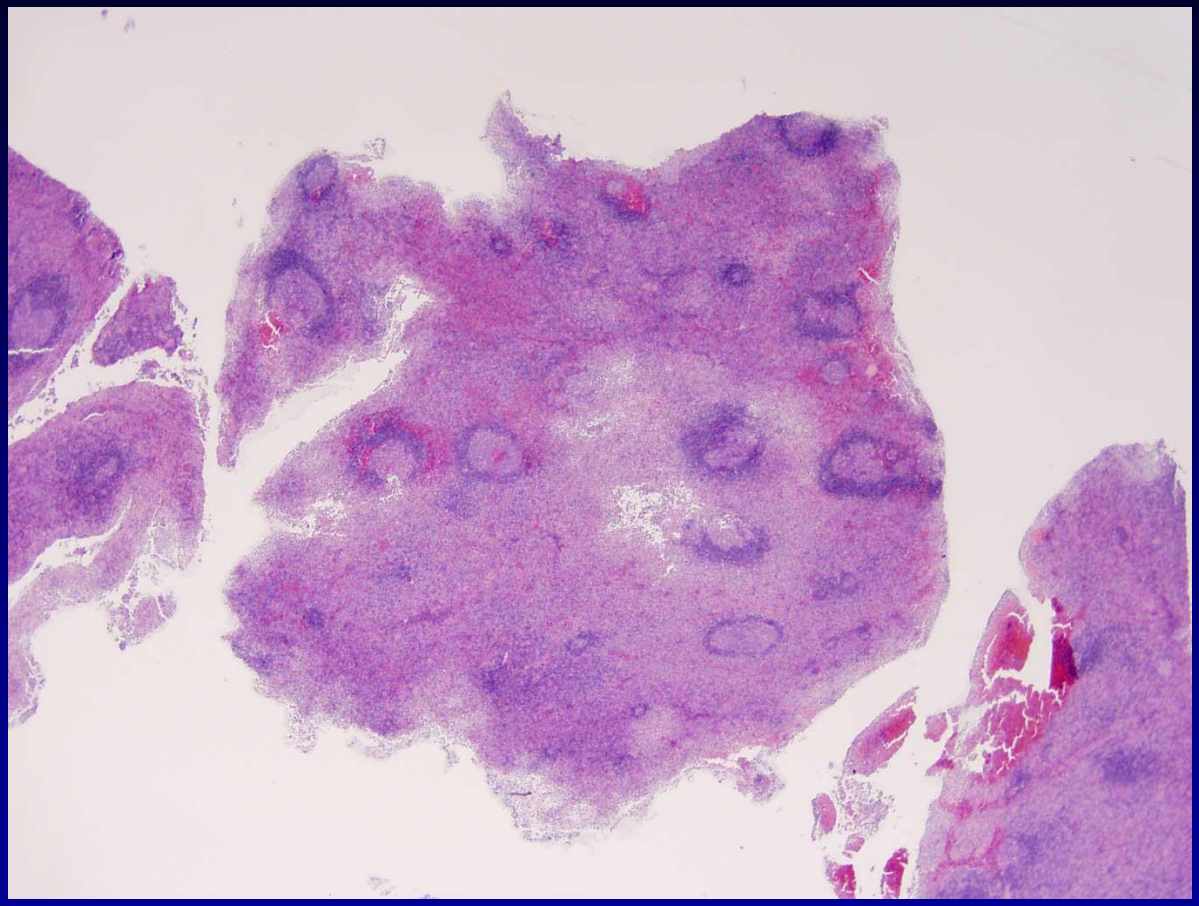
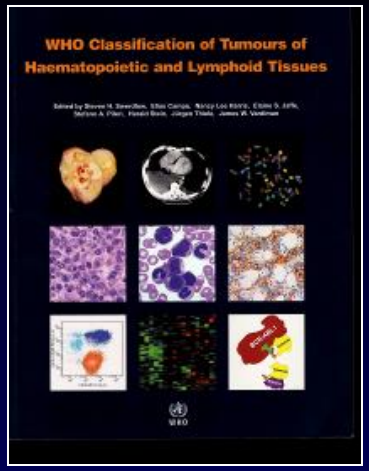
Marginal Zone Lymphomas



L. Jeffrey Medeiros, MD
MD Anderson Cancer Center

Indolent B-Cell Lymphomas in WHO Classification



Lymphoma Type	Frequency
Follicular lymphoma	29 %
Small lymphocytic lymphoma/CLL	12 %
Extranodal MZL/MALT lymphoma	9 %
Nodal marginal zone lymphoma	2 %
Lymphoplasmacytic lymphoma/WM	1.4 %
Splenic marginal zone lymphoma	0.9 %

WHO book, p. 164

What do normal MZ lymphocytes do?

First line of defense against foreign organisms

- T-cell independent
- Bulk of primary antibody response

Short-lived antibody production

No memory B-cells are not generated

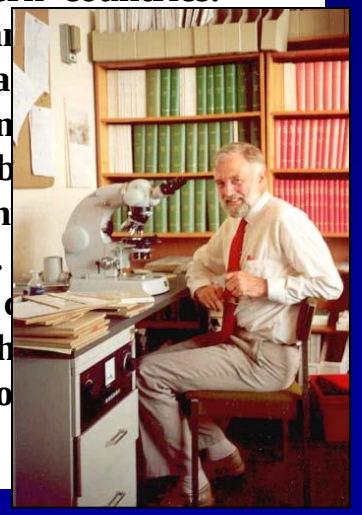
Extranodal MZL/MALT Lymphoma
First Description

Malignant Lymphoma of Mucosa-Associated Lymphoid Tissue

A Distinctive Type of B-Cell Lymphoma

PETER ISAACSON, DM, MRC PATH, AND DENNIS H. WRIGHT, MD, FRC PATH

As illustrated in the two cases described in this paper close morphologic and immunohistochemical similarities exist between Mediterranean lymphoma (MTL) and primary gastrointestinal lymphoma of follicle center (FCC) origin as it occurs in Western countries. tween the two conditions include a dense noninvasive monotypic la iltrate, present in all cases of MTL and in some cases of Western ga a, and an invasive infiltrate of FCCs morphologically distinct fro ctive lesion produced by individual gland invasion characterizes b clonal relationship between the lamina propria plasma cells and the in but never proved in MTL, can be demonstrated in Western cases. clinical features common to these lymphomas can be explained in the ation sequences of gut associated lymphoid tissue. It is suggested th of primary FCC gastrointestinal lymphoma share a common histo ted lymphoid tissue.

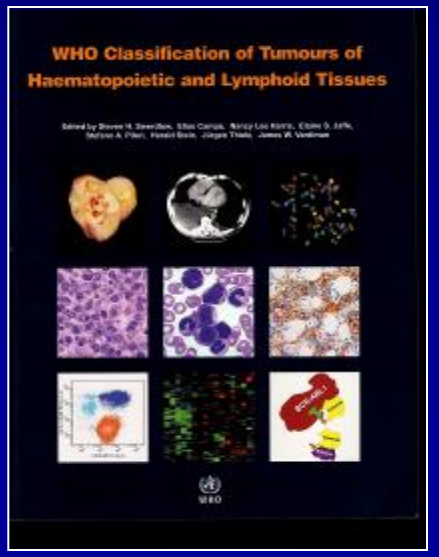


Peter Isaacson | Cancer 52: 1410, 1983 | Dennis Wright

Extranodal Marginal Zone Lymphoma of Mucosa-associated Lymphoid Tissue (MALT Lymphoma)

Definition

An extranodal lymphoma composed of morphologically heterogeneous small B-cells including marginal zone cells, monocytoid cells, small lymphocytes and scattered immunoblasts and centroblast-like cells. There is plasmacytoid differentiation in a proportion of cases. The infiltrate is in the marginal zone of reactive B-cell follicles… In epithelial tissues lymphoepithelial lesions can be present.



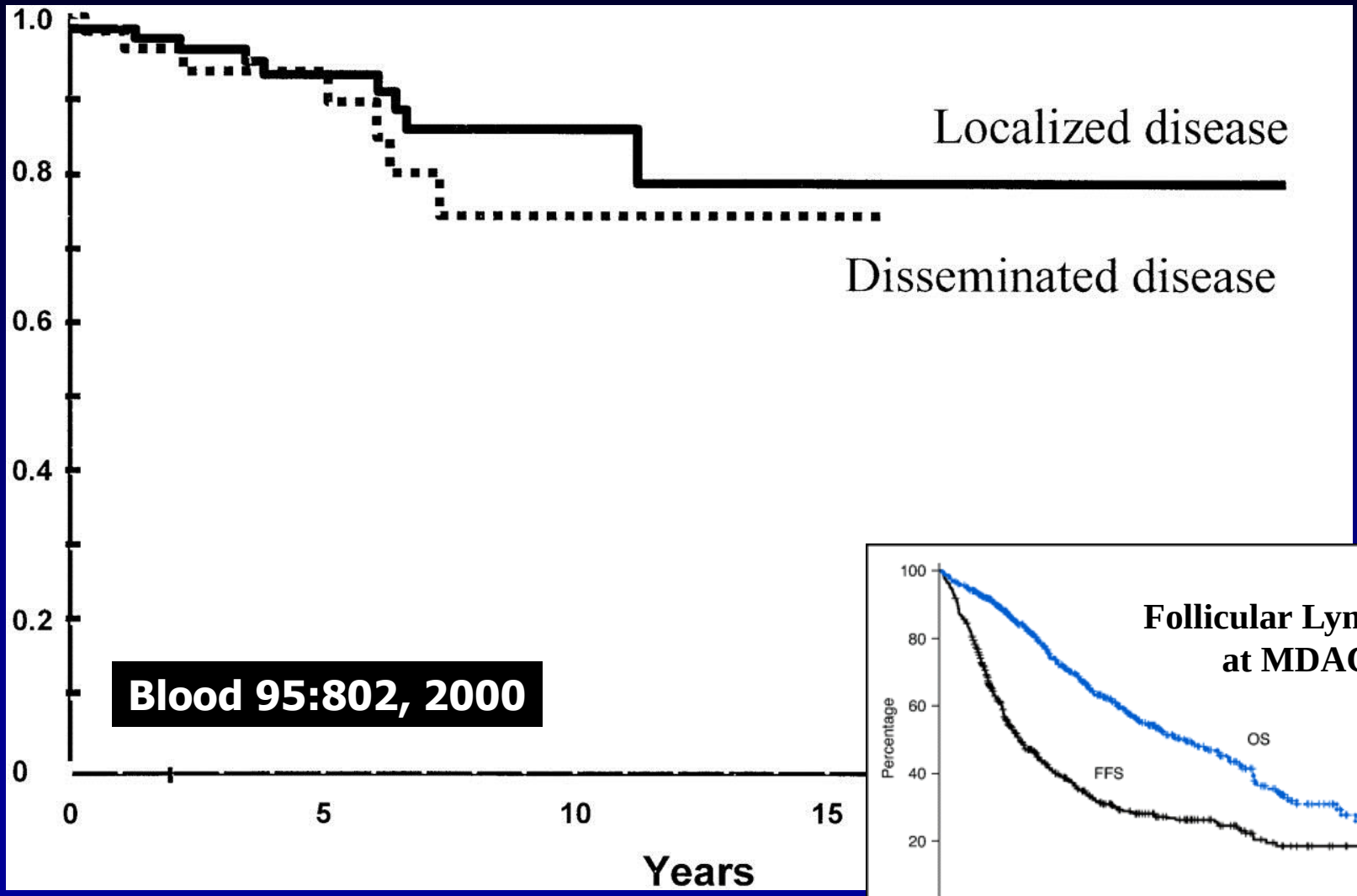
WHO book, p. 214

MALT Lymphoma
Clinical Findings

	EMZL	FL
Median age	60 yrs	59 yrs
Male	48 %	42 %
BM+	14 %	42 %
B symptoms	19 %	28 %
Stage		
I-II	67 %	33 %
III-IV	33 %	67 %

Blood 89: 3909, 1997

MALT Lymphoma
Freedom from progression



MALT Lymphomas

Relative Frequency of Involved Sites

Stomach	28 %
Skin	20 %
Salivary gland	17 %
Ocular adnexae	15 %
Intestine	6 %
Lung	6 %
Thyroid gland	2 %
Breast	2 %
Liver	2 %
Other	2 %

Leukemia 18: 1722, 2004

MALT Lymphoma
Unusual Sites

Almost any site can be involved

- Dura
- Tongue
- Thymus gland
- Pleura
- Muscle
- Gallbladder
- Kidney
- Cervix
- Endometrium
- Ovary
- Testis

