European Association for Haematopathology

XV EBMWG 2022

LUND SWEDEN

MAY 28th - 31st

14.30-15.00 Update on T-prolymphocytic Leukemia, Hepatosplenic T-cell lymphoma and Adult T-cell leukemia/lymphoma *Elena Sabattini, Bologna*

LUNDS UNIVERSITET

DISCLOSURES

I have no COI to declare related with the addressed topic

TPLL	HTLV1-ATLL	HSTCL
2%	2-5% of HTLV1 carriers	2%
most common in Western	endemic in southwest Japan, Central/South America, central Africa, Middle/Far East, central Australia, Romania ***sporadic*** in North America, Europe: ***incidence raising in nonendemic areas due to immigration***	*>West (USA>EU)* *extremely rare in other countries*
older adults (65yrs)	*43–65* yrs; rare in children (>Brasil)	Adolescents, *young adults (34yrs)*
slight >M	Slight >F	***>strong M*** predominance
unknown *In spite of a patognomonic TCR-activation, the lack of a common TCR clonotype across cases make the hypothesis of an* ***antigen-driven disease unlikely*** *(either a low avidity autoantigen or antigen independent tonic signals)*	***HTLV1 infection Retrovirus*** *HAM/TSP (HTLV-1–associated myelopathy/tropical spastic paraparesis)* *infective dermatitis associated (IDH)* *HTLV-1 associated uveitis* *Immunesuppressed status* *Association with variety of inflammatory, autoimmune and additional infectious diseases* *(strongyloides stercoralis)*	***>70% de novo*** (***unknown***) - 18% ***immunocompromised*** (AI, hematologic / solid malignancies, SOT (>kidney after median of 6yrs) - 10% in ***IBD*** *possibly implicated :* ***combined anti-TNF therapies****, thiopurine immunomodulators (>azathioprine and 6-mercaptopurine).* *likely not a direct result of treatment but more disease* ***severity/degree of inflammatory activity related and increased immunosuppression***

HSTCL: Risk factors for HSTCL in IBD: young age, concomitant use of anti-TNFs and thiopurines, Crohn disease, male sex, long-term thiopurine therapy (≥2 years).

TPLL : uniform presentation	HTLV1-ATLL: protean presentation	HSTCL : uniform presentation
Aggressive ➢few indolent cases or possible prodromal initially indolent course (like in ATM pts)	***Aggressive*** ➢ ***"Indolent"*** *Smouldering, Chronic variants* ➢ ***Aggressive*** *Acute, Lymphomatous, EPC* ➢recent new targeted therapies provided with encouraging responses.	***Aggressive*** ➢durable remissions reported if prompt reduction of immunosuppression and intensive chemotherapy regimens.

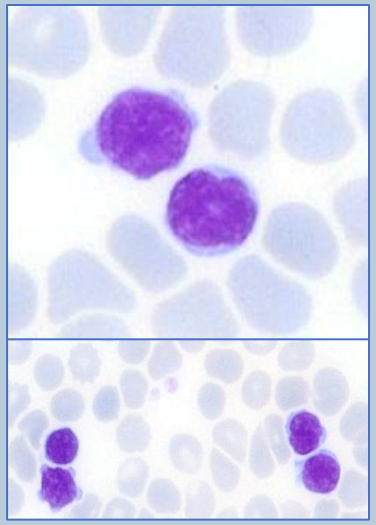
TPLL: uniform presentation

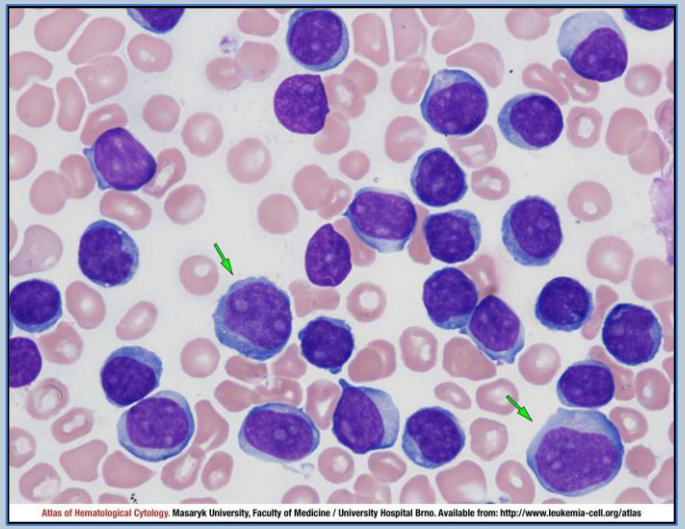
Leukaemia >100.000/ul
rapidly increasing

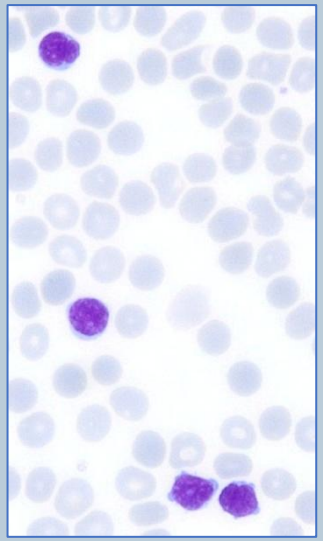
BMB or pb smear
>prolymphocyte-like fairly monomorphic)
25% small/mature looking
no granules
Interstitial/diffuse pattern

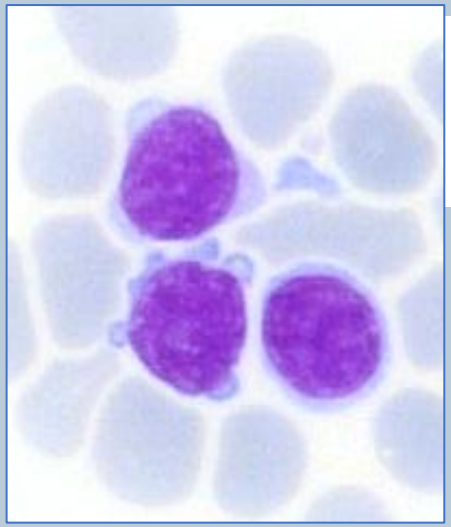
Cytopenia
(Anemia, Thrombocytopenia)

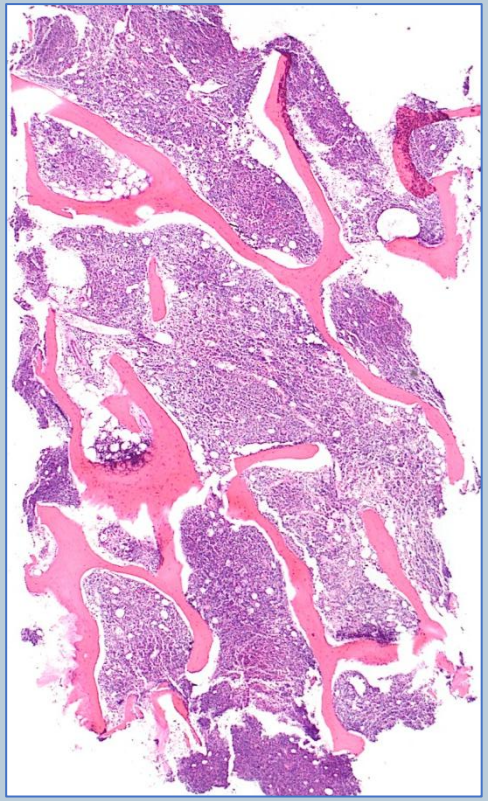
Liver and **spleen enlargement**
lymphadenopathies
(generalized small nodes)

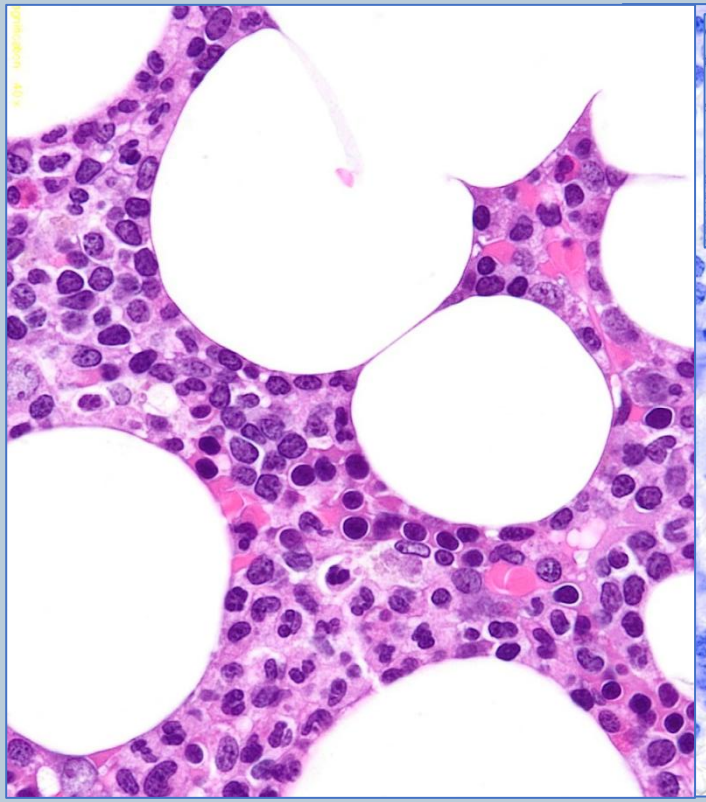


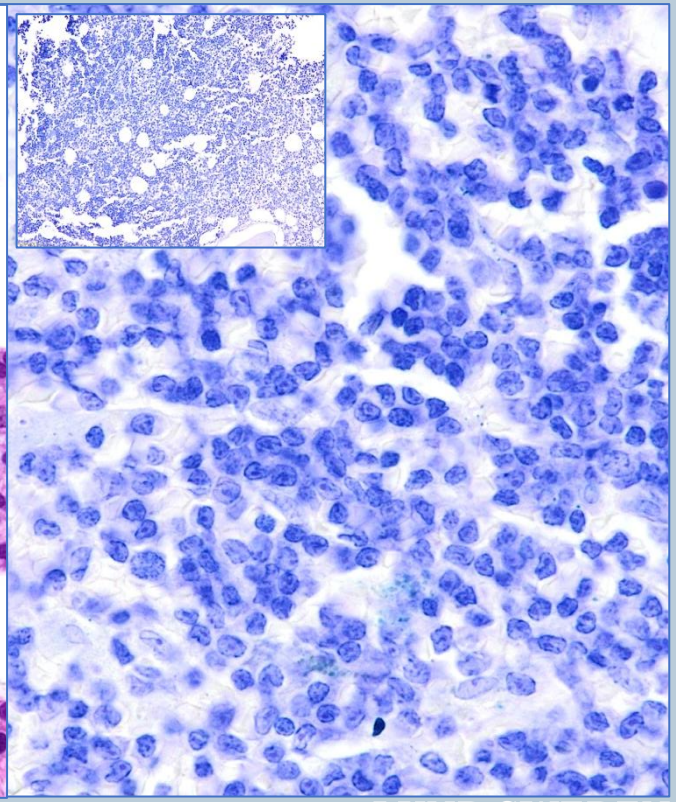




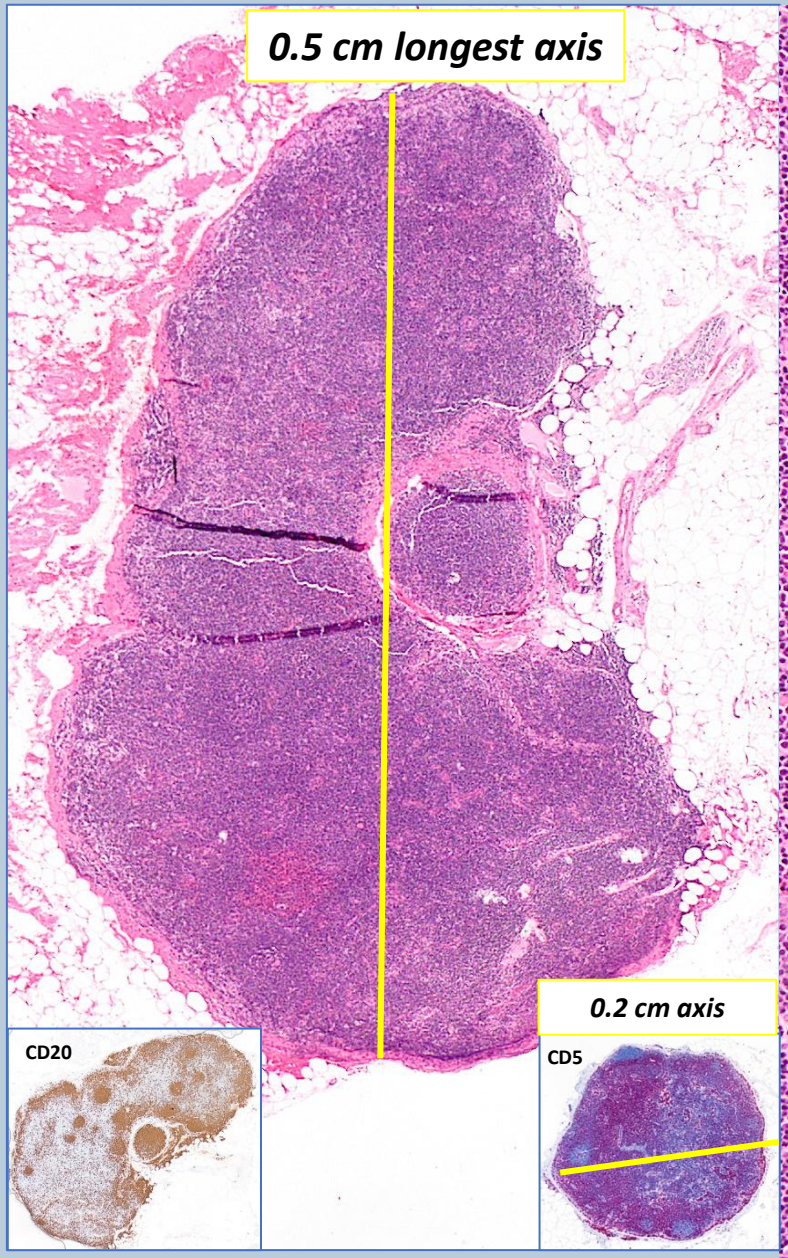


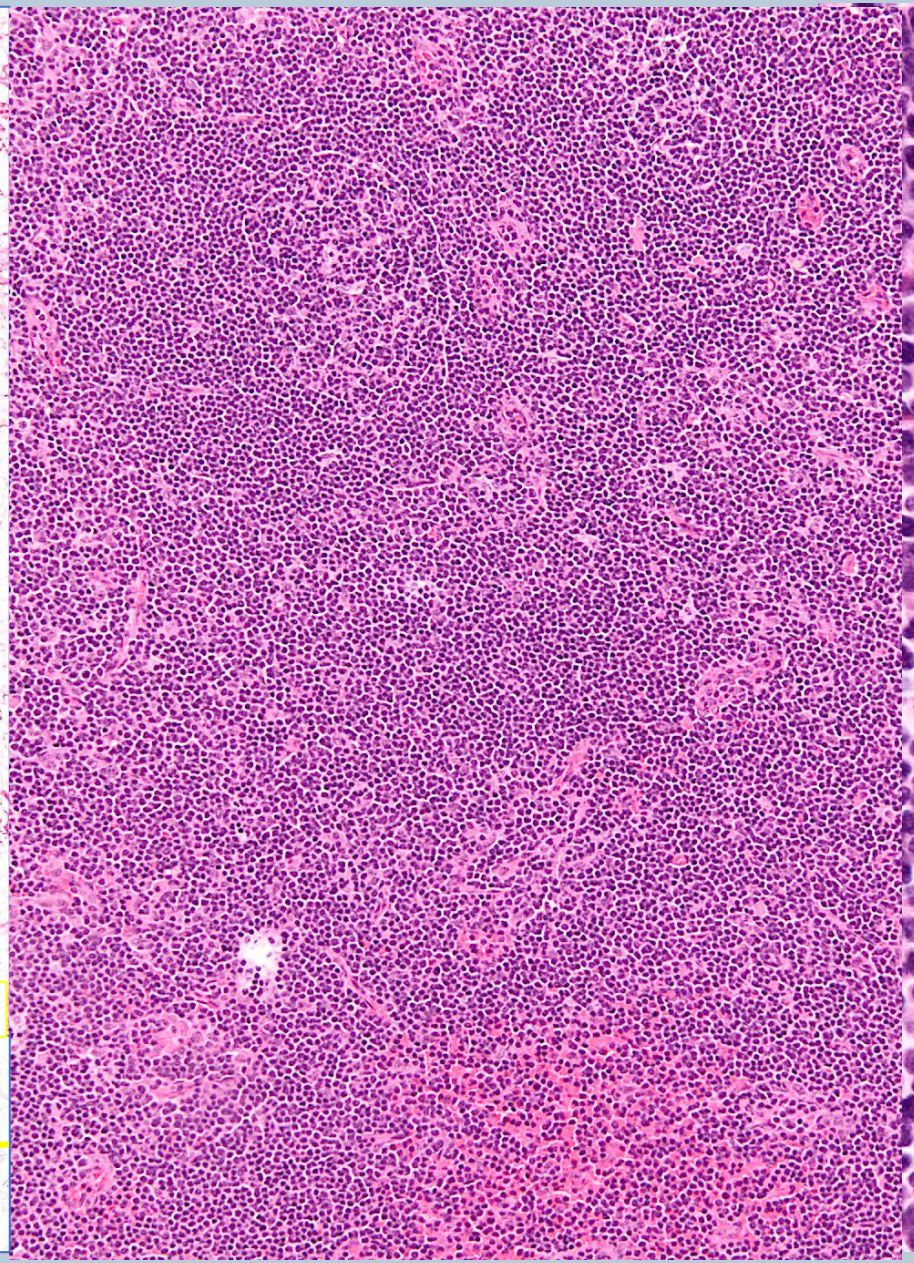


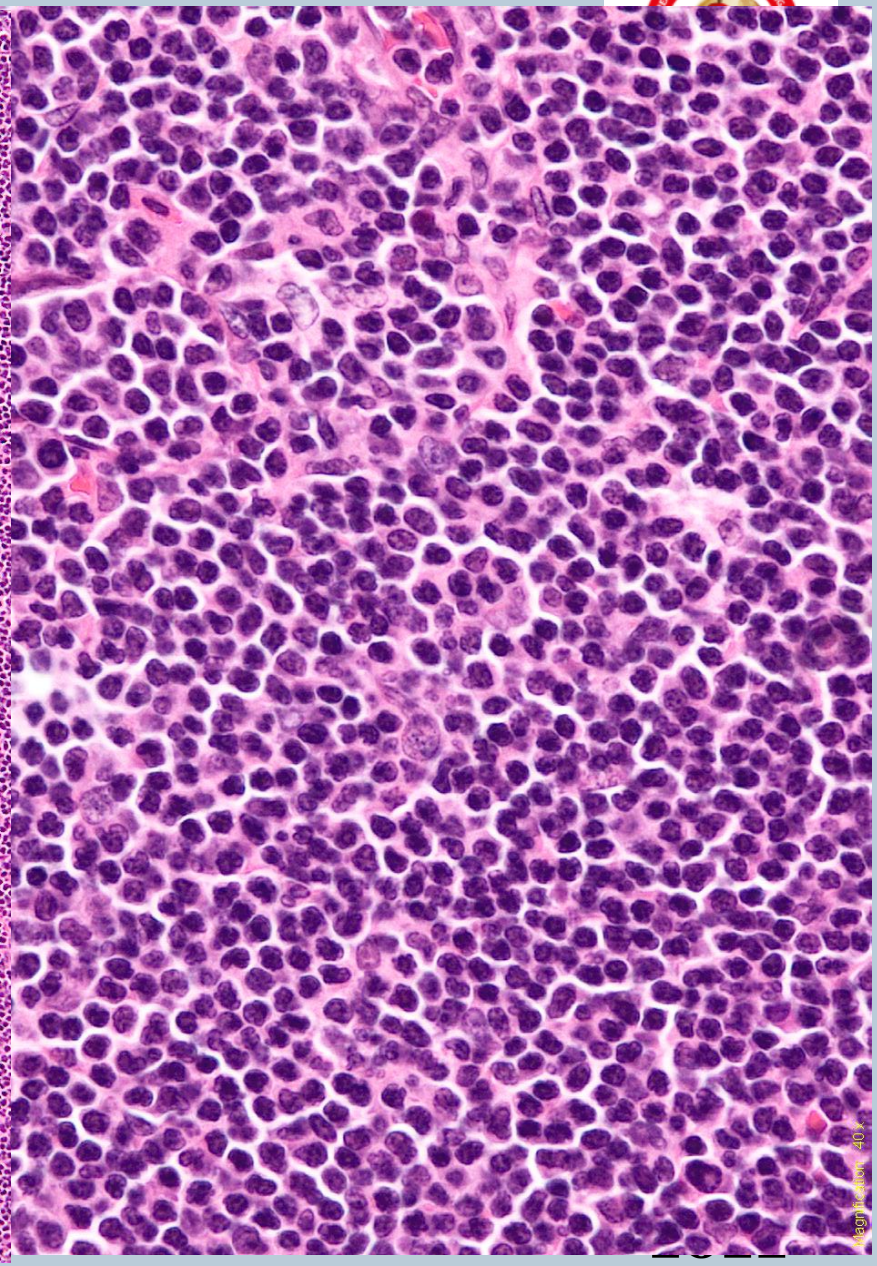




Lymphadenopathies : generalized small nodes







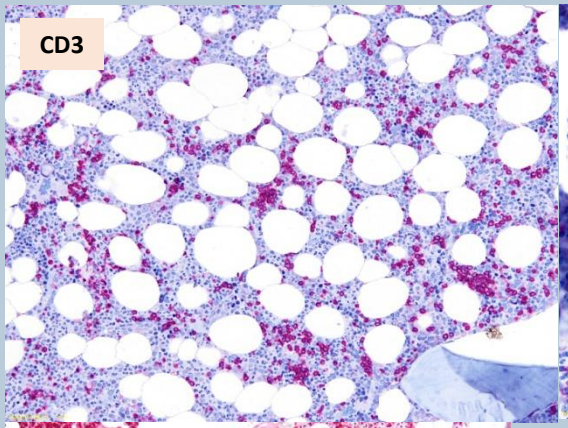
TPLL :
αβ mature,
antigen experienced
non-conventional memory T-cell, >helper

