Changing concepts:
T-cell lymphomas (including pitfalls)

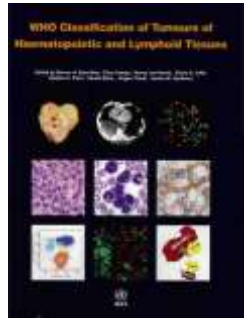
Ayoma Attygalle

Consultant Histopathologist

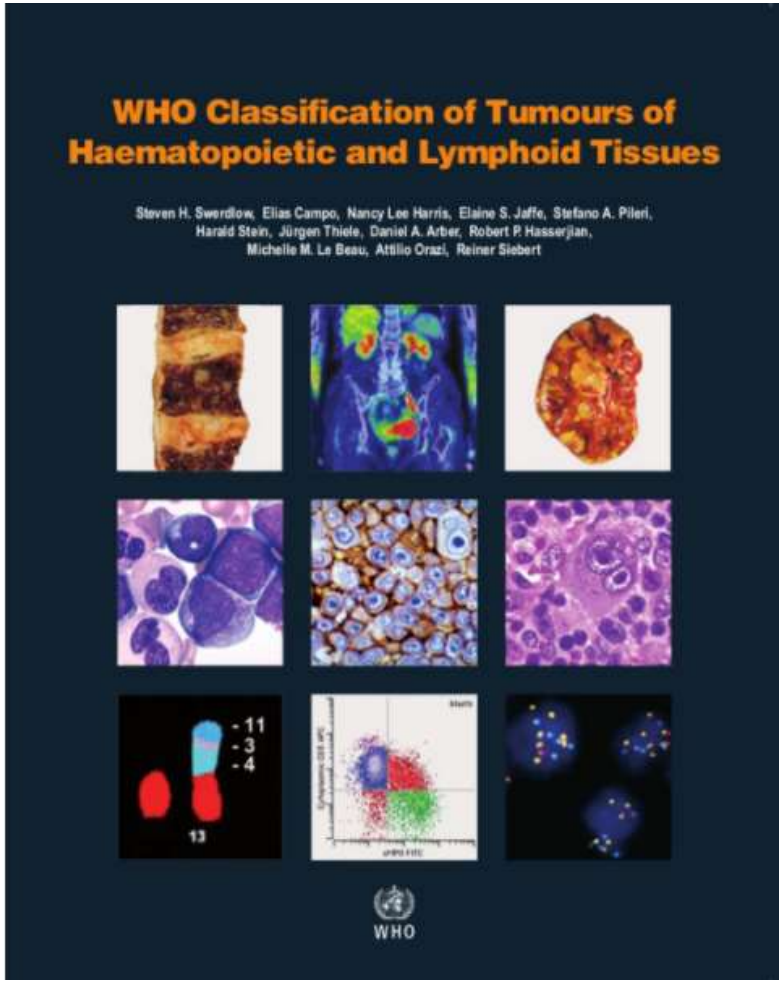
Royal Marsden Hospital

London

Mature T-and NK-cell neoplasms



- Significant advances have occurred since 2008
- Many changes are result of genomic studies
- Revisions to existing classification and introduction of new provisional entities



Volume 2

(2017)

Mature T-and NK-cell neoplasms (revision to 4th Edition)

- Grouping entities (previously separated) under a single umbrella category
- Separating previously grouped entities
- Introduction of new provisional entities
- Down-grading entities from lymphoma to lympho-proliferative disorder (LPD)
- Upgrading entities from LPD to lymphoma
- Increasing recognition of indolent T-cell lymphoproliferations

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

Mature T and NK neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV$^+$ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8$^+$ T-cell lymphoma**
- *Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK$^+$
- Anaplastic large-cell lymphoma, ALK$^-$*
- *Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

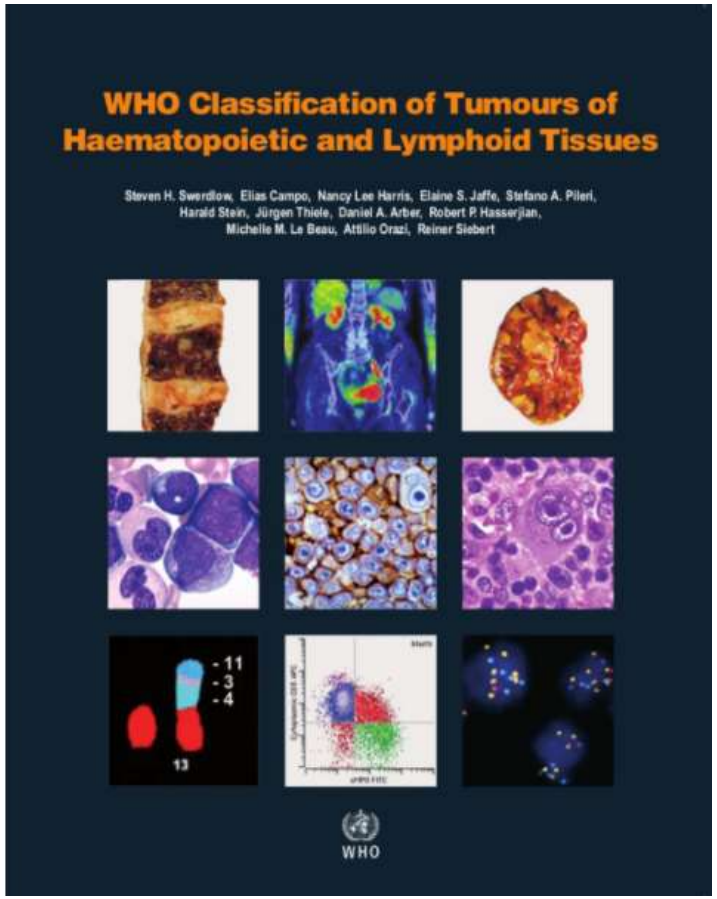
Swerdlow et al. Blood 2016;127:2375-2390

Mature T and NK neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV$^+$ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8$^+$ T-cell lymphoma**
- *Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK$^+$
- Anaplastic large-cell lymphoma, ALK$^-$*
- *Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

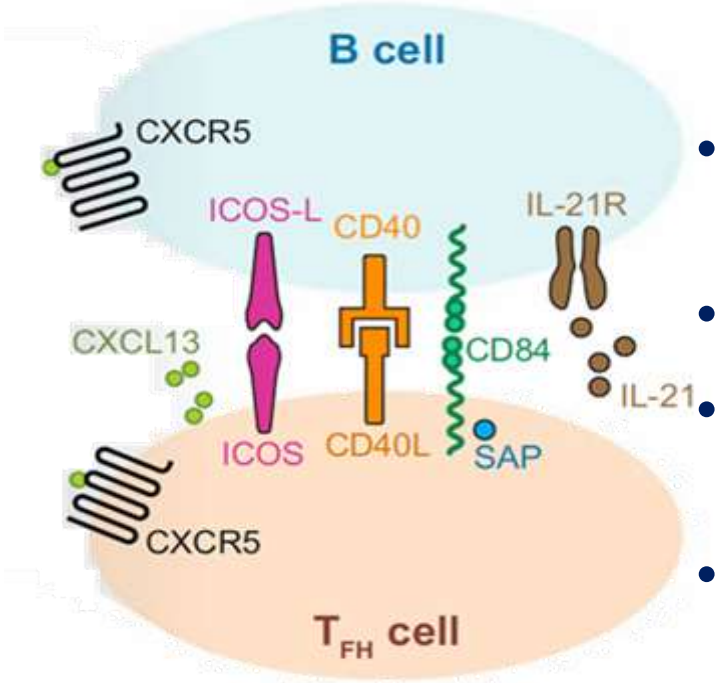


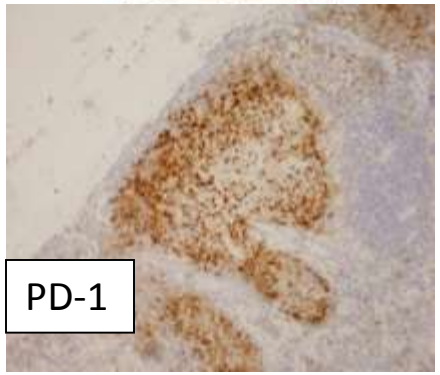
Volume 2

Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper origin

- *Angioimmunoblastic T-cell lymphoma*
- *Follicular T-cell lymphoma*
- *Nodal peripheral T-cell lymphomas with a T follicular helper phenotype*

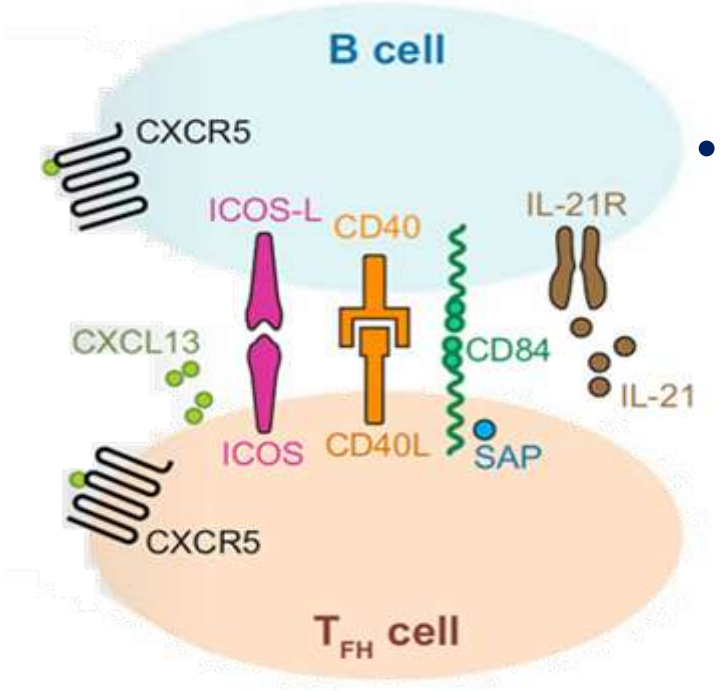
Follicular helper-T-cells (T_{FH} cells)





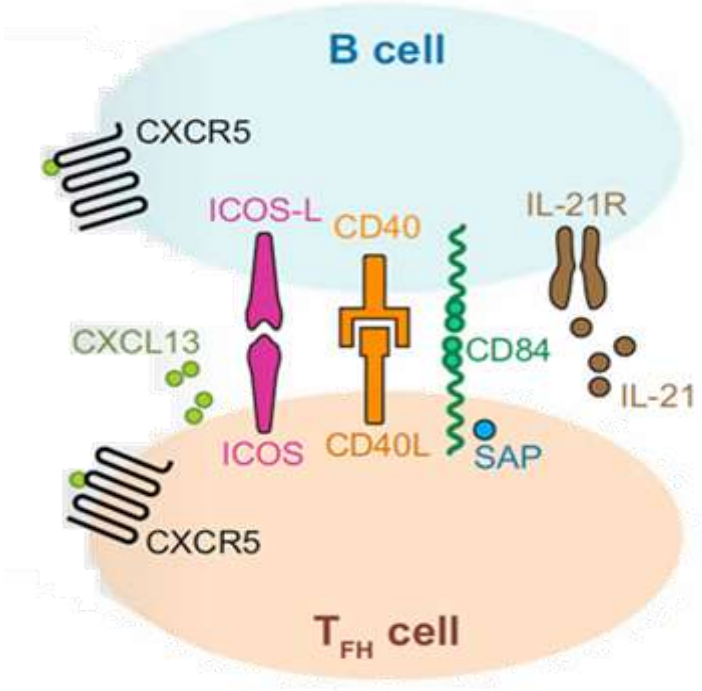
- Distinct functional subset of effector T-helper cells
- Reside in reactive germinal centres
- Specialise in providing help to B-cells during the germinal centre reaction
- Interactions b/w T_{FH} cells and B-cells critical to promote B-cell differentiation and survival (Ig class switch, somatic hypermutation)

Follicular helper-T-cells (T_{FH} cells)



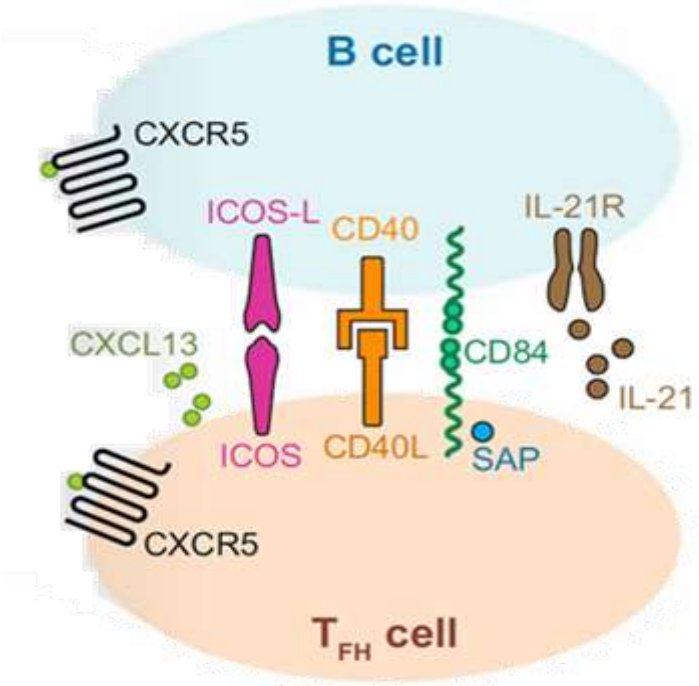
- Functions mediated through cytokines/chemokines (IL-10, IL-21, IL-4, CXCL13) and via co-stimulatory molecules (ICOS, CD28, CD40L, PD1) and other receptors (SAP, CXCR5)

Follicular helper-T-cells (T_{FH} cells) – functional properties



- CXCR5 is expressed by T_{FH} cells and GC B-cells
- CXCL13 (ligand for CXCR5) is expressed by T_{FH} cells and FDC
- CXCL13 crucial to **recruit B-cells** into GCs and for **B-cell activation**

Follicular helper-T-cells (T_{FH} cells)



- PD-1
- ICOS
- CXCL-13
- CD10 (subset)
- BCL-6
- c-MAF
- CD200
- CXCR5
- SAP

Angioimmunoblastic T-cell lymphoma (AITL)

- Lennert (1973) –

  - lymphogranulomatosis X

- Lukes (1973) -

  - immunoblastic lymphadenopathy

- Frizzera (1974) -

  - angioimmunoblastic lymphadenopathy with dysproteinaemia (AILD)

Angioimmunoblastic T-cell lymphoma (AITL)

- Lennert (1973) –
  - lymphogranulomatosis X
- Lukes (1973) -
  - immunoblastic lymphadenopathy
- Frizzera (1974) -
  - **angioimmunoblastic lymphadenopathy with dysproteinaemia (AILD)**

"Angioimmunoblastic lymphadenopathy with dysproteinaemia" (AILD)

? Atypical reactive "lymphoma – like"

? Disorder of immunoregulation

Deregulated response to antigen stimulation

Proliferating T- and B-cell clones

Lymphoma

REAL classification -1994
and
WHO classification - 2001

- Nodal peripheral T-cell lymphoma

WHO classification - 2001

- Nodal peripheral T-cell lymphoma

de novo T-cell lymphoma

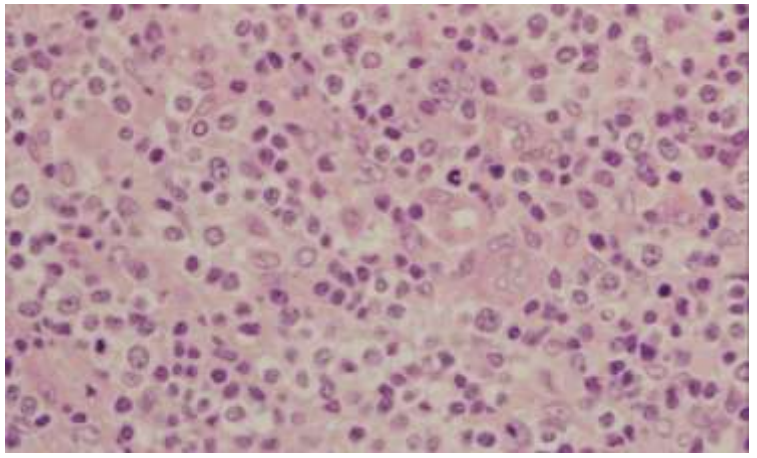
or

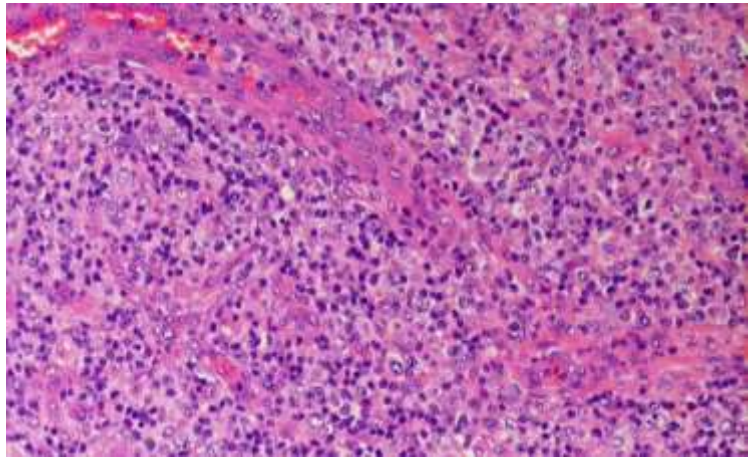
? preceded by atypical/oligoclonal proliferations

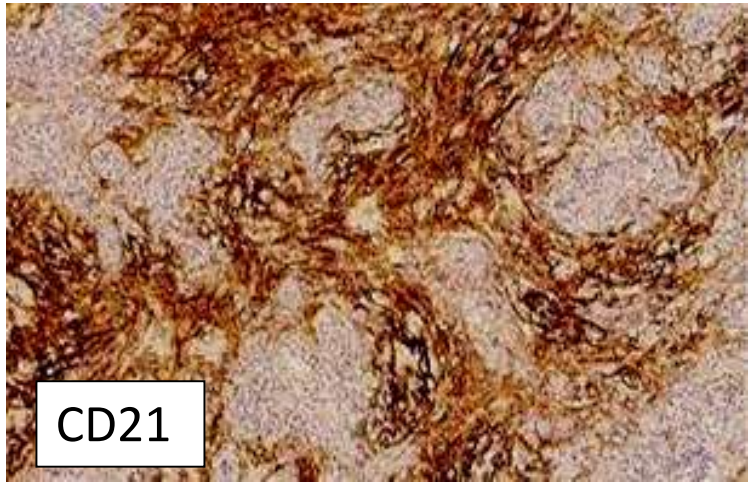
Definition (WHO, 2001,2008)

AITL is a peripheral T-cell lymphoma characterised by

- Systemic disease
- Polymorphous infiltrate involving lymph nodes
- Prominent proliferation of HEV
- Prominent proliferation of FDC



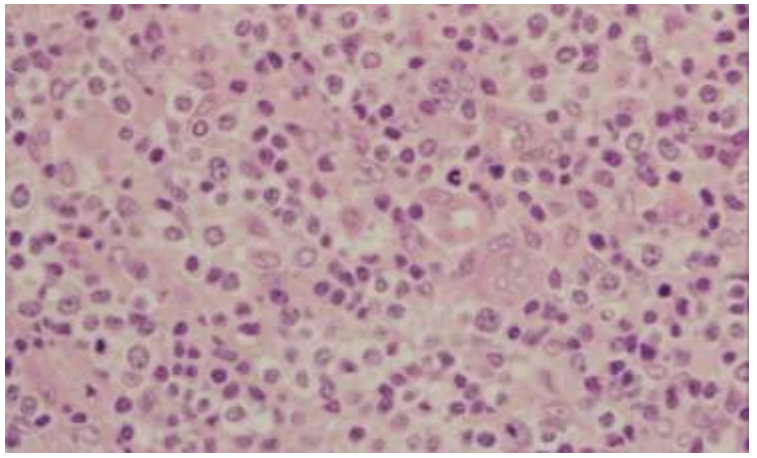


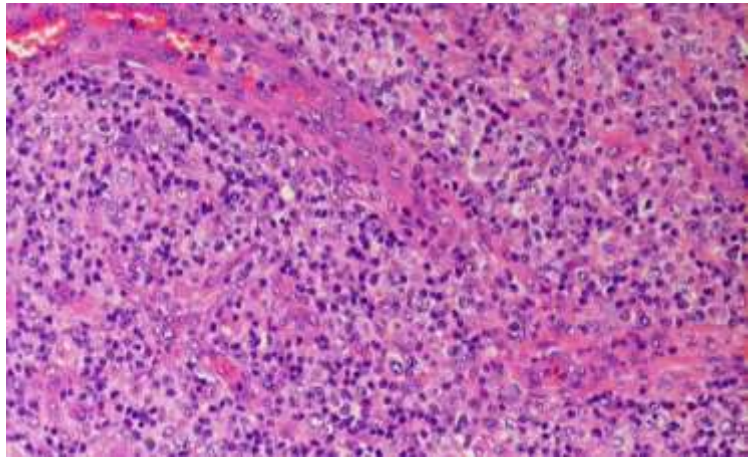


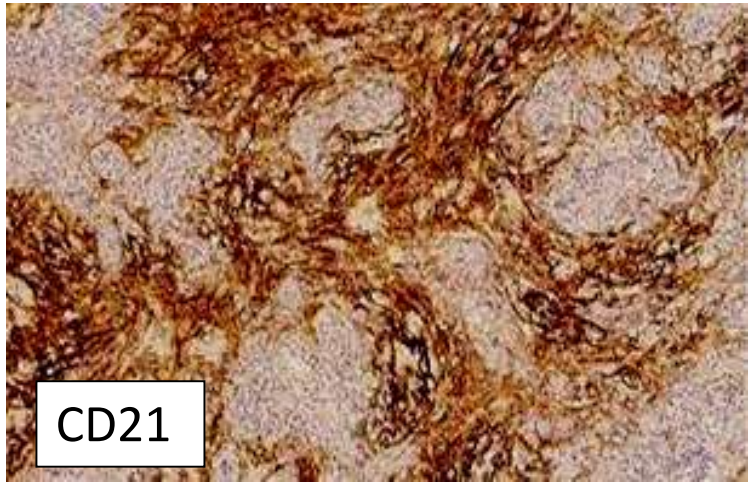
Definition (WHO, 2001,2008)

AITL is a peripheral T-cell lymphoma characterised by

- **Systemic disease**
- Polymorphous infiltrate involving lymph nodes
- Prominent proliferation of HEV
- Prominent proliferation of FDC







Angioimmunoblastic T-cell lymphoma (AITL)

Clinical features and sites of involvement

Age range (median age)	20-89 (62-65)
Sex ratio (M:F)	1.3
B-symptoms	69-72%
Stage III to IV (generalised LAD)	80-90%
Hepatomegaly	25%
Splenomegaly	55%
Skin rash (often pruritic)	44%
Effusions /oedema	26%
Arthritis	16%
Bone marrow involvement	28-47%

Mourad et al 2008, Federico et al 2013

Angioimmunoblastic T-cell lymphoma (AITL)

Laboratory findings

Anaemia	39-65%
Positive Coomb's test	15-33%
Polyclonal hypergammaglobulinaemia	44-50%
Lymphopaenia	49%
Thrombocytopaenia	20%
Hypereosinophilia	32%
Raised serum LDH	66%

Mourad et al 2008, Federico et al 2013

Angioimmunoblastic T-cell lymphoma (AITL)

Laboratory findings

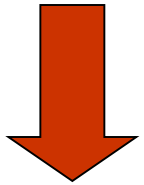
Anaemia	39-65%
Positive Coomb's test	15-33%
Polyclonal hypergammaglobulinaemia	44-50%
Lymphopaenia	49%
Thrombocytopaenia	20%
Hypereosinophilia	32%
Raised serum LDH	66%

Mourad et al 2008, Federico et al 2013

Systemic/Lab findings - characteristic but **NOT MANDATORY** for diagnosis!

Angioimmunoblastic T-cell lymphoma (AITL)

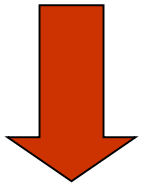
Functional properties of T_{FH} cells



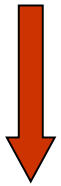
Expansion of normal B-cells and plasma cells

Angioimmunoblastic T-cell lymphoma (AITL)

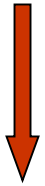
Underlying immune dysfunction



Expansion of (often EBV-infected) B-cells (>90%)



B-cell clone (24%)



secondary

Diffuse large B-cell lymphoma (most often EBV+)

B-cell proliferations in AITL

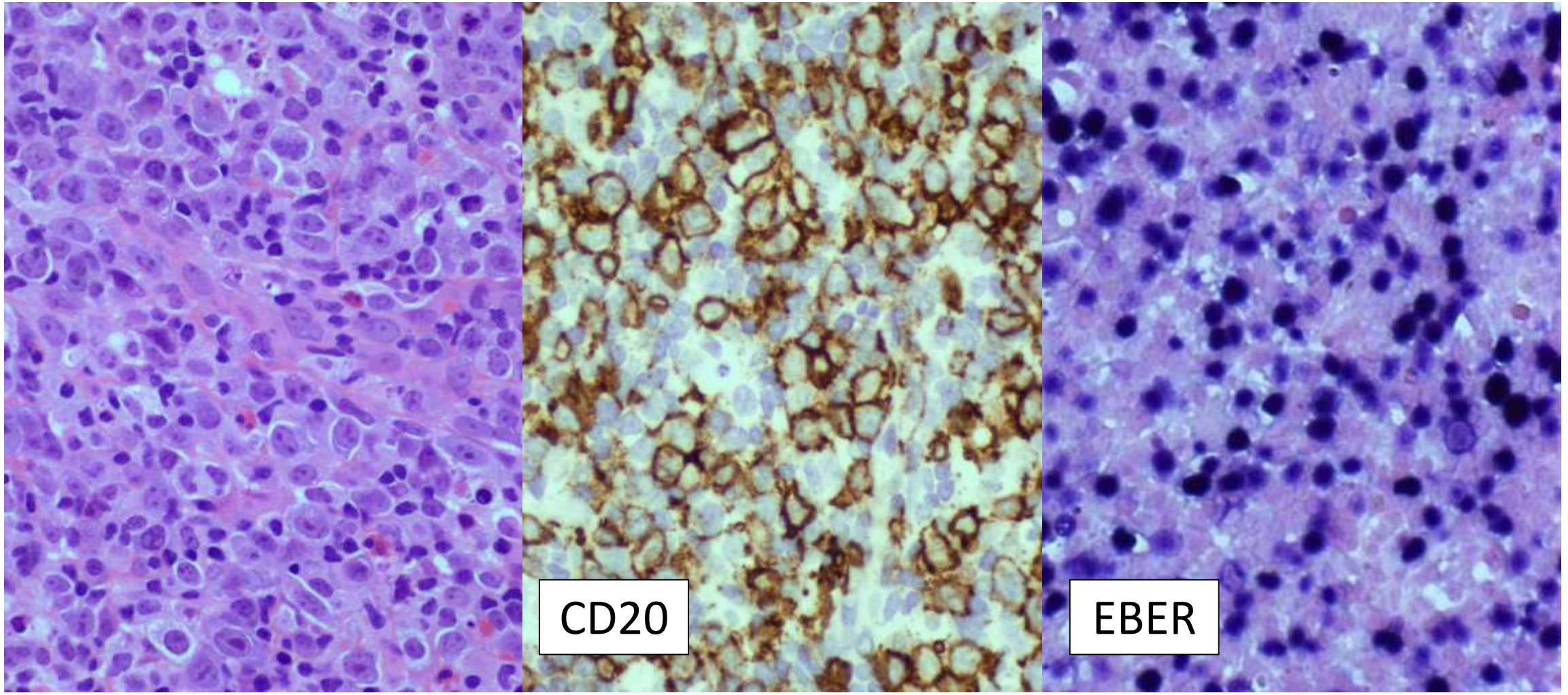
- Scattered EBV+ large B-cells
- Polyclonal proliferation of EBV+ large B-cells
- Clonal proliferation of EBV+ large B-cells

