"Low-grade B-cell NHL"

Dr. Leticia Quintanilla-Martinez
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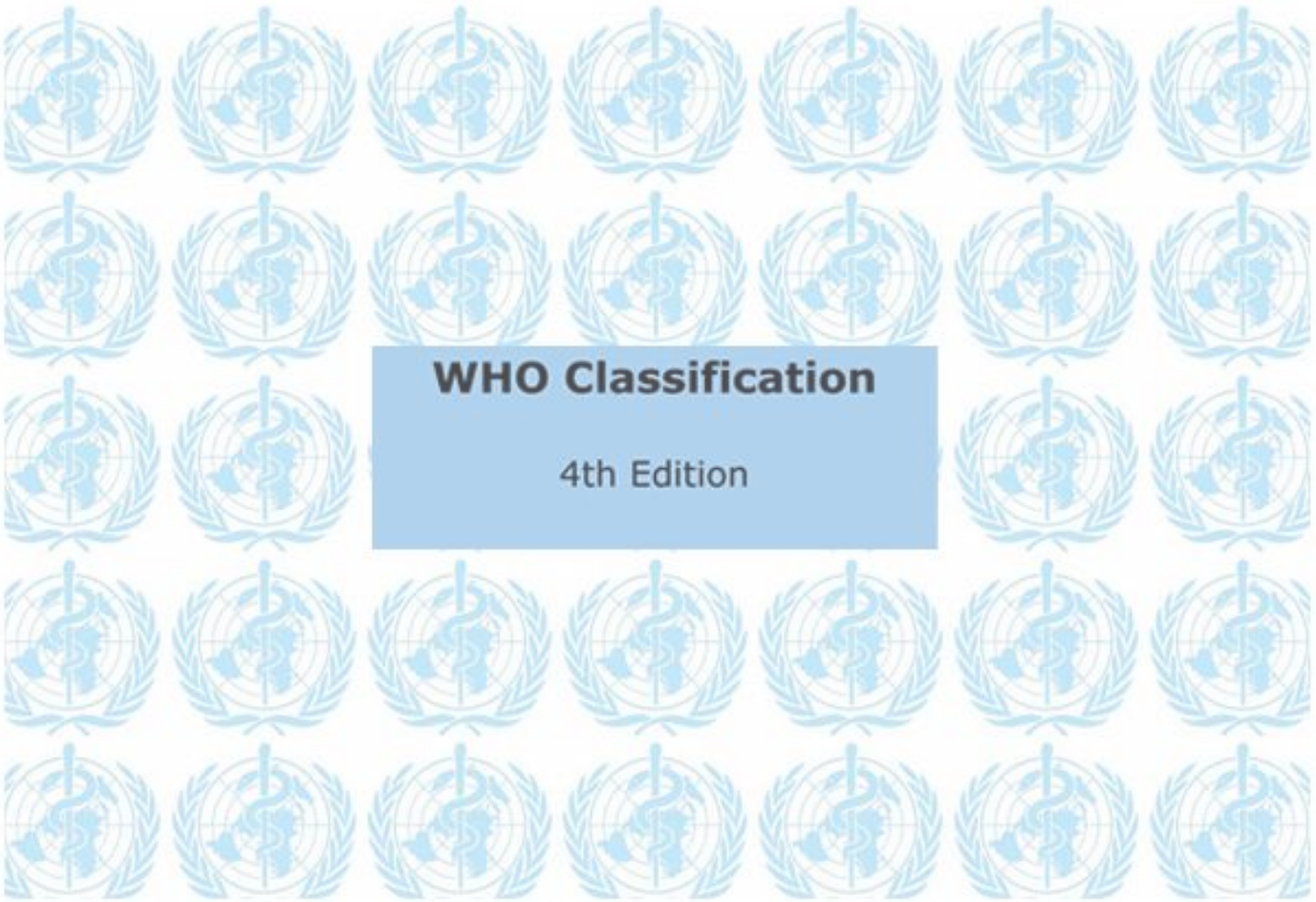

WHO Classification
4th Edition

Principles of the WHO Classification

- Lineage is the starting point of disease definition
  - ✓ B, T, NK

- Each disease is a distintict entity based on a constellation of clinical and laboratory features
  - ✓ Morphology
  - ✓ Immunophenotype
  - ✓ Genetic features
  - ✓ Clinical presentation

- Site of involvement is often a signpost for important biological distinctions

- Distinguishes between grade and aggressiveness within the same diseae

Principles of the WHO Classification

- The WHO classification does not attempt to stratify lymphomas according to „grade" either histological or clinical.

- Low cytological grade does not necessarily translate into indolent clinical behaviour
  - -Mantle Cell Lymphoma
  - -Angioimmunoblastic T-cell Lymphoma

- Lymphomas have within them a spectrum of histologic grade and clinical behavior
  - Follicular lymphoma (G1-3)
  - CLL and Richters Transformation
  - Mantle cell lymphoma (Classic vs Blastic)

WHO classification 2008

MATURE B-CELL NEOPLASMS	
Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	9823/3
B-cell prolymphocytic leukaemia	9833/3
Splenic marginal zone lymphoma	9689/3
Hairy cell leukaemia	9940/3
Splenic lymphoma/leukaemia, unclassifiable	9591/3
Splenic diffuse red pulp small B-cell lymphoma	9591/3
Hairy cell leukaemia-variant	9591/3
Lymphoplasmacytic lymphoma	9671/3
Waldenström's macroglobulinemia	9761/3
Heavy chain diseases	9762/3
Alpha heavy chain disease	9762/3
Gamma heavy chain disease	9762/3
Mu heavy chain disease	9762/3
Plasma cell myeloma	9732/3
Solitary plasmacytoma of bone	9731/3
Extraosseous plasmacytoma	9734/3
Follicular lymphoma	9690/3
Paediatric follicular lymphoma	9690/3
Primary cutaneous follicle centre lymphoma	9597/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma (DLBCL), NOS	9680/3
T-cell/histiocyte rich large B-cell lymphoma	9688/3
Primary DLBCL of the CNS	9680/3
Primary cutaneous DLBCL, leg type	9680/3
EBV positive DLBCL of the elderly	9680/3
DLBCL associated with chronic inflammation	9680/3
Lymphomatoid granulomatosis	9766/1
Primary mediastinal (thymic) large B-cell lymphoma	9679/3
Intravascular large B-cell lymphoma	9712/3
ALK positive ~~DLBCL~~	9737/3
Plasmablastic lymphoma	9735/3
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease	9738/3
Primary effusion lymphoma	9678/3

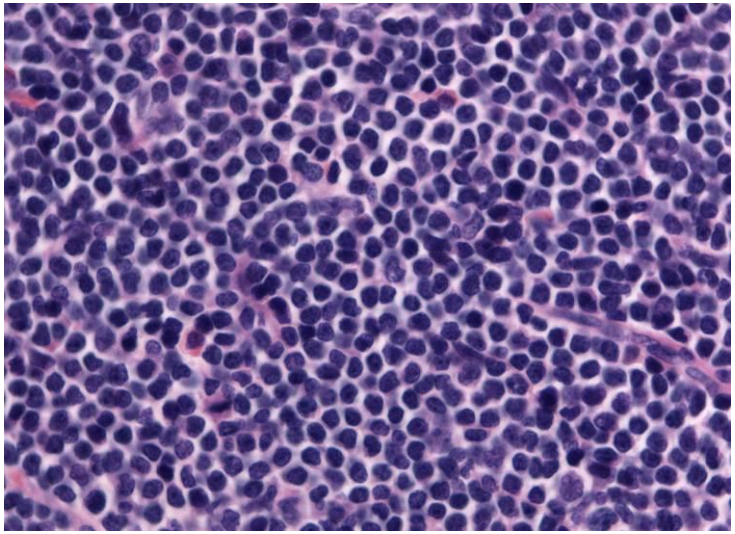
„Low grade“ B-cell non-Hodgkin Lymphoma

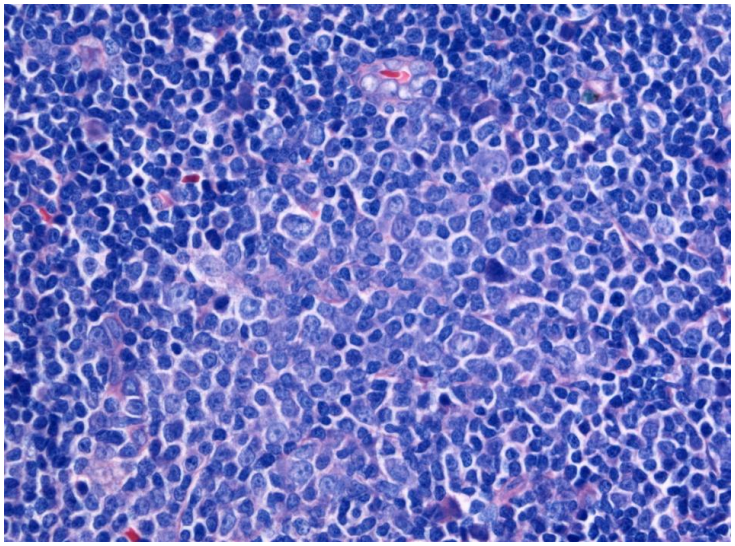
- Chronic lymphocytic leukemia/small lymphocytic leukemia
- Follicular lymphoma
- Mantle cell lymphoma
- Marginal cell lymphoma
- Lymphoplasmacytic lymphoma
- Hairy cell leukemia

Chronic lymphocytic Leukemia/Small lymphocytic lymphoma

Definition:

- Monomorphic small, round to slightly irregular B-cells
- Involved PB, BM, LN, spleen
- Proliferation centers composed of prolymphocytes and paraimmunoblasts
- $\geq 5x10^9/L$ monoclonal lymphocytes in PB (CLL)
- $<5x10^9/L$ monoclonal B-cell lymphocytosis (MBL)
- Non-leukemic manifestations with tissue involvement, small lymphocytic lymphoma (SLL)





Monoclonal B-cell lymphocytosis

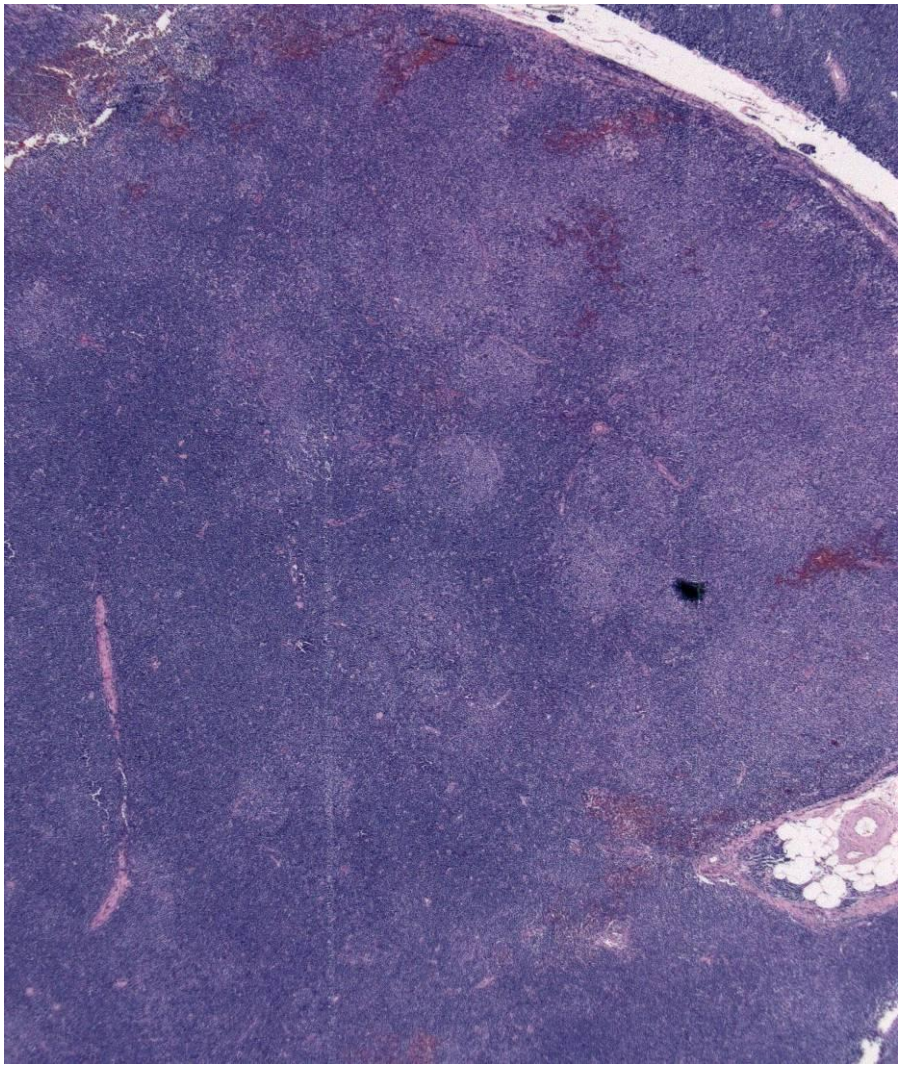
- Healthy individuals with monoclonal expansion of B-cells
- Phenotype of CLL (CD20+CD23+CD5+)
- $<5x10^9/L$ (To distinguish from Rai Stage 0 CLL)
- The absence of palpable lymphadenopathy and /or organomegaly (to distinguish from SLL)
- 3.5% > 40 years, 12% > 50 years, and 50-75% > 90 years
- The risk to develop CLL is 1-2% per year

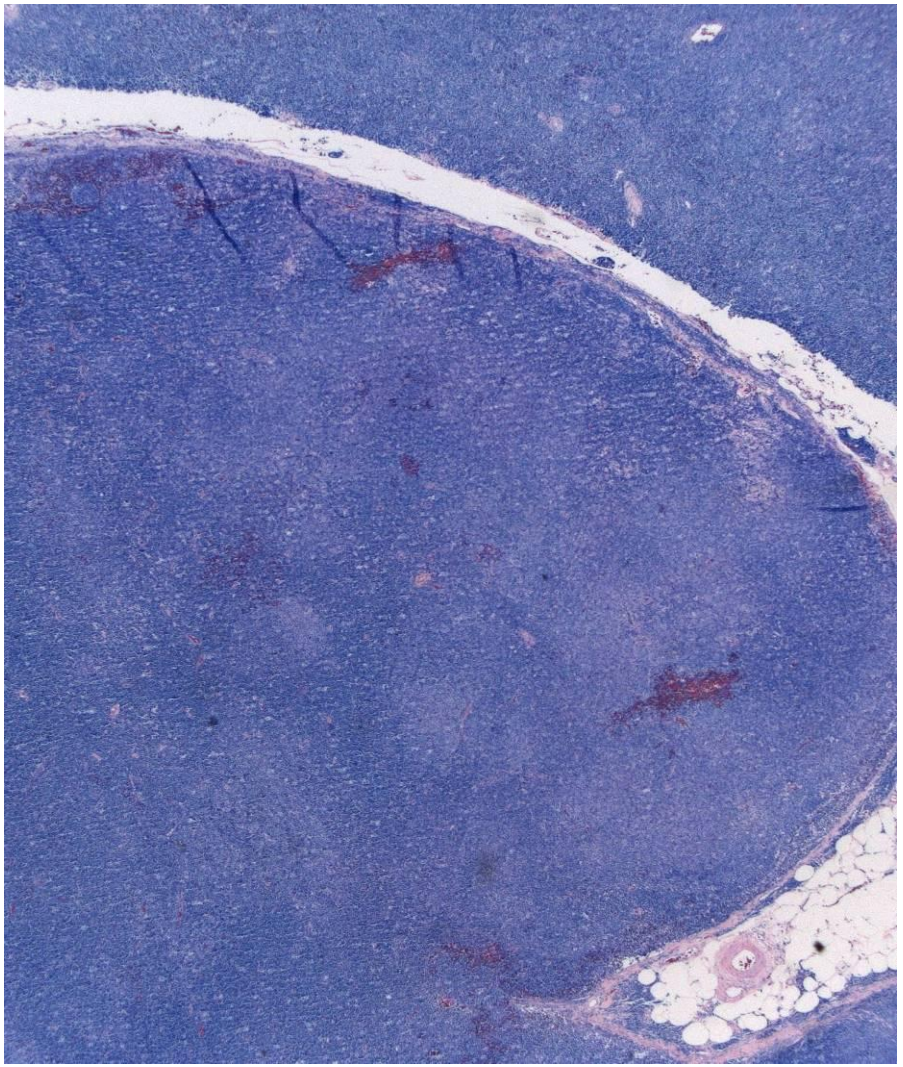
Chronic lymphocytic Leukemia/Small lymphocytic lymphoma

- Epidemiology:
- CLL is the most common leukemia of adults
- Median age of diagnosis is 65 years
- Male : Female ratio 1.5 – 2.1
- In biopsies 6.7% of all NHL
- PB and BM are usual involved
- Clincal features:
- Most patients are asymptomatic
- Some present with hemolytic anemia, fatigue

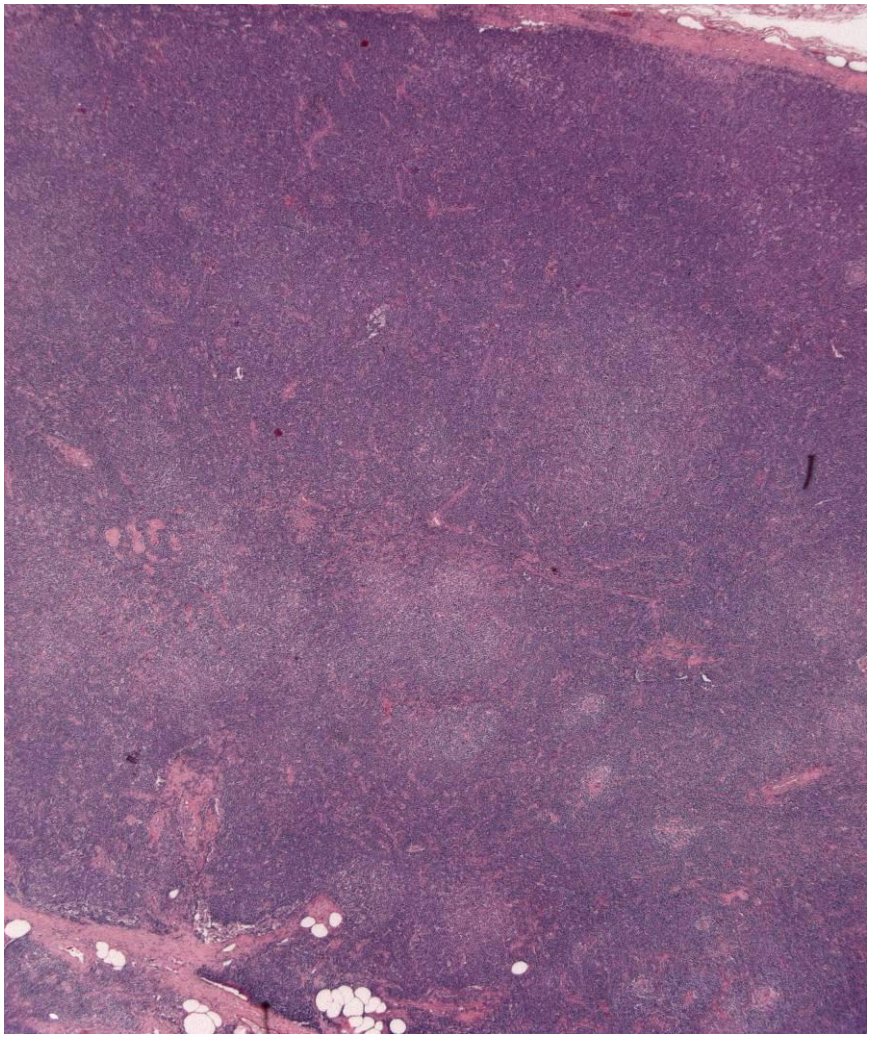
Müller-Hermelink, WHO 2008

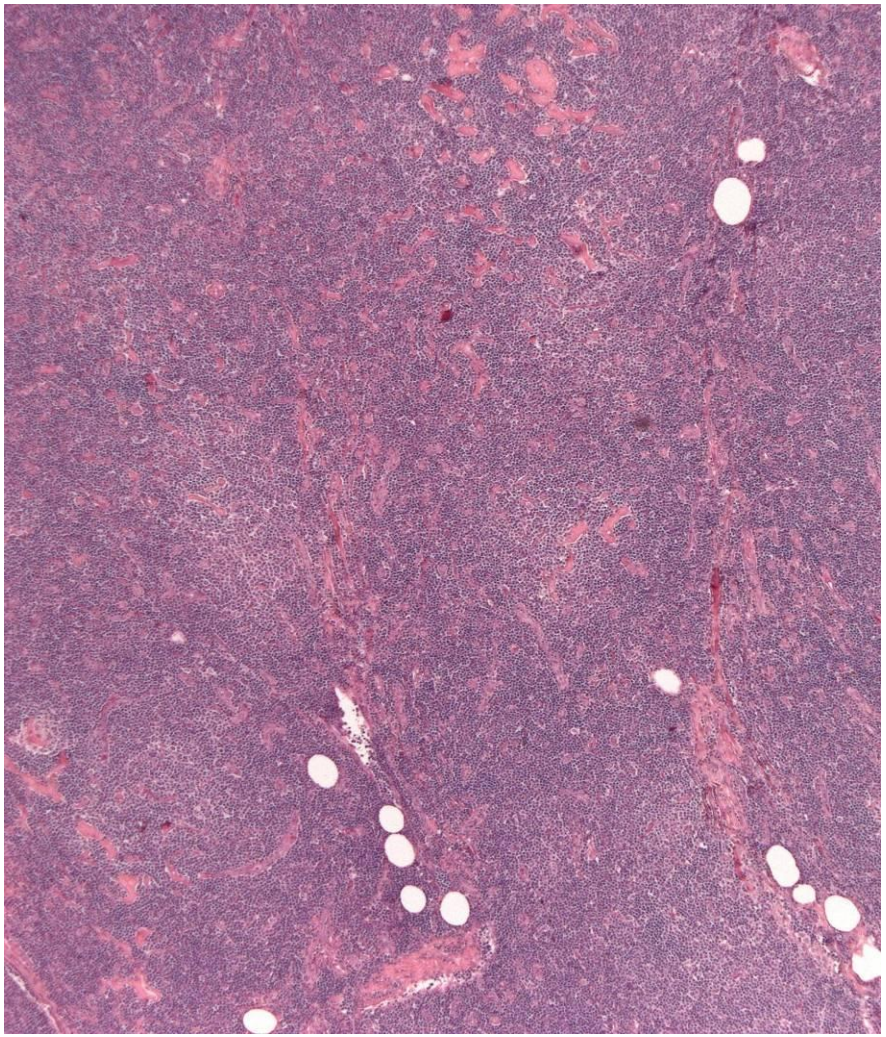
Chronic lymphocytic leukemia. Morphology



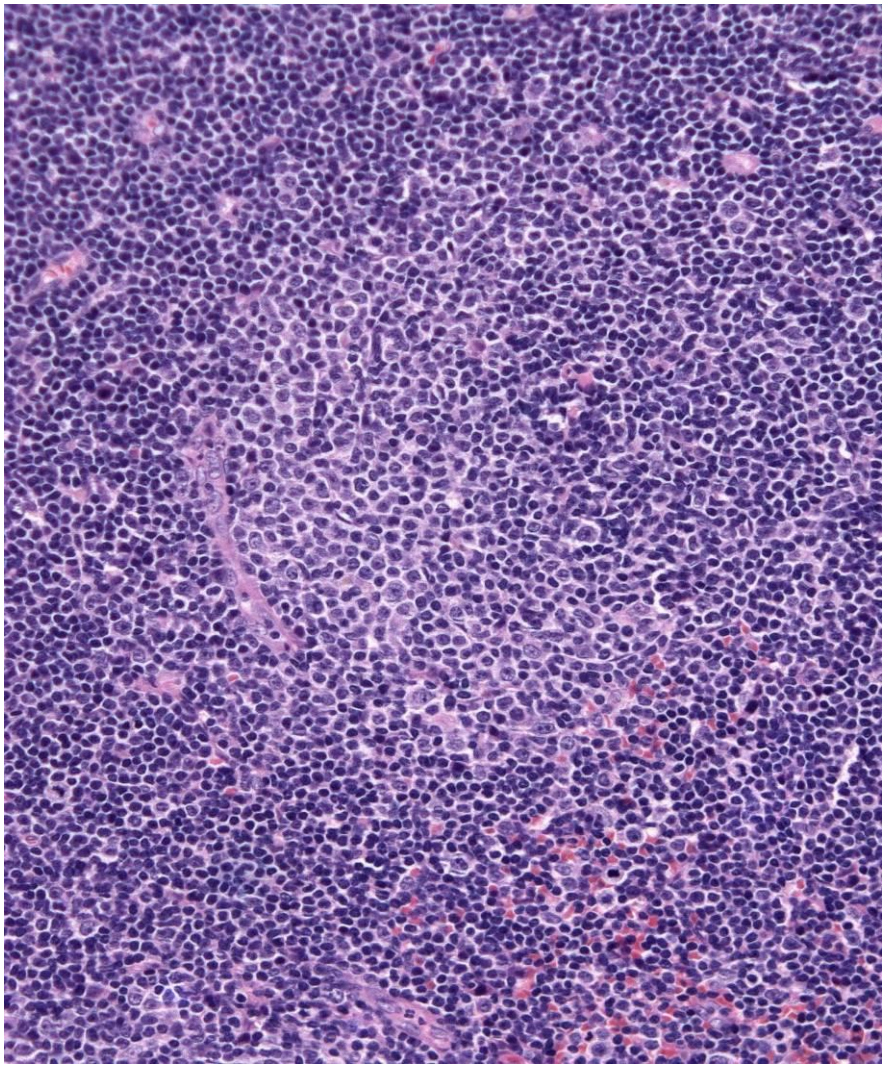


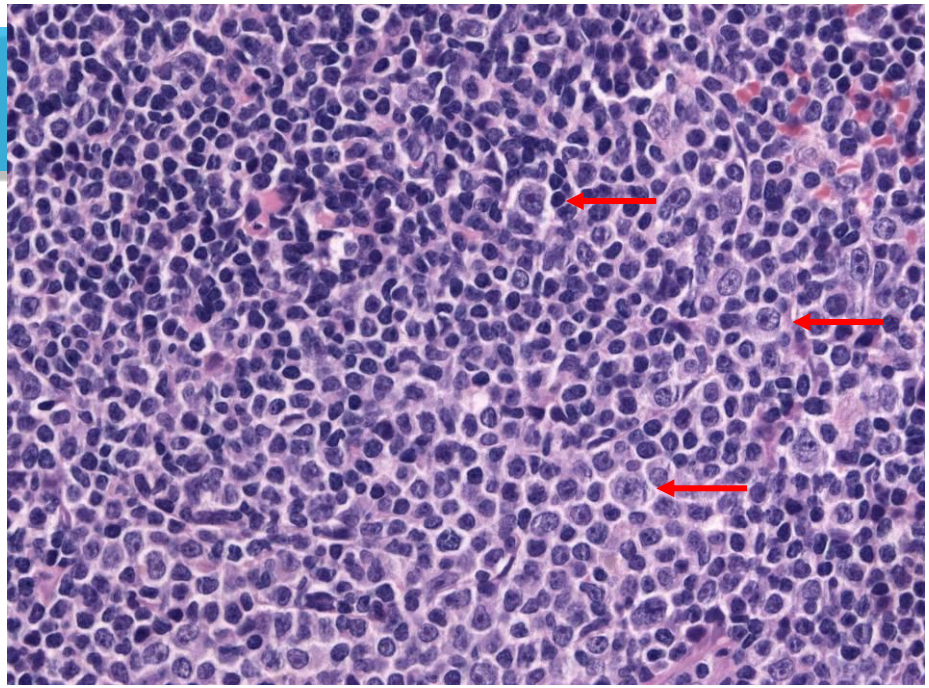
Chronic lymphocytic leukemia. Morphology

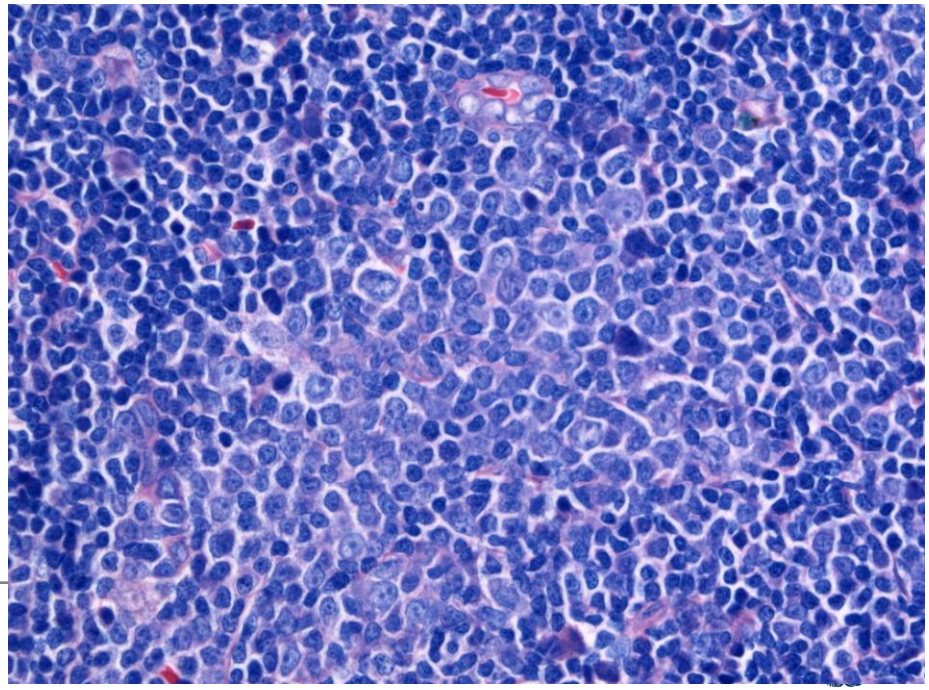




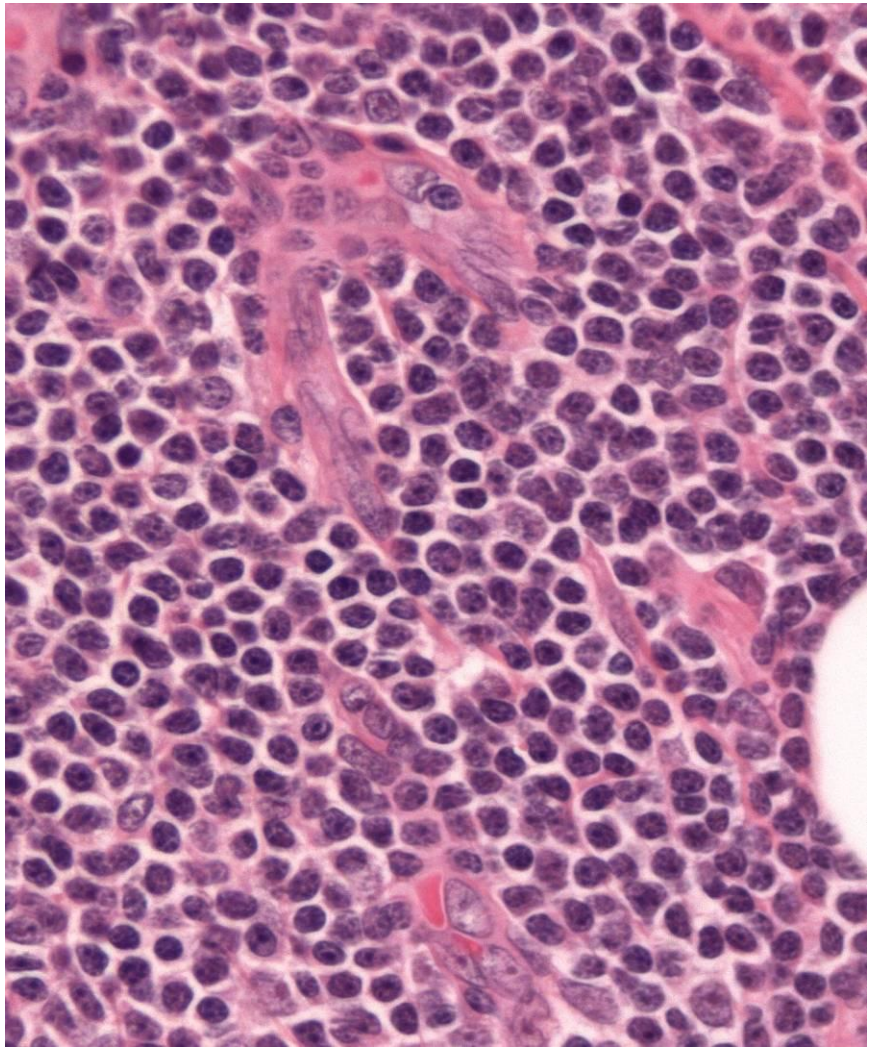
Proliferation centers

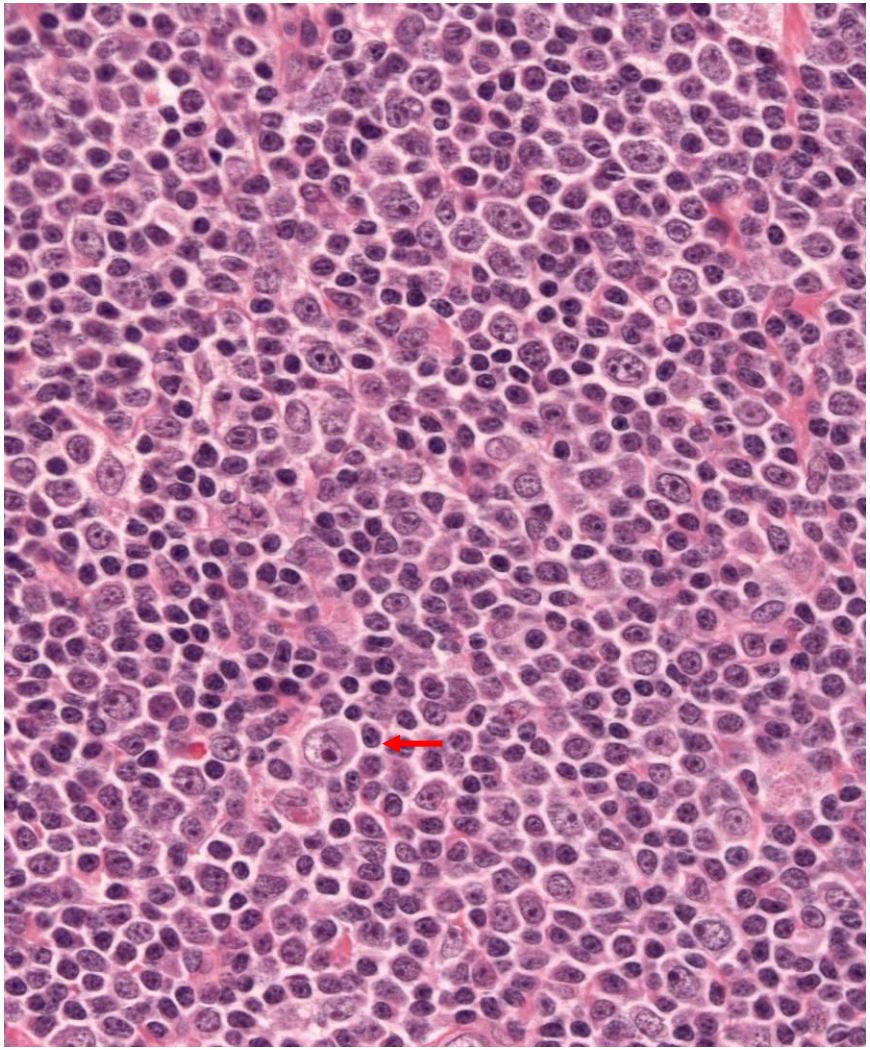






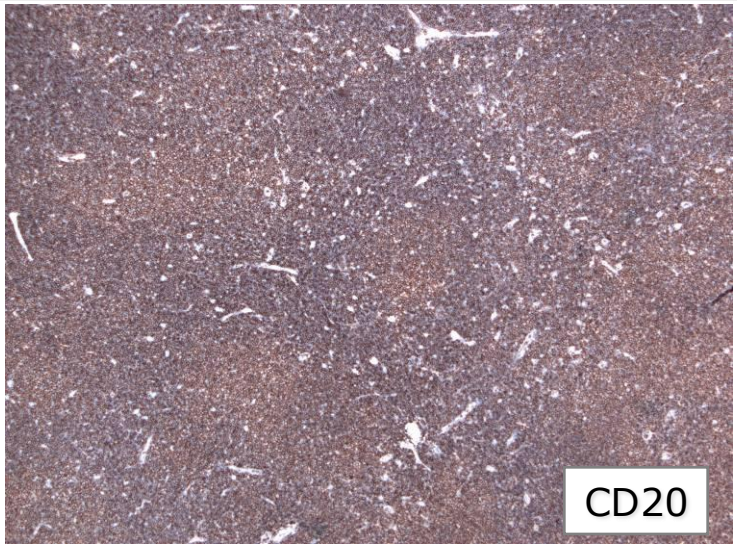
Chronic lymphocytic leukemia. Morphology

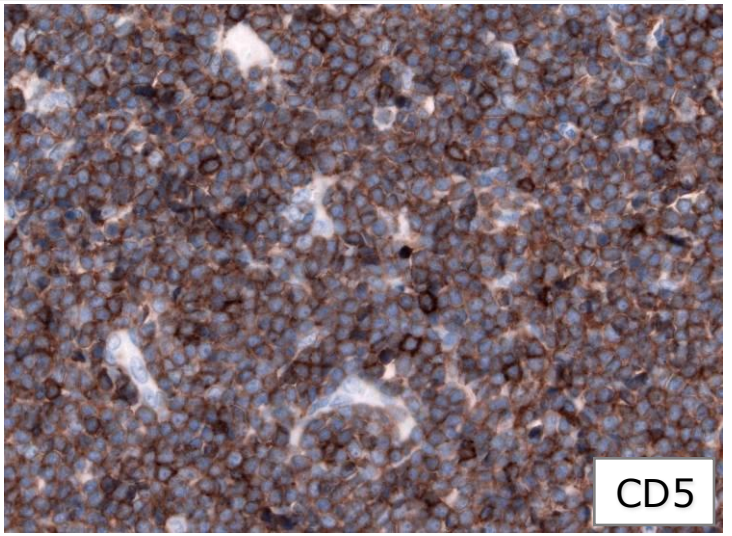


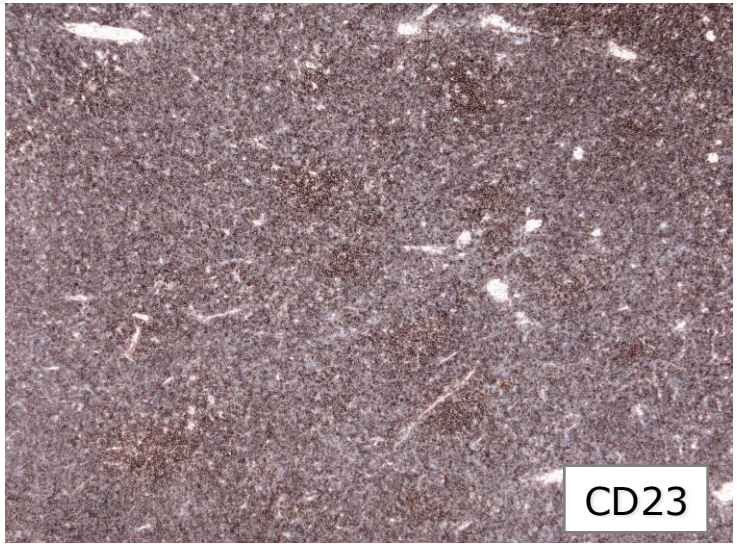


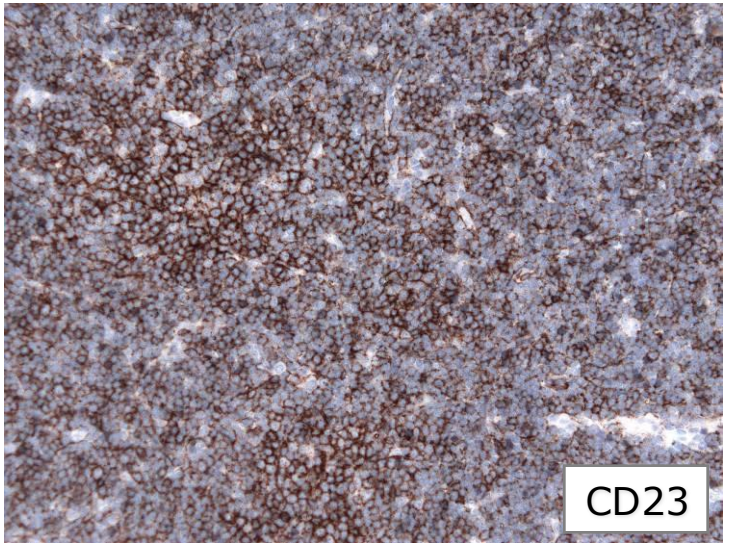
Chronic lymphocytic leukemia - Immunophenotype