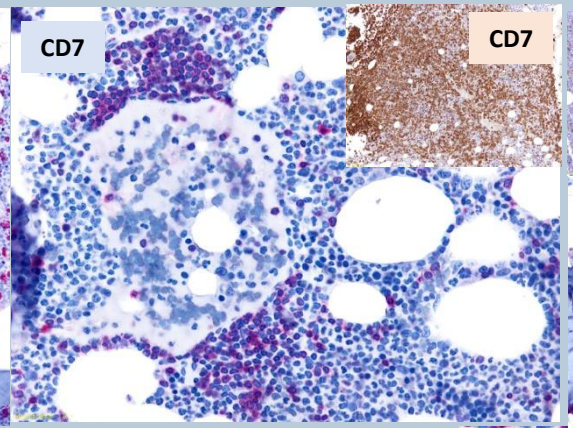
CD3+ (rare negative cases)
CD2+, CD5+, CD7+ (rare absence of one panT)

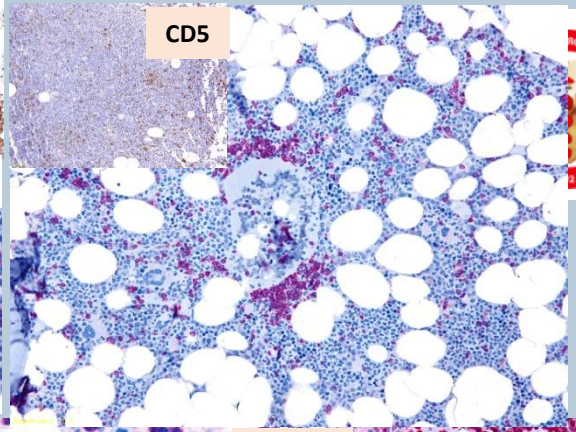
- **CD4+**/CD8-
  <*CD4+/CD8*+ or CD8+
  <<DN
- **non cytotoxic**
  (15% CD4-CD8+ cytotoxic)

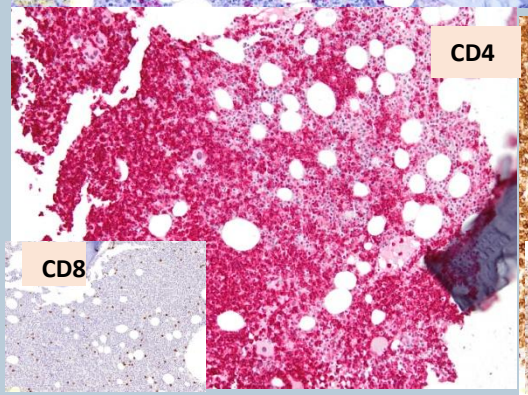
TCL1+ less useful in FU

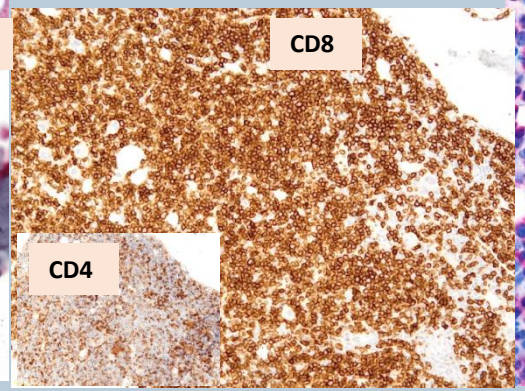
CD52 consistently strongly expressed
S100 + (30%)

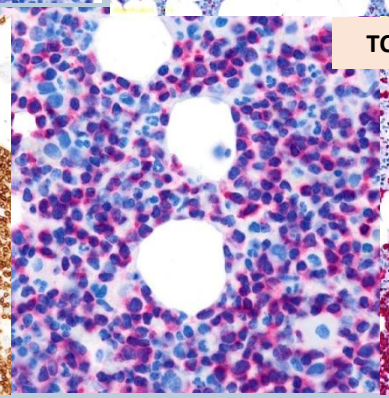


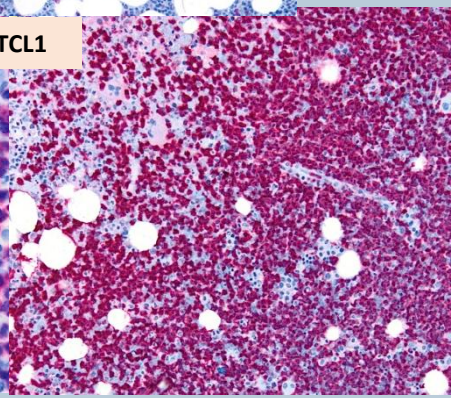


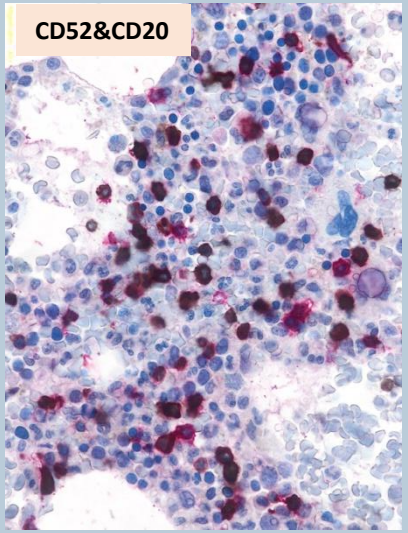


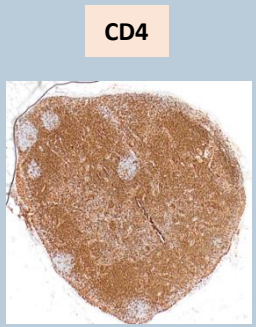


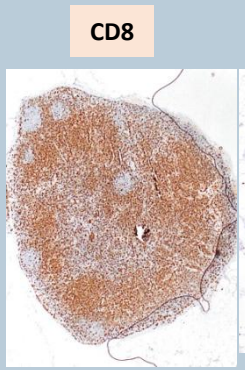


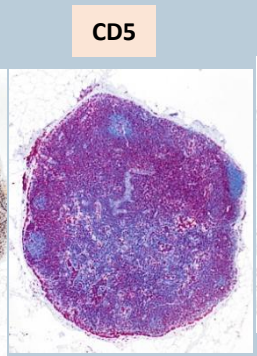


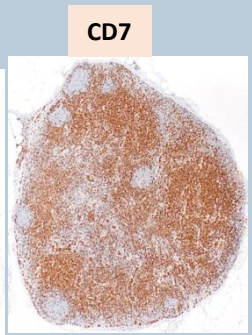












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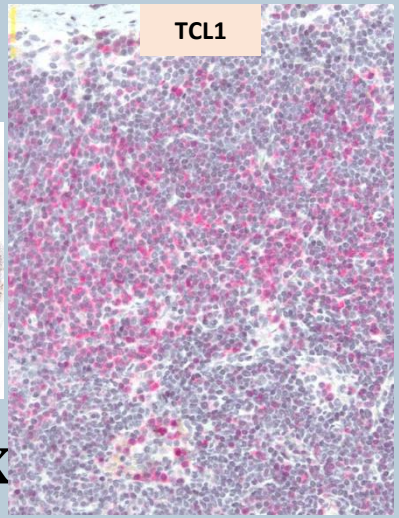
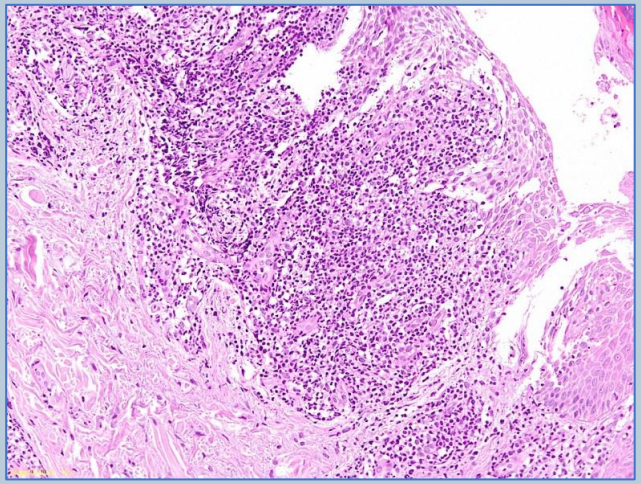
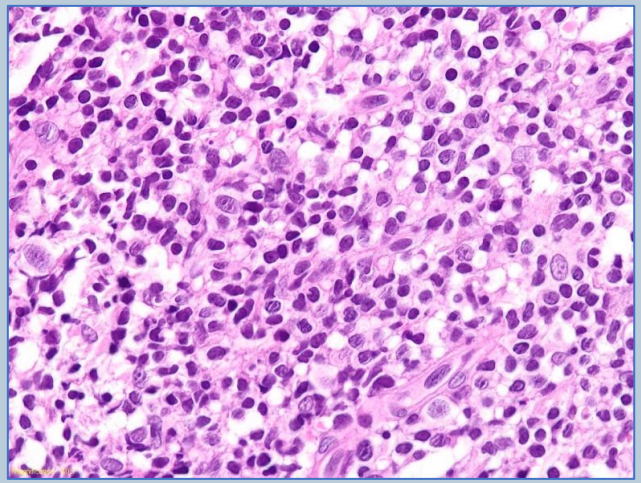
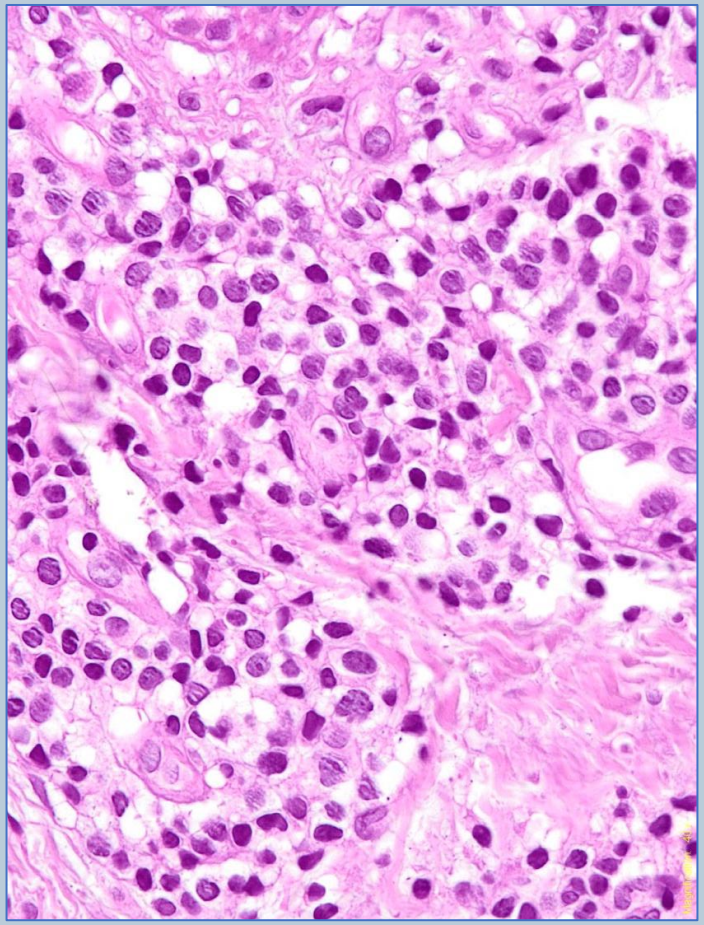
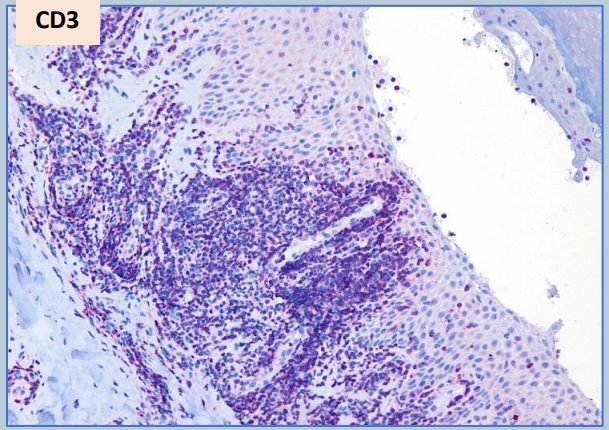


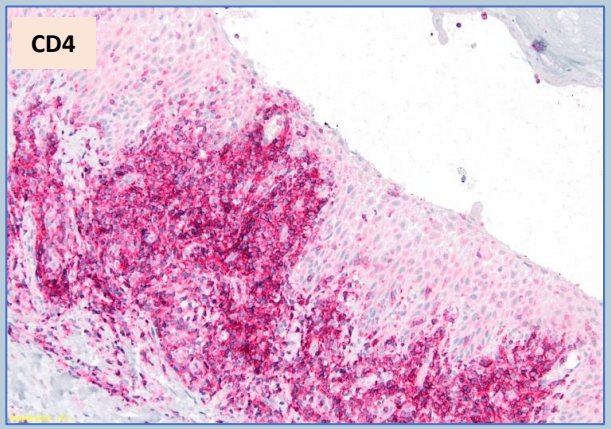




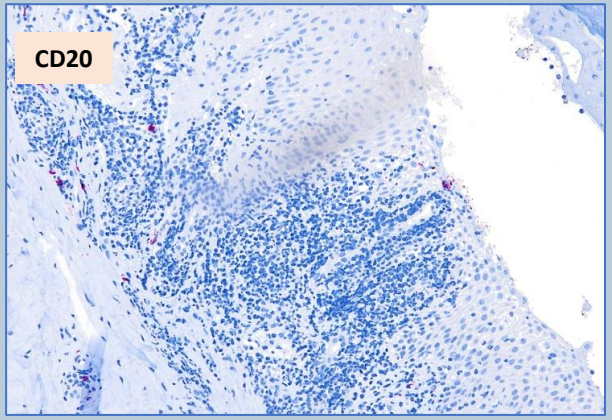


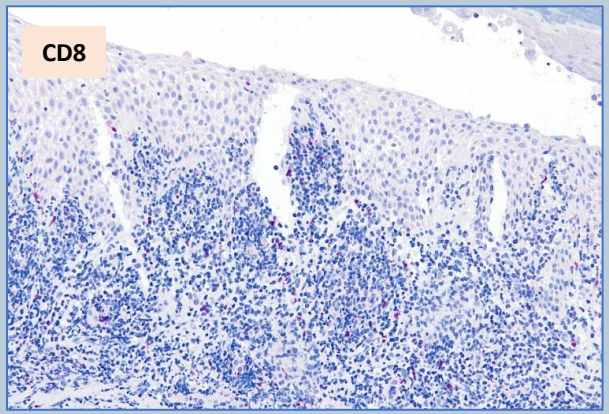
Male 82 years
Onset: cutaneous lesion in anterior thoracic area with suspicion of B-cell lymphoma.