MALT Lymphoma

Tonsils and Ileum

Uncommon sites for MALT lymphoma

These sites have abundant MALT tissue

Many lymphoepithelial lesions

Tonsils

Usually we receive bigger specimens

Can assess architecture

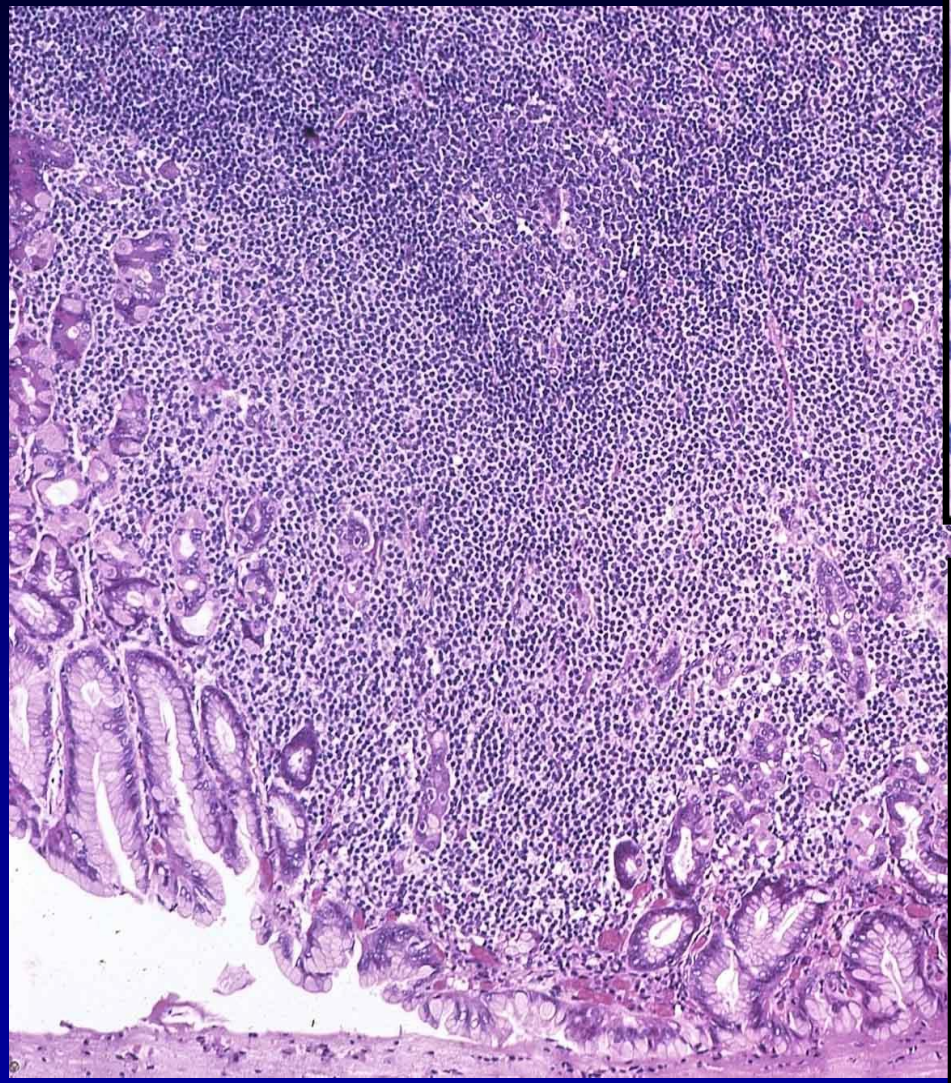
Ileum

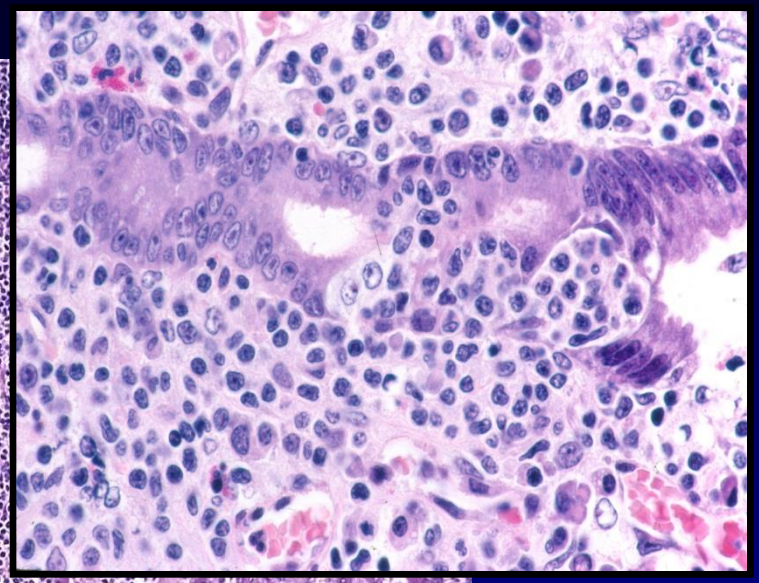
Tiny endoscopic biopsy specimens

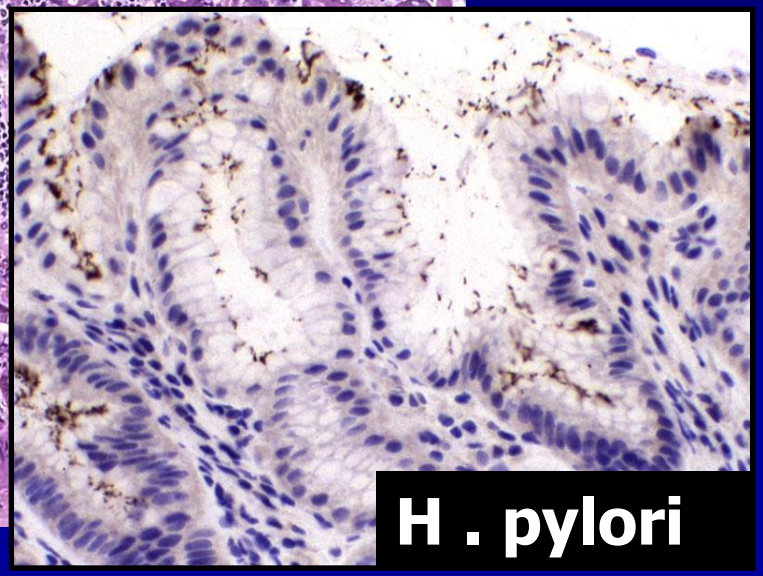
No architecture to assess

I cannot diagnose MALT lymphoma

MALT Lymphoma of Stomach

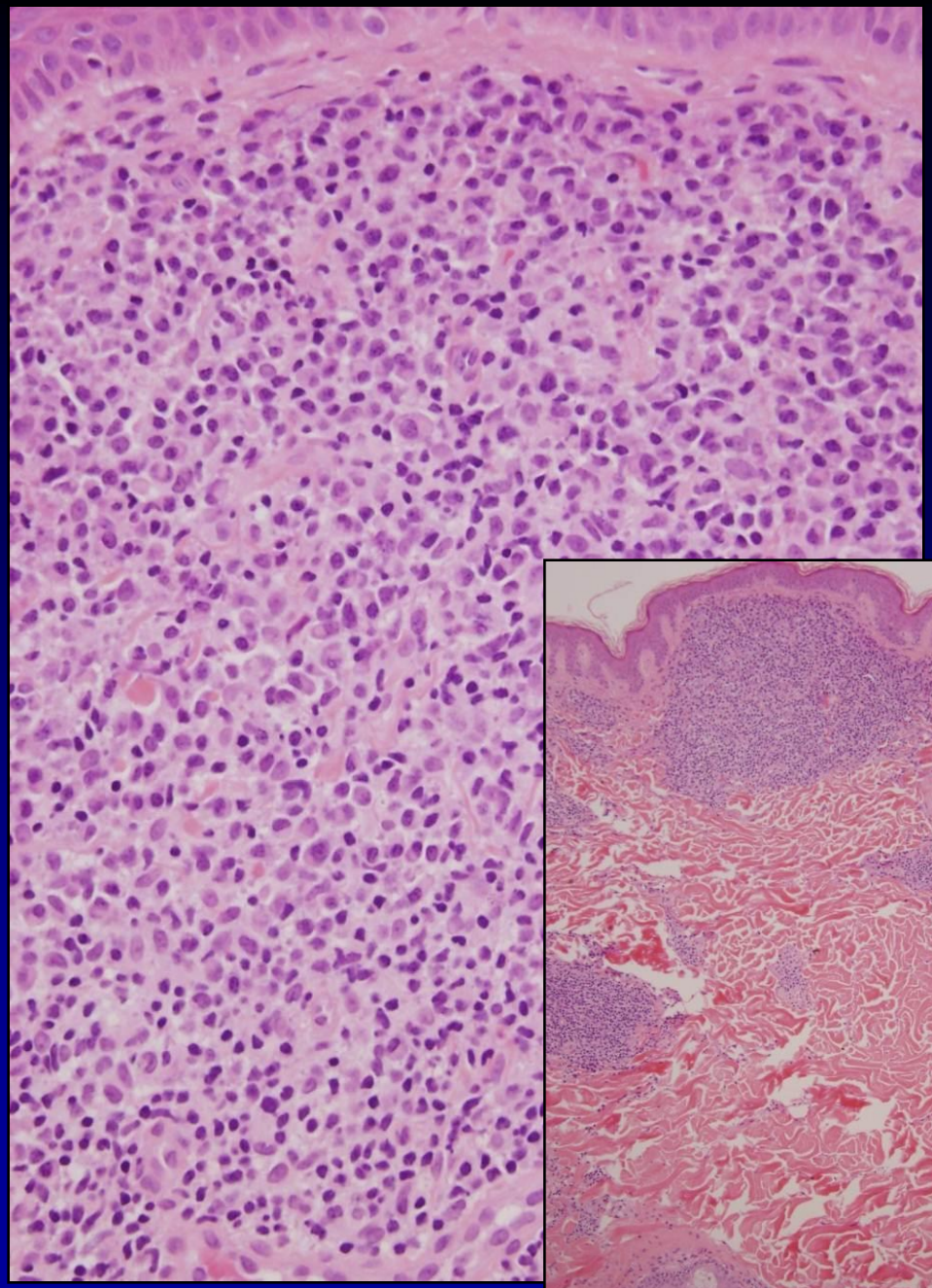


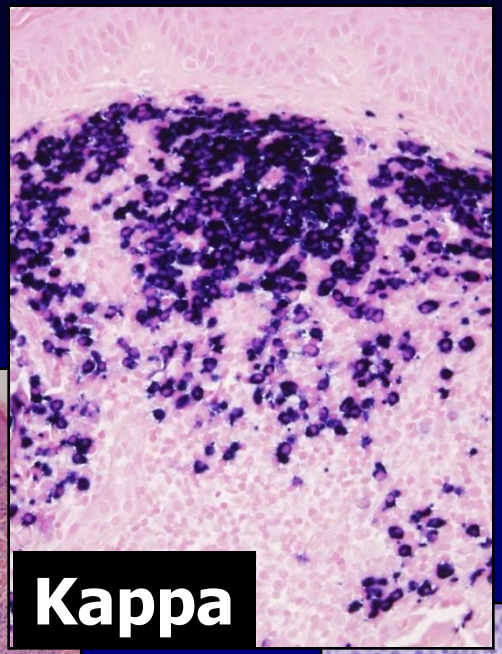




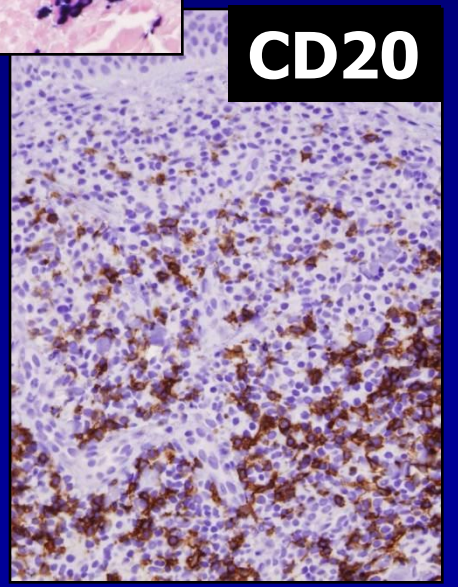
MALT Lymphoma of Skin

Immunocytoma Pattern



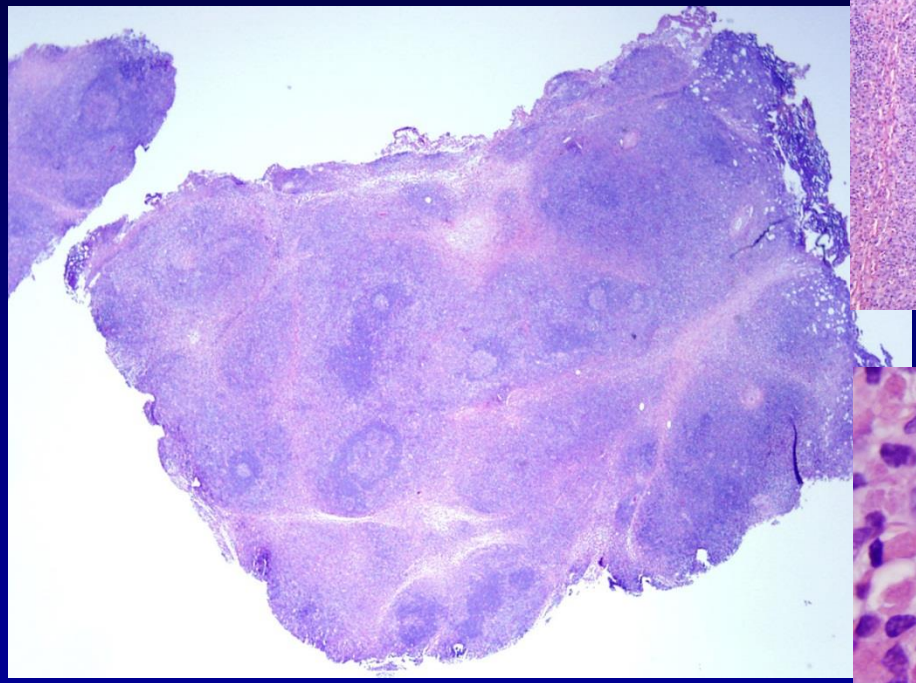


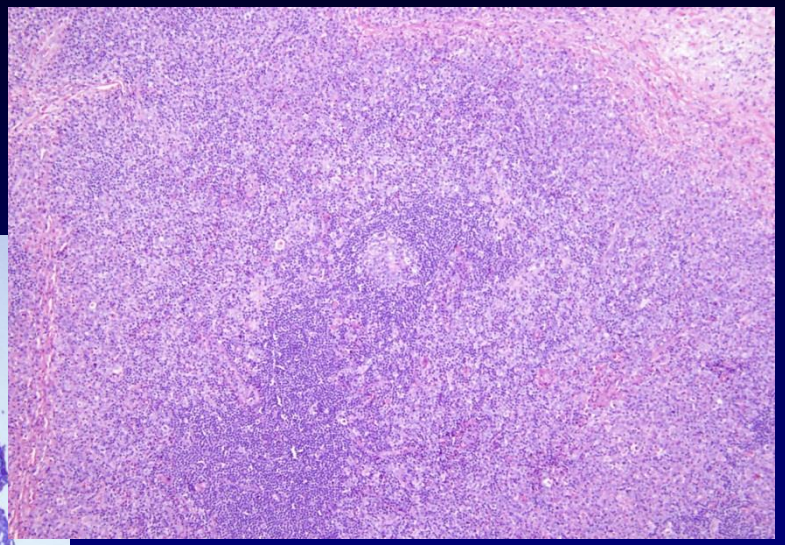
Kappa

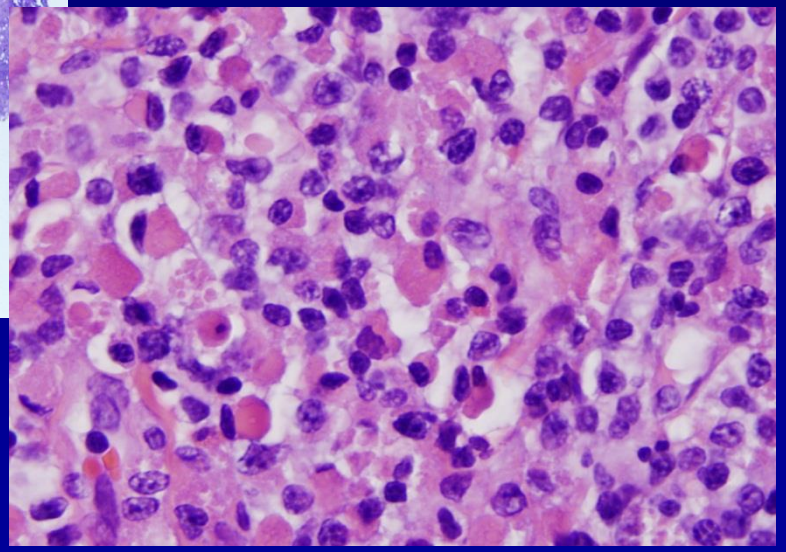


CD20

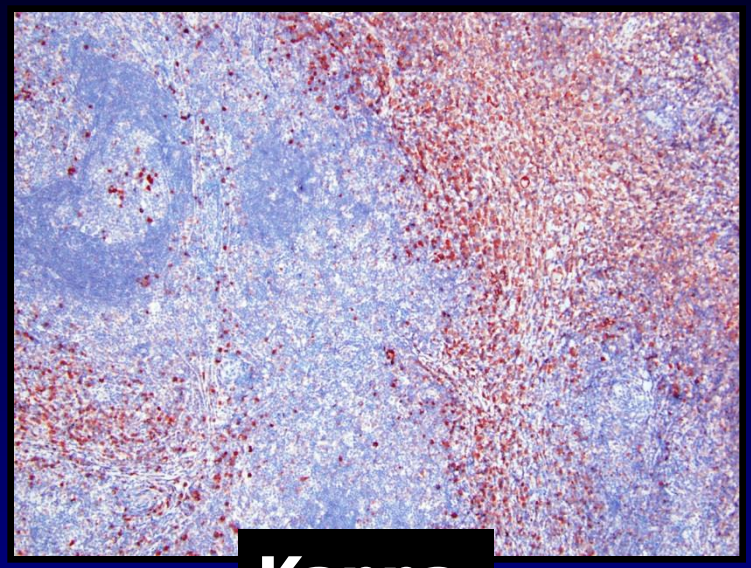
MALT Lymphoma of Orbit







MALT Lymphoma of Orbit



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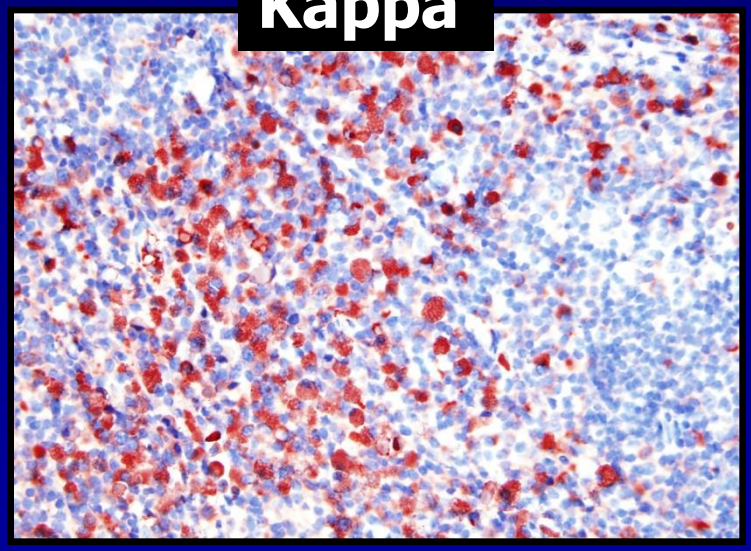
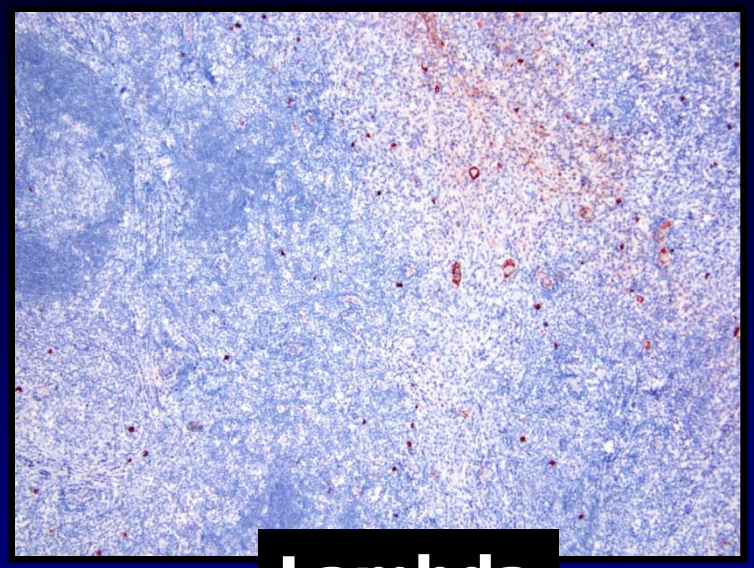
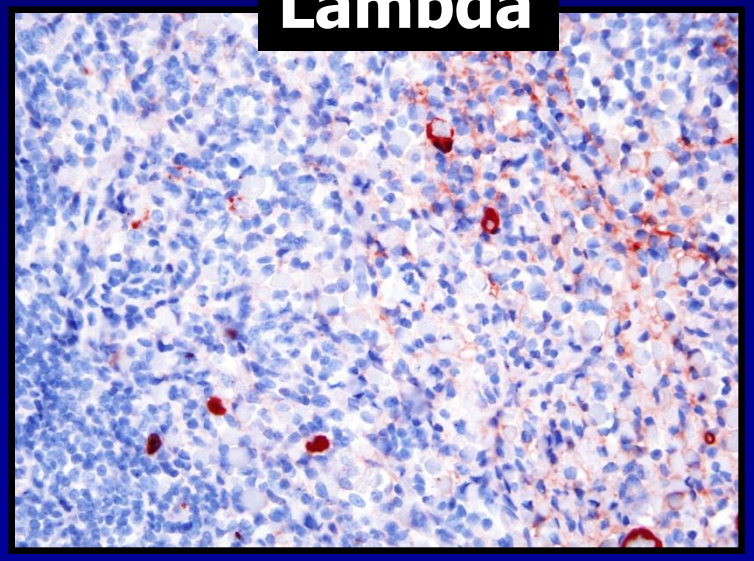