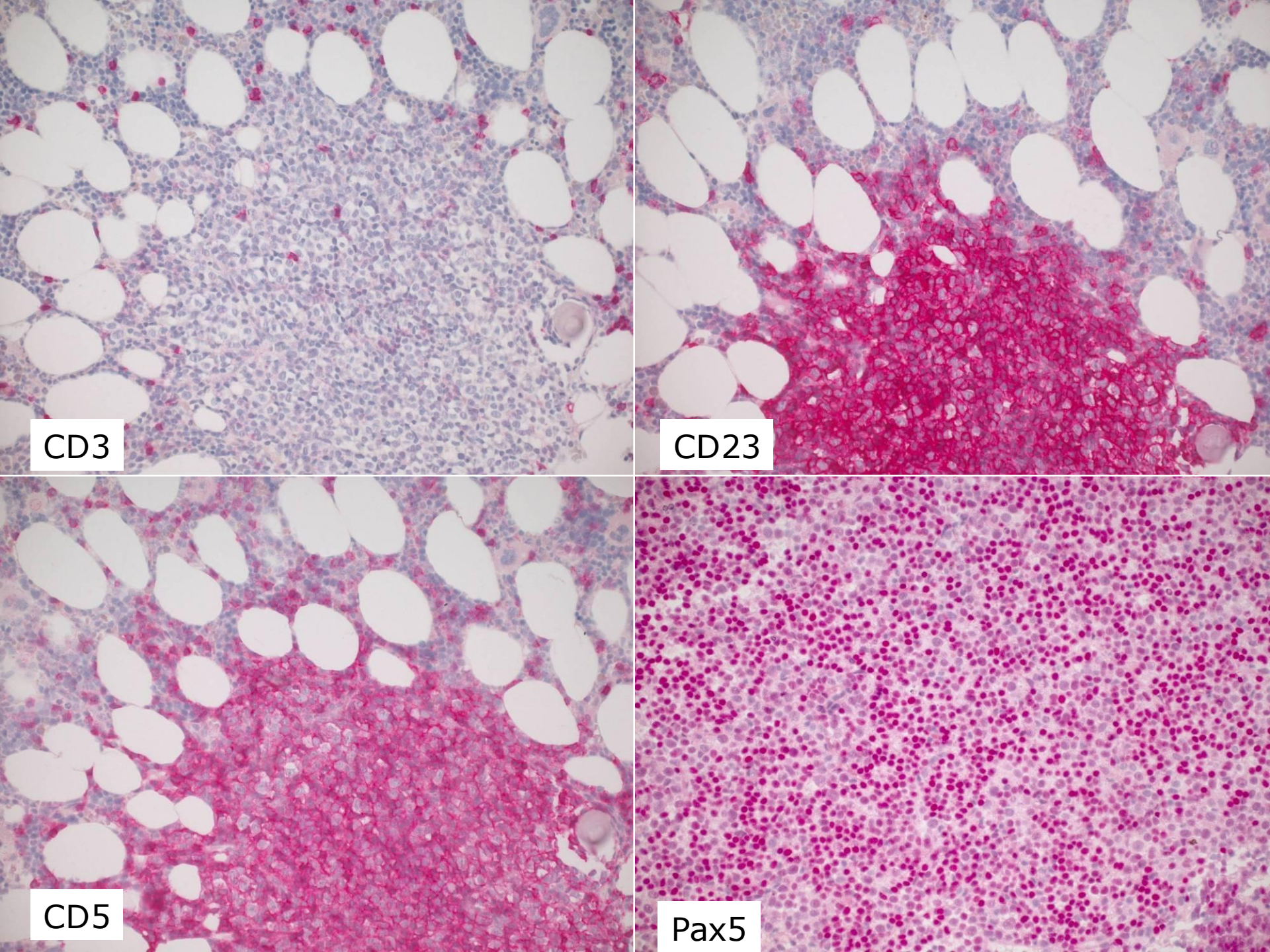
- Phenotype:
- IgM+, IgD+
- CD20+++
- CD22++
- CD23+
- CD5 +
- CD10-
- Cyclin D1-*



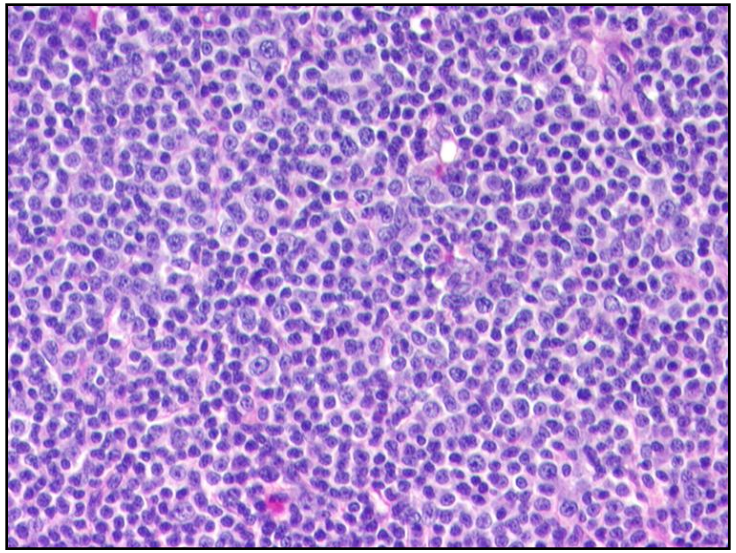


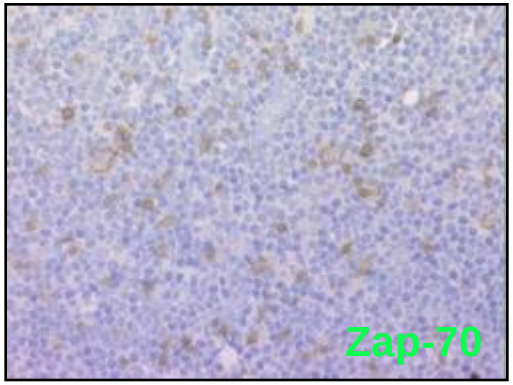


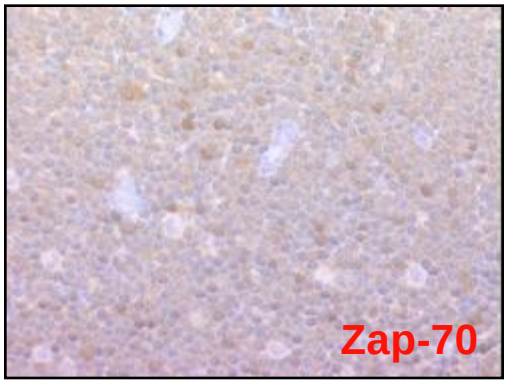


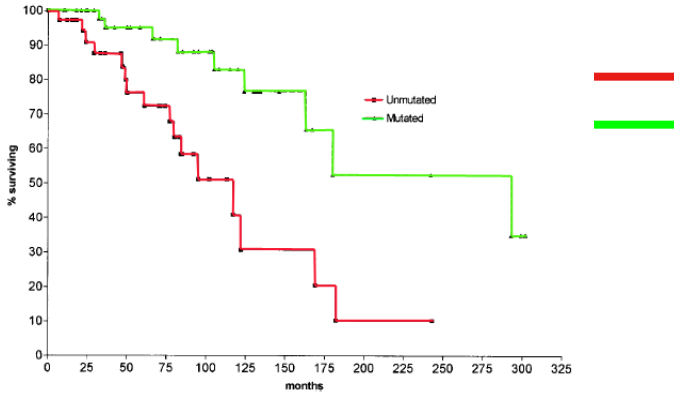

CD3
CD23
CD5
Pax5

Genetic findings in CLL/SLL

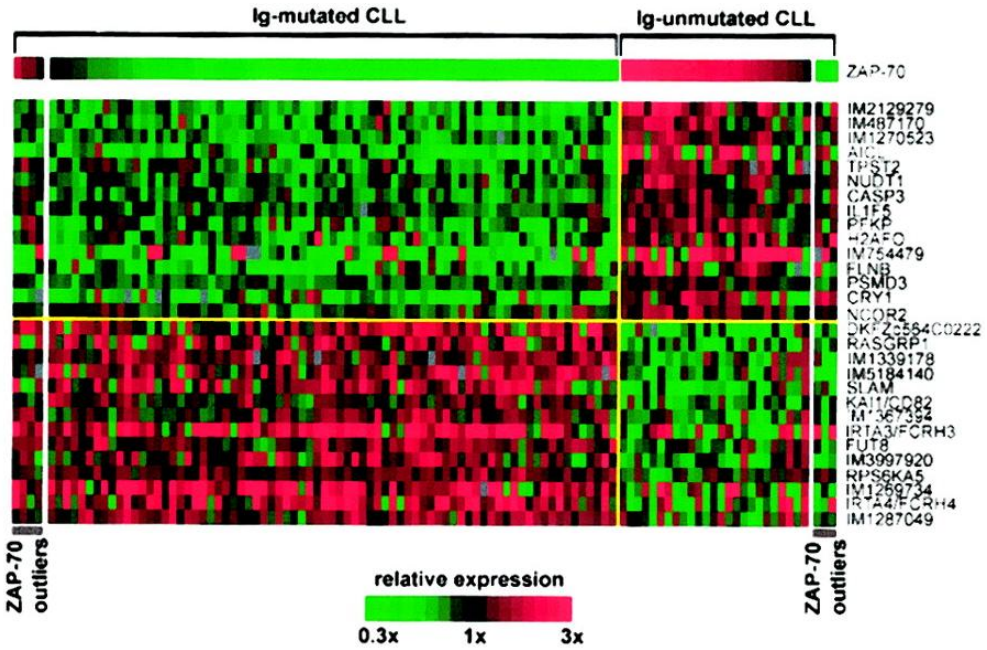








Hamblin et al Blood 1999;94:1848



Wiestner et al Blood 2003; 101:4944

Cytogenetic abnormalities and oncogenes

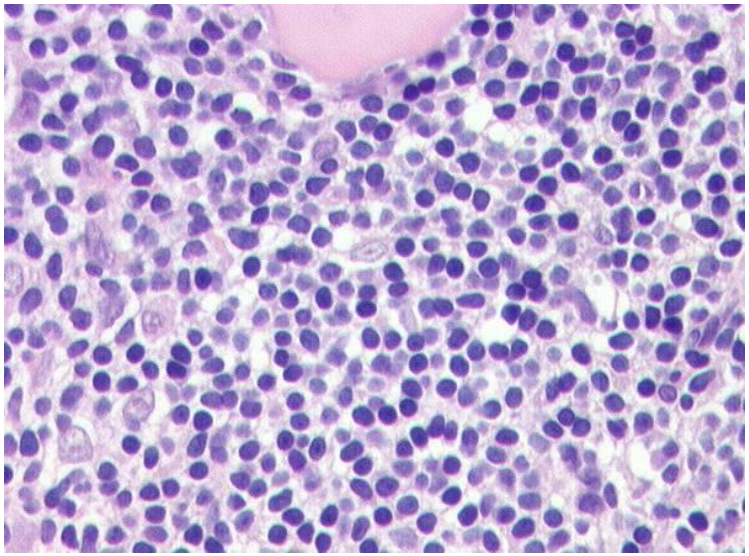
Aberration	Mutated *VH* 44%	Unmutated *VH* 56%
Clonal aberrations	80%	84%
13q deletion*	65%	48%
Isolated 13q del*	50%	20%
Trisomy 12	15%	19%
11q deletion* (*ATM*)	4%	27%
17p deletion* (p53)	3%	10%
17p or 11q del*	7	35%

13q14.3: miR-16.1 and miR-15a

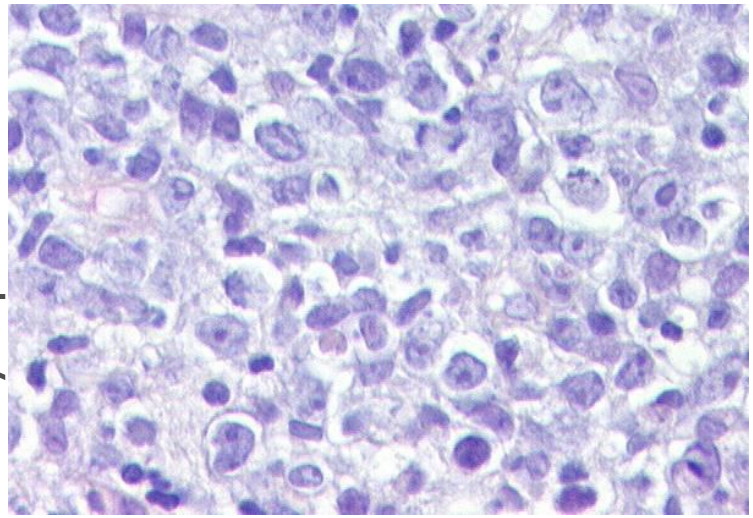
Müller-Hermelink, WHO 2008

Progression and Transformation of CLL

Bone Marrow



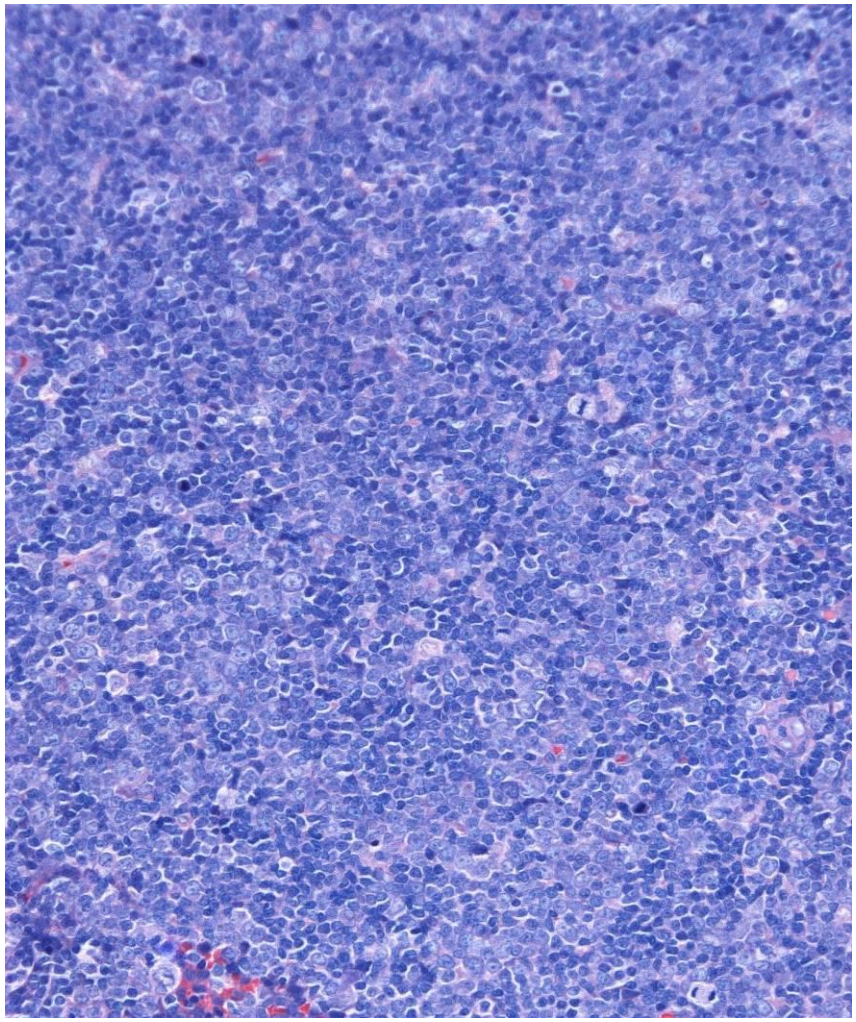
Lymph node

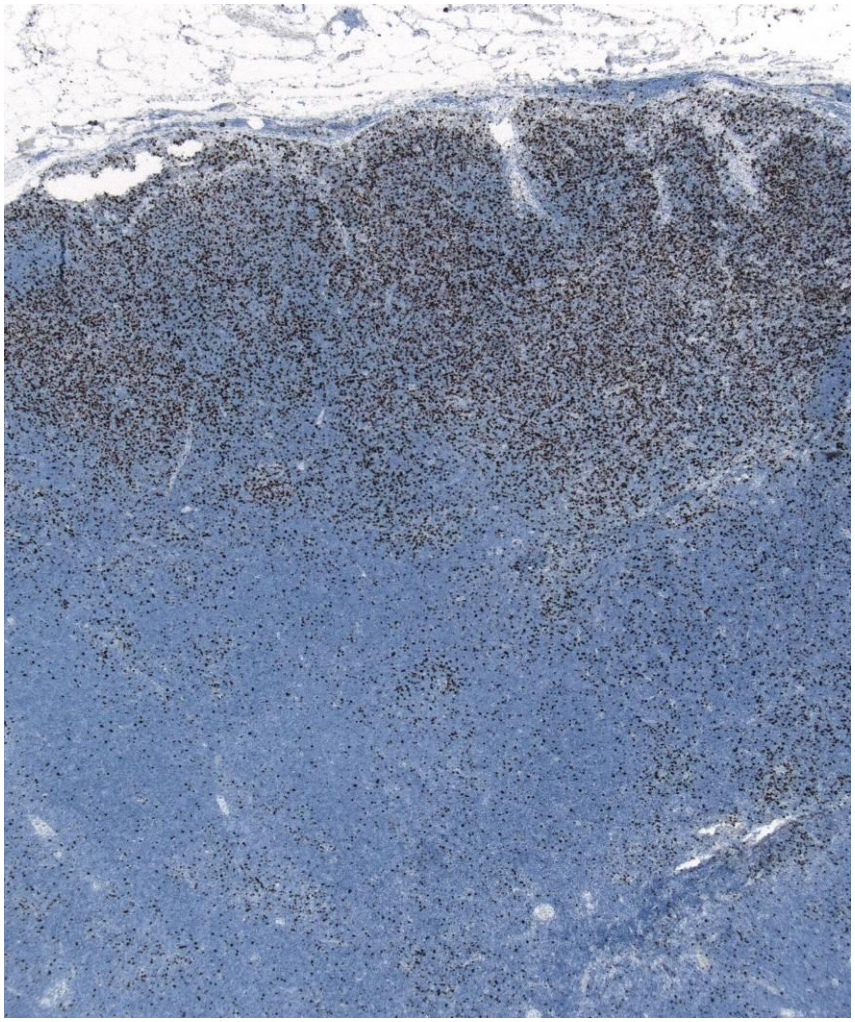


- Classical Richter´s syndrome: Diffuse large B-cell lymphoma, frequently immunoblastic morphology
  - Usually poor prognosis
  - 2-8% of CLL
  - 70% unmutated CLL
  - p53
- Paraimmunoblastic transformation or Tumor forming CLL
  - Extremely rare
- Classical Hodgkin‘s disease, frequently EBV+
  - T-cell dominated, mixed background
  - <1% of CLL

Mao Z, Quintanilla-Martinez L, AJSP 2007;31:1605

Tumor forming CLL

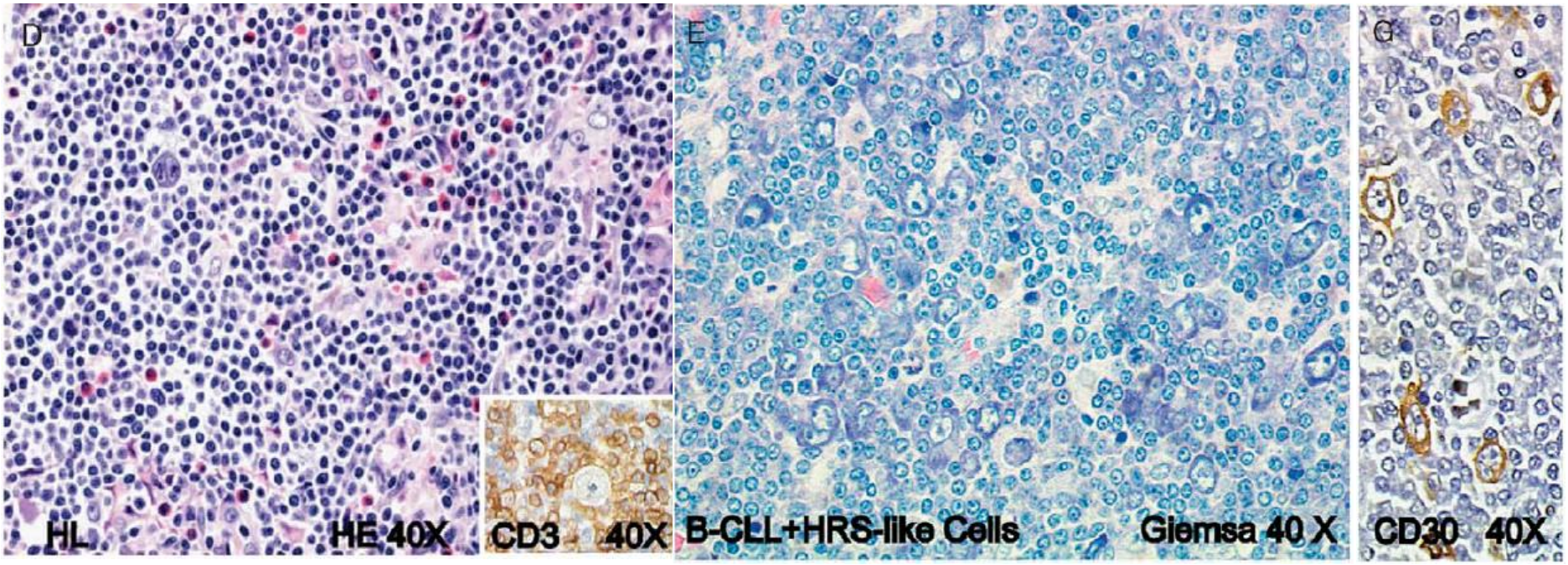




Progression and Transformation of CLL

Hodgkin Transformation

CLL with R-S-like cells



EBV might be positive or negative
Clonally unrelated are EBV+

Mao Z, Quintanilla-Martinez L, AJSP 2007;31:1605

„Nodal" monoclonal B-cell lymphocytosis

Original Articles

Reassessment of small lymphocytic lymphoma in the era of monoclonal B-cell lymphocytosis

Sarah E. Gibson,[1] Steven H. Swerdlow,[1] Judith A. Ferry,[2] Urvashi Surti,[1,3] Paola Dal Cin,[4] Nancy Lee Harris,[2] and Robert P. Hasserjian[2]

[1]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Department of Pathology, Massachusetts General Hospital, Boston, MA; [3]Pittsburgh Cytogenetics Laboratory, Magee-Women's Hospital of UPMC, Pittsburgh, PA, and [4]Center for Advanced Molecular Diagnostics, Brigham and Women's Hospital, Boston, MA, USA

Conclusions

Our findings suggest that biopsies containing chronic lymphocytic leukemia-type cells, but lacking proliferation centers and with non-enlarged or only slightly enlarged lymph nodes on imaging, represent a very indolent disease that may best be considered a tissue equivalent of monoclonal B-cell lymphocytosis rather than overt small lymphocytic lymphoma. We propose that such cases be designated as *tissue involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma-like cells of uncertain significance.*

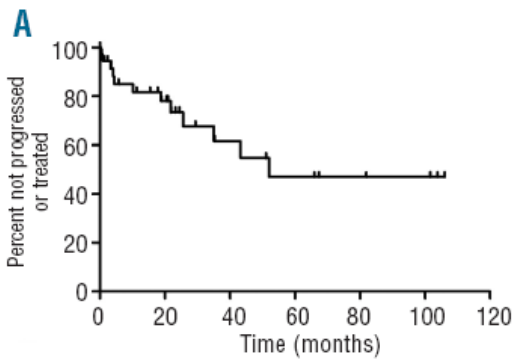
G.E. Gibson *et al.* haematologica | 2011; 96(8)

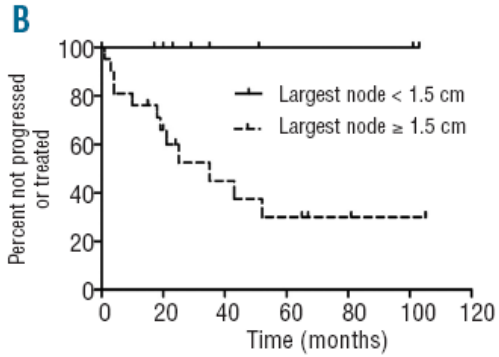
„Nodal" monoclonal B-cell lymphocytosis

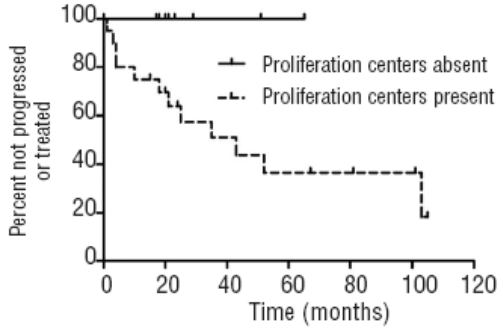
Table 3. Proposed classification scheme for CLL/SLL cells in blood and tissues.

	Peripheral blood monoclonal B-cell count	Biopsy-proven tissue infiltrate of cells with CLL phenotype	Proliferation centers	Lymphadenopathy
Chronic lymphocytic leukemia (CLL)*	≥5×10⁹/L	Present or Absent	Present or Absent	Present or absent
Monoclonal B-cell lymphocytosis (MBL)*	<5×10⁹/L	Absent	NA	No palpable lymphadenopathy or splenomegaly
Small lymphocytic lymphoma (SLL)	<5×10⁹/L	Present	Present or Absent	Enlarged lymph nodes (≥1.5 cm) on CT staging
Tissue involvement by CLL/SLL-like cells of uncertain significance	<5×10⁹/L	Present	Absent	No lymph nodes ≥1.5 cm on CT staging

*NA: not applicable. *Definitions according to the WHO 2008 classification.*[1]







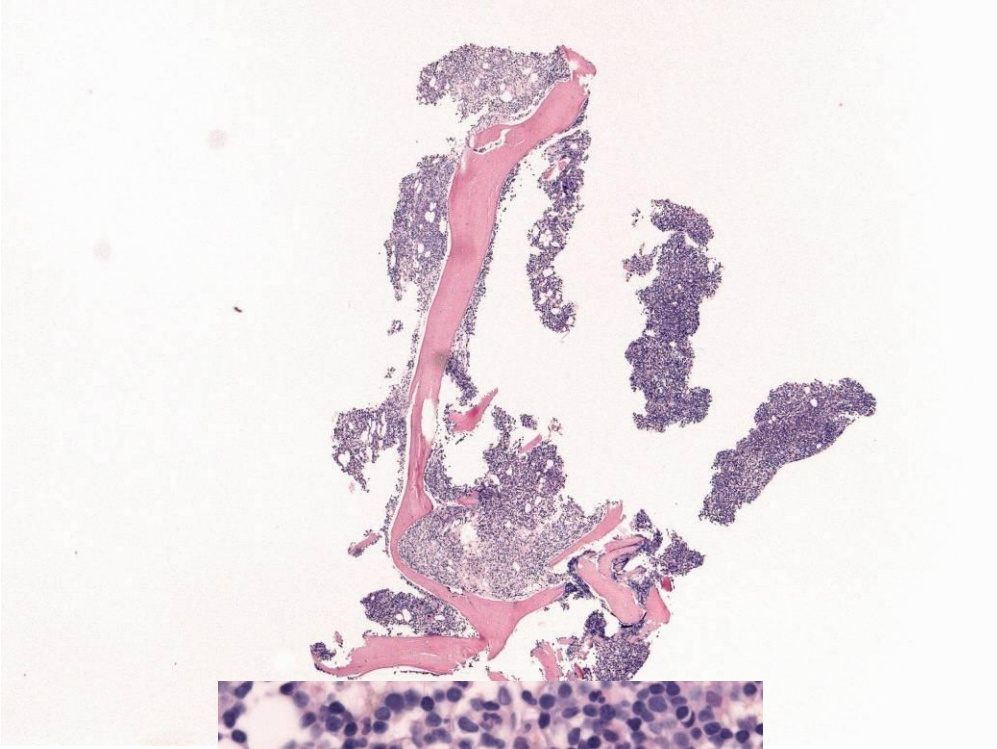
G.E. Gibson *et al.* haematologica | 2011; 96(8)

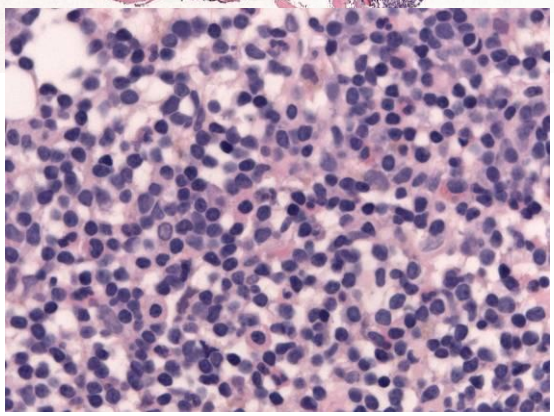
Terminology

- CLL or SLL in situ??
- nodal manifestation of monoclonal B-cell lymphocytosis??
- CLL lymphoma like-cells of uncertain significance

- Do we need the BM and PB for making a definitive diagnosis?

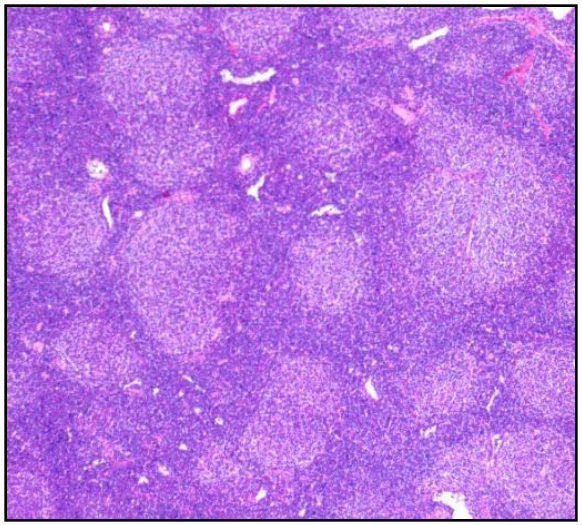
- Should we look for these lesions??

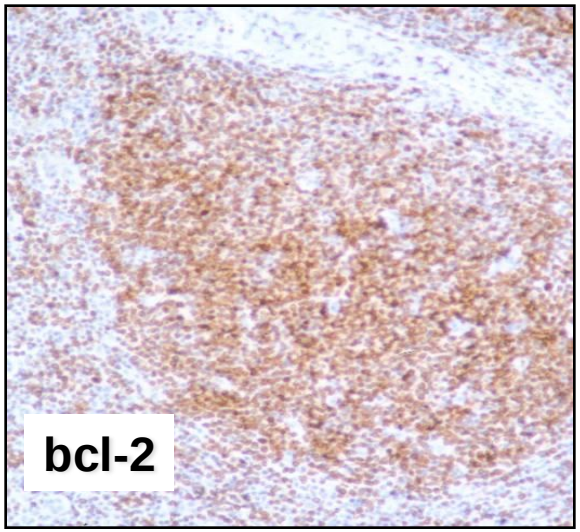




Necker River, Tübingen

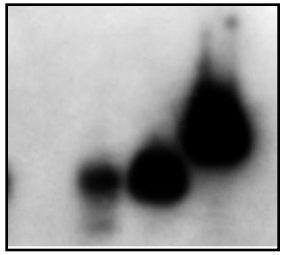
Follicular Lymphoma





Morphology: Follicular proliferation of centrocytes and centroblasts associated with FDC

Immunophenotype: CD20+, CD19+, CD79a+
IgM, IgG, IgA
CD10+, Bcl-2+, BCL-6+



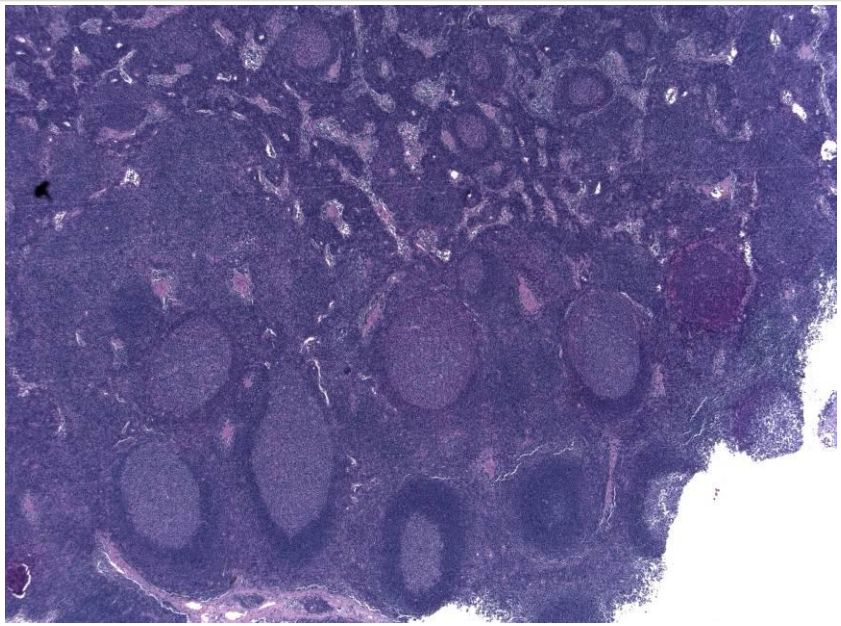
Genetics: JH/BCL-2 rearrangement
t(14;18)

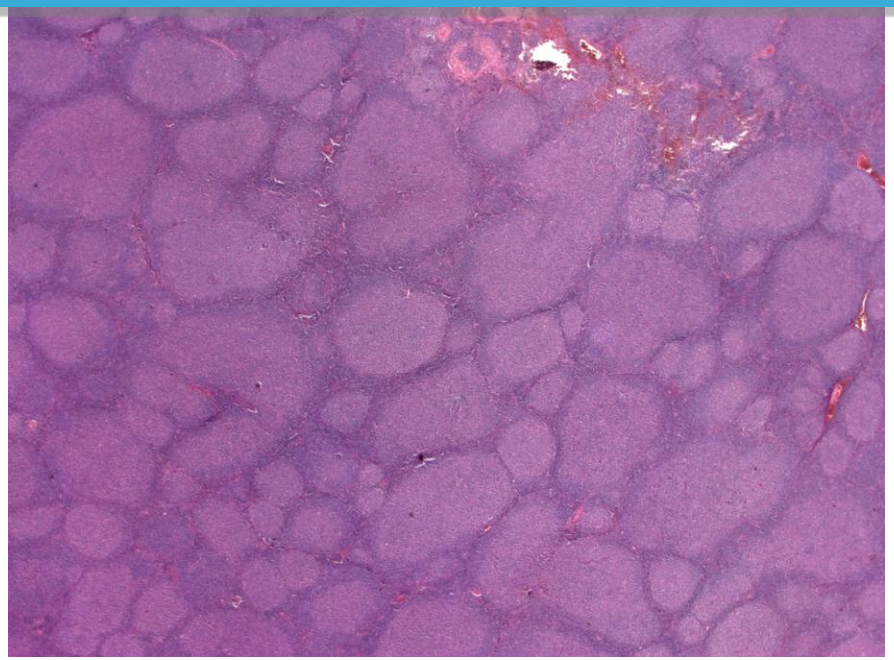
Clinical: Adults, indolent course but generally incurable. Most patients present with advanced Stage disease, III/IVA

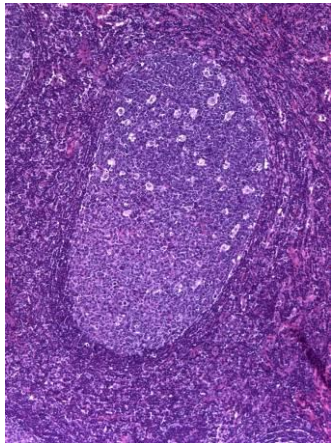
Follicular Lymphoma

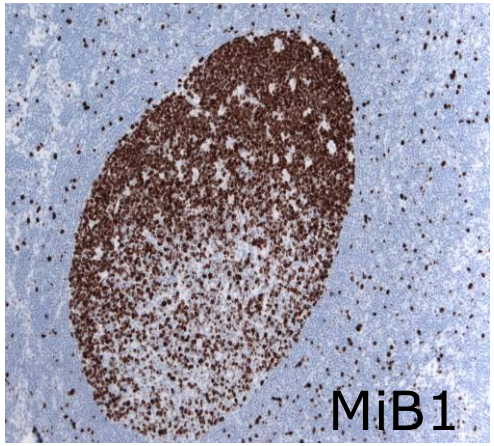
- Epidemiology:
- FL accounts for about 20% of all lymphomas with the highest incidence in USA and Western Europe
- Less frequent in Asia and Latin America
- Median age in the 6th decade
- Male:Female ratio 1:1.7
- The BM is involved in 40-70% of the cases

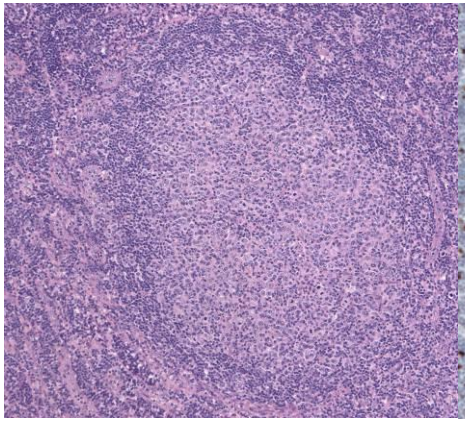
Reactive hyperplasia Follicular Lymphoma

