Carrefour Pathologie 2016

Palais des Congrès de Paris 7 au 10 novembre

SYMPOSIUM SFP
Lymphomes T périphériques non cutanés: Problèmes pratiques et diagnostic différentiel

Modérateurs

Prof. Philippe Gaulard, Hôpital Henri Mondor, Créteil

Prof. Laurence de Leval, Institut Universitaire de Pathologie, Lausanne

Déclarations d’intérêts

L’objectif de cette déclaration est d’exposer aux congressistes l’existence d’éventuels liens qui pourraient influencer, d’une façon ou d’une autre, votre intervention.

Je déclare ne pas avoir de conflits d’intérêts en rapport avec mon intervention

Lymphomes T périphériques non cutanés: Problèmes pratiques et diagnostic différentiel

- Lymphomes T globalement rares mais regroupent de nombreuses entités
- Maladies généralement agressives doivent être correctement identifiées
- Diagnostic de lymphome T reste difficile
- Modifications introduites dans la révision 2016 de la classification OMS
- Objectifs de l'histoséminaire: update sur la classification, recommandations pratiques sur l'approche diagnostique

Lymphomes T périphériques non cutanés: Problèmes pratiques et diagnostic différentiel

PROGRAMME

- Actualités sur la classification OMS 2016 et lymphomes dérivés des lymphocytes T folliculaires (T_{FH}) – Laurence de Leval, Lausanne
- Les lymphomes T CD30+ en 2016 : quelles entités ? - Céline Bossard, Nantes
- Le spectre des lymphoprolifération cytotoxiques T et NK extra-ganglionnaires de l'adulte – Marie Parrens, Bordeaux
- Que reste-t-il du lymphome T périphérique sans spécificité en 2016 ? – Philippe Gaulard, Créteil

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Actualités sur la classification OMS 2016 et lymphomes dérivés des lymphocytes T folliculaires (T_{FH})

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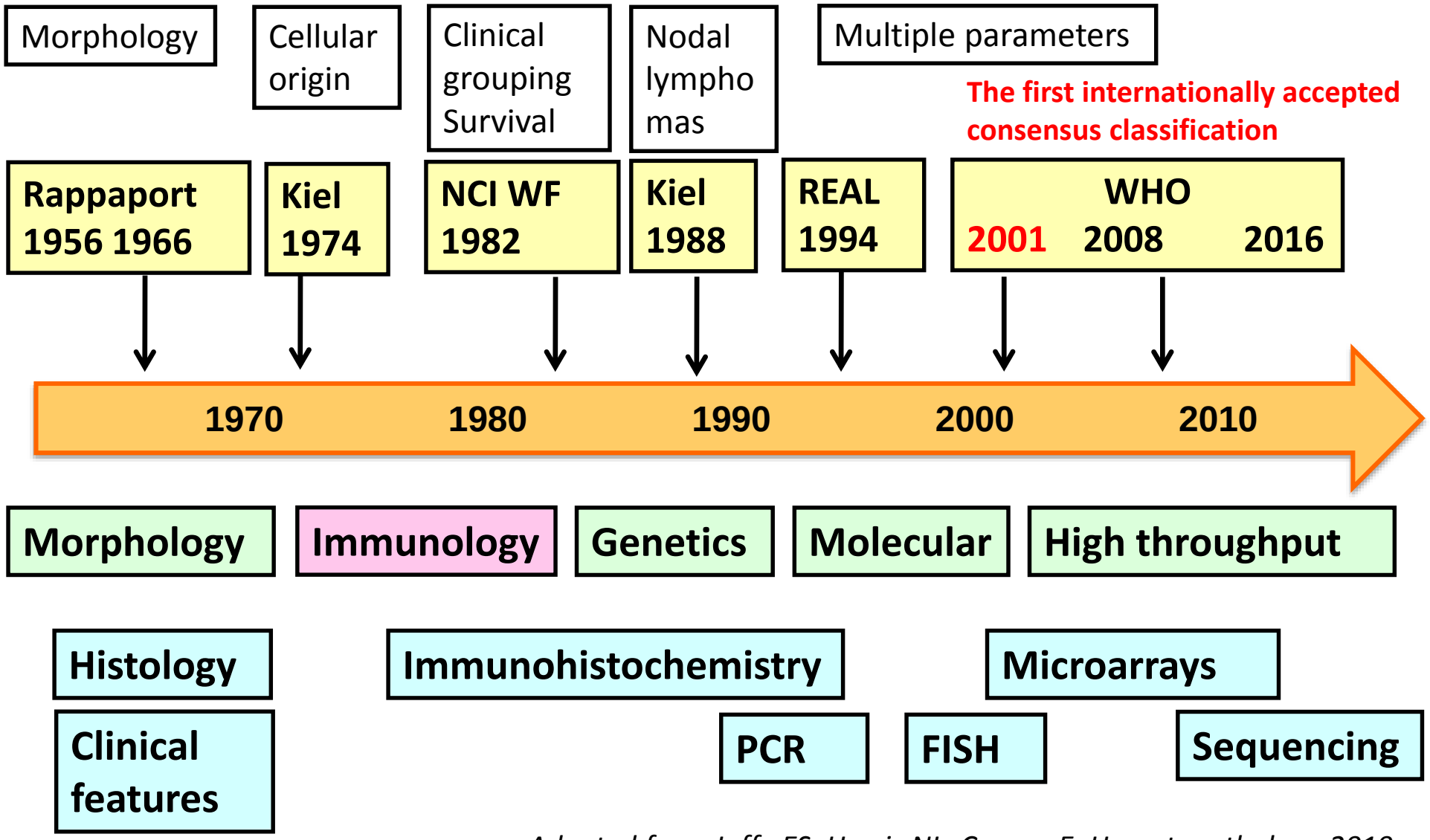
The evolution of lymphoma classification



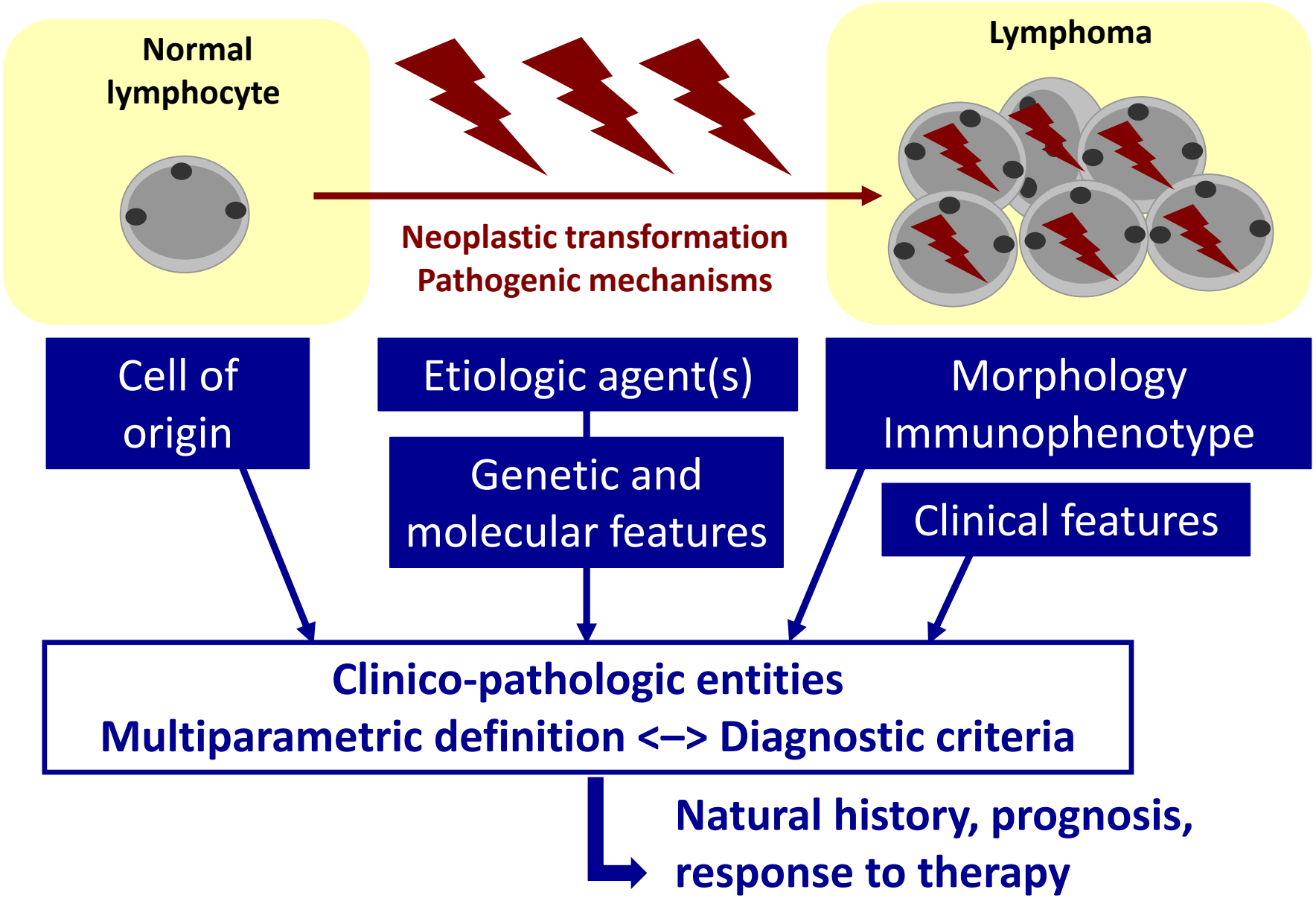
Adapted from Jaffe ES, Harris NL, Campo E, Hematopathology 2010

The 2016 revision of the WHO classification

- Incorporation of new molecular discoveries impacting on diagnosis, prognosis and therapeutic implications
- An update of the 2008 classification
  - Some provisional entities promoted to definitive
  - Some new novel provisional entities
  - No new definitive entity
  - Some changes in nomenclature
- Maintains the goal to delineate well-characterized entities
- Clinical advisory comittee

Swerdlow SH et al. Blood Volume 127(20):2375-2390 May 19, 2016

Principles of the REAL/WHO classification



Mature T/NK-cell neoplasms

Leukemic

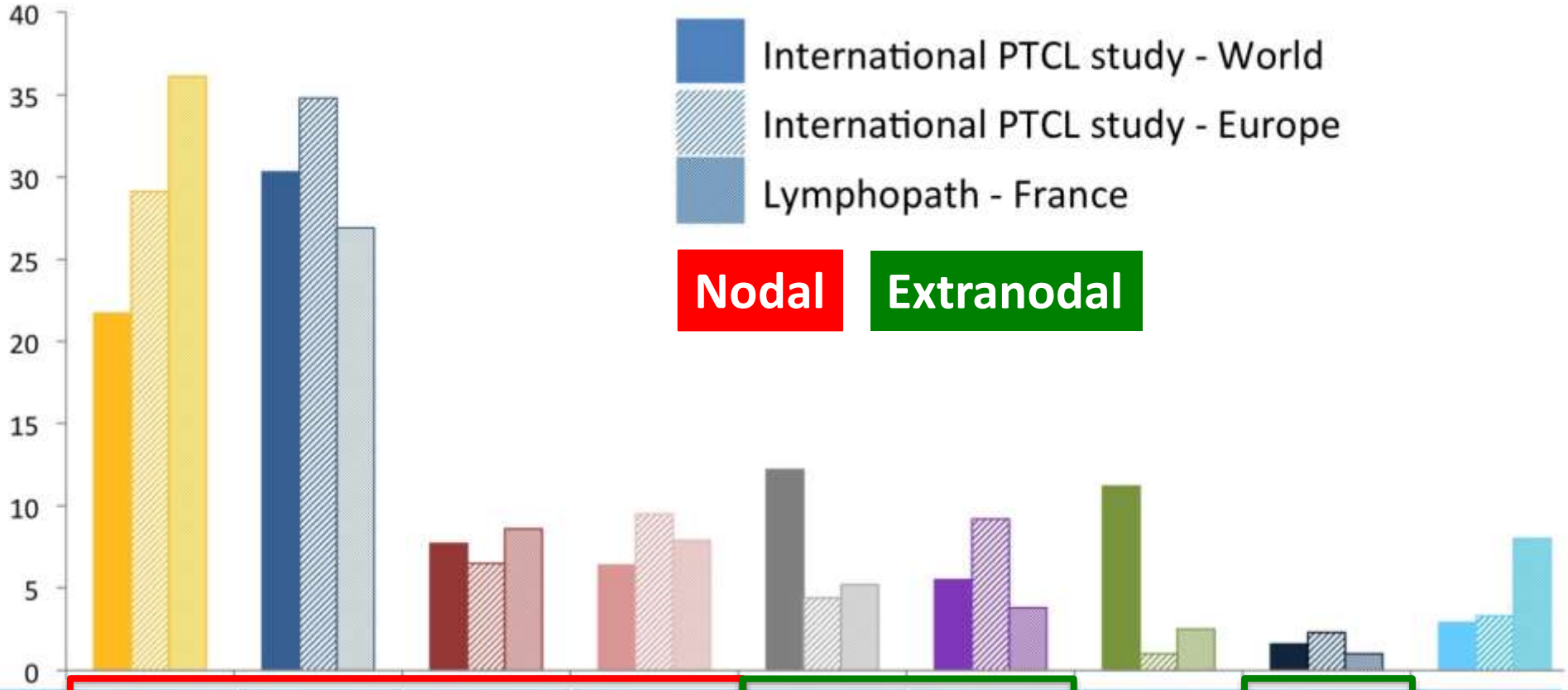
- T-cell PLL
- T-cell LGL leukemia
- *Chronic LPDs of NK cells*
- Aggressive NK-cell leukemia
- ATLL
- Systemic EBV+ T-cell lymphoma of childhood
- Hydroa vacciniforme-like lymphoproliferative disorder

Nodal

- PTCL-NOS
- AITL (angioimmunoblastic)
- *Follicular T-cell lymphoma*
- *Nodal PTCL with TFH phenotype*
- ALCL, ALK-positive
- ALCL, ALK-negative

Extra-Nodal

- Extranodal NK/TCL, nasal type
- Enteropathy-associated TCL
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- *Indolent T-cell proliferative disorder of the GI tract*
- Subcutaneous panniculitis-like TCL
- Hepatosplenic TCL
- MF/Sezary Syndrome
- Primary cutaneous CD30+ LPD
- LyP, pcALCL
- *Breast implant-associated ALCL*
- Primary cutaneous $\gamma\delta$ TCL
- *Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL*
- *Primary cutaneous acral CD8+ TCL*
- *Primary cutaneous CD4+ small/medium T-cell LPD*



%	AITL	PTCL-NOS	ALK+ ALCL	ALK- ALCL	NKTCL	EATL	ATLL	HSTL	Others
World	21.7	30.4	7.7	6.5	12.2	5.5	11.3	1.6	2.9
Europe	29.1	34.8	6.5	9.5	4.4	9.2	1	2.3	3.3
France	36.1	26.9	8.6	7.9	5.2	3.8	2.5	3.3	8

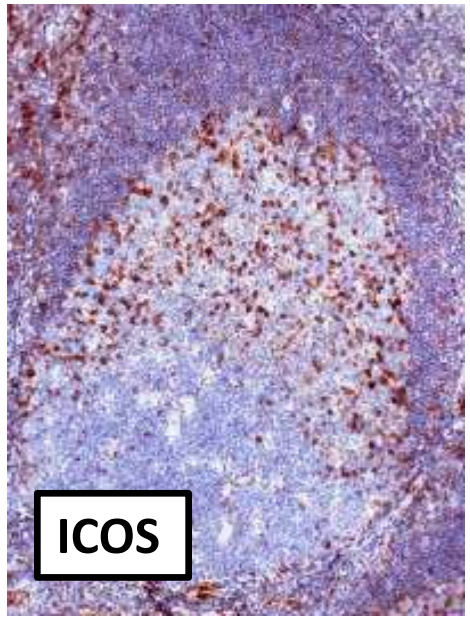
Lymphopath data, de Leval L, et al. Haematologica 2015

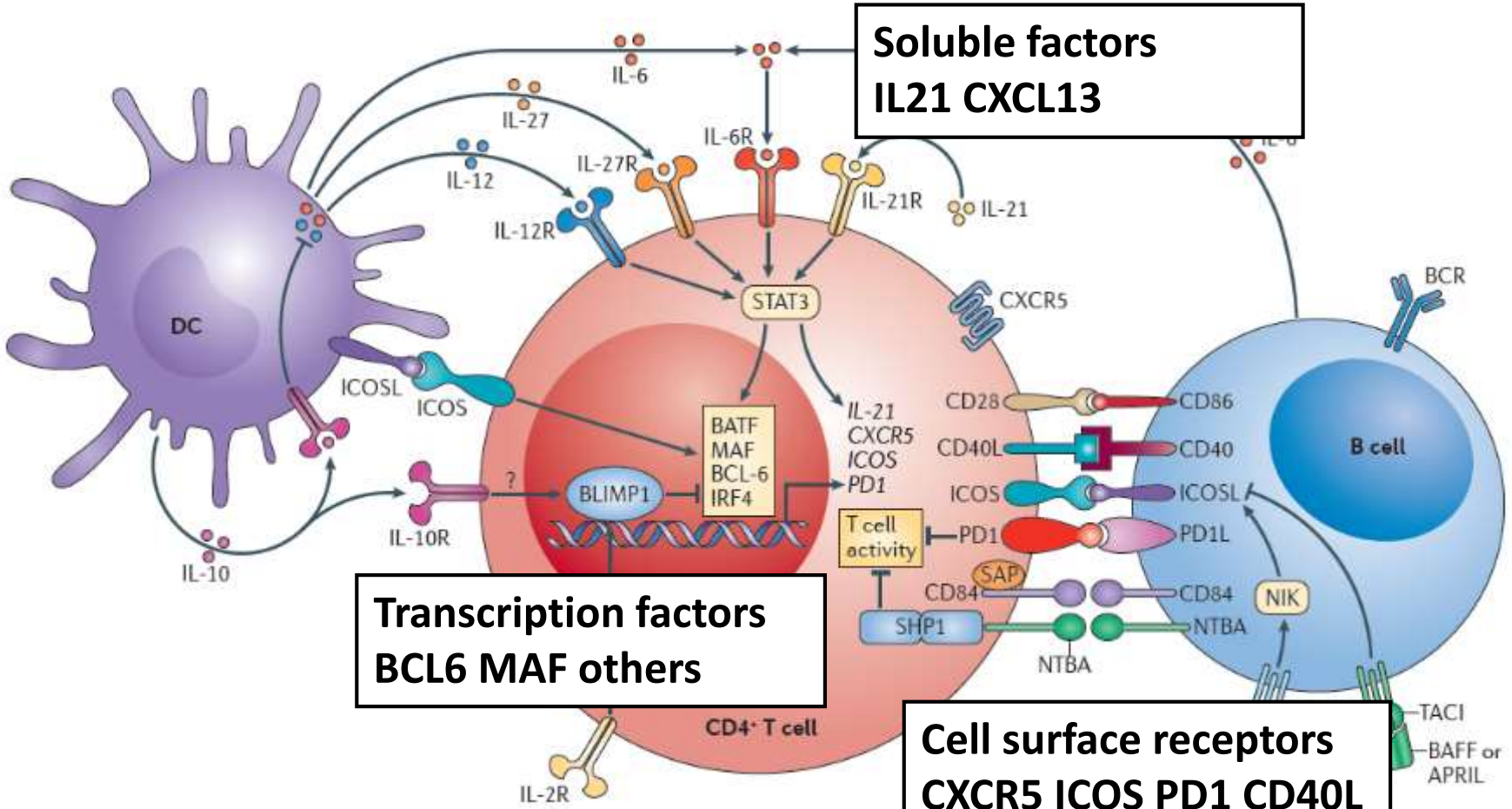
Nodal lymphomas of T_{FH} origin

AITL : angioimmunoblastic T-cell lymphoma

F-TCL: follicular T-cell lymphoma

PTCL-TFH: nodal PTCL with TFH phenotype



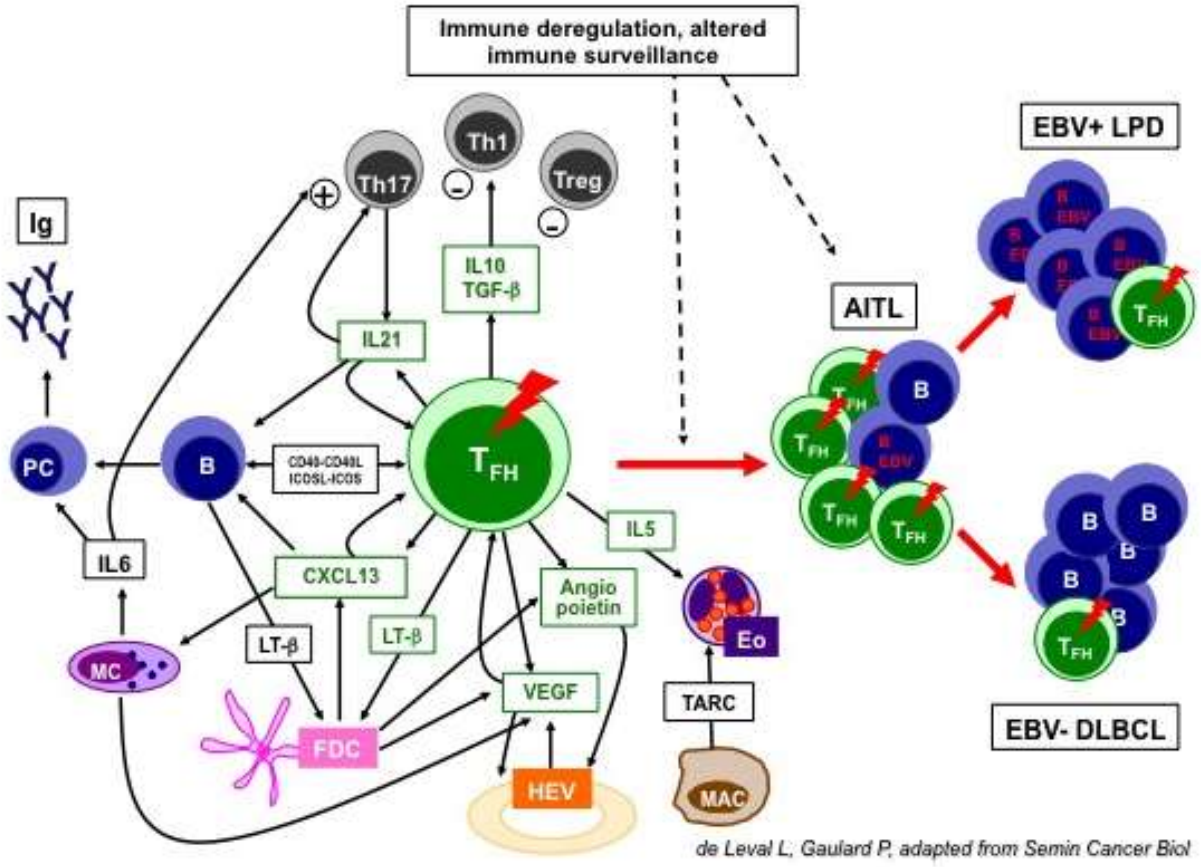


Tangye SG et al, Nature Rev Immunol 2013

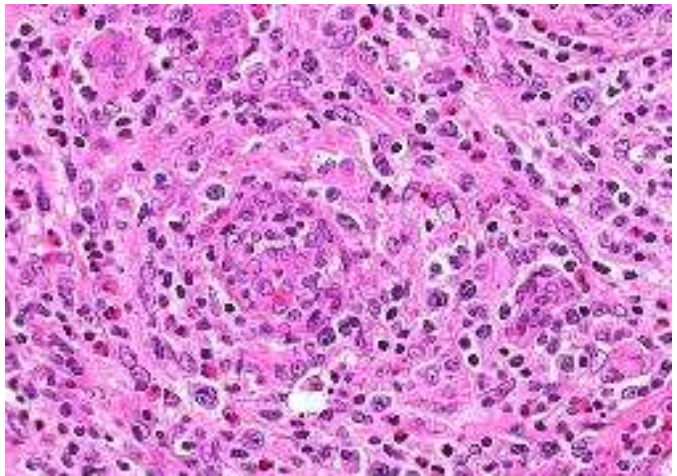
Angioimmunoblastic T-cell lymphoma - WHO 2016

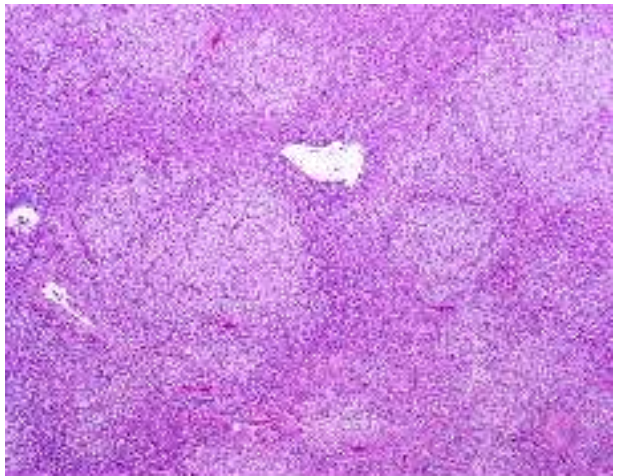
A neoplasm of mature TFH cells characterized by **systemic disease**, a **polymorphous** infiltrate involving lymph nodes with a prominent proliferation of high endothelial **venules** and **follicular dendritic cells,** and frequent expansion of **EBV+ B cells**

