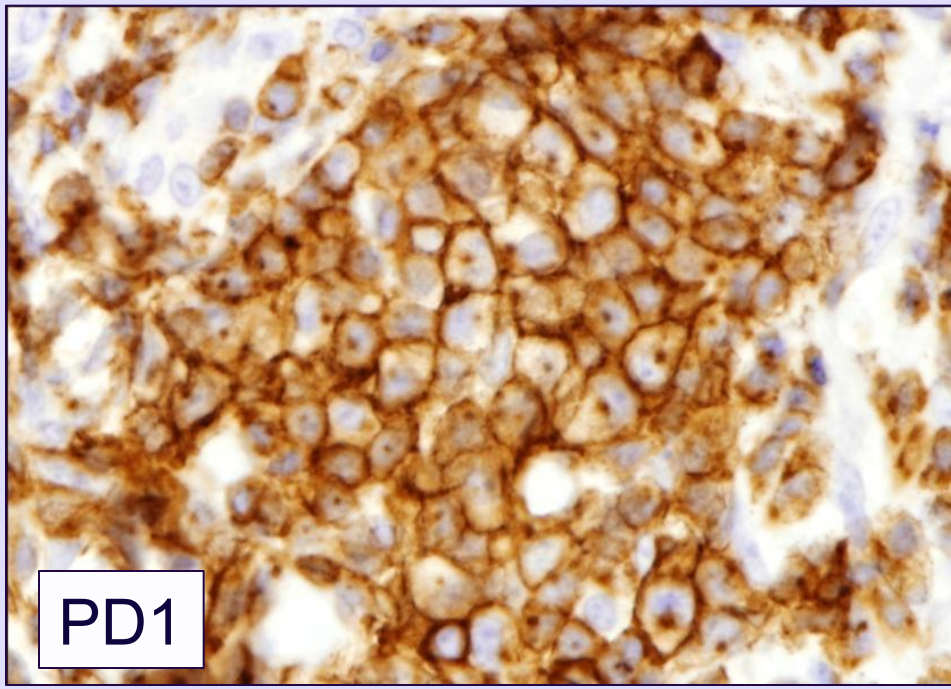




TFH phenotype, PD-1+
rarely CD10+

Contains abundant B-cells, fewer plasma cells

Clonal TCR with rare B-cell clonality



Primary cutaneous small/medium CD4 positive T-cell proliferations

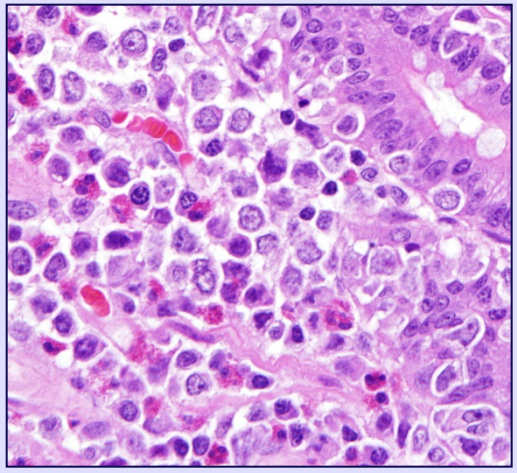
Grogg (2008) Garcia Herrerra (2008) Beltraminelli (2009)

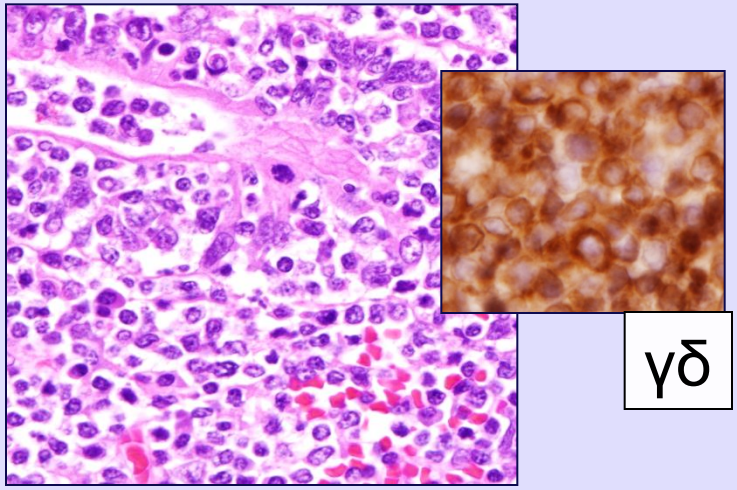
- Vast majority of patients have an isolated single lesion
- 75% head and neck area
- Excellent prognosis following simple excision
  - Only patients with multiple or bulky disease had an aggressive clinical course
- Proposal: Primary cutaneous CD4+ T-cell lymphoproliferative disease (not lymphoma)

Enteropathy Associated T-cell Lymphoma, Types I & II are distinct

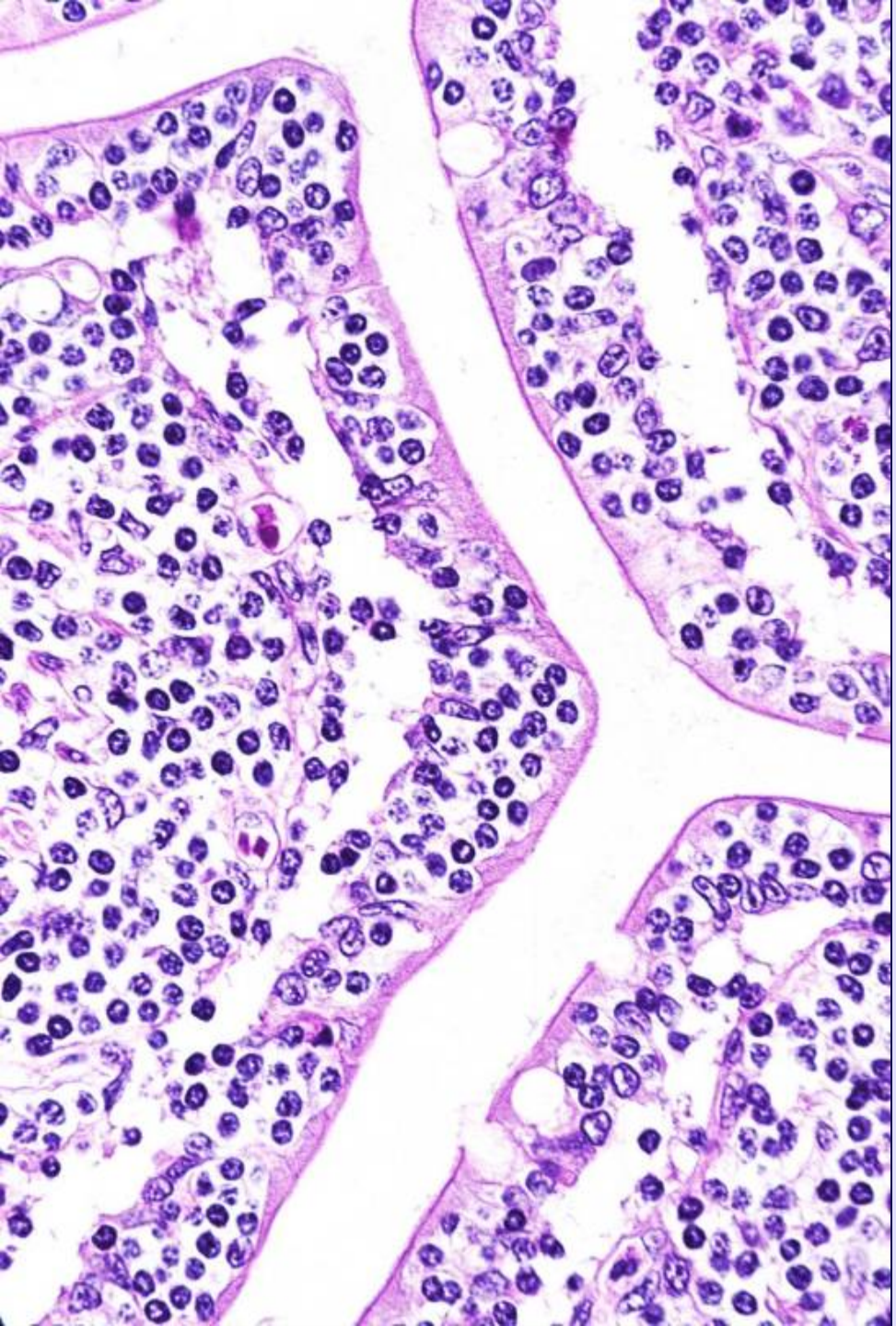
EATL I
Usually αβ
Celiac disease
N European

EATL II
Usually γδ
Epitheliotropic
Asian, Hispanic





γδ

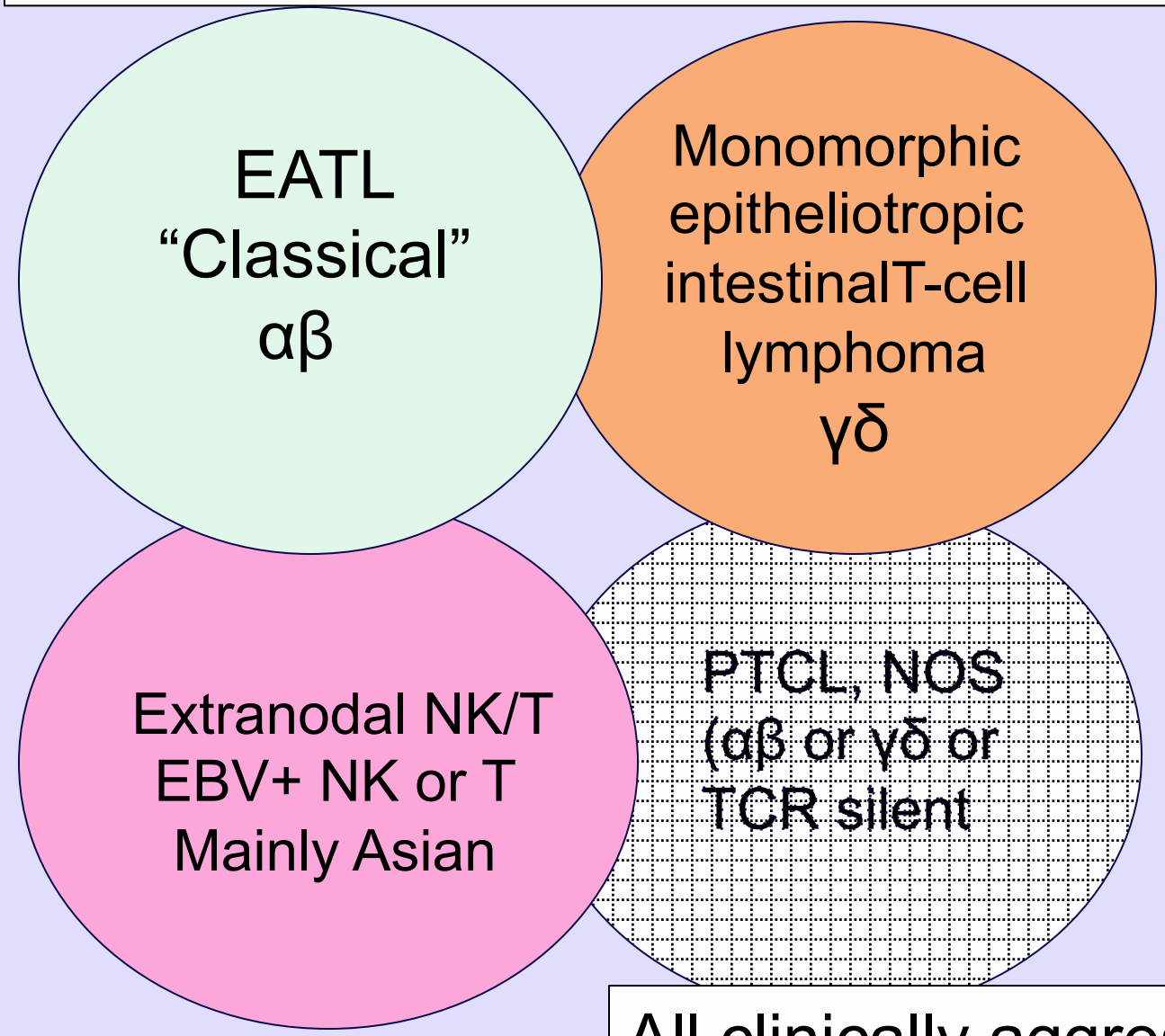


Monomorphic epitheliotropic intestinal T-cell lymphoma

(EATL II)

