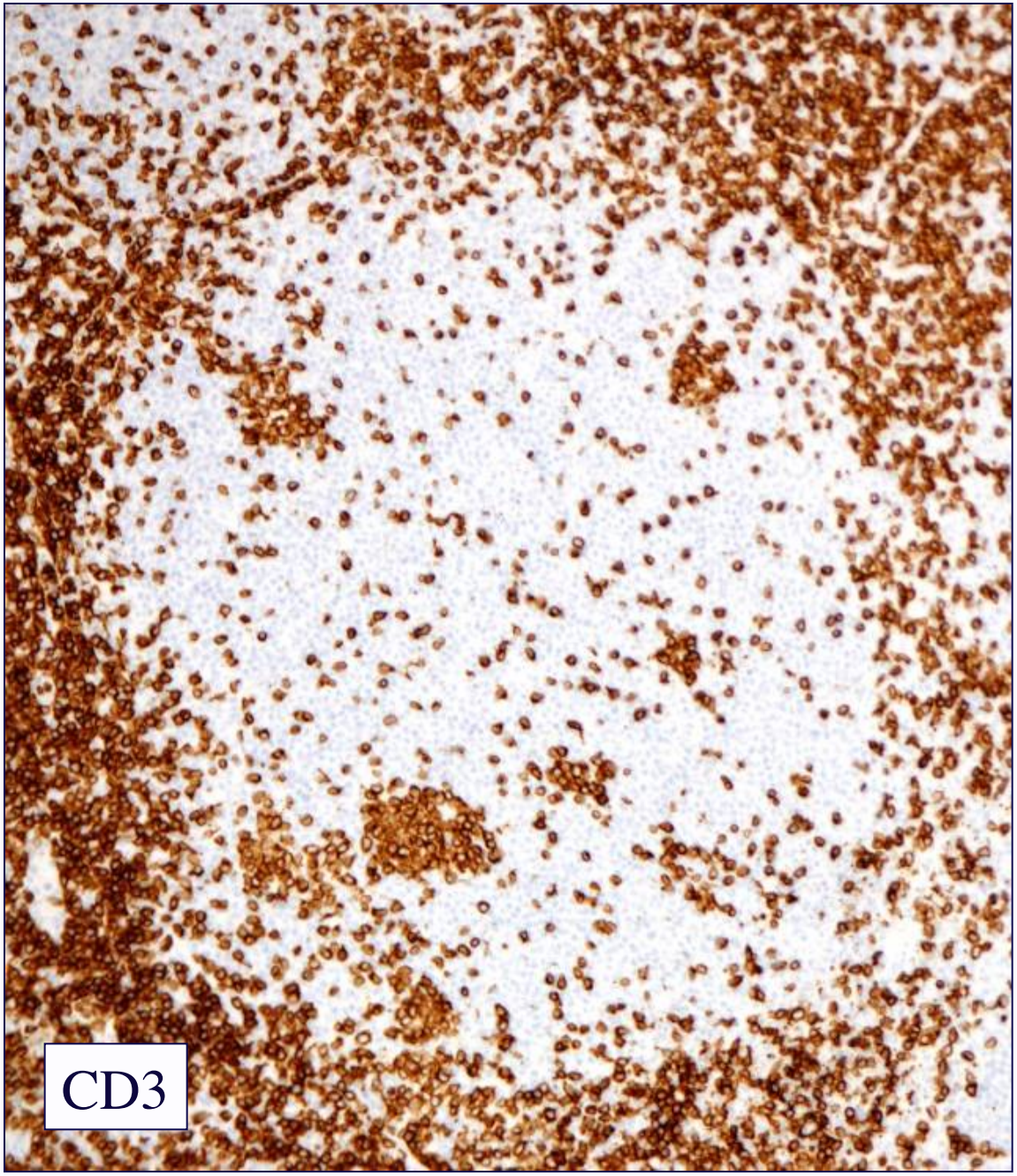
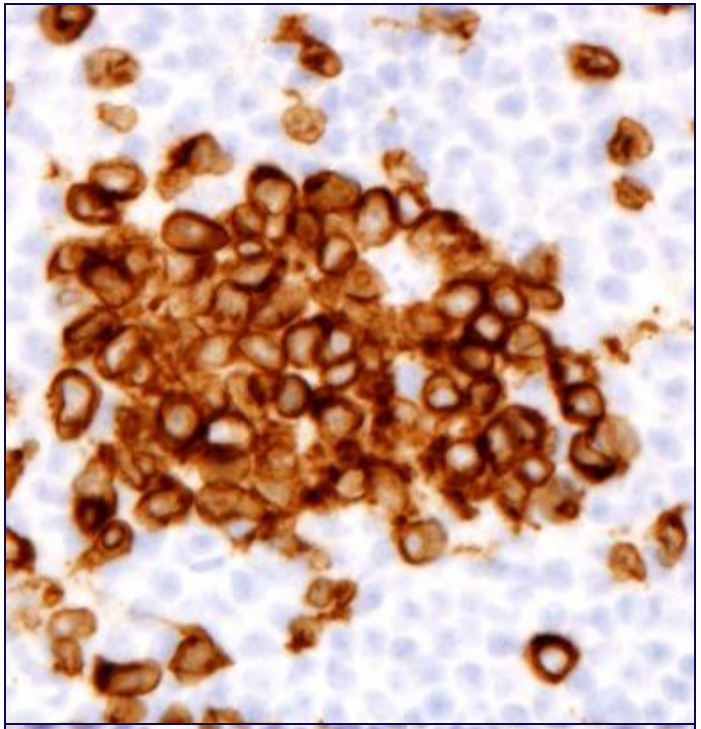
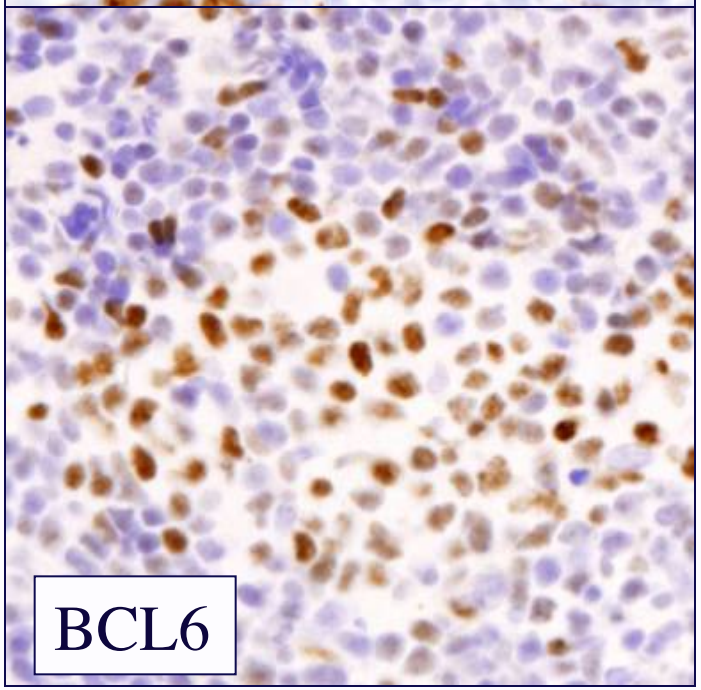
Follicular Variant of PTCL

de Leval AJSP 2001

- Intrafollicular T-cell lymphomas derived from T_{FH} cells
- Usually CD4+, BCL-6+, CD10+
- Clusters of clear cells within GCs
- May simulate follicular lymphoma
- Lack typical clinical findings of AITL


CD3




BCL6

Genomic Findings in AITL and TFH derived lymphomas

- 20-45% mutations in *IDH2 (*isocitrate dehydrogenase2) and *TET2 in AITL*
  - *Genes involved in pathogenesis of gliomas, AML*
- *TET2* mutations also seen in other PTCL of TFH origin, including PTCL, follicular variant (up to 60%)
- *ITK/SYK* fusion mainly in PTCL, follicular variant

Lemonnier et al, Blood2012, Cairns et al Blood 2012; Couronne NEJM 2012; Streubel Leukemia 2006

Genotypic Analysis of AITL

TCR γ R (90 %)

Why is clonal TCR not detected in all cases?

- CD10+ T-cells may represent a minority of cells present in some cases
- Some cases may be misdiagnosed
  - Differential diagnosis of atypical paracortical hyperplasia and AITL a problem, especially in older series
- Small false negative rate by PCR

