



Society for Hematopathology & European Association for Haematopathology
SH/EAHP Workshop 2017
September 7-9, 2017 • Chicago, IL

ASCP2017
ANNUAL MEETING



Clonal evolution of a TET2 mutated angioimmunoblastic T-cell lymphoma (AITL) towards an EBV-associated TFH-PTCL

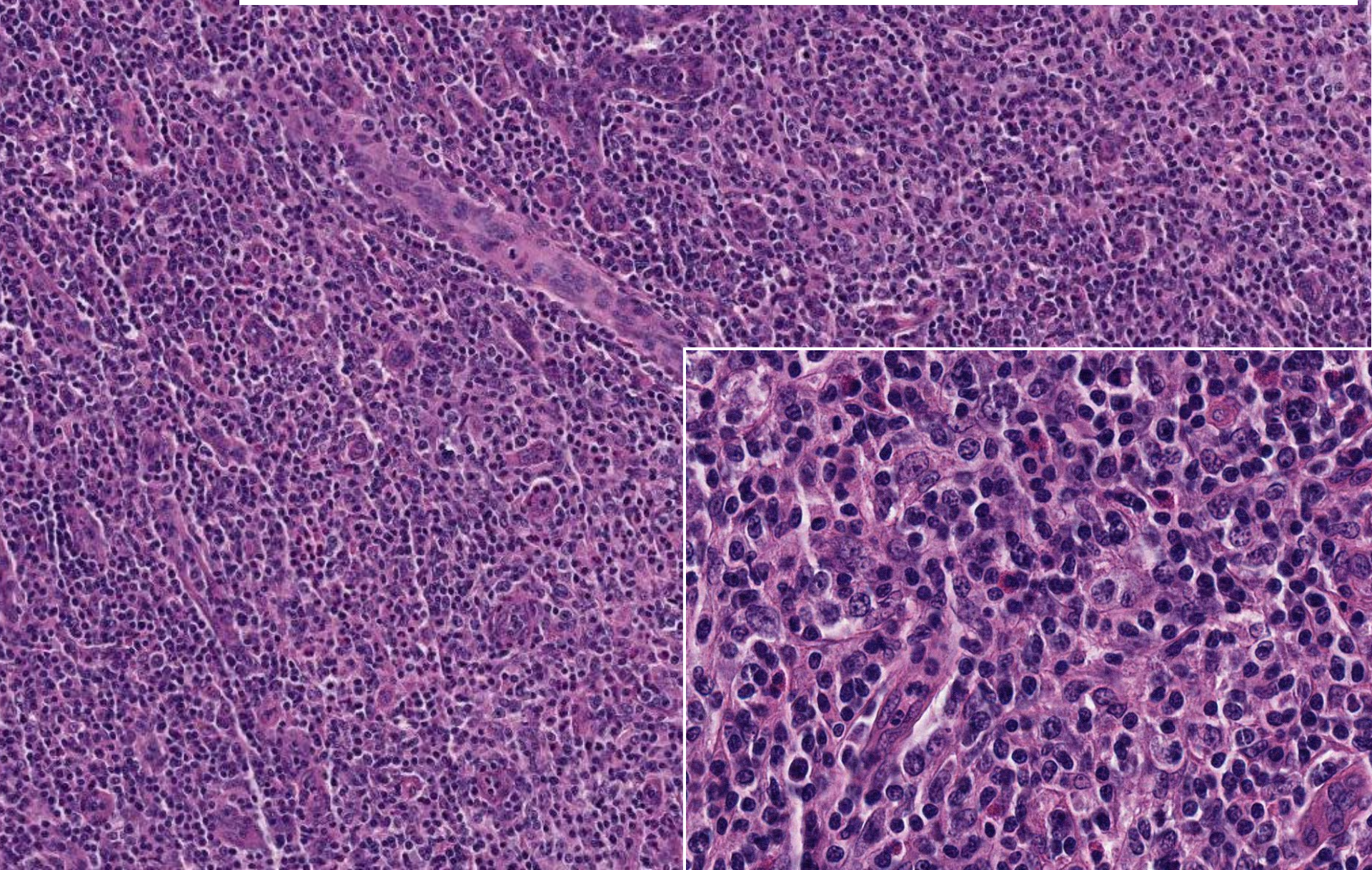
Case SH 2017- 0377

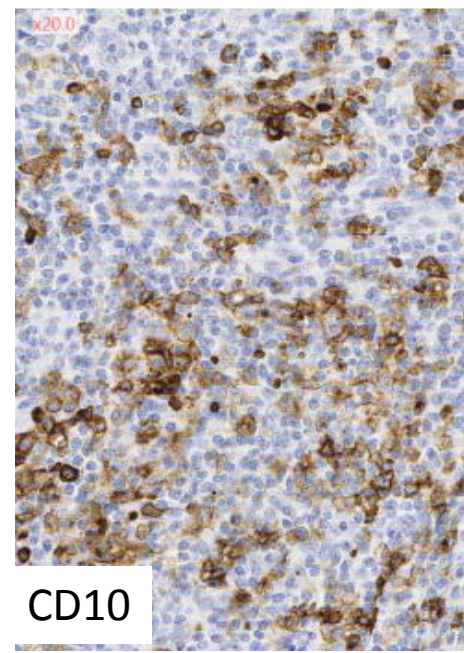
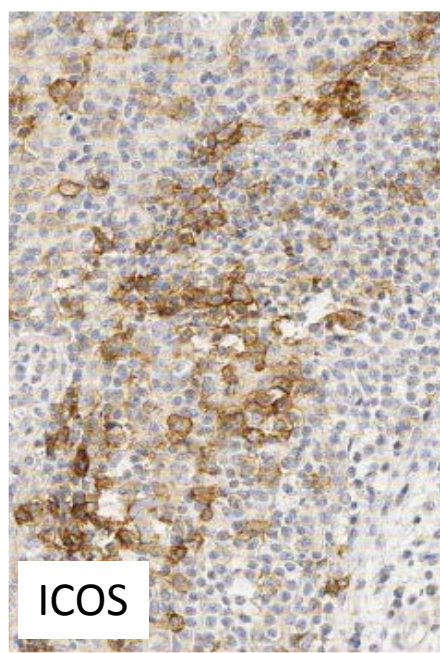
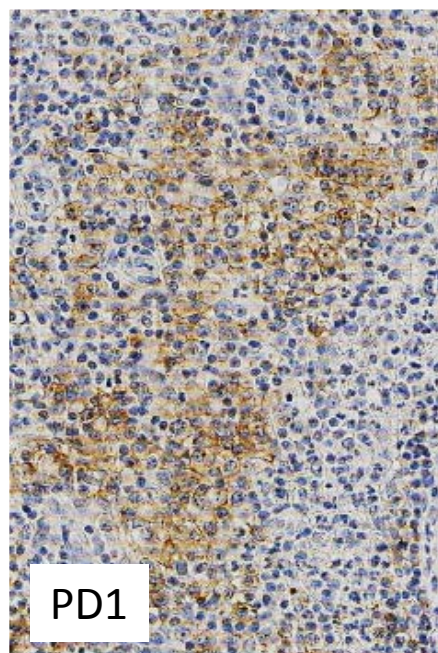
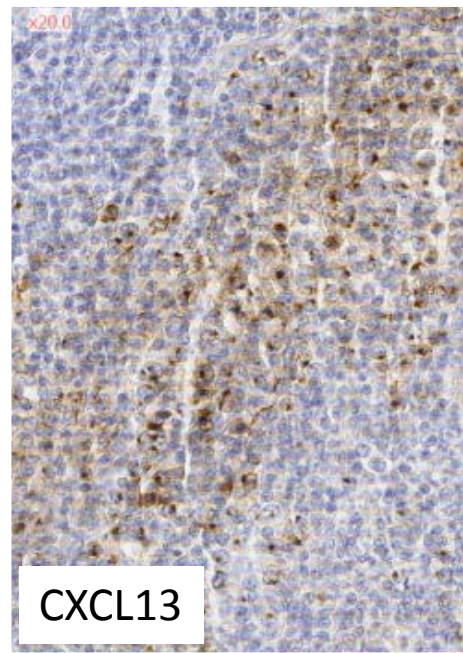