- Medium sized cells with clear cytoplasm
- CD56 +, CD8+, CD4-
- Gamma delta +
- MAT kinase +
- 8q24(myc) amplifications

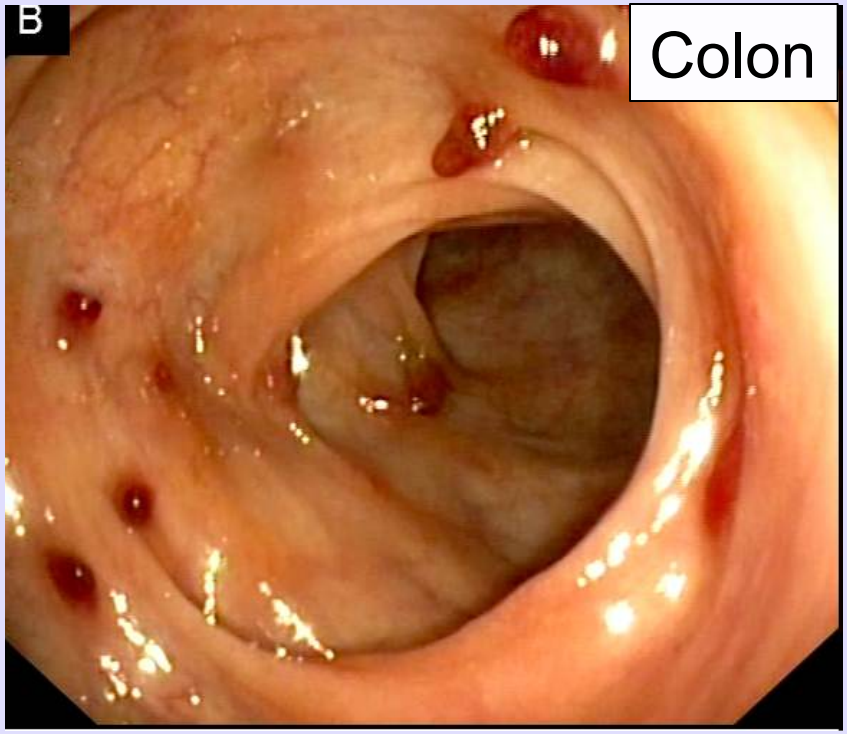
T-cell & NK cell Lymphomas of Gastrointestinal Tract



All clinically aggressive

Indolent T-cell Lymphoproliferative diseases of low malignant potential

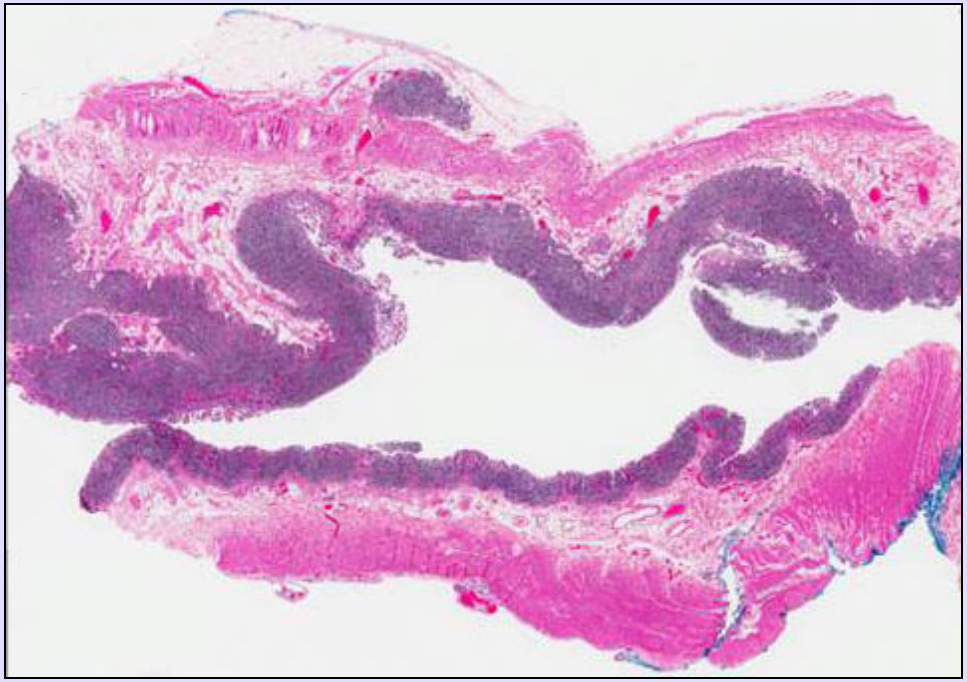
Indolent T-LPD of the GI Tract
Perry et al., Blood 2013