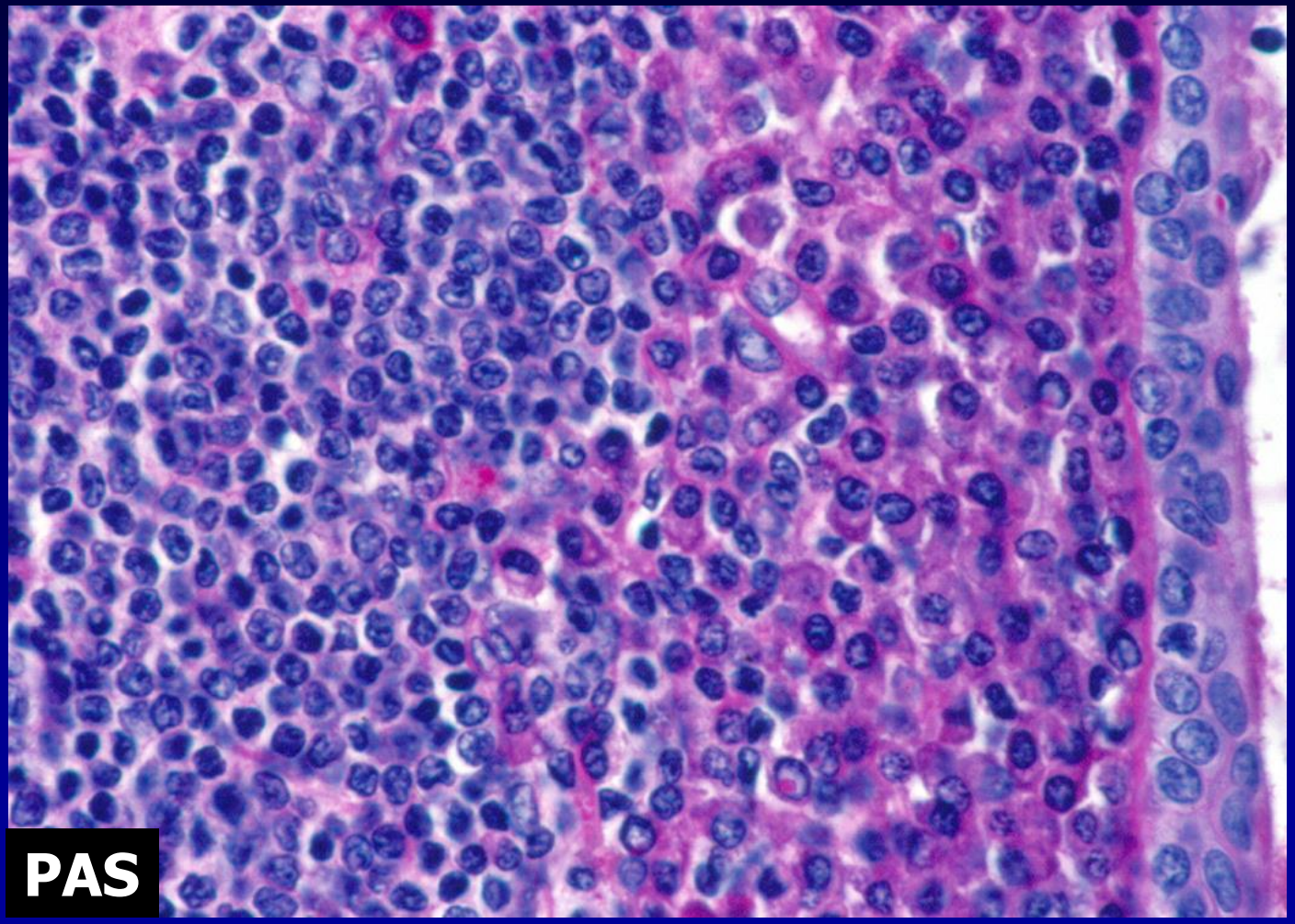


Lambda



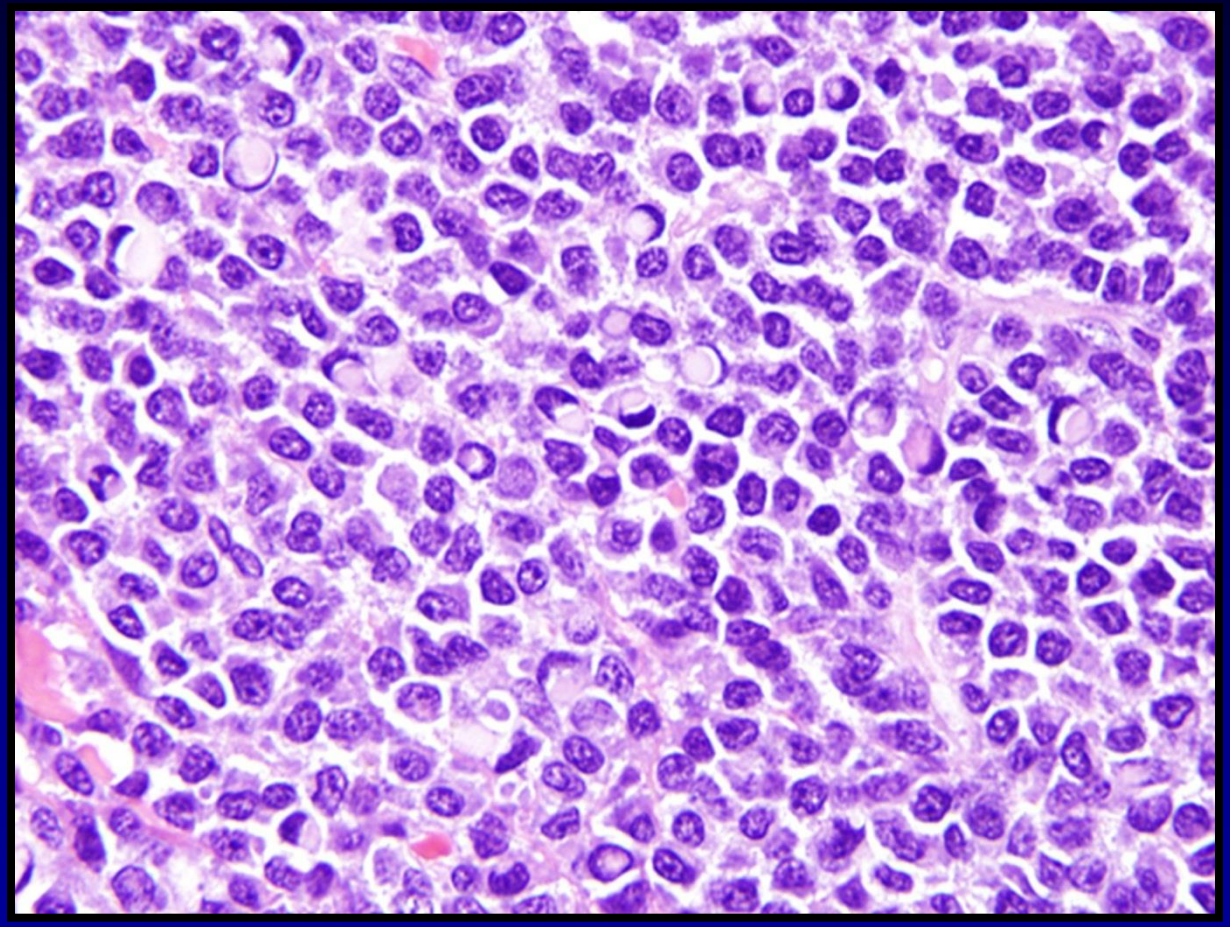
MALT Lymphoma of Conjunctiva

Plasmacytoid Differentiation Can be Prominent



MALT Lymphoma

Dutcher Bodies are Helpful for Dx



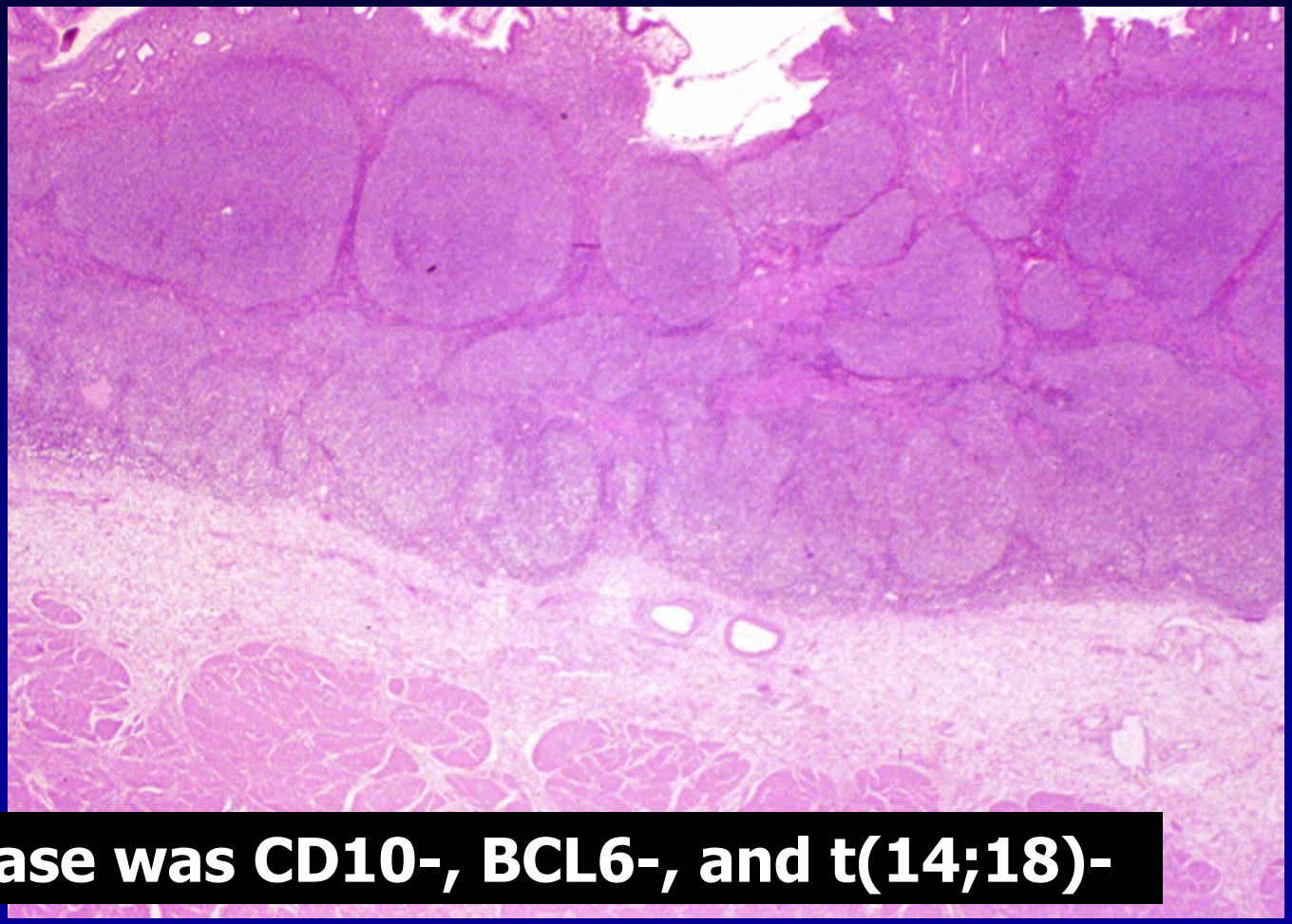
Dutcher bodies = nuclear pseudoinclusions of cytoplasm
Numerous Dutcher bodies support lymphoma

MALT Lymphomas

Histologic Features

- Neoplastic small lymphoid cells
  - Small round lymphocytes
  - Monocytoid cells
  - Centrocyte-like cells
  - Plasmacytoid lymphocytes
- Occasional large cells (blasts)
- Lymphoepithelial lesions
- Reactive follicles

MALT Lymphoma of Stomach
Follicular Colonization

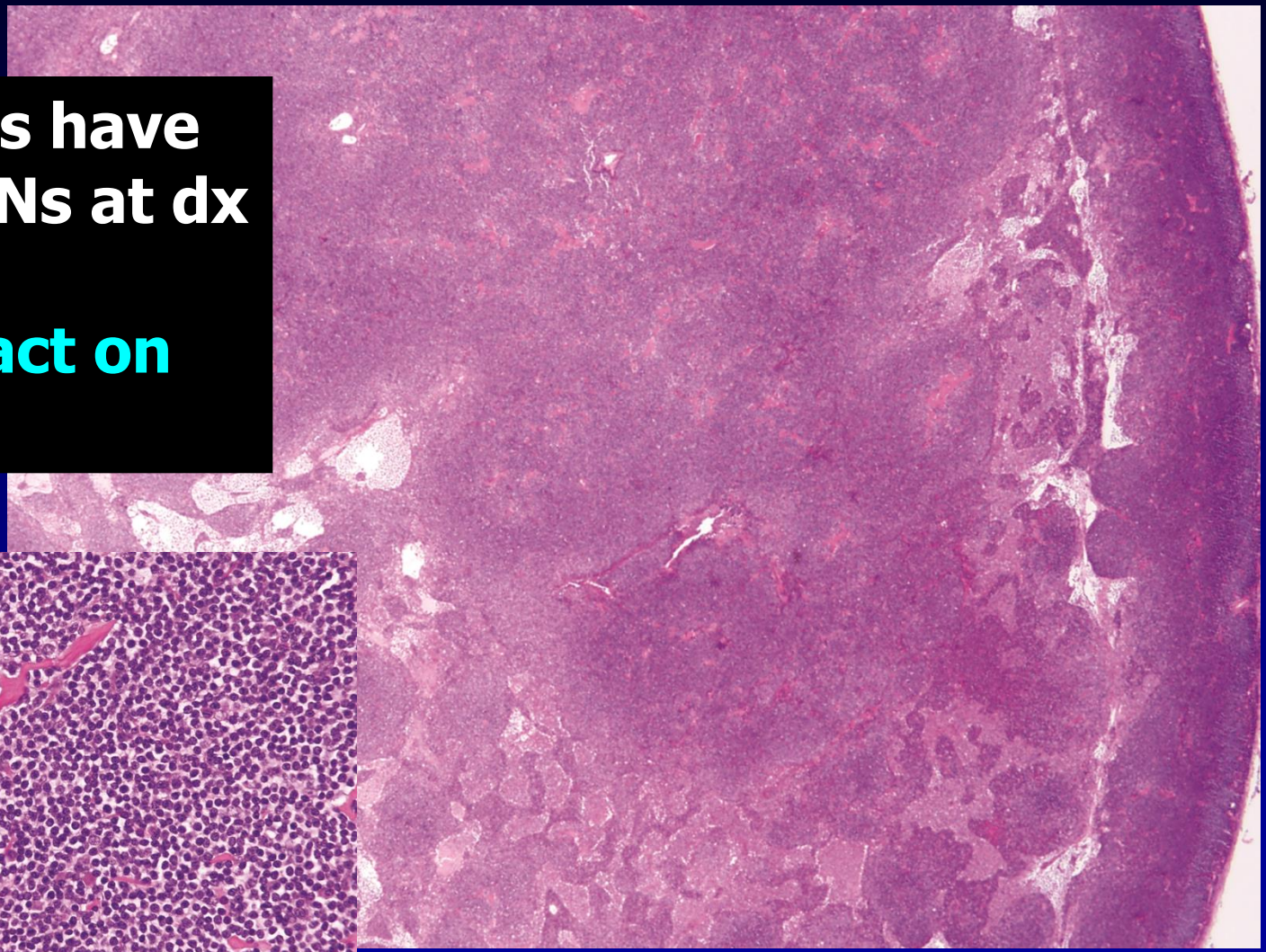


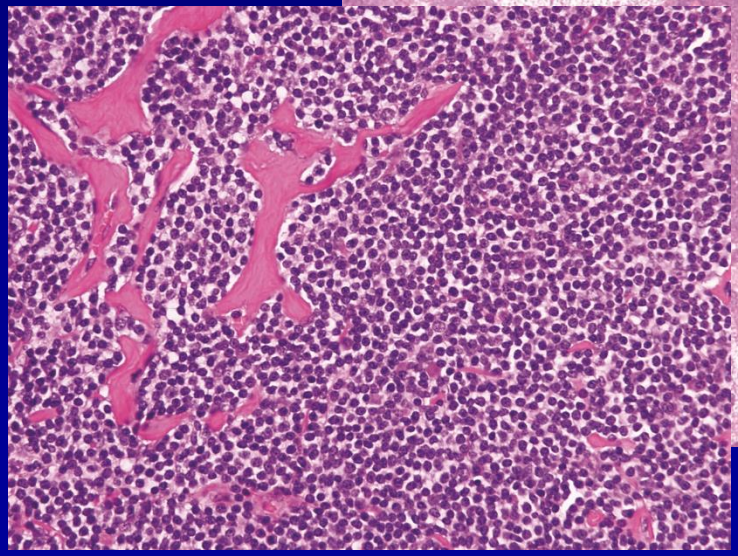
This case was CD10-, BCL6-, and t(14;18)-

MALT Lymphoma in Regional Lymph Node

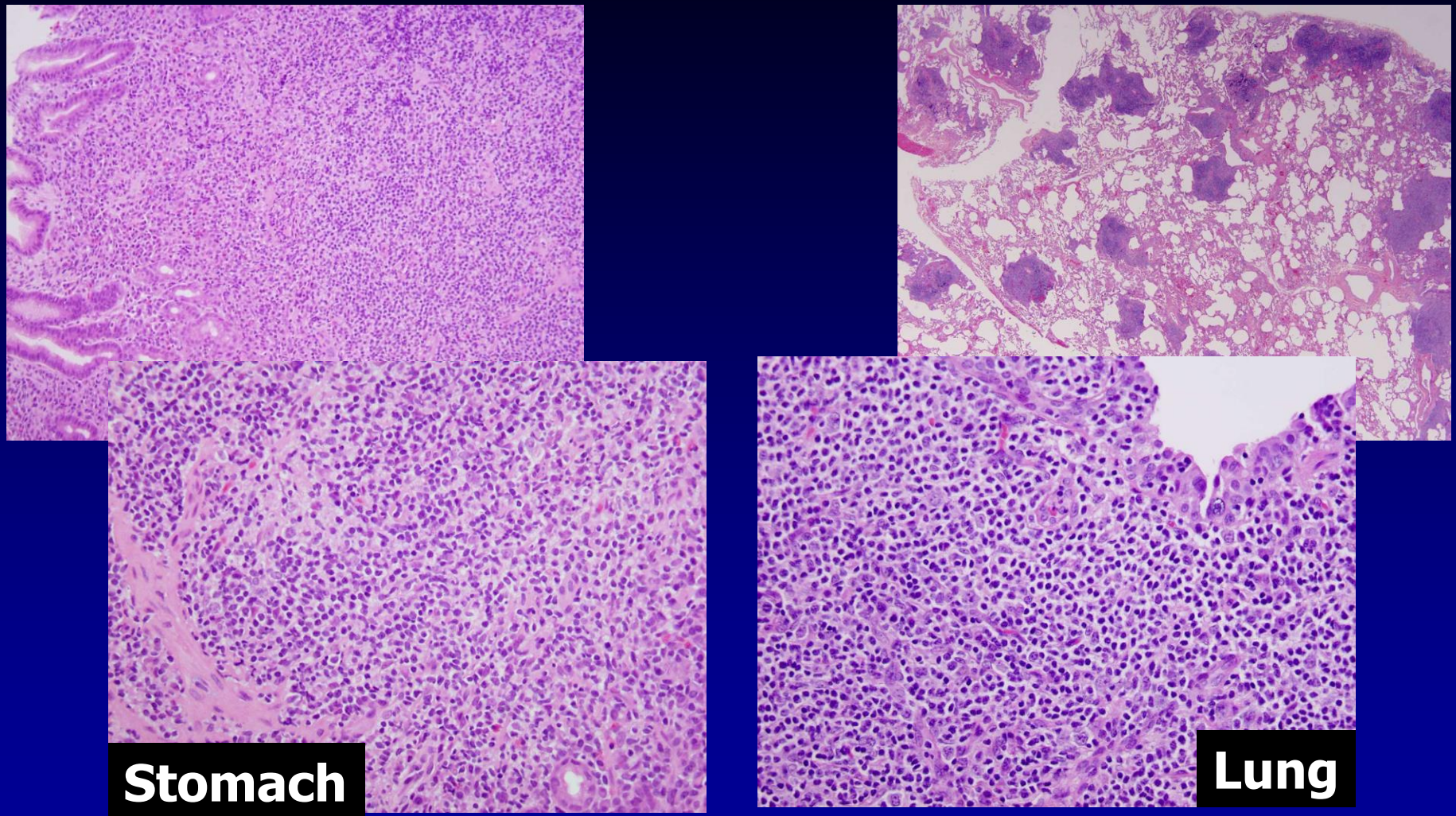
20% of pts have regional LNs at dx

Little impact on prognosis





MALT Lymphoma Can be Multicentric



~ 25% of pts

May not be clonally related (true in this case)