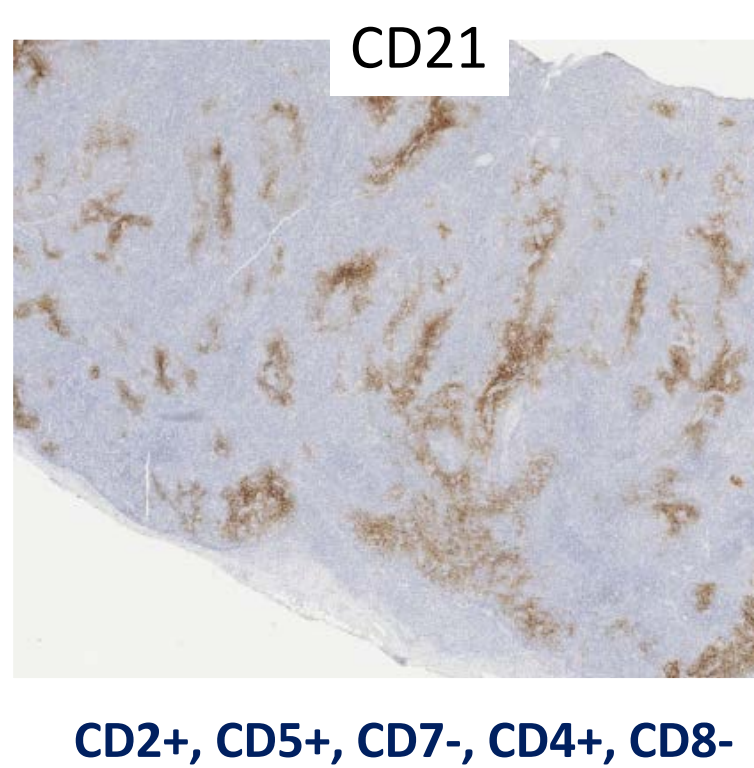
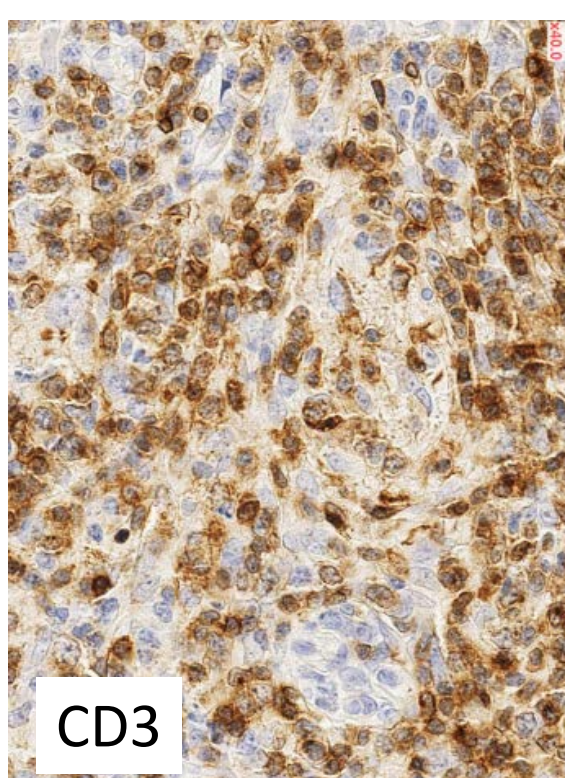
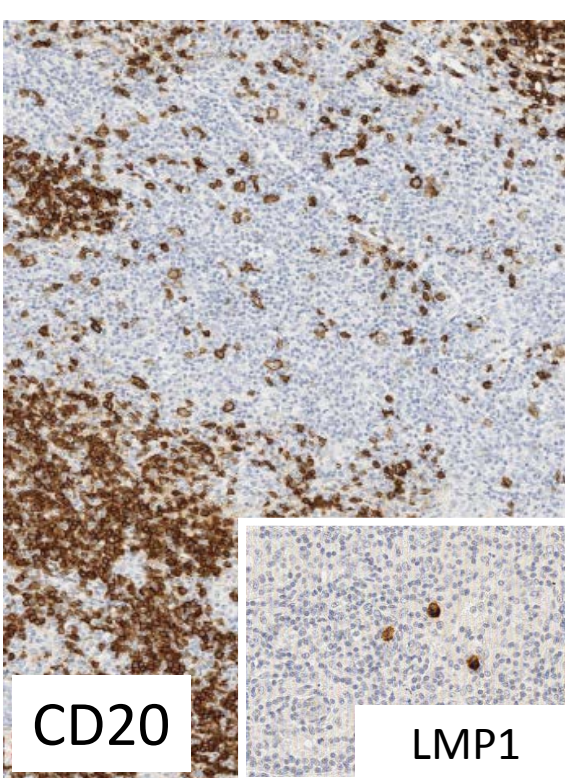
C Bossard (°), C Copie-Bergman (*), F Lemonnier (*), P Gaulard (*)
(*) University Hospital Henri Mondor, Créteil, France
(°) University Hospital, Nantes, France



1995

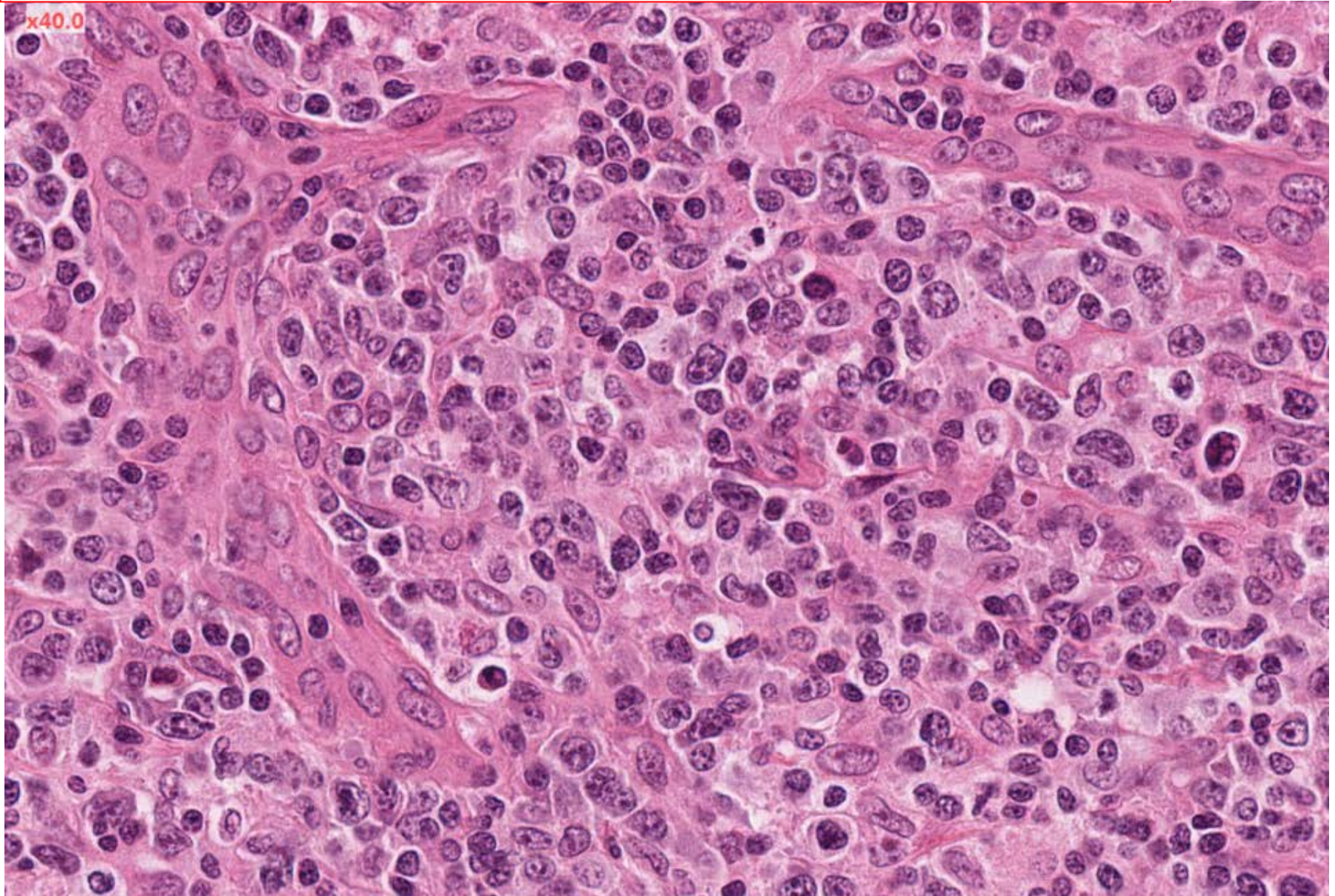
- ° A 37 yo woman without medical past history
- ° Polyadenopathies, B symptoms, BM involvement
- **First lymph node biopsy (iliac)**