Multiple mucosal polyps
Can affect entire GI Tract

Most common in:
- small intestine
- colon

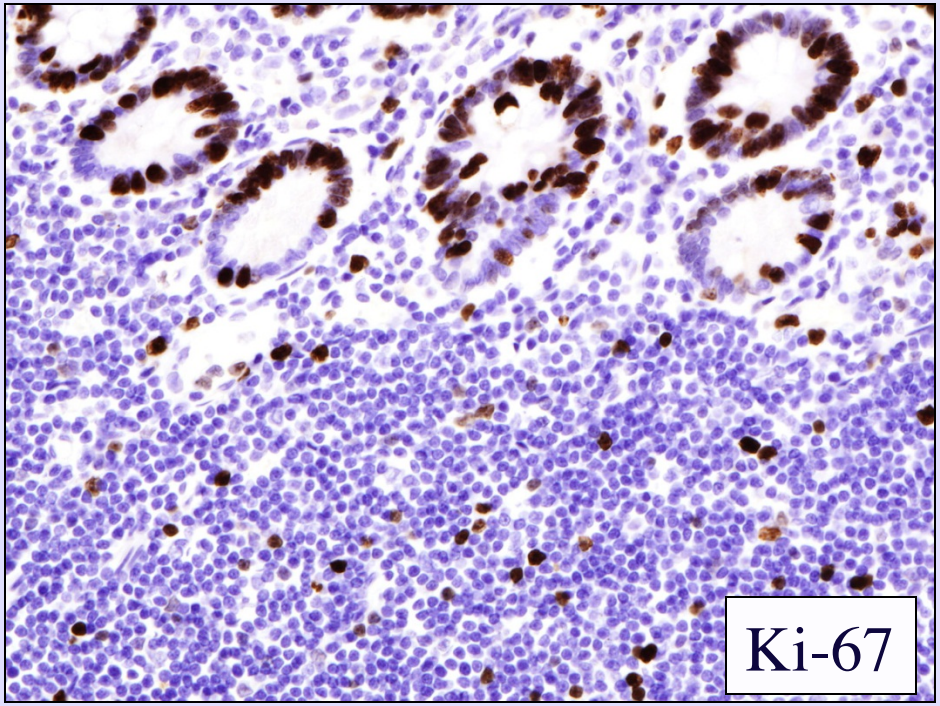
Less often:
- stomach
- oral mucosa

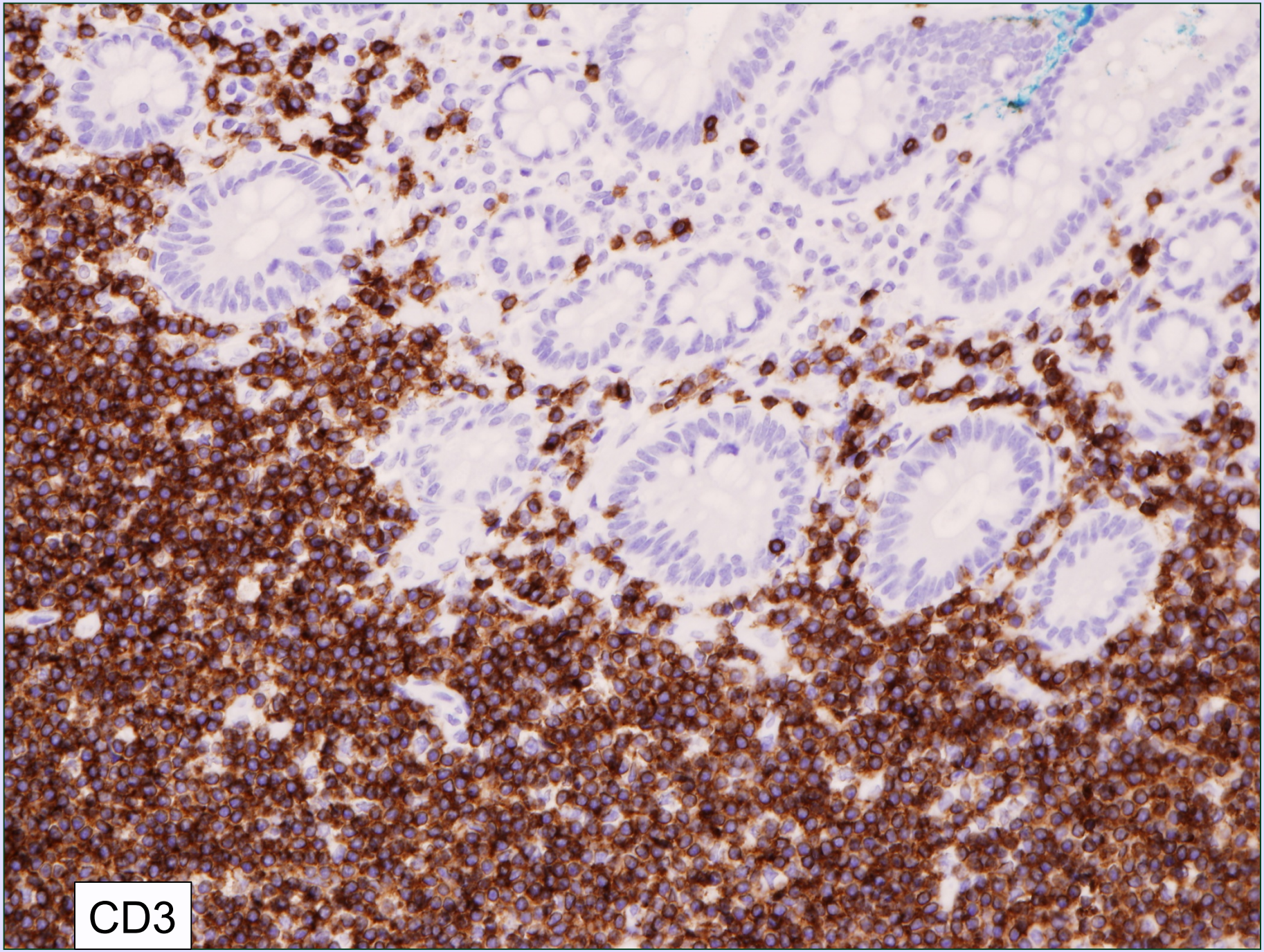


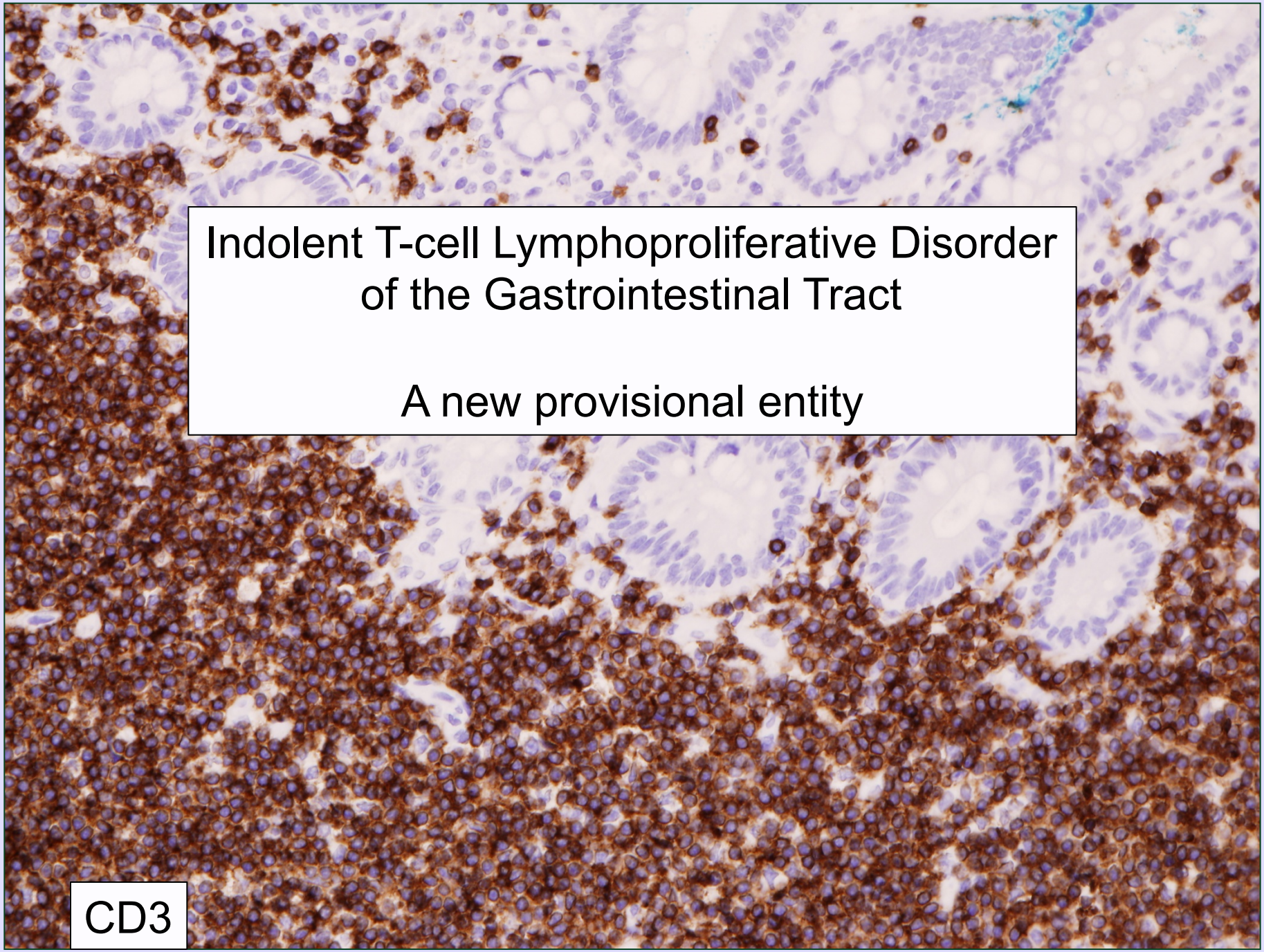
Superficial infiltrate
Confined to mucosa
No invasion of the wall

Very low proliferation rate
No destruction of the glands
No cytological atypia
Very bland infiltrate

