Integrated approach to PTCL diagnosis

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APOYO

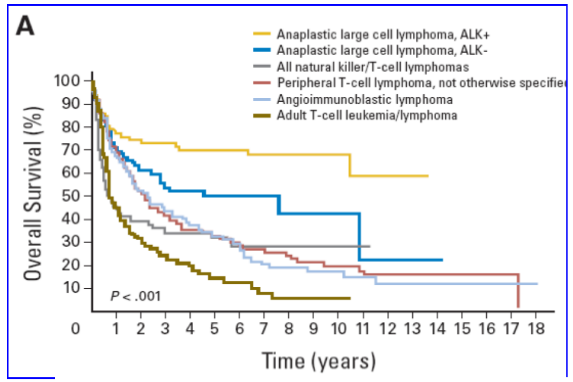
PTCL : yet a diagnostic challenge & an unmet medical need

✓ Rare diseases (geographic variations)
✓ Great clinico-pathologic heterogeneity
✓ >30 entities in the updated classifications

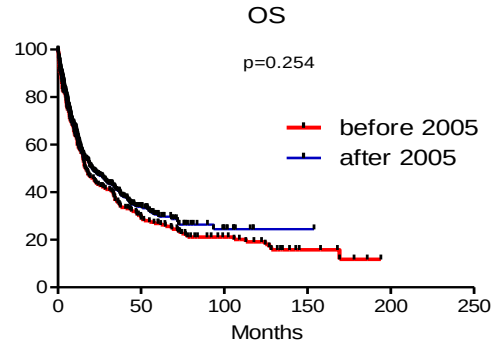
Diagnostic challenges

- Tumors cells can be sparse, abundant reactive infiltrate, ± respect of the architecture
- Tumors cells can be accompanied by atypical cells of other lineage, (ex HRS-like cells in TFHL)
- Patients can present clinically without obvious tumor

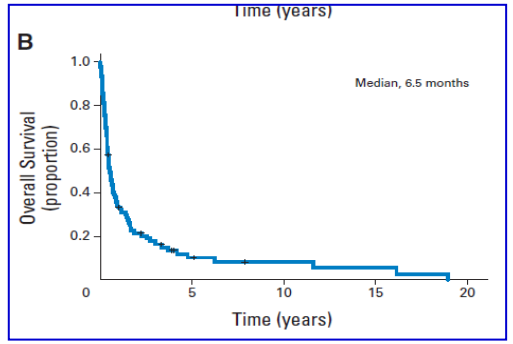
Unmet medical need



International T-cell lymphoma project, J Clin Oncol, 2008



TENOMIC cohort (569 pts, *unpublished)*



Mak et al. J Clin Oncol, 2013

Classification(s) of mature T- and NK-cell neoplams

Leukemic

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia (LGL)
- Chronic LPD of NK cells
- **Adult T-cell leuk/lymphoma (ATL/L, HTLV1)**

EBV

EBV+ T/NK lymphomas/leukemias

- Extranodal NK/T-cell lymphoma, nasal type
- Aggressive NK cell leukemia
- **Primary nodal EBV+ T-cell/NK-cell lymphoma**

EBV+ T/NK LPDs of childhood

- **Hydroa vacciniforme LPD**
- Severe mosquito bite allergy
- **Chronic active EBV disease**, systemic (T& NK)
- Systemic EBV+ T-cell lymphoma of childhood

Nodal

Follicular helper TCL (TFH Lymph)

- **TFH lymphoma, AITL-type (AITL)**
- **TFH lymphoma, follicular type**
- **TFH lymphoma, NOS**

Peripheral TCL, NOS

ALCL, ALK +

ALCL, ALK –

Breast-implant-associated ALCL

Extranodal

- Extranodal NK/T nasal-type
- **Enteropathy-associated TCL**
- **Type II refractory celiac disease**
- **Monomorphic epitheliotropic intestinal TCL**
- **Intestinal T-cell lymphoma, NOS**
- **Indolent clonal T-LPD of the GI tract**
- **Indolent NK-cell LPD of the GI tract**
- **Hepatosplenic TCL**

Cutaneous

- Mycosis fungoides
- Sézary syndrome
- Primary cut. CD30+ LPD
  - -LyP
  - - Iry cut ALCL
- Primary cut small/med CD4+ LPD
- Subcut panniculitis-like TCL
- Primary cut γ/δ TCL
- Primary cutaneous acral CD8+ T-cell **LPD**
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL

And in the practice ?

PTCL in a few questions….

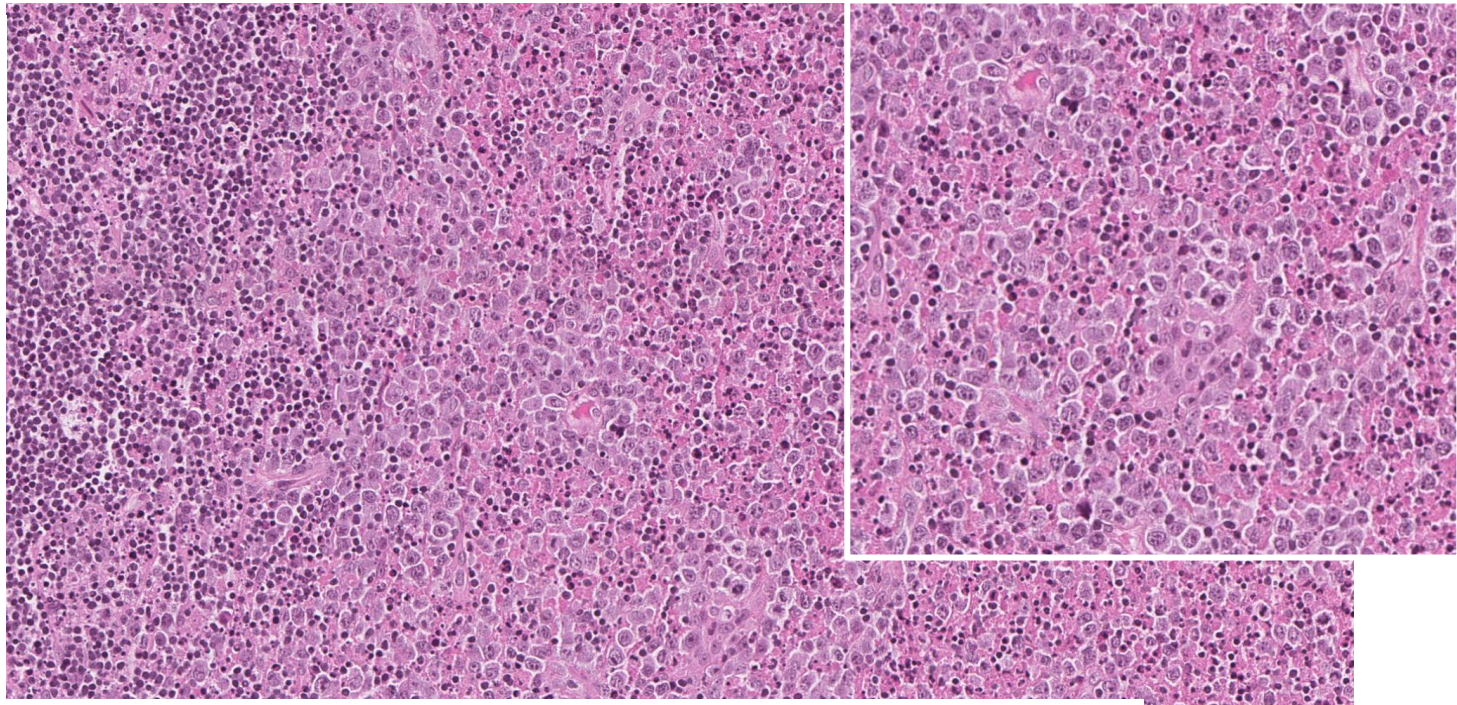
1 - Reactive or PTCL… ?

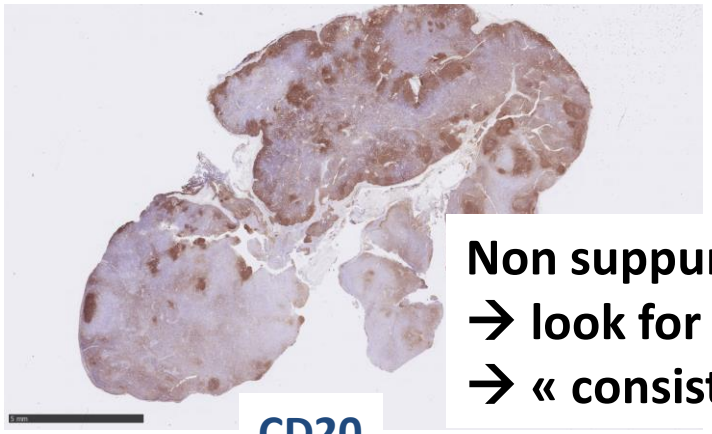
- Dense T-cell **infiltrate # T-cell lymphoma**
  - **Even when cytological atypia**
  - **almost when cytotoxic (CD8+)**
- Viral infections, dysimmunes conditions
  - **IM (EBV, ….)**
  - HSV…
- Non suppurative histiocytic necrotizing lymphadenitis (Kikuchi & Fujimoto)
  - ALPS,…

Not over interpret core biopsies ++!

- ✓ A 15 y-o girl, B symptoms, hypermetabolic polyADP,…
- ✓ Absence of infectious context

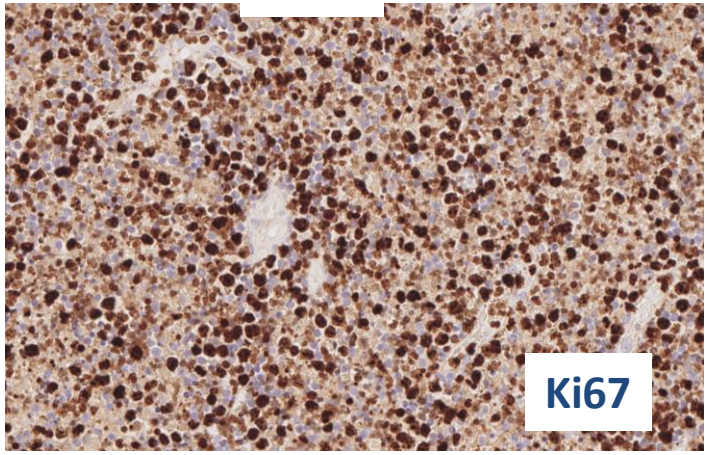
- ➢ **CD20 follicles**
- ➢ **CD68+ histiocytes expressing MPO**
- ➢ **CD123+ plasmocytoid cells**
- ➢ **No T-cell clone**



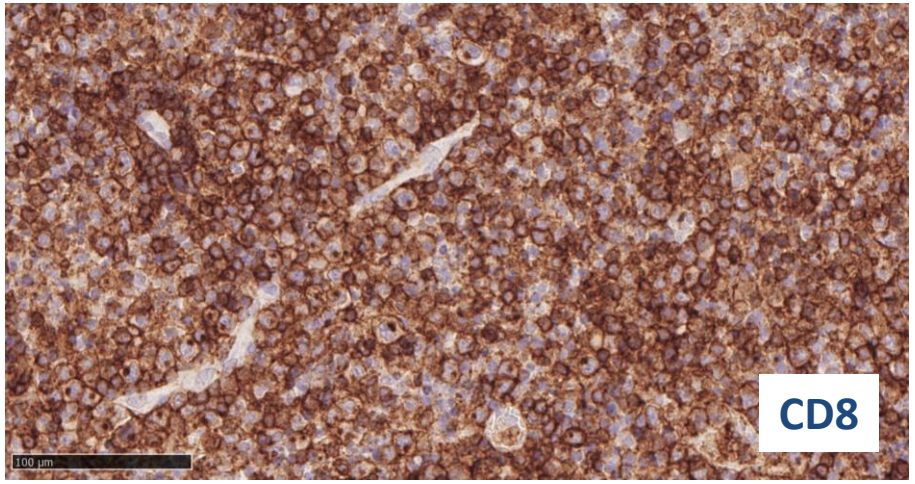


CD20

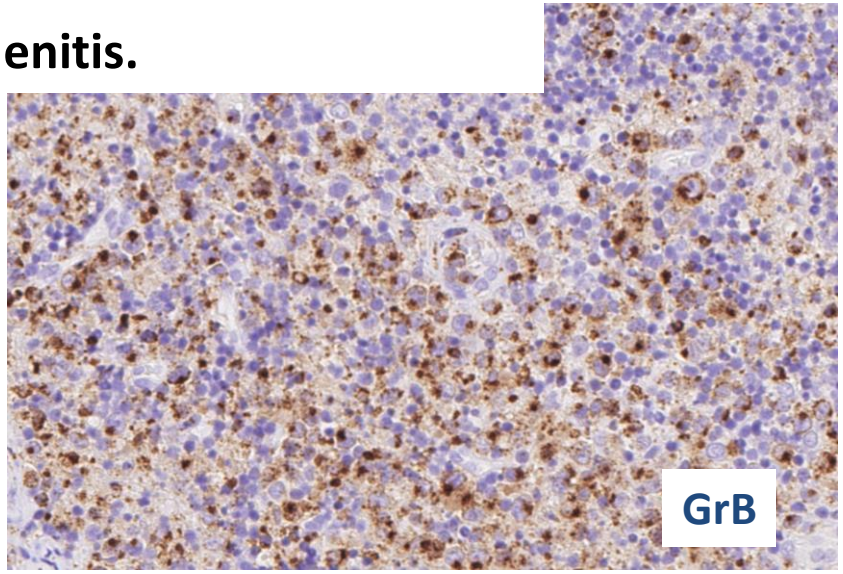
Non suppurative histiocytic necrotizing lympadenitis (proliferative phase)
→ look for auto-immune disease (Lupus)
→ « consistent with » Kikuchi and Fujimoto lymphadenitis.



Ki67



CD8



GrB

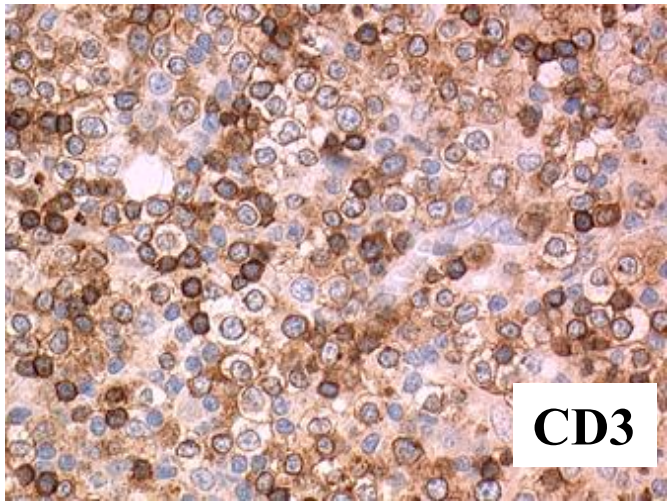
1 - Reactive or PTCL… ?

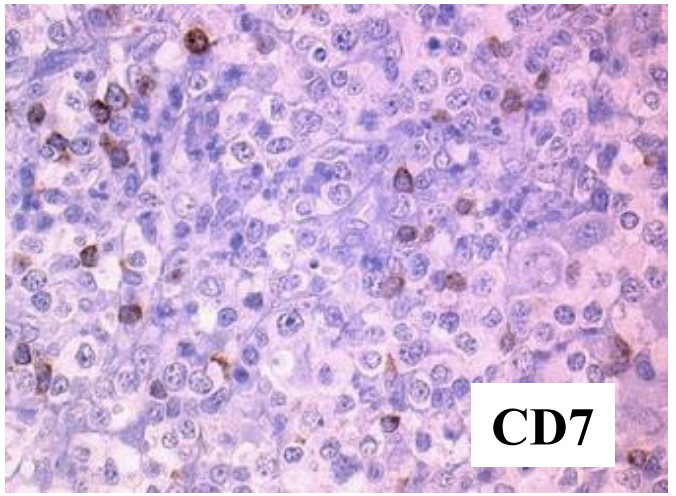
- Even if dense infiltrate with atypia
- Above all when CD8+

Virus : IM,…
Kikuchi
ALPS

- ✓ Importance architecture
  - focal!!
  - cytology
- ✓ « Aberrant» T-cell phenotype
- ✓ EBV
- ✓ Clonality
- ✓ Sequencing (NGS)
- ✓ **Clinical context!!!**

Antigen loss
CD3, CD5, CD2, CD7





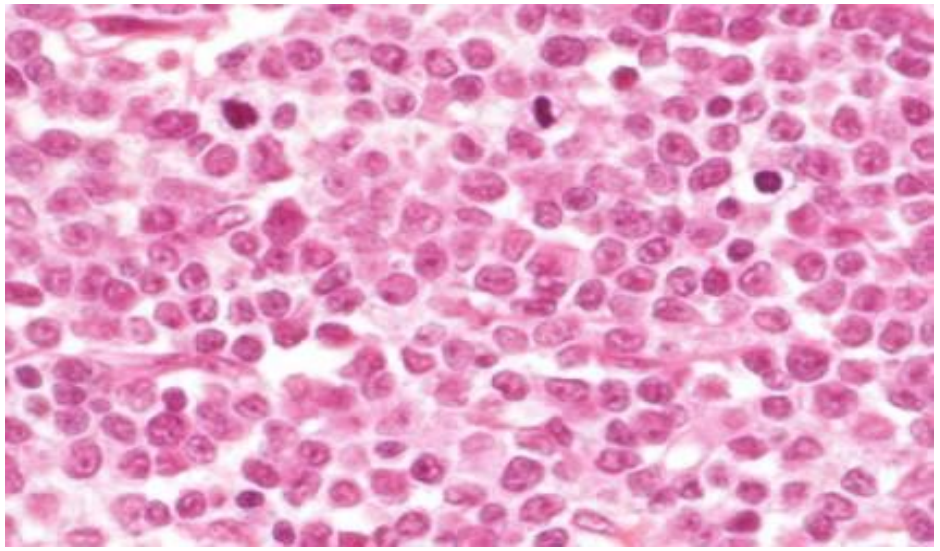
Good internal positive controls

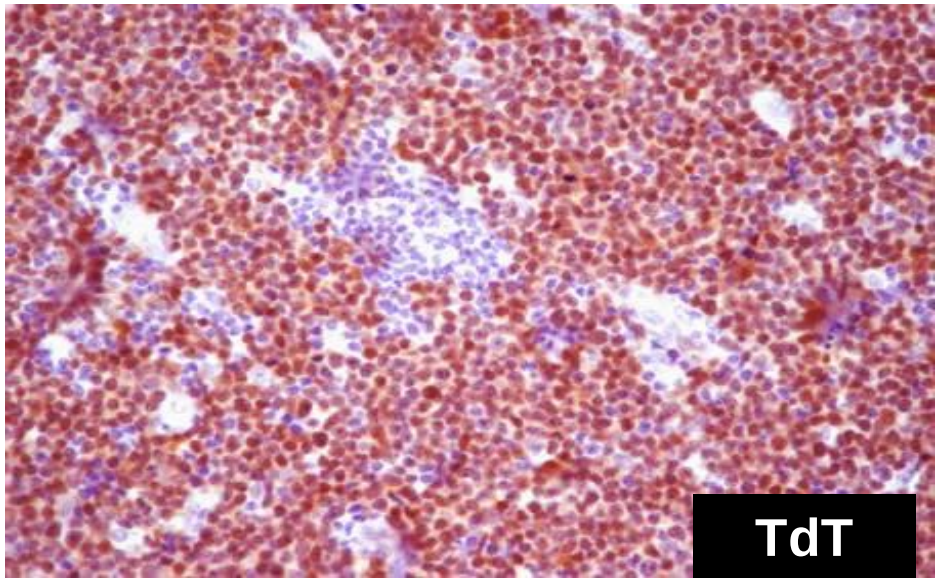
Classifying PTCL - In first approach…

- (clinical context)
- **age,**
- **site of the biopsy**
- **morphology**

- Leukemic ?
- Lymphoblastic or mature (PTCL) ?
- If PTCL, nodal or cutaneous or extranodal presentation ?

2 – Exclude a lymphoblastic T-cell lymphoma/leukaemia



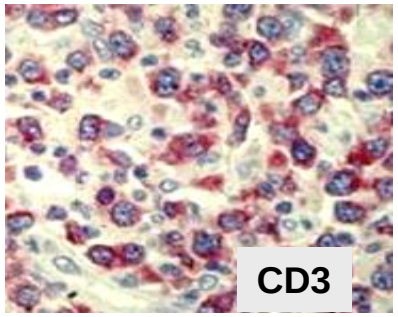


- Children, young adults, **mediastinal mass**, cervical adenopathies, ± leukemic features
- **Monotonous, « blastic », mitoses**
- **TdT +, CD1a+ (50%), CD10+/-, CD34 -/+,** Ki67 high
- Translocations TCR genes; deletion/translocation TAL1; *NOTCH1* mutations….

Mediatinal biopsies: Absence of epithelial meshwork (CK)!

3 – Which PTCL entity?

Morphology
Age
Biposy site
Clinical context



Iry cutaneous TCL (CTCL)

nodal

Extranodal

Hepatosplenic TCL (HSTL)

TFH Lymphoma AITL….