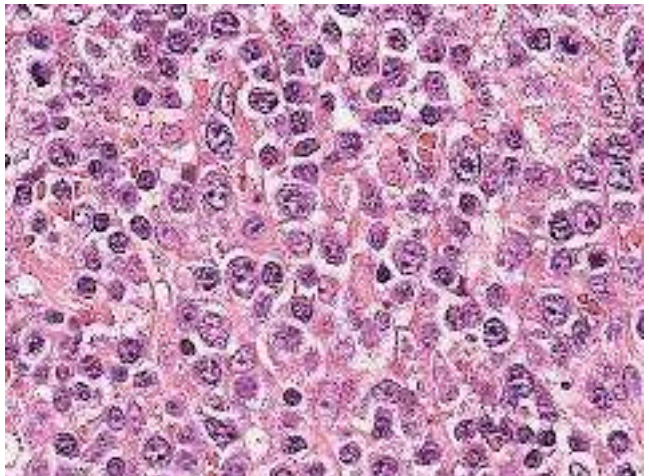
- Elderly, disseminated disease, B symptoms
- Lymphadenopathies, spleen and liver involvement, skin rash, effusions
- Anemia (Coombs positive), cytopenias, hypereosinophilia, hyperγglobulinemia



	AITL	F-TCL	TFH-PTCL
Epidemiology	First or second most common PTCL	Very rare (variant of PTCL-NOS in WHO 2008)	20% of PTCL-NOS
Pattern	Diffuse (perifollicular)	**FL-like or PTCG-like**	**Diffuse (T-zone)**
Neoplastic cells	Small to medium, clear cells	Variable	Medium to large
Polymorphic infiltrate	Abundant	Absent or minimal	Absent or minimal
FDC	Diffuse proliferation	**Restricted to follicules**	**Minimal or absent**
Vascular proliferation	Abundant	Absent or minimal	Absent or minimal
EBV+ blasts	Typically present	May be present	May be present
TFH phenotype	Several TFH markers, heterogeneous	**Several TFH markers, strong**	**At least 2 TFH markers**





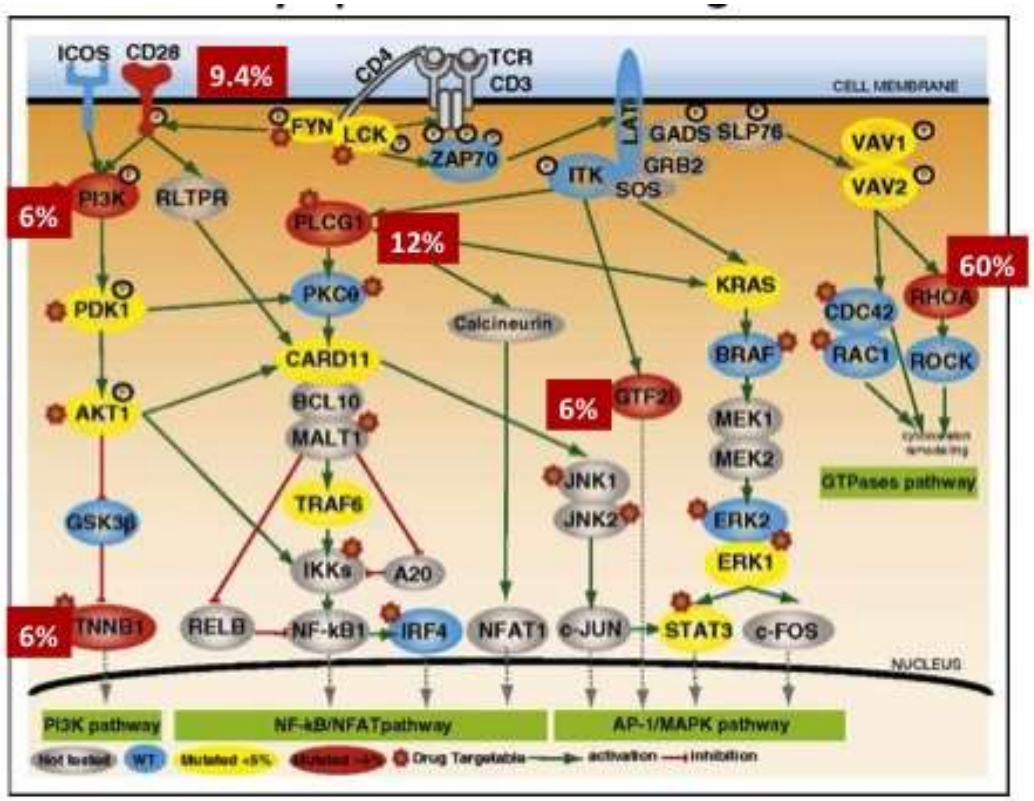


Genetic alterations in AITL and PTCL of TFH origin

Gene	Alteration	Freq.
TET2 *Lemonnier F et al. Blood 2012*	Inactivating mut.	50-75%
DNMT3	Inactivating mut.	30%
IDH2* *Cairns R et al. Blood 2012*	R172 (R140)	25%
RHOA *Palomero T Sakata M et al. Nat Genet 2014*	G17V	60-70%
t(5;9)(q33;q22) *Streubel B et al. Leukemia 2006*	*ITK-SYK* fusion	20% FTCL (AITL)
CD28 *Rohr J et al. Leukemia 2016; Lee SH et al. Haematologica 2015*	Activating mut. @ residues 124 195	10% AITL
PLCG1, CARD11, FYN… *Vallois D et al. Blood 2016*	Activating mut.	50%

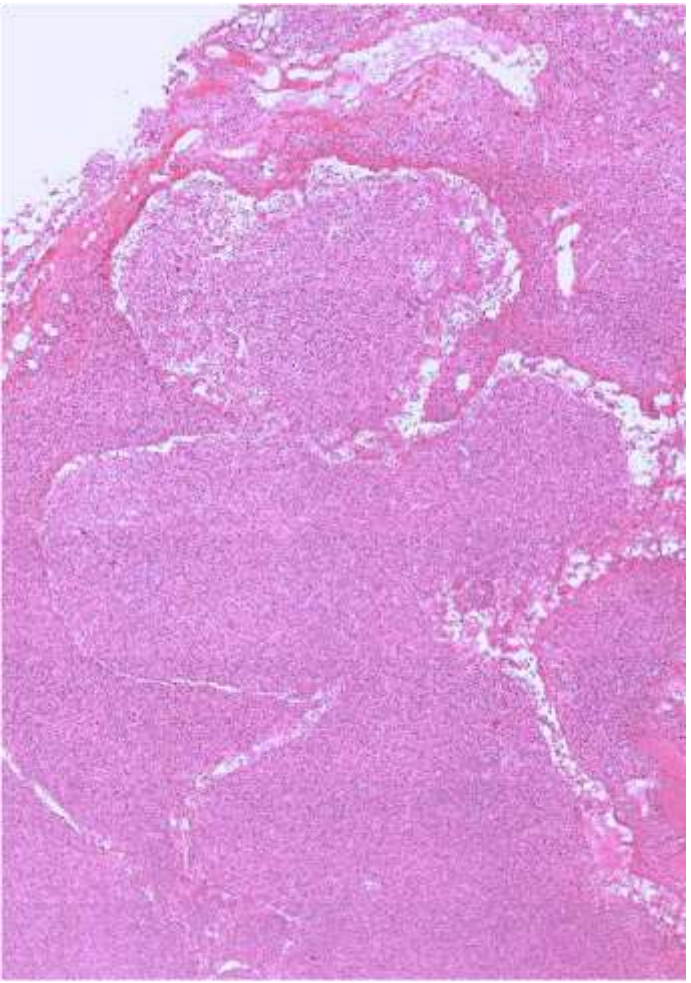
Epigenetics Hypermethylation

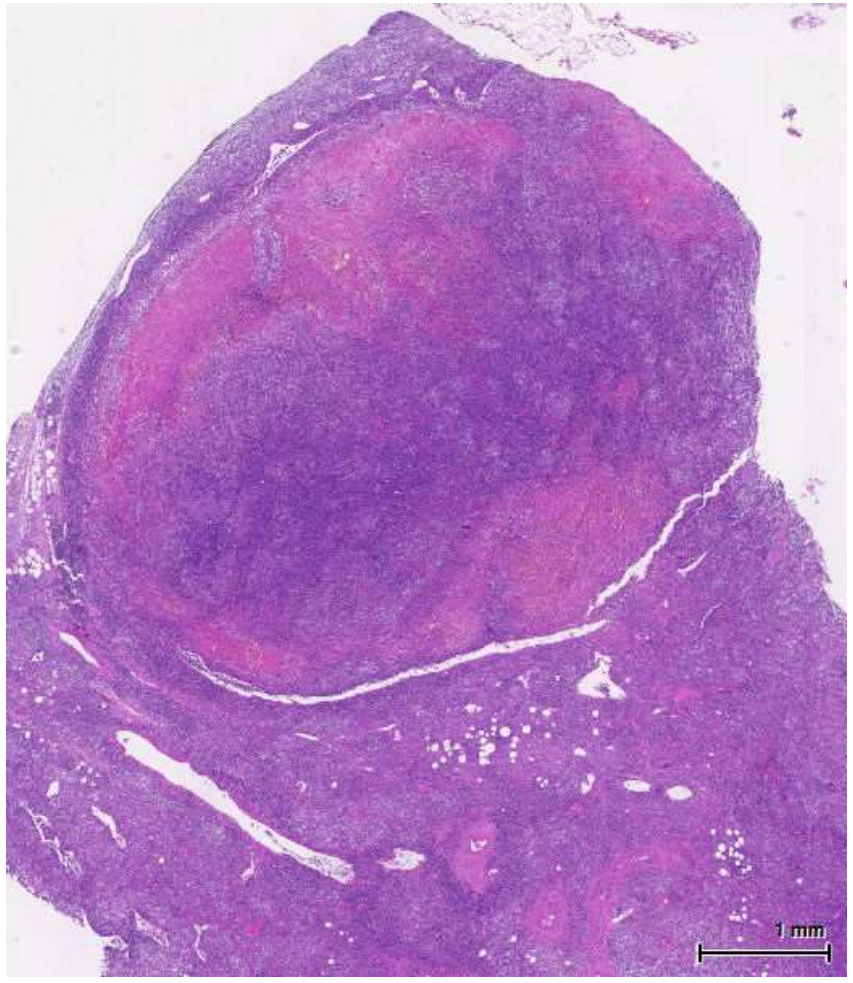
TCR signaling

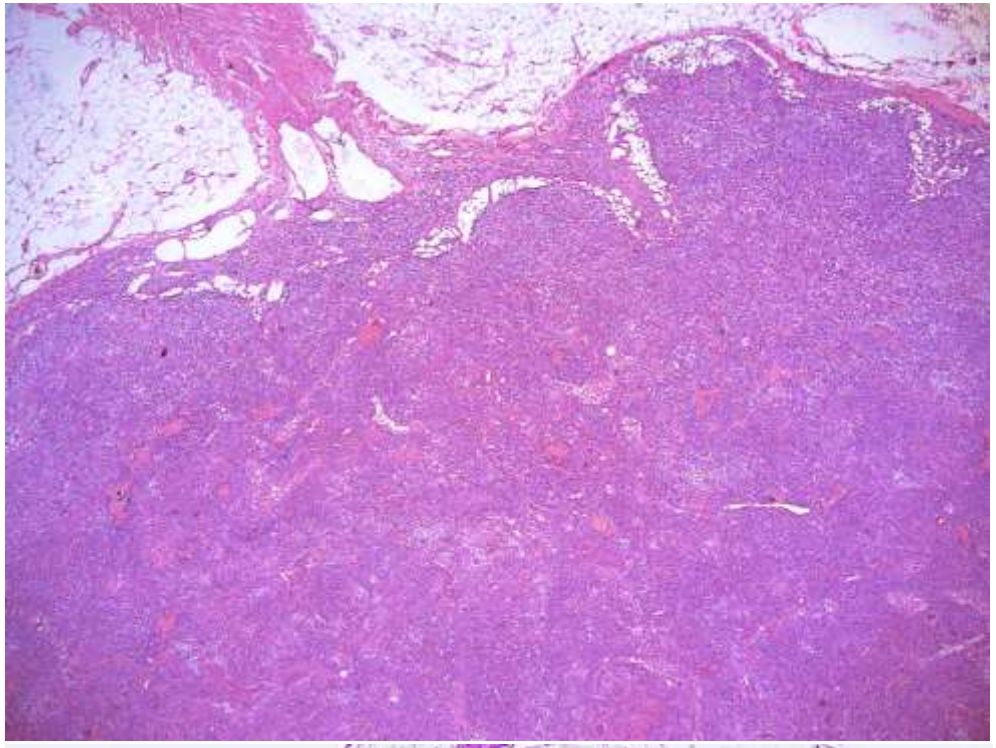


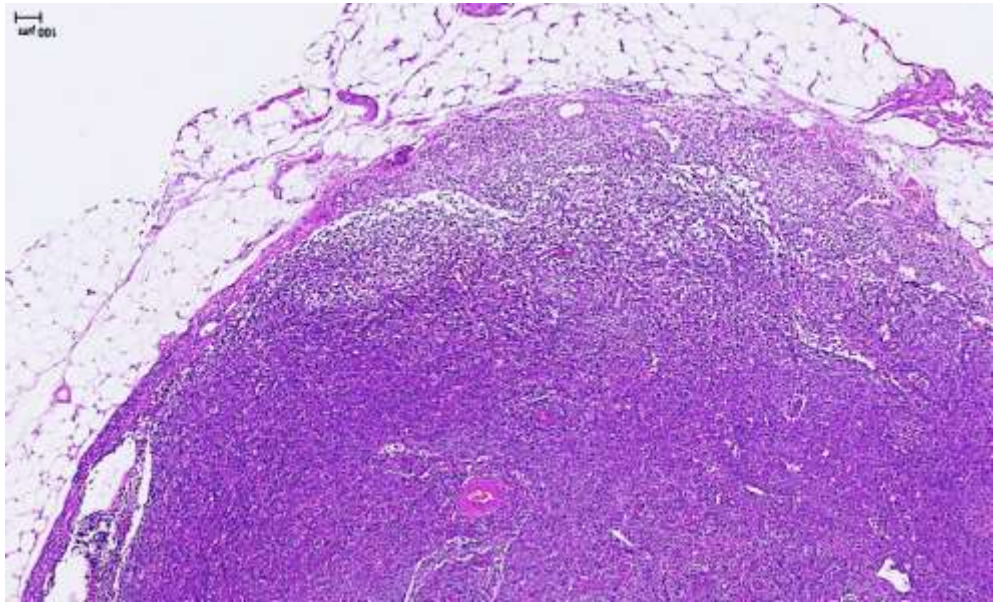
David Vallois et al. Blood 2016;128:1490-1502