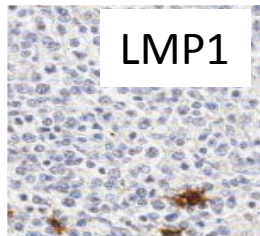
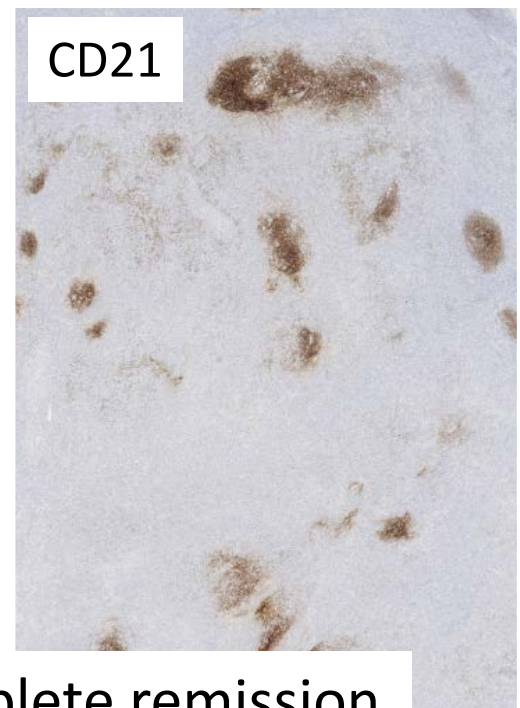
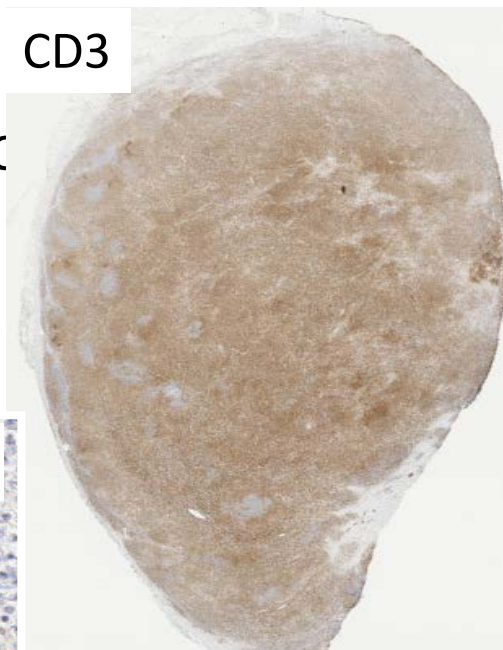
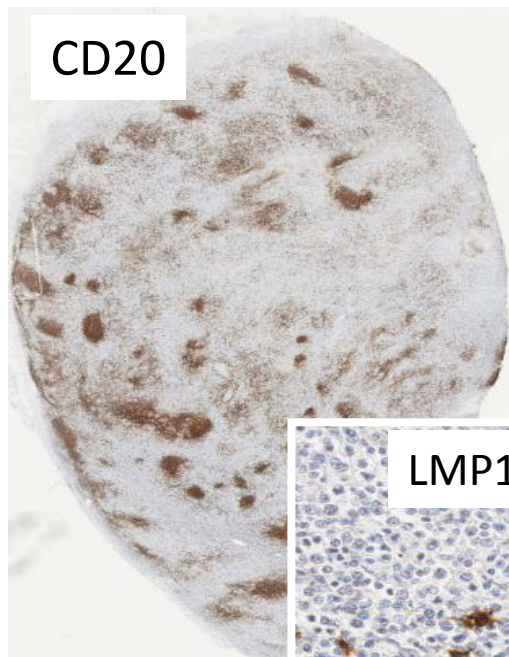


- Diagnosis of AITL
- The patient was given 4 cycles of CHOP followed by aracytine, VP16, cisplatin and then BEAM conditioning autologous stem cell transplantation
- She underwent a CR till 1998

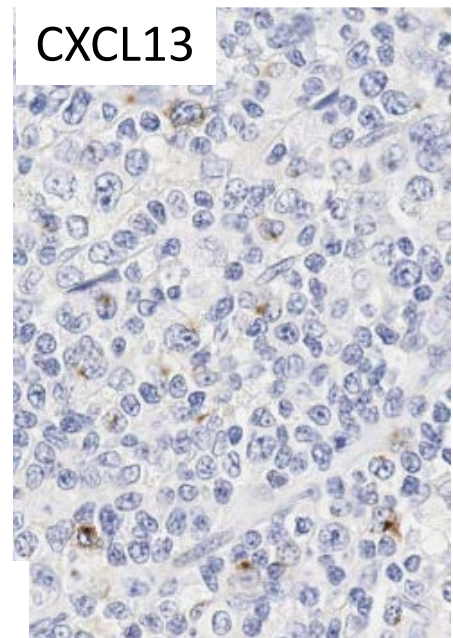
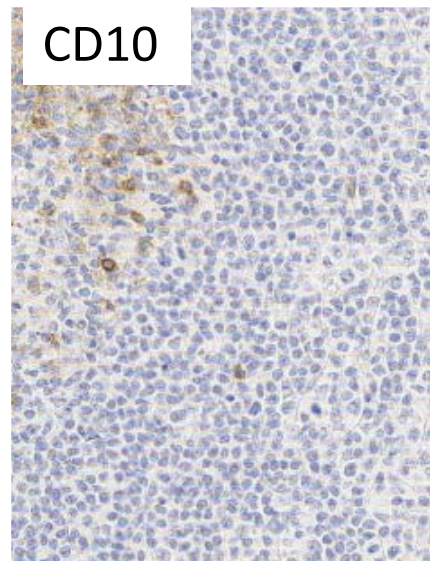
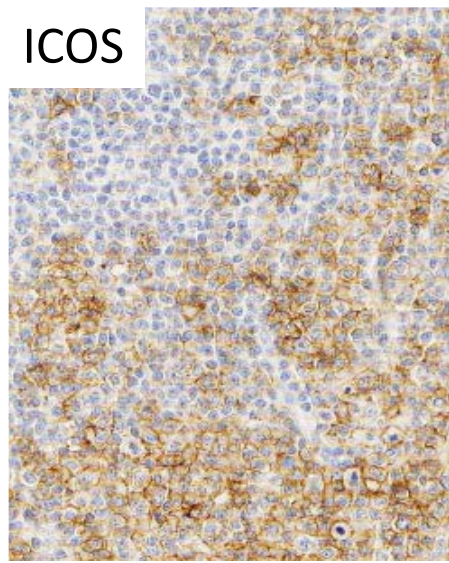
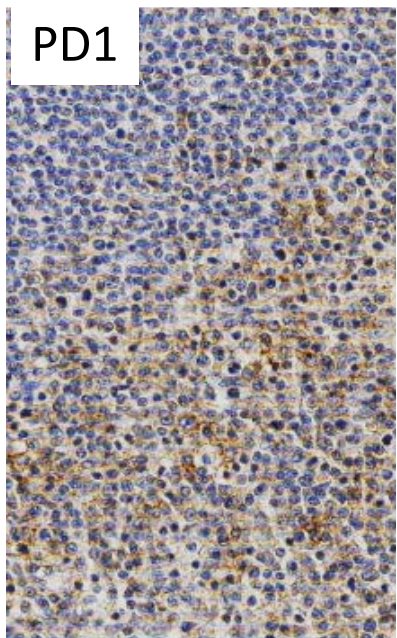
1998 – Second lymph node biopsy (inguinal)