MEITL

ALCL ALK+
ALCL ALK-

Nasal-type NK/T-cell L

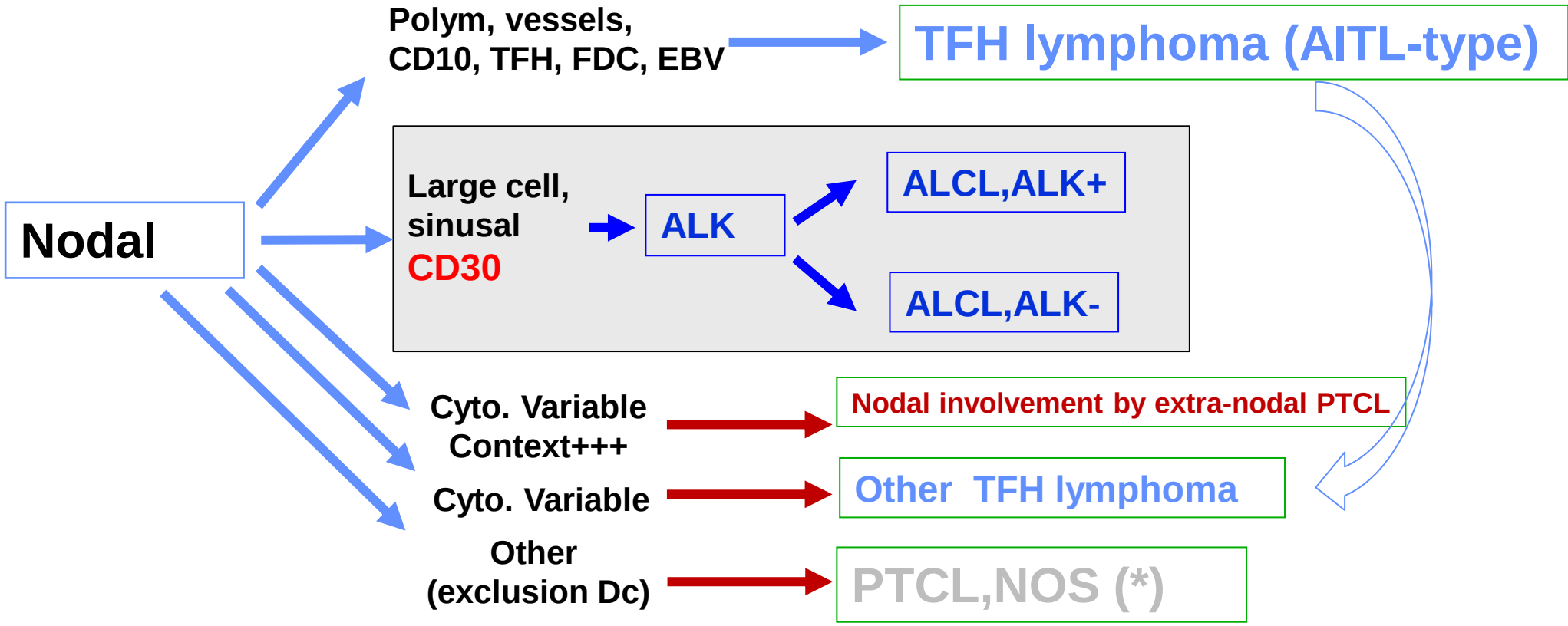
EATL

Indolent clonal T-cell LPD of the GI tract

PTCL-NOS ?

!!! Adult T-cell lymphoma/leukaemia (HTLV1) can show a wide spectrum of pathological aspects!

4 – PTCL with nodal presentation



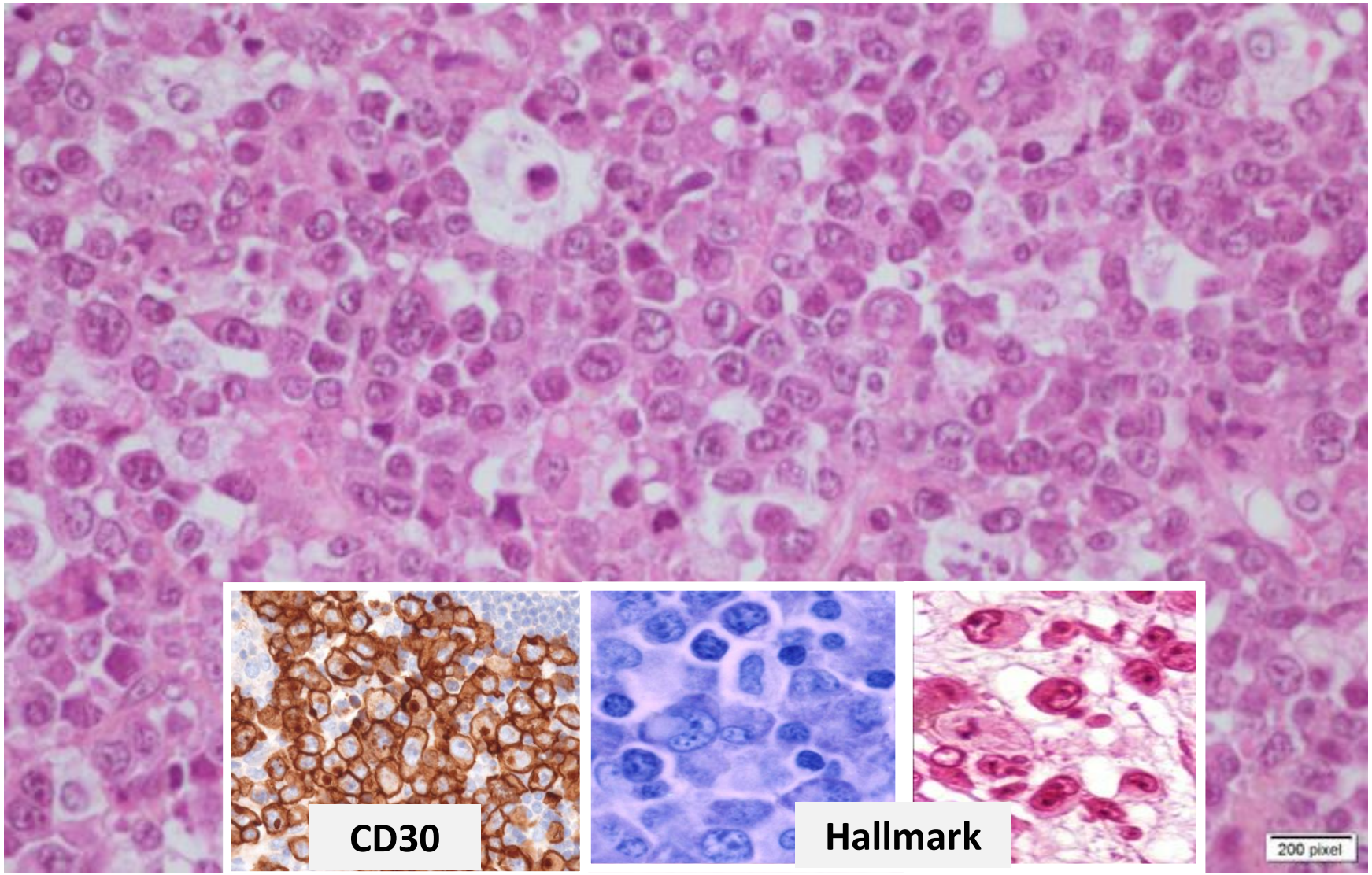
Small lymphocytes (monomorphic) :

- is it a lymphoma?

! ATLL can reproduce almost the full morphological spectrum of PTCLs..

(*) EBV+ : primary nodal T/NK cell lymphoma

5 – Anaplastic large cell lymphoma (ALCL)



ALCL, ALK-positive

ALCL, ALK-negative

DUSP22

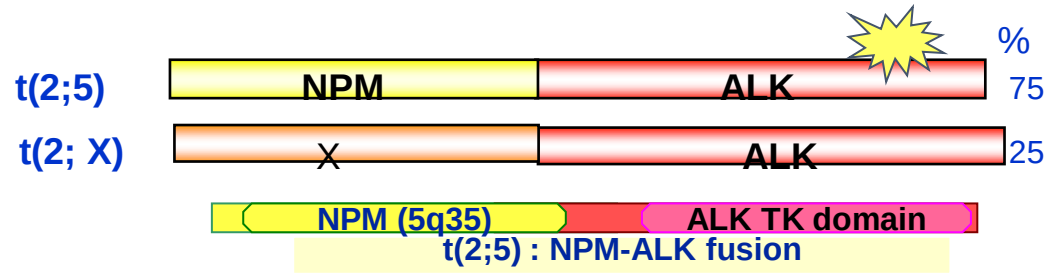
Cutaneous ALCL (ALK-negative)

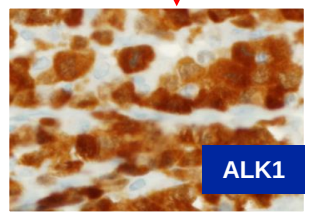
Breast implant ALCL (ALK-negative)

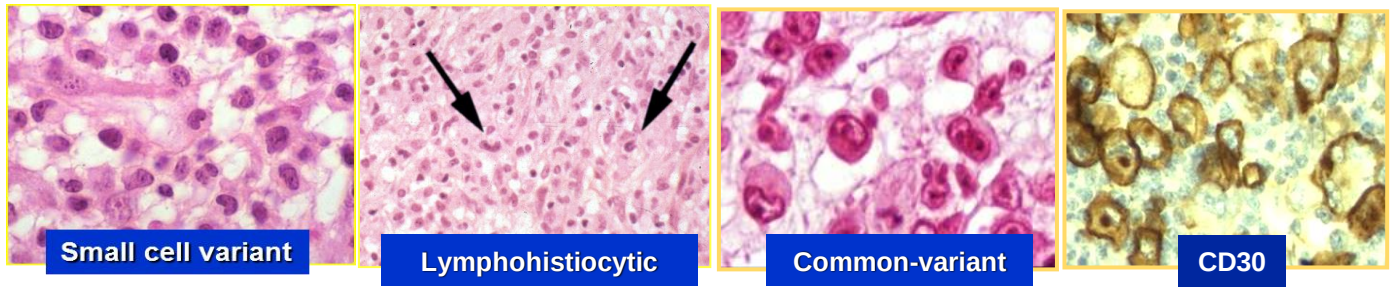
A uniform morphology but .. several diseases

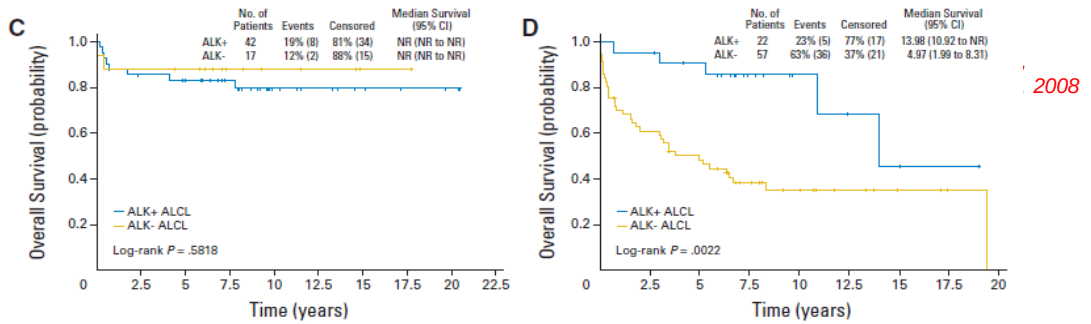
The best delineated entity: ALCL, ALK+

- **Translocation involving the *ALK* gene**
  → ALK fusion proteins
- **CD30+ (all cells), ALK+,** EMA+,
- often CD20-/CD3-/CD5-/CD2-/CD7-, CD4+/-, TIA1+GrB+/prf+
- Children and young adults
- Adenopathies, extranodal sites frequent (skin, bone,…)
- **Critical to perform ALK staining!**
  - Diagnostic utility
  - Prognostic relevance
  -Targetable for therapy (Crizotinib)
- Rare forms of ALK+ ALCL limited to the skin with an indolent outcome (°)









2008

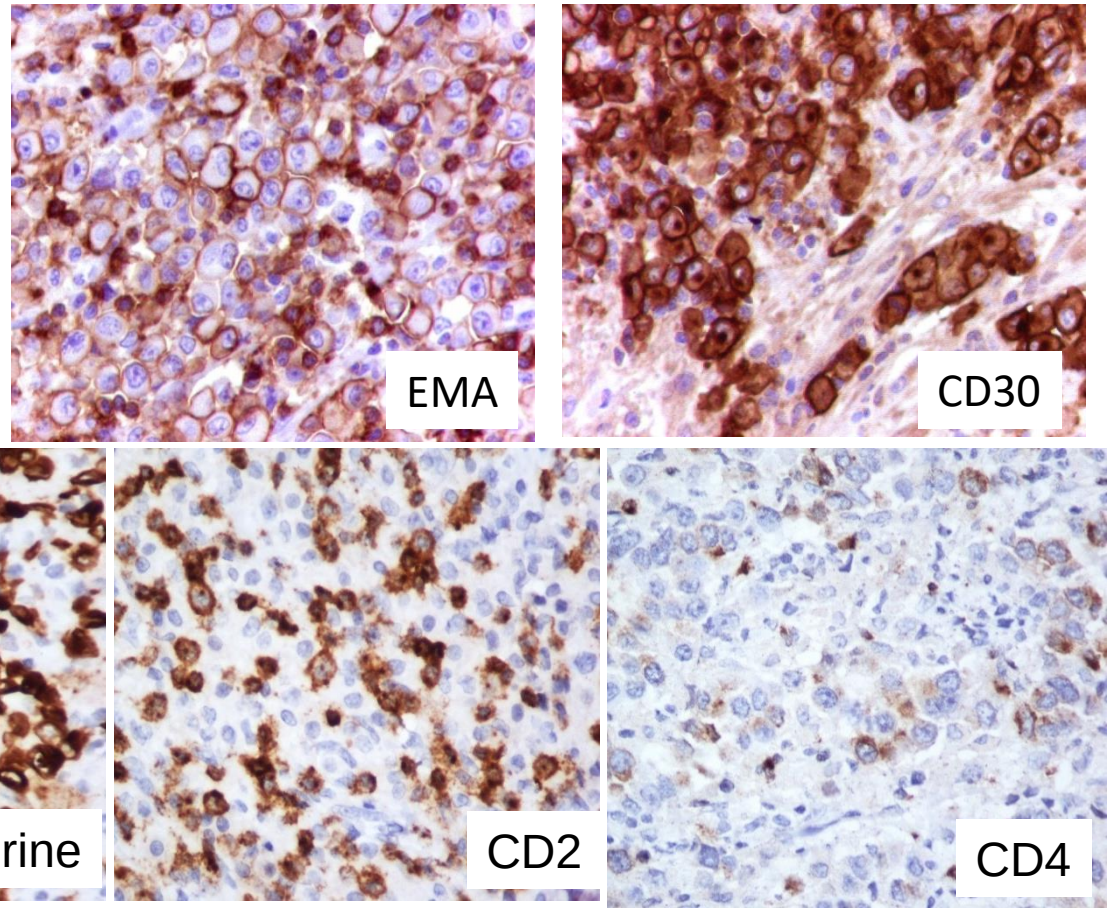
(°)Oschlies et al. Haematologica 2013

Sibon D et al.. J Clin Oncol, 2012

ALCL, ALK + > ALK- : often « null »-cell phenotype

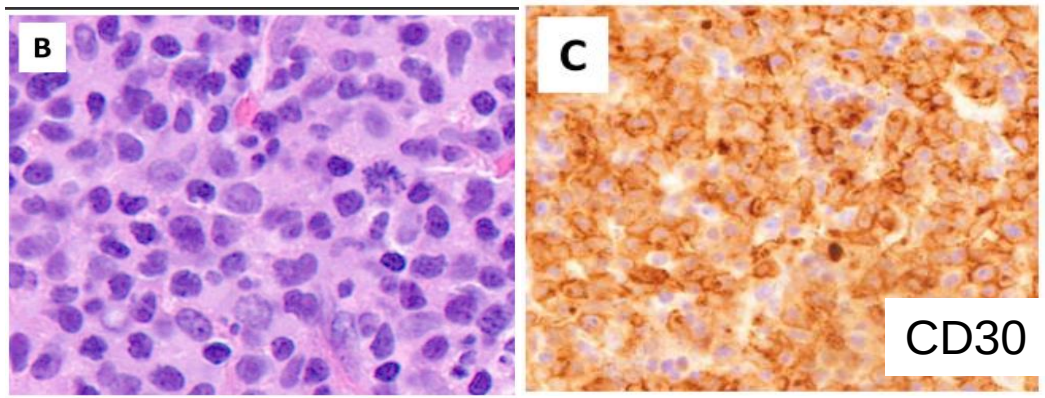
- ✓ **CD30+, EMA+, ALK +**
- ✓ CD3 – (~75%)
- ✓ CD4+ (50-70%)
- ✓ **Activated cytotoxic profile**
- ✓ TCR rearrangement (90%)
- ✓ **EBV-**

- ✓ **!! CD45 often negative!**

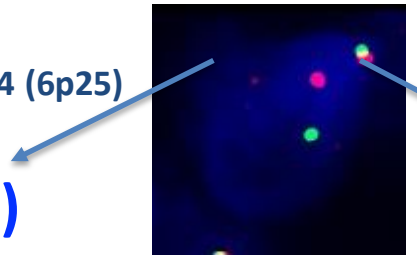


!! Even when CD45, CD20, CD3 are negative and EMA +, ALCL is possible and perform CD30 staining !!!

ALCL, ALK- : a distinct entity, but genetically heterogeneous



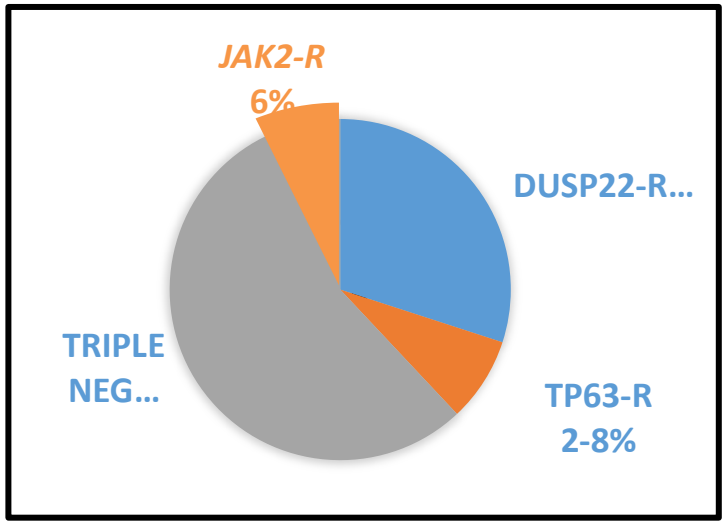
Sibon D et al/ Haematologica 2022



DUSP22-rearranged ALCLs (25-40%)

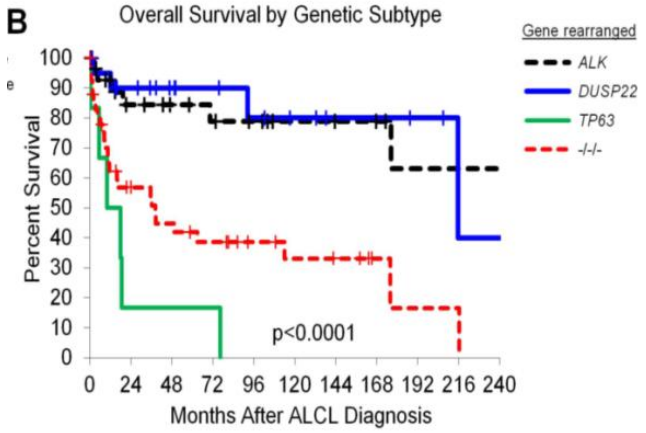
- **Systemic ALK- ALCL with unique molecular features**
  - some morphologic differences
  - less EMA+, less cytotoxic profile
  - distinct gene signature, lack of STAT3 activation
  - DNA hypomethylation
  - expression of CT antigens
  - *MSC E116K* mutation (35%)
  - clinical relevance debated
- Also seen in cut-ALCL and Lymphomatoid papulosis

DUSP22-non rearranged ALCLs (60-70%)

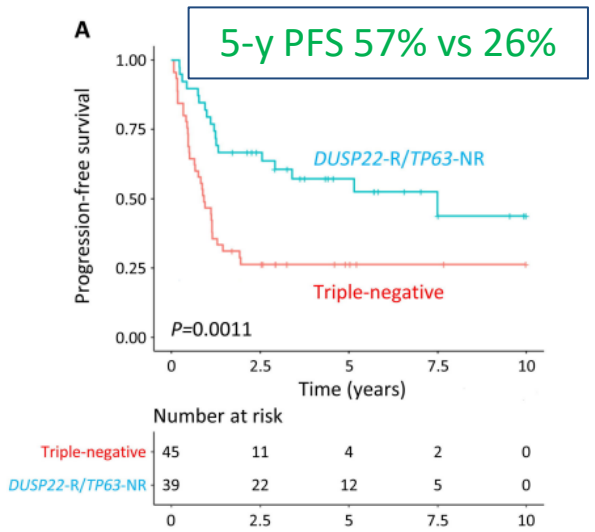


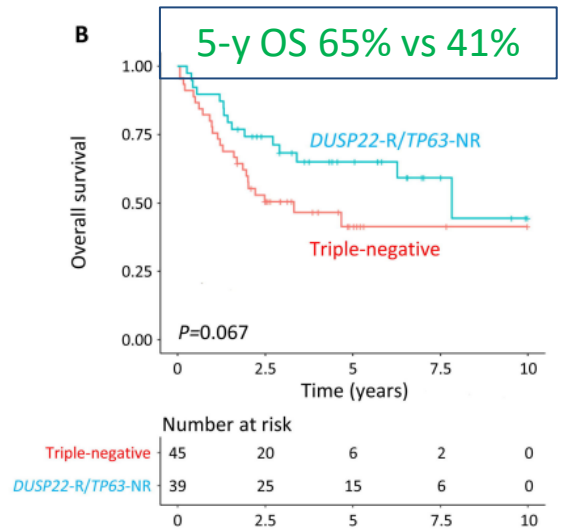
Fldman et al. Blood, 2019; Luchtel RA et al. Blood 2018; Luchtel et al. Blood 2019; Fitzpatrick M et al. AJSP 2021