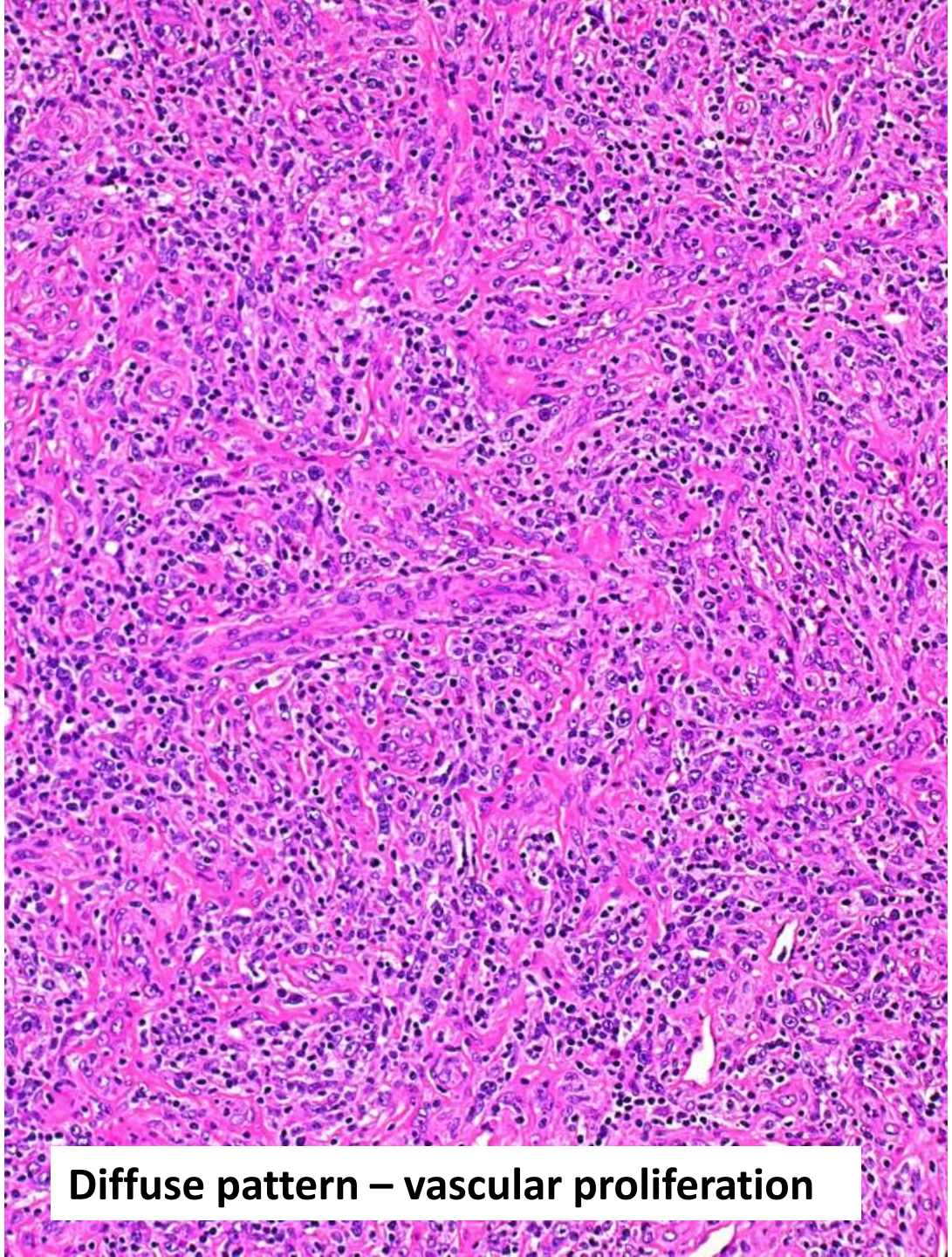
AITL – sinus sign



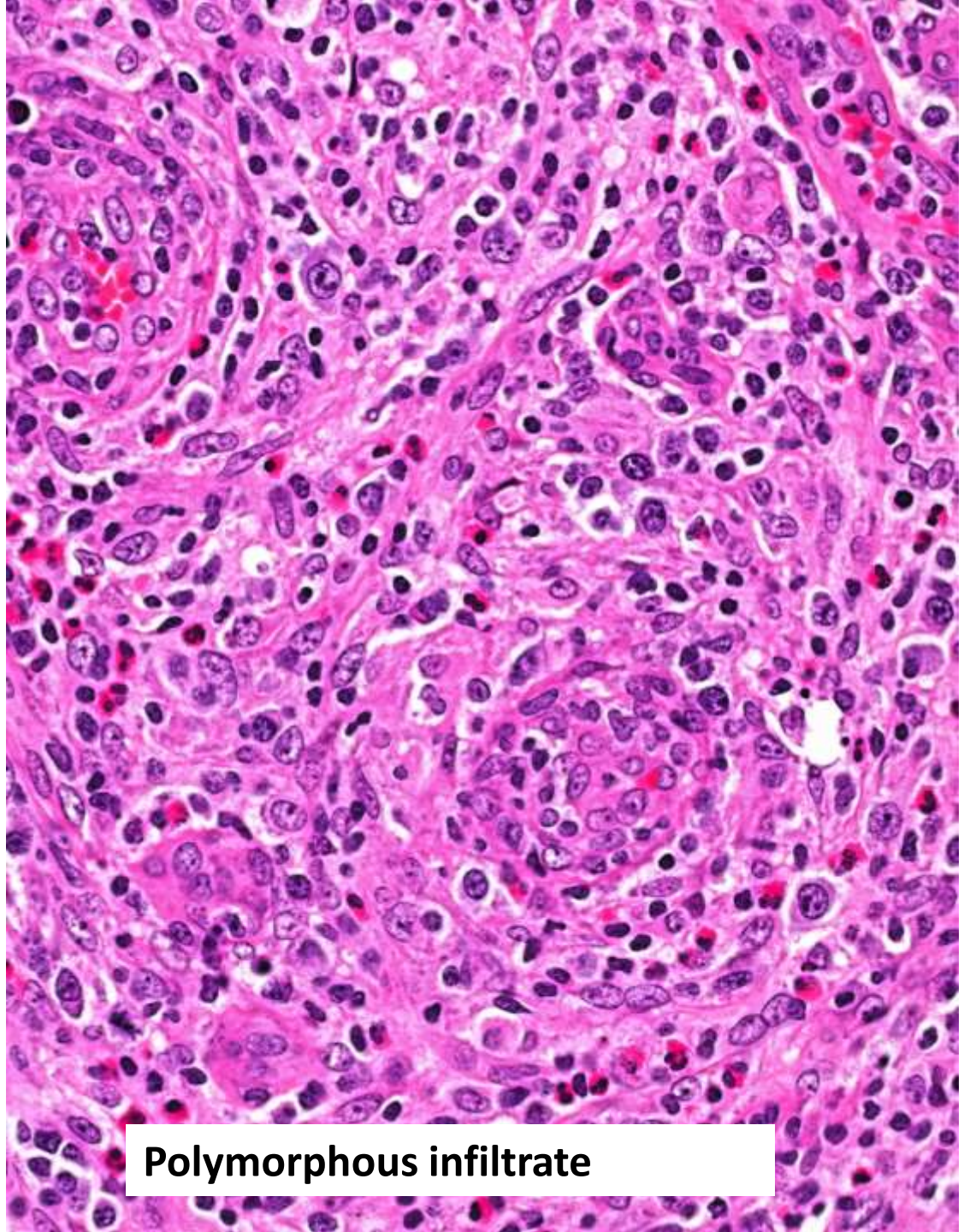




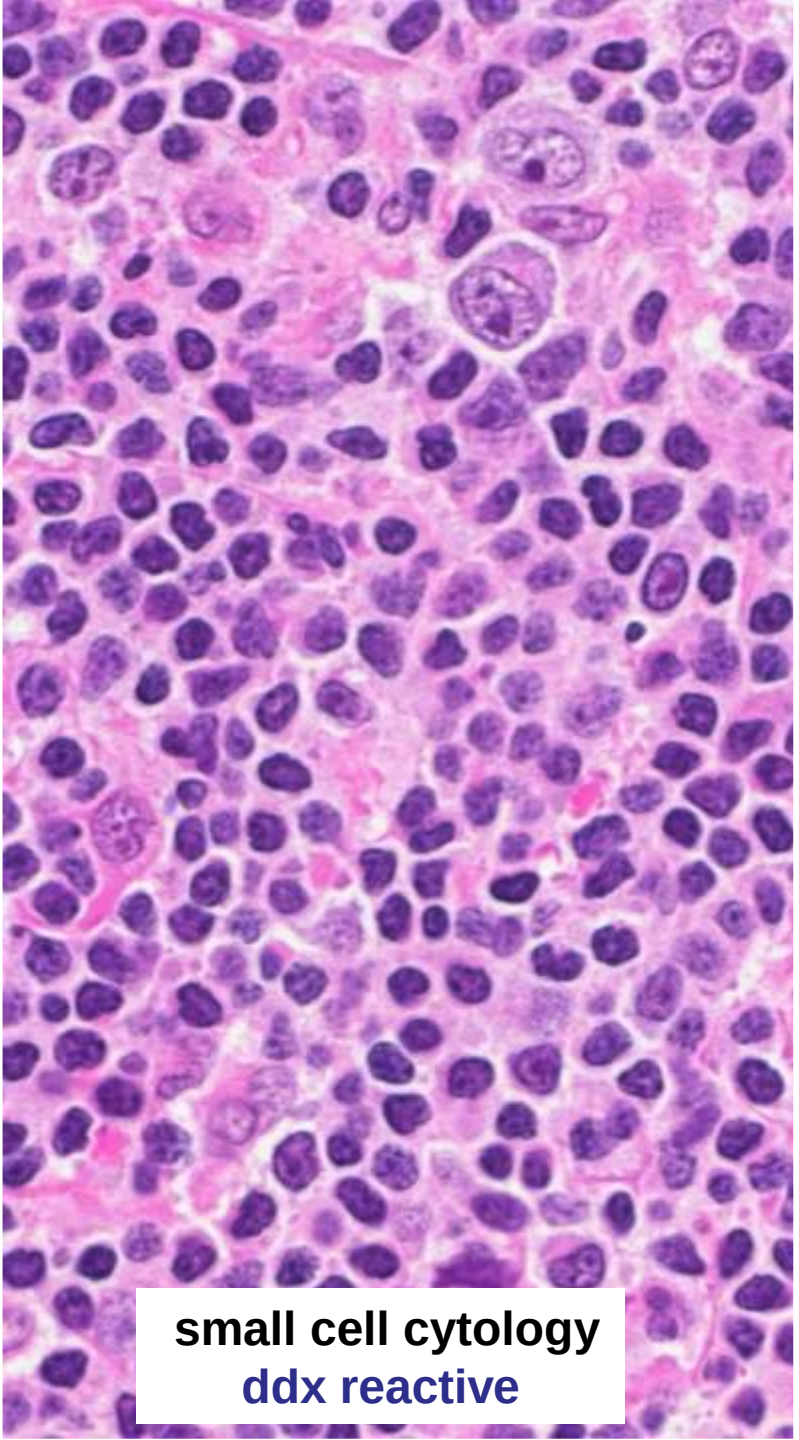


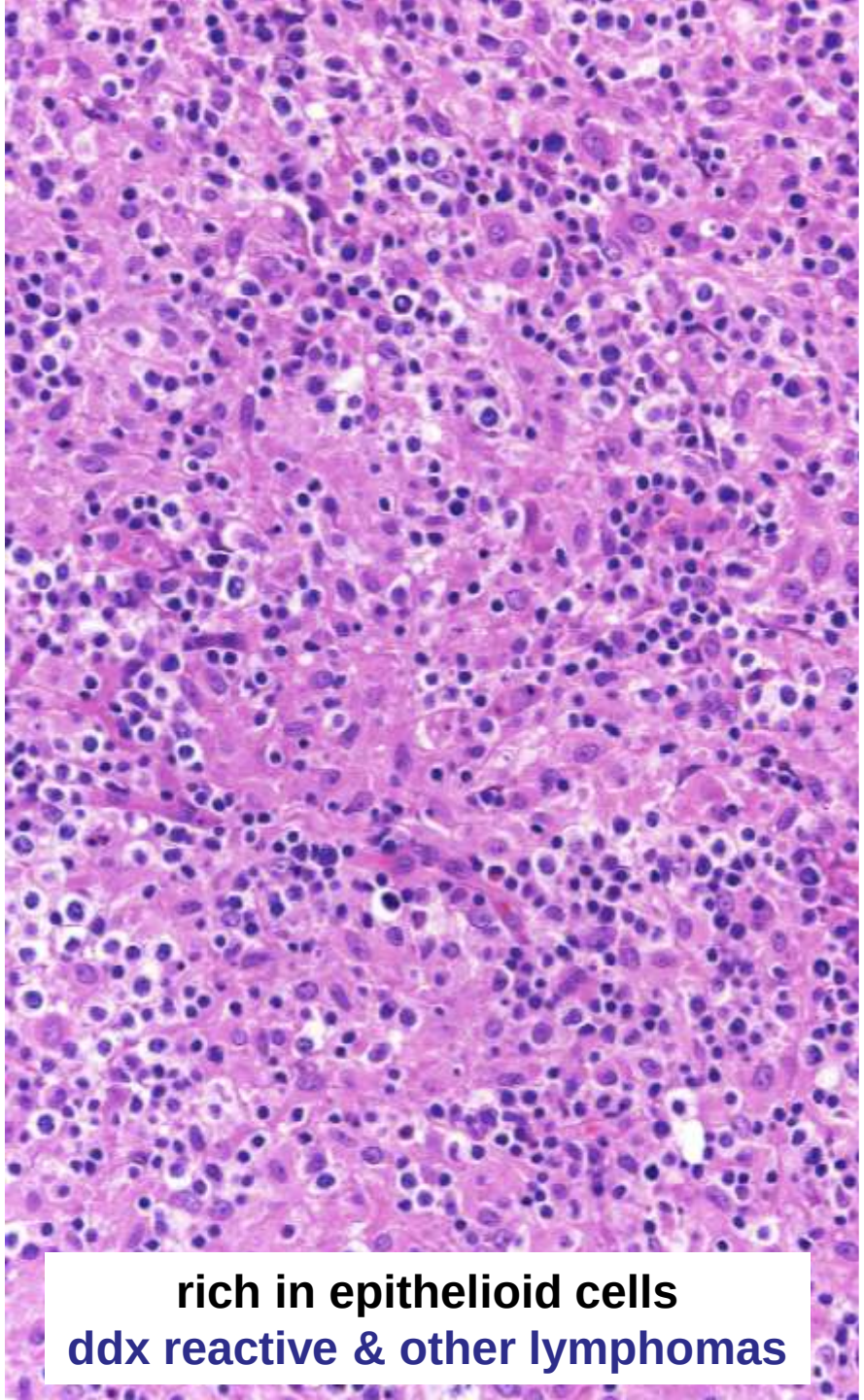


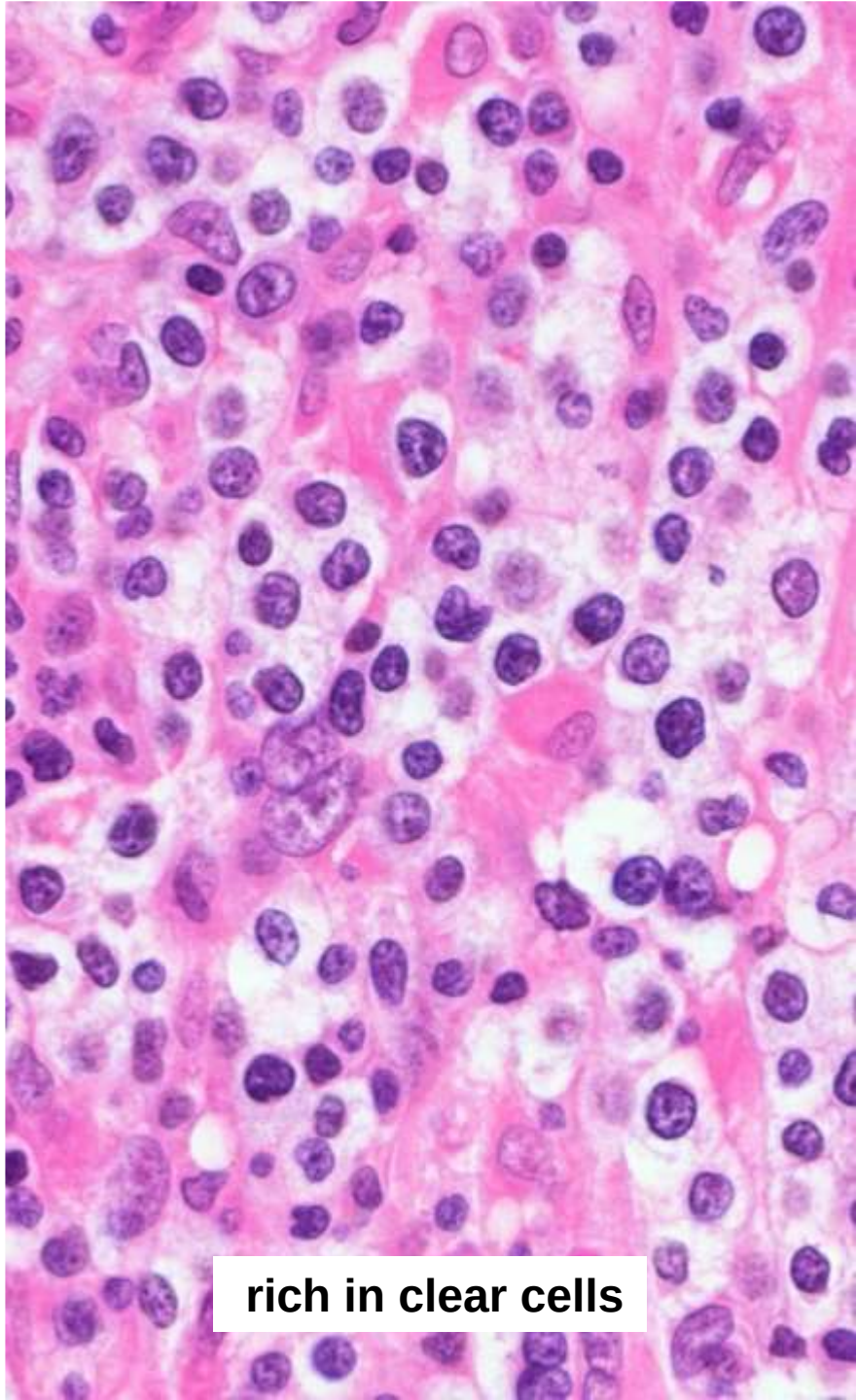
Diffuse pattern – vascular proliferation



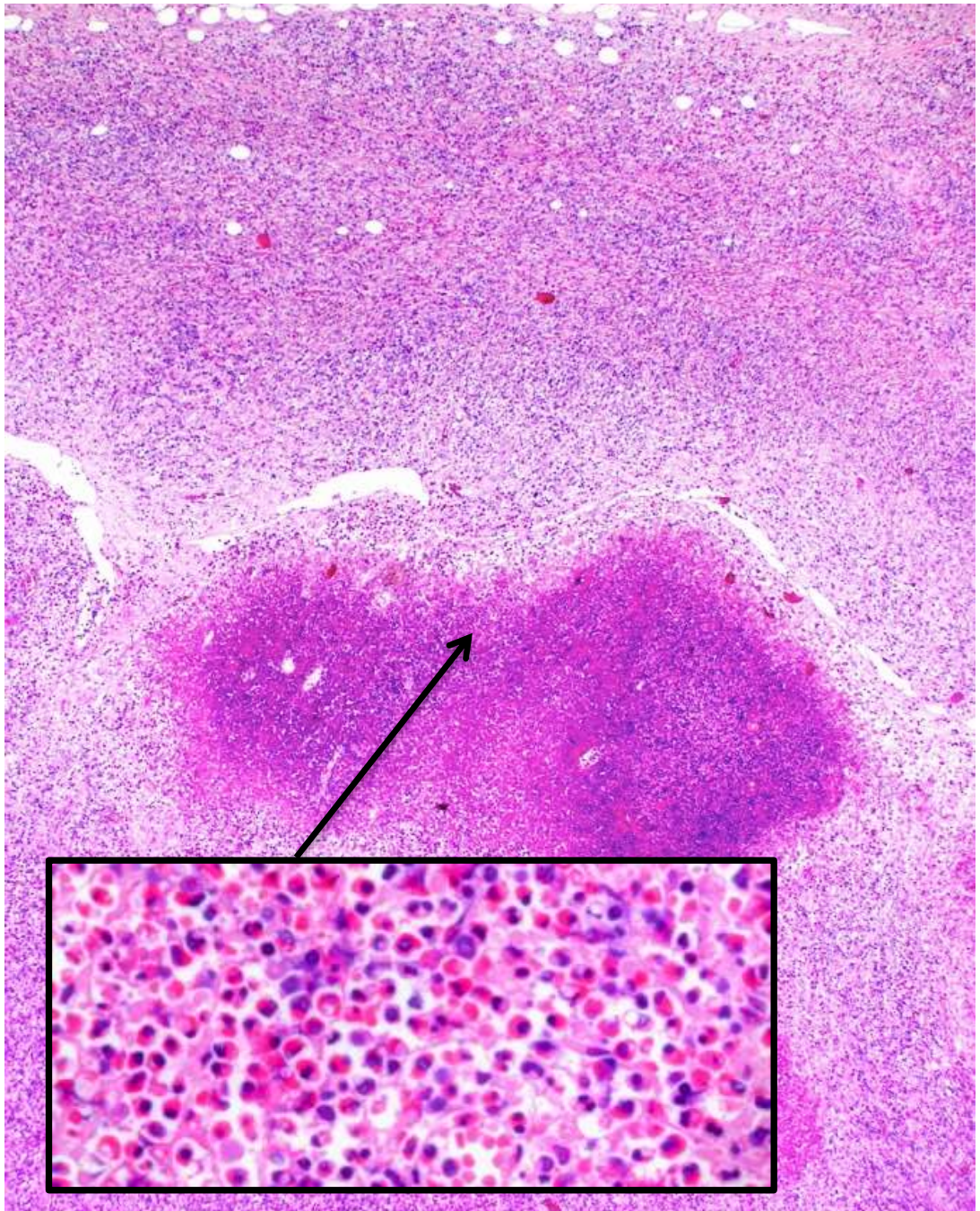
Polymorphous infiltrate

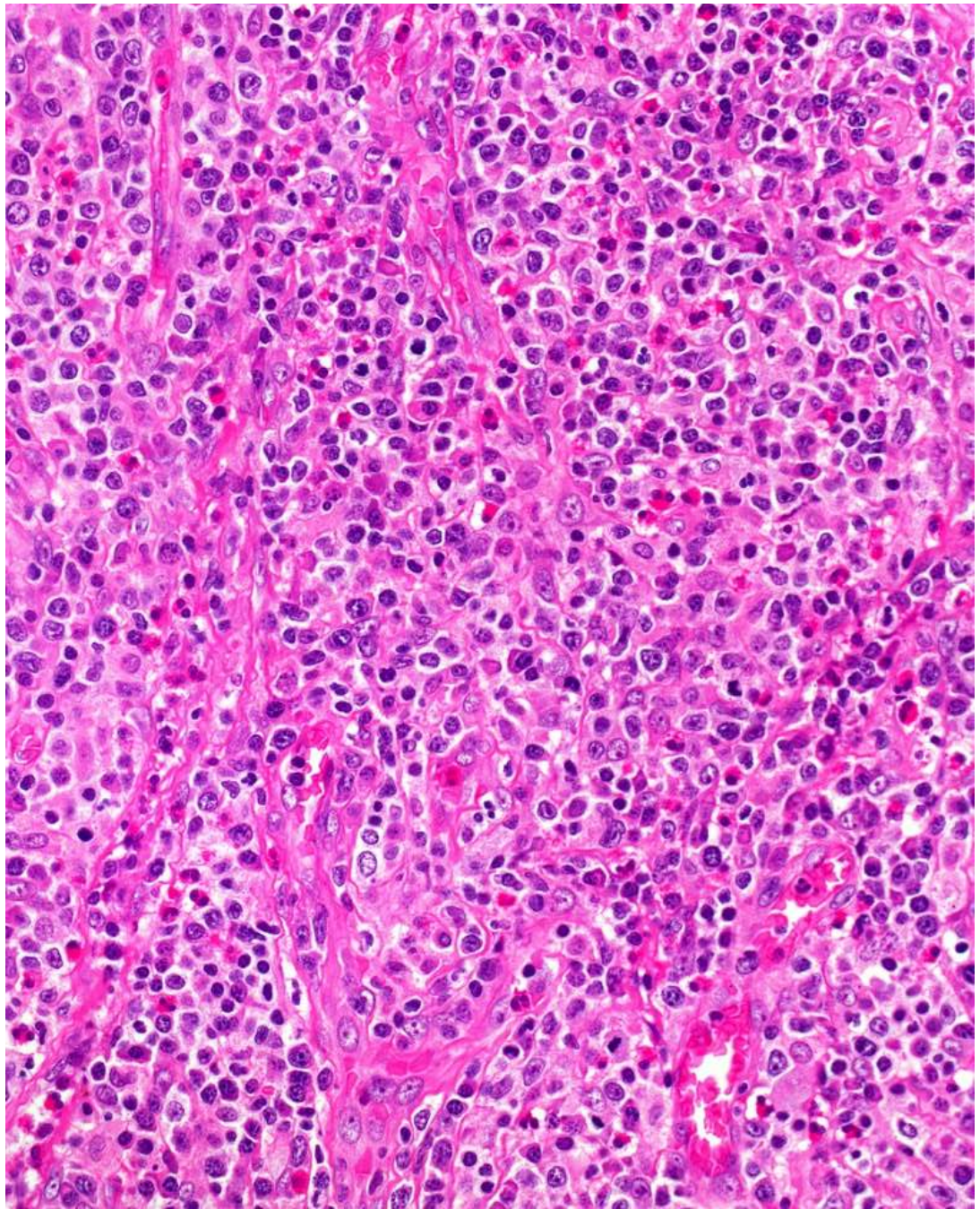

small cell cytology
ddx reactive


rich in epithelioid cells
ddx reactive & other lymphomas

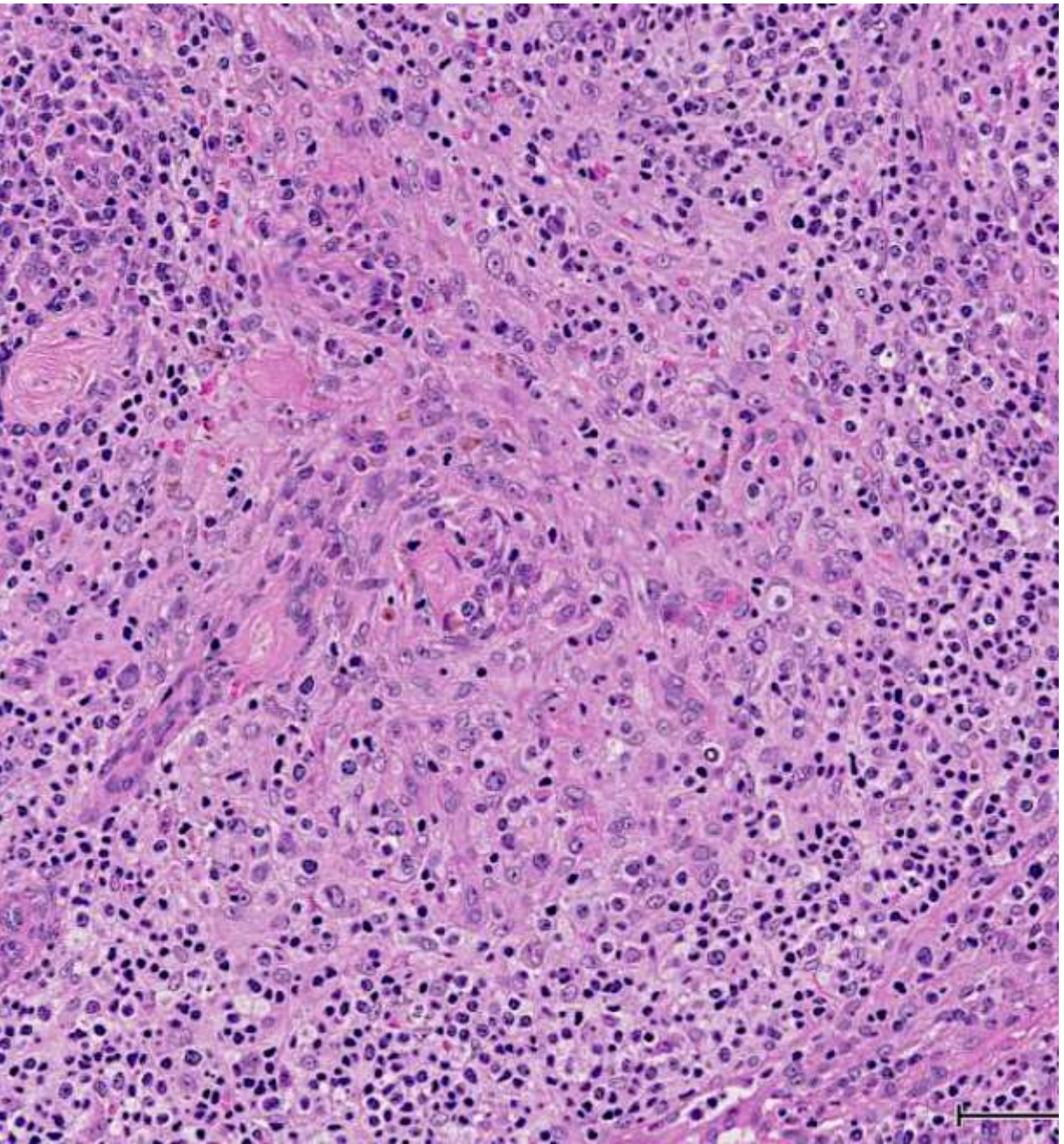

rich in clear cells

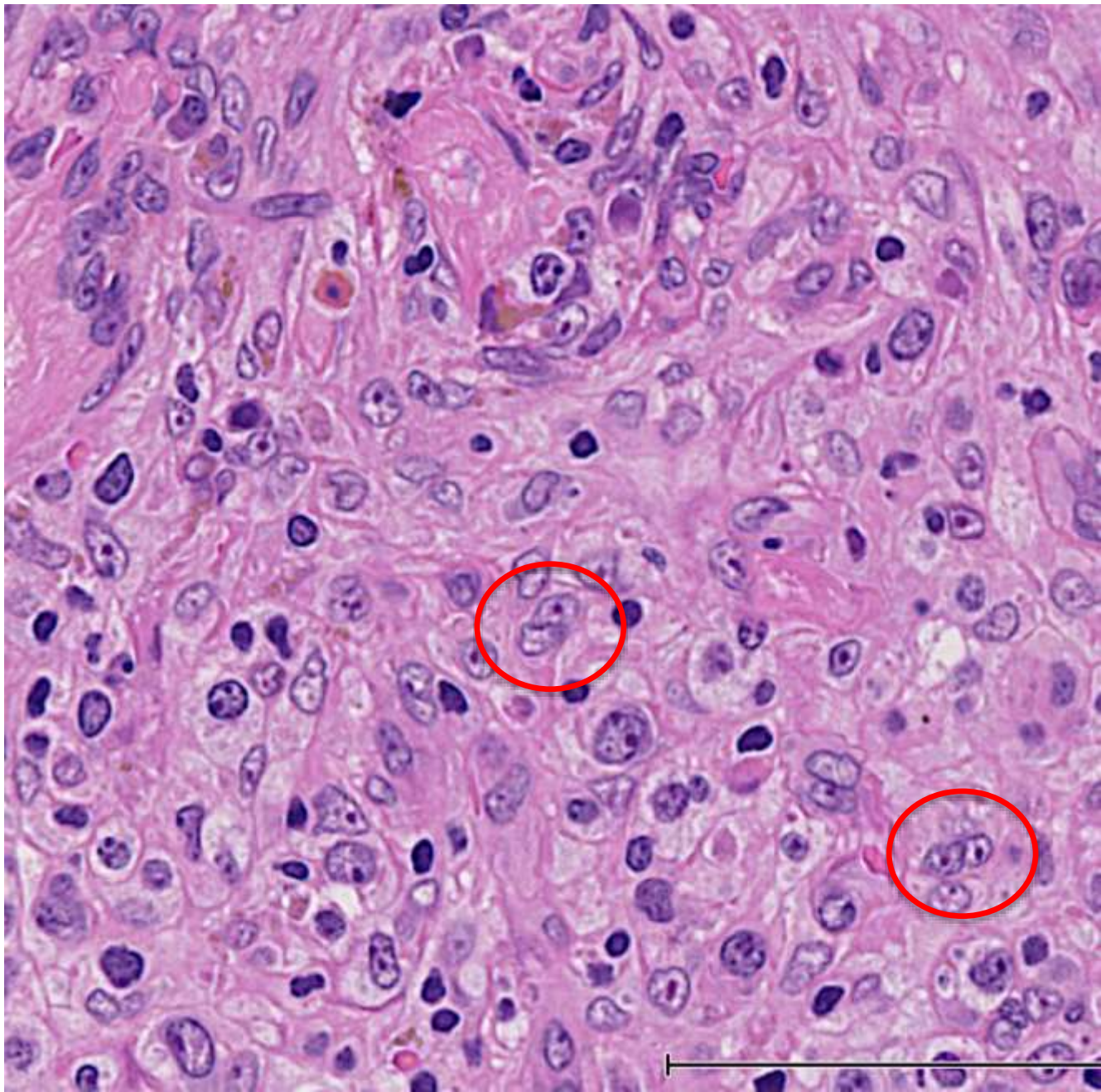
AITL in a patient with marked blood eosinophilia