Relapse with cervical, axillary, inguinal bilateral adenopathies



12 cycles of Pentostatine → Complete remission



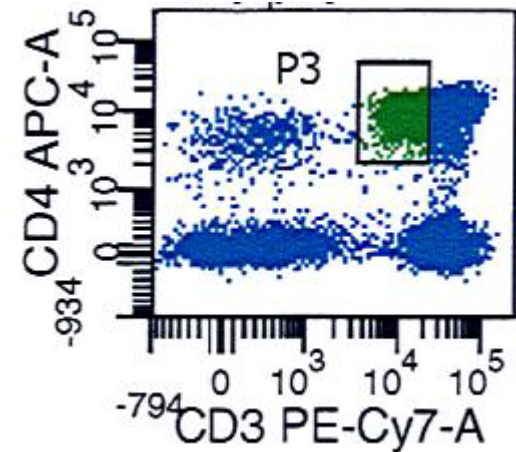
CD2+, CD5+, CD7-, CD4+, CD8-, CD10-

1998 -→ 2014-2015

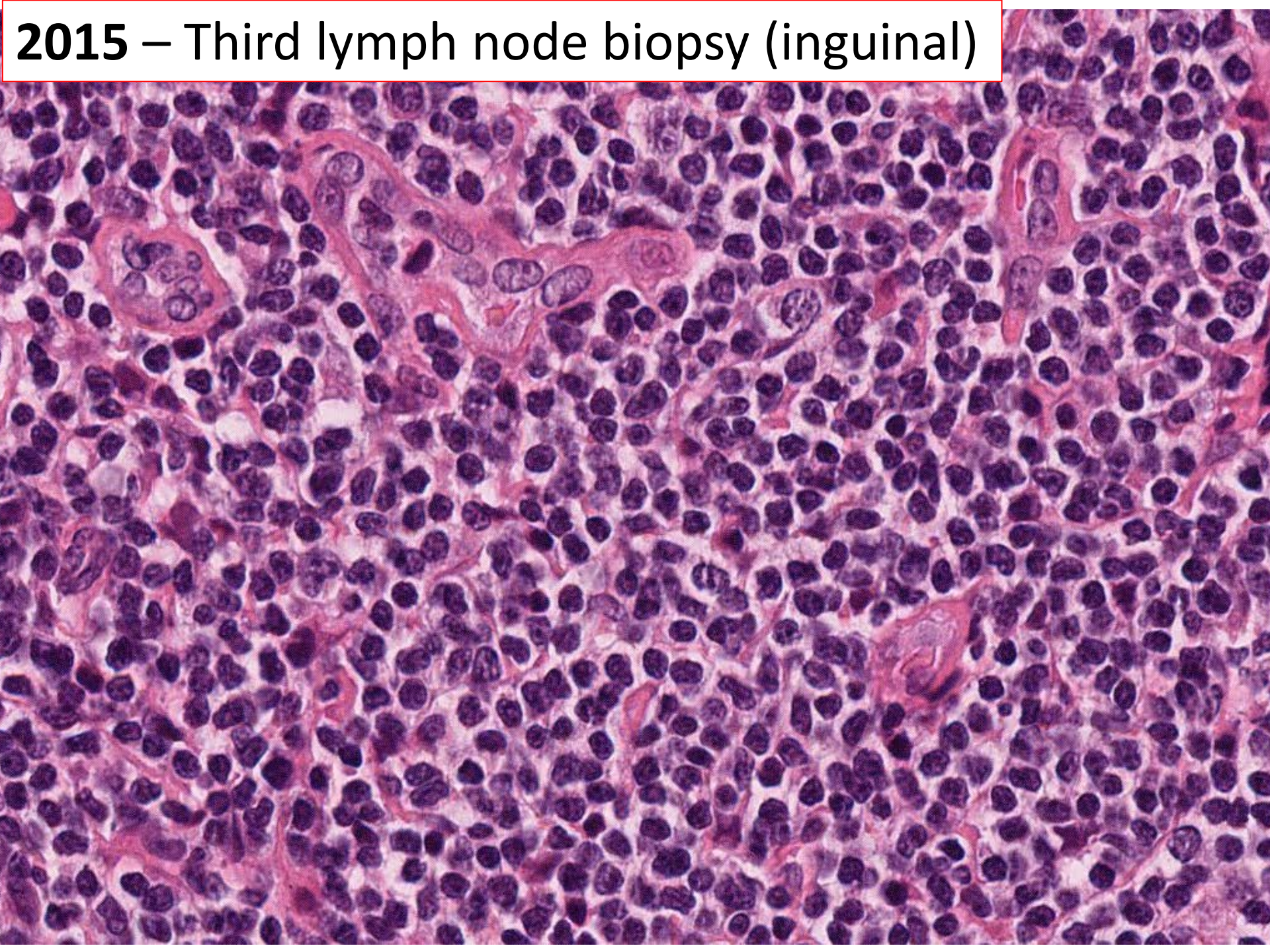
- The patient was well till 2014, when she presented with
 - multiple adenopathies, asthenia, lymphopenia, increased EBV load and high LDH level,
 - a minimal population of atypical lymphocytes in the PB with an “abnormal “ CD3 dim, CD4+, TCRab+ phenotype.

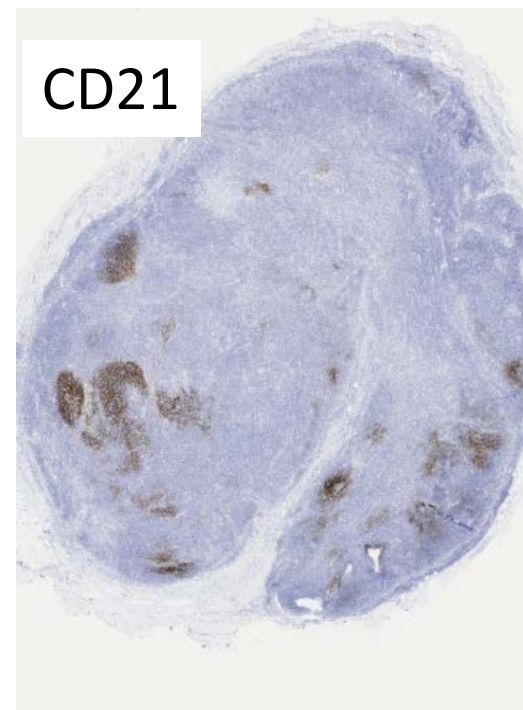
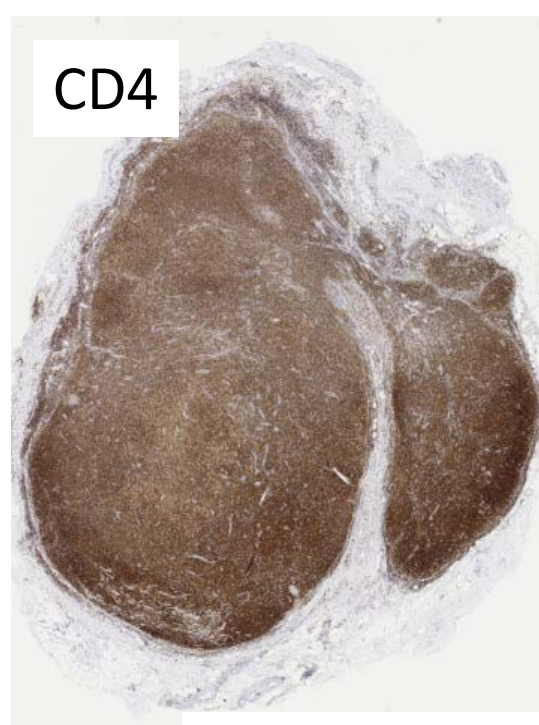
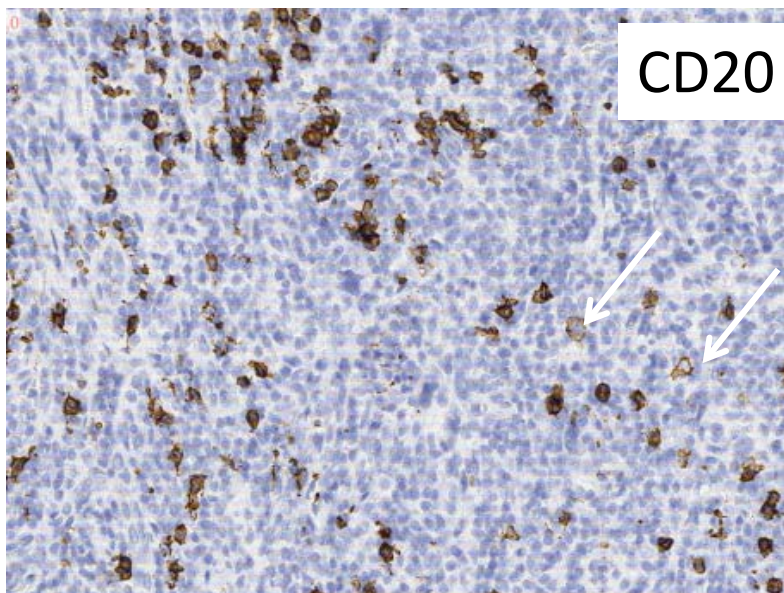
→ A cervical lymph node biopsy (3rd biopsy) was performed in January 2015.

