Current Concepts in Hematopathology

Nodal Small B-cell Lymphomas

Challenging Situations and Potential Pitfalls

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SMALL B-CELL LYMPHOMAS

Classification

CD5+

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - Monoclonal B-cell lymphocytosis
- Mantle cell lymphoma
  - Leukemic non-nodal mantle cell lymphoma
  - In situ mantle cell neoplasia

CD10+

- Follicular lymphoma
  - Testicular follicular lymphoma
  - In situ follicular neoplasia
  - Duodenal-type follicular lymphoma
- Pediatric-type follicular lymphoma
- Large B-cell lymphoma with IRF4 rearrangement
- Primary cutaneous follicle center lymphoma

CD5-/CD10-

- Lymphoplasmacytic lymphoma
- Hairy cell leukemia
- Splenic B-cell lymphoma/leukemia, unclassifiable
  - Splenic diffuse red pulp B-cell lymphoma
  - Hairy cell leukemia, variant
- Splenic marginal zone lymphoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - Pediatric nodal marginal zone lymphoma

CD5-/+

- B-cell prolymphocytic leukemia

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Gray areas/caveats

Monoclonal B-cell lymphocytosis (MBL)

- circulating clonal B cells <$5x10^9$/L
- no documented lymphadenopathy, organomegaly, other extramedullary disease
- patients with MBL can have bone marrow involvement (interstitial, non-paratrabecular lymphoid aggregates, diffuse) – ranges, but on average accounts for ~20% of the cellularity
- difference in definitions:
  - *International Workshop on CLL* (iwCLL):* "the presence of a cytopenia caused by a typical marrow infiltrate establishes the diagnosis of CLL regardless of the number of peripheral blood B lymphocytes or of the lymph node involvement"
  - WHO: "the [4th ed] revision will eliminate the option to diagnose CLL with <$5x10^9$/L peripheral blood CLL cells in the absence of extramedullary disease, even if there are cytopenias or disease-related symptoms"

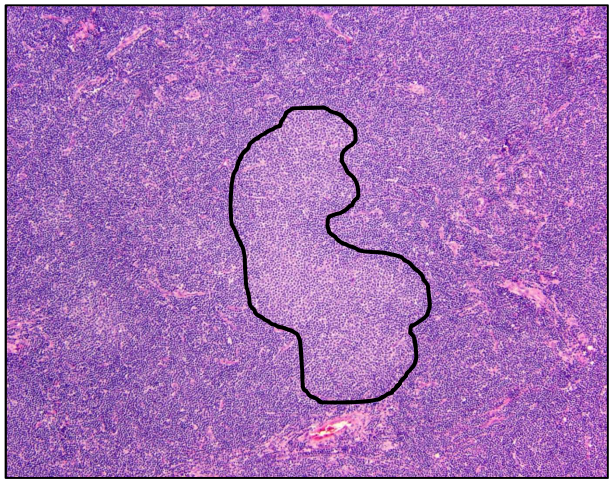
Limited nodal involvement by CLL-like cells

- sometimes this is an incidental flow finding in lymph nodes taken out for other reasons (subtle by morphology/IHC) → recommend PB flow cytometry evaluation to exclude circulating component at ≥$5x10^9$/L
- if circulating CLL-like count is <$5x10^9$/L, probably best considered "nodal MBL" (*not* SLL) <u>if</u>: architecture not effaced; proliferation centers not identified; lymph nodes are <1.5cm by imaging

Hallek M et al. *Blood*. 2018;131(25):2745-2760.
Ganapathi KA et al. *Haematologica*. 2014; 99(9).
Gibson SE et al. *Haematologica*. 2011;96(8):1144-1152.
Strati P, Shanafelt TD. *Blood*. July 23 2015;126(4).
Randen U et al. *Am J Clin Pathol*. 2013;139:390-395.

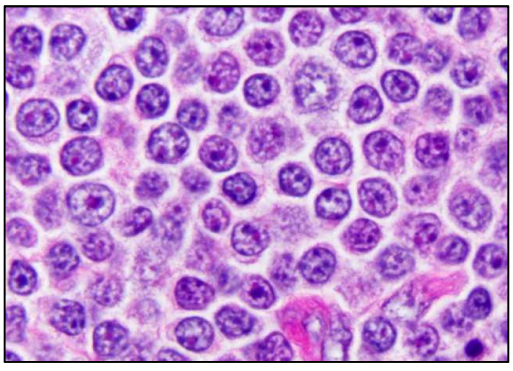
CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Proliferation centers



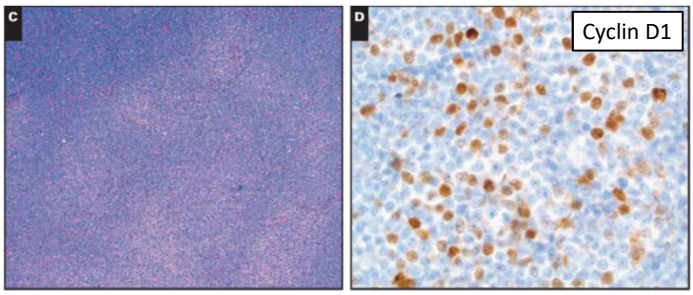
Lymph node:

- diffuse effacement; occasionally vaguely nodular
- proliferation centers: small lymphocytes, prolymphocytes and paraimmunoblasts

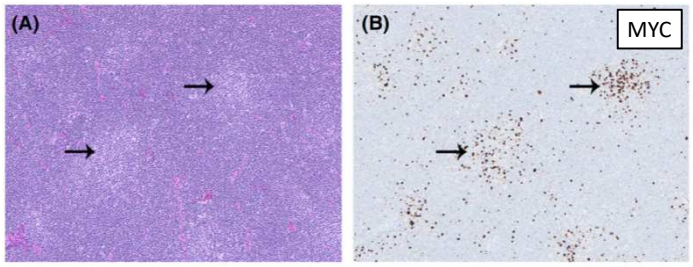


CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Proliferation centers – potential pitfalls



- proliferation centers in up to 30% of cases of CLL/SLL can have cyclin D1 expression
- no t(11;14)
- no SOX11 expression by IHC
- does not = mantle cell lymphoma



- proliferation centers in the majority of cases of CLL/SLL have at least subset MYC expression by IHC
- no MYC rearrangement by FISH; few cases with MYC hyperdiploidy by FISH
- does not = transformation to large-cell lymphoma

Gibson SE et al. *Br J Haematol*. 2016;175, 161–175.
Gradowski JF et al. *Am J Clin Pathol*. 2012;138:132-139.

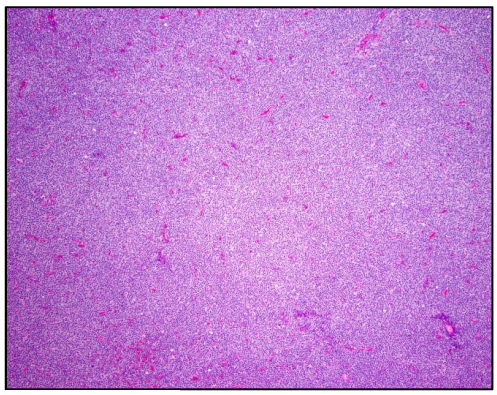
CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

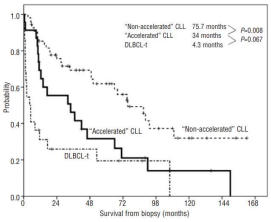
Proliferation centers - confluent

- proliferation centers broader than 20x field or becoming confluent and/or Ki67 >40% or mitoses >2.4/PC
- association with deletion in 17p13 or trisomy 12
- has been referred to as "accelerated CLL"
- not an official category in the current WHO

- challenging "gray zone" histologically
- distinct from DLBCL (often requires excisional biopsy)
  - DLBCL = confluent sheets of large B cells with a nuclear size equal to or exceeding that of normal macrophage nuclei or more than twice the size of a normal lymphocyte
- clinical trial study showed that only 33 of 40 (82.5%) cases submitted as Richter transformation were consistent with RT following expert central review
  - large proliferation centers
  - variably confluent and serpiginous proliferation centers
  - high proliferation index (sometimes thick section or associated normal bone marrow)
- comment upon in report given association with more aggressive clinical course
  - note that outcomes studies were before the current therapy era

Confluent



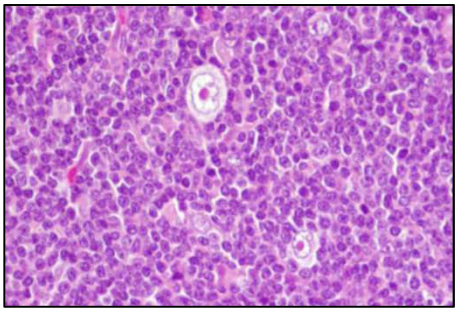


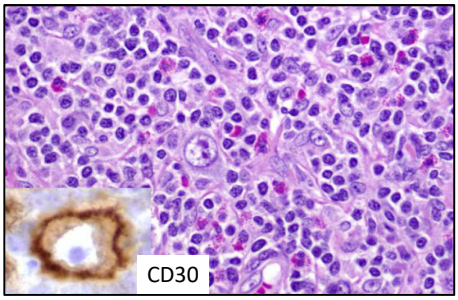
Soilleux EJ et al. *Histopathology*. 2016;69, 1066–76.
Gine E et al. *Haematologica*. 2010:95(9):1526-33.
Ciccone M et al. *Leukemia*. 2012;26:499–508.
Oscier D et al. *Br J Haematology*. 2016;174, 767–775.
Chabot-Richards D et al. Chp 14. *Hematopathology 2nd ed*. 2016.

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Hodgkin/Reed-Sternberg (HRS) cells

- "Type I" pattern, or CLL/SLL with HRS-like cells (CLL-HRS)
  - HRS cells sparsely distributed amongst CLL cells
    - median 4 HRS cells/high-powered field; often with T-cell rosette
  - no evidence of inflammatory background typical of classic Hodgkin lymphoma
    - per 2017 WHO, does not fulfill criteria for CHL/not "Richter transformation"
  - most EBV+
  - may or may not be clonally related to CLL
- "Type II" pattern, or Richter transformation as CHL (RT-CHL)
  - requires diagnostic RS cells in an inflammatory background typical of CHL per WHO
  - most EBV+
  - ~50% related to the CLL clone; clonally-unrelated cases associated with unmutated CLL
  - uncommon type of Richter transformation (~5%)
  - inferior prognosis compared to *de novo* HL

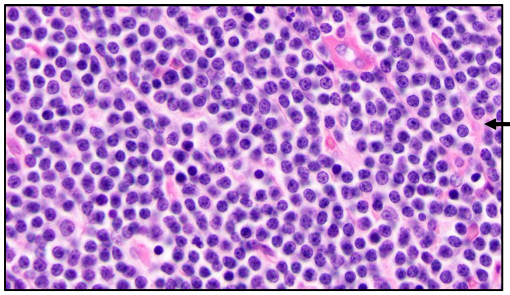


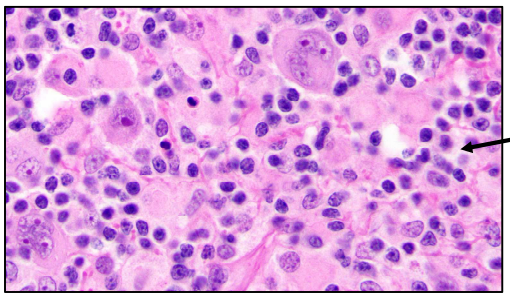


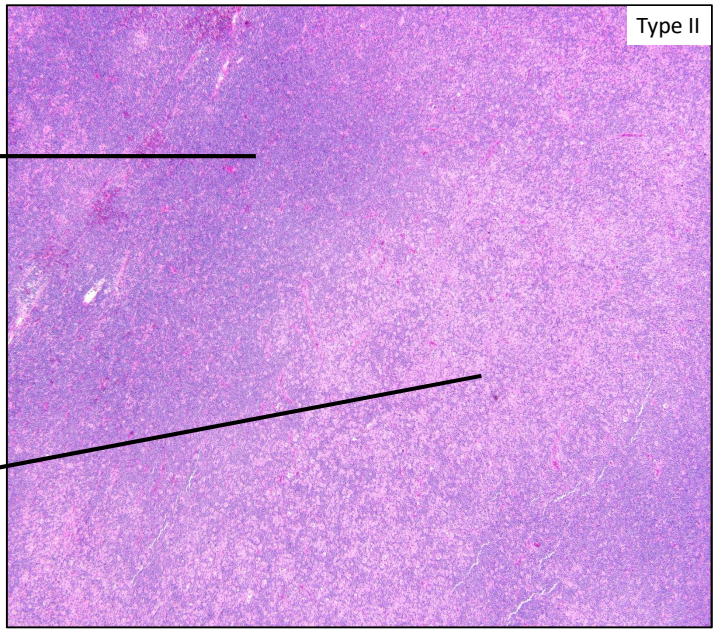
King RL et al. *Blood Cancer Journal.* 2022;12:18.
Xiao W et al. *Hum Pathol*. 2016 September;55: 108–116.
Chabot-Richards D et al. Chp 14. *Hematopathology 2nd ed.* 2016.