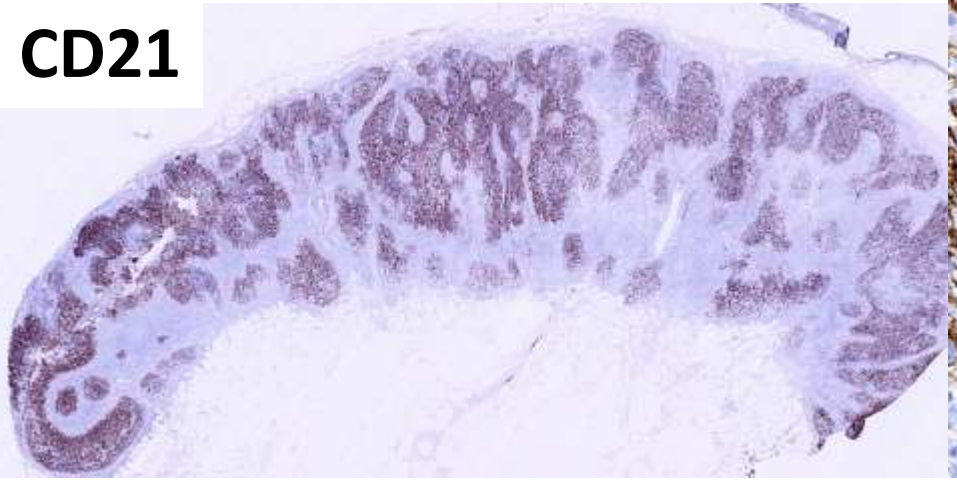


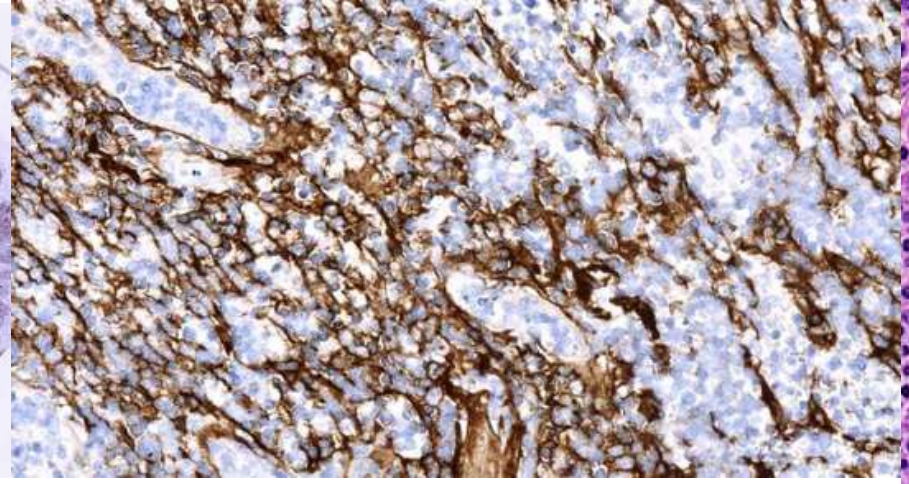


FDC proliferation in AITL

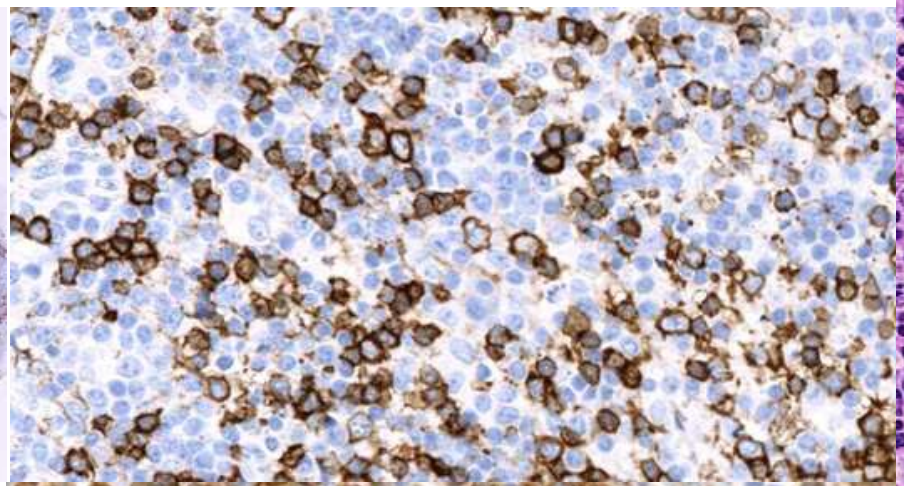




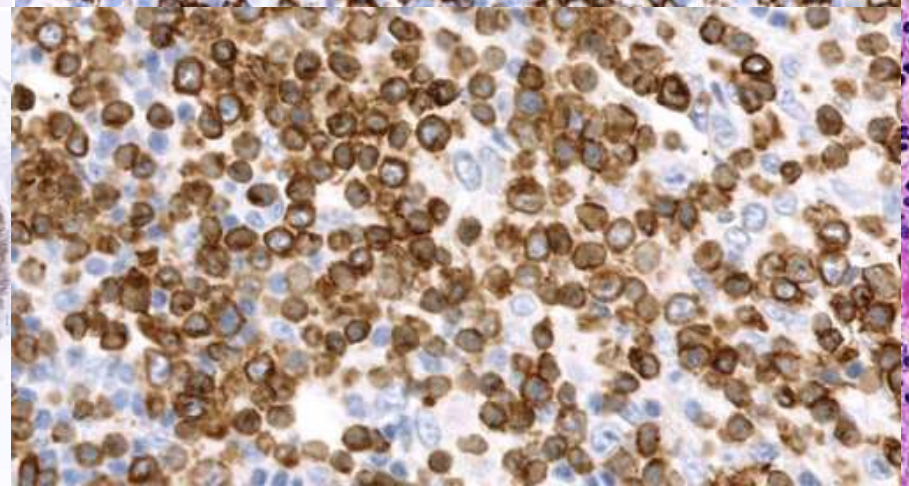

CD21

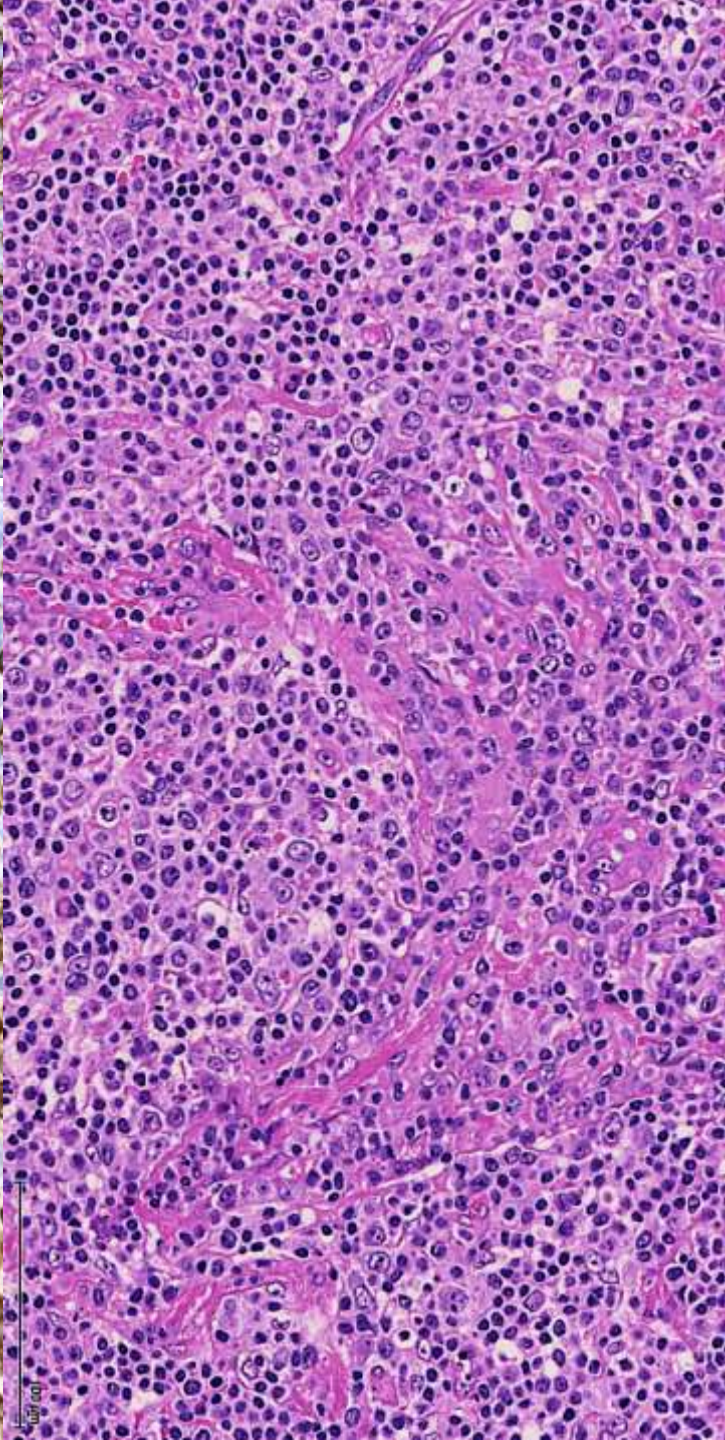



CD20

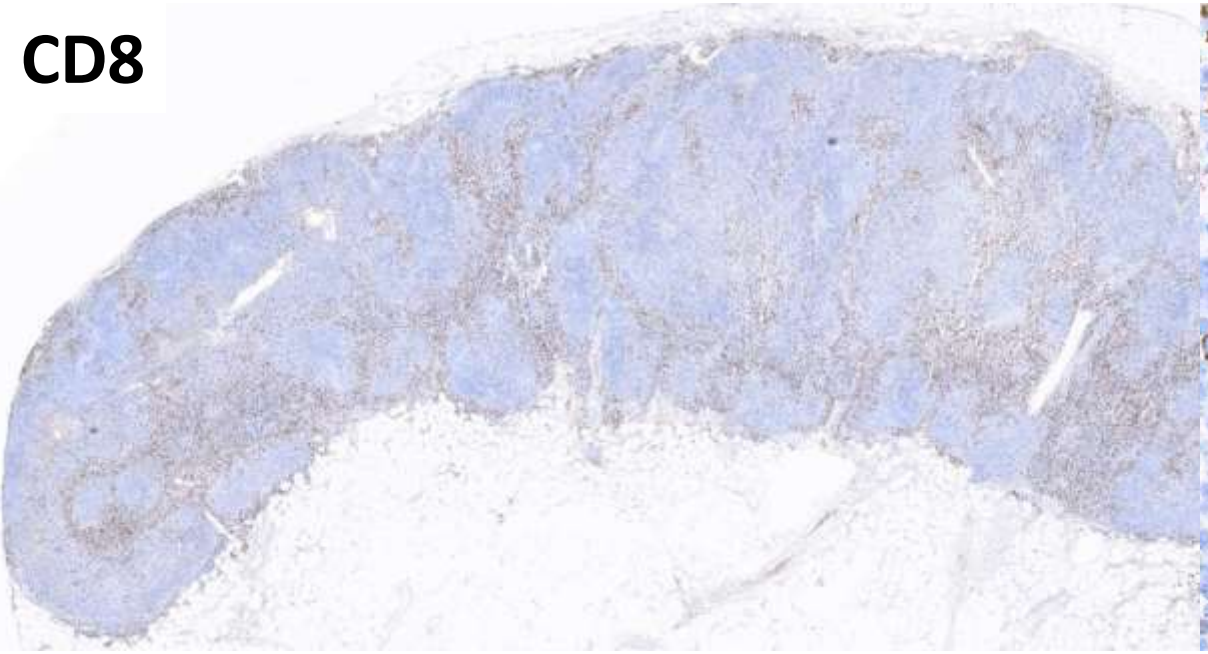


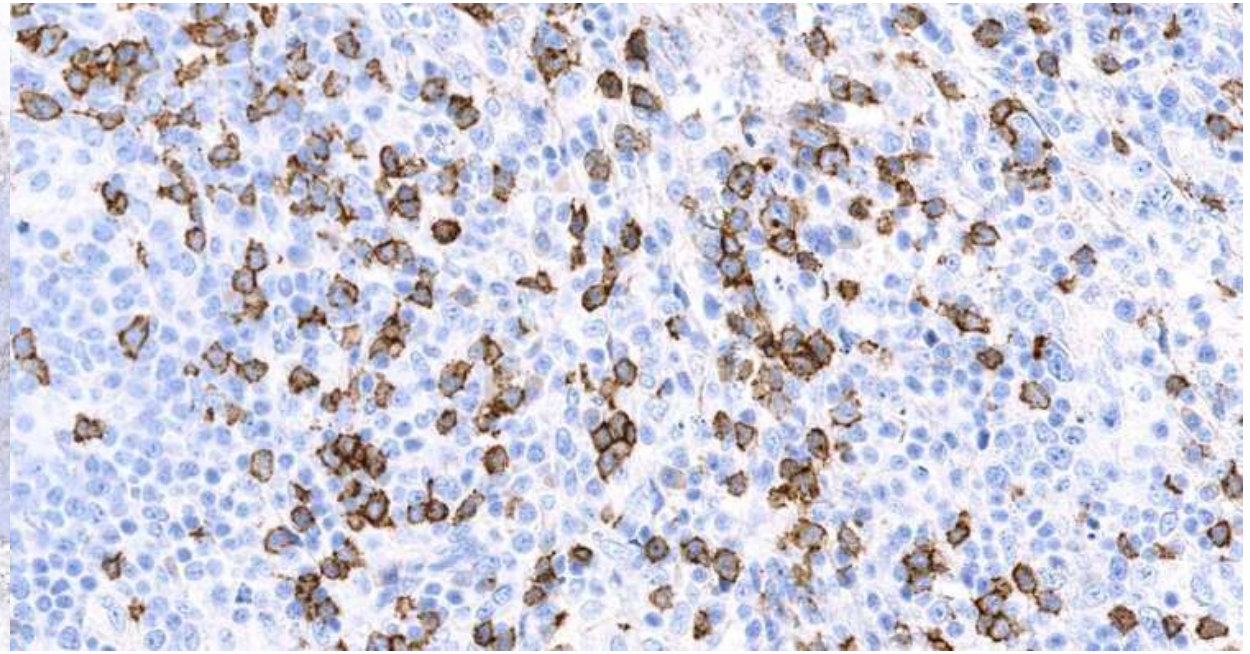

CD3



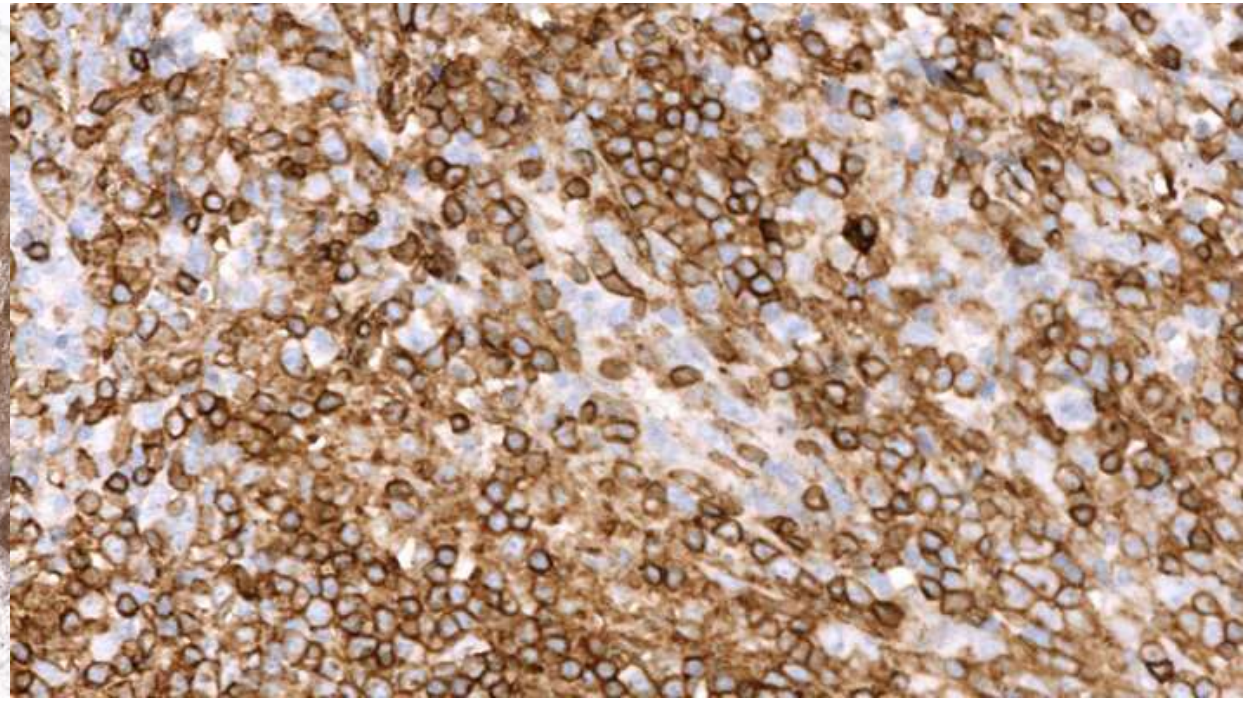


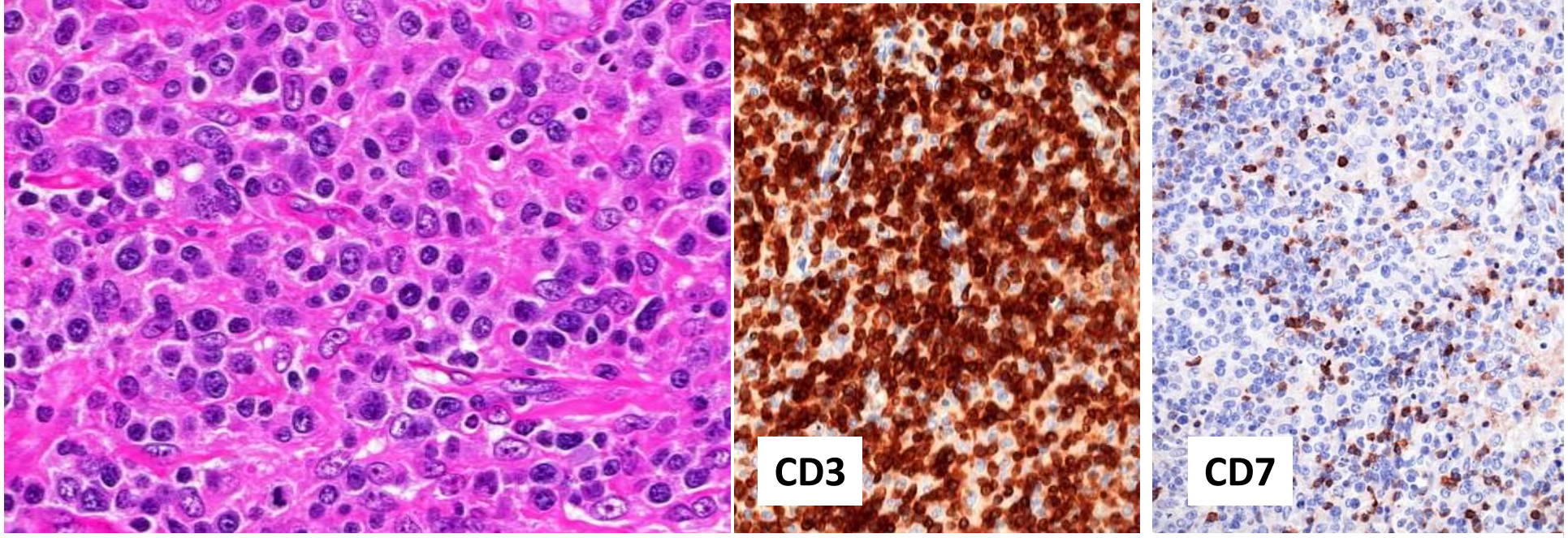
CD8



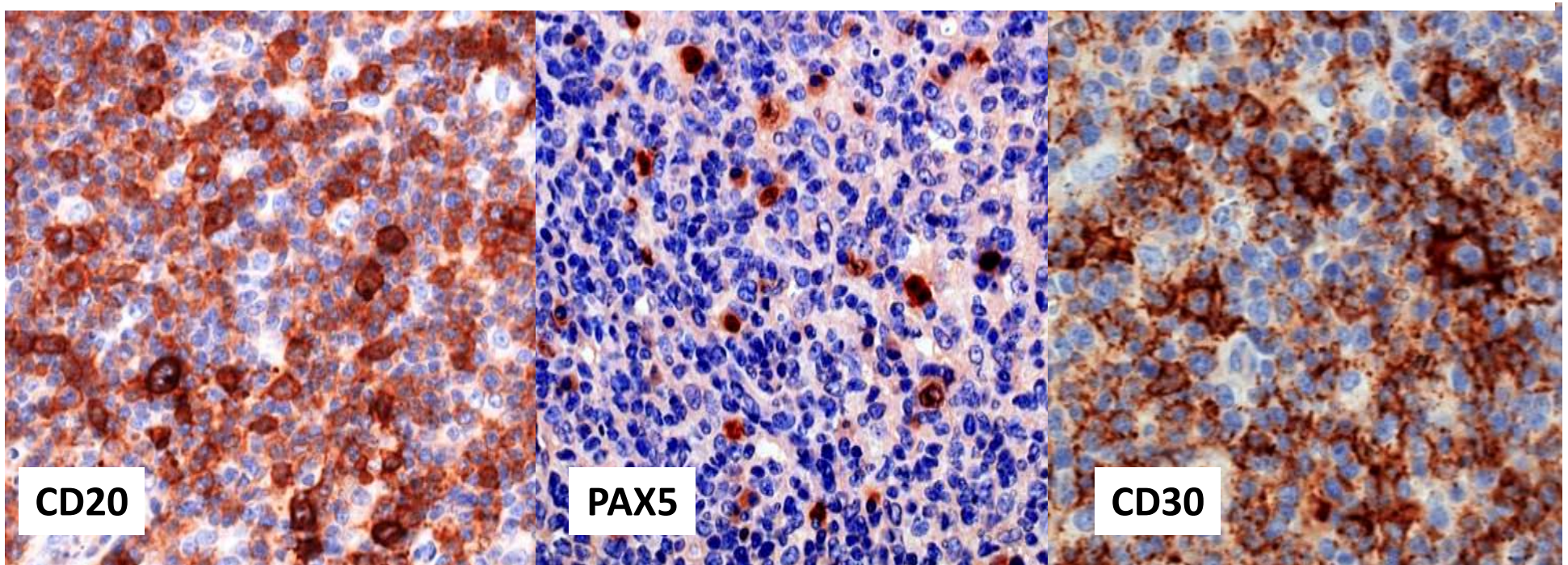


CD4

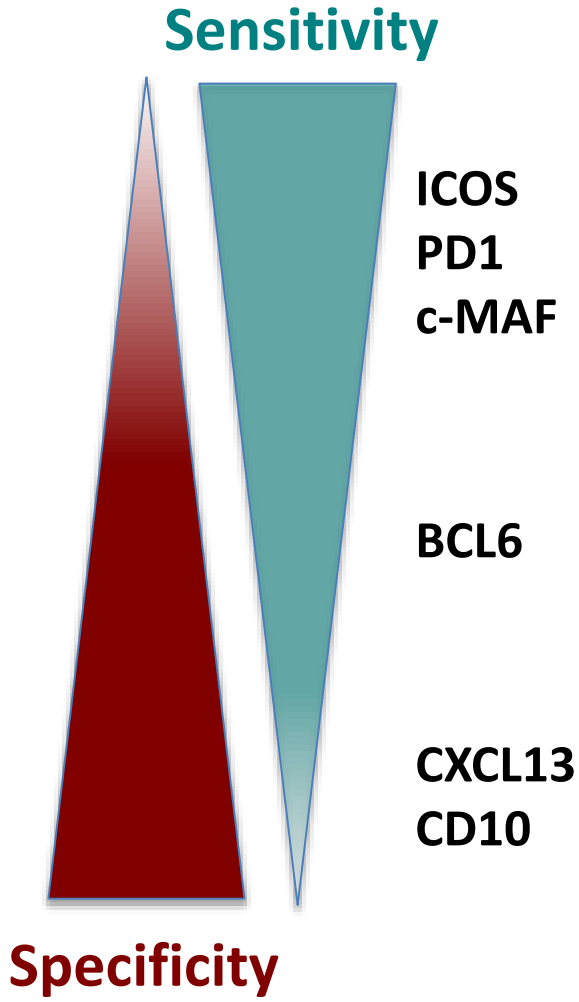


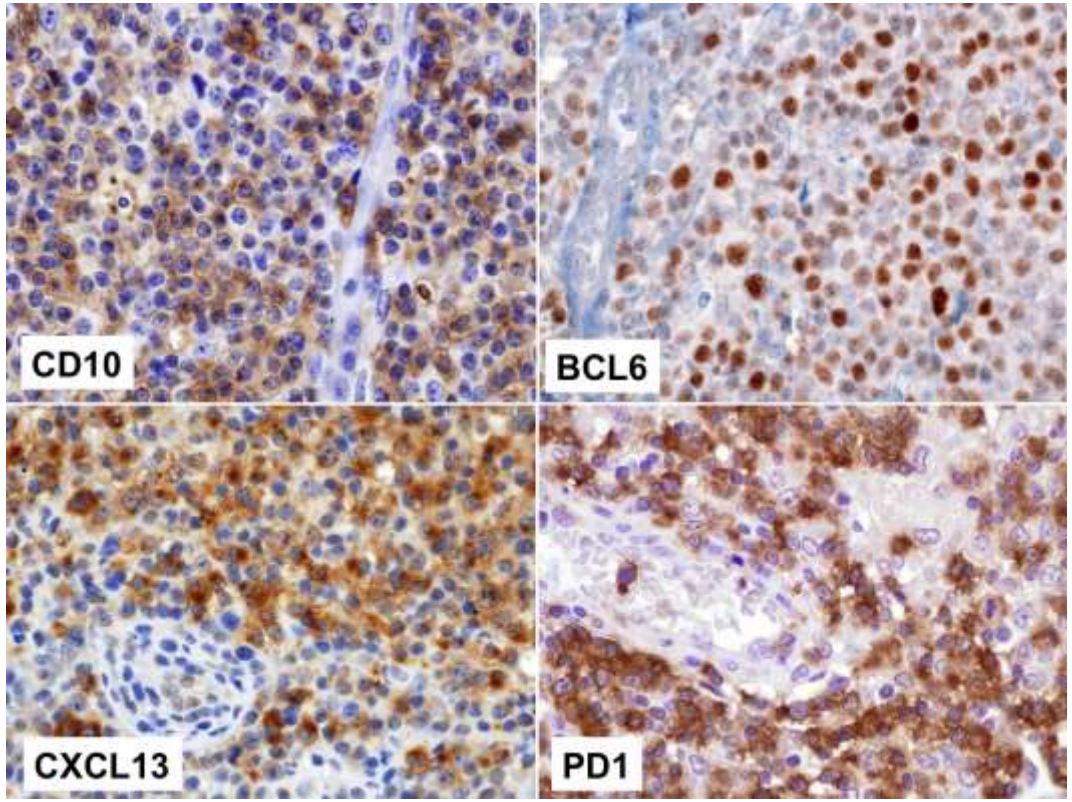


AITL with aberrant immunophenotype



Immunohistochemistry for T_{FH} cell markers

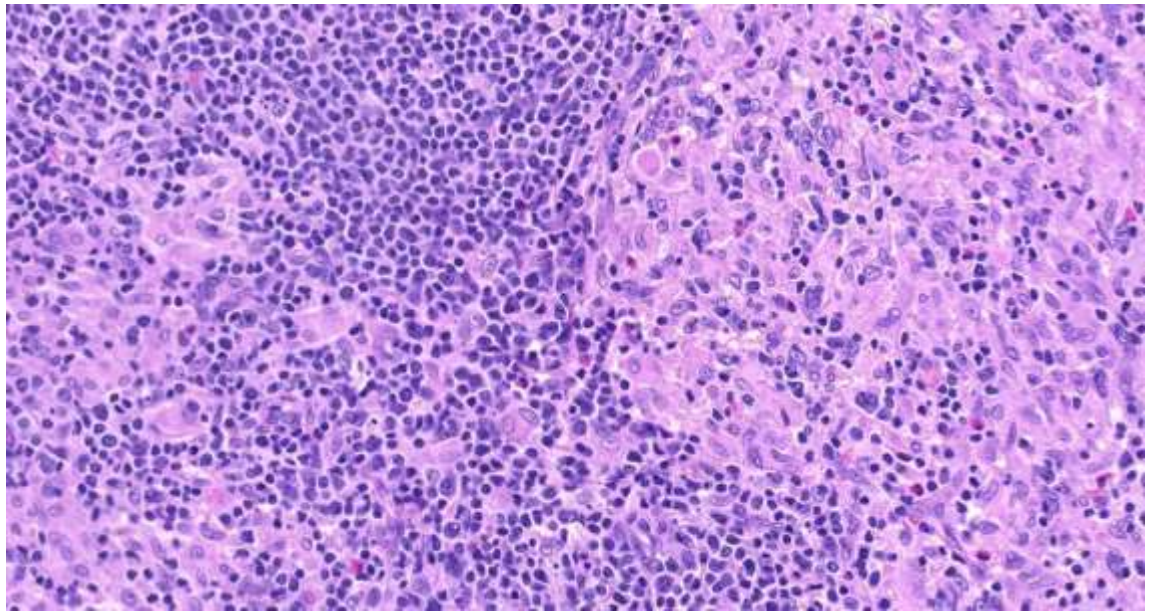


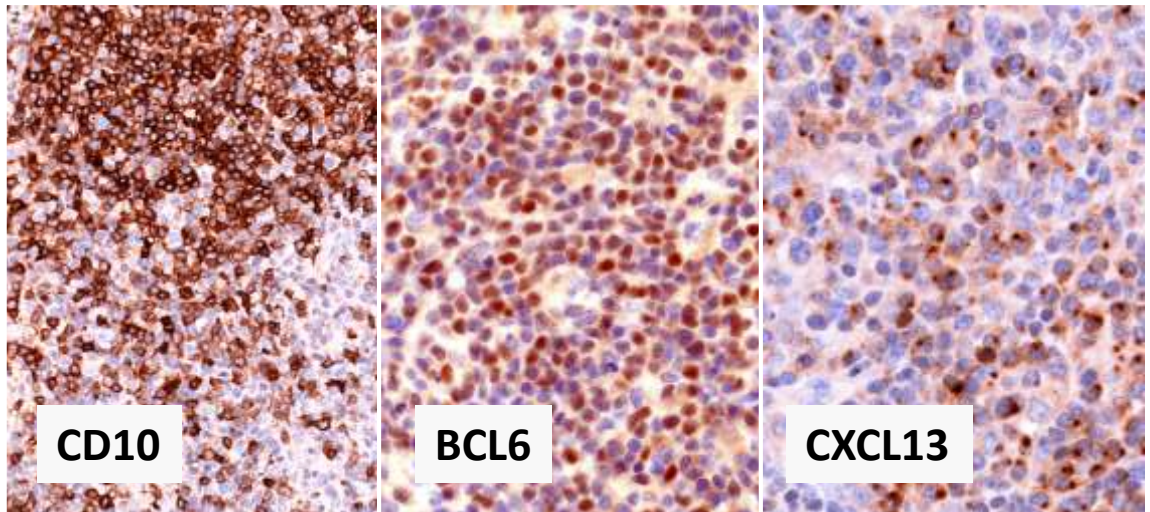


A combination of several markers (3 or more) must be used
CD10 most often stains only 10-30% tumor cells
Other markers usually produce a more extensive staining
Compare to staining intensity in normal GC (PD1)