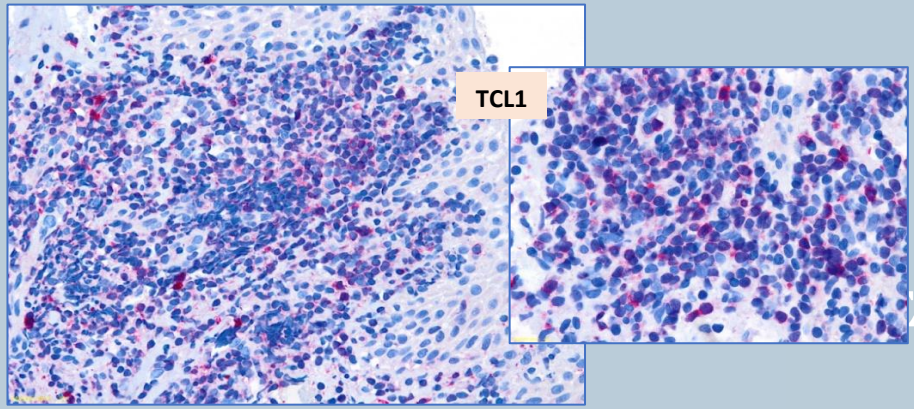




Possible/rare
skin,
serosa effusions,
CNS (<5%)







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2022
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HSTCL : uniform presentation

Cytopenia common
(thrombocytopenia almost always present and tend to relate to progression)

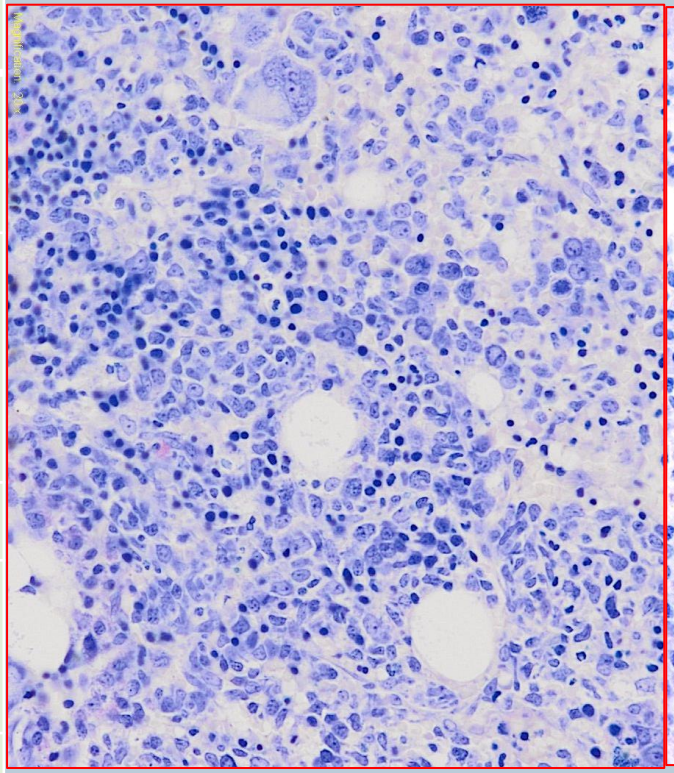
➢No leukaemia at onset
advanced cases, leukemic and blastic evolution reported
small population of atypical lymphocytes at flow in ~50% pts

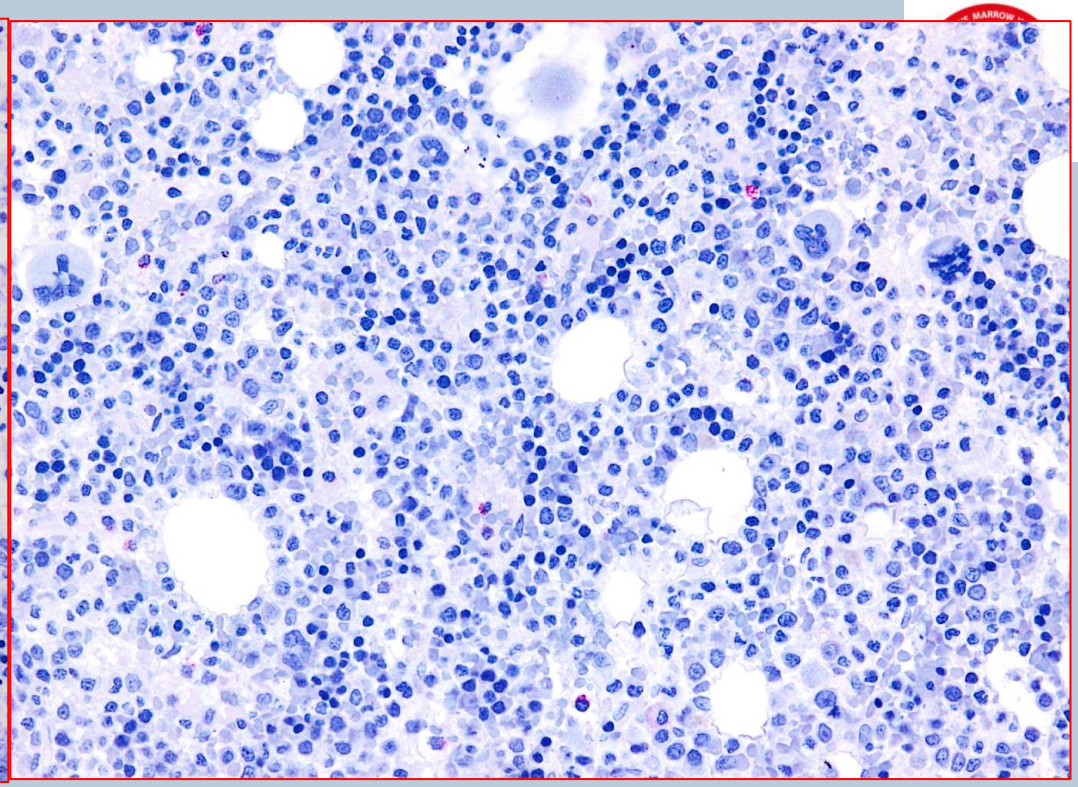
Liver and spleen enlargement

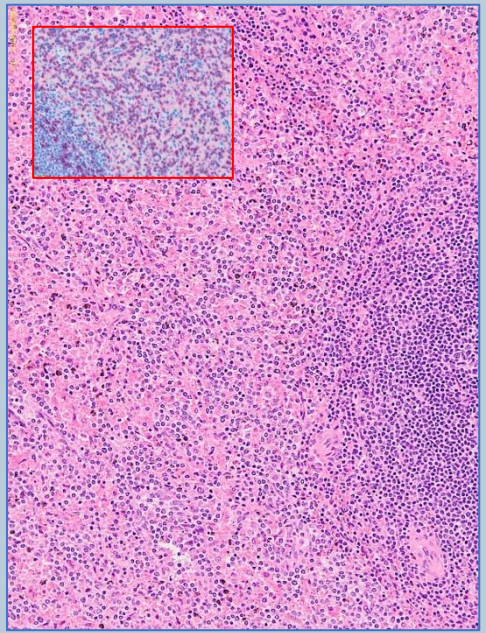
Bone marrow : *involved 65% at diagnosis, > frequently in advanced disease*

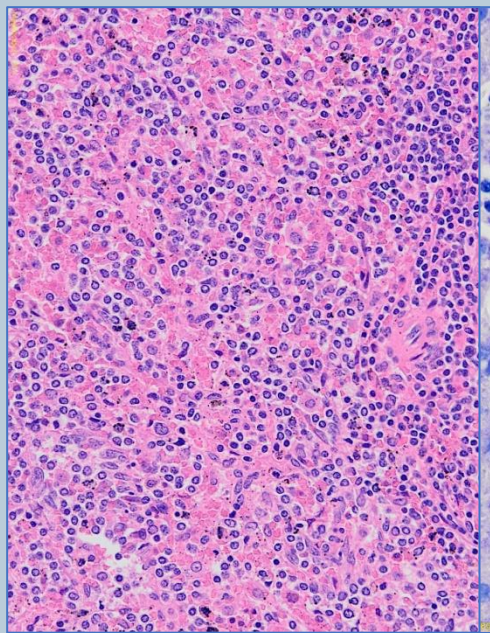
variability in size & morphology

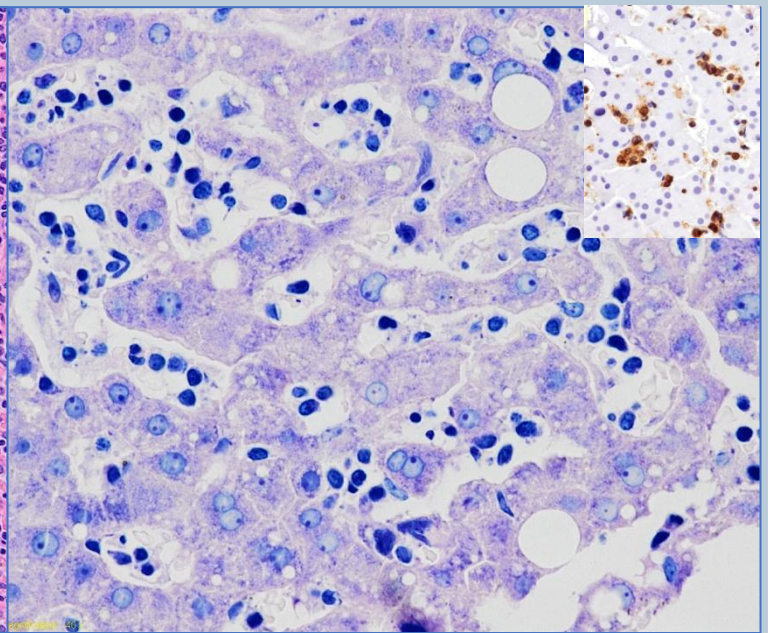
- small to medium; irregular nuclei, inconspicuous nucleoli, moderate cytoplasm; possible large or *blastoid variants (at progression)*
- no granules (possible fine granules at smears and/or hairy projections)
- **sinusoidal > interstitial** pattern; increasingly interstitial at progression; usually discrete, but subtle; splenic red pup
- Hemophagocytosis 5%











HSTCL: γδ T-cell from splenic pool ; >Vδ1 gene usage; functionally immature

CD3⁺
CD2+, **CD5−**, CD7+/−

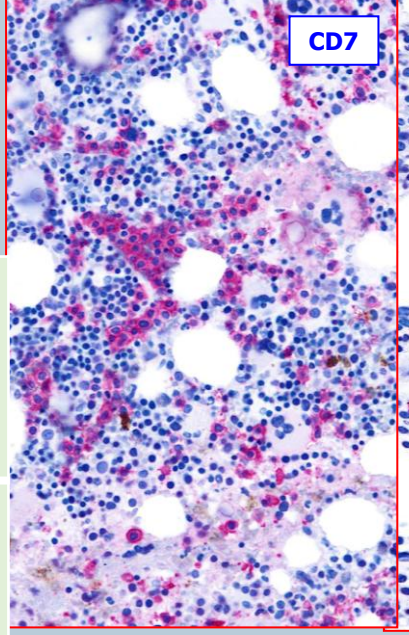
CD4−/CD8− (<CD8+)

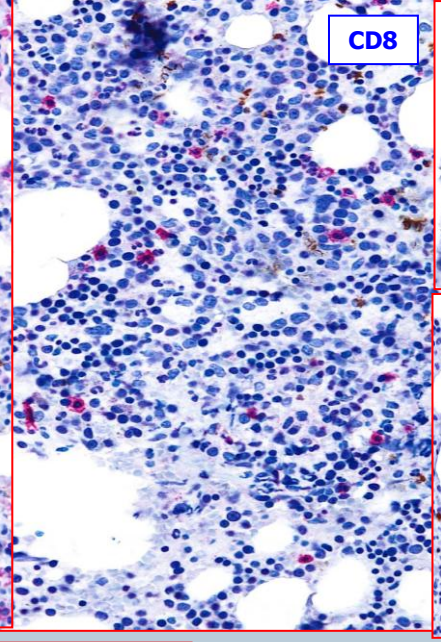
cytotoxic non activated
Tia1+GyM+/non activated
(**GyB-Perf-**)

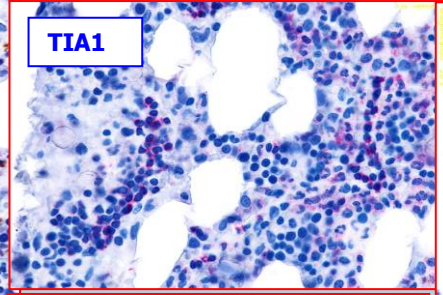
CD56+-, CD57−, CD16-

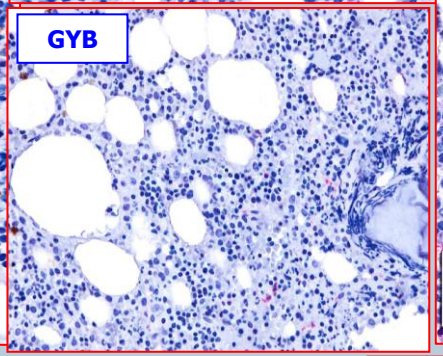
CD30/CD25 neg

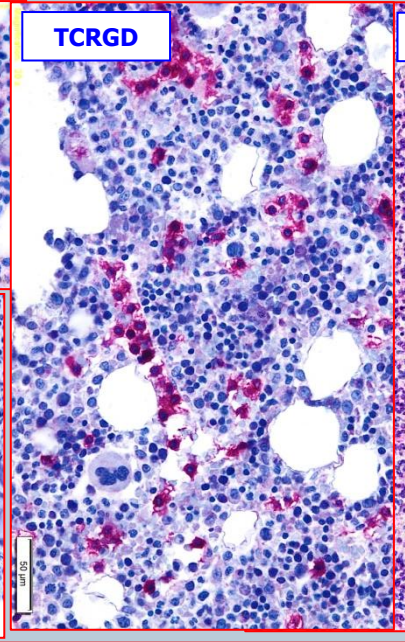
20% αβ (DN cells)
minor cases with silent TCR

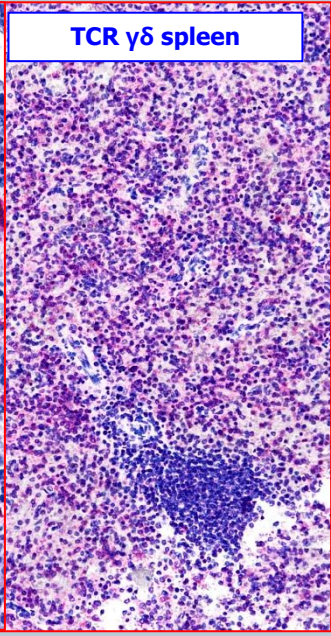


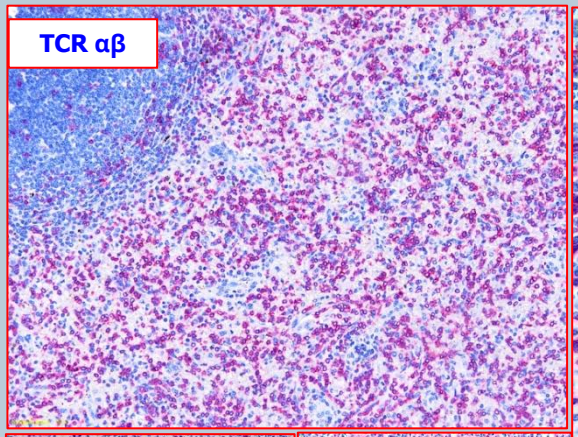


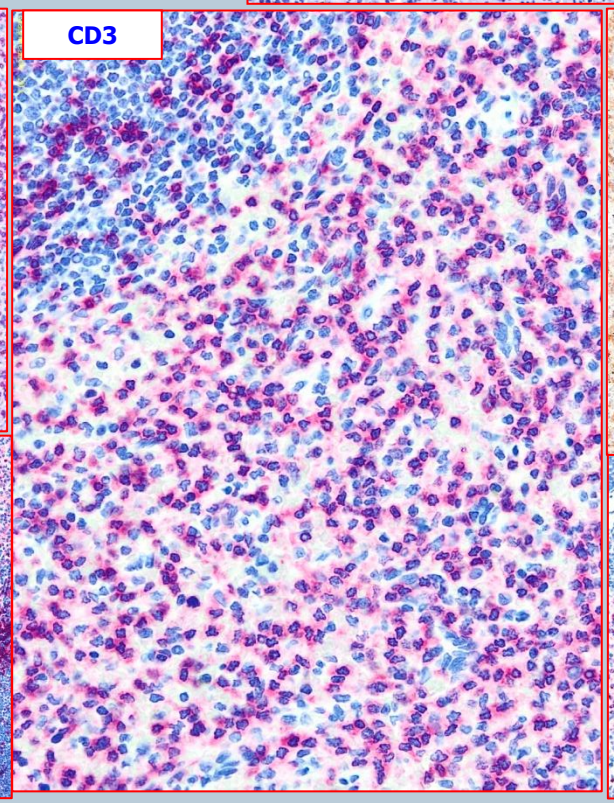


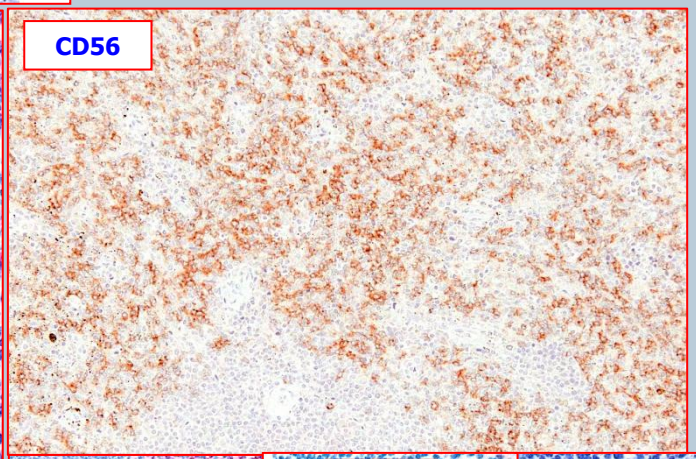


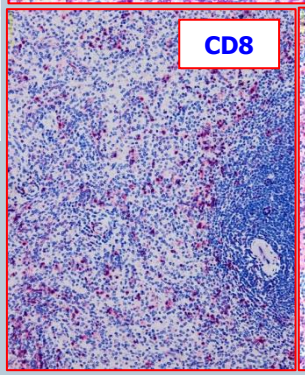


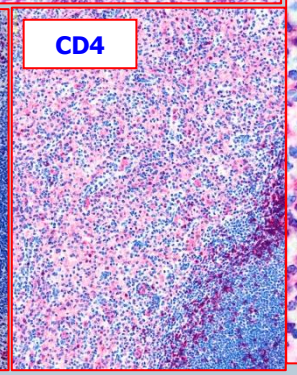


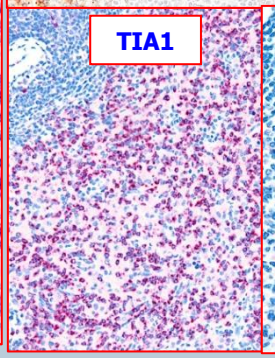


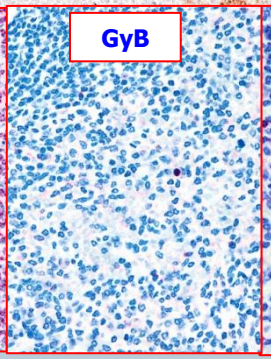


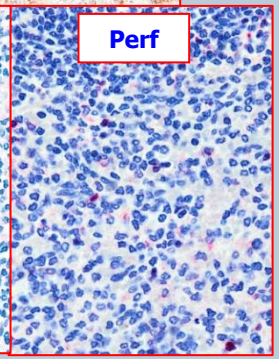












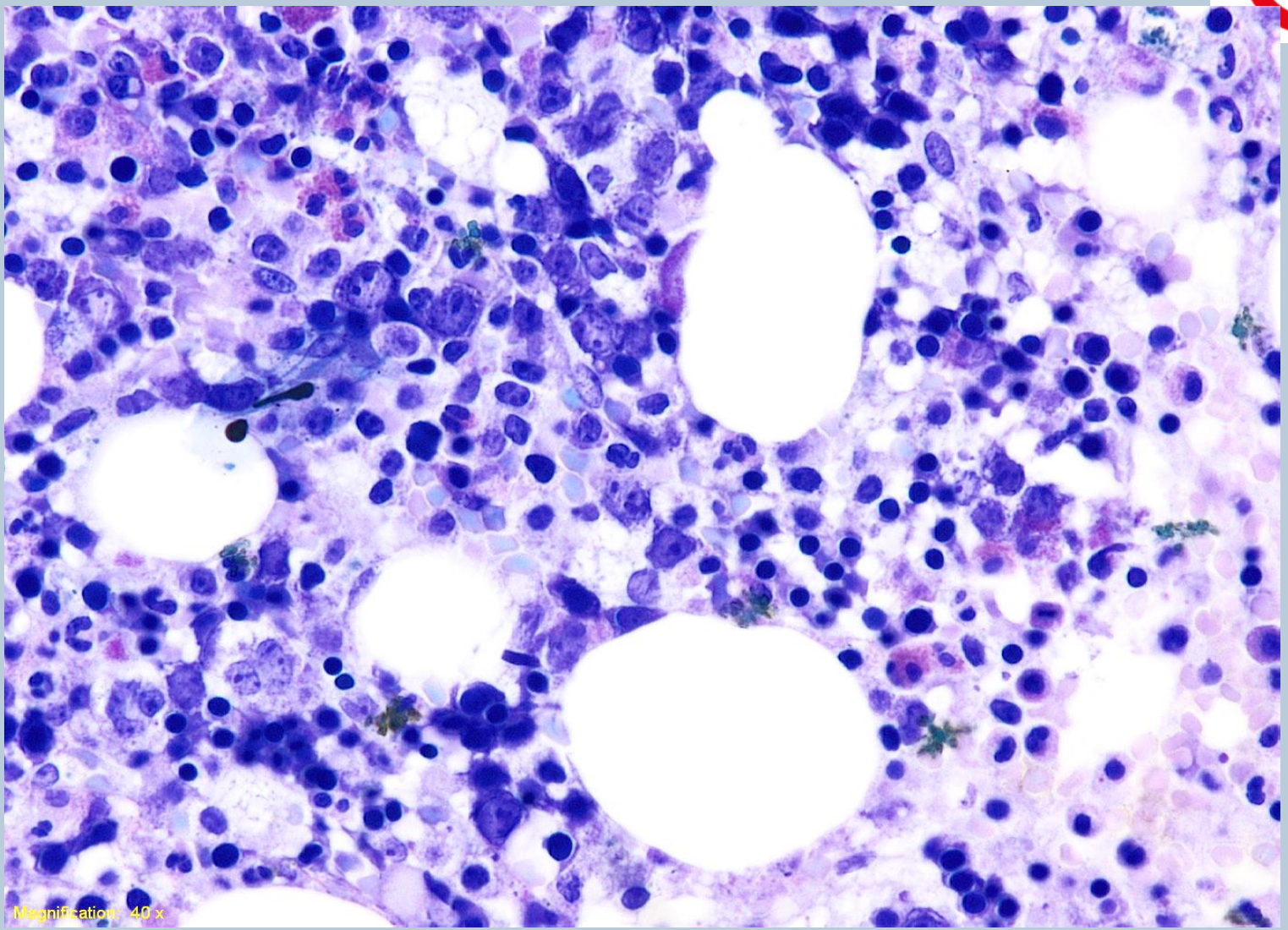
Dyspoietic changes associated with hepatosplenic T-cell lymphoma are not a manifestation of a myelodysplastic syndrome: analysis of 25 patients.