? Optimal management
Do not respond to chemorx

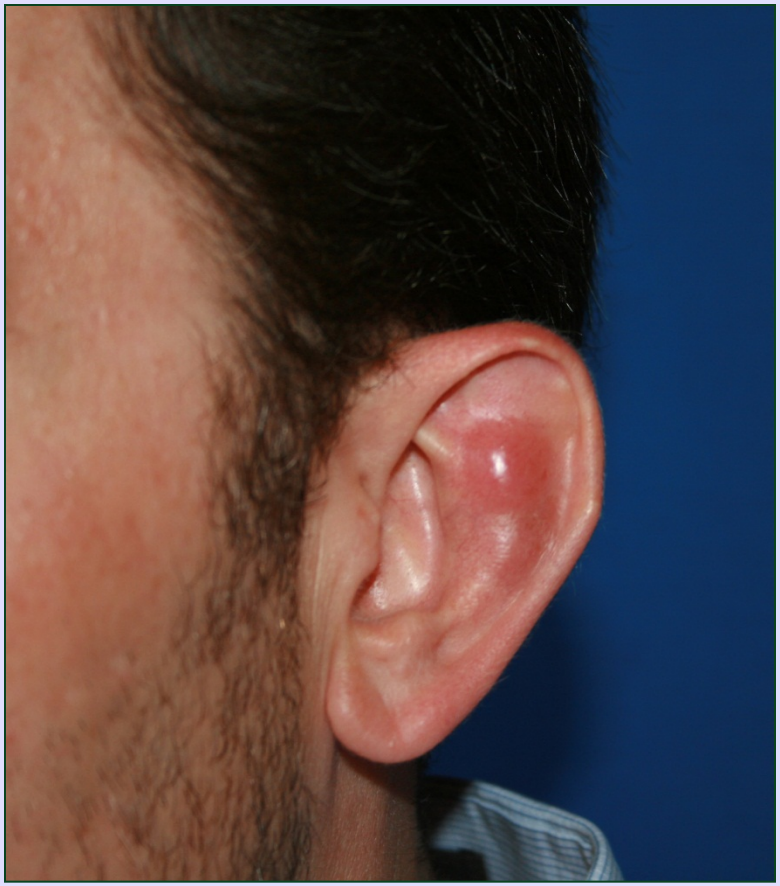


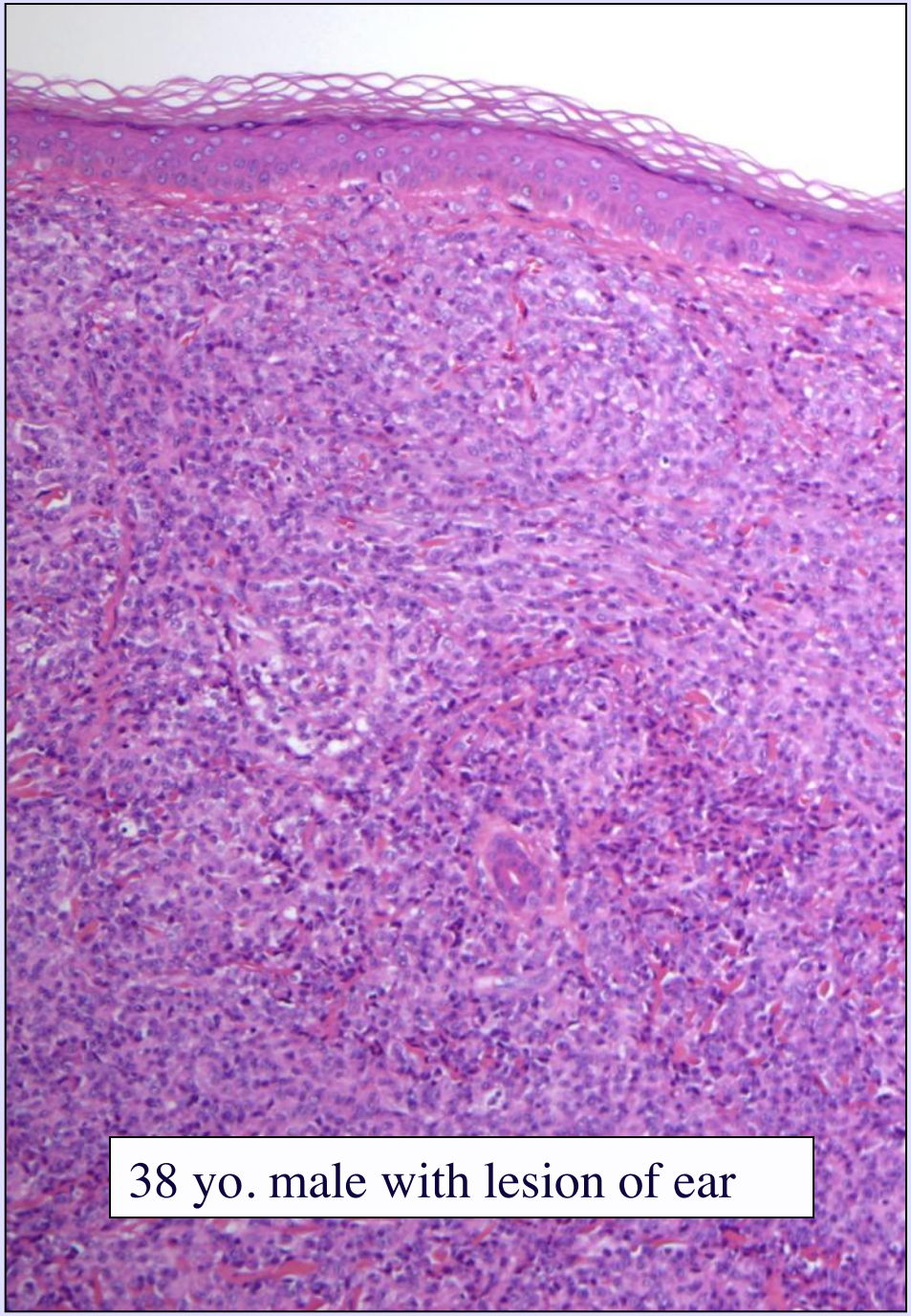

CD3

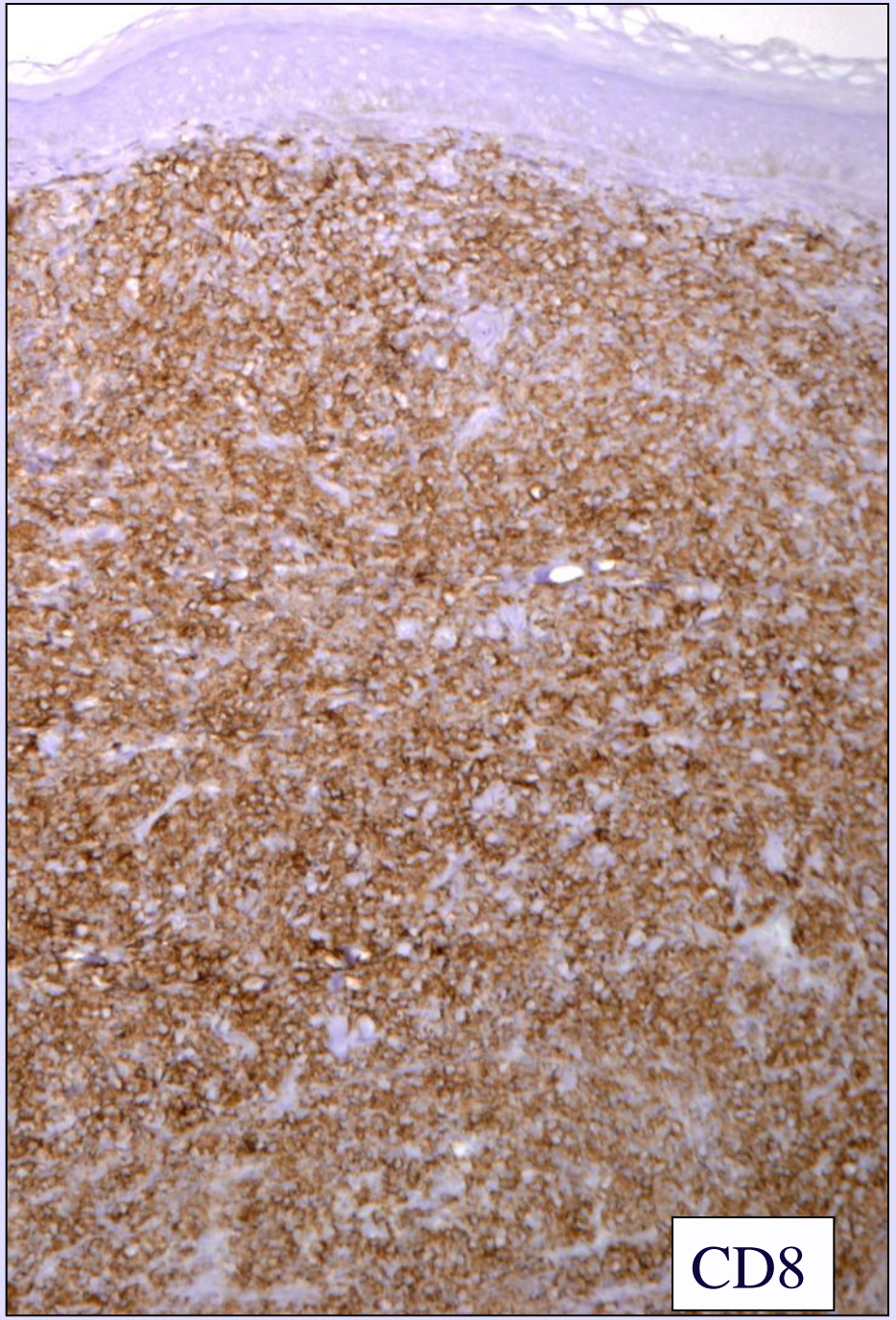

Indolent T-cell Lymphoproliferative Disorder of the Gastrointestinal Tract
A new provisional entity
CD3

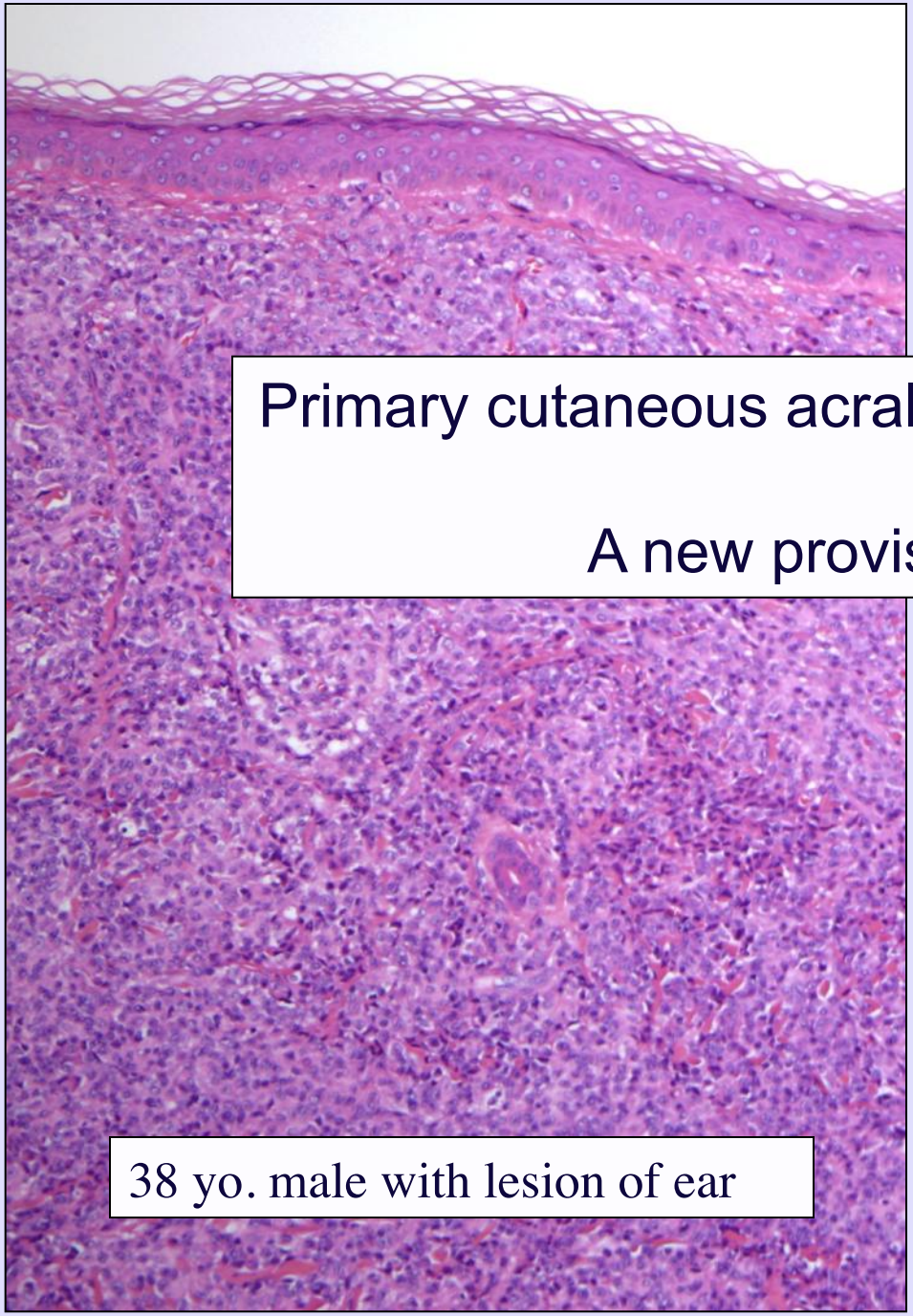
Indolent CD8+ lymphoid proliferation of the ear (Petrella et al, 2007)

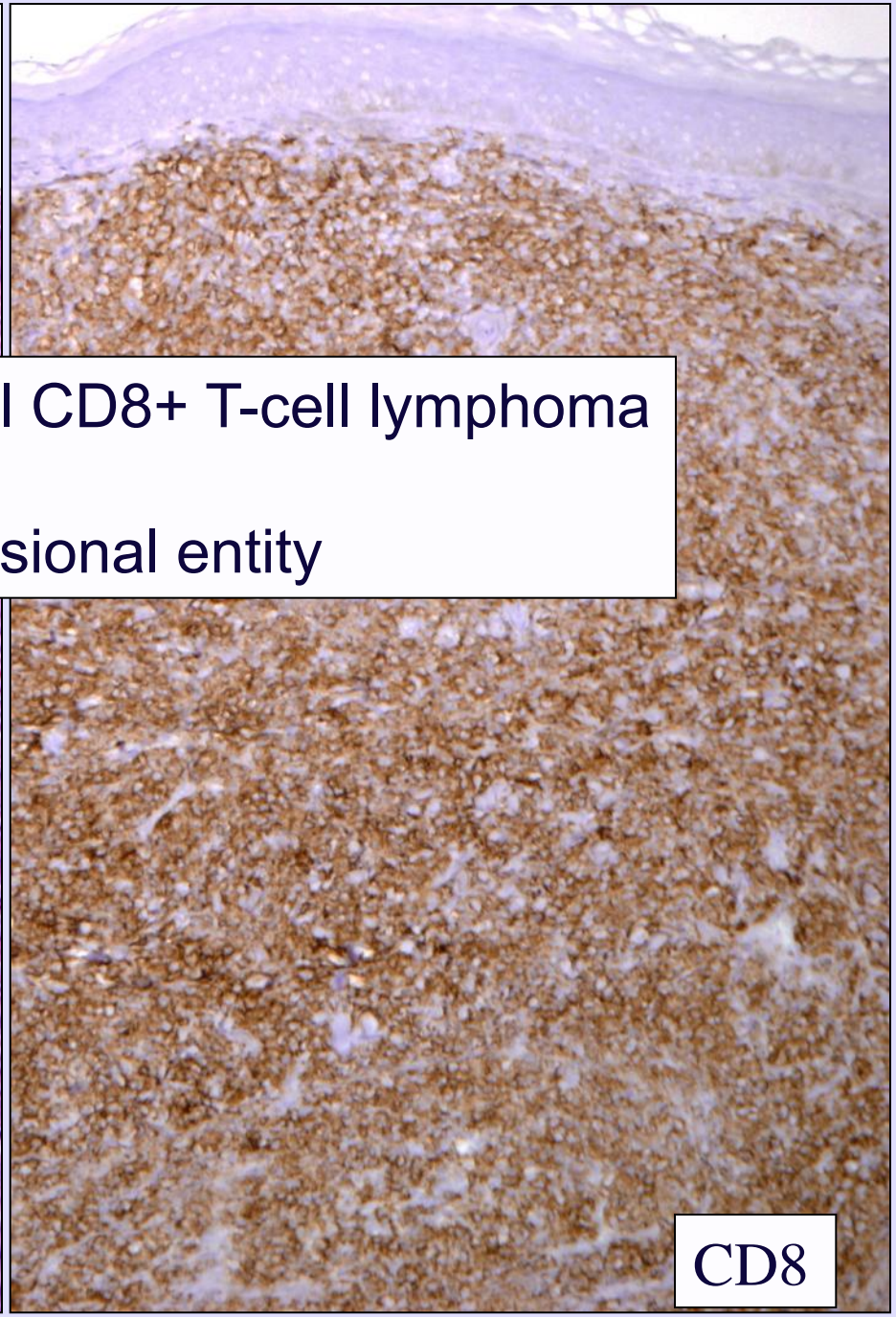
- Dense, non-epidermotropic; Clonal
- Rx with local radiotherapy or excision
- Local recurrence in some, but no progression
- Also involves other acral cutaneous sites