Prognostic relevance of genetic alterations in systemic ALCL



Castellar et al. Blood 2014



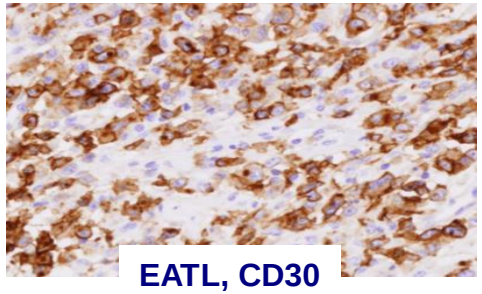


Sibon D et al. Haematologica, 2022

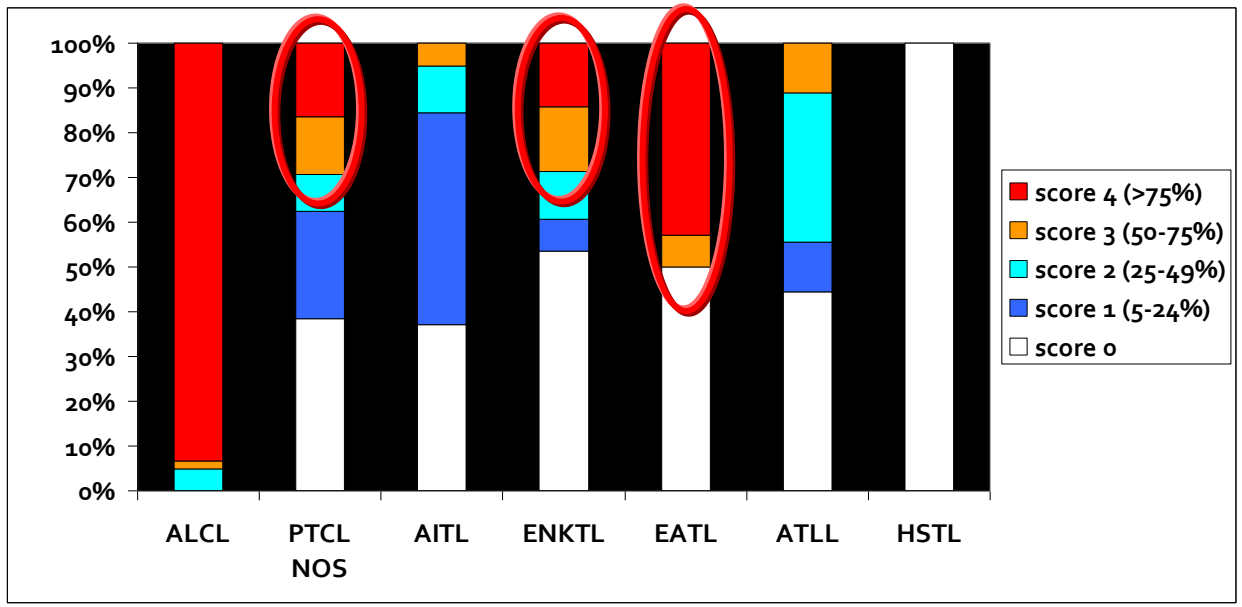
Implications for therapy
- BV (CH(O)EP)
- Crizotinib, BETi (?)…

Horwitz et al. Lancet 2018
Sibon et al. Haematologica 2019
Horwitz et al. Annals Oncol 2022

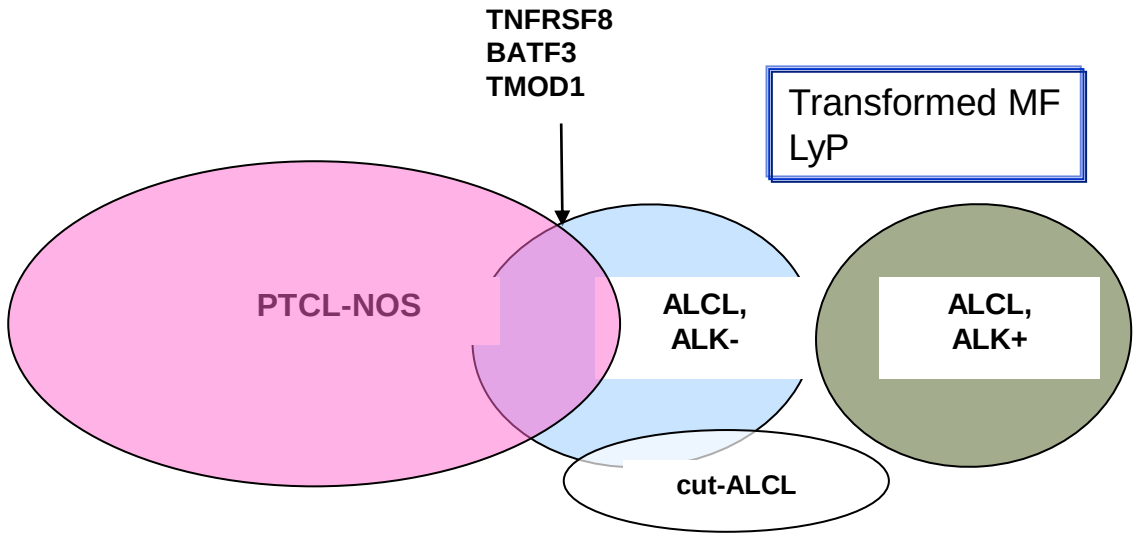
Many (other) PTCLs may express CD30



EATL, CD30



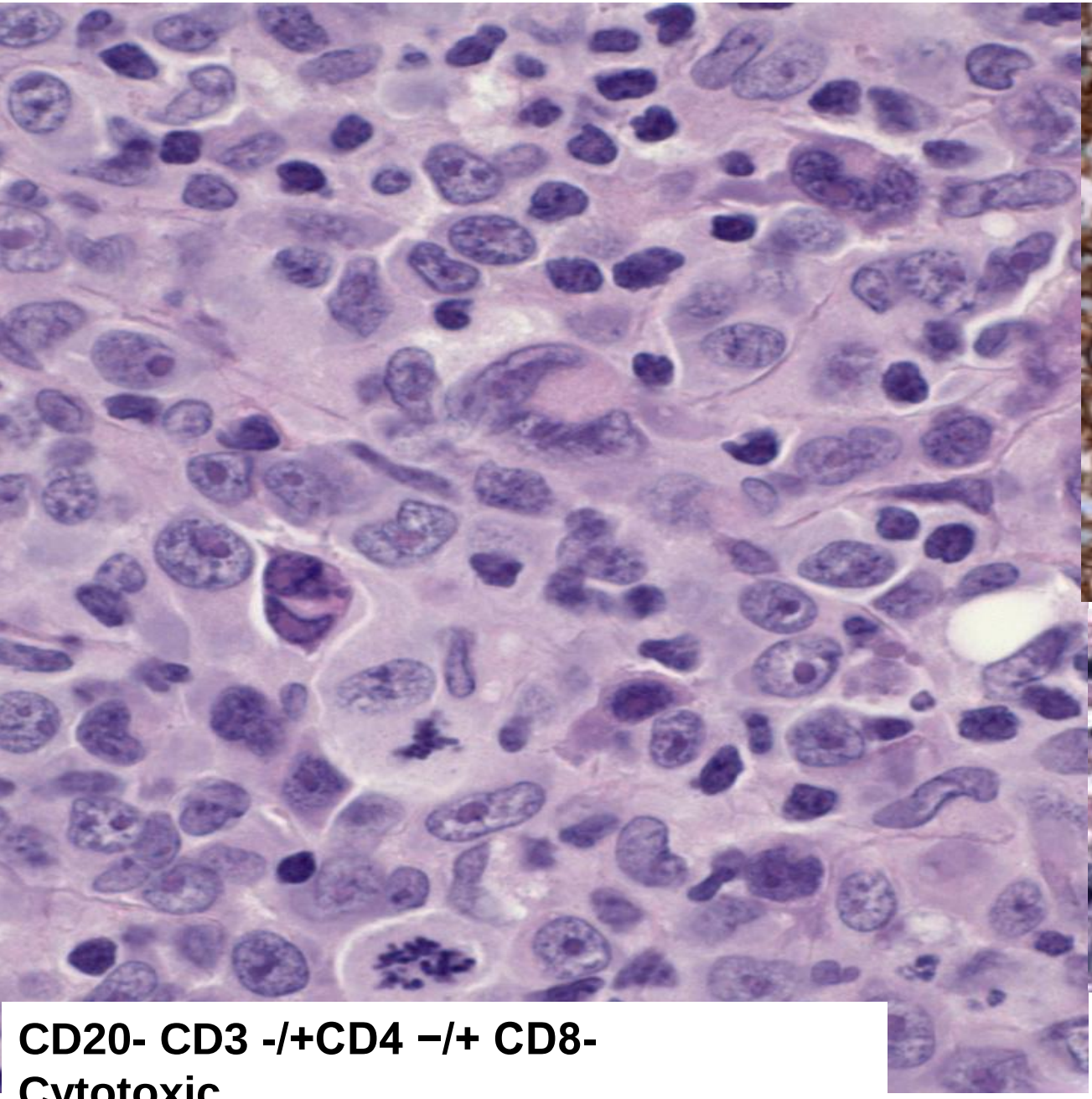
Bossard C , Blood, 2014



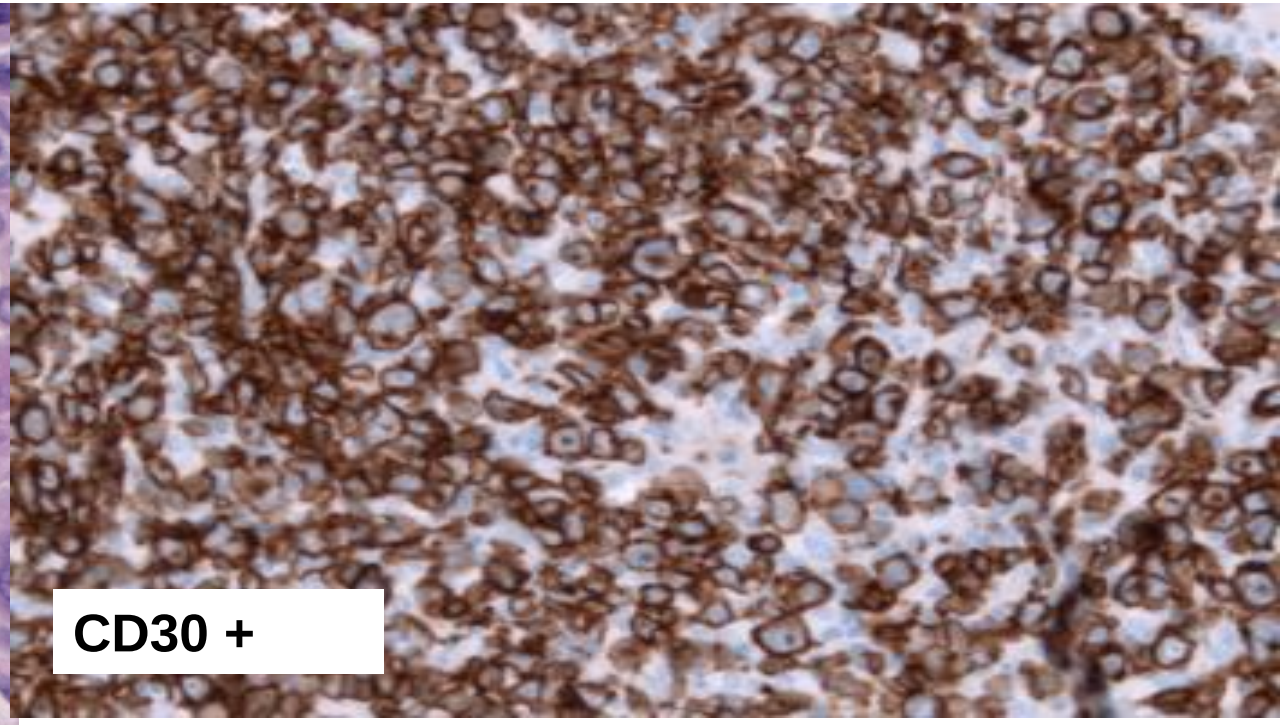
The appropriate cut-off value of CD30 expression correlating with the antitumor activity of B-vedotin still needs to be determined

Bossard et al. Blood 2014; Sabattini, Hematologica 2013
Agnelli et al. Blood 2012; Bisig et al. Haematologica 2013

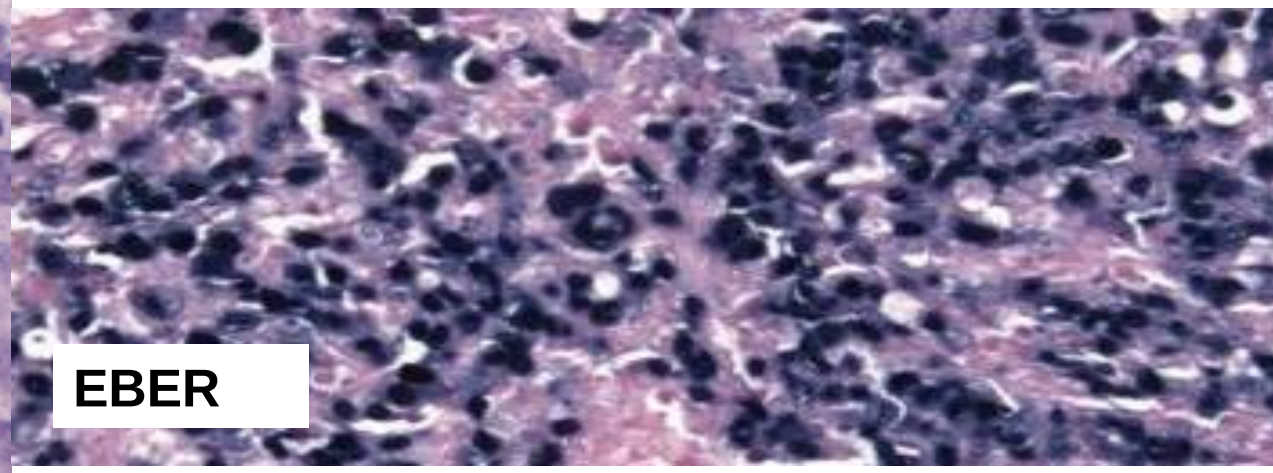
- 35-year-old man with large sinonasal mass



CD20- CD3 -/+CD4 –/+ CD8-
Cytotoxic



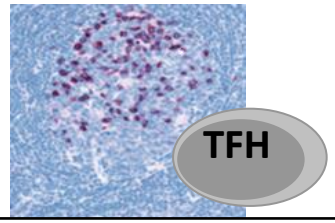
CD30 +



EBER

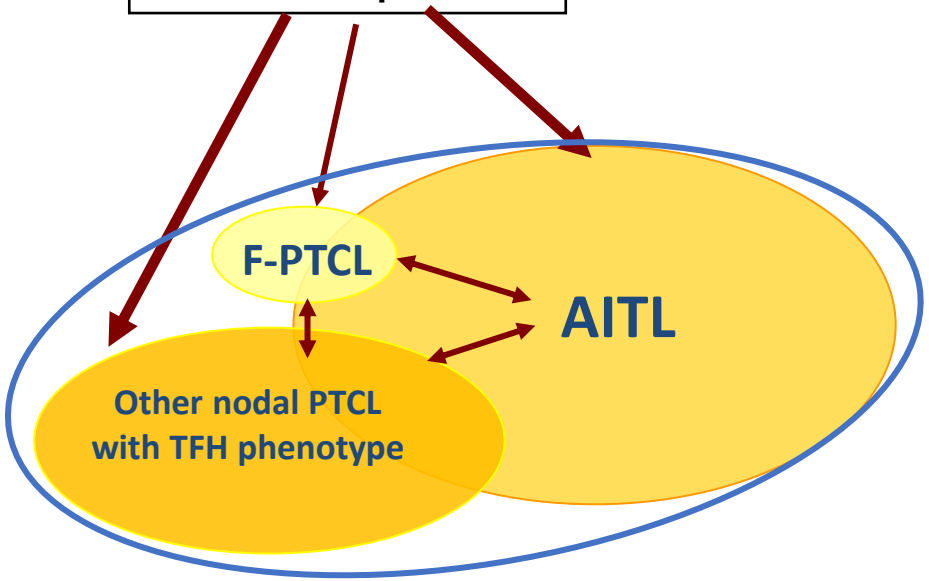
Extranodal NK/T cell Lymphoma

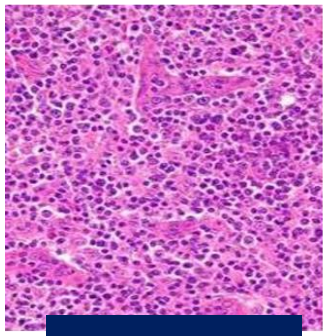
5 – (Nodal) TFH lymphoma



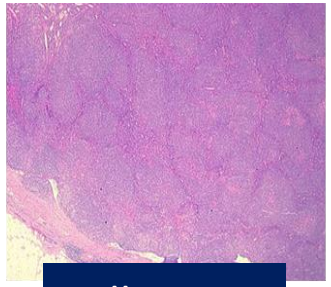
Follicular helper T cell

- ✓ Localize in germinal center
- ✓ Provide help to B cells
- • Class switch
- • Somatic hypermutation

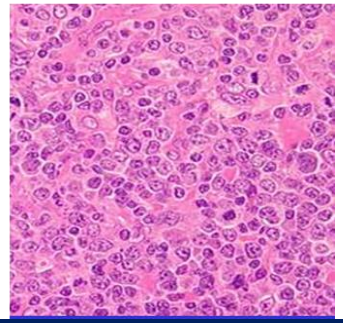




AITL(-type)



Follic-type

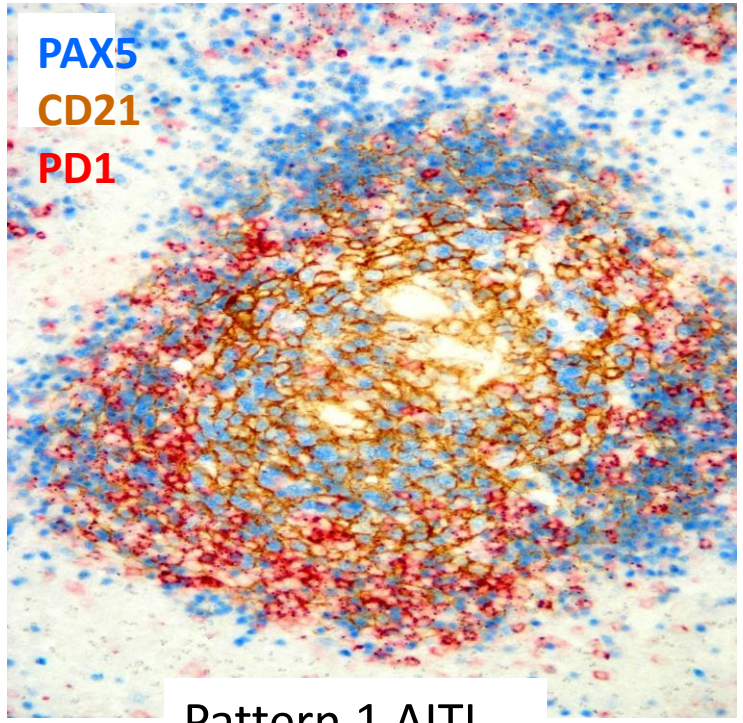


TFH lymphoma, NOS

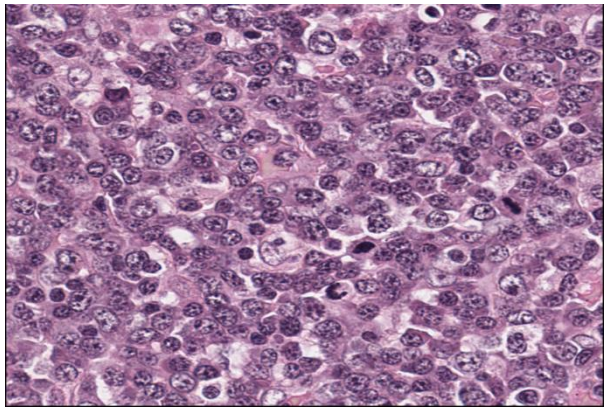
- **• The largest PTCL disease, with 3 subtypes**
- **• Share a unique TFH profile and genetic landscape:**
  - •TFH markers (CD10, BCL6, CXCL13, PD1, ICOS..)
  - •TFH gene signature,
  - • Mutational landscape
- **• A large pathological spectrum and combination of patterns**

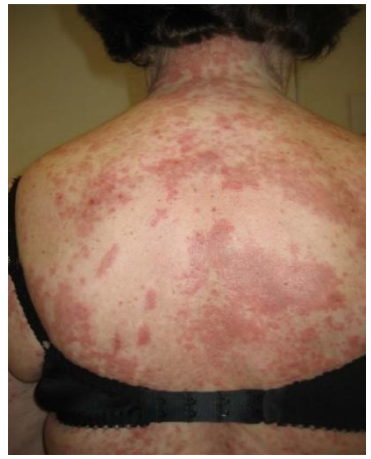
TFH lymphoma

A TFH derivation which imprints the pathological and clinical features



Pattern 1 AITL



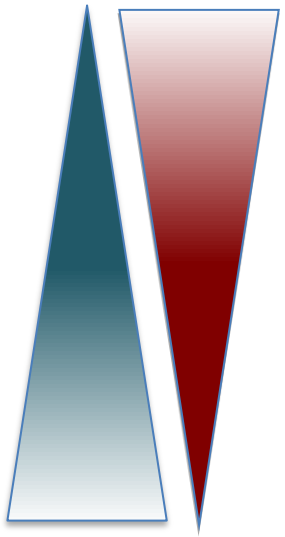


- Advanced stage (III/IV)	68 – 94 %
- B symptoms	52 – 86 %
- Polyadenopathies	81 – 100%
- Skin rash	38 – 58 %
- Positive Coombs test	**32 – 75 %**
- Hyperγglobulinemia	**30 – 83 %**