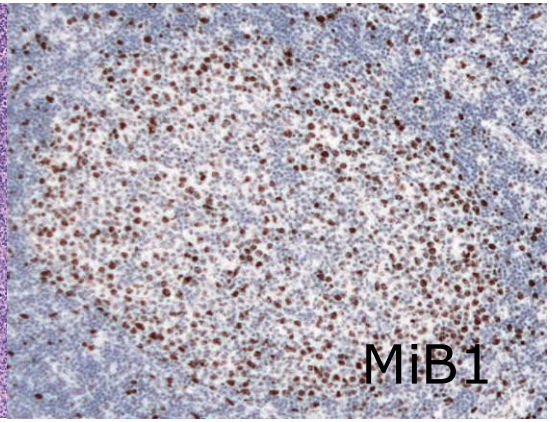












Cytological grading of follicular lymphoma

- Historical basis of grading - empiric
- counting blasts in 10 neoplastic follicles with 40x
- grade 1 = 0-5 blasts per HPF; grade 2= 6-15 blasts per HPF; grade 3 = >15 blasts per HPF

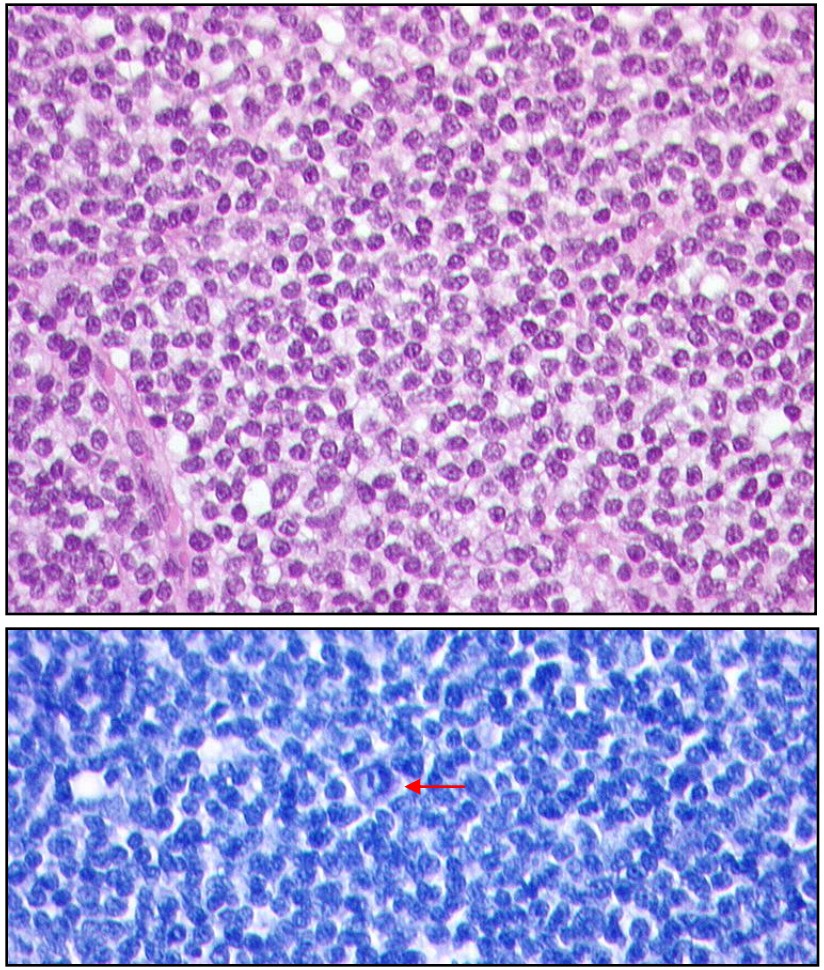
- Most studies show lack of reproducibility among pathologists

- Most studies show difference in natural history and overall survival among different cytological grades in FL

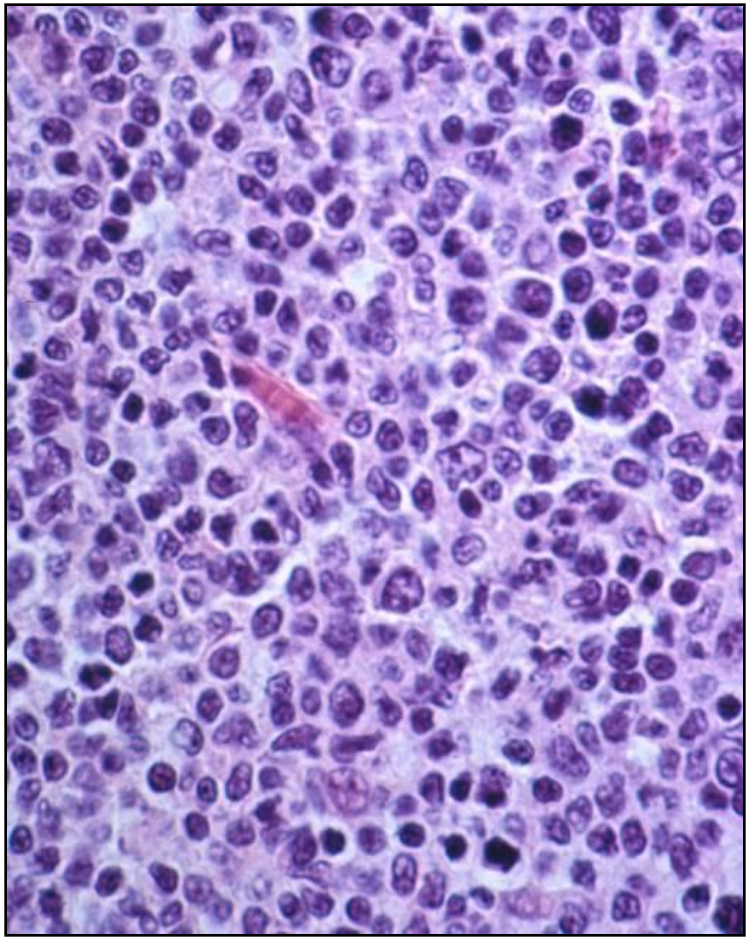
- Long-term significance of grade is still controversial

Cytological grading of follicular lymphoma

Grade 1

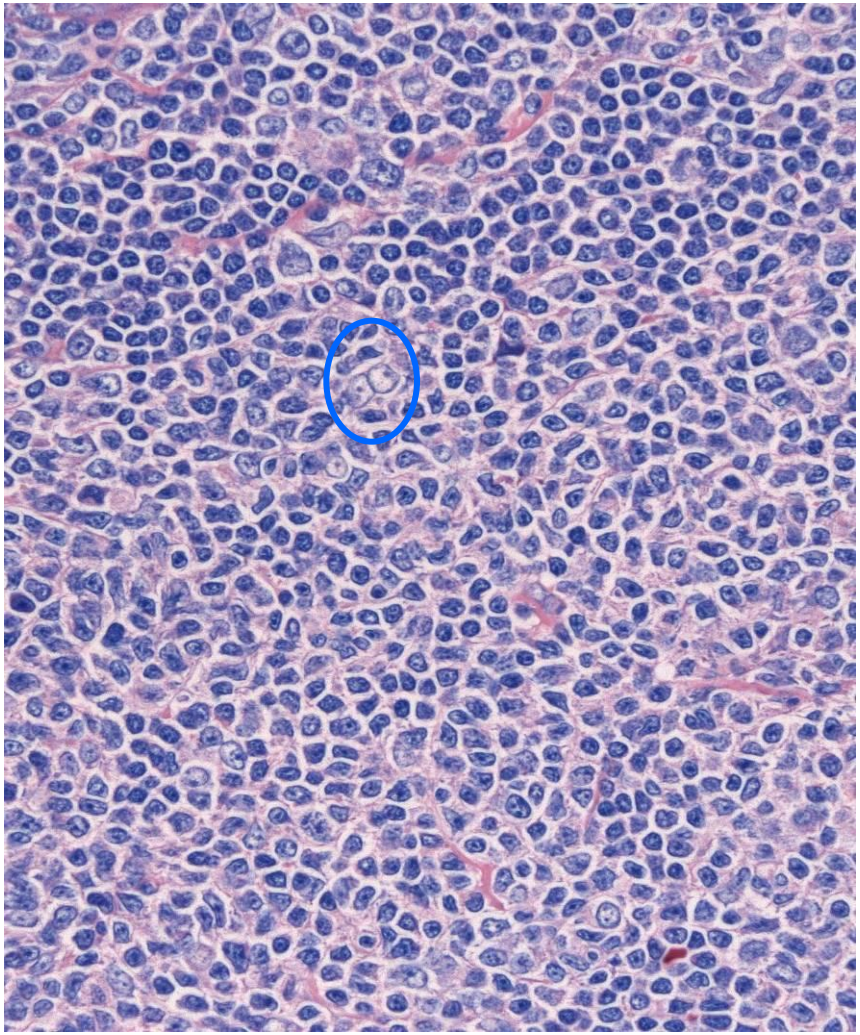


Grade 2

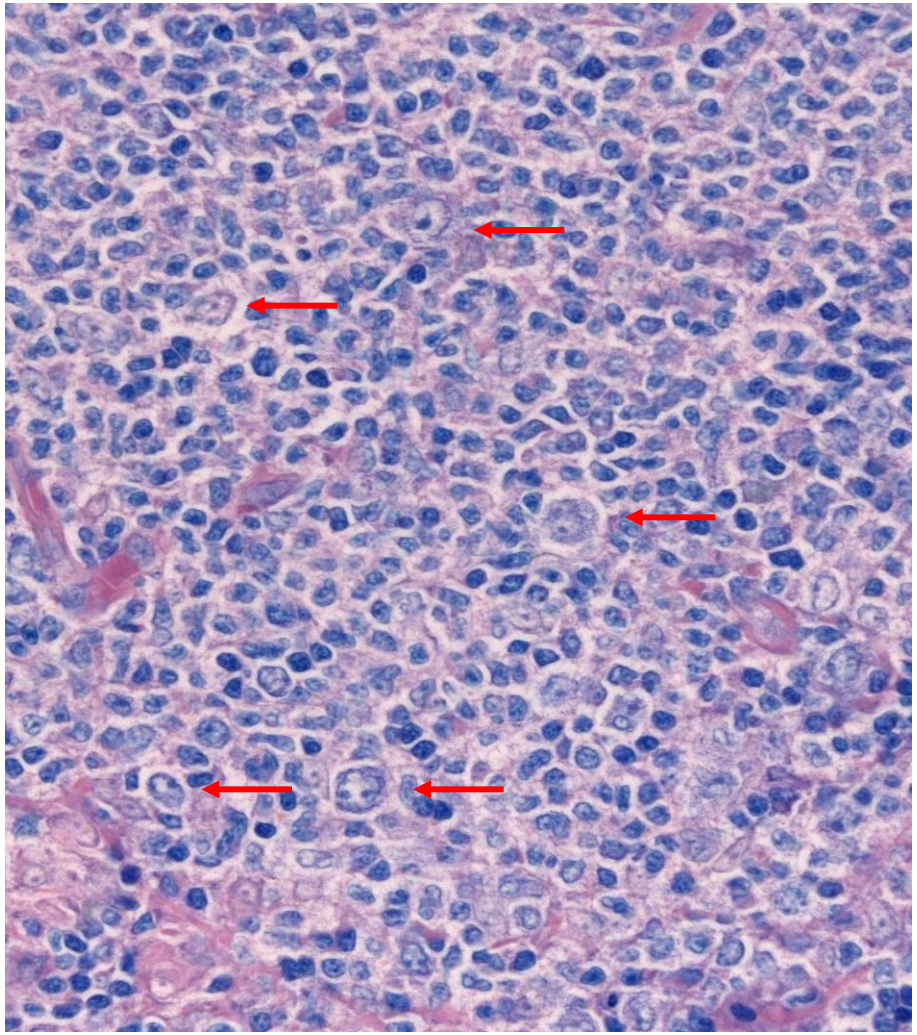


Cytological grading of follicular lymphoma

Grade 1

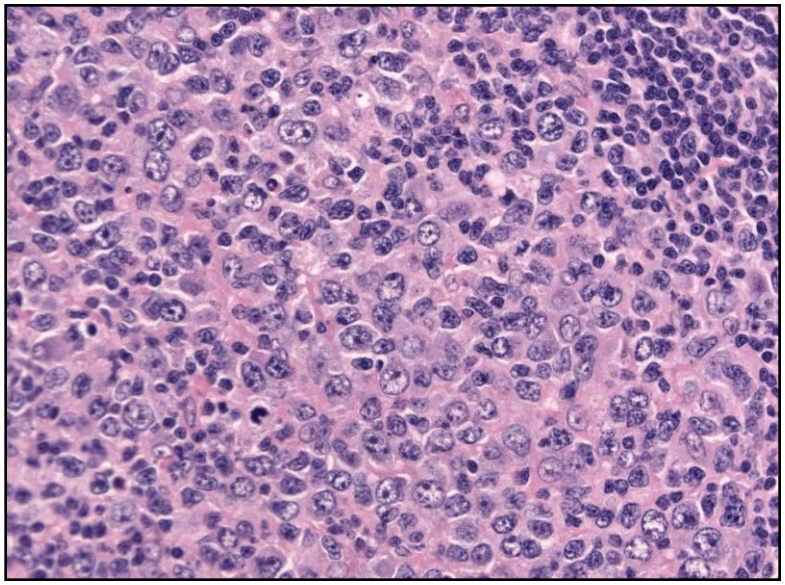


Grade 1-2



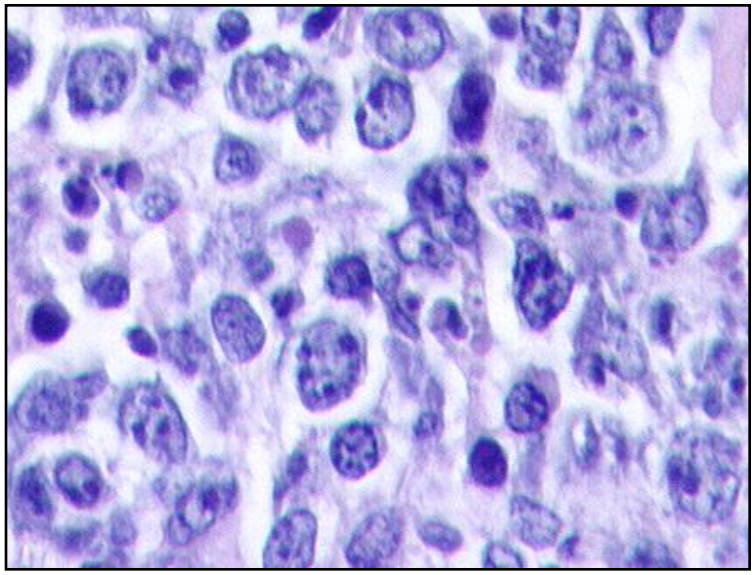
Cytological grading of follicular lymphoma

Grade 3A



- 15 per HPF with centrocytes
- Diffuse areas uncommon
- BM commonly involved
- CD10+,BCL6+,BCL2+,MUM1-
- P53 usually negative
- T(14;18) common

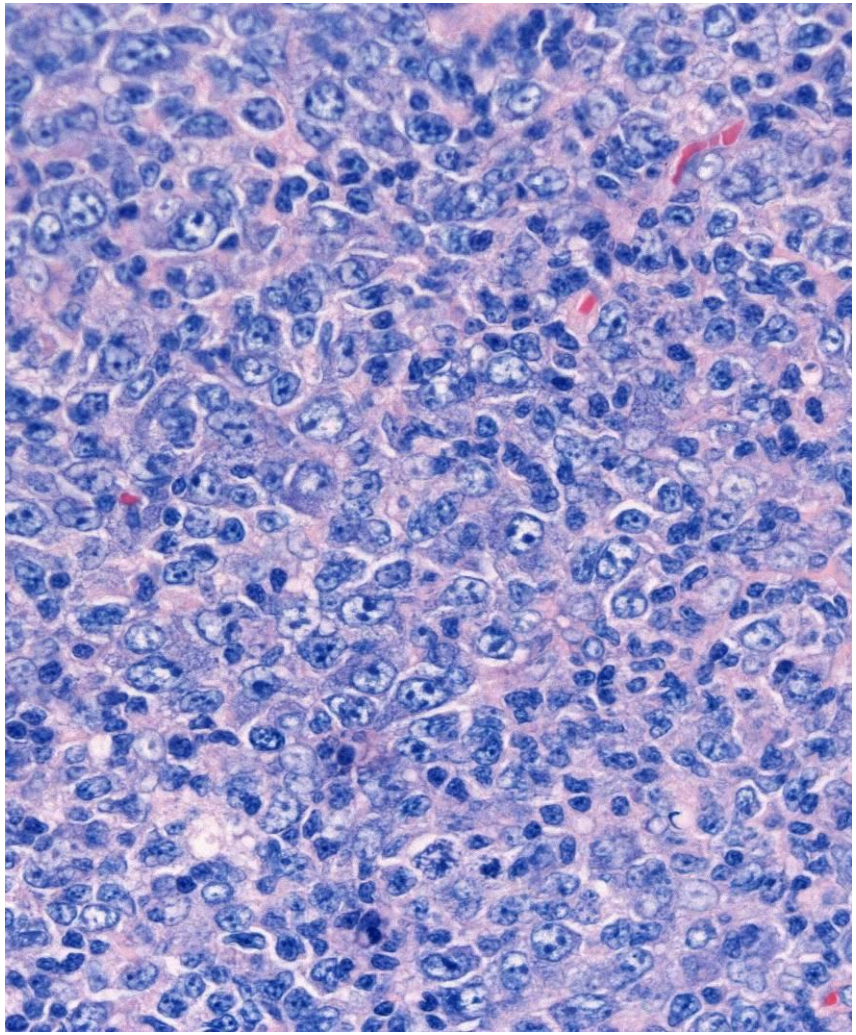
Grade 3B



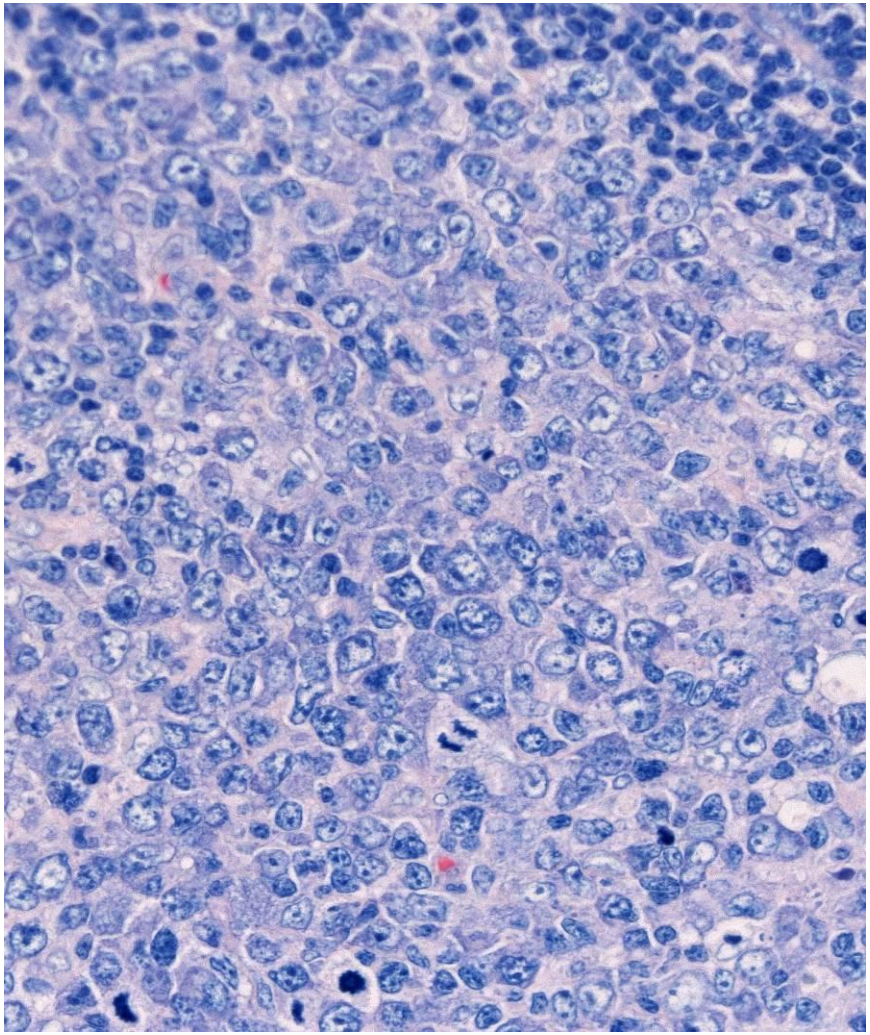
- Almost exclusively centroblasts
- Diffuse areas common
- BM infrequently involved
- CD10-,BCL6+,BCL2-/+,MUM1+/-
- P53 + in 30% of the cases
- T(14;18) uncommon

Cytological grading of follicular lymphoma

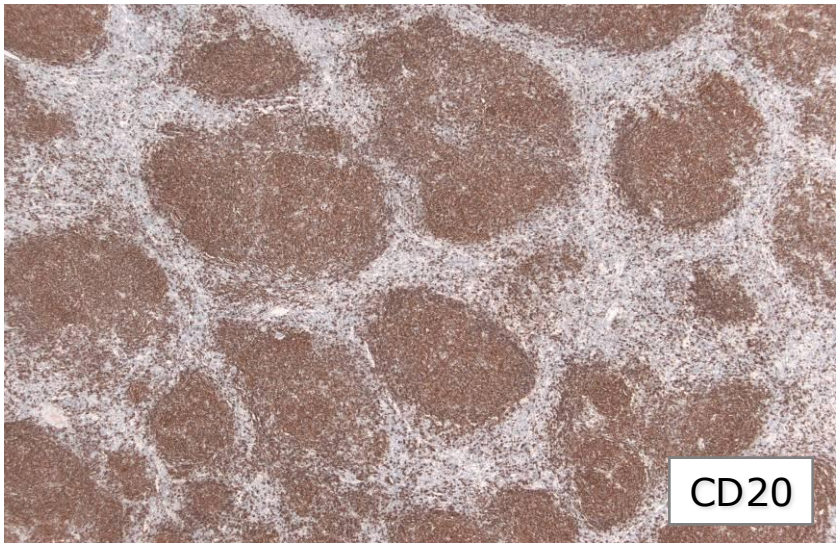
Grade 3A

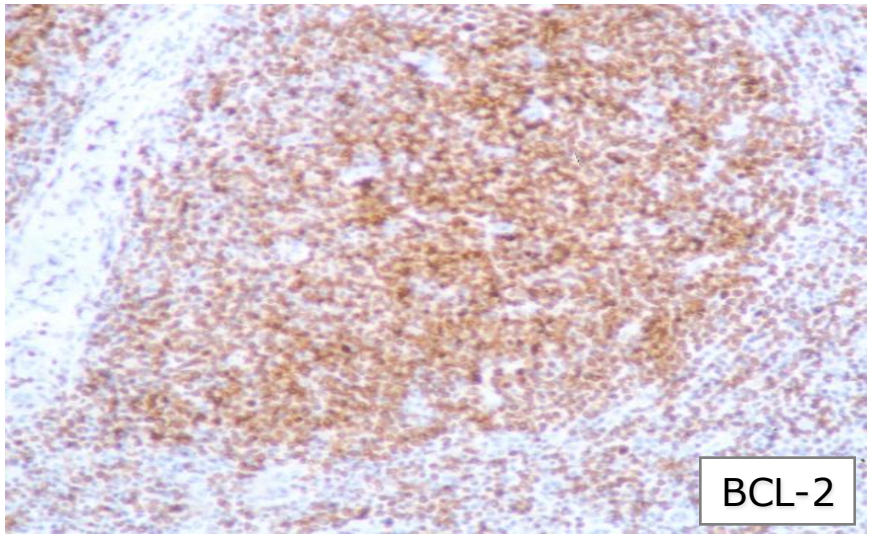


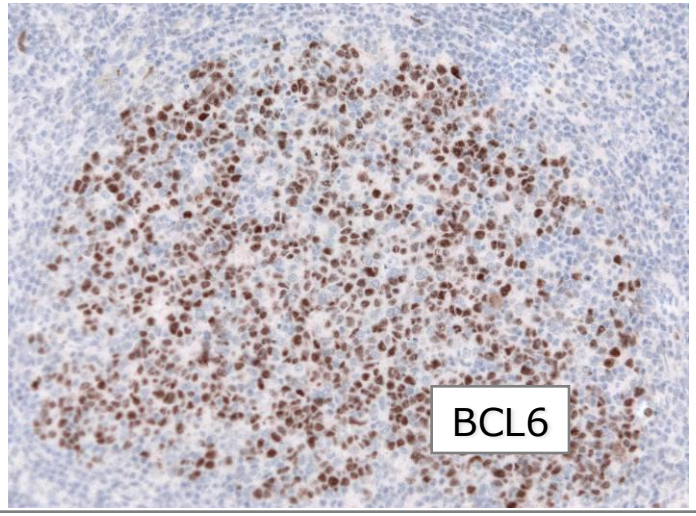
Grade 3B

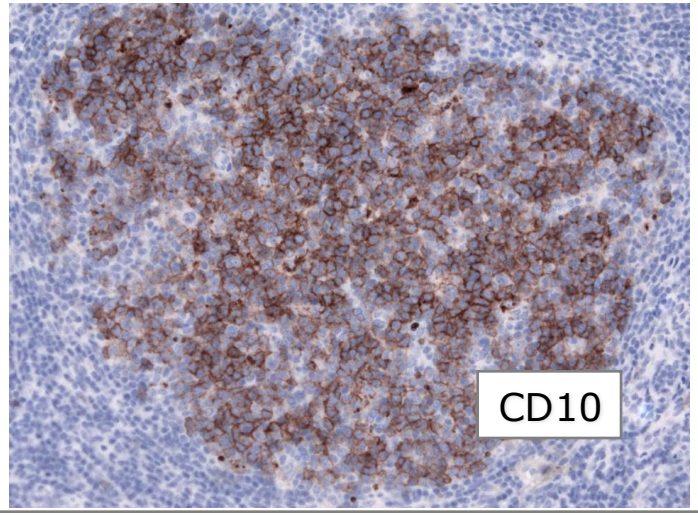


Immunophenotype of Follicular lymphoma

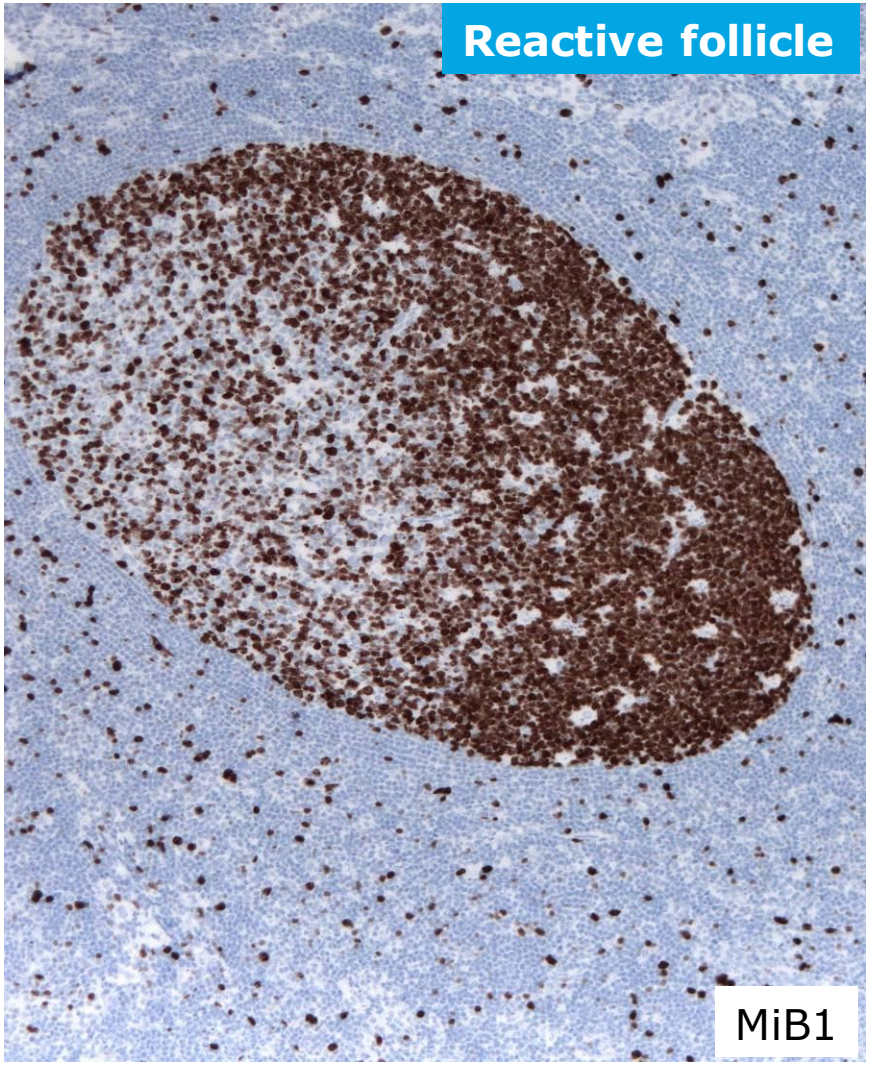


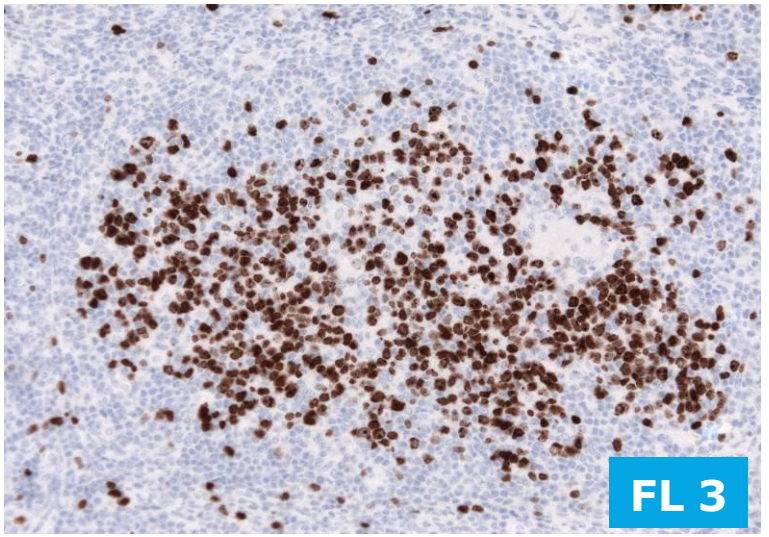




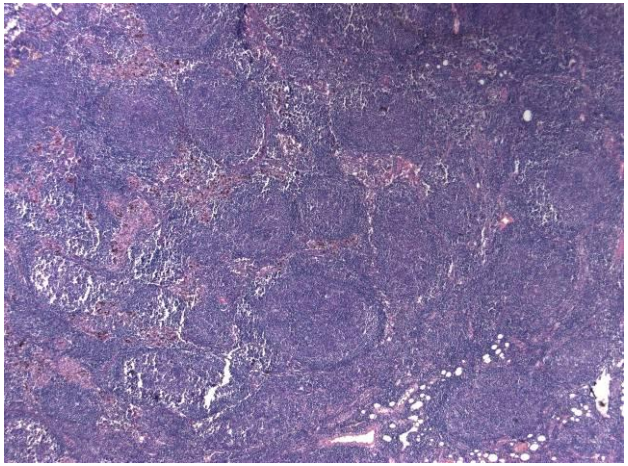


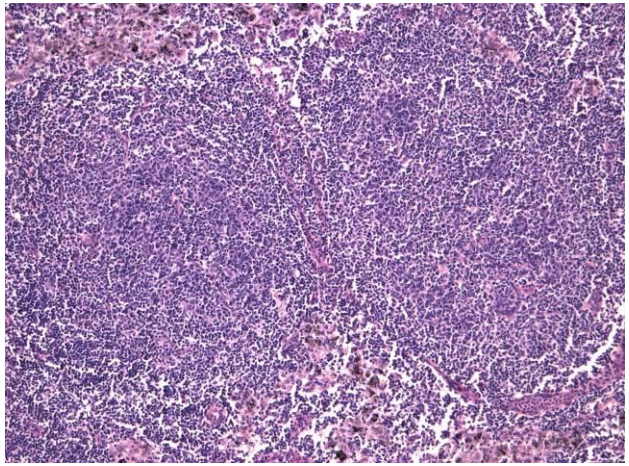
Proliferation in Follicular Lymphoma

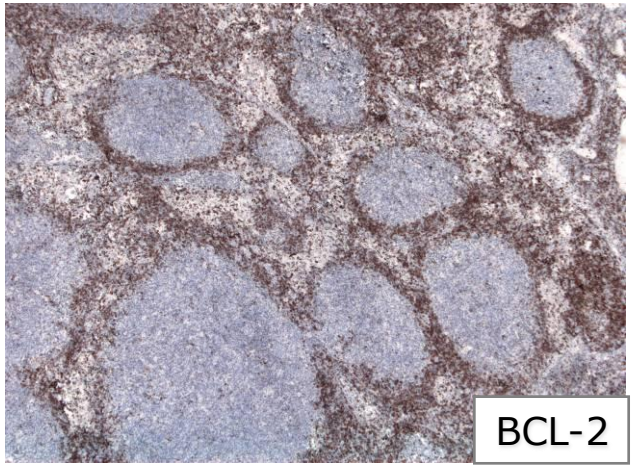


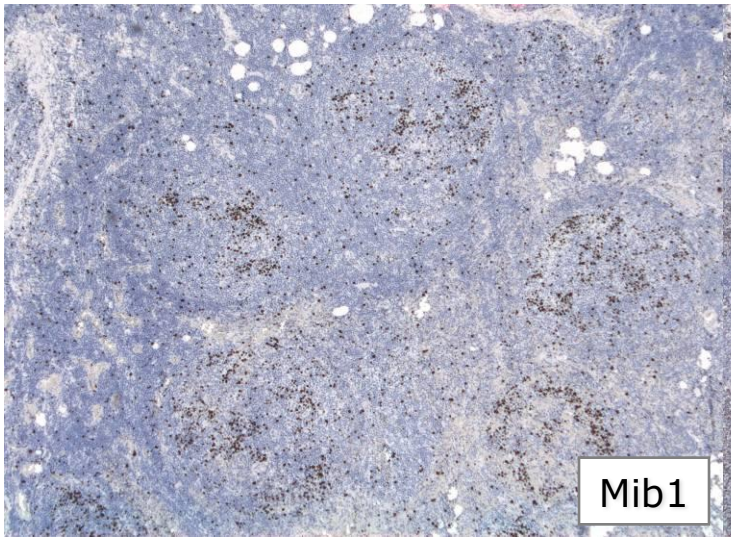


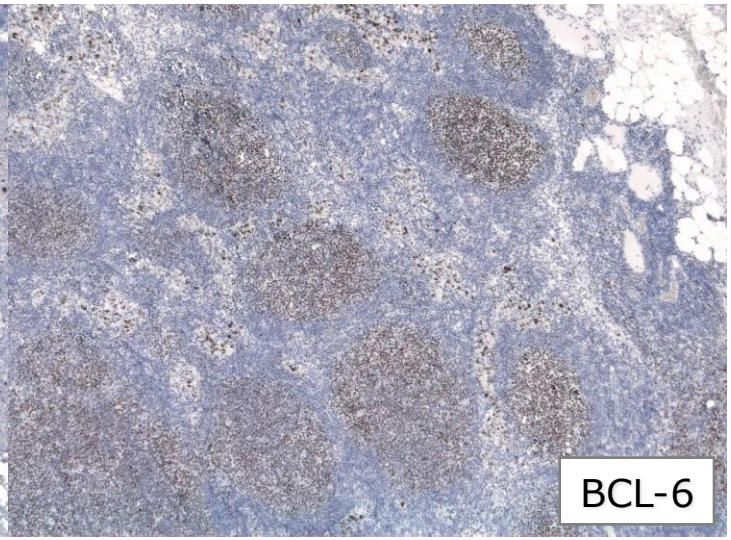
BCL2 negative Follicular lymphoma 1/2

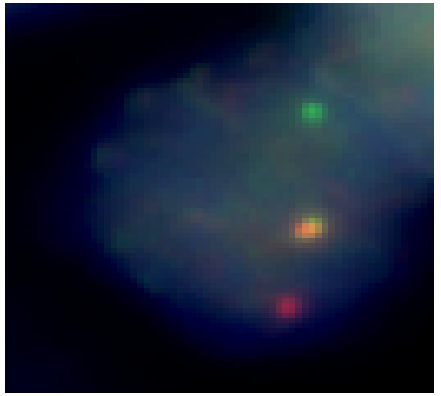






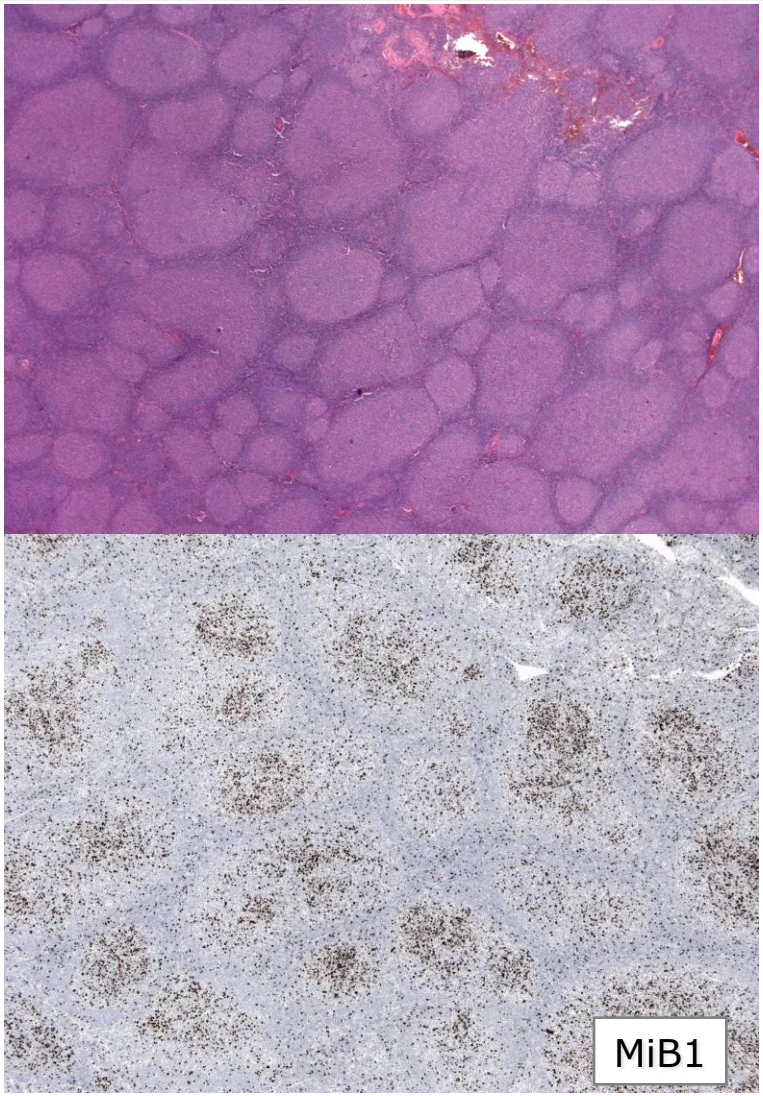


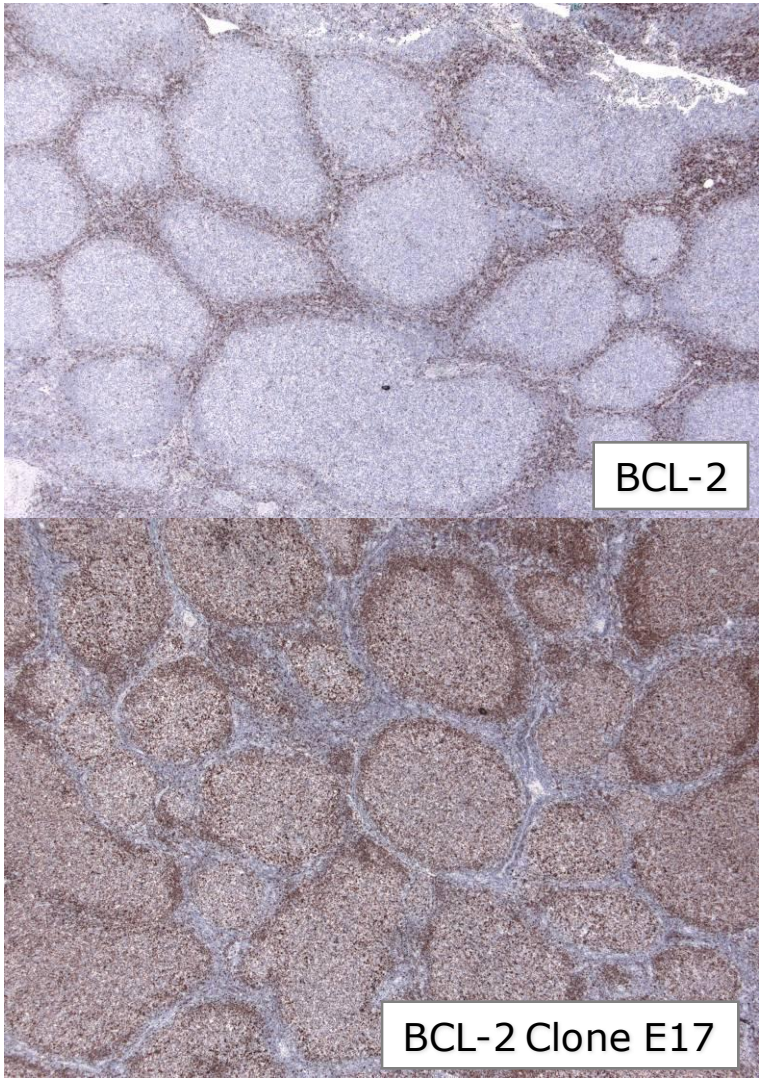




t(14;18)