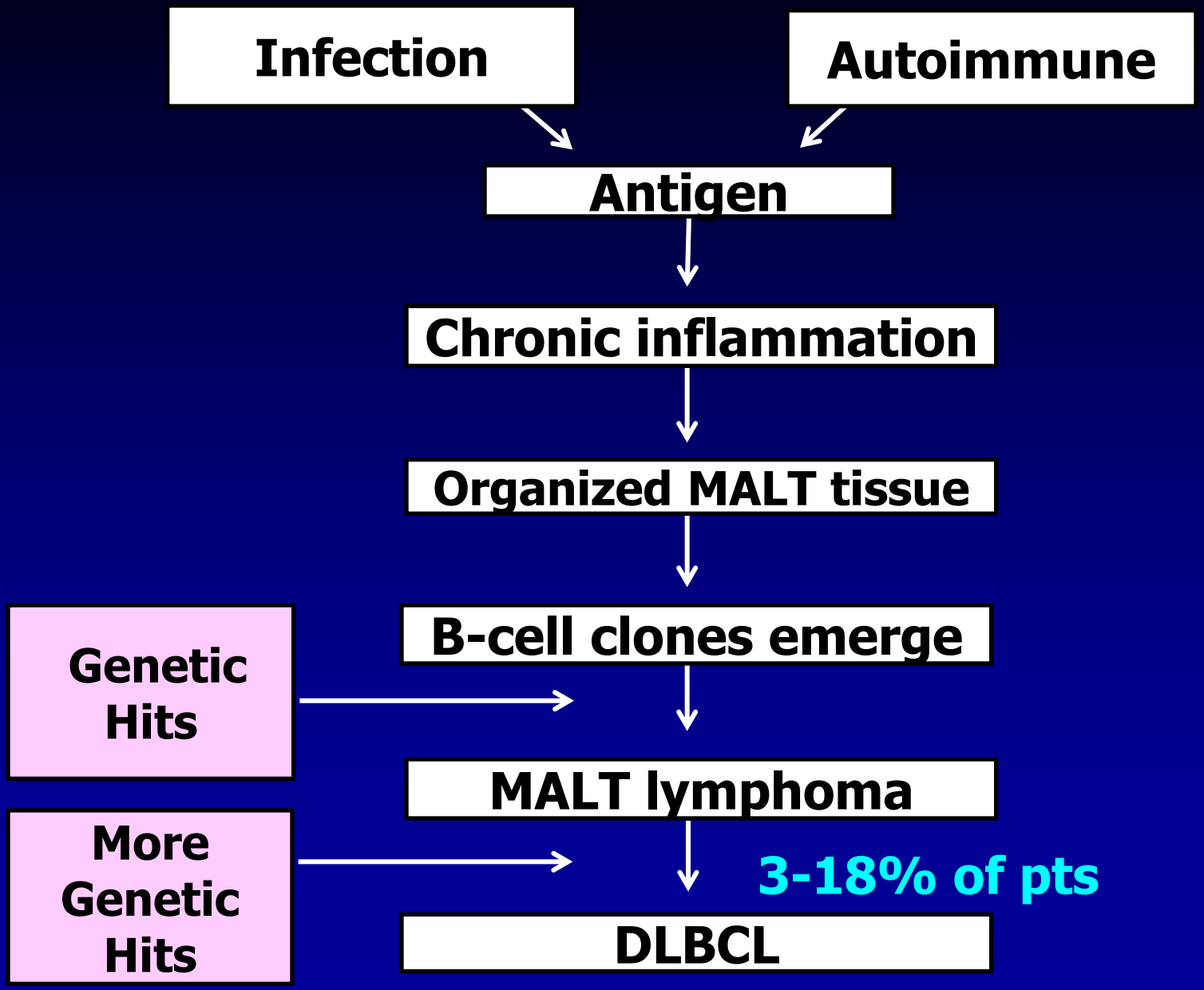
MALT Lymphoma

Associated Infections and Autoimmune Diseases

Stomach	*Helicobacter pylori*
Skin	*Borrelia burgdorferi* (Europe)
Jejunum	*Campylobacter jejuni*
Ocular adnexa	*Chlamydia psittaci*
Lung	*Achromobacter xylosoxidans*
	Lymphoid interstital pneumonia
Thyroid	Hashimoto thyroiditis
Salivary gland	Sjogren syndrome

Hepatitis C may have a role for non-gastric cases (Italy)

Pathogenesis of MALT Lymphoma



MALT Lymphoma

Immunophenotype

Positive	Negative
Immunoglobulin	CD3, CD5
CD19, CD20, CD22, CD79A, PAX5	CD10
BCL2	CD23 -/+
IRTA*	BCL6
MNDA*	Cyclin D1

* Less than 100% sensitive

CLONALITY IN MALT LYMPHOMA

Sensitivity of detection depends on method

Method	Sensitivity	Comment
Paraffin IHC (kappa, lambda)	~10%	Need plasmacytoid lymphocytes/plasma cells
Flow cytometry	~ 0.1-001%	% clonal cells important
PCR IGH	~ 0.1%	Many false negatives Size of clone important

Chromosomal Translocations in MALT Lymphoma

The Famous 4

Abnormality	Genes	Frequency
t(11;18)(q21;q21)	*API2 (BIRC3)* and *MALT1*	20-30%
t(14;18)(q32;q21)	*IGH* and *MALT1*	10-15%
t(3;14)(p14.1;q32)	*FOXP1* and *MALT1*	~10%
t(1;14)(p22;q32)	*BCL10* and *IGH*	~5%

Cytogenetic/Molecular Abnormalities in MALT Lymphoma

Abnormality	Genes	Frequency
3q27/BCL6 rearrangements	*BCL6*	<5%
t(X;14)(p11.2;q32)	*GPR34* and *IGH*	2-3%
t(1;2)(p22;p12)	*BCL10* and *IGK*	~1%
t(1;14)	*CNN3* and *IGH*	Rare
t(5;14)(q34;q32)	*ODZ2* and *IGH*	Rare
t(9;14)(p24;q32)	*JMJD2C* and *IGH*	Rare
t(6;7)(q25;q11)	Unknown	Rare
Del(6p23)	*TNFAIP3*/A20	10-20%
Trisomy 3 and 18	Unknown	40-60%
Trisomy 7 and 12	Unknown	~30%

MALT Lymphomas

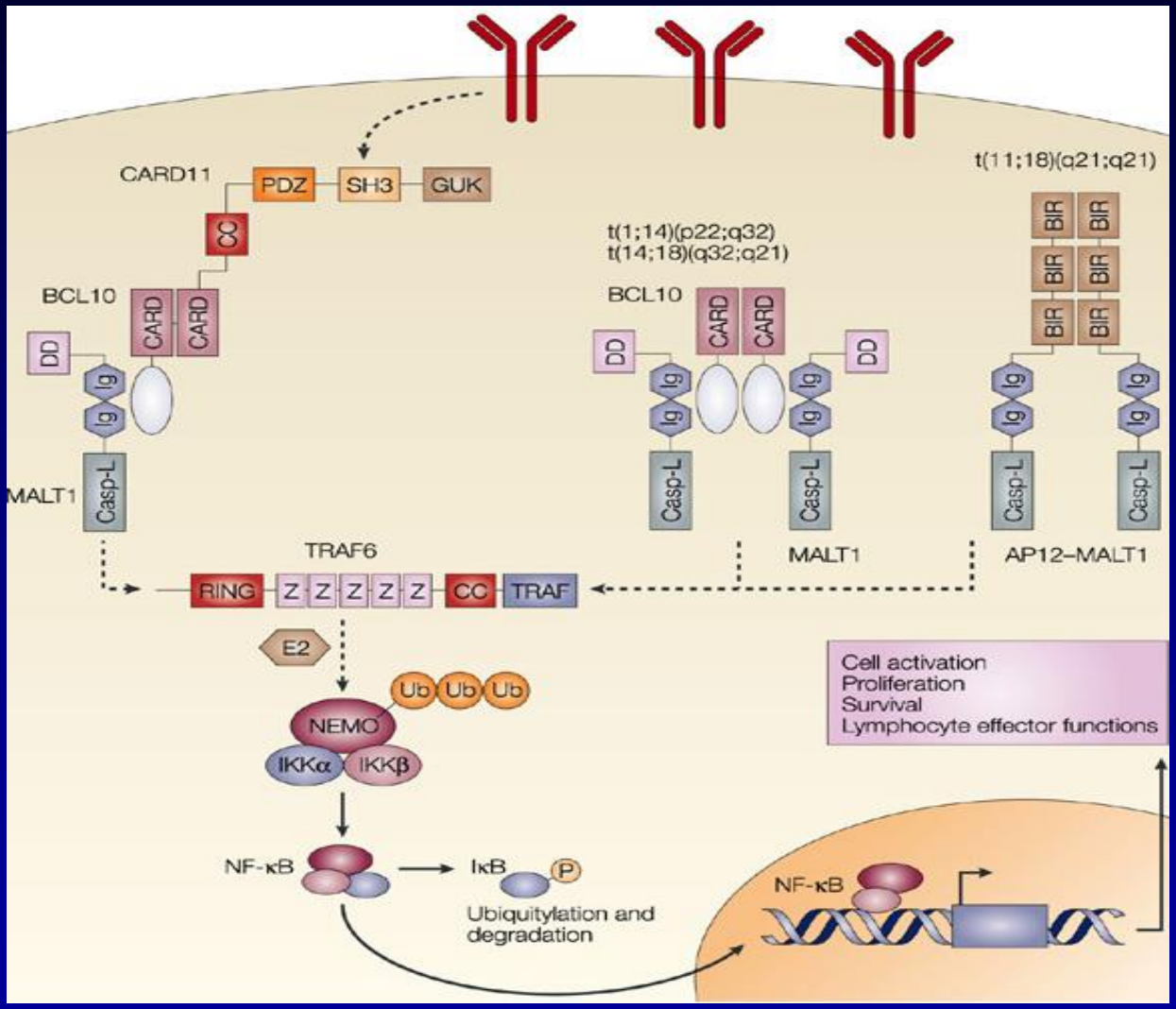
Translocation Frequency Related to Site

Site	t(11;18)	t(14;18)	t(1;14)
Stomach	24 %	1 %	0 %
Skin	8 %	14 %	0 %
Salivary gland	2 %	12 %	2 %
Ocular adnexae	3 %	24 %	0 %
Intestine	13 %	0 %	12 %
Lung	53 %	7 %	7 %

Leukemia 18: 1722, 2004

MALT Lymphoma

Common Activation of NF-κB pathway



Nat Rev Cancer 4: 644, 2004

MALT-Lymphoma of Stomach

Clinical Implications of t(11;18)

t(11;18) +

- Poorer response to antibiotics for *H. pylori*
- Higher stage
- Often do not progress to large cell lymphoma

t(11;18) -

- Usually respond to antibiotic therapy
- Lower stage
- May progress to large cell lymphoma

Clues to Diagnosis of MALT Lymphoma

Extranodal site

History of infection or autoimmune disease

Monocytoid or plasmacytoid lymphocytes

Dutcher bodies (many)

Too many B-cells by IHC

Appropriate immunophenotype

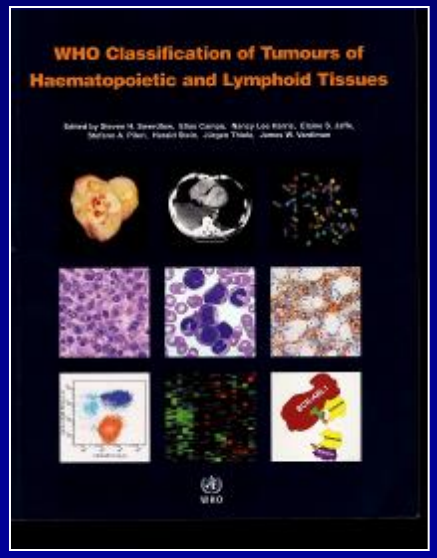
CD20+, CD5-, CD10-, BCL6-, cyclin D1-

Warning: systemic B-cell lymphomas can initially present in an extranodal site – need to exclude

Nodal Marginal Zone B-cell Lymphoma
Definition

A primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by MZL of extranodal or splenic types but without evidence of extranodal or splenic disease

Old name: monocytoid B-cell lymphoma



WHO book, p. 218

Nodal Marginal Zone Lymphoma
Clinical Findings

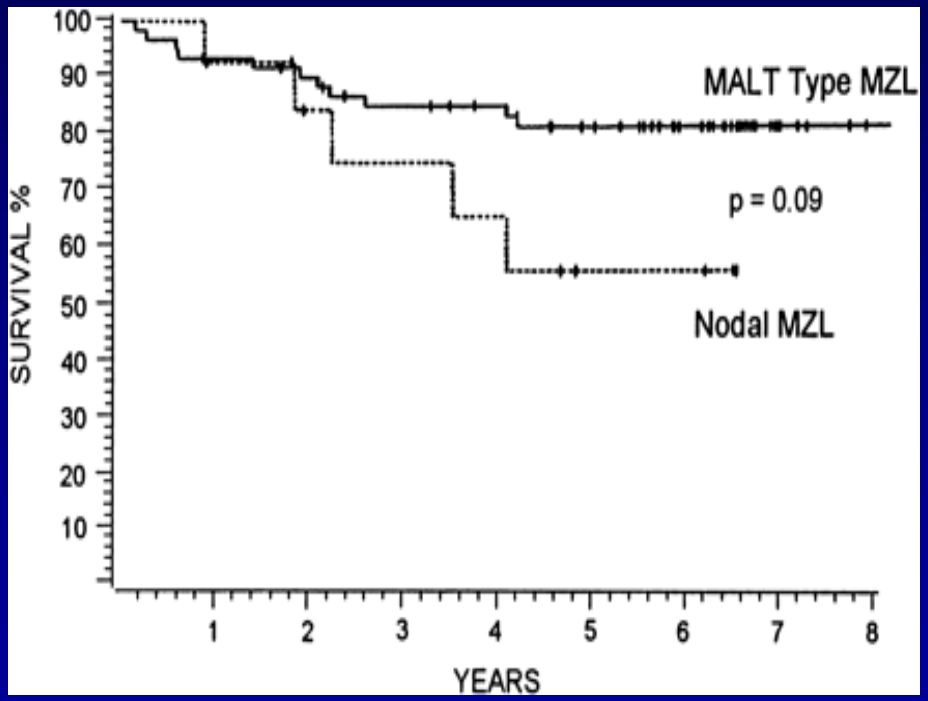
	NMZL	FL
Age	58 y	59 y
Male	42 %	42 %
BM+	32 %	42 %
B symptoms	37 %	28 %
Stage		
I-II	26 %	33 %
III-IV	74 %	67 %