38 yo. male with lesion of ear


CD8





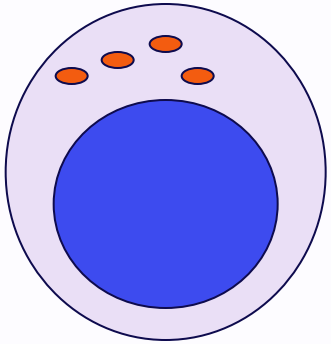
Primary cutaneous acral CD8+ T-cell lymphoma

A new provisional entity

38 yo. male with lesion of ear

CD8

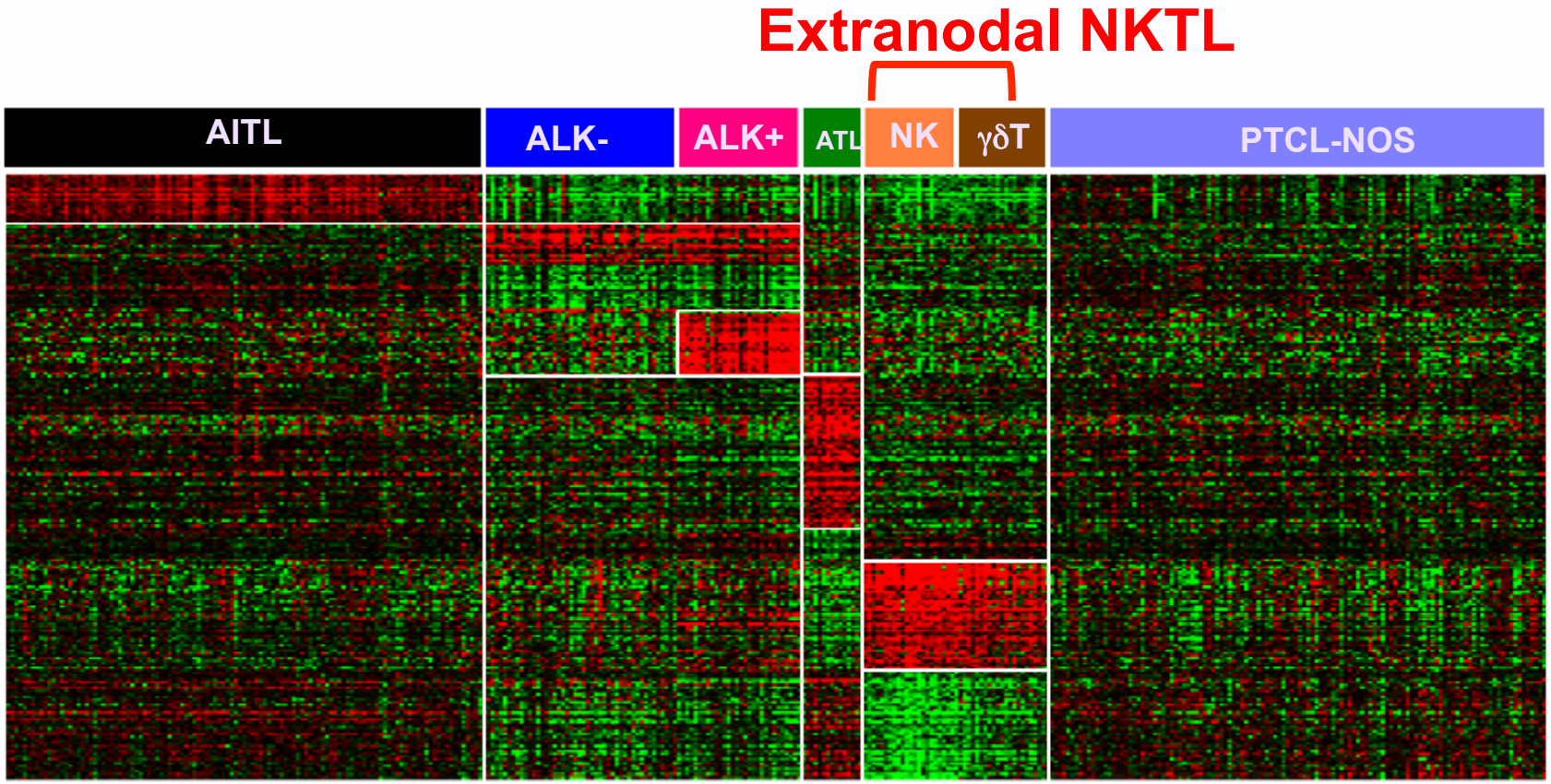
Lymphomas of the Innate Immune System



- Includes γδ T-cells, NK-like T-cells, NK-cells
- Commonly involve
  - Skin, mucosa & other extranodal sites
  - Spleen & BM
- Infrequent lymphadenopathy

Similarities in gene expression profile and in genetic features

Overlap in the Gene Expression Profile of γδ T-cell and NK-cell lymphomas

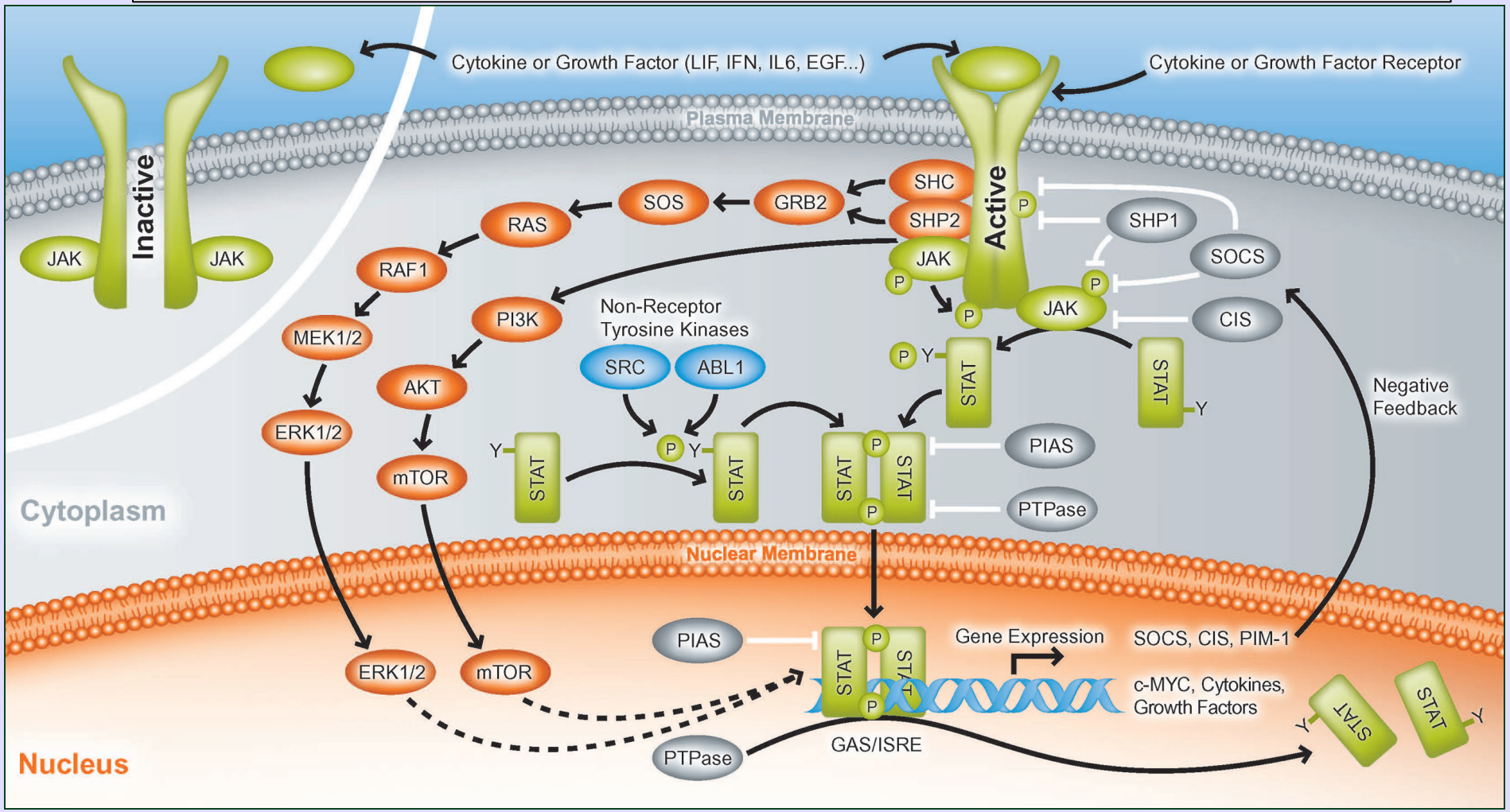


Gene expression signatures in peripheral T-cell lymphoma; Iqbal et al. Blood 2014