- DLBCL EBV+ /rarely EBV-
- Clonal plasmacytic proliferations EBV+/-

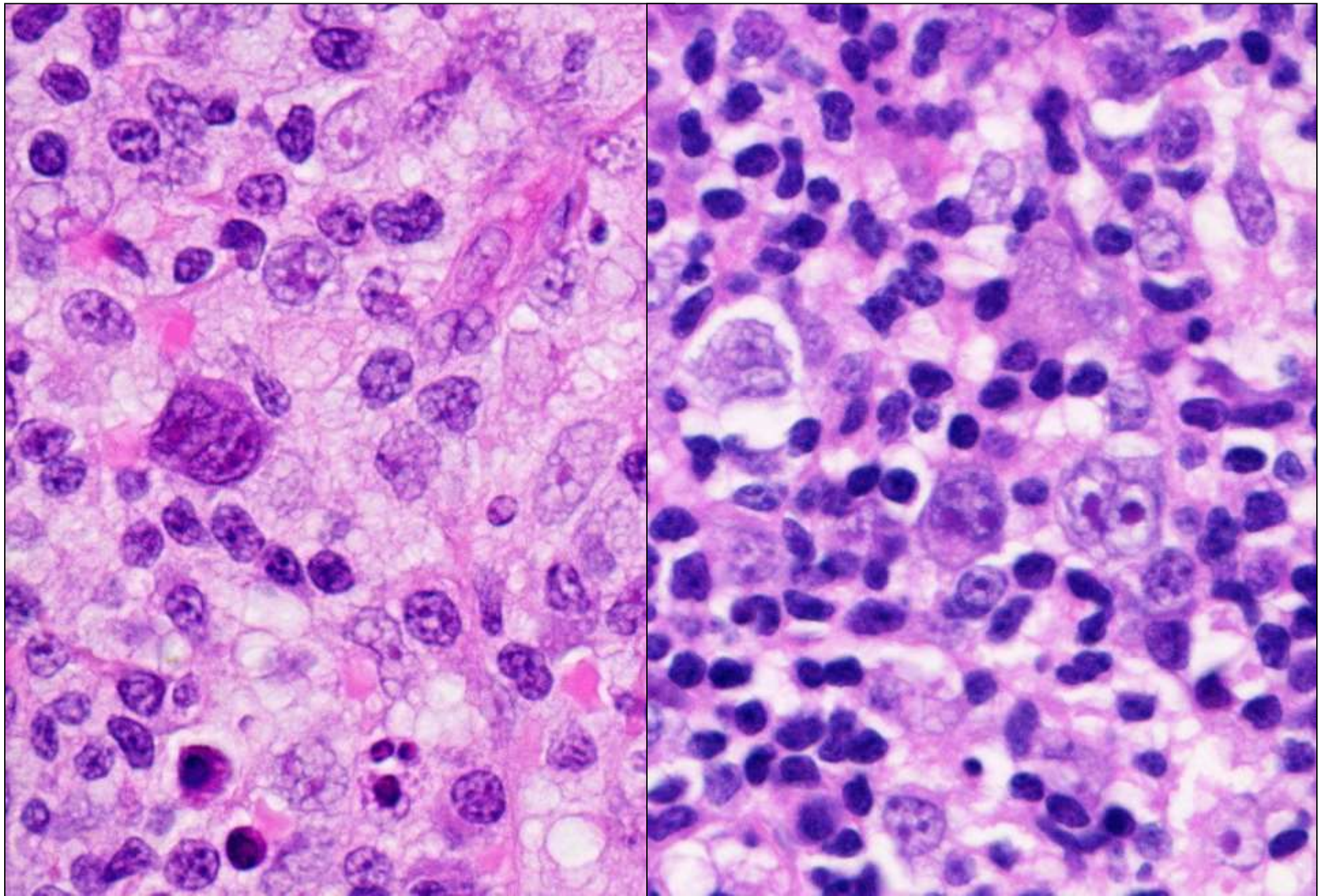
} **Masks underlying AITL – pitfall!**

- Hodgkin/Reed Sternberg-like cells EBV+ /less commonly EBV- **– may be misdiagnosed as classic Hodgkin lymphoma (pitfall!)**

Clonal EBV+ large B-cell proliferation ? DLBCL, masking underlying AITL

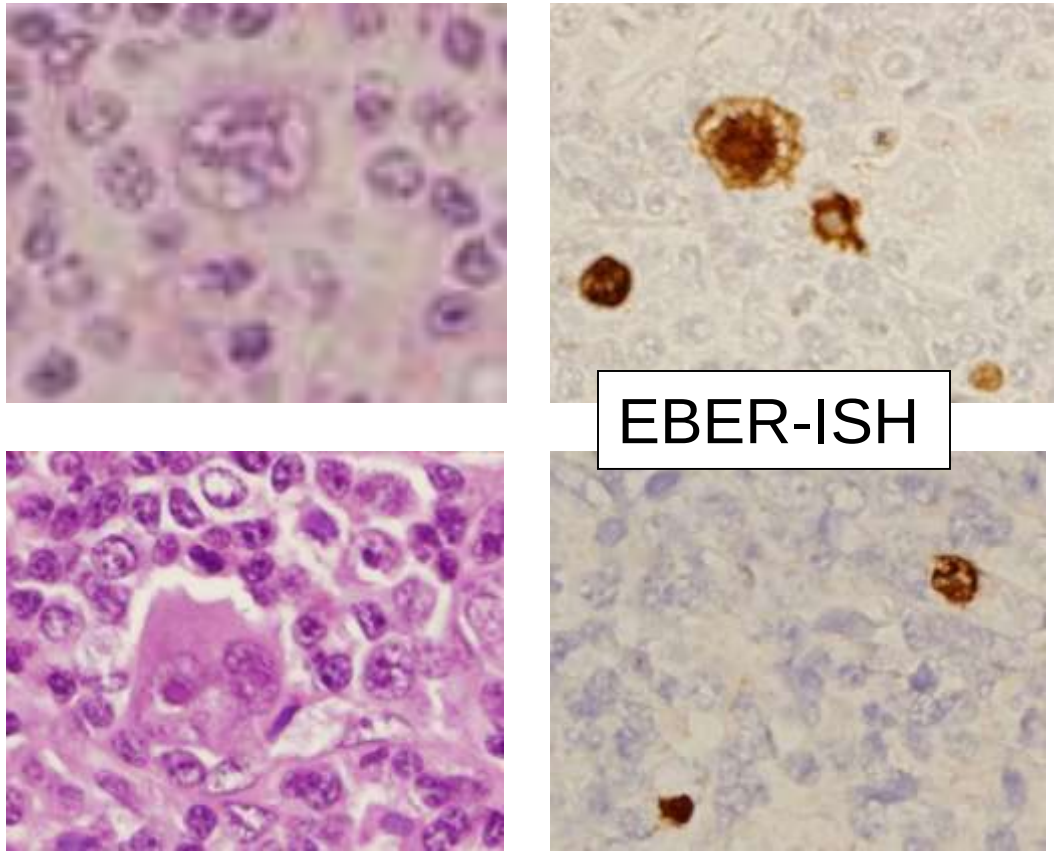


AITL-RS-like B-cells



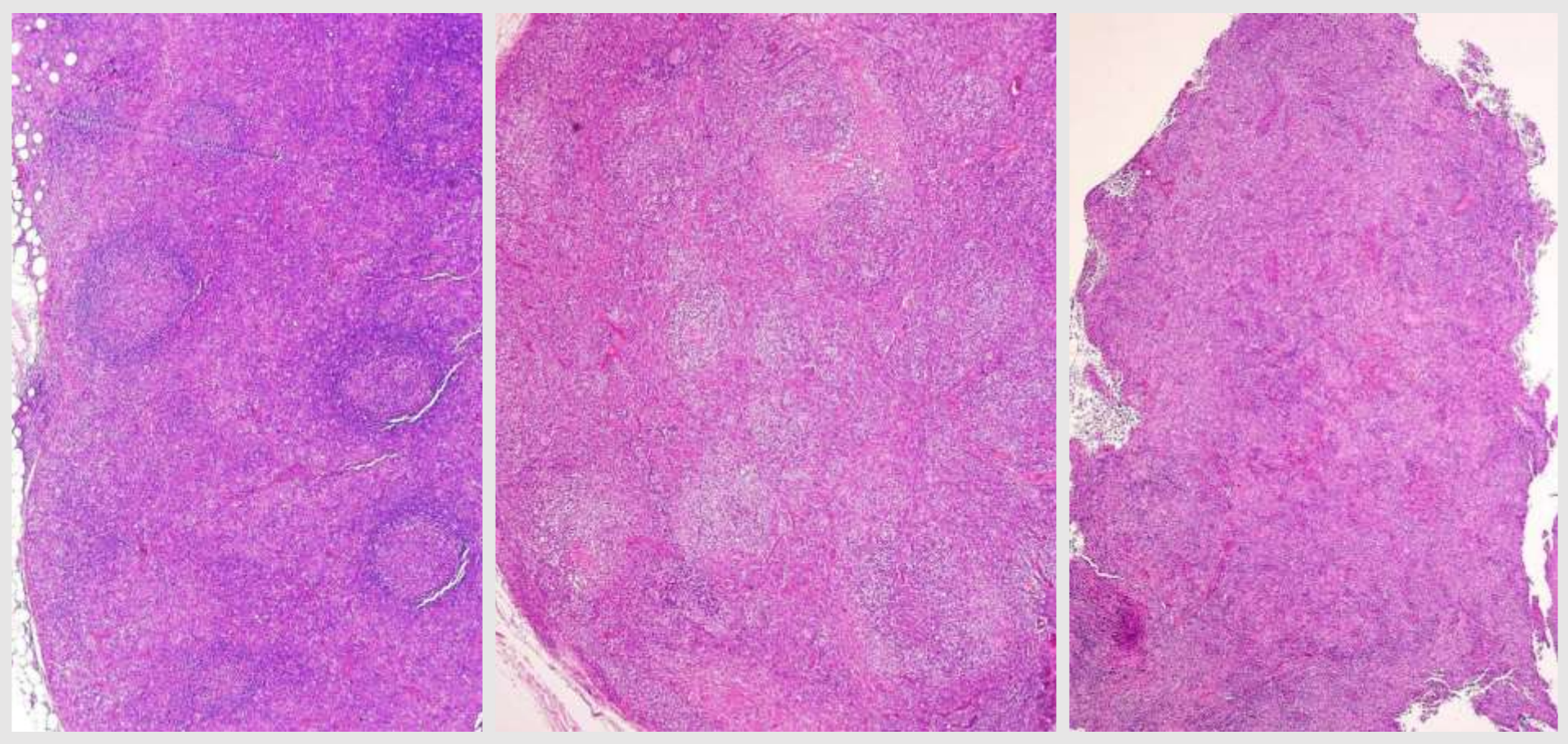
HRS-like cells :

- mostly EBV positive, but may be EBV negative



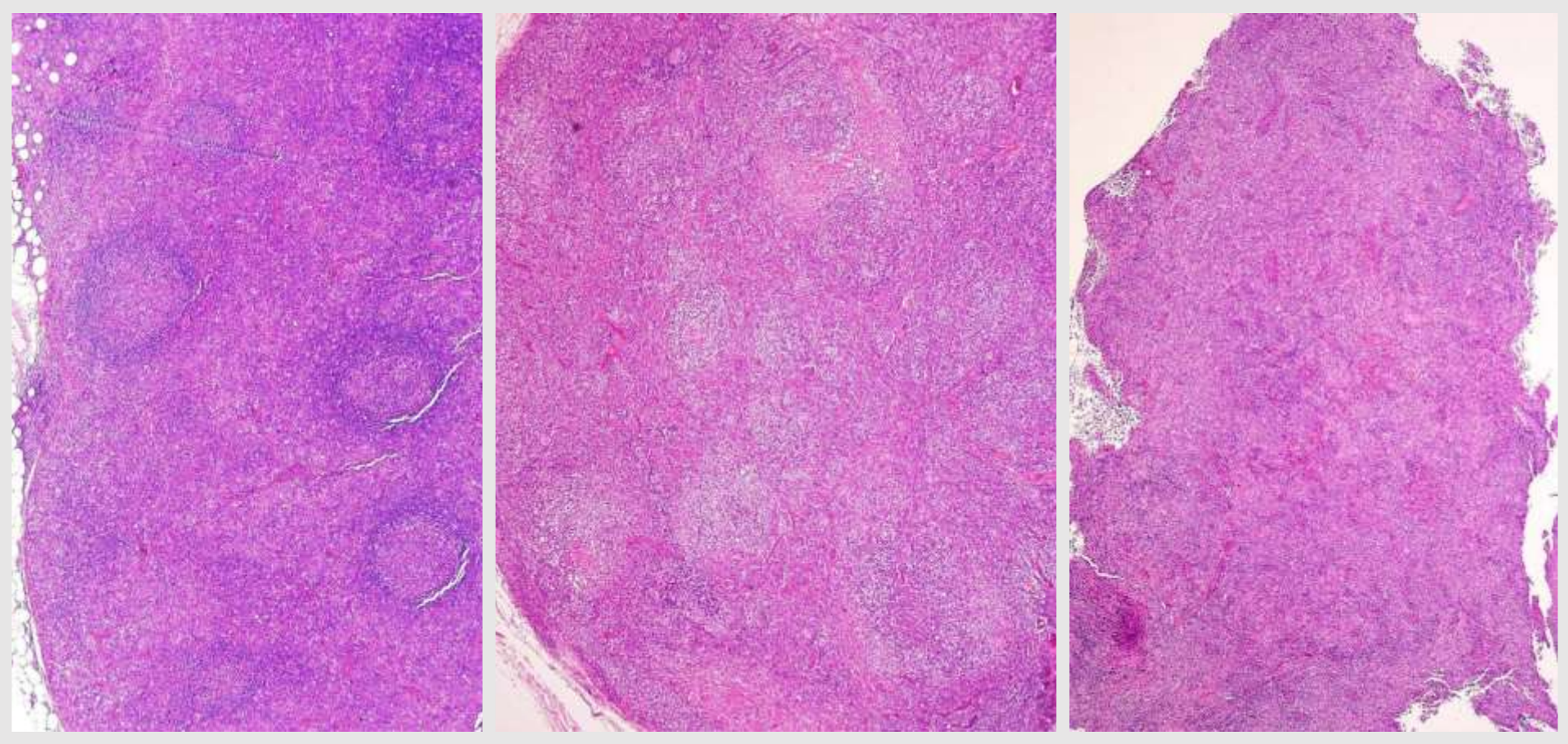
Quintanilla-Martinez 1999, Nicolae et al 2013

AITL- (often overlapping) histological patterns



Attygalle et al 2002

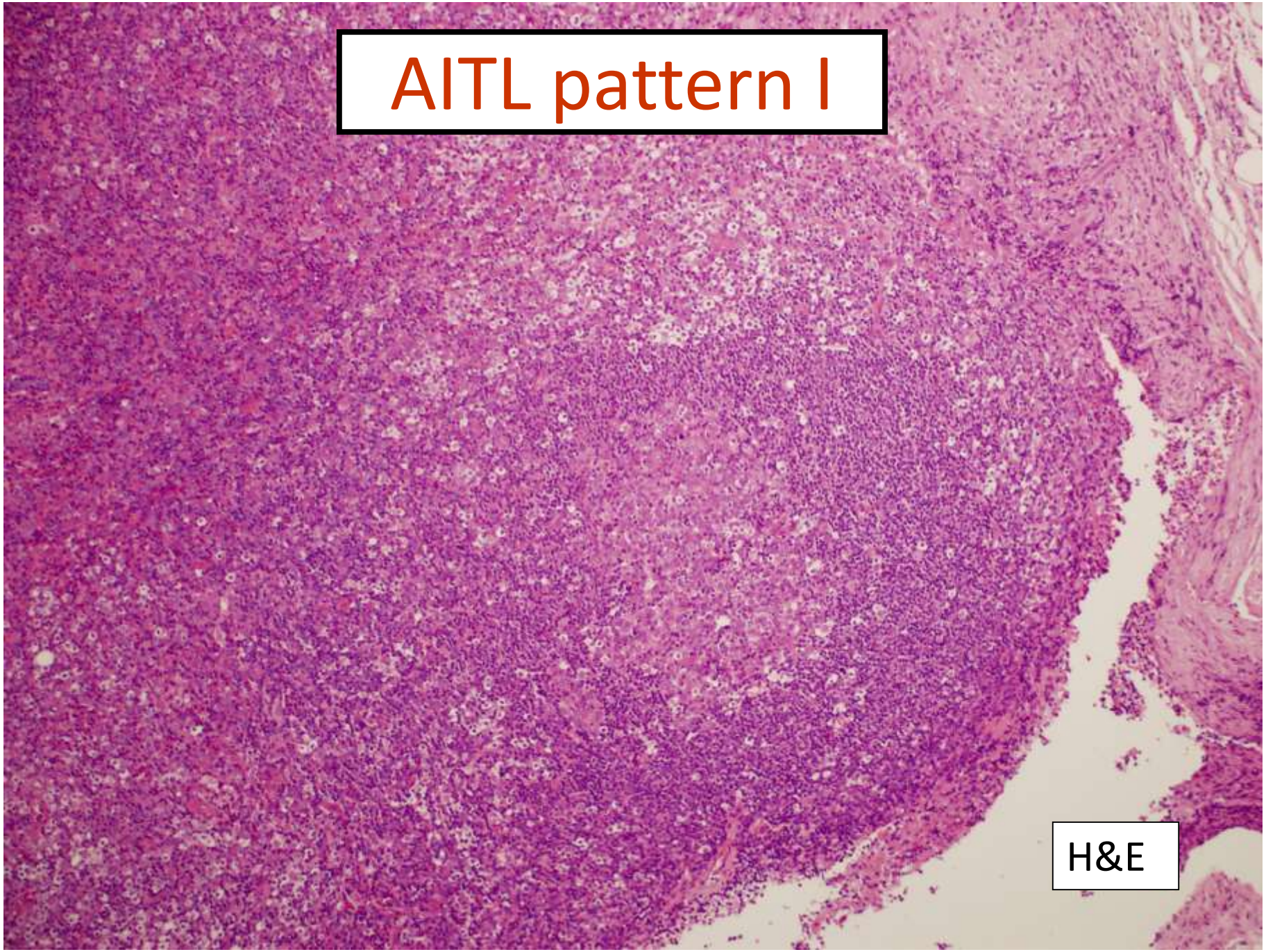
Patterns 2 and 3 = “Typical AITL”



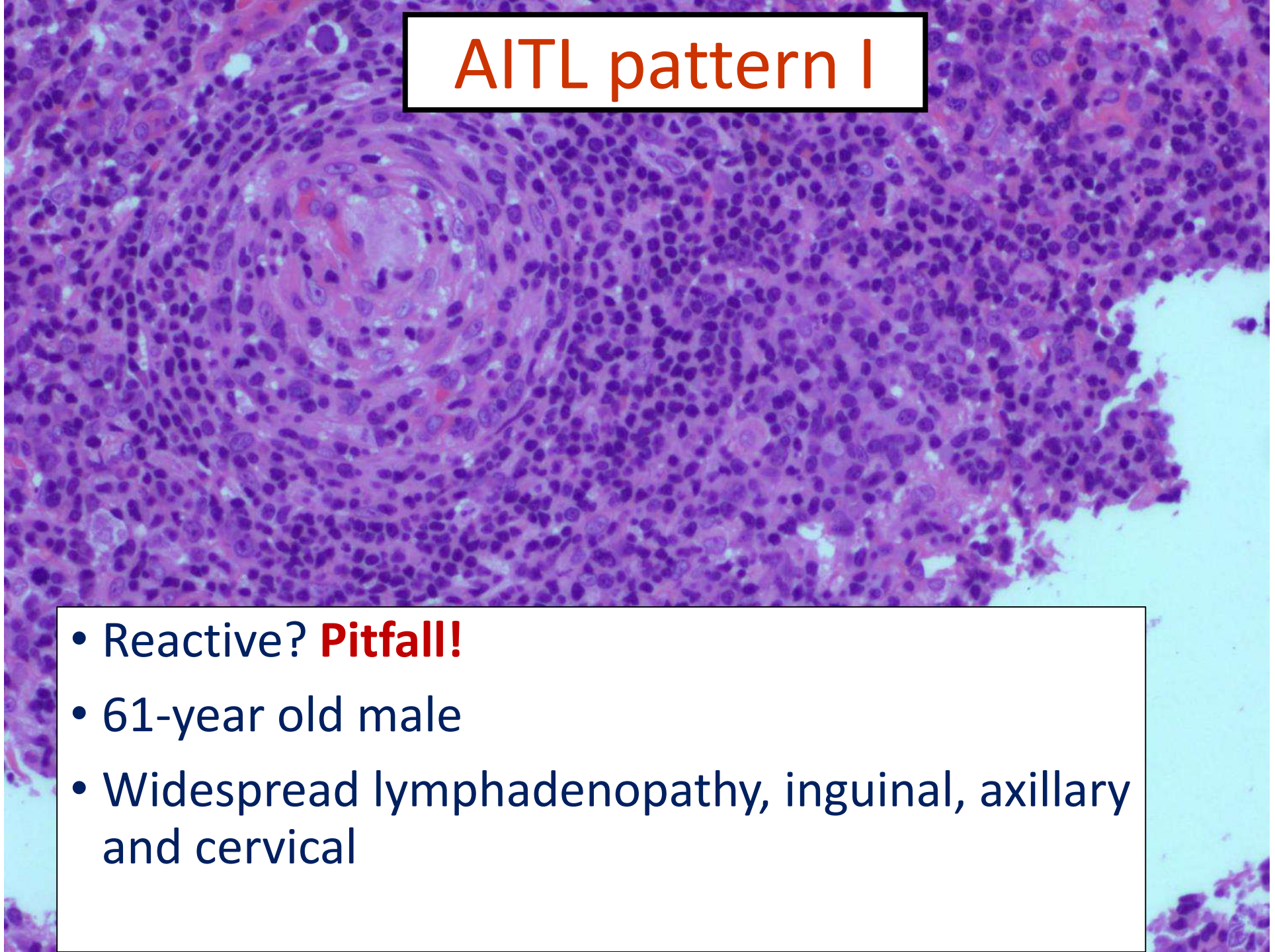
Attygalle et al 2002

AITL pattern I

- Partial nodal involvement, but usually disseminated (stage III or IV) disease
- Systemic/immune manifestations often present.
- May relapse as pattern I, II or III or overlap of patterns

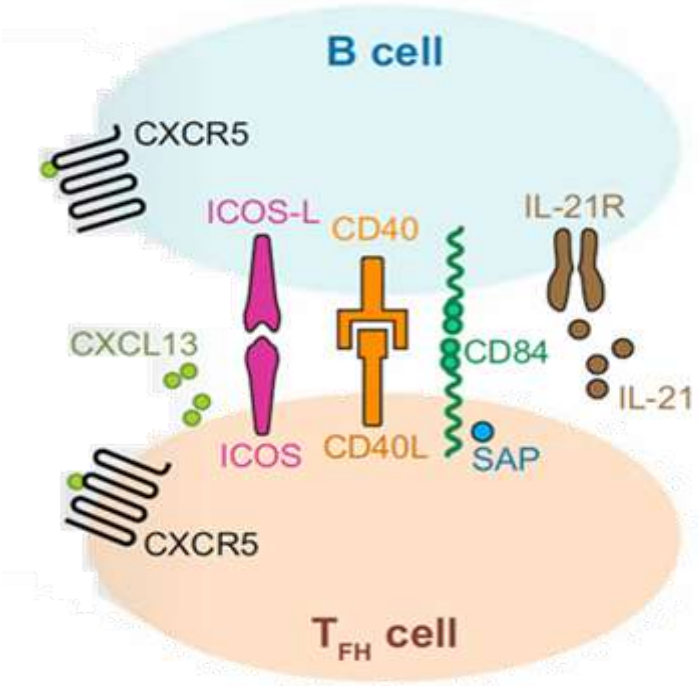

AITL pattern I
H&E

AITL pattern I



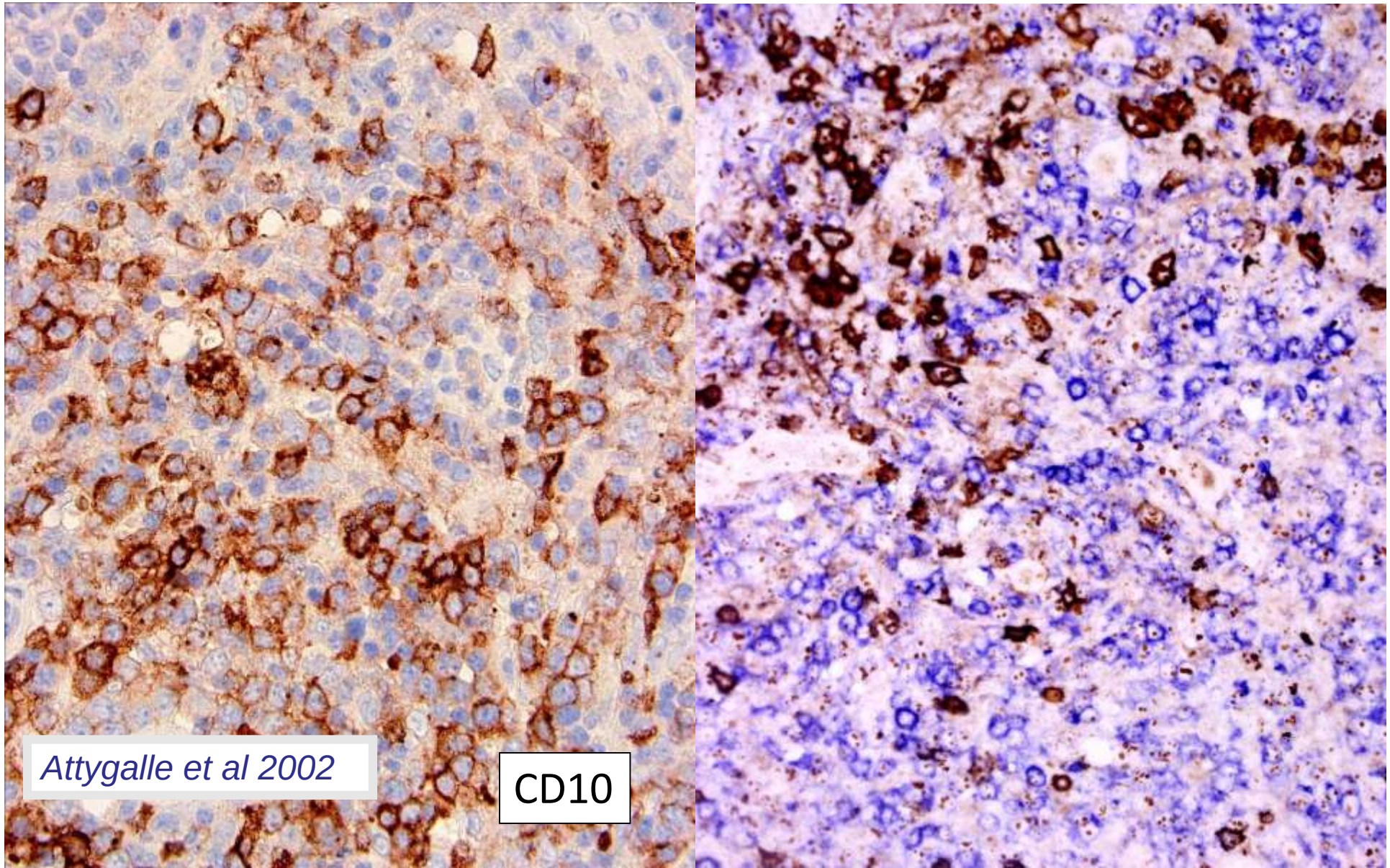
- Reactive? **Pitfall!**
- 61-year old male
- Widespread lymphadenopathy, inguinal, axillary and cervical

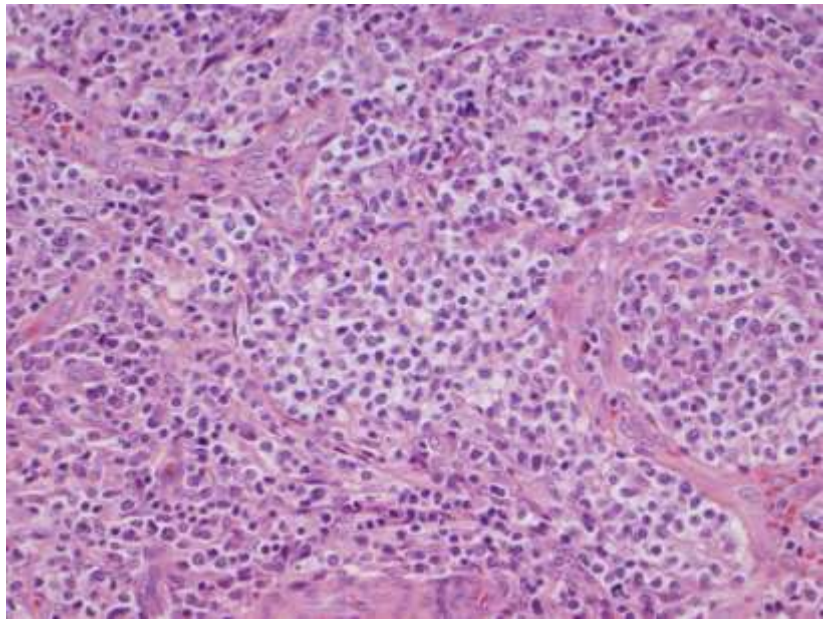
Follicular helper-T-cells (T_{FH} cells)