Yabe M et al. Hum Pathol. 2016

pathogenesis of cytopenias not well defined.

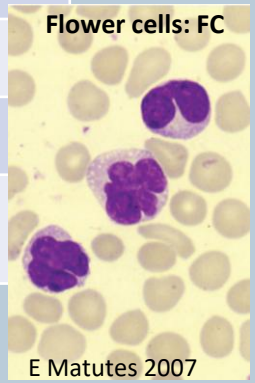
Likley not related to splenic sequestration
(severity of cytopenias correlates with disease progression, even in patients who have undergone splenectomy)

Likely not-MDS related:
morphologic dysplasia do not correlate with severity of cytopenias or cytogenetic abnormalities associated with MDS



Comparison of clinical variants of ATLL: 2019 Revised ATVLL International Consensus Meeting Report (Cook et al. JCO 2019)

	Smouldering	Chronic	Acute	Lymphoma	Extranodal Primary Cutaneous
Lymphocytosis	-	+ Mild **(>4x10^9/L)**	**+**	- (1% cells)	-
TCR rearrangement	+-	+	+	+	+
Elevated LDH	-	-/minimal	+	+	na
hypercalcemia	-	-	+ **lytic bone lesions**	+-	-
Skin lesions	**+erythematous rash**	**+rash, papules**	>50%	>50%	**+papules,nodules, tumors**
Lymphadenopathy	-	+ mild	+-	**+**	-
Heopatosplenomegaly	-	+ mild	+-	+-	-
BM infiltration	-	-	+	-	-
Median Survival	>2 years	2 years	<1year	<1 year	<2years
Morphology	>small cell **minimal atypia**	>small, few FC **mild atypia**	pleomorphic, FC, **marked atypia**	pleomorphic, FC, **marked atypia**	pleomorphic, FC **marked atypia**



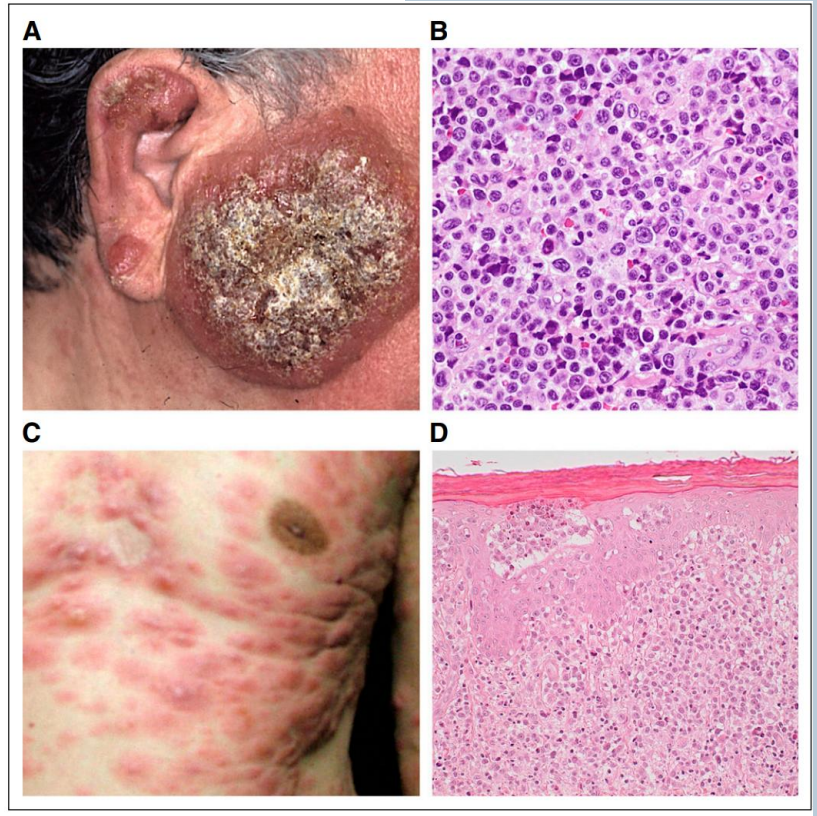
10-20% aggressive ATL progress to CNS (incorporate CNS prophylaxis);
progression from chronic and smoldering types to acute forms reported;
hemophagocytic syndrome as one of the first signs of transformation

Modified from Adkins et al. Sem Diagn Pathol 2020

Shimoyama et al. BJH 1991, Adkins et al. Sem Diagn Pathol 2020, Cook et al JCO 2019, Tsukasaki et al. JCO 2009

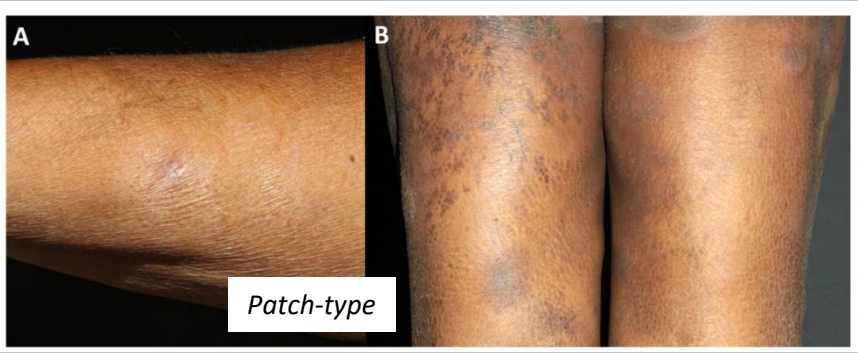
Cutaneous-type ATLL

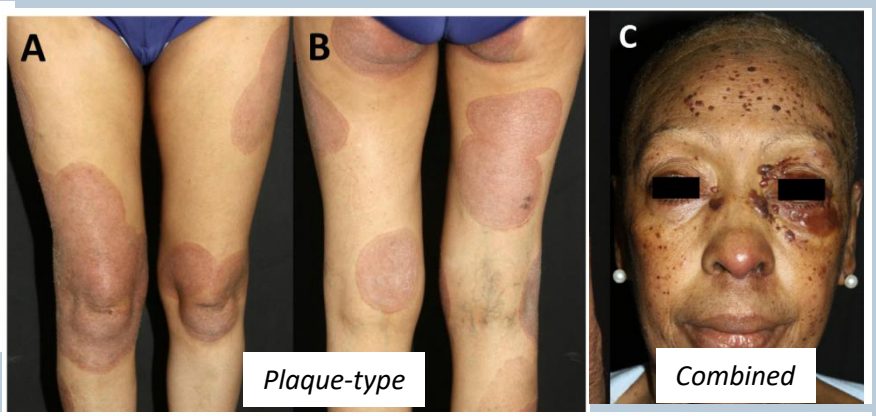
- *Classified as "smouldering" until 2019*
- *erythematopapular: median survival time 60 months (within smouldering variant)*
- *tumoral types: median survival time 19 months*
  Extranodal primary cutaneous variant of lymphoma type
  - no leukemic, lymph node, and other organ involvement
  - once into smoldering ATL but considered poor prognostic factor by univariable analyses.
  - nodules
  - high-grade T-cell lymphoma pathology
  - perivascular infiltration, scant epidermotropism
  - consider for immediate treatment

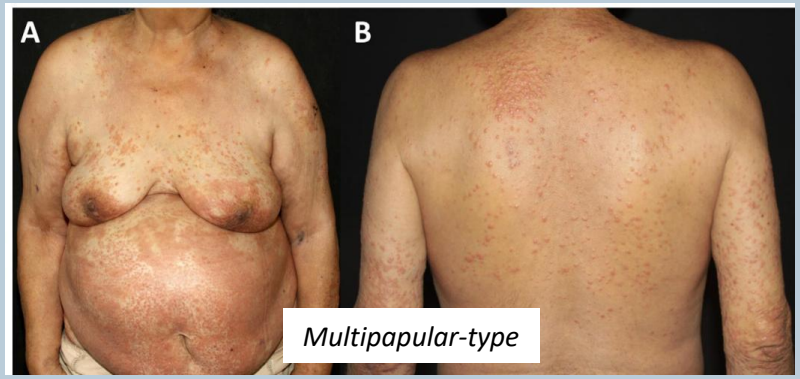


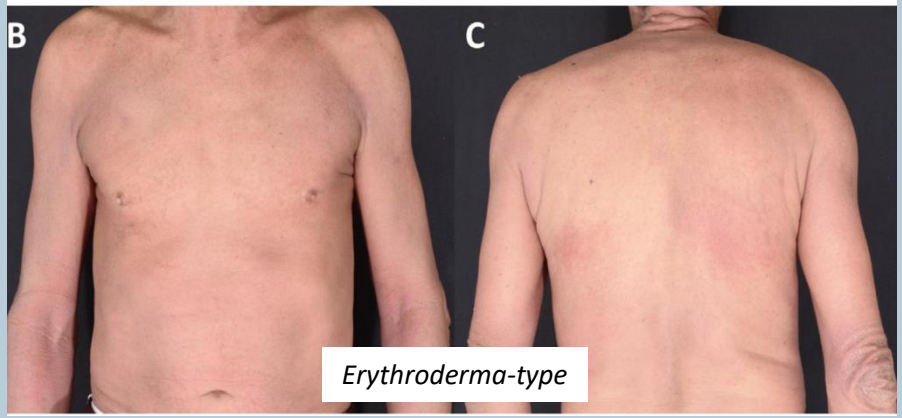
from Cook JCO 2019

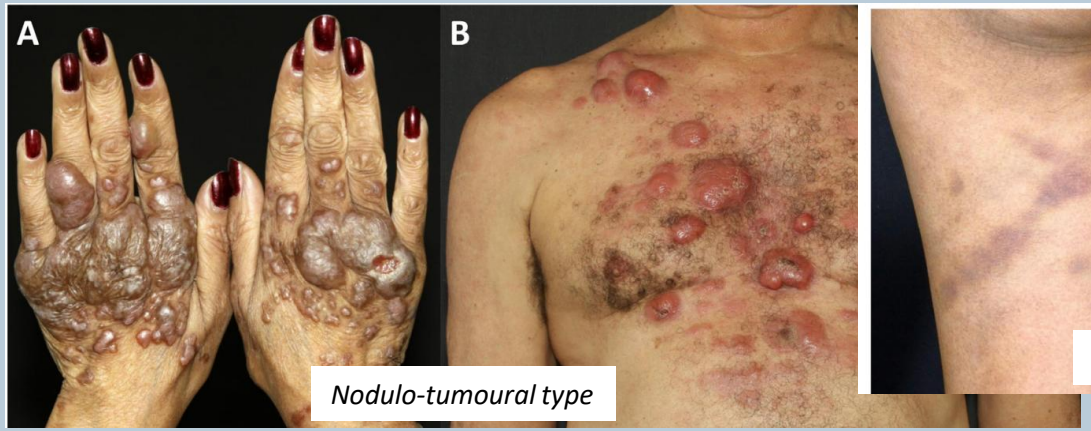
Cook et al JCO 2019; Bittencourt et al 2007 (first descritpion of EPC-ATLL cutaneous-type ATLL (cATLL) and subdivision into erythematopapular and tumoral types)

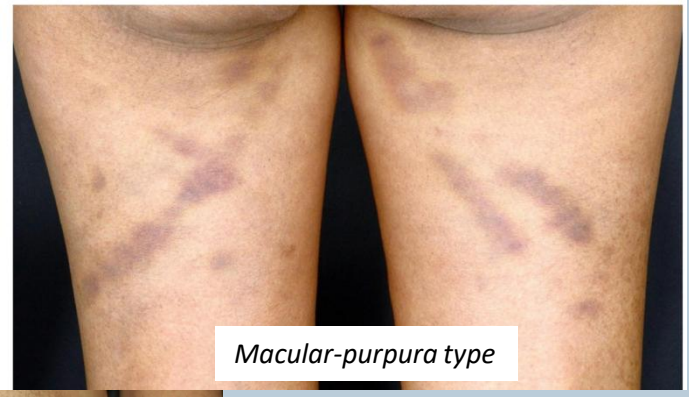












SPECIFIC LESIONS: NEOPLASTIC CELLS

- *39% to 72% pts*
- *can be first manifestation: importance of early recognition*
- *>multiple and disseminated*
- *>pruriginous*
- *different types may coexist in 50% pts*

- *P/P more common in indolent variants*
- *N and erythroderma more common in aggressive variants*


Contents lists available at ScienceDirect

2019

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Cutaneous manifestations of adult T-cell leukemia/lymphoma

Denis Miyashiro, Jose Antonio Sanches*

Oshima et al. Cancer Scie 2007, Bittencourt et al Acta Oncol 2009, Sawada et al Blood 2011 , Tsukasaki K et al. J Dermatol. 2014,Marchetti et al. J Am Acad Dermatol 2015

Overt-ATLL: non preserved architecture mimic of other PTCL; FC not always detectable at histology

Pleomorphic (medium&large cell)

>common; giant/HRS cells frequent

Pleomorphic small cell type

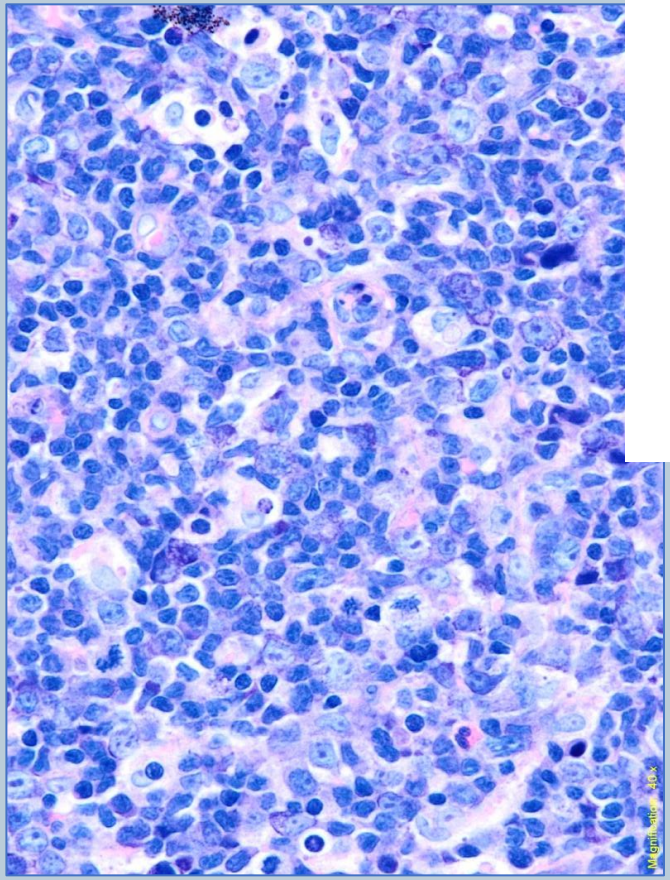
mild nuclear irregularities, few mitoses

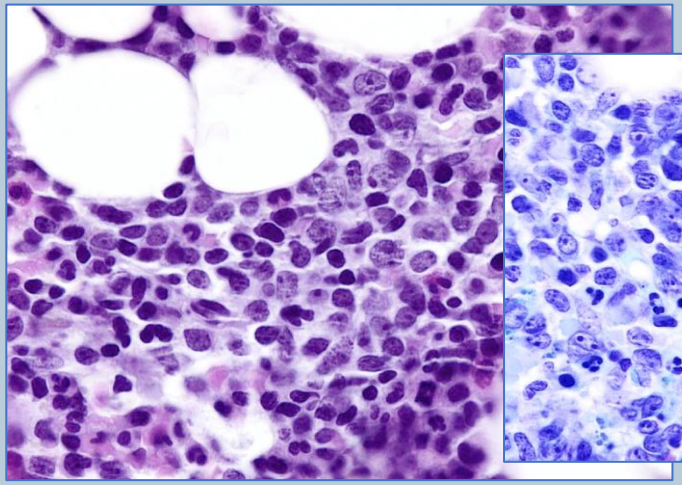
ALCL-like type

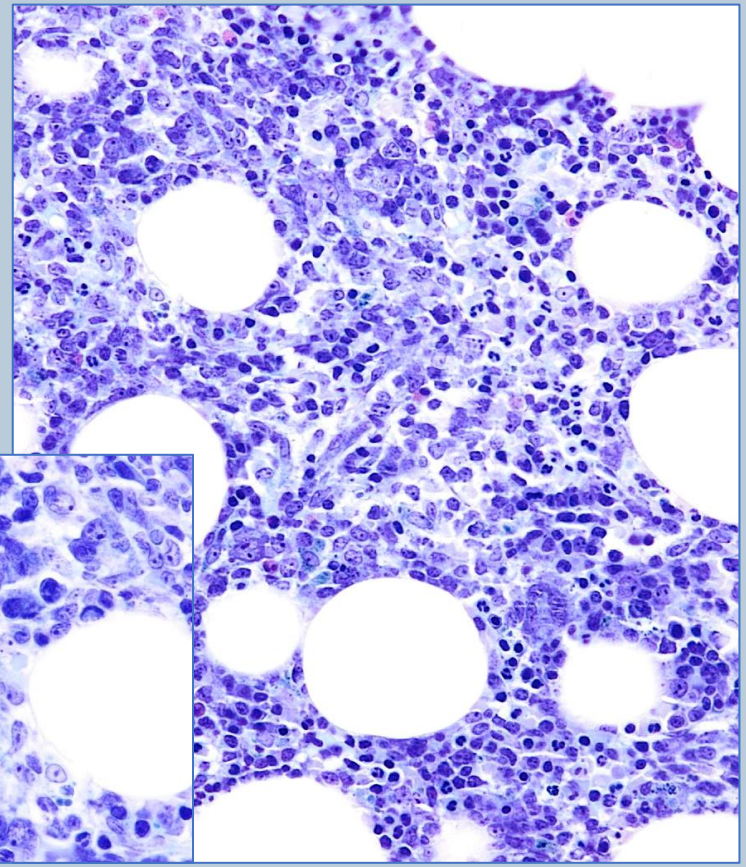
possible CD30 pos and sinusoidal pattern.