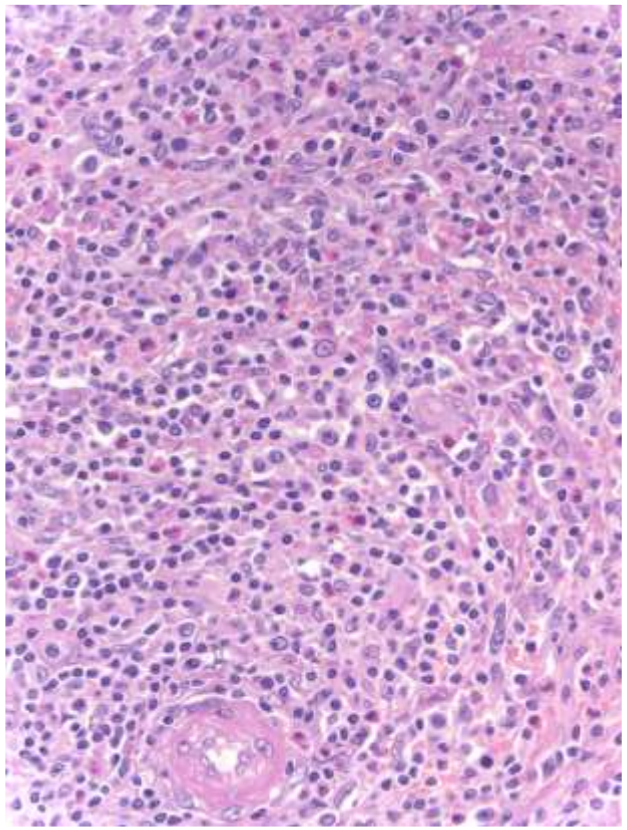
Epithelioid cell –rich lymphoproliferations

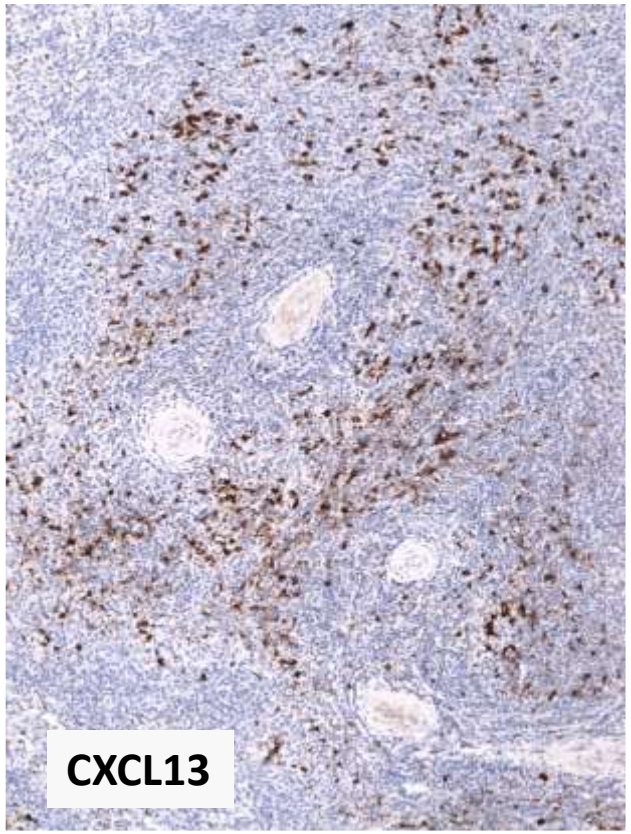
- Lennert lymphoma
- AITL
- T-cell/histiocyte rich LBCL

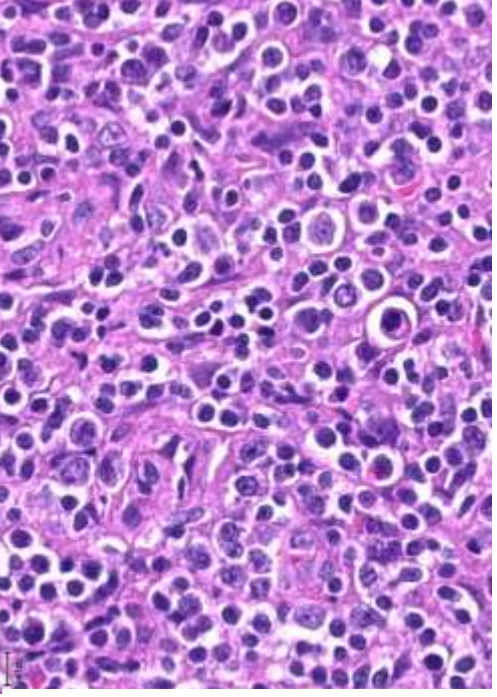


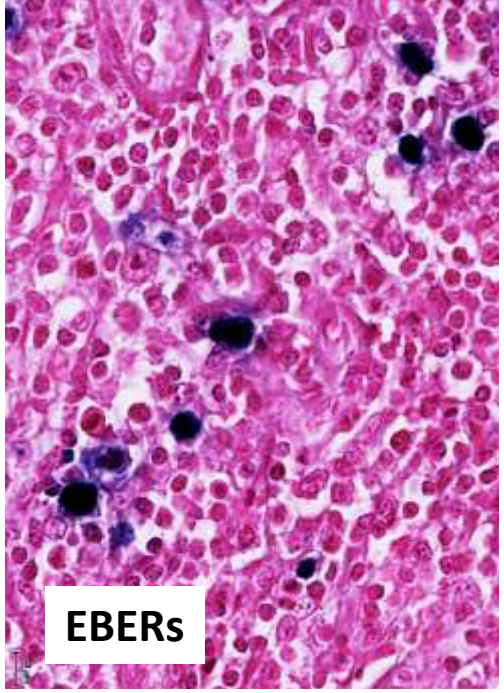


TFH markers helping identification of AITL in extranodal sites

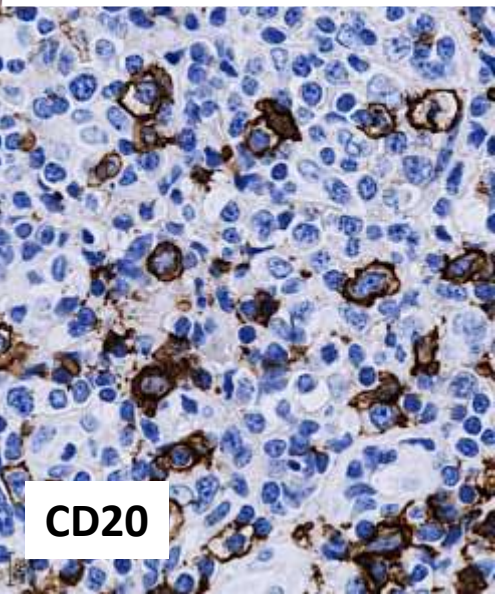


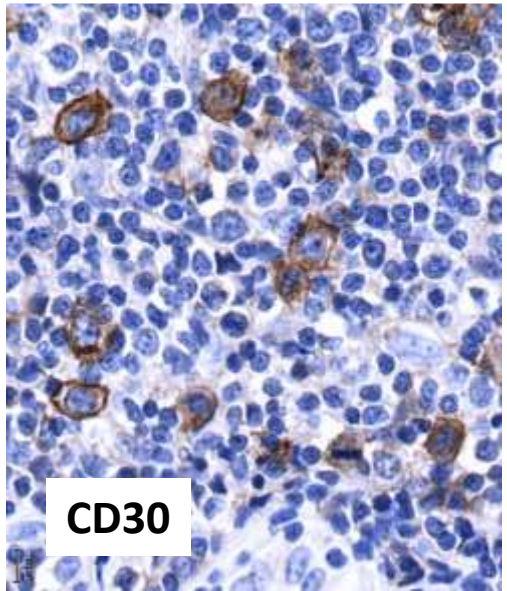






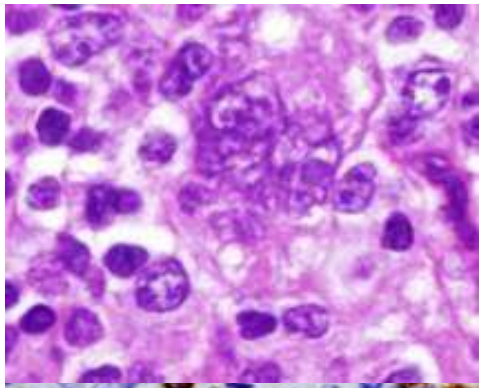
Scattered EBV-positive (or negative) B-cell immunoblasts in >90% cases

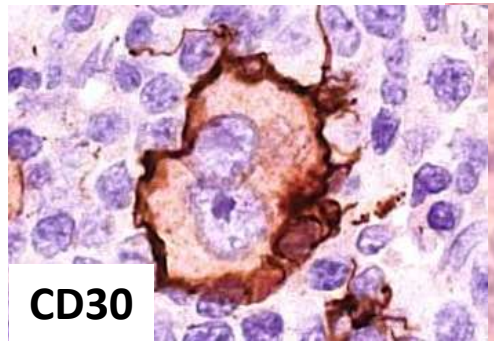


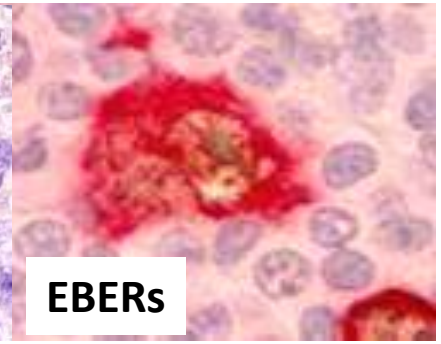


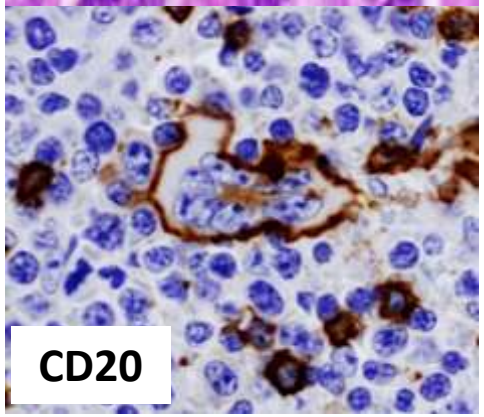
Differential diagnosis: AITL versus EBV+(-) cHL

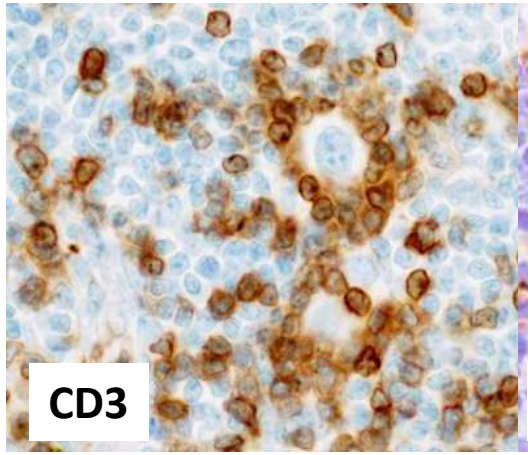
- **AITL-associated blasts may resemble HRS cells**
- CD30+ CD15-/+ CD20 +/- PAX5+ EBV+/-
- Rimming of atypical TFH cells around HRS-like cells
- Clonality studies (*TCR* and *IG*)
- No indication to diagnose composite lymphoma