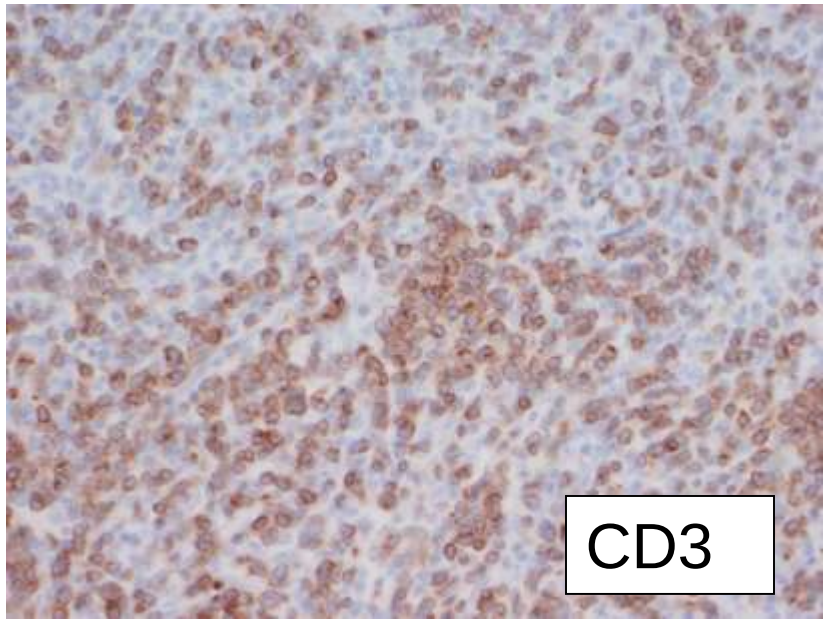


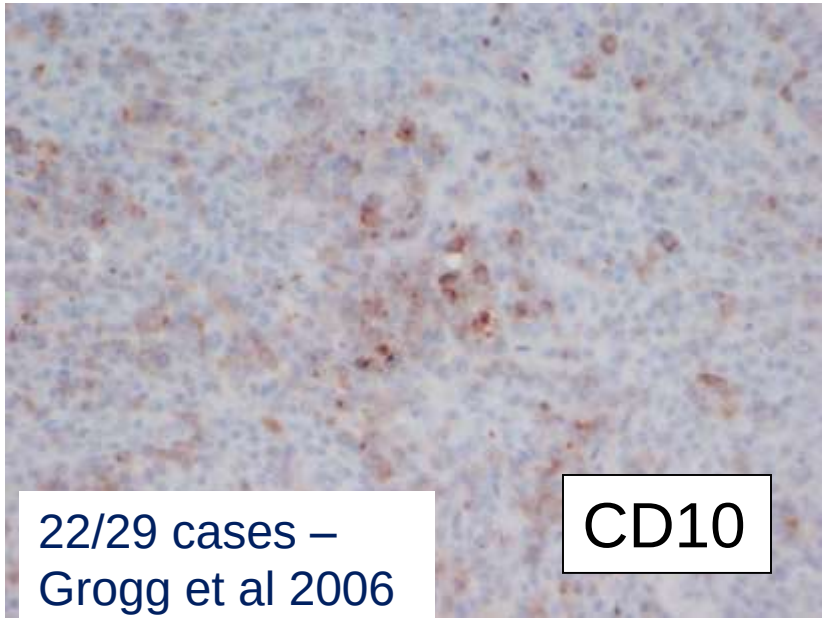
- PD-1
- ICOS
- CXCL-13
- CD10 (subset)
- BCL-6
- c-MAF
- CD200
- CXCR5
- SAP

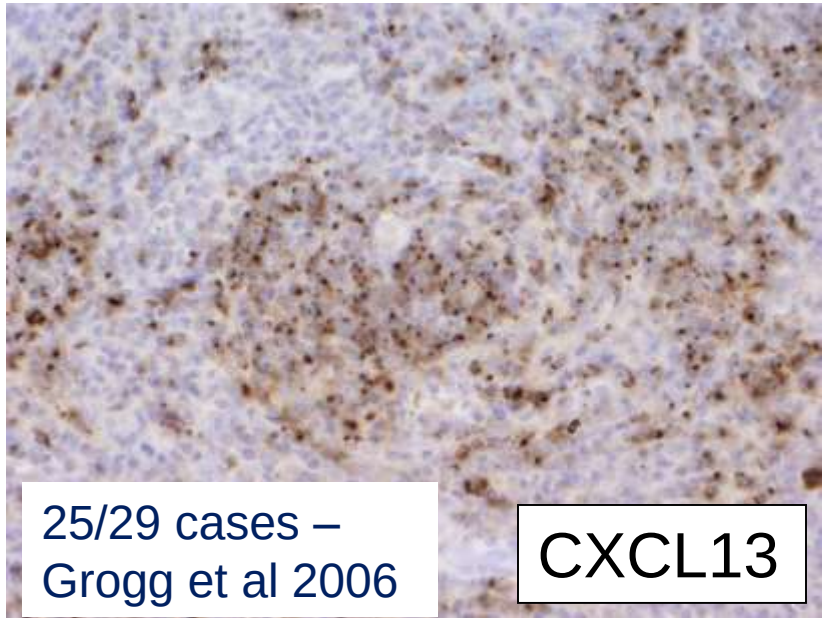
CD10 expression in angioimmunoblastic T-cell lymphoma







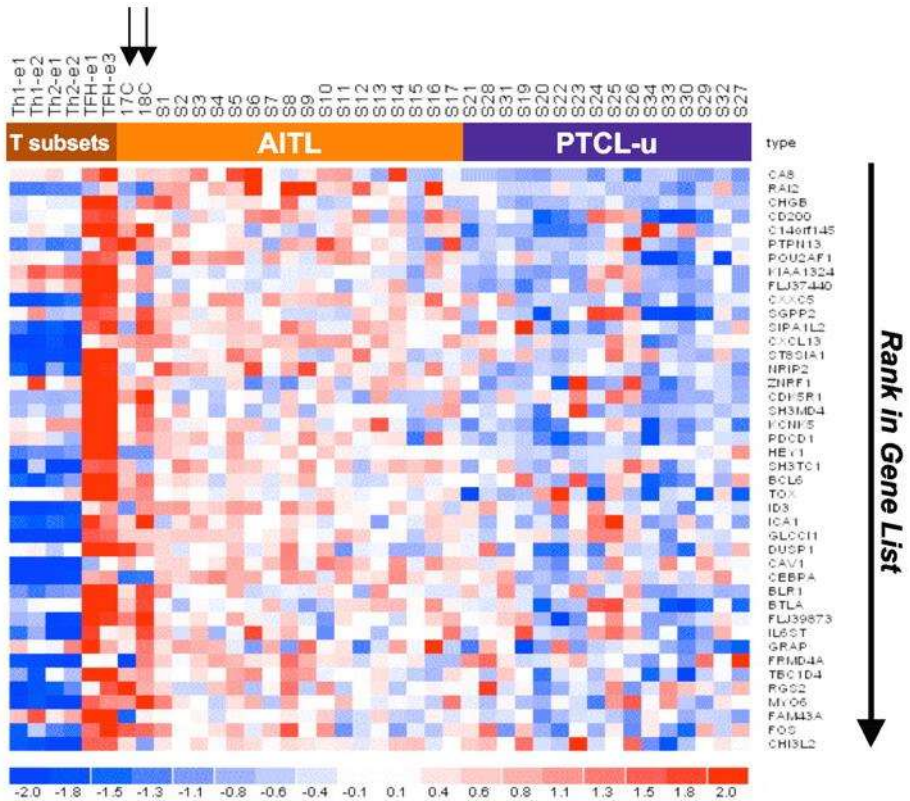




Grogg, et al Blood 2006, Dupuis et al 2006

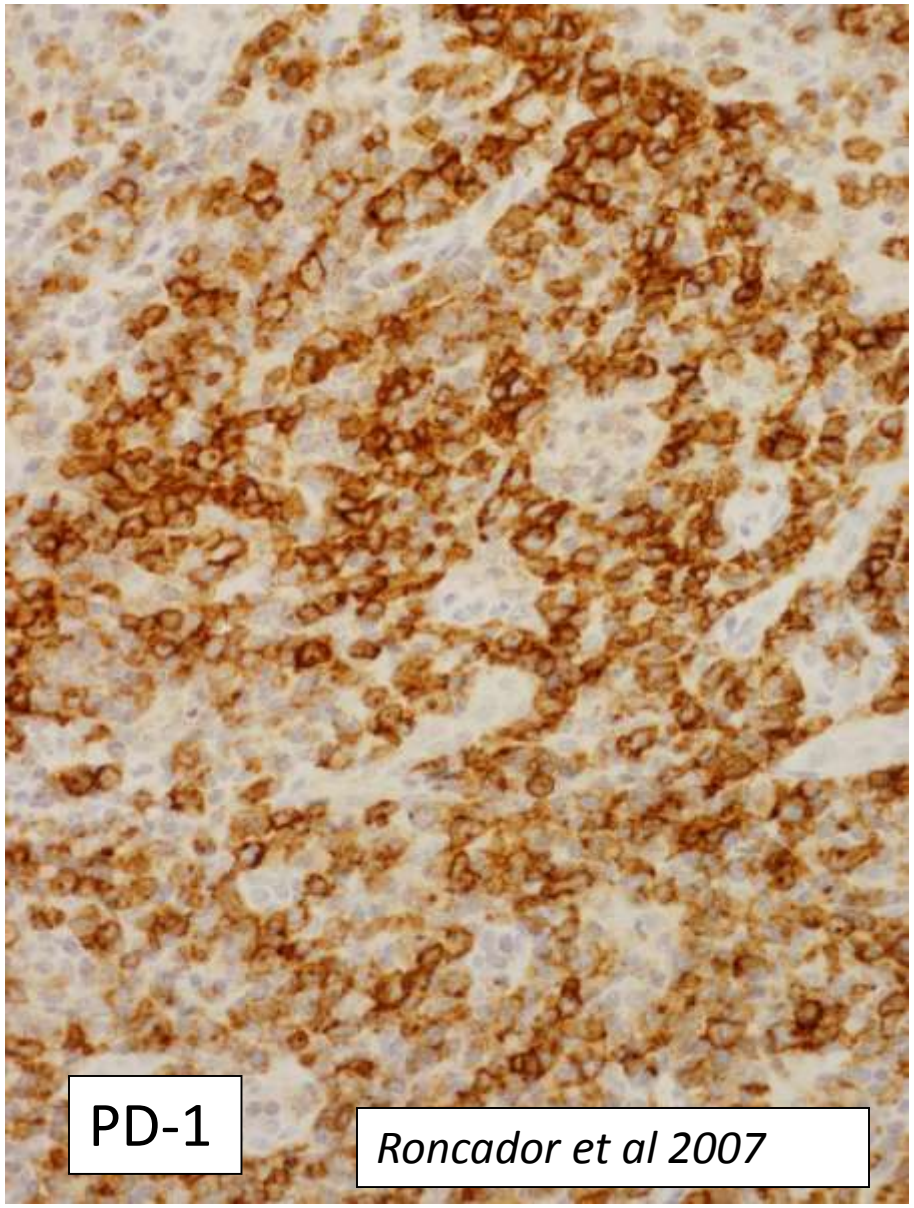
The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (T_{FH}) cells

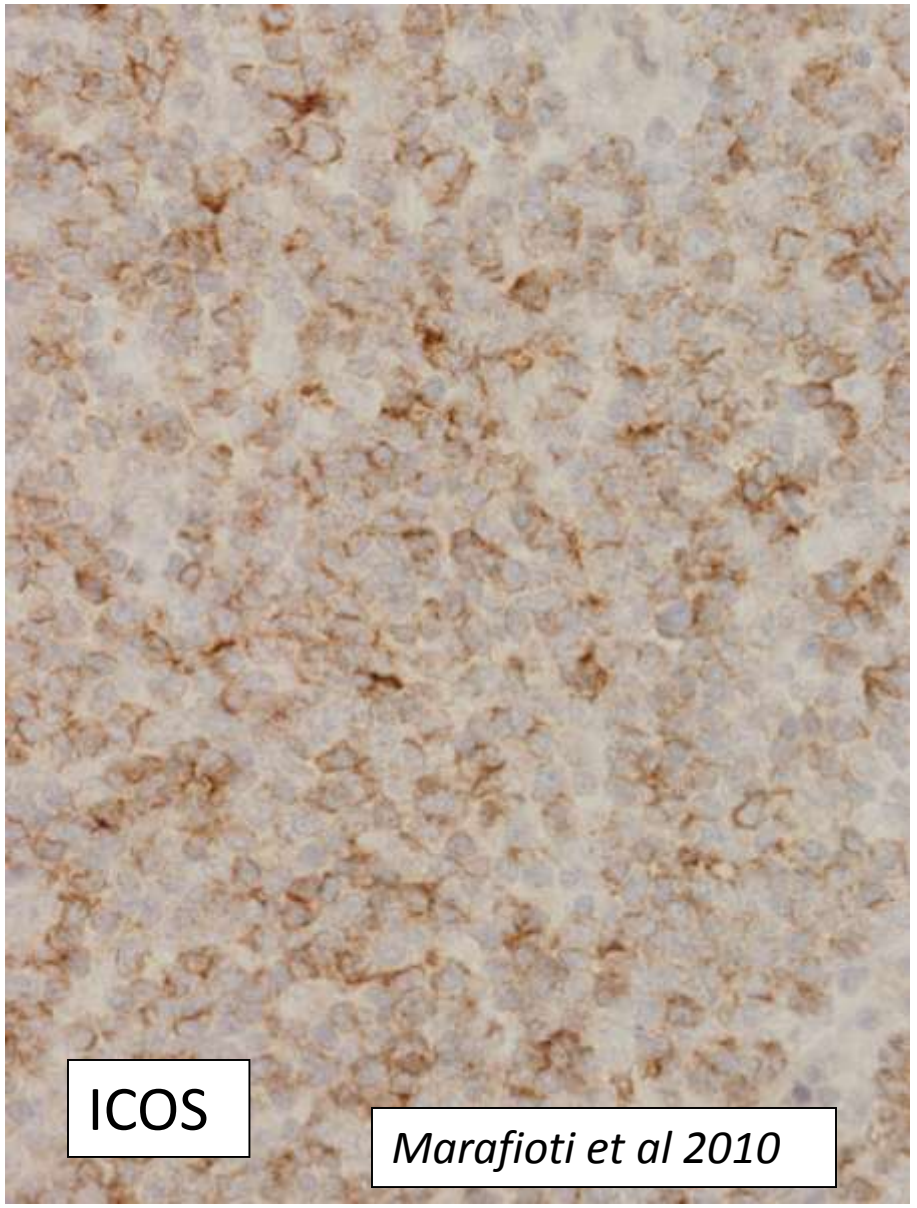
Laurence de Leval,[1] David S. Rickman,[2] Caroline Thielen,[1] Aurélien de Reynies,[2] Yen-Lin Huang,[3,5] Georges Delsol,[6] Laurence Lamant,[6] Karen Leroy,[3,4,5] Josette Brière,[7] Thierry Molina,[8] Françoise Berger,[9] Christian Gisselbrecht,[10] Luc Xerri,[11] and Philippe Gaulard[3,4,5]



Blood 2007;109:4952-4963

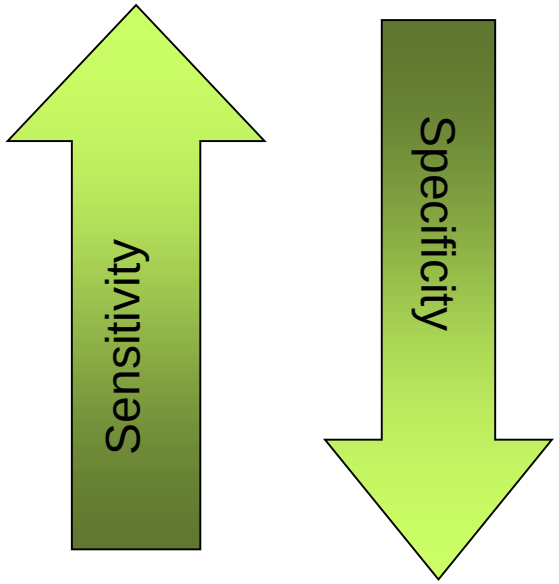
Other T_{FH} markers



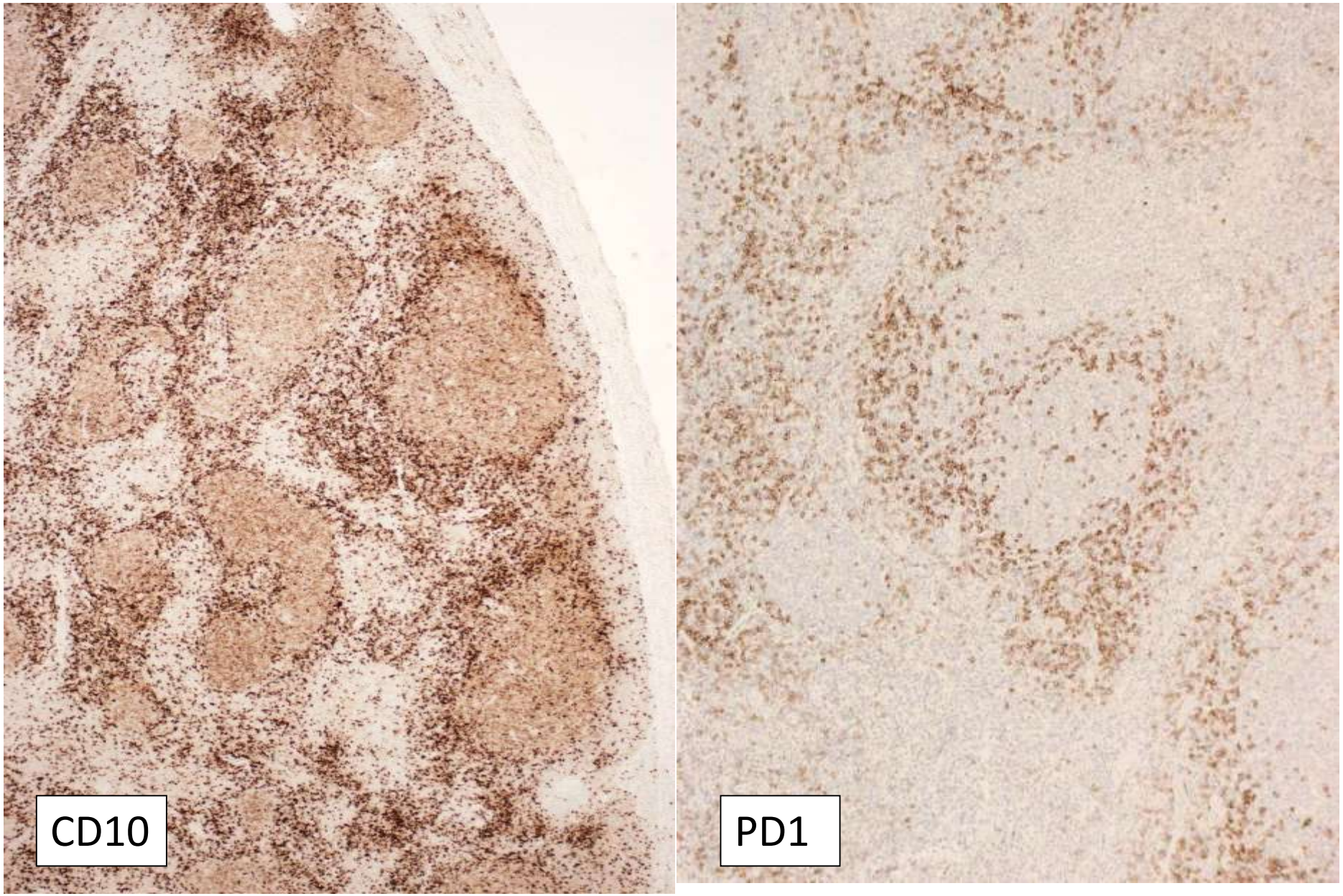


How useful is the T_{FH} phenotype in diagnosis?

- ICOS
- PD-1
- CXCL13
- CD10

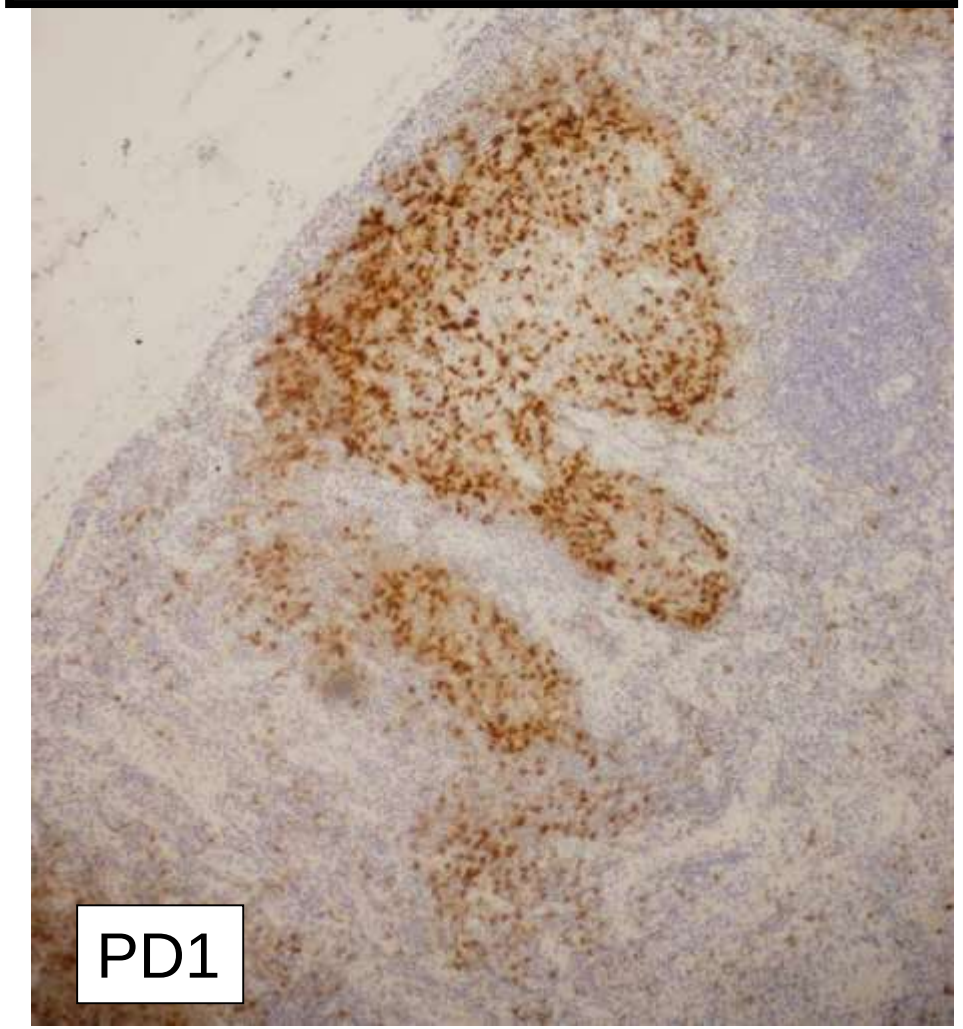


Marafioti et al 2010, Krishnan et al 2010, Grogg et al 2005, Grogg et al 2006, Dupuis et al 2006, Yu et al 2009, Attygalle et al 2007,

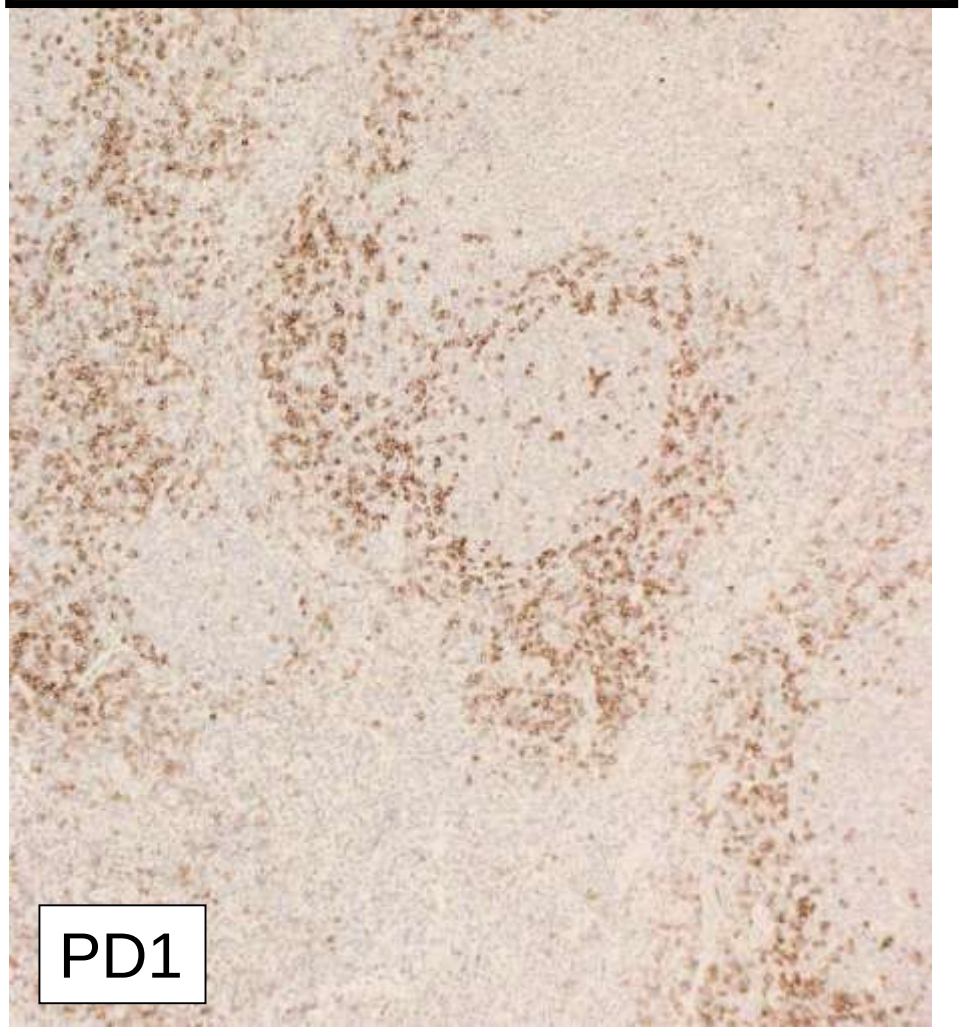

CD10
PD1

Differential diagnoses

Reactive LN



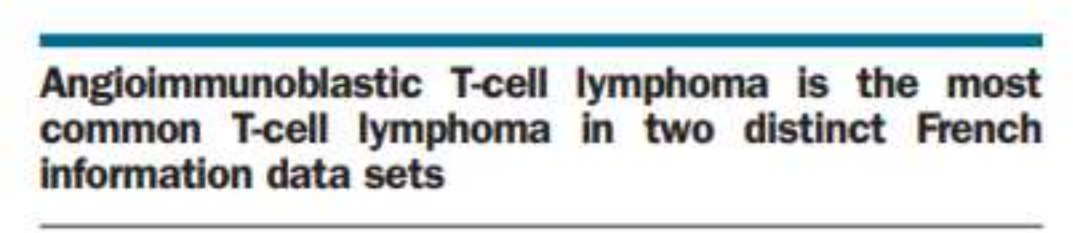
AITL pattern I



T-cell and NK-cell neoplasms account for 12% of all non-Hodgkin lymphomas

AITL

- 18.5% of all mature T-cell lymphomas (International T-cell lymphoma project, 2008)
- Europe :29% of all mature T-cell lymphomas
- Asia: 18% of all mature T-cell lymphomas

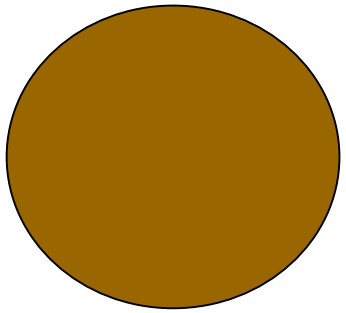

Angioimmunoblastic T-cell lymphoma is the most common T-cell lymphoma in two distinct French information data sets

AITL 36.1 % vs PTCL,NOS 26.9%

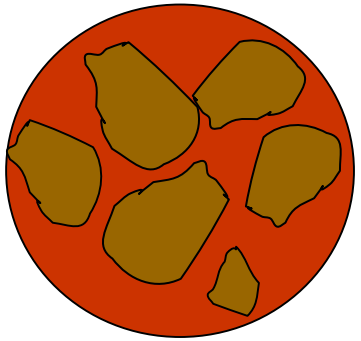
de Leval et al 2015

PTCL, NOS, follicular variant (PTCL-F) (2008)

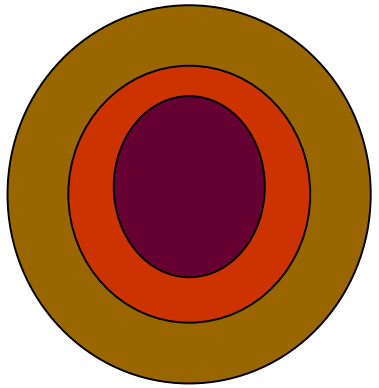
"Folliculotropic" T_{FH} neoplasms with no significant FDC expansion,



mimicking follicular lymphoma



mimicking nodular LPHL



mimicking nodal MZL

Peripheral T-cell lymphoma with distinct perifollicular growth pattern: a distinct subtype of T-cell lymphoma?
The American Journal of Surgical Pathology. 24(1):117-22, JAN 2000
Rudiger et al