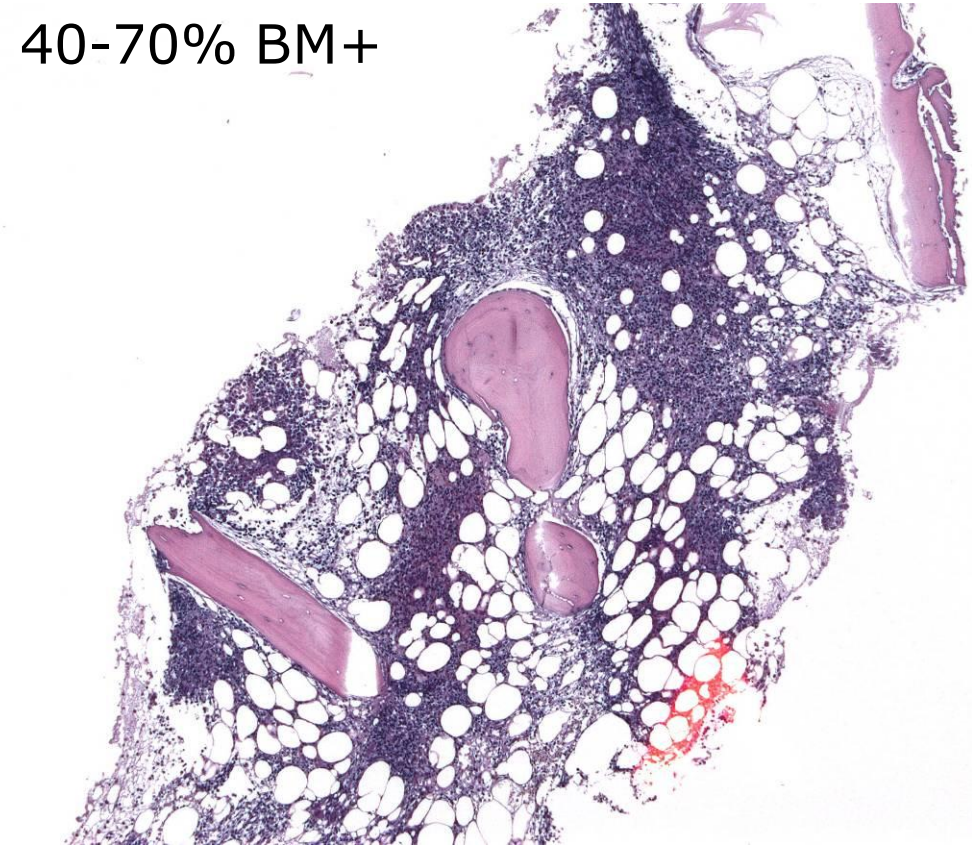
BCL2 „negative“ Follicular lymphoma 1/2

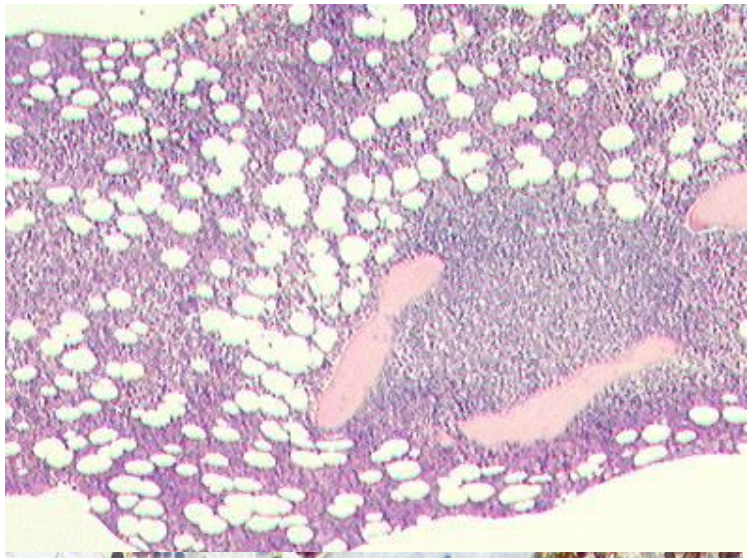


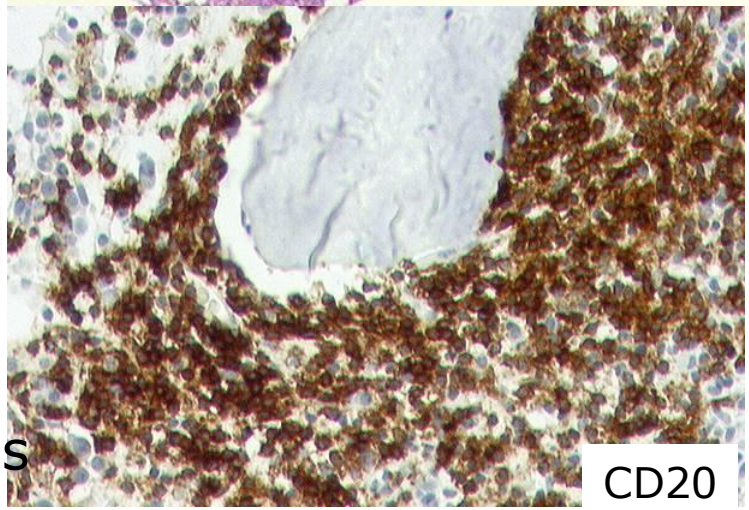


BM infiltration by Follicular Lymphoma

40-70% BM+





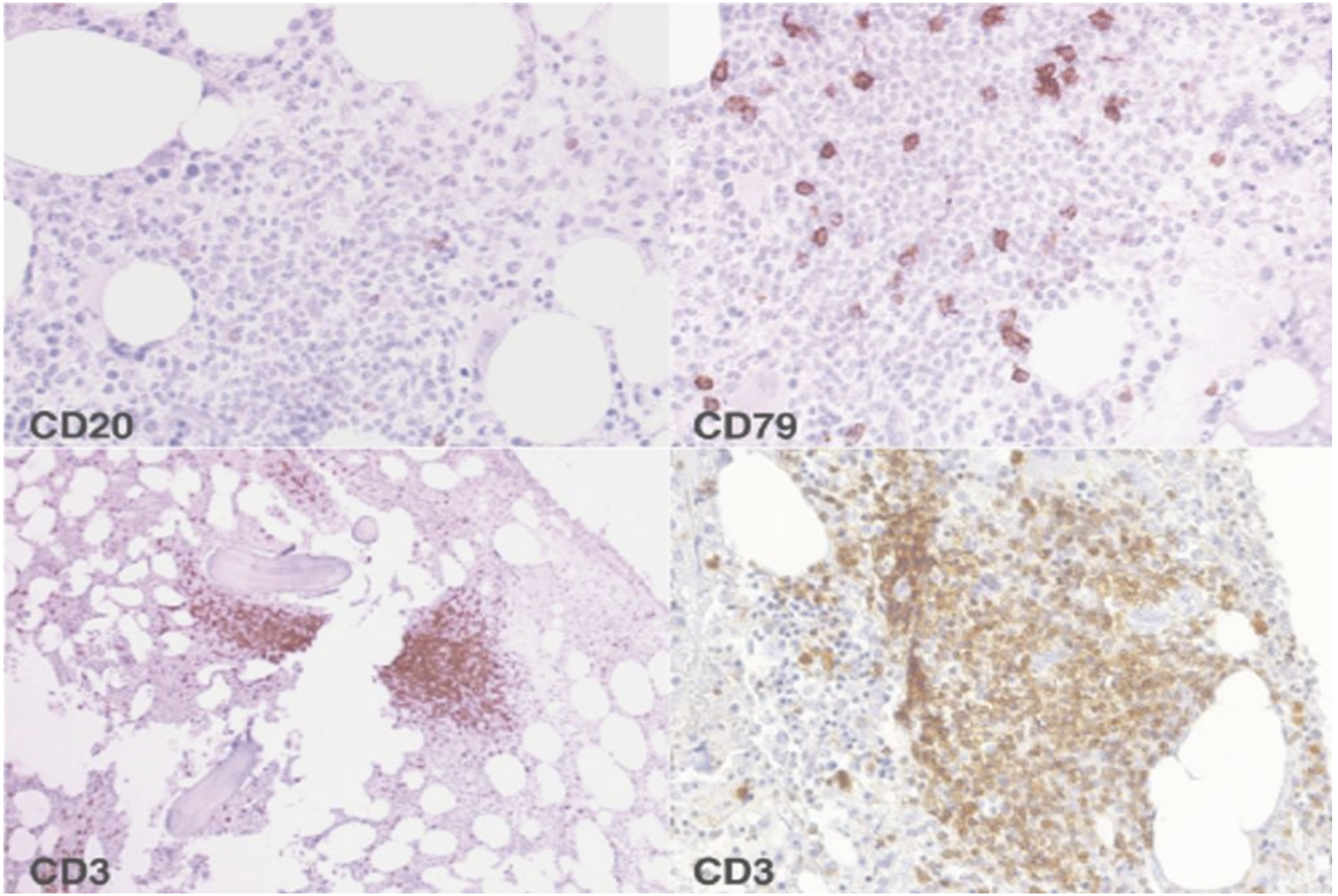


CD20

After Rituximab therapy:

- Do more than 1 B-cell marker
- Be careful with reactive T-cell infiltrates

T-cell aggregates mimicking residual lymphoma in BM



Prognostic markers in follicular lymphoma

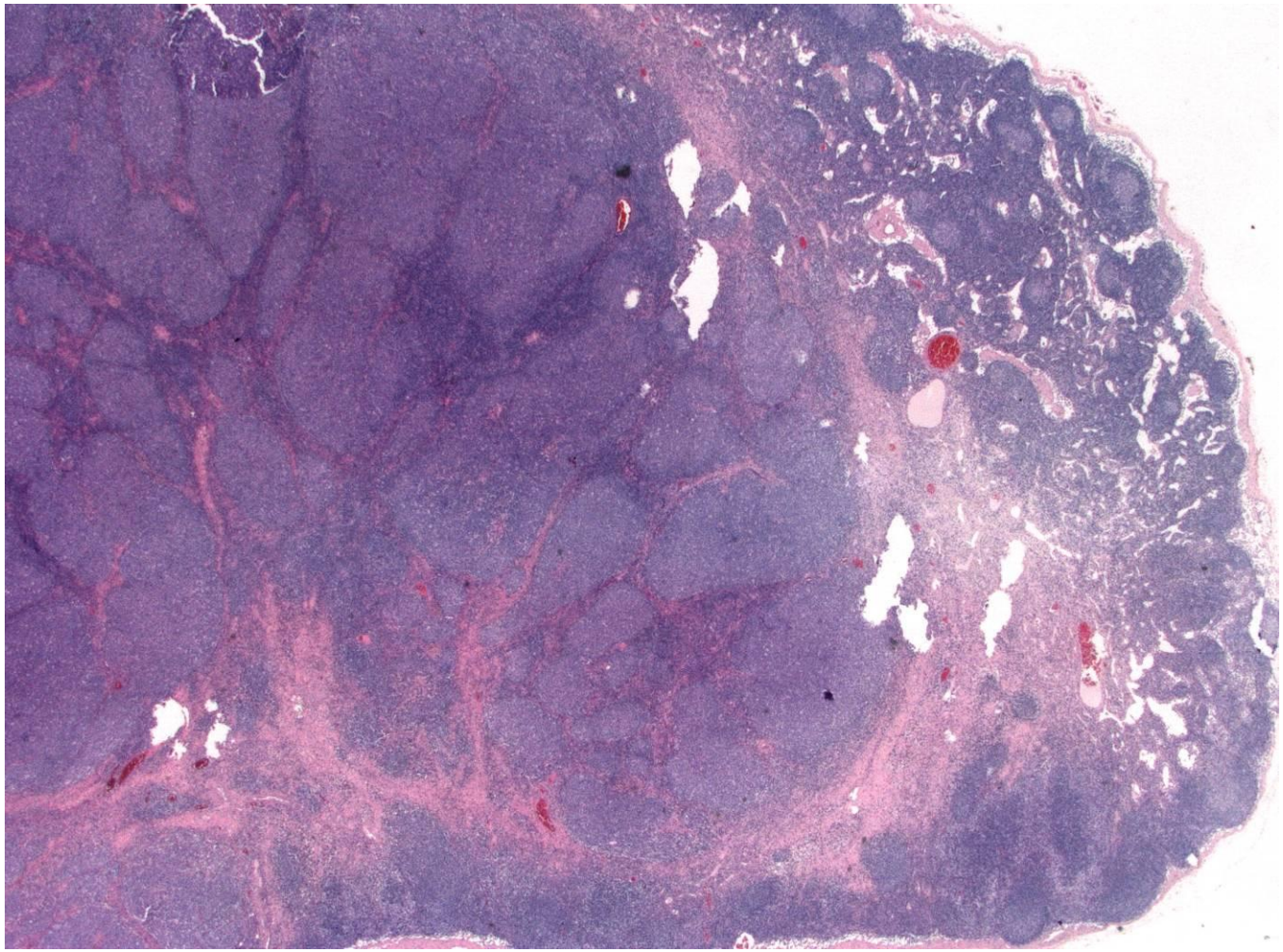
- FLIPI:
  - Clear separation of three risk groups
  - does not identify patients with early treatment failure
  - does not give information on the biology of tumors

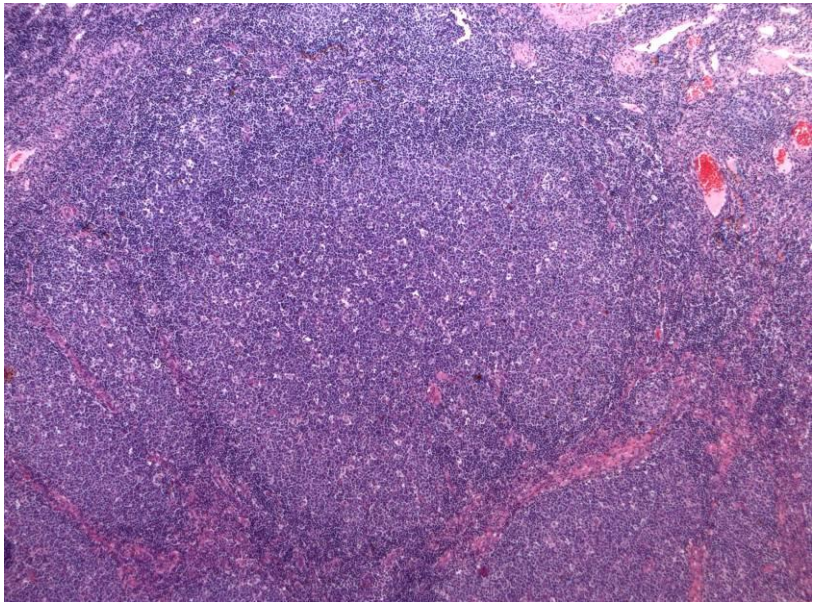
- Cytologic grading system:
  - No clinical difference between grade 1-2
  - Important to differentiate grade 3A - 3B

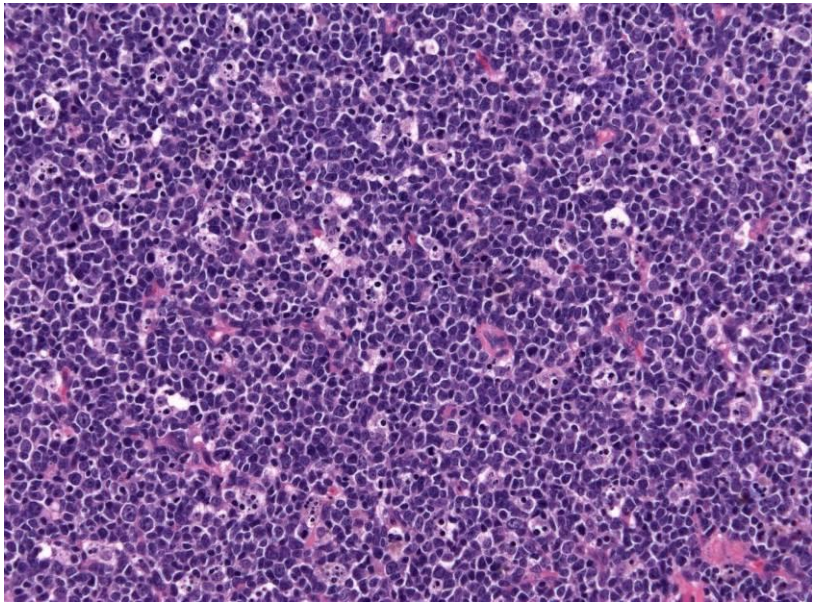
- Proliferation:
  - Ki-67 <20% G1-2; >20% G3

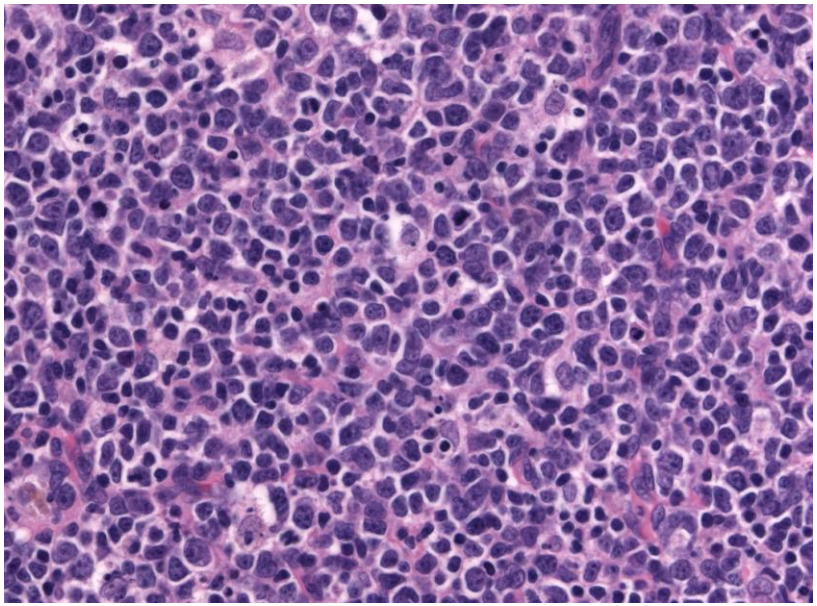
- Bystander cell within the tumor:
  - Macrophage content as prognostic marker

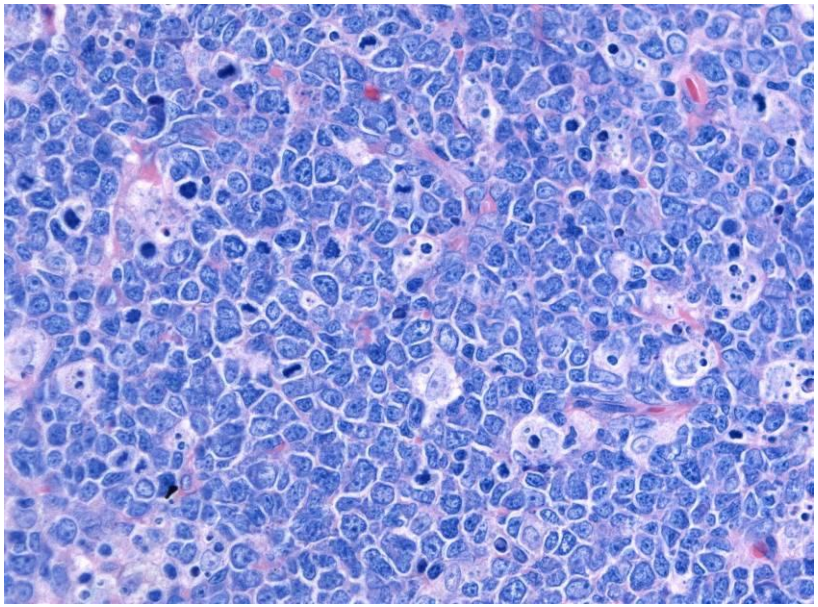
- A 16 year-old boy presents with an enlarge cervical lymph node without additonal symptoms

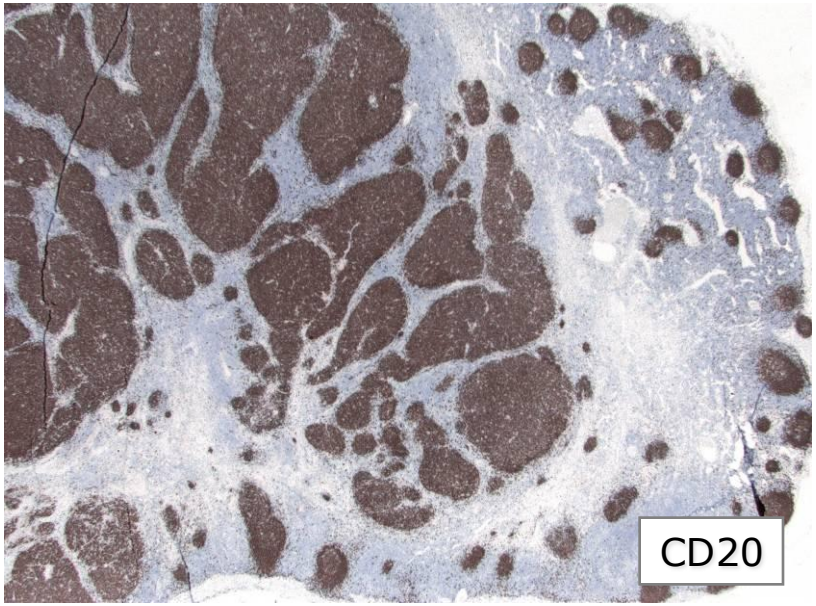


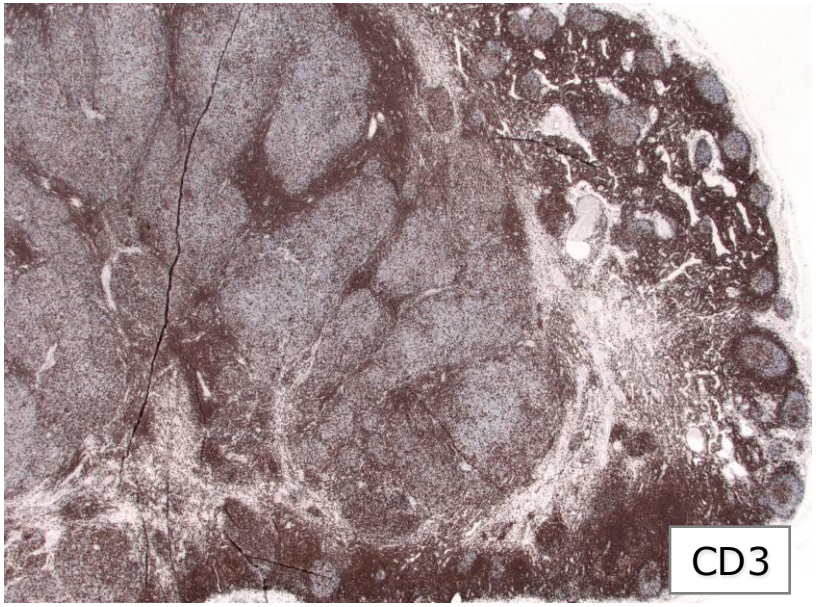









CD20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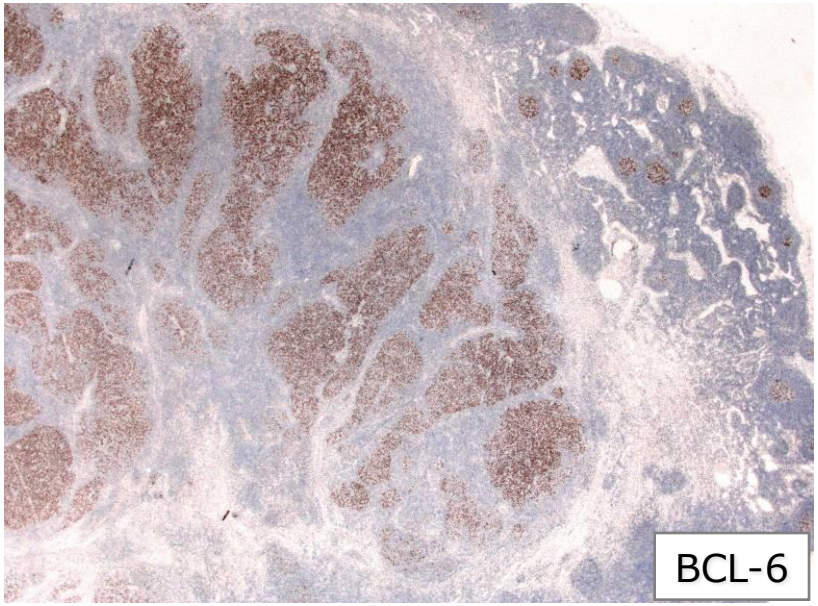
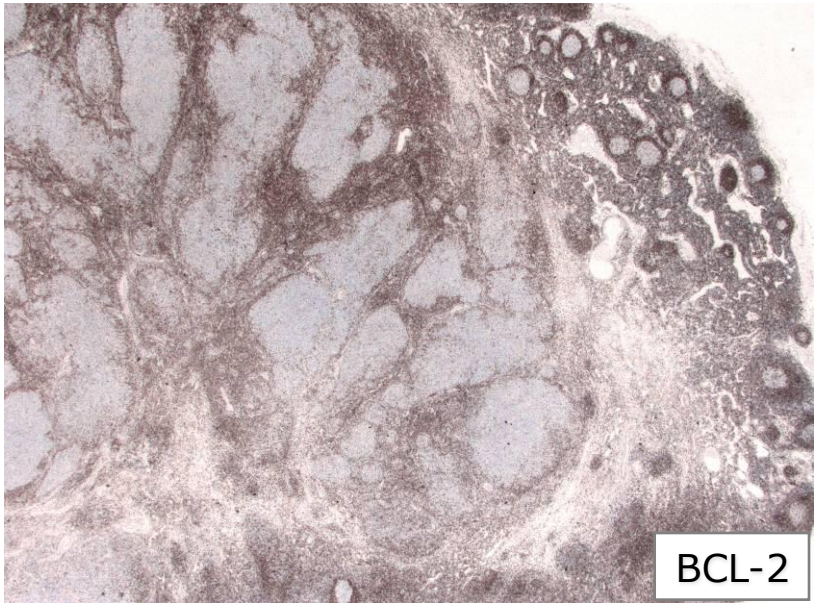
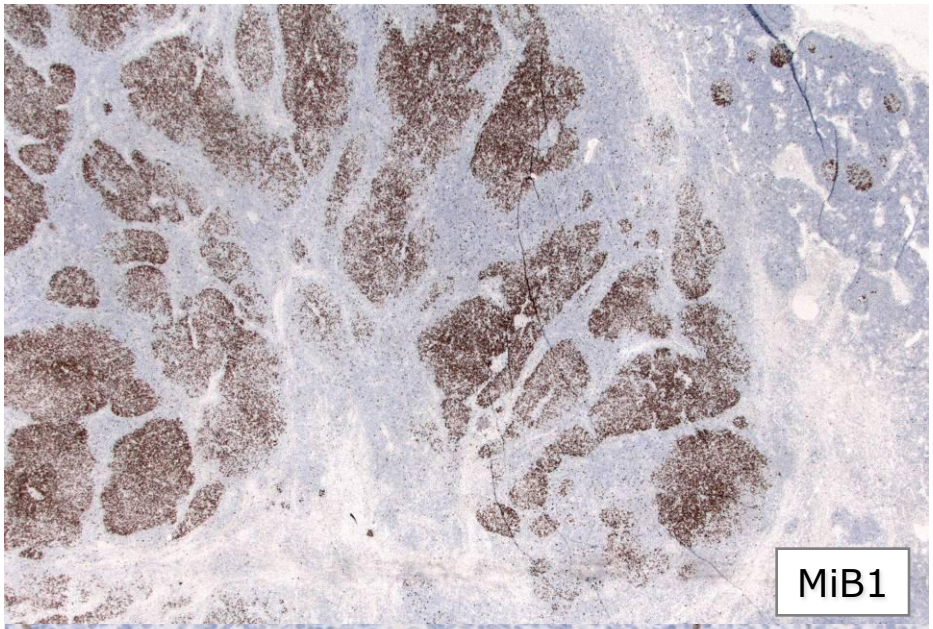
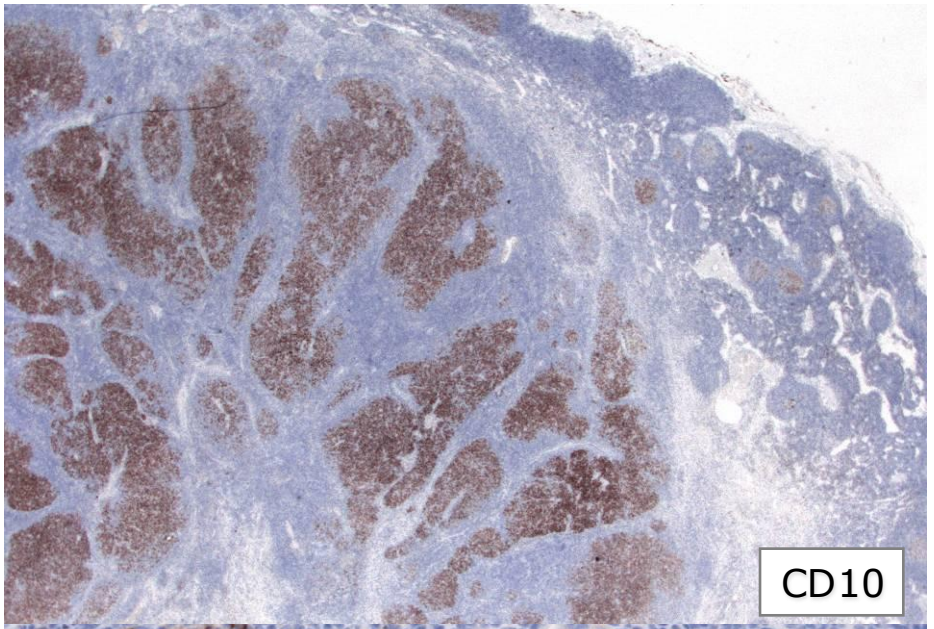
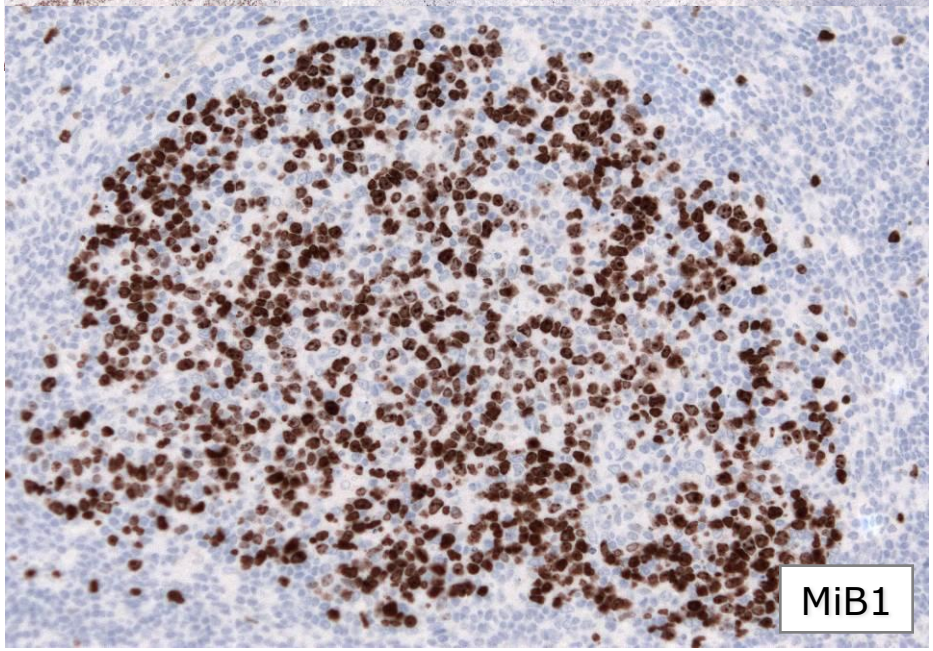
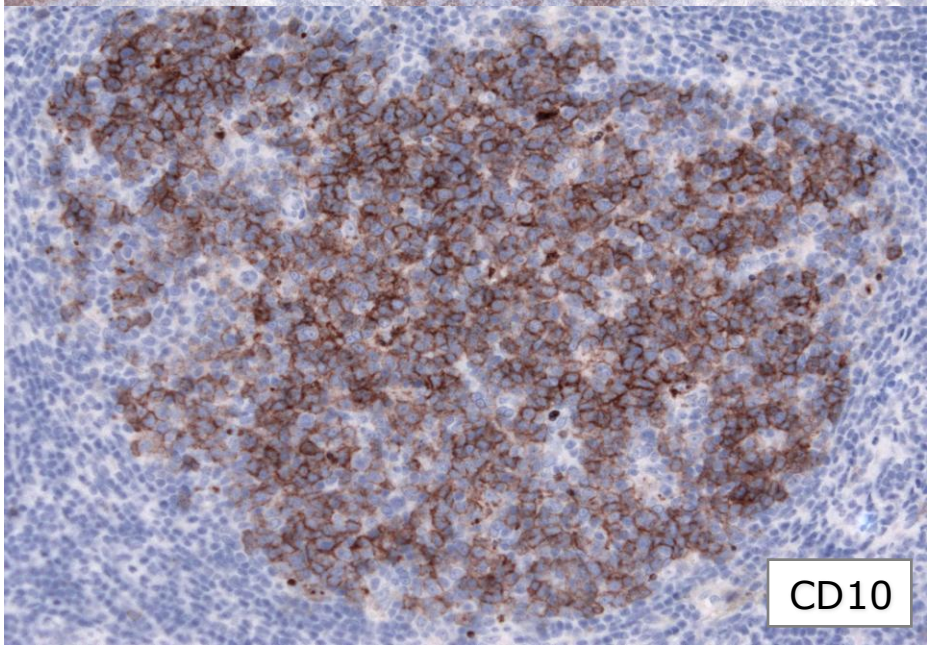

