



*Better health through  
laboratory medicine.*

## PEARLS OF LABORATORY MEDICINE

### Mature B-cell Neoplasms

*Michael Moravek, MD*

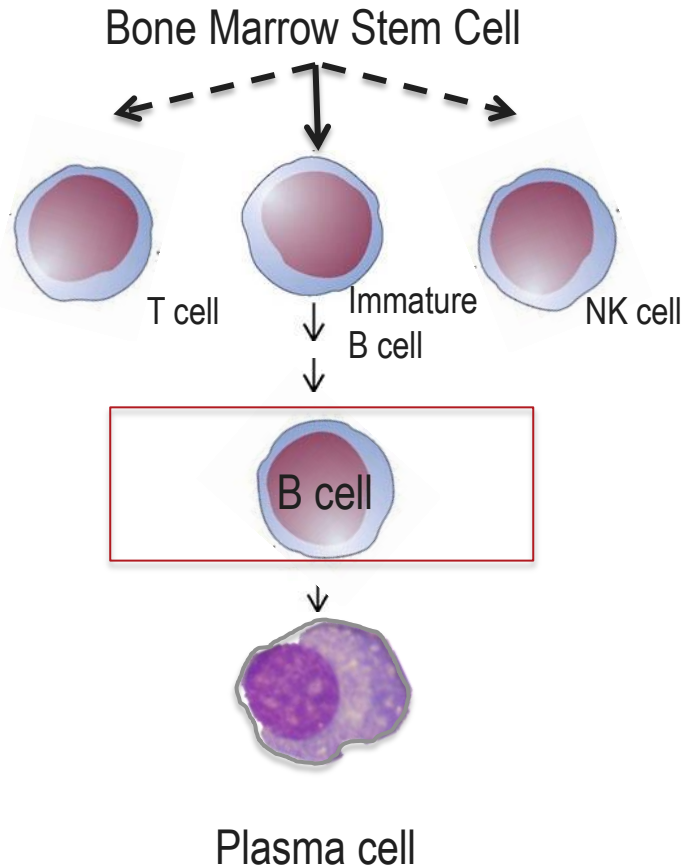
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DOI: 10.15428/CCTC.2018.287706

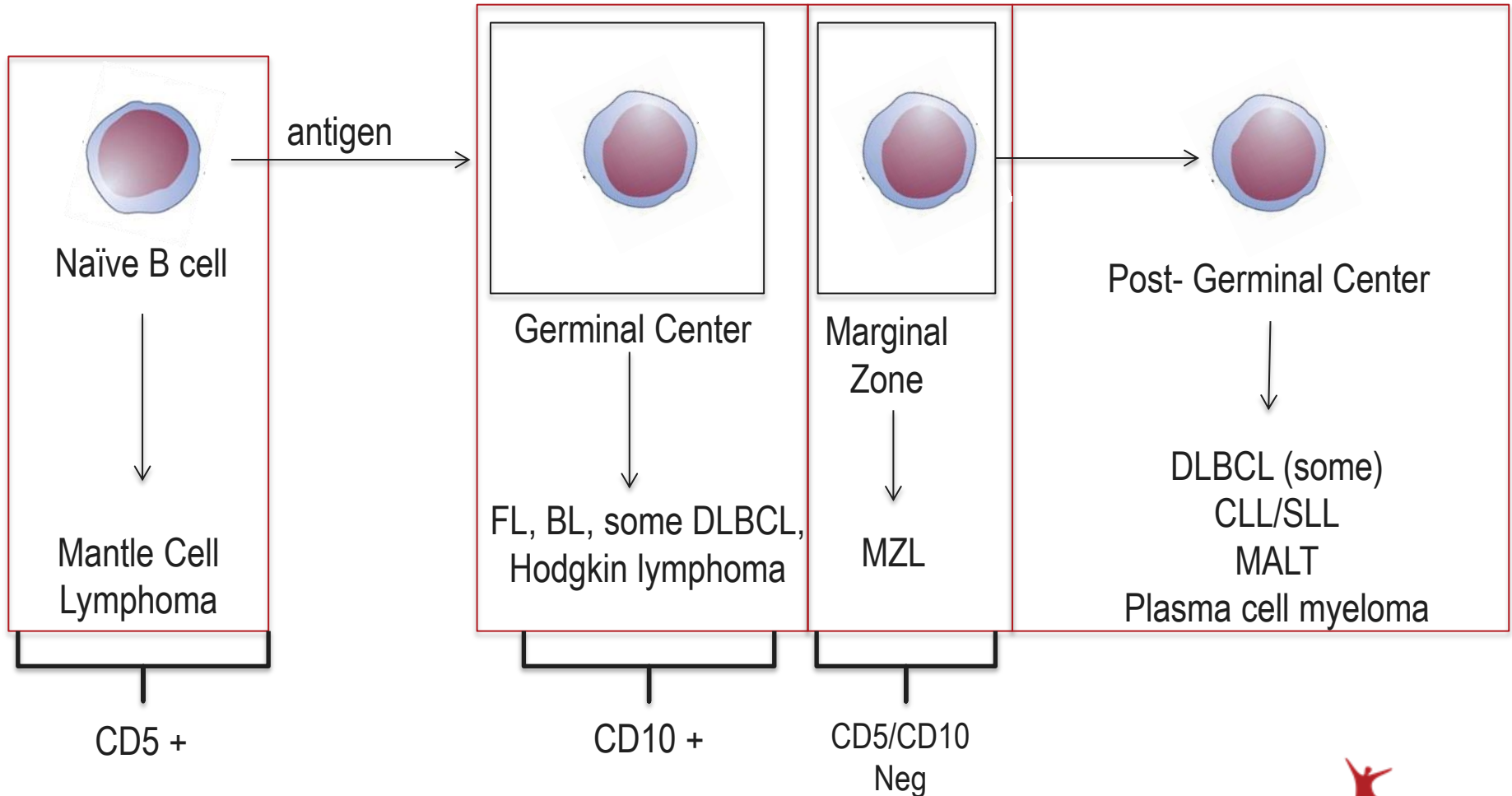


# The Lymphoid System



- Mature B-cell lymphomas comprise approximately 75% of all lymphoid neoplasms
- Genetic alterations lead to deregulation of cell proliferation or apoptosis
- Low-grade lymphomas typically present as painless lymphadenopathy, hepatosplenomegaly, or incidental lymphocytosis
- High-grade lymphomas typically present with a rapidly enlarging mass and “B” symptoms (fever, weight loss, night sweats)