Peripheral T-cell lymphoma with follicular involvement and a CD4+/bcl-6+phenotype.
The American Journal of Surgical Pathology. 25(3):395-400, MAR 2001
de Leval et al

Peripheral T-cell lymphoma with distinct perifollicular growth pattern: a distinct subtype of T-cell lymphoma?
The American Journal of Surgical Pathology. 24(1):117-22, JAN 2000
Rudiger et al

Peripheral T-cell lymphoma with follicular involvement and a CD4+/bcl-6+phenotype.
The American Journal of Surgical Pathology. 25(3):395-400, MAR 2001
de Leval et al

Leukemia (2006) 20, 313–318

www.nature.com/leu

ORIGINAL ARTICLE

Novel t(5;9)(q33;q22) fuses *ITK* to *SYK* in unspecified peripheral T-cell lymphoma

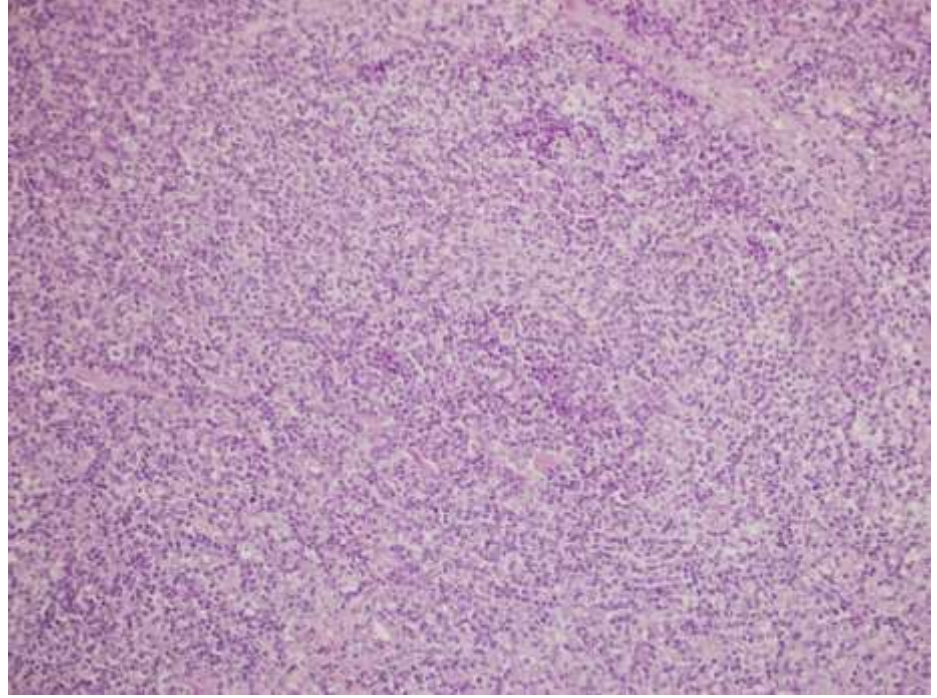
B Streubel[1], U Vinatzer[2], M Willheim[3], M Raderer[4] and A Chott[1]

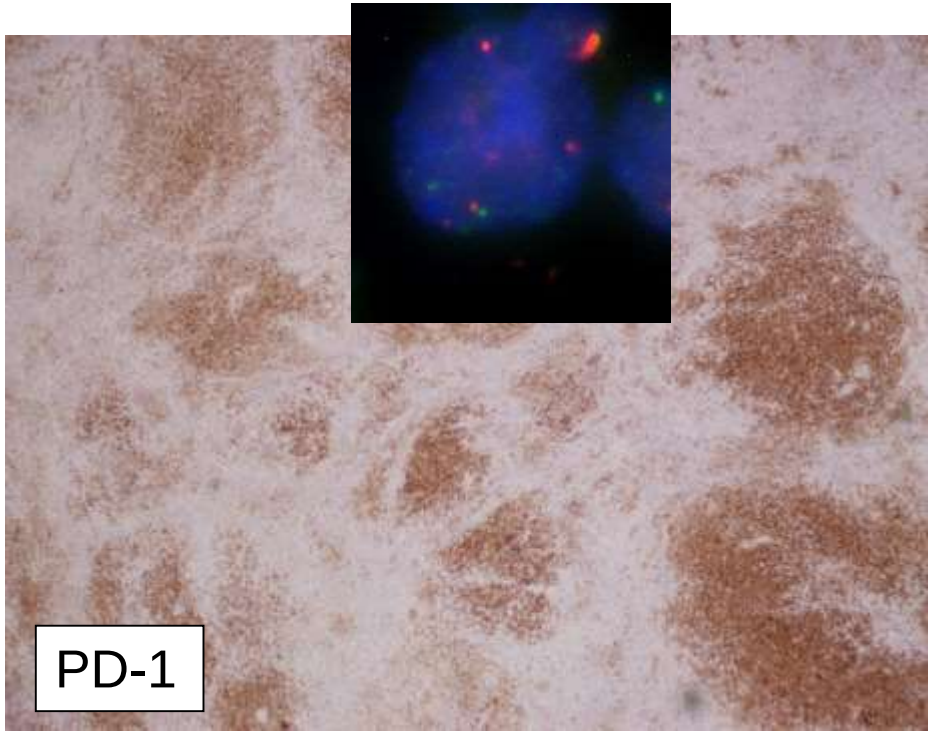
[1]*Department of Pathology, Medical University of Vienna, Vienna, Austria;* [2]*Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria;* [3]*Department of Physiology and Pathophysiology, Medical University of Vienna, Vienna, Austria and* [4]*Department of Internal Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria*

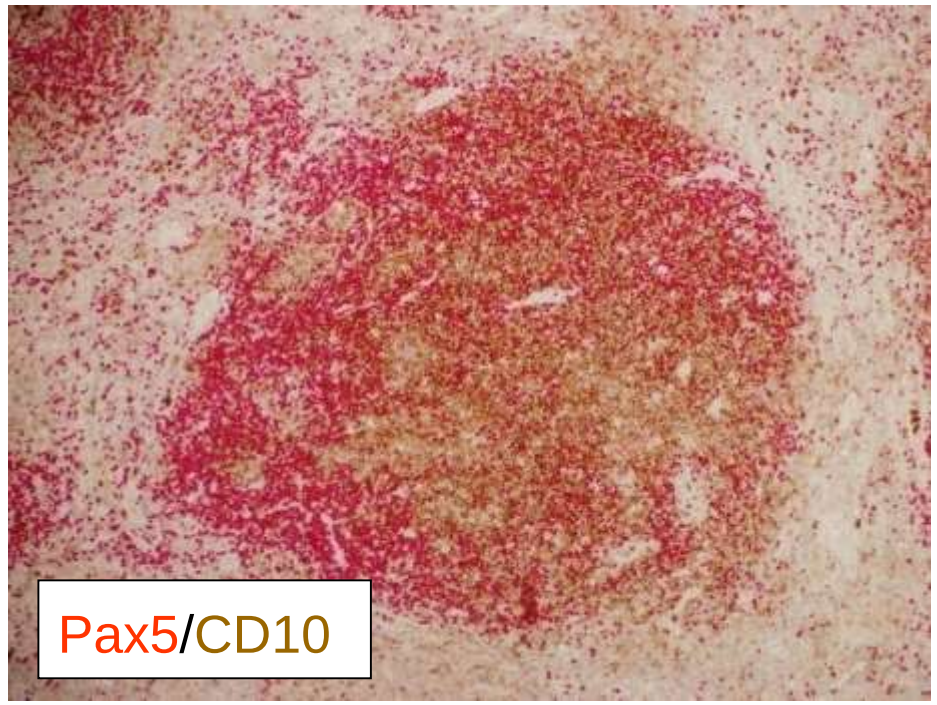
Peripheral T-cell lymphoma (NOS), follicular variant (WHO 2008)

Rudiger et al 2000, de leval et al 2001, Hatano et al 2002, Uherova et al 2002, Jiang et al 2005, Hu et al 2012

- Early stage, partial involvement, lack of FDC proliferation, lack of prominent HEV (WHO, 2008)
- t(5;9)(q33;q22) ITK/SYK – in proportion of cases - *Streubel et al 2006*







PTCL-F (FTCL)

Clinical features and laboratory findings

Age range (median age)	27-90 years (62yrs)
Sex ratio (M:F)	1.2:1
B-symptoms	29%
Stage III to IV	73%
Multiple lymphadenopathies	86%
Hepatomegaly	23%
Splenomegaly	24%
Skin rash (often pruritic)	23%
Bone marrow involvement	26%
Elevated LDH	45%
Hypergammaglobulinaemia	19%
Coomb's positive AIHA	50%

Hu et al 2012

Table 1. Summary of clinical features, mutational status and copy number variations in AITL, other PTCL of TFH origin and PTCL-NOS.

	Nodal lymphomas of TFH cell origin (TFH-PTCL)				
	AITL	Other TFH-PTCL		PTCL-NOS	*P* (Fisher test) across four entities
		TFH-like PTCL	F-PTCL*		
Clinical variables					
Median age at diagnosis	67.8	65	67	62.5	
Sex (M)	53/94 (56%)	9/16 (60%)	2/5 (40%)	23/34 (68%)	0.54
Stage III-IV	84/85 (99%)	14/15 (93%)	4/4 (100%)	29/34 (85%)	0.02
ECOG ≥ 2	67/83 (53%)	3/12 (25%)	1/4 (25%)	11/33 (33%)	$< 1.0 \times 10^{-2}$
IPI ≥ 3	63/79 (80%)	11/15 (73%)	2/4 (50%)	20/31 (65%)	0.21
Coombs (+)	25/56 (45%)	1/3 (33%)	1/2 (50%)	0/6 (0%)	0.14*
Anemia	47/71 (66%)	5/10 (50%)	2/4 (50%)	10/27 (37%)	0.17*
Hypergammaglobulinemia (≥16 g/dl)	23/48 (48%)	1/8 (12.5)	1/3 (33%)	4/19 (21%)	0.08
Mutations (%)					
TET2	31/64 (48%)	7/11 (64%)	3/4 (75%)	4/24 (17%)	$< 1.0 \times 10^{-2}$
DNMT3A	19/64 (30%)	1/10 (10%)	1/4 (25%)	1/24 (4%)	0.02
IDH2	22/66 (33%)	1/11 (10%)	0/5 (0%)	0/23 (0%)	$< 1.0 \times 10^{-3}$
RHOA (G17V)	42/72 (58%)	8/14 (57%)	3/5 (60%)	0/23 (0%)	$< 1.0 \times 10^{-4}$
Copy number variations					
Events per patient (average)	3.17	3.94	2.36	10.8	
Patients with events	23/60 (38%)	4/12 (33%)	1/3 (33%)	17/27 (63%)	0.78
Heavily-rearranged (>10 events) patients	6/60 (8%)	3/12 (25%)	0/3 (0%)	11/27 (41%)	$< 1.0 \times 10^{-2}$
Patients with homozygous deletions or amplifications	3/60 (5%)	3/12 (25%)	0/3 (0%)	12/27 (44%)	$< 1.0 \times 10^{-4}$

*Two out of 5 F-PTCL (40%) had *ITK-SYK* translocation by FISH, 1/5 (20%) was negative and 2/5 (40%) had non- interpretable results. None of the other PTCL with interpretable signals (9 AITL, 5 TFH-like PTCL, and 4 PTCL-NOS) disclosed *ITK-SYK* rearrangement. *P-value < 0.05 when TFH-like PTCL and F-PTCL are calculated as a single entity (Other TFH-PTCL).

Dobay et al 2017

Peripheral T-cell Lymphomas With a Follicular Growth Pattern are Derived From Follicular Helper T Cells (T_{FH}) and may Show Overlapping Features With Angioimmunoblastic T-cell Lymphomas

Yenlin Huang, MD,†‡ Anne Moreau, MD,§ Jehan Dupuis, MD,‖ Berthold Streubel, MD,¶ Barbara Petit, MD,# Steven Le Gouill, MD, PhD,** Nadine Martin-Garcia, BSc,*†‡ Christiane Copie-Bergman, MD, PhD,*†‡ Fanny Gaillard, MD,§ Marwan Qubaja, MD,†† Bettina Fabiani, MD,‡‡ Giovanna Roncador, BSc,§§ Corinne Haioun, MD,‖ Marie-Hélène Delfau-Larue, MD, PhD,*†‖‖ Teresa Marafioti, MD, FRCPath,¶¶ Andreas Chott, MD,¶ and Philippe Gaulard, MD*†‡*

(*Am J Surg Pathol* 2009;33:682–690)

4/23 cases positive for t(5;9)

Huang et al 2009

- 1 case presented with generalised lymphadenopathy, haemolytic anaemia, splenomegaly typically associated with AITL

- 1 case presented with disseminated disease with multiple lymphadenopathy with PTCL-F appearance and on relapse had areas reminiscent of AITL

ITK/SYK translocation in AITL

- EAHP/SH meeting 2012: A single case of pattern I AITL positive was for t(5;9)

- One case of typical AITL positive for t(5;9)

–Attygalle et al 2013

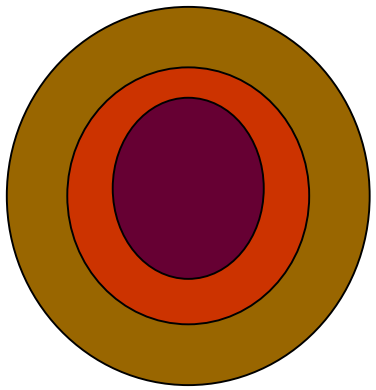
EAHP/SH meeting Lisbon 2012 –
3 cases that showed overlapping features between AITL and PTCL-F

AITL –pattern I vs PTCL-F (perifollicular/MZL-like)

- “in particular, cases of PTCL-F with a MZL-like pattern have similarities with early phase AITL, so called pattern I and II, as summarized by *Attygalle et al*”

Hu et al 2012

PTCL-F (perifollicular/MZL-like)?
Or
spectrum of AITL (pattern I)?



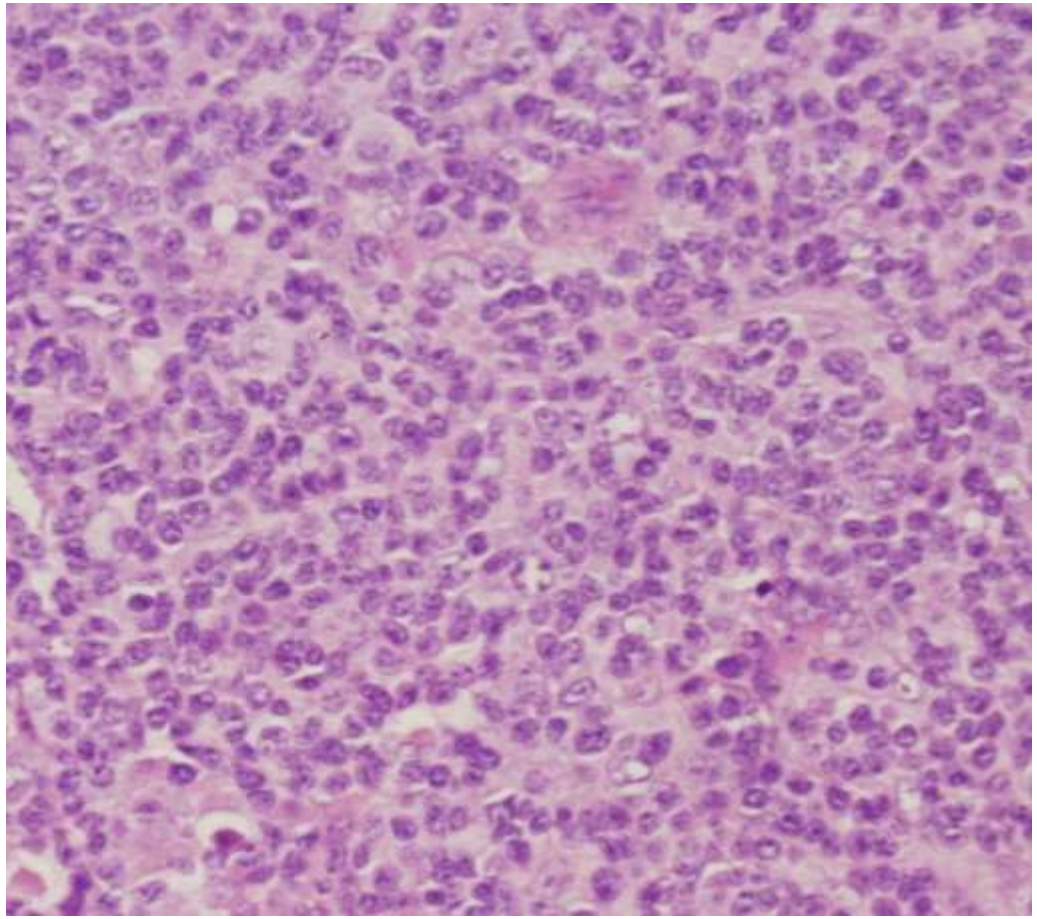
AITL that deviates from existing diagnostic criteria, but categorised as AITL in WHO 2008

- AITL (pattern 1) - there is no/subtle FDC expansion

Are there other cases of “AITL” that deviate from existing diagnostic criteria?

AITL or PTCL (NOS)?

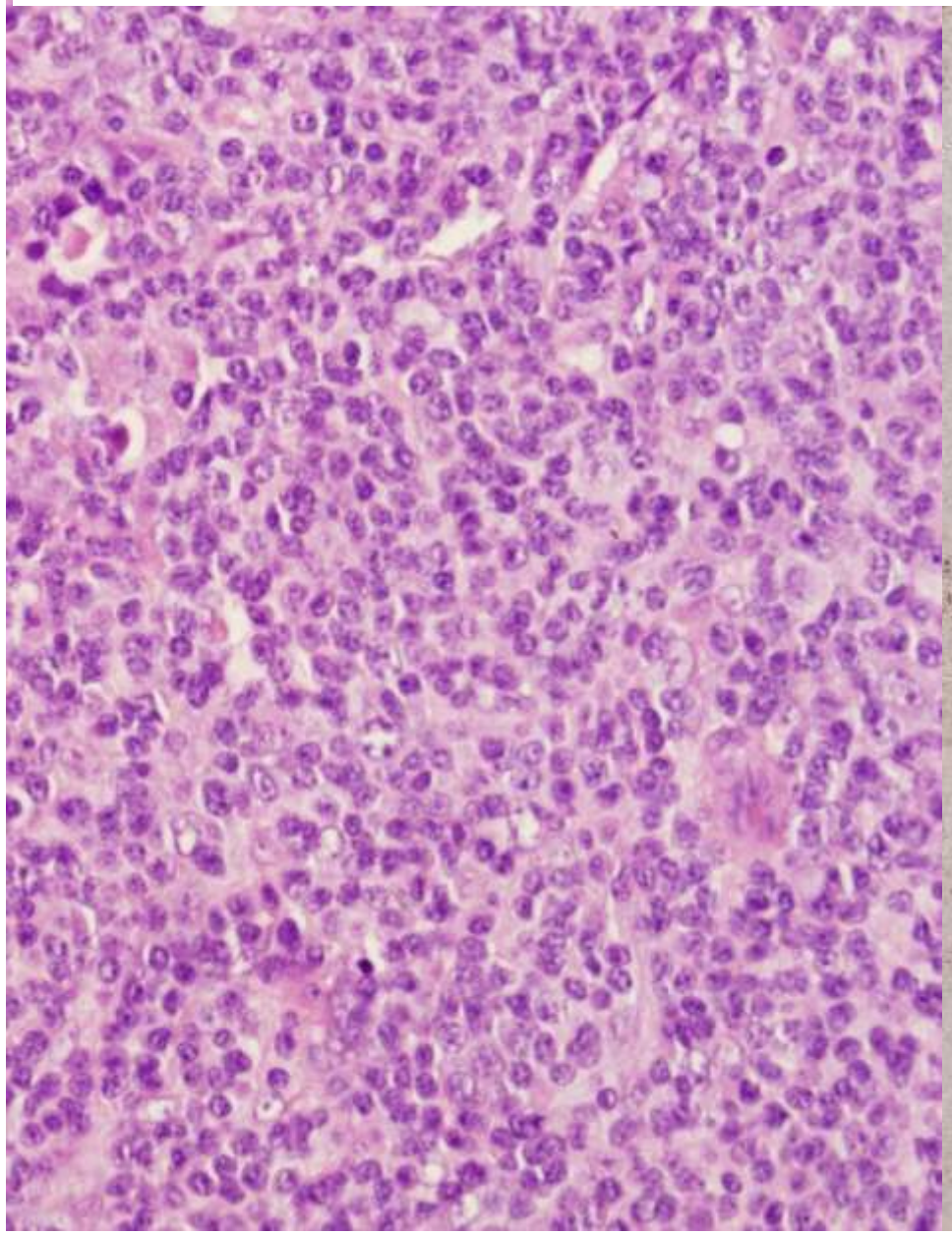
When infiltrate is monomorphous and HEV hyperplasia limited – ? PTCL (NOS)

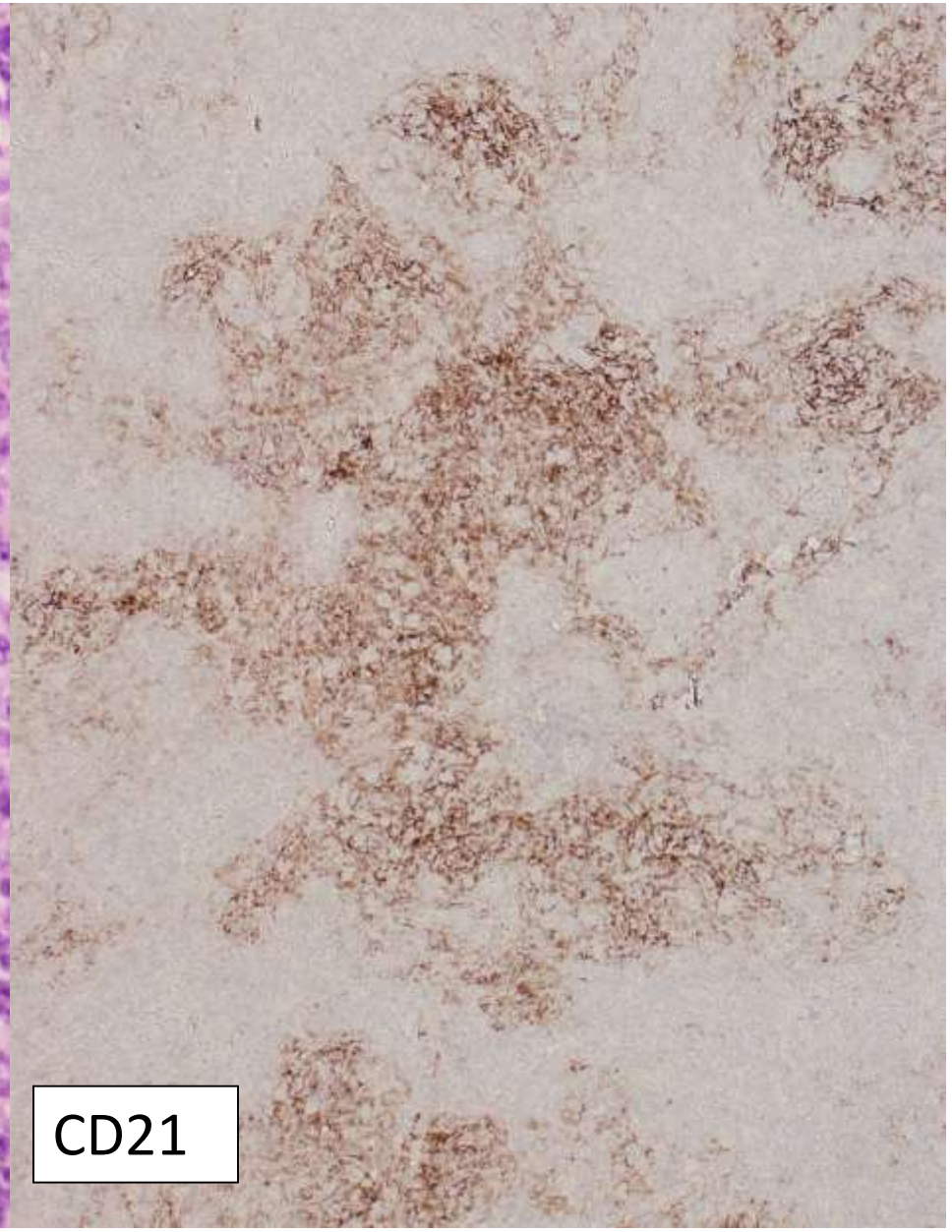


EAHP/SH 2012 - AITL "tumour cell rich"

Case# Submittor	Clinical syndrome /B symp /skin rash	LN	infiltrate	HEV	Clear cells	FDC	EBER	CD10/ TFH marker
332 Kansal	None	Inguinal pelvic	mono	+/-	+	increase	-	ICOS+ PD1 wk CXCL13+ CD10+
145 Li	None	gen	mono	++	+	increase	+	ICOS+ PD1+ CXCL13+ CD10+
55 Tzankov	Syn ? B-symp+ Rash+	gen	1st – Poly 2nd mono	1st ++ 2nd -	+	Increase	-	ICOS+ PD1+ CXCL13+ CD10 ND
39 van Krieken	N/A	N/A	Limited poly	+	-	Increase	++	ICOS+ PD1+ CXCL13+ CD10+
296 Ambrose	None	gen	mono	-	-	increase	+	ICOS+ PD1 wk CXCL13+ CD10 f+

58 yrs old male, progressive disease: - generalized lymphadenopathy and splenomegaly, no skin lesions