Blood 89: 3909, 1997

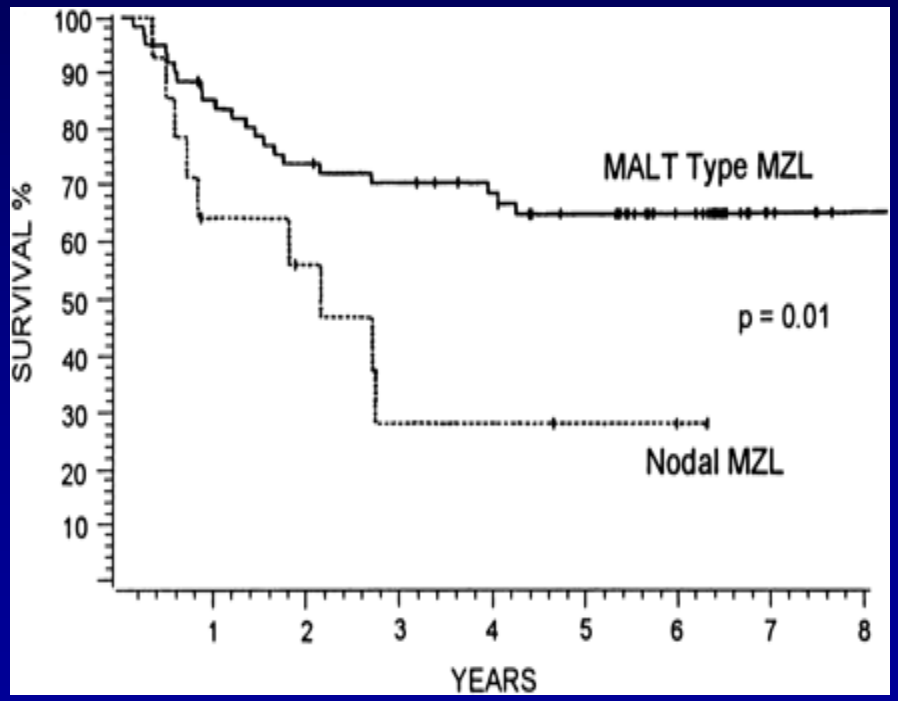
Nodal Marginal Zone Lymphoma

Survival

Overall



Failure-Free



J Clin Oncol 17: 2486, 1999

Nodal Marginal Zone Lymphoma
Histologic Features

Marginal zone distribution

Abundant cytoplasm

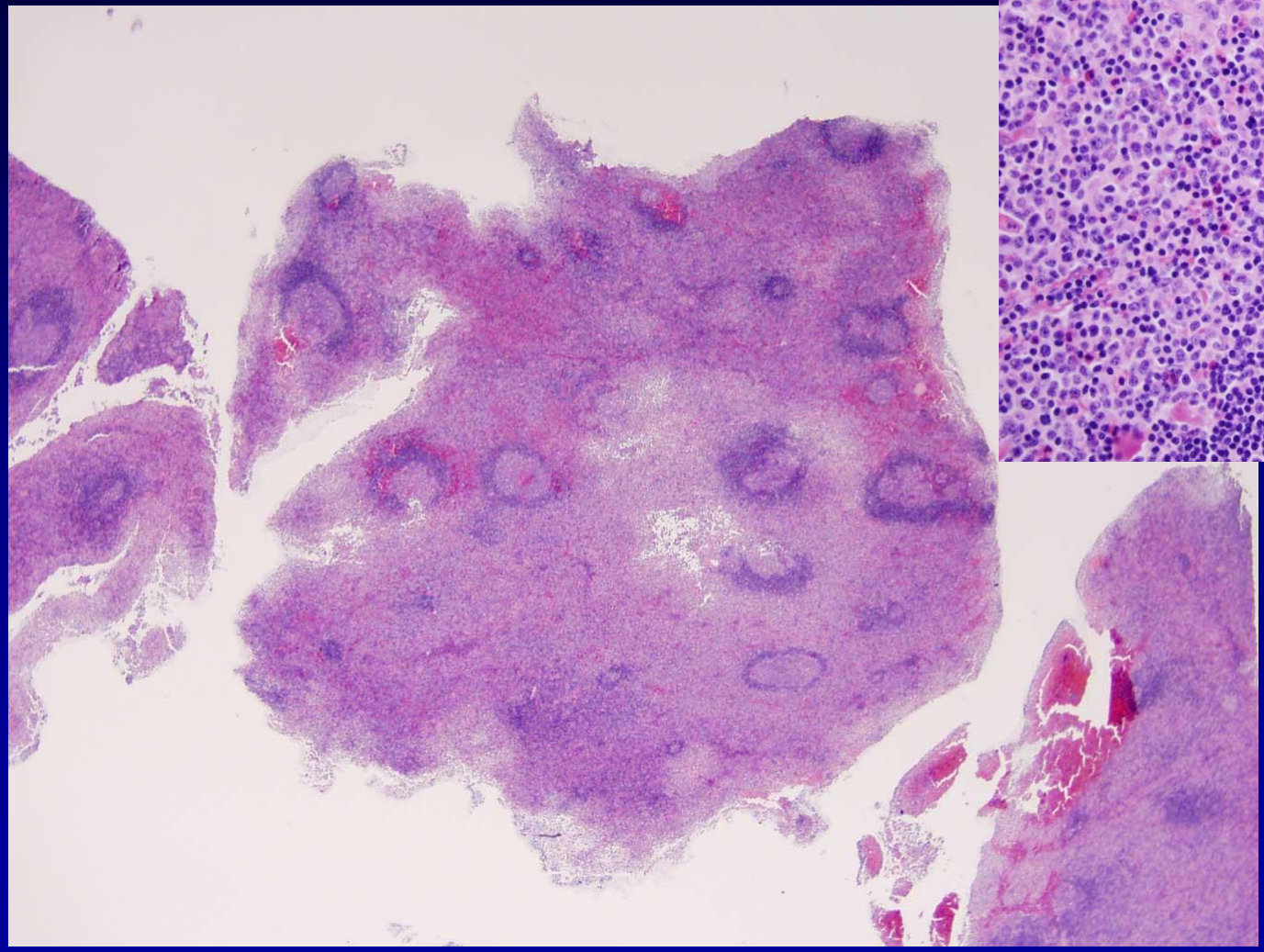
- Often pale at low power

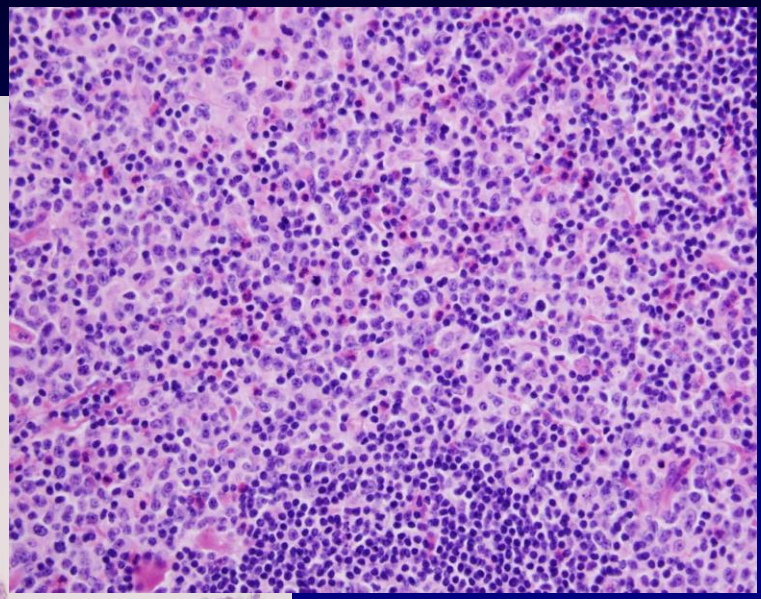
Plasmacytoid differentiation +/-

Follicular colonization +/-

Nodal Marginal Zone Lymphoma

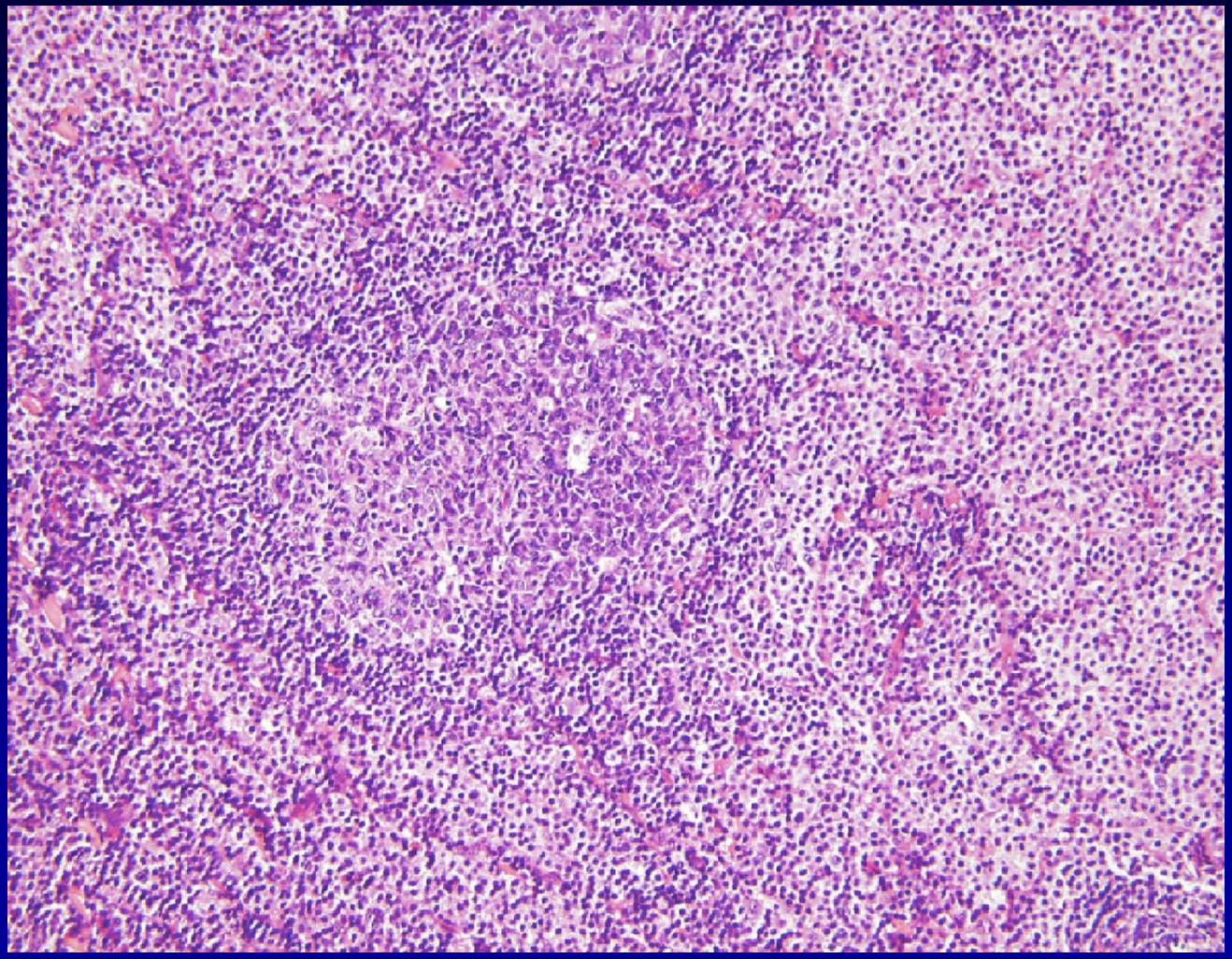
Marginal Zone Pattern and Pale Cytoplasm