Genotypic Analysis of AITL

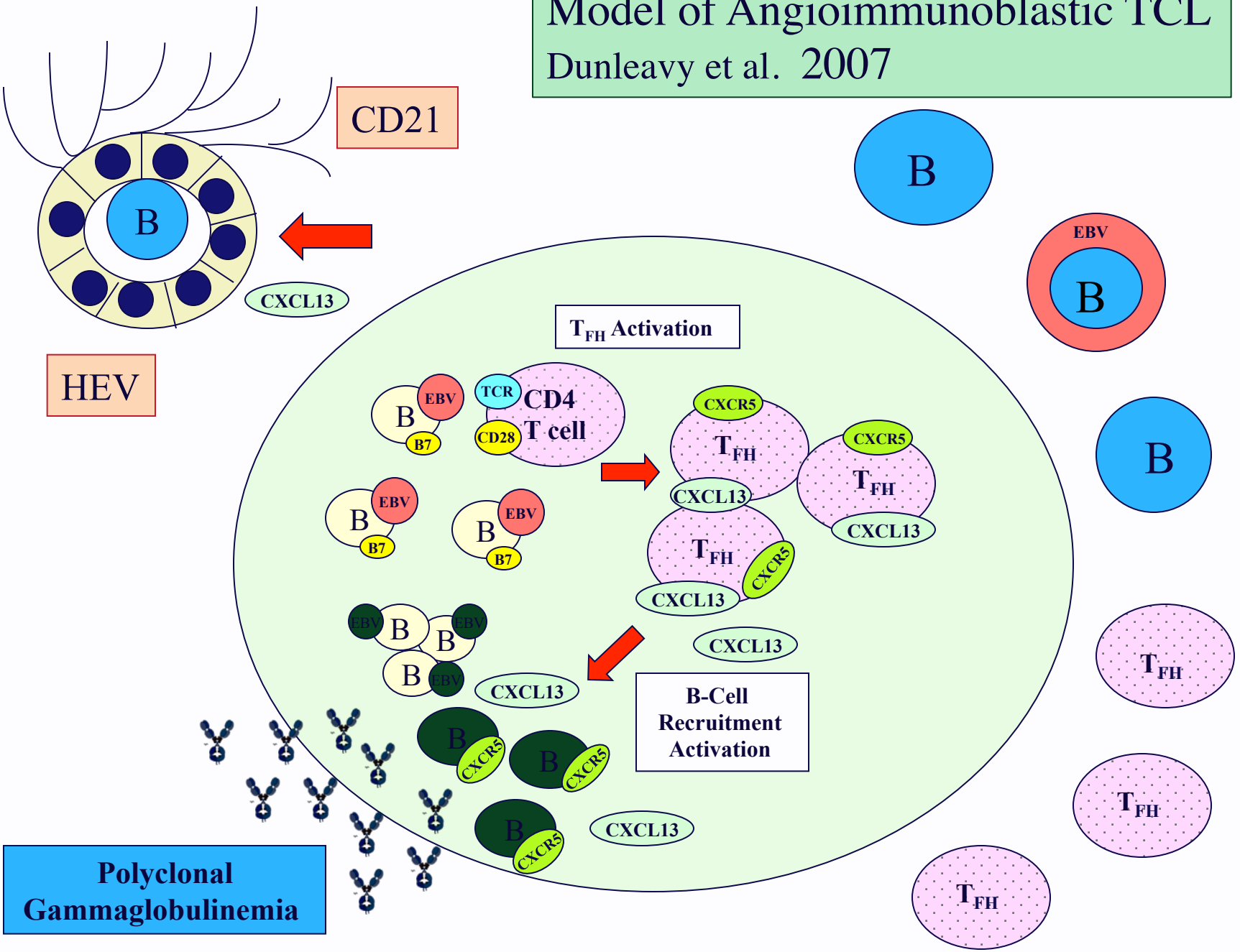
IgH R (10-40%)

Why does a T-cell lymphoma contain clonal B-cell expansion?

- B-cell/ plasma cell proliferation is a constant feature of AITL, may be monoclonal in some cases
- Expansion of EBV+ and EBV- B-cells may lead to B-cell clones

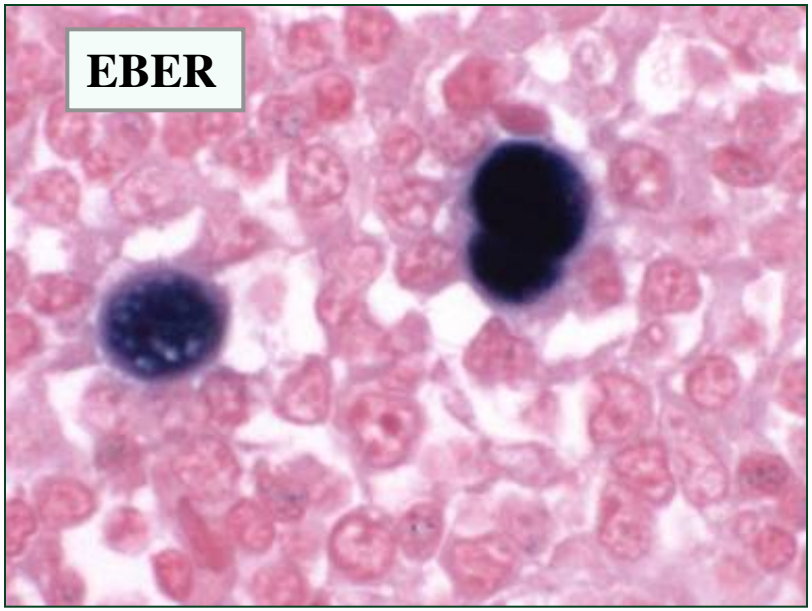
Model of Angioimmunoblastic TCL

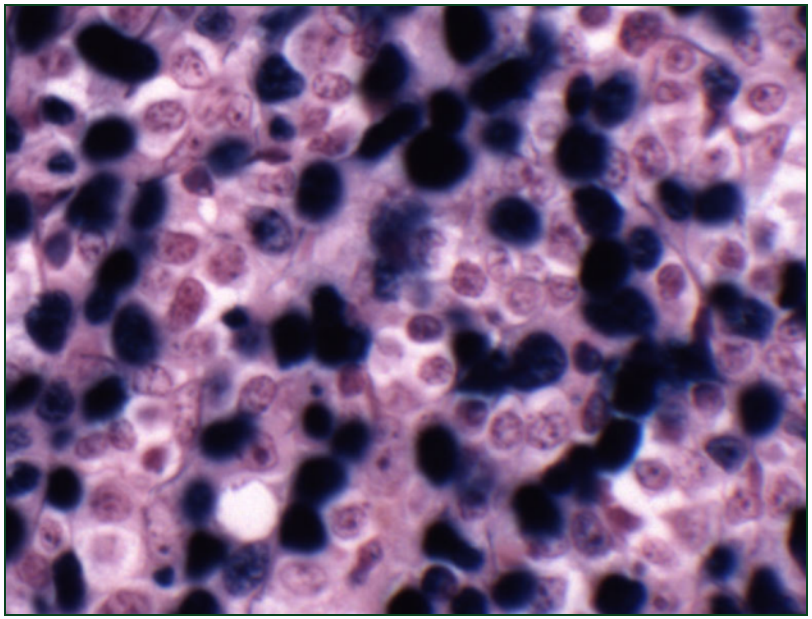
Dunleavy et al. 2007

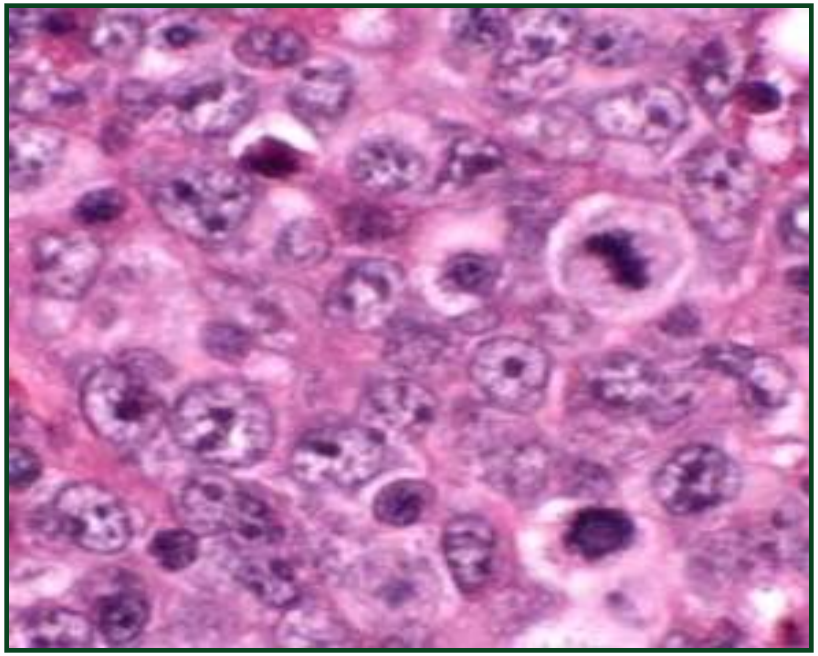


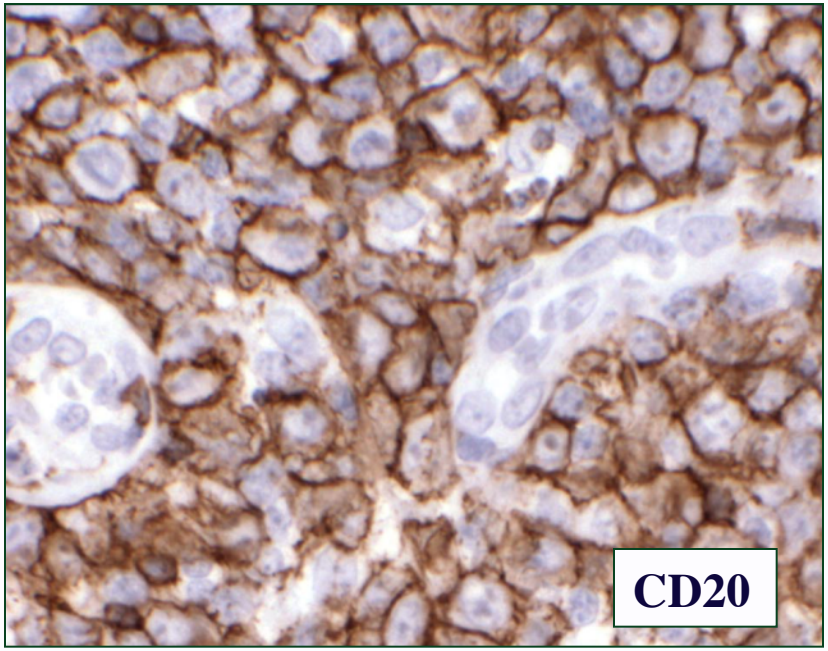
B-cell proliferations in AITL

- EBV-positive
  - Variable numbers of EBV+ blasts, may be dominant picture
  - Hodgkin/Reed-Sternberg like cells
- EBV-negative
  - B-immunoblasts
  - Polyclonal plasma cells
  - Monotypic/ Monoclonal plasma calls
  - Hodgkin/Reed-Sternberg like cells