# B-Cell Maturation



## Frequency among mature B-cell neoplasms

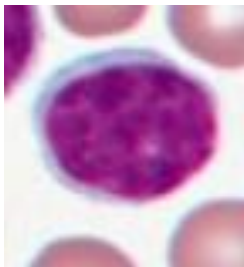
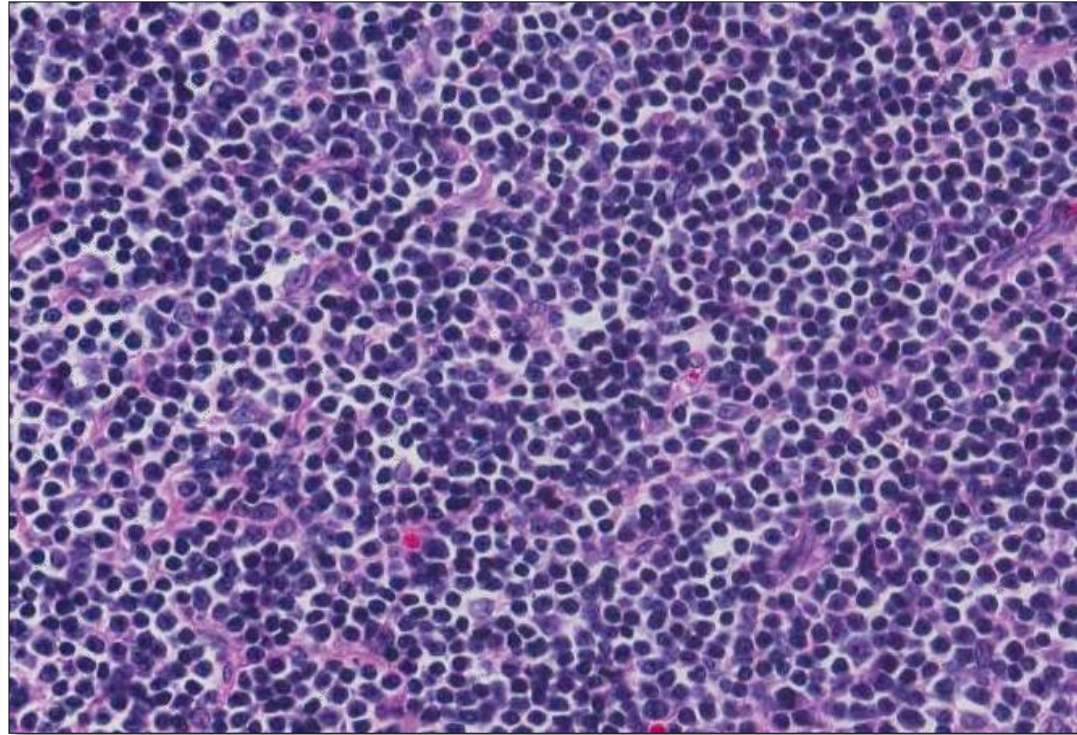
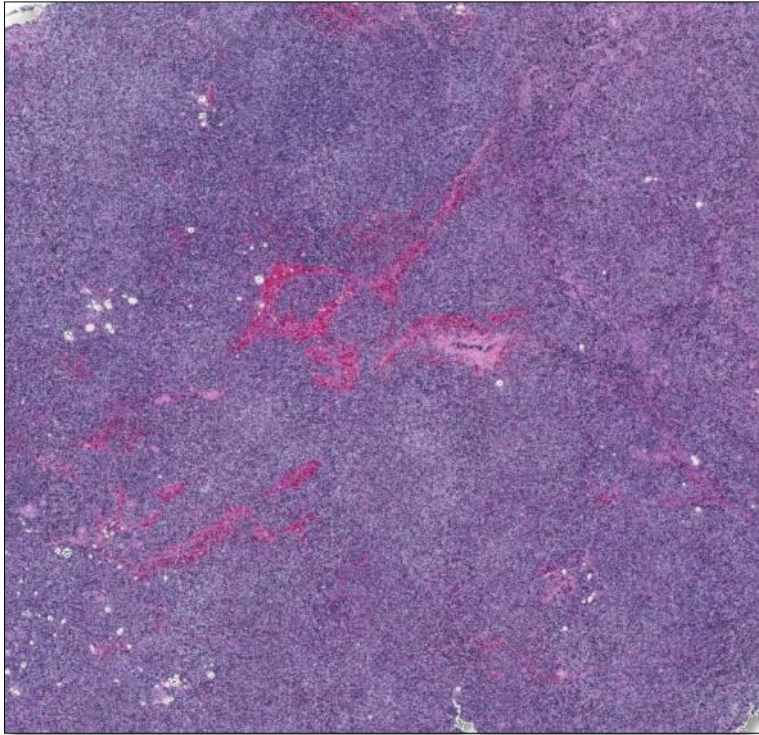
## Mature B-cell neoplasms

DLBCL	27.6%		
CLL/SLL	19.4%		
Follicular Lymphoma	12.2%	hocyctic lymphoma	Primary cutaneous follicle center lymphoma
Marginal Zone Lymphoma	3.7%		Mantle cell lymphoma
Mantle Cell Lymphoma	1.9%		-Leukemic non-nodal mantle cell lymphoma
Burkitt Lymphoma	1.3%		-In situ mantle cell neoplasia
			Diffuse large B-cell lymphoma (DLBCL), NOS
		ssifiable	-Germinal center B-cell type
		mphoma	-Activated B-cell type
			T-cell/histiocyte-rich large B-cell lymphoma
			Primary DLBCL of the central nervous system (CNS)
			Primary cutaneous DLBCL, leg type
			EBV+ DLBCL, NOS
			EBV+ mucocutaneous ulcer
			DLBCL associated with chronic inflammation
			-Fibrin-associated DLBCL
			Lymphomatoid granulomatosis
			Primary mediastinal (thymic) large B-cell lymphoma
			Intravascular large B-cell lymphoma
			ALK+ large B-cell lymphoma
			Plasmablastic lymphoma
			Primary effusion lymphoma
			HHV8-associated lymphoproliferative disorders
			-Multicentric Castleman disease
			-HHV8+ diffuse large B-cell lymphoma, NOS
			-HHV8+ germinotropic lymphoproliferative disorder
			Burkitt lymphoma
			Burkitt-like lymphoma with 11q aberration
			High-grade B-cell lymphoma,
			High-grade B-cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements
			High-grade B-cell lymphoma, NOS
			B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid Tissues. Lyon: International Agency for Research on Cancer; 2017.

# Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

- Most common leukemia in Western countries with an incidence of approximately 5/100,000 per year
- Median age of 70 years
- Commonly presents with unintentional weight loss, night sweats, fatigue and fevers without evidence of infection
- Patient's can have WBC  $>100,000/\mu\text{L}$ , diagnostic threshold is  $>5000/\mu\text{L}$  monoclonal B-cells
- Pathogenesis is a complex, multi-step process involving cytogenetic abnormalities and genetic alterations
- There are no specific genetic markers, however, 80-90% of cases have cytogenetic abnormalities



CLL cells with soccer ball  
chromatin pattern

## Immunophenotype

CD20	+
CD5	+
CD23	+
Cyclin D1	-

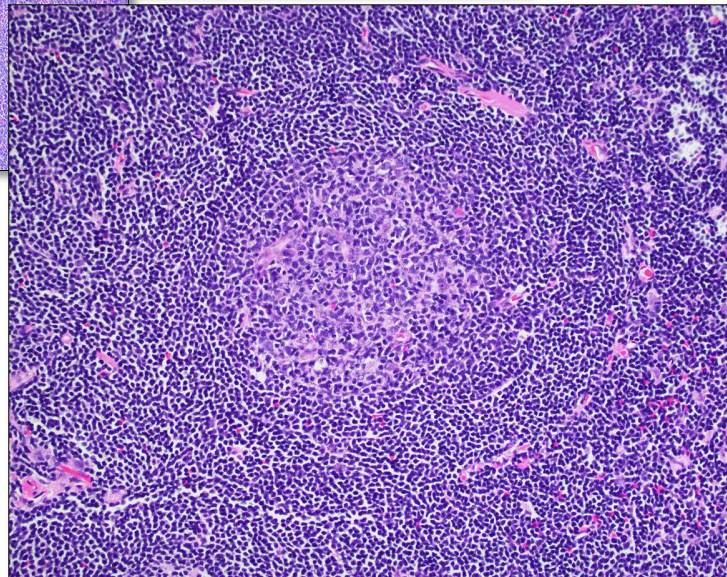
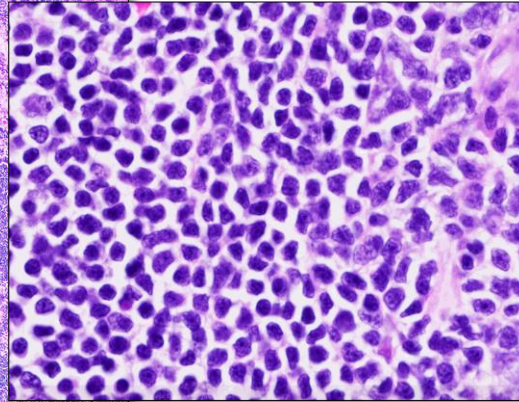
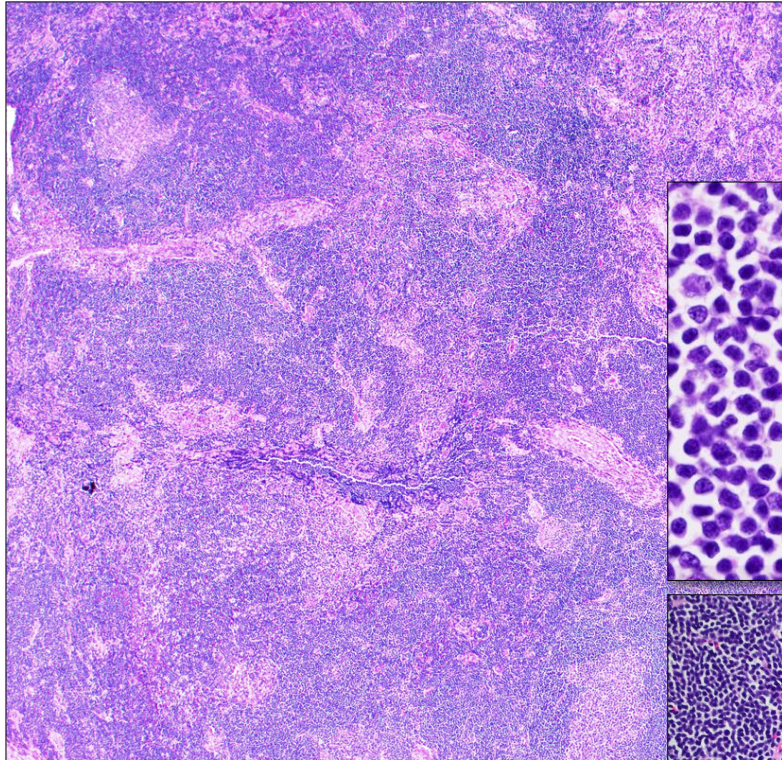
# Adverse Prognostic Factors in CLL/SLL

- High stage disease (Rai/Benet), High  $\beta 2$  microglobulin, Unmutated IgV<sub>H</sub>, Expression of CD38, ZAP70, CD49d, deletion of 11q, deletion of 17p
- Molecular: *TP53*, *BIRC*, *NOTCH1* and *SF3B1* mutations
- Large-cell transformation of CLL/SLL is known as Richter's transformation
- Factors predisposing to transformation include:
  - TP53 disruption, c-MYC abnormality, Unmutated IgV<sub>H</sub>, Non-del13q cytogenetics, CD38 gene polymorphisms, antigen-receptor Stereotypy, VH4-39 gene usage

# Mantle Cell Lymphoma

- Median age of about 60 years
- Most patients present with lymphadenopathy, hepatosplenomegaly, and bone marrow involvement
- Poor prognosis with a median survival time of 3-5 years
- Extranodal and peripheral blood involvement is common
- The  $t(11;14)(q13;q32)$  translocation between the *IGH* and *CCND1* genes is found in >95% of cases and leads to overexpression of the cyclin D1 protein