Manifestations of immune dysregulation

Mourad et al. Blood 2008
L de Leval et al. Haematologica 2015
Tokunaga, Blood 2012
Advani, Blood 2021

A unique TFH derivation and mutational landscape with pathological correlations



CD10

BCL6

CXCL13

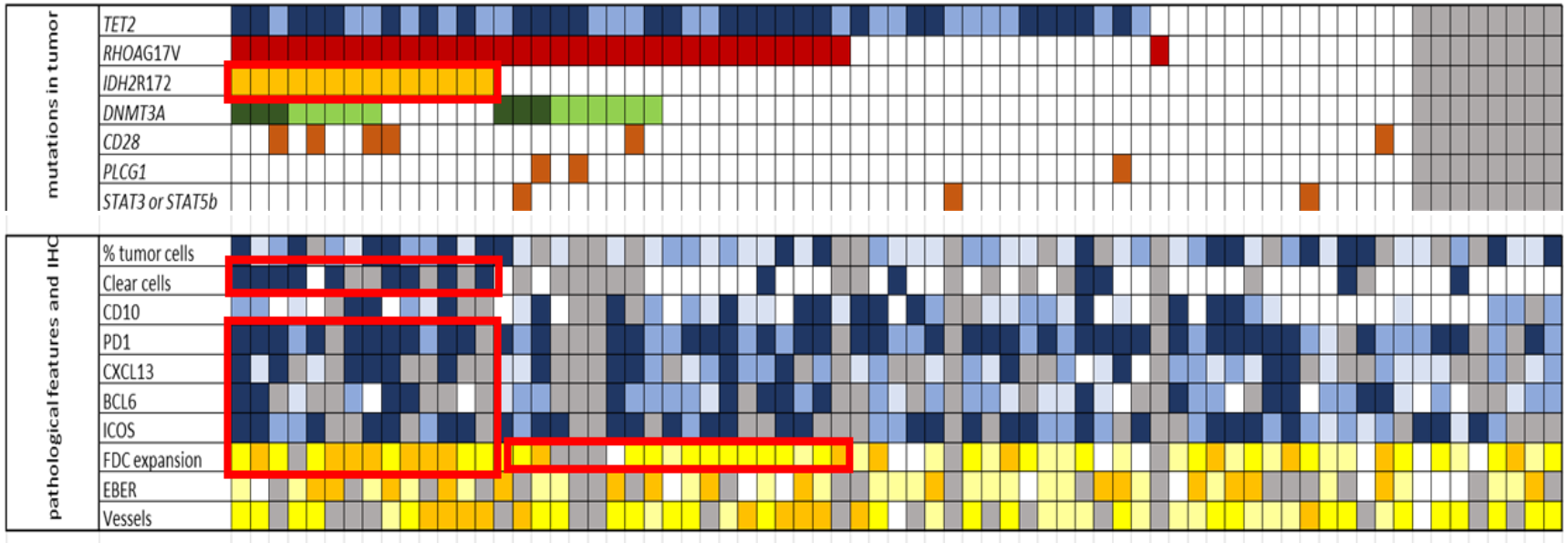
PD1

ICOS

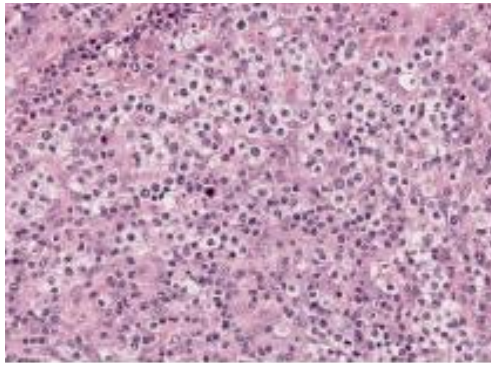
Sens Spec.

.

CXCR5
CD200
....



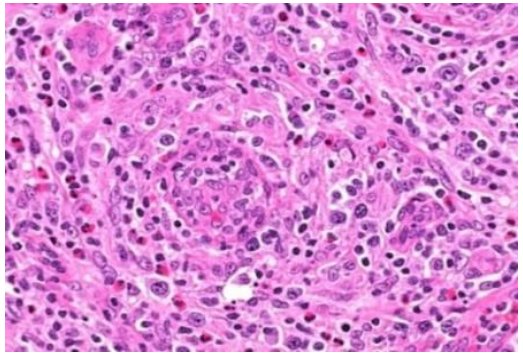
Adapted from F Lemonnier et al. REVAIL study, Blood Advances, 2021

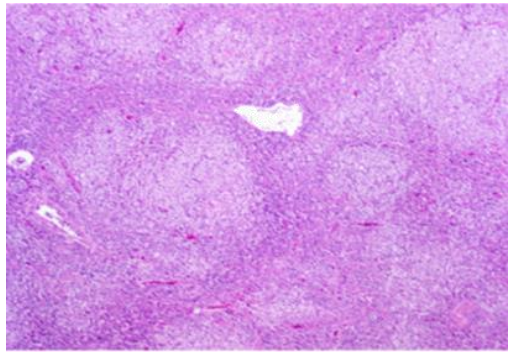


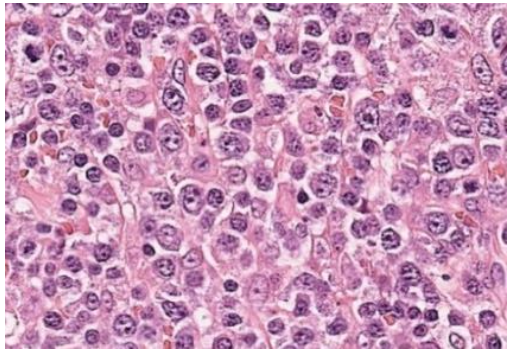
H Miyoshi et al. Pathology Intern 2020; MP Dobay et al. Haematologica 2017; Steinhilber et al. Modern Pathol 2018

TFH lymphoma:
a new designation for a single entity with 3 subtypes

Angioimmunoblastic-type	Follicular-type	Not otherwise specified (NOS)
Diffuse involvement and FDC expansion **Or** perifollicular without FDC expansion	Follicular lymphoma-like **Or** PTGC-like (with FDCs & IgD+ B cells)	Diffuse and no FDC expansion **Or** T-zone pattern
EBV +/- B-blasts	EBV +/- B-blasts -/+	EBV +/- B-blasts –/+
Increased vascularity (+)	Increased vascularity -/+	Increased vascularity (-)
Polymorphous environment	Polymorphous environment -/+	Polymorphous environment -



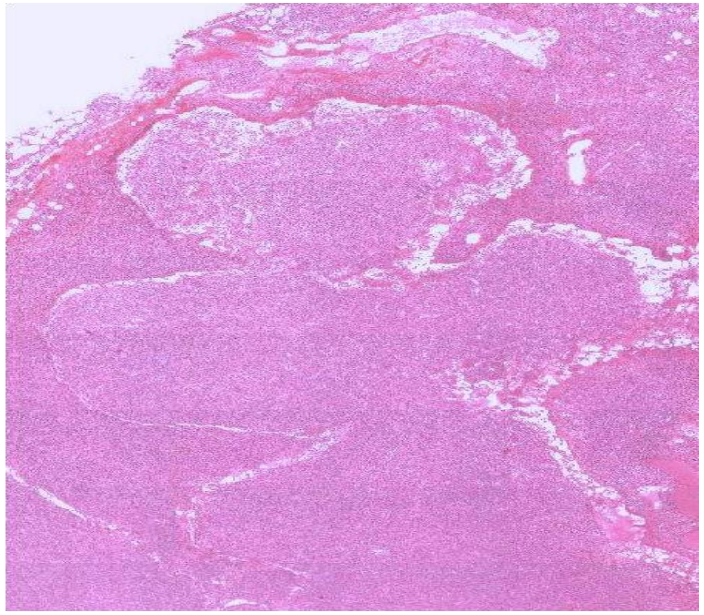


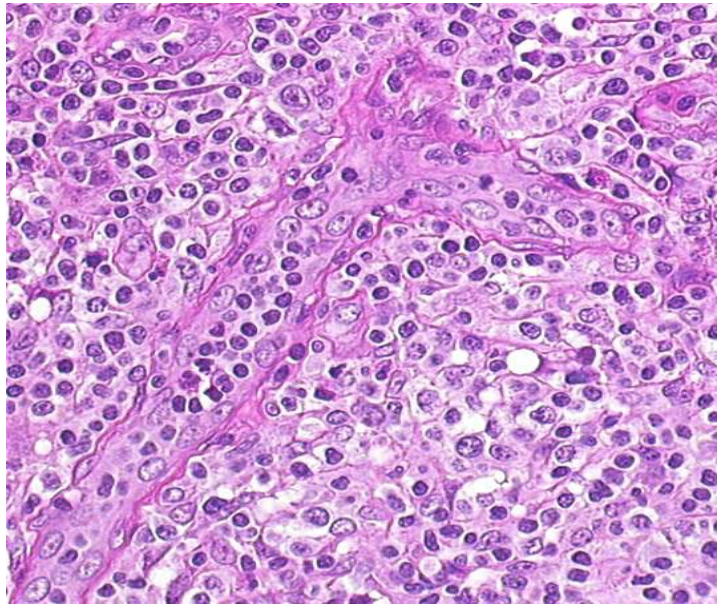


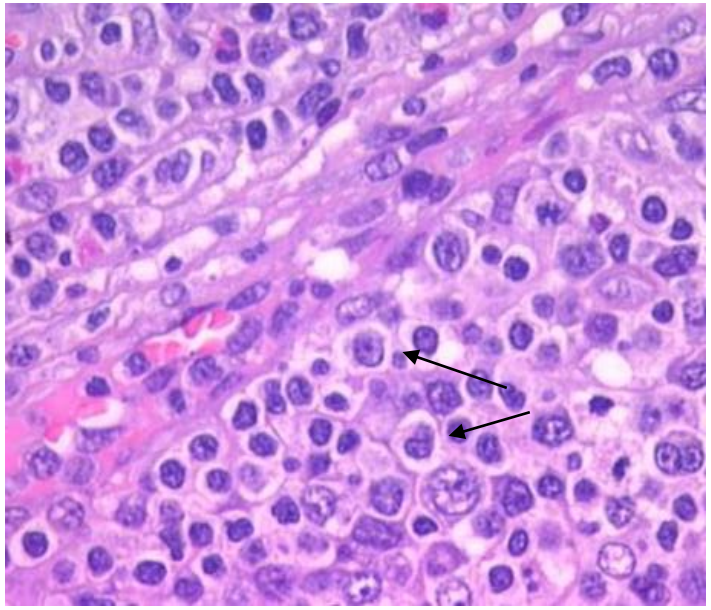
ICC: TFH lymphoma
WHO: Nodal TFH lymphoma

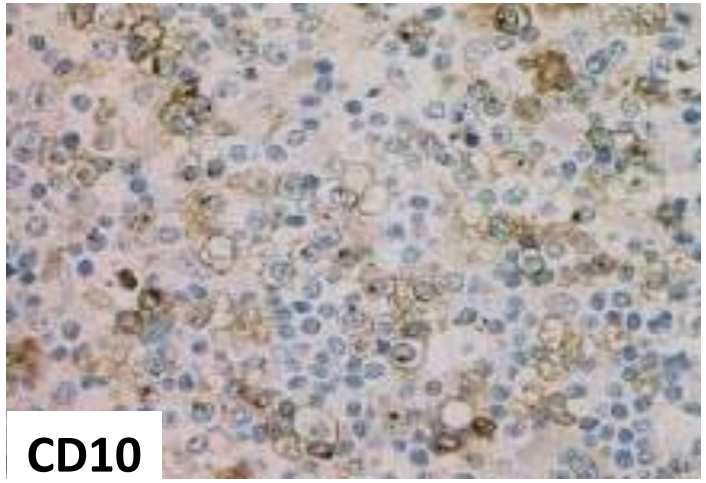
Campo E et al. ICC Classification… . Blood 2022;
Alaggio R et al. WHO classification… .Leukemia 2022

Angioimmunoblastic T-cell lymphoma (AITL-type)

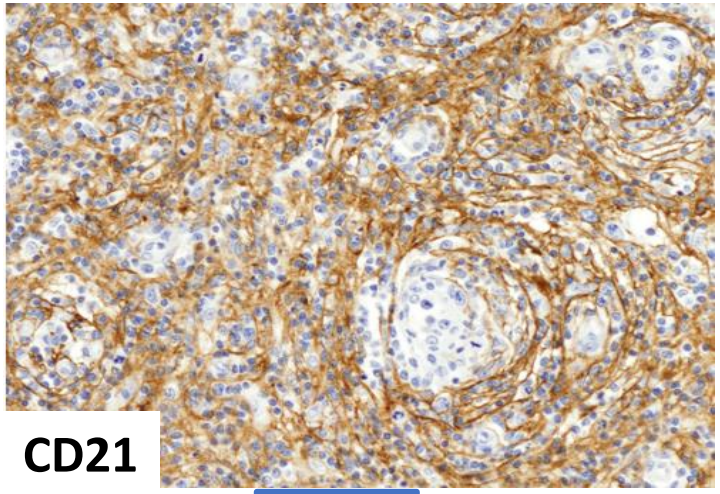




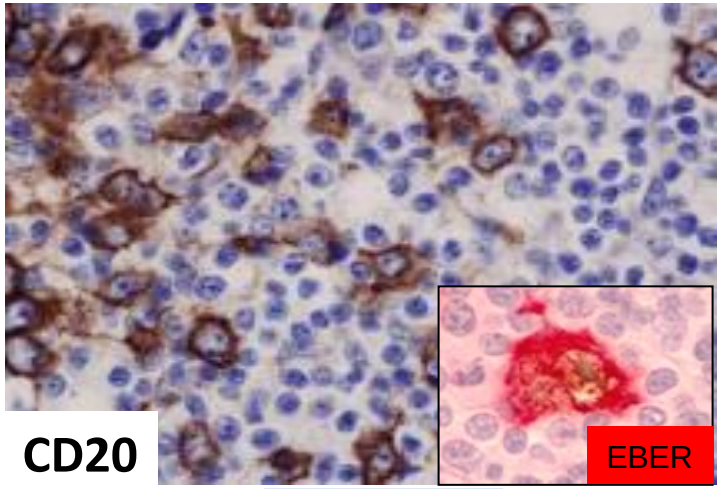




CD4 TFH



FDC



B Cells

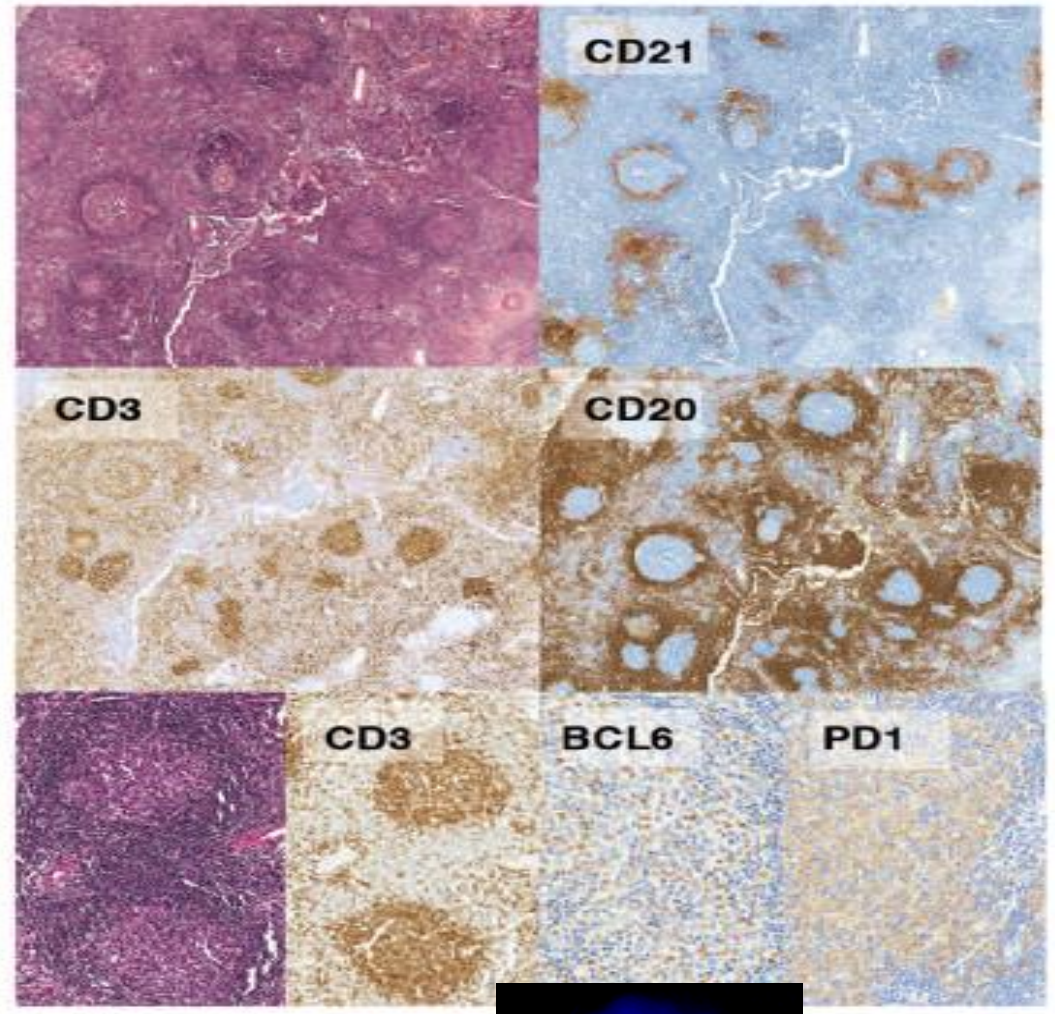
AITL – Diagnostic criteria-

- **Architecture**, vascular hyperplasia (HEV), open sinus
- **Clear cells,** (moderate) atypias highlighted by IHC with T-cell markers CD3+, CD5+ (small:medium-sized nuclei, abundant cytoplasm):
  - **CD10+**
  - Expression of other **TFH markers** (CXCL13, BCL6, PD1, ICOS)
  - Weakly CD30-positive
- Irregular hyperplastic FDC meswork (CD21, CD23, ...)
- Scattered CD20+/PAX5 large B cells dispersées
- Variable number of EBV-positive cells (B) with large nuclei (EBER>LMP1+) (but inconstant)
- Clonal T-cell population (PCR g) (! Sometimes with B-cell clone (IgH))
- **Clinical & biological features**
- Molecular studies : mutations in ***RHOAG17V (50-65%),*** *IDH2R172 > TET2+/- DNMT3A*..)