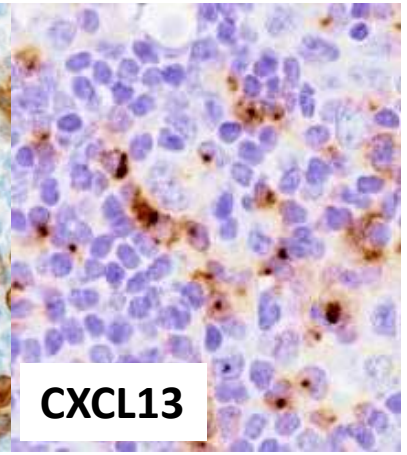


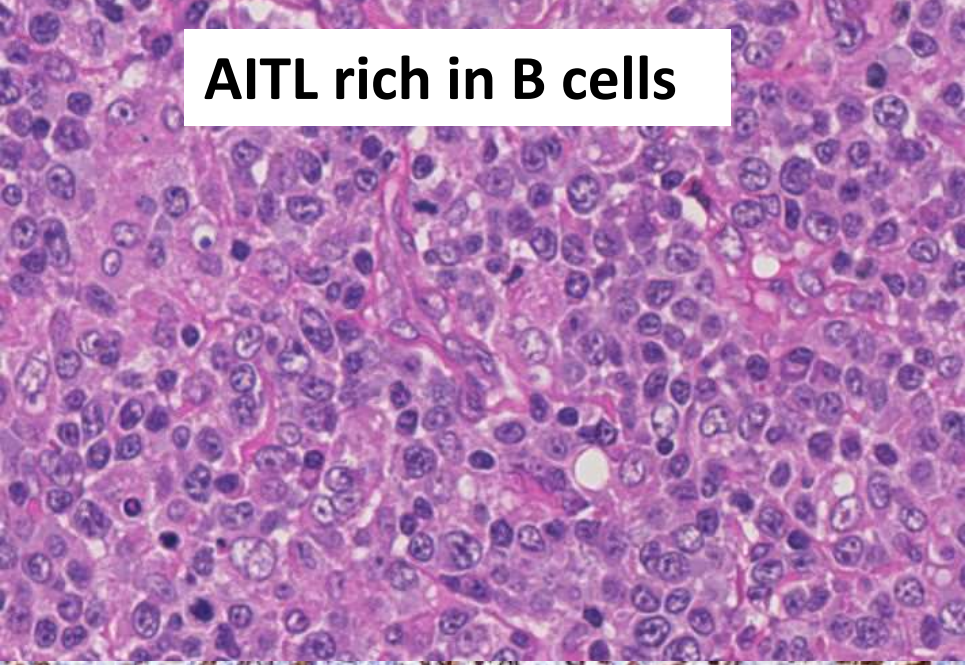


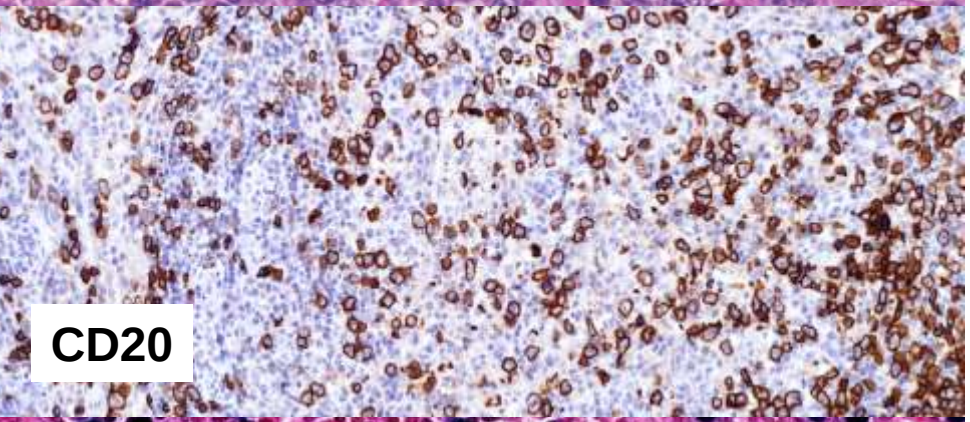


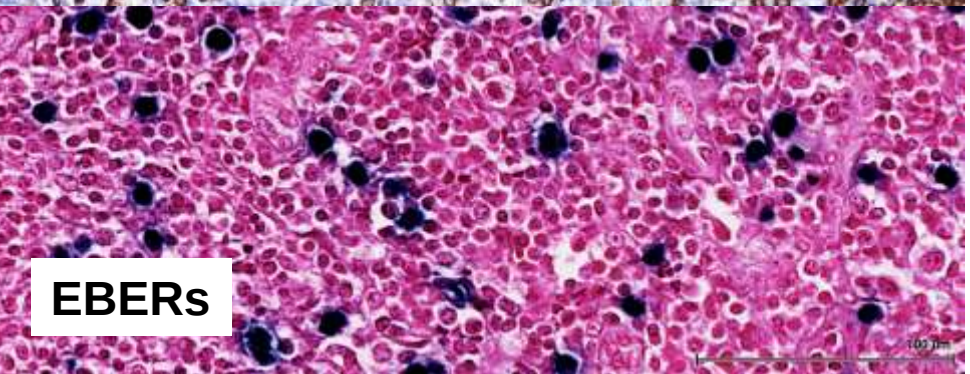


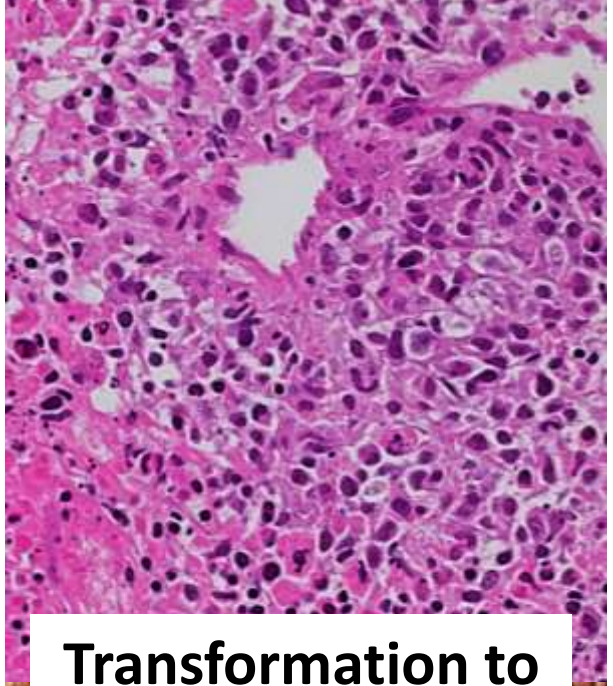




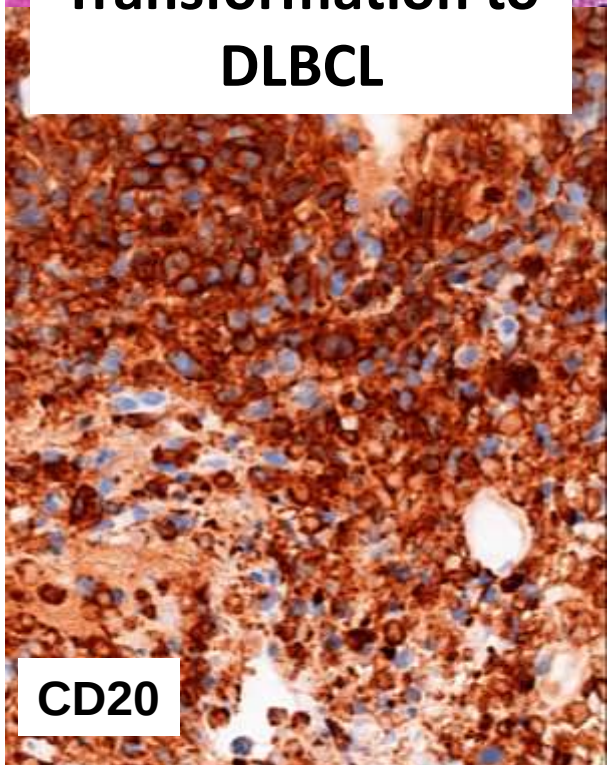


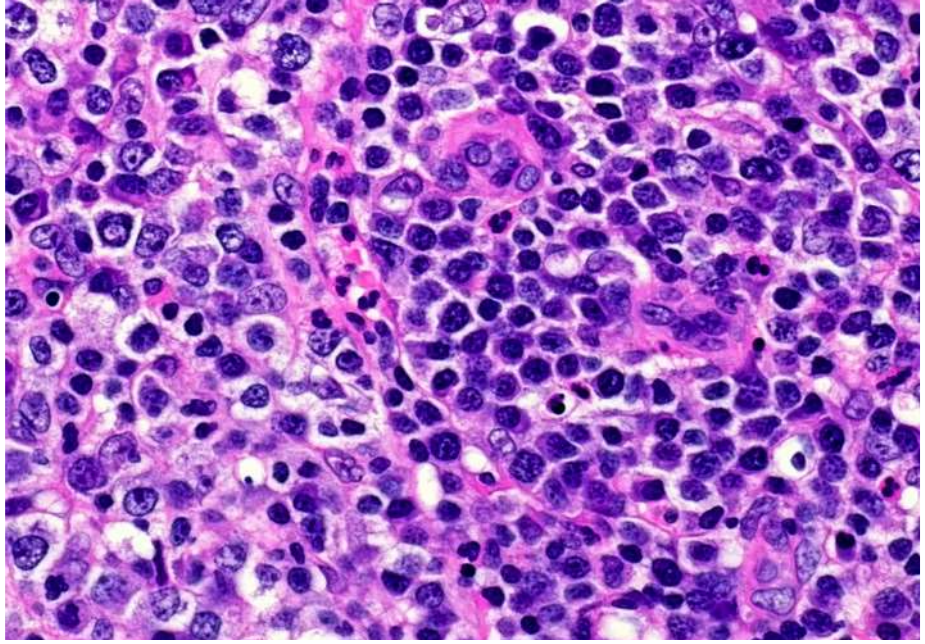




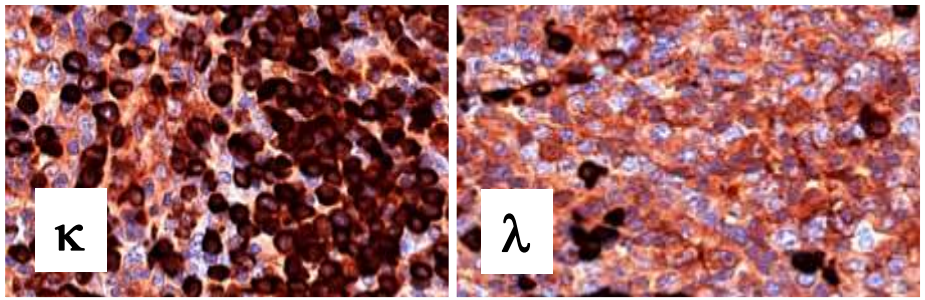


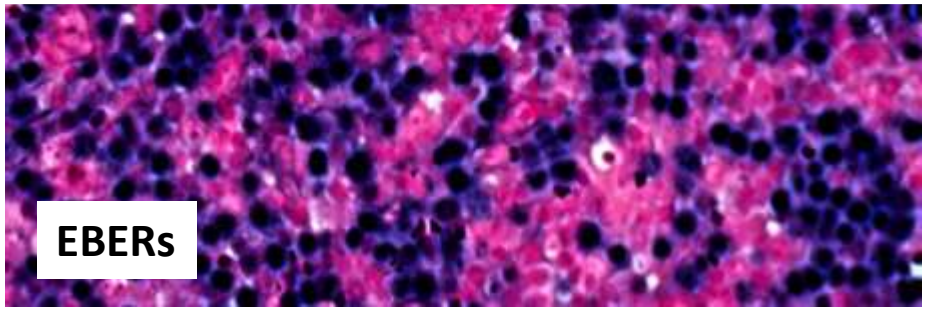
Transformation to DLBCL





AITL with plasma cell proliferation

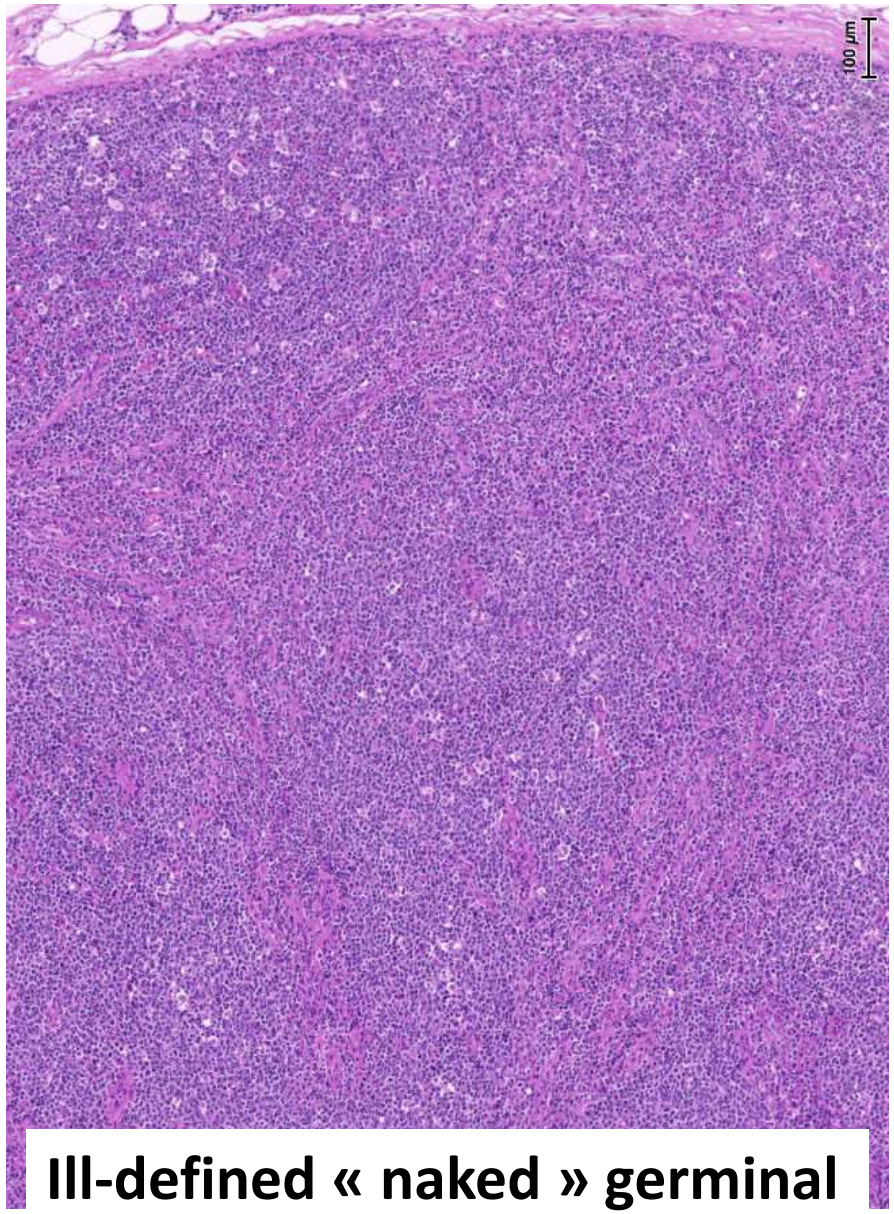




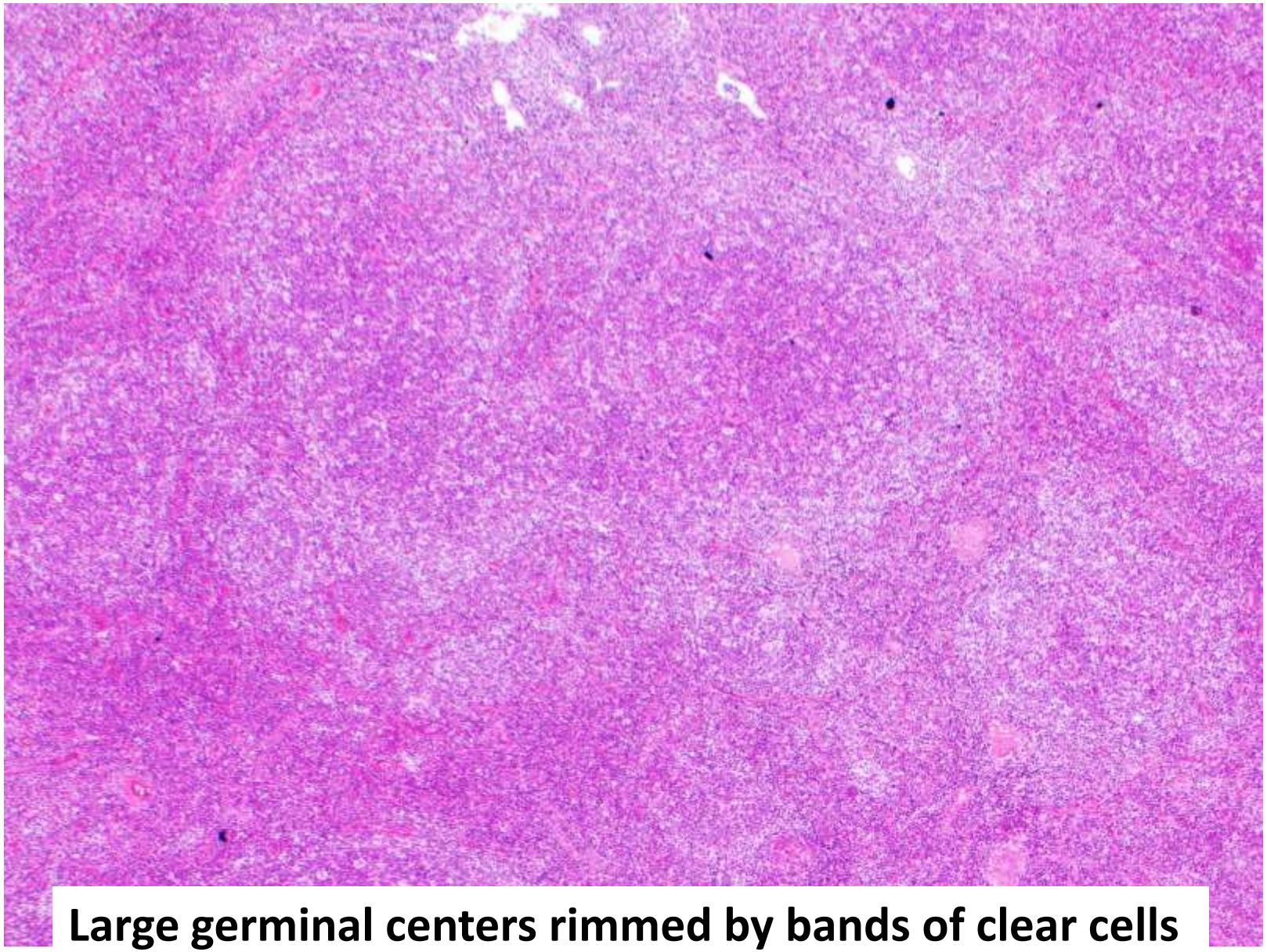
Correlation with monoclonal *IG* rearr.

AITL pattern 1: perifollicular / with hyperplastic follicles

Differential diagnosis: reactive lymphadenopathy; marginal zone lymphoma

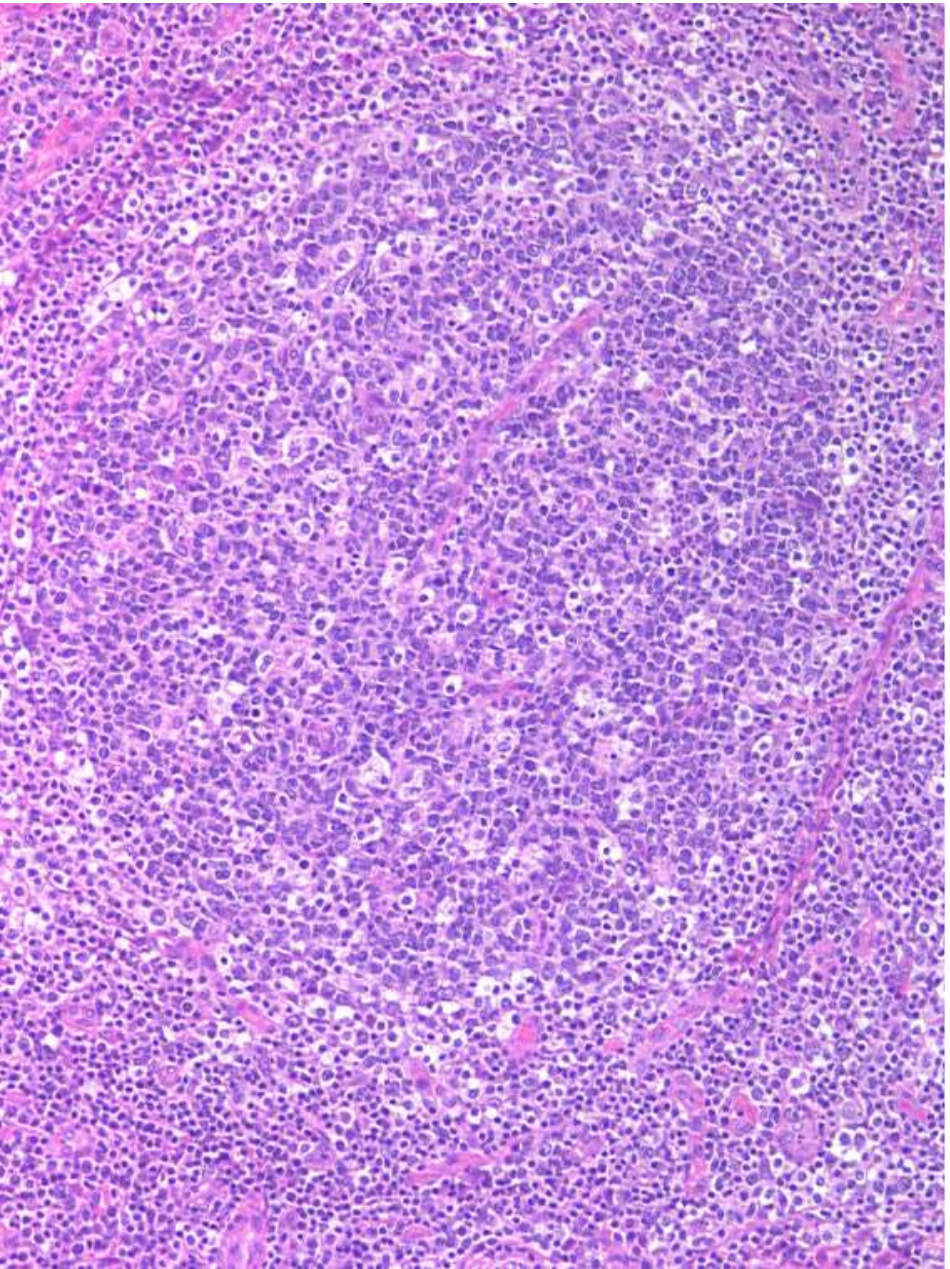


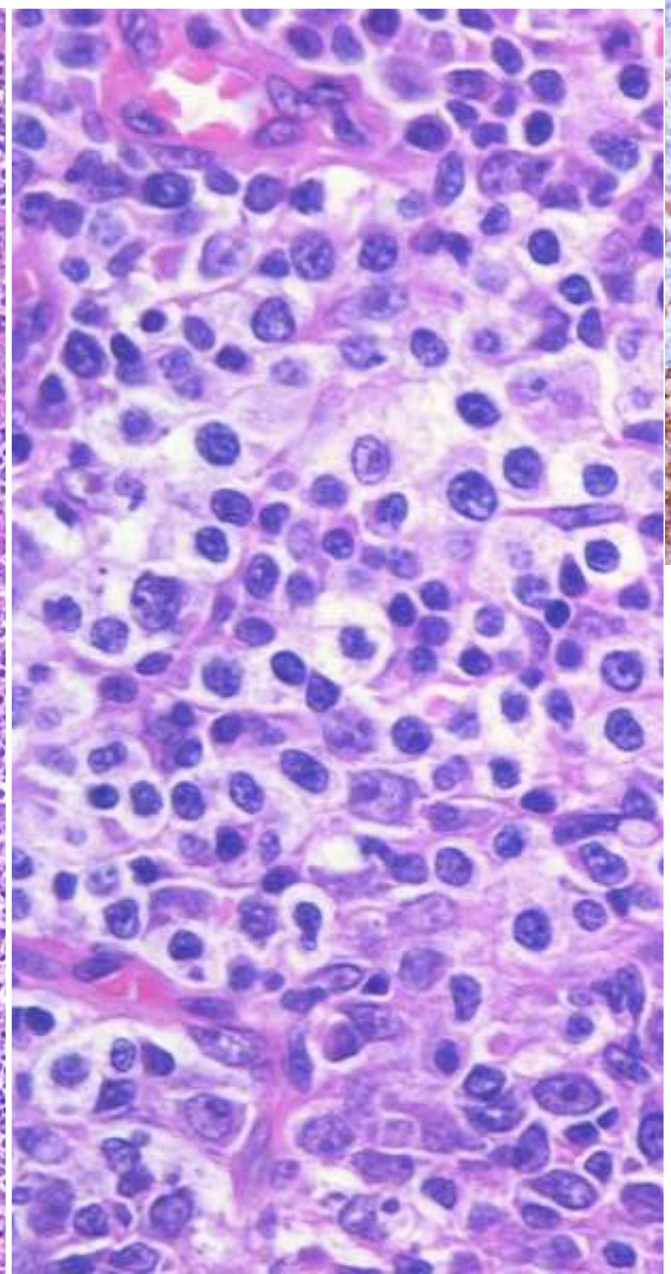
Ill-defined « naked » germinal

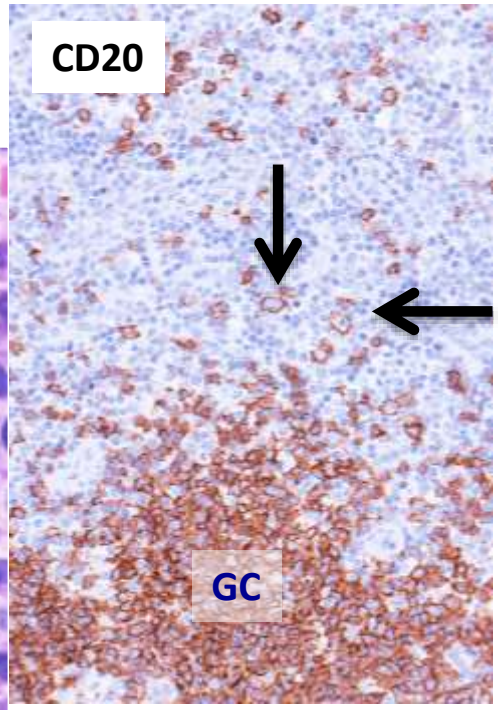


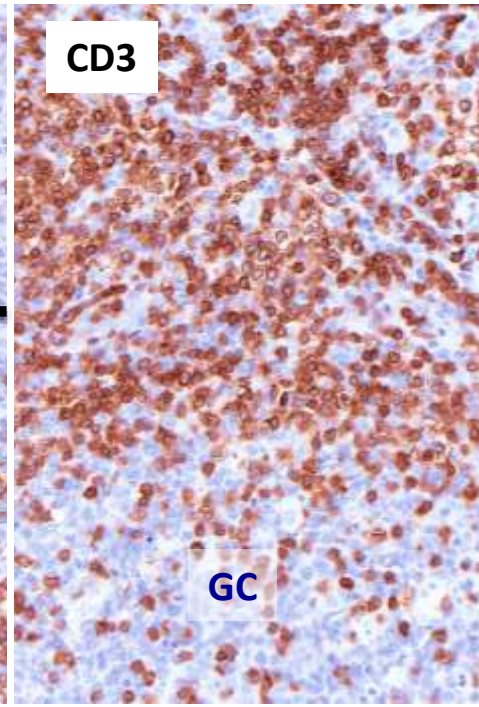
Large germinal centers rimmed by bands of clear cells

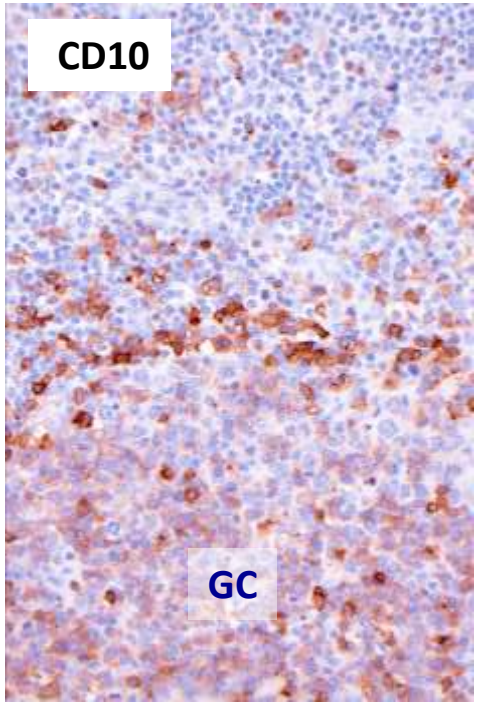
AITL pattern 1: perifollicular with hyperplastic follicles