# Mantle Cell Lymphoma

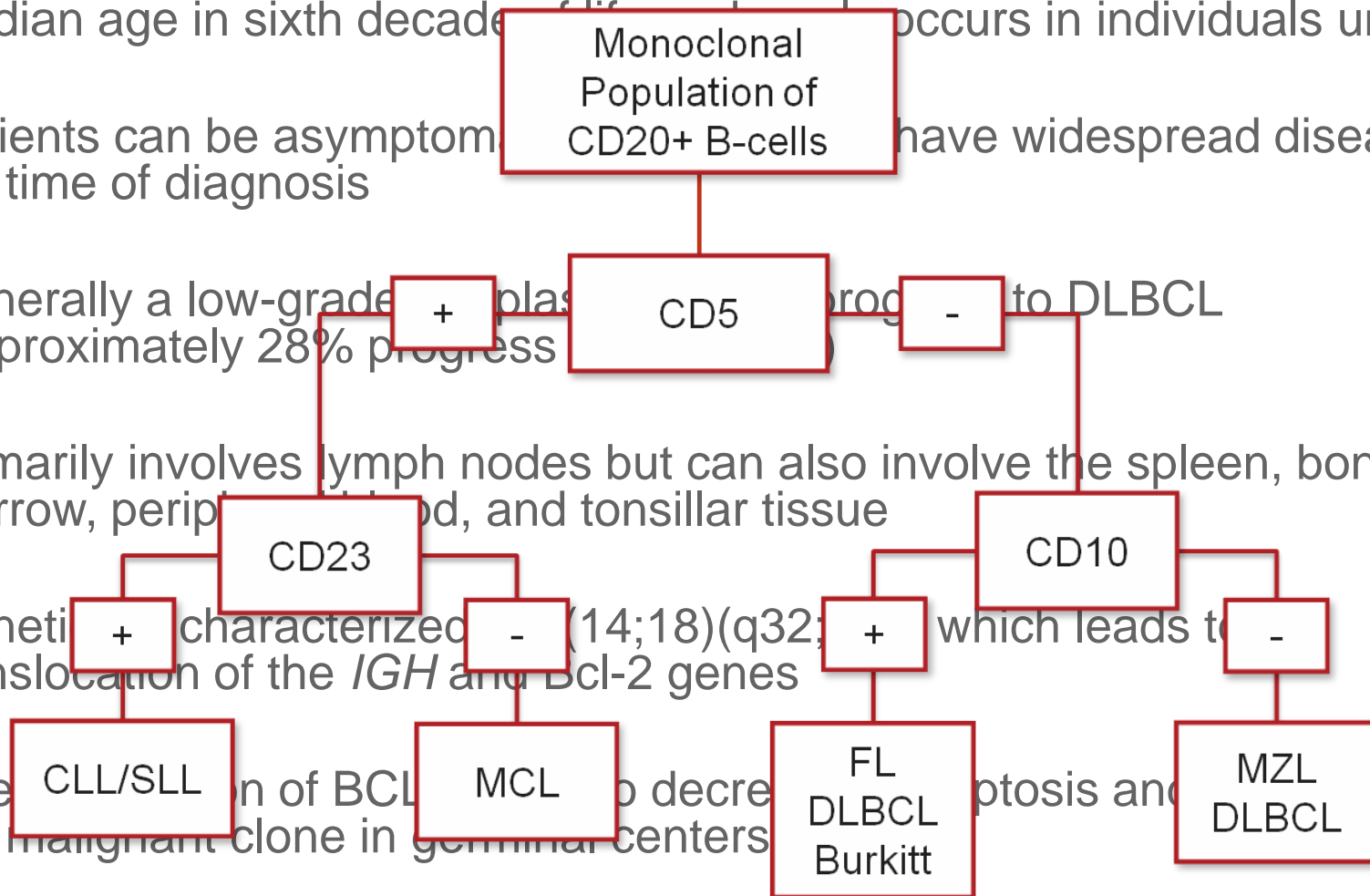


## Immunophenotype

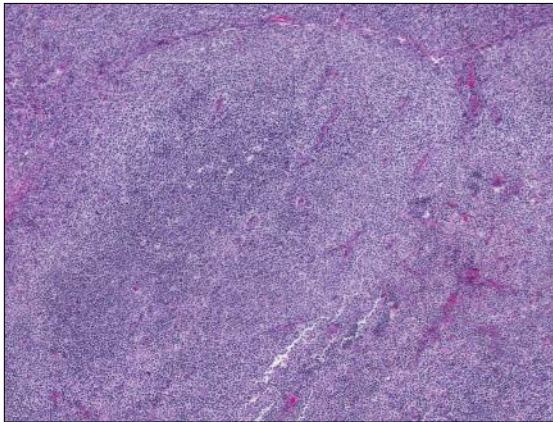
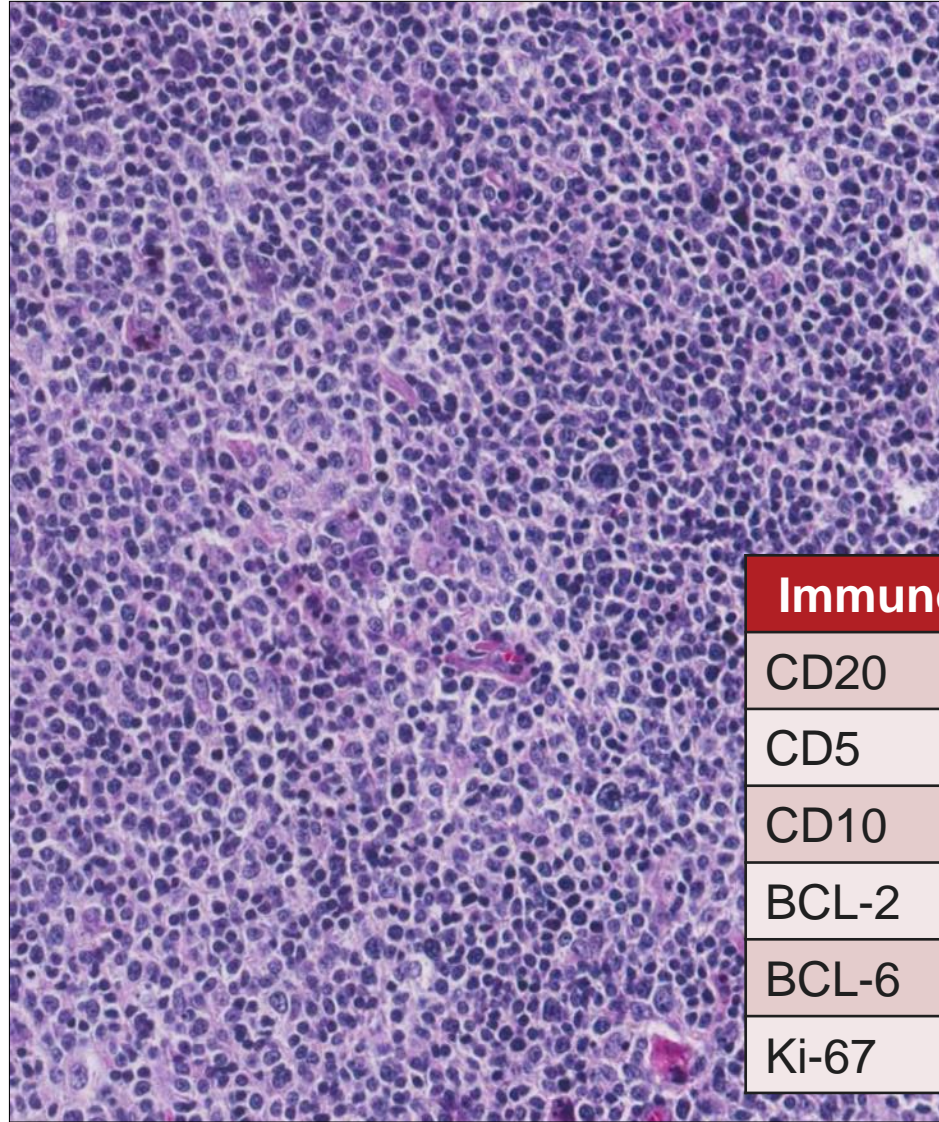
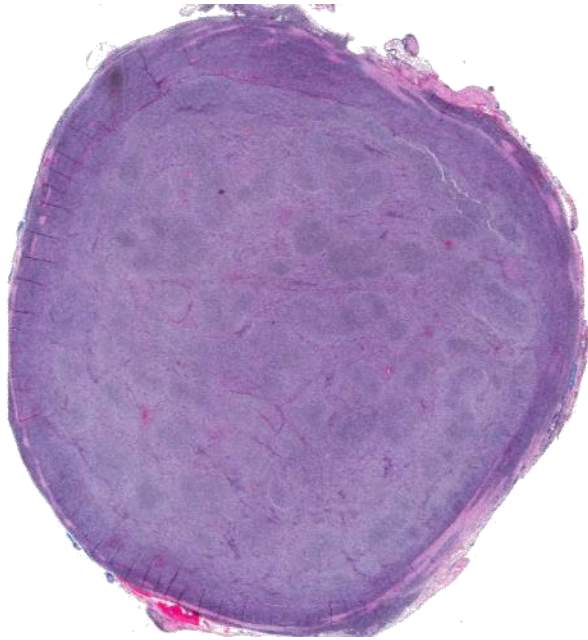
CD20	+
CD5	+
Cyclin D1	+
SOX11	+
CD23	-
FMC7	+

# Follicular Lymphoma

- Median age in sixth decade of life; occurs in individuals under 18
- Patients can be asymptomatic; have widespread disease at the time of diagnosis
- Generally a low-grade neoplasm (approximately 28% progress to DLBCL)
- Primarily involves lymph nodes but can also involve the spleen, bone marrow, peripheral blood, and tonsillar tissue
- Genetically characterized by t(14;18)(q32;q24) which leads to translocation of the *IGH* and *Bcl-2* genes
- Overexpression of *BCL-2* to decrease apoptosis and proliferation of the malignant clone in germinal centers