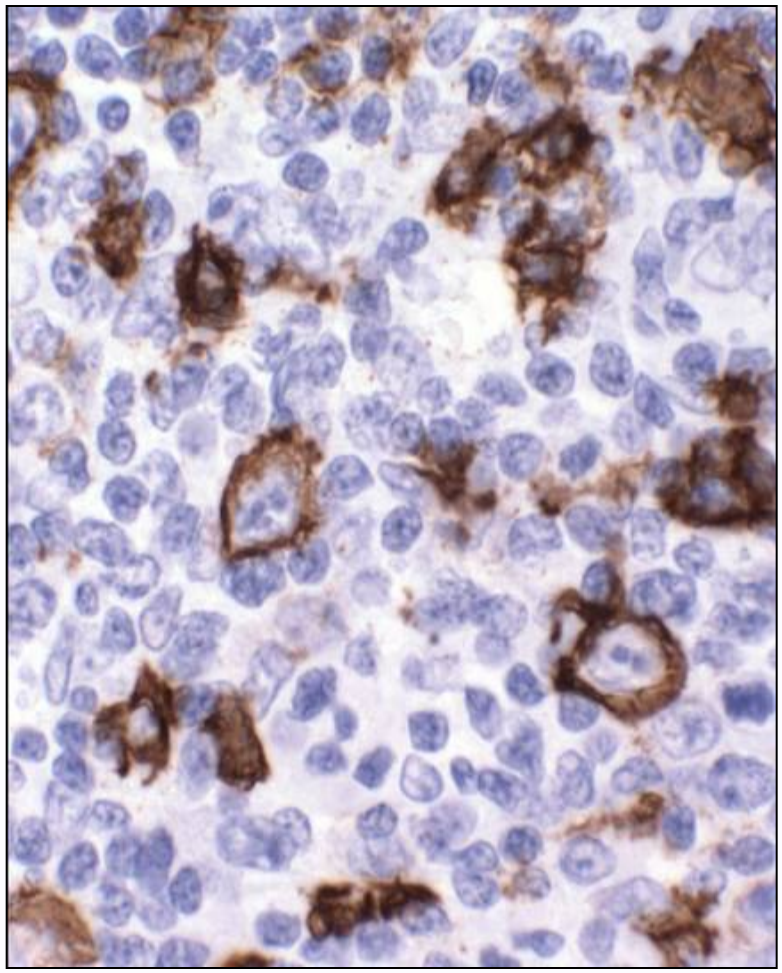

EBER



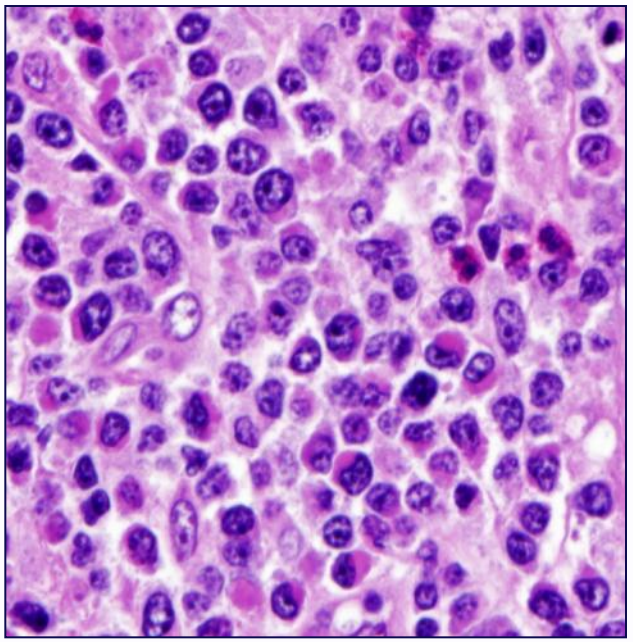


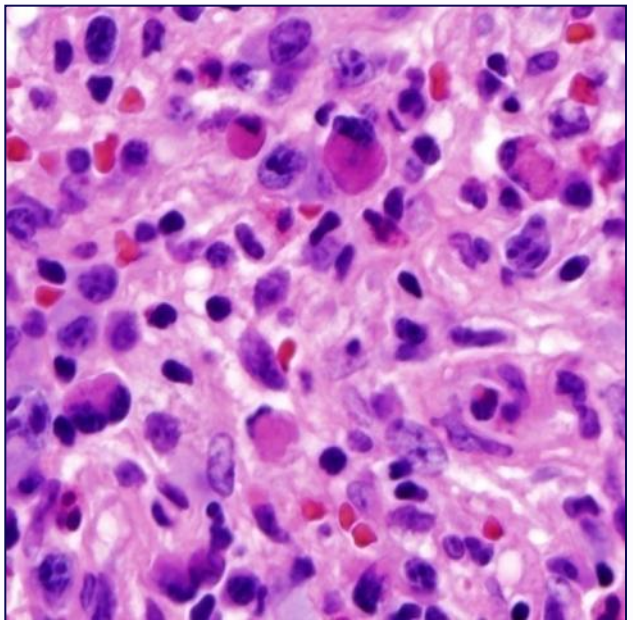

CD20

B-cell proliferations in Angioimmunoblastic T-cell lymphoma



CD20 + B-immunoblasts



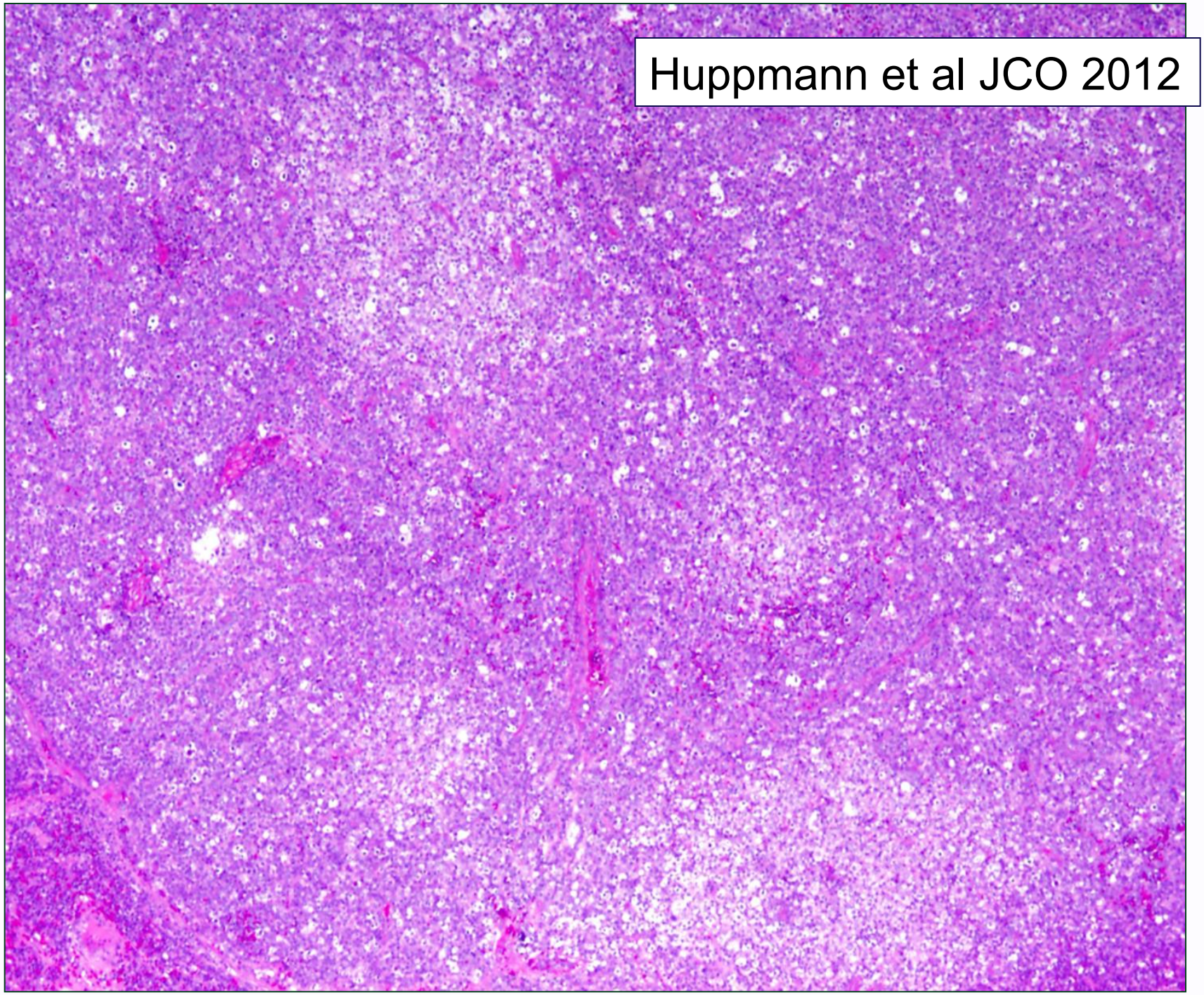


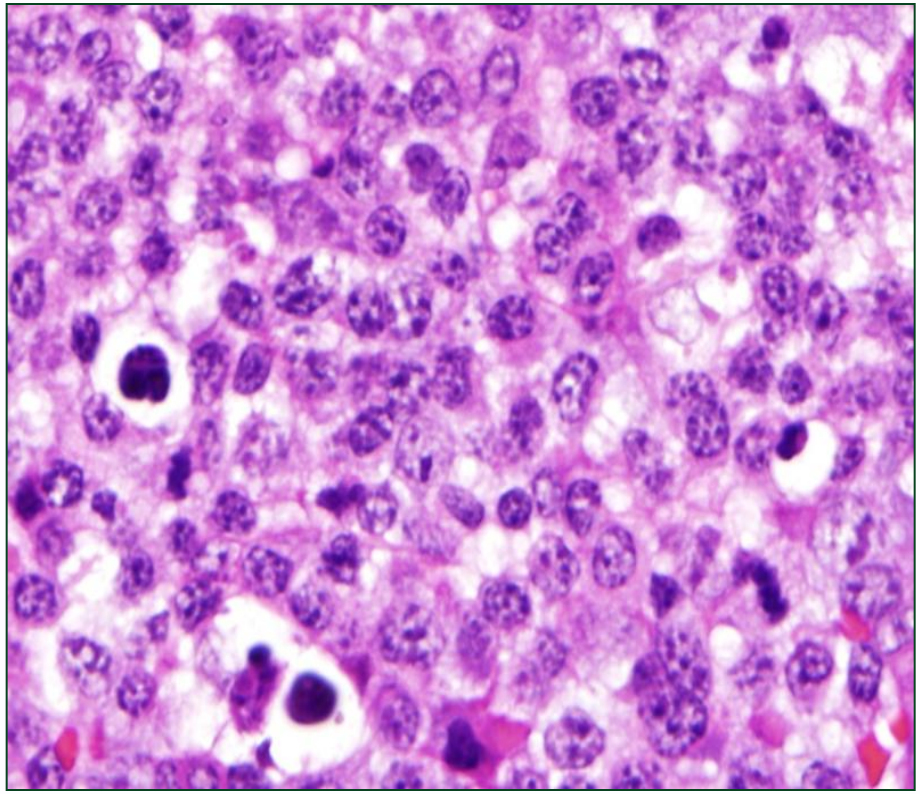