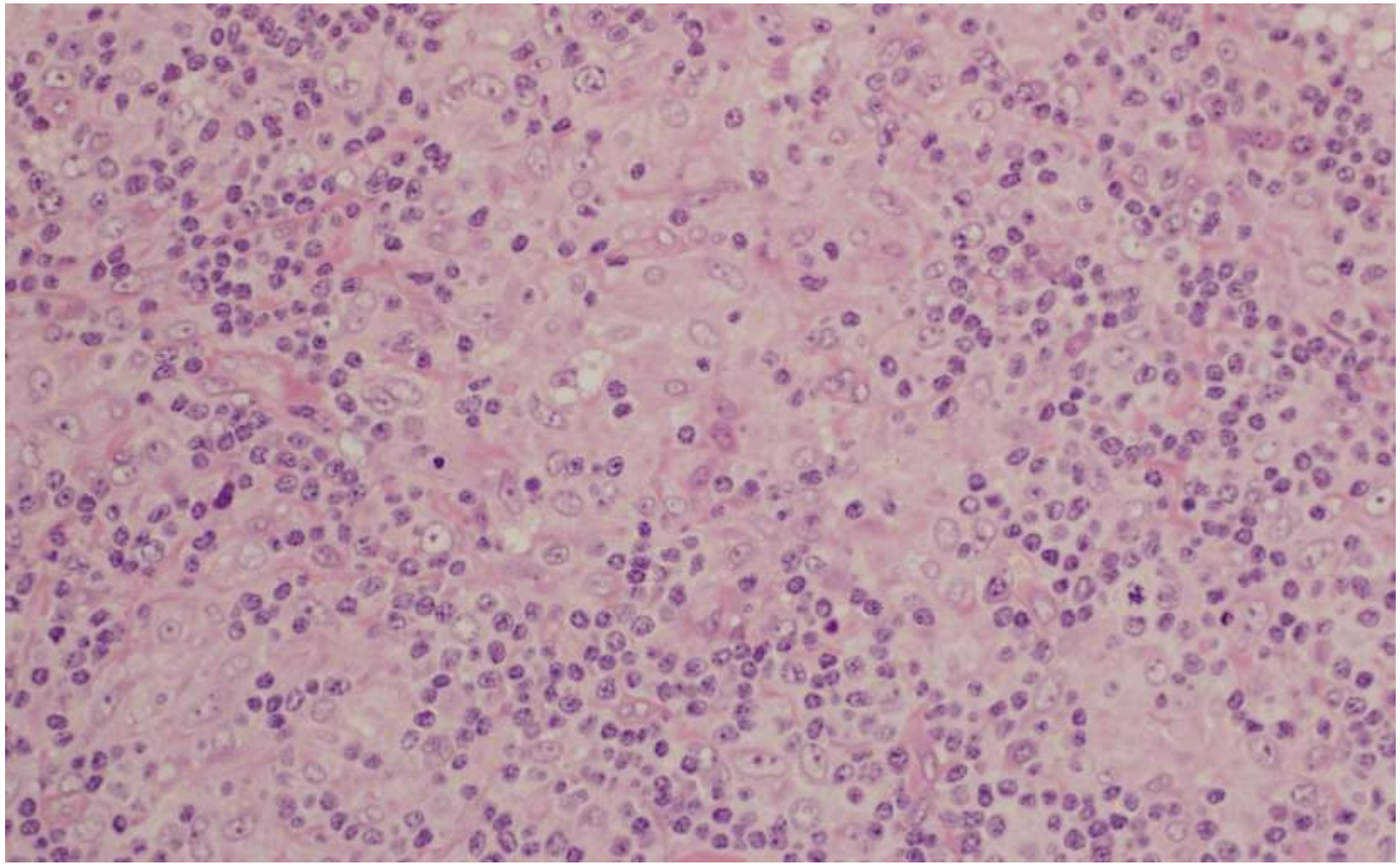


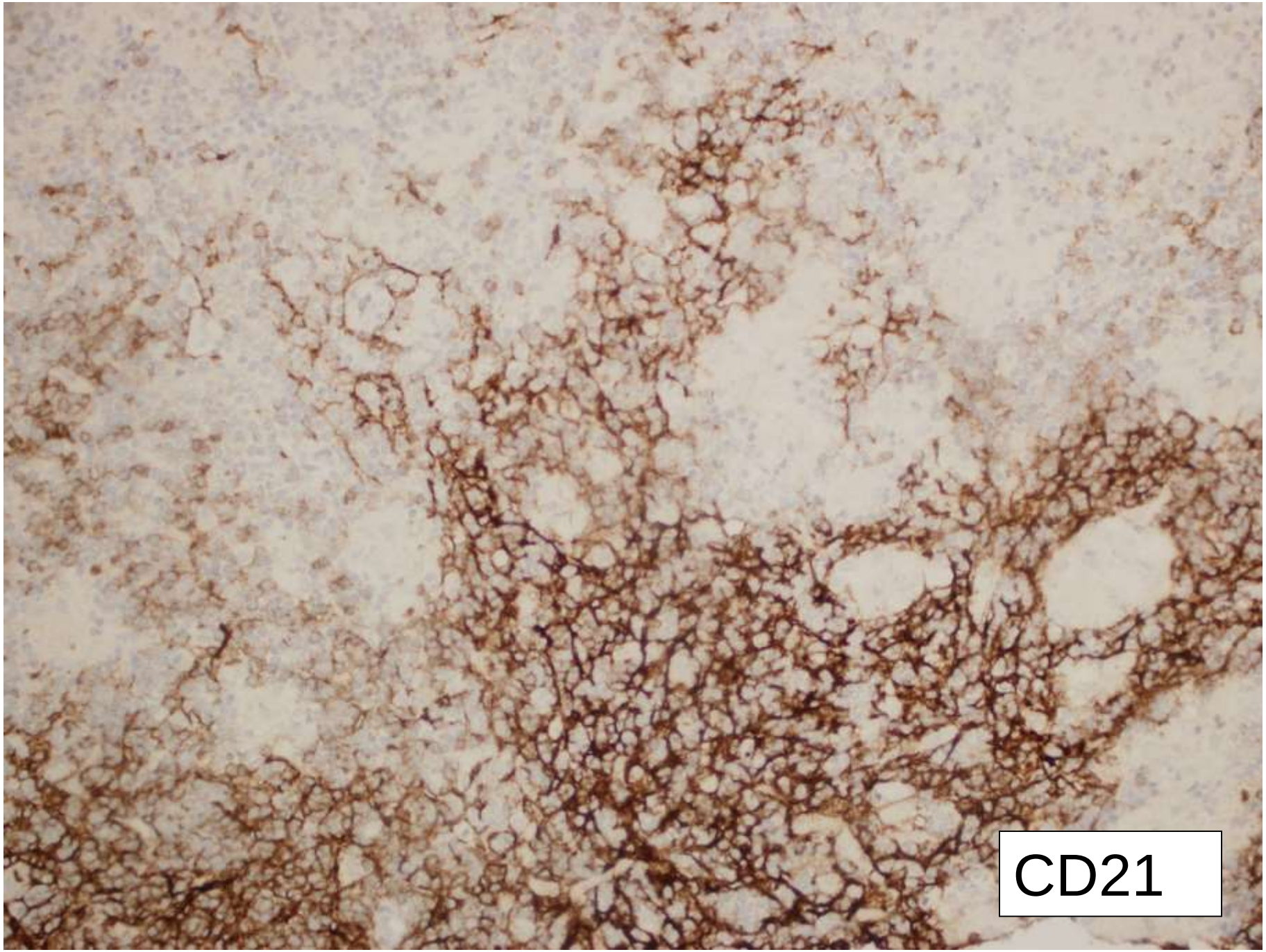
PTCL , rich in epithelioid histiocytes

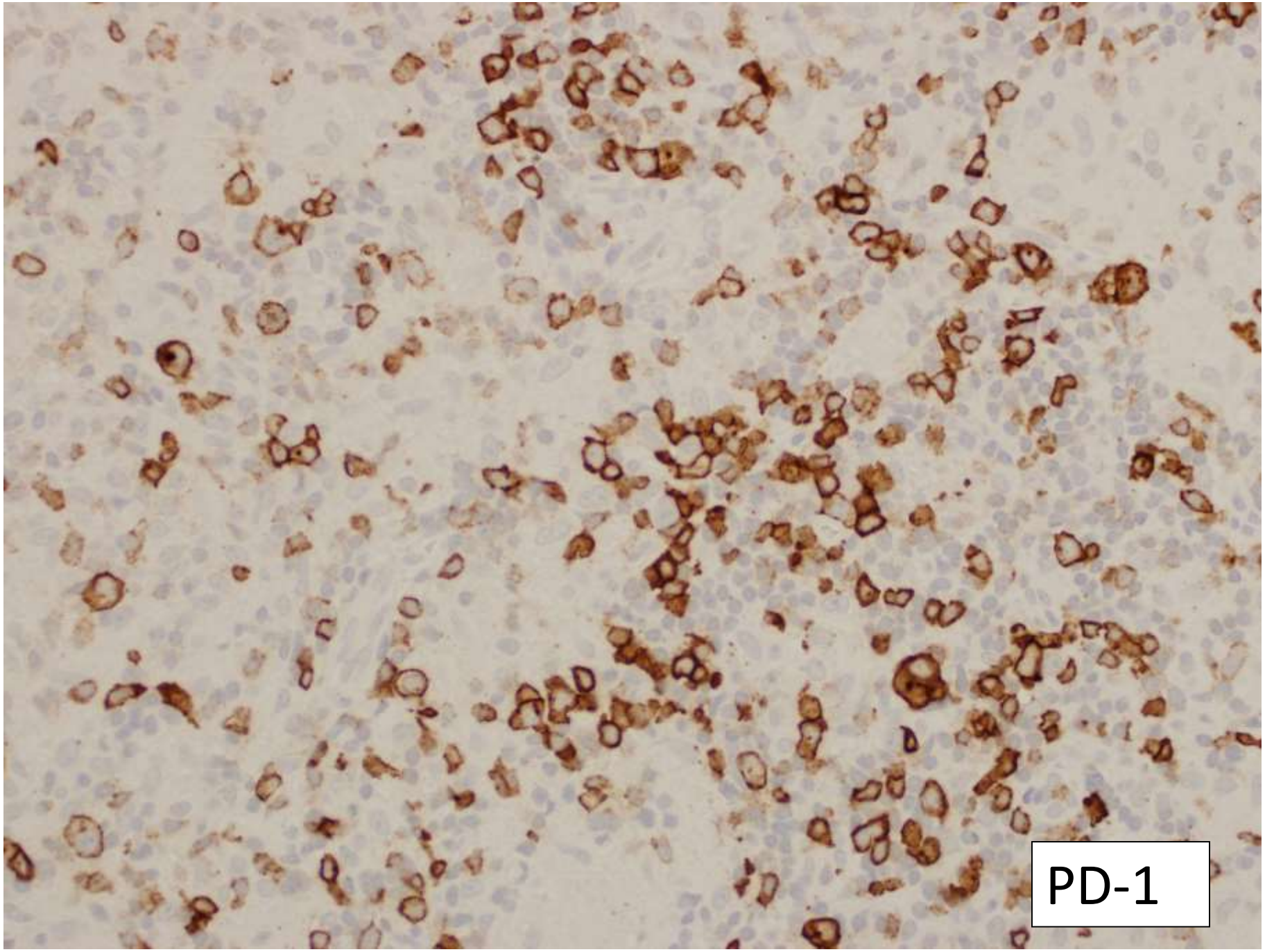
?AITL

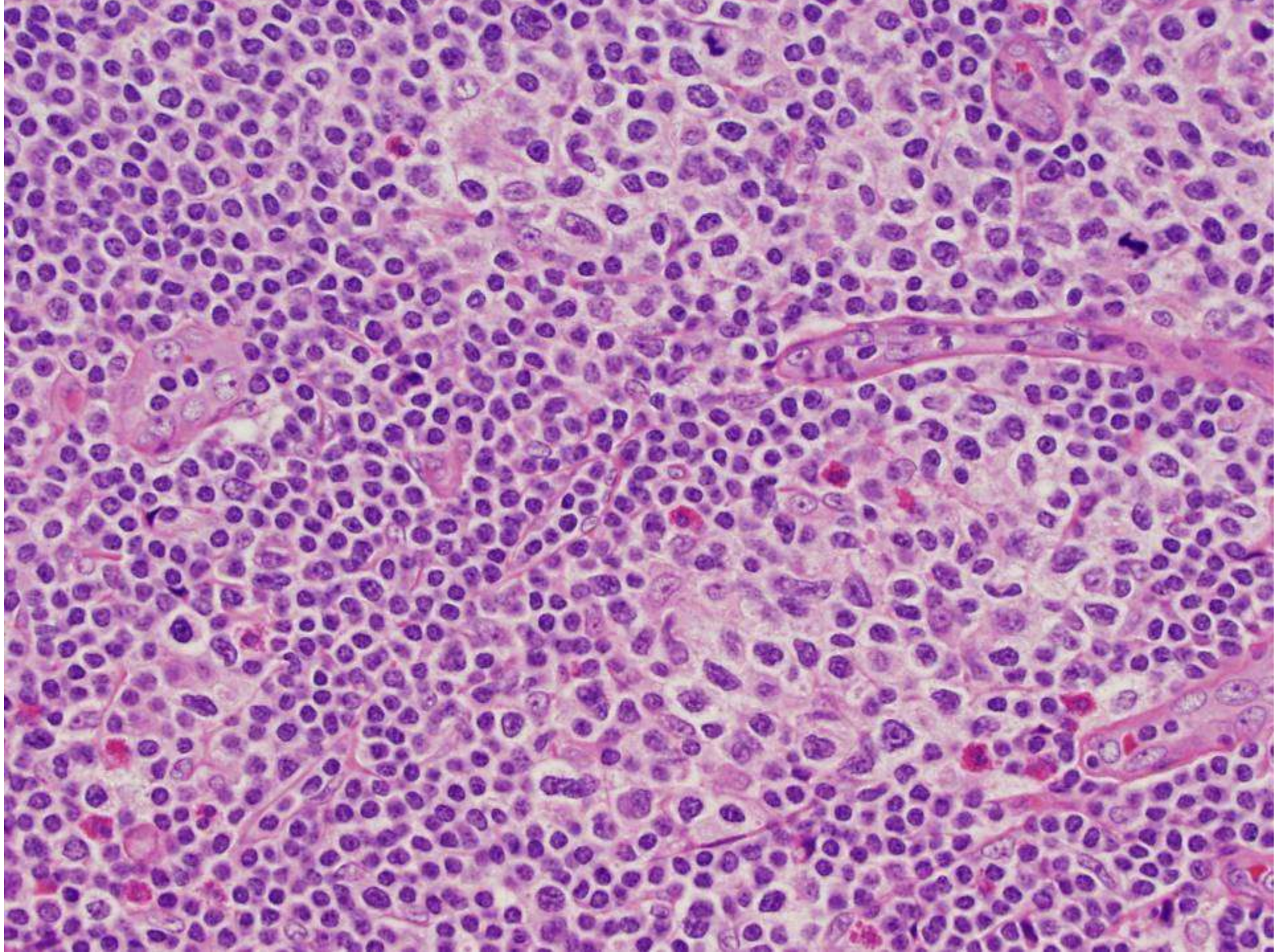
or

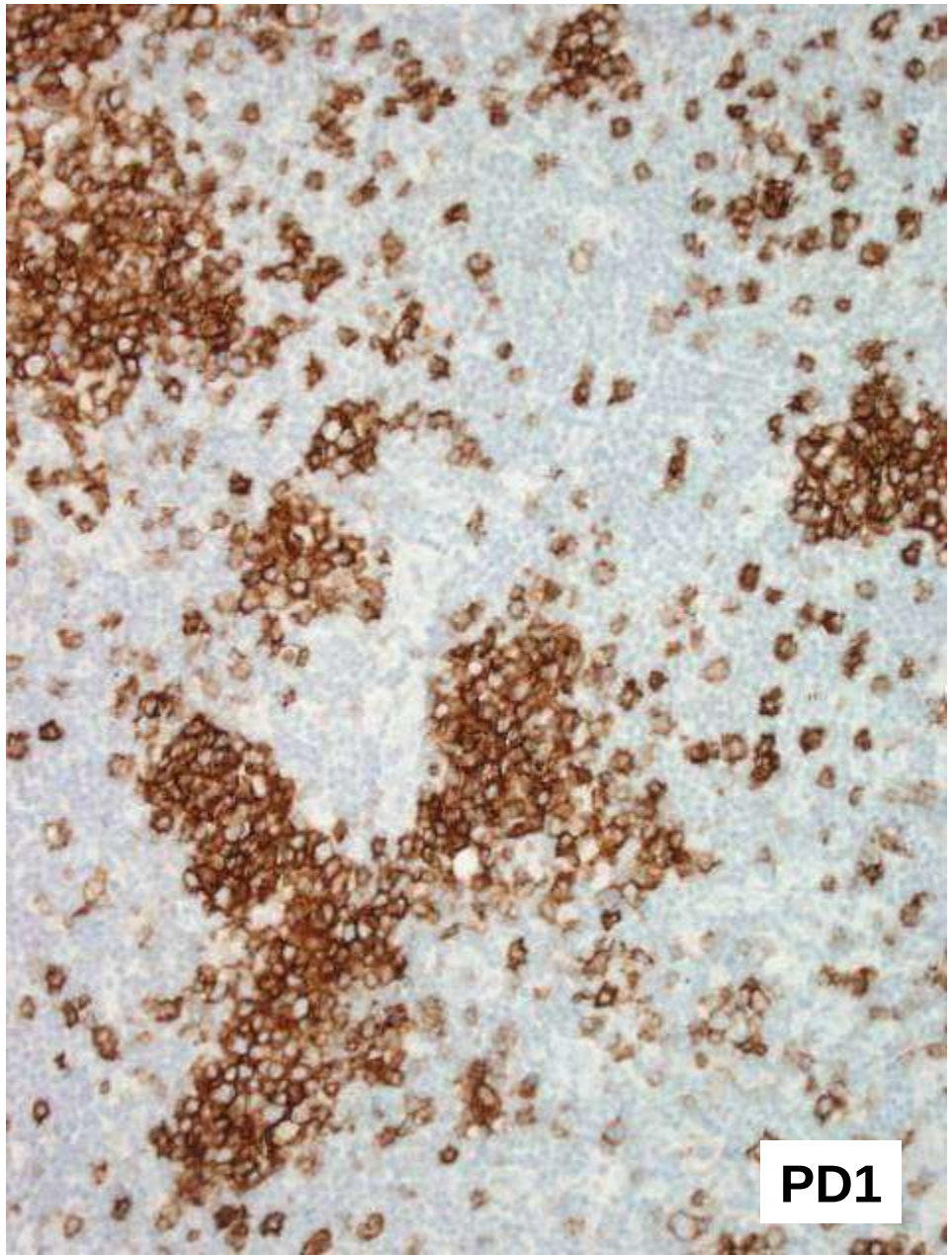
?PTCL(NOS), lymphoepithelioid variant (Lennert lymphoma)

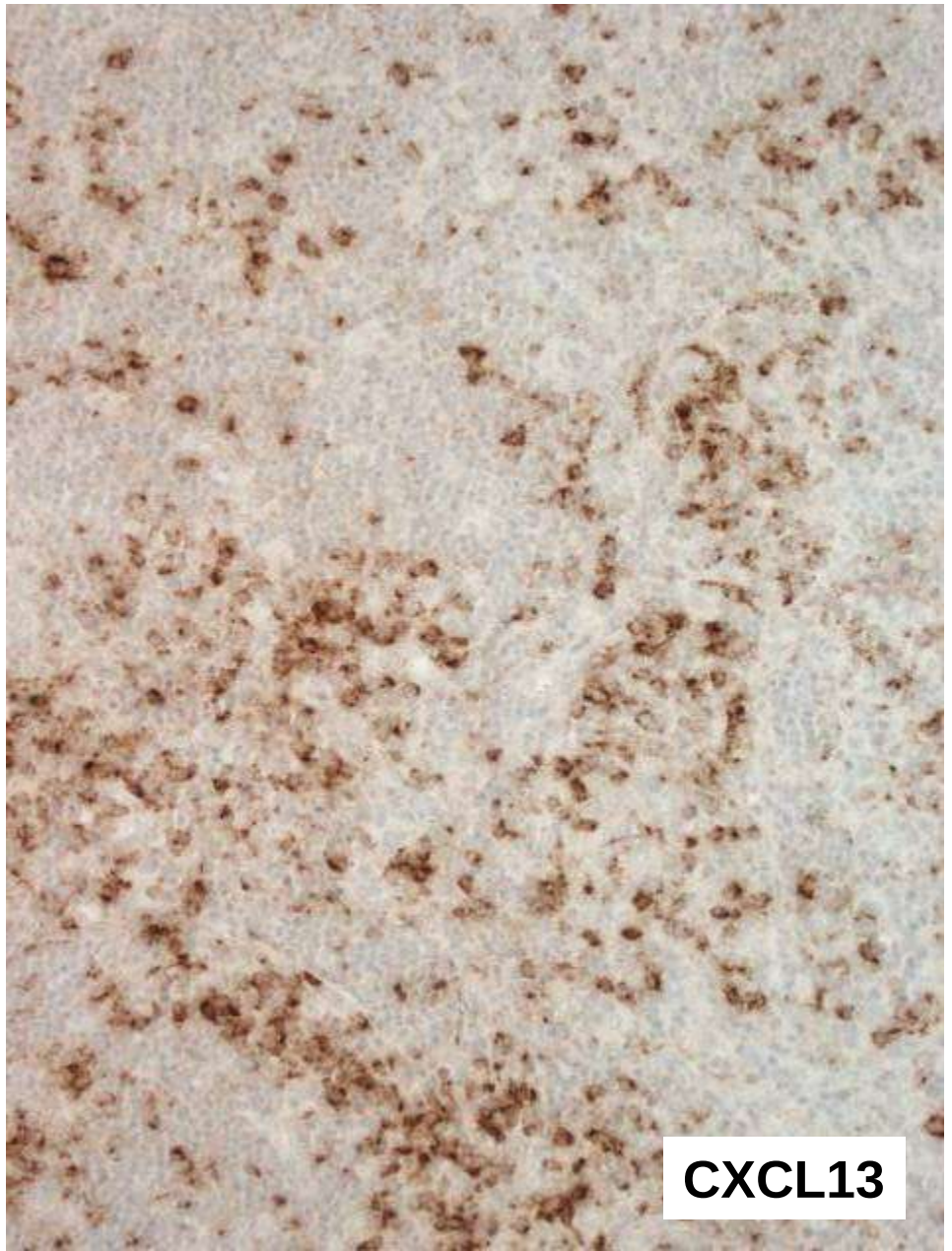



CD21


PD-1




PD1


CXCL13

Conclusion at EAHP/SH 2012: Spectrum of AITL broader than currently recognised

AITL – variants

- Hyperplastic follicles (pattern 1)
- ***Tumour cell rich/clear cell rich***
- ***Epithelioid cell rich***
- ***Associated with IgD positive small B-cells/primary follicles***

EAHP 2012 (Attygalle et al 2014)

Table 1. Summary of clinical features, mutational status and copy number variations in AITL, other PTCL of TFH origin and PTCL-NOS.

	Nodal lymphomas of TFH cell origin (TFH-PTCL)				
	AITL	Other TFH-PTCL		PTCL-NOS	*P* (Fisher test) across four entities
		TFH-like PTCL	F-PTCL*		
Clinical variables					
Median age at diagnosis	67.8	65	67	62.5	
Sex (M)	53/94 (56%)	9/16 (60%)	2/5 (40%)	23/34 (68%)	0.54
Stage III-IV	84/85 (99%)	14/15 (93%)	4/4 (100%)	29/34 (85%)	0.02
ECOG ≥ 2	67/83 (53%)	3/12 (25%)	1/4 (25%)	11/33 (33%)	$< 1.0 \times 10^{-7}$
IPI ≥ 3	63/79 (80%)	11/15 (73%)	2/4 (50%)	20/31 (65%)	0.21
Coombs (+)	25/56 (45%)	1/3 (33%)	1/2 (50%)	0/6 (0%)	0.14[a]
Anemia	47/71 (66%)	5/10 (50%)	2/4 (50%)	10/27 (37%)	0.17[a]
Hypergammaglobulinemia (≥16 g/dl)	23/48 (48%)	1/8 (12.5)	1/3 (33%)	4/19 (21%)	0.08
Mutations (%)					
TET2	31/64 (48%)	7/11 (64%)	3/4 (75%)	4/24 (17%)	$< 1.0 \times 10^{-3}$
DNMT3A	19/64 (30%)	1/10 (10%)	1/4 (25%)	1/24 (4%)	0.02
IDH2	22/66 (33%)	1/11 (10%)	0/5 (0%)	0/23 (0%)	$< 1.0 \times 10^{-3}$
RHOA (G17V)	42/72 (58%)	8/14 (57%)	3/5 (60%)	0/23 (0%)	$< 1.0 \times 10^{-4}$
Copy number variations					
Events per patient (average)	3.17	3.94	2.36	10.8	
Patients with events	23/60 (38%)	4/12 (33%)	1/3 (33%)	17/27 (63%)	0.78
Heavily-rearranged (>10 events) patients	6/60 (8%)	3/12 (25%)	0/3 (0%)	11/27 (41%)	$< 1.0 \times 10^{-3}$
Patients with homozygous deletions or amplifications	3/60 (5%)	3/12 (25%)	0/3 (0%)	12/27 (44%)	$< 1.0 \times 10^{-4}$

Dobay et al 2017

Nodal PTCLs with a T_{FH} phenotype (classified on WHO 2008)

- Angioimmunoblastic T-cell lymphoma (AITL)
- PTCL, (NOS) follicular variant
- PTCL (NOS) with a T_{FH} phenotype

Unified under one umbrella term?

Unification under a broader category

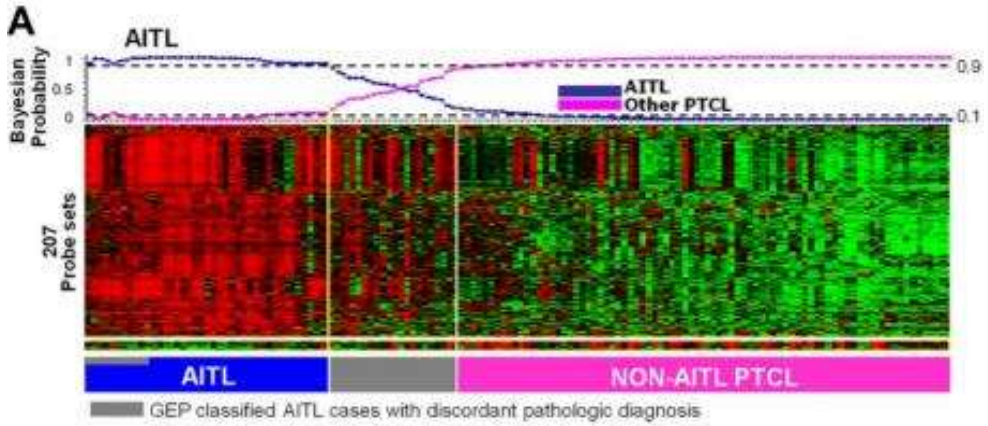
- ✓Clinical features
- Morphology - variation
- ✓Immunophenotype
- ✓Postulated normal counterpart
- Genetic profile **?**

Molecular genetics

Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma

Javeed Iqbal,[1] Dennis D. Weisenburger,[1] Timothy C. Greiner,[1] Julie M. Vose,[2] Timothy McKeithan,[2] Can Kucuk,[1] Huimin Geng,[1] Karen Deffenbacher,[1] Lynette Smith,[3] Karen Dybkaer,[4] Shigeo Nakamura,[5] Masao Seto,[5] Jan Delabie,[6] Francoise Berger,[7] Florence Loong,[8] Wing Y. Au,[8] Young-Hyeh Ko,[9] Ivy Sng,[10] James Olen Armitage,[2] and Wing C. Chan,[1] for the International Peripheral T-Cell Lymphoma Project

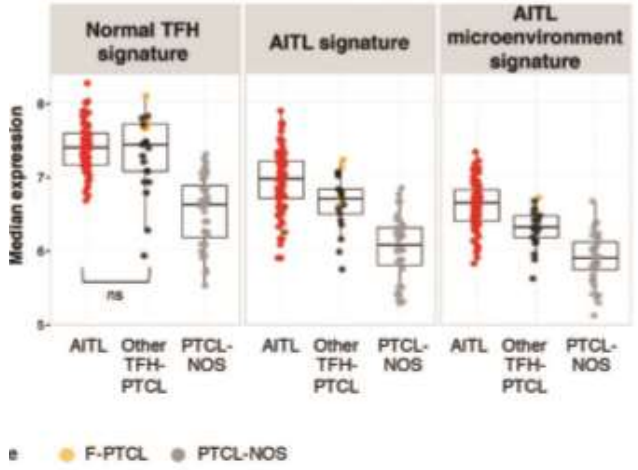
(Blood. 2010;115:1026-1036)



AITL: related to microenvironment and T_{FH} origin

- B-cell signature
- FDC signature
- Cytokine signature – prominent group of immunosuppressive cytokines/receptors
  - genes expressed by T_{FH} cells (CXCL13, CXCR5)

- **AITL microenvironment signature** expressed at lower levels in PTCL of T_{FH} origin than in AITL on average, but higher than in PTCL-NOS,
- Findings consistent with the lack of the characteristic AITL microenvironment in other PTCLs of T_{FH} origin.



Dobay et al 2017

Table 1. Summary of clinical features, mutational status and copy number variations in AITL, other PTCL of TFH origin and PTCL-NOS.

	Nodal lymphomas of TFH cell origin (TFH-PTCL)				
	AITL	Other TFH-PTCL		PTCL-NOS	*P* (Fisher test) across four entities
		TFH-like PTCL	F-PTCL*		
Clinical variables					
Median age at diagnosis	67.8	65	67	62.5	
Sex (M)	53/94 (56%)	9/16 (60%)	2/5 (40%)	23/34 (68%)	0.54
Stage III-IV	84/85 (99%)	14/15 (93%)	4/4 (100%)	29/34 (85%)	0.02
ECOG ≥ 2	67/83 (53%)	3/12 (25%)	1/4 (25%)	11/33 (33%)	$< 1.0 \times 10^{-7}$
IPI ≥ 3	63/79 (80%)	11/15 (73%)	2/4 (50%)	20/31 (65%)	0.21
Coombs (+)	25/56 (45%)	1/3 (33%)	1/2 (50%)	0/6 (0%)	0.14[a]
Anemia	47/71 (66%)	5/10 (50%)	2/4 (50%)	10/27 (37%)	0.17[a]
Hypergammaglobulinemia (≥16 g/dl)	23/48 (48%)	1/8 (12.5)	1/3 (33%)	4/19 (21%)	0.08
Mutations (%)					
TET2	31/64 (48%)	7/11 (64%)	3/4 (75%)	4/24 (17%)	$< 1.0 \times 10^{-3}$
DNMT3A	19/64 (30%)	1/10 (10%)	1/4 (25%)	1/24 (4%)	0.02
IDH2	22/66 (33%)	1/11 (10%)	0/5 (0%)	0/23 (0%)	$< 1.0 \times 10^{-3}$
RHOA (G17V)	42/72 (58%)	8/14 (57%)	3/5 (60%)	0/23 (0%)	$< 1.0 \times 10^{-4}$
Copy number variations					
Events per patient (average)	3.17	3.94	2.36	10.8	
Patients with events	23/60 (38%)	4/12 (33%)	1/3 (33%)	17/27 (63%)	0.78
Heavily-rearranged (>10 events) patients	6/60 (8%)	3/12 (25%)	0/3 (0%)	11/27 (41%)	$< 1.0 \times 10^{-3}$
Patients with homozygous deletions or amplifications	3/60 (5%)	3/12 (25%)	0/3 (0%)	12/27 (44%)	$< 1.0 \times 10^{-4}$

Dobay et al 2017

Unification under a broader category

- ✓Clinical features
- Morphology - variation
- ✓Immunophenotype
- ✓Postulated normal counterpart
- ✓Genetic profile

Revision to 4th edition of WHO classification of lymphoid neoplasms

Nodal T-cell lymphomas with T-follicular helper (TFH) phenotype

- An umbrella category created to highlight the spectrum of nodal lymphomas with a T_{FH} phenotype including ***AITL, FT-cell lymphoma, and other nodal PTCL with a T_{FH} phenotype*** (specific diagnoses to be used to due to clinicopathologic differences)

- Overlapping recurrent molecular/cytogenetic abnormalities recognized that could impact on therapy

Revision to 4th Edition of WHO classification of lymphoid neoplasms *(Blood 2016)*

- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma (provisional entity)*
- *Nodal PTCL with TFH phenotype (provisional entity)*

Follicular T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

Definition:

FTCL is a lymph node-based neoplasm of T_{FH} cells with a predominantly follicular growth pattern and lacking characteristic features of AITL such as proliferation of high endothelial venules or extrafollicular follicular dendritic cells.