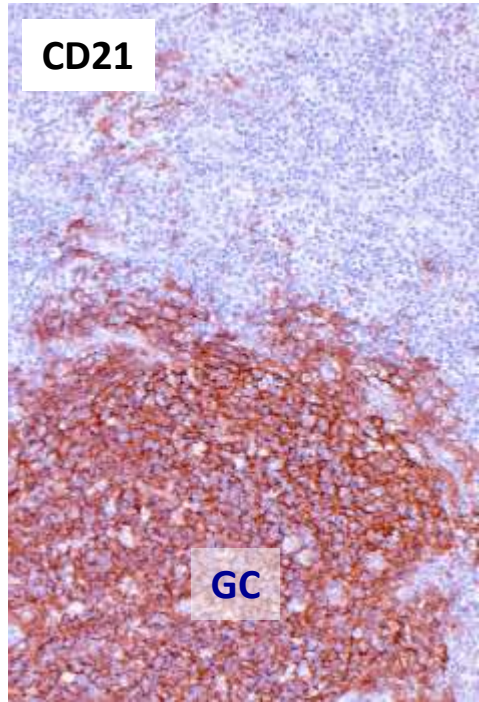




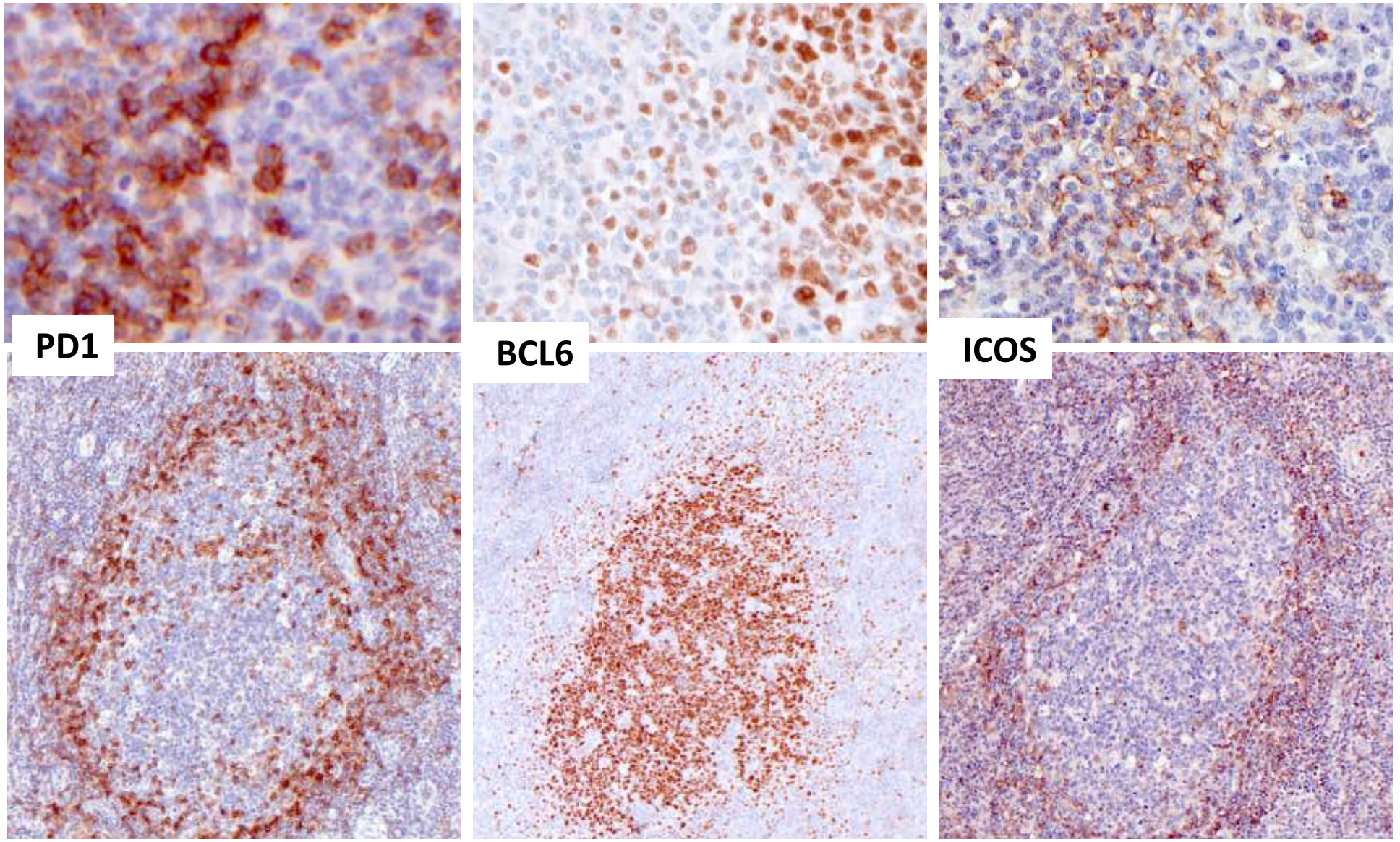








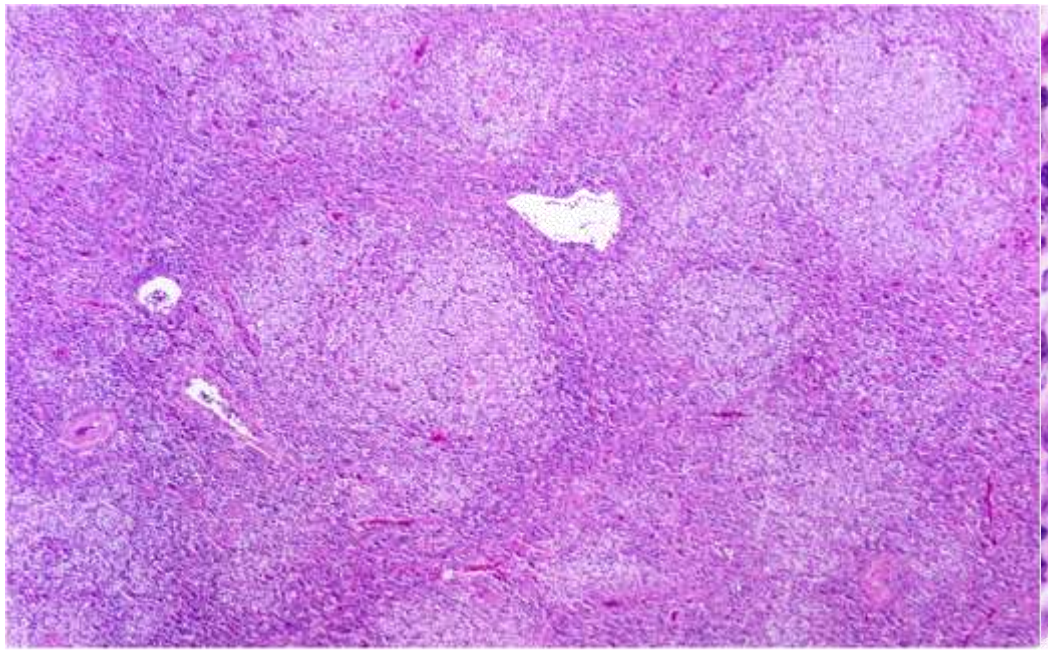
AITL pattern 1: perifollicular/with hyperplastic follicles: utility of TFH markers

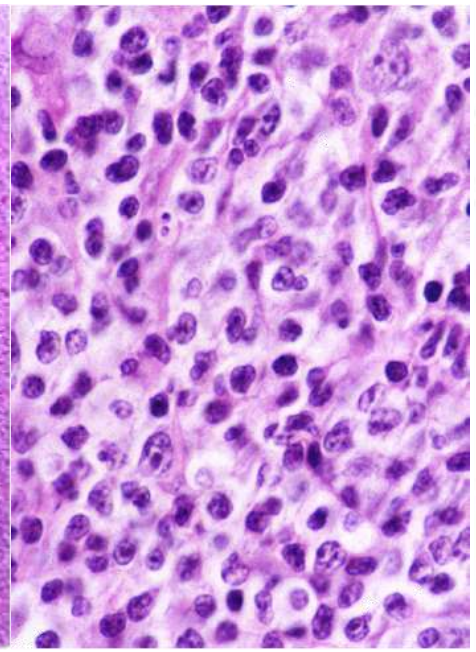


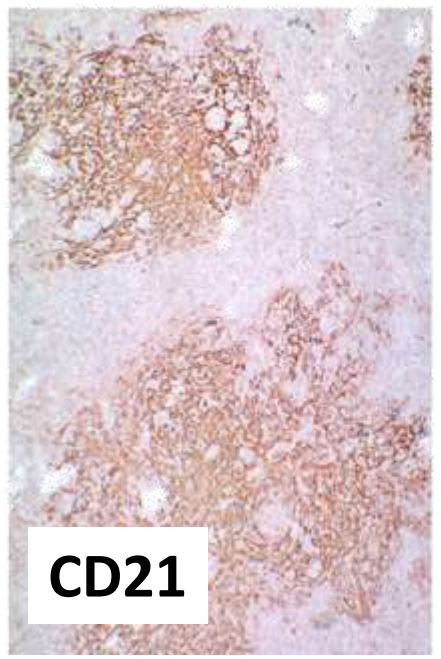
early morphological phase / partial involvement

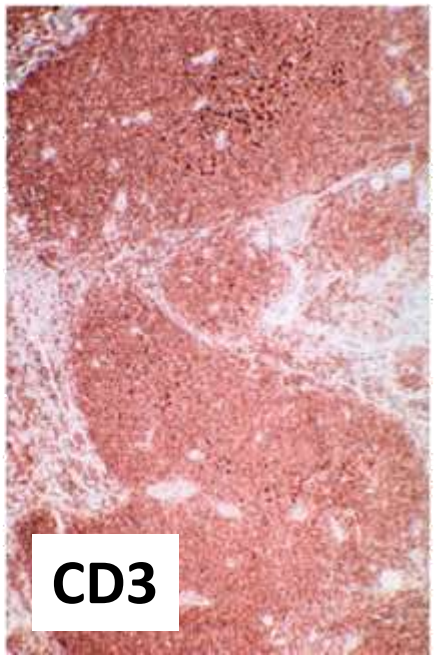
Not early stage, many patients already have clinically advanced stage disease

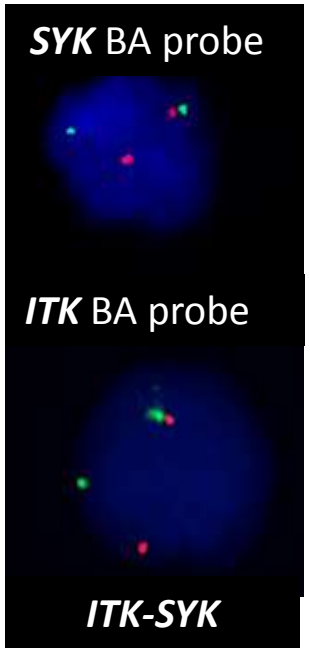
F-TCL: Follicular lymphoma-like

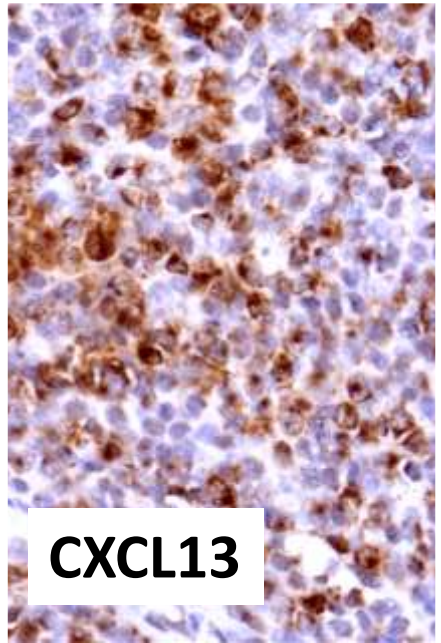


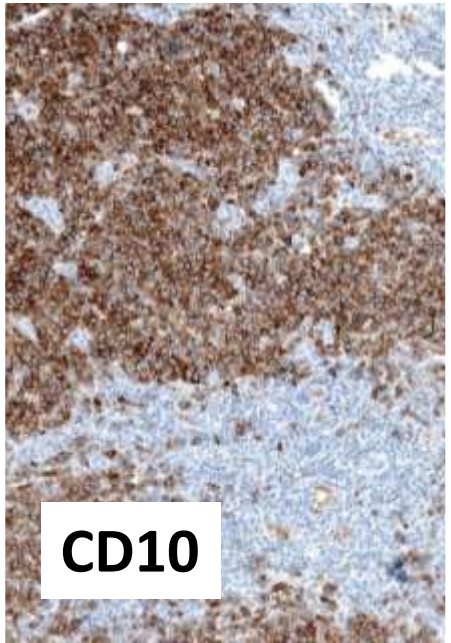








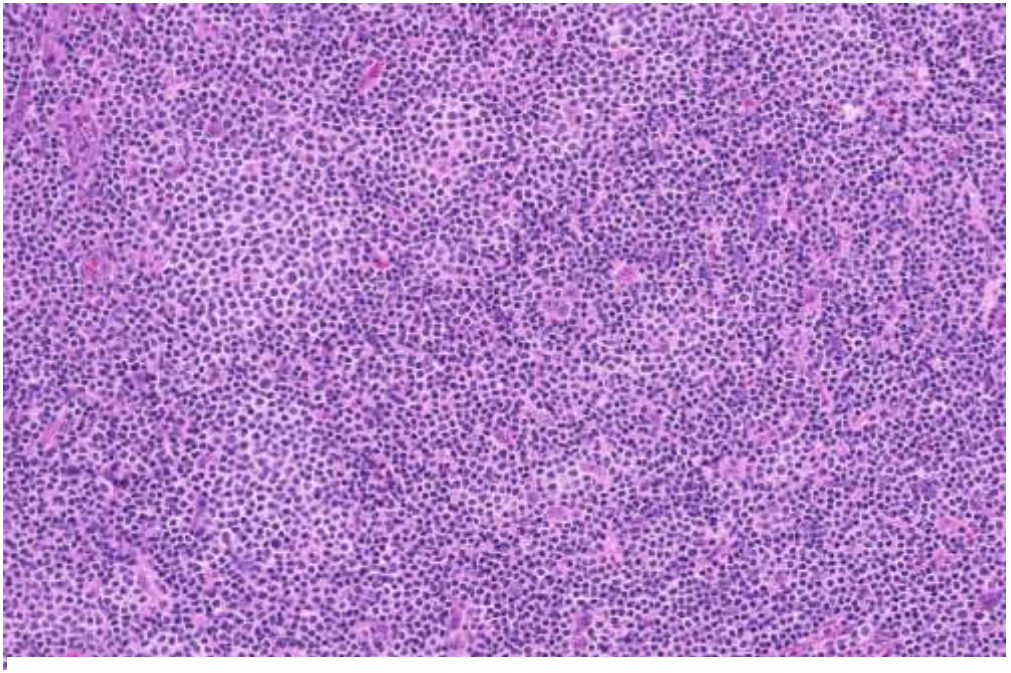


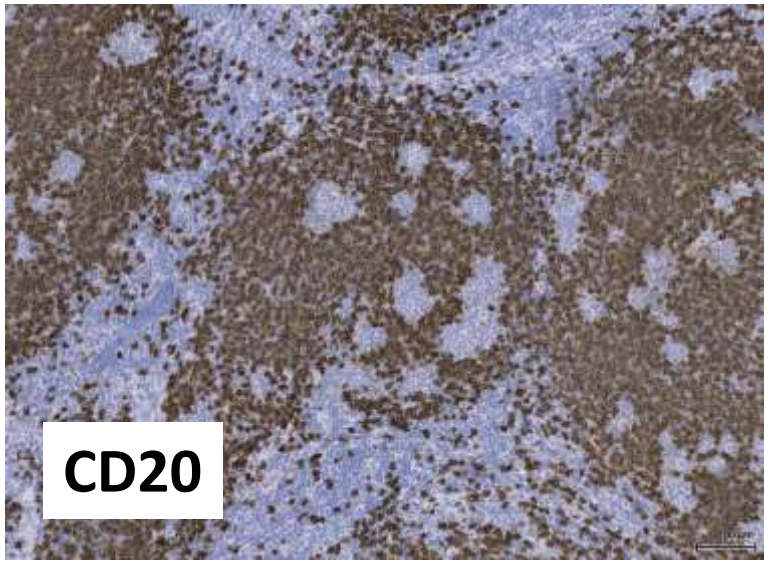


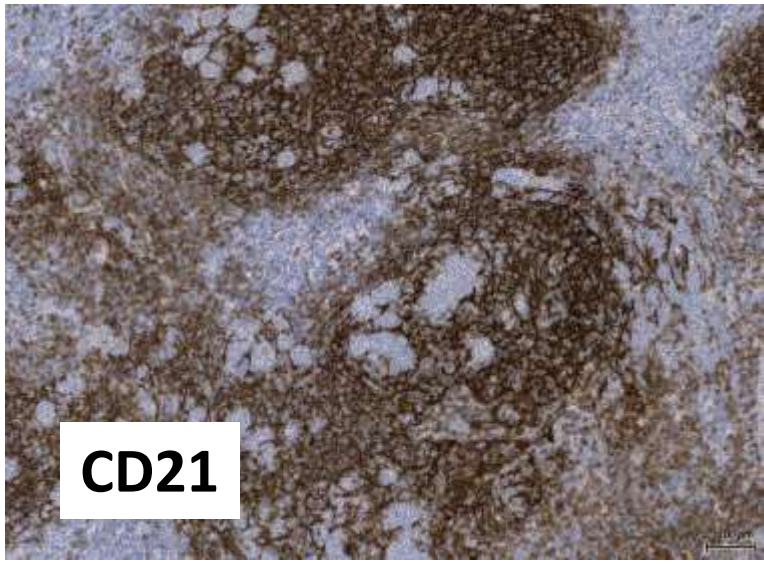
Differential diagnosis

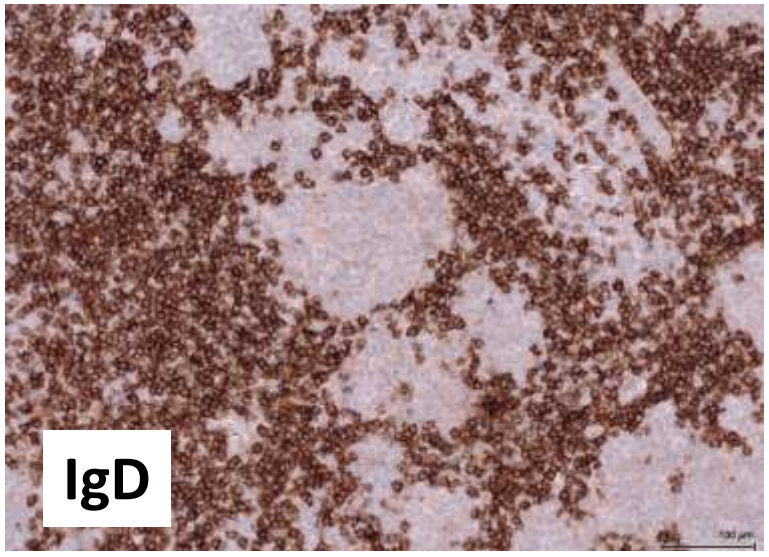
- (B-cell) follicular lymphoma: IHC; confirm T-cell phenotype by several T-cell markers; clonality studies
- Overlapping feaures with AITL

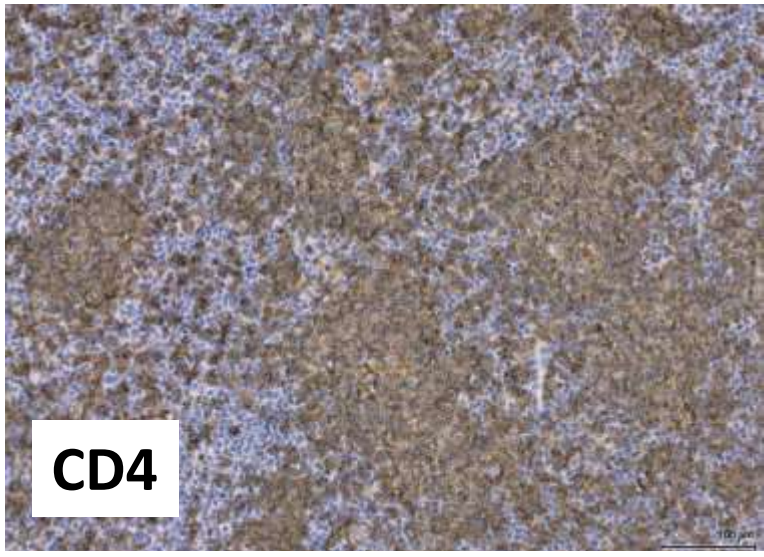
F-PTCL: PTGC-like cellular aggregates within expanded mantle zones



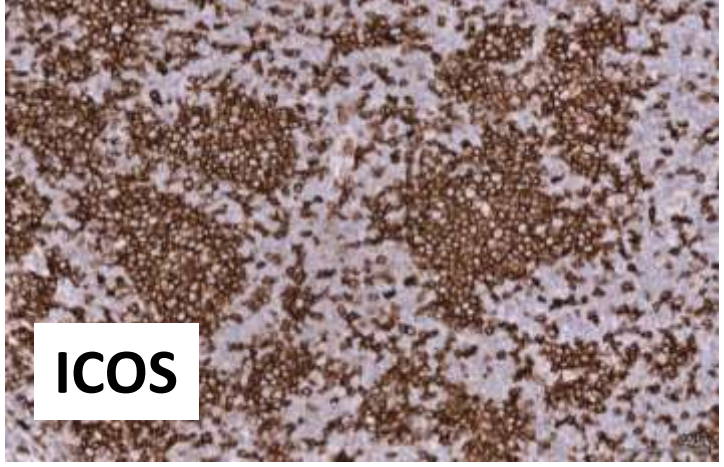


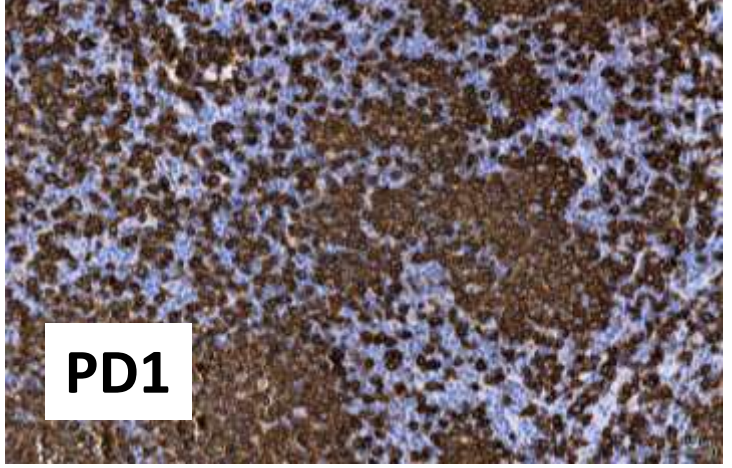


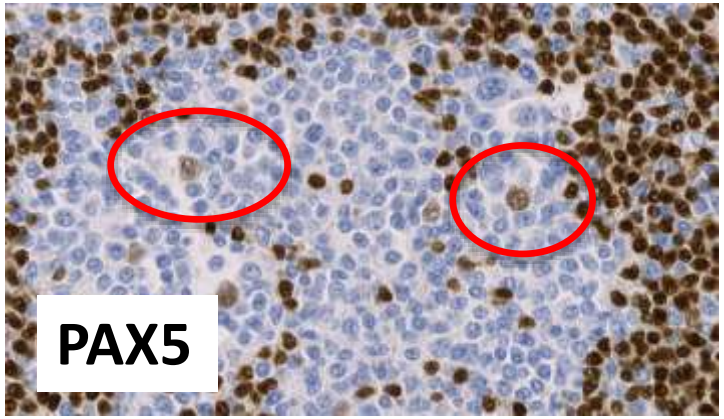


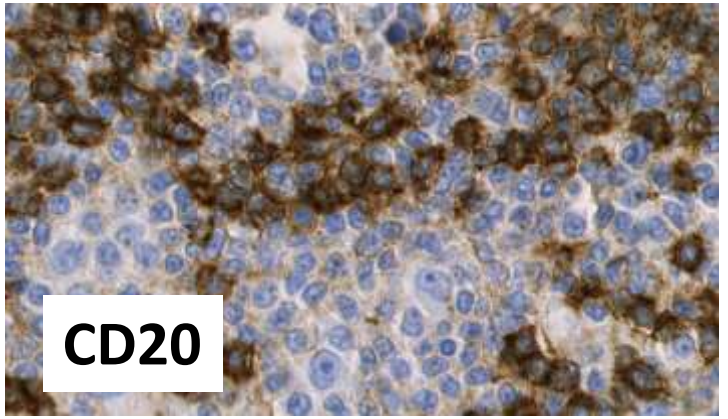


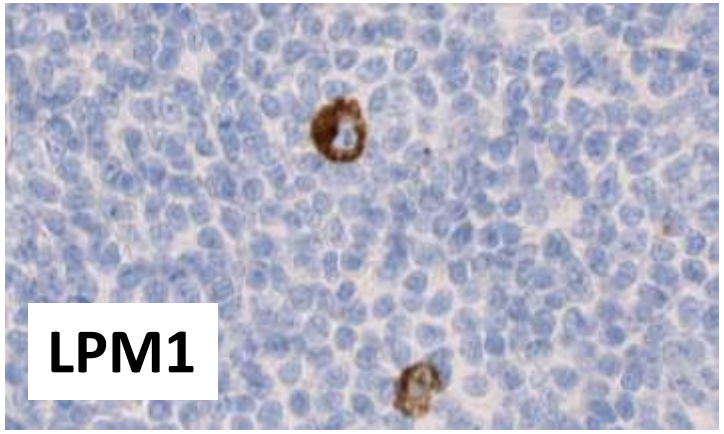
Differential diagnosis: PTGC, NLPHL, small B-cell lymphoma (MZL)