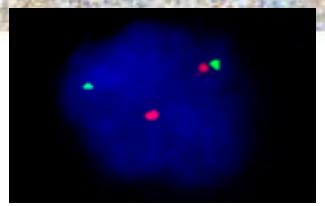
Not a single criteria is fully specific
An integration of features/criteria is required

TFH lymphoma, Follicular-type

- ✓ Rare variant
- ✓ Nodular growth pattern (**FL-like or TPCG-like**)
- ✓ small/medium sized CD4+ T cells
- ✓ **T_{FH} phenotype**
- ✓ **FDC restricted to follicles**
- ✓ t(5;9) translocation (SYK-ITK fusion) in 20-30% of cases
- ✓ Overlapping features with AITL
- ✓ HL-like B blasts possible



Dobay et al. Haematologica 2017

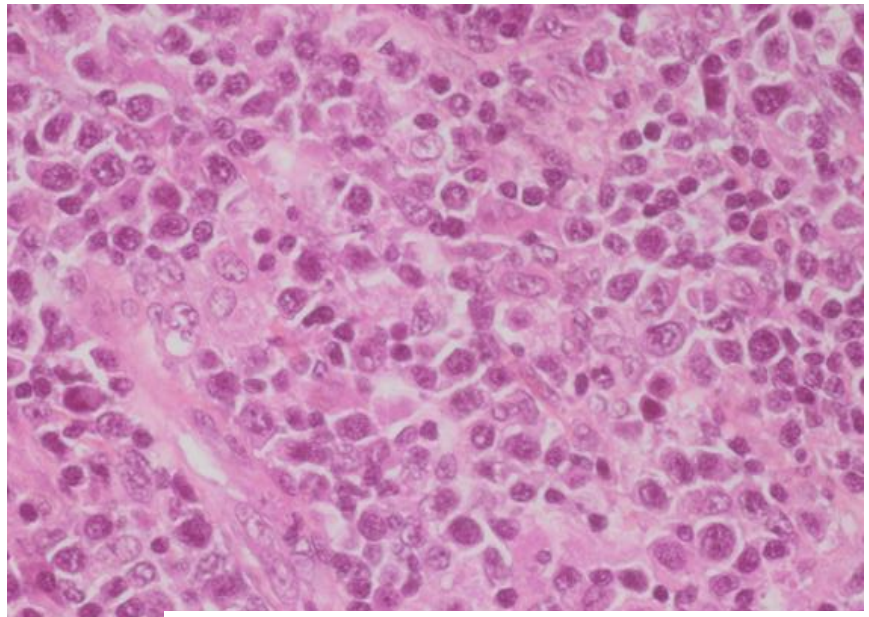


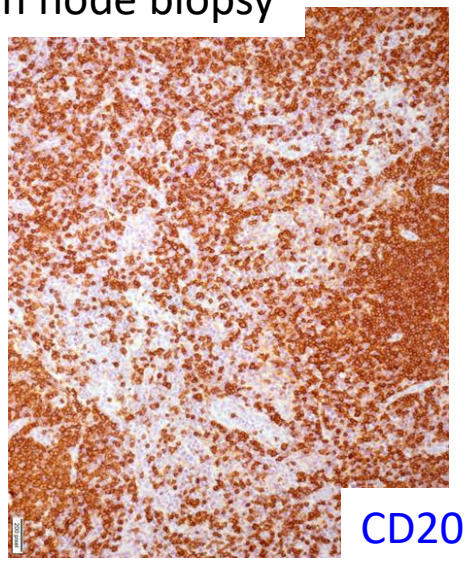
t(5;9)

de Leval L et al. AJSP 2001
Streubel B et al. Leukemia 2006
Bacon C et al. Br J Haematol 2008
Qubaja M et al. Human Pathol 2008
Huang L et al. AJSP 2009
Moroch et al. AJSP 2012
Alikhan et al. Modern Pathol 2016

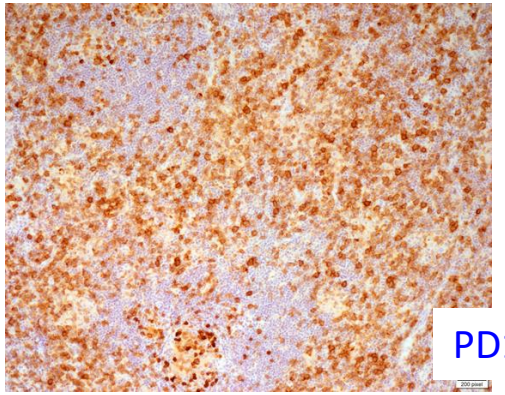
TFH lymphoma, NOS

A 47 yo man, polyADP, B Symptoms, surgical lymph node biopsy

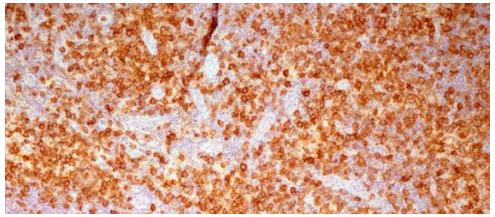




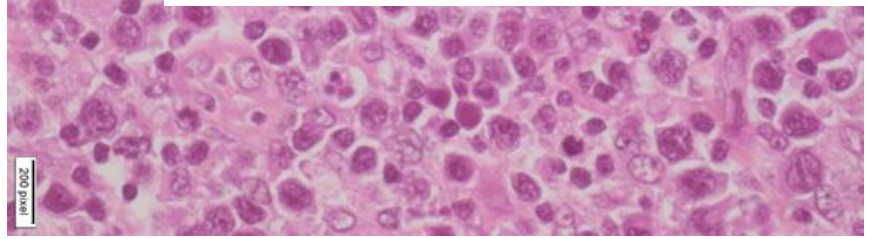
CD20

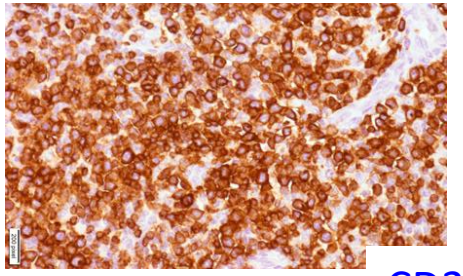


PD1

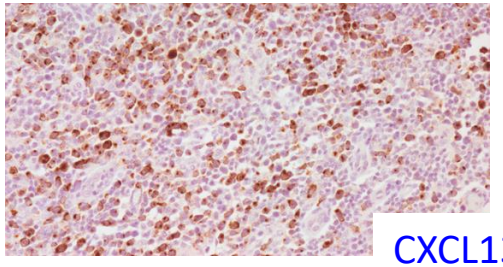


- Morphologically « PTCL, NOS » with T_{FH} molecular signature and/or expression of <u>≥2</u> T_{FH} immunophenotypic markers (CD10, PD1, ICOS, CXCL13, BCL6)
- May have some (not all) AITL morphological features (no FDC)





CD3

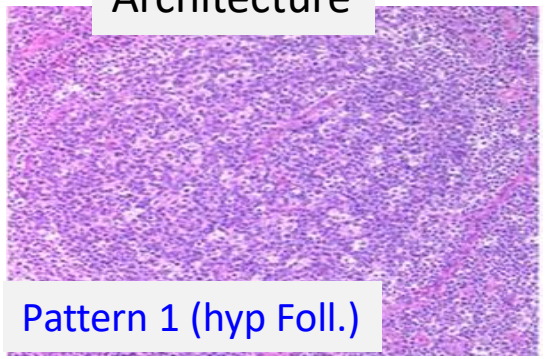


CXCL13

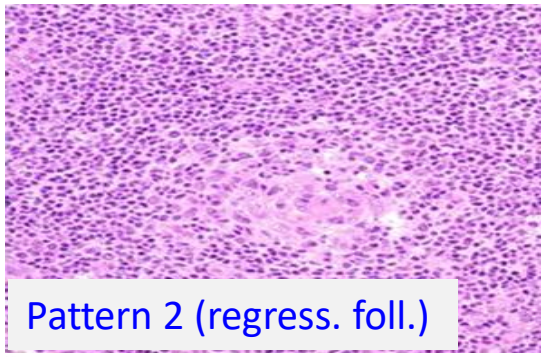
- ✓ T-cell clone
- ✓ EBV –
- ✓ No FDC expansion
- ✓ TET2 mut (2), DNMT3A mut, CD28 mut

A TFH derivation that recapitulates the wide pathological spectrum of AITL & TFHL

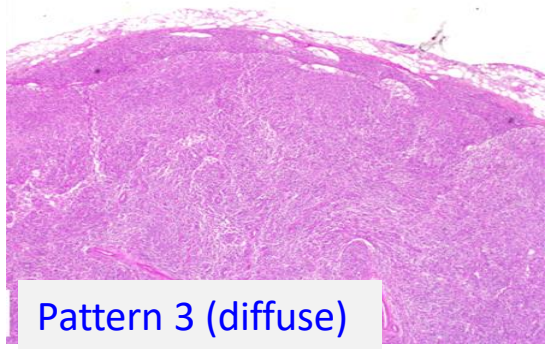
Architecture



Pattern 1 (hyp Foll.)

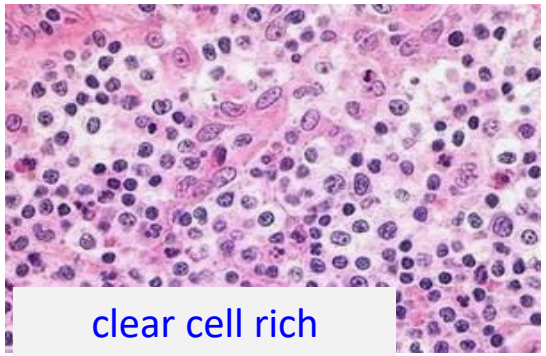


Pattern 2 (regress. foll.)

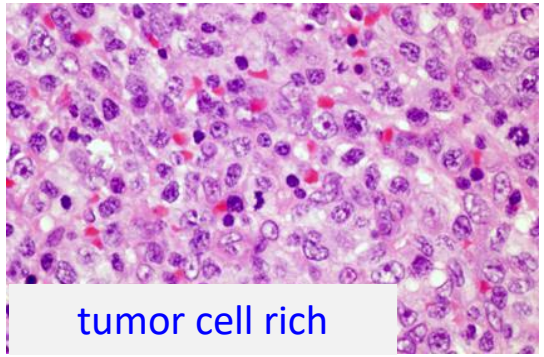


Pattern 3 (diffuse)

Tumor cells



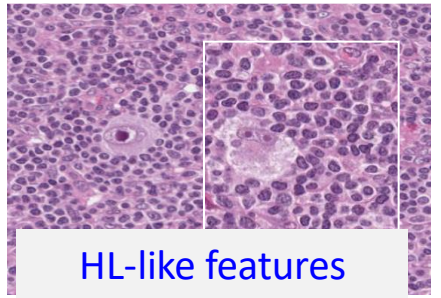
clear cell rich



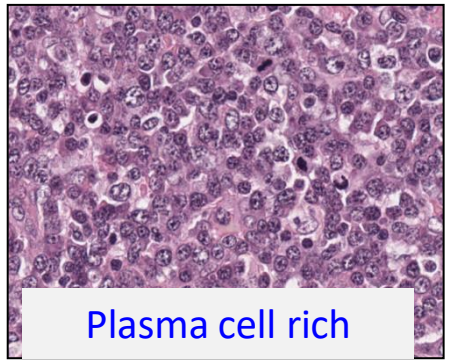
tumor cell rich

B cells

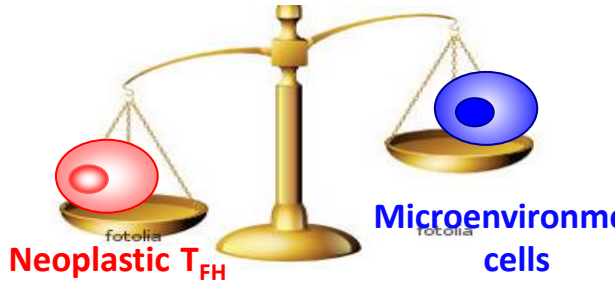
B-LPD/DLBCL

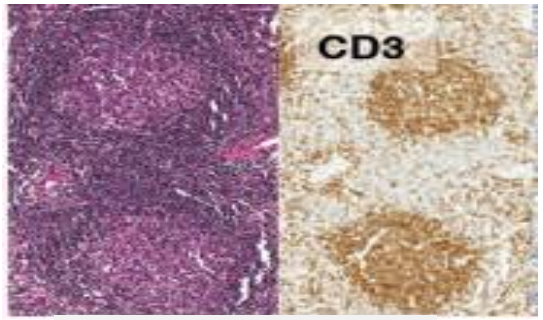


HL-like features

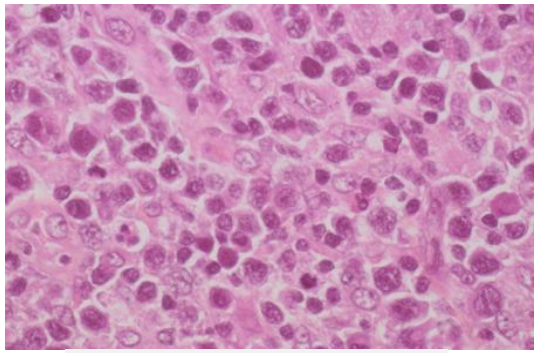


Plasma cell rich





TFHL, follic-type



TFHL, NOS

TFH lymphoma (AITL) & differential diagnoses

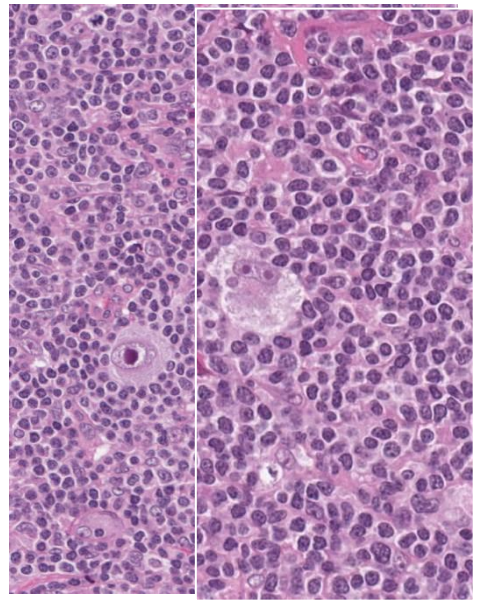
1 - **Reactive « dysimmune » lymphadenopathies** :
--------> absence of atypical CD3+ cells, CD10, T-cell clone, FDC expansion, RHOA mutation…

2 - **T-cell rich large B-cell lymphoma**:
--------> absence of eosinophils, plasma cells, HEV, atypical CD3+ cells, CD10, T-cell clone, FDC expansion, EBV, …

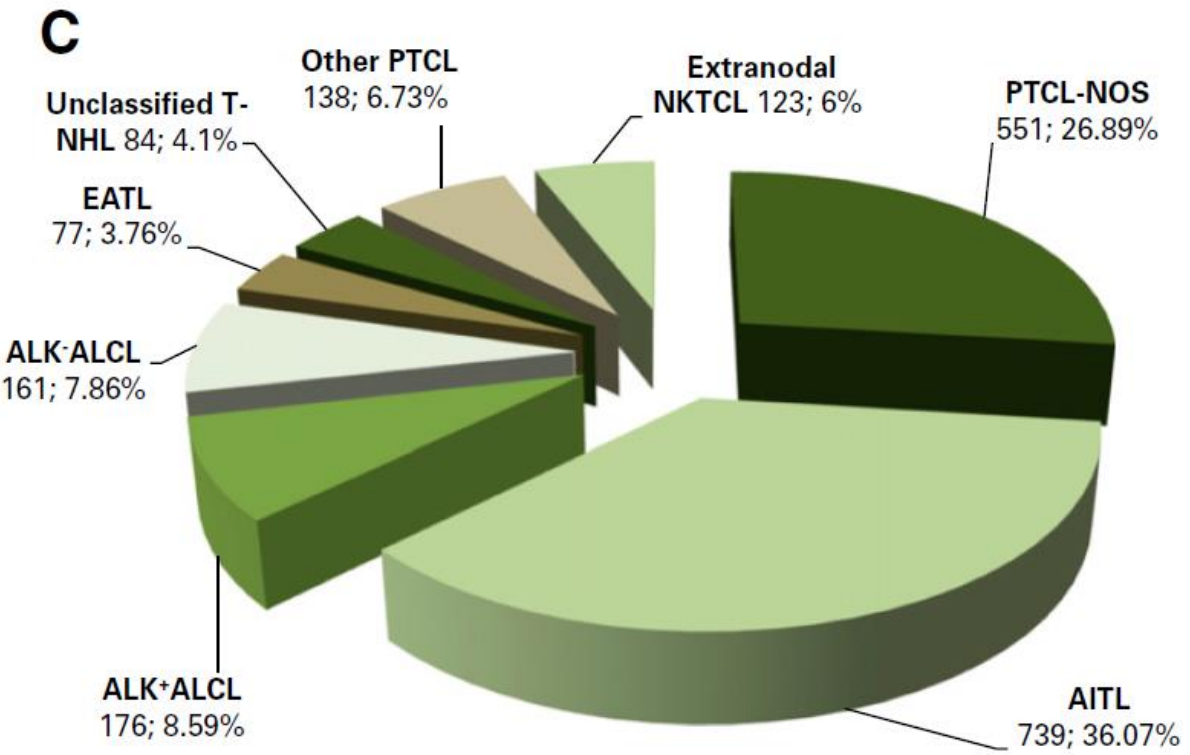
3 - **Hodgkin ’s disease** (when atypical polylobated CD30+ cells)

4 - **Other T-cell lymphomas**:
- if numerous pleomorphic T cells: TFHL, NOS or PTCL, NOS
- if « epitheliod rich »: PTCL, NOS (Lennert ’s variant, very rare, CD8+)

5- **EBV-positive LPD in the elderly**



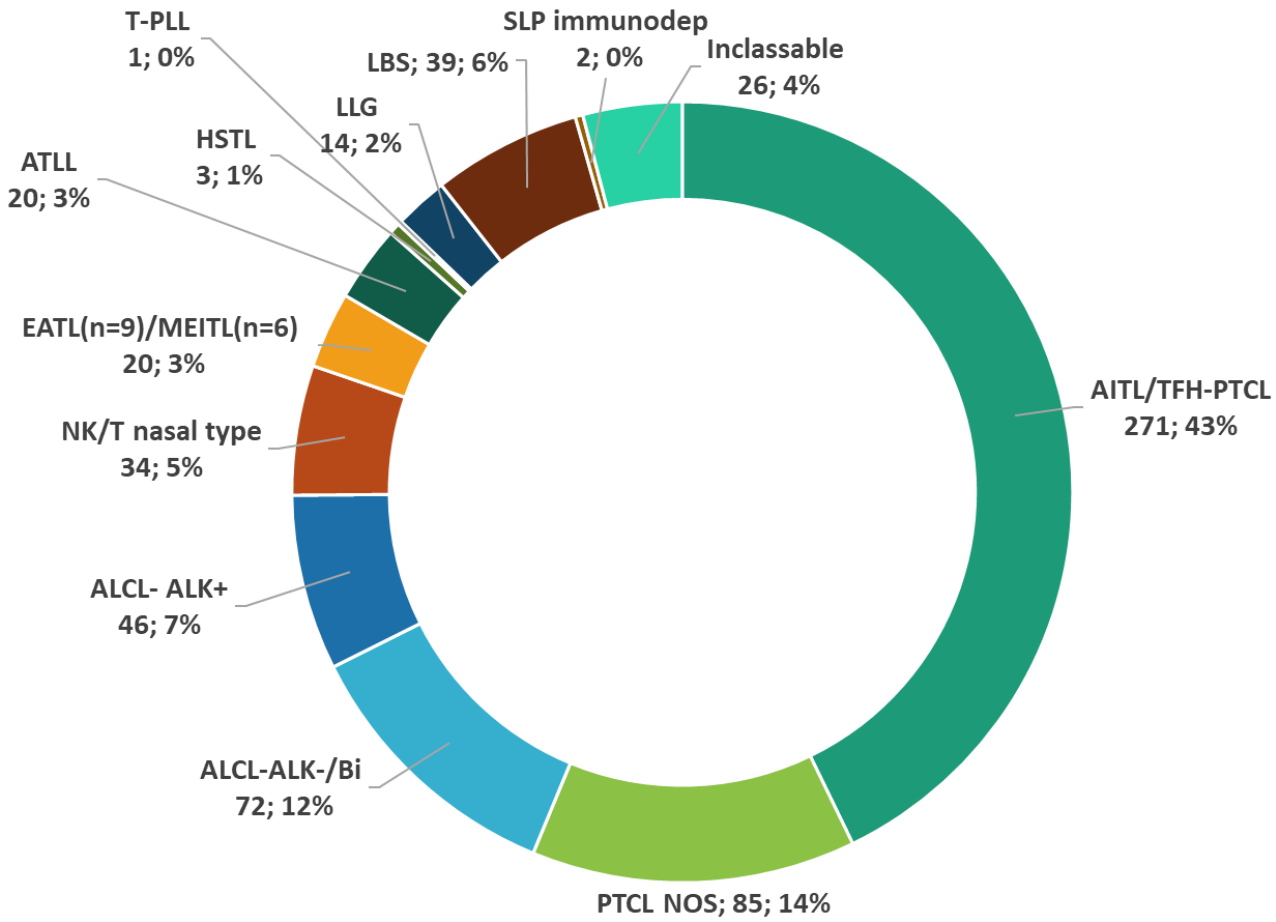
The most prevalent PTCL…..!