BCL-6


BCL-2


MiB1

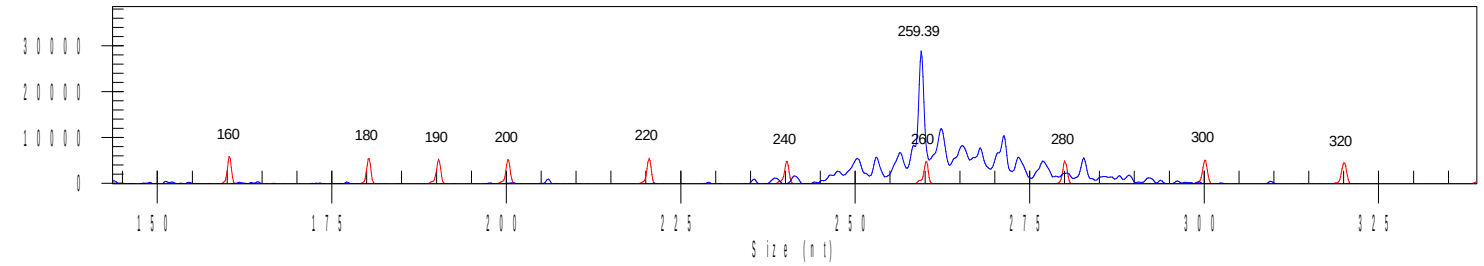

CD10


MiB1

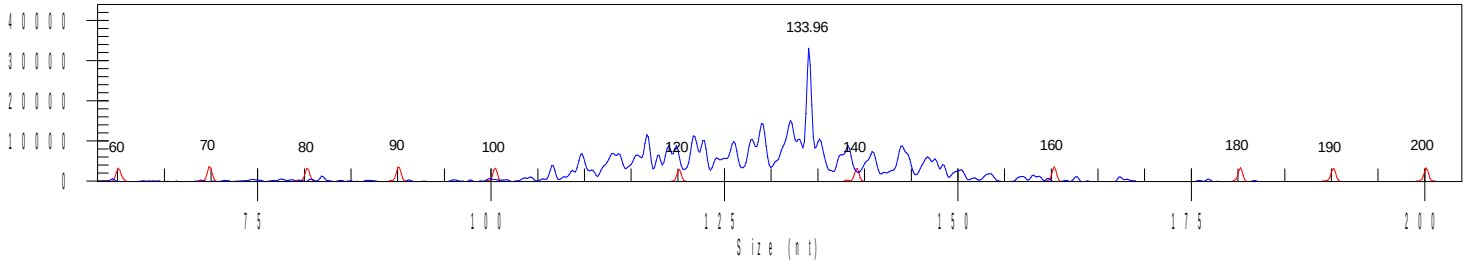

CD10

Pediatric Follicular Lymphoma

FR 2



FR 3

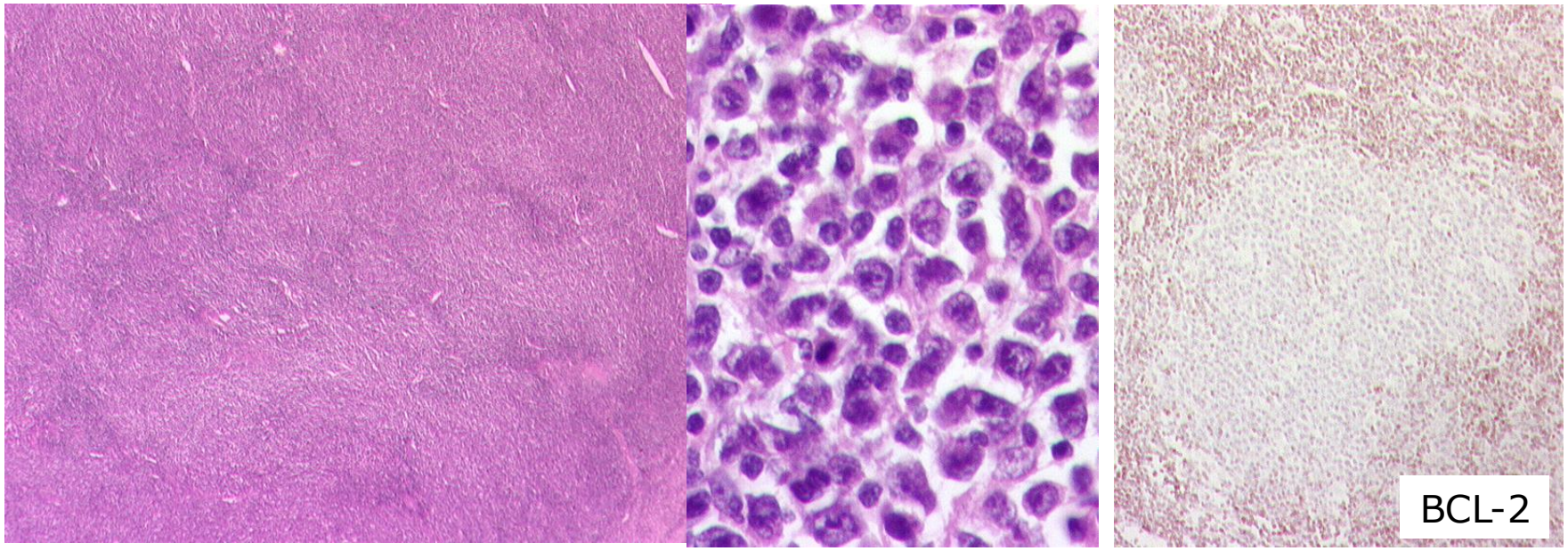


IGH

Pediatric Follicular lymphoma

A 22 year-old boy presented with intraparotideal lymph node

Follicular lymphoma grade 3B

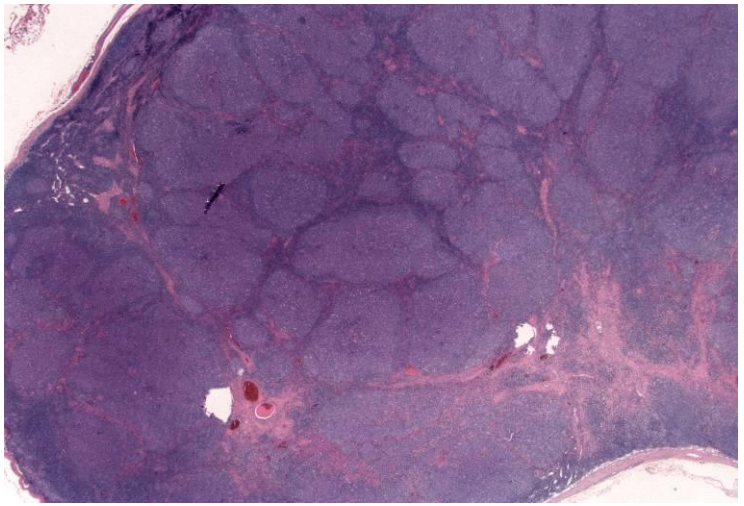


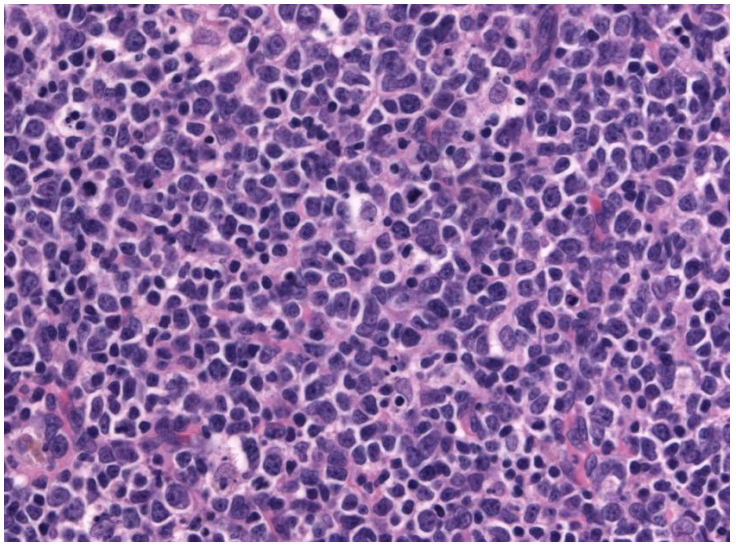
Usually BCL2 – t(14;18) neg.
MUM1 often positive
CD10 negative

BCL6 chromosomal alterations
MYC chromosomal alterations

Pediatric Follicular lymphoma

- Often involves cervical lymph nodes
- Extranodal sides also often, testis
- Clinically:
  - Early stage disease
  - Predominates in male patients
- Morphologically:
  - grade 3
  - Large expansile follicules
- Molecular: BCL2 negative, no t(14;18)





In situ localization of follicular lymphoma: description and analysis by laser capture microdissection

(Blood. 2002;99:3376-3382)

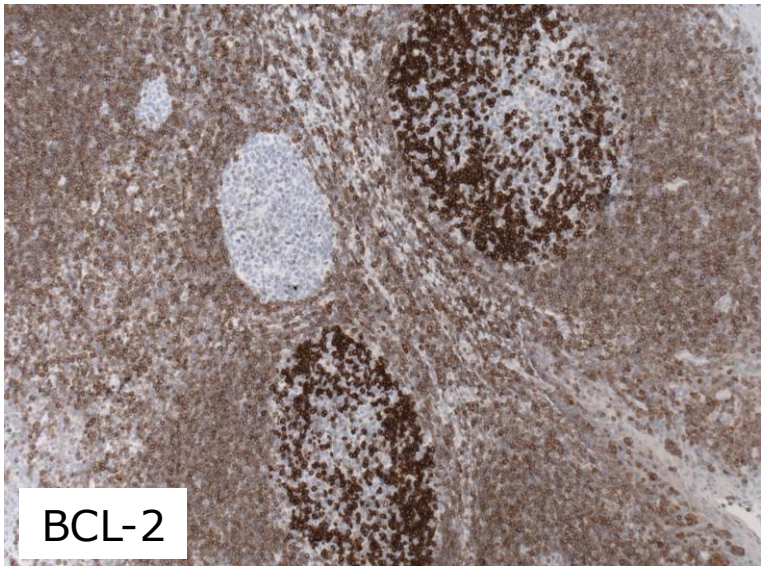
Peijie Cong, Mark Raffeld, Julie Teruya-Feldstein, Lynn Sorbara, Stefania Pittaluga, and Elaine S. Jaffe

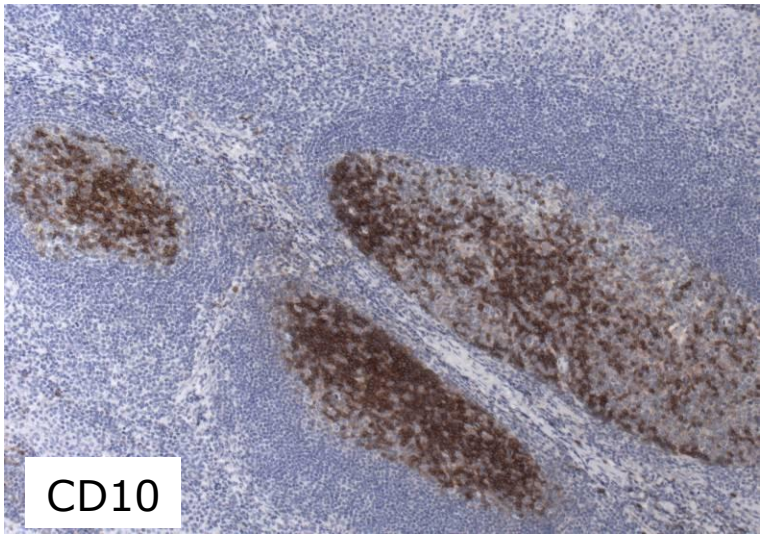
- Strongly bcl-2 protein staining germinal centers in otherwise architecturally and phenotypically normal lymph nodes
- 23 cases identified in 15.000 LN Bx
  - 4/5 cases with clonal Ig gene rearrangements studied by laser microdissection
  - 6/14 with bcl-2 gene rearrangement by PCR (MBR primers)
  - 5 with synchronous FL at other site
  - 13 with further follow-up
- 3/13 with development of FL in 12 to 72 months

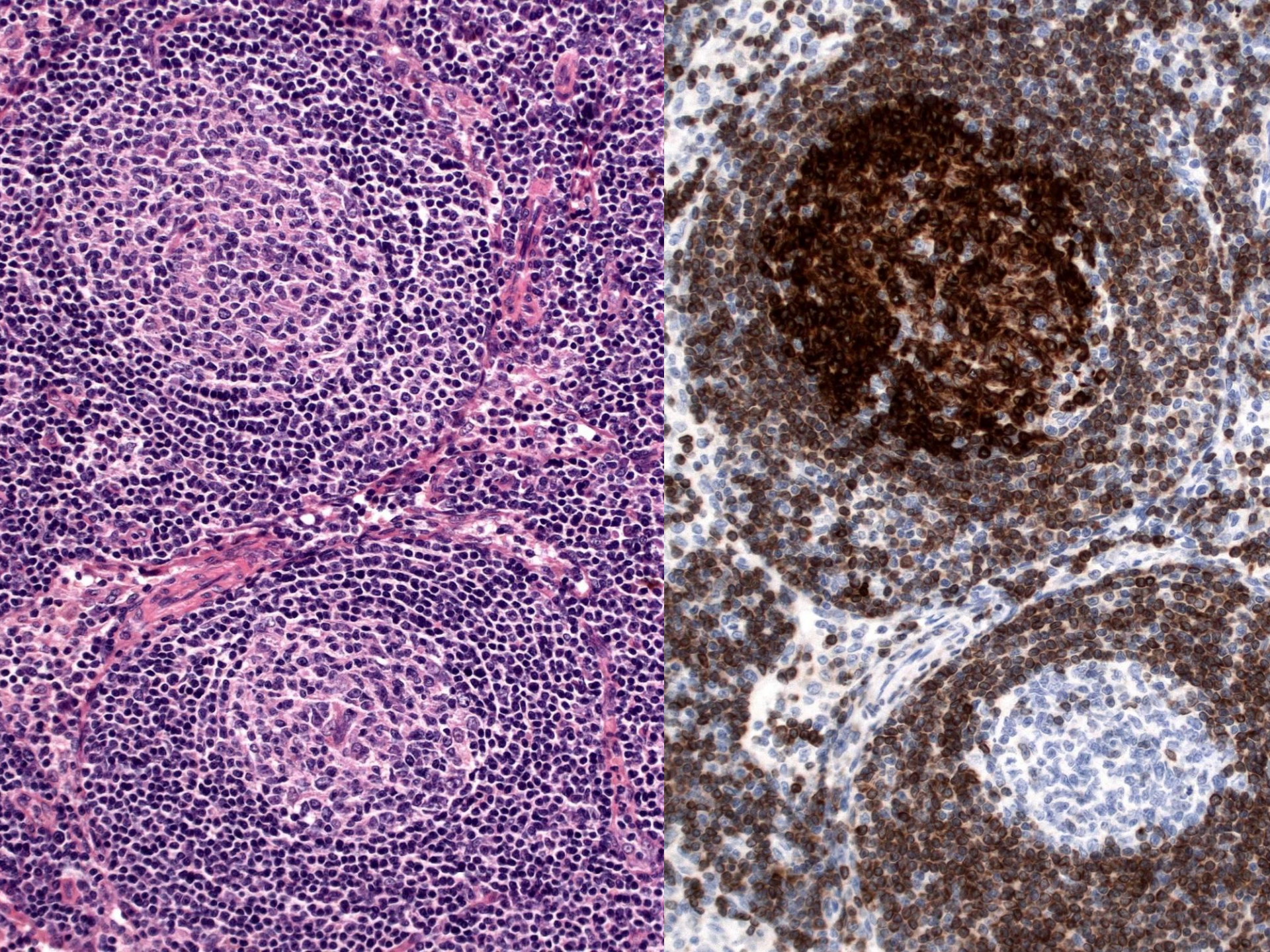
Follicular Lymphoma in situ

- Definition:

-Normal LN architecture
-Normal sized follicles
-Well demarkated GC,
-Dominance of centrocytes
-GC cells bcl-2+++
-CD10+++,
-Ki-67 low proliferation

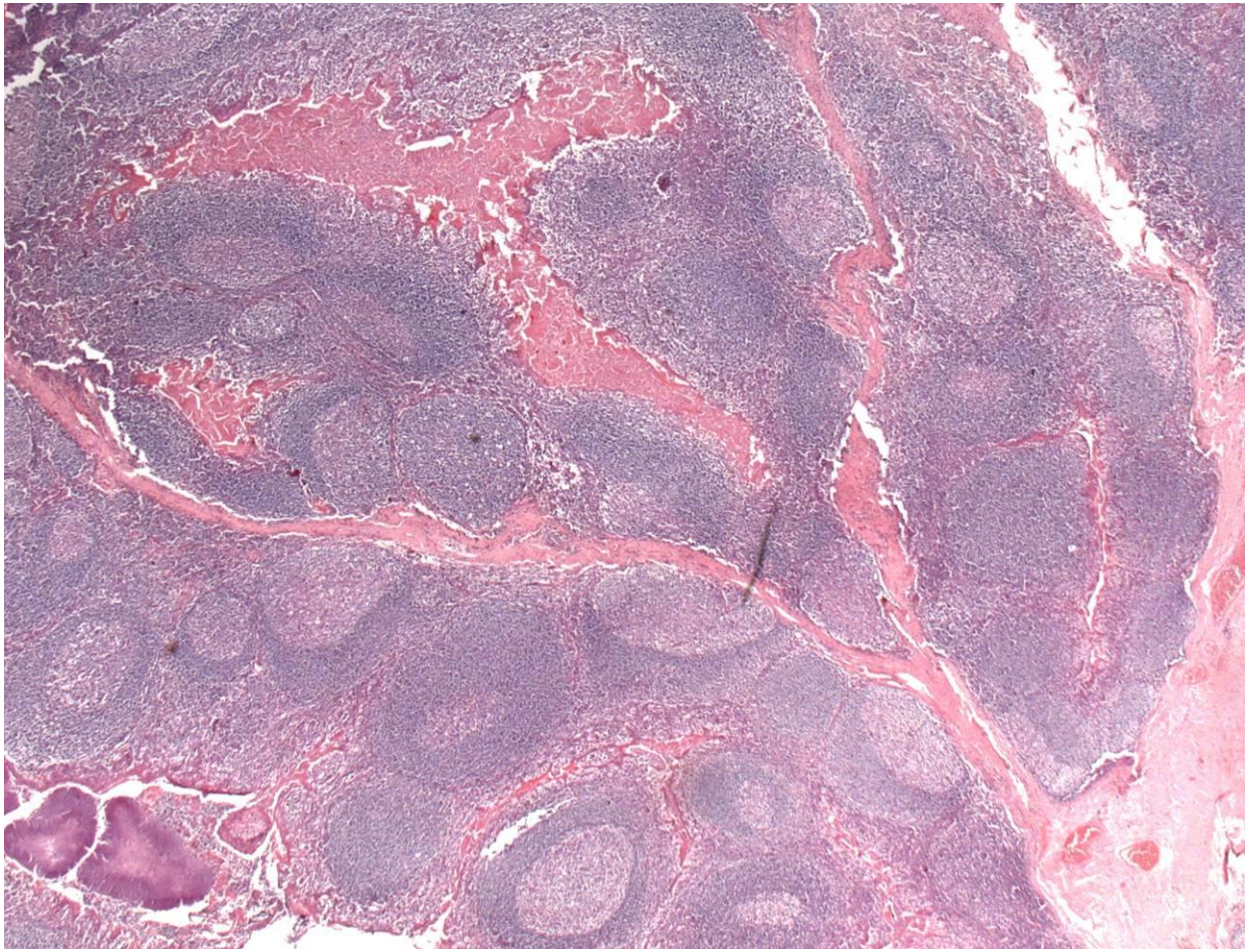




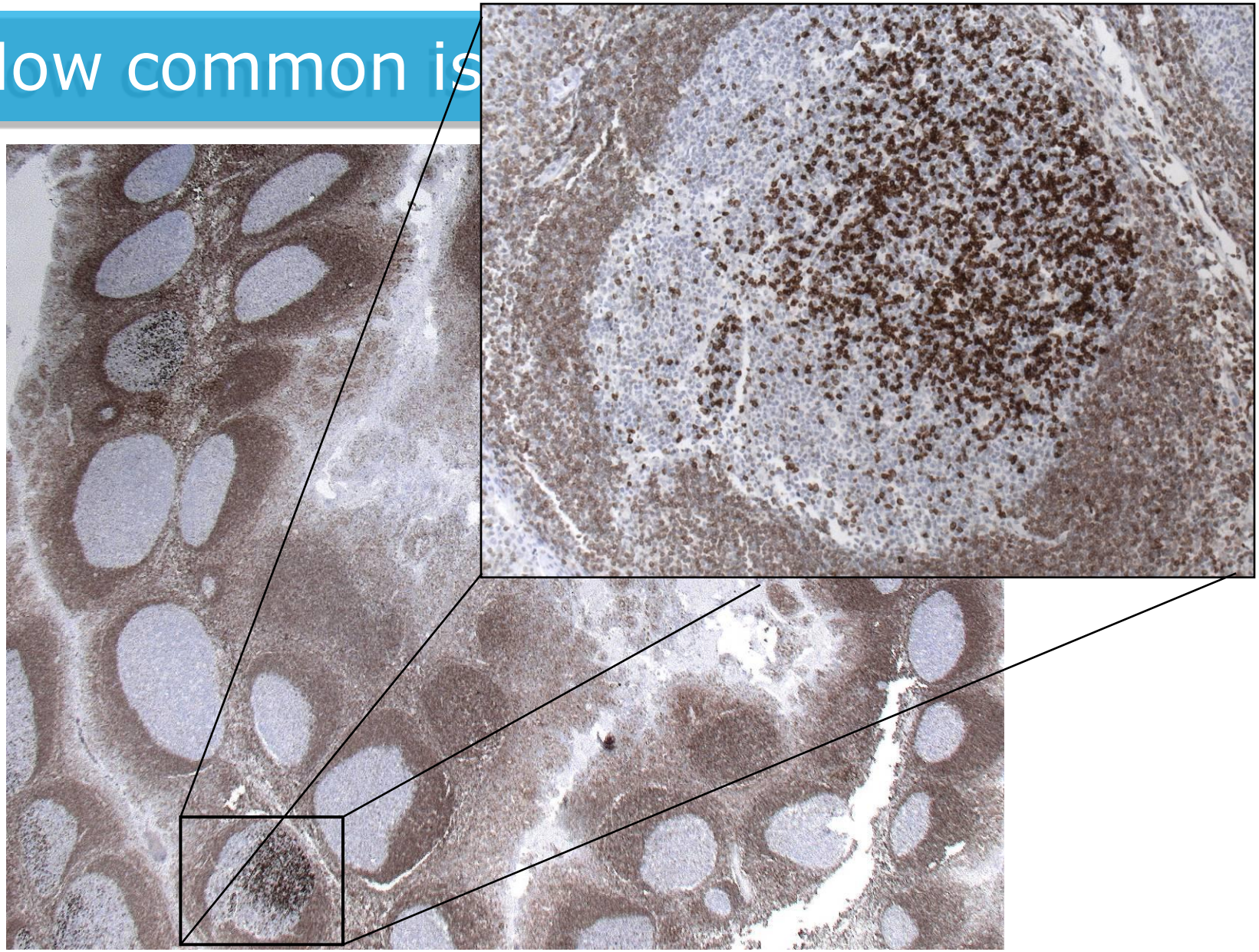


How common is FLIS in FL patients?

- 50-year-old male, 6 years previously Dx of FL grade 1/2 in LN biopsy
- 3 years later recurrence, FL G1/2
- Now bilaterally enlarged tonsils



How common is



How common is FLIS?

- All reactive lymph nodes with a least one germinal center over a 3-month period stained for bcl-2
- 1294 lymph nodes from 132 patients
  - Median 61 years - av. 5 LN/patient
  - 3/132 (2.4%) pats. with FLIS in 2-16 LN
  - 3/3 with break in bcl-2 locus

Henopp et al, Histopathology 2011

Age (years)/sex	Specimen	Primary disease	Associated lymphoma	LN	LN with FLIS
71/male	Whipple resection	Intraductal papillary mucinous neoplasm of the pancreas with invasive adenocarcinoma	No	7	4
69/male	Lobectomy	Lung cancer	No	27	16
42/male	Lymphadenectomy	Lymphadenitis (relapse)	No	4 (2007 = 1)	2 (2007 = 1)

How is the progression risk of FL?

- 34 cases of FLIS, usually incidental finding
  - 40-60 y, M:F=1:1
  - Only two cases with extranodal manifestation (thyroid, jejunum)
  - 6 cases with concurrent FL (3 BCL2 neg. by immunostaining)
  - 5 cases within composite lymphoma (4 low grade B-NHL, 1 cHL)
- 17/17 tested positive for BCL2 translocation by FISH
- 1/21 patients developed manifest FL after 29 mo (median follow up 41 mo)

Jegalian et al, Blood 2011

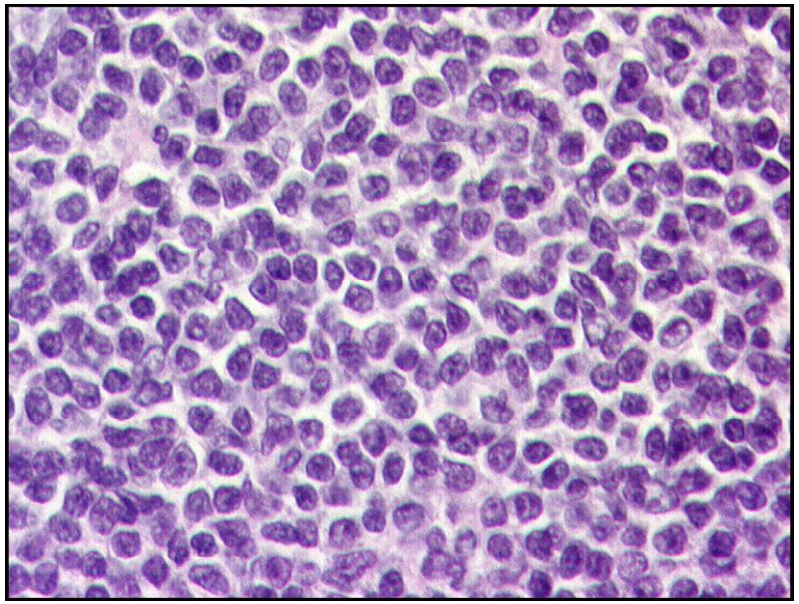
	FL partial involvement	FLBUS (FLIS)
Histopathology		
architectural alteration	focal	no
germinal centers (GC)	occasionally enlarged, ill-defined	normal size, well defined borders
follicle mantles	focally attenuated and ill defined	well defined, normal configuration
cytology of GC	monotonous, mostly centrocytes	monotonous, mostly centrocytes
perifollicular spread	occasionally	absent
Distribution within LN	Affected follicles often clustered	Affected follicles widely scattered
Immunohistochemistry		
BCL2	positive, variable intensity, whole GC	strongly positive, sometimes only partial GC involvement
CD10	positive, occasional interfollicular tumor cells	strongly positive, restricted to involved GC
MIB1	low proliferation	low proliferation
Clinical		
manifest FL at other site	possible	FLIS may involve more than one node

Castle Hohentübingen

Friedrich Miescher

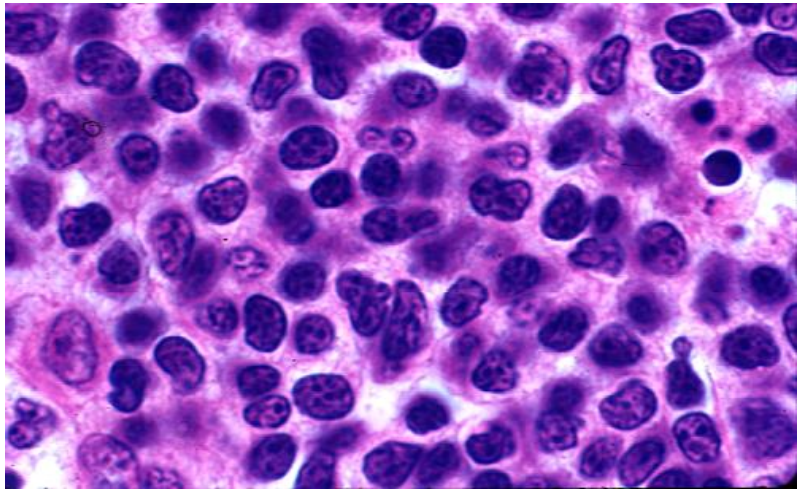
Mantle cell lymphoma
WHO classification

- **Definition:**
- Mantle cell lymphoma (MCL) is a B-cell neoplasm generally composed of monomorphous small to medium-sized lymphoid cells with irregular nuclei and *CCND1* translocation.
- Centroblasts, paraimmunoblsts and proliferation centers are absent

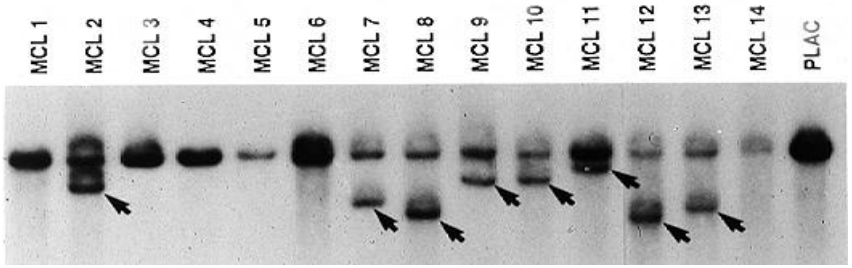


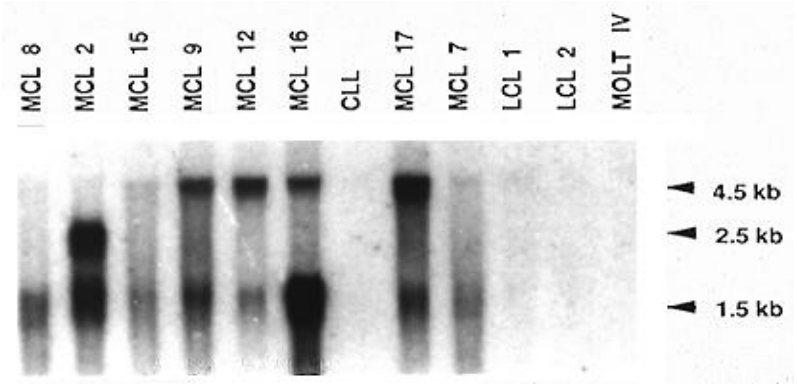
Swerdlow et al, WHO classification 2008

Biology of Mantle cell lymphoma

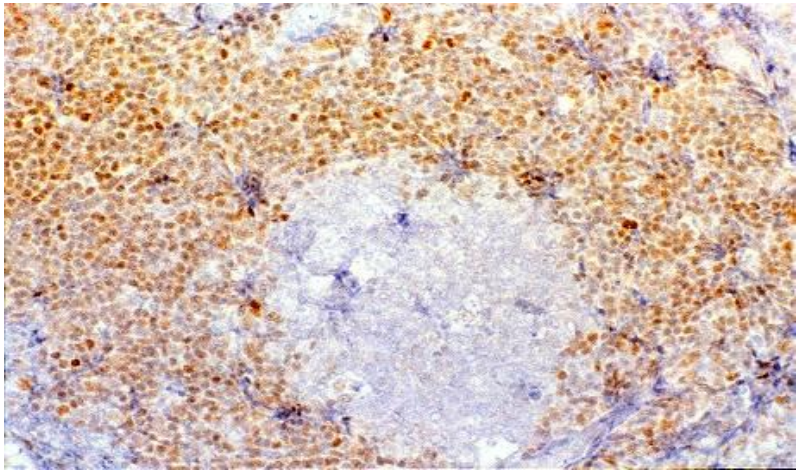


t (11;14)





Northern blot cyclin D1



Cyclin D1

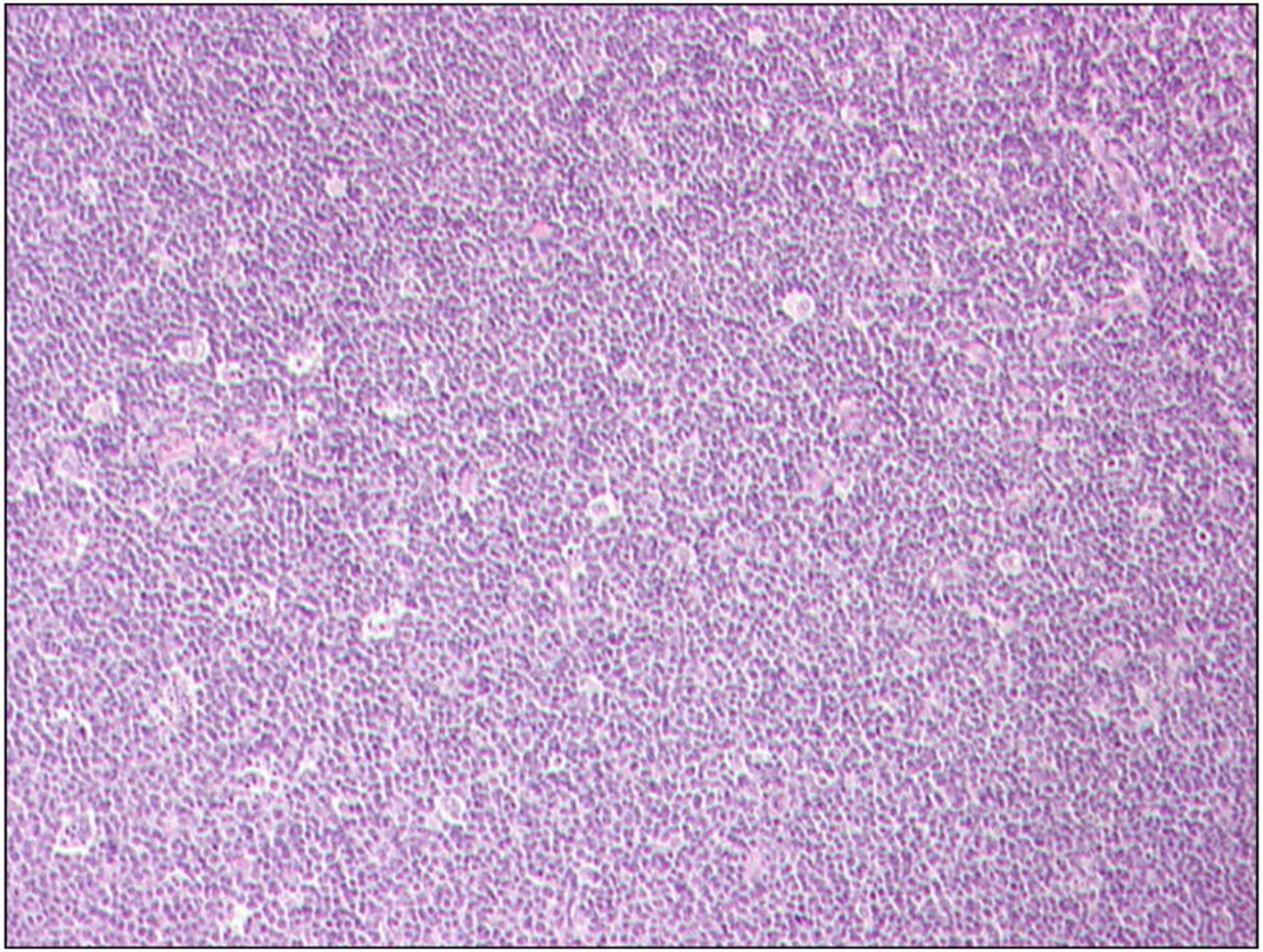
Mantle cell lymphoma
WHO classification

- proliferation of mature B-lymphocytes
  - Naive B-cell CD5+, IgD+
- **Clinically**
  - Represents 3-10% of NHL
  - Median age of 60 years
  - Predominates in male patients
  - Familial aggregation has been reported
  - Involves predominantly LN, spleen and BM
    - 30% involve the GI tract and Waldeyer´s ring
  - Aggressive with poor response to conventional chemotherapy

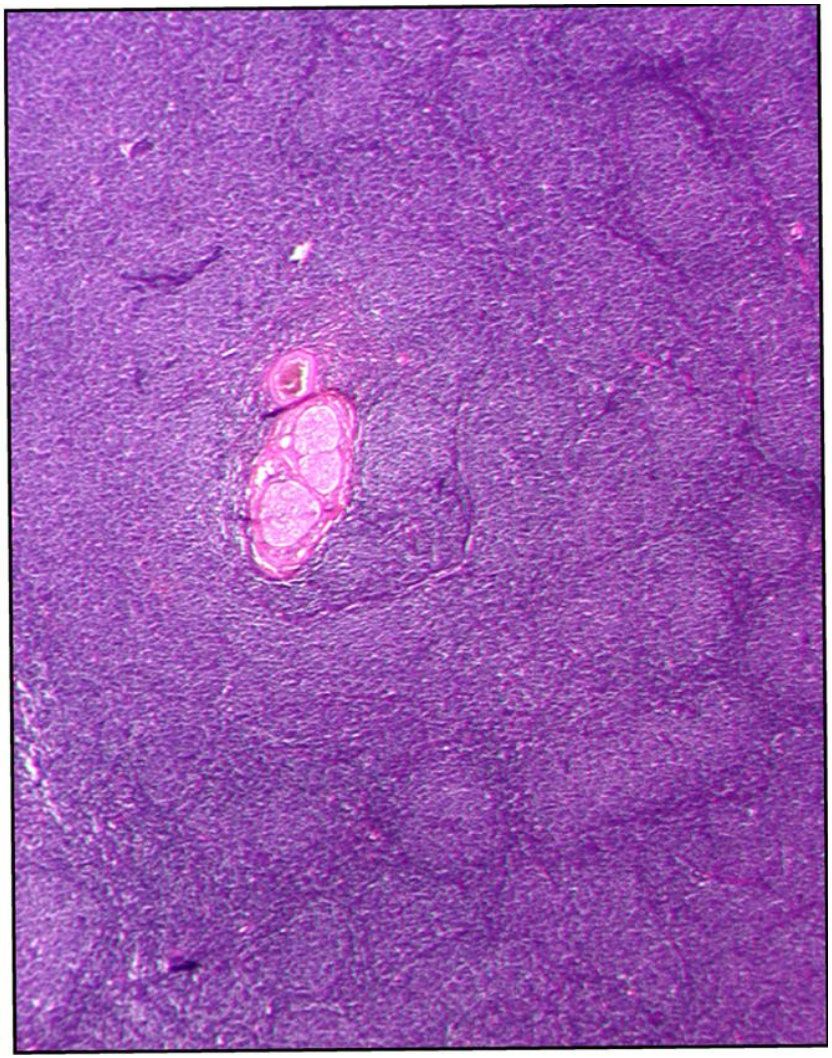
Mantle cell lymphoma
WHO classification

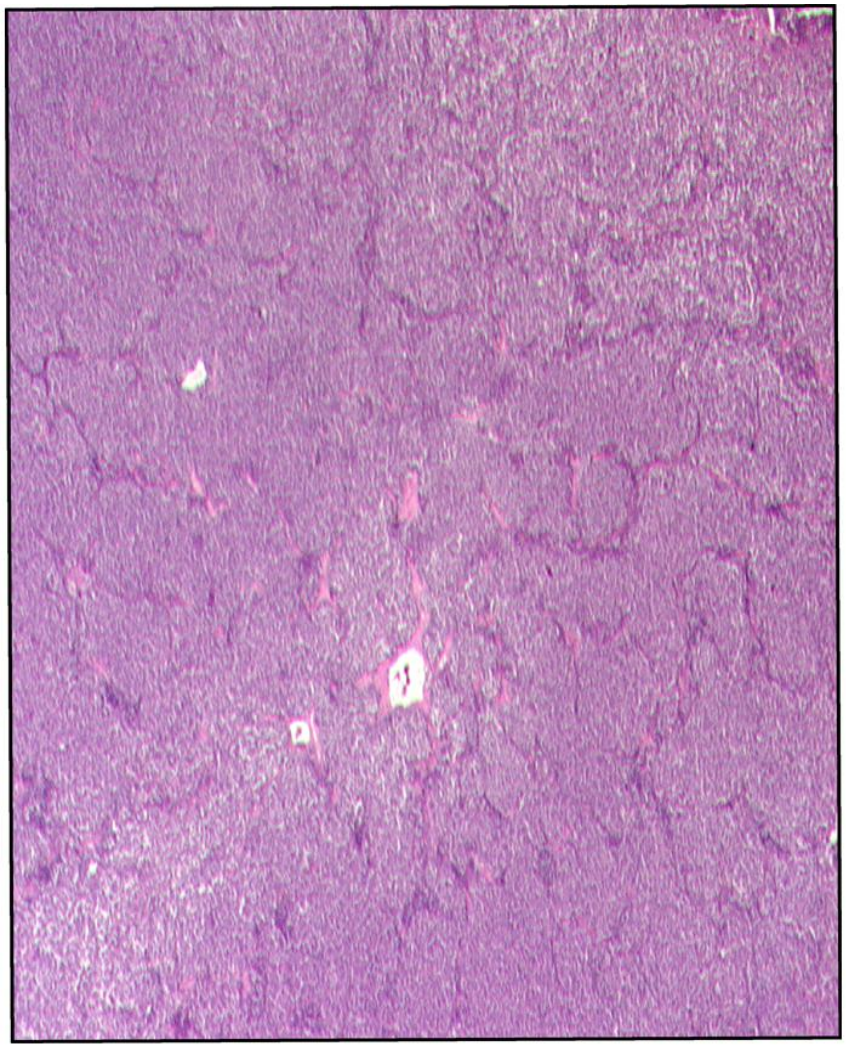
- **Morphologically:**
- Growth pattern:
  - Diffuse
  - Nodular (follicular lymphoma)
  - Mantle zone (marginal cell lymphoma)
  - *In situ*
- Cytologically
  - Classic
    - Small cell (CLL), marginal zone-like
  - Blastoid variants
    - Blastic variant (lymphoblastic lymphoma)
    - Pleomorphic (Diffuse large B-cell lymphoma)