# Follicular Lymphoma



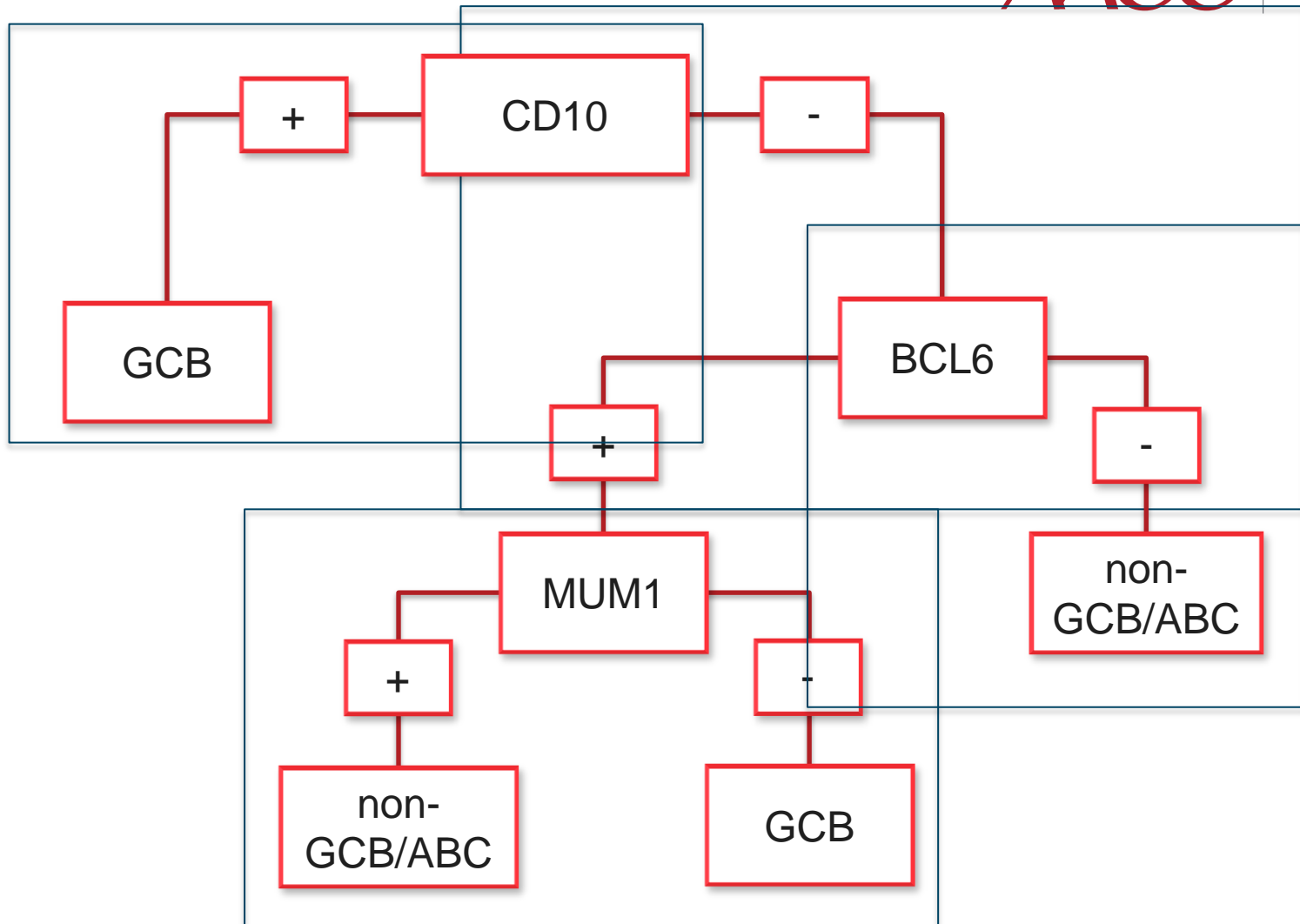
## Immunophenotype

CD20	+
CD5	-
CD10	+
BCL-2	+
BCL-6	+
Ki-67	<40%

# Diffuse Large B-Cell Lymphoma

- Most common nodal and extra-nodal histologic subtype of non-Hodgkin lymphoma (NHL)
- Median age of 70
- High grade with poor prognosis
- Can arise de novo, through transformation of a low-grade B-cell lymphoma, or in the setting of immunodeficiency or chronic inflammation
- GCB vs. non-GCB/ABC
- *MYC*, *BCL2*, and/or *BCL6* gene rearrangement/expression has prognostic significance

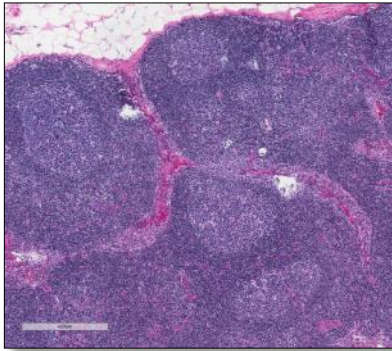




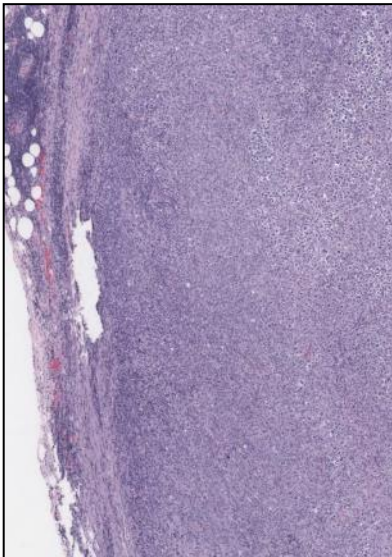
Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004 Jan 1;103(1):275-82.