***Lymphopath* 2010-13**

(36.920 (non-cutaneous) lymphomas, **2.049 PTCL**)

Laurent C et al. J Clin Oncol 2017

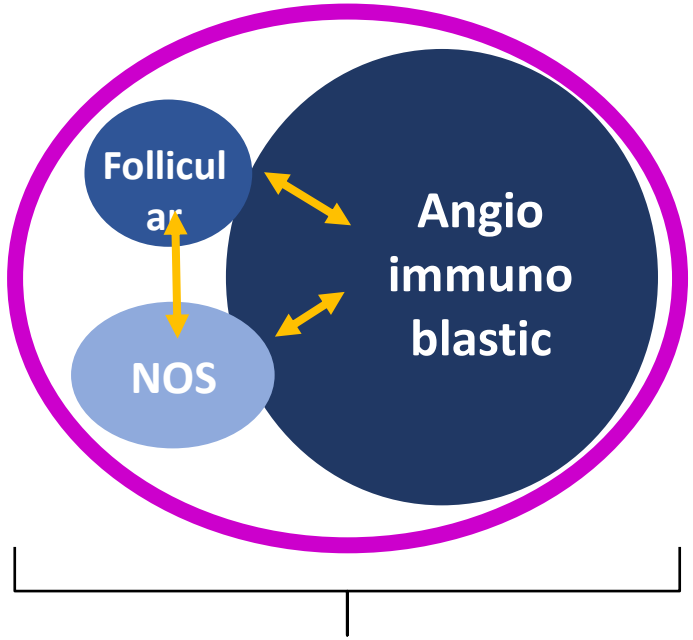


Lymphopath 2019

(NODAL) TFH LYMPHOMAS – Summary

- **Applies to CD4+ non primarily cutaneous lymphoproliferations**
- **Unique TFH signature and genetic landscape (except IDH2 only in AITL)**
- **A large pathological spectrum and combinations of patterns**
  - Overlapping features
  - FDC expansion is a key feature of AITL
  - Multiple patterns can be seen in individual patients
- **Differences in microenvironment signature which may impact diagnosis**
- **No evidence that the distinction between AITL and other nodal TFH lymphomas has clinical importance, and a <u>diagnosis of nodal TFH lymphoma is acceptable</u>**
- **Sensitivity to demethylating agents, HDACi….**

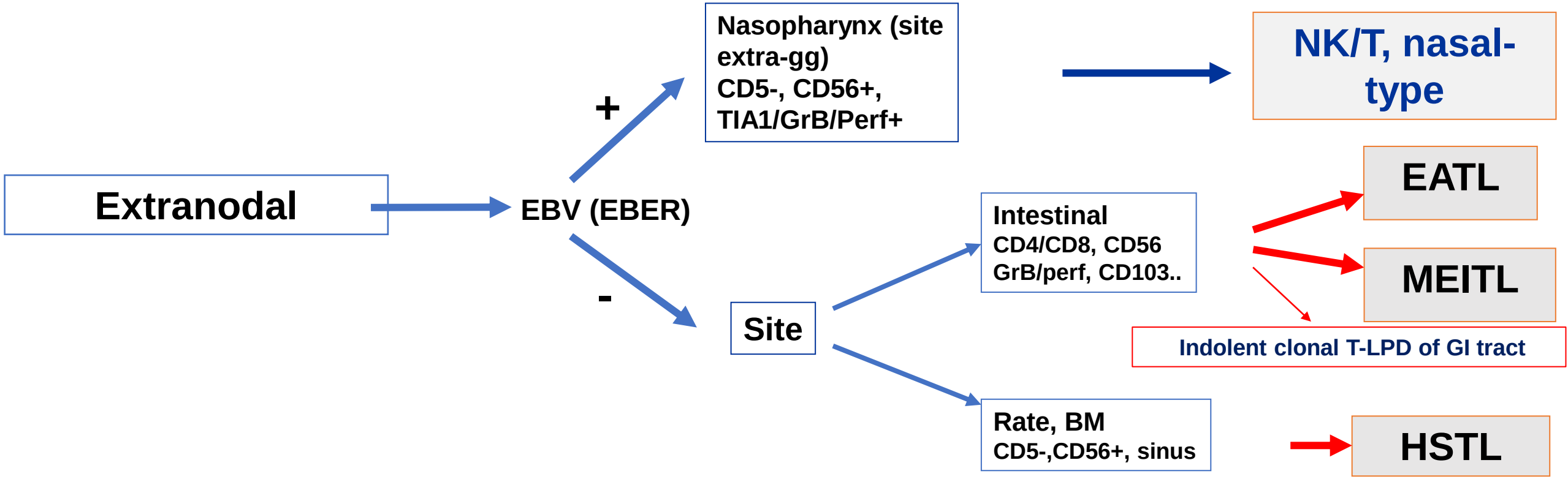
<u>ICC 2022</u>
TFH lymphoma
One entity - three subtypes



TFH signature and phenotype
Clinico-pathological features
Mutational landscape, clinical relevance

Attygalle AD et al.AJSP 2007; Attygalle A et al. Histopathology 2014; Dobay MP et al Haematologica 2017
(°) Iqbal et al. Blood 2010; Amador et al. J Clin Oncol 2022

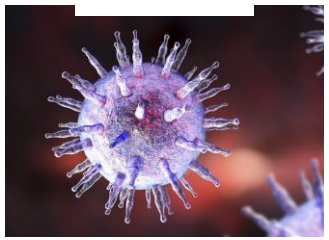
6- Extra-nodal T or NK-cell lymphomas (non cutaneous)

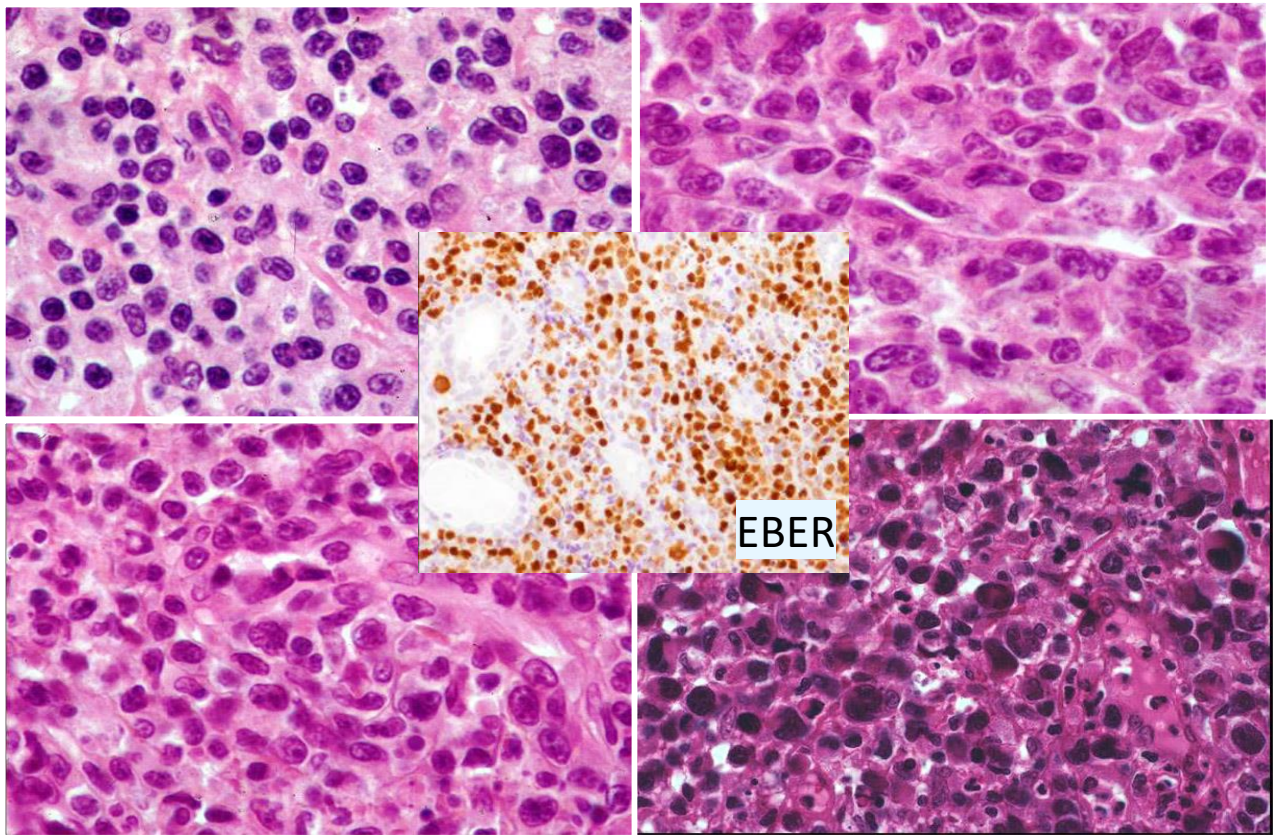


! ATLL can present in the skin, bone or other extranodal site..
!! Any other specific nodal entities can present with extranodal (rarely prominent) localisations (ex: skin in AITL…)
!!! By exclusion of any other diagnosis, PTCL, NOS

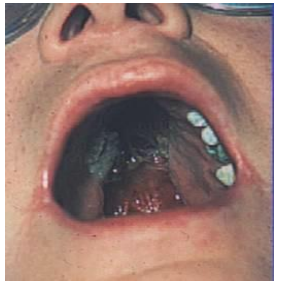
Extranodal NK/T cell lymphoma, nasal-type

EBV



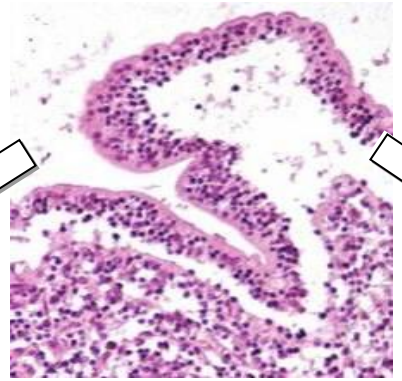


Bossard C et al. Blood 2007

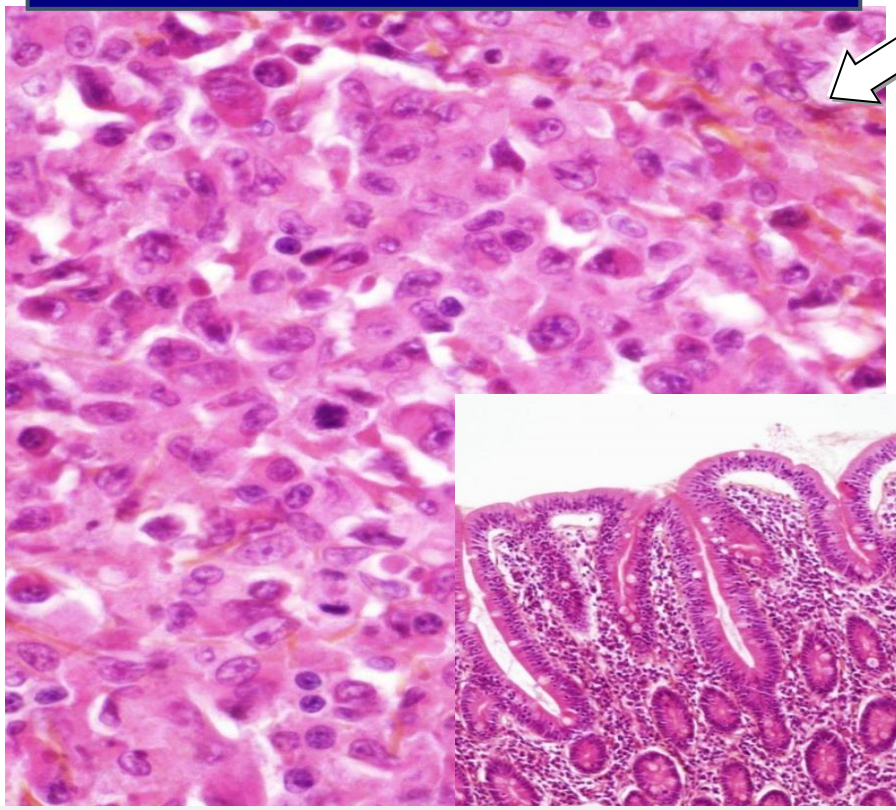


- ✓ **Asia, Central & South America**
- ✓ Median age, 40y
- ✓ Angiocentrism, necrosis, wide cytological spectrum…
- ✓ CD3+/CD5-, CD56+(-), cytotoxic
- ✓ **NK >> T (γδ, αβ)**
- ✓ **EBV (100%) (EBER>LMP1)**
- ✓ Genetic susceptibility
- ✓ 40-50 % 5y OS
- ✓ **Mutations** : *STAT5-STAT3, JAK3, DDX3X, BCOR,…*
- ✓ **6q21-25 deletion (TSG)**
- ✓ **"Nasal-type"** : similar cases is skin, GI tract, testis, …..

Intraepithelial lymphocytes (IEL) CD103+

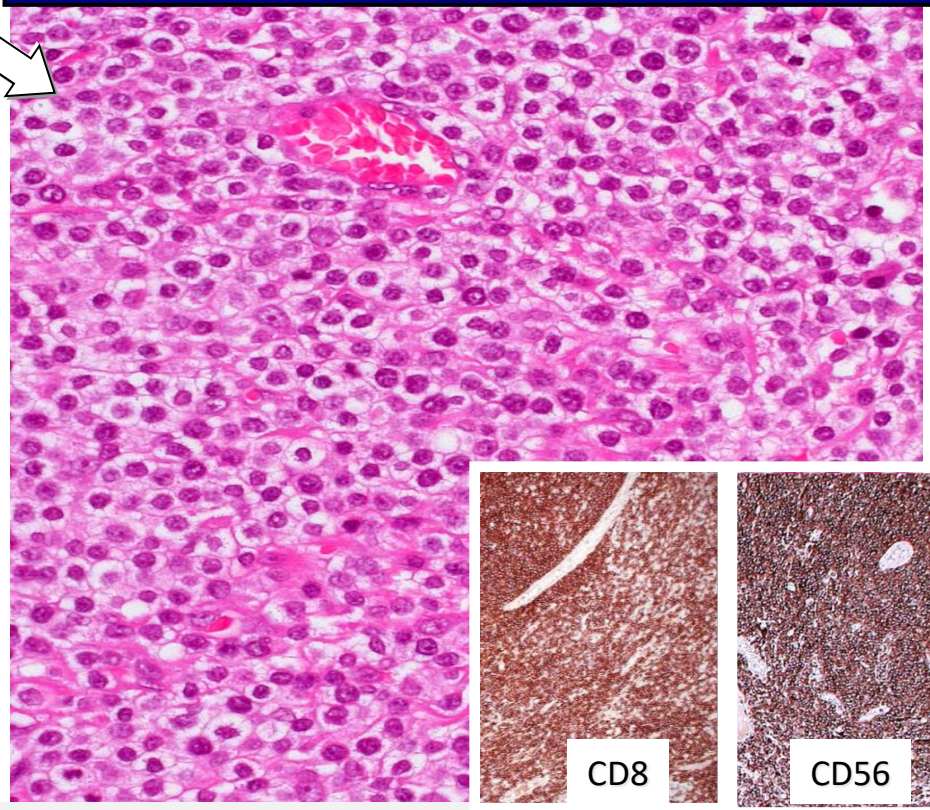


Enteropathy-associated TL (EATL)



- Complication of CD or *de novo* (50%), **possible stage of RCD/Intraepithelial EATL**
- Environmental factor: **gliadine**
- **Mostly** αβ or TCR silent, CD8-, CD56-, often CD30+
- Frequent mutations in JAK1, STAT3, but STAT5B/SETD2 rare

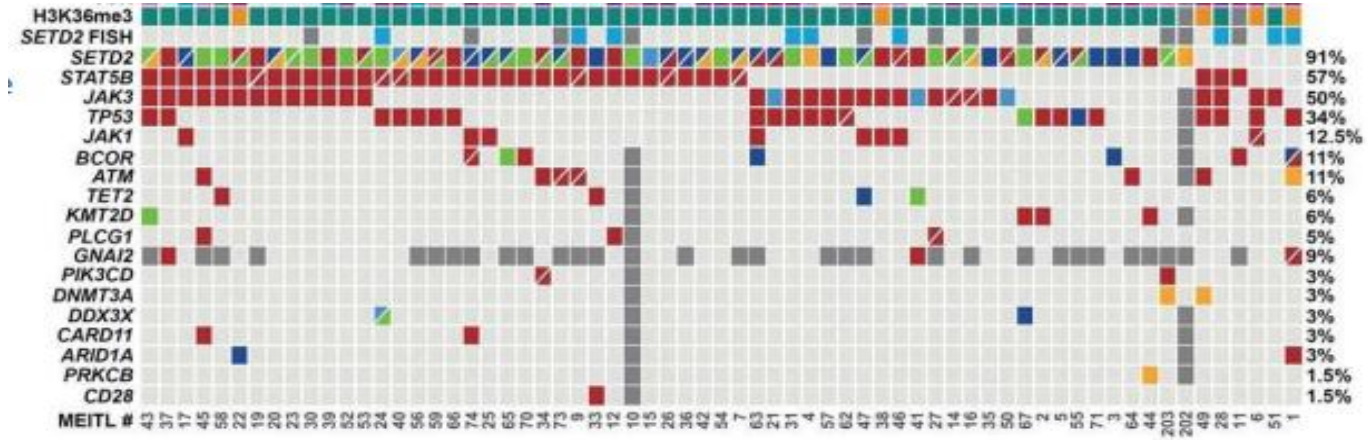
Monomorphic epitheliotropic ITL (MEITL)



- Absence of CD (so far), no clinical & histologic features of enteropathy
- Environmental factor (ag) ?
- **Often** γδ, more rarely ab or TCR silent, CD8+, CD56+
- Frequent mutations in SETD2 (95%), STAT5B, JAK3

EATL and MEITL are phenotypically and genetically distinct diseases

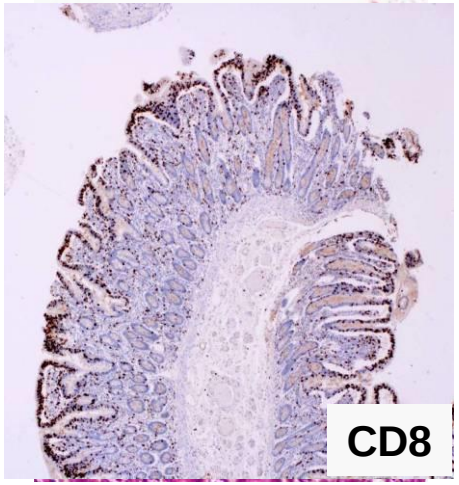
	EATL	MEITL
Phenotype	CD8-, CD56- CD30+ MATK-, SYK- NKP46+	CD8+, CD56+ CD30- MATK+, SYK+ NKP46- (?)
TCR	TCR silent > αβTCR > γδTCR	γδTCR > αβTCR > TCR silent/double
Epigenetics	*SETD2 rare* *KMTD2, TET2*	***SETD2 (~90%)***
JAK-STAT pathway	***JAK1 (20-70%)*** ***STAT3 (20-50%)*** *JAK3 (10%)* *STAT5B rare*	*JAK1 (~10%)* *STAT3 rare* ***JAK3 (~50%)*** ***STAT5B (50-70%)***
Others		*GNAI2* mut (9-25%)



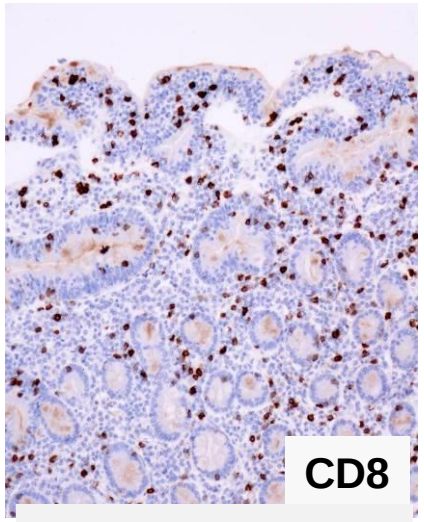
Roberti et al. Nature Comm 2016; Nicolae et al. Leukemia 2016; Moffitt et al. JEM 2017; Cheminant et al. Gastroenterol 2019; Cording et al. Gut 2020; Nairismagi et al. Leukemia 2016; Huang et al. Blood Adv 2020; Tomita et al. Cancers 2020; Veloza et al. Haematologica 2022

L Veloza et al. Haematologica 2022

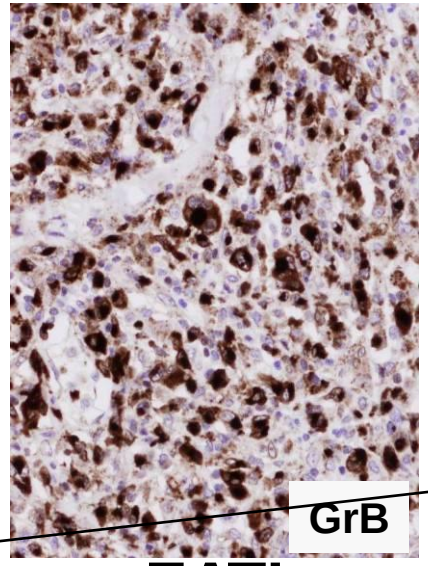
EATL, not MEITL, can be preceded by celiac disease …



Celiac disease



RCDII/ Intraepith EATL



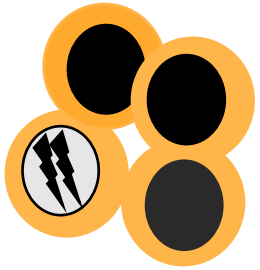
EATL

ICC 2022

Environmental fr (gliadin,..) HLA context

Cytokines (IL-15,…)

Refractory CD /intraepithelial TCL



EATL

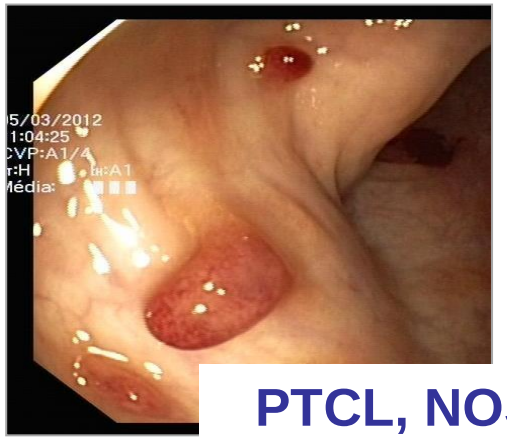
Poor prognosis

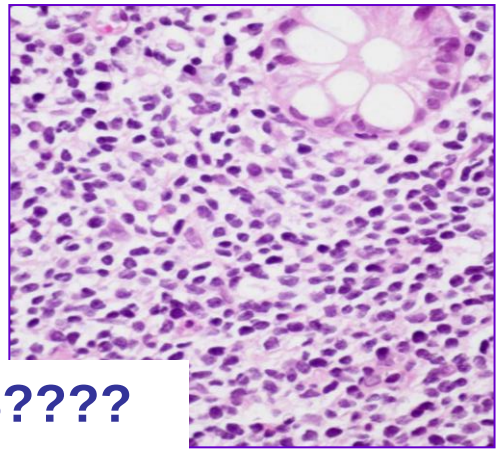
EBV
CD3, CD7
CD8, CD56
TIA1/GrB
!CD30

A 71-year-old female was submitted to emergency for acute abdominal pain → peritonitis
No peculiar clinical history

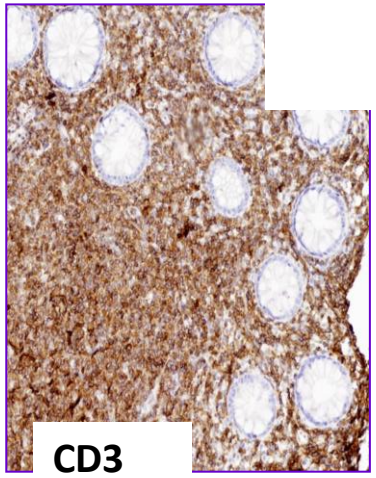
But…..

