

*WHO WHAT WHERE & WHEN –*

THE UPDATED WHO CLASSIFICATION OF T-CELL  
LYMPHOMAS IS NOW

Elaine S Jaffe, NCI, NIH





2015... 2018  
T-Cell Lymphomas:  
we are close to the  
finalization



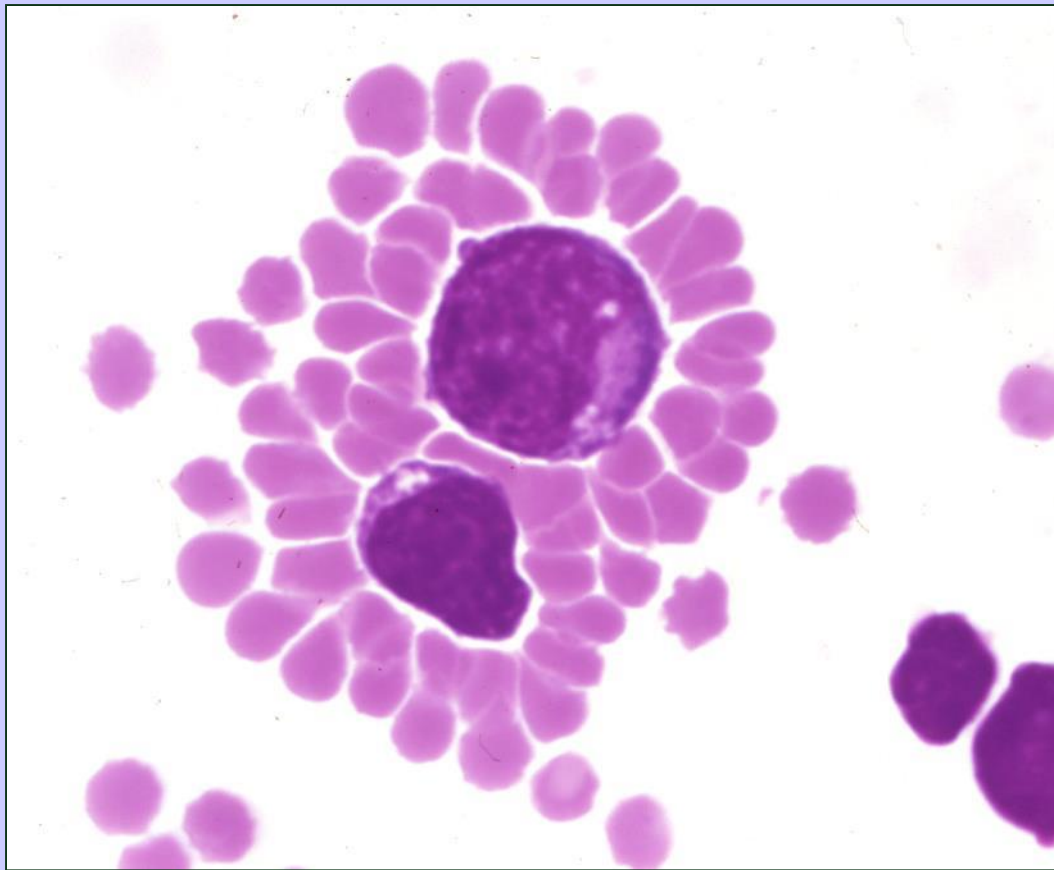
Bologna  
ROYAL HOTEL CARLTON  
May 7-9, 2018

President: **Pier Luigi Zinzani**  
Co-President: **Michele Cavo**  
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**Disclosures of Elaine Jaffe**

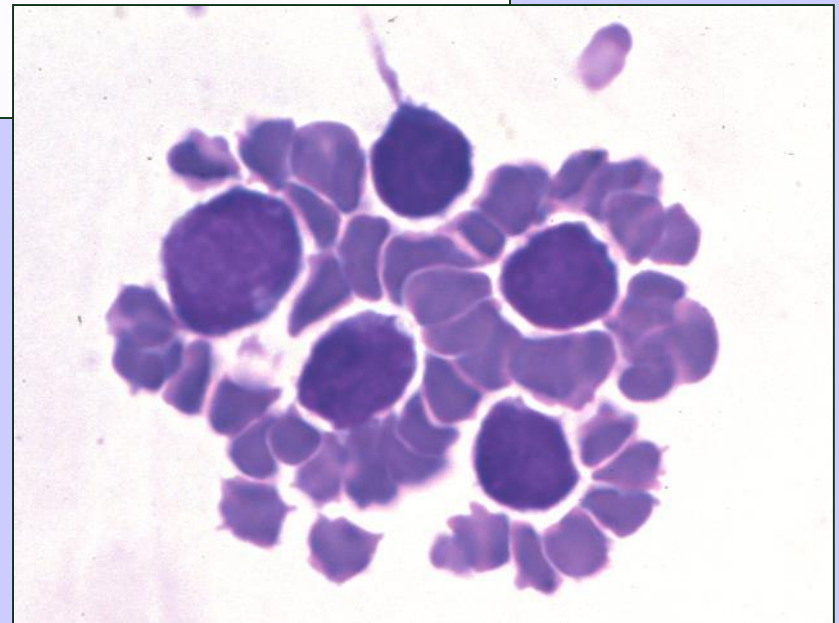
Nothing to Declare

# Identifying T-cells in the Olden Days



# Identifying the First Confirmed T-cell Lymphoma

- Smith et al. (Lancet, Jan 1973)
  - Characterization of mediastinal “Sternberg Sarcoma” as thymic in origin
  - Single case report of a 2 yr. old boy with thymic mass (86% E-rosette +, 9% slg +)





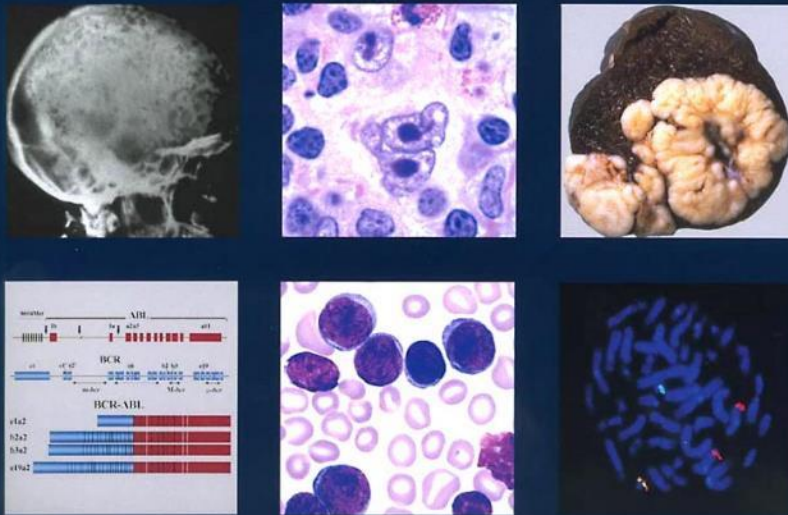
World Health Organization Classification of Tumours



## Pathology & Genetics

### Tumours of Haematopoietic and Lymphoid Tissues

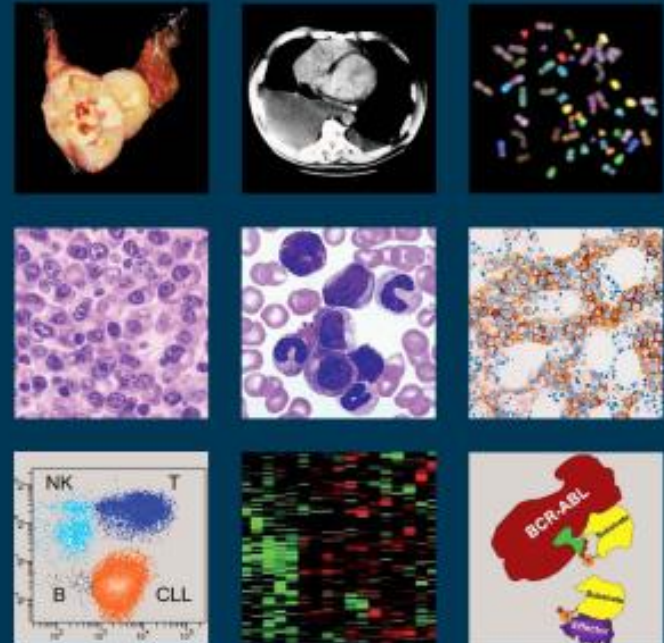
Edited by Elaine S. Jaffe, Nancy Lee Harris, Harald Stein, James W. Vardiman



3<sup>rd</sup> Ed 2001

## WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman



4<sup>th</sup> Ed 2008

# WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues

## A new taxonomy of disease\*

- Build a biomedical information network to promote disease discovery & pathogenetic insights
- Provide a framework for “Precision Medicine”
- Facilitate clinical trials
- Improve the standard of diagnosis and treatment in the community

\* (2011). **IOM report:** Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease, The National Academies Press.