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Hodgkin/Reed-Sternberg (HRS) cells



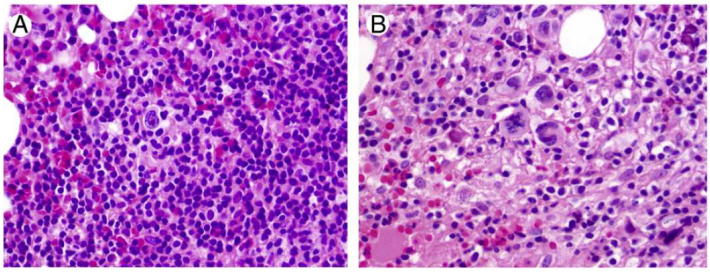




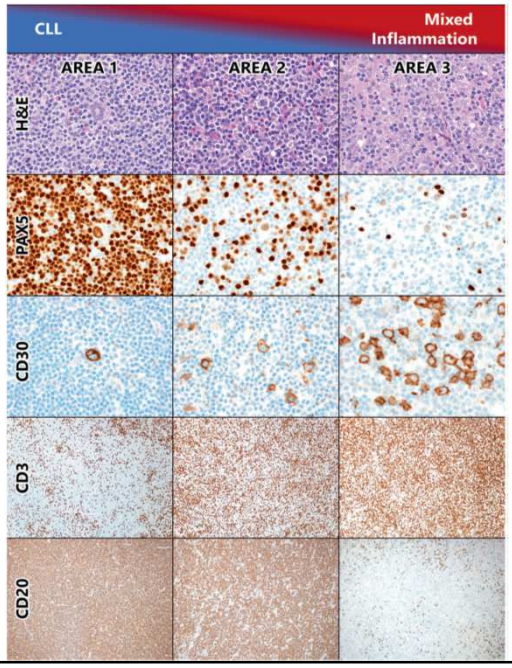
CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Hodgkin/Reed-Sternberg (HRS) cells

- however, other cases can present as a histologic continuum or can progress over time



Type I | Same patient, 2 years later (Type II)



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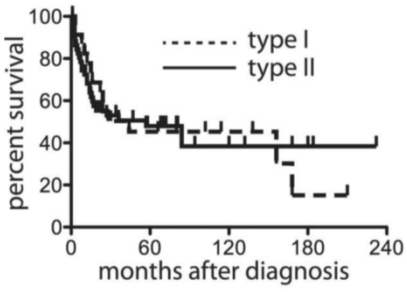
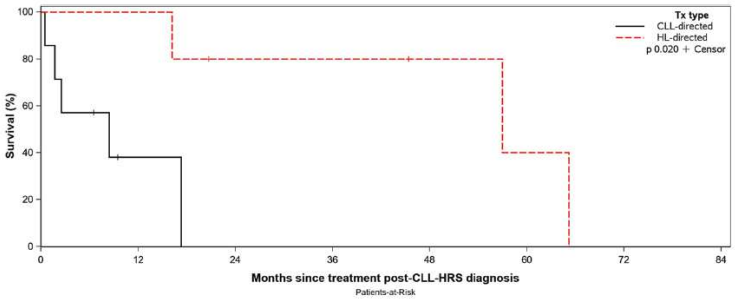
Xiao W et al. *Hum Pathol*. 2016 September; 55: 108–116.

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Hodgkin/Reed-Sternberg (HRS) cells

- Do we need to make a distinction between CLL-HRS and RT-CHL?





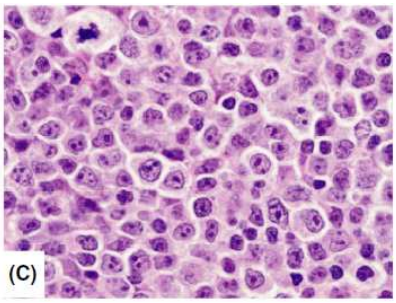
(retrospective study spanning 3 decades)

King RL et al. *Blood Cancer Journal.* 2022;12:18.
Xiao W et al. *Hum Pathol*. 2016 September; 55: 108–116.

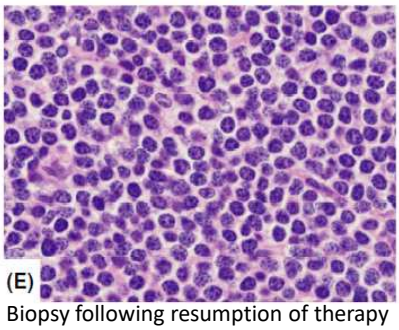
CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Pseudo-Richter transformation

- RT occurs at a similar rate with novel agents like ibrutinib (BTK inhibitor) as traditional chemotherapy agents, although rate is lower if front-line
- If RT occurs, it is usually an early event (within the first year) and clonally related to CLL
- recent report of 5 patients with CLL/SLL receiving ibrutinib who underwent brief interruption of therapy due to upcoming surgery → developed lymphadenopathy, lymphocytosis or progressive cytopenias
- biopsies (LN or bone marrow) revealed findings morphologically consistent with RT
- histologic findings resolved upon resumption of therapy



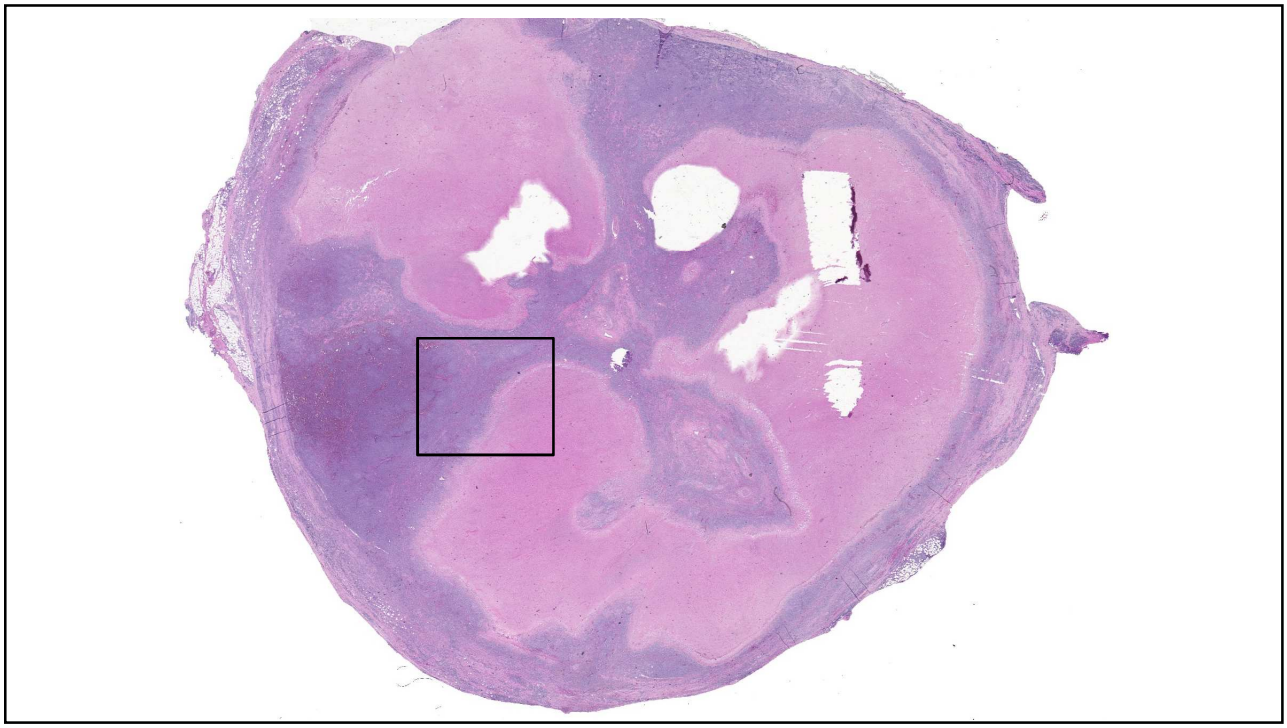
Biopsy 7-13 days into therapy interruption