- Pentostatine was started again. She died of disease progression in September 2015.

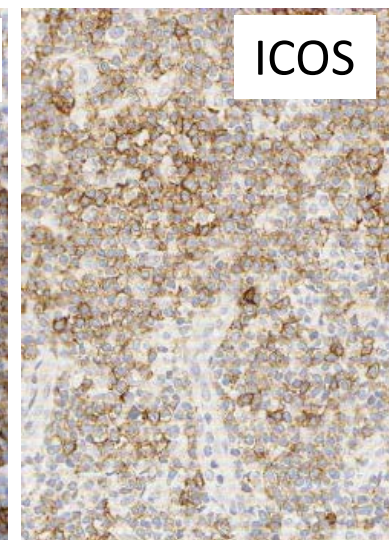
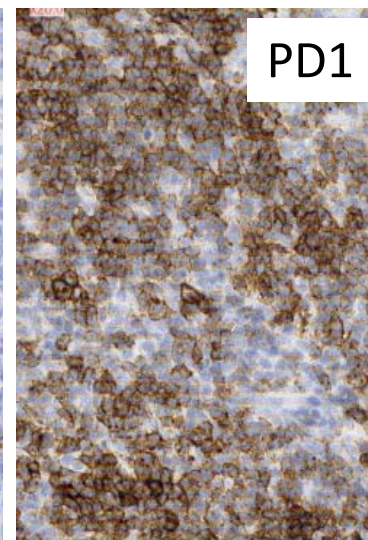
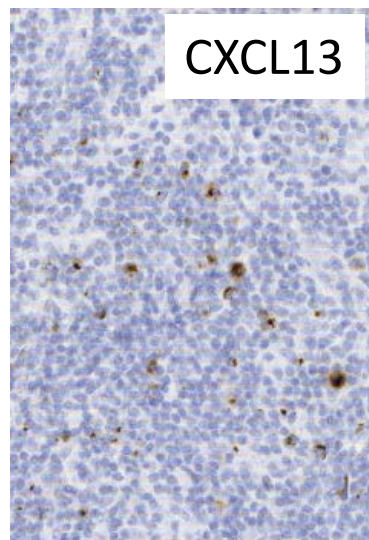
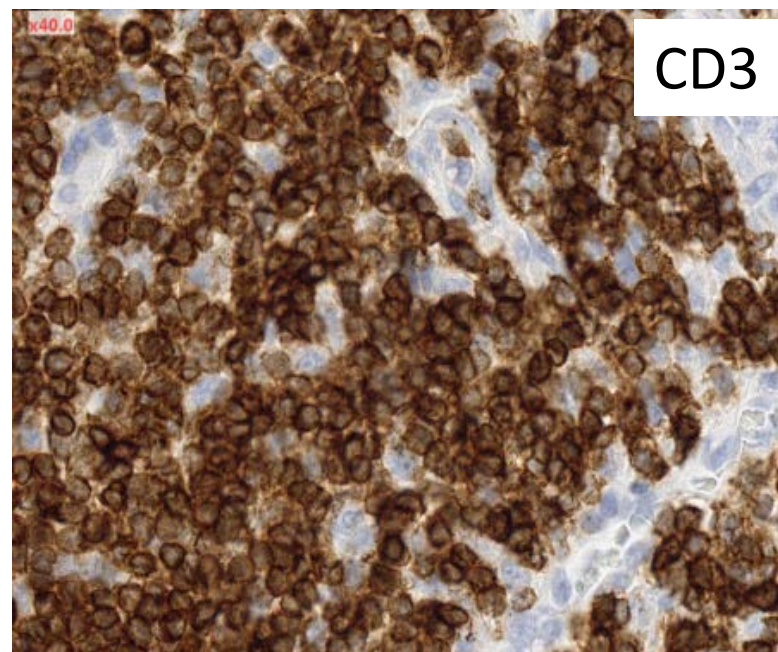


2015 – Third lymph node biopsy (inguinal)