## New Insights Since 4<sup>th</sup> Edition (2008)

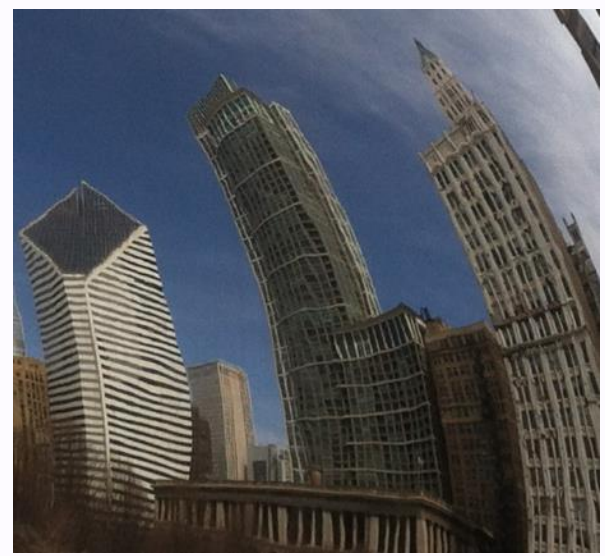
- Rapid progress in understanding of molecular pathogenesis
  - NGS studies, Nanostring, RNAseq
  - Allow high throughput investigation of paraffin embedded samples
- Large scale clinical studies led to new insights into clinical behavior
  - Interest in more targeted therapy
- IARC authorized a “Revised 4<sup>th</sup> WHO classification”

# Clinical Advisory Committee

## Integral Part of the Process since the 2001 Edition

- Classification should be useful to both pathologists and clinicians
- Classification should be suitable for daily practice and clinical trials
- Has remained an integral part of the process





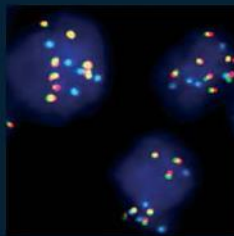
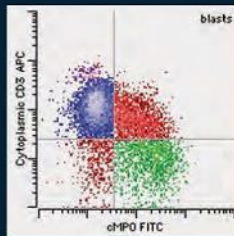
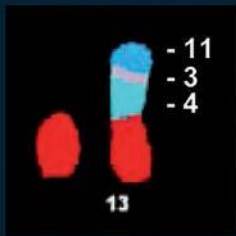
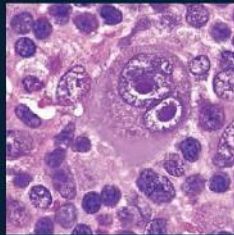
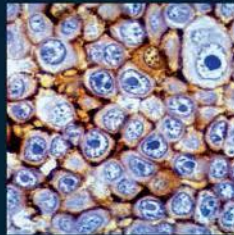
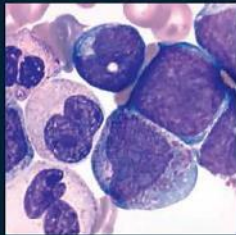
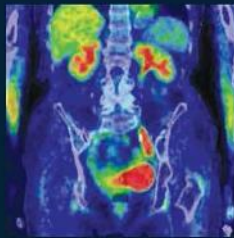
Clinical Advisory Meeting, March 31-April 1, 2014





# WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, Daniel A. Arber, Robert P. Hasserjian, Michelle M. Le Beau, Attilio Orazi, Reiner Siebert



Summaries of revisions

*Swerdlow et al. (Lymphoid Neoplasms)*

*Arber et al. (Myeloid and Acute Leukemia)*

Blood May 19, 2016

Bluebook published  
September 2017

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*From the USA*

Stylus Publishing

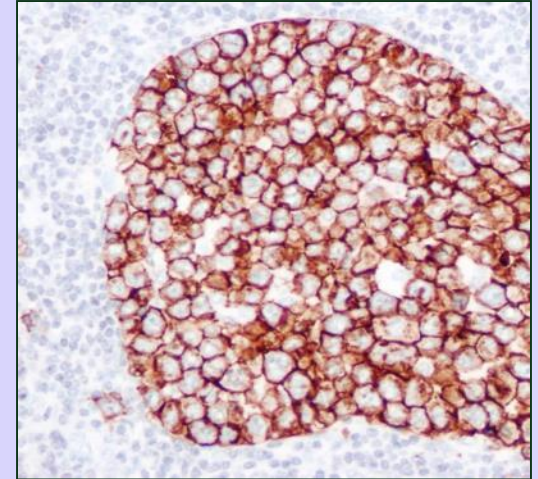
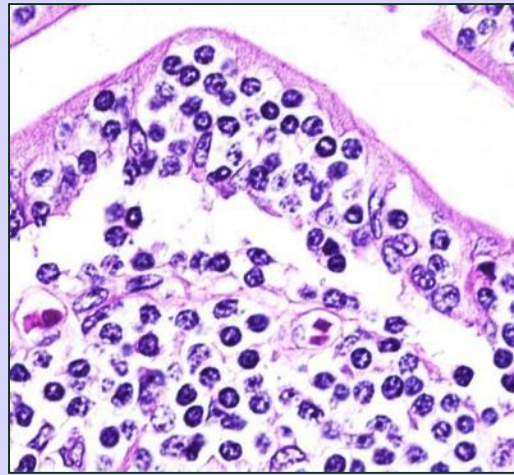
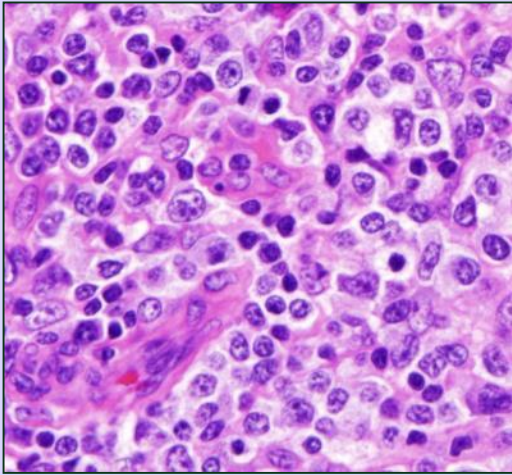
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Herndon VA 20172-05

[stylusmail@presswarehouse.com](mailto:stylusmail@presswarehouse.com)

[www.styluspub.com](http://www.styluspub.com)

# What's new in the Peripheral T-cell lymphomas

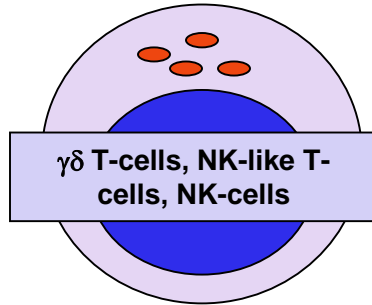


AITL & other nodal  
TFH lymphomas

Intestinal T-cell lymphomas

ALCL, ALK-negative

## Innate Immune System



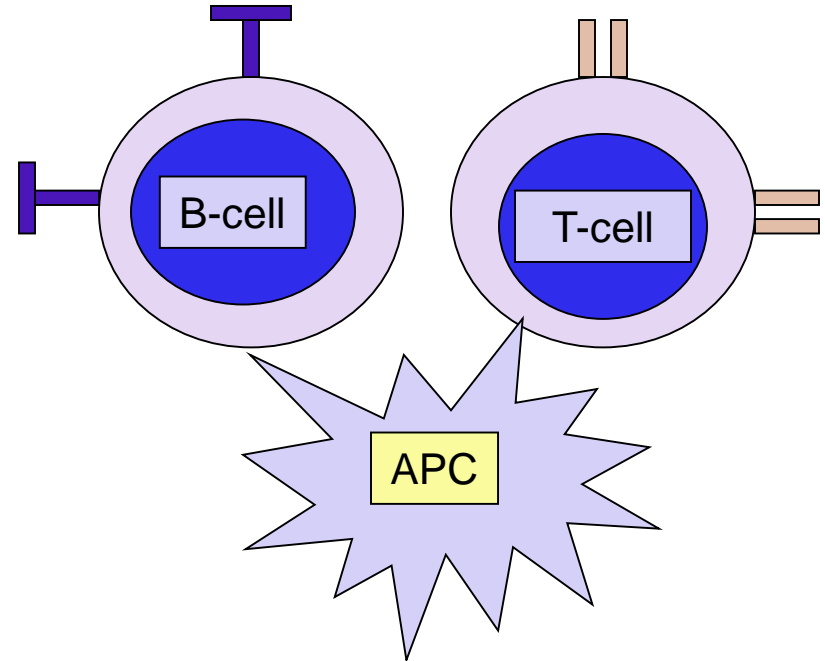
Toll like receptors  
Not MHC restricted

Cytokines  
Chemokines  
Complement

Apoptotic & necrotic  
cell death pathways

First line of defense with  
a major role in barrier immunity

## Adaptive Immune System

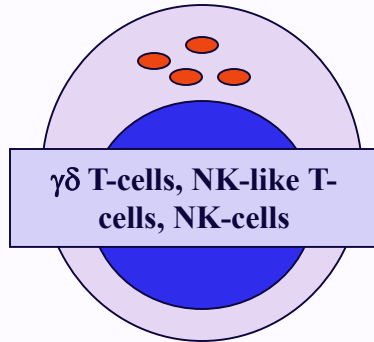


Ag specific  
receptors  
on B + T-cells

Antigen presentation to  
T-cells in the  
context of MHC

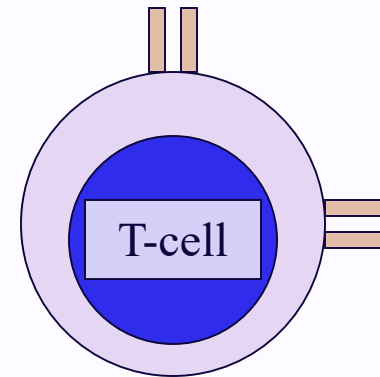
Immunological defense  
characterized by *specificity & memory*

## Innate Immune System



- Often cutaneous, mucosal, spleen & BM
- Cytotoxic
- Activated cells show frequent apoptosis, necrosis
- Includes most extranodal PTCLs