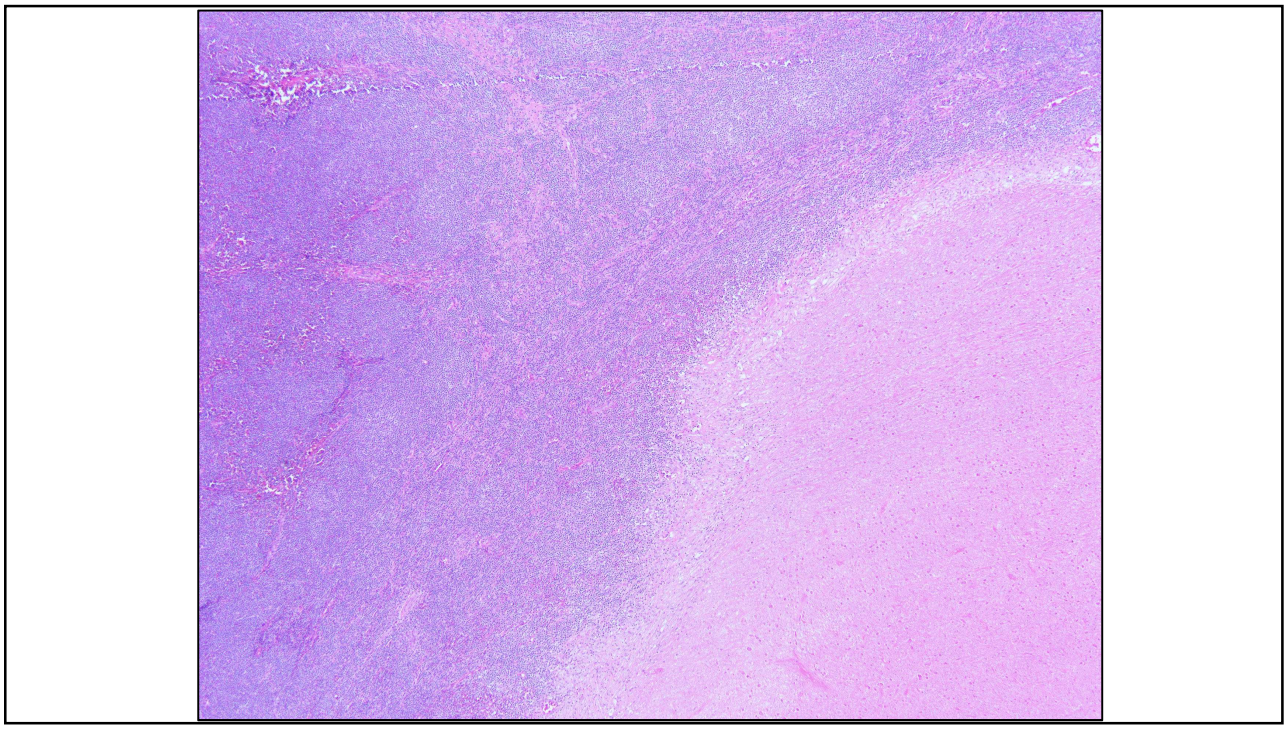


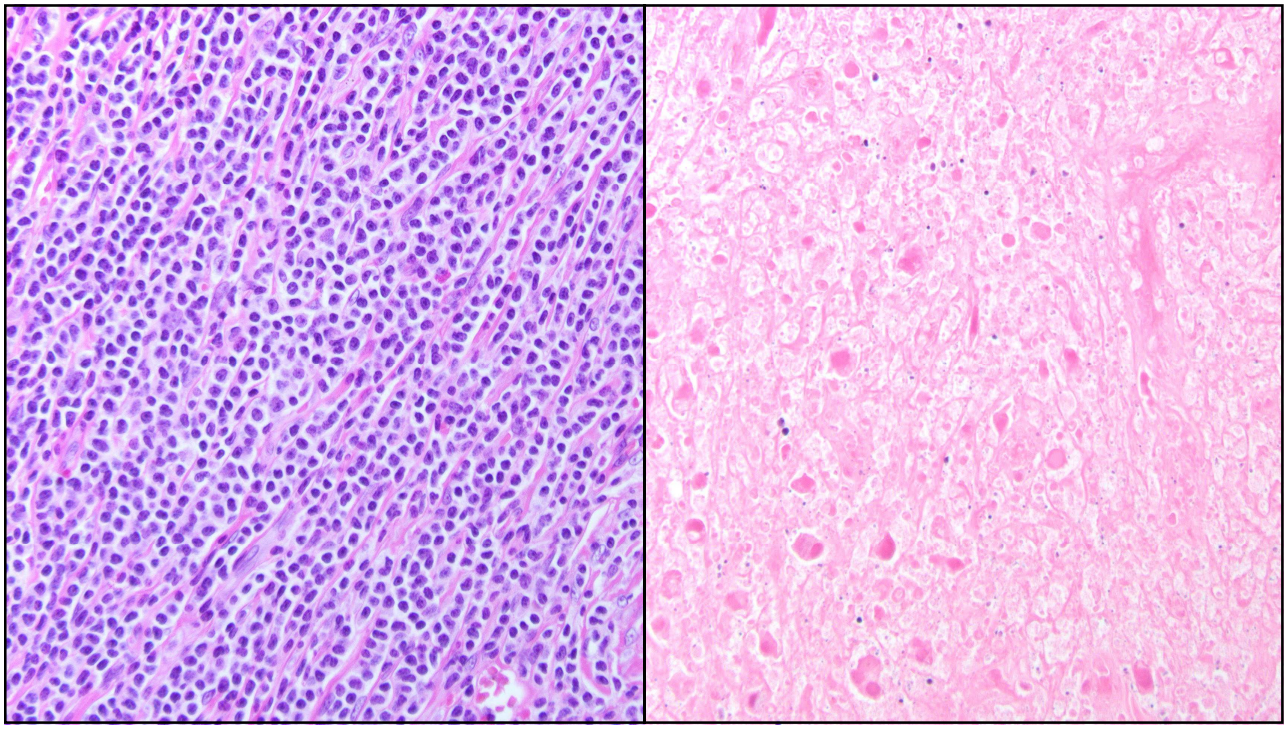
Biopsy following resumption of therapy

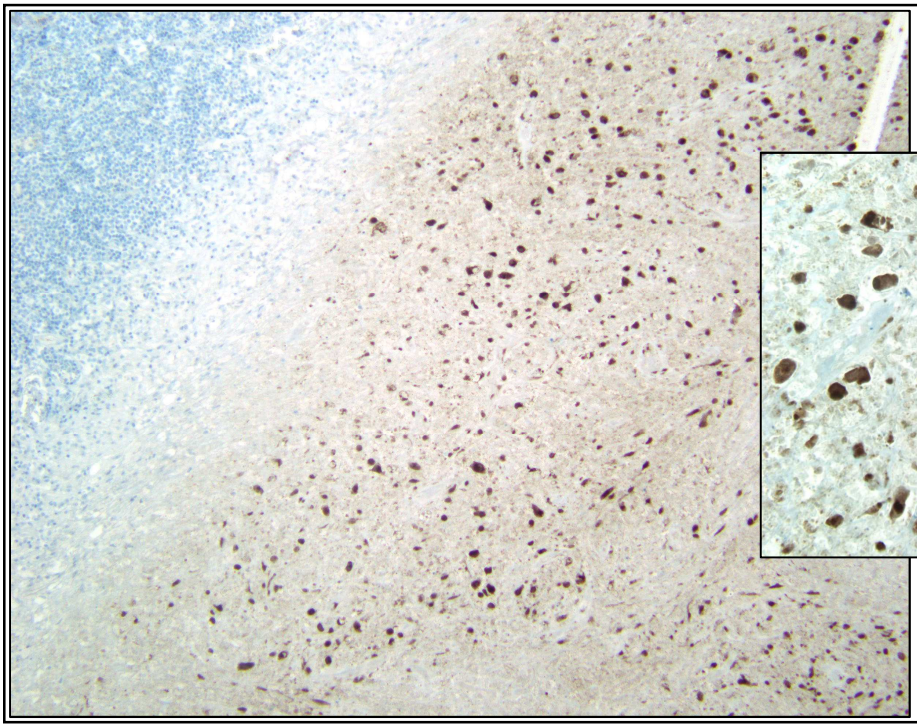
Petrackova A et al. *Blood Reviews*. 2021;49: 100824.

Slonim LB et al. Br J Haematol. 2020;191, e5–e3





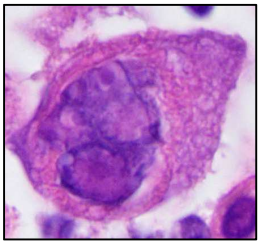




HSV immunostain

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Necrosis – potential pitfall

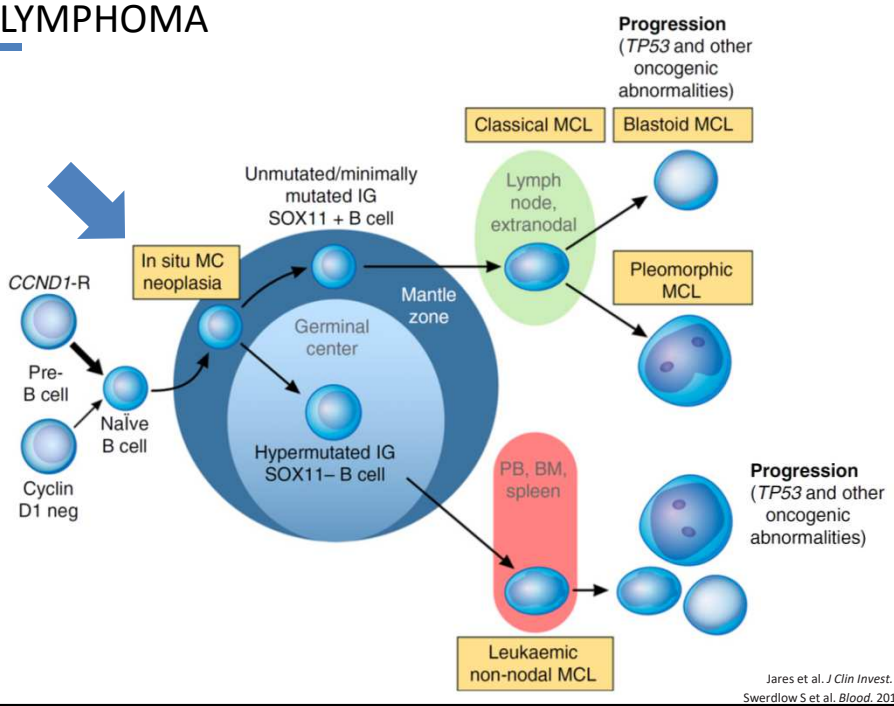


Herpes simplex virus (HSV) lymphadenitis

- well-circumscribed areas of necrosis with nuclear dust/debris, eosinophilic ghost cells, viral inclusions, neutrophils
- HSV-infected cells can be mononuclear or multinucleated, and show eosinophilic, “ground-glass” intranuclear inclusions
- can infect any cell type
- reactivation of HSV associated with lymphadenopathy is particularly seen in patients with CLL/SLL (?secondary to immunosuppression)
- can also be seen in other hematologic malignancies
- *do not interpret necrosis as unequivocal evidence of Richter transformation – may be HSV!*

MANTLE CELL LYMPHOMA

New paradigm

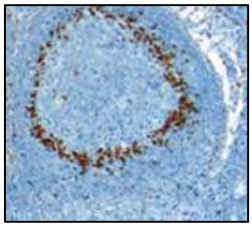


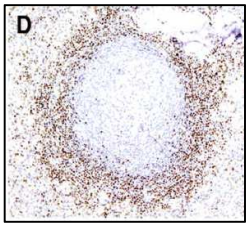
Jares et al. *J Clin Invest.* 2012;122:3416–3412.
Swerdlow S et al. *Blood.* 2016;127(20):2375-2390.

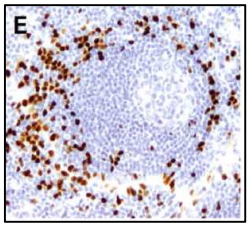
MANTLE CELL LYMPHOMA

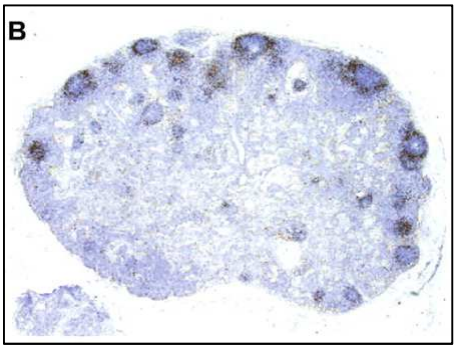
*In situ mantle cell **neoplasia***

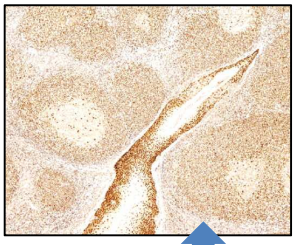
- non-expanded mantle zones
- cyclin D1⁺ cells in inner, outer or entire mantle zone
- no other features in the lymph node of MCL
- often found incidentally, particularly in association with a true lymphoma
- t(11;14) present; SOX11+/-
- low rate of progression
- the term “neoplasia” emphasizes need for conservative clinical approach → not equal to MCL/typically does not show progression to MCL









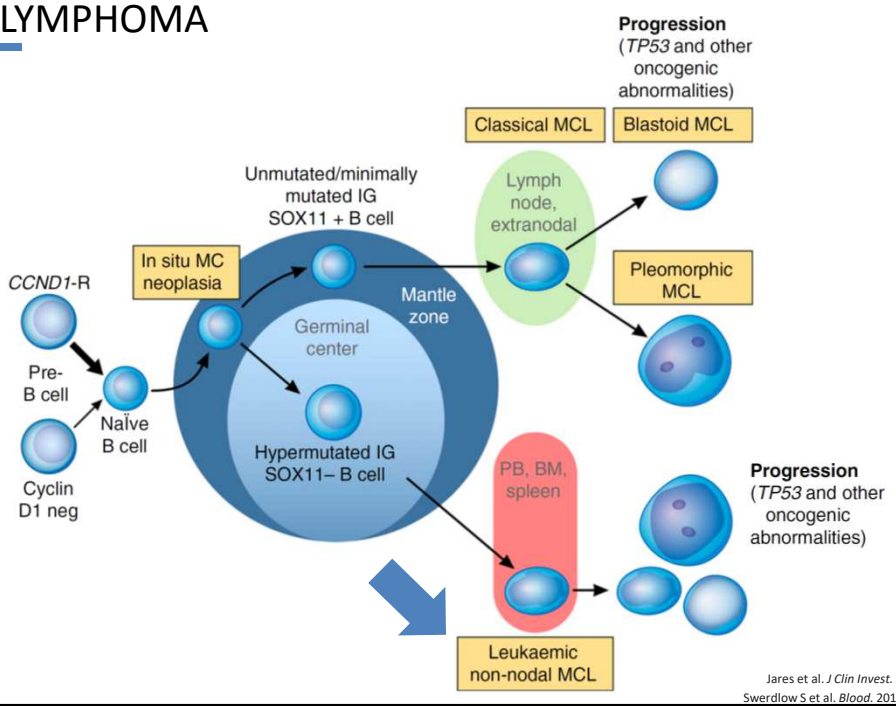


Caveat! Must be distinguished from overt MCL with a mantle zone growth pattern = expanded mantle zones

Carvajal-Cuenca A et al. *Haematologica.* 2012;97:270-278.