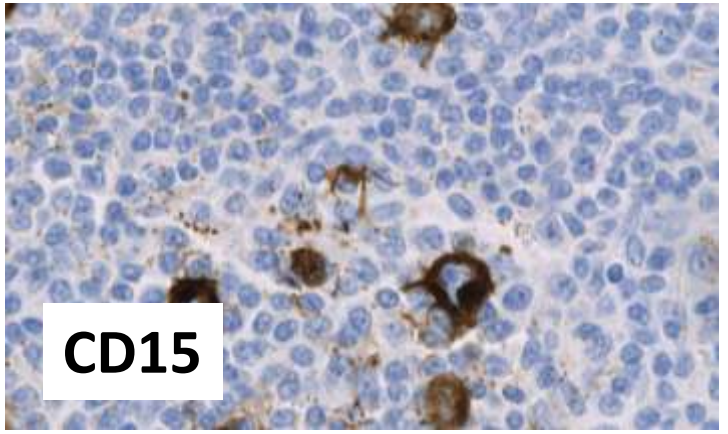








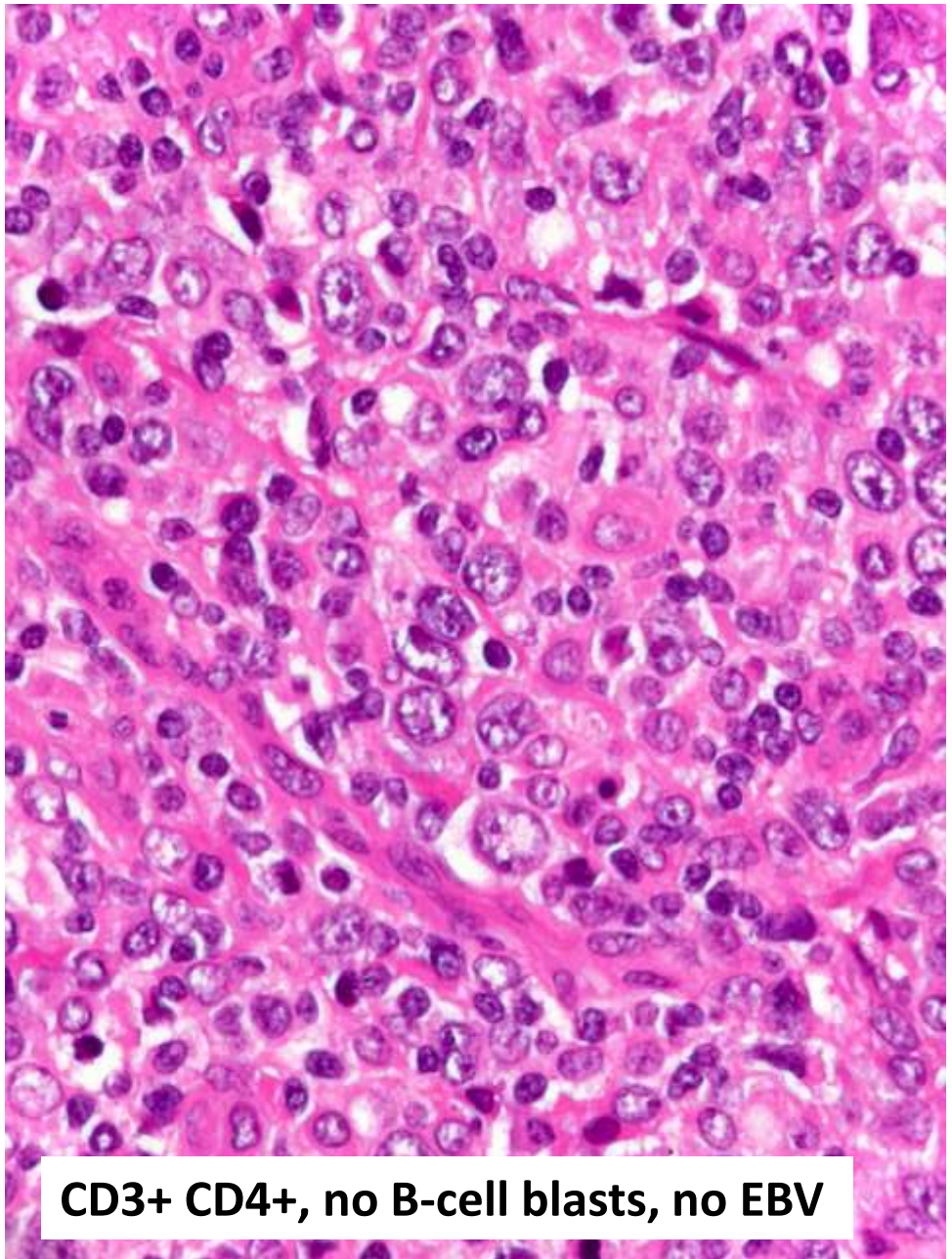


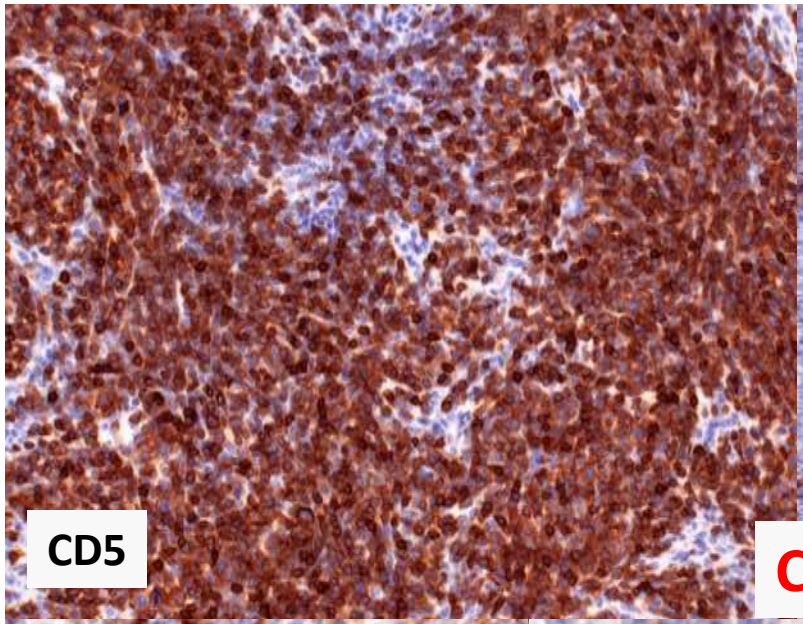


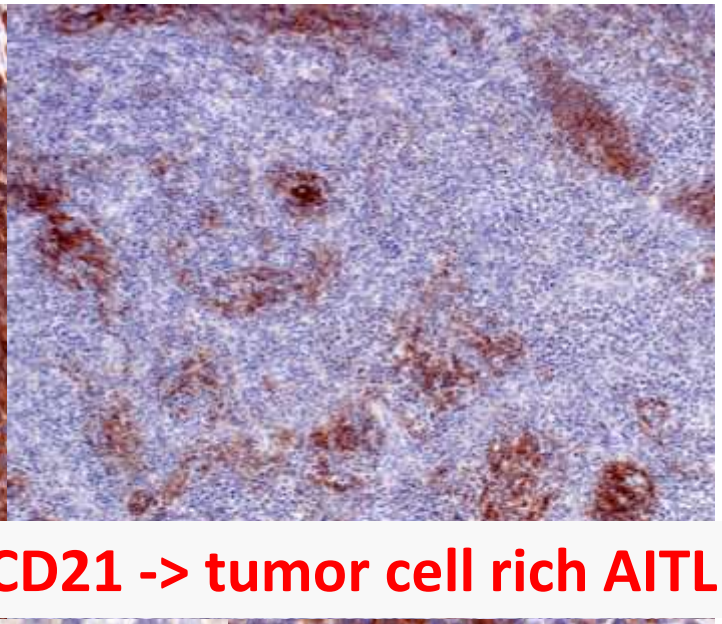
F-PTCL: PTGC-like

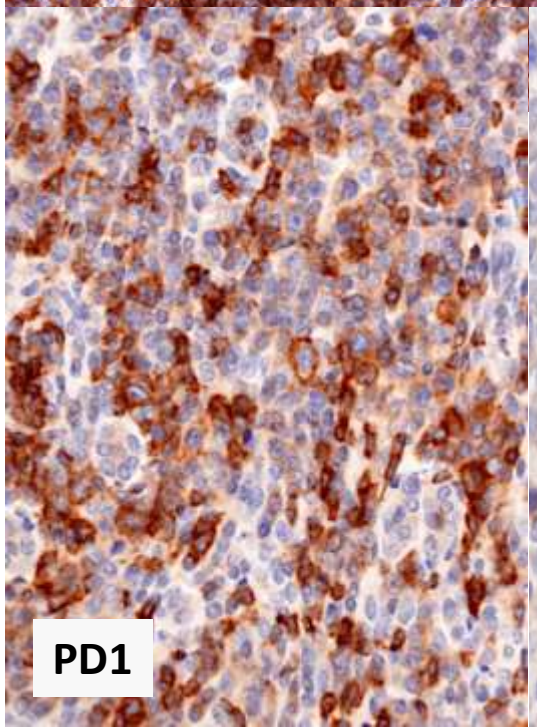
Differential diagnosis: classical HL

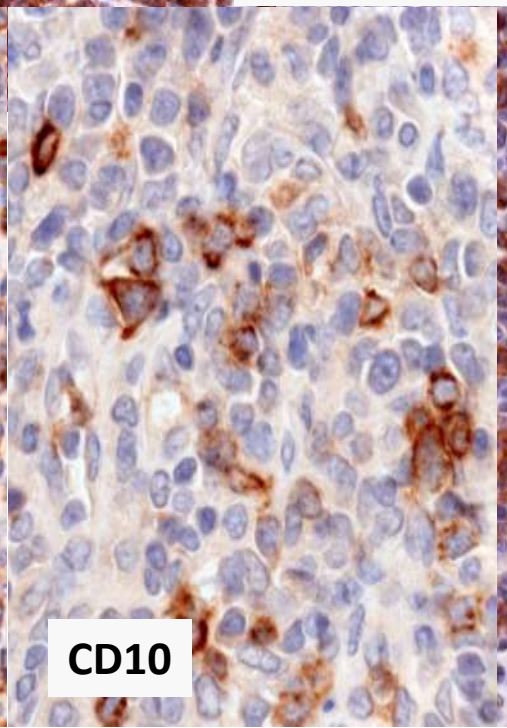
58 y-old M, LN biopsy sent for review as PTCL NOS -> Nodal PTCL with TFH phenotype

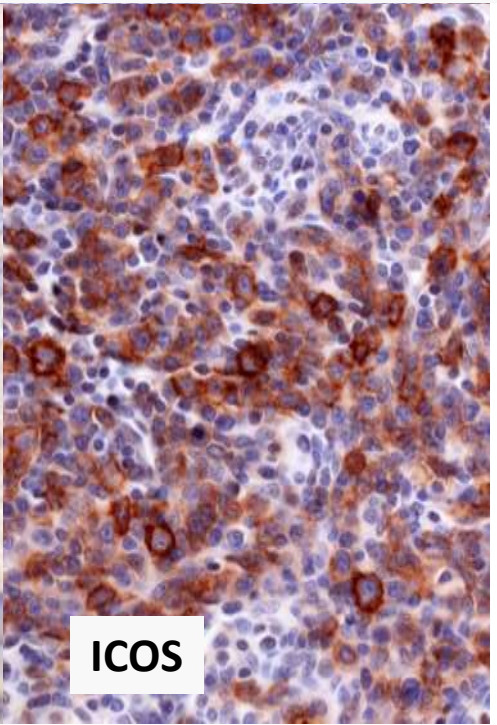




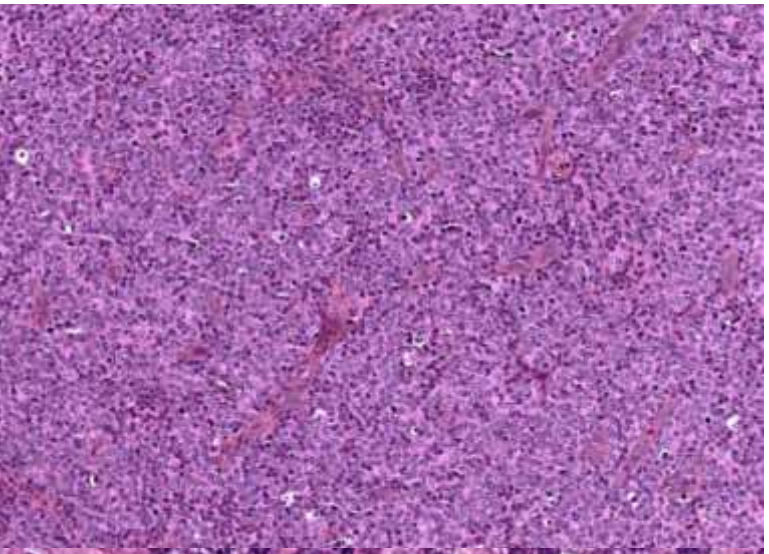


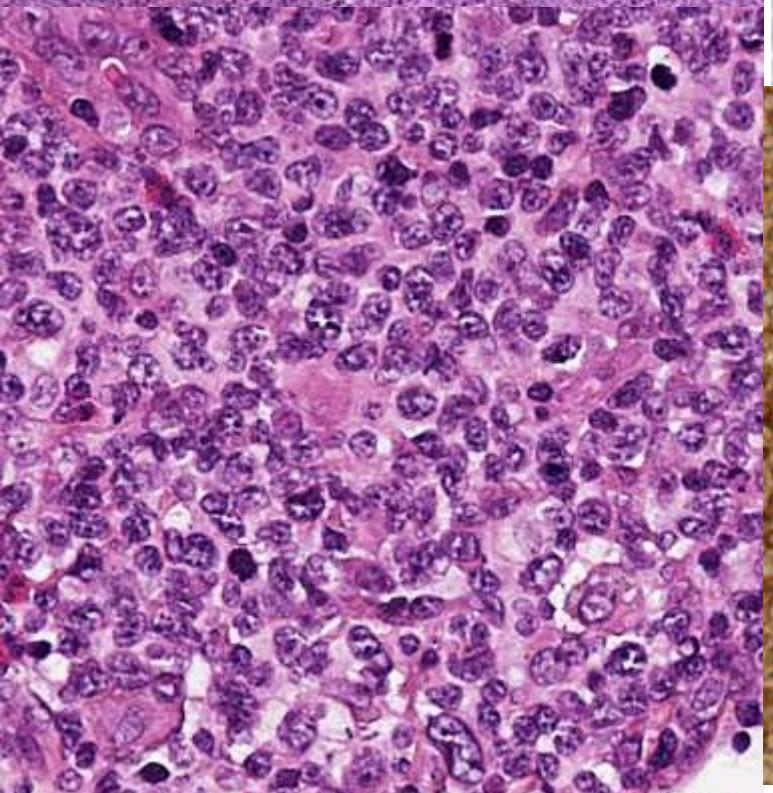


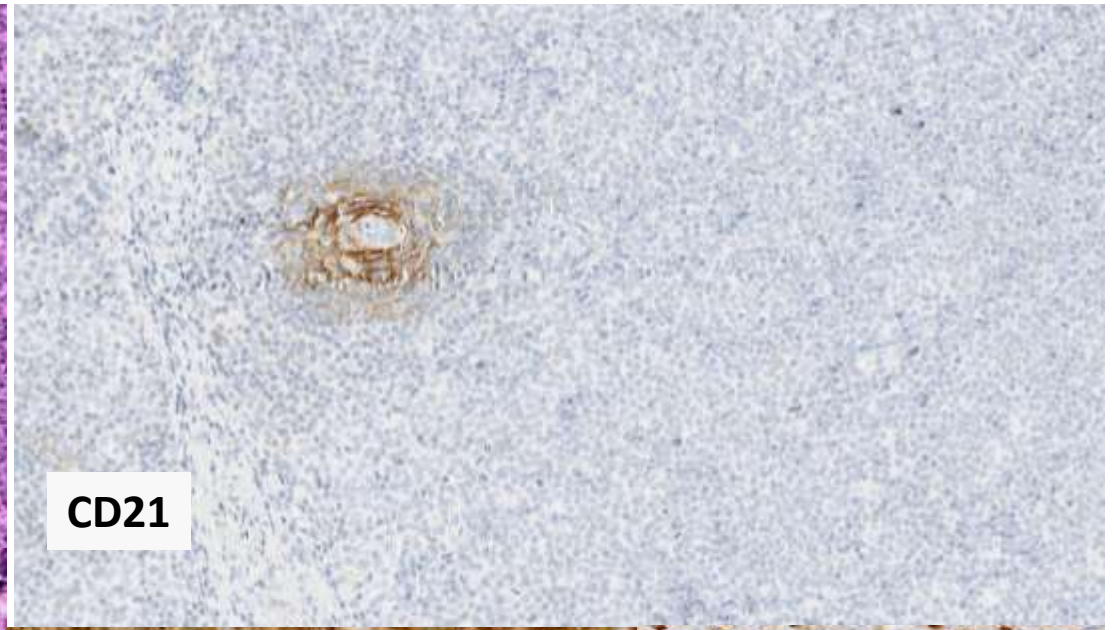


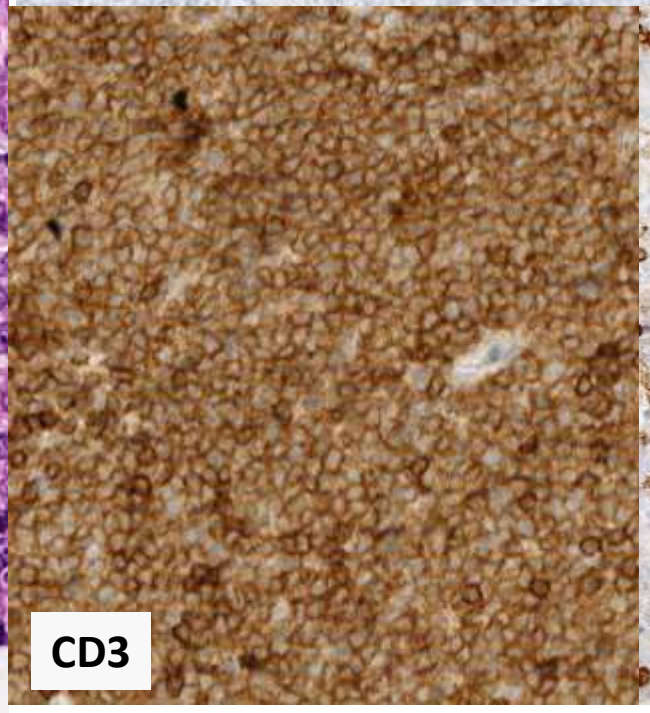


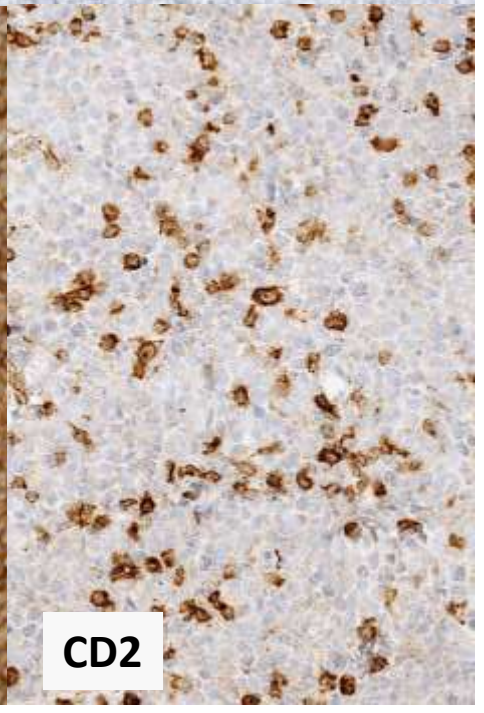
Nodal PTCL with TFH phenotype

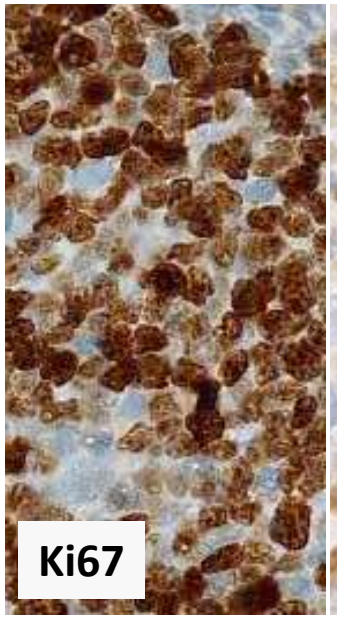


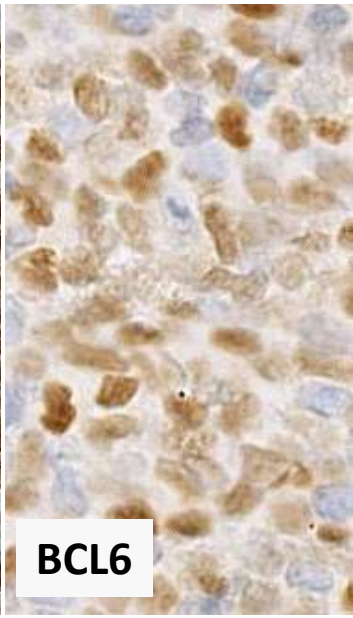


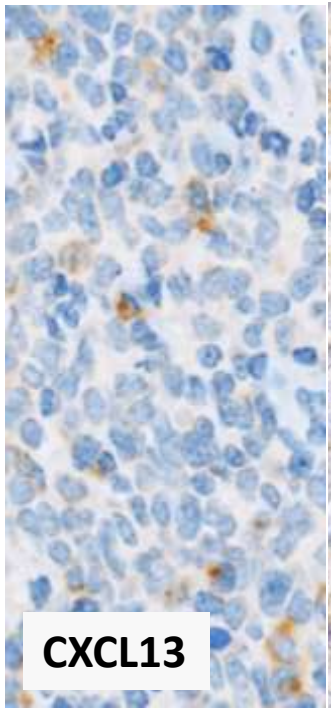


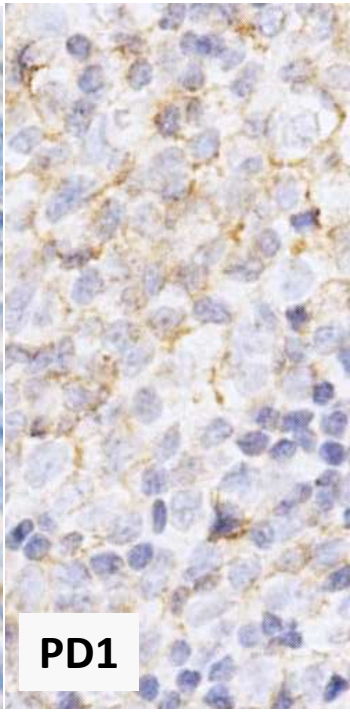












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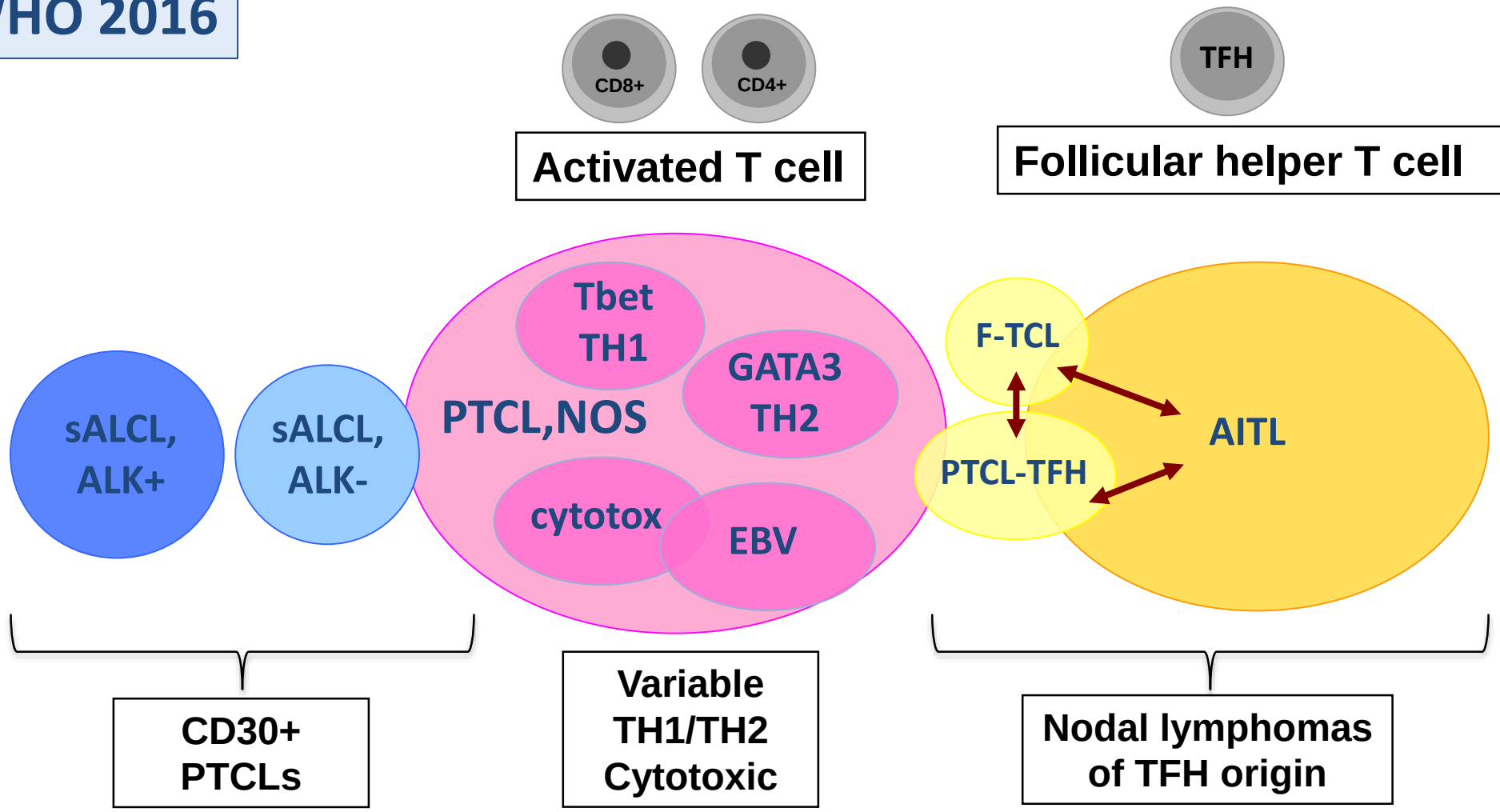

AITL : angioimmunoblastic T-cell lymphoma
F-TCL: follicular T-cell lymphoma
PTCL-TFH: nodal PTCL with TFH phenotype

Concluding remarks

- AITL is the most common PTCL and exhibits a wide pathological spectrum
- Importance of FDC expansion as a diagnostic criterion for AITL, TFH markers for identification of morphological variants and spectrum of neoplasms derived from TFH cells
- AITL and F-TCL must be distinguished from reactive and neoplastic mimics
- Nodal PTCLs must be explored for expression of TFH imarkers, as PTCL-NOS category excludes nodal PTCL with TFH phenotype
- Molecular testing
  - Clonality analysis
  - Identification of molecular aberrations (*RHOA, TET2, IDH2*, others..) as an adjunct to diagnosis

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