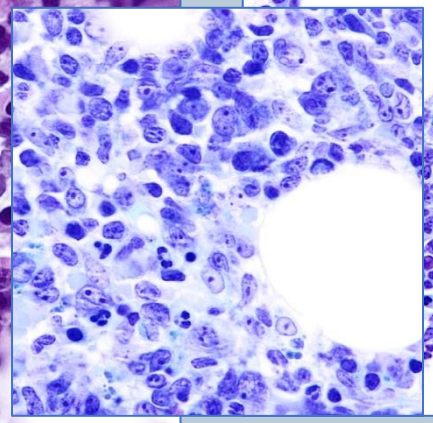
AILT-like ATLL:

very rare; inflammatory cells









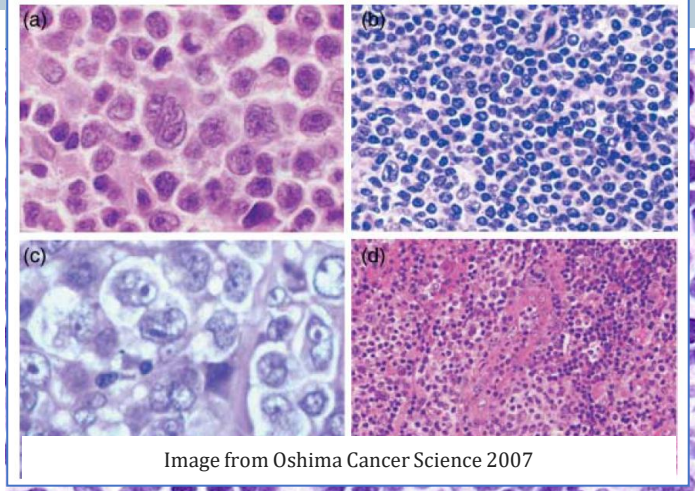
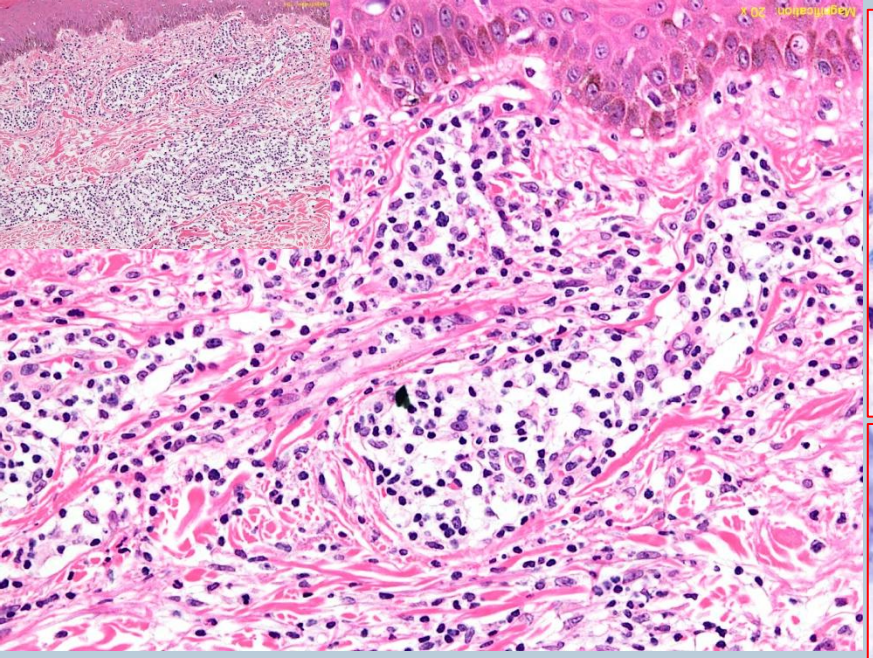
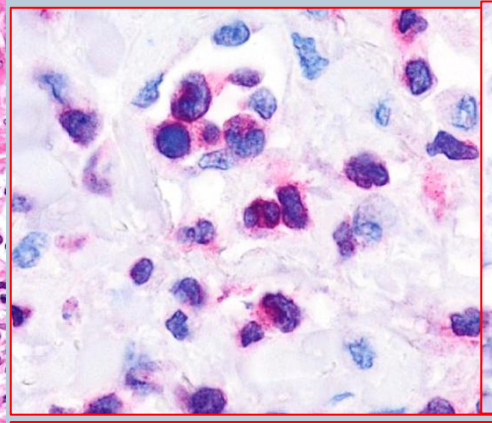
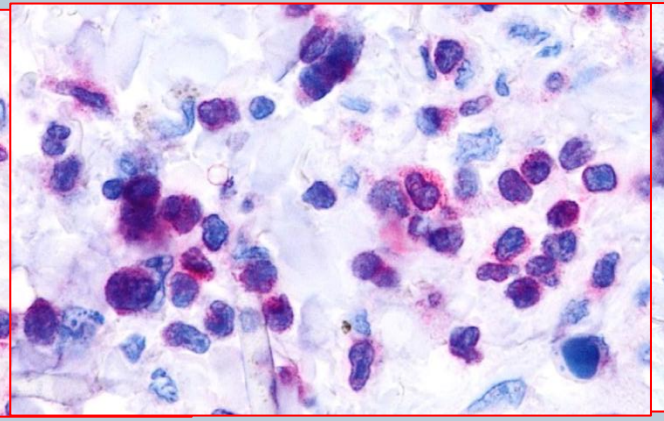


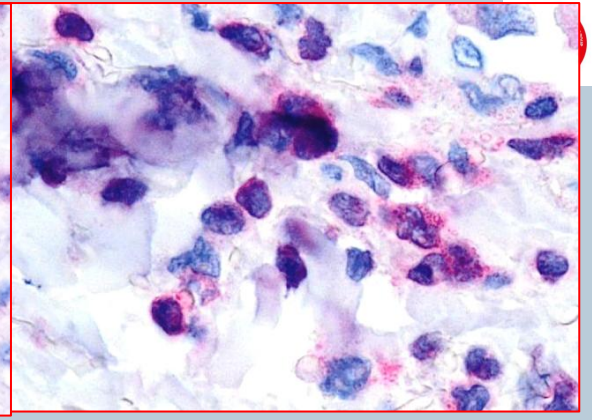
Image from Oshima Cancer Science 2007

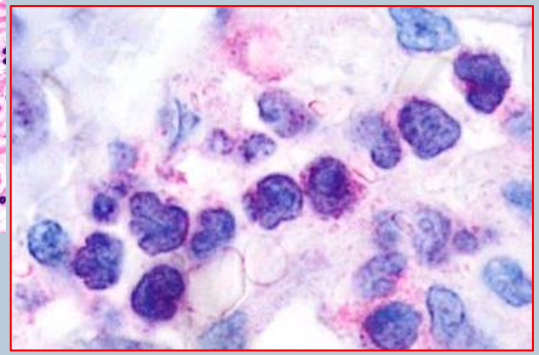
WHO classification 2008-2017

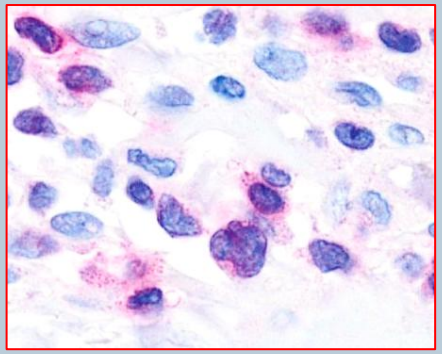


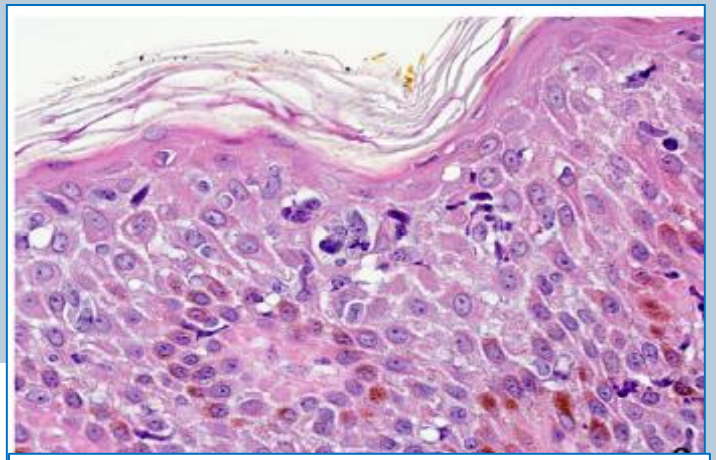




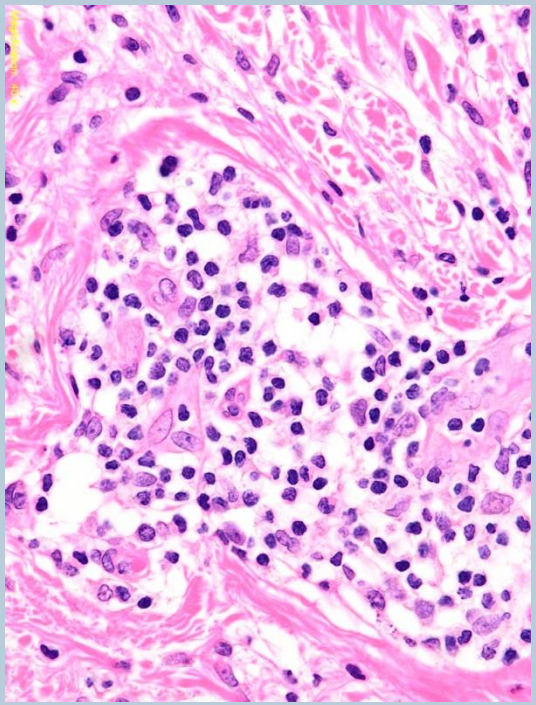








Miyashiro D et al. Semin Diagn Pathol. 2019



Heterogeneity of skin manifestations and pathologic lesions

- <u>Superficial banded dermal infiltrate w/wo epidermotropism</u>

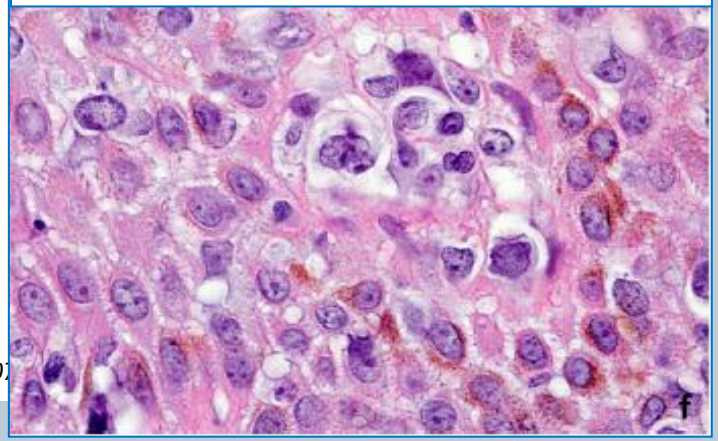
(mimic MF; possible Daurier-Pautrier-like microabsesses)

- <u>Diffuse dermal</u>
- <u>Nodular dermal</u>

often perivascular; possible eosinophils and plasma cells;

cytologic findings similar to those seen in other tissues
challenge in patches in smouldering cases: minimal atypia

Miyashiro Semin Diagn Pathol 2019; Adkins Sem Diagn Pathol 2020, *Sawada Blood 2011, Oshima Cancer Science 200*



ATLL: αβ mature antigen experienced T cell, with possible T-regulatory phenotype

CD3+ CD2+, CD5+, **CD7-/-+** (nearly all cases)

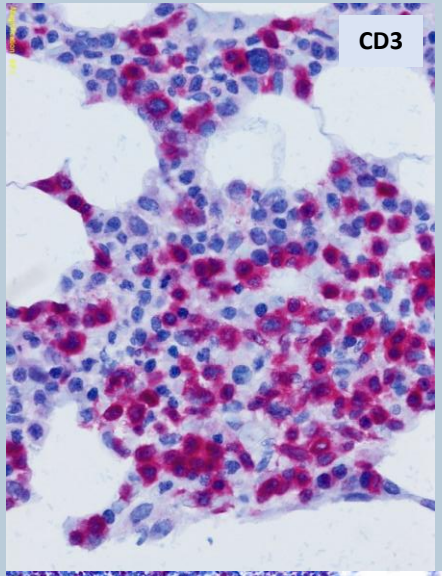
CD4+ CD8-
CD8+(29% but no cytotoxicity); CD4+/CD8+ or +- (partial or fully), CD4-/CD8- (~10%)
non cytotoxic

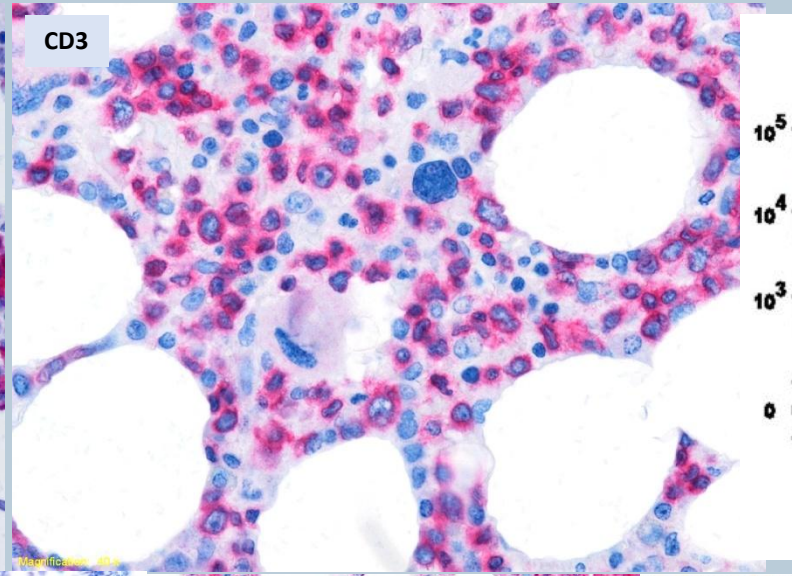
CD25/IL-2R, FOXP3+ (T-regs like)
not always present (68%; only some cells, usually a minority; related to poorer prognosis)
CD25 sensitive non-specific (71% to 93%)

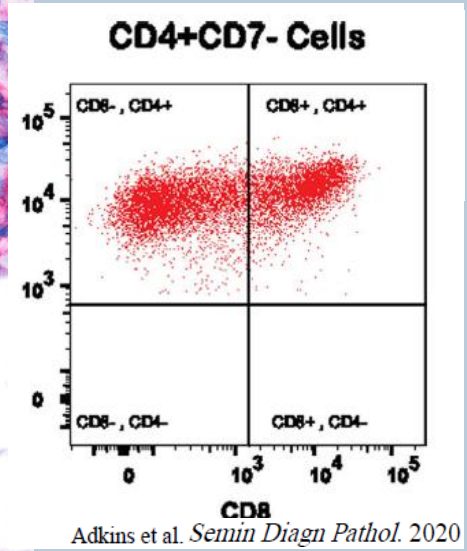
CCR4 (expressed 90% cases; mutated 26%; target protein of mogamulizumab)

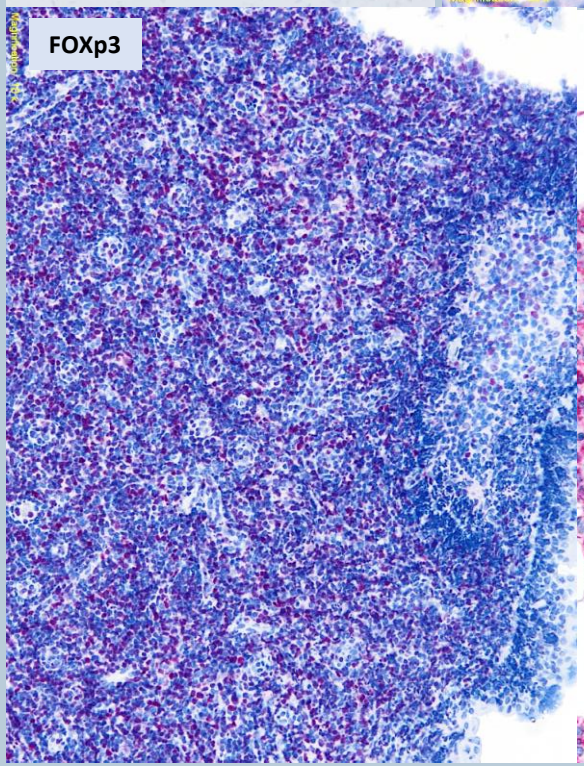
PD-1 positive in neoplastic and non-neoplastic CD4 positive T-cells in pb and skin; also in CD8+ reactive T cells

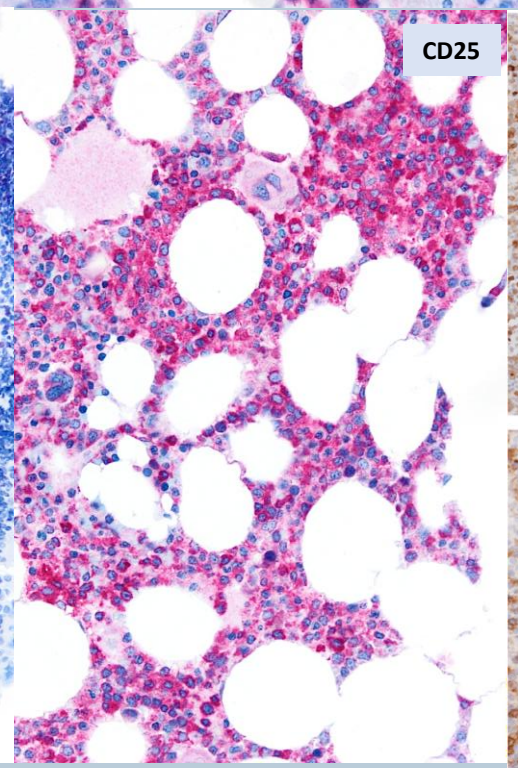
CD30 variable (up to 30%)