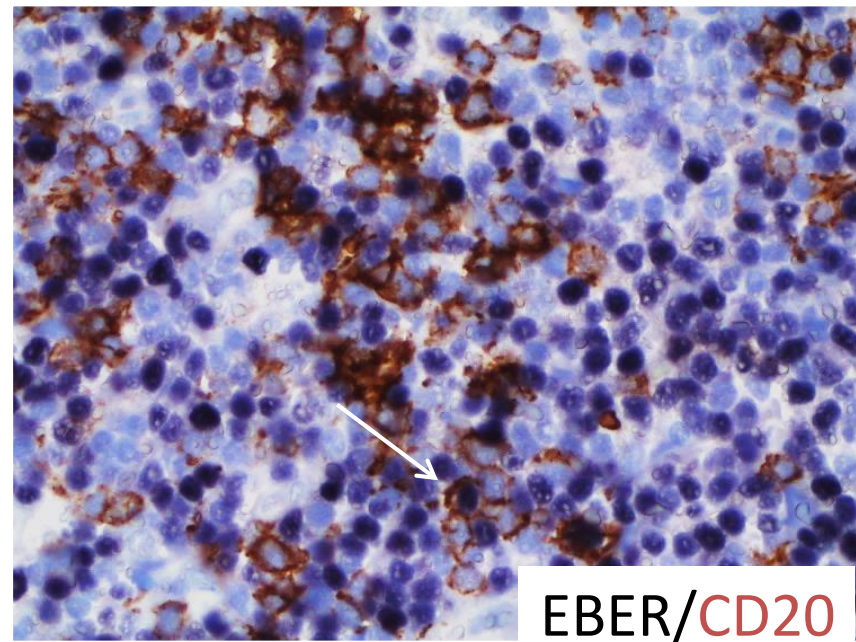
CD2+, CD5+, CD7+, CD4+, CD8-



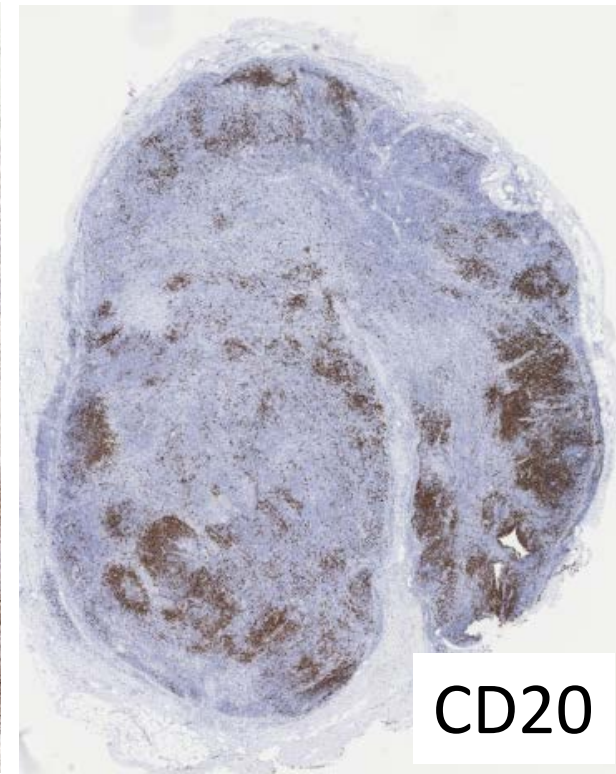
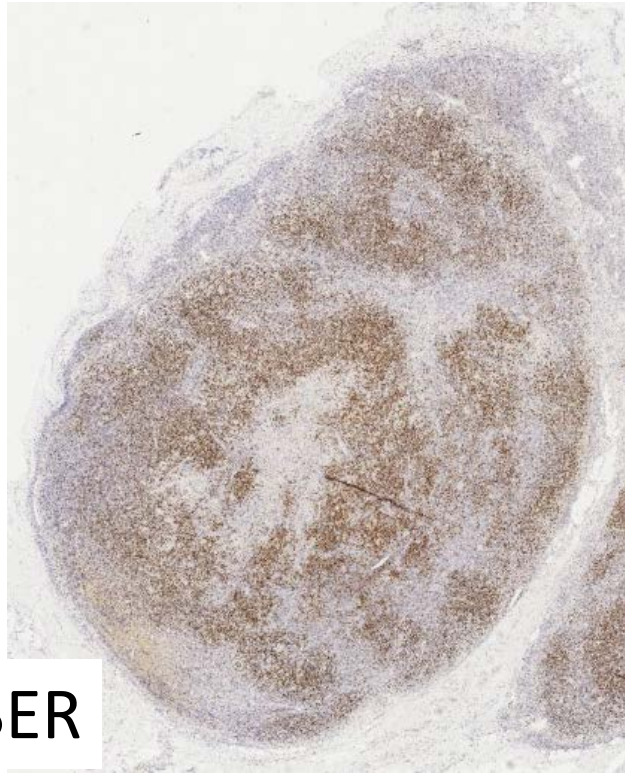
→ Nodal PTCL with a TFH phenotype
(WHO 2016)

HOWEVER....

EBER-positive cells did not overlap with the remaining CD20+ B cell compartment but with the atypical small T cell population with a TFH phenotype



EBER



CD20

MOLECULAR STUDIES

	Clonality PCR (TCR γ)	<i>TET2</i> (%VAF)	<i>DNMT3A</i> (%VAF)	<i>RhoA</i> <i>G17V</i> (%VAF)	<i>IDH2</i> (%VAF)	EBV (T cells)
Initial diagnosis 1995	NI	+ (6.4%)	+ (3.3%)	+ (7.4%)	R172S + (4.2%)	- (°)
Early relapse 1998	T-cell clone	+ (30%)	+ (26.1%)	+ (31.2%)	R172W + (29.8%)(*)	- (°)
Late relapse 2015	T-cell clone (similar 1998) Identical in lymph node&blood	+ (20.6%)	+ (21.5%)	+ (19.7%)	-	+

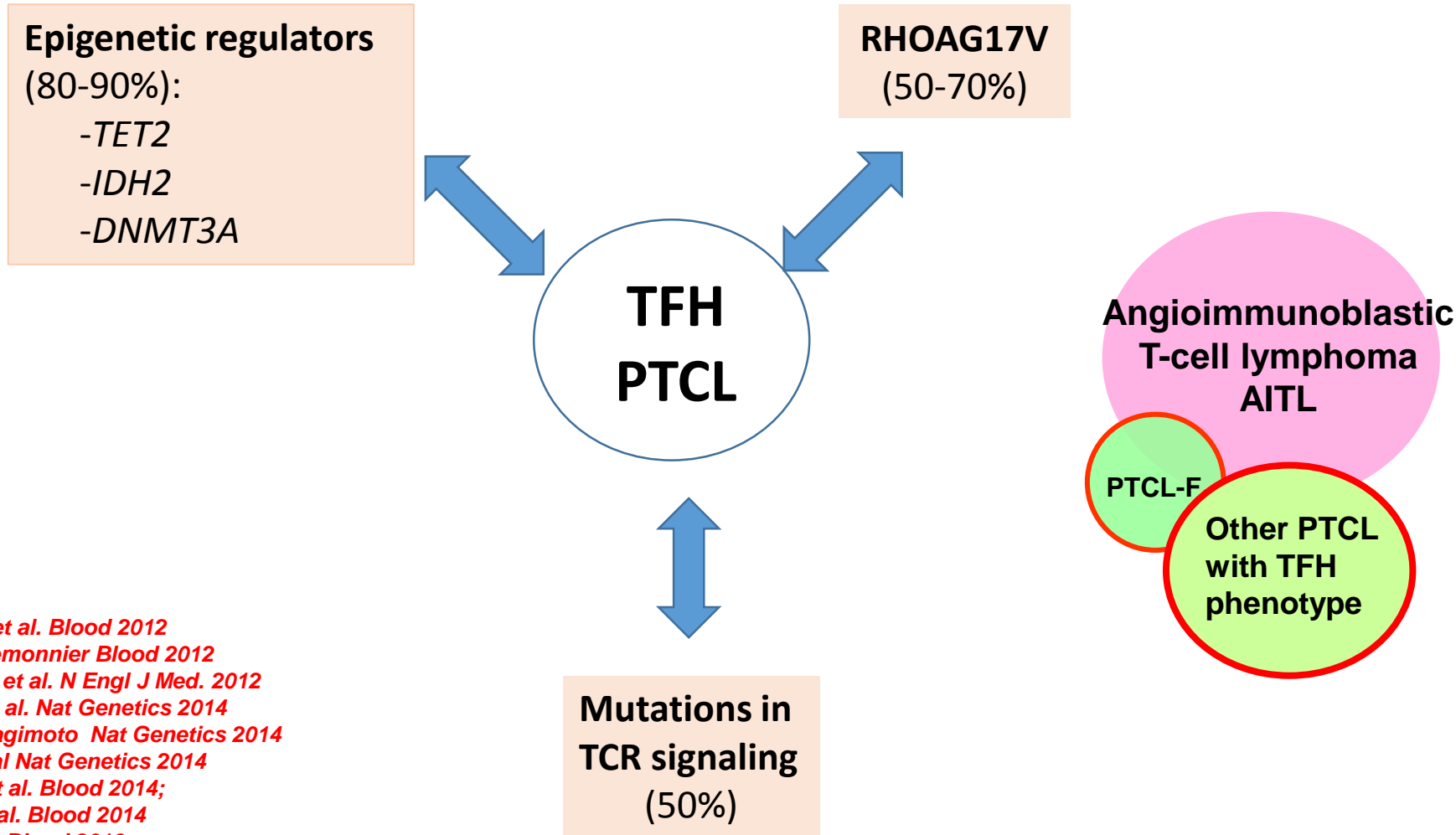
- **Similar *TET2*, *DNMT3A* mutants and presence of *RHOA(G17V)* in the 3 lymph nodes from 1995, 1998 & 2015**
- (°) *large scattered likely B-immunoblasts EBV+*

(*) *validation pending*

Discussion points

- Please discuss the significance of mutational events in AITL, and genetic events that occur in T-cell lymphoma progression
- Please discuss the role of molecular disease monitoring in T-cell lymphoma