Recurrent Mutations in γδ T-cell & NK-cell lymphomas and T-LGL leukemia

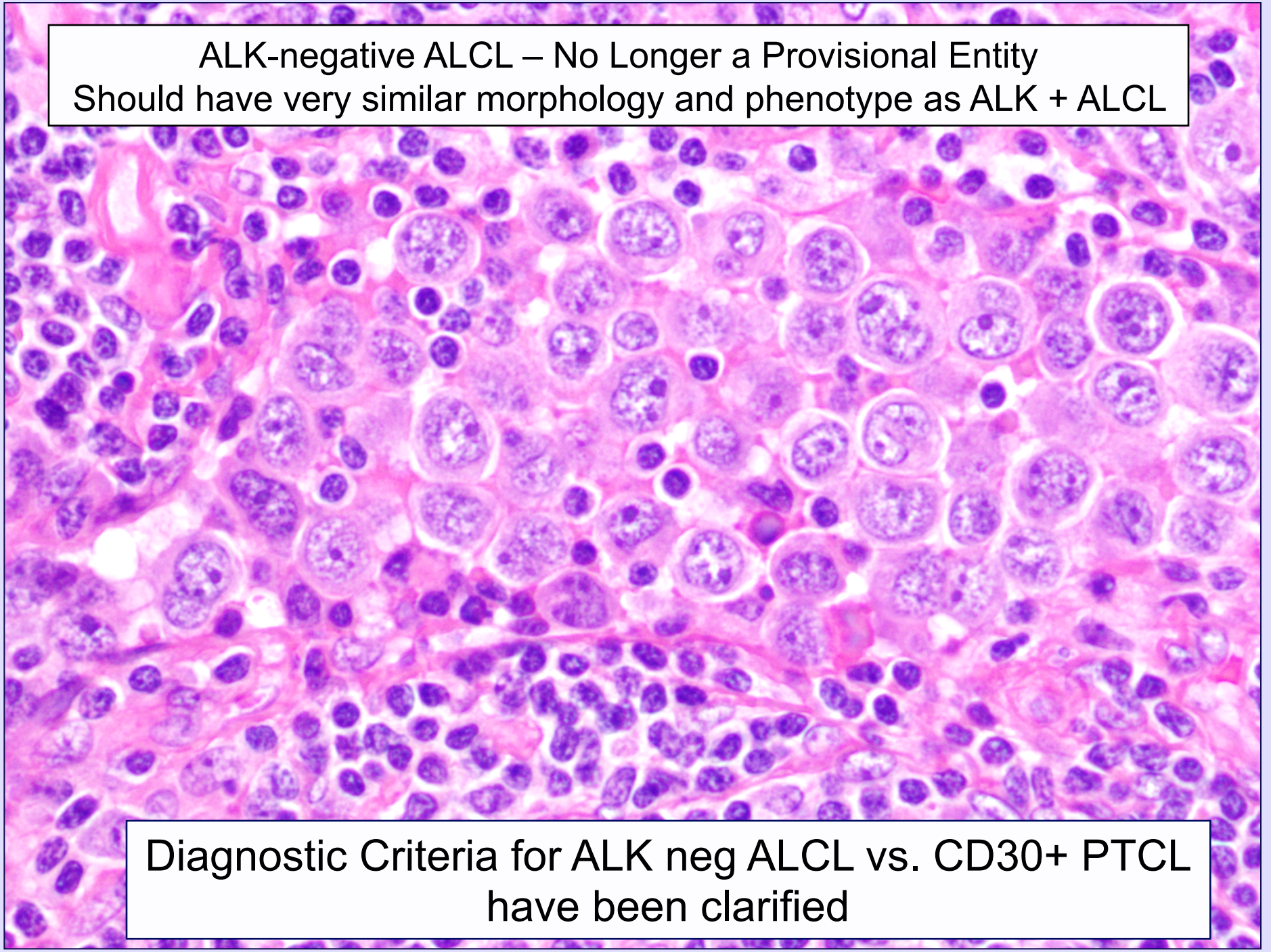
	Mutations
Nicolae, et al. 2014	
• γδ HSTCL	• 33% STAT5B, 10% STAT3
Kucuk et al. 2015	
• γδ cutaneous & HSTCL	• 33% STAT5B; 8% STAT3
• EATL, II (γδ)	• 36% STAT5B
• NKTCL	• 6% STAT3; 6%STAT5B
Koskela et al., Jerez et al.2012	
• T-cell & NK-cell LGL	• 40% STAT3; 2% STAT5B

Similar rate of mutations in STAT5B (33%) in most γδ T-cell lymphomas (Hepatosplenic, Intestinal, Cutaneous)

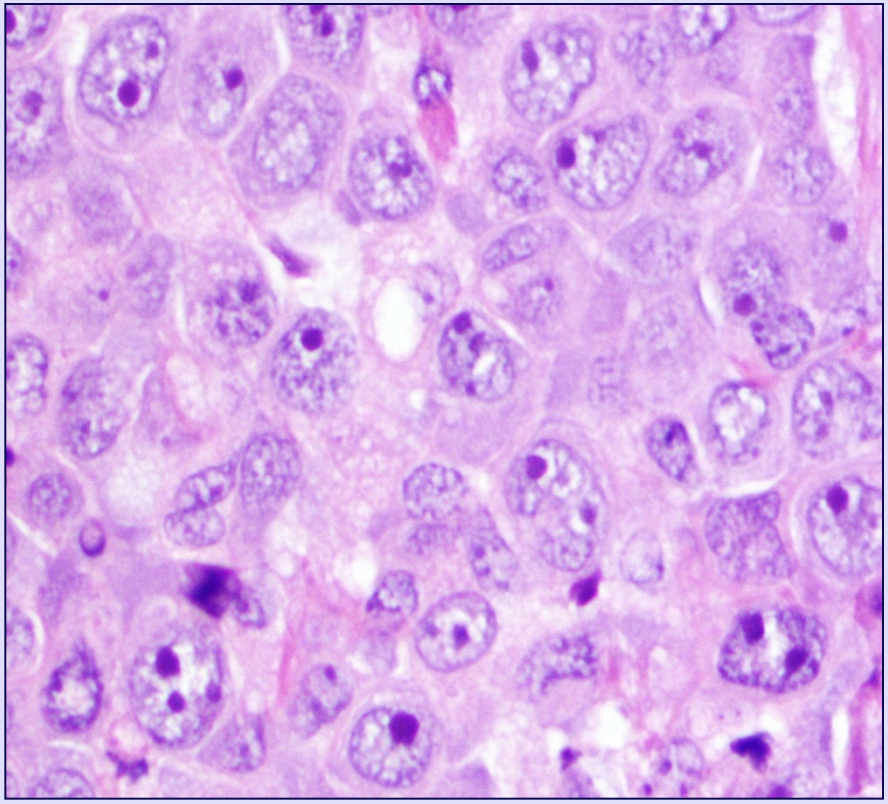


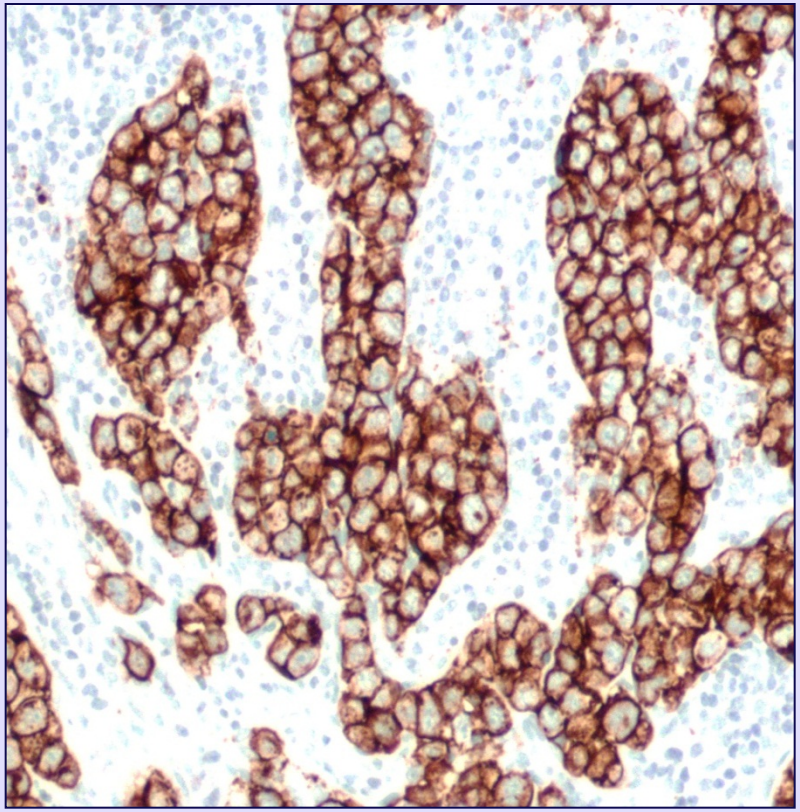
JAK/STAT Pathway is an attractive target for therapy of Cytotoxic T-cell Lymphomas and Leukemias

ALK-negative ALCL – No Longer a Provisional Entity
Should have very similar morphology and phenotype as ALK + ALCL



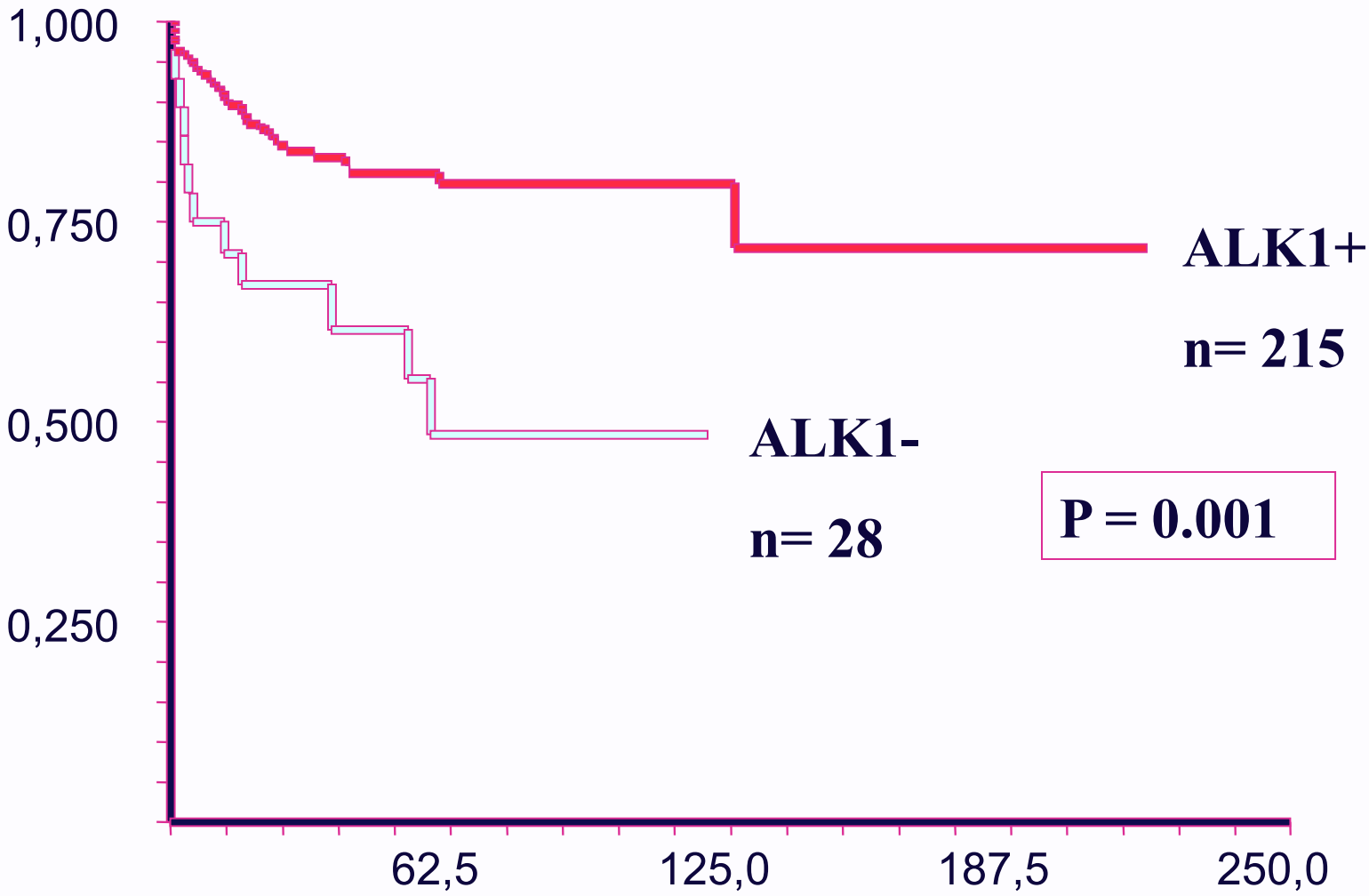
Diagnostic Criteria for ALK neg ALCL vs. CD30+ PTCL have been clarified