Follicular T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

Clinical features

- Resembles AITL and other nodal peripheral T-cell lymphomas
- Advanced stage of disease with generalised lymphadenopathy, splenomegaly, B-symptoms and skin rash
- Subset: lab abnormalities typical of AITL (e.g. hypergammagolobulinaemia, Coombs + haemolytic anaemia etc)
- Clinical course not well characterised, but appears to be aggressive, median survival <24 months

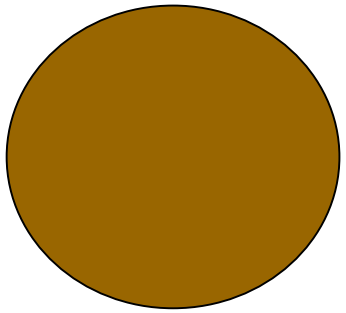
Follicular T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

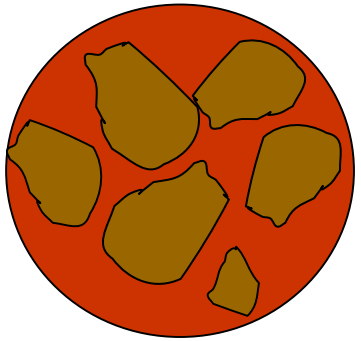
Clinical features

- Resembles AITL and other nodal peripheral T-cell lymphomas
- Advanced stage of disease with generalised lymphadenopathy, splenomegaly, B-symptoms and skin rash
- Subset: lab abnormalities typical of AITL (e.g. hypergammagolobulinaemia, Coombs + haemolytic anaemia etc)
- Clinical course not well characterised, but appears to be aggressive, median survival <24 months
- **Few patients have localised disease and/or no B symptoms – rationale for separation from AITL?**

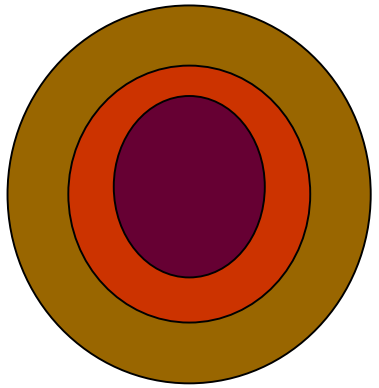
PTCL, NOS, follicular variant (PTCL-F) – **WHO 2008**



mimicking follicular lymphoma

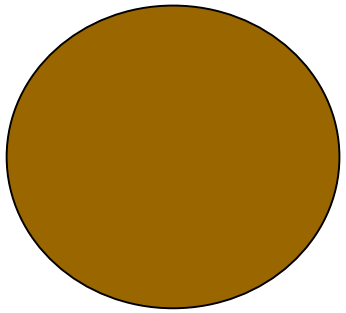


mimicking nodular LPHL

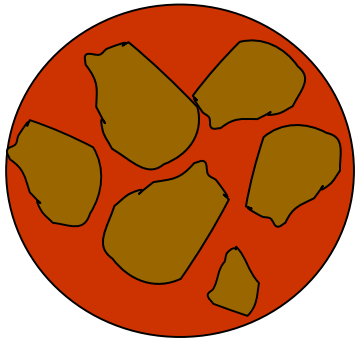


mimicking nodal MZL

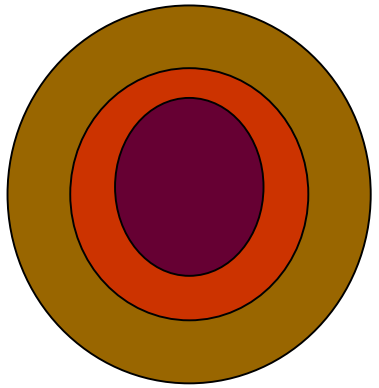
PTCL, NOS, follicular variant (PTCL-F) – **WHO 2008**



mimicking follicular lymphoma



mimicking nodular LPHL



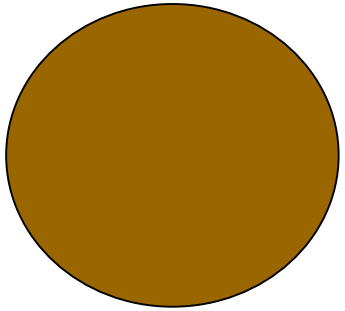
mimicking nodal MZL

AITL- pattern I

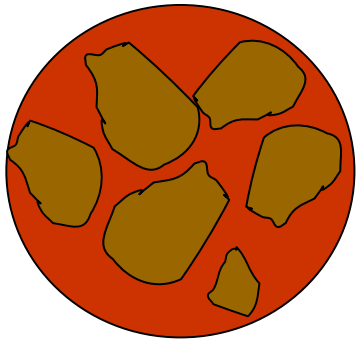
Follicular T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

Histology



mimicking follicular lymphoma



mimicking nodular LPHL

- Interfollicular areas lack polymorphous infiltrates and HEV, characteristic of AITL
- A subset may have HRS-like cells
- **Consecutive biopsies may show change of morphology from FTCL to AITL or vice versa suggesting the two entities may constitute different morphological representations of the same biological process**

Nodal peripheral T-cell lymphoma with a T_{FH} phenotype

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

- A subset of PTCL classified as NOS have a T_{FH} phenotype (positive for CD4, PD1, CD10, BCL6, CXCL13 and ICOS) and some pathological features of AITL
- Minimum criteria for assignment of T_{FH} phenotype: at least 2, preferably 3, T_{FH} markers in addition to CD4

Nodal peripheral T-cell lymphoma with a T_{FH} phenotype

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

- Diffuse pattern without the prominent polymorphic inflammatory background - **tumour cell rich**
- Without prominent vascular proliferation or expansion of FDCs
- Some cases: T-zone pattern
- Share some genetic alterations seen in AITL (mutations in TET2, DNMT3A and RHOA)

Angioimmunoblastic T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

- In advanced cases, the inflammatory component may be diminished and the proportion of clear cells and large cells increase

  - the so called **tumour cell rich variant of AITL**

- In such cases the T_{FH} phenotype and the expanded FDC meshworks helps diagnosis

Angioimmunoblastic T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

- In advanced cases, the inflammatory component may be diminished and the proportion of clear cells and large cells increase

  - the so called **tumour cell rich variant of AITL**

- In such cases the T_{FH} phenotype and **the expanded FDC meshworks** helps diagnosis

Nodal peripheral T-cell lymphoma with a T_{FH} phenotype

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

- Are they related to AITL? Do they constitute tumour cell rich AITL?
- Until further evidence: classify as PTCL with T_{FH} phenotype

Summary of AITL and other nodal lymphomas of TFH origin

- Despite some morphological differences, there is extensive overlap in clinical features, recurrent mutations, GEP patterns
- Cases may present as AITL and relapse with features of FTCL and vice versa
- Cases may present as AITL and relapse as nodal PTCL with T_{FH} phenotype

- which suggests that AITL, FTCL and nodal PTCL with T_{FH} phenotype likely to be are part of a spectrum.

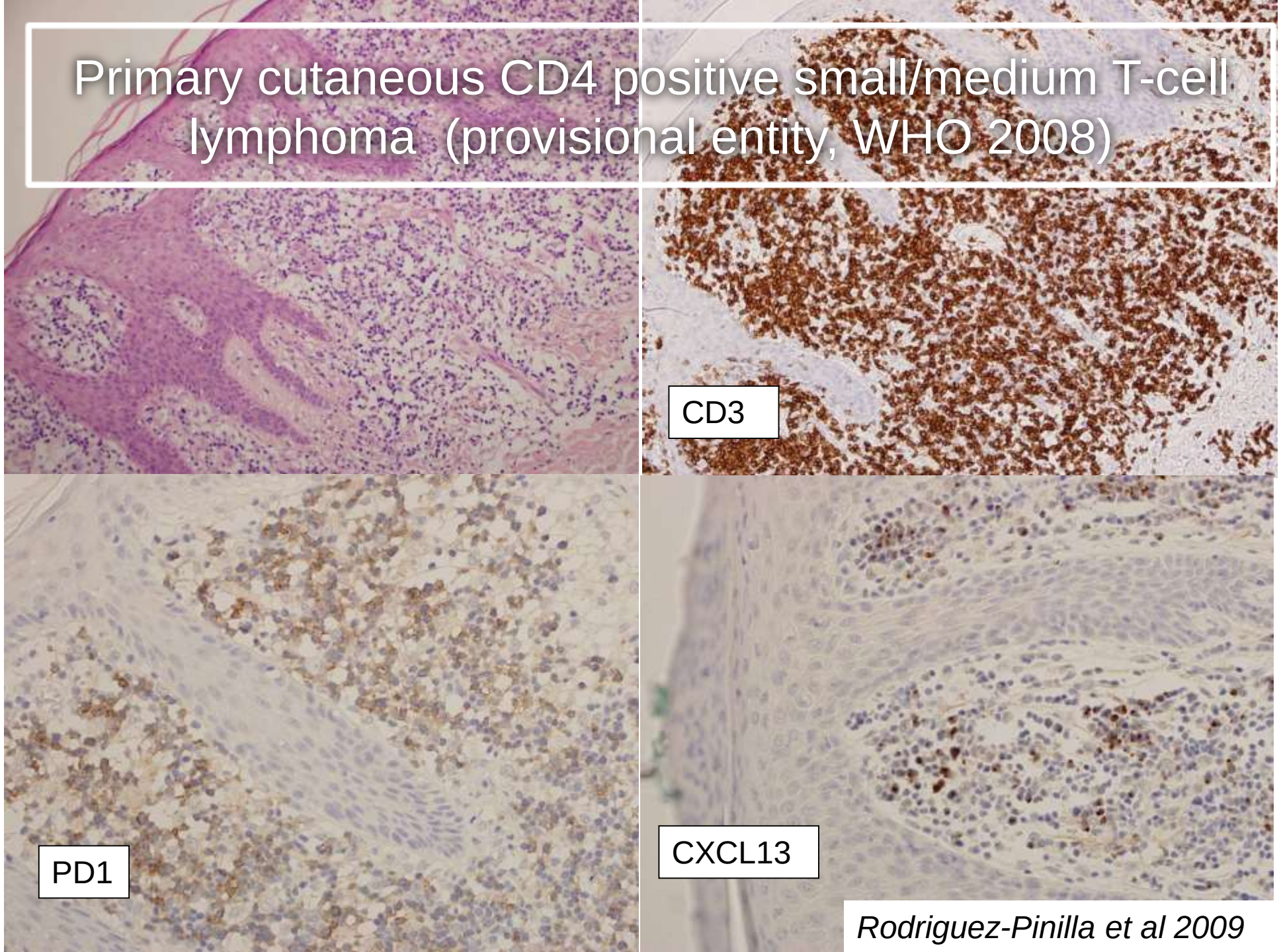
Will the distinction between these entities be maintained in future classifications?

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

Primary cutaneous CD4 positive small/medium T-cell lymphoma (provisional entity, WHO 2008)

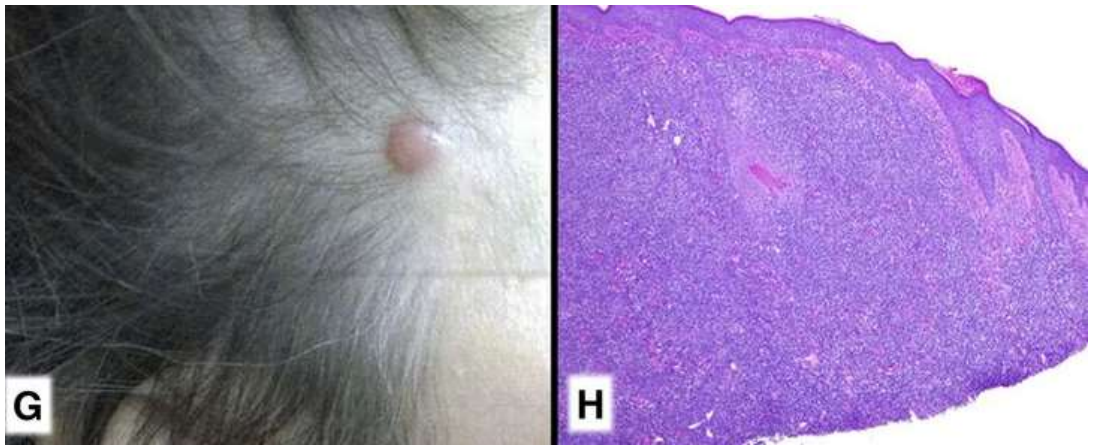


Rodriguez-Pinilla et al 2009

Revised 4th Edition of WHO Classification of Tumours of Haematopoietic and Lymphoid tissues

Primary cutaneous CD4+ small/medium T-cell **lymphoproliferative disorder**

- No longer diagnosed as an overt lymphoma, due to limited clinical risk, localised disease and similarity to clonal drug reactions
- Remains a provisional entity



Swerdlow et al. Blood 2016;127:2375-2390

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

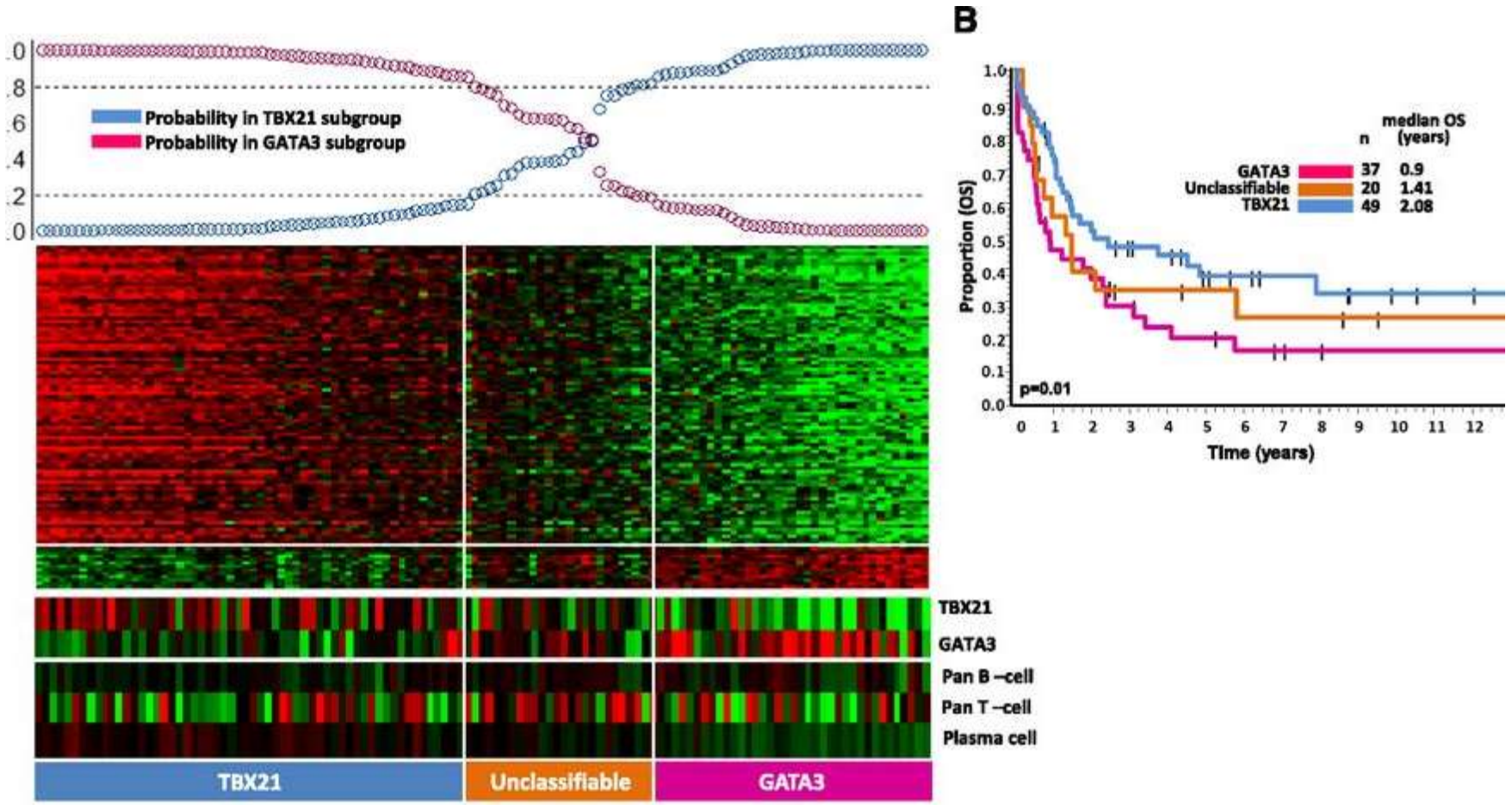
PTCL, NOS

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

Peripheral T-cell lymphoma (NOS)

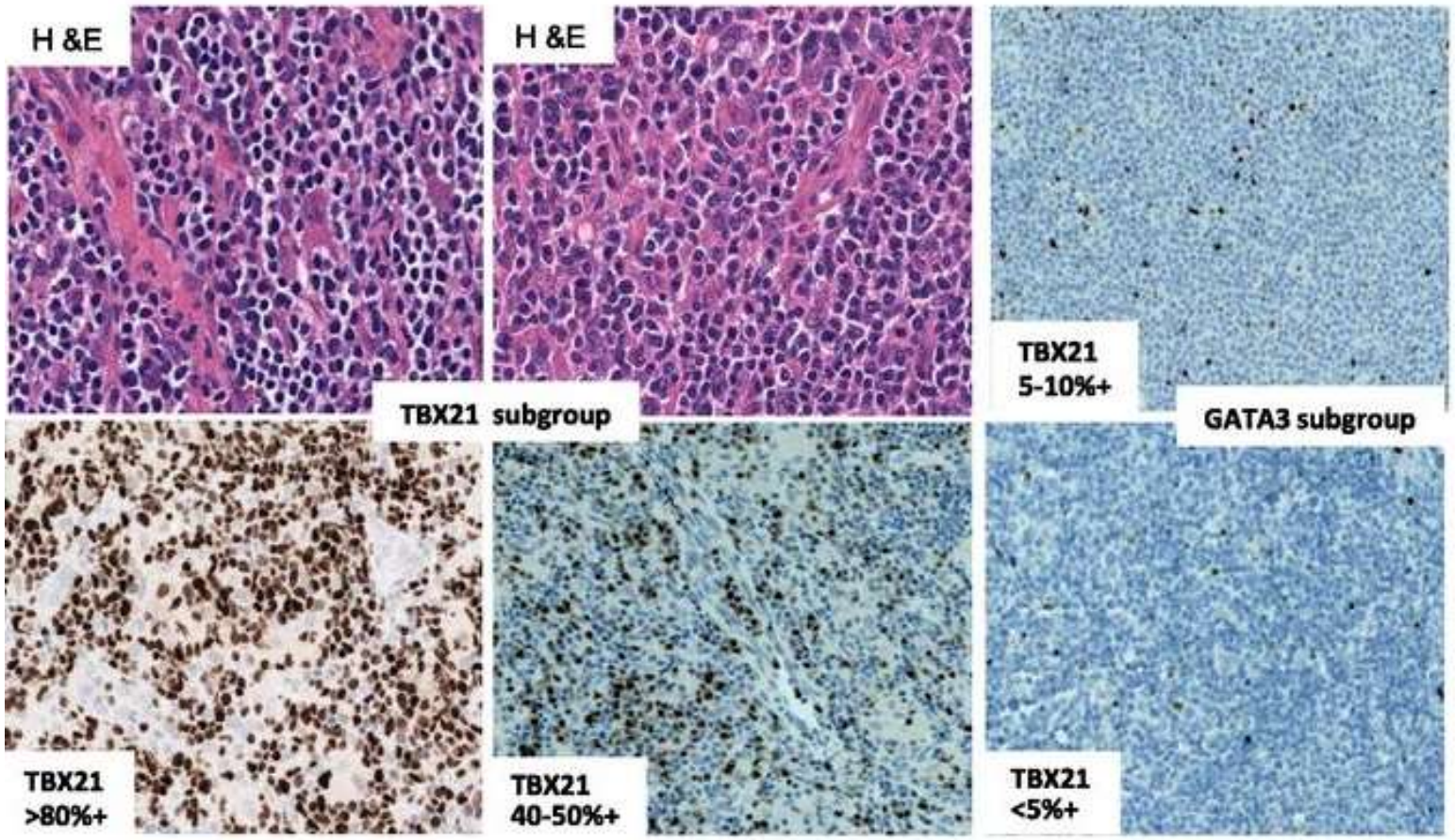
- Subsets based on phenotype and molecular abnormalities being recognised that may have clinical implications, but most not part of routine practice at this time

Two major molecular subgroups within PTCL-NOS with biological and overall survival differences.



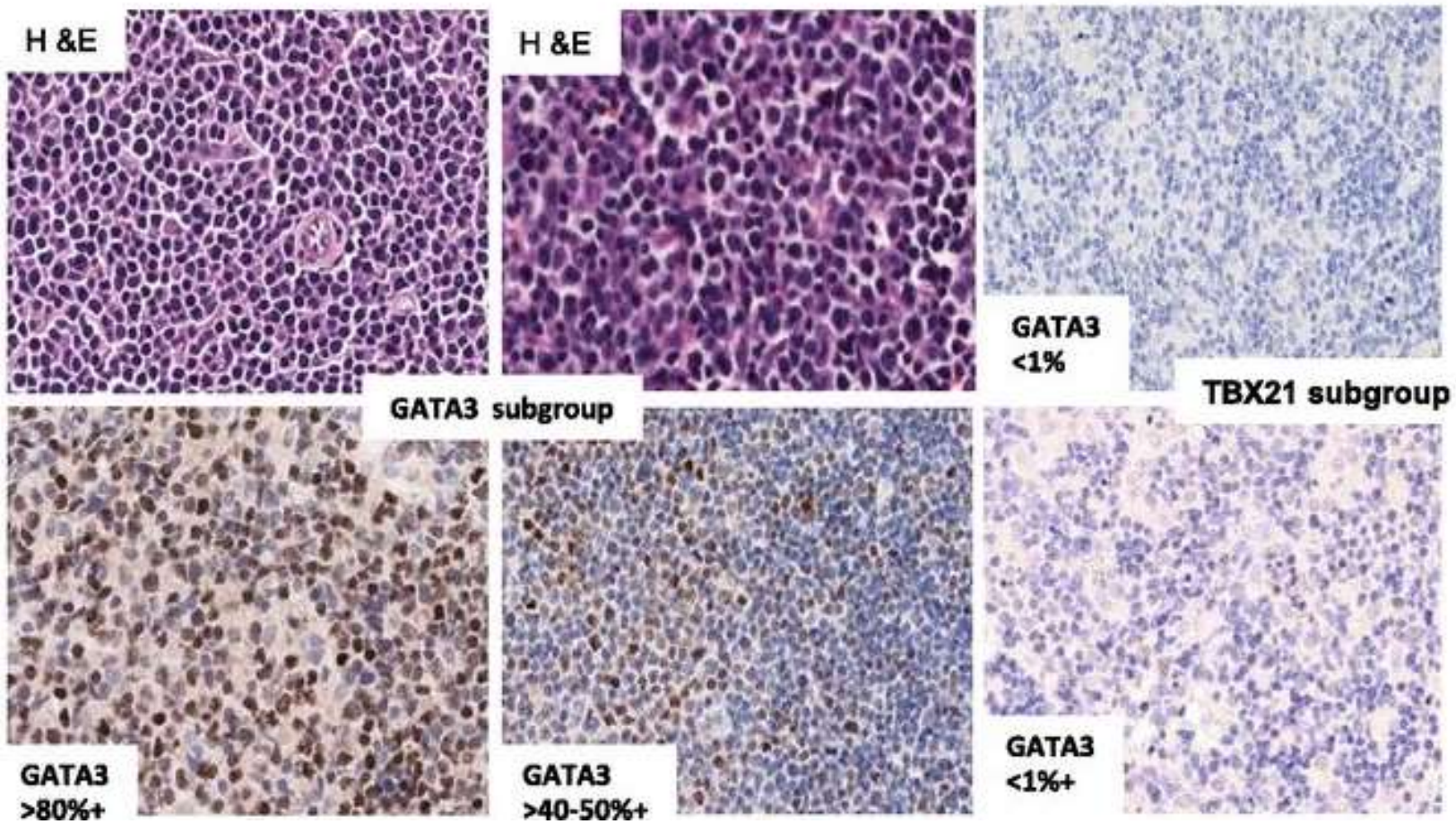
Javeed Iqbal et al. Blood 2014;123:2915-2923

Two major molecular subgroups within PTCL-NOS with biological and overall survival differences.



Javeed Iqbal et al. Blood 2014;123:2915-2923

Two major molecular subgroups within PTCL-NOS with biological and overall survival differences.



Javeed Iqbal et al. Blood 2014;123:2915-2923

GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features

Tianjiao Wang,[1] Andrew L. Feldman,[2] David A. Wada,[3] Ye Lu,[1] Avery Polk,[1] Robert Briski,[1] Kay Ristow,[4] Thomas M. Habermann,[4] Dafydd Thomas,[5] Steven C. Ziesmer,[4] Linda E. Wellik,[4] Thomas M. Lanigan,[6] Thomas E. Witzig,[4] Mark R. Pittelkow,[7] Nathanael G. Bailey,[5] Alexandra C. Hristov,[5] Megan S. Lim,[5] Stephen M. Ansell,[4] and Ryan A. Wilcox[1]

[1]Division of Hematology and Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [3]Department of Dermatology, University of Utah, Salt Lake City, UT; [4]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN; [5]Department of Pathology, and [6]Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; and [7]Department of Dermatology, Mayo Clinic, Rochester, MN

(*Blood*. 2014;123(19):3007-3015)

PTCL, NOS

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

Variants:

-Lymphoepithelioid lymphoma

Other variants

- follicular variant (2008), now classified as FTCL and under 'AITL and other nodal lymphomas of T_{FH} origin'

-T-zone (2008)now regarded as a non-specific morphological pattern and not as a variant; a proportion classified as nodal PTCL with T_{FH} phenotype

-Primary nodal EBV positive T cell and NK cell lymphoma, 'for the time being' regarded as variant of PTCL, NOS, but may be designated as a separate entity with more data

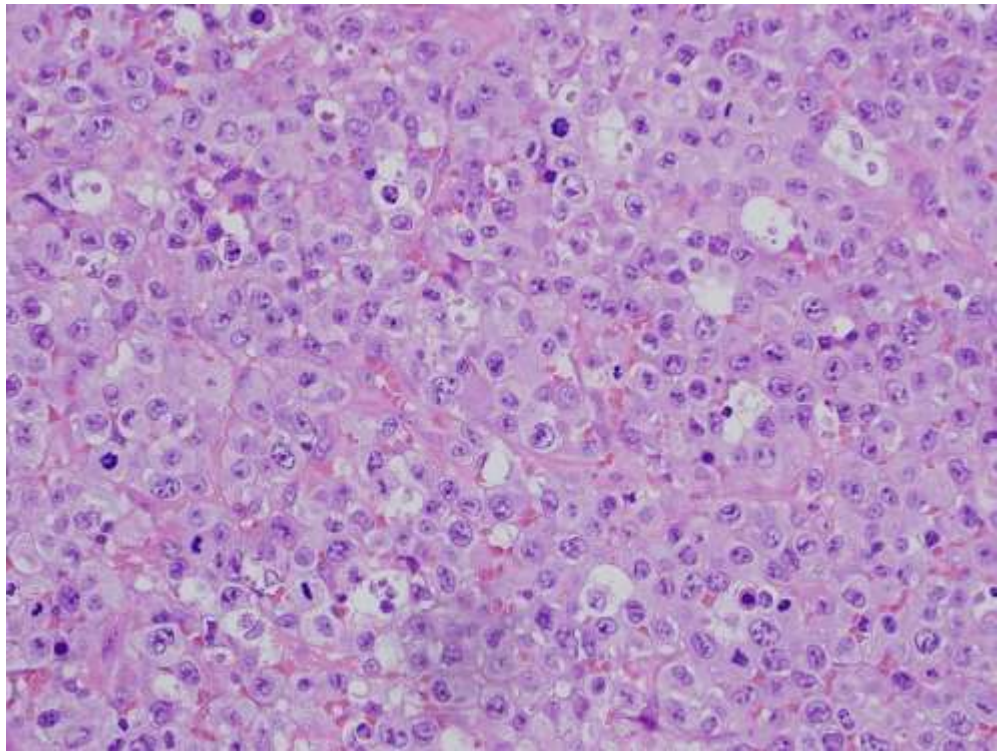
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

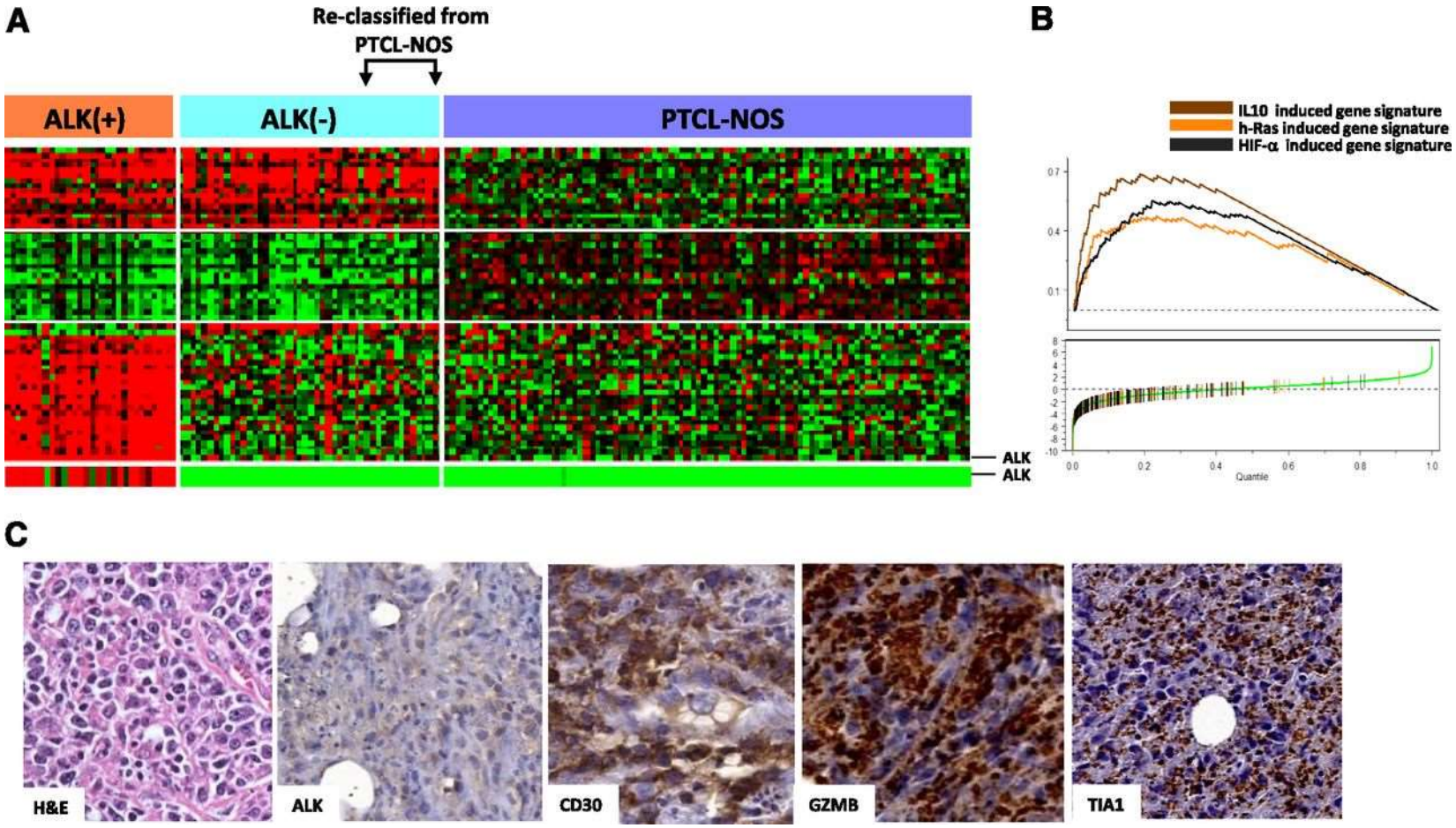
Swerdlow et al. Blood 2016;127:2375-2390

Anaplastic large cell lymphoma (WHO 2008)

- Anaplastic large cell lymphoma, ALK+
- Anaplastic large cell lymphoma, ALK- (provisional entity)



ALK(–)ALCL is molecularly distinct from PTCL-NOS and ALK(+)ALCL.