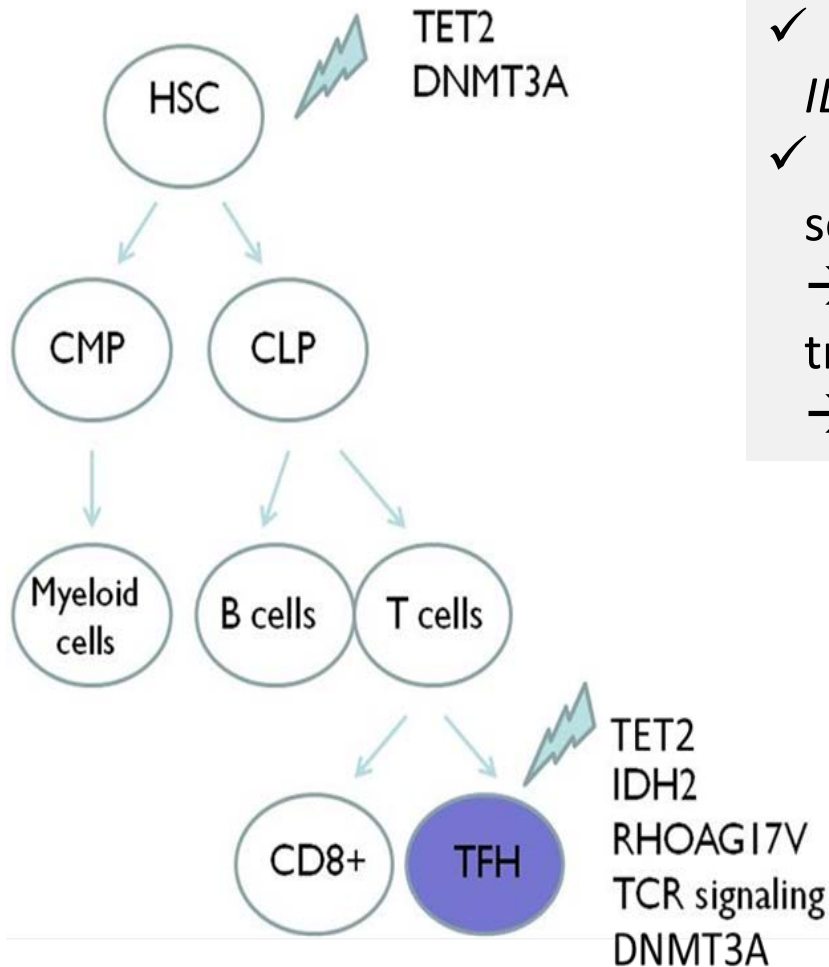
TFH-PTCL mutational Landscape



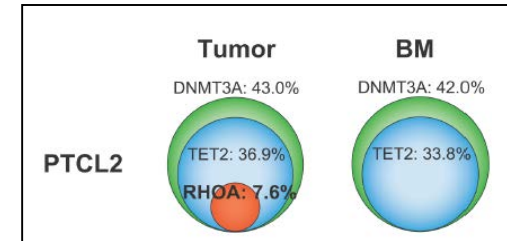
Lemonnier et al. Blood 2012
Cairns & Lemonnier Blood 2012
Couronné L et al. N Engl J Med. 2012
Palomero et al. Nat Genetics 2014
Sakata-Yanagimoto Nat Genetics 2014
Yoo H-Y et al Nat Genetics 2014
Odejide O et al. Blood 2014;
R Manso et al. Blood 2014
Vallois et al. Blood 2016
Dobay et al. Haematologica 2017
Nguyen et al. Blood Cancer Journal 2017
Schwartz et al. J Pathol 2017

TFH-PTCL : a multistep oncogenesis

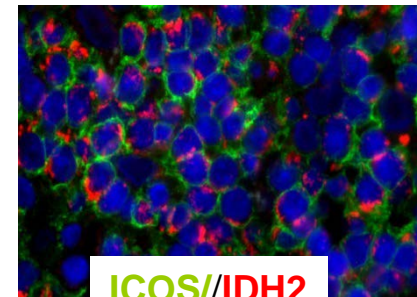
Clonal hematopoiesis



- ✓ Not mutually exclusive (*TET2*, *DNMT3A* and *IDH2*) in AITL (# CMML, AML)
- ✓ *TET2* mutations in up to 80-90% following sensitive techniques
 - Necessary but not sufficient for transformation
 - mice models (*TET2*^{KO}, *RHOA*^{G17V}) → TFH-PTCL



Sakata-Yanagimoto.. Nat Genetics 2014



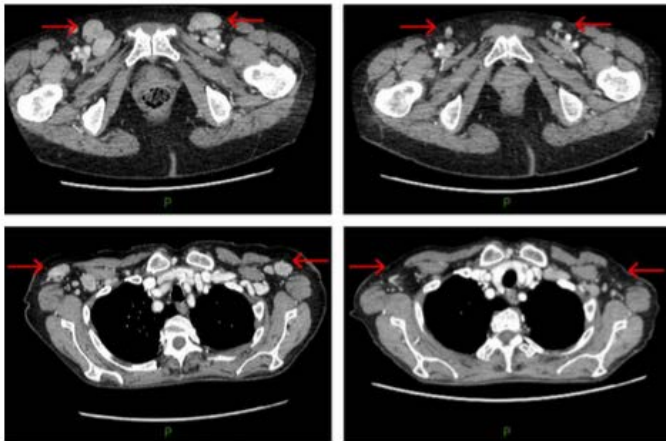
Lemonnier, et al. PNAS 2016

Quivoron et al. Cancer cell 2011; Couronne et al. NEJM 2012; Sakata-Yanagimoto et al. Nat Genetics 2014

Nguyen TB et al. Blood Cancer Journal 2017; Lemonnier et al. PNAS 2016; Schwartz et al. J Pathol 2017; Zang S et al. JCI 2017

Implications for therapy...?

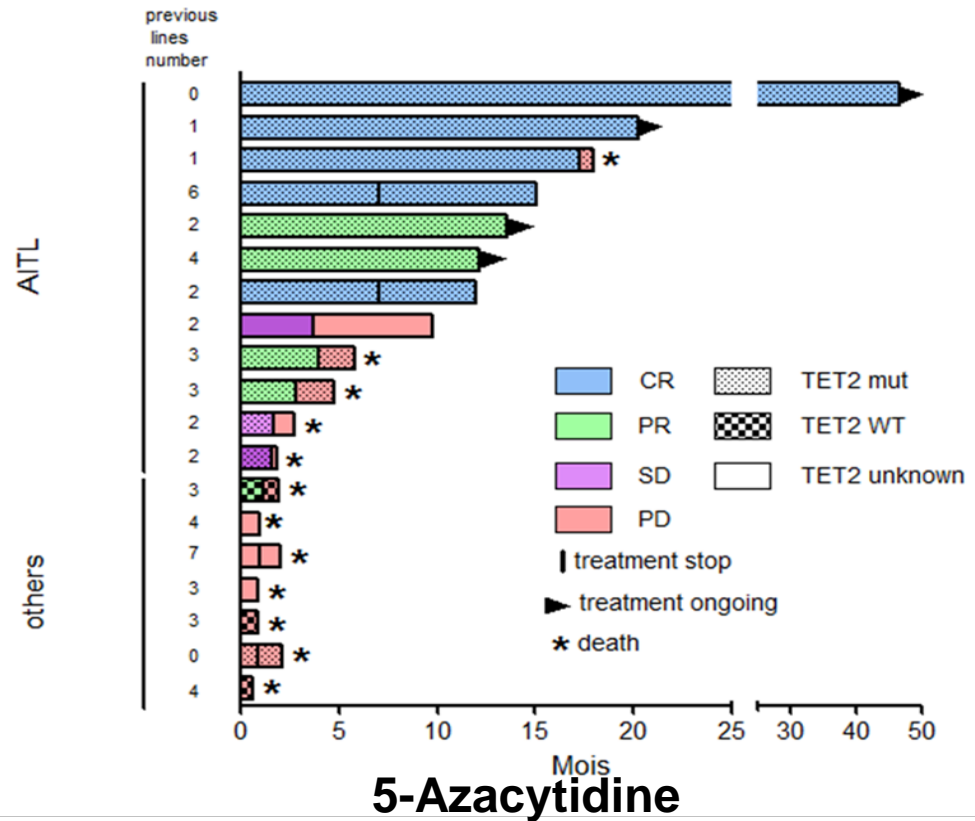
- Demethylating agents?