Plasma cells

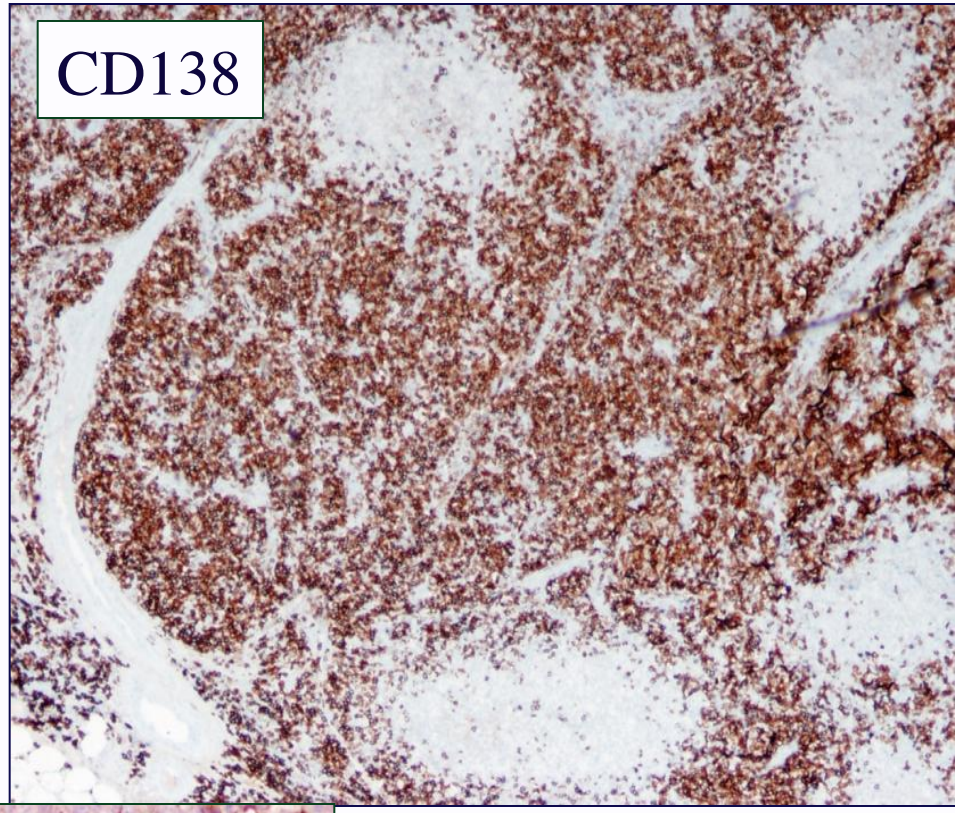
Often Abundant

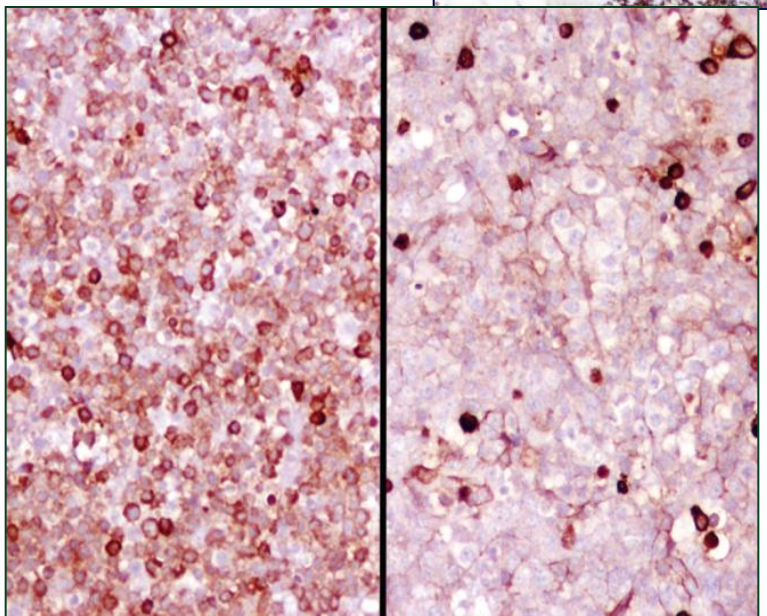
May be monoclonal & atypical

Balague et al. Am J Surg Path 2007


Huppmann et al JCO 2012







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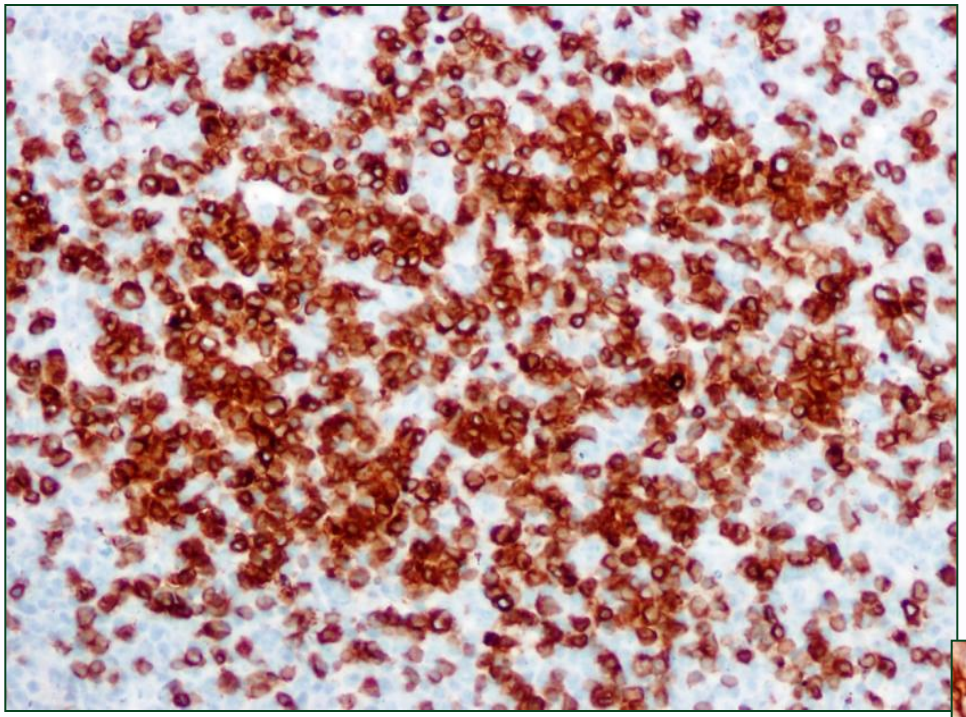