MANTLE CELL LYMPHOMA

New paradigm



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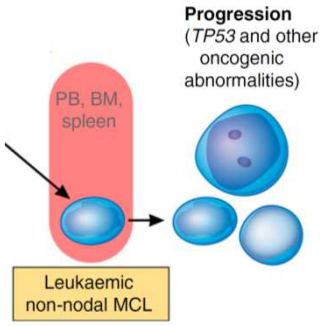
Swerdlow S et al. *Blood.* 2016;127(20):2375-2390.

MANTLE CELL LYMPHOMA

Leukemic non-nodal MCL

- peripheral blood, bone marrow and splenic involvement without significant adenopathy
- SOX11-negative
- may be CD5-negative, CD200+
- morphologically may resemble CLL/SLL
- somatic hypermutation
- t(11;14) present; few if any additional karyotypic abnormalities
  - ATM mutation/11q22 deletion rare to absent
- more indolent course/better overall survival
- acquisition of *TP53* mutation or other oncogenic gene abnormalities may result in more aggressive behavior

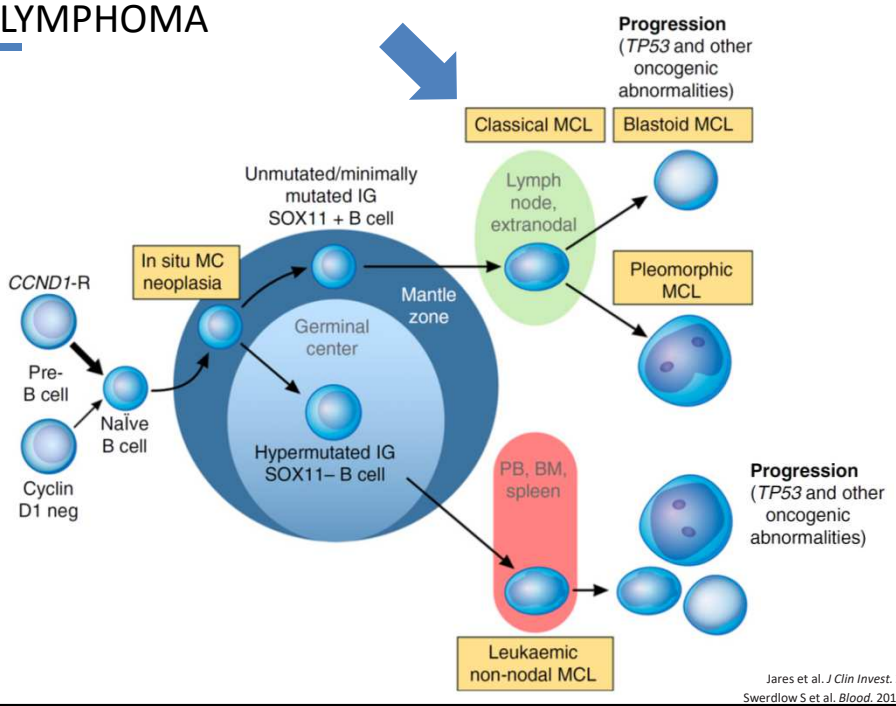


Consider this entity in evaluation of leukemic lymphomas – always perform cytogenetic evaluation for t(11;14) in this setting

Swerdlow S et al. *Blood.* 2016;127(20):2375-2390.

MANTLE CELL LYMPHOMA

New paradigm

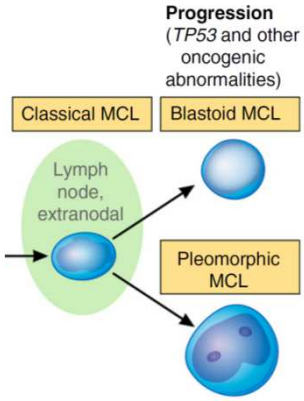


Jares et al. *J Clin Invest.* 2012;122:3416–3412.
Swerdlow S et al. *Blood.* 2016;127(20):2375-2390.

MANTLE CELL LYMPHOMA

"Classical" MCL

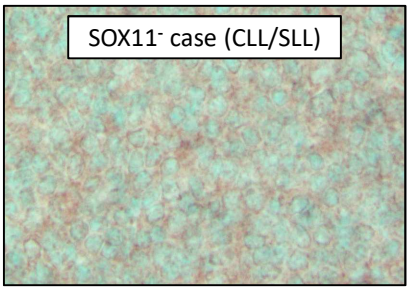
- involves lymph nodes and extranodal sites
- SOX11+, CD200-negative
- no evidence of transit through germinal center (unmutated)
- genetically unstable and acquires secondary driver mutations in cell cycle regulatory genes, DNA damage response pathway, cell survival mechanisms
  - ATM mutation/11q22 deletion common
- clinically aggressive course
- may progress to blastoid or pleomorphic MCL

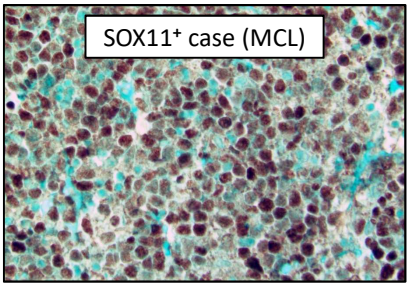


Swerdlow S et al. *Blood.* 2016;127(20):2375-2390.

MANTLE CELL LYMPHOMA

SOX11





The choice of SOX11 antibody matters!

TABLE 1. IHC SOX11 Expression in a Series of Cyclin D1-positive or Cyclin D1-negative Lymphomas, Using the Mouse Monoclonal anti-SOX11^{MRQ-58}, Anti-SOX11^{143}, and the Goat Polyclonal Anti-SOX11$^{sc-17347}$ Antibody

CCND1	Diagnosis	Mouse Monoclonal Anti-SOX11^{MRQ-58} SOX11 Positive/Total Cases (%) (n = 205)	Mouse Monoclonal Anti-SOX11^{143} SOX11 Positive/Total Cases (%) (n = 209)	Goat Polyclonal Anti-SOX11$^{sc-17347}$ SOX11 Positive/Total Cases (%) (n = 177)
Negative	B-LBL	0/4	2/4 (50) ←	0/4
	T-LBL	0/4	4/4 (100) ←	1/3 (33) ←
	CLL	0/9	0/9	0/9
	HCL	0/3	0/3	1/3 (33) ←
	PCM/Plasmacytoma	0/4	0/4	0/3
	MZL	0/10	0/10	0/10
	FL	0/8	0/8	0/1
	MCL	9/9 (100)	9/9 (100)	9/9 (100)
	DLBCL	0/43	2/43 (5) ←	1/35 (3) ←
	PBL	0/9	0/9	0/7
	PEL	0/2	0/2	0/2
	BL	0/32	22/32 (69) ←	6/32 (19) ←
	BCLU	0/5	0/5	1/4 (25) ←
	T-PLL	0/2	1/2 (50) ←	0/2
	Extranodal NK/T-cell lymphoma	0/1	0/1	0/1
	EATL II	0/1	0/1	0/1
	HSTL	0/3	0/3	0/3
	PTCL, NOS	0/11	0/11	0/10
	AITL	0/6	0/6	0/4
	ALCL ALK$^+$	0/3	0/3	0/3
	ALCL ALK$^-$	0/1	0/1	0/1
	NLPHL	0/1	0/1	—
	cHL	0/5	0/5	0/1
Positive	HCL	0/2	0/2	0/2
	PCM/Plasmacytoma	0/4	0/4	0/4
	MCL	20/23 (87)	20/27 (74)	18/23 (78)

AITL indicates angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; BCLU, B-cell lymphoma unclassified with features intermediate between DLBCL and BL; B-LBL, B-lymphoblastic lymphoma; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; EATL II, enteropathy-associated T-cell lymphoma type II; FL, follicular lymphoma; HSTL, hepatosplenic T-cell lymphoma; MZL, marginal zone lymphoma; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; PBL, plasmablastic lymphoma; PCM, plasma cell myeloma; PEL, primary effusion lymphoma; PTCL NOS, peripheral T-cell lymphoma not otherwise specified; T-LBL, T-lymphoblastic lymphoma; T-PLL, T-cell prolymphocytic leukemia.

Soldini D et al. *Am J Surg Pathol*. 2014;38:86–93.

MANTLE CELL LYMPHOMA

Infrequent IHC and FISH variations

	Cyclin D1 IHC+ t(11;14) FISH-
Possible explanations	MCL with cryptic *CCND1* insertion into *IGH* locus (very rare) or MCL with *CCND1* fusion with *IGK* or *IGL* instead of *IGH* or other entity: plasma cell neoplasm, CLL with expanded proliferation centers, hairy cell leukemia (weak)
Next steps	NGS evaluation Break-apart probes Full IHC work-up for other entities

Sethi S et al. *Front Oncol*. 2021;11:739441.

MANTLE CELL LYMPHOMA

Infrequent IHC and FISH variations

	Cyclin D1 IHC+ t(11;14) FISH-	Cyclin D1 IHC- t(11;14) FISH+
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Next steps	NGS evaluation Break-apart probes Full IHC work-up for other entities	SOX11 expression with classic morphologic features confirms MCL diagnosis

Sethi S et al. *Front Oncol.* 2021;11:739441.

MANTLE CELL LYMPHOMA

Infrequent IHC and FISH variations

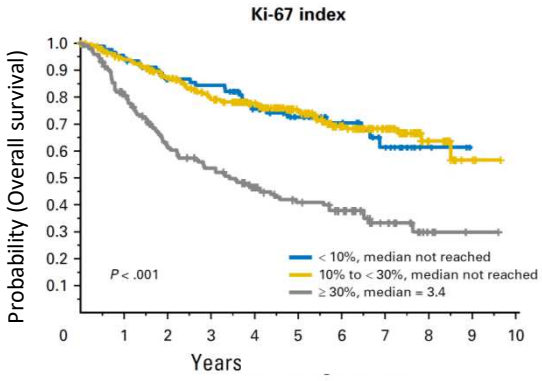
	Cyclin D1 IHC+ t(11;14) FISH-	Cyclin D1 IHC- t(11;14) FISH+	Cyclin D1 IHC- t(11;14) FISH-
Possible explanations	MCL with cryptic *CCND1* insertion into *IGH* locus (very rare) or MCL with *CCND1* fusion with *IGK* or *IGL* instead of *IGH* or other entity: plasma cell neoplasm, CLL with expanded proliferation centers, hairy cell leukemia (weak)	epitope not recognized by commercial antibody	>50% of these cases have *CCND2* rearrangements, with *IGK*, *IGL* or *IGH*
Next steps	NGS evaluation Break-apart probes Full IHC work-up for other entities	SOX11 expression with classic morphologic features confirms MCL diagnosis	SOX11 expression with classic morphologic features confirms MCL diagnosis may be positive for CCND2 and CCND3 by IHC, but these are non-specific (CLL, follicular lymphoma, splenic marginal zone lymphoma) NGS evaluation, FISH for *CCND2* or *3* translocation

Sethi S et al. *Front Oncol.* 2021;11:739441.