Mantle cell lymphoma. Diffuse pattern

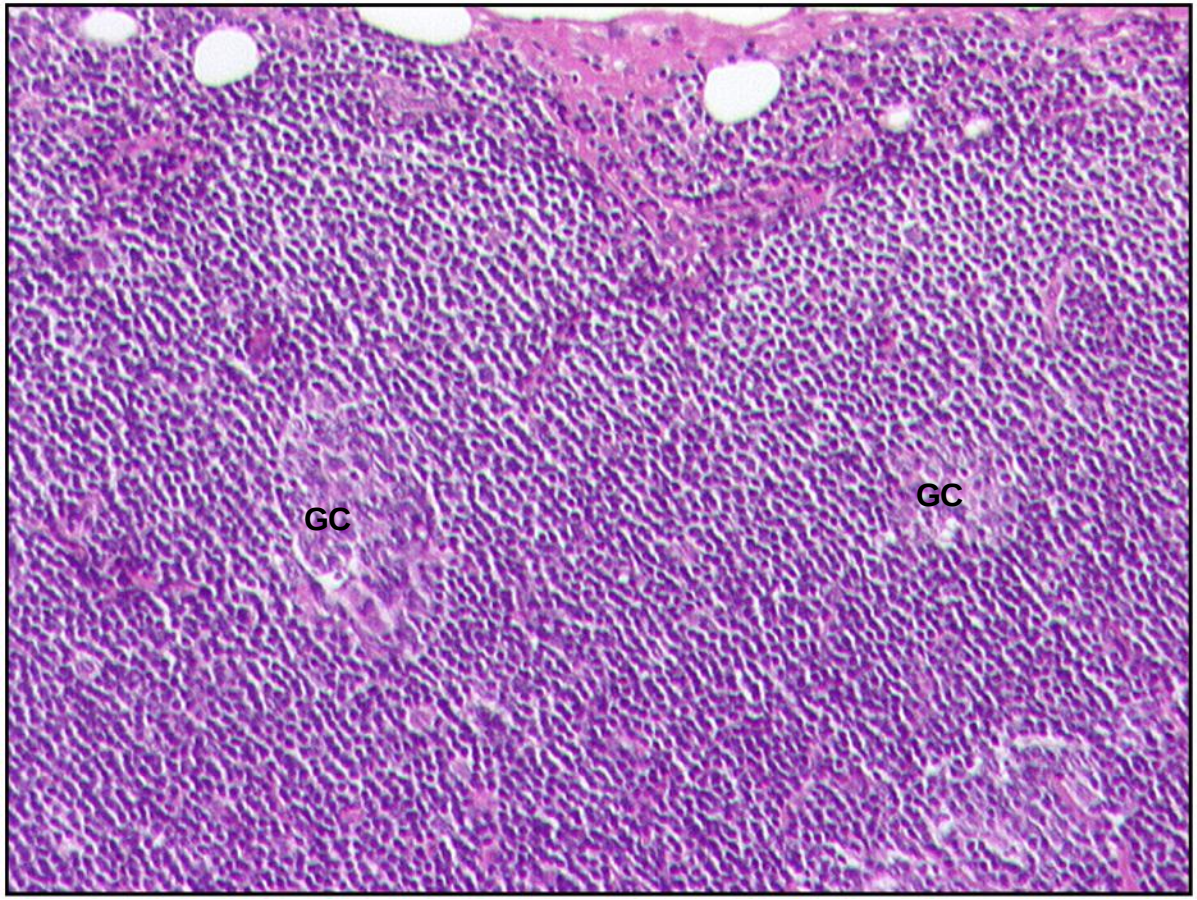


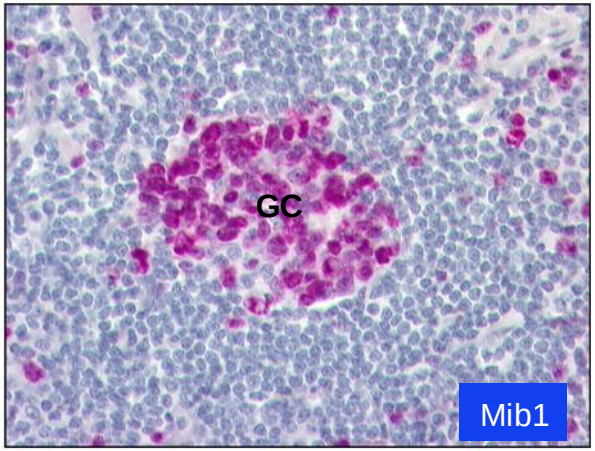
Mantle cell lymphoma. Nodular pattern

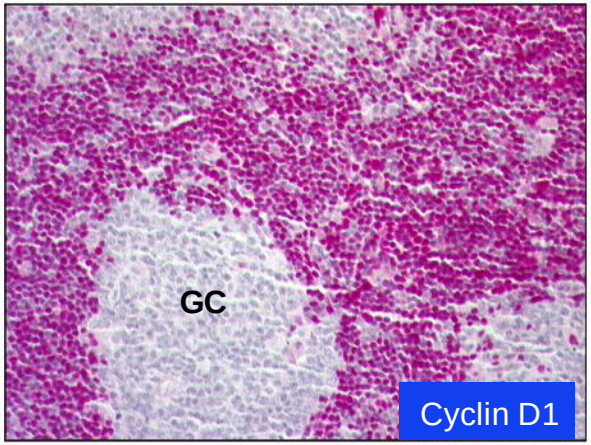




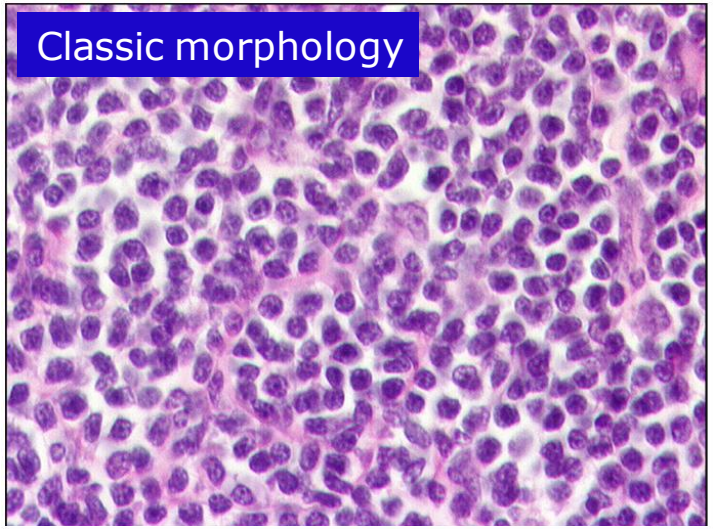
Mantle cell lymphoma. Mantle zone pattern

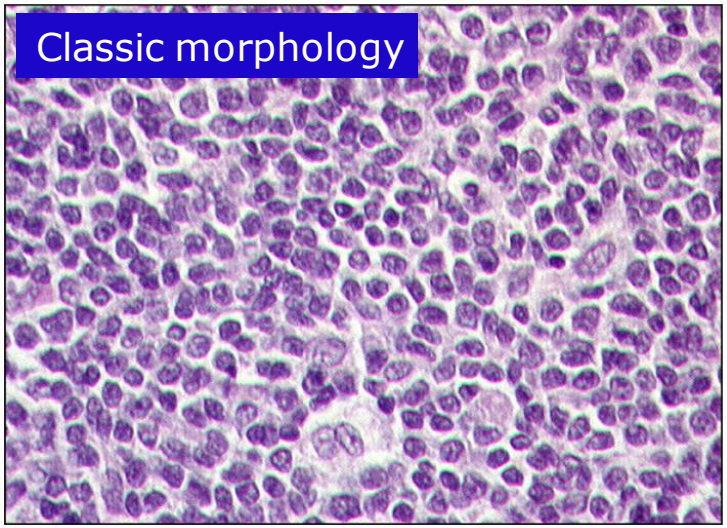


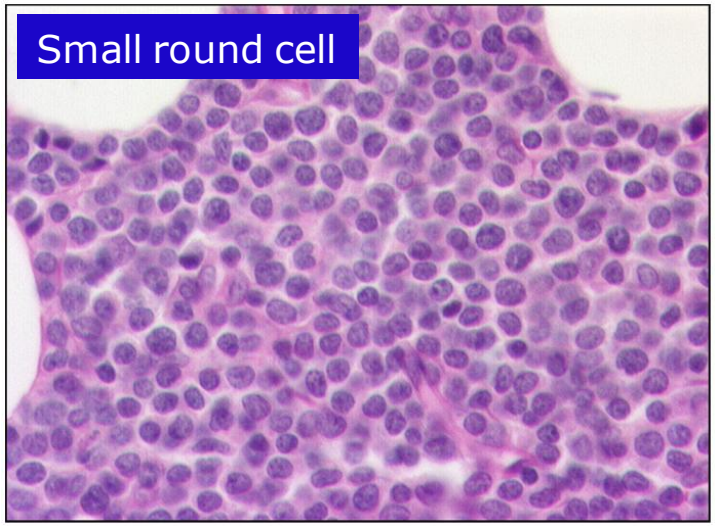


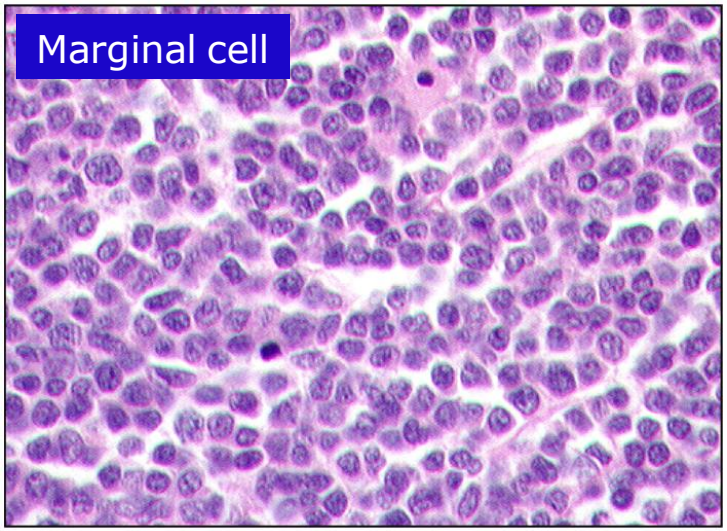


Mantle cell lymphoma. Cytology

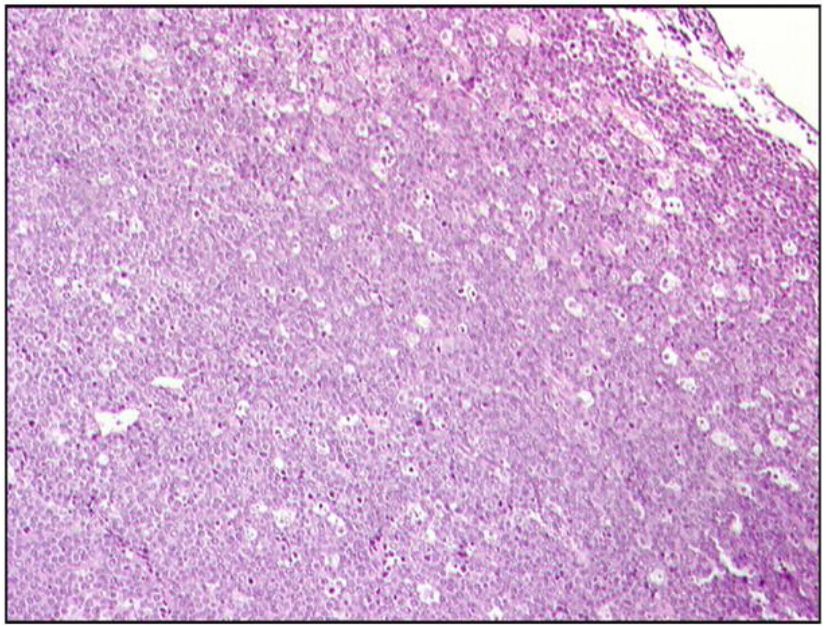


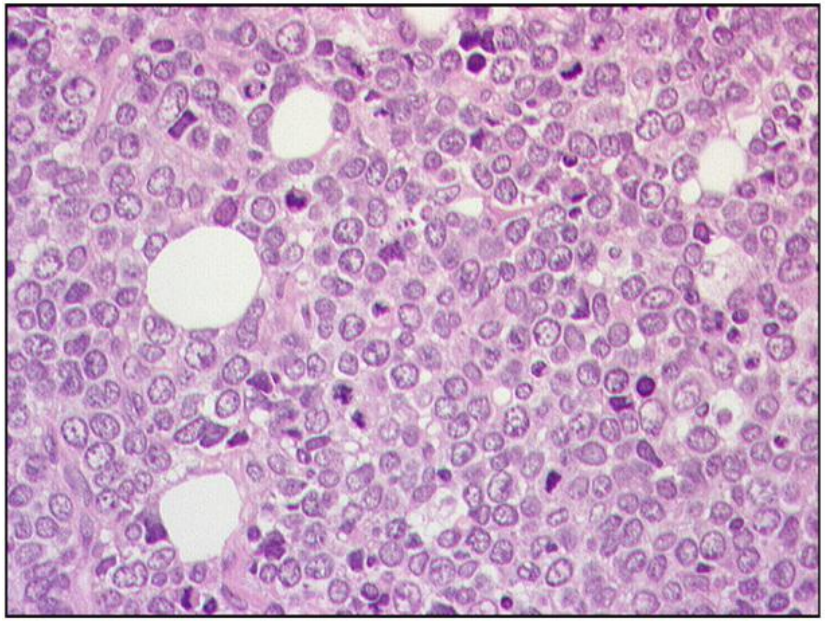


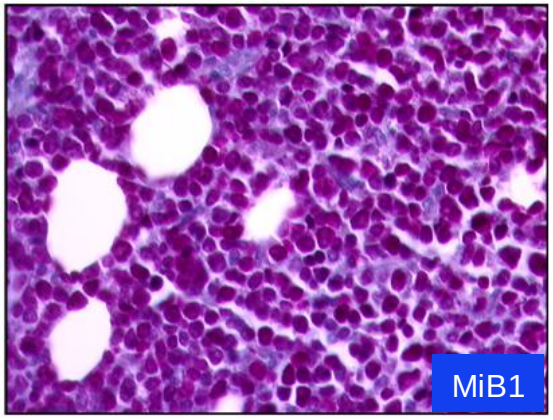


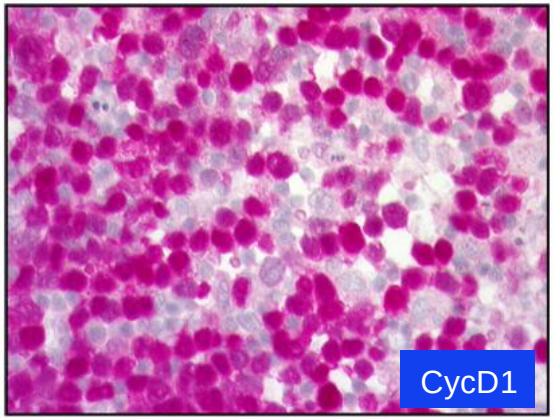


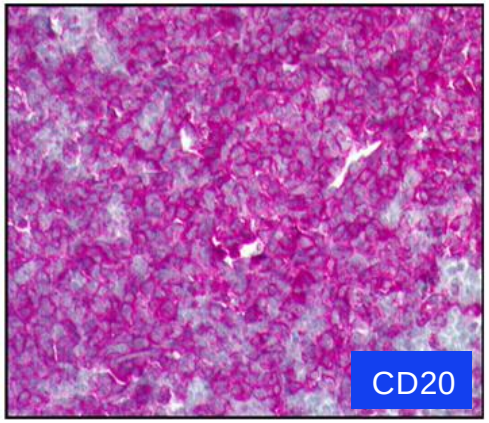
Mantle cell lymphoma. Blastic variant



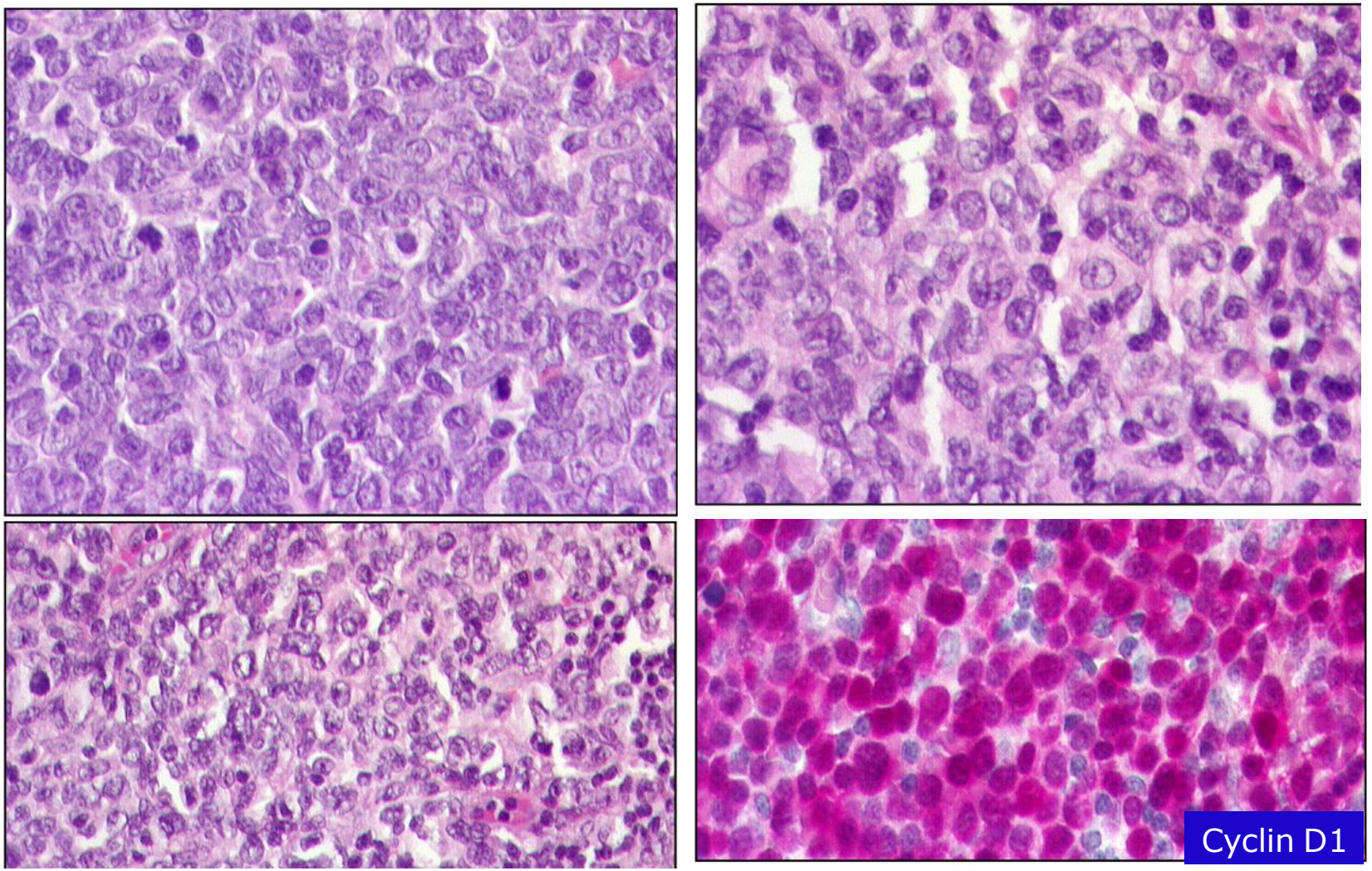




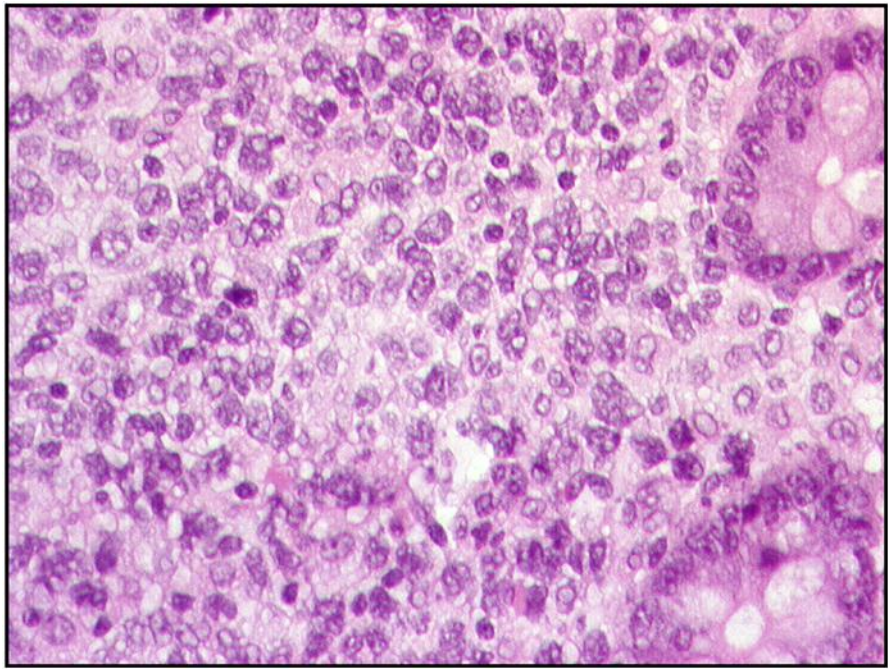


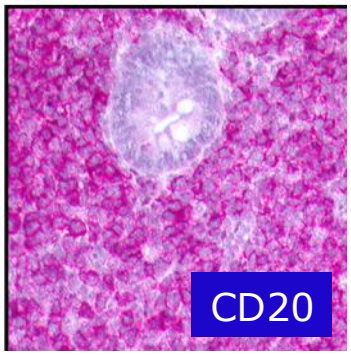


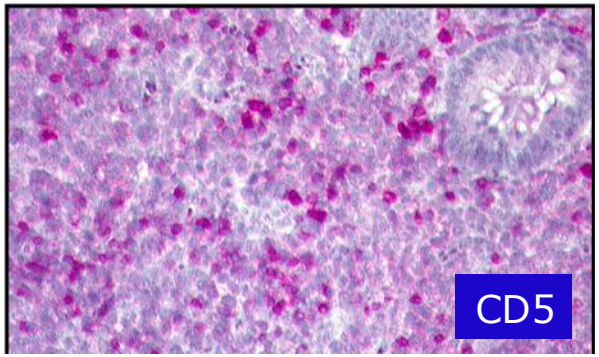
Mantle cell lymphoma. Pleomorphic variant

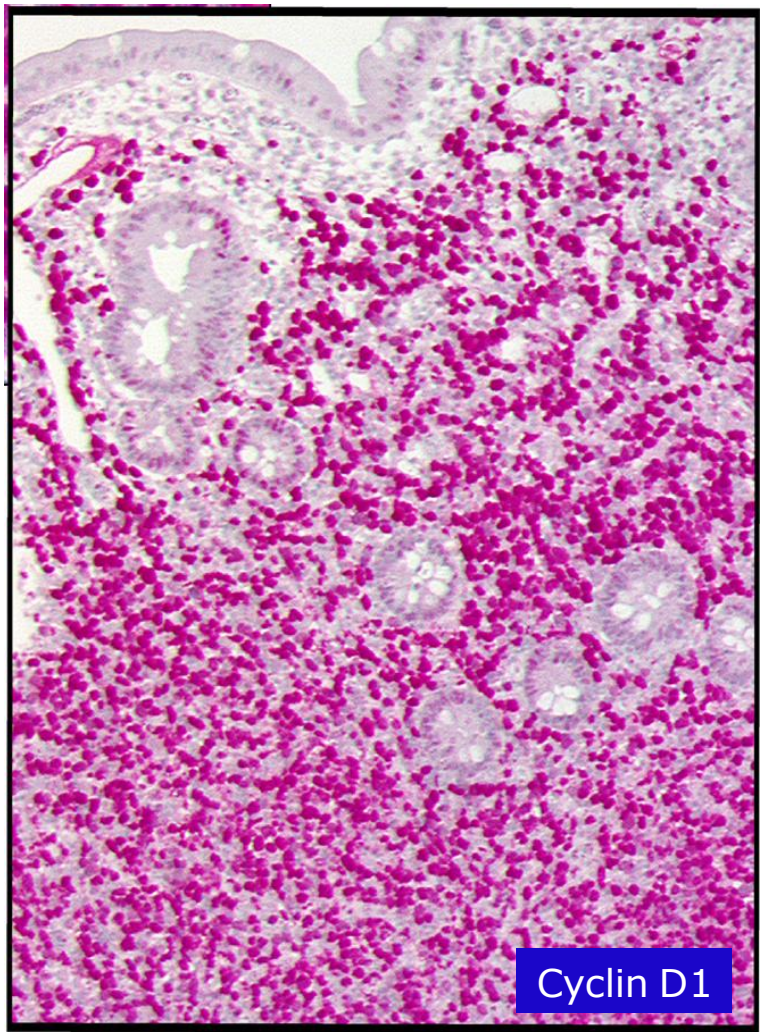


Mantle cell lymphoma: Lymphomatous polyposis



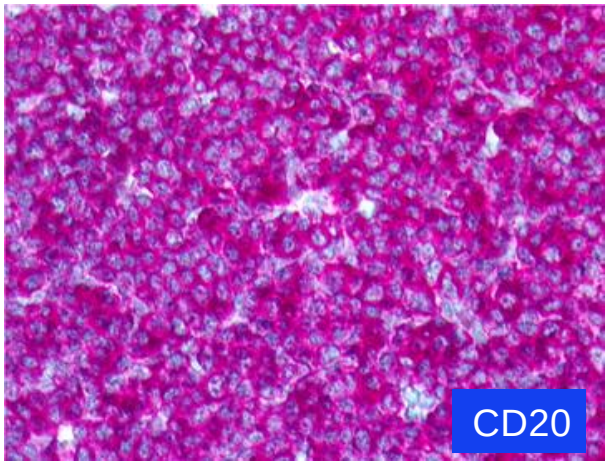


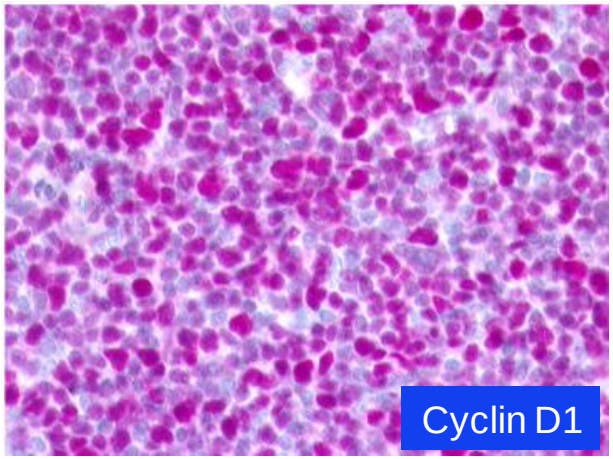


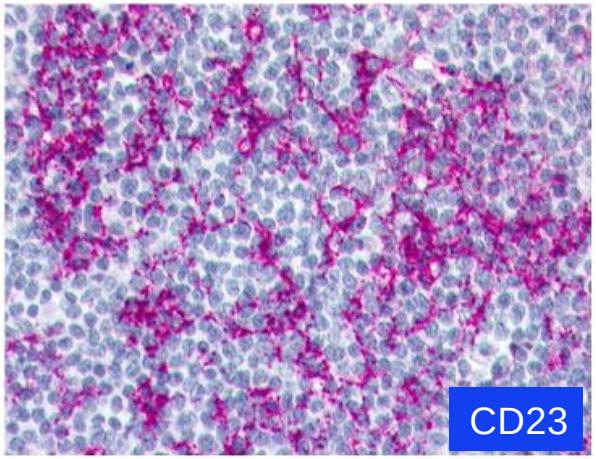


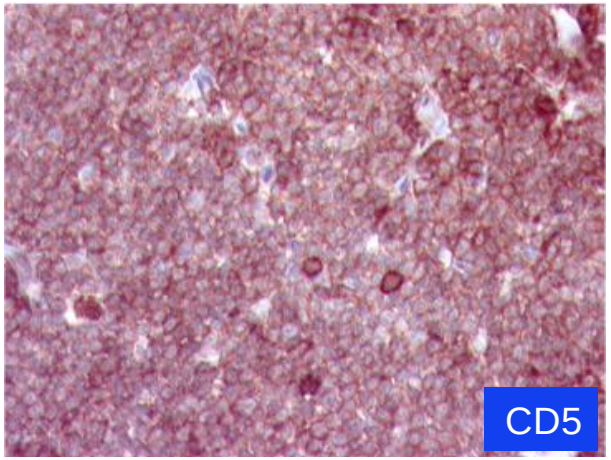
Mantle cell lymphoma

- Immunophenotype:
- IgM+, IgD+
- Cyclin D1++
- CD5 +/ -
- CD10-/+
- bcl-6 -/+
- Bcl-2++
- CD23-*

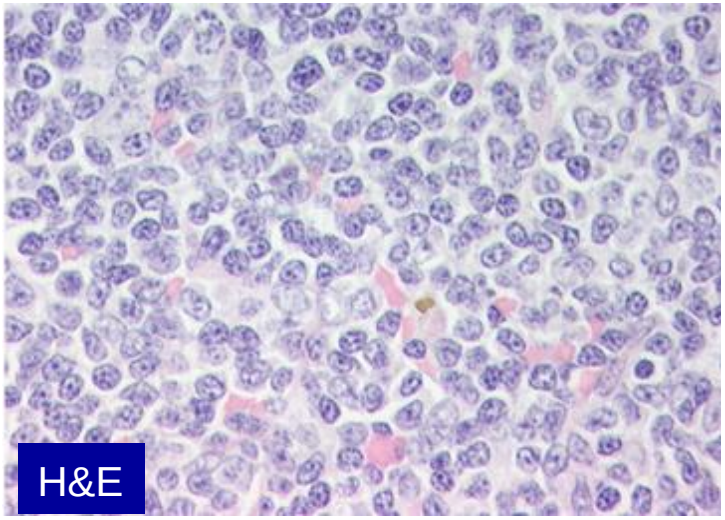


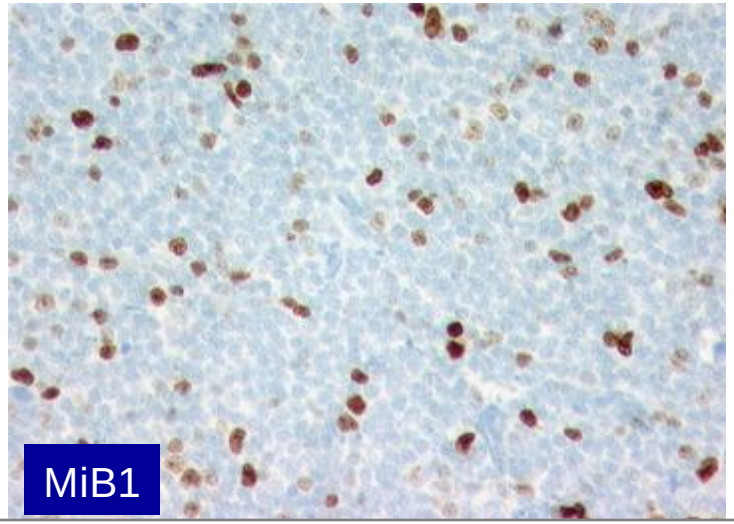




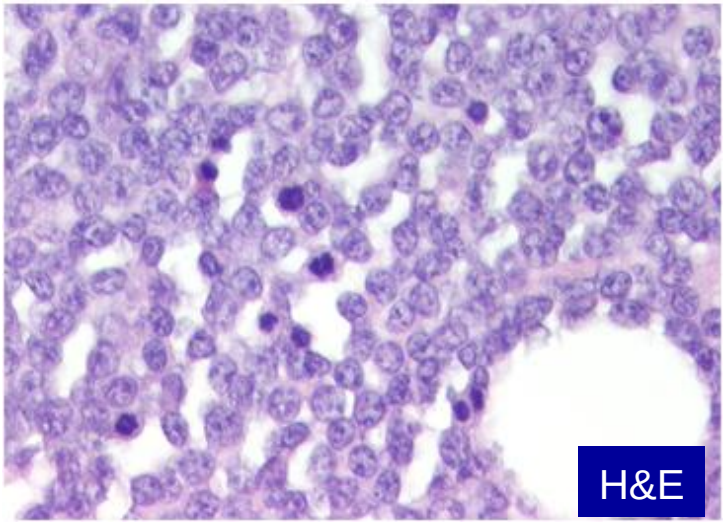


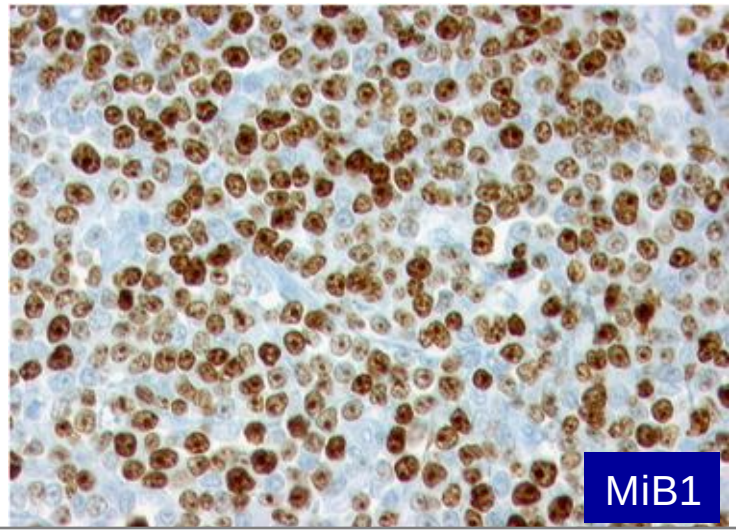
MCL - Classical type



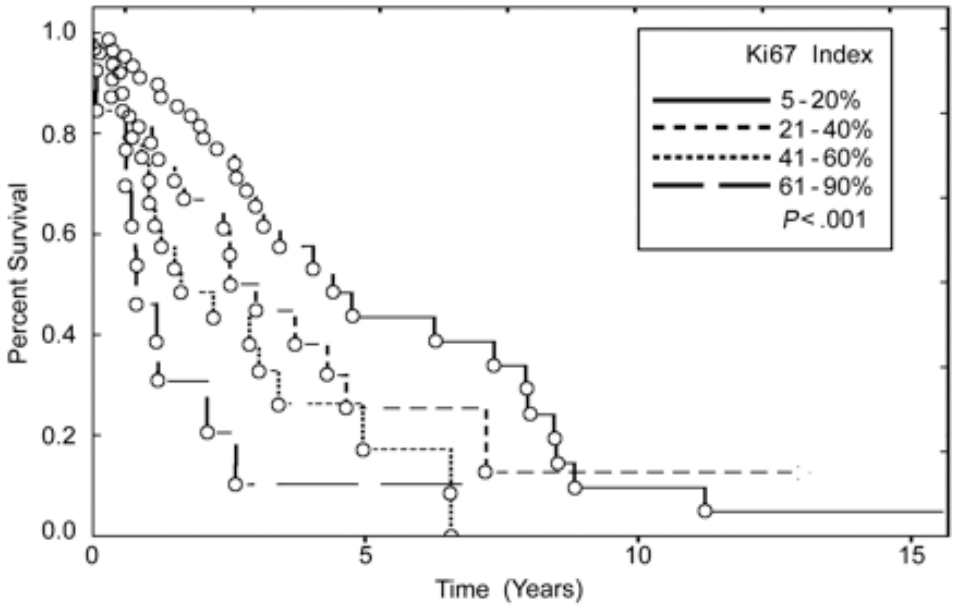


MCL - Blastoid type



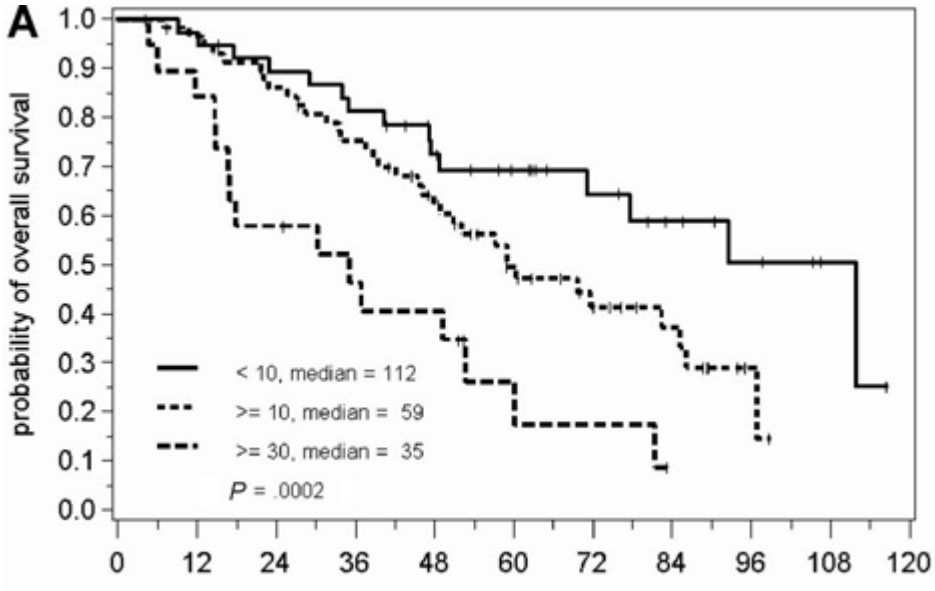


Ki-67 proliferation index in mantle cell lymphoma



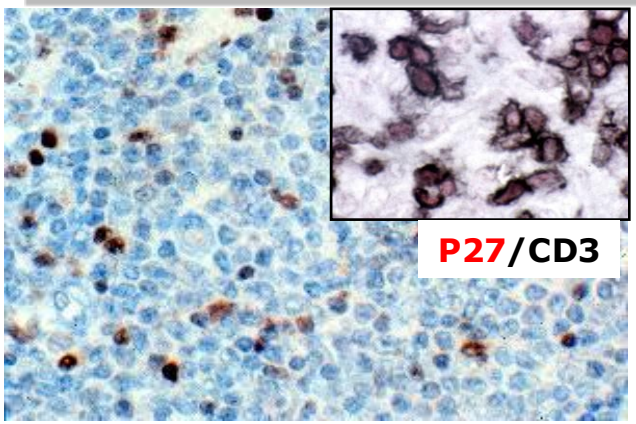
Katzenberger T et al, Blood 2006,107:3407