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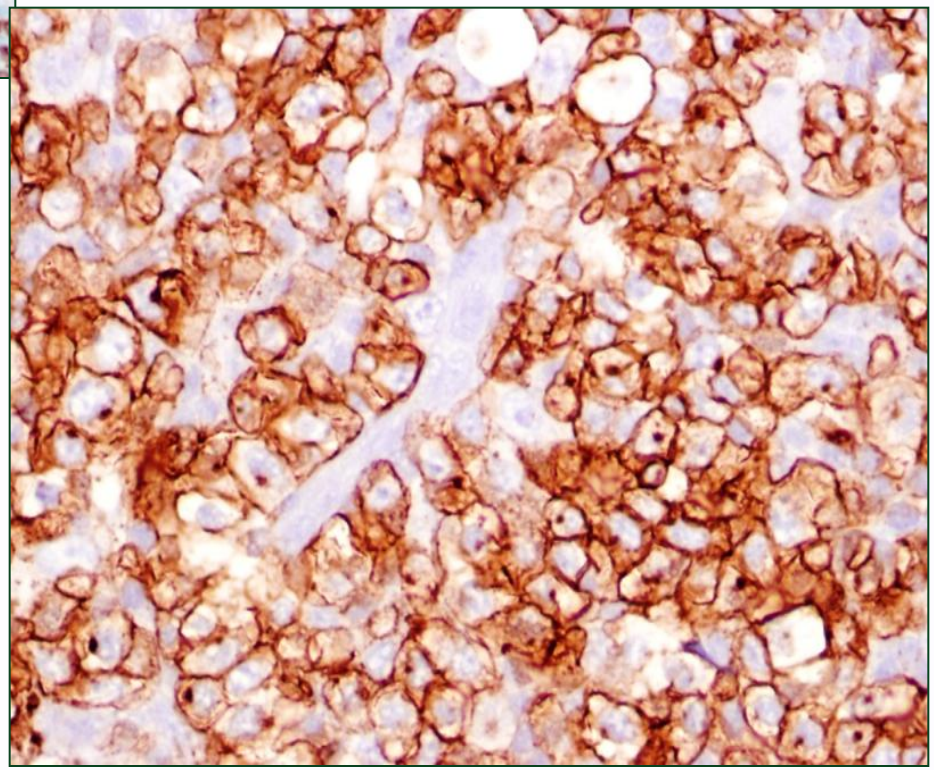
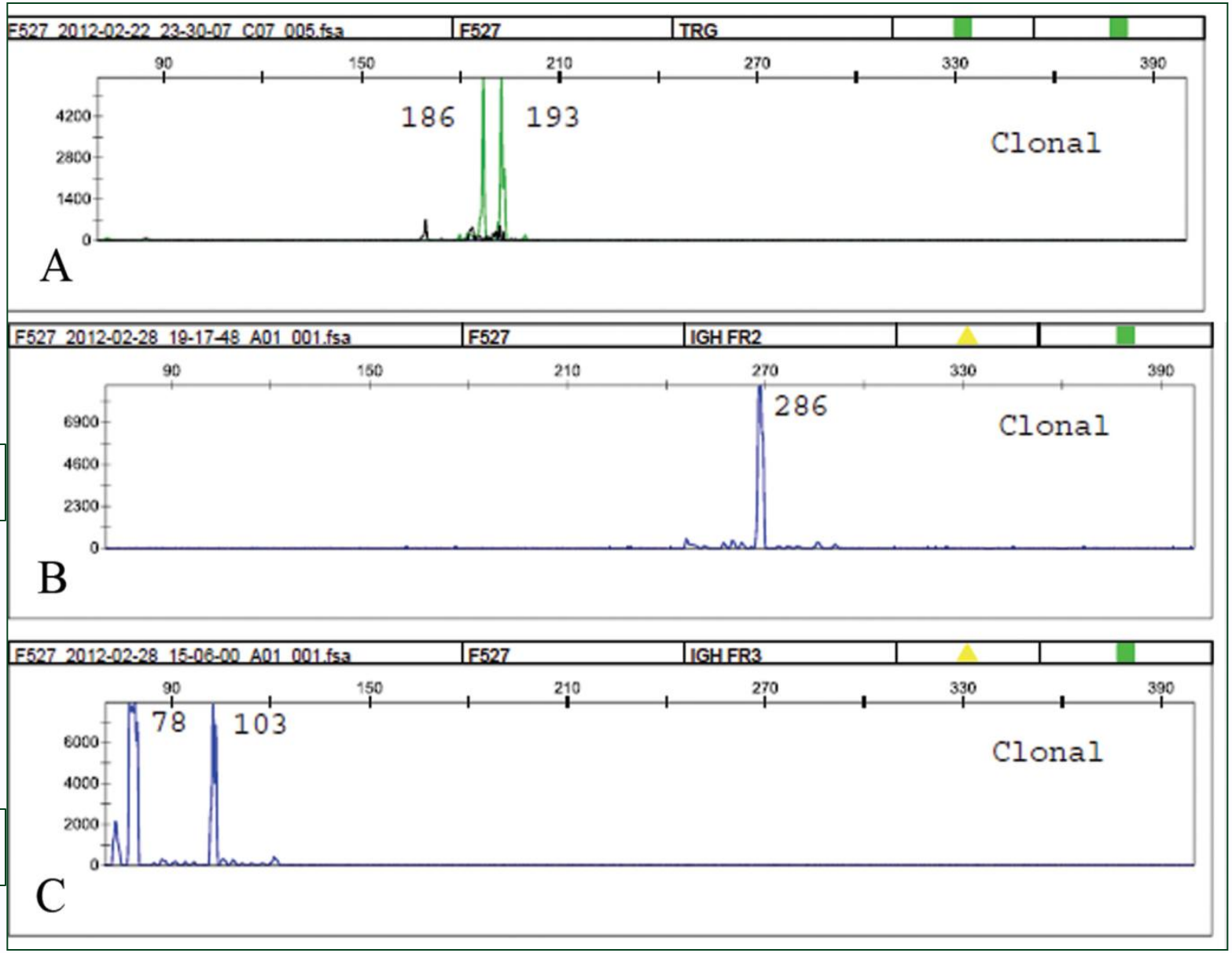


CD279/ PD-1

TCR

IGH FR2

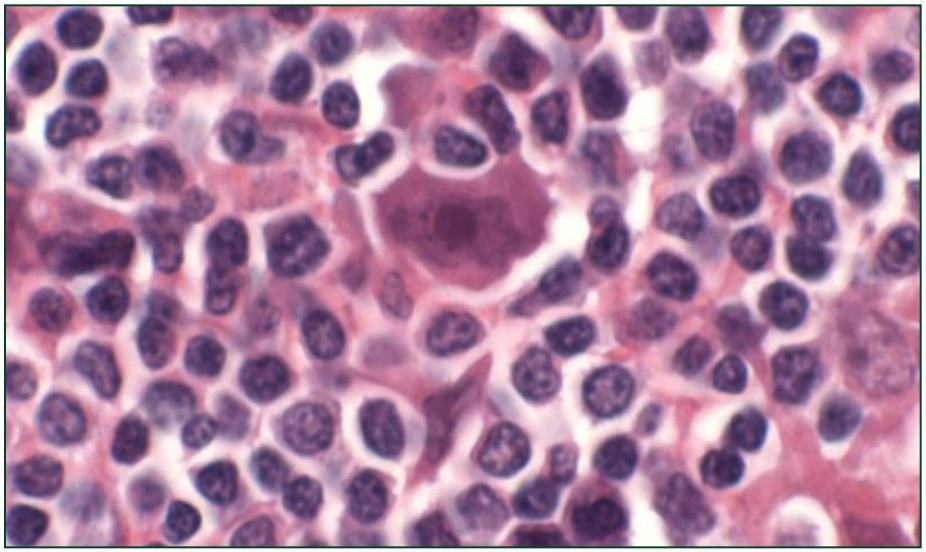
IGH FR3

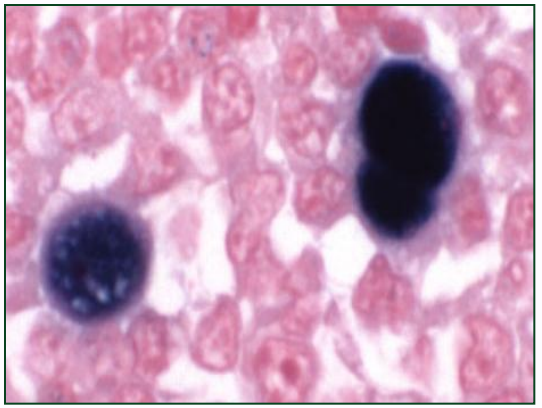


Huppmann et al JCO 2012

Peripheral T-cell lymphoma with EBV+ HRS cells

Quintanilla-Martinez et al. Am J Surg Pathol 1999

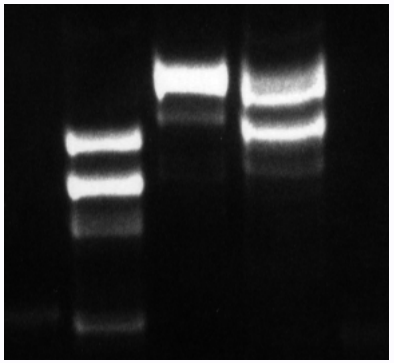




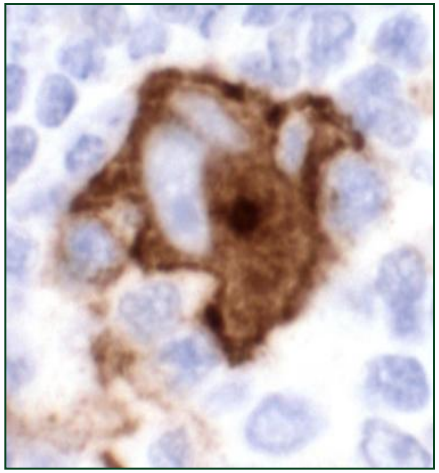
EBER

HRS cells

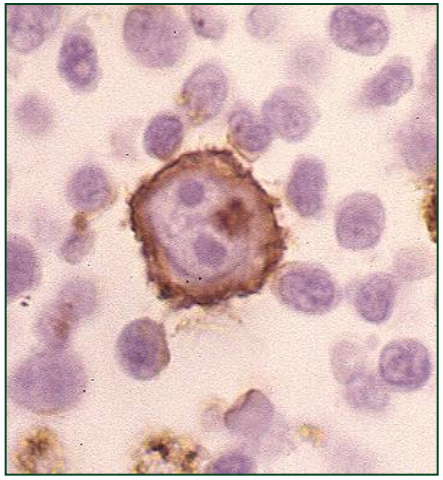
1 2 3



IgH-PCR



CD30



CD15

Laser capture microdissection of HRS cells (oligoclonal)

PTCL of TFH Origin with EBV+ HRS-like cells – a mimic of Lymphocyte Rich Classical Hodgkin Lymphoma