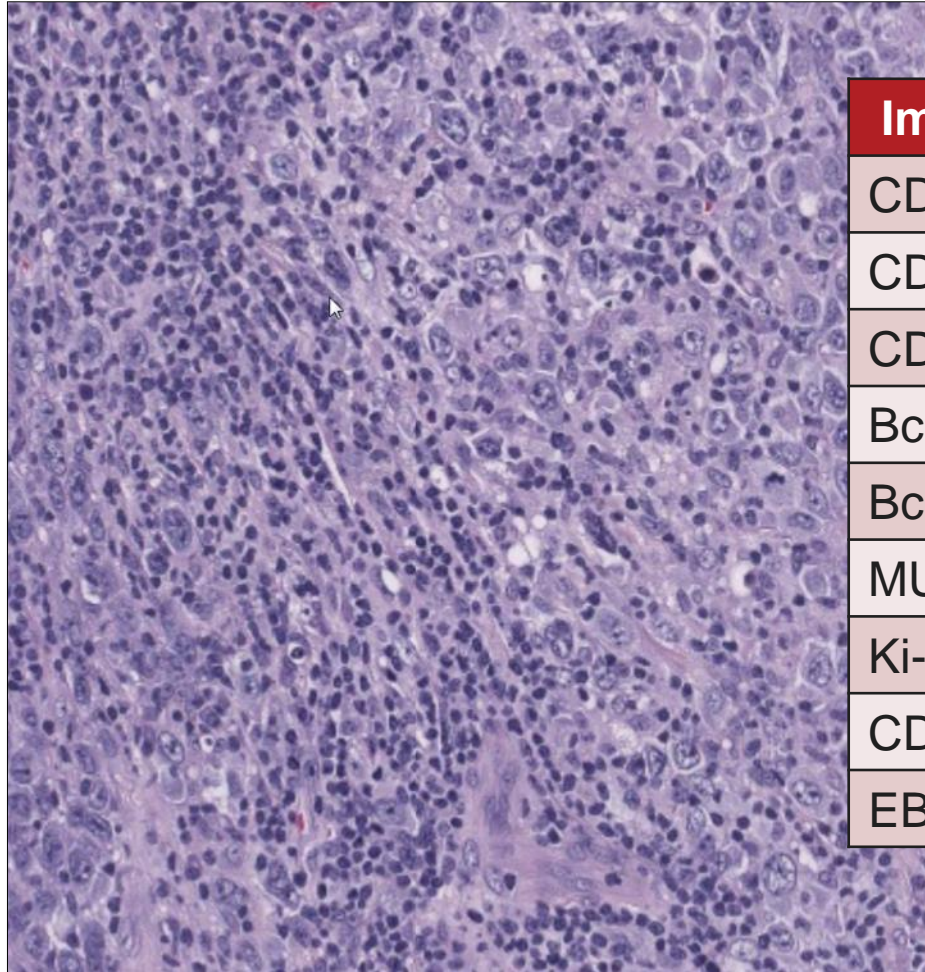
# Diffuse Large B-Cell Lymphoma



Reactive Node



Diffuse effacement

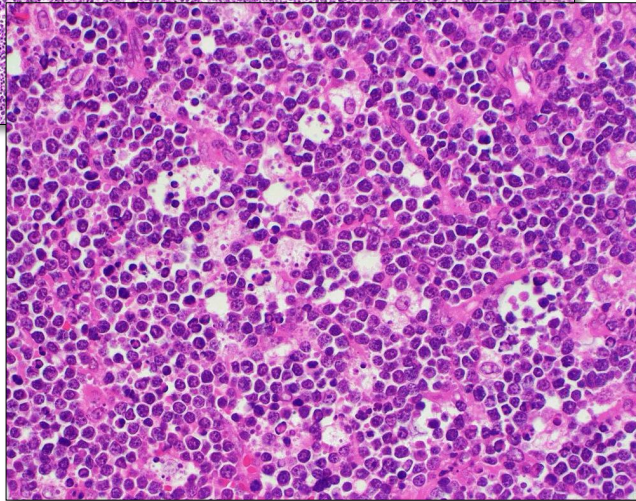
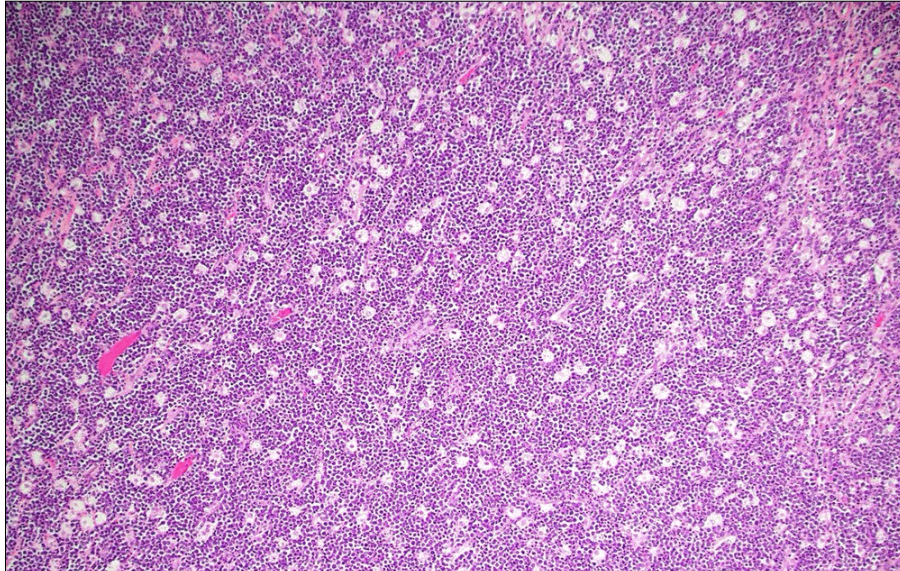


Immunophenotype	
CD20	+
CD5	+/-
CD10	+/-
Bcl-2	+/-
Bcl-6	+/-
MUM-1	+/-
Ki-67	>40%
CD30	+/-
EBV	+/-

# Burkitt Lymphoma

- Highly aggressive but curable with a long-term overall survival rate of 70-90%
- Endemic variant is primarily seen in equatorial Africa and new guinea, has a peak incidence of 4-7 years of age
- Polymicrobial disease with interaction between EBV, *Plasmodium falciparum* and other organisms has been implicated in the pathogenesis of the endemic variant