Required: Cohesive growth pattern with hallmark-like cells
Strong and uniform CD30 expression
Desirable but not essential: EMA+, Cytotoxic +, Sinusoidal growth, Loss of "T-cell ag"

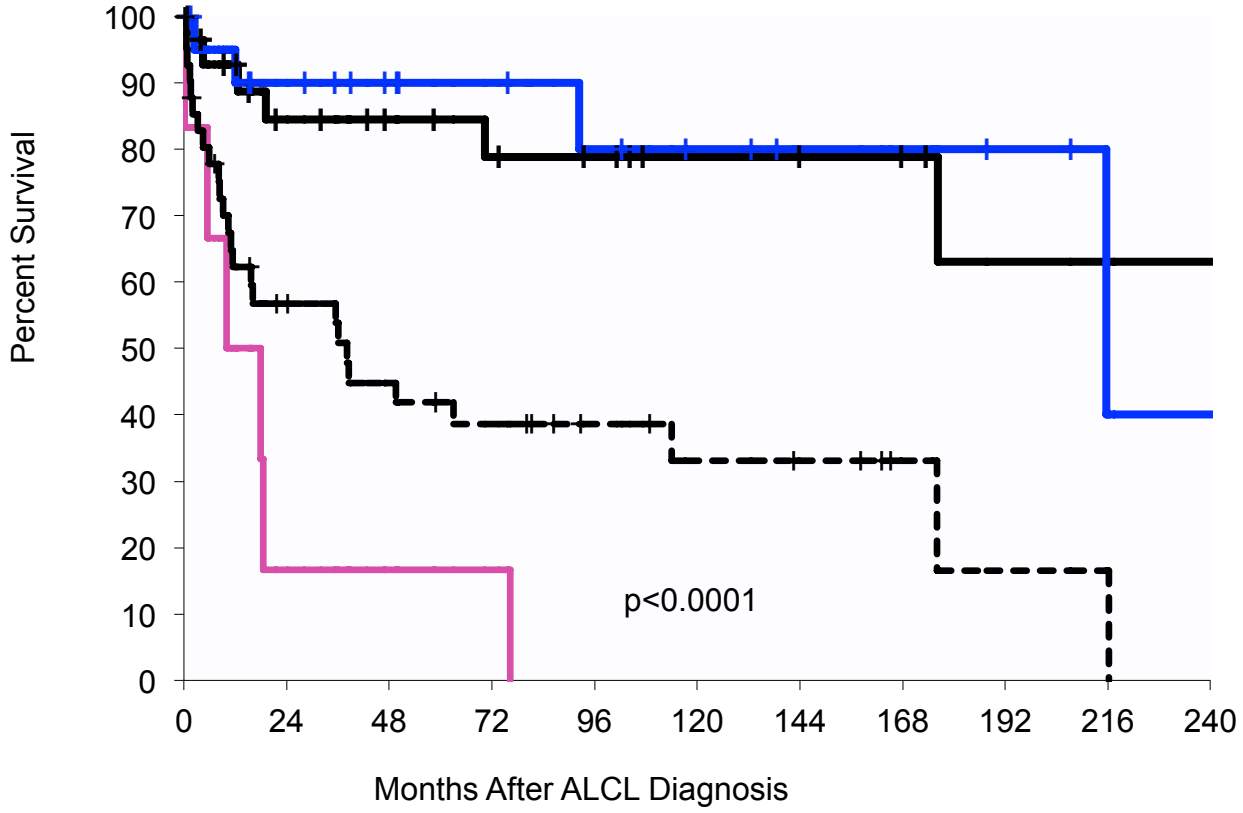
Overall survival of ALCL, ALK+ / ALK-
Pediatric and Adult cases



G Delsol

Genetic correlates with survival in ALCL, ALK+/ ALK-

Feldman et al. Blood 2014

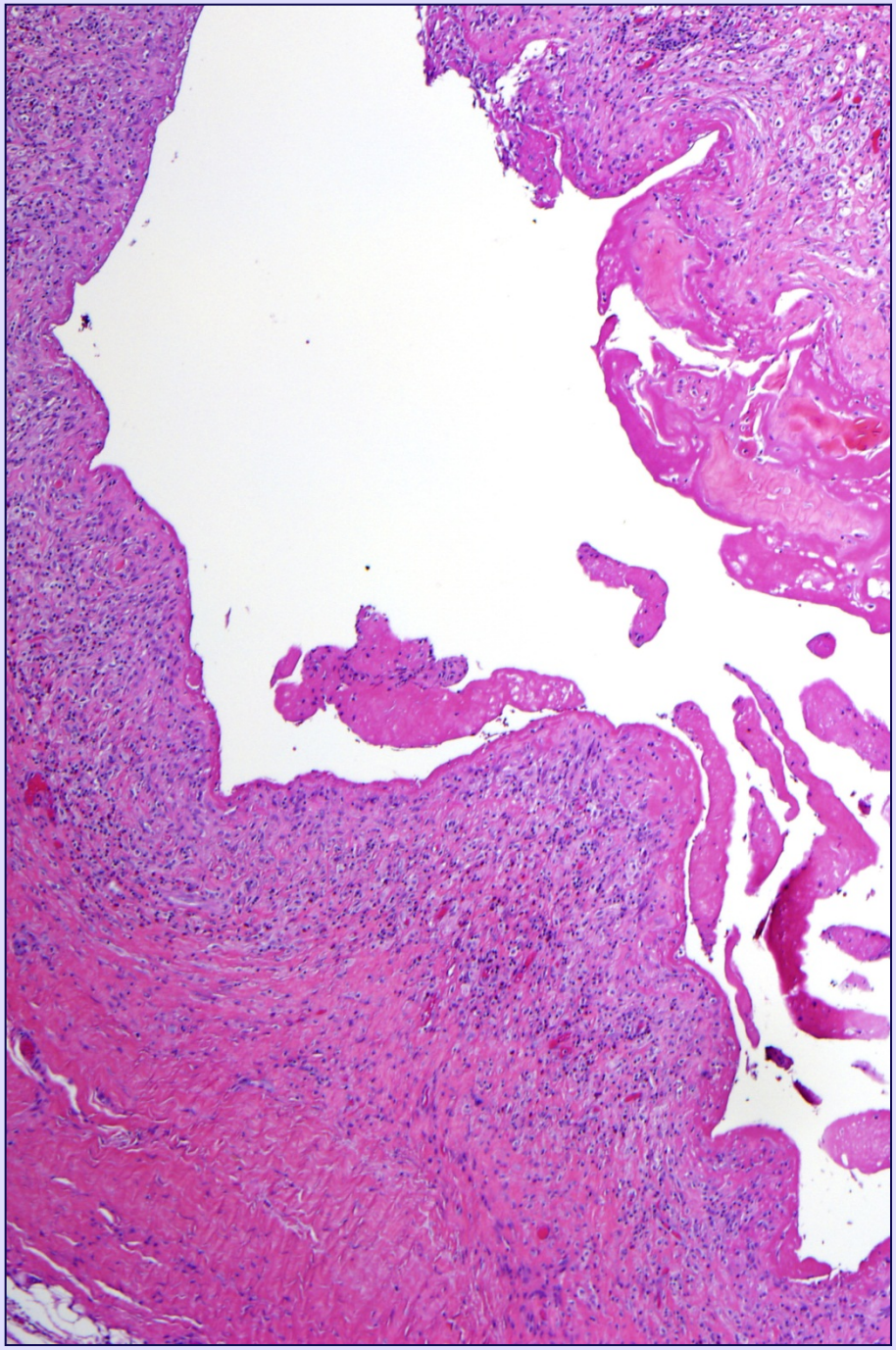


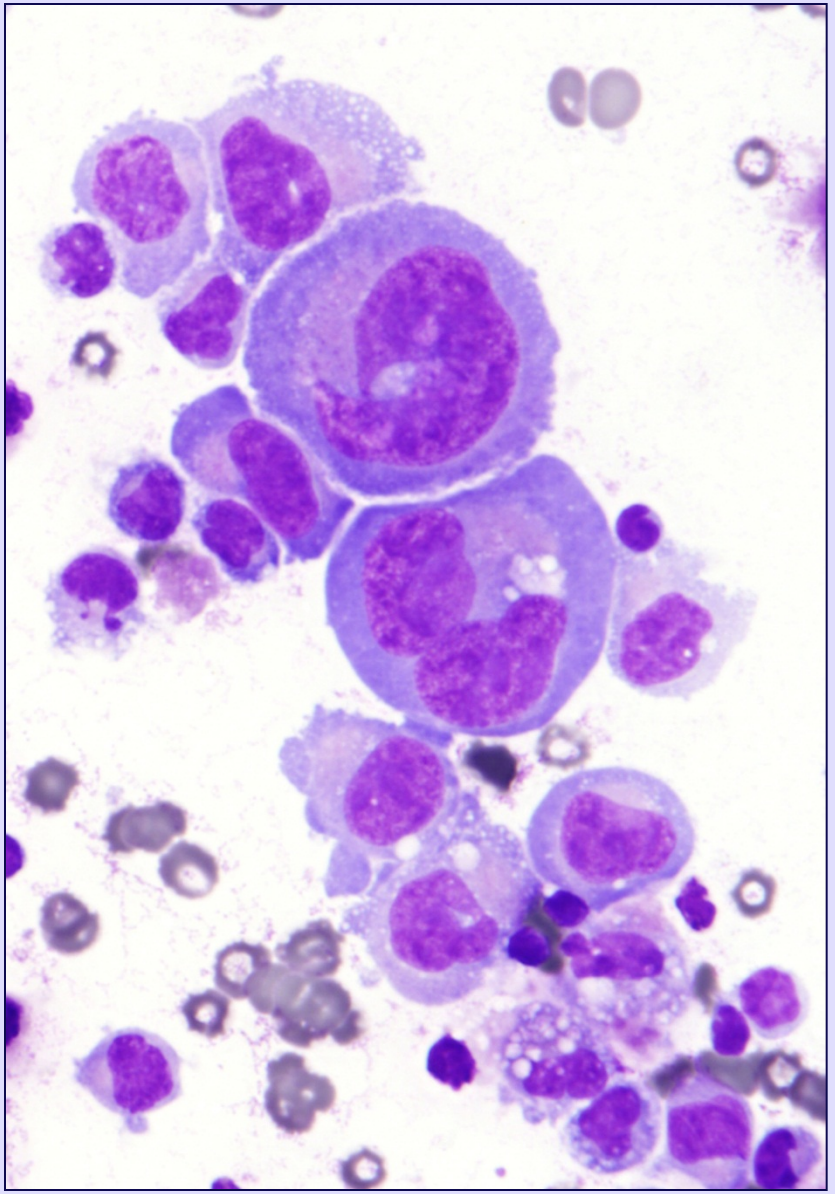
DUSP22 (# 22)
ALK+ (# 32)
P63 (# 6)
ALK neg, no aberrations (#45)