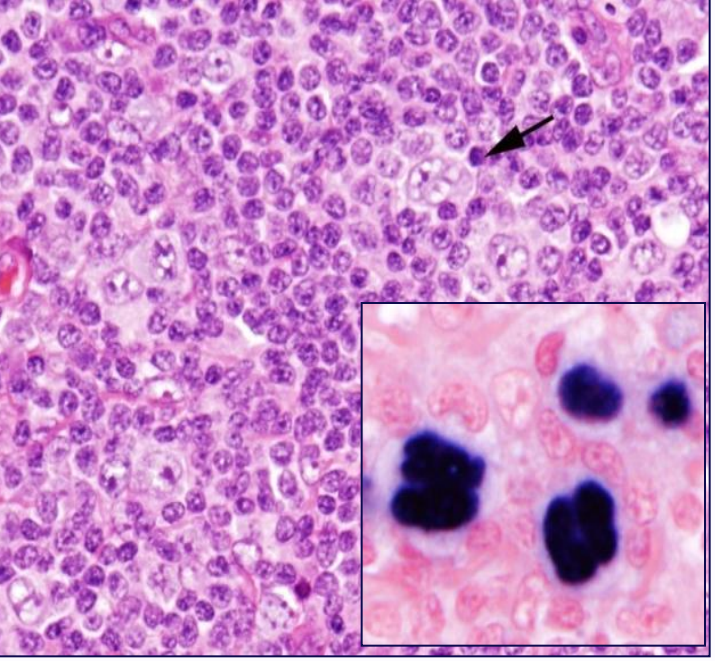
Moroch et al. AJSP 2013

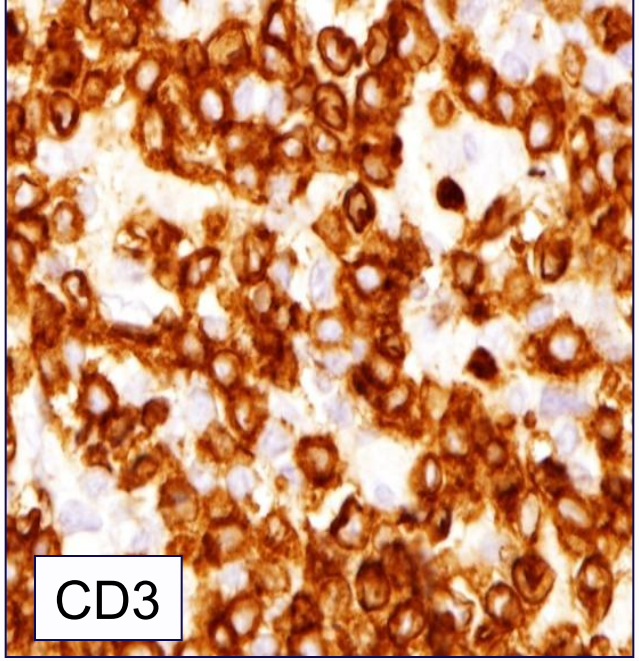
- 5 cases of PTCL with TFH phenotype
  - Classified as PTCL, follicular variant
- Nodular growth pattern mimics CHL, LR
- HRS cells all EBV+
- Clonal T-cells expressed BCL6, PD1, CXCL13 and CD10 (4/5)

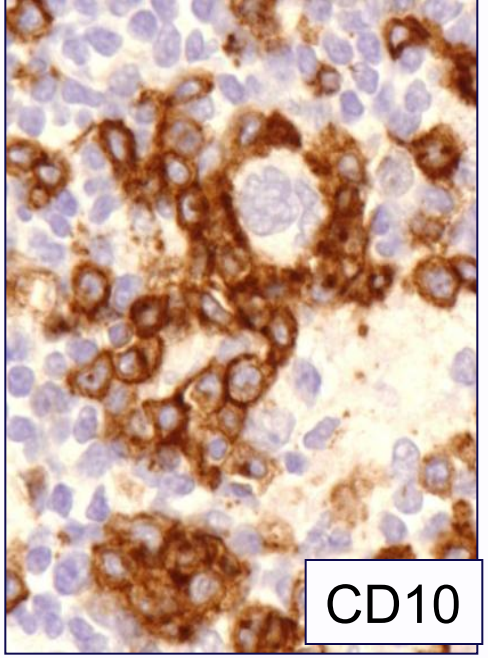
PTCL with HRS-like cells – An Update (57 cases)

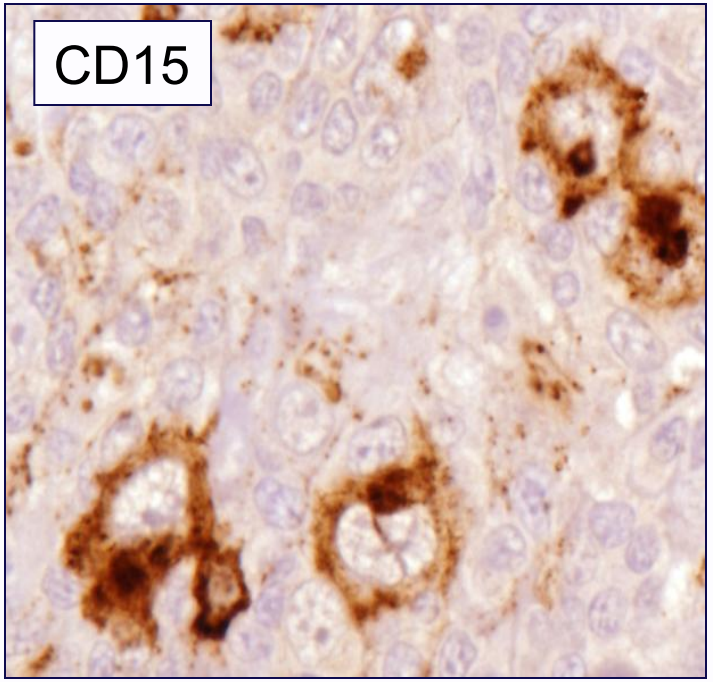
Nicolae et al AJSP 2013

- PTCL classified as AITL, PTCL, often with T_{FH} markers
- Intimate relationship between the HRS-like cells & neoplastic T-cells
- HRS-like cells
  - EBV-positive (52 cases)
  - EBV-negative (5 cases)
- Progression to classical Hodgkin's lymphoma not observed