R-CHOP

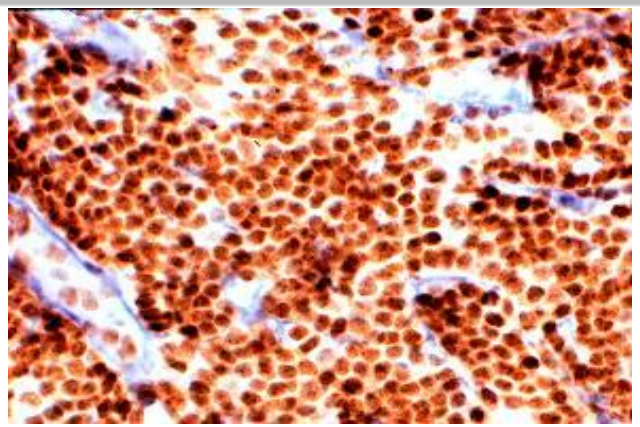


Determann et al, Blood 2008,111:2385

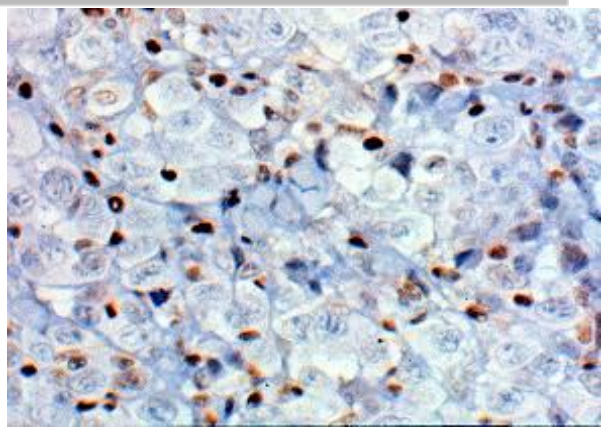
Loss of p27Kip1 in MCL



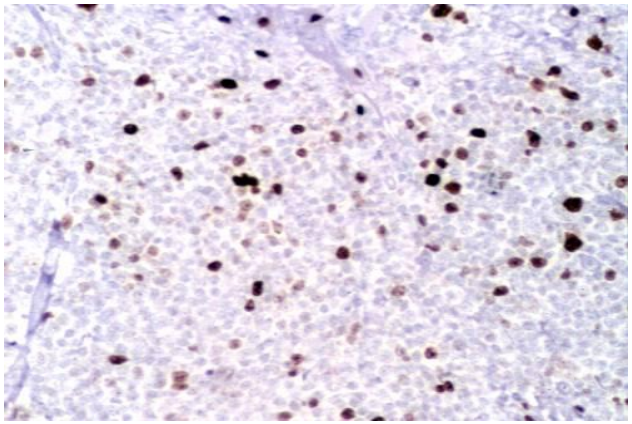
Typical MCL, p27



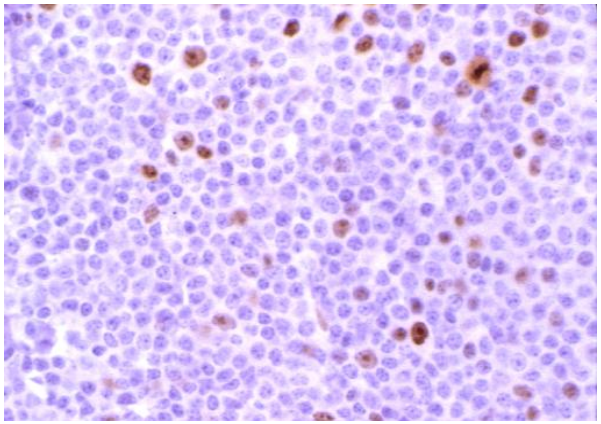
CLL/SLL, p27



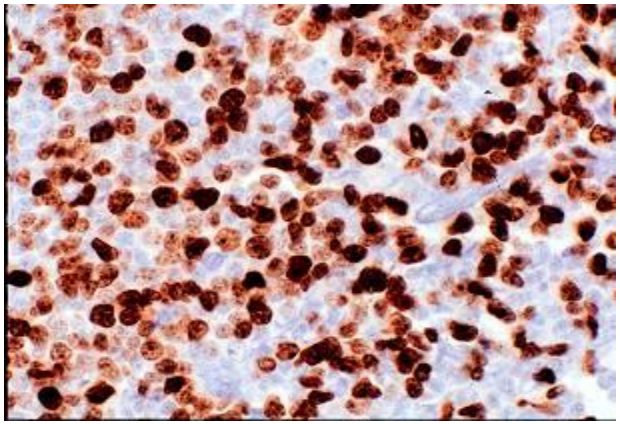
Large B-cell lymph, p27



Typical MCL, MIB1



CLL/SLL, MIB1



Large B-cell lymph, MIB

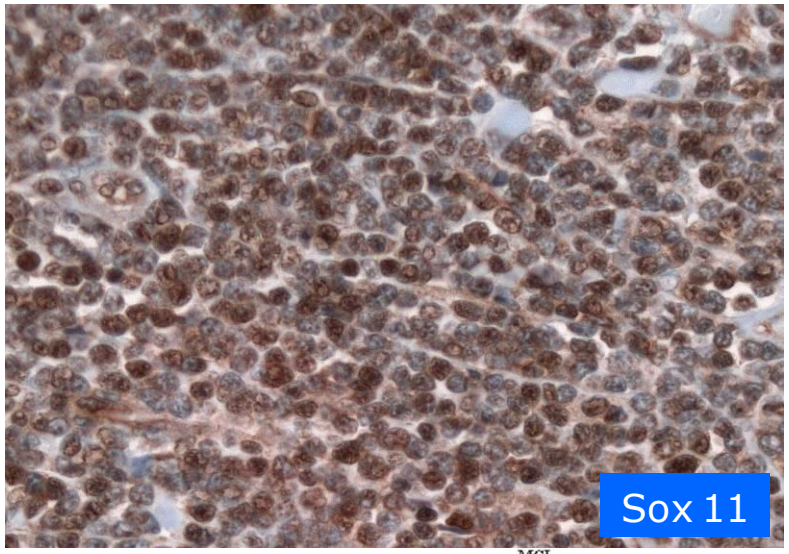
Südwestdeutsches Tumorzentrum
Comprehensive Cancer Center Tübingen

Eberhard-Karls-Universität UKT Universitätsklinikum Tübingen

Quintanilla-Martinez, et al AJP 1998
Quintanilla-Martinez, et al Blood 2003

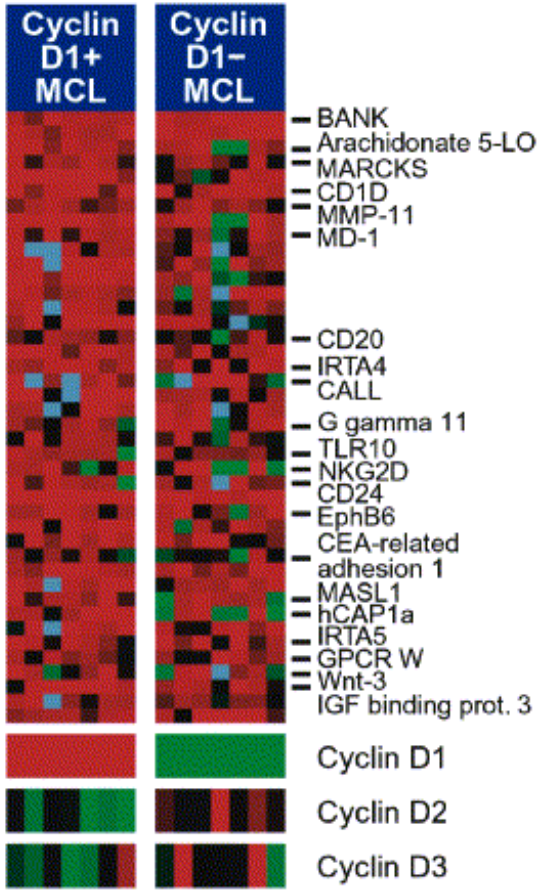
Sox 11 expression in Mantle cell lymphoma

- Most MCL are positive including the cases of cyclin D1 negative
  - (CycD1-,CD5+.Sox11+)
- Other „Low grade“ lymphomas are negative
- Some Burkitt lymphoma, lymphoblastic lymphomas and T-prolylmphocytic leukemias are postive

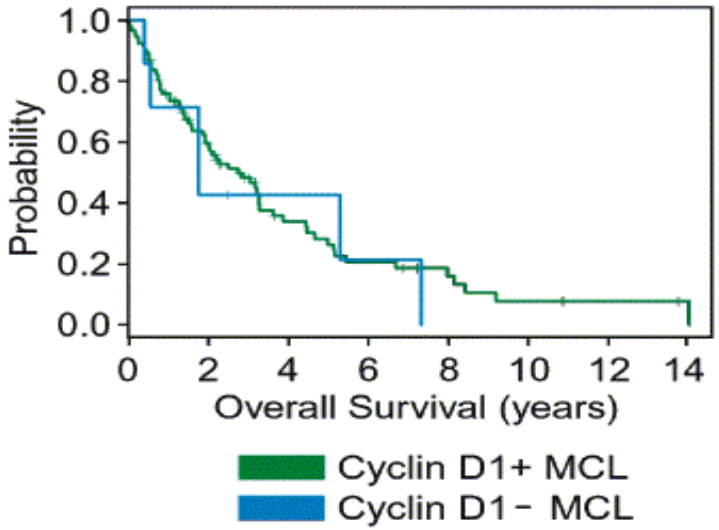


Mozos A et al. Haematologica 2009;94:1555-1562

Cyclin D1 negative MCL



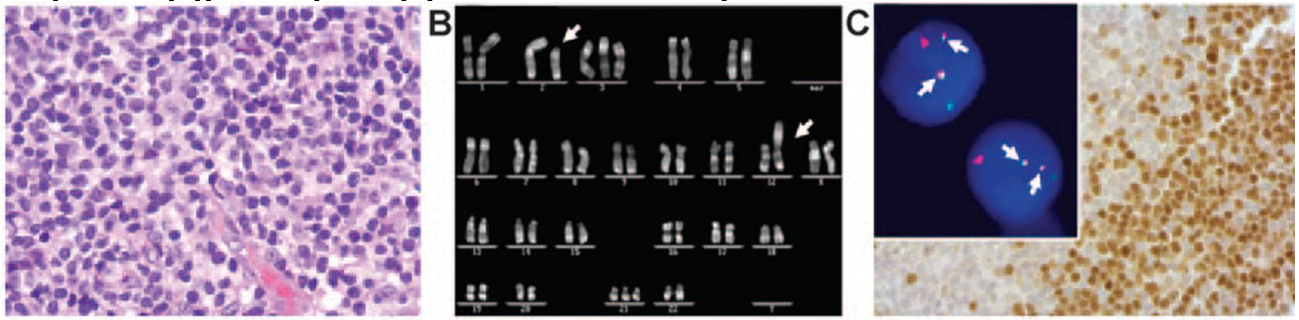
- Rare cases of MCL are cyclin D1-
- Survival is similar to cyclin D1+
- Cyclin D2 or D3 may substitute



Rosenwald A et al, Cancer Cell 2003,3:185

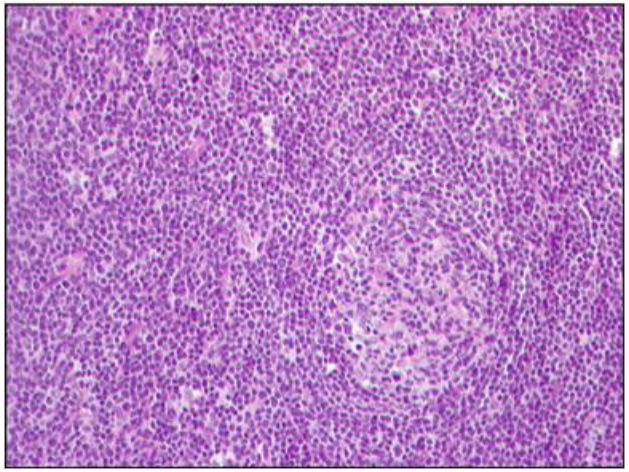
Cyclin D1 negative MCL

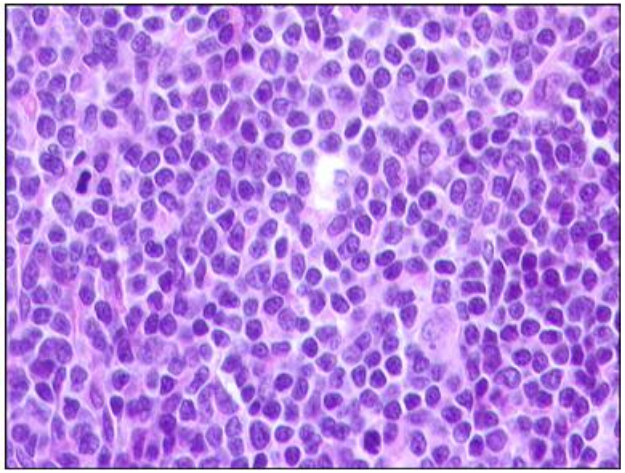
- Fu et al published 6 cases of Cyclin D1- MCL
  - 2 cases expressing cyclin D2 by IHC
  - 4 cases expressisng cyclin D3 by IHC
  - None of these cases showed any genetic alteration
- Gesk et al published 2 cases of "*bona-fide"* cyclin D2 positive MCL
  - t(2;12)(p13-p12)(*IGκ;CCND2*)

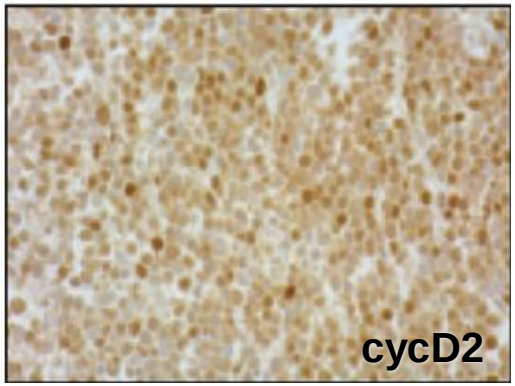


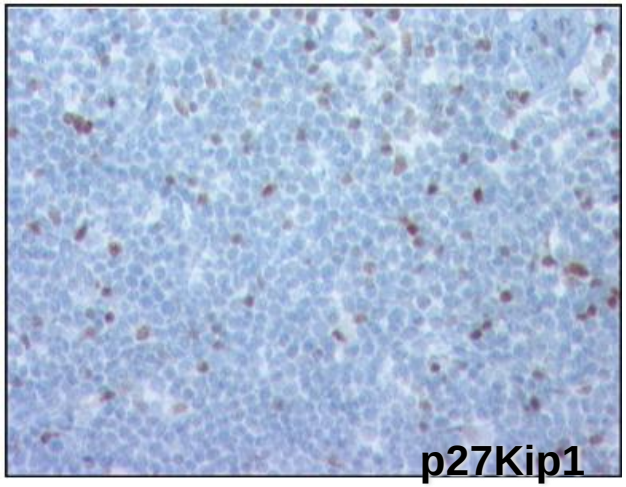
Fu K et al., Blood 2005, 106:4315
Gesk S et al., Blood 2006:108; 1109

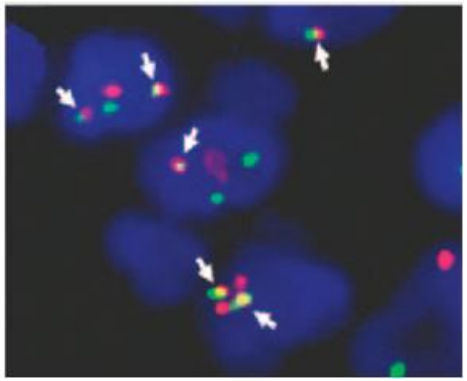
Cyclin D2 positive MCL







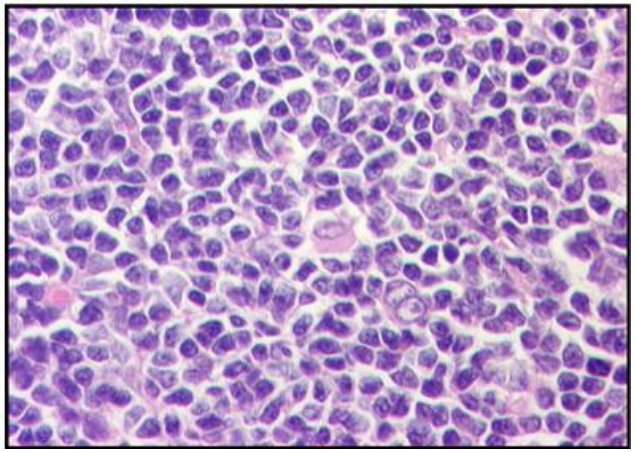


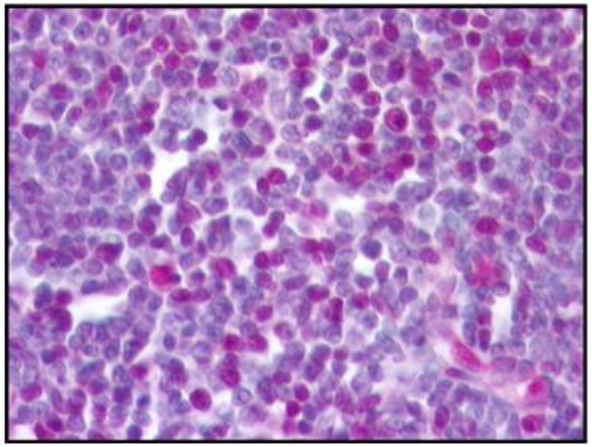


t(2;12)(p12-p13)

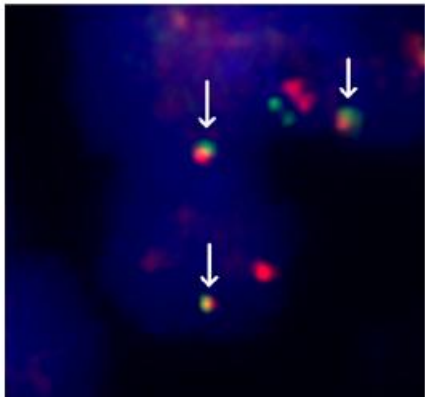
Clinical history:
70 year-old man with Stage IV disease.
Immunophenotype:
CD20+CD5+CD10-CD23-P27 & CyclinD1 negative

Cyclin D2 positive MCL

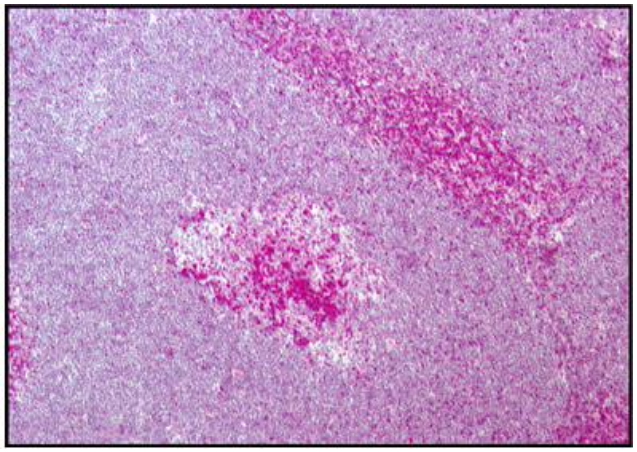




Cyclin D2



t(2;12)(p12-p13)

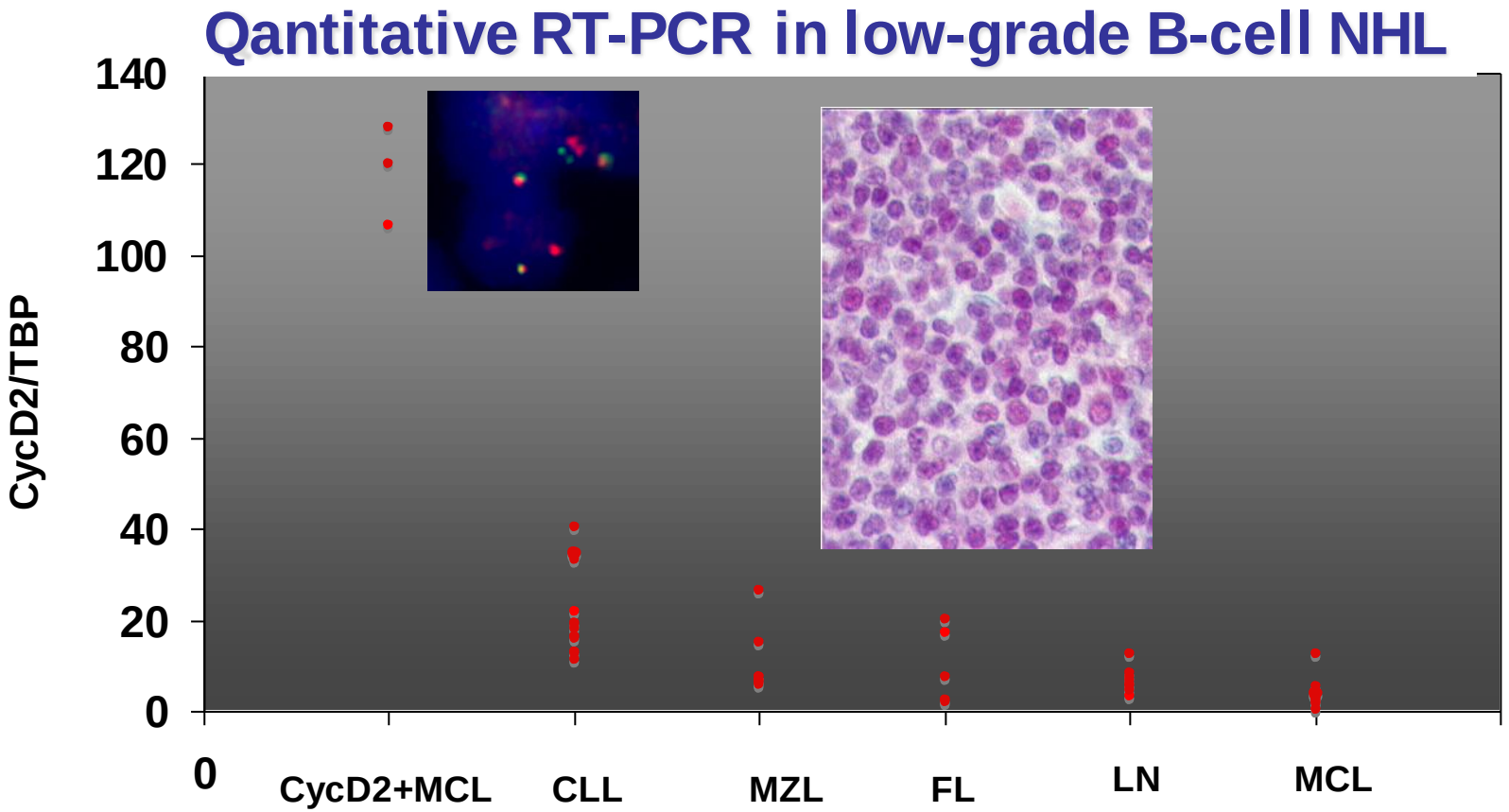


p27Kip1

Clinical history:
45 year-old man with Stage IV disease.

Immunophenotype:
CD20+CD5+CD10-CD23-
P27 & CyclinD1 negative

Cyclin D2 mRNA expression

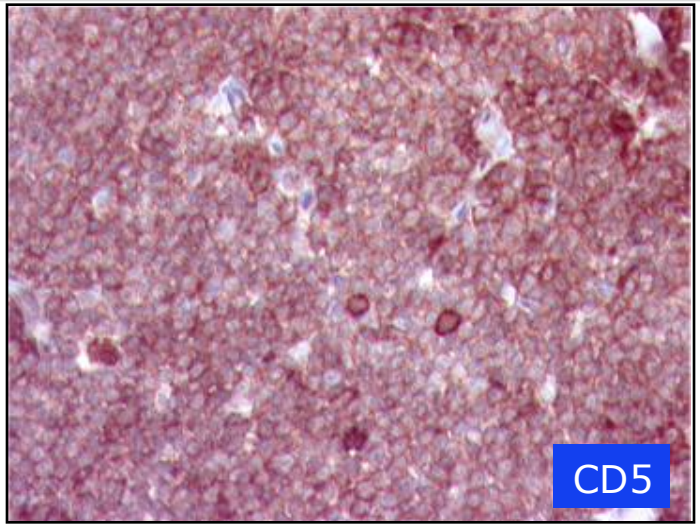


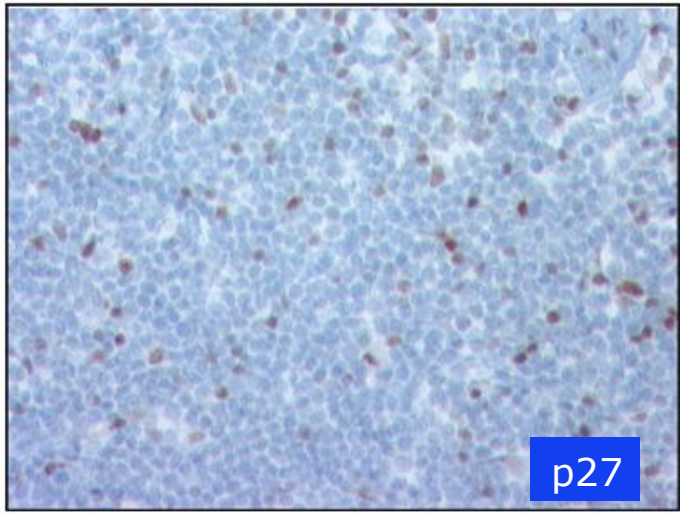
Quintanilla-Martinez et al Haematogica, Nov 2009

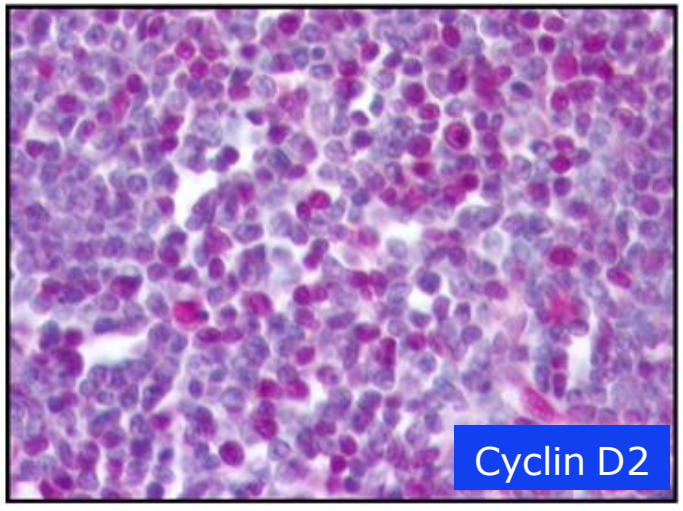
Cyclin D1 negative MCL

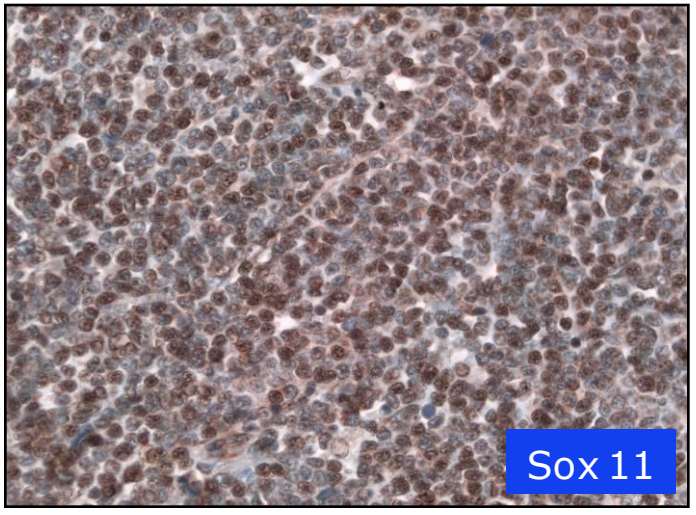
CD5+CycD1-
Diff. Dx:

- MCL
  P27-Sox11+
  CycD2+
- CD5+MZL
  P27+Sox11-
- CLL
  P27+Sox11-
  CD23+









Secondary genetic events in MCL

- Mantle cell lymphoma is one of the malignant lymphoid neoplasia with the highest levels of Chromosomal alterations
  - Recurrent losses, gains and amplifications
  - Frequent tetraploid clones
    - Pleomorphic variant (80%)
    - Blastic variant (36%)
    - Classical variant (8%)

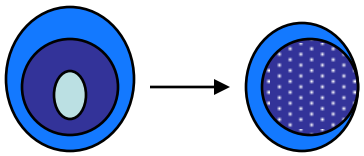
Jares et al., Nature Cancer Review 2007, 7:750

Secondary genetic events in MCL

Chromosomal region	Candidate gene	Function
Gains		
8q21	MYC	Cell growth, proliferation apoptosis
9q22	SYK	Cell signaling
10p11-12	BMI1	DNA damage response, cell cycle
12q13	CDK4	Cell cycle
18q11-q23	BCL2	Anti-apoptosis
Losses		
1p13-31	??	
2q13	BIM	Pro-apoptosis
9p21-p22	CDKN2A	Cell cycle and anti-senescence
11q22-q23	ATM	DNA damage response
13q11-13 & q14-34	??	
17p13-pter	TP53	Cell cycle, DNA damage response

Jares et al., Nature Cancer Review 2007, 7:750

Pathogenetic molecular model for the development and progression of MCL

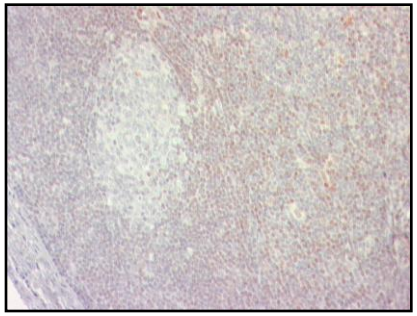


t(11;14)
Cyclin D1

RB1

p27

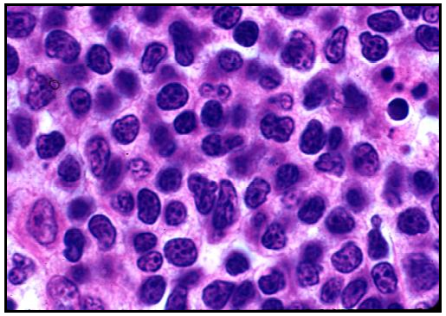
Early MCL



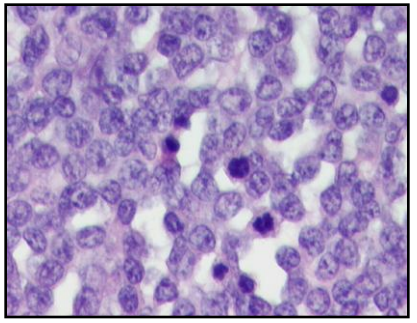
ATM
CHK2

Complex Karyotypes

Classical MCL



Blastoid MCL

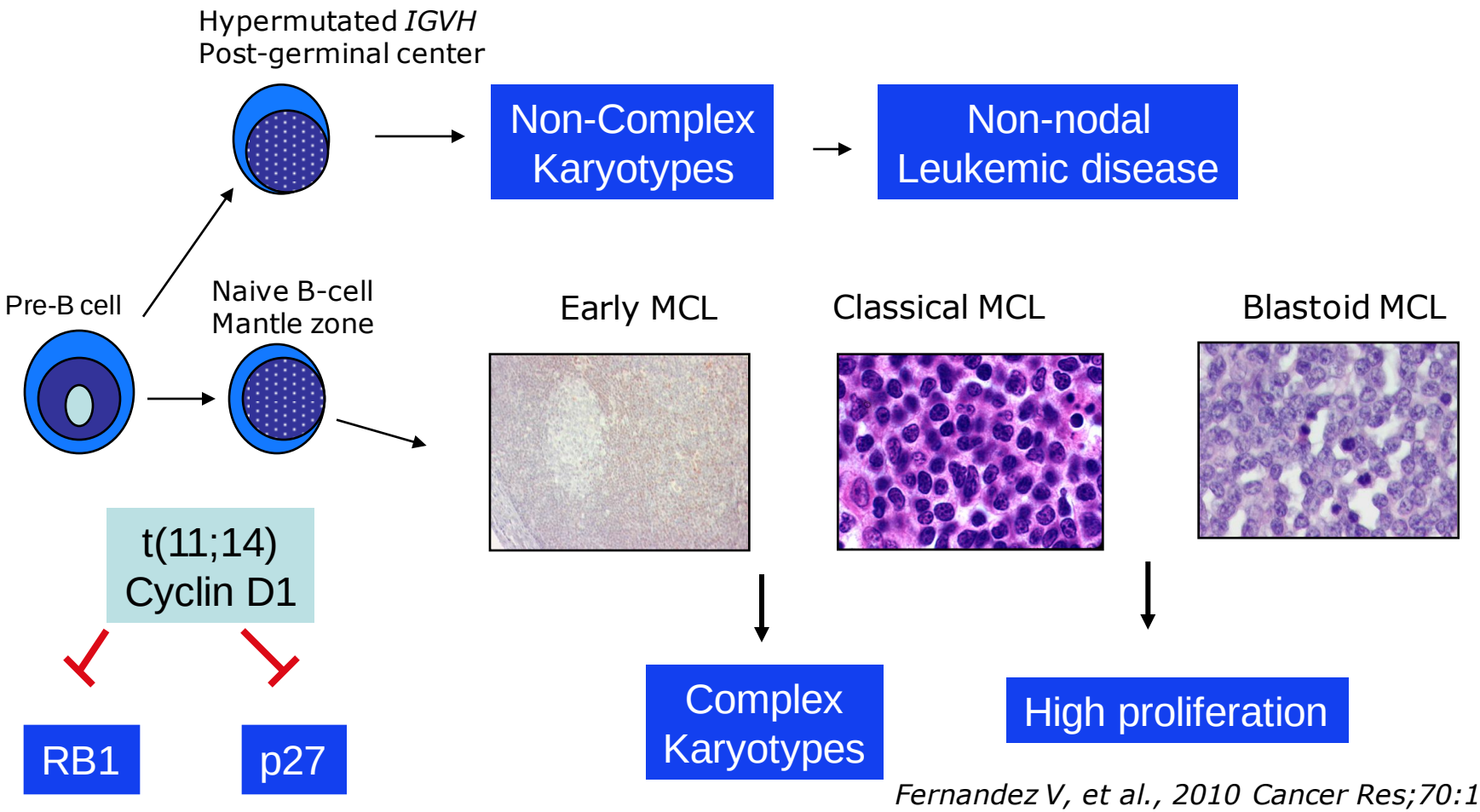


INKA4/CDK4/RB1
ARF/MDM2/p53

High proliferation

Jares et al., Nature Cancer Review 2007, 7:750

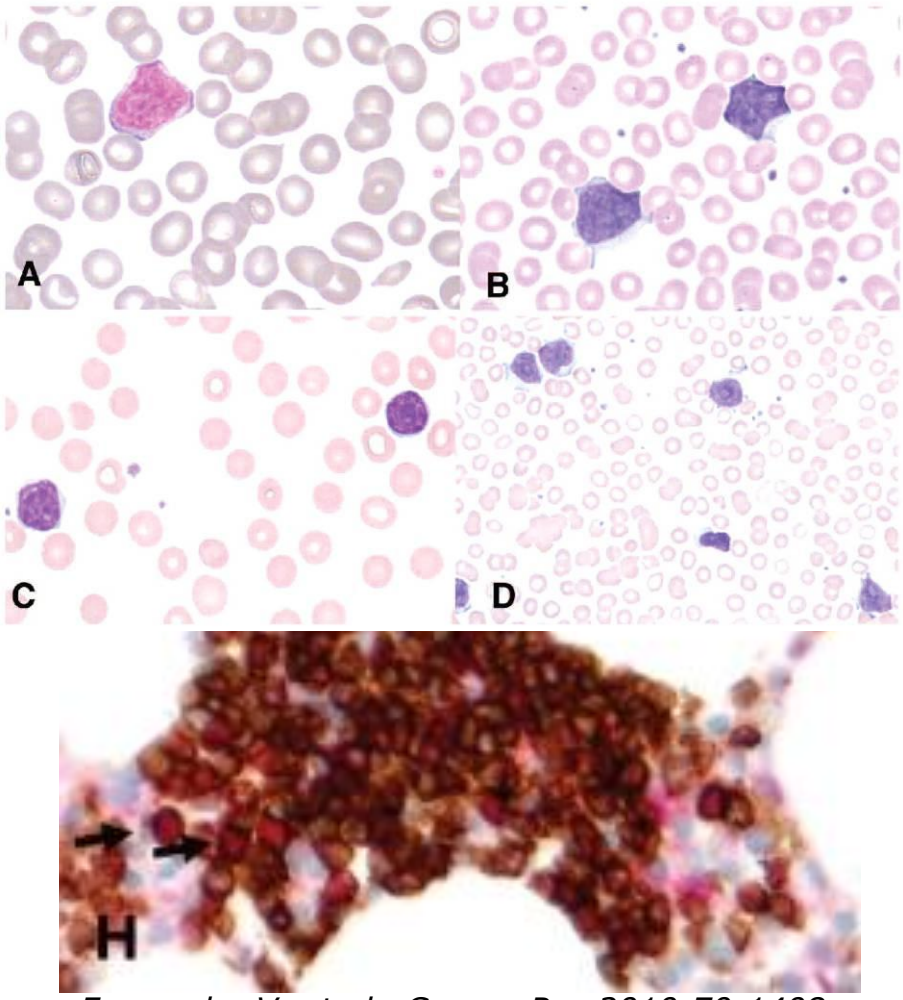
Indolent Mantle cell lymphoma



Fernandez V, et al., 2010 Cancer Res;70:1408

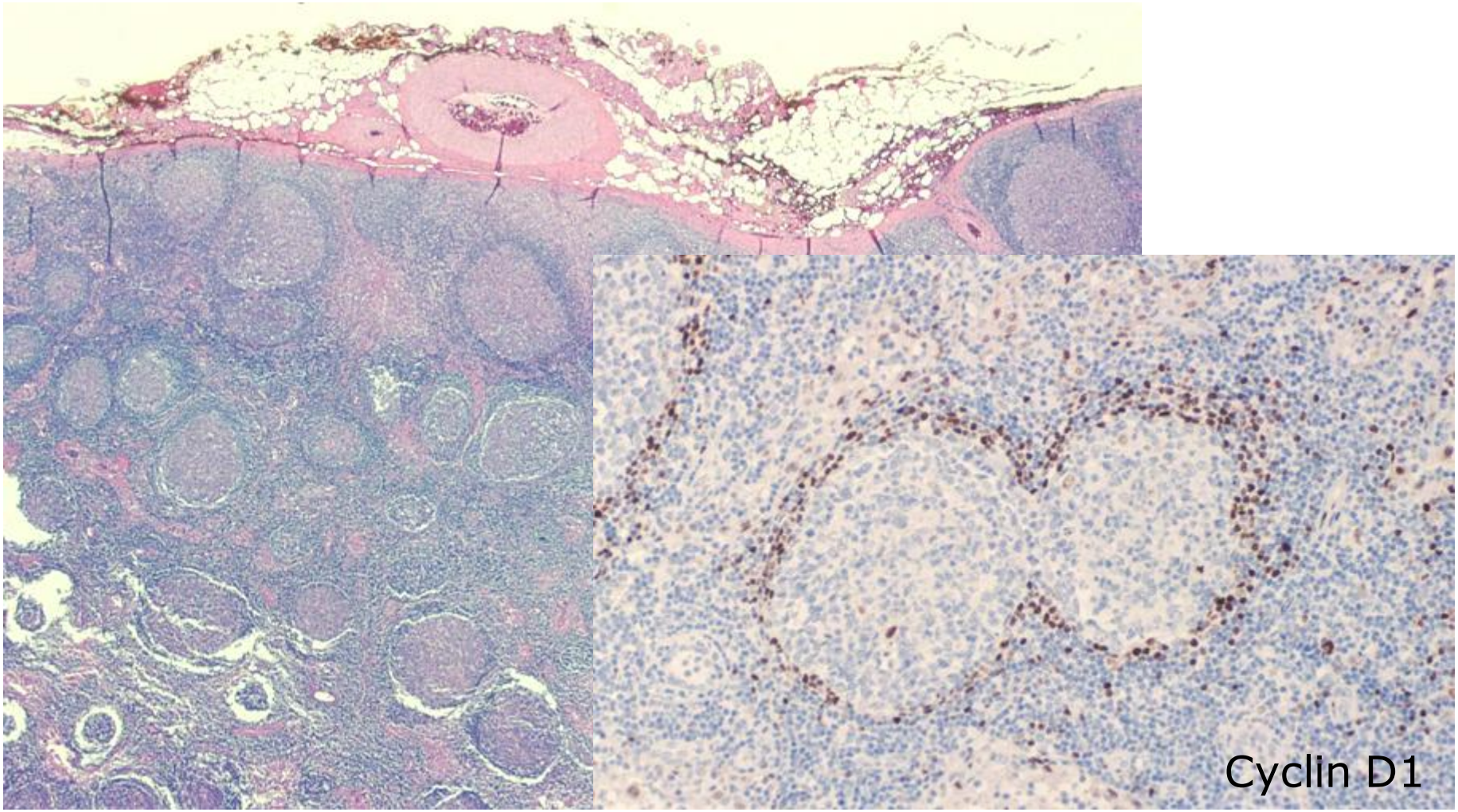
Indolent Mantle cell lymphoma

- Non-nodal leukemic disease
- Indolent clinical behaviour
- No treatment at diagnosis
- Different GEP signature
- SOX11 negative