## Adaptive Immune System

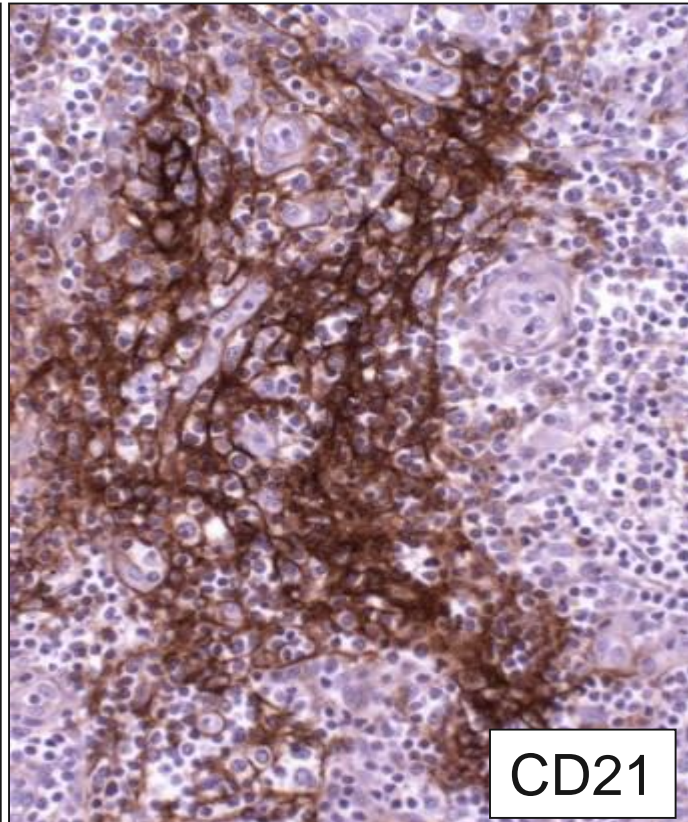
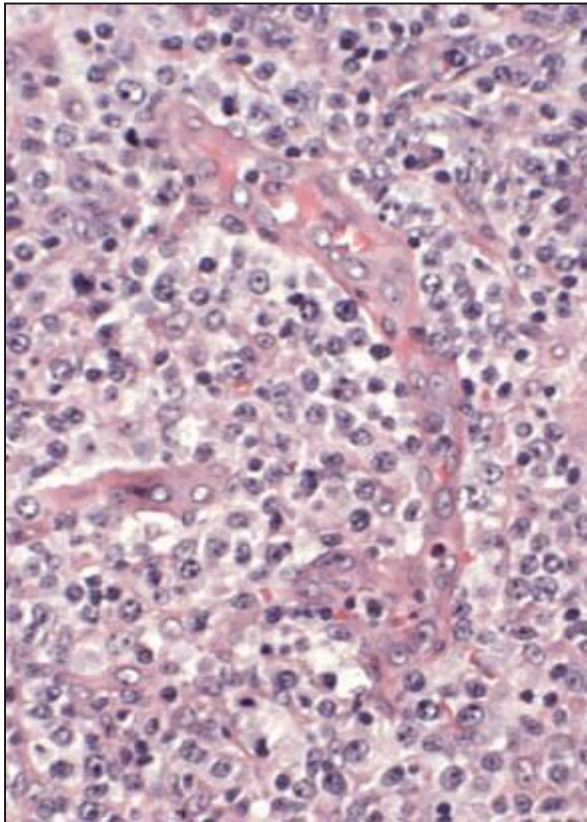


- Lymphomas may relate to specific effector T-cells
- $T_{FH}$ , Treg
- Functional consequences may be clinically apparent
- Includes most nodal PTCLs in adults



# Angioimmunoblastic T-cell Lymphoma

is a disease of germinal center  
derived T-cells ( $T_{FH}$  cell)



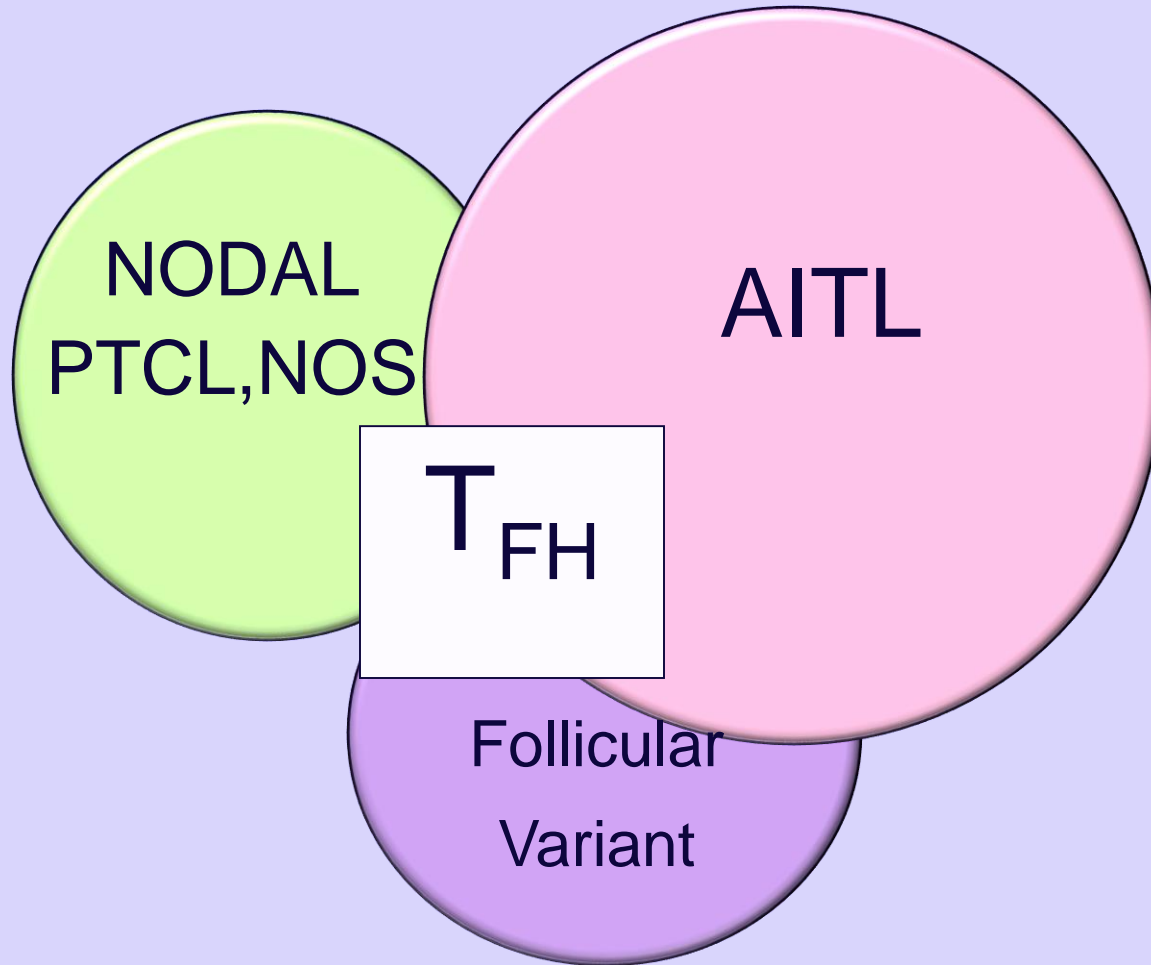
CD3+  
CD10+  
BCL6 +/-  
CD279/PD-1+  
CXCL13 +