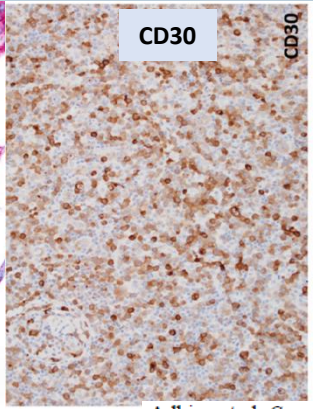


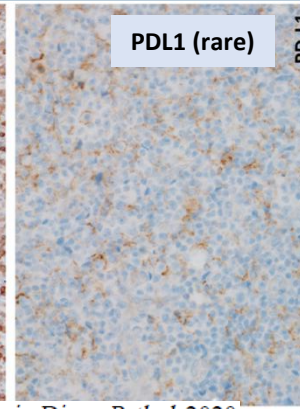




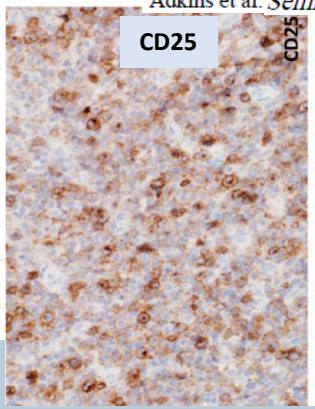


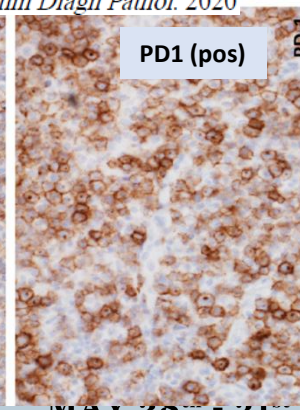






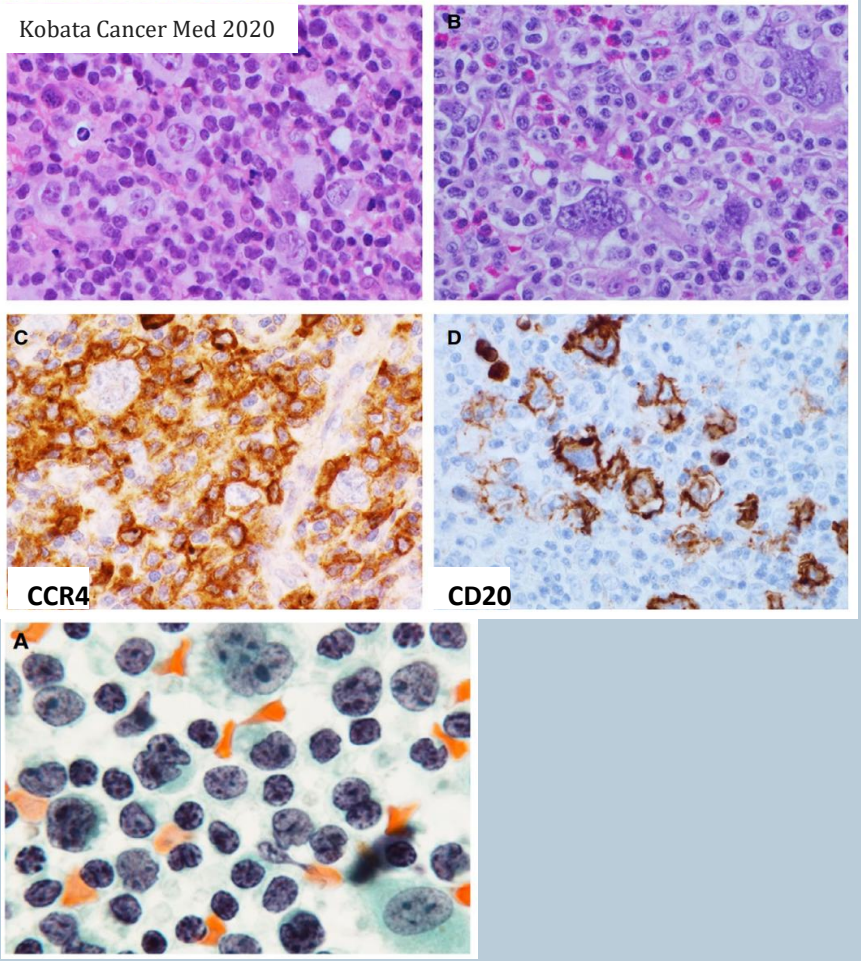
Adkins et al. Semin Diagn Pathol. 2020





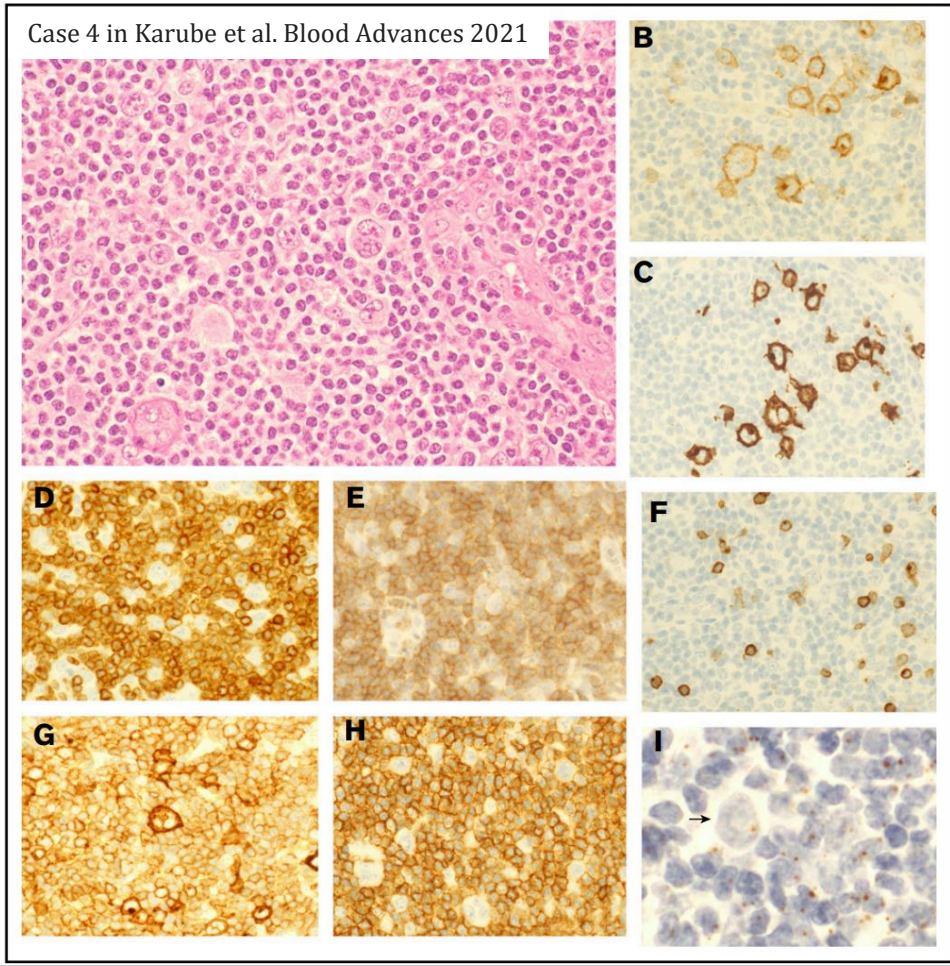
MAY 28 - 31

HL-like ATLL “conventional”



ATLL & HRS cells

HL-like ATLL «unconventional»



Atypical T-cell proliferation

defective phenotype (CD4+/CD25+/CCR4+), high KI67 (60-80%), TCR rearr. no/few B cells; HBZ/proviral HTLV1 DNA* positive/weakly pos

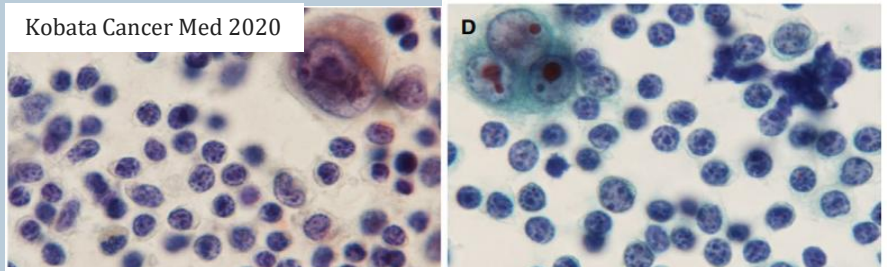
HRS cells : CD30+/CD15+, **B+-/Pax5+, EBV+-, HBZneg** Possible as precursor /preovert lesion	HRS cells: CD30+/CD15+, **B- (Pax5neg), EBV-, HBZpos**

Oshima Cancer Science 2007; Oshima Cancer 1991; Oshima Int J Cancer 1997; Oshima Int J Cancer 2003; Venkataram Hum Pathol 2012; Kobata Cancer Med 2020; Karube Blood Advances 2021; *Southern Blot or ISH

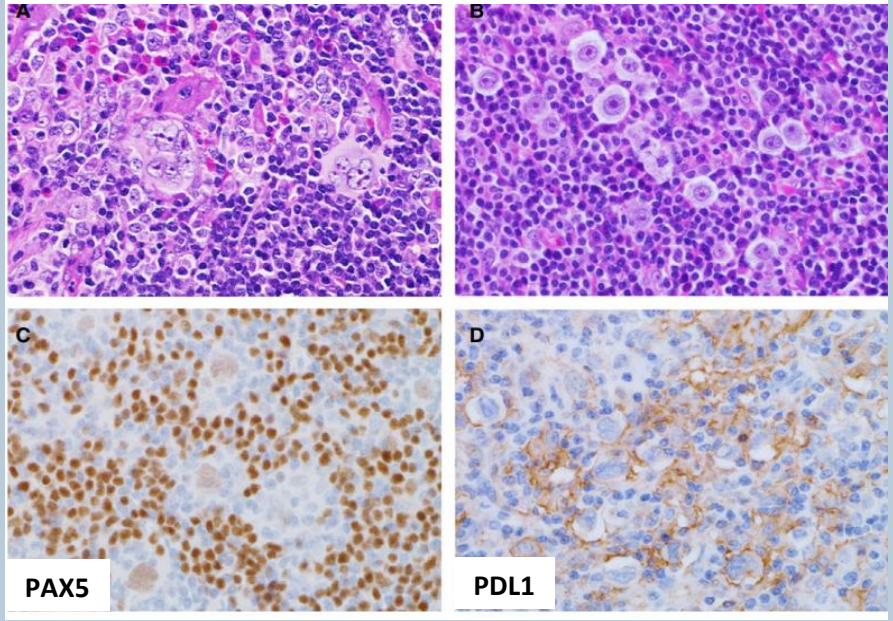
Classic Hodgkin Lymphoma in HTLV1 carriers

ATLL
&
HRS cells

Kobata Cancer Med 2020

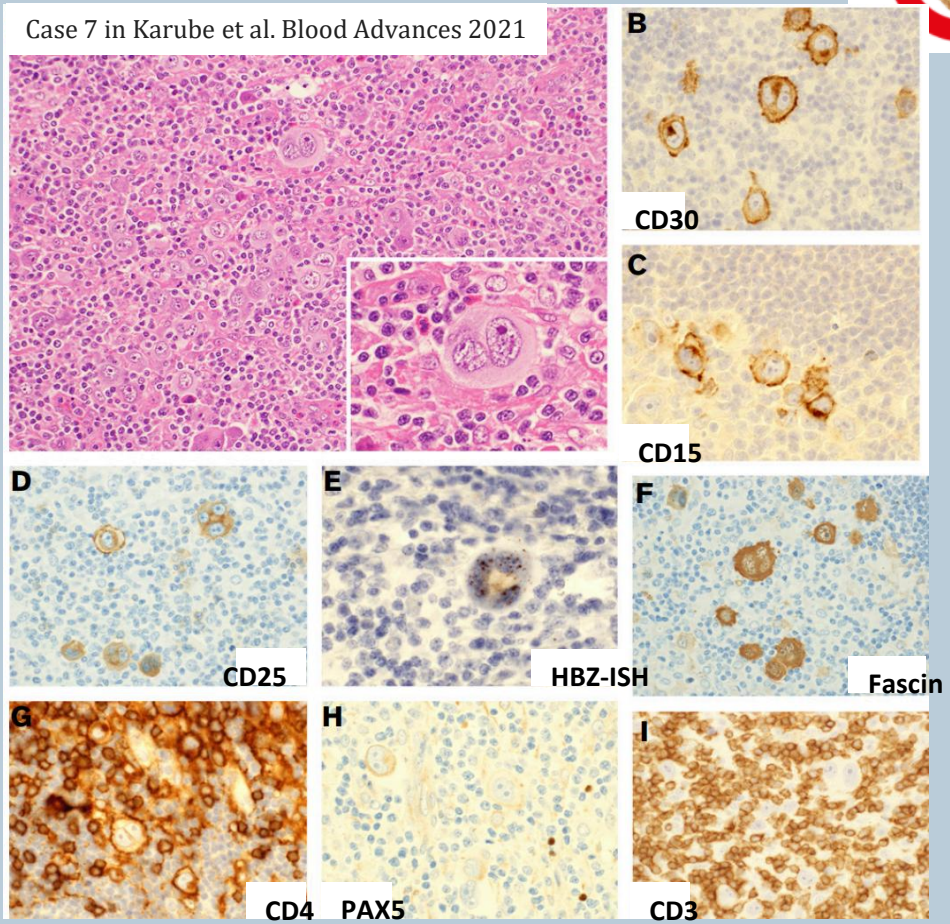


Kobata et al. Cancer Med 2020



CHL-like lesion in HTLV1 carriers

Case 7 in Karube et al. Blood Advances 2021



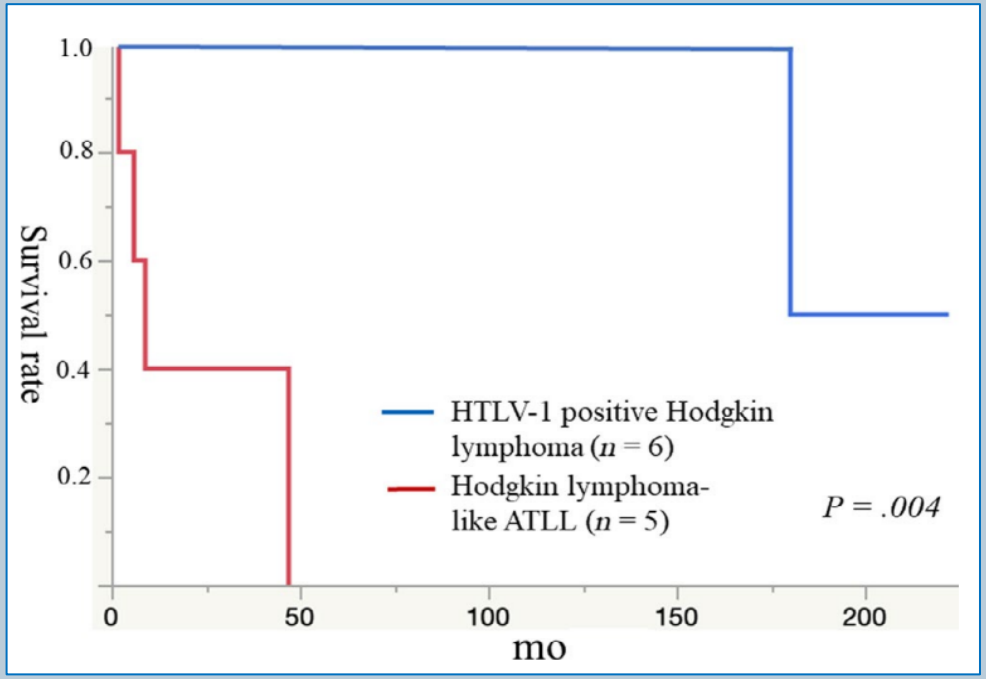
Typical T lymphocytes likely/definitely reactive

T-markers preserved, CD4>CD8/CD4=CD8, CD25-/CCR4-, KI67 low/mod., TCR WT; HBZ/proviral HTLV1 DNA*neg or weaker than classic ATLL

HRS cells : CD30+/CD15+, **B+-/Pax5+, EBV+-, HBZneg**

HRS cells: CD30+/CD15+, **B- (Pax5neg), EBV-, HBZpos**
Another precursor lesion?

Oshima Cancer Science 2007; Oshima Cancer 1991; Oshima Int J Cancer 1997; Oshima Int J Cancer 2003; Venkataram Hum Pathol 2012; Kobata Cancer Med 2020; Karube Blood Advances 2021; *Southern Blot or ISH



Kobata Cancer Med 2020

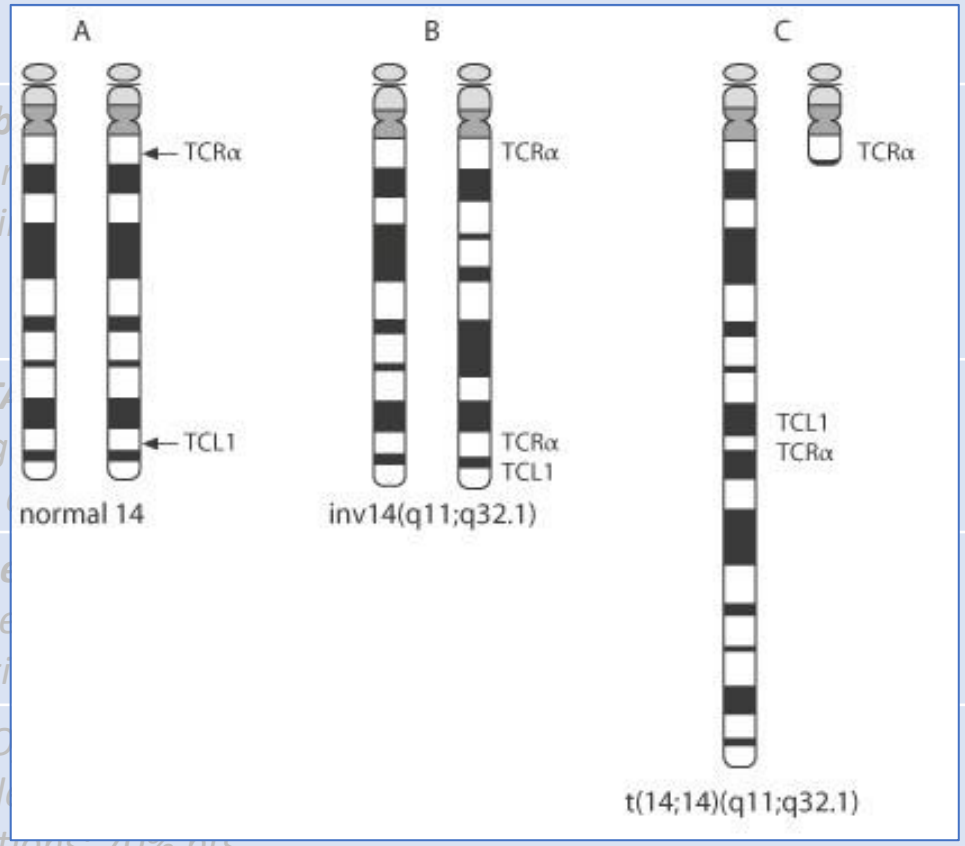
TPLL	HTLV1-ALL	HSTCL
TCR: almost invariably upregulated gene: defined as initiating event inv(14)(q11q32) or t(14;14)(q11;q32) involving the TCR alpha/delta gene locus (TRA/TRD) at 14q11 and the TCL gene cluster at 14q32.1. Few alternative translocations t(X;14)(q28;q11) (TRA/TRD; MTCP1 gene at Xq28; encodes a TCL1A paralog) promotion of cell proliferation (activate Akt, enhances Akt1 kinase activity, promotes nuclear transport)	***Tax mediated alterations*** *NK-KappB (Canonical&non-canonical)* *Inhibit anti-NF-KappaB mechanisms* *Inhibit proteasome degradation*	***i(7q) or ring chr7*** *25%-68%, likely secondary event* *•can occur with trisomy 8* *•only known driver cytogenetic events*
perturbed responses to DNA damage •>85% cases with mono-allelic deletion or mutation of ATM (11q22.3); TP53 is mostly unmutated •germline ATM defects: high occurrence of TPLL		***trisomy 8*** *8%-53%; likely primary event* *•Can occur with i(7q)*
JAK/STAT signaling pathway •JAK3 gain-of-function mutations (highest frequency); •STAT5 and JAK1 genomic losses	***STAT3 mutation*** *more frequent in indolent ATL*	***STAT3*** *mutations in 10%;* ***STAT5B*** *mutations in 30%* *•Almost always mutually exclusive;* *•oncogenic driver mutations*
Epigenetics massive epigenetic reprogramming with •mutations in modifiers (e.g. EZH2, TET2, KMTs)	***genetic and epigenetic abnormalities targeting antigen presentation machinery*** *90% of cases related to immune evasion*	***Chromatin modifers*** *SETD2, INO80, TET3, and SMARCA2: 62%* *SETD2 most commonly mutated in 25% (loss-of-function mutations that occur in biallelic fashion)*
•Gains Of chromosome 8q (AGO2 at 8q24.3); •Complex karyotypes (≥3 structural or numerical cytogenetic aberrations: 70% pts	***chemokine receptors*** *CCR4*	***Mutations in PIK3CD***

TPLL

TCR:

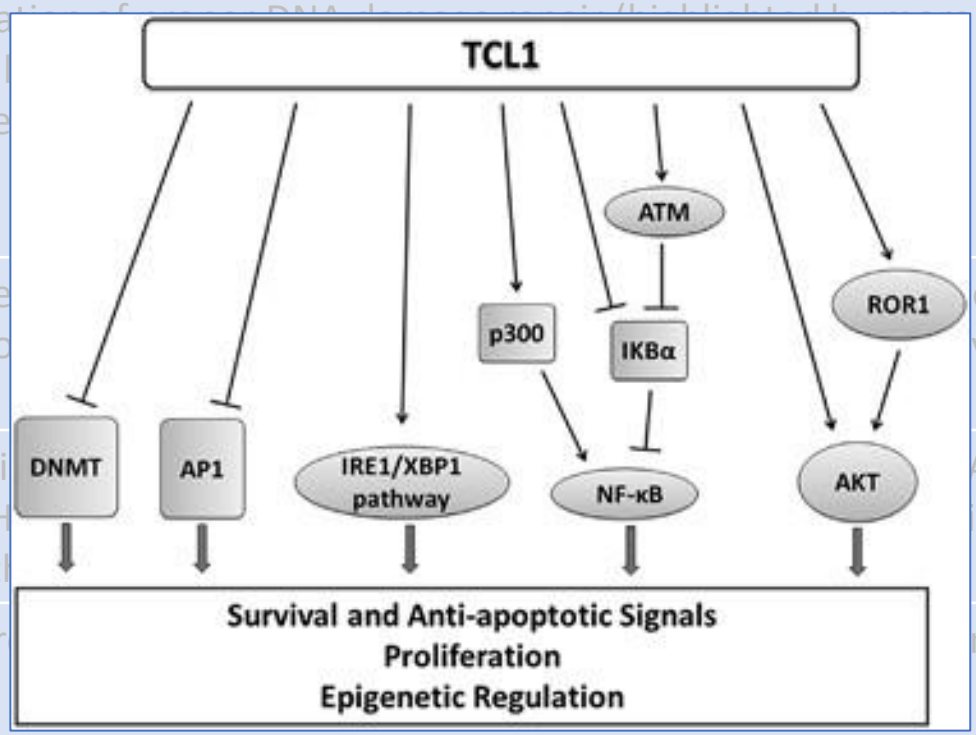
almost invariably upregulated gene

•inversions or translocations of TCL1A (at 14q32.1) or MTCP1 (atXq28) to 14q11.2 at TRA/T-cell Receptor alfa/delta gene