MANTLE CELL LYMPHOMA

Proliferation index

- MCL is not graded, but elevated proliferation index is associated with adverse prognosis
  - Ki67 staining: ≥ 30% associated with decreased overall survival
  - # of mitoses per 15 high-powered fields (HPFs): >10
  - *assessment of proliferation index should be performed in all cases of MCL*

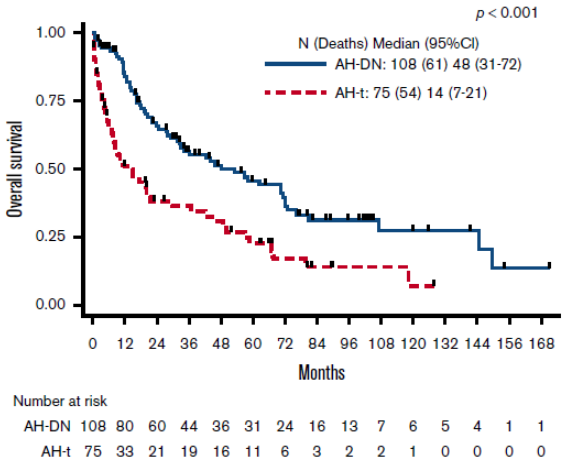


Hoster E et al. *J Clin Oncol.* 2016; 34(12):1386-1394.

MANTLE CELL LYMPHOMA

Blastoid and pleomorphic variants

- certain morphologies are associated with more aggressive behavior:
  - **blastoid variant** = cells resemble lymphoblasts; often ≥20-30 mitoses per 10 HPFs
  - **pleomorphic variant** = large cells with pleomorphic nuclei and often prominent nucleoli
- may arise *de novo* or as transformation from MCL with classical morphology

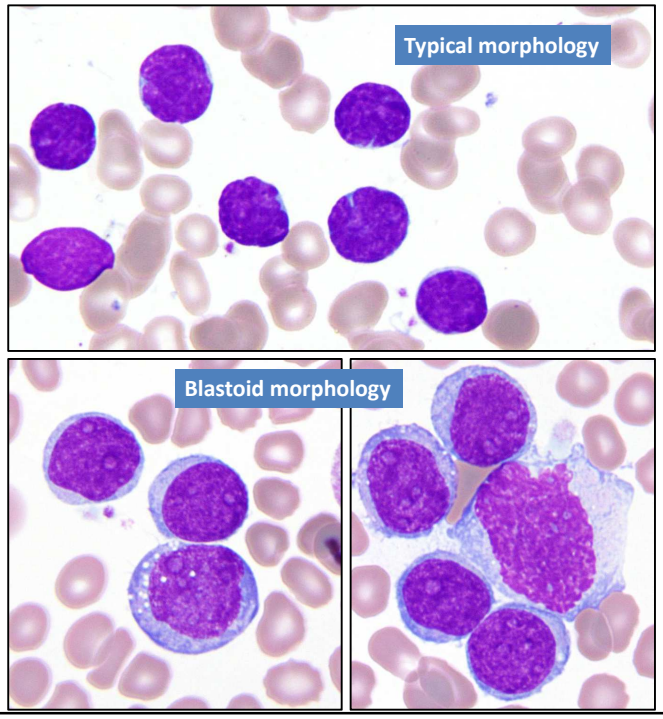


Jain P et al. *Blood Adv.* 2020;4(6): 1038–1050.
Hoster E et al. *J Clin Oncol.* 2016;34(12):1386-1394.

MANTLE CELL LYMPHOMA

Blastoid and pleomorphic variants

- morphology can be deceiving, particularly *de novo* cases
- recommend cyclin D1 in routine work-up of DLBCL and B-cell neoplasms with immature cytologic features



MANTLE CELL LYMPHOMA

TP53

- numerous recurrent gene mutations (including *ATM* and *TP53*) and chromosomal gains and losses have been described in MCL
- *TP53* gene aberrations (mutation or 17p deletion) in MCL → aggressive disease features such as blastoid/pleomorphic histology, high Ki-67, complex karyotype, high-risk MIPI (MCL International Prognostic Index) → predict poor outcomes

NCCN Guidelines B-cell lymphomas Version 2.2022

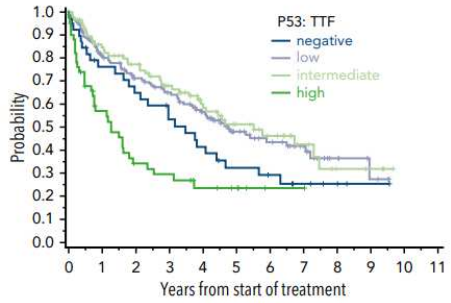
ESSENTIAL:
- **Adequate immunophenotyping to establish diagnosis[a]**
  - **IHC panel: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, SOX11, Ki-67[b] with or without**
  - **Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen: kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD200**
- ***TP53* sequencing[c]**

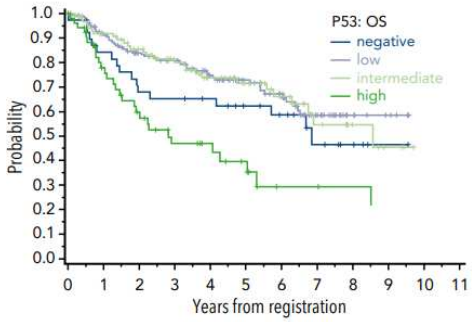
Jain P et al. *J Clin Oncol*. 2022;38(36):4302-4317.
Sethi S et al. *Front Oncol*. 2021;11:739441.

MANTLE CELL LYMPHOMA

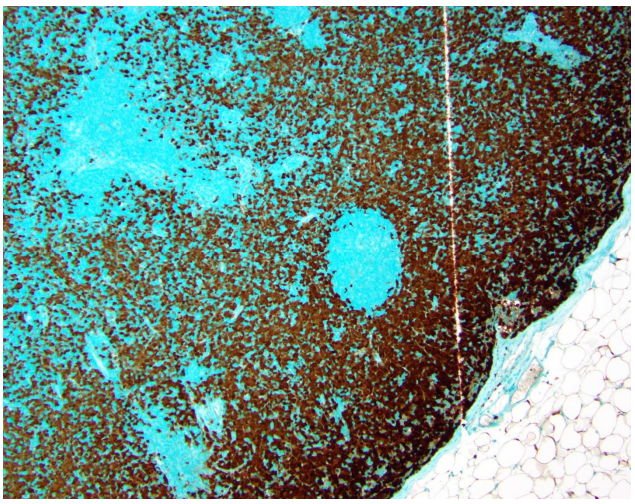
To p53 IHC or not to p53 IHC

- Aukema et al *Blood* 2018: patients with high p53 expression by IHC (>50% positive lymphoma cells) had a shorter time to treatment failure and poor OS independent of both MIPI score and Ki-67 index
  - negative (0% positive lymphoma cells)
  - low (1%-10% positive lymphoma cells)
  - intermediate (10%-50% positive lymphoma cells)
  - high (>50% positive lymphoma cells)
- our clinicians have asked us to perform p53 IHC on mantle cell cases for prognostic information → affects management decisions, including re: transplant

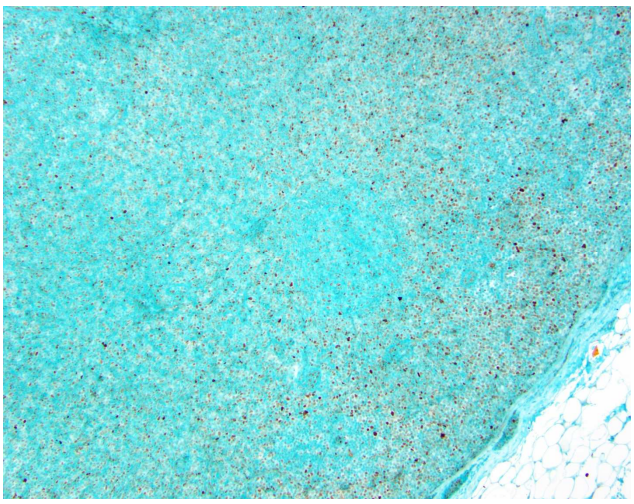




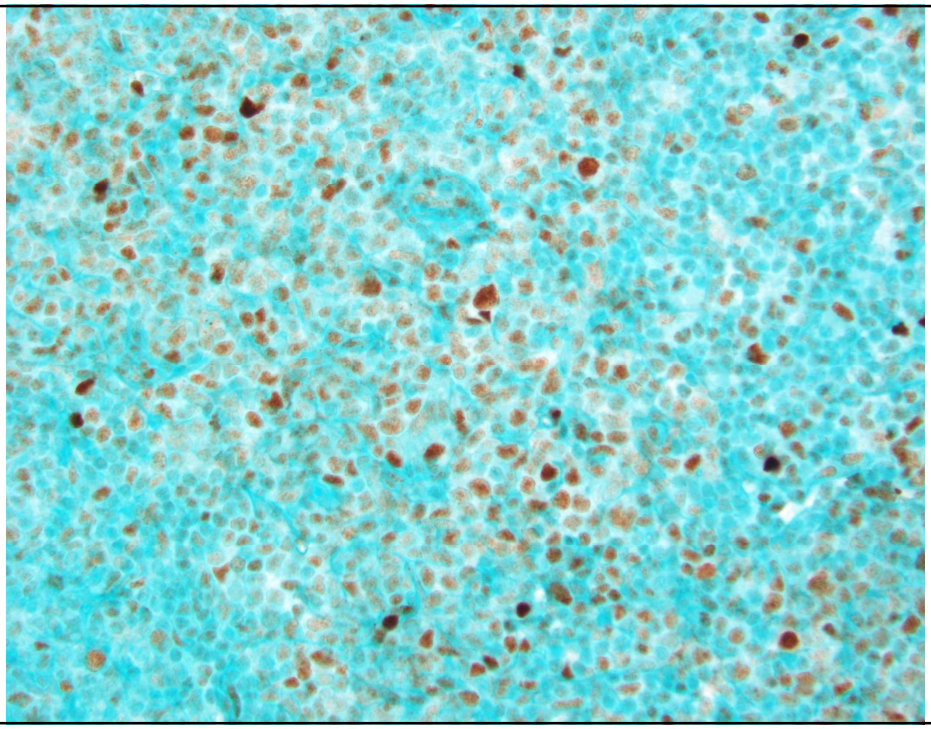
Aukema SM et al. *Blood*. 2018;131(4):417-420.