Inc. B-cells - both  
EBV pos and neg

B-cells often  
clonal



## 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

# Nodal Peripheral T-cell Lymphomas (2008)

PTCL, NOS

T-zone variant

Follicular variant

Lymphoepithelioid  
cell variant

Angioimmunoblastic  
T-cell lymphoma

# Nodal Peripheral T-cell Lymphomas (2017)

PTCL, NOS

Lymphoepithelioid  
cell variant

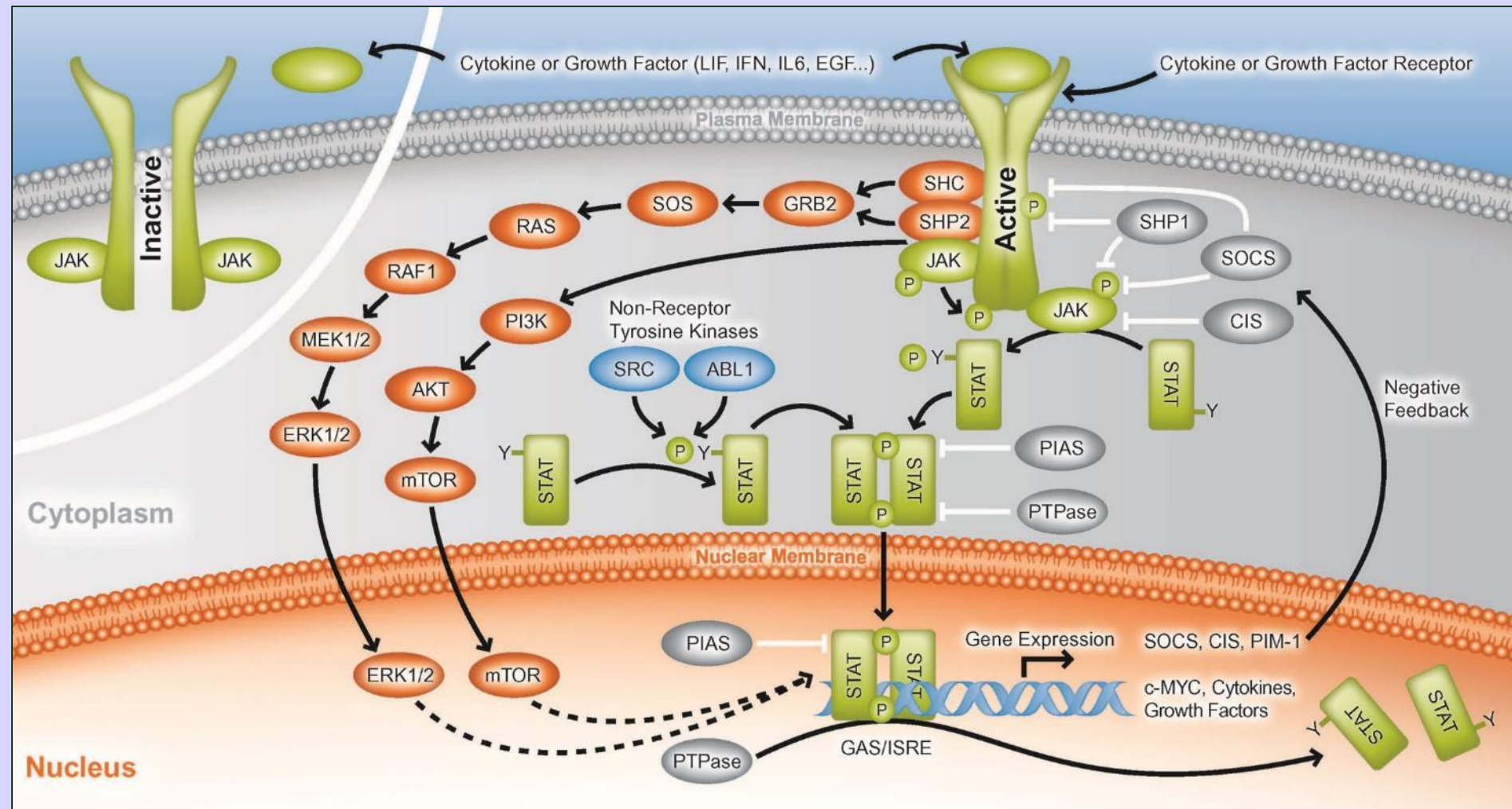
Angioimmunoblastic  
T-cell lymphoma

Follicular T-cell lymphoma

Nodal peripheral T-cell  
lymphoma with TFH  
phenotype

T-zone variant

# JAK/STAT Pathway is a frequent target in Cytotoxic T-cell Lymphomas and Leukemias



# Recurrent Mutations in T/NK-LGL leukemia & Cytotoxic T-cell & NK-cell lymphomas

## Authors/ Diagnosis

Koskela et al., Jerez et al.2012

T-cell & NK-cell LGL

Nicolae, et al. 2014/ 2016

$\gamma\delta$  HSTCL/ Intestinal TCLs

Kucuk et al. 2015

$\gamma\delta$  T-cell lymphomas

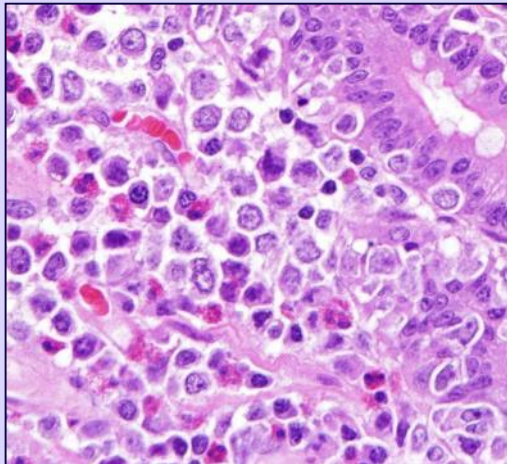
HSTCL, intestinal, cutaneous

## Mutations

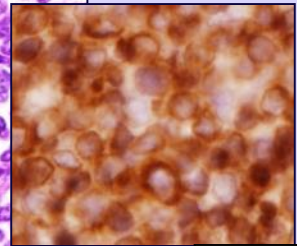
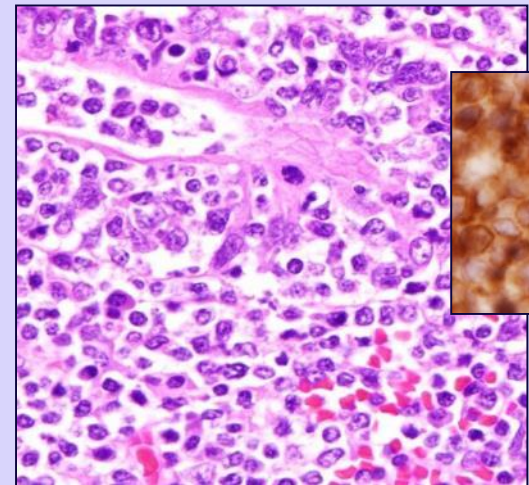
- 40% STAT3; 2% STAT5B
- 33% STAT5B, 10% STAT3
- ~ 75% JAK/STAT pathway
- ~ 35% STAT5B;
- ~ 8% STAT3

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

EATL I  
Usually  $\alpha\beta$   
Celiac  
disease  
N European

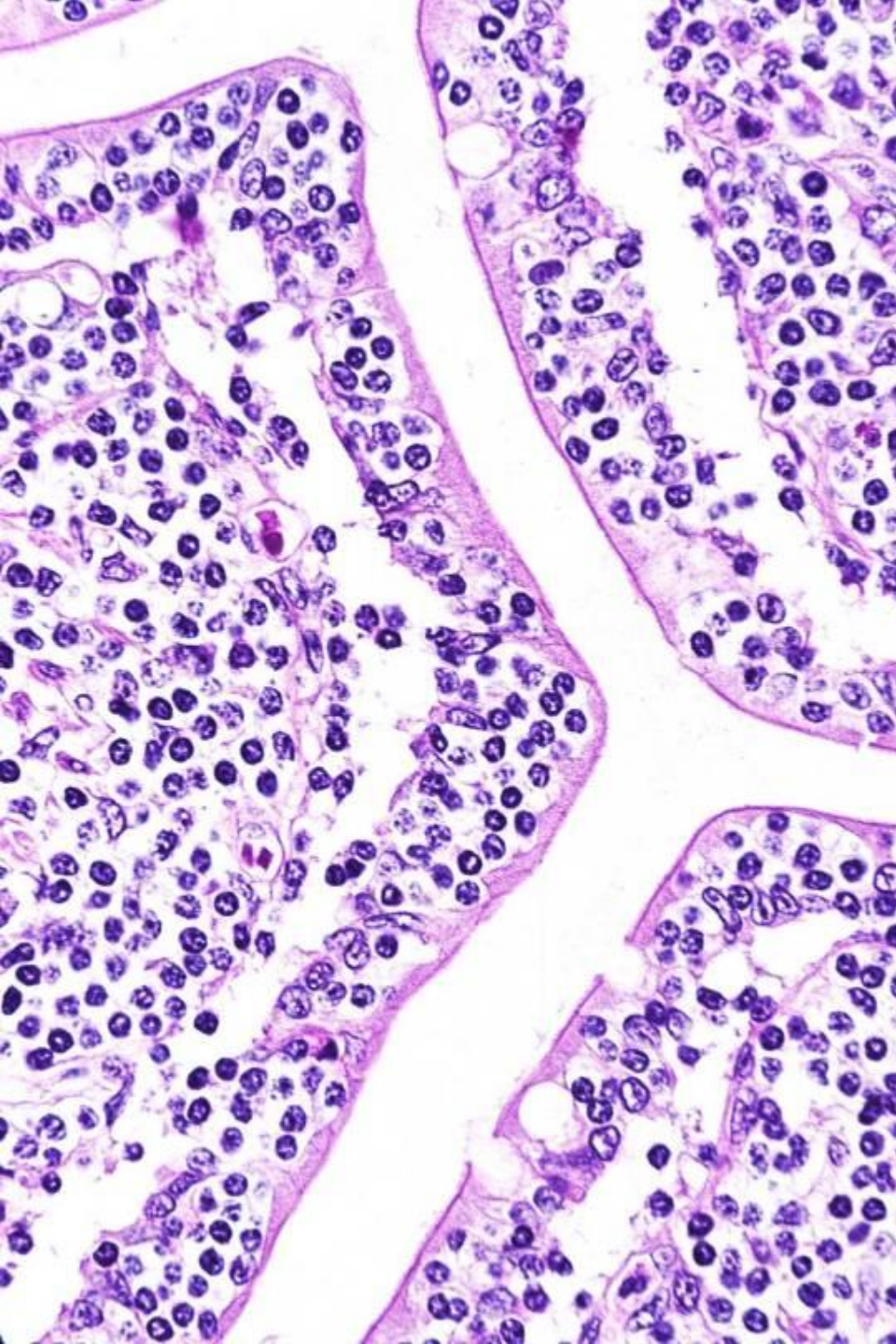


EATL II  
Usually  $\gamma\delta$   
Epitheliotropic  
Asian, Hispanic



$\gamma\delta$





Monomorphic  
epitheliotropic intestinal  
T-cell lymphoma  
(EATL II)

- Medium sized cells with clear cytoplasm
- CD56 +, CD8+, CD4-
- Usually  $\gamma\delta$ +
- MAT kinase +
- *SETD2* mutations (>90%)

# T-cell & NK cell Lymphomas of Gastrointestinal Tract

EATL  
"Classical"

$\alpha\beta > \gamma\delta$

Monomorphic  
epitheliotropic  
intestinal T-cell  
lymphoma  
 $\gamma\delta > \alpha\beta$