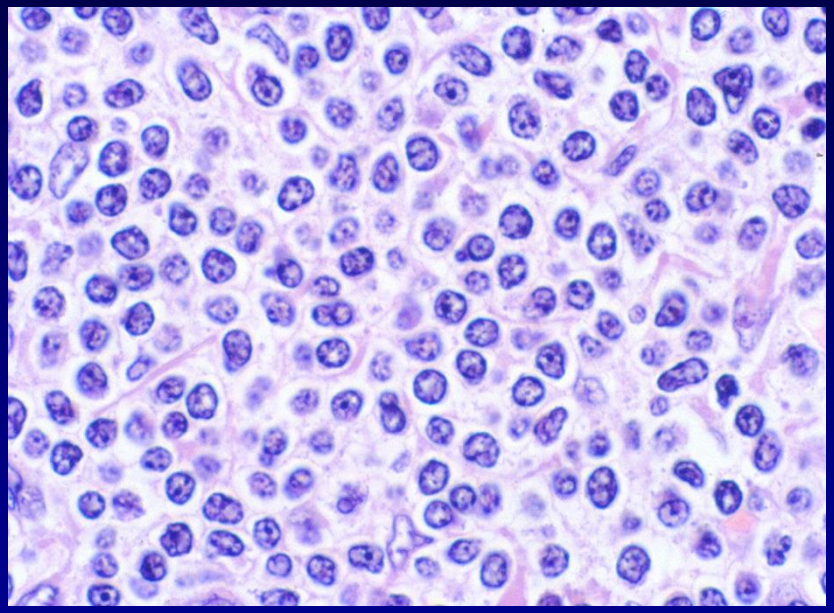
Nodal Marginal Zone Lymphoma

Marginal Zone Pattern and Clear Cytoplasm

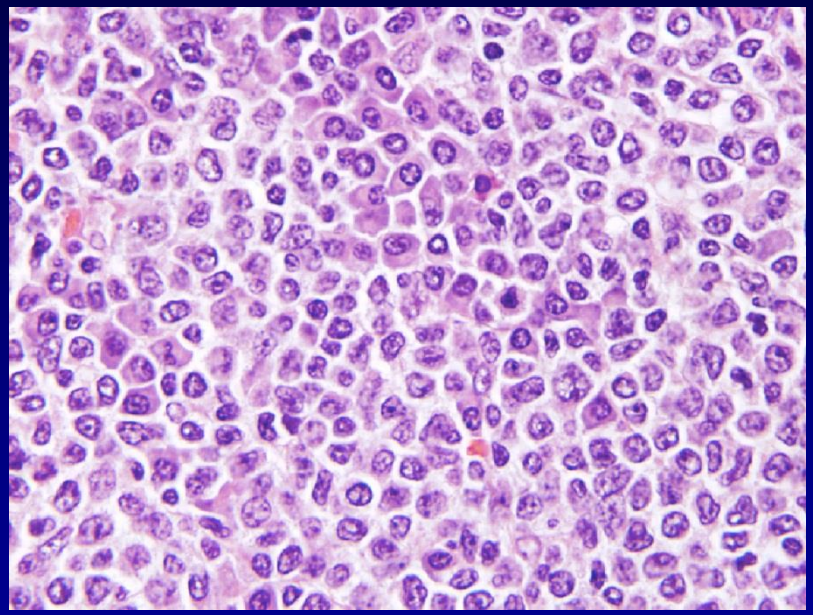


Nodal Marginal Zone Lymphoma

Cytologic Spectrum



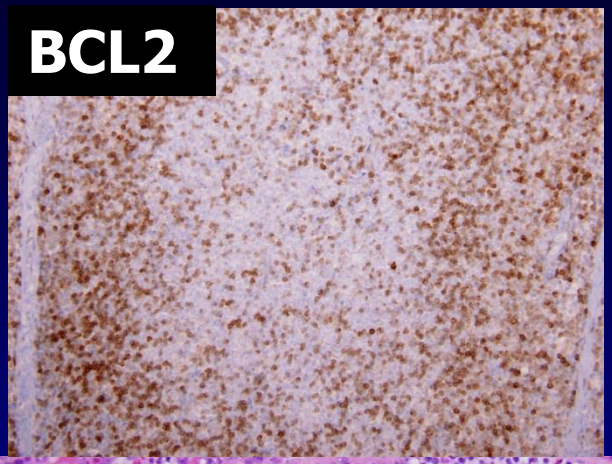
Monocytoid

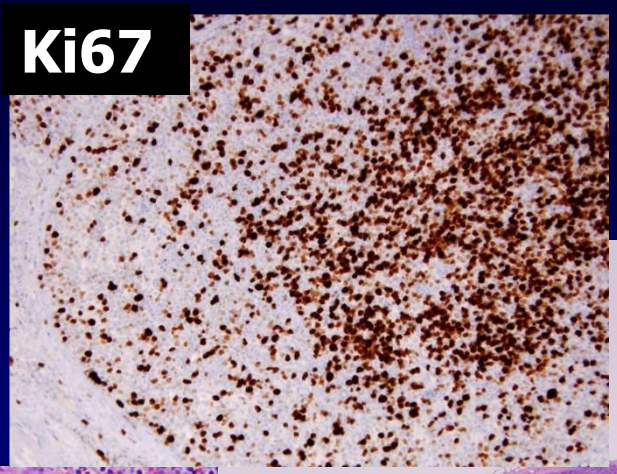


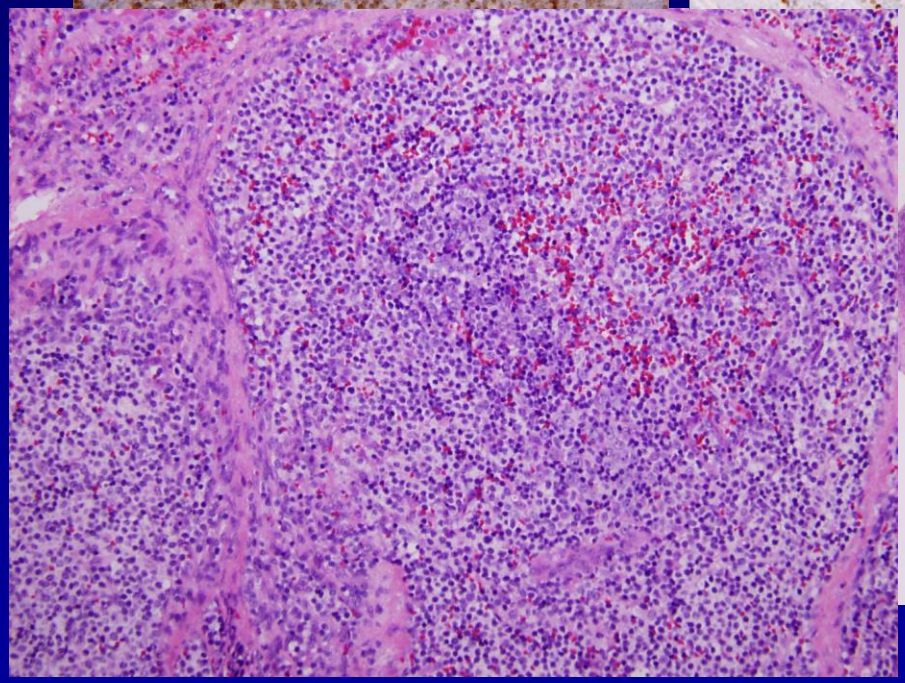
Plasmacytoid

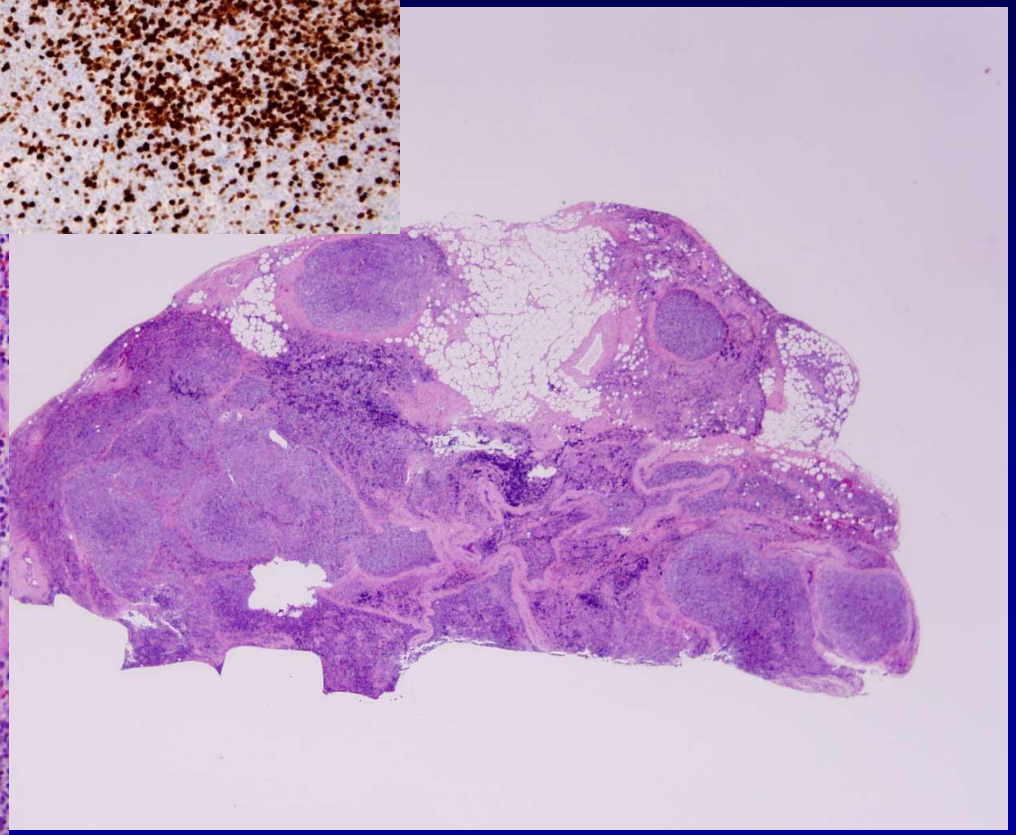
Nodal Marginal Zone Lymphoma

Hint of Residual Germinal Centers



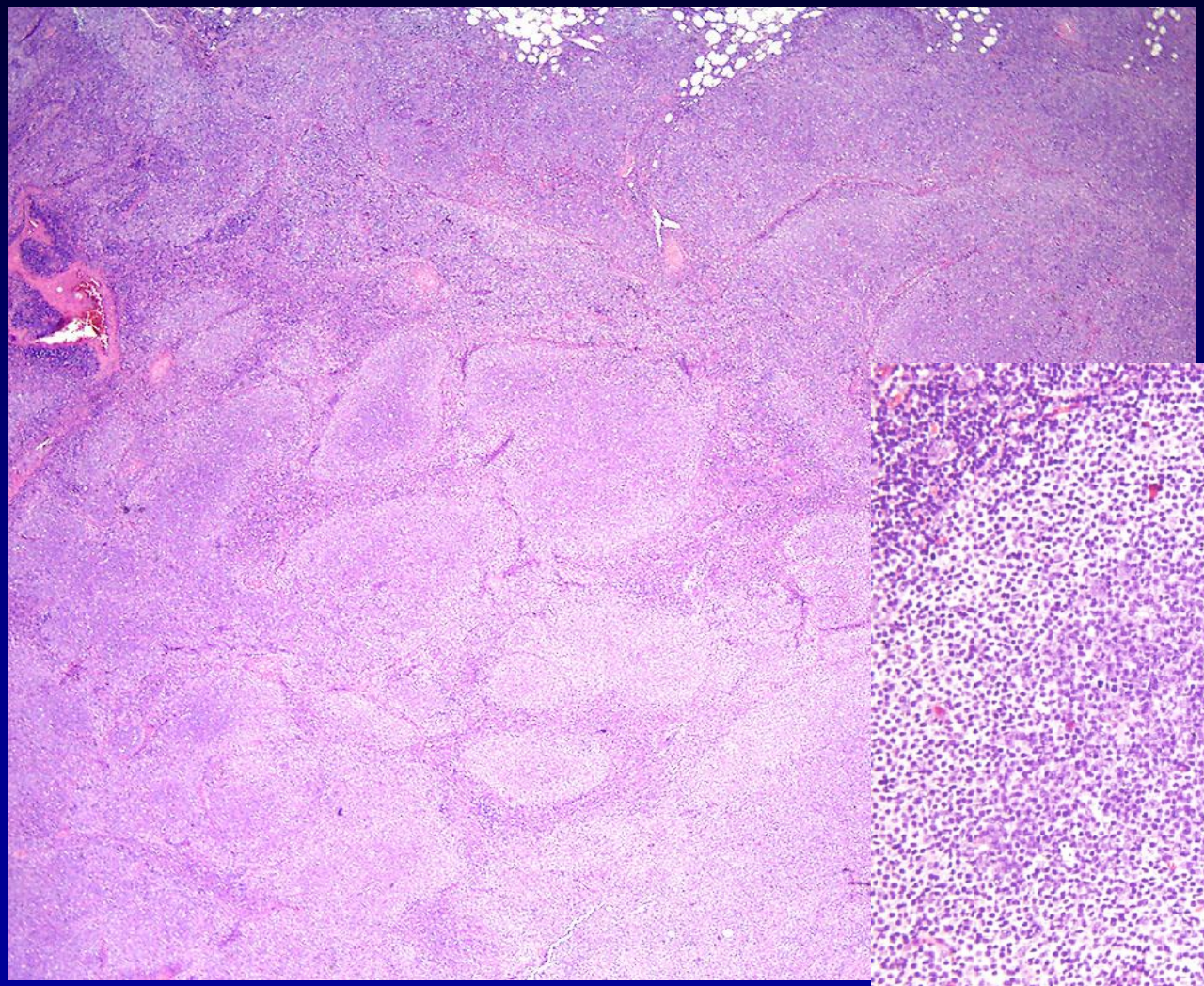


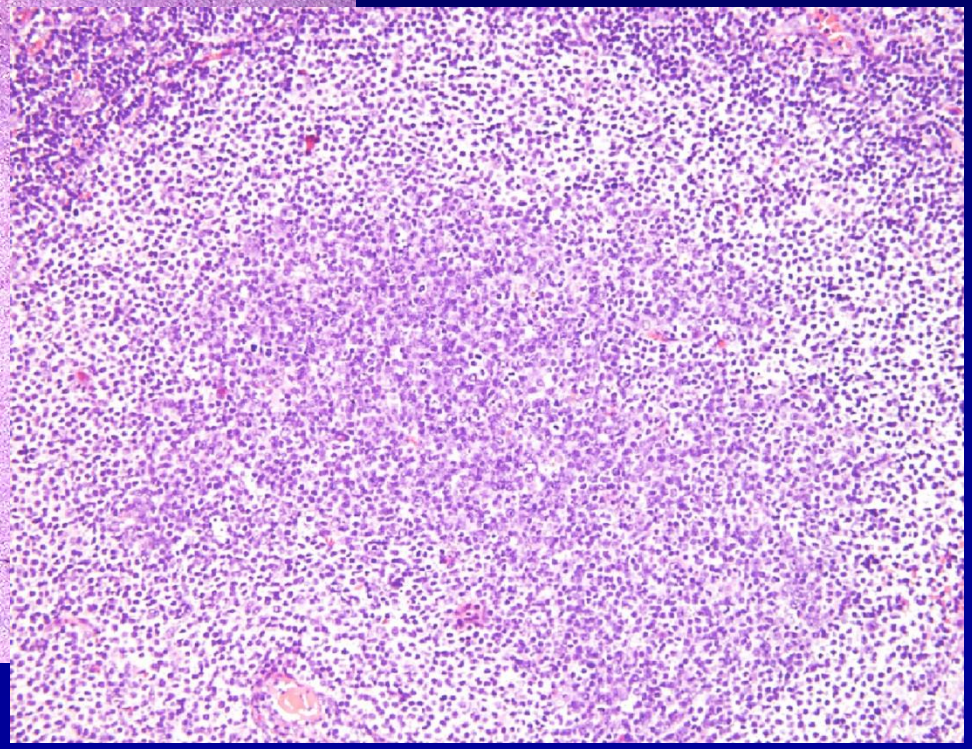




Nodal Marginal Zone Lymphoma

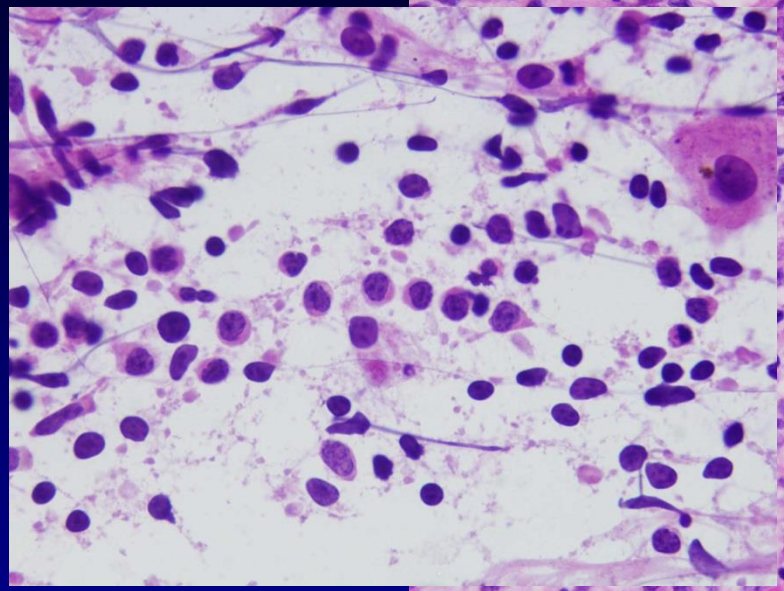
Follicular Colonization

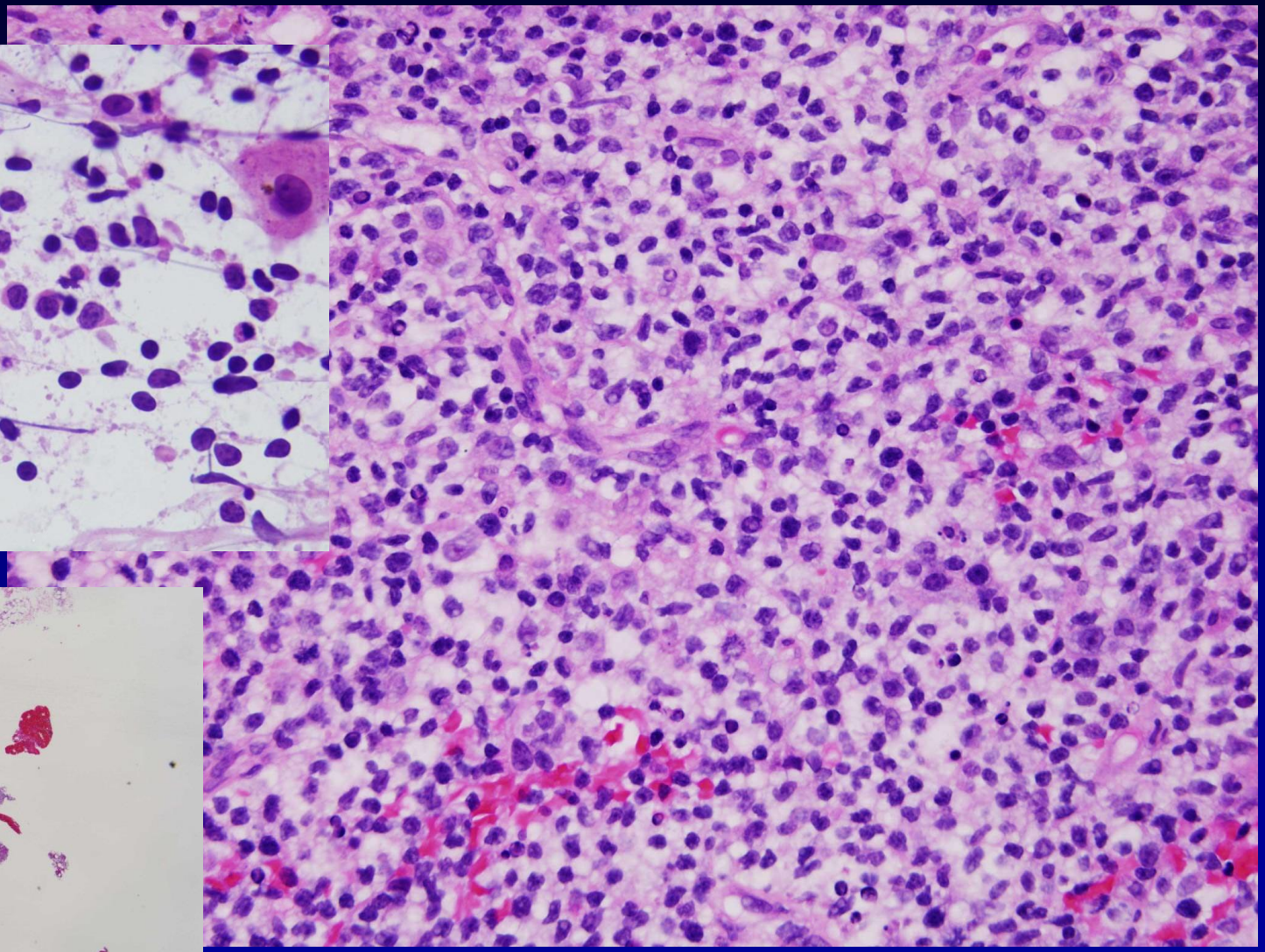


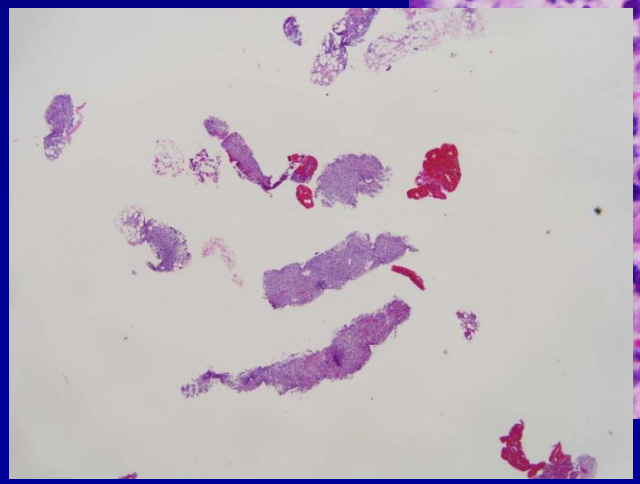


Nodal Marginal Zone Lymphoma

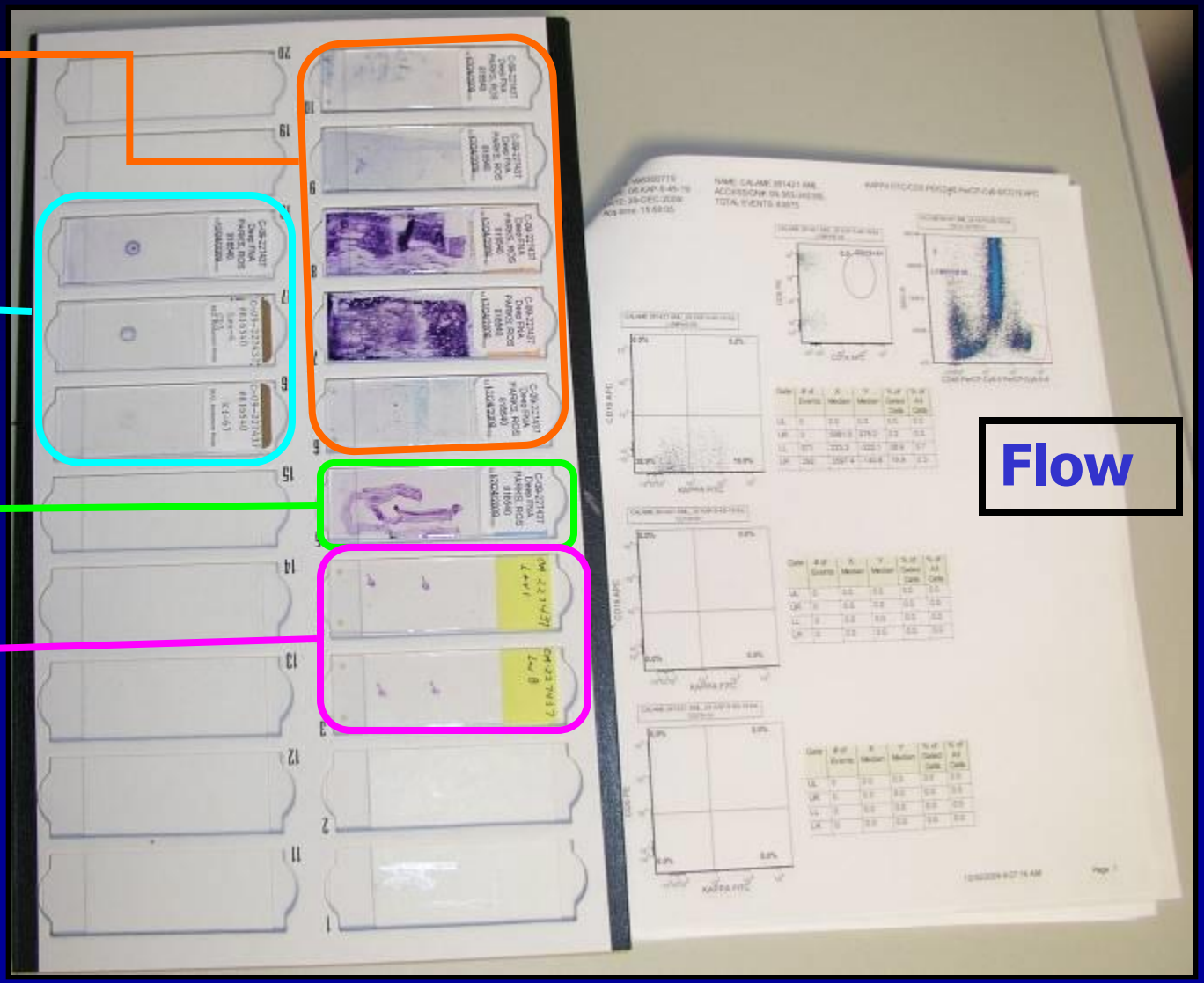
Can do by FNA with Flow/Ipox







Fine Needle Aspiration of LN - Components



Nodal Marginal Zone Lymphoma

Immunophenotype

Ipox CD19, CD20, PAX5, BCL2

Flow CD11c+/- CD23-/+ CD25-/+ FMC7+/-

CD5- ,CD10-

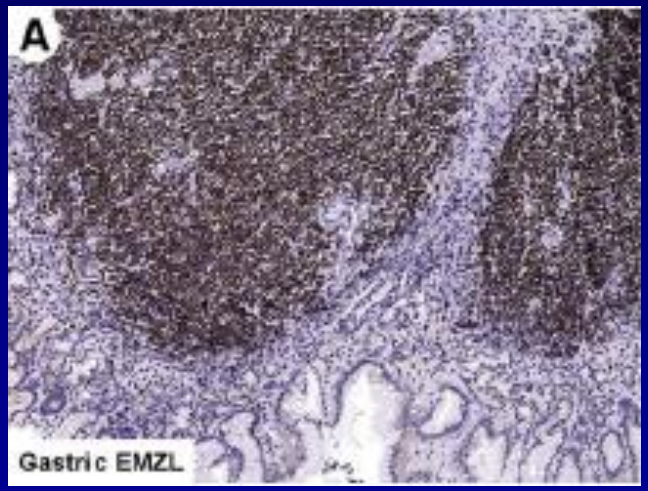
Molecular Features

No characteristic translocations

Myeloid cell nuclear differentiation antigen is expressed in a subset of marginal zone lymphomas and is useful in the differential diagnosis with follicular lymphoma☆

Ryan A. Metcalf MD[a], Ahmad Monabati MD[a], Monika Vyas MD[a], Giovanna Roncador BS[b], Gabriela Gualco MD[c], Carlos E. Bacchi MD[c], Sheren F. Younes MD[d], Yasodha Natkunam MD, PhD[a,*], Aharon G. Freud MD, PhD[a]

Hum Pathol 45: 1730, 2014



Diagnosis	MNDA Positive
NMZL	16 / 24 (66.7%)
EMZL	27 / 44 (61.4%)
SMZL	5 / 21 (23.8%)
CLL/SLL	4 / 31 (12.9%)
MCL	9 / 140 (6.4%)
LPL	2 / 8 (25.0%)
FL	6 / 110 (5.5%)
DLBCL	2 / 61 (3.3 %)

IRTA1 is selectively expressed in nodal and extranodal marginal zone lymphomas

Brunangelo Falini, Claudio Agostinelli,[1] Barbara Bigerna, Alessandra Pucciarini, Roberta Pacini, Alessia Tabarrini, Flavio Falcinelli, Milena Piccioli,[1] Marco Paulli,[2] Marcello Gambacorta,[3] Maurilio Ponzoni,[4] Enrico Tiacci, Stefano Ascani,[5] Maria Paola Martelli, Riccardo Dalla Favera,[6] Harald Stein[7] & Stefano A Pileri[1]

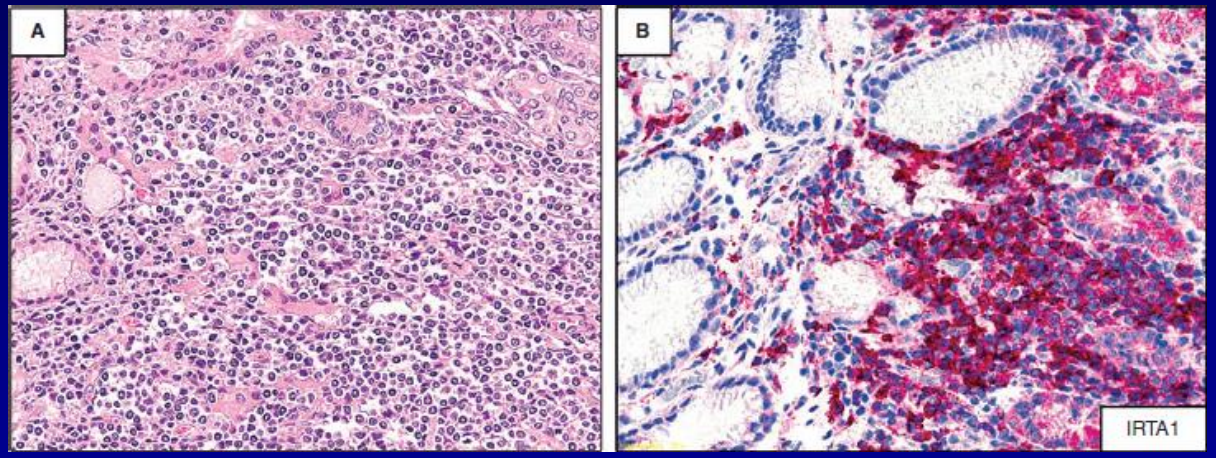
Immunoglobulin superfamily receptor translocation-associated 1

EMZL 307/329 (93%)

NMZL 154/210 (73%)

SMZL 0/21 (0%)

DLBCL 69/256 (27%)



All other B- and T-NHLs are negative for IRTA1

Histopathology 61: 930, 2012

The genetics of nodal marginal zone lymphoma

Valeria Spina,[1,*] Hossein Khiabanian,[2,*] Monica Messina,[3] Sara Monti,[1] Luciano Cascione,[4] Alessio Bruscaggin,[1] Elisa Spaccarotella,[1] Antony B. Holmes,[5] Luca Arcaini,[6] Marco Lucioni,[7] Fabrizio Tabbò,[8] Sakellarios Zairis,[2] Fary Diop,[1] Michaela Cerri,[1] Sabina Chiaretti,[3] Roberto Marasca,[9] Maurilio Ponzoni,[10] Silvia Deaglio,[11] Antonio Ramponi,[12] Enrico Tiacci,[13] Laura Pasqualucci,[5] Marco Paulli,[7] Brunangelo Falini,[13] Giorgio Inghirami,[8,14,15] Francesco Bertoni,[4] Robin Foà,[3] Raul Rabadan,[2] Gianluca Gaidano,[1] and Davide Rossi[1,4]

KMT2D 34%
PTPRD 20%
NOTCH 20%
KLF2 17%

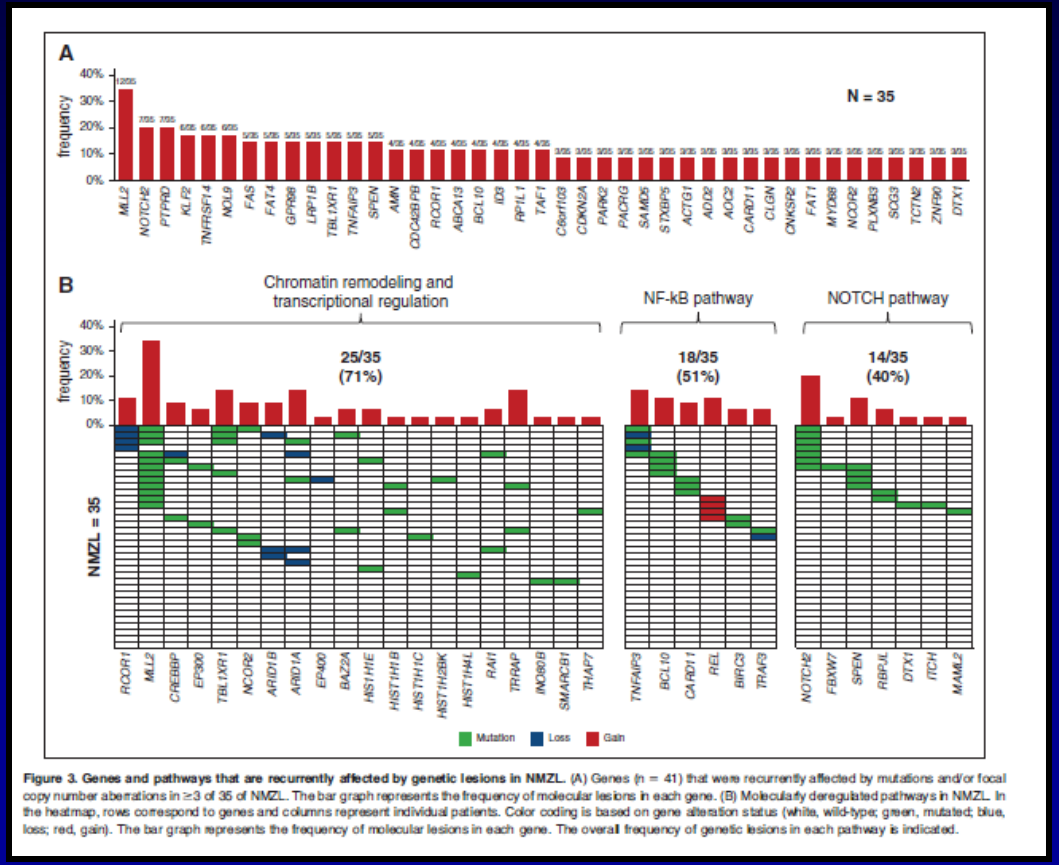


Figure 3. Genes and pathways that are recurrently affected by genetic lesions in NMZL. (A) Genes (n = 41) that were recurrently affected by mutations and/or focal copy number aberrations in ≥3 of 35 of NMZL. The bar graph represents the frequency of molecular lesions in each gene. (B) Molecularly deregulated pathways in NMZL. In the heatmap, rows correspond to genes and columns represent individual patients. Color coding is based on gene alteration status (white, wild-type; green, mutated; blue, loss; red, gain). The bar graph represents the frequency of molecular lesions in each gene. The overall frequency of genetic lesions in each pathway is indicated.