- The sporadic variant is primarily seen in the USA and Western Europe and has a peak incidence of 11 years of age
- The immunodeficiency-associated variant is often seen in the setting of HIV infection.

# Burkitt Lymphoma



## Immunophenotype

CD20	+
CD5	-
CD10	+
BCL2	-
Ki-67	~100%
MYC	+

Characterized by translocation of the *MYC* gene to the *IGH* region  
 $t(8;14)(q24;q32)$

Less frequently involves *MYC* translocation to the *IGK*  $t(2;8)(p12;q24)$  and *IGL*  $t(8;22)(q24;q11)$  loci

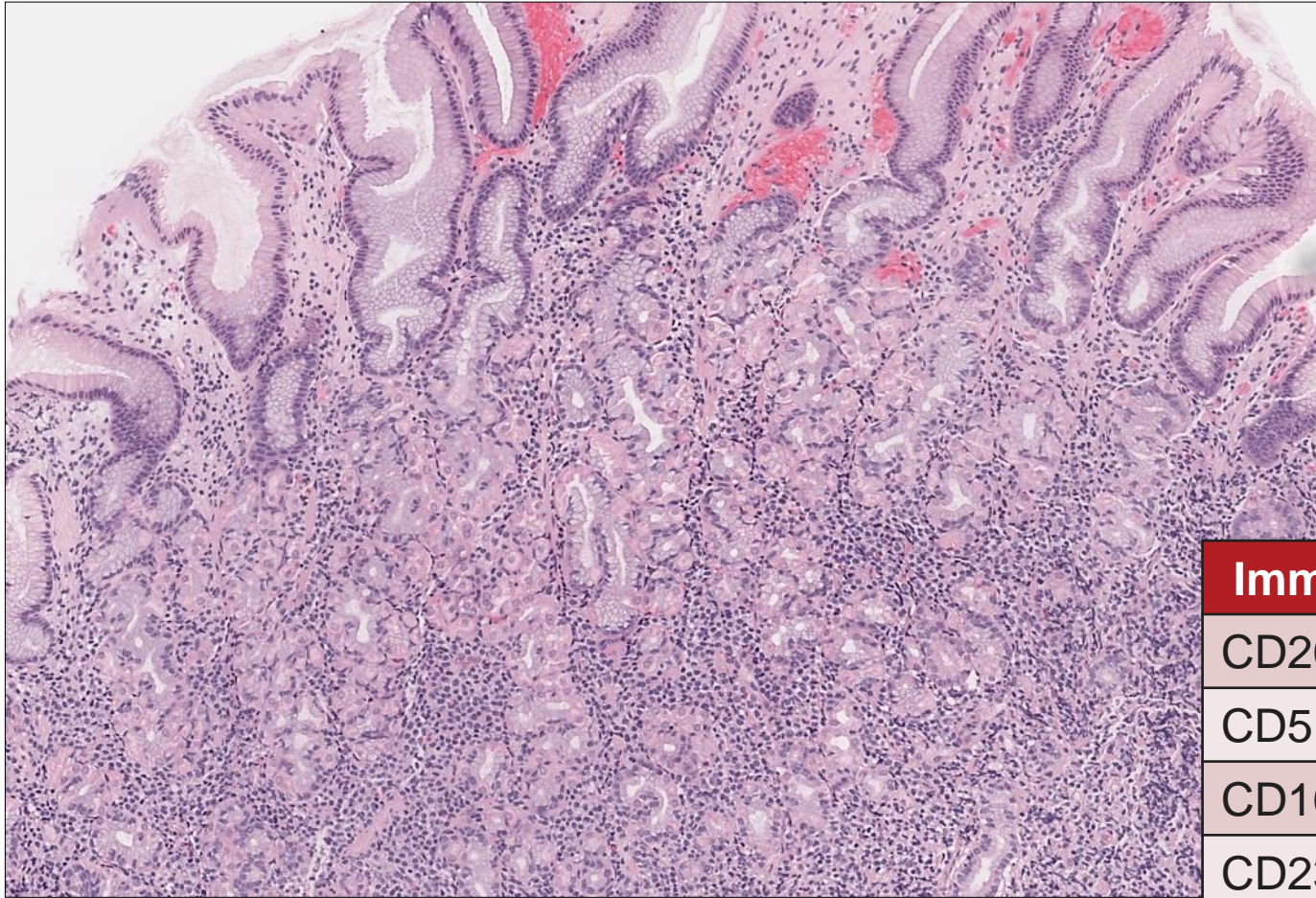
# Marginal Zone Lymphoma (MZL)