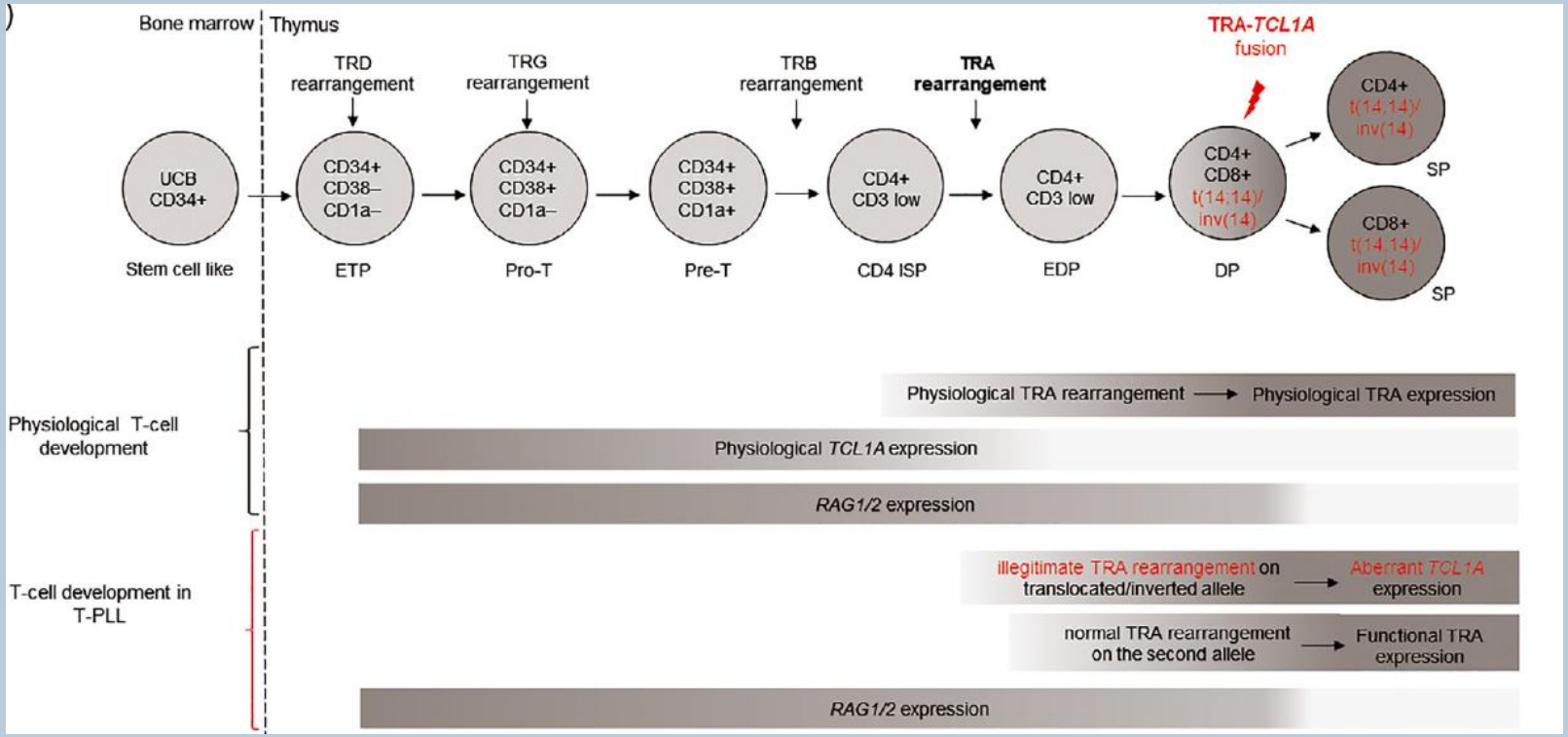


>95% T-PLL; aberrant expression of the proto-oncogenes TCL1A or MTCP1; transition of naïve T-cells into an expanding pool of memory T-cells is accelerated

- promotion of cell proliferation through activation of the protein kinase B Akt (of which it is a cofactor), enhancement of Akt1 kinase activity, promotion of its nuclear transport.



TPLL	
TCR: *almost invariably upregulated gene* *•inversions or translocations (juxtapose TCL1A (at 14q32.1) or MTCP1 (atXq28) loci to 14q11.2 locus under control of highly active TRA (T-cell Receptor alfa/delta gene) gene enhancer elements*	>95% of T-PLL, aberrant constitutive expression of the proto-oncogenes TCL1A or MTCP1; transition of naïve T-cells into an expanding pool of memory T-cells is accelerated promotion of cell proliferation through activation of the protein kinase B (Akt); cofactor of Akt1, enhances Akt1 kinase activity, and promotes its nuclear transport.
perturbed responses to DNA damage *•>85% mono-allelic deletion or mutation of ATM (11q22.3);* *•germline ATM defects: high occurrence of TPLL*	➢ dysregulation of proper DNA damage repair (highlighted by more complex karyotypes in ATM deleted) ➢ downstream effector of ATM, p53, is only disrupted in a minority of T-PLL
JAK/STAT signaling pathway *•JAK3 gain-of-function mutations (highest frequency);* *•STAT5 and JAK1 genomic losses*	Inhibit negative regulators of this pathway (e.g. DUSP4, SOCS genes) basal phosphorylation of distal STAT5 is observed in virtually every T-PLL case
Epigenetics *massive epigenetic reprogramming with mutations in chromatin modifiers (e.g. EZH2, TET2, KMTs)*	changes in expression of frequently deregulated genes (e.g. TCL1A, MYC, EZH2, AGO2) ➢ additional ways of their deregulation beyond the genomic aberrations
Gains Of chromosome 8q (AGO2 at 8q24.3); *Complex karyotypes (≥3 structural or numerical cytogenetic aberrations: 70% pts*	Overexpression of AGO2, which centrally regulates RNA interference

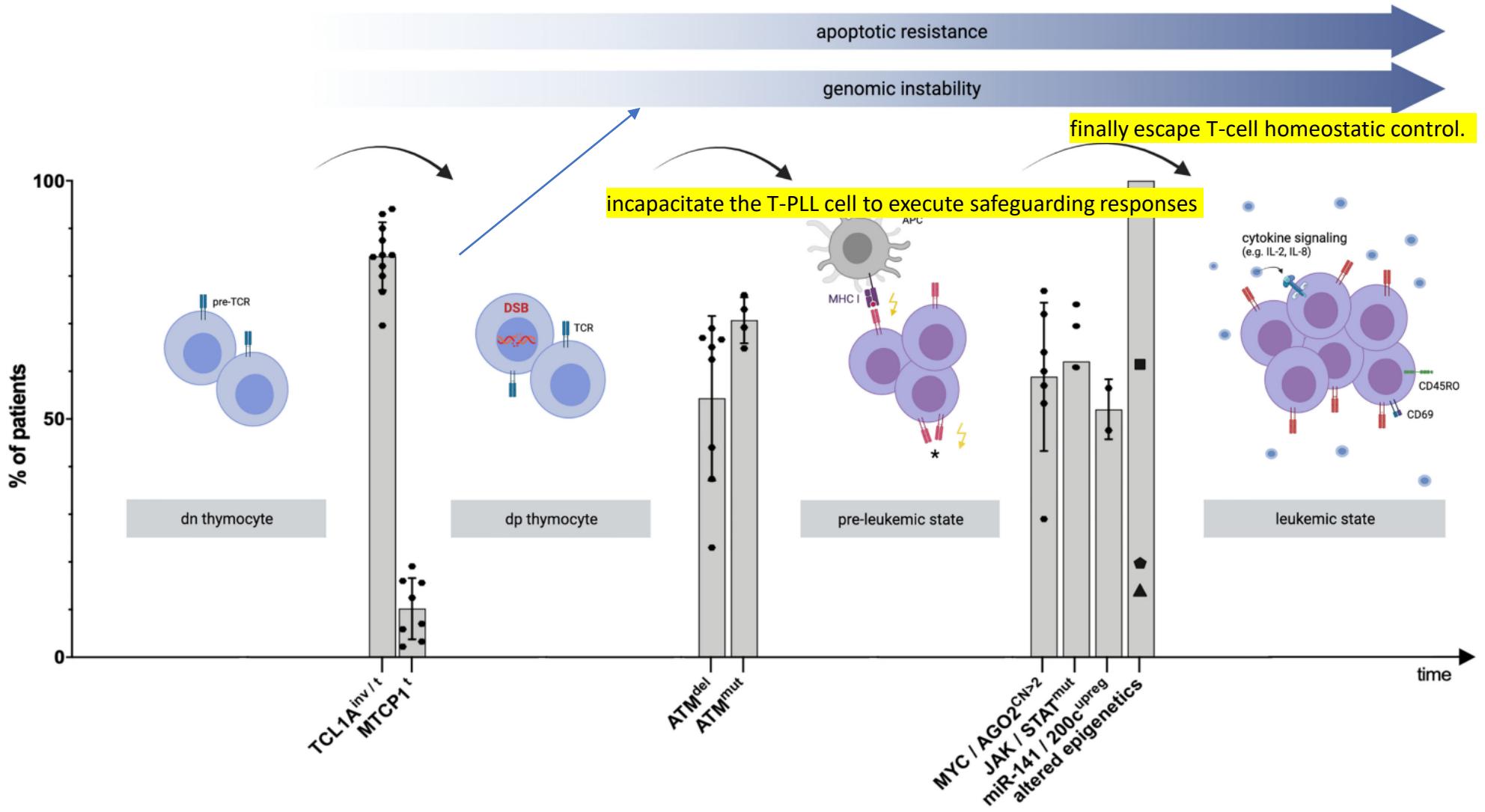


- *TCL-1 is expressed in normal immature B and T cells and also associated with the MTCP1 gene) and silenced after TCR-A rearrangement (last in TCR ontogenesis)*
- *the oncogenic translocation between TRA/TCL1A or MTCP1 genes occur during opening of the TRA locus, at transition between SP/CD4+ to early DP thymocyte and just before TCL1A expression is silenced.*
- *As result 1) TCL1 is overexpressed 2) TCR-A rearrangement not productive.*
- *A correct TCR-A rearrangement is produced and functional on the second allele that explain why the cell can mature to later stages of differentiation and why TCR-mediated activation is the key-genetic hallmark of TPLL*

Reconstruction of rearranged T-cell receptor loci by whole genome and transcriptome sequencing gives insights into the initial steps of T-cell prolymphocytic leukemia

Paurnima Patil[1] | Agata Cieslak[2] | Stephan H. Bernhart[3] | Umut H. Toprak[4,5,6] | Rabea Wagener[1,7] | Cristina López[1,7] | Laura Wiehle[1] | Susanne Bens[1,7] | Janine Altmüller[8] | Marek Franitza[8] | Ingrid Scholz[9] | Sandrine Jayne[10] | Matthew J. Ahearne[10] | Annika Scheffold[11] | Billy M. C. Jebaraj[11] | Christof Schneider[11] | Dolors Costa[12] | Till Braun[13] | Alexandra Schrader[13] | Elias Campo[12] | Martin J. S. Dyer[10] | Peter Nürnberg[8] | Jan Dürig[14] | Patricia Johansson[14] | Sebastian Böttcher[15] | Matthias Schlesner[4] | Marco Herling[13] | Stephan Stilgenbauer[11] | Elizabeth Macintyre[2] | Reiner Siebert[1,7]

TPLL : possible pathogenetic hypothesis

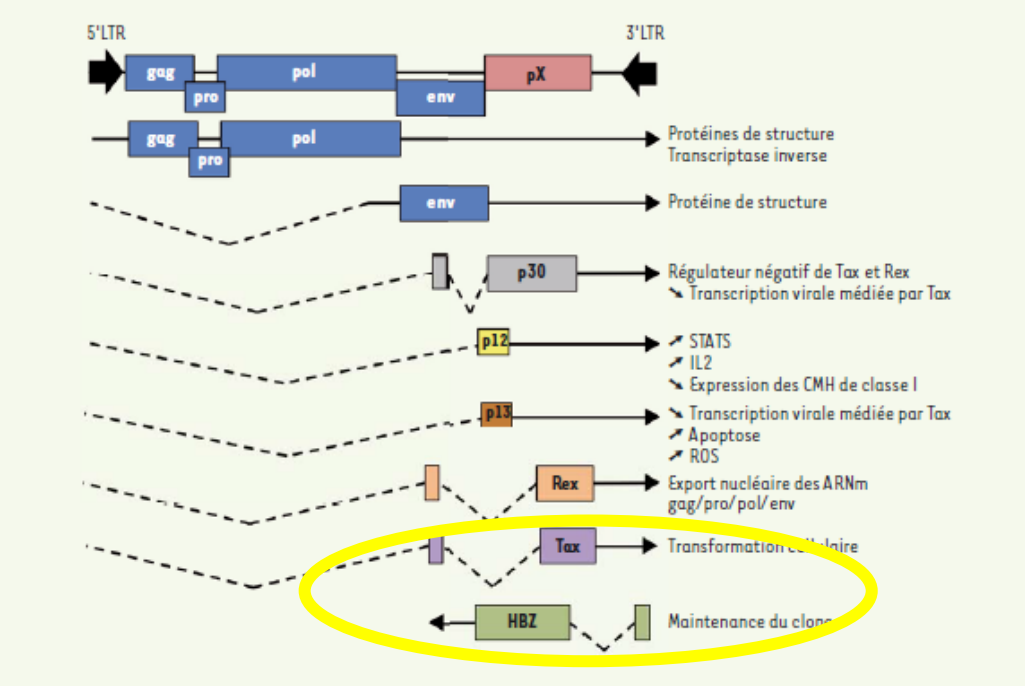


Braun et al. Frontiers in Oncology 2021

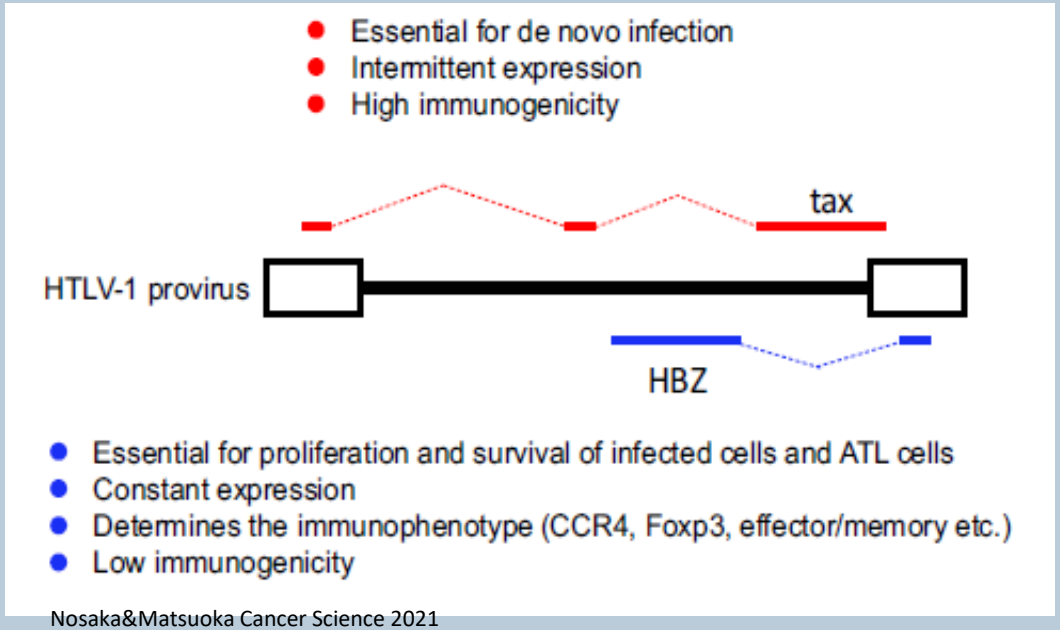
HTLV1-ATLL

Tax mediated alterations

NK-KappB (Canonical&non-canonical), Inhibit anti-NF-KappaB mechanisms, Inhibit proteasome degradation