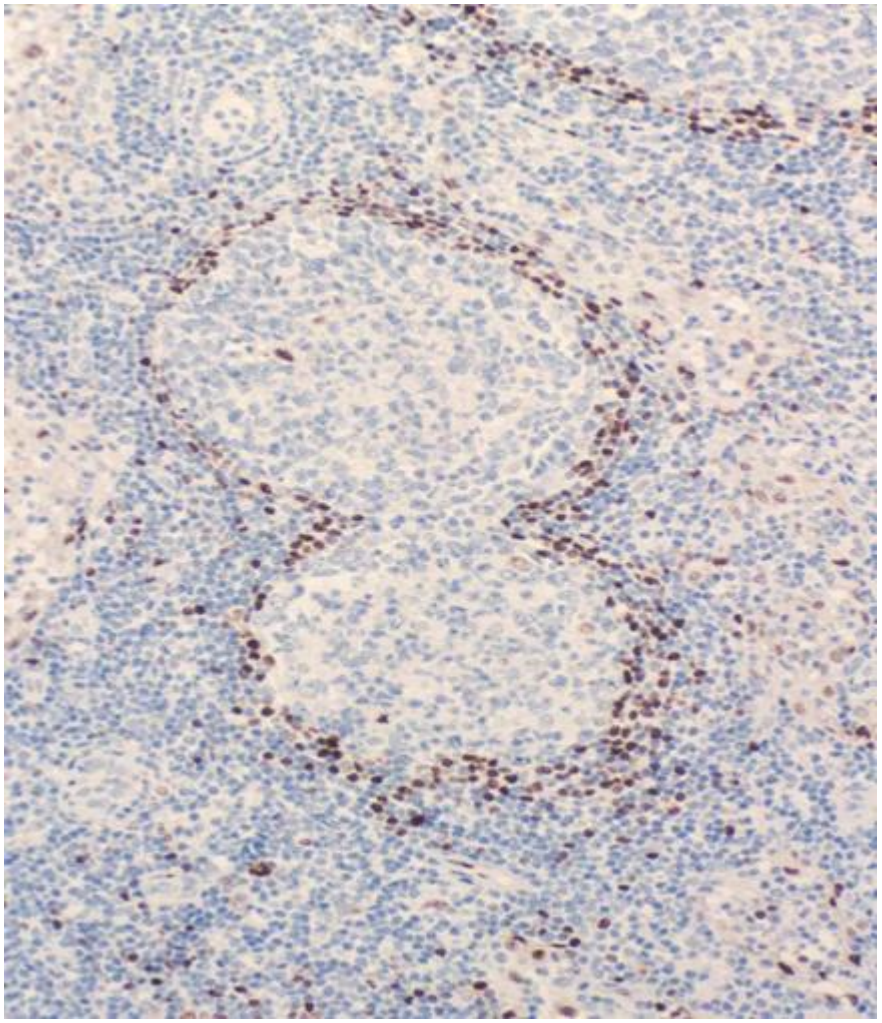


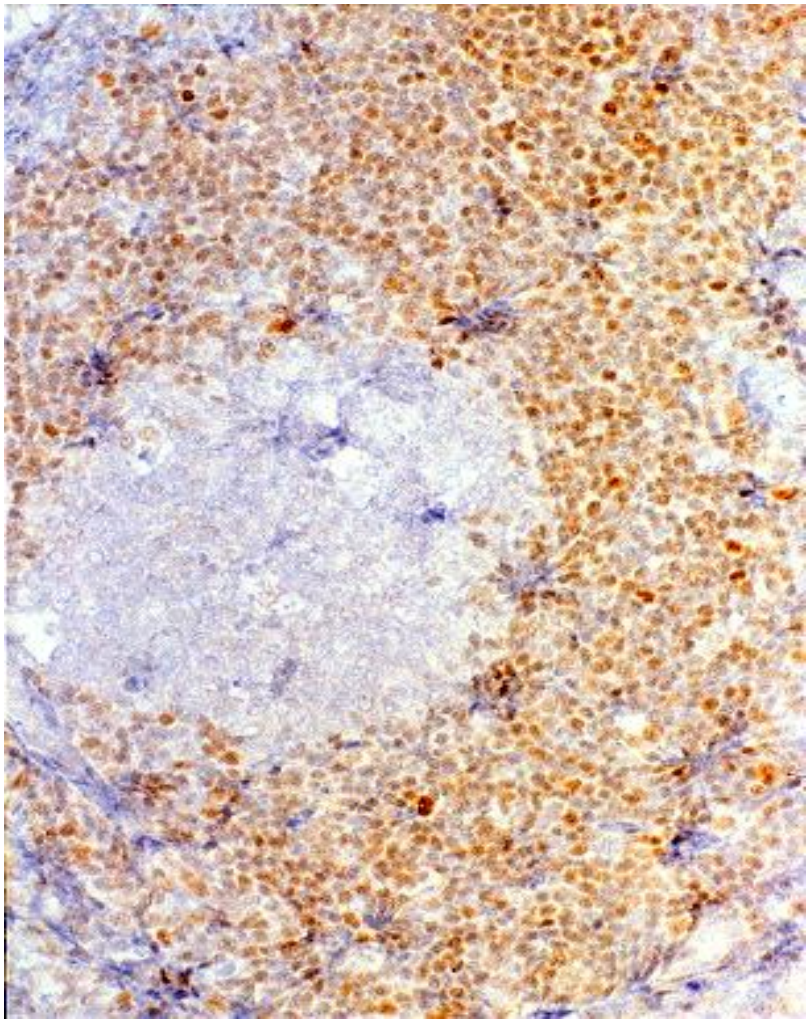
Fernandez V, et al., Cancer Res 2010;70:1408
Ondrejka SL, et al., Haematologica 2011;96:1121

Mantle cell lymphoma „in situ“

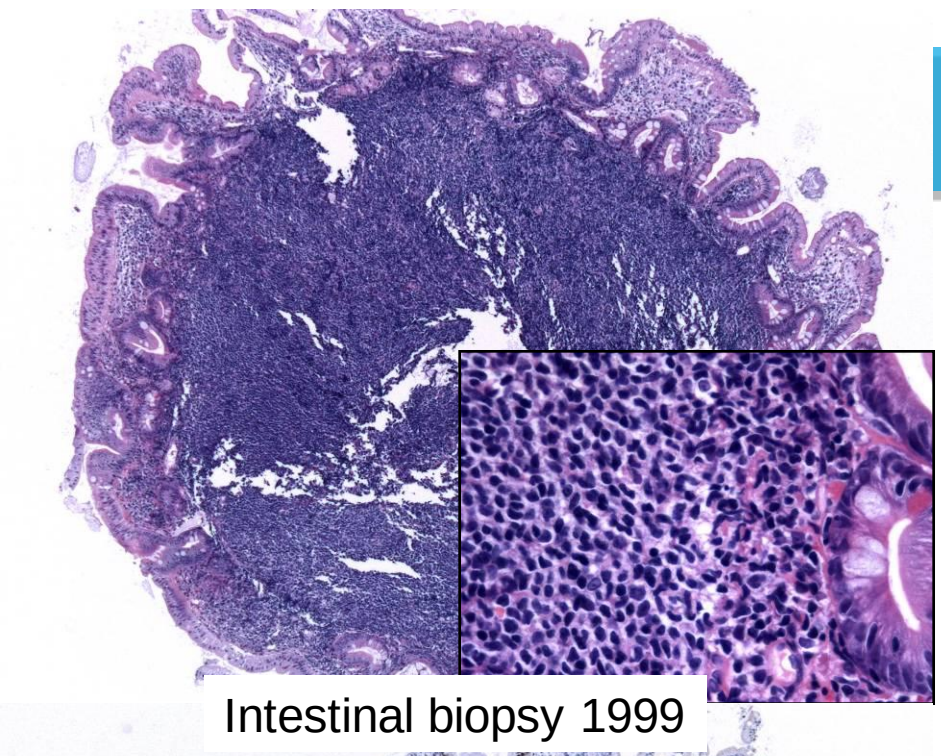


Mantle cell lymphoma in situ Mantle zone pattern

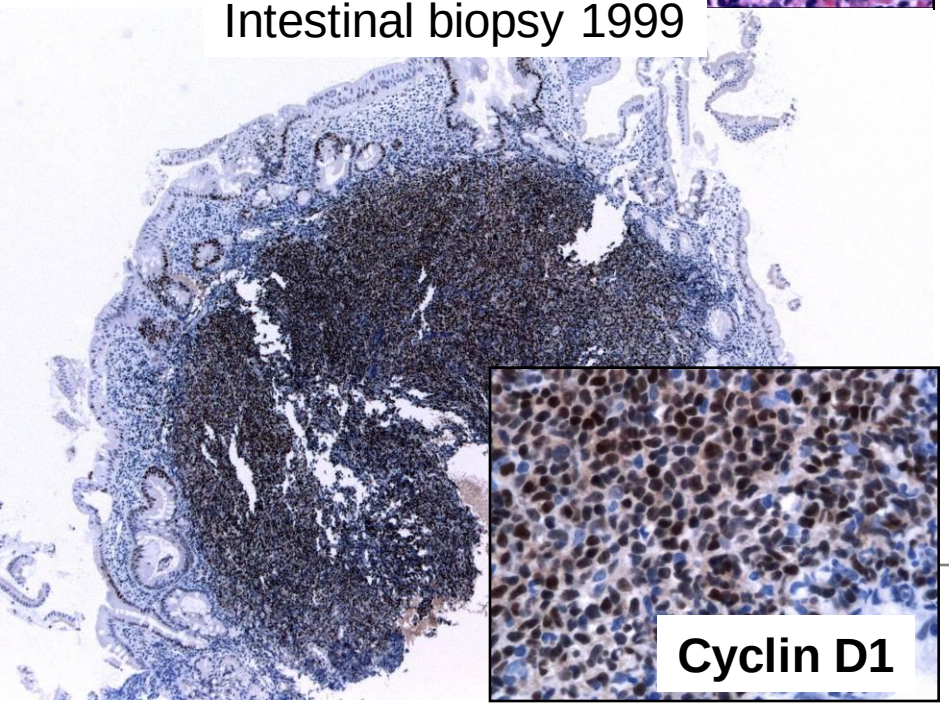




Clinical history



Intestinal biopsy 1999

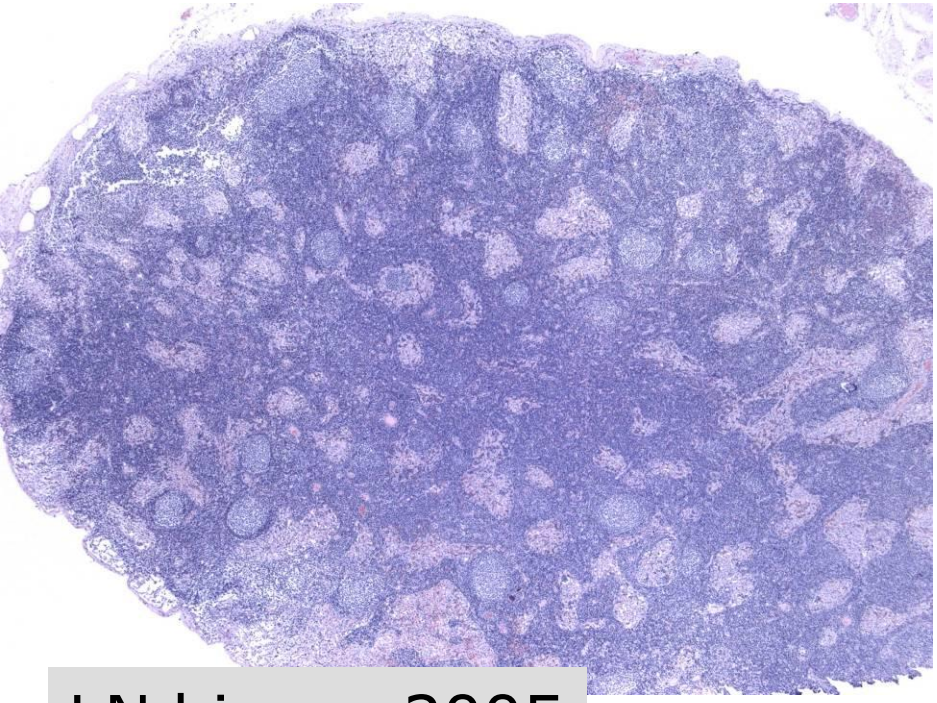


67-year old male
Dx of mantle cell lymphoma in intestinal biopsy (lymphomatous polyposis) Stage IVa

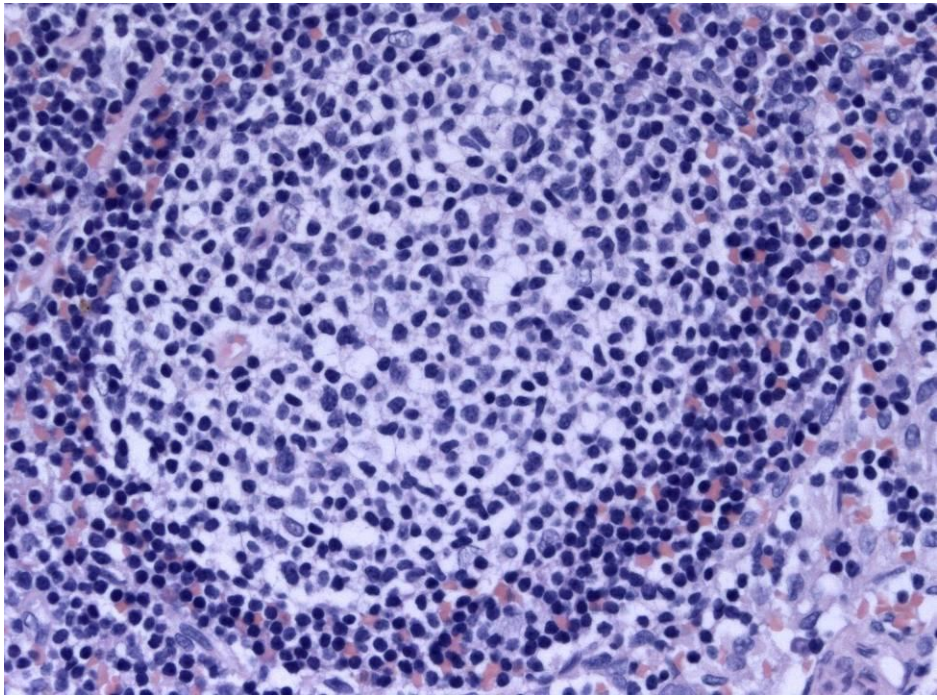
Treatment with CHOP

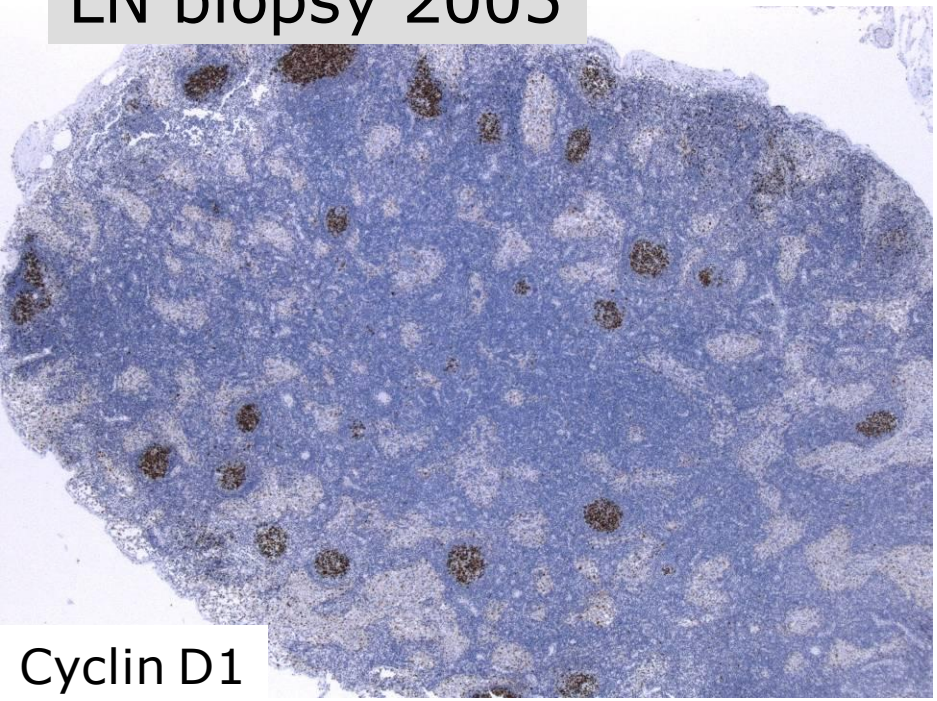
2005: salivary gland enlargement
Treatment with R-CHOP

2008: succumbed to pneumonia
Probably progressive disease

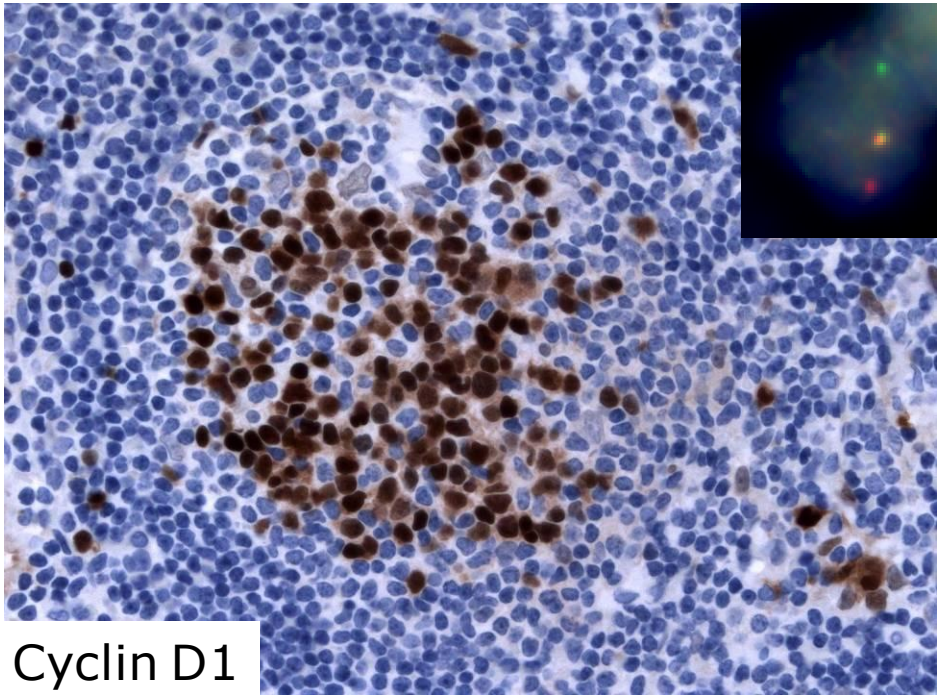


LN biopsy 2005

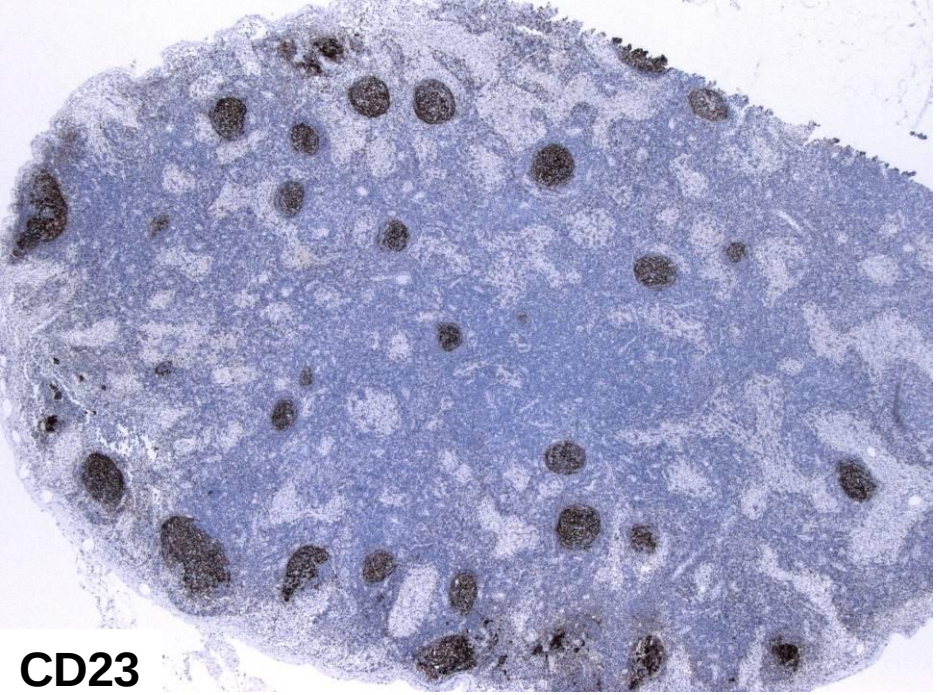




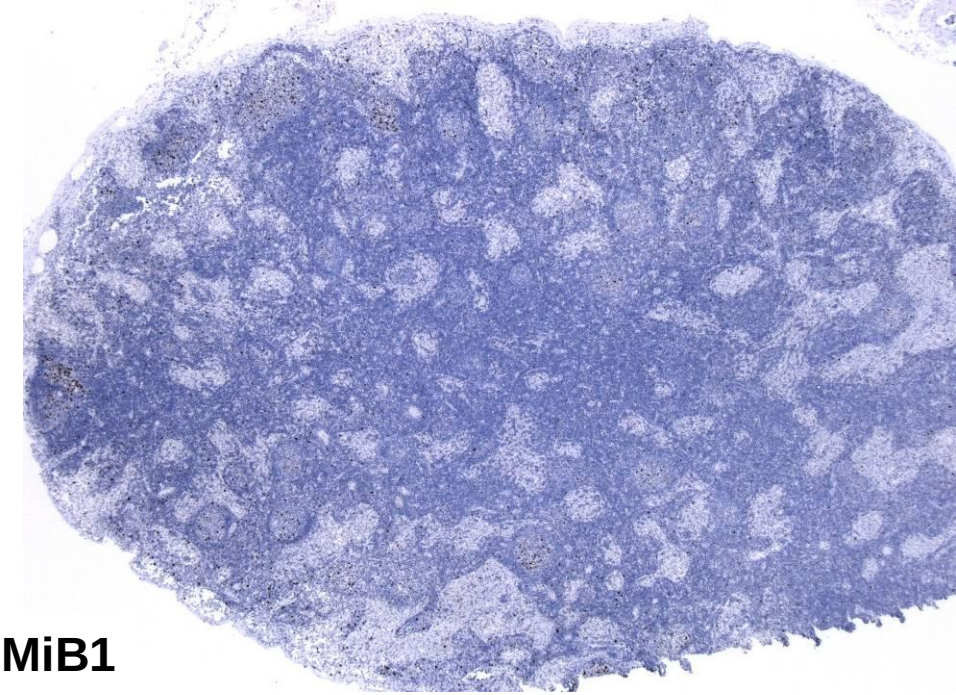
Cyclin D1



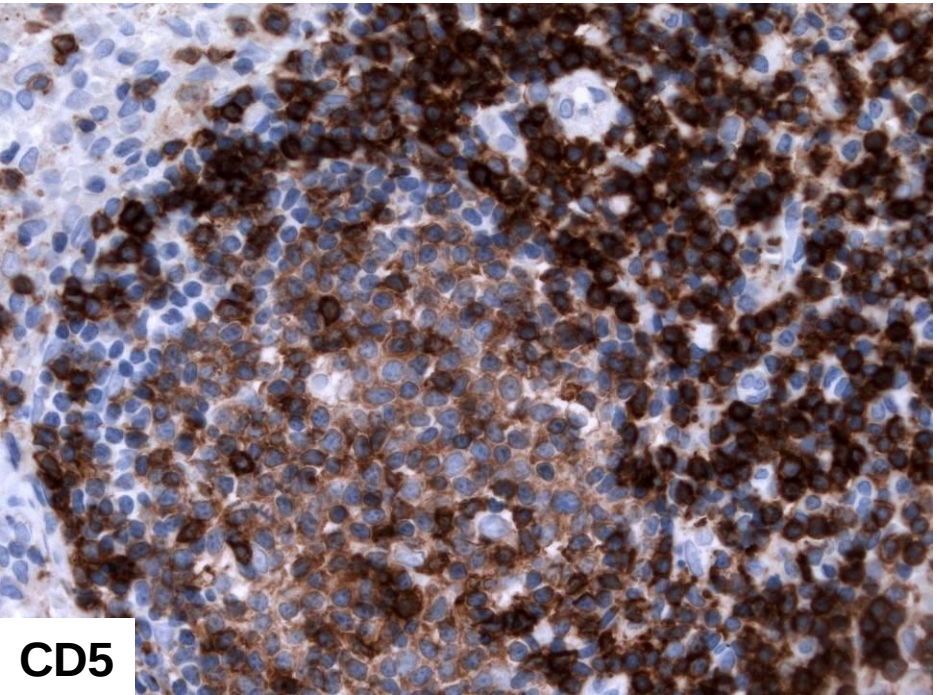
Cyclin D1



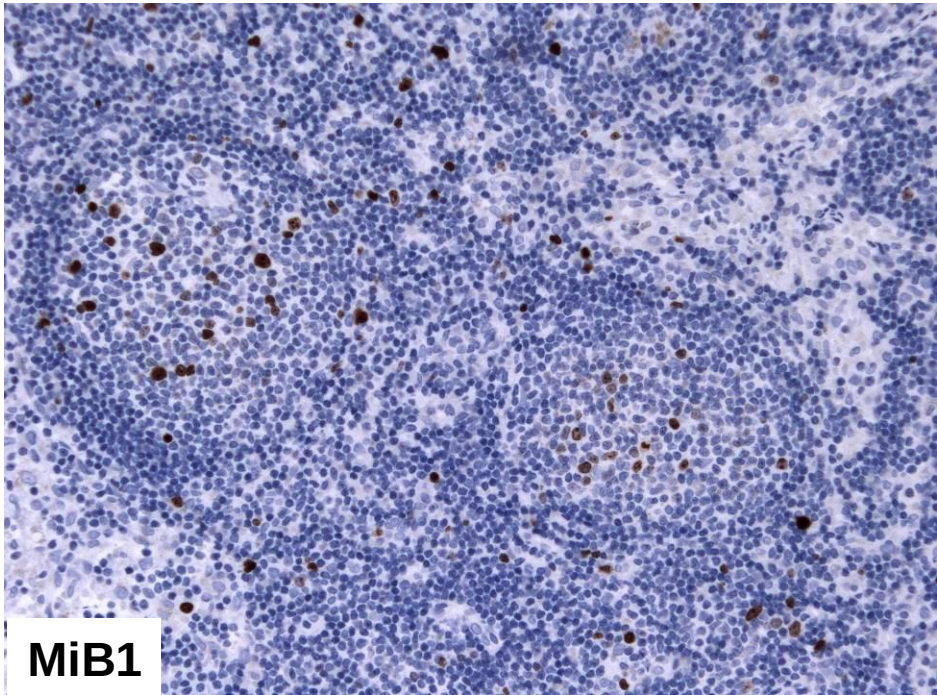
CD23



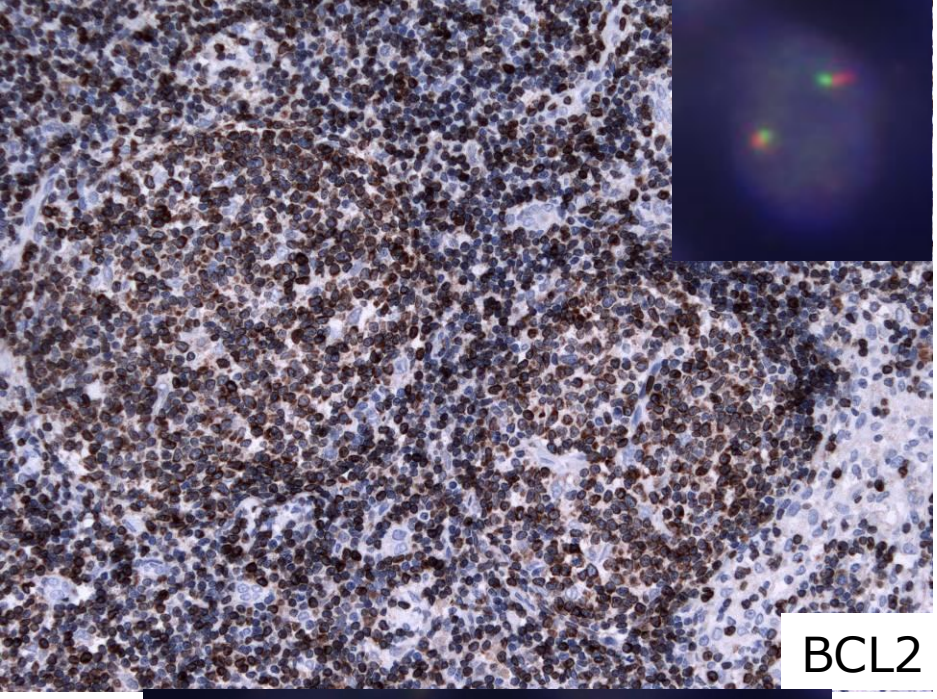
MiB1

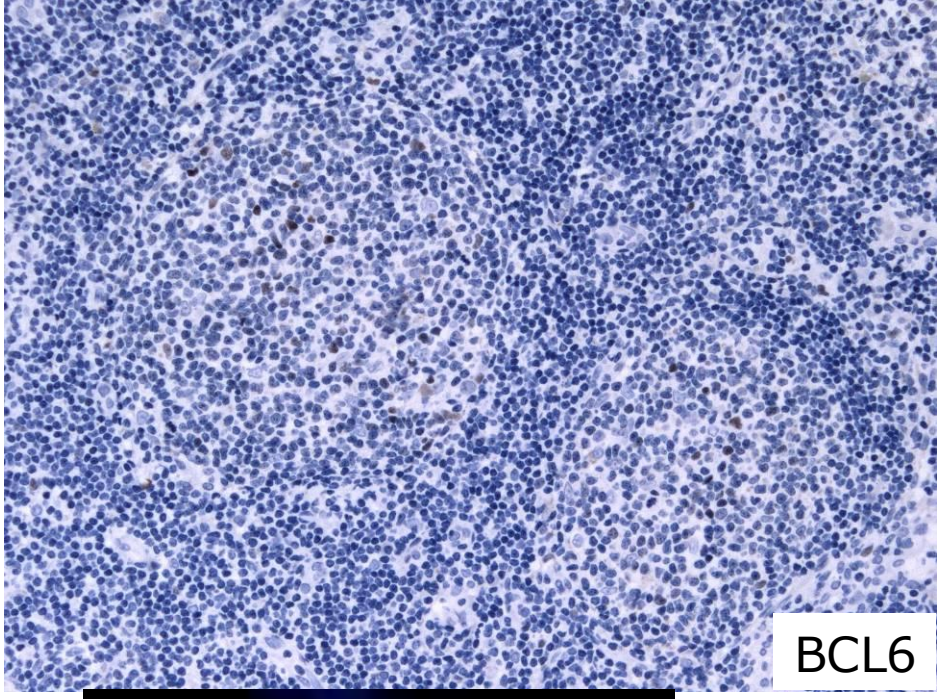


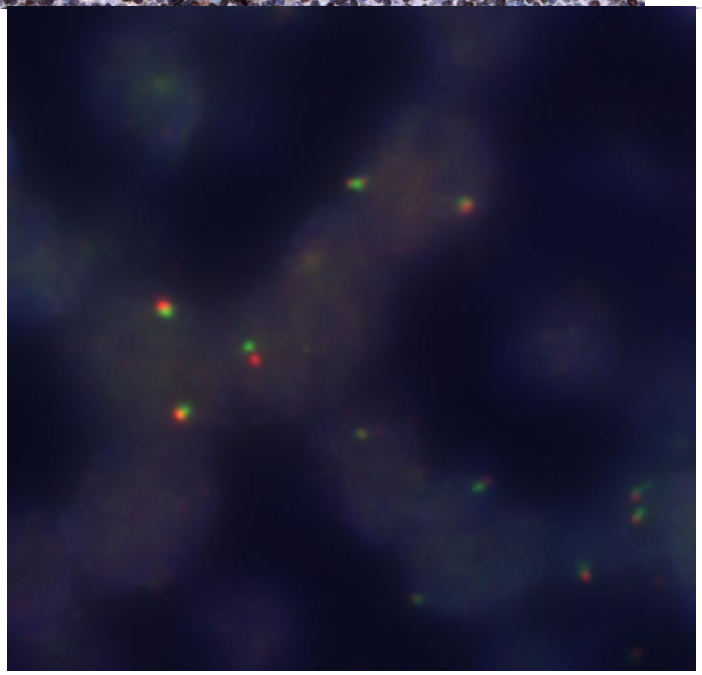
CD5



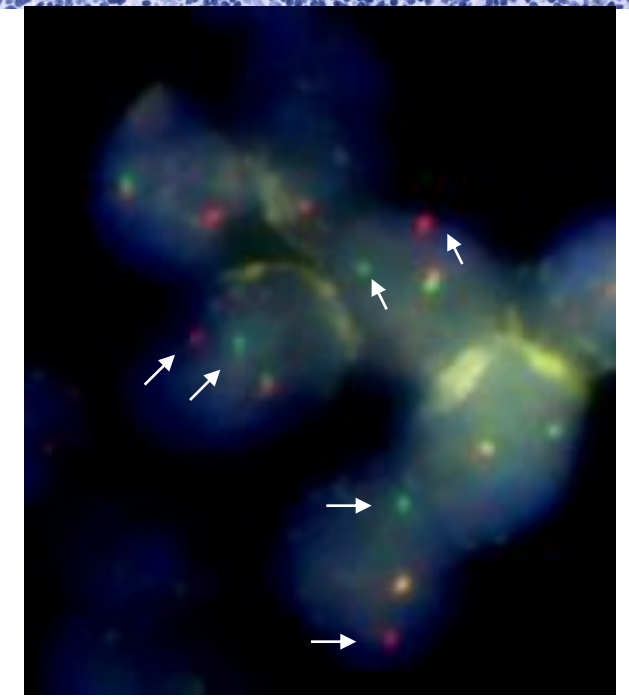
MiB1







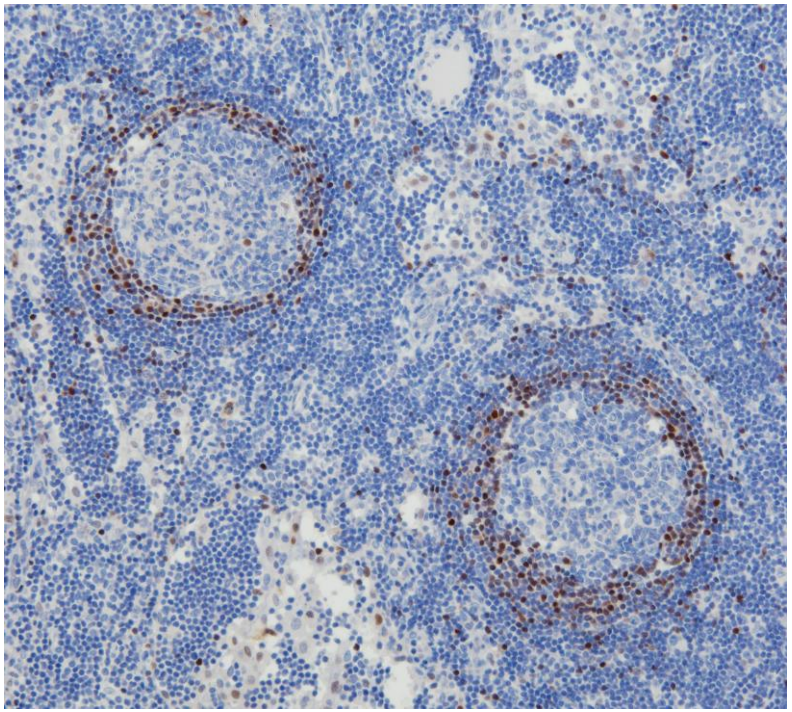
Break-apart *BCL2* probe



Break-apart *CCND1* probe

Mantle cell lymphoma „in situ“

- Usually localized in mantle zone, may be found extranodal
- Identical phenotype as classical MCL (Sox11+/-)
- May be associated with manifest MCL at other site
- Probably rarer than FLIS
  - No MCL in situ in our study of reactive LN
- 1/100 healthy individuals with t(11;14)+ PBBC vs. 39/85 t(14;18)+ PBBC (Hirt et al, Blood 2004)
- 7% in healthy individuals with long-time persistence of clone

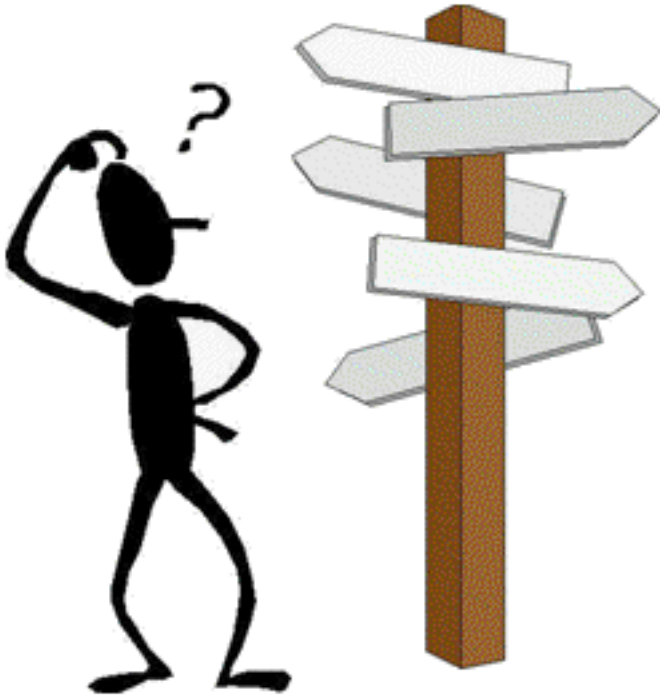


Sox 11 in MCLis

Adam et al, in prep

„Low grade“ Lymphomas

- „New“ definitions of SLL and „nodal“ monoclonal B-cell lymphocytosis
- Follicular lymphoma in situ, BCL2 negative FL and Pediatric FL
- Mantle cell lymphoma, indolent variant, in situ MCL, cyclin D1 negative MCL



Terminology of early lesions

- Should the term „lymphoma“ appear in the diagnosis?
  - Unwarranted treatments
  - Insurance coverage (USA)
  - Psycological impact
- Proposal from Uppsala workshop
  - FL-like B-cells of undetermined significance (FLBUS) MCL-like B-cells of undetermined significance (MCLBUS) and CLL/SLL-like B-cells of undetermined significance
  - **Communicate the clinical meaning of this finding!**

What are the clinical consequences?

- Possibility of fully developed lymphoma at other site – perform staging
  - Clinical / Imaging / BM biopsy ?
- Risk for progression low – no indication for therapy –
- indication for and spacing of follow-up examination??
  - Risk for progression not known!
- No indication for molecular staging

Tübingen