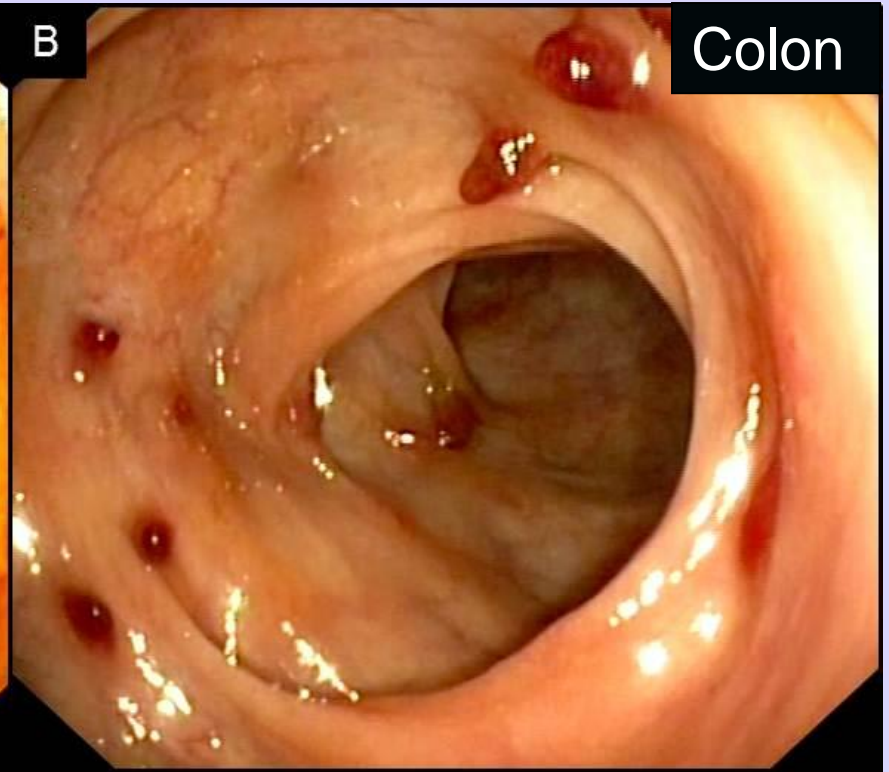
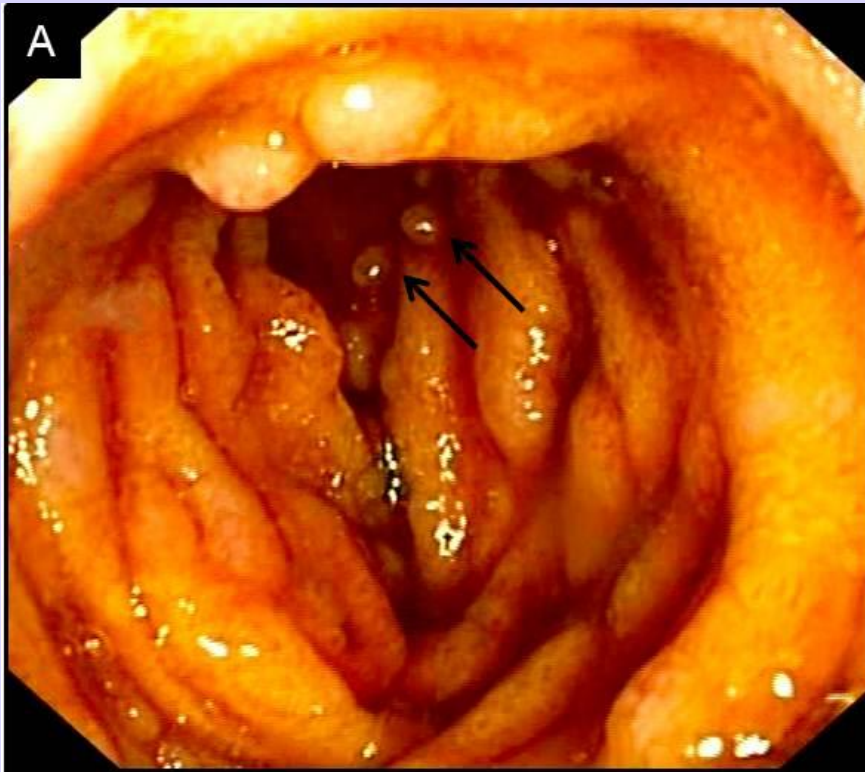
Extranodal NK/T  
EBV+ NK or T  
Mainly Asian

PTCL, NOS  
( $\alpha\beta$  or  $\gamma\delta$  or  
TCR silent)

All clinically aggressive  
All cytotoxic

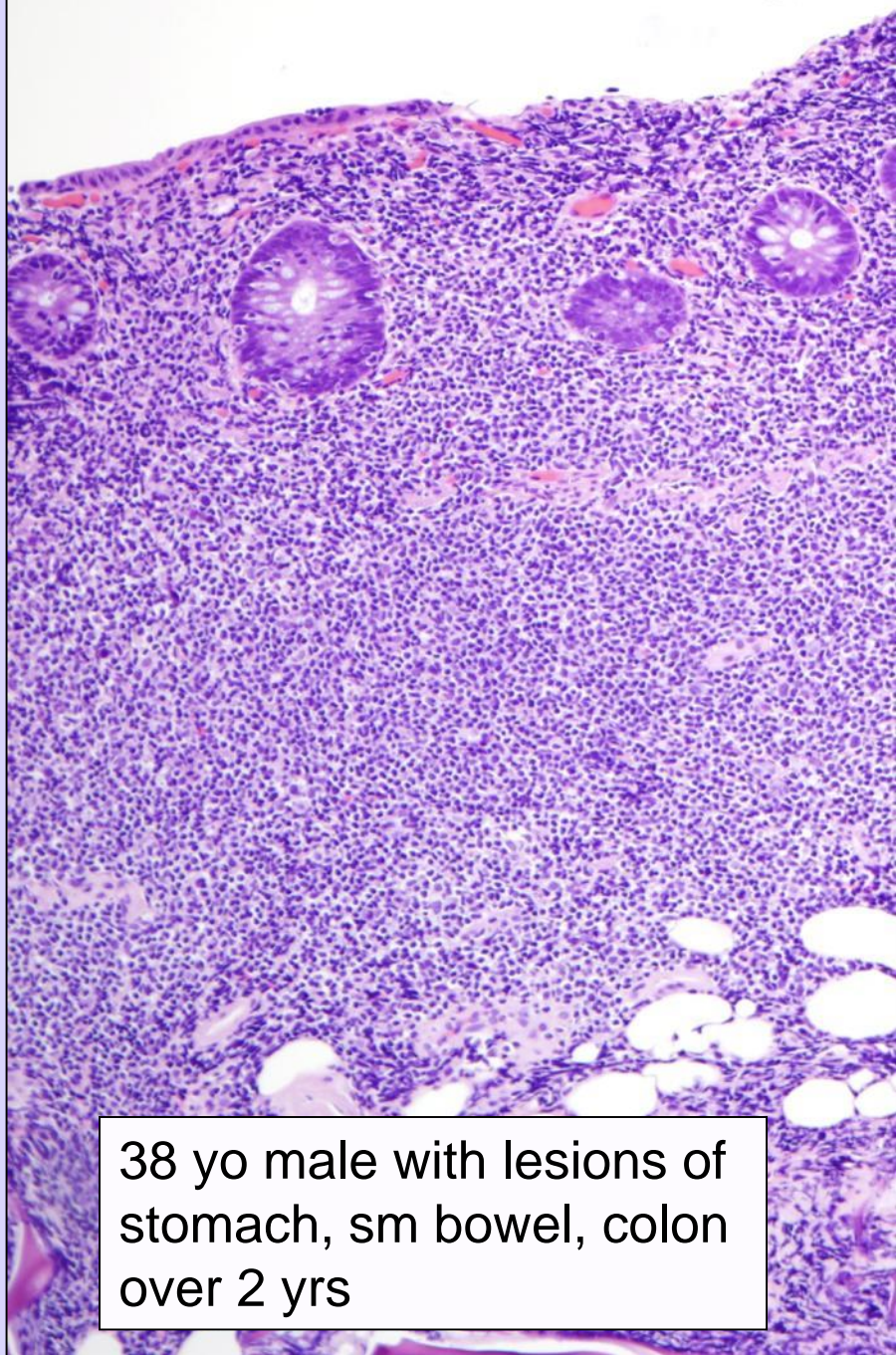
## Indolent T-cell lymphoproliferative disease of the GI tract (Provisional entity 2017)

- Adults, rare under age 20; M=F
- Oral cavity, stomach, small intestine, colon
- Diarrhea, pain, rectal bleeding
  - History of “IBD” in few patients
- Chronic, indolent course
- Lack of dissemination outside GI tract, except in rare cases
- Chemotherapy not effective

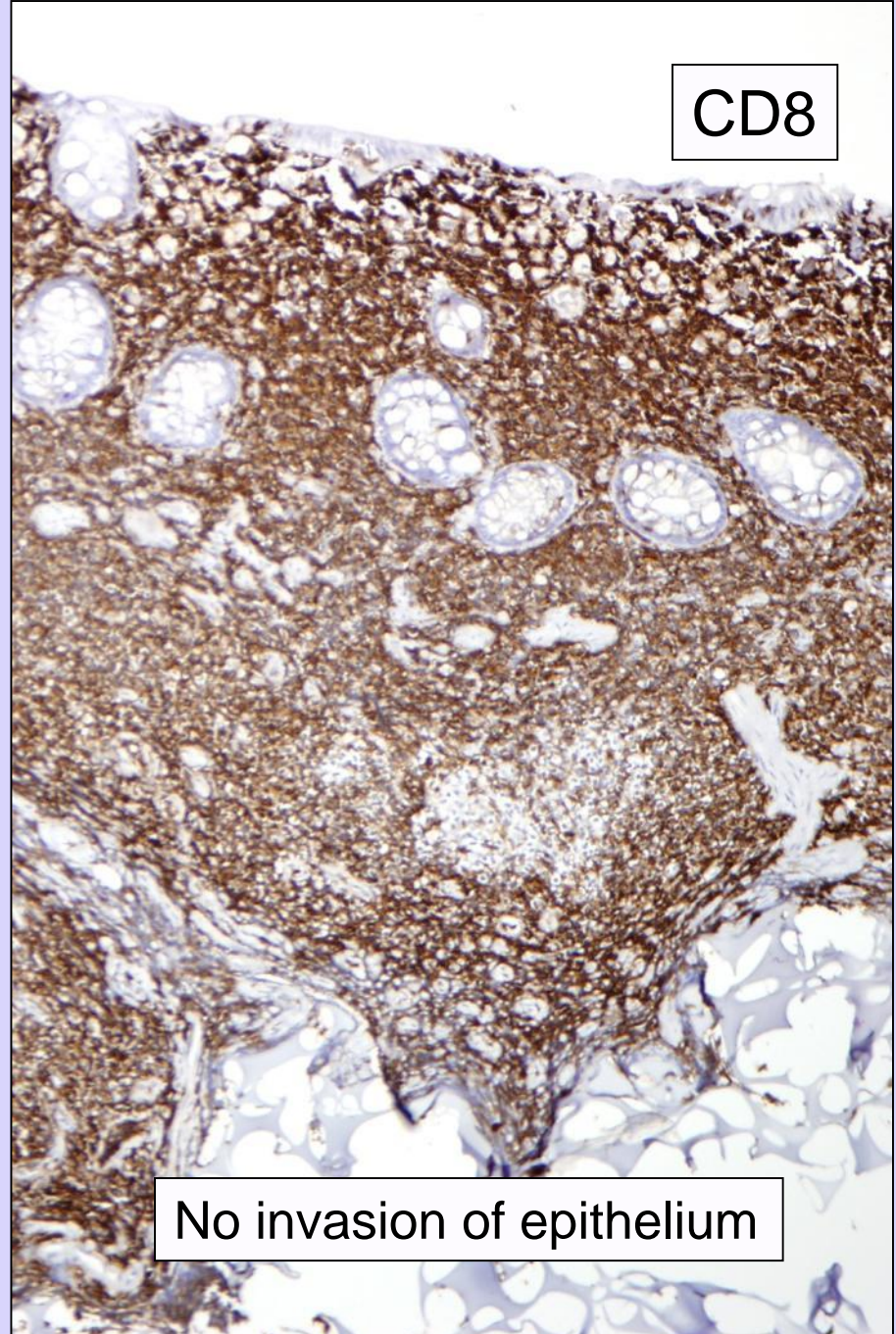


Indolent T-cell lymphoproliferative disease  
of the gastrointestinal tract  
Perry et al. Blood 2013