Subset with DUSP22 R Comparable to ALK+

Implant-associated anaplastic large cell lymphoma, ALK-negative

- Seen with a variety of breast implants, both saline and silicone
- Usually years after implant
- Symptoms related to accumulation of seroma fluid in cavity surrounding the implant
- Diagnosis best made by cytology
- Cells grow within cavity and on surface of cavity lining, usually without invasion

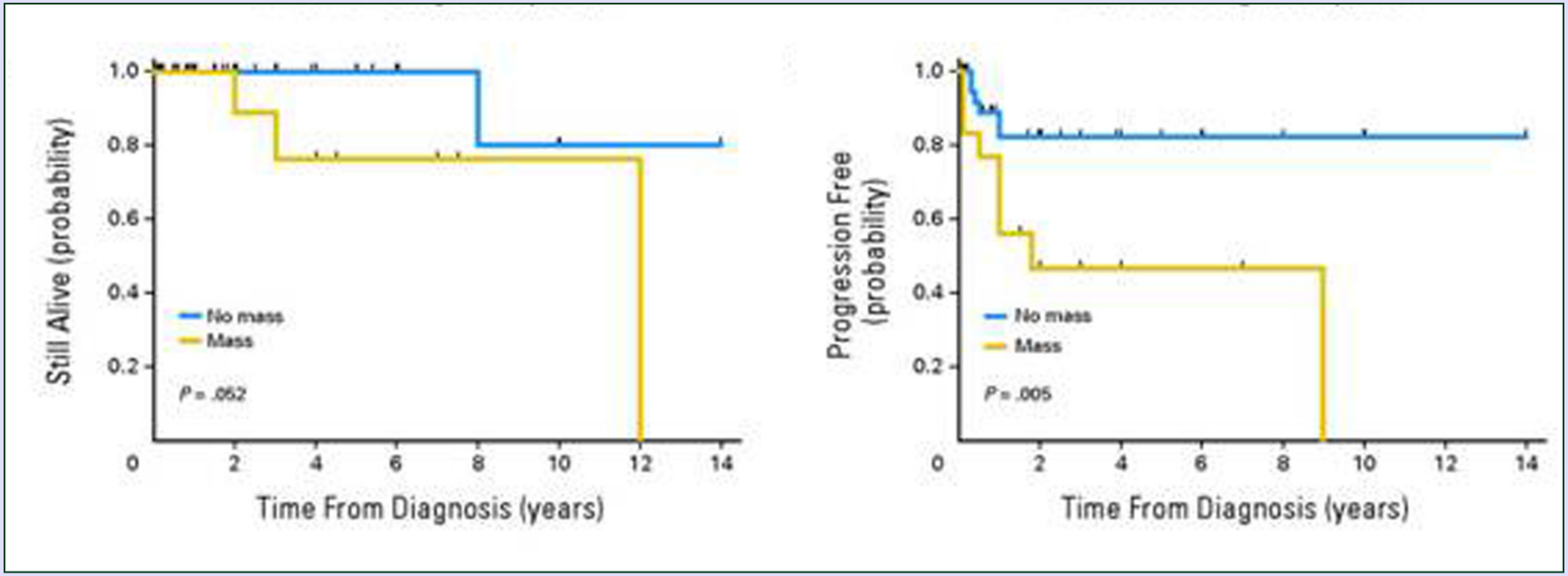




Breast implant assoc. ALCL
A provisional entity

Breast implant–associated anaplastic large-cell lymphoma Long Term Follow up in 60 Patients

Miranda R N et al. JCO 2014;32:114-120



93% CR in patients with disease confined to the capsule
72% CR in patients with a mass
No difference in OS or PFS in patients who had chemorx

Recommended rx: Implant removal with capsulectomy

Biological & Clinical Features

- Clonal TCR reported in most but not all cases
- Surprisingly indolent course, despite very atypical cytological features
- Therapy varies in literature
  - Chemo, Radiation, Observation following removal
- Removal of implant & capsule is probably adequate therapy in most cases, e.g. no invasion
  - Miranda et al. JCO 2014 (review of 60 cases from literature)

Most EBV+ T-cell and NK-cell neoplasms share a similar epidemiology *(WHO 2008)*

- *Chronic Active EBV-infection*
  - *Systemic CAEBV of T or NK cell type*
  - *Hydroa vacciniforme-like lymphoma (T>NK)*
  - *Mosquito-bite allergy (NK >T)*
- *Extranodal NK/T-cell lymphoma, nasal type*
- *Aggressive NK-cell leukemia*
- *Systemic EBV+ T-cell lymphoproliferative disease of childhood*

CAEBV *vs* acute EBV-associated HLH *vs* Systemic EBV+ T-cell Lymphoma

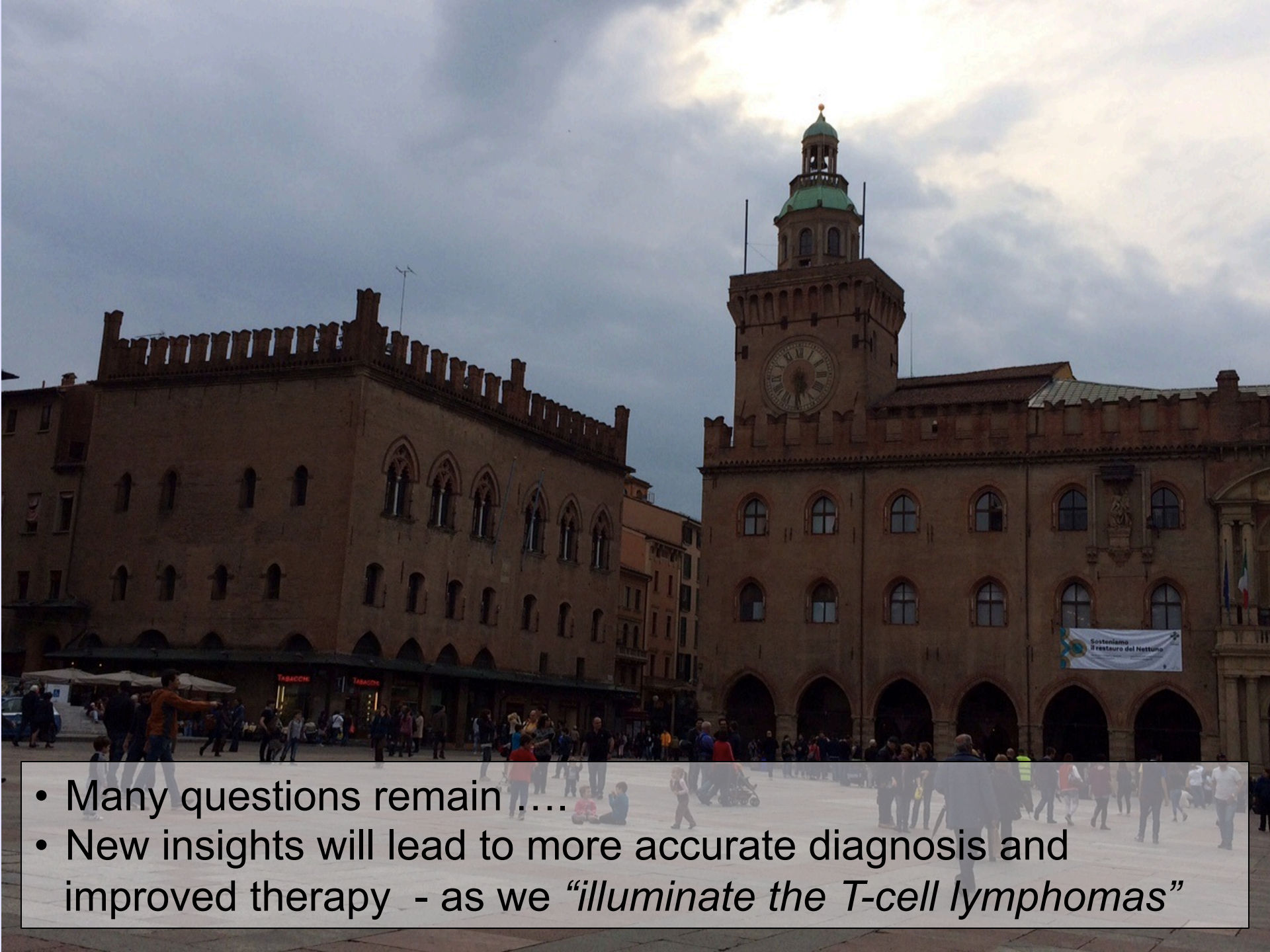
- Challenging differential diagnosis
  - All can have clonal EBV-infection of T-cells or NK-cells
- CAEBV requires > 3-6 mos symptoms
- Poor prognostic factors in HLH include marked elevations of Ferritin, Bilirubin (Kogawa et al. 2014)
- Clonality of T-cells is helpful but not definitive

(2016) EBV+ T/NK - Variation in Clinical Aggressiveness from Chronic to Fulminant

- *Chronic Active EBV-infection*
  - *Systemic CAEBV of T or NK cell type*
  - *Hydroa vacciniforme-like lymphoma*
  - *Mosquito-bite allergy*
- *Extranodal NK/T-cell lymphoma, nasal type*
- *Aggressive NK-cell leukemia*
- *EBV+ Nodal T/NK cell lymphoma (new)*
- *Systemic EBV+ T-cell lymphoma of childhood*
  - *Terminology changed from systemic EBV+ T-cell LPD to emphasize the aggressive clinical course*

What's new in the WHO classification ….

- Integrated approach to AITL and other TFH lymphomas
- Altered terminology for primary cutaneous CD4+ T-cell LPD
- Formal separation of EATL Types I and II
- Introduction of new provisional entities for indolent T-cell LPD's in the GI tract & Skin
- New Insights into the genetics of γδ T-cell lymphomas
- ALK-negative ALCL no longer provisional entity
  - More clearly defined & new genetic findings
- Breast implant associated ALCL - a provisional entity
- Improved definition of EBV+ T-cell and NK-cell malignancies



- Many questions remain ….
- New insights will lead to more accurate diagnosis and improved therapy - as we *“illuminate the T-cell lymphomas”*