CD3


CD10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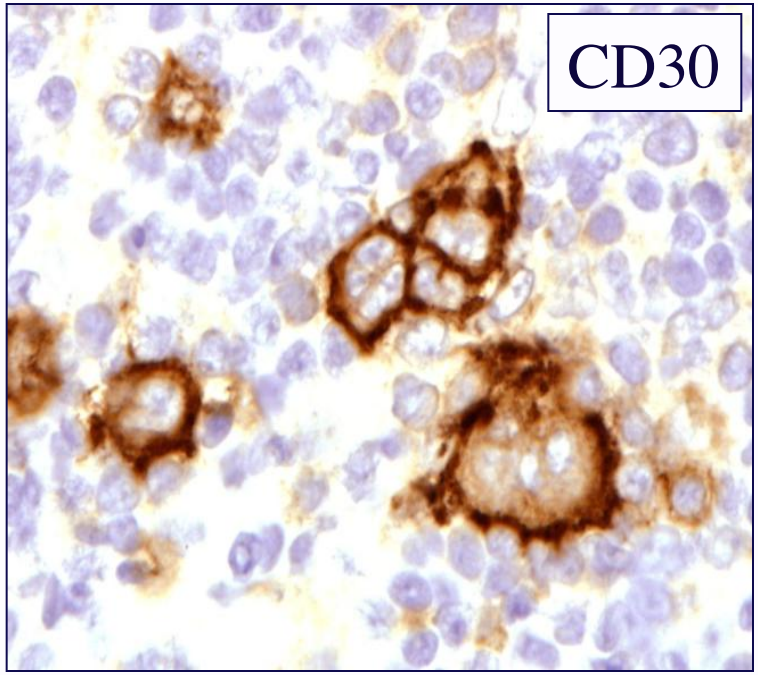
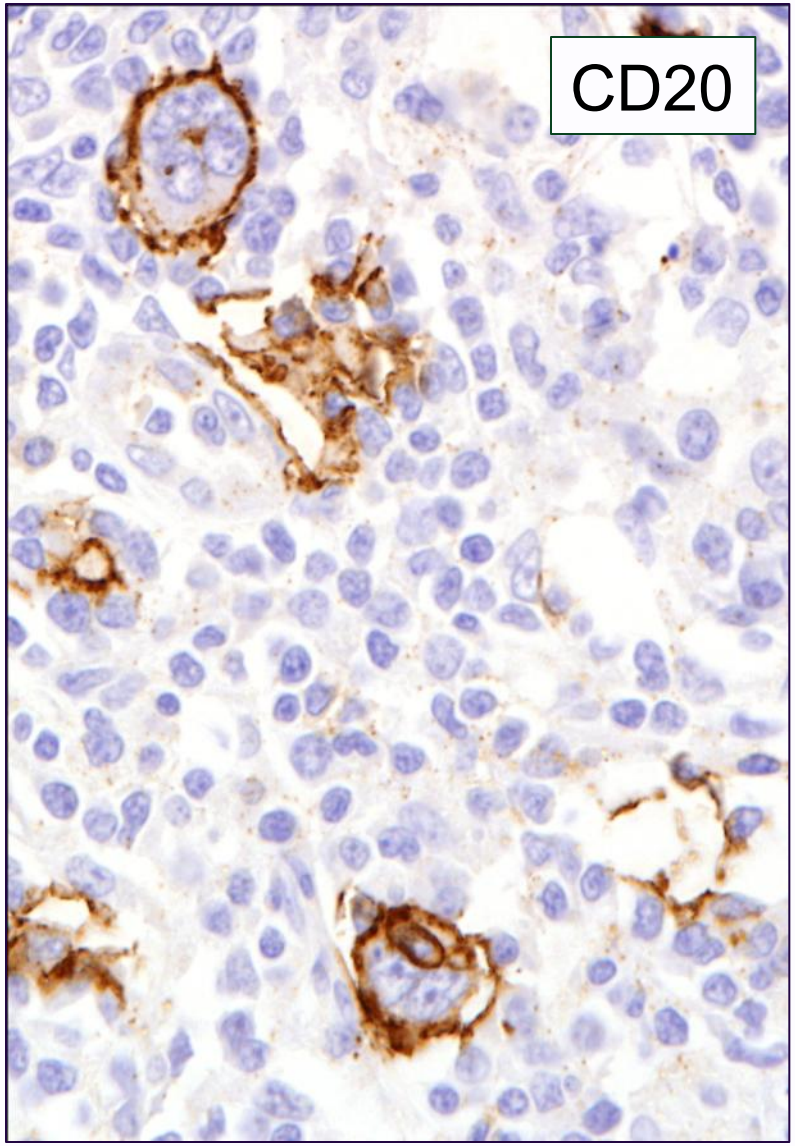
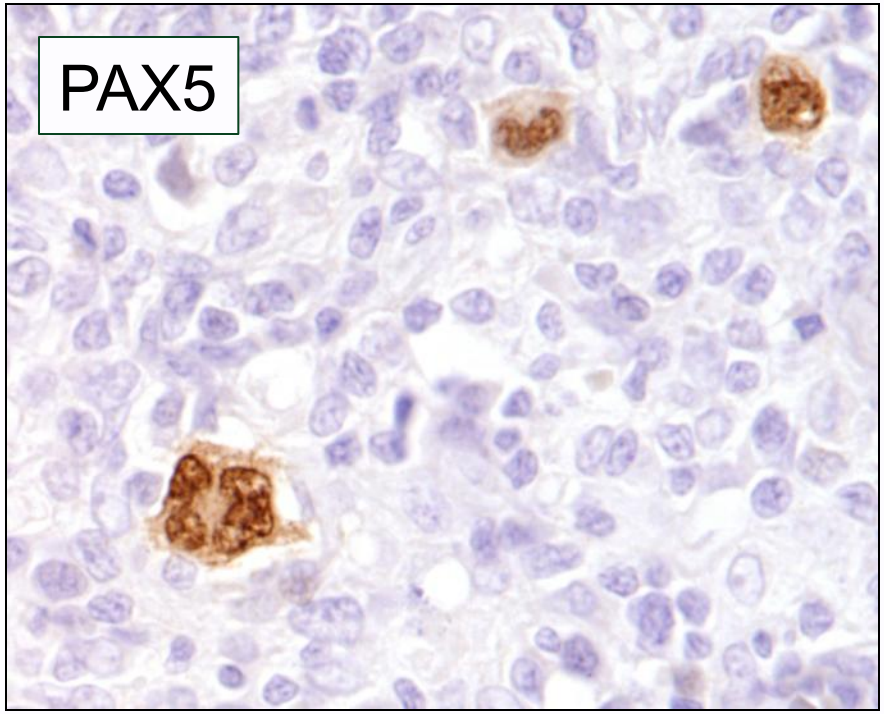
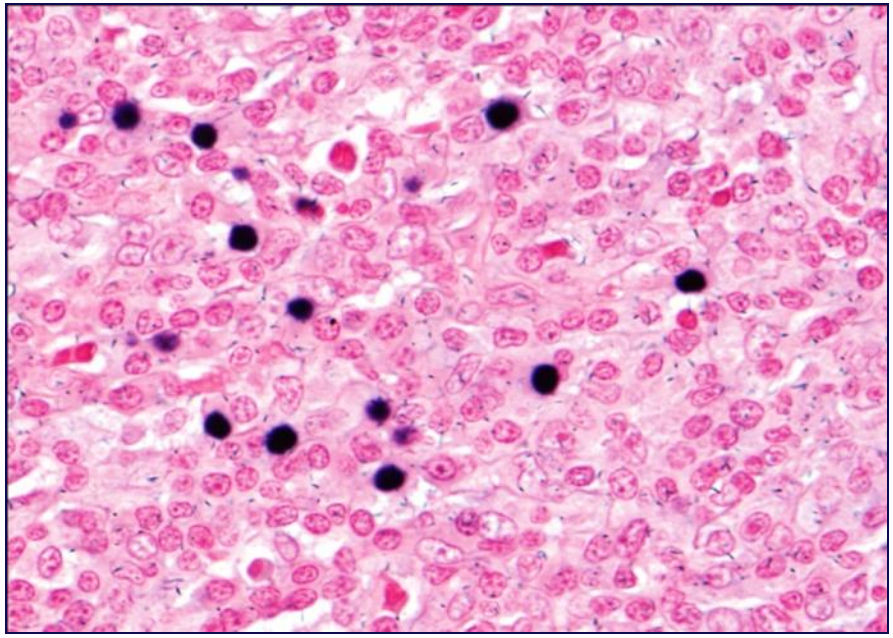
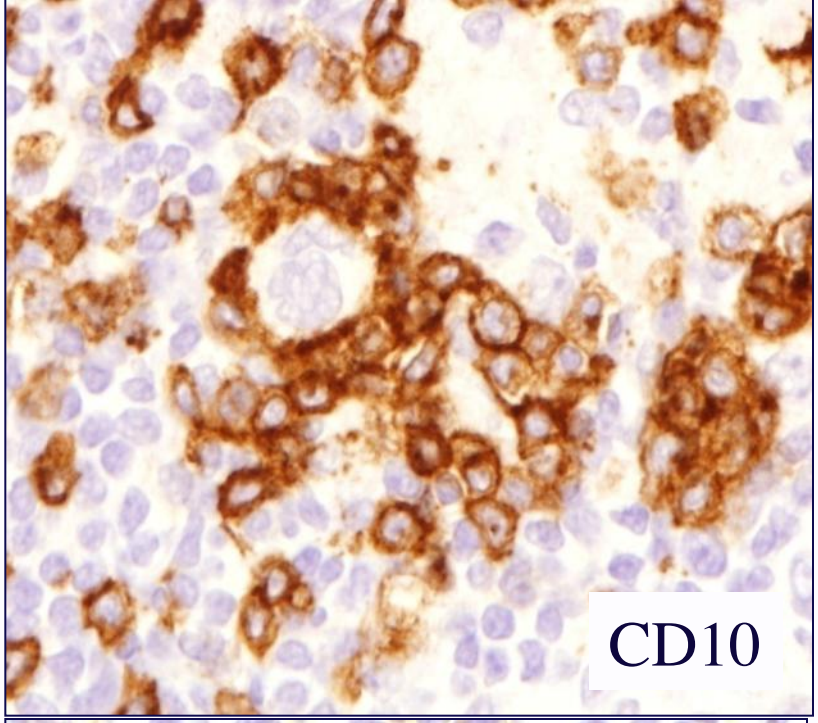