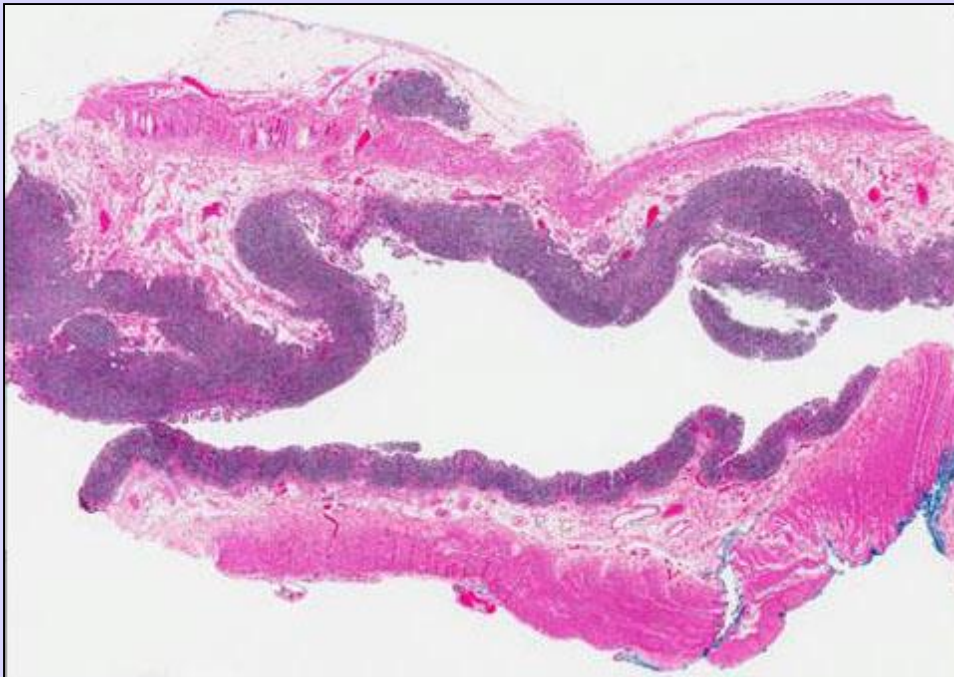
38 yo male with lesions of stomach, sm bowel, colon over 2 yrs



CD8

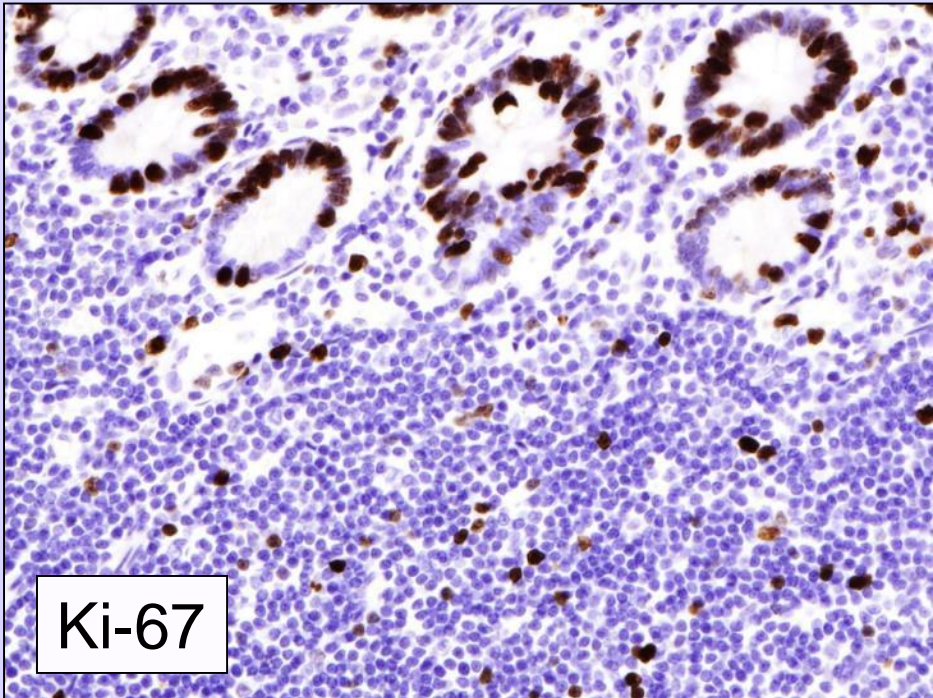
No invasion of epithelium





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



Ki-67

CD8+ > CD4+;  
TIA1+, GranB, Perforin neg  
EBV neg, TCR  $\alpha\beta$

Recurrent *STAT3-JAK2* fusions  
seen in CD4 but not CD8 pos  
cases (*Sharma et al Blood 2018*)



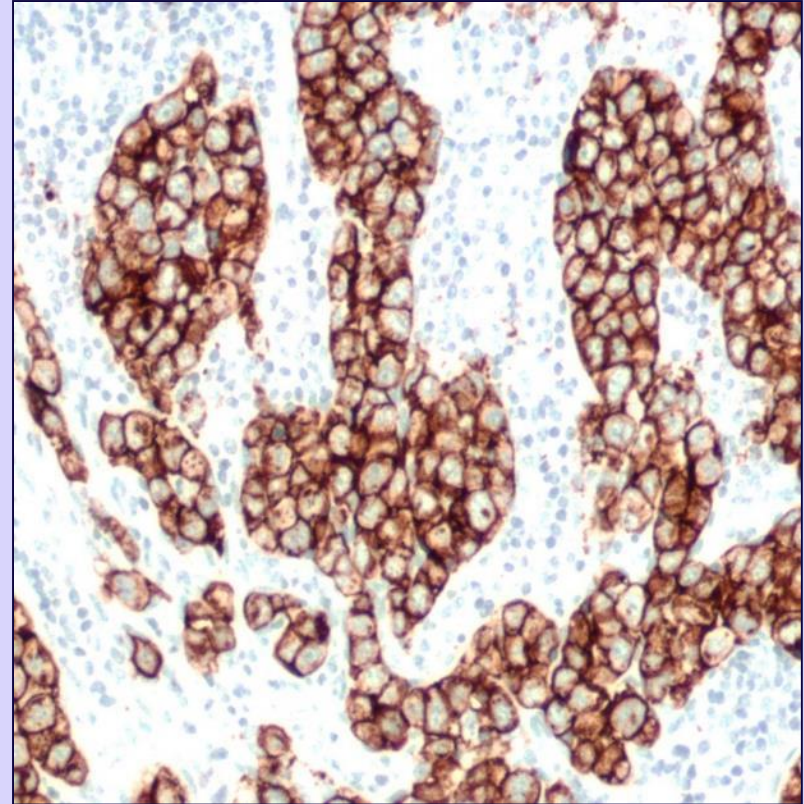
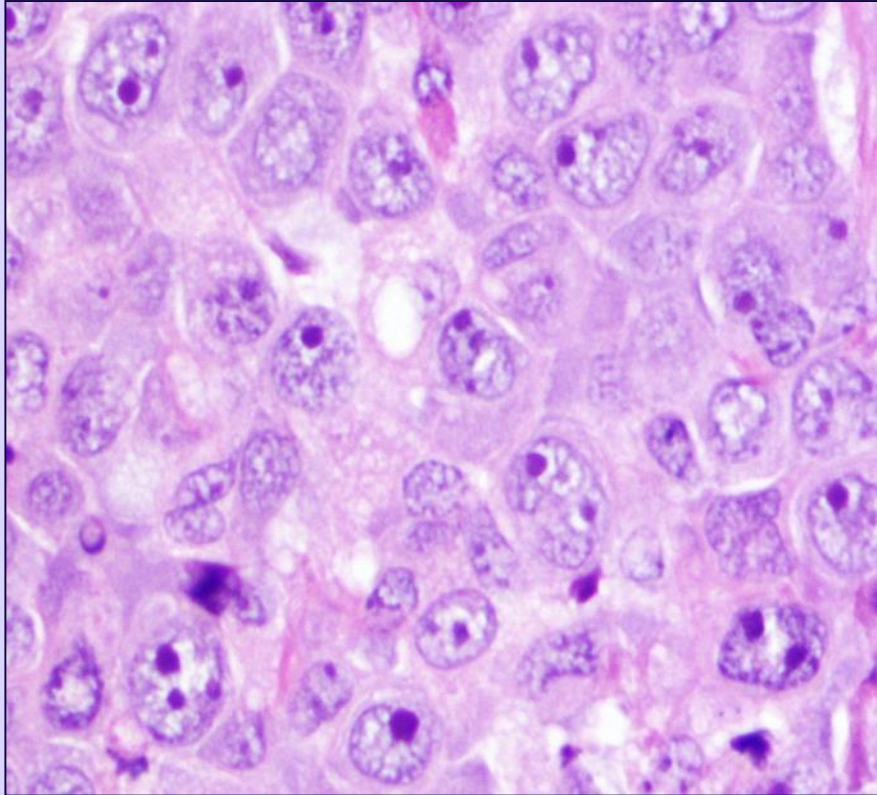
# Anaplastic Large Cell Lymphomas

overlapping clinical and biological features

- ALCL, ALK-positive
- ALCL, ALK-negative
- Primary cutaneous anaplastic large cell lymphoma & Lymphomatoid papulosis
- Breast implant associated anaplastic large cell lymphoma