Cheminant et al. BJH 2014

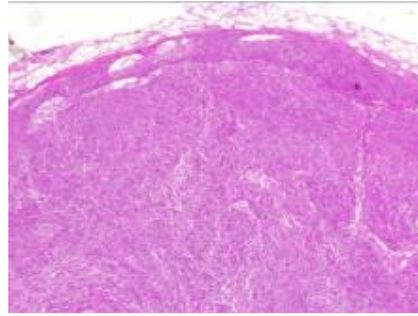
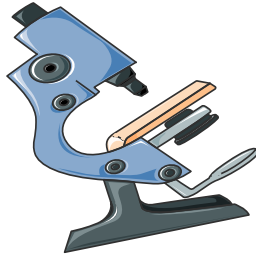
- IDH2 Inhibitors?

ORR 75% in AITL vs 15%



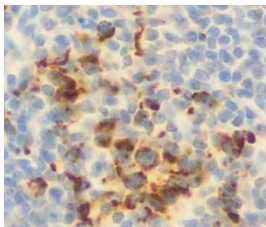
Delarue, Dupuis et al, in preparation

2 – Molecular disease monitoring in T-cell lymphoma: what do we need in the routine practice ?



Immunohistochemistry

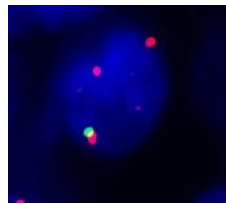
ALK
IDH2(R172K)....



Diagnostic

FISH

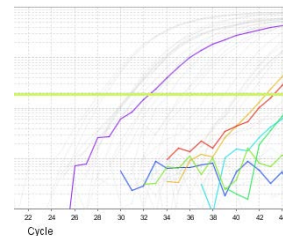
DUSP22
TP63(?),....



Prognostic

Molecular tool(s) (As-PCR, NGS)

- Clonality analysis
- Hotspots: *RHOAG17V*, *IDH2R172*
- Throughout the genes: *TET2*, *DNMT3A*, *STATs*,..

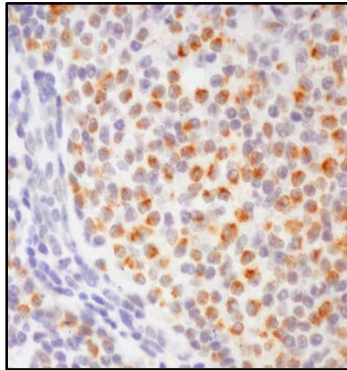


Predictive/Therapy

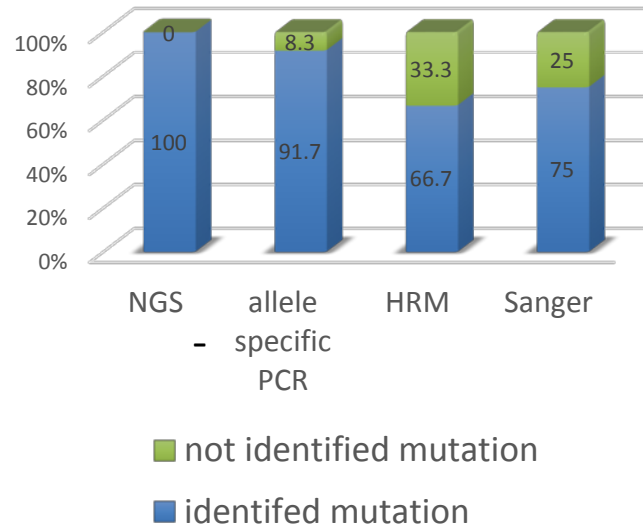
(°) sensitive techniques due to the low tumor cell content: As-PCR, NGS (\geq x1000X)

(°°) Liquid biopsy (follow-up)?

2 – Molecular disease monitoring in TFH-PTCL : example of *IDH2 (R172)* mutation identification

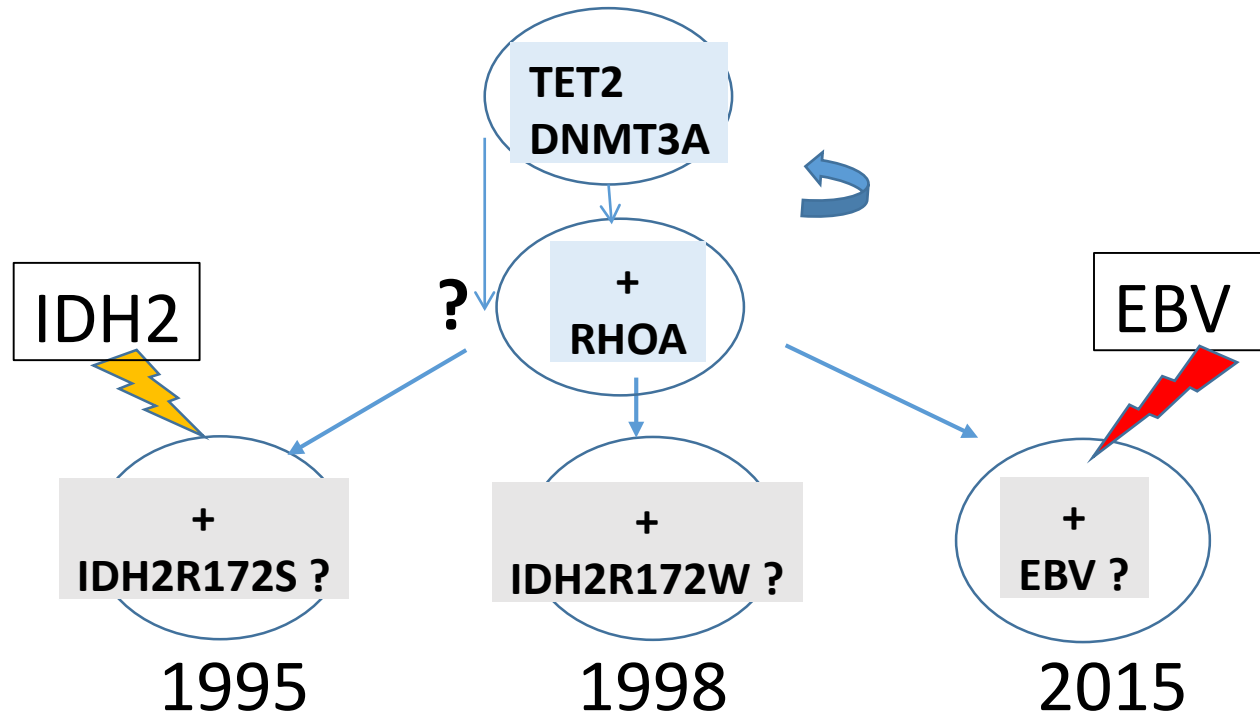


IDH2R172K



- Some of these mutations (*RHOAG17V*, *IDH2R172*) are very characteristic of TFH-PTCL
 - Gene mutations analysis (AS-qPCR-NGS) may be more sensitive than TCR gene rearrangement (conventional PCR γ) which fails to detect clonality in up to 10-20 % of AITL ?
 - Role in the disease follow-up (MRD, VAFs): sequential biopsies, liquid biopsy?

Current case: Hypothetical scheme ?



- It is suggested that the “lymphoma initiating cell”, which has proceeded to TCR rearrangement, bears *TET2*, *DNMT3A* (+/-*RHOA*) mut and can survive for a long time in a quiescent form.
- *IDH2R172* mutations, or EBV infection likely are secondary oncogenic events that support the lymphoma development.
- **EBV infection in TFH cells** is not described (# B-blasts in AITL):
→? Mechanism of infection (**crosstalk TFH-B cells**, trogocytosis, ? CD21??) , role of immunosuppression (?)



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Panel diagnosis

Angioimmunoblastic T-cell lymphoma,
latest recurrence with EBV expression by
tumoral T cells