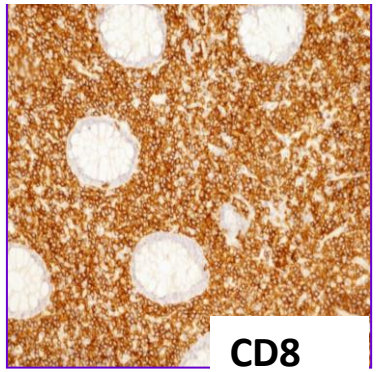
• A 31 year-old man, presenting without chonic diarrhea, without B symptoms
• Multiple polypoid lesions (ileon, colon) at endocopy
• Clinical staging & laboratory tests: normal

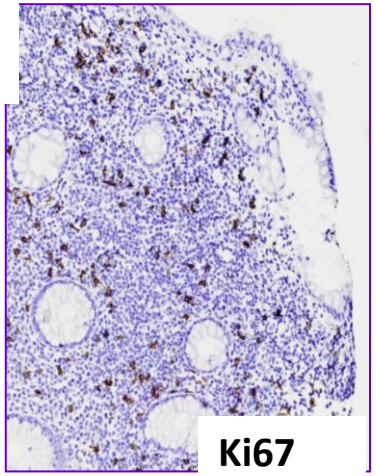




PTCL, NOS????
MEITL
Or…?







- CD20-, CD2+, CD3+, CD5+, CD7+, CD4-/CD8+, TCRab+, CD56-, TiA1+, GrB-, **Ki67<5%, EBERs** -
- **T cell clone.**

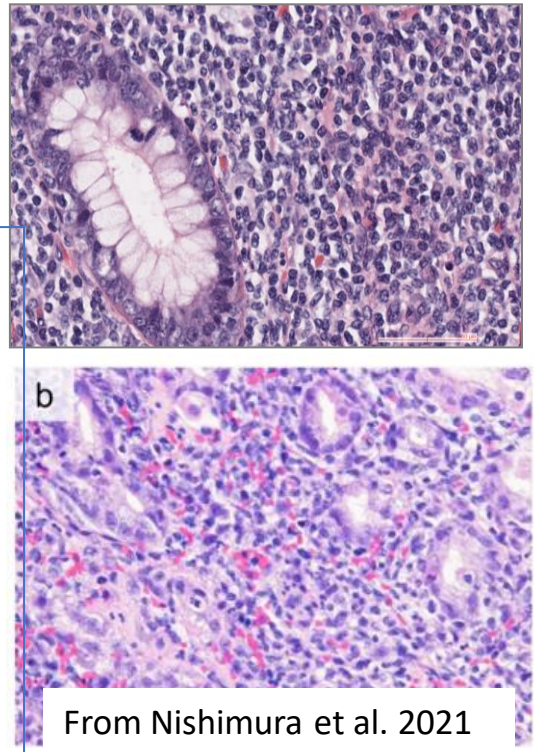
Indolent T-cell clonal LPD of the GI tract

Takeuchi et al. Blood 2010; Mansoor et al. Blood 2011;
Perry et al. Blood 2013; Sharma et al. Blood 2018; Craig et al Haematologica 2020;
Montes-Moreno et al. Virchows Arch 2020

Indolent T or NK cell LPDs of the GI tract

Indolent clonal T-cell LPD of the GI tract

- ✓ Adults, M>F
- ✓ **Intestine, colon** > stomach
- ✓ Context of Crohn's possible
- ✓ May disseminate/transform
- ✓ **Small lymphocytes**, no epitheliotropism
- ✓ **CD4 or CD8, TCRαβ, low Ki67 (<10%)**
- ✓ **Clonal TR Rearragt**
- ✓ JAK-STAT mutations
- ✓ JAK2-STAT3 fusions (CD4+)



From Nishimura et al. 2021

Indolent NK-cell LPD of the GI tract (formally NK cell enteropathy, lymphomatoid gastropathy)

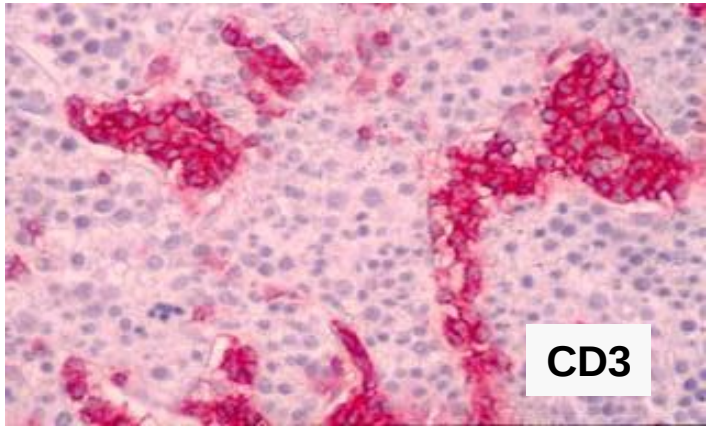
- ✓ Adults, children, M/F
- ✓ **Stomach**, duodenum, colon
- ✓ No specific context
- ✓ May persist, recur or resolve
- ✓ **Atypical medium/large cells**
- ✓ H Pylori frequent
- ✓ **NK cell phenotype (CD3ε +, TCR-), KI67 variable**
- ✓ **Absence of clonal TR Rearragt**
- ✓ JAK3 mutations (30%)

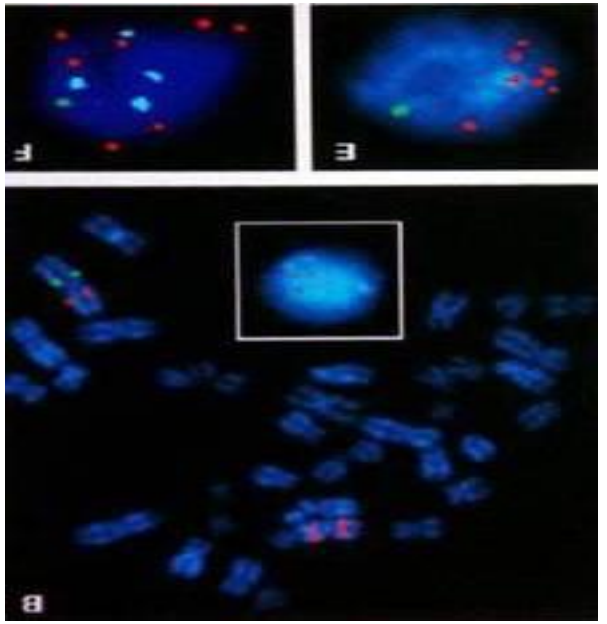
- Do not respond to anthracycline-based chemotherapy
- **« Clonality »** to avoid overcalling florid reactive T-cell infiltrates
- Homogeneize nomenclature and keep distinction according to cell lineage

Carbonnel F et al. Cancer 1994; Perry AM et al. Blood 2013; Sharma A et al. Blood 2018; Perry AM et al. Int J Surg Path 2019; Soderquist CR et al. Haematologica 2019; Xiao WB et al. Blood 2019; Montes-Moreno S et al. Virchow Archiv 2020; Dargent JL et al. Virchow Archiv 2021; Nishimura et al. Cancers 2021

Hepatosplenic T-cell lymphoma

- ✓ Rare, very aggressive disease
- ✓ Young adults & children
- ✓ B symptoms, pancytopenia
- ✓ Splenomegaly, hepatomegaly, BM (sinusoidal distribution)
- ✓ $\gamma\delta > \alpha\beta$
- ✓ Non activated cytotoxic (TIA1+, GrB-) CD56+ phenotype
- ✓ Context: chronic ag stimulation (PTLD, dysimmune conditions: Crohn's disease $\pm$ Infliximab)
- ✓ Isochromosome 7q +, $\pm$ Trisomy 8
- ✓ Distinct gene signature
- ✓ Recurrent mutations : *STAT5B-STAT3, SETD2, IN080, ARID1,..*
- ✓ Very poor outcome



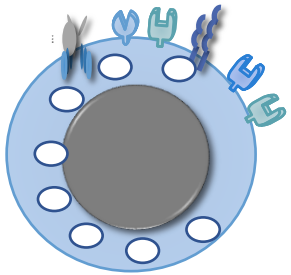


Belhadj et al. Blood 2003; Yabe et al. Human Pathol 2018; Pro et al. Blood 2020;
Travert M et al. Blood 2012; Nicolae et al. Leukaemia 2014; Mc Kinney et al. Cancer Discov 2017

Common features of PTCL from the innate immune system

- Extranodal NK/T cell lymphoma, nasal-type (NKTCL)
- Enteropathy-associated T-cell lymphoma (EATL)
- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
- Hepatosplenic T cell lymphoma (HSTL)

- Intestinal T-cell lymphoma, NOS
-Indolent T cell LPD of the GI tract



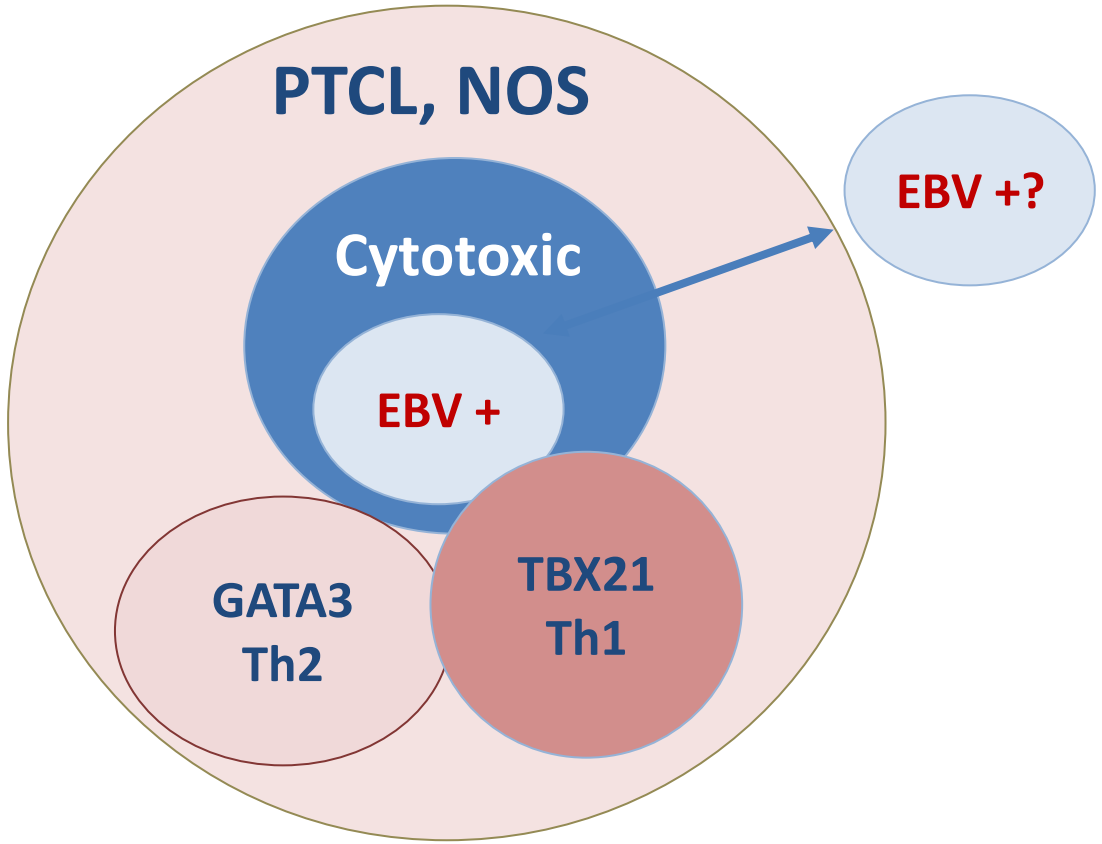
NK receptors (incl KIR3DL2)

NK, Tγδ, (Tαβ)

- Extranodal sites
- Cytotoxic
- **Plasticity** in cell counterpart (NK, Tγδ, Tαβ)
- **Chronic antigenic stimulation**
- Genetic susceptibility (?)
- Activation of the **JAK-STAT pathway**
- With the exception of T-LGL, poor prognosis

7 - What remains of “PTCL, NOS” in 2023?

- PTCL, NOS is mainly a nodal lymphoma that remains a **diagnosis of exclusion**
- Two molecular subgroups, namely PTCL-TBX21 and PTCL-GATA3,
- Expression of cytotoxic molecules delineates a subgroup of aggressive PTCL, NOS which tend to occur in patients with impaired immunity and mostly cluster to PTCL-TBX21.
- **Designation of PTCL, NOS according to the molecular subgroups is not routinely incorporated into clinical diagnosis and requires further studies for clinical validation.**
- **Investigation for EBV NEEDED -→ Primary nodal EBV-positive T/NK cell lymphoma, a distinct entity (ICC, WHO)**

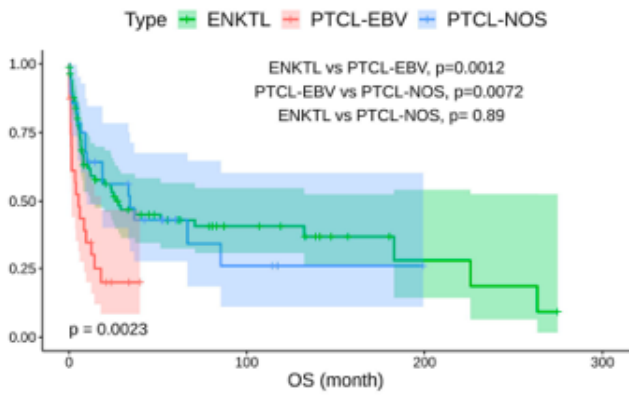


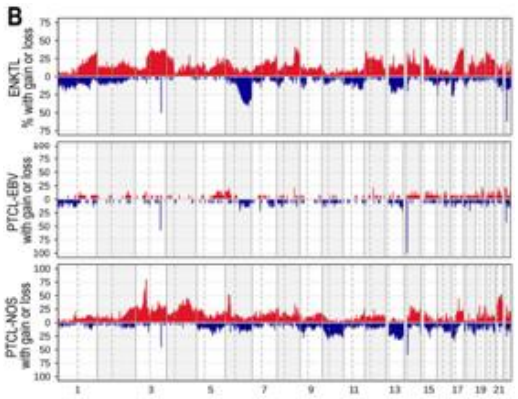
Iqbal et al. Blood 2010; Drieux et al. Haematologica 2020; Alinae et al. Modern Pathol 2022; Amador et al. J Clin Oncol 2022

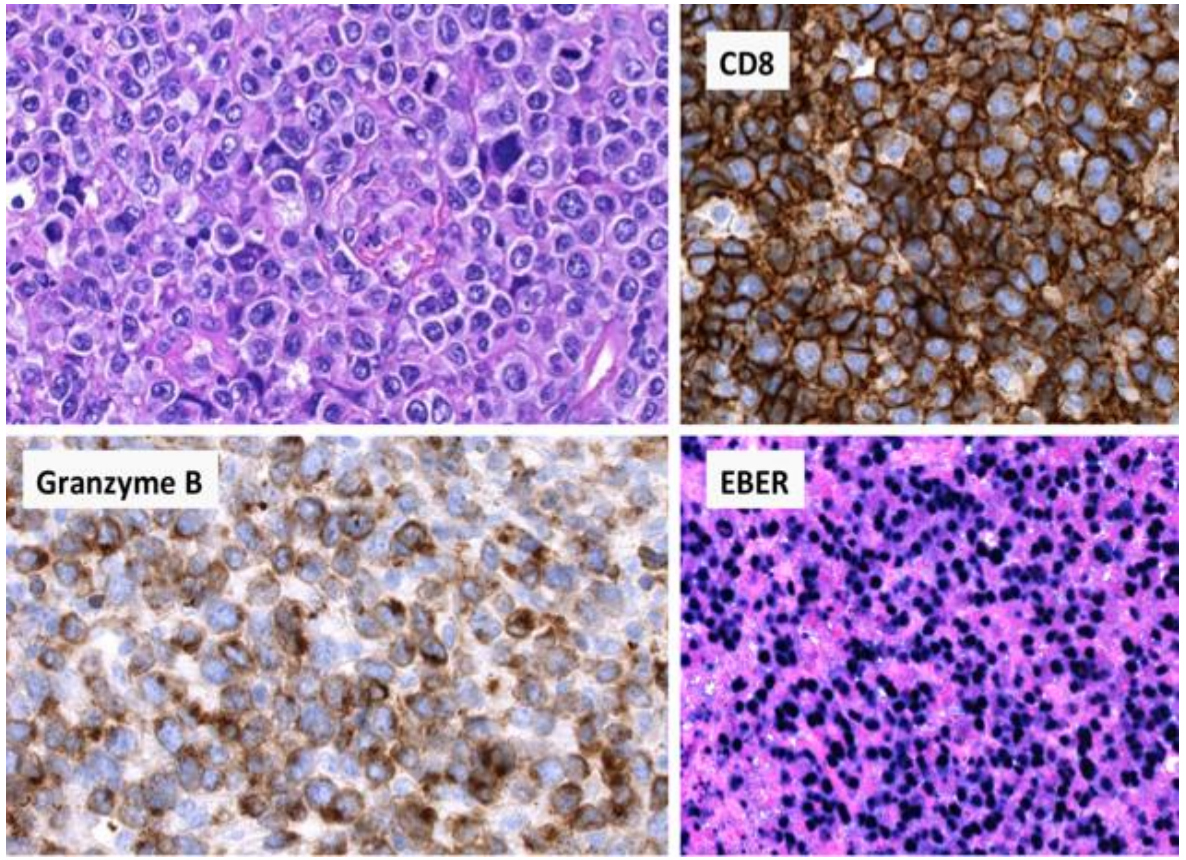
Primary nodal EBV+ T-cell/NK-cell lymphoma

ICC 2022: provisional entity

- ✓ **Formerly variant of PTCL-NOS**
- ✓ Most reports from Asia
- ✓ Adults, +/- immune suppression
- ✓ No nasal involvement
- ✓ Large cells +/- pleomorphic
- ✓ CD3+ CD5-/+ CD8+, activated cytotoxic phenotype
- ✓ frequent T> NK derivation
- ✓ In contrast to ENKTCL:
  - ° Angiocentricity and necrosis infrequent, CD56-
  - ° Lower genomic complexity, immune pathway activation and worse prognosis







Reviewed in Kato S et al. J Clin Exp Hematopathol 2020
Mai MM et al. Haematologica 2021

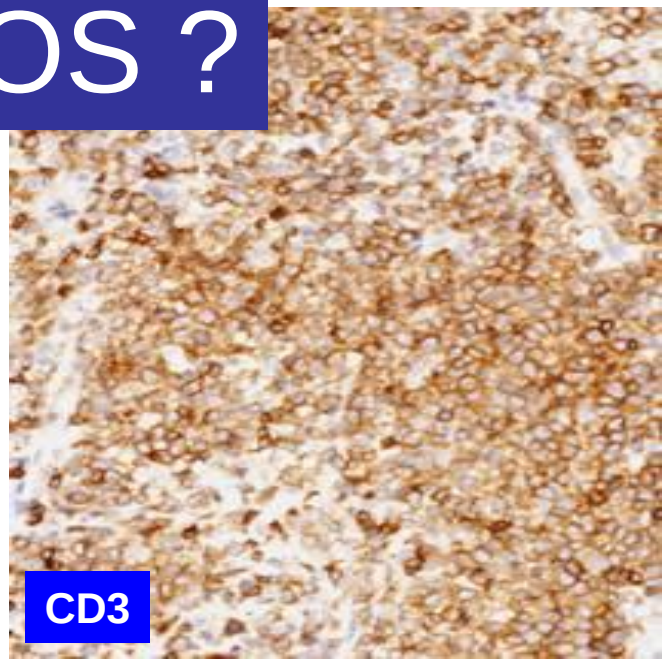
7 - What remains of “PTCL, NOS” in 2023?