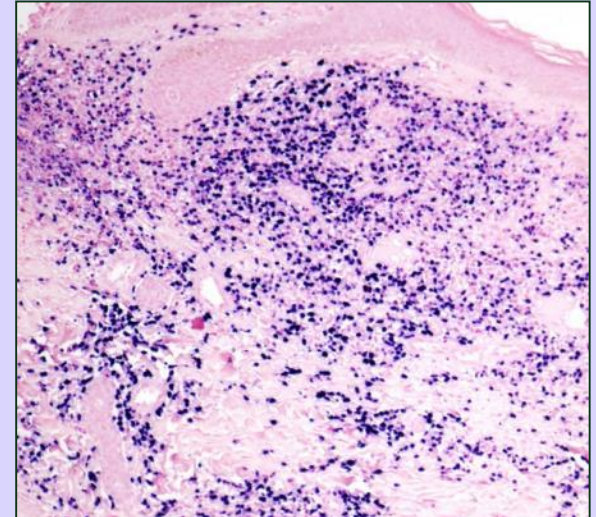
*All show activation of the JAK-STAT pathway*

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



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

# What's new in the Peripheral T-cell lymphomas



Cutaneous T-cell lymphomas

EBV-associated T/NK cell

# 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







Primary cutaneous acral CD8+ T-cell lymphoma

A new provisional entity

38 yo. male with lesion of ear

CD8

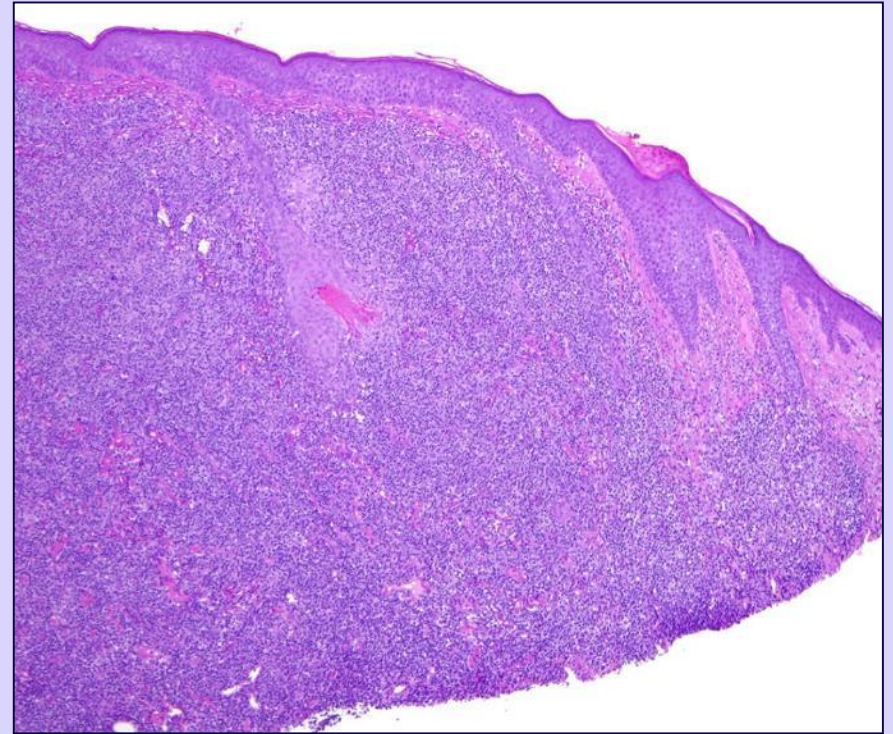




Primary cutaneous acral CD8+ T-cell lymphoma

Other acral sites (contributed by T. Petrella)





Primary cutaneous CD4 positive small/medium T-cell lymphoma  
*(Provisional 2008)*

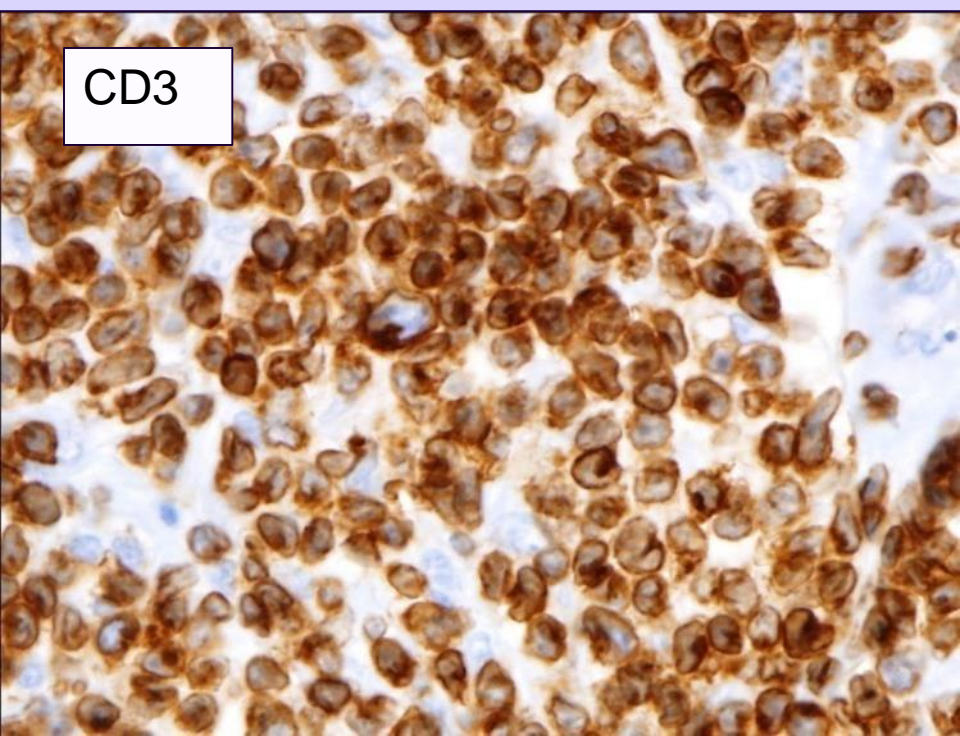
*Primary cutaneous CD4 positive small/medium T-cell  
lymphoproliferative disorder (not lymphoma in 2017)*

## Primary cutaneous CD4+ small/ medium T-cell LPD

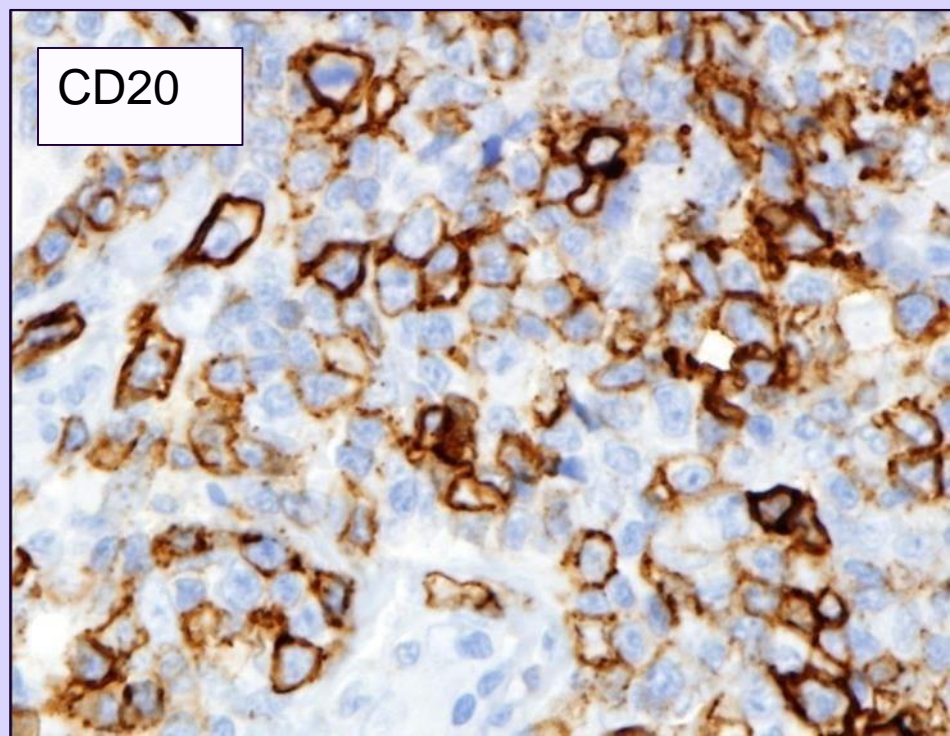
- Usually localized, often involving head and scalp
- Distinction with atypical hyperplasia often difficult
- Lesions sometimes contain numerous B-cells
- Good prognosis if single lesion, most < 3 cm
  - Infrequent recurrences, no deaths
  - Patients with bulky or advanced disease (very few) had aggressive course