PTPRD mutations are unique to nodal MZL

Blood 128: 1362, 2016

Differential Diagnosis of Nodal MZL

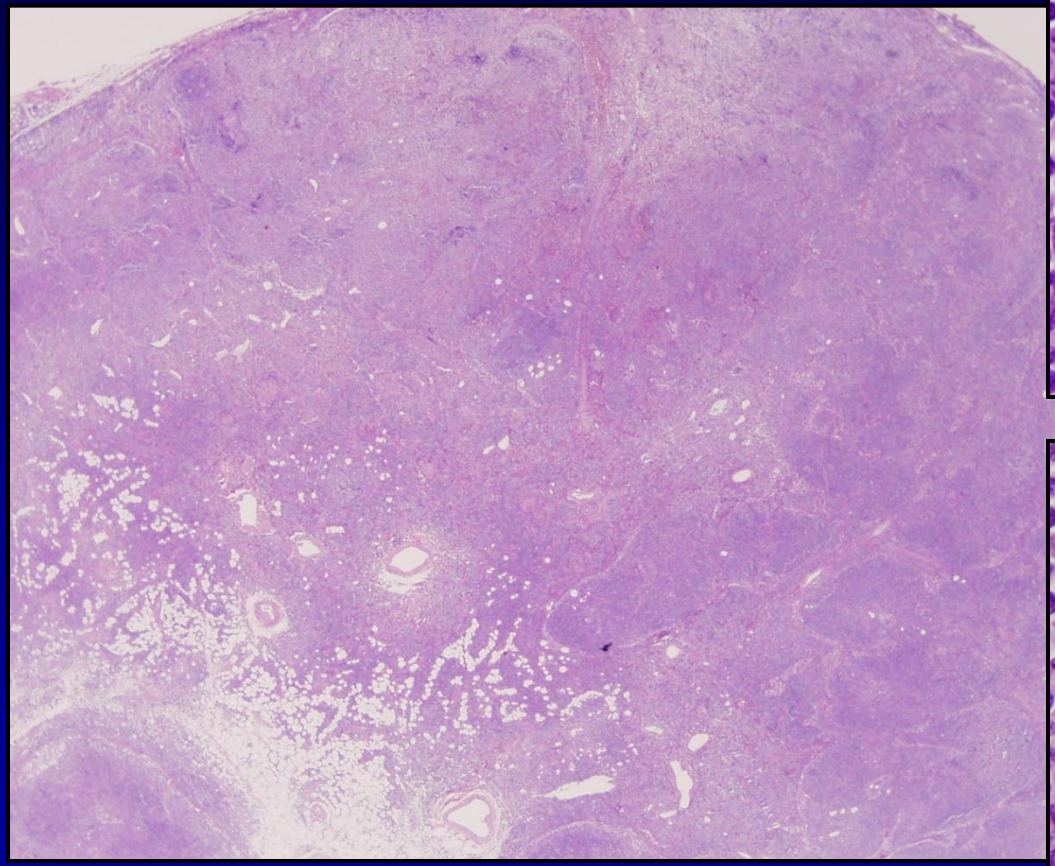
Other types of MZL

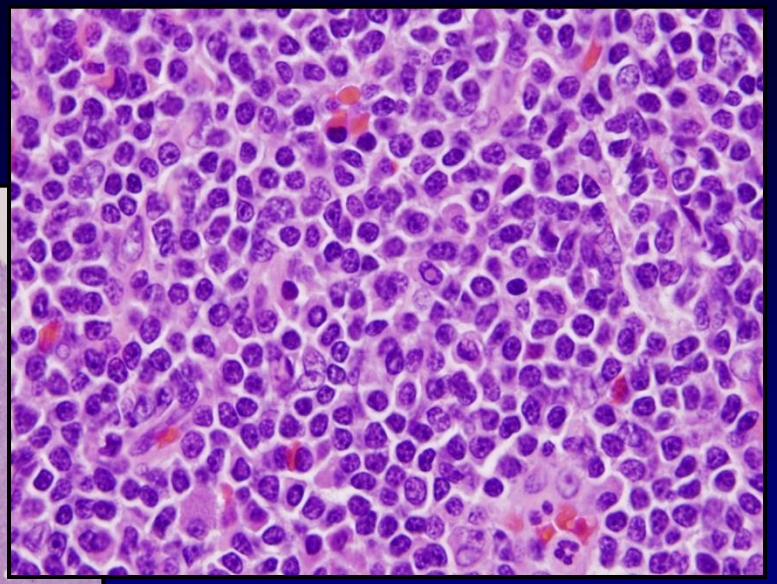
Usually not too difficult because there are extranodal sites or spleen

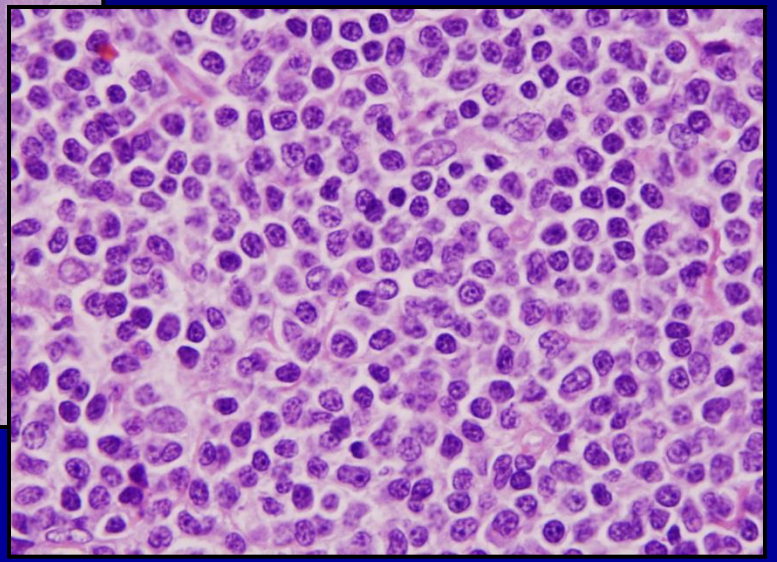
Lymphoplasmacytic lymphoma/Waldenstrom

Follicular Lymphoma

Lymphoplasmacytic Lymphoma/ Waldenstrom Macroglobulinemia





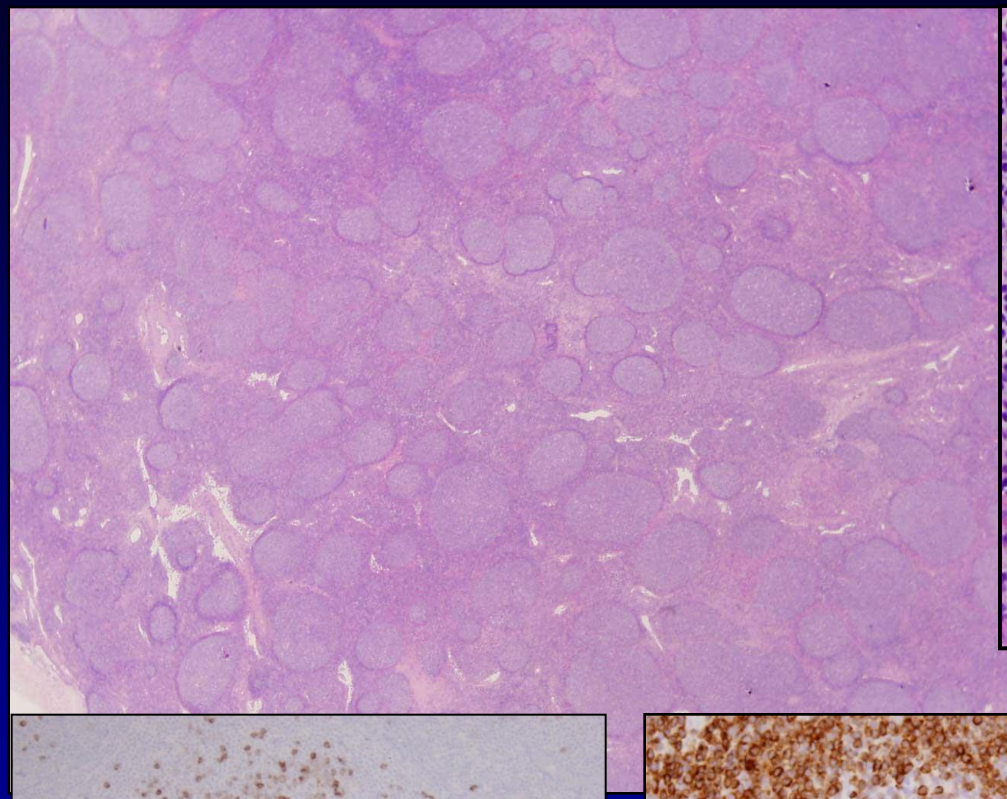


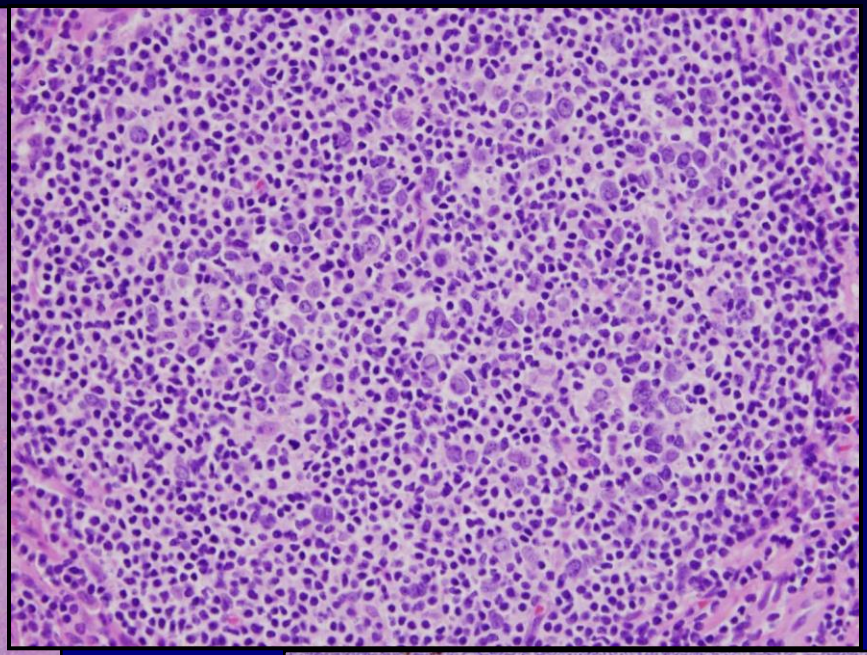
Nodal MZL versus LPL/WM

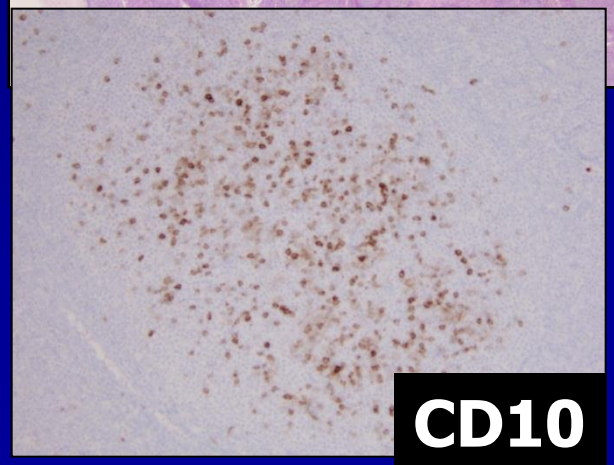
Feature	Nodal MZL	LPL/WM
Serum IgM	~ 5-10% pts	100% of WM
Bone marrow +	30-40% of pats	100%
Distribution	Cortical	Medullary
Sinuses	Often effaced	Usually patent
Follicles	Large, reactive	Usually small
Cell cytoplasm	Pale (monocytoid)	Darker (purple)
Dutcher bodies	Uncommon	Common
IRTA1, MNDA	+/-	Negative
MYD88 L265P	Very rare	>90%

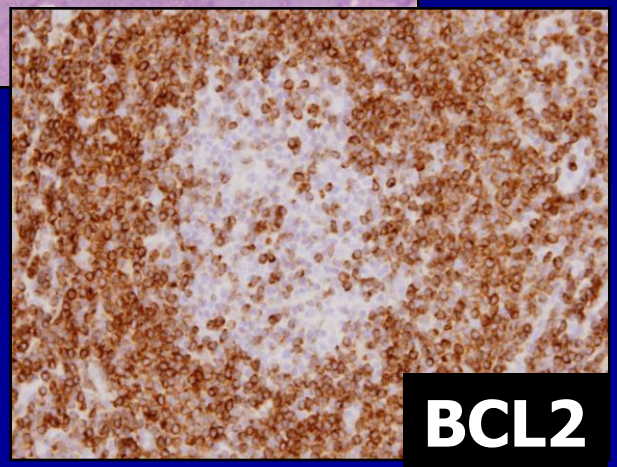
Nodal Marginal Zone Lymphoma

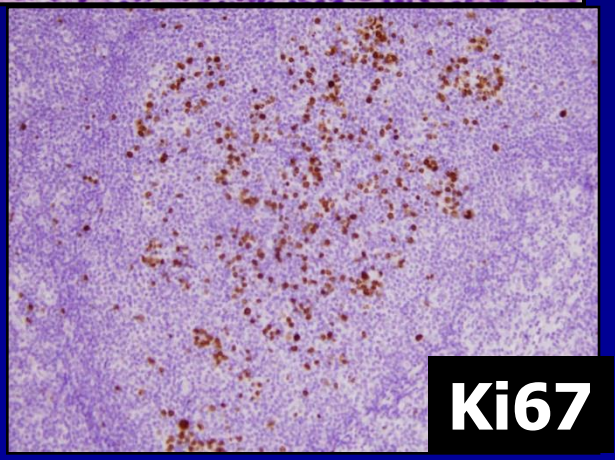
Can Colonize Follicles and mimic FL









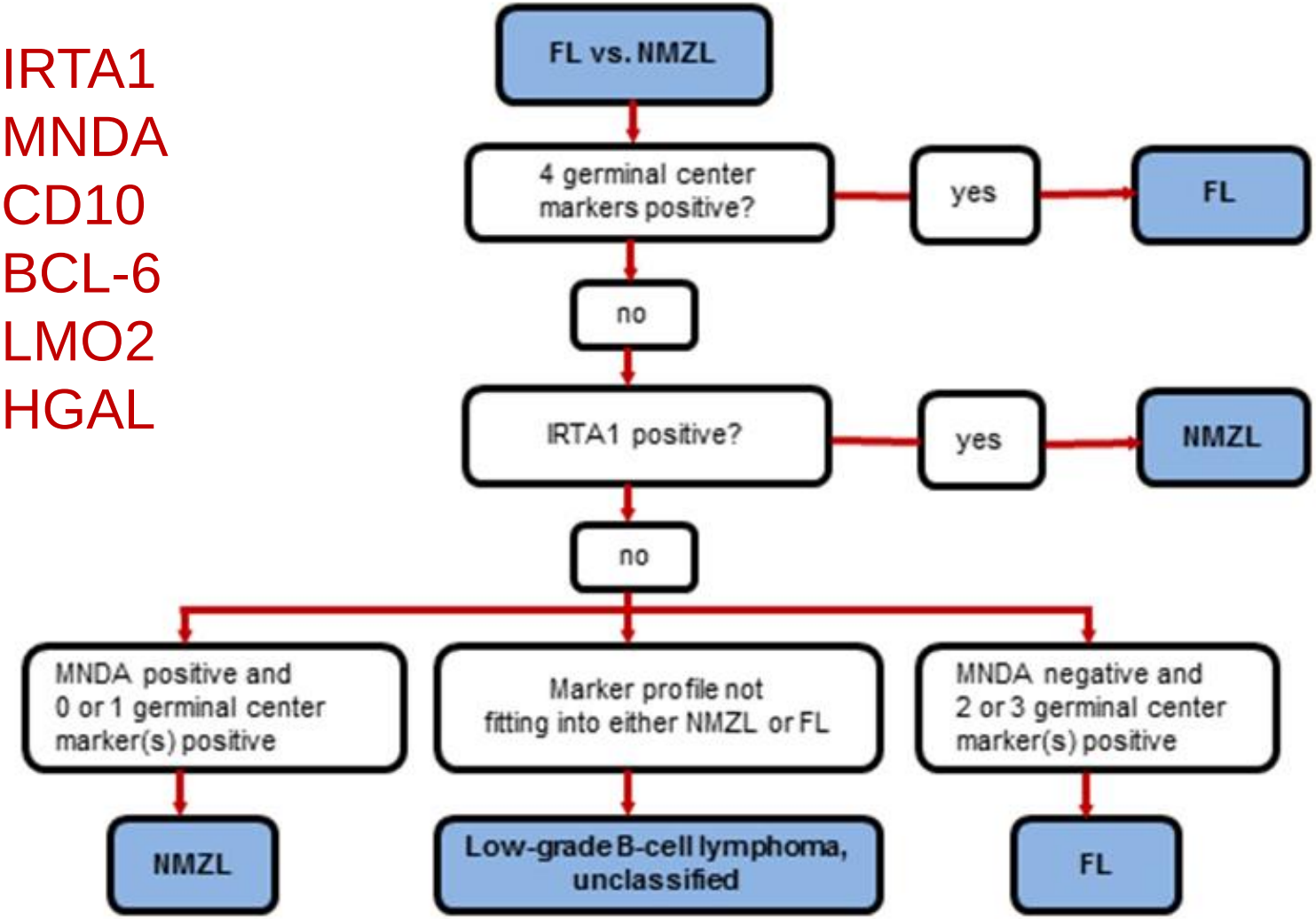


Nodal MZL with Follicular Colonization versus FL

Feature	Nodal MZL	Follicular Lymphoma
Distribution of follicles	Confined to lymph node	Extend into perinodal fat
Growth pattern	Tumor begins outside follicle and grows in	Tumor begins in follicle and grows out
Cytology	Often rounder cells +/- plasm differentiation	Centrocytes/centroblasts Plasm diff is rare
Cell cytoplasm	Pale (pink)	Darker (blue)
CD10/BCL6	Germinal centers+ Tumor cells-	+/-
BCL-2	Germinal centers - Tumor cells+	+/-
Ki-67	Germinal centers high Tumor low	Usually low (unless grade 3 FL)
IGH-BCL2	Absent	Present

Follicular Lymphoma vs Nodal MZL

IRTA1
MNDA
CD10
BCL-6
LMO2
HGAL



Brand and Van Krieken, Haematologica 100: e359, 2015

Nodal MZL versus Follicular Lymphoma
Does It Matter Clinically?