Cyclin D1



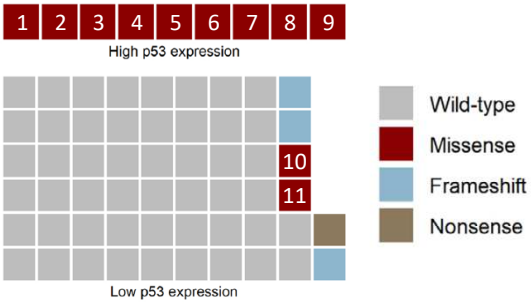
p53



MANTLE CELL LYMPHOMA

To p53 IHC or not to p53 IHC

- How does IHC correlate with mutation status?
  - p53 is overexpressed in the setting of missense mutations (due to protein accumulation)
  - Rodrigues et al *Br J Haematol* 2020:
    - >30% dark brown nuclei = p53 overexpression (faint staining was not considered)
    - p53 overexpression detected in 9 of 11 cases with p53 missense mutations



NCCN Guidelines B-cell lymphomas Version 2.2022

ESSENTIAL:

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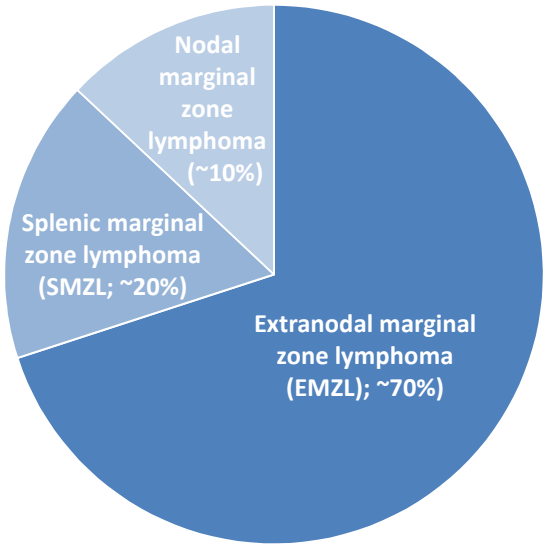
  - **Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen: kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD200**
- ***TP53* sequencing[c]**

[c] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly recommended for these patients. TP53 by IHC is not a proven surrogate for *TP53* mutation status or del(17p) status.

Rodrigues J et al. *Br J Haematol.* 2020;191(5):796-805.

MARGINAL ZONE LYMPHOMA



Nodal marginal zone lymphoma (NMZL)

- peripheral lymphadenopathy, often stage III or IV, often head & neck
- bone marrow involvement in ~1/3rd of cases
- does not involve extranodal sites or (rarely) peripheral blood
- marked splenomegaly uncommon
- may be associated with IgM monoclonal gammopathy (~10%)
- may be associated with autoimmune disease or hepatitis C infection

NODAL MARGINAL ZONE LYMPHOMA

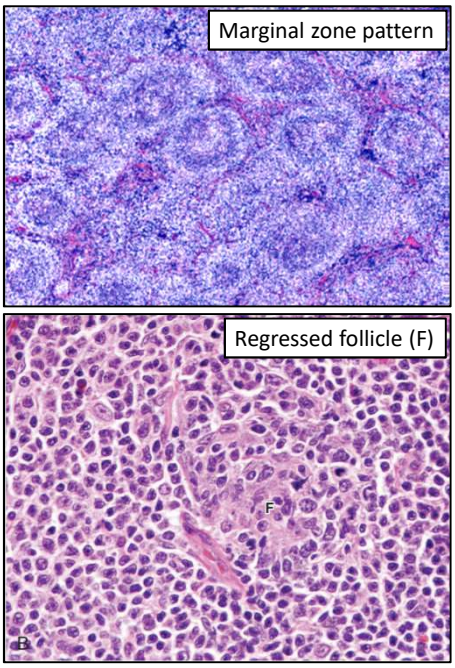
Challenges in diagnosis

Multiple architectural patterns

- marginal zone pattern (cells surrounding secondary follicles)
- follicular colonization pattern (neoplastic invasion of GCs)
- vaguely nodular pattern with absent/atrophic GCs
- diffuse pattern

Variable cytologic appearance

- centrocyte-like
- monocytoid
- plasmacytoid
- admixed larger, centroblast-like cells



Angelopoulou MK et al. *Leukemia & Lymphoma*. 2014;55:6, 1240-1250.

NODAL MARGINAL ZONE LYMPHOMA

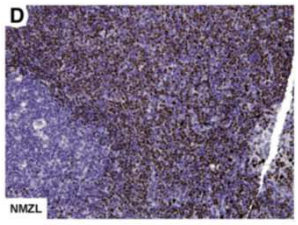
Challenges in diagnosis

Nodal marginal zone lymphoma	
CD20	+
CD5	- (~15% +)
CD10	-
BCL6	-
CD43	up to 50%
BCL2	+
CD23, CD21	negative in lesional cells but helpful to ID follicular dendritic cells
Plasmacytoid cells	
MUM-1	subset +
cytoplasmic light chain	restricted

Myeloid cell nuclear differentiation antigen (MNDA)

Table 1 MNDA expression analysis in extramedullary tissues involved by lymphoma

Diagnosis	Number MNDA+	Percent MNDA+
FL, grade 1-2	3/69 [a]	4.3%
FL, grade 3	3/41	7.3%
DLBCL	2/61	3.3%
NMZL	16/24	66.7%
EMZL	27/44	61.4%
SMZL	5/21	23.8%
Splenic diffuse red pulp small B-cell lymphoma	1/1	100%
CLL/SLL	4/31	12.9%
MCL	9/140	6.4%
LPL	2/8	25%%



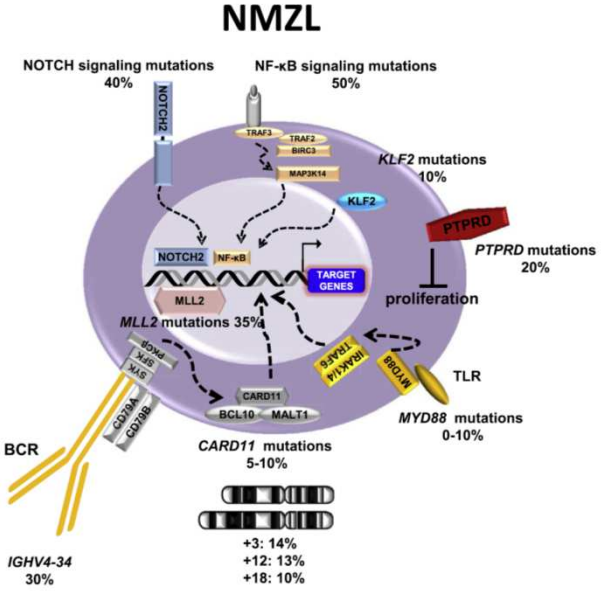
- myelomonocytic cells
- non-neoplastic B cells in spleen, in marginal zone distribution

Metcalf RA et al. *Human Pathology*. 2014;45, 1730–1736.
Angelopoulou MK et al. *Leukemia & Lymphoma*. 2014;55:6, 1240-1250.

NODAL MARGINAL ZONE LYMPHOMA

Challenges in diagnosis

- majority of recurrent genetic aberrancies are non-specific
  - trisomy 3
  - trisomy 12
  - trisomy 18
  - *NOTCH2* mutations
  - *NF-κB* signaling mutations
- *PTPRD* mutations appear to be specific for nodal MZL (~20% cases)

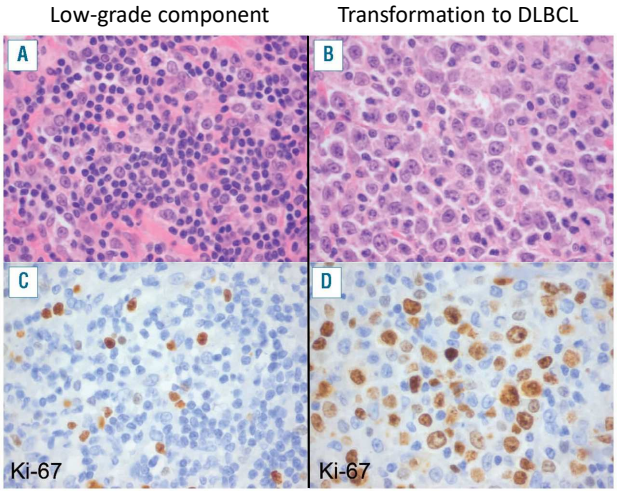


Spina V et al. *Best Practice & Research Clinical Haematology*. 2017;30:5e12.

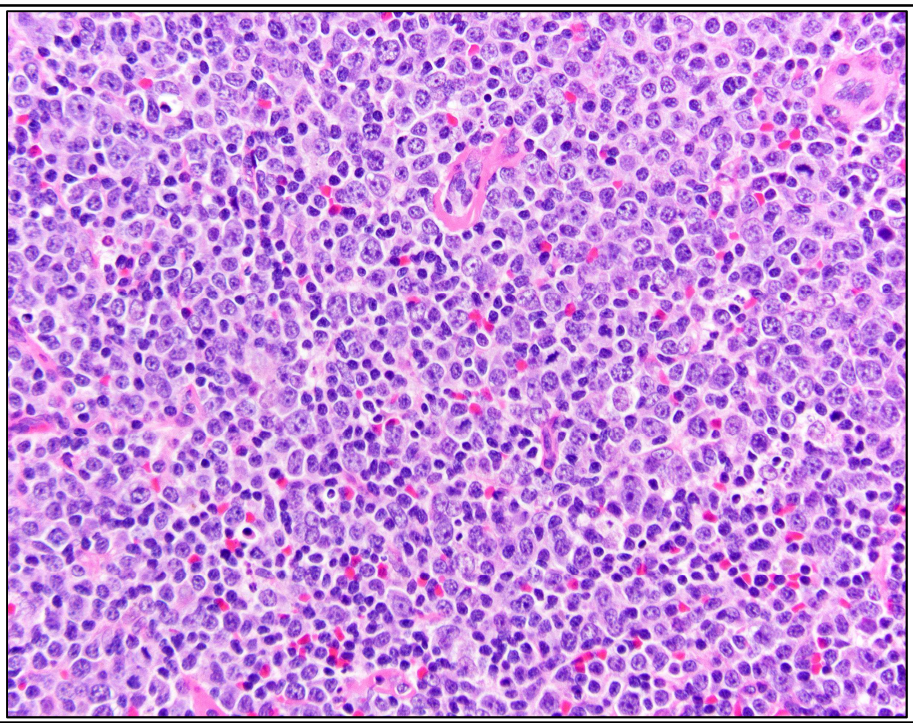
NODAL MARGINAL ZONE LYMPHOMA

Transformation

- transformation to DLBCL has been described in 15% of patients with NMZL at median 4.5 years from diagnosis
- caveat: morphologic distinction between NMZL and DLBCL can be challenging
  - NMZL can show an increased number of centroblasts, particularly in cases with follicular colonization
  - NMZL is not graded; higher proportion of large-sized cells does not definitively correlate with outcome
  - WHO recommends reserving diagnosis of DLBCL for cases with sheets of centroblasts



van den Brand M et al. *Hematologica*. 2013;98(7):1003-1013.

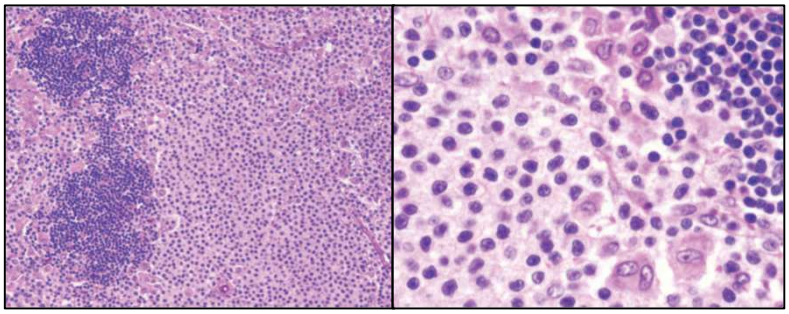


NODAL MARGINAL ZONE LYMPHOMA

Differential diagnosis

- 2° nodal involvement by EMZL or SMZL
  - exclusion requires careful clinical and radiologic correlation
  - large numbers of monocytoid cells and well-preserved reactive follicles favor nodal spread from an undetected EMZL

2° nodal involvement by EMZL



Jaffe ES. Chp 21. *Hematopathology 2nd ed.* 2016.