Javeed Iqbal et al. Blood 2014;123:2915-2923

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

Edgardo R. Parrilla Castellar,[1] Elaine S. Jaffe,[2] Jonathan W. Said,[3] Steven H. Swerdlow,[4] Rhett P. Ketterling,[1] Ryan A. Knudson,[1] Jagmohan S. Sidhu,[5] Eric D. Hsi,[6] Shridevi Karikehalli,[7] Liuyan Jiang,[8] George Vasmatzis,[9] Sarah E. Gibson,[4] Sarah Ondrejka,[6] Alina Nicolae,[2] Karen L. Grogg,[1] Cristine Allmer,[10] Kay M. Ristow,[11] Wyndham H. Wilson,[12] William R. Macon,[1] Mark E. Law,[1] James R. Cerhan,[10] Thomas M. Habermann,[11] Stephen M. Ansell,[11] Ahmet Dogan,[1] Matthew J. Maurer,[10] and Andrew L. Feldman[1]

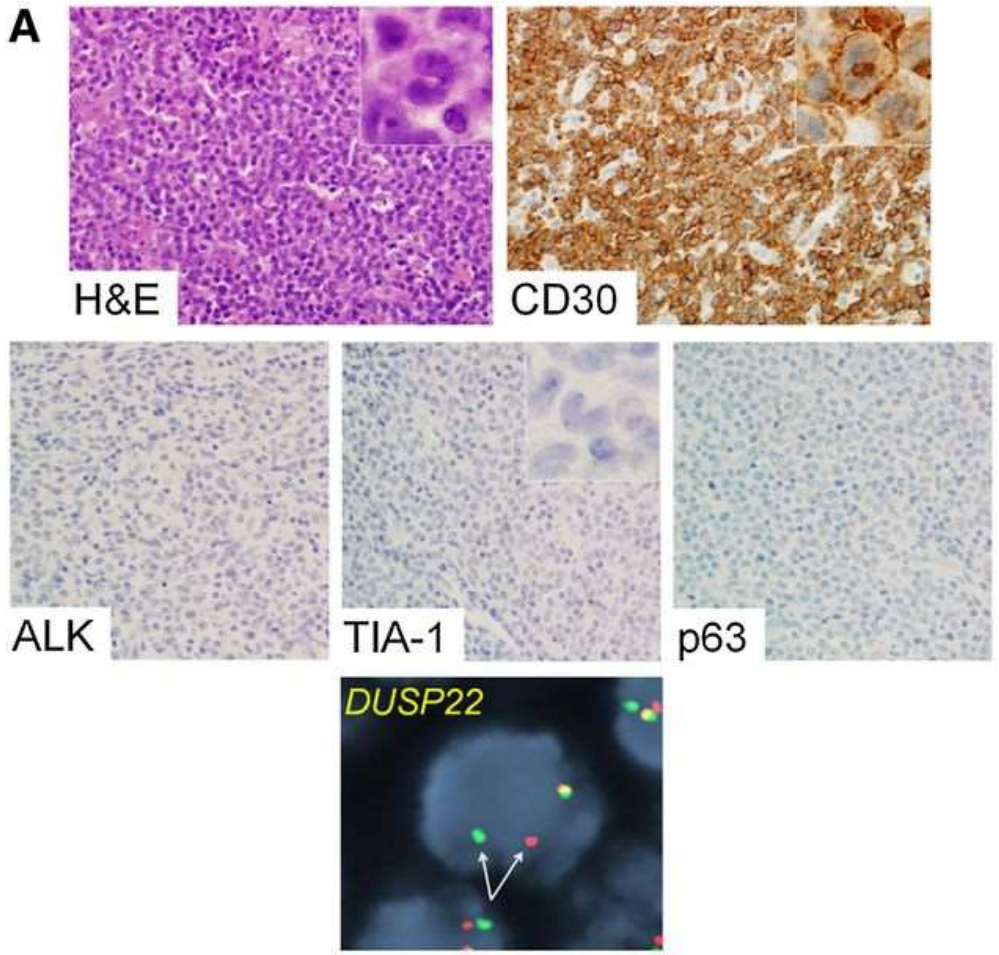
(*Blood*. 2014;124(9):1473-1480)

Key Points

- ALK-negative ALCLs have chromosomal rearrangements of *DUSP22* or *TP63* in 30% and 8% of cases, respectively.
- *DUSP22*-rearranged cases have favorable outcomes similar to ALK-positive ALCLs, whereas other genetic subtypes have inferior outcomes.

Representative cases of genetic subtypes of ALCL.

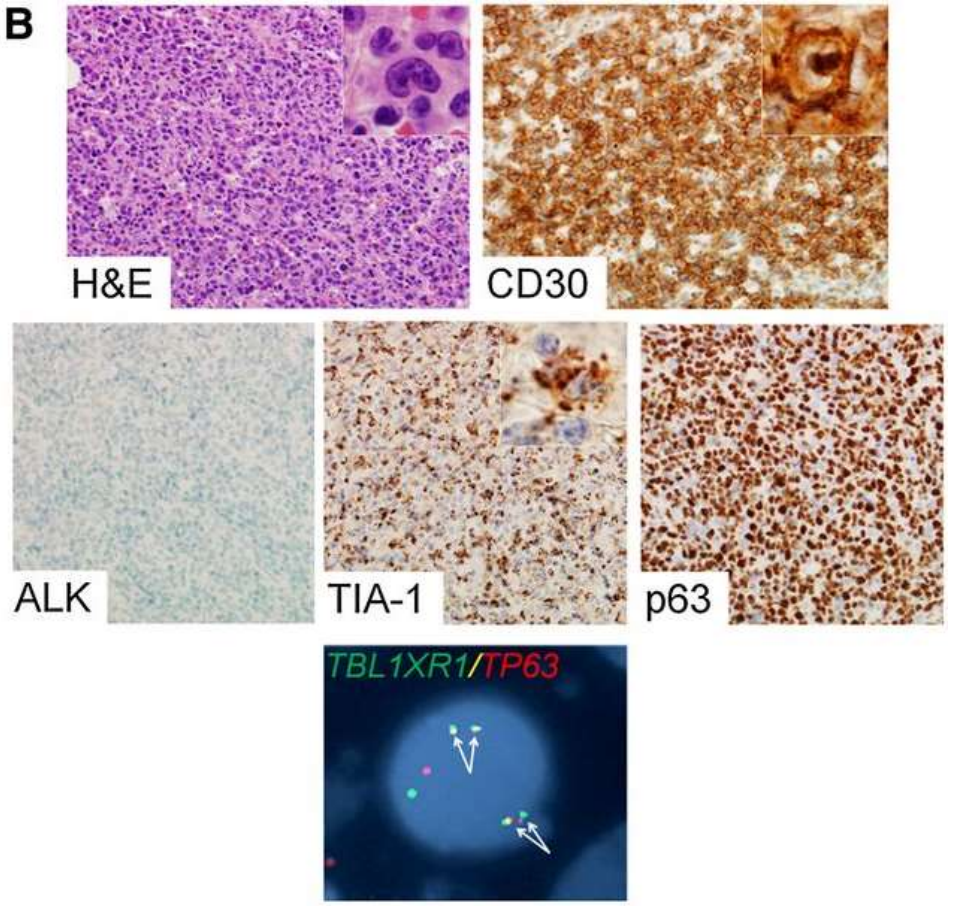
(A) ALK-negative ALCL with DUSP22 6p25 rearrangement



Edgardo R. Parrilla Castellar et al. Blood 2014;124:1473-1480

Representative cases of genetic subtypes of ALCL

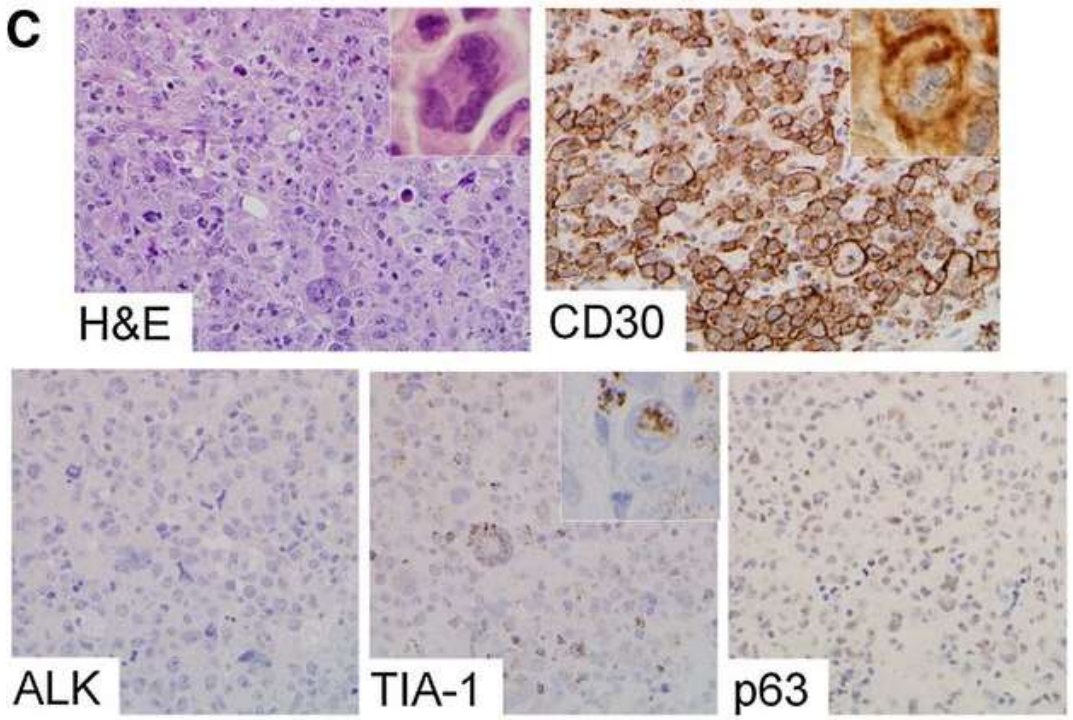
(B) ALK-negative ALCL with TP63 rearrangement



Edgardo R. Parrilla Castellar et al. Blood 2014;124:1473-1480

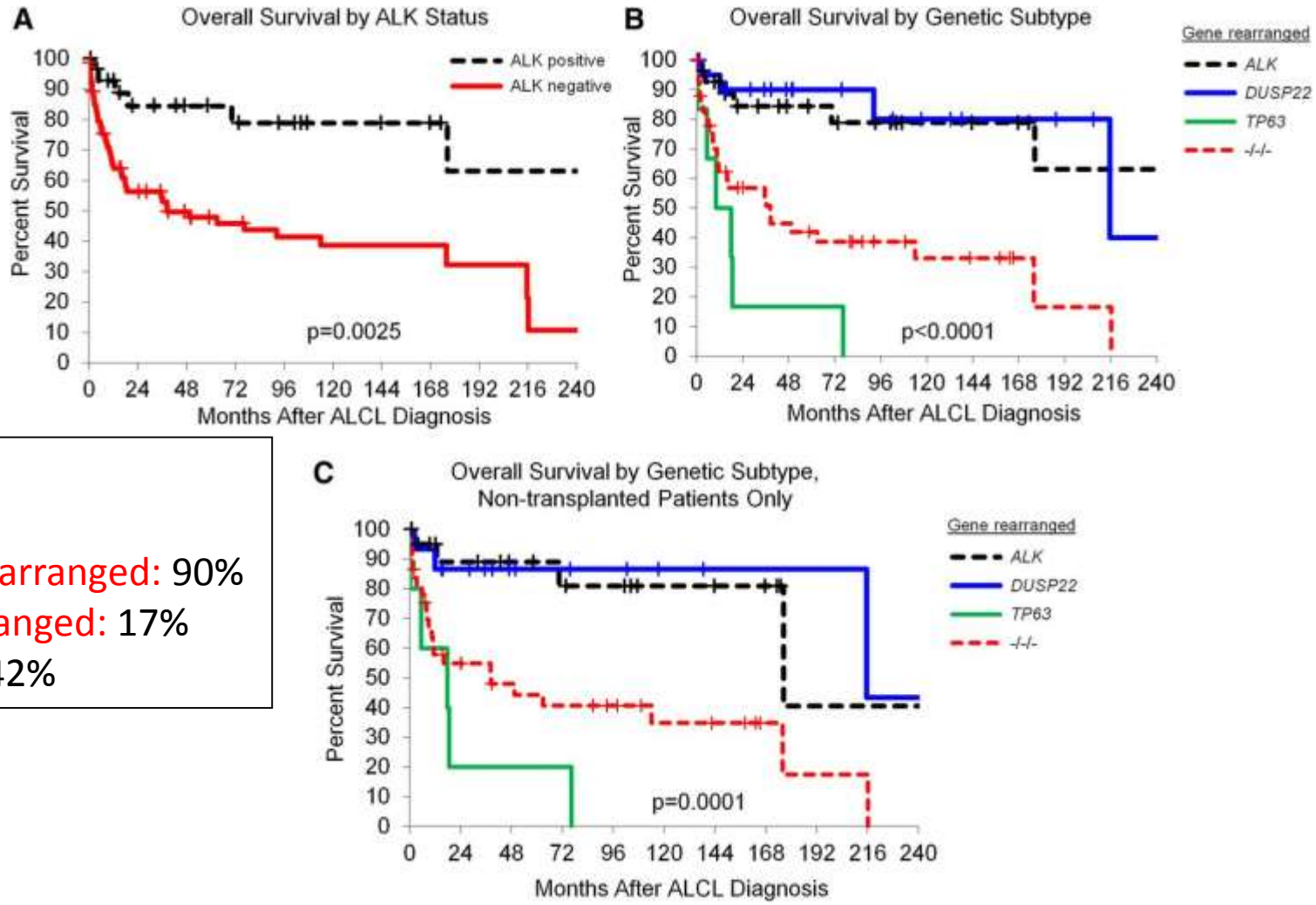
Representative cases of genetic subtypes of ALCL

(C) ALK-negative ALCL, triple negative



Edgardo R. Parrilla Castellar et al. Blood 2014;124:1473-1480

Outcomes in patients with ALCL based on genetic subtype.



5-year survival
ALCL, ALK+: 85%
ALCL, ALK-, DUSP22-rearranged: 90%
ALCL, ALK-, TP63 rearranged: 17%
ALCL, triple negative: 42%

Edgardo R. Parrilla Castellar et al. Blood 2014;124:1473-1480

Anaplastic large cell lymphoma (WHO 2017)

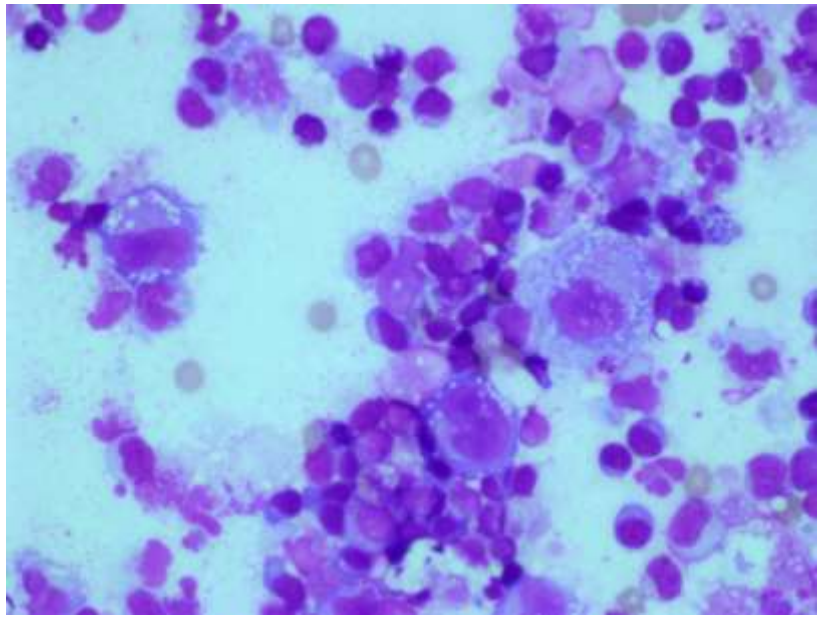
- Anaplastic large cell lymphoma, ALK+
- Anaplastic large cell lymphoma, ALK- ~~(provisional entity)~~

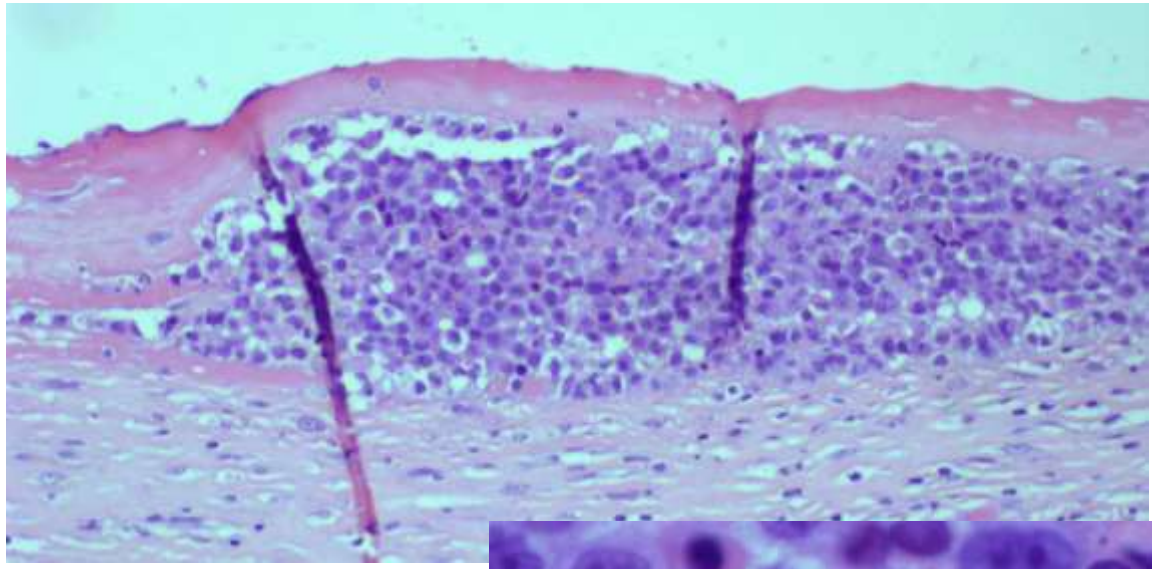
Anaplastic large cell lymphoma (WHO 2017)

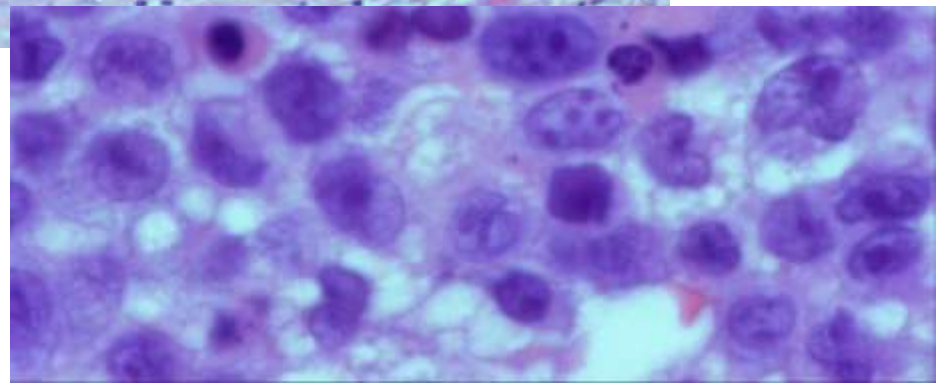
- Anaplastic large cell lymphoma, ALK+
- Anaplastic large cell lymphoma, ALK- ~~(provisional entity)~~
- *Breast implant associated anaplastic large cell lymphoma (provisional entity)*

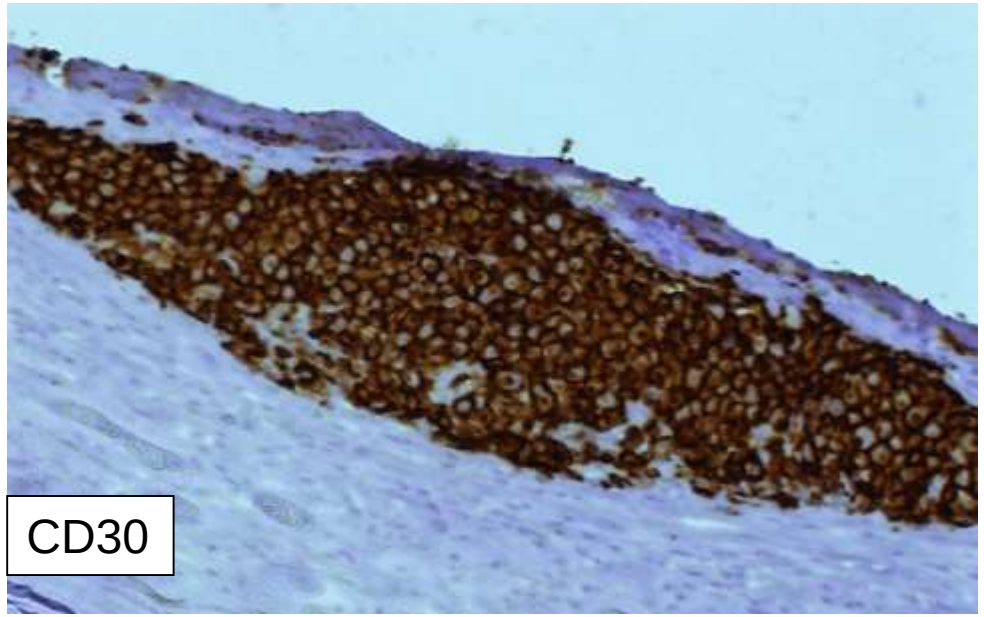
Breast implant associated ALCL

- Unique form of ALCL ALK-, associated with breast implants
- Median interval to development of lymphoma, 10 yrs
- Most cases confined to seroma fluid with no invasion of capsule (treat conservatively; remove capsule)
- Most important adverse feature: solid mass
- If invasion of capsule, risk of LN and systemic spread – treat with chemotherapy








CD30

Mature T and NK neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV$^+$ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8$^+$ T-cell lymphoma**
- *Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK$^+$
- Anaplastic large-cell lymphoma, ALK$^-$*
- *Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

Cutaneous CD30+ LPD – (WHO 2017 updates)

Lymphomatoid papulosis

- New histopathological subtypes:

➢ **Type D:** mimics cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

➢ **Type E:** angioinvasive

➢ **with 6p25 rearrangement:** histologically may resemble tumour stage of mycosis fungoides

Histologically may mimic very aggressive TCLs but clinically similar to other forms of LYP **(potential pitfall!)**

IRF4/DUSP22 locus at chromosome 6p25.3

- Rearranged in 30% of systemic ALCL, ALK-
- Rearranged in 30% of primary cutaneous ALCL
- Rearranged in small subset of Lymphomatoid Papulosis

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

Enteropathy-associated T-cell lymphoma (WHO 2008)

- Type I, closely linked with coeliac disease, primarily affecting those of northern European origin

- Type II, no association with coeliac disease, more frequent in Asian/Hispanic, monomorphic and prominent epitheliotropism

Intestinal T-cell lymphoma

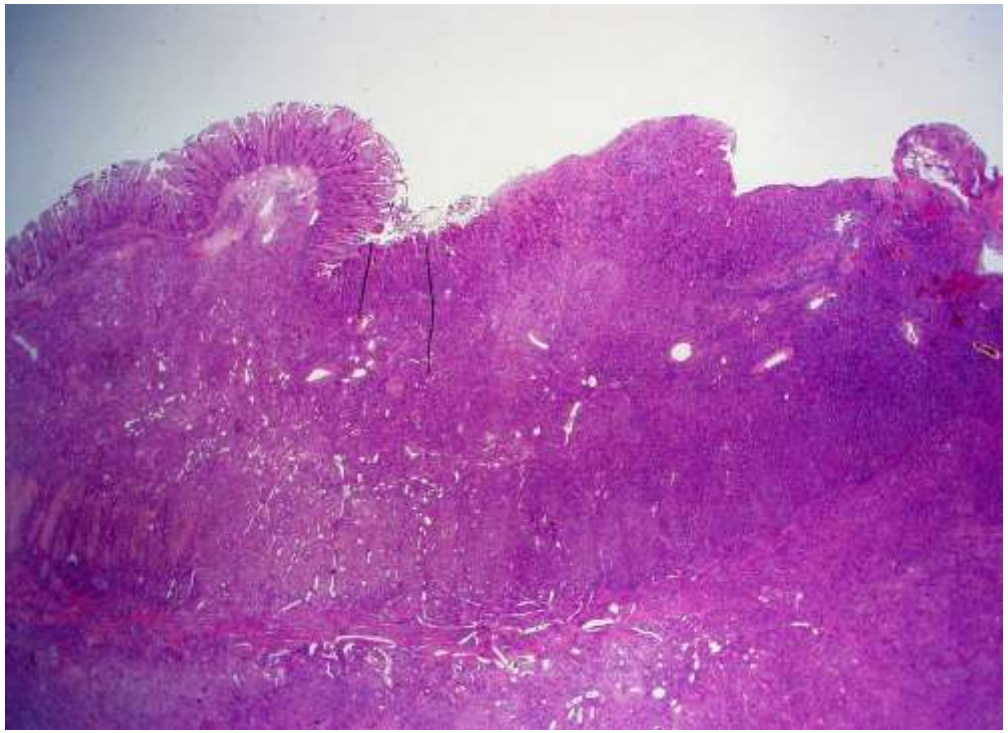
WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

- **Enteropathy-associated T-cell lymphoma (EATL)** (previously EATL, type I)
- **Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)** (previously EATL, type II)

- **Intestinal T-cell lymphoma NOS** – does not conform to EATL or MEITL. It may be because biopsy is inadequate, not a specific disease entity.