Couronné et al. Médecine/sciences 2015

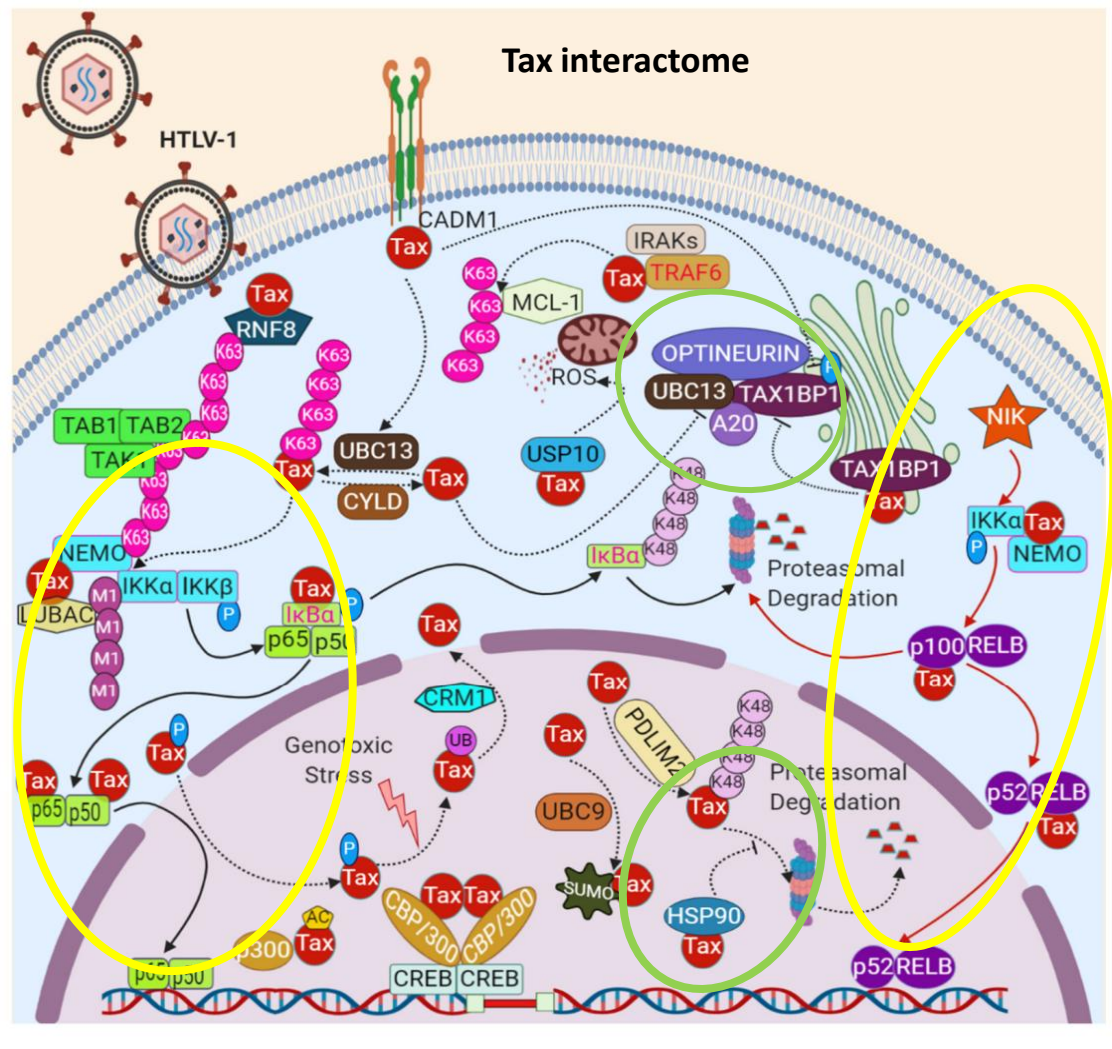


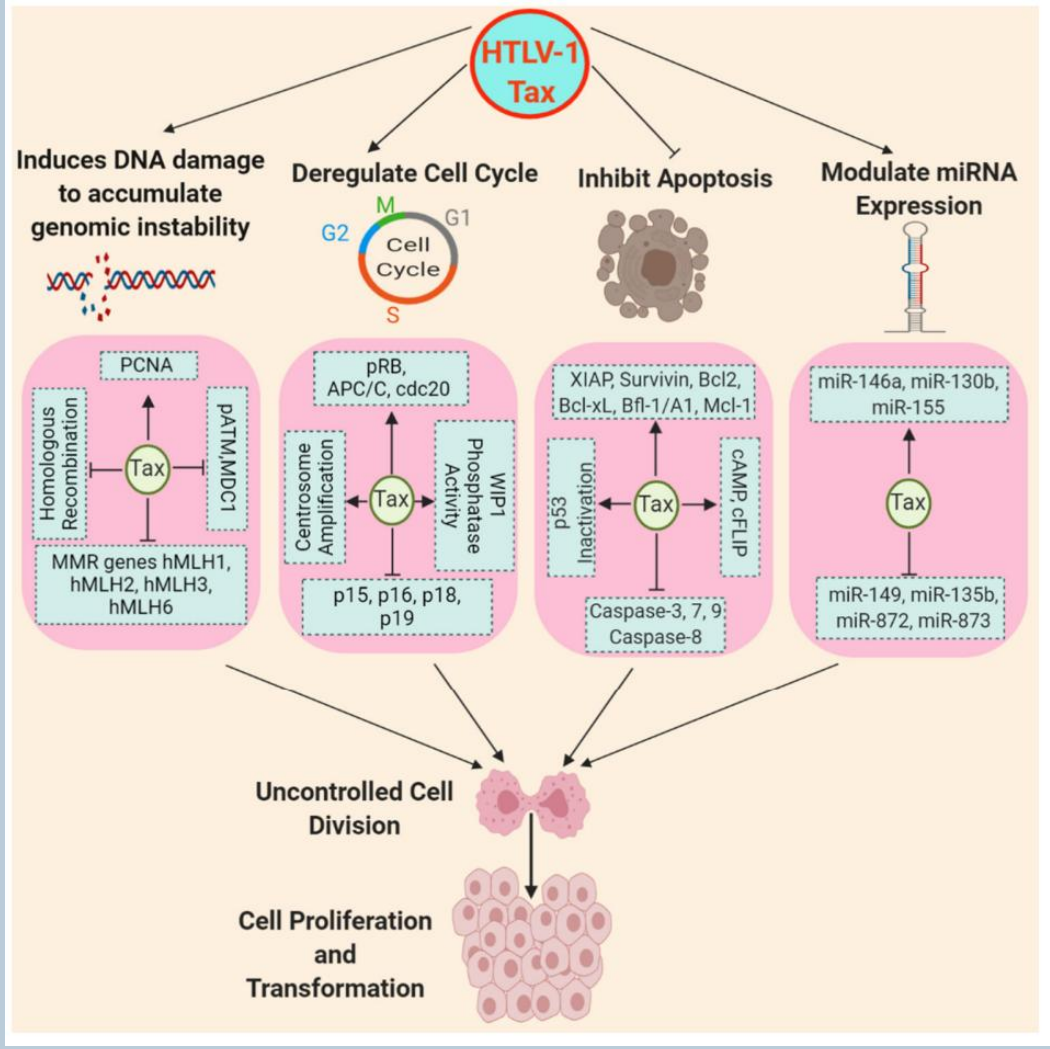
Nosaka&Matsuoka Cancer Science 2021

- HTLV1 infection is the primary event detected in cells from virtually all cases (exceedingly rare exceptions)
- Infection mostly contracted at birth; 2–5% infected individuals develop aggressive ATLL, 40–60 years after infection (>remain asymptomatic)

Multiple factors at play for ATLL development (virus + immunesuppression + additional genetic events + immune evasion)

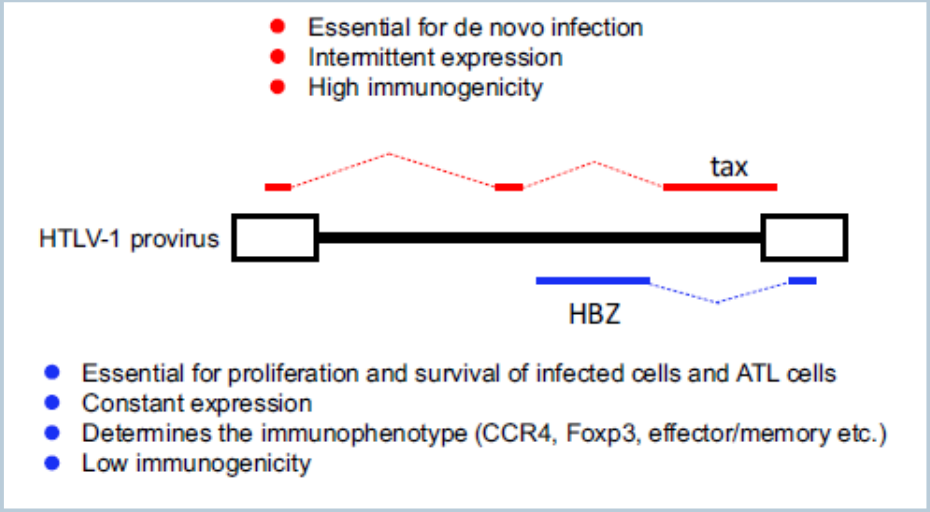
- **TAX** and **HTLV-1 bZIP factor (HBZ) :** critical proteins for the infection and leukemogenesis with different roles and different expressions

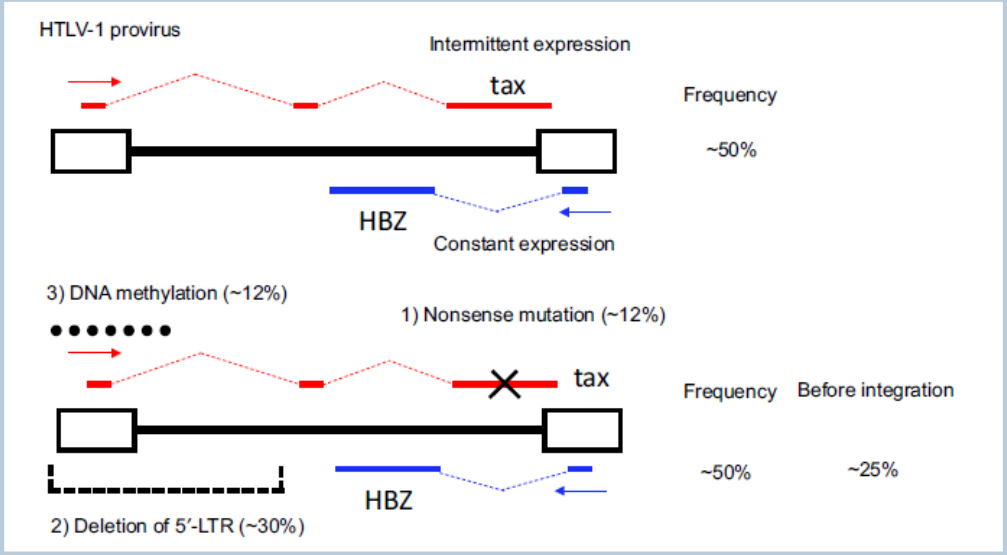




Tax induces a profound perturbation of the cell homeostasis driving the activation and/or silencing of different cell mechanisms

Mohanty & Harhaj Pathohens 2020





HTLV1 related immunosuppression

Unknown molecular events driving polyclonality to monoclonality

Genetic events that suppress Tax protein expression in >50% cases increasing immune evasion; additional transforming events

Polyclonal Tax+,HBZ+ CD4+ T cell expansion *Carriers*

Oligoclonal Tax+,HBZ+ CD4+ T cell LPD *Carriers*

Oligo/monoclonal Tax+,HBZ+ CD4+ T cell LPD *Carriers/indolent ATLL*

Monoclonal Tax-/-+, HBZ+ CD4+ T cell *ATLL*

Nosaka&Matsuoka Cancer Science 2021; Murata K et al Int Rev Immuno 2007

Large-scale integrated genetic analysis ***unexpected complexity*** *of cellular gene alterations in ATL, with predominance of gain-of-function mutations*

Chemokine receptor	*CCR4*	31%
	CCR7	11%
	GPR183	7%
Tumor suppressor	*TP53*	25%
	CDKN2A	22%
	TP73	1%
Transcriptional regulation	*IRF4*	16%
	IRF2BP2	10%
	GATA3	14%
	PRDM1	12%
	IKZF2	4%
Other signaling	*NOTCH1*	10%
	STAT3	23%
Immune evasion	*PD-L1*	10%
	PDCD1	12%
	CD58	20%
	B2M	4%
	HLA-A	10%
	HLA-B	7%
	FAS	10%
Epigenetic regulation	*TET2*	11%
	DNMT3A	2%
	IDH2	2%
	EP300	5%

Kataoka & Koya
J Clin Experimental Hematopathology
2020

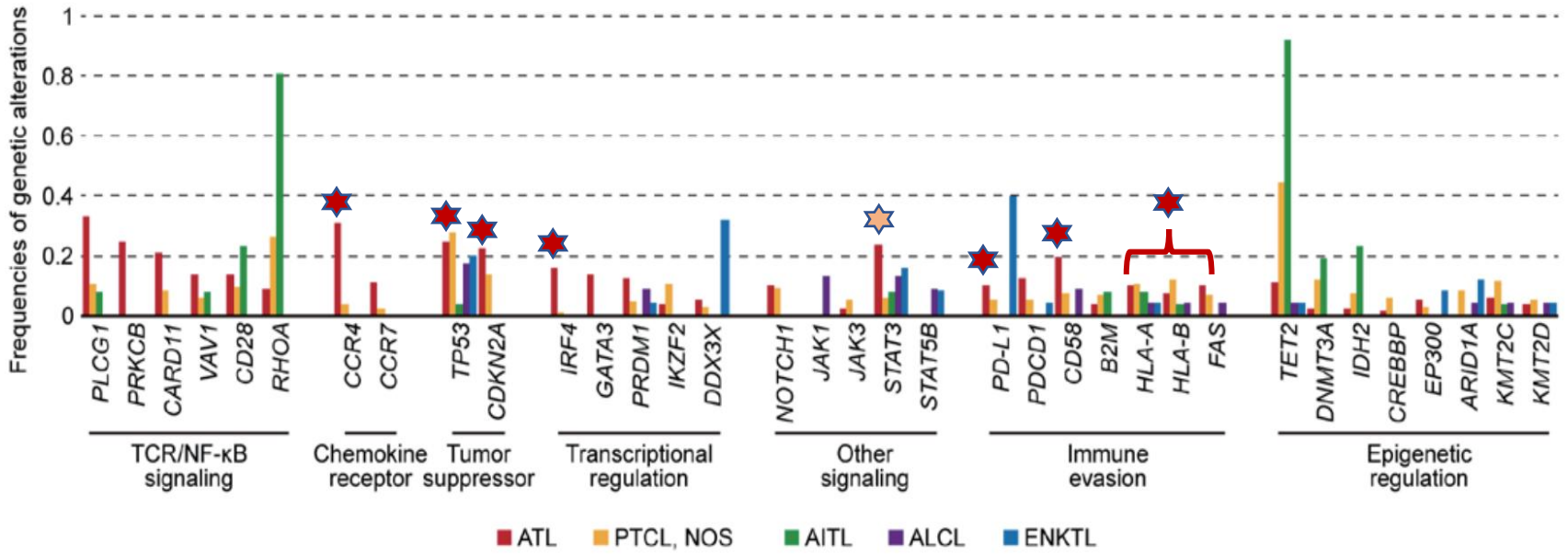


Fig. 2. Comparison of frequencies of genetic alterations among ATL (n = 81),[6] PTCL, NOS (n = 133),[27] AITL (n = 26),[27] ALCL (n = 23),[29] and ENKTL (n = 25)[31] analyzed by whole-exome or targeted sequencing.

predominance of gain-of-function mutations: CCR4 mutations; mutations&amplification IRF4-6p25 locus; STAT3 mutations; PDL1 expression amplification; Ag presentation through MHC class 1 (HLA-A, HLA-B and B2M): mutations or deletions and epigenetic regulation (hypermethylation) and T/NK cell-mediated immune response (CD58 and FAS): overall 90% of ATL

Kataoka & Koya J Clin Experimental Hematopathology 2020; Kogure & Kataoka Cancer Science 2017; Kataoka et al Nat Genet 2015

HSTCL: pathogenesis remains largely unknown

- ***Cluster separately from other PTCL*** **(NOS, AITL, NKTCL) but profile closer to NKTCL** (extranodal entity derived from cytotoxic cells) than to that of PTCL-NOS and AITL
- ***γδ and αβ HSTL cluster together***
- ***NK-cell associated molecules*** (NCAM1 and **CD244**) and ***NK –cell mediated cytotoxicity genes*** specifically overexpressed

Both variants derive from innate cell

- ***no oncogene or TSG has been identified*** **in HSTL, but several candidate genes are upregulated and potentially associated with pathophysiology of HSTL**
  oncogenes FOS, VAV3, MAF, BRAF, TCR signaling, cell cycle, sonic hedgehog GLI3, PRKAR2B, PRKACB, PRKAR1A; cell adhesion VCAM1, CD11d, ICAM1, tyrosine kinases (SYK), signal transduction SPRY2, RHOB, MAP4K3, SPRY1; sprouty regulation of tyrosine kinase pathways, WNT pathway FRZB, TCF7L2, BAMBI, TLE1, CTNNB1, APC, FZD5;

ABCB1/encoding for the p-glycoprotein multidrug transporter MRD
export drugs out of the cytoplasm

Cytarabine not affected by MRD: rationale for cytarabine-containing regimens

S1PR5 (sphingosine-1- phosphatase receptor 5): involved in T- and B-cell exit from lymphoid organs and NK cells homing to spleen

- **AIM1** tumour suppressor gene: dramatically downregulated by means of methylation

Might explain clinic pathologic features

- **SyK overexpressed** (not amplified or ITK-SYK fusion)
  normal mature T lymphocytes lack Syk expression; involved in BCR signaling

demethylating agents could reverse AIM1 function

potential usage of anti-SYk agent

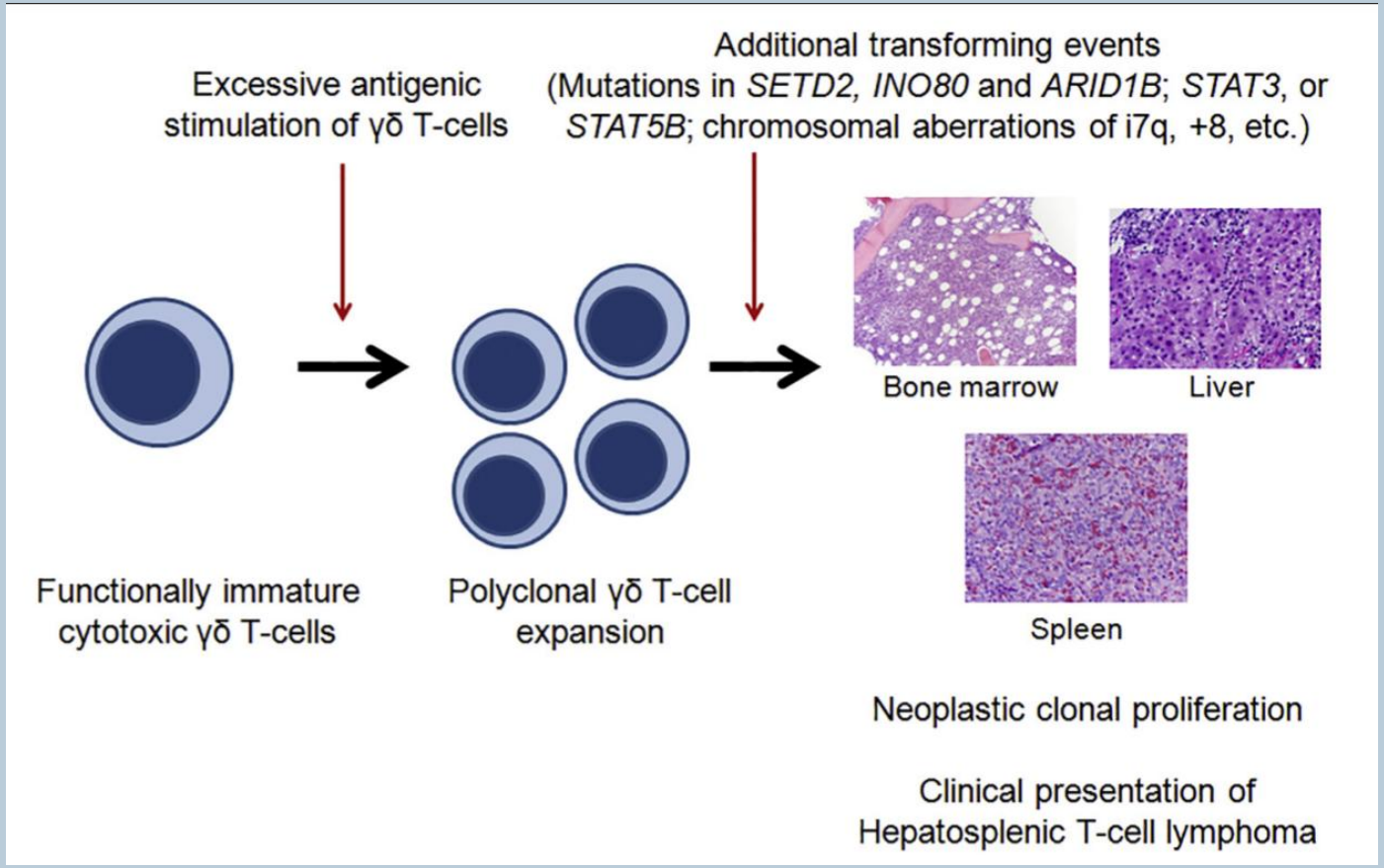
Travert et al. Blood 2012

i(7q) or ring chr7	▪ **25%-68%** ; can occur with trisomy 8 likely secondary event; can occur later at time of relapse or disease progression. ▪ not entirely specific (AML, ALL, MDS, WilmsT, few NKCL or ALCL) ▪ significant enrichment of genes of **apoptosis-related pathways**, overexpression of putative oncogene PTPN12; down regulation of 7p genes (CYCS and IKZF1: regulation of apoptosis, HUS1 and CBX3 (DNA repair)
trisomy 8	▪ 8%-53%; likely primary event; can occur with i(7q)
STAT3 mutations in 10% (mutated in other γδ TCL) **STAT5B** mutations in 30% (not mutated in >αβ TCL)	▪ Almost always mutually exclusive; occurring in the SH2 domains Enable STAT5 phosphorilation; JAK/STAT pathway activation
Mutations in PIK3CD	Activate PI3K/AKT signaling
Chromatin modifiers	▪ SETD2, INO80, TET3 62% fair **SETD2** : TSG; most commonly mutated (25% cases) loss-of-function in biallelic fashion proliferation as major oncogenic process affected by SETD2 loss; not specific for HSTCL (MEITL, subset of acute leukemias; clear cell Carcinoma) ▪ SMARCA2 (mostly observed in B-CL)

•Potential usage of STAT5B inhibitor (with CAS 285986-31-4)
•Potential usage of PI3K inhibitor (idelalisib)

Yabe et al. Human Pathology 2018; Travert et al. Blood 2012; ***Mc Kinney et al Cancer Discovery 2017***

Yabe et al. Human Pathology 2018



Expansion of GD-T cells has been reported particularly in patients after kidney transplantation, systemic lupus, Hodgkin lymphoma, or malaria and, more recently, also after treatment with anti-TNF agents: Belhadj K et al. Blood. 2003; Kelsen J et al PLoS One. 2011

European Association for Haematopathology

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MAY 28th - 31st

Thank you

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