- Median age in seventh decade of life
- Sub classified as extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), nodal MZL marginal zone lymphoma (NMZL), and splenic MZL (SMZL) depending on localization of the neoplastic cells
- Can present with marked splenomegaly (splenic marginal zone B-cell lymphoma)
- Extranodal marginal zone lymphoma is associated with t(11;18), t(14;18), t(1;14), and t(3;14) which lead to activation of NF-kappa B which leads to increased survival of extranodal MZL cells

Burkitt



# Marginal Zone Lymphoma



Immunophenotype	
CD20	+
CD5	-
CD10	-
CD23	-
CD43	+ (often)

# References

1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. *Blood* 2008;111(12):5446-56.
2. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-82.
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# Disclosures/Potential Conflicts of Interest

*Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:*

- **Employment or Leadership:** No disclosures
- **Consultant or Advisory Role:** No disclosures
- **Stock Ownership:** No disclosures
- **Honoraria:** No disclosures
- **Research Funding:** No disclosures
- **Expert Testimony:** No disclosures
- **Patents:** No disclosures

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### QUESTION BANK TEMPLATE

Field	Instructions	
Stem	Write one question <i>Refer to Guide for Presenters for guidance (Page 5)</i>	A translocation between which two genes characterizes mantle cell lymphoma?
Responses	Provide 5 responses <i>Refer to Guide for Presenters for guidance (Page 5)</i>	A. <i>IgH</i> and <i>MYC</i> B. <i>IgH</i> and <i>CCND1</i> C. <i>BCR</i> and <i>ABL1</i> D. <i>PML</i> and <i>RARA</i> E. <i>IgH</i> and <i>Bcl-2</i>
Answer	Indicate one correct response	B. <i>IGH</i> and <i>CCND1</i>
Discussion	Provide a discussion of the correct response with main points explaining why it is the best choice	The t(11;14)(q13;q32) translocation is found in most cases of mantle cell lymphoma and leads to constitutive cyclin D1 expression. The genes involved in this translocation are <i>IgH</i> and <i>CCND1</i> .
Source(s)	Provide the source(s) of information for further study <i>Refer to Guide for Presenters for full citation formatting (Page 3)</i>	Li JY, Gaillard F, Moreau A, Harousseau JL., et al. Detection of translocation t (11; 14)(q13; q32) in mantle cell lymphoma by fluorescence in situ hybridization. The American journal of pathology. 1999 May 1;154(5):1449-52.
Difficulty	Select one level of difficulty: <i>Easy, intermediate, advanced</i>	Intermediate
Category	Select one category ( <i>Refer to list in Guide for Presenters - Page 6</i> )	Hematology
Sub-category	Select one sub-category ( <i>Refer to list in Guide for Presenters - Page 6</i> )	Hematopathology
Keywords	Include at least 1-2 keywords <i>Keywords should describe a subtopic to the sub-category selected. Examples include, thyroid, electrolytes, diabetes, pregnancy, etc.</i>	Lymphoma, Cytogenetics, FISH
Field	Instructions	

## Question Bank Template

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Stem	Write one question <i>Refer to Guide for Presenters for guidance (Page 5)</i>	A 70 year-old-man presents for an annual check-up. On physical examination, an enlarged cervical lymph node is palpated. CBC demonstrates marked leukocytosis. An excisional biopsy of the lymph node is performed. Flow cytometry of the specimen demonstrates a monoclonal population of CD20 (dim), CD19 (dim) B-cells that co-express CD5 (dim) and also express CD23. What is the most likely diagnosis?
Responses	Provide 5 responses <i>Refer to Guide for Presenters for guidance (Page 5)</i>	A. Plasma cell myeloma B. Mantle cell lymphoma C. Follicular lymphoma D. Diffuse large B-cell lymphoma E. Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL)
Answer	Indicate one correct response	E. Chronic lymphocytic leukemia/Small lymphocytic lymphoma
Discussion	Provide a discussion of the correct response with main points explaining why it is the best choice	Flow cytometry analysis of an excised lymph node involved by chronic lymphocytic leukemia/small lymphocytic lymphoma will typically demonstrate this phenotype. This pattern can also be visualized with immunohistochemistry.
Source(s)	Provide the source(s) of information for further study <i>Refer to Guide for Presenters for full citation formatting (Page 3)</i>	Gong JZ, Lagoo AS, Peters D, et al. Value of CD23 determination by flow cytometry in differentiating mantle cell lymphoma from chronic lymphocytic leukemia/small lymphocytic lymphoma. American journal of clinical pathology. 2001 Dec 1;116(6):893-7.
Difficulty	Select one level of difficulty: <i>Easy, intermediate, advanced</i>	Easy
Category	Select one category ( <i>Refer to list in Guide for Presenters - Page 6</i> )	Hematology
Sub-category	Select one sub-category ( <i>Refer to list in Guide for Presenters - Page 6</i> )	Hematopathology
Keywords	Include at least 1-2 keywords <i>Keywords should describe a subtopic to the sub-category selected. Examples include, thyroid, electrolytes, diabetes, pregnancy, etc.</i>	Lymphoma, Flow Cytometry