NODAL MARGINAL ZONE LYMPHOMA

Differential diagnosis

- lymphoplasmacytic lymphoma
  - similarities include IgM monoclonal gammopathy, absence of CD5/CD10 expression, plasmacytoid differentiation
  - *MYD88 L265P* mutations are found in >90% LPL cases but in only 0-10% of NMZL
- follicular lymphoma
  - NMZL with extensive follicular colonization can be difficult to distinguish from follicular lymphoma
  - in NMZL, the infiltrating NMZL cells will be BCL2+ whereas the residual follicular cells express BCL6, CD10 and stathmin but are negative for BCL2
- reactive conditions
  - marginal zone hyperplasia (reactive marginal zone cells are BCL2+ so this does not help distinguish)
  - hyperplasia of monocytoid B-cells (toxoplasmosis or other infections)

Often a diagnosis of exclusion given absence of defining immunophenotypic or genetic markers

Jaffe ES. Chp 21. *Hematopathology 2nd ed.* 2016.

HAIRY CELL LEUKEMIA

Nodal and extranodal involvement

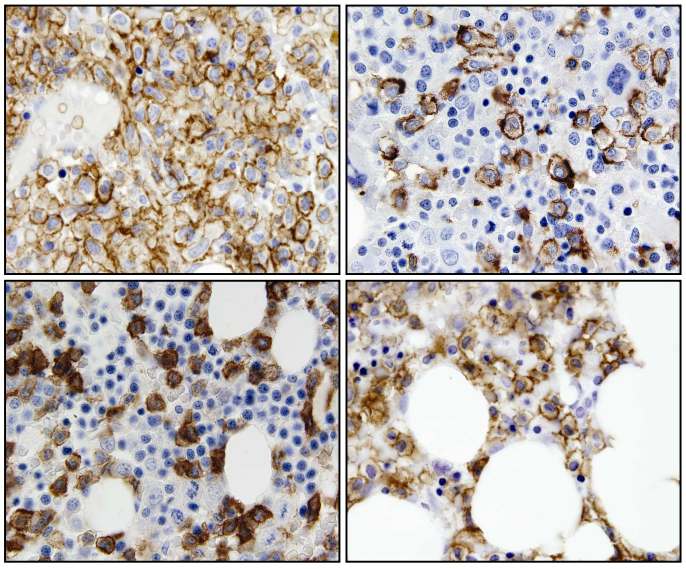
- lymph node involvement considered uncommon
  - often associated with advanced disease and splenectomy
- extranodal involvement is rare
  - can occur at presentation or in patients with longstanding disease
  - variable anatomic sites
    - lytic bone lesions
    - central nervous system
    - skin
    - breast
    - salivary gland
    - pleura

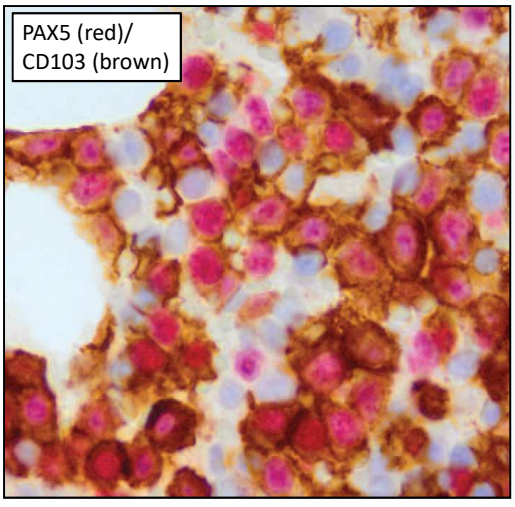
Cortazar JM et al. *Histopathology*. 2017;71, 112–124.

Hairy cell leukemia	
CD20	+
CD5	-
CD10	-
CD23	-
CD43	-/+
LEF1	-
CD200	+
FMC7	+
cyclin D1	+ (weak)
SOX11	-
light chain	+
TRAP	+
CD11c	+ (bright)
CD25	+
CD103	+
DBA.44	+
CD123	+
T-bet	+
Annexin A1	+
CD1d	+

HAIRY CELL LEUKEMIA

CD103



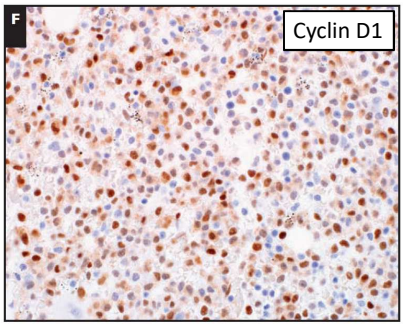


Rozenvald IB et al. *Arch Pathol Lab Med*. 2017;141(6):837-840.
Morgan EA et al. *Am J Clin Pathol*. 2013;139:220-230.

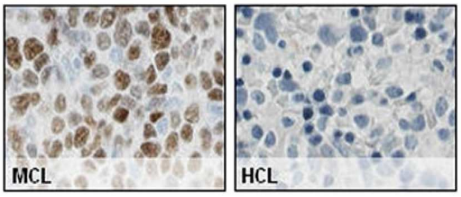
HAIRY CELL LEUKEMIA

IHC pitfalls

- cyclin D1+
  - weaker, less uniform than mantle cell lymphoma
  - not associated with t(11;14)
- SOX11-negative
  - earlier literature suggested HCL was SOX11+
  - this was using polyclonal SOX11 antibody
  - HCL does not express SOX11 when using a monoclonal antibody
- up to 25% express CD10
  - BCL6-negative
- rarely CD5+

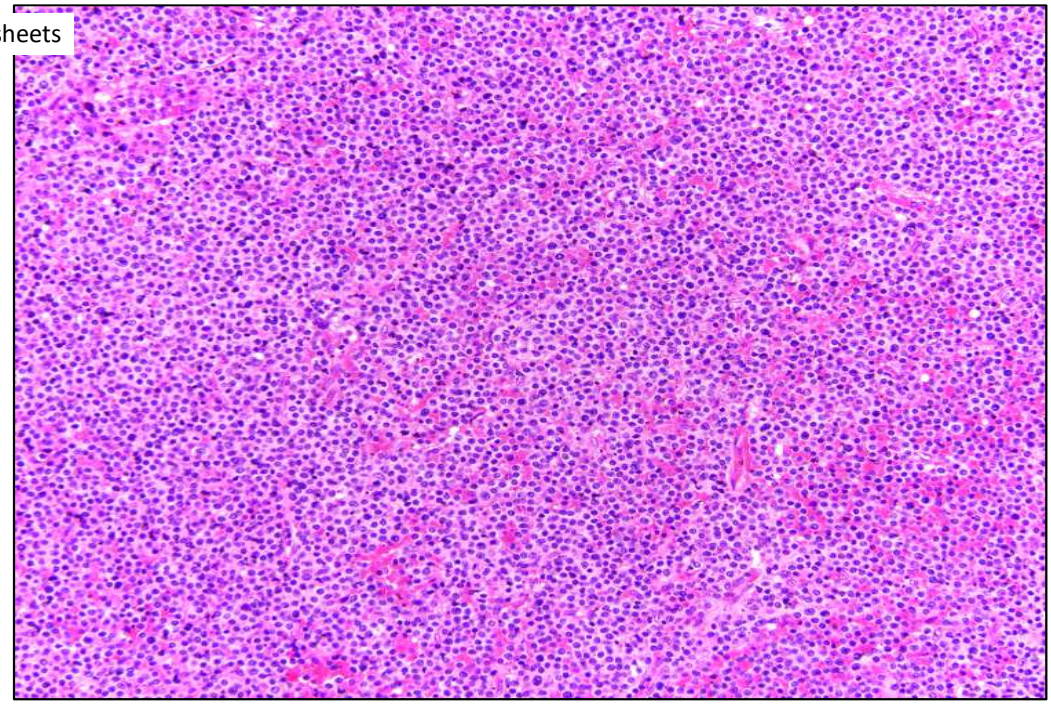


Monoclonal SOX11 (C-terminal peptide):

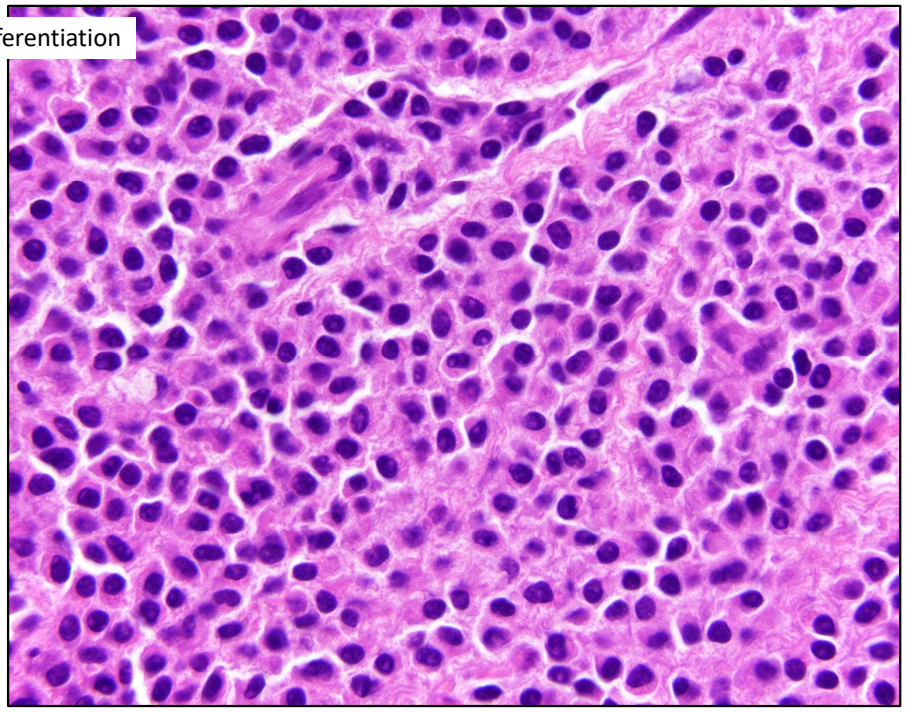


Jasionowski TM et al. *Am J Clin Pathol.* 2003;120:228-235.
Basso K et al. *J Exp Med.* 2004;199(1):59-68.
Cortazar JM et al. *Histopathology.* 2017;71, 112–124.
Bosch F et al. *Br Haematol.* 1995;91:1025-30.
Miranda RN et al. *Mod Pathol.* 2000;13(12):1308–1314.
Sherman MJ et al. *Am J Clin Pathol.* 2011;136:390-399.
Dictor M et al. *Haematologica.* 2009;94:1563-1568.
Nordström L et al. *BMC Cancer.* 2012;12:269.