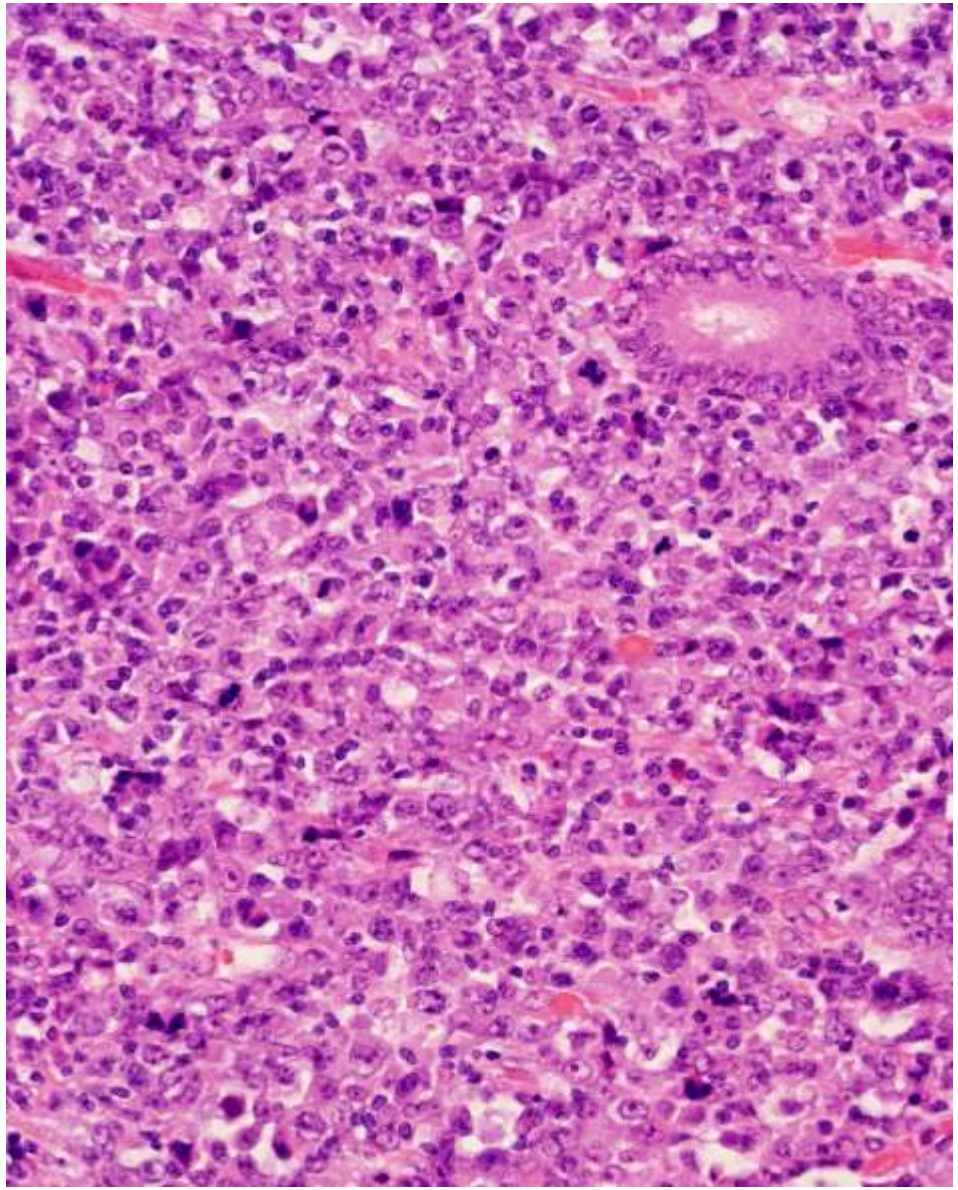
- **Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract**

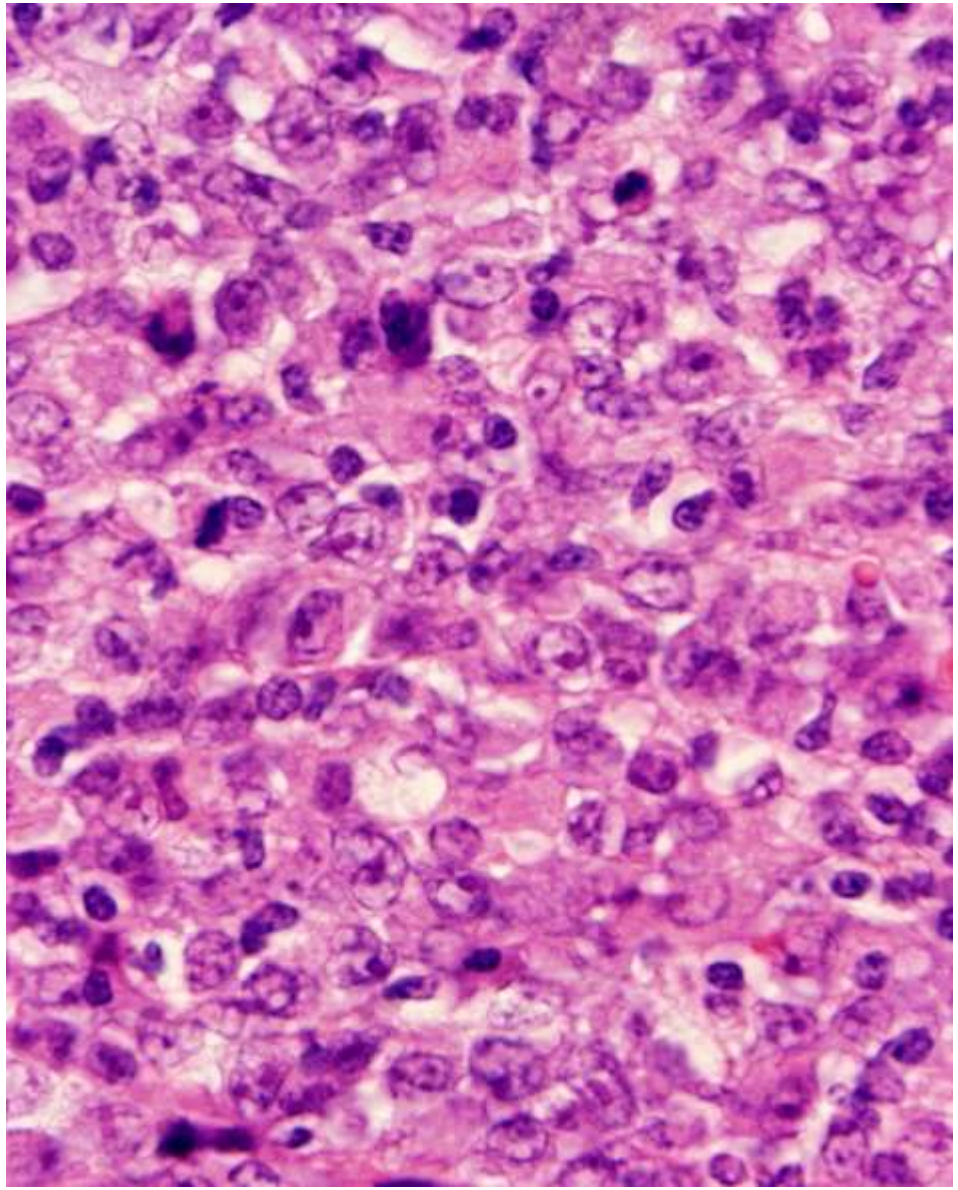
EATL



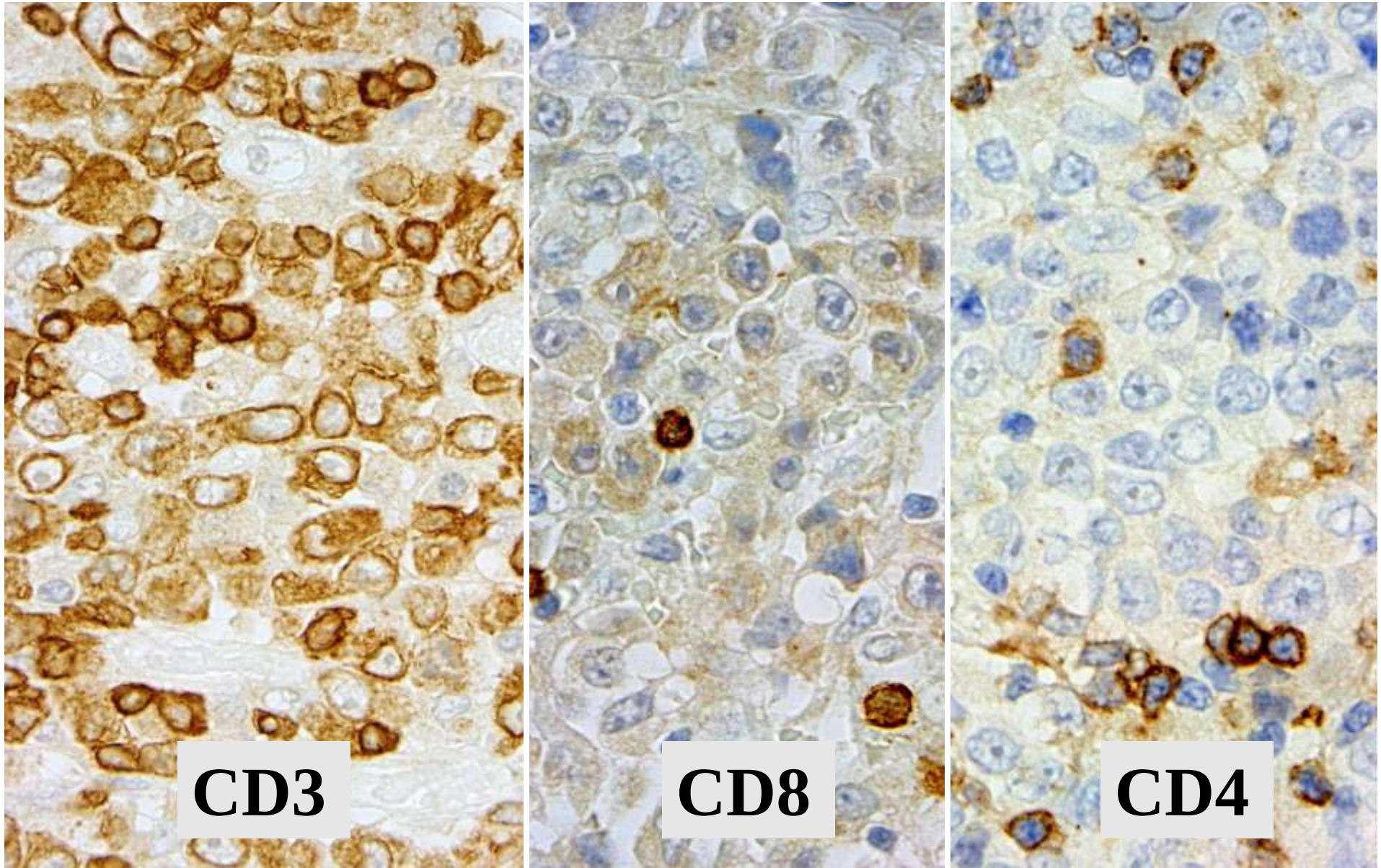
- Closely linked to coeliac disease
- Primarily in Northern Europeans
- Polymorphous infiltrate
- Most $\alpha\beta$, but $\gamma\delta$ variants exist

EATL

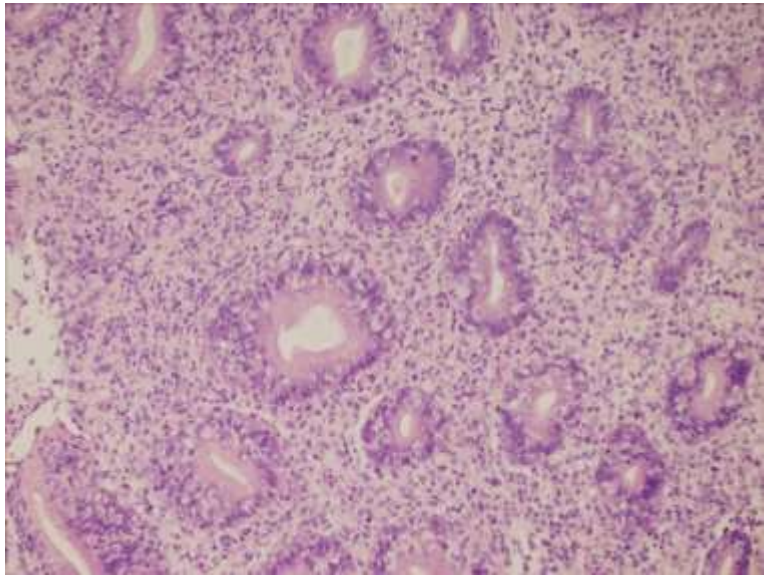


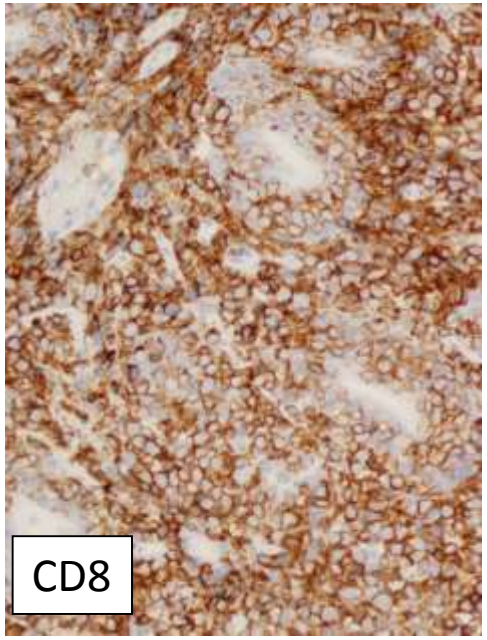


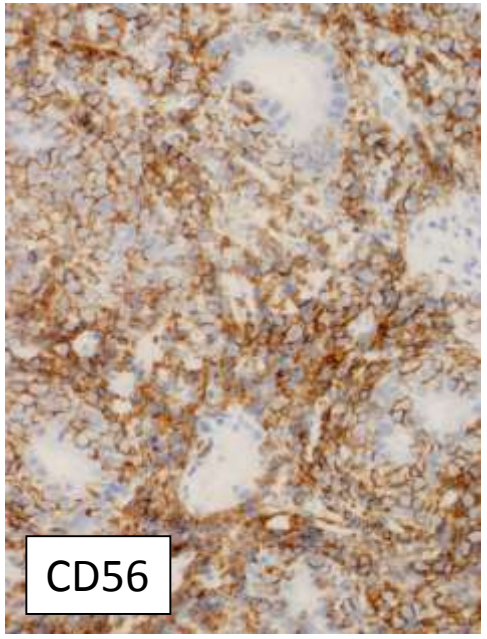
EATL



Monomorphic eptheliotropic intestinal T-cell lymphoma (MEITL)







- No association with coeliac disease
- World wide. Increased incidence in Asians/Hispanics

- Monomorphic
- Highly epitheliotropic

- CD8+, CD56+, MATK+
- Most are of $\gamma\delta$ origin

- Gains in 8q24 involving MYC in high proportion; STAT5B mutations in 36%; SETD2 mutations in >90%

Indolent T-cell lymphoproliferative disease of the gastrointestinal tract

Anamarija M. Perry,[1] Roger A. Warnke,[2] Qinglong Hu,[3] Philippe Gaulard,[4] Christiane Copie-Bergman,[4] Serhan Alkan,[5] Huan-You Wang,[6] Jason X. Cheng,[7] Chris M. Bacon,[8] Jan Delabie,[9] Erik Ranheim,[10] Can Kucuk,[11] XiaoZhou Hu,[11] Dennis D. Weisenburger,[12] Elaine S. Jaffe,[13] and Wing C. Chan[11]

[1]Department of Pathology, University of Manitoba, Winnipeg, MB, Canada; [2]Department of Pathology, Stanford University School of Medicine, Palo Alto, CA; [3]Tucson Pathology Associates, Carondelet St. Joseph Hospital, Tucson, AZ; [4]Department of Pathology, Hospital Henri Mondor, Créteil, France; [5]Department of Pathology and Laboratory Medicine, Cedars Sinai Medical Center, Los Angeles, CA; [6]Department of Pathology, University of California San Diego, San Diego, CA; [7]Department of Pathology, University of Michigan, Ann Arbor, MI; [8]Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom; [9]Department of Pathology, The Norwegian Radium Hospital, Oslo, Norway; [10]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI; [11]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE; [12]Department of Pathology, City of Hope National Medical Center, Duarte, CA; and [13]Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

Key Points

- Ten cases of an indolent T-cell lymphoproliferative disease of the gastrointestinal tract are reported.
- It is important to recognize this condition because it can be mistaken for aggressive T-cell lymphoma, which may lead to unnecessary therapy.

Primary gastrointestinal (GI) T-cell lymphoma is an infrequent and aggressive disease. However, rare indolent clonal T-cell proliferations in the GI tract have been described. We report 10 cases of GI involvement by an indolent T-cell lymphoproliferative disease, including 6 men and 4 women with a median age of 48 years (range, 15-77 years). Presenting symptoms included abdominal pain, diarrhea, vomiting, food intolerance, and dyspepsia. The lesions involved oral cavity, esophagus, stomach, small intestine, and colon. The infiltrates were dense, but nondestructive, and composed of small, mature-appearing lymphoid cells. Eight cases were $CD4^-/CD8^+$, 1 was $CD4^+/CD8^-$, and another was $CD4^-/CD8^-$. T-cell receptor-γ chain gene rearrangement identified a clonal population in all 10 cases. There was no evidence of *STAT3* SH2 domain mutation or activation. Six patients received chemotherapy because of an initial diagnosis of peripheral T-cell lymphoma, with little or no response, whereas the other 4 were followed without therapy. After a median follow-up of 38 months (range, 9-175 months), 9 patients were alive with persistent disease and 1 was free of disease. We propose the name "indolent T-LPD of the GI tract" for these lesions that can easily be mistaken for intestinal peripheral T-cell lymphoma, and lead to aggressive therapy. (*Blood.* 2013;122(22):3599-3606)

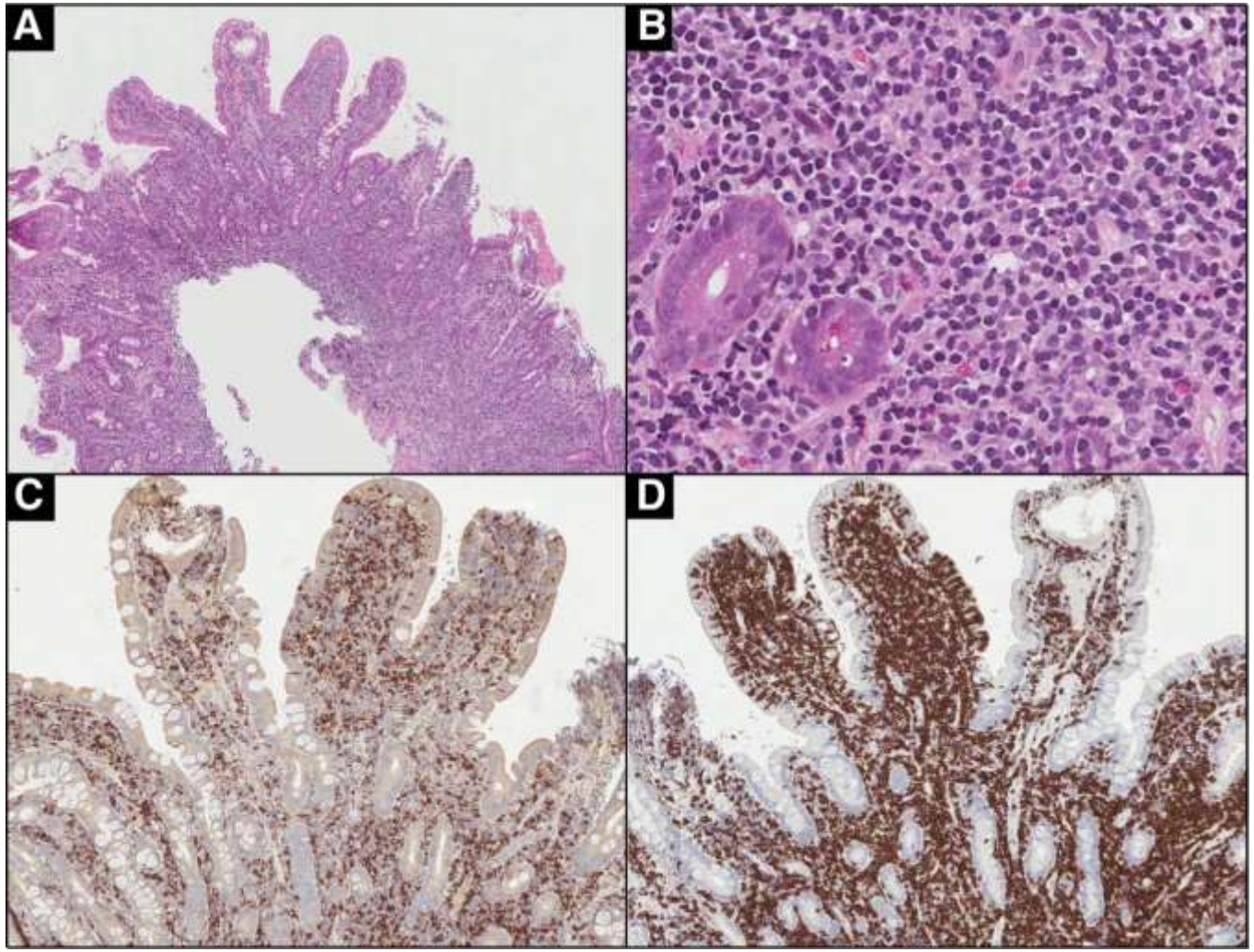
Intestinal T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid tissues, Volume 2

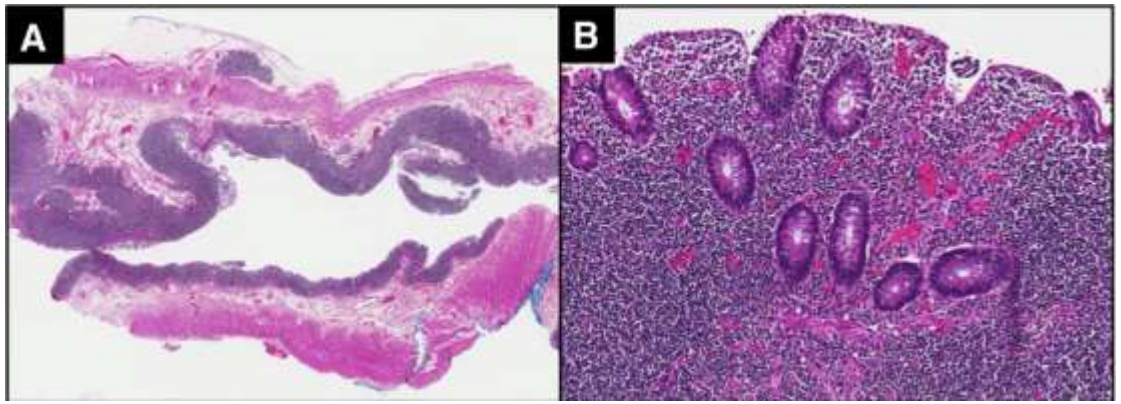
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

- A clonal T-cell LPD that can involve mucosa in all sites of GIT, but most common in small intestine and colon.
- Infiltration of lamina propria; usually no invasion of epithelium
- Course indolent, but most patients do not respond to conventional chemotherapy.
- A subset may progress to higher grade T-cell lymphoma and spread beyond the GI tract

Indolent T-LPD of the duodenum (case 9).



Indolent T-LPD of the ileum (case 10).



Perry et al. Blood 2013;122:3599-3606

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

Primary cutaneous γδ T-cell lymphoma (revised 4th edition of WHO classification)

- Emphasises the importance of excluding other T-cell lymphomas/LPD that may be derived from γδ T-cells such as mycoses fungoides, lymphomatoid papulosis

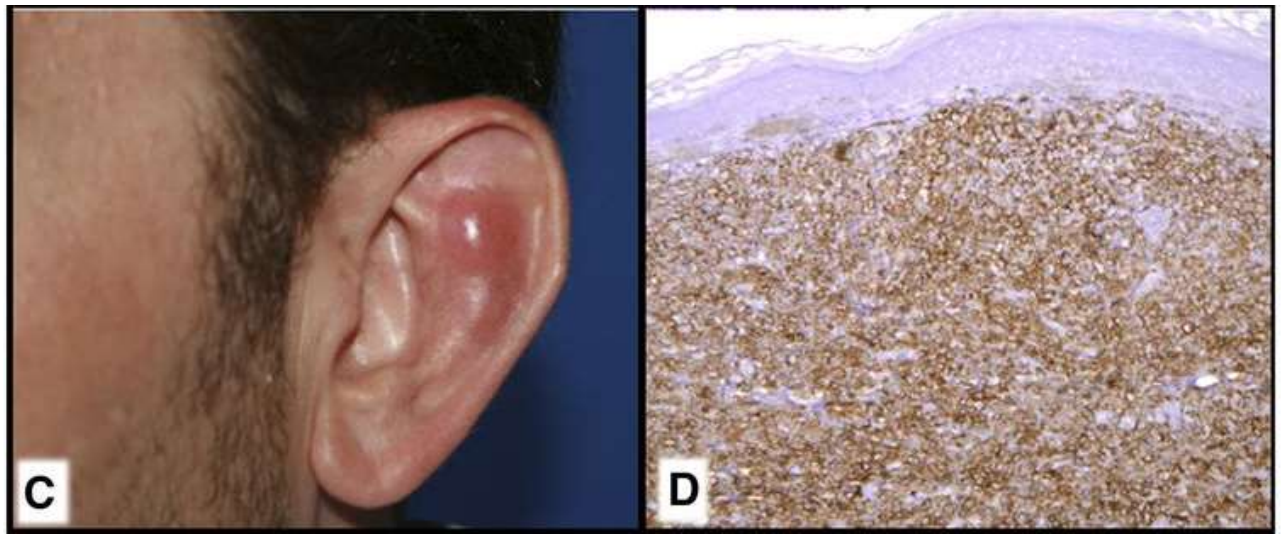
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

New indolent T-LPD/lymphomas (provisional entities) in revised 4th edition of WHO classification

- Primary cutaneous acral CD8+ T-cell lymphoma



- Indolent
- Nearly always localised to single site
- Originally described in the ear, but may involve other sites
- Can be managed conservatively

- Indolent T-cell lymphoproliferative disorder of the GI tract

Swerdlow et al. Blood 2016;127:2375-2390

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Swerdlow et al. Blood 2016;127:2375-2390

EBV+ T-cell and NK-cell lymphomas -changes in revised 4th Edition of WHO classification

- Systemic EBV+ T-cell lymphoma of childhood (no longer, referred to as LPD), as it has a fulminant clinical course
- Hydroa vaccinforme-like LPD, name changed from lymphoma to LPD, due to its relationship with chronic active EBV infection and a spectrum in terms of clinical course
- Node based EBV+ PTCL, included under broad heading of PTCL, NOS

Summary -changes in WHO 2017 update -1

- Nodal T-cell lymphomas with a T-follicular helper phenotype

  -umbrella category created to highlight spectrum of nodal lymphoma with T_{FH} phenotype. Include entities, AITL, *FTCL and nodal PTCL with a T_{FH} phenotype*

- PTCL (NOS) subsets based on phenotype/molecular abnormalities being recognised; may have clinical impact, but not part of routine practice at this time

Summary -changes in WHO 2017 update -2

- Anaplastic large cell lymphoma, ALK-, now definite entity that includes subsets that have prognostic implications
- *Breast implant associated ALCL – new provisional entity*

- *Primary cutaneous small/medium T-LPD* (name change: no longer diagnosed as lymphoma) (*remains a provisional entity)*

Summary -changes in WHO 2017 update -3

- Enteropathy-associated T-cell lymphoma (EATL) (name change: previously EATL, type I)
- Monomorphic epitheliotrophic intestinal T-cell lymphoma (MEITL), (name change: previously, EATL, type II)

- *Indolent T-cell LPD of GI tract (new provisional entity)*
- *Primary cutaneous acral CD8+ T-cell lymphoma (new indolent provisional entity)*

Summary -changes in WHO 2017 update -4

- Systemic EBV+ T-cell lymphoma of childhood (name changed from LPD to lymphoma)
- Hydroa vaccinforme-like LPD (name changed from lymphoma to LPD)


The Centre
For Molecular
Pathology
NHS
National Institute for
Health Research
NHS
National Institute for
Health Research