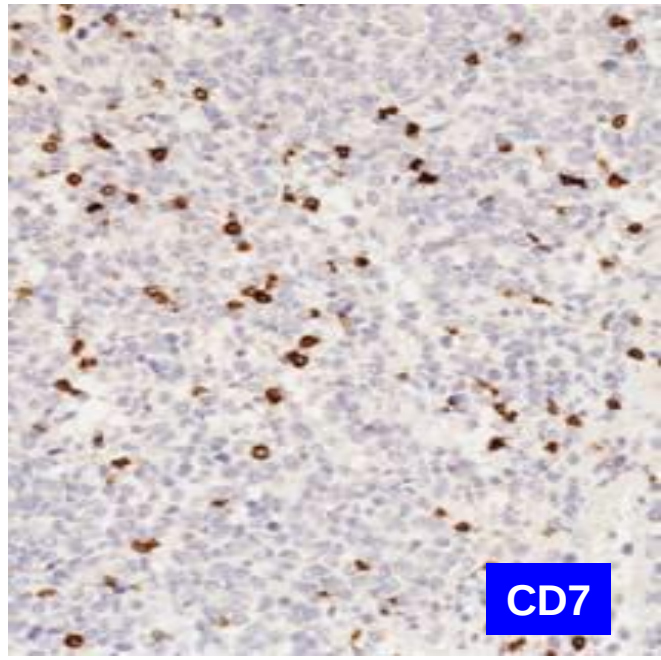
Every case of “PTCL-NOS” - a diagnosis of exclusion- requires in the routine practice the most extensive panel of IHC markers (TFH markers, FDC, EBV, CD30, cytotoxic,..) to exclude a better defined PTCL entity, especially a PTCL of TFH origin, ALCL, or involvement by an extranodal PTCL

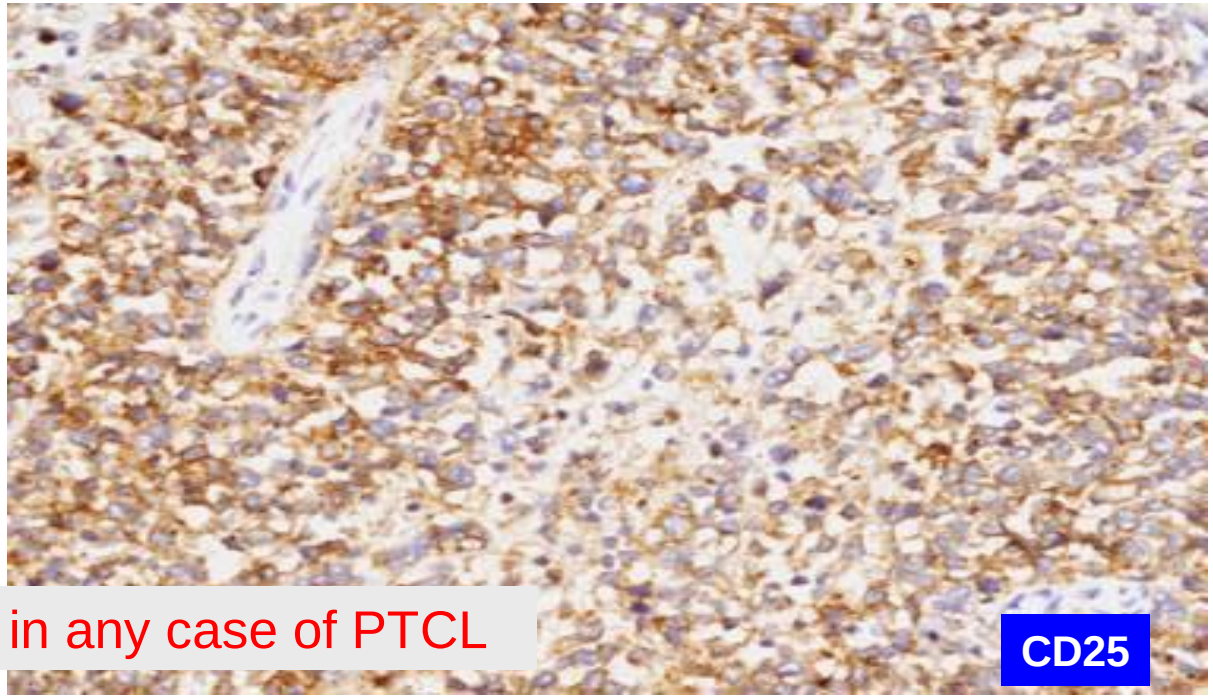
PTCL, NOS ?

A 57 yo man,
French Carribean islands
B symptoms,
large tumor mass in the spleen
No other ADP

HTLV1 + → Lymphome/leucémie T de l'adulte (HTLV1+)



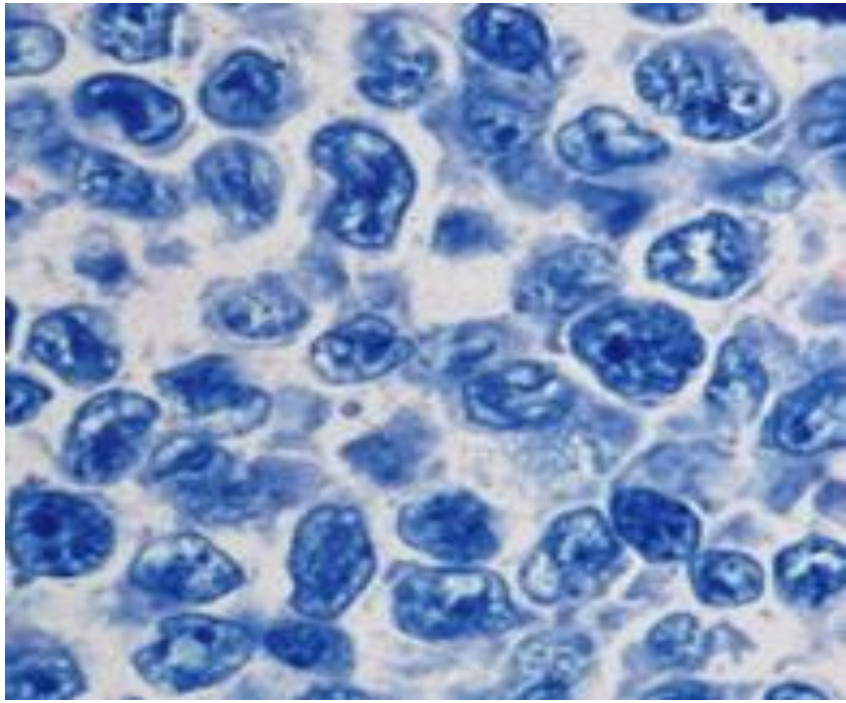




Serological tests for HTLV1 to be performed in any case of PTCL

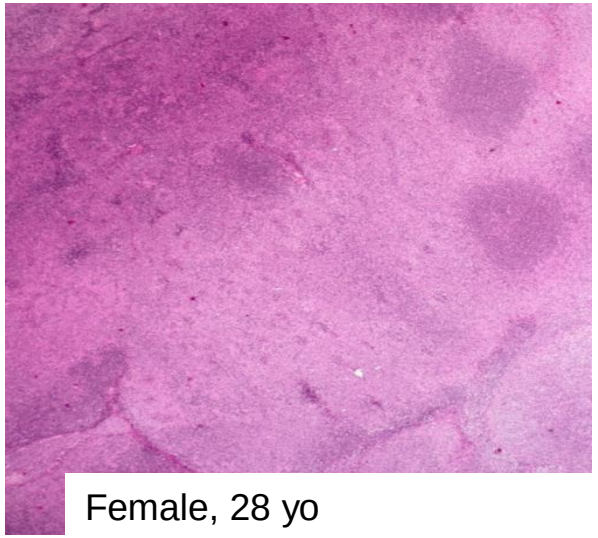
Adult T-cell leukaemia/lymphoma (HTLV1+) (ATLL)

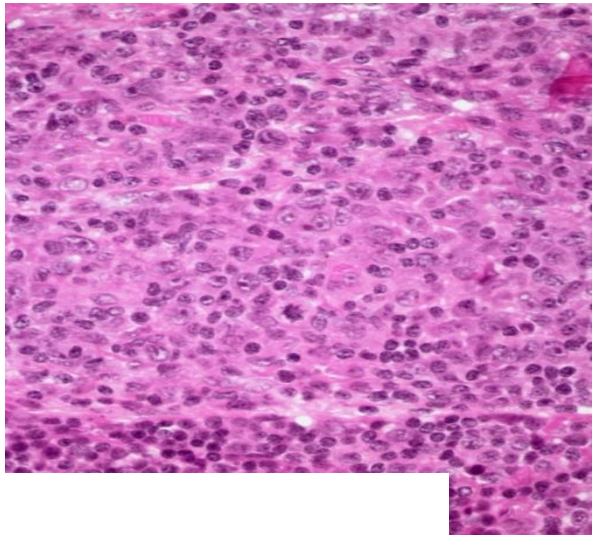
- A peripheral T-cell neoplasm caused by HTLV1
- Endemic : South Japan, Caribbean islands, Central Africa
- Adults (long latency ≥ 20y)
- Morphology highly variable: pleomorphic small, medium or large; convoluted nuclei (« flower » cells)
- Phenotype: CD3+, CD4+, CD7-, **CD25+, FoxP3+**
- Genotype: clonal integration of the viral HTLV1 genome
- Clinical variants with critical prognostic relevance:
  - smoldering (skin)
  - chronic
  - lymphomatous
  - acute (leukemic)



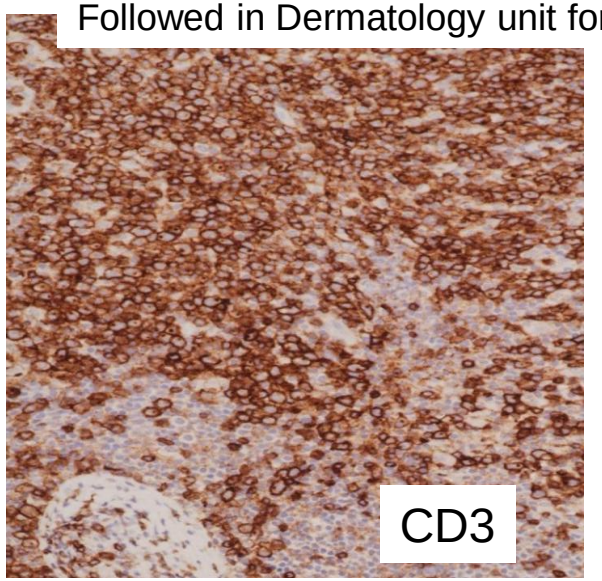
Serological tests for HTLV1 to be performed in any case of PTCL

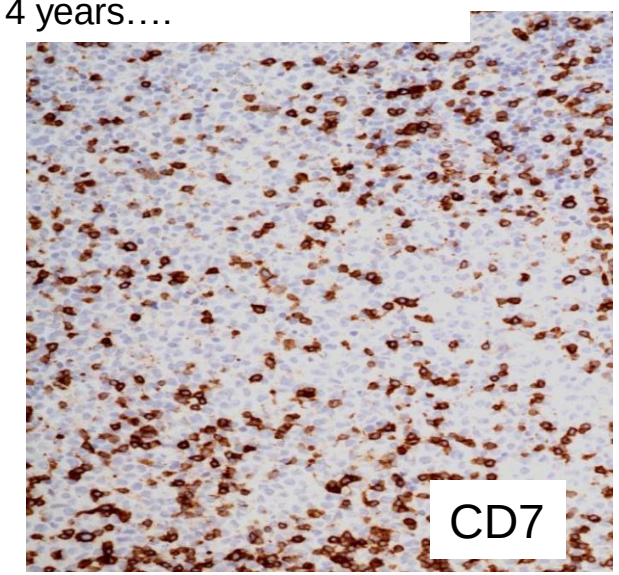
~~PTCL-NOS~~ – Lymph node involvement by Mycosis fongoïdes (transformed) !

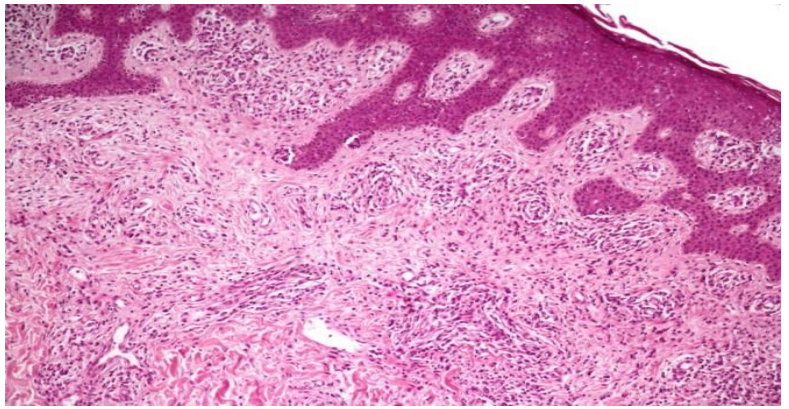




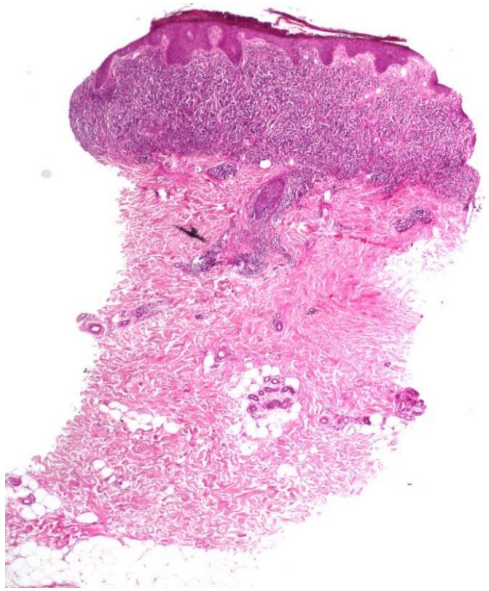
Female, 28 yo
Followed in Dermatology unit for 4 years….

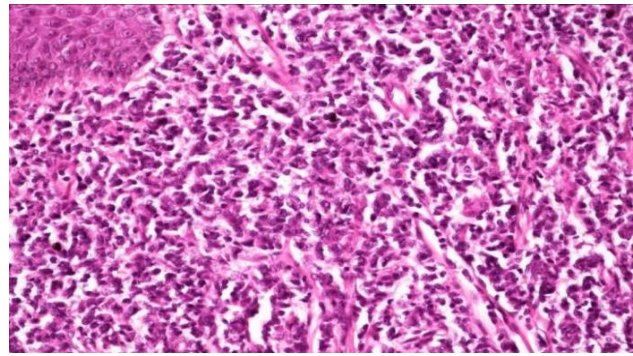






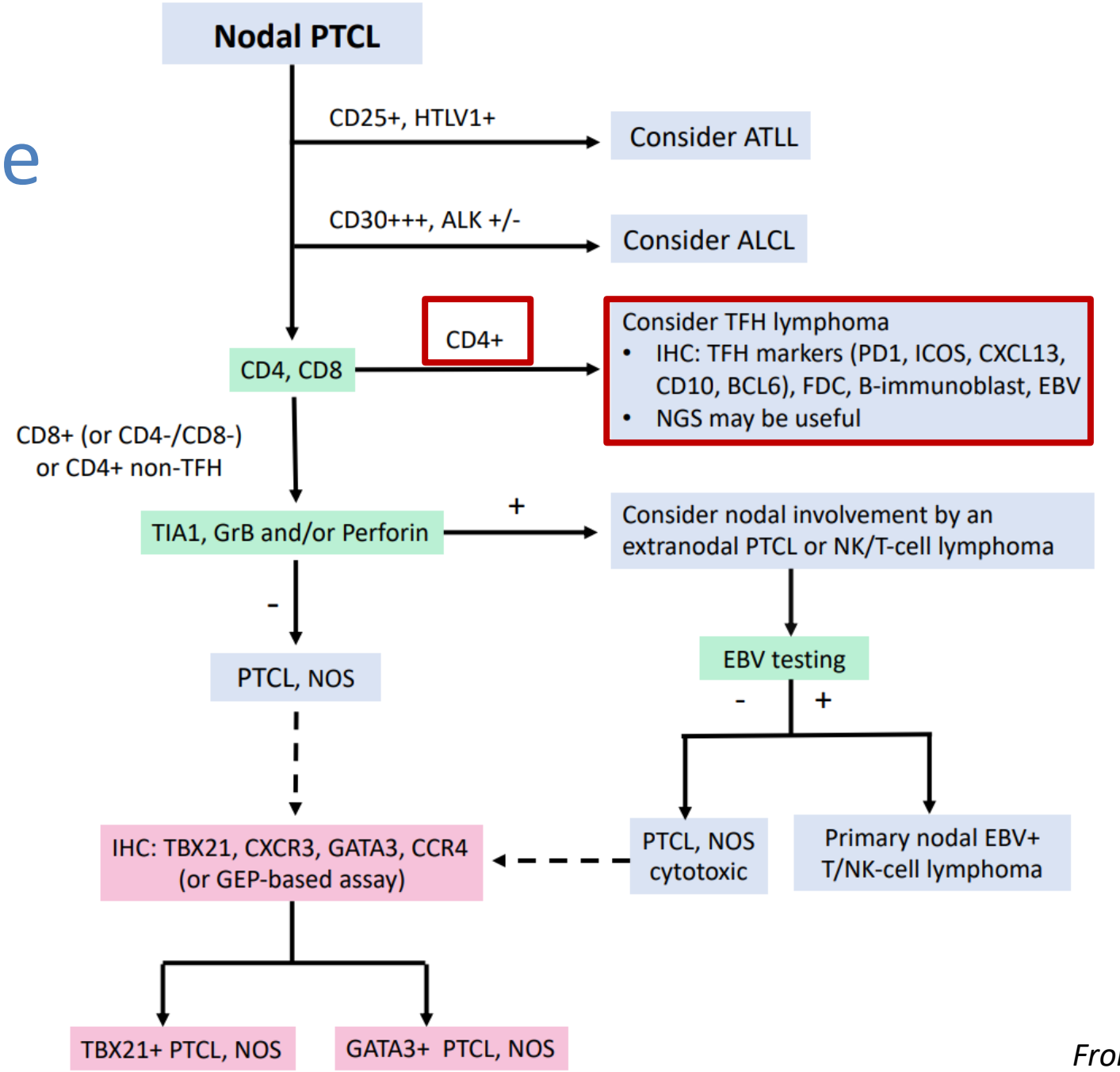
2011





2015

In practice



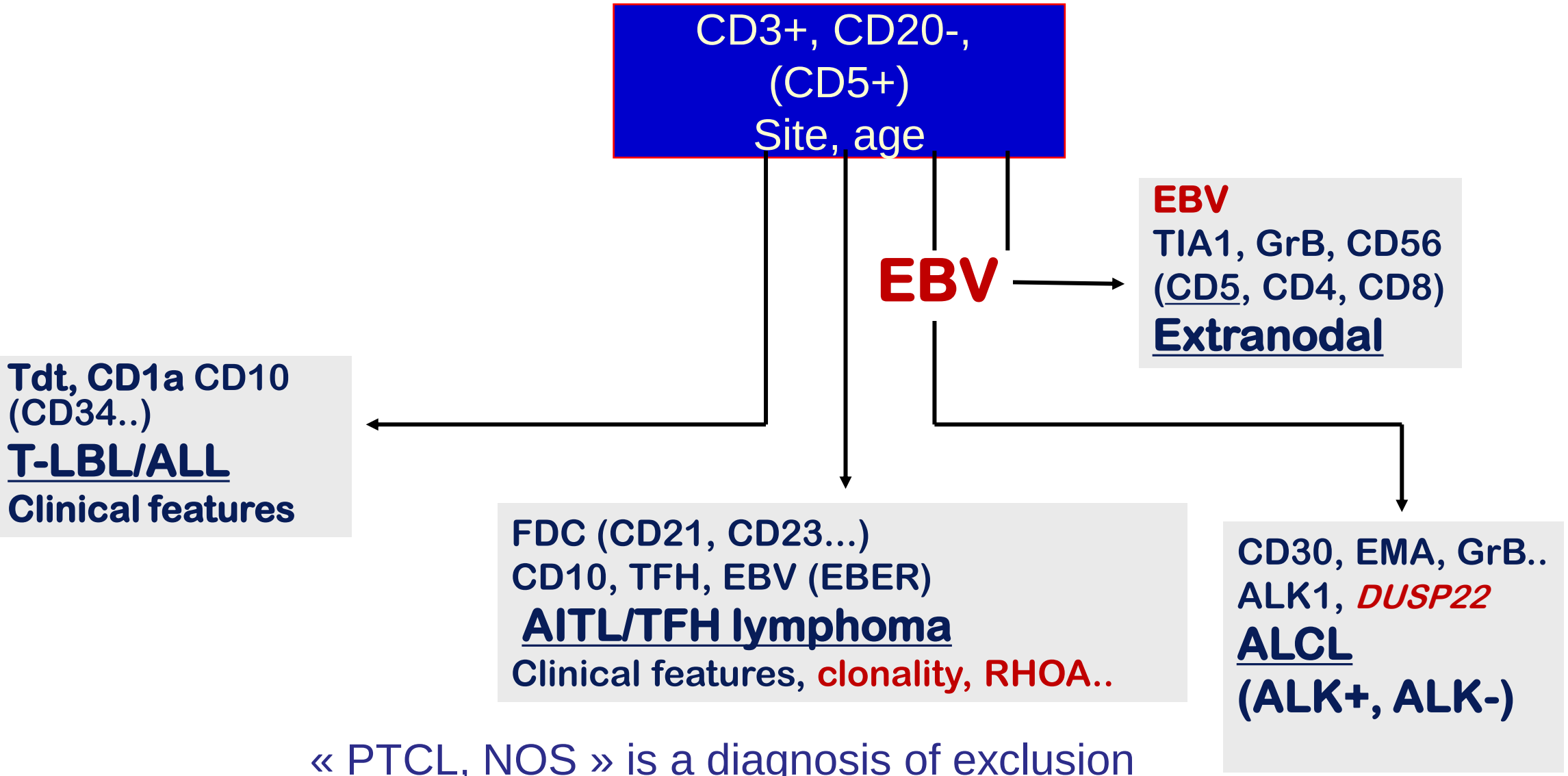
From Campo E et al.. Blood 2022

8 – What can we expect from molecular studies in PTCLs ?

- **EBV+++** (HIS EBER >LMP1)
- **Clonality (PCR γ),** to interpret according to the pathological & clinical context
- **Genetic alterations** :
  - ***IHC*** : ALK1 (IDH2R172K)
  - ***FISH*** : DUSP22 (ALCL, ALK-) (TP63)
  - ***Sequencing***
    - Targeted (possible) : ***RHOA (G17V), IDH2*** *(TFH lymphoma)*
    - *NGS (mutations) (in practice, gene panels are often large and not PTCL specific) :*
      - ***RHOA (G17V), IDH2,*** *TET2, DNMT3A* in TFH-PTCL
      - JAK-STAT pathway : *JAK3, STAT3, STAT5B*.. in HSTL, EATL, MEITL, ALK- ALCL, T-LGL…
      - others (*SETD2, BCOR,…*)
- Gene expression (Nanostring, RT-MLPA..), fusions: yet, limited impact in the routine practice

Diagnostic & therapeutic relevance

9 - Diagnostic Algorythme of non-cutaneous PTCL



« PTCL, NOS » is a diagnosis of exclusion

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