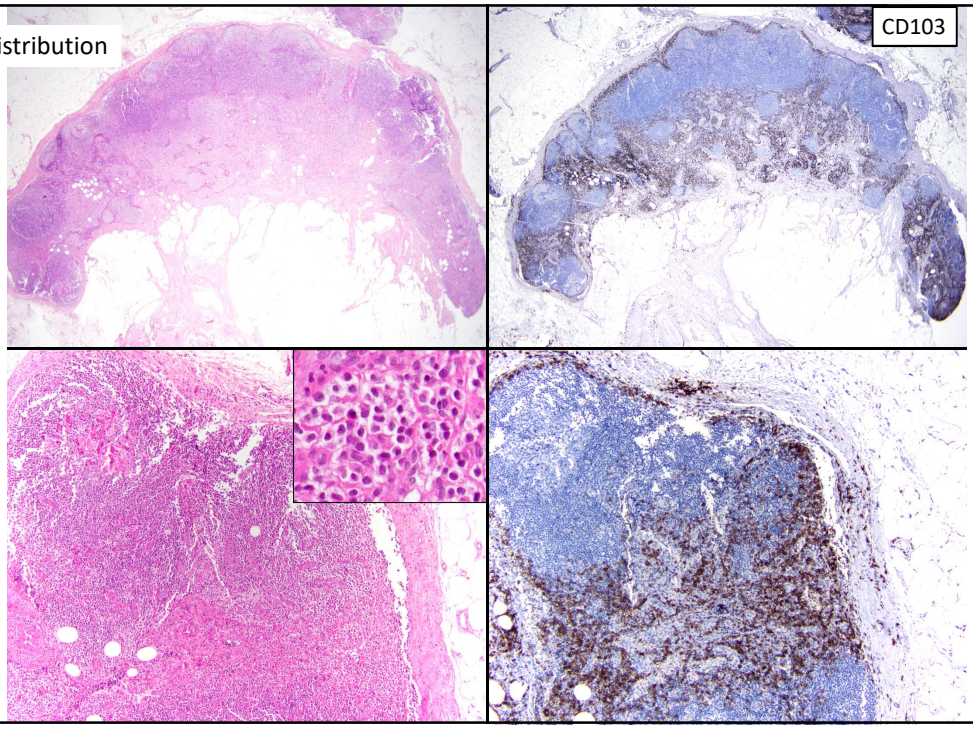
Diffuse sheets



Plasmacytic differentiation

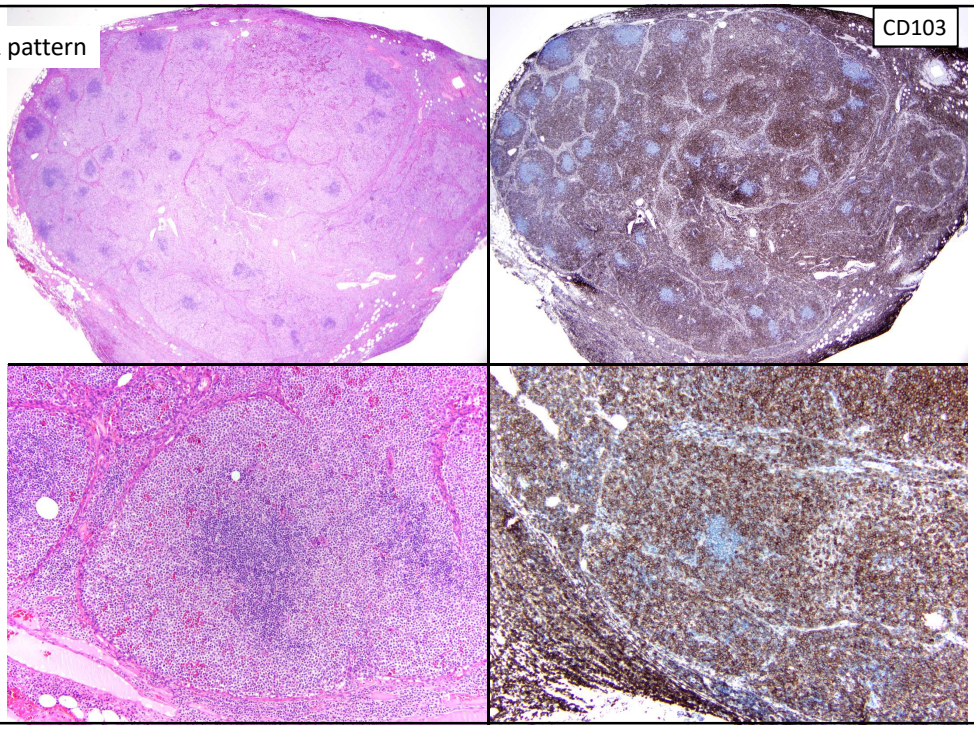


Sinusoidal distribution



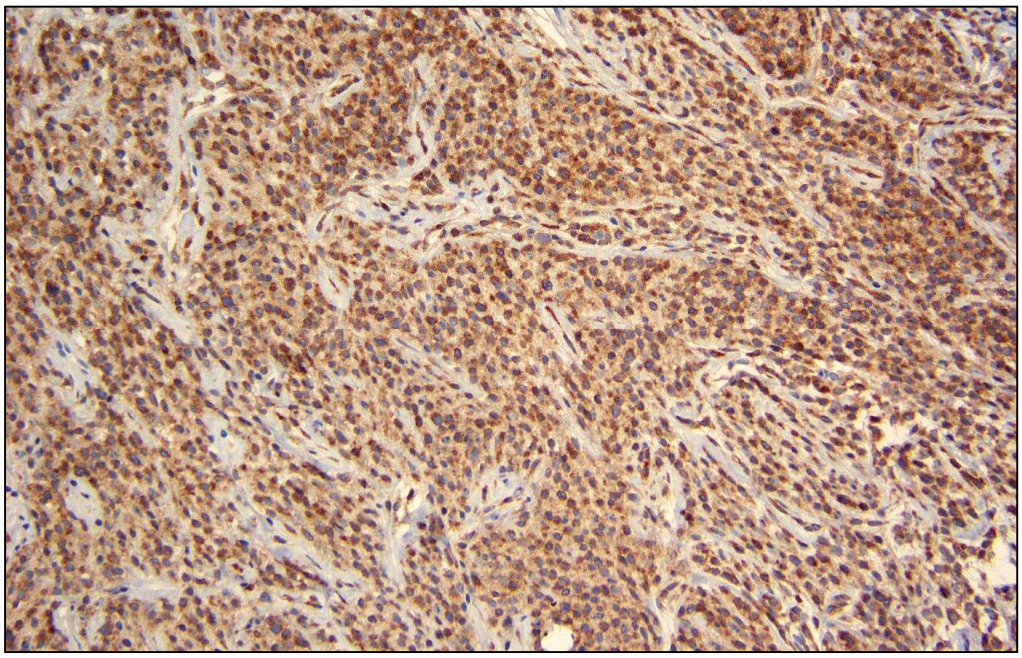
Cortazar JM et al. *Histopathology.* 2017; 71, 112–124.

Pseudo-MZL pattern



Cortazar JM et al. *Histopathology.* 2017; 71, 112–124.

BRAF V600E



SUMMARY

Transformation caveats

- expanded proliferation centers can be misinterpreted as Richter transformation
- HRS cells in CLL/SLL without mixed inflammatory background does not equal Richter transformation per WHO criteria, but should be reported
- necrosis is CLL/SLL does not always = transformation; consider HSV lymphadenitis
- blastoid or pleomorphic MCL, particularly *de novo*, can resemble large cell or immature process; perform cyclin D1 liberally in work-up of B-cell entities
- NMZL may have many centroblast-like cells, particularly in the setting of follicular colonization; diagnosis of DLBCL is reserved for sheets of centroblast-like or large-sized cells

SUMMARY

IHC pitfalls and helpful hits

- see tables in appendix for typical IHC profiles in small B-cell lymphomas, and for frequency of “aberrant” expression of CD5 and CD10 in B-cell neoplasms
- SOX11 is helpful for diagnosis of MCL but care is needed when choosing antibody clone
- cyclin D1 is not only positive in MCL but also plasma cell myeloma with t(11;14) which are often IgM+ and CD20+; HCL (weak); and proliferation centers of CLL/SLL
- p53 IHC is not a proven surrogate for *TP53* mutation or del(17p) status
- myeloid cell nuclear differentiation antigen (MNDA) is positive in approximately 60% of NMZL and EMZL but is also expressed in smaller subset of most other small B-cell lymphomas

IMMUNOHISTOCHEMISTRY (APPENDIX)

Table 14-7 Classic Immunophenotypic Profile of B-Chronic Lymphoproliferative Neoplasms

Disorder	SIg	CD20	CD22	CD23	CD25	CD5	FMC7	CD11c	CD10	CD79b	CD103	CD200	LEF1	Cyclin D1	SOX11
CLL/SLL	w	w	w	+	–	+	–/w	w	–	–/w	–	+ bright	+	–	–
PLL	+	+	+	–	–	v	v	–	–	+	–	–/+	ND	–	ND
MCL	+	+	+	–, w	–	+	+	–	–	+	–	–	–	+	+
FL	+	+	+	–	–	–	+	–	+	+	–	+ dim/ mod	–	–	–
SMZL	+	+	+	–	–	v	+	v	v	+	–	+ dim/ mod	ND	–	–
HCL	+	+	+	–	+	–	+	+	s	–	+	+ bright	ND	+s	–
LPL	+/CIg	+	+	–	–	–	–	–	–	+	–	+/– dim	–	–	–

References 1, 36, 40, 68, 71, and 199-203.

CIg, cytoplasmic immunoglobulin; *CLL/SLL,* chronic lymphocytic leukemia/small lymphocytic leukemia; *FL,* follicular lymphoma; *HCL,* hairy cell leukemia; *LPL,* lymphoplasmacytic; *MCL,* mantle cell lymphoma; *ND,* not done; *PLL,* prolymphocytic leukemia; *+s,* subset of cases positive; *SMZL,* splenic marginal zone lymphoma, lymphoma; *v,* variable expression; *w,* weakly expressed

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Table 1. Expression Pattern and Frequency of CD5 and CD10 in Common, Mature B-Cell Lymphomas

Immunophenotype	Type of Mature B-Cell Lymphoma	Approximate % Staining	Source, y
$CD5^+/CD10^-$	MCL	93–95	Dorfman and Shahsafaei,[6] 1997; Gualco et al,[7] 2010
	SLL/CLL	80–92	Kurec et al,[4] 1992; Geiler et al,[5] 1991
	LPL	9–43	Hunter et al,[20] 2005; Morice et al,[21] 2009
	MZBCL		
	Splenic MZBCL	20	Gimeno et al,[24] 2005; Matutes et al,[25] 2008
	Nodal MZBCL	8.6	Jaso et al,[22] 2013
	MALT lymphoma	1	Jaso et al,[23] 2012
	De novo DLBCL NOS	10	Tagawa et al,[27] 2005
$CD10^+/CD5^-$	BL	100	Dogan et al,[37] 2000
	FL (low grade)	80	Eshoa et al,[31] 2001
	DLBCL, NOS	10–40	Colomo et al,[46] 2003; Berglund et al,[47] 2005; Visco et al,[48] 2012
	HCL	10–20	Jasionowski et al,[43] 2003; Gupta et al,[44] 2015
	FL (grade 3)	17	Eshoa et al,[31] 2001
	MCL	0–7	Akhter et al,[45] 2015
$CD5^-/CD10^-$	MZBCL		
	MALT lymphoma	>99	Jaso et al,[23] 2012
	Nodal MZBCL	92	Jasoco et al,[22] 2013
	Splenic MZBCL	80	Gimeno et al,[24] 2005; Matutes et al,[25] 2008
	LPL	57–91	Hunter et al,[20] 2005; Morice et al,[21] 2009
	HCL	80–90	Jasionowski et al,[43] 2003; Gupta et al,[44] 2015
	DLBCL, NOS	50–70	Tagawa et al,[27] 2005; Colomo et al,[46] 2003; Berglund et al,[47] 2005; Visco et al,[48] 2012
	FL (grade 3)	83	Eshoa et al,[31] 2001
	FL (low grade)	20	Eshoa et al,[31] 2001
	SLL/CLL	8–20	Kurec et al,[4] 1992; Geiler et al,[5] 1991

Abbreviations: BL, Burkitt lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; LPL, lymphoplasmacytic lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MZBCL, marginal zone B-cell lymphoma; NOS, not otherwise specified; SLL, small lymphocytic lymphoma.

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