CD3



CD20

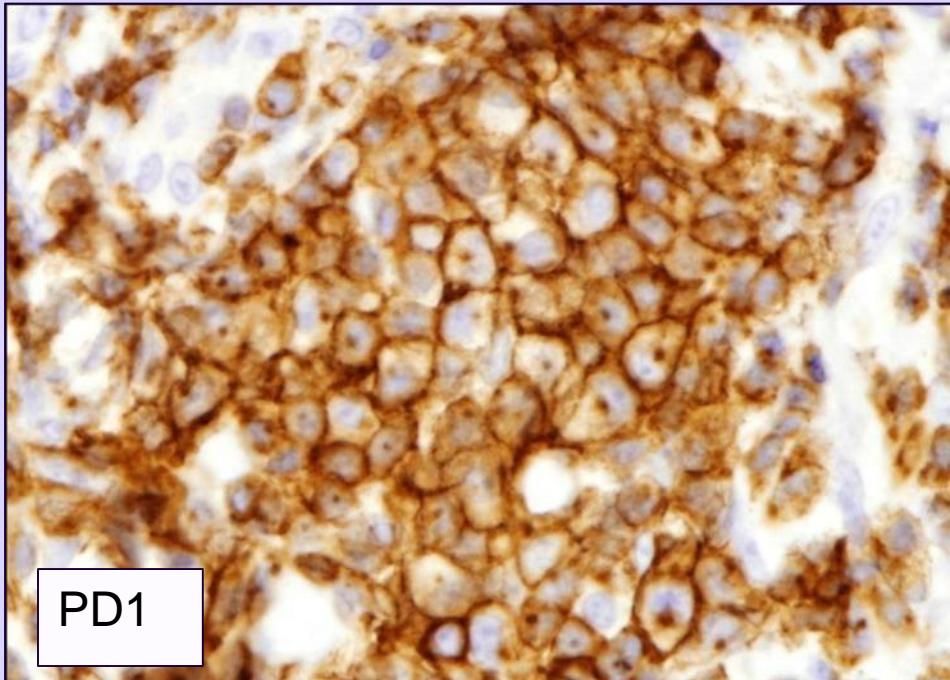


TFH phenotype, PD-1+, more rarely  
CD10+

Contains abundant B-cells, fewer  
plasma cells

Lack genetic changes of other TFH  
lymphomas

PD1



# EBV+ T/NK cell lesions – WHO update (2017)

*Y-H Ko, L Quintanilla Martinez, H Kimura, ES Jaffe*

- *EBV-associated hemophagocytic lymphohistiocytosis (HLH) (non-neoplastic)*
- Cutaneous CAEBV
  - Hydroa Vacciniforme **LPD** (T/NK)
  - Severe Mosquito Bite Allergy (NK)
- Systemic CAEBV, T-cell or NK-cell
- Systemic EBV+ T-cell **lymphoma** of childhood
- Aggressive NK-cell leukemia
- Extranodal NK/T-cell lymphoma, nasal type

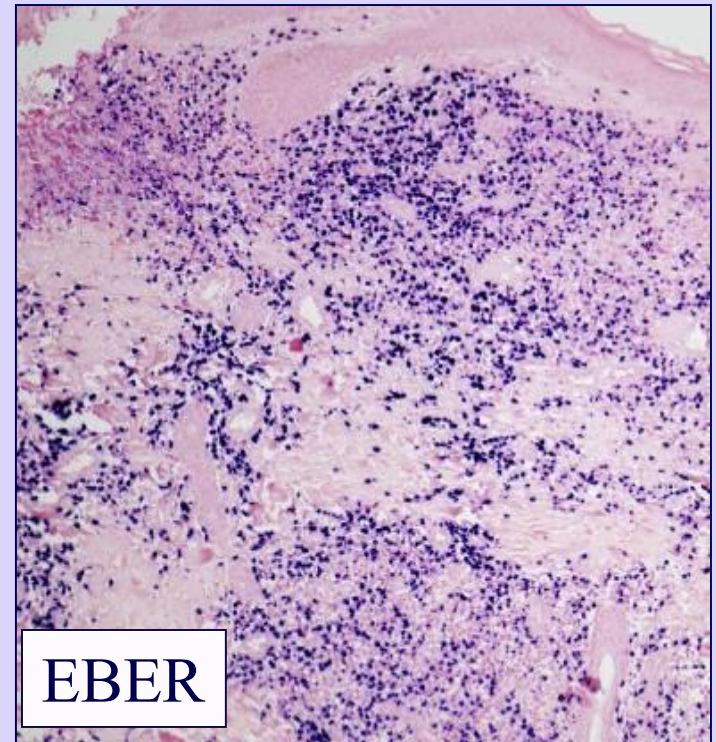
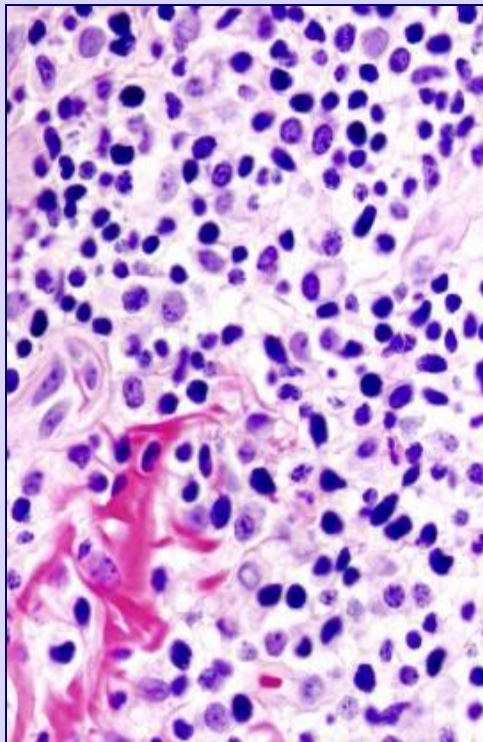
*Marked variation in clinical behavior from indolent to highly aggressive*  
*Similar epidemiological profile: Asian, Hispanic*



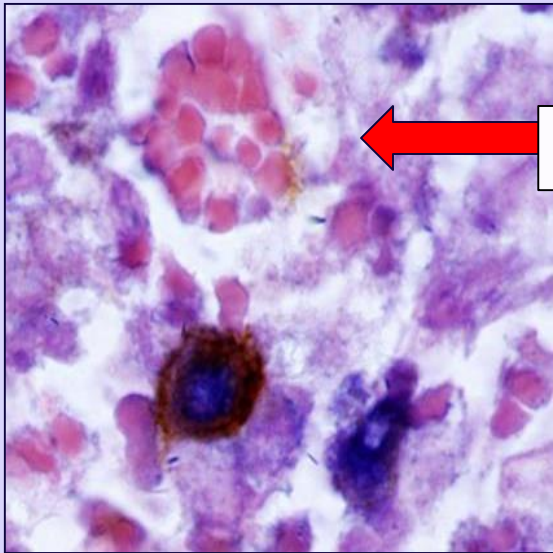


- Hydroa-vacciniforme-like *LPD*
- Asian or Hispanic children
- Lesions in sun exposed areas
- Chronic course but may progress to acute phase with systemic disease

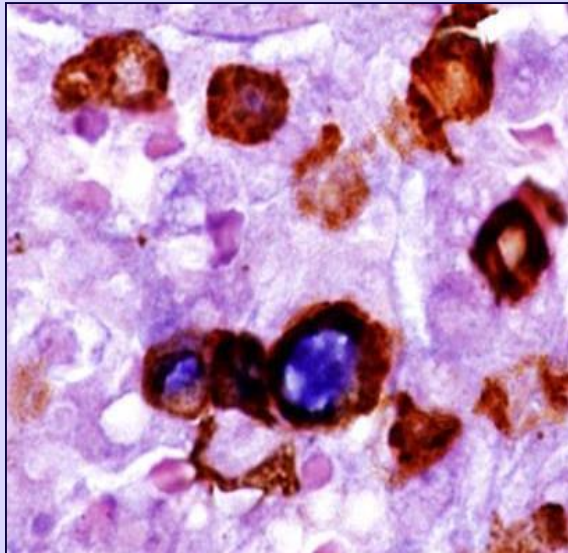
Cells of T-cell or less often NK cell origin



## Systemic EBV+ T-cell lymphoproliferations +/- clinical HLH



HPS



EBER/CD3

- Often challenging to predict clinical behavior at initial presentation
- T-cell clonality not always predictive
- Follow EBV viral load following treatment for HLH

*Bollard C and Cohen J, How I treat T-cell CAEBV disease, Blood 2018*



# WHO Classification of T/NK cell neoplasms

## Leukemic/ Systemic

T-cell prolymphocytic leukaemia

T-cell large granular lymphocytic leukaemia

Chronic lymphoproliferative disorder

Aggressive NK cell leukaemia

Systemic EBV+ T-cell Lymphoma of the GI tract

Hydroa vacciniforme-like lymphoproliferative disorder

Adult T-cell leukaemia/lymphoma

Hepatosplenic T-cell lymphoma

## Extranodal

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Monomorphic epitheliotropic intestinal T-cell lymphoma

Indolent T-cell lymphoproliferative disorder of the GI tract

Breast implant-associated anaplastic large cell lymphoma

## Cutaneous

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides/ Sézary syndrome

Primary cutaneous CD30 positive T-cell lymphoproliferative disorders

Lymphomatoid papulosis

Primary cutaneous anaplastic large cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous CD8 positive aggressive cytotoxic T-cell lymphoma

Primary cutaneous acral CD8+ T-cell lymphoma

Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder

## Nodal/ Extranodal

Peripheral T-cell lymphoma, NOS

Angioimmunoblastic T-cell lymphoma

Follicular T-cell lymphoma

Nodal peripheral T-cell lymphoma with TFH phenotype

Anaplastic large cell lymphoma, ALK positive

Anaplastic large cell lymphoma, ALK negative

With acknowledgment to the many contributors &

Lymphoid Editors

Steven H. Swerdlow

Elias Campo

Stefano Pileri

Nancy Lee Harris

Harald Stein

Reiner Siebert

CAC Chairs

Ranjana Advani

Michele Ghilmini

Gilles Salles

Andrew Zelenetz

**WHO Classification of Tumours of  
Haematopoietic and Lymphoid Tissues**

Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri,  
Harald Stein, Jürgen Thiele, Daniel A. Arber, Robert P. Hasserjian,  
Michelle M. Le Beau, Attilio Orazi, Reiner Siebert