CD30







EBER only in small lymphs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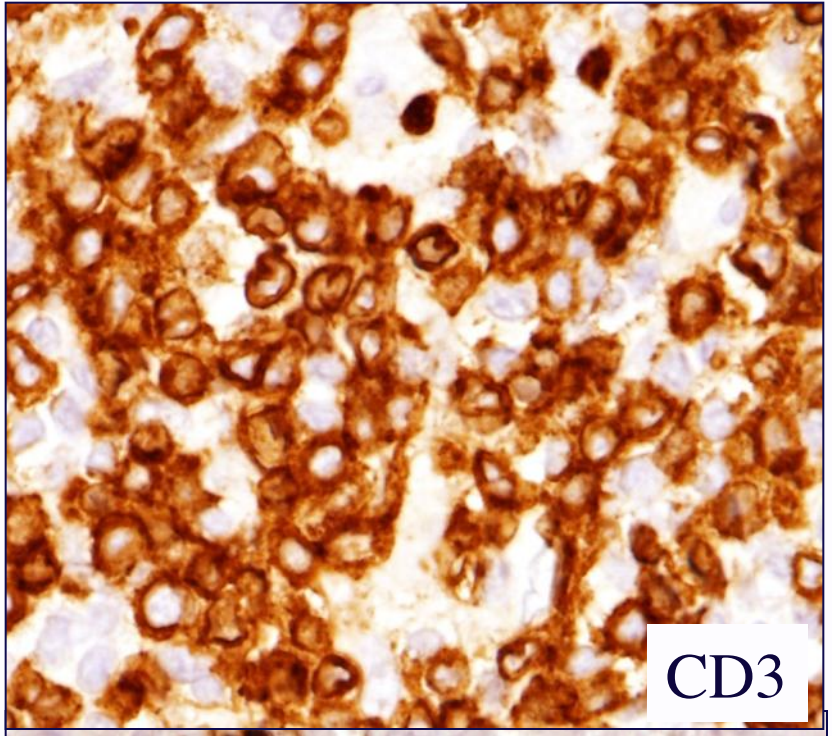
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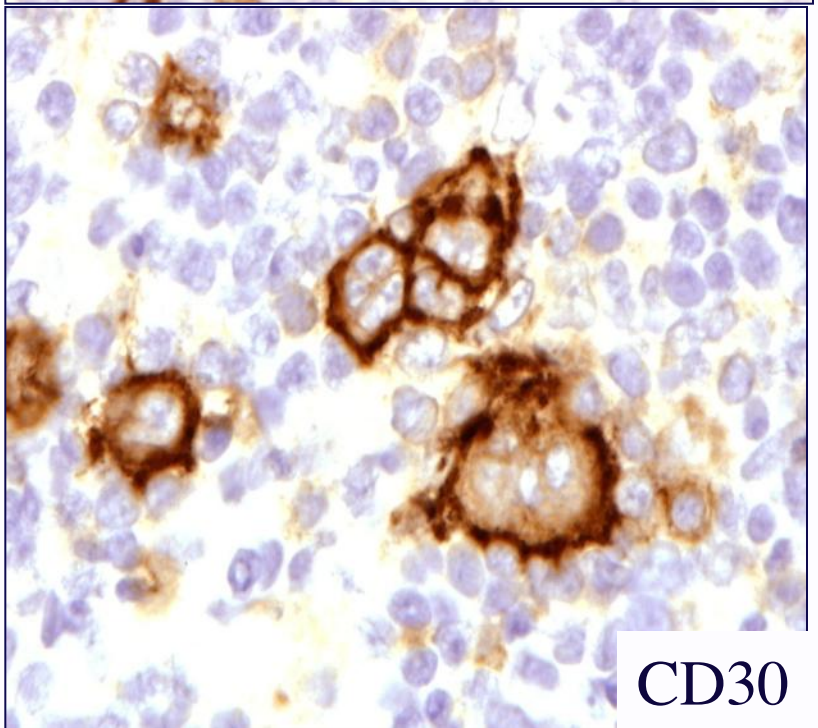
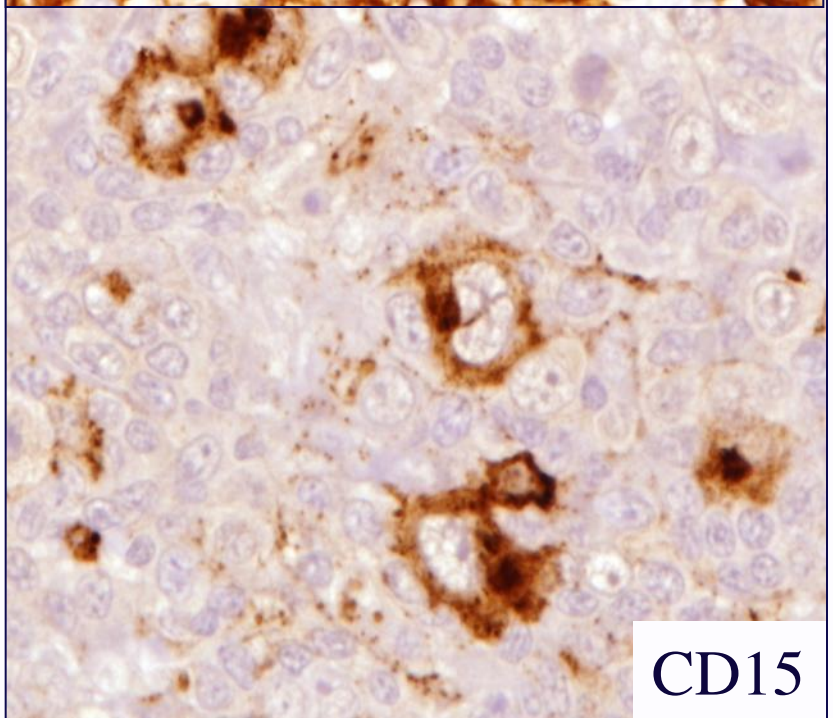
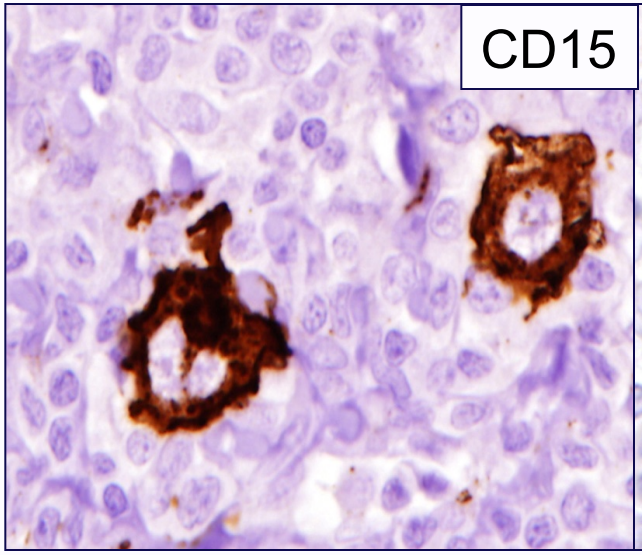
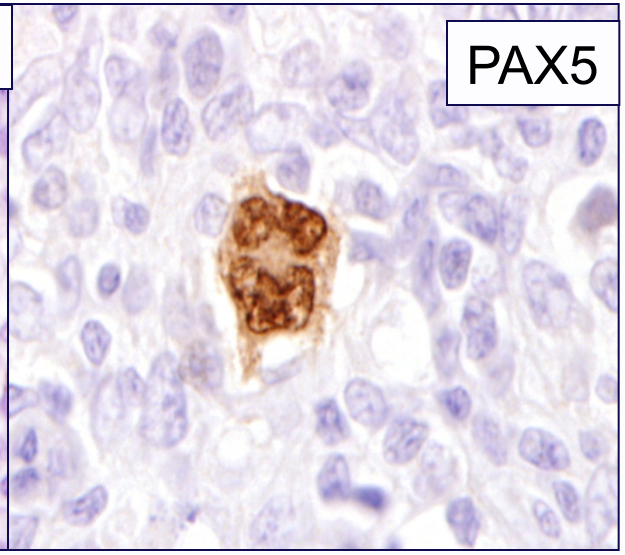
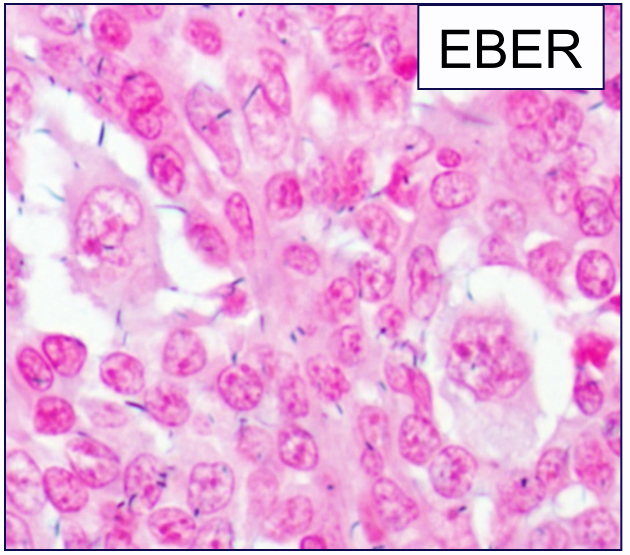
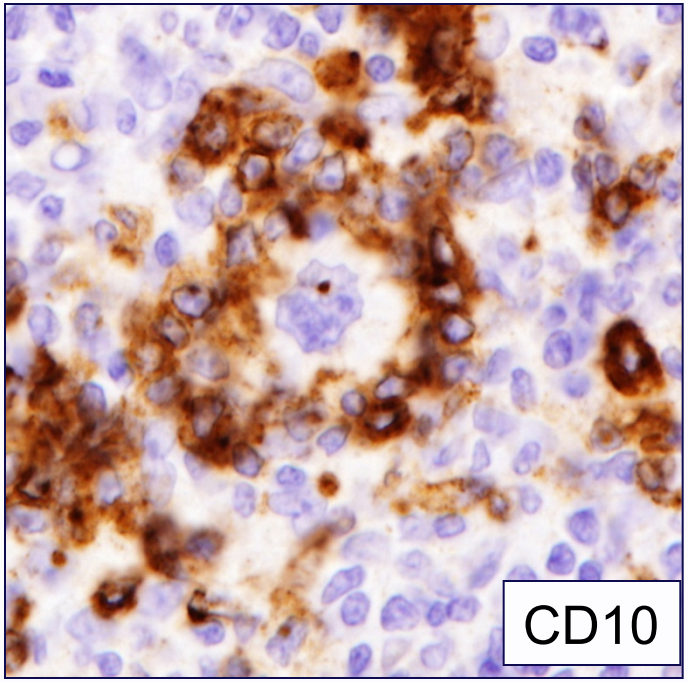

CD30

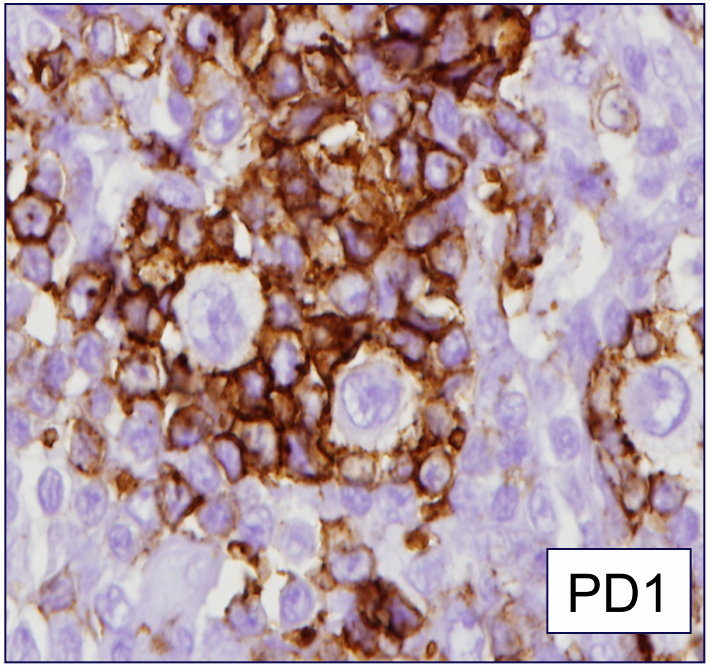

CD15











EBV-negative HRS like cells are also rosetted by neoplastic TFH cells

HRS-like cells rosetted by neoplastic TFH cells Significance and Possible Mechanisms

Nicolae A. et al AJSP

- T_{FH} promote the expansion of B-cells in the immune response, thus T_{FH} might aberrantly expand B-cells outside of normal physiological control.
- PD-1 with its ligand (PDL-1) helps to maintain an immunosuppressive microenvironment
- Rosetting PD-1+ T-cells might protect aberrant B-cell clones from immune surveillance, leading to emergence of the HRS-cells

Angioimmunoblastic T-cell Lymphoma Take Home Points & Remaining Questions

- AITL is characterized by proliferation and sometimes clonal expansion of B-cells, as well as neoplastic T_{FH}-cells
- If B-cells are passively expanded secondary to function of T_{FH} cells, why do they appear so atypical, or evolve to a clonal proliferation in some cases?