Patients with FL have

- Higher stage
- More frequent BM +
- More abdominal LNs +
- More frequent transformation to DLBCL

FL usually transforms to DLBCL of GCB type
NMZL usually transforms to DLBCL of non-GCB type

May not matter much for patient at diagnosis
Few therapeutic implications
Does have prognostic meaning

Leuk Lymphoma 57: 1649, 2016

Clues to Diagnosis of Nodal MZL

No extranodal sites of disease

Adundant pale cytoplasm

Marginal zone distribution

Dutcher bodies (many)

Appropriate B-cell immunophenotype

CD20+, CD5-, CD10-, BCL6-, cyclin D1-

IRTA1+ and MDNA+

NMZL is often a diagnosis of exclusion

There is overlap with lymphoplasmacytic lymphoma

Splenic Marginal Zone Lymphoma
Clinical Features

Median Age	**65 years**
Symptoms	**Fatigue** **Abdominal discomfort** **May be asymptomatic**
Laboratory	**33 % paraprotein** **10% autoimmune phenomena** **? association with hepatitis C**

Splenic Marginal Zone Lymphoma

Characteristic Disease Distribution

Spleen and hilar lymph nodes

Abdominal lymph nodes

Bone marrow (80-90%)

Peripheral blood ±

Liver ±

Splenic Marginal Zone Lymphoma
Pathologic Findings

Spleen

- Usually massive
- Red and white pulp
- ± Plasmacytoid differentiation

Bone marrow

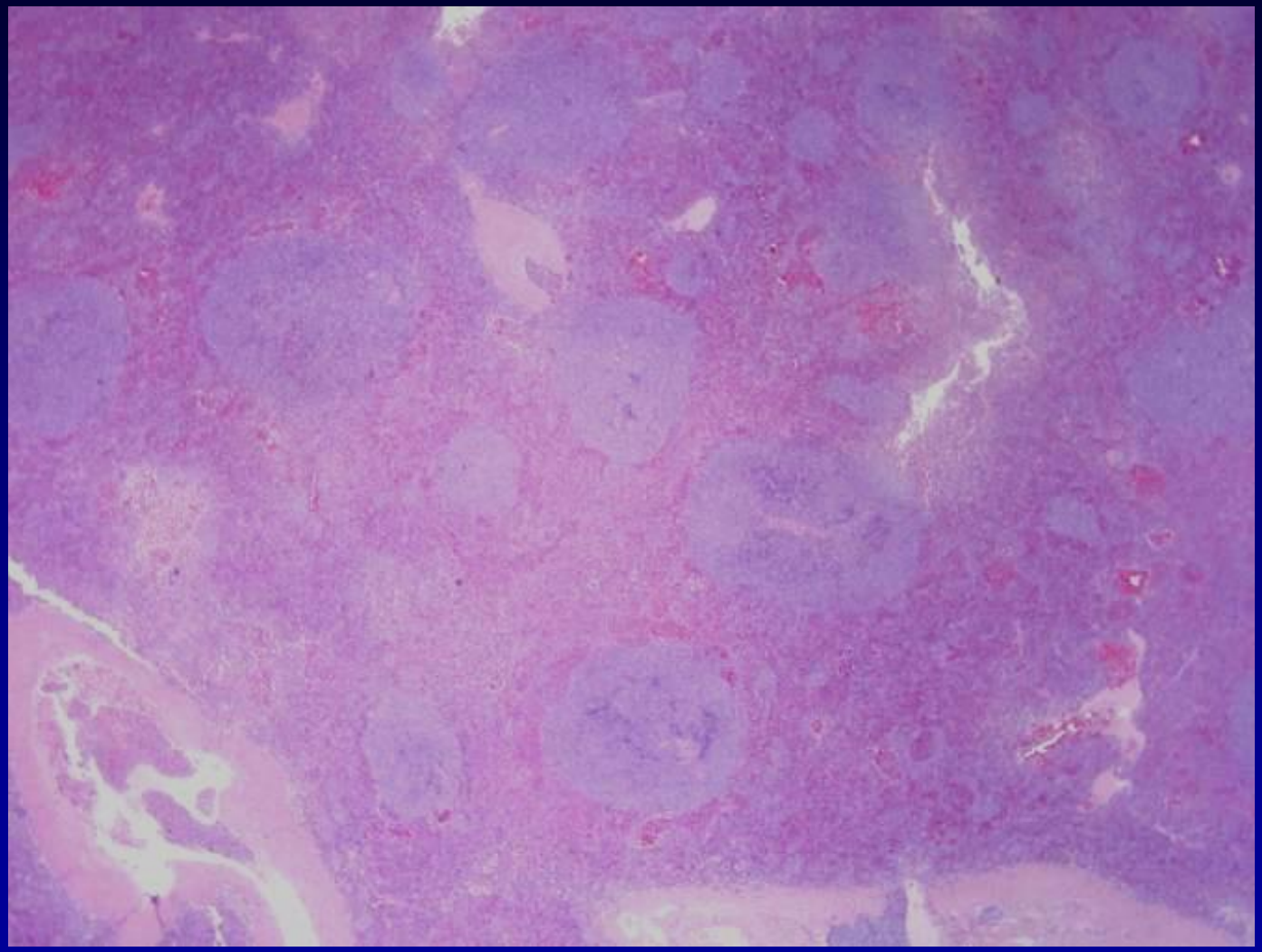
- Paratrabecular and non-paratrabecular
- ± Germinal centers
- ± Intrasinusoidal (~33%)

Peripheral blood

- ± Villous lymphocytes

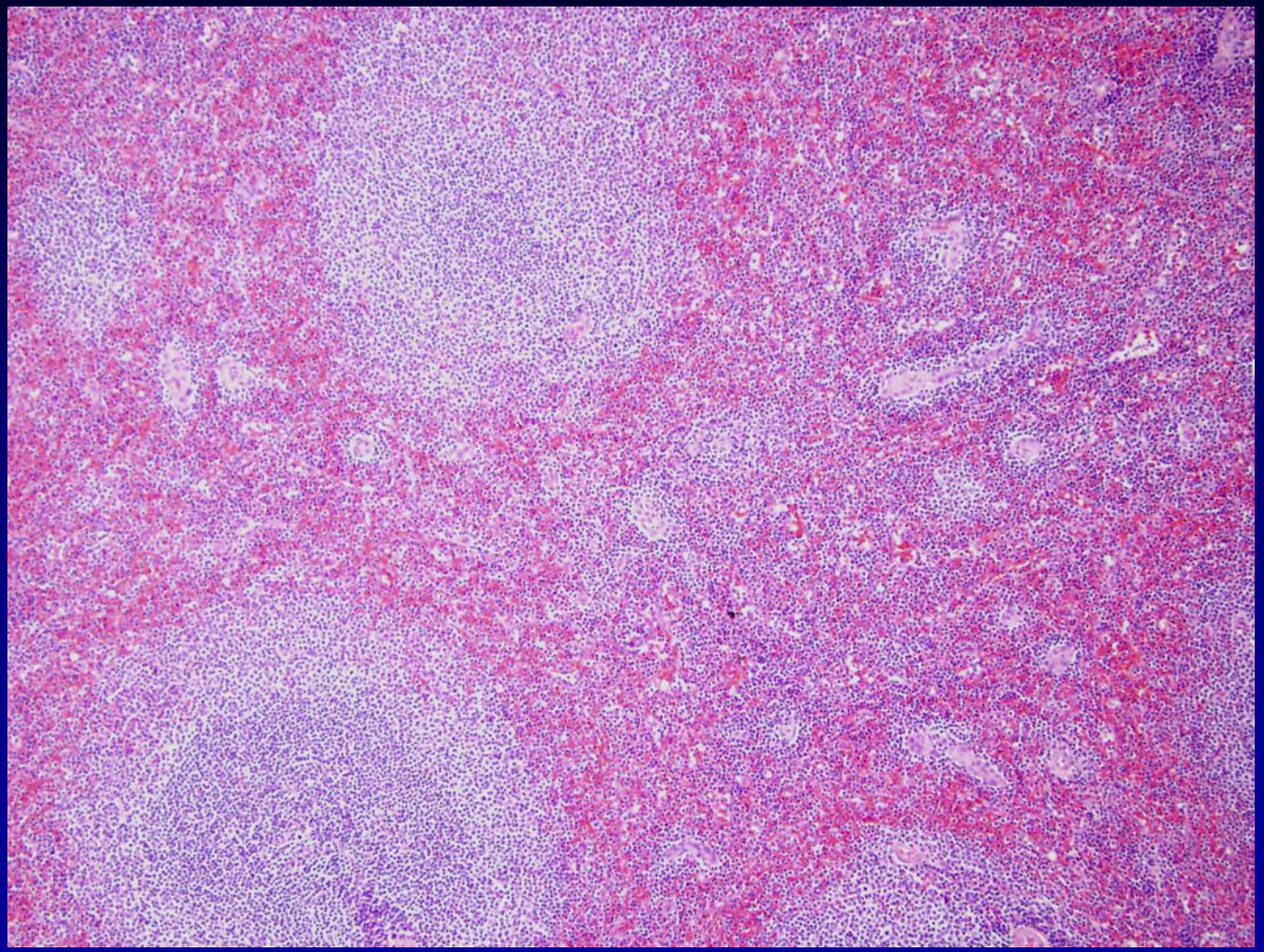
Splenic Marginal Zone Lymphoma

Spleen



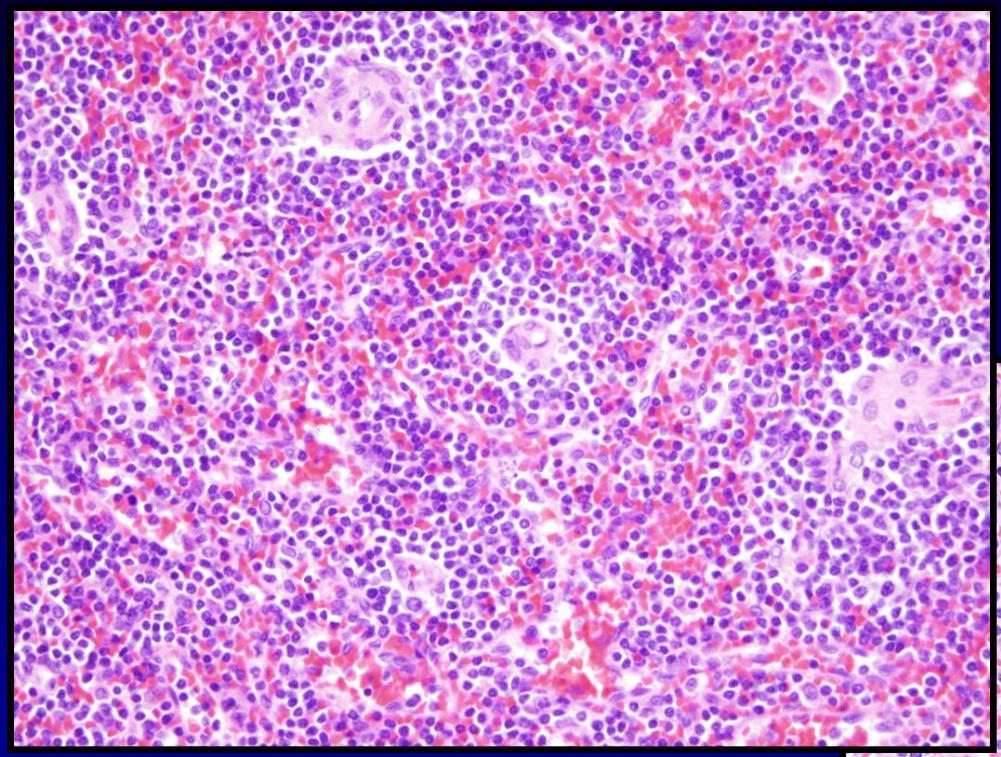
Splenic Marginal Zone Lymphoma

Spleen

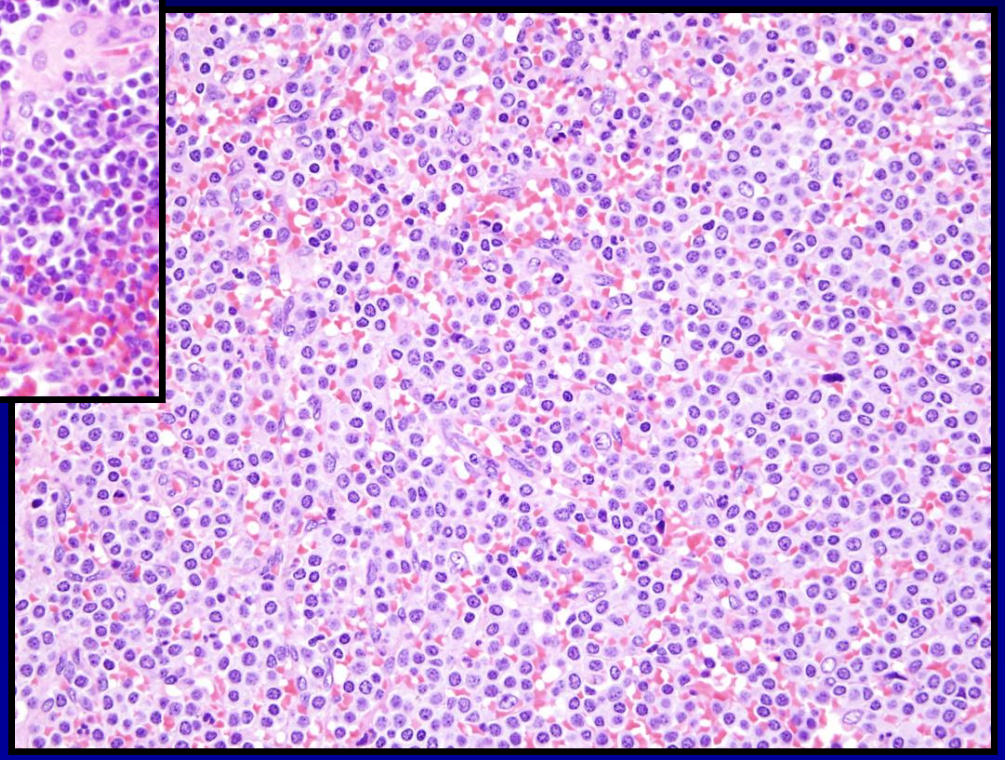


Splenic Marginal Zone Lymphoma

Splenic Red Pulp



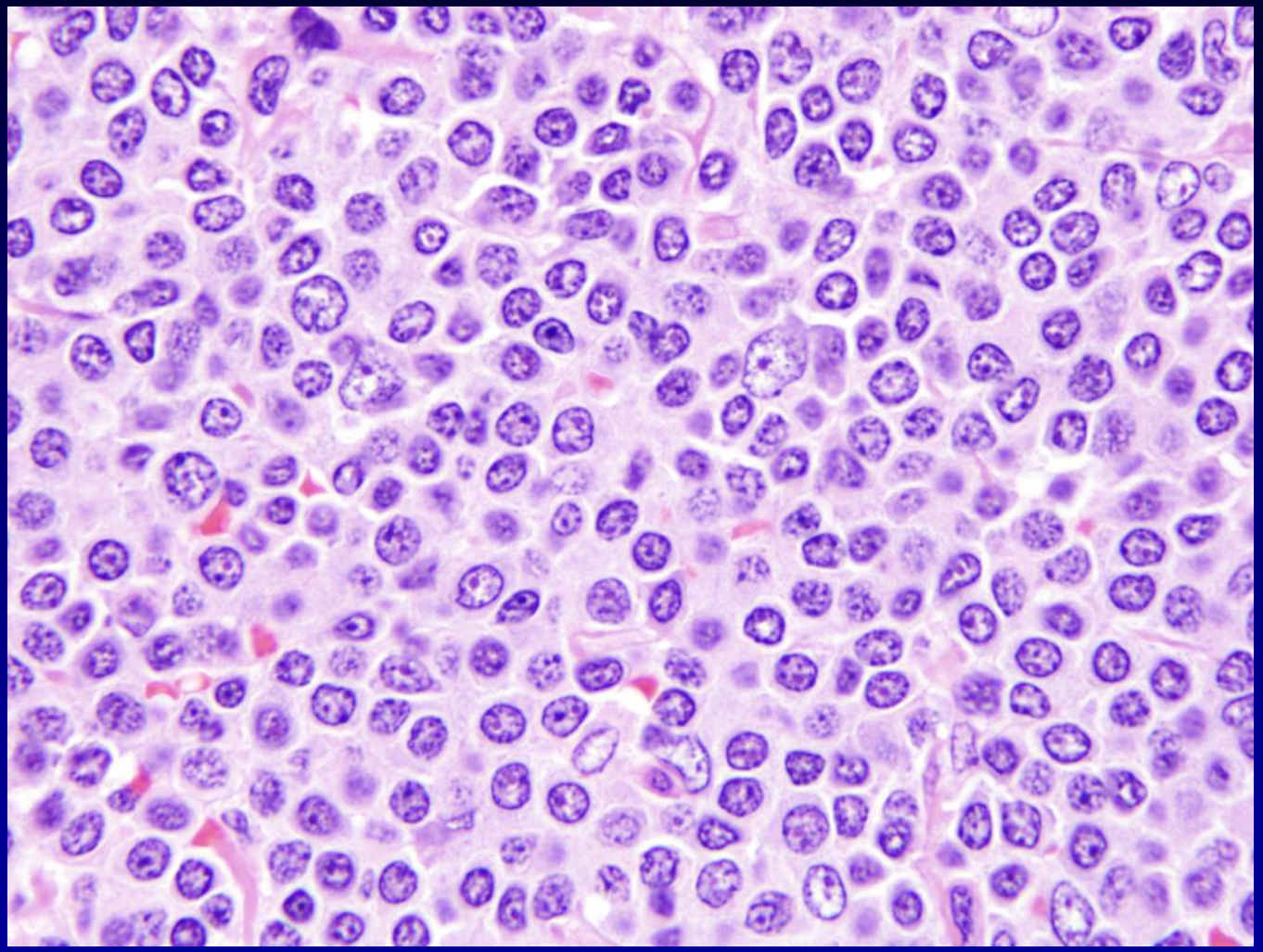
⇦ Partial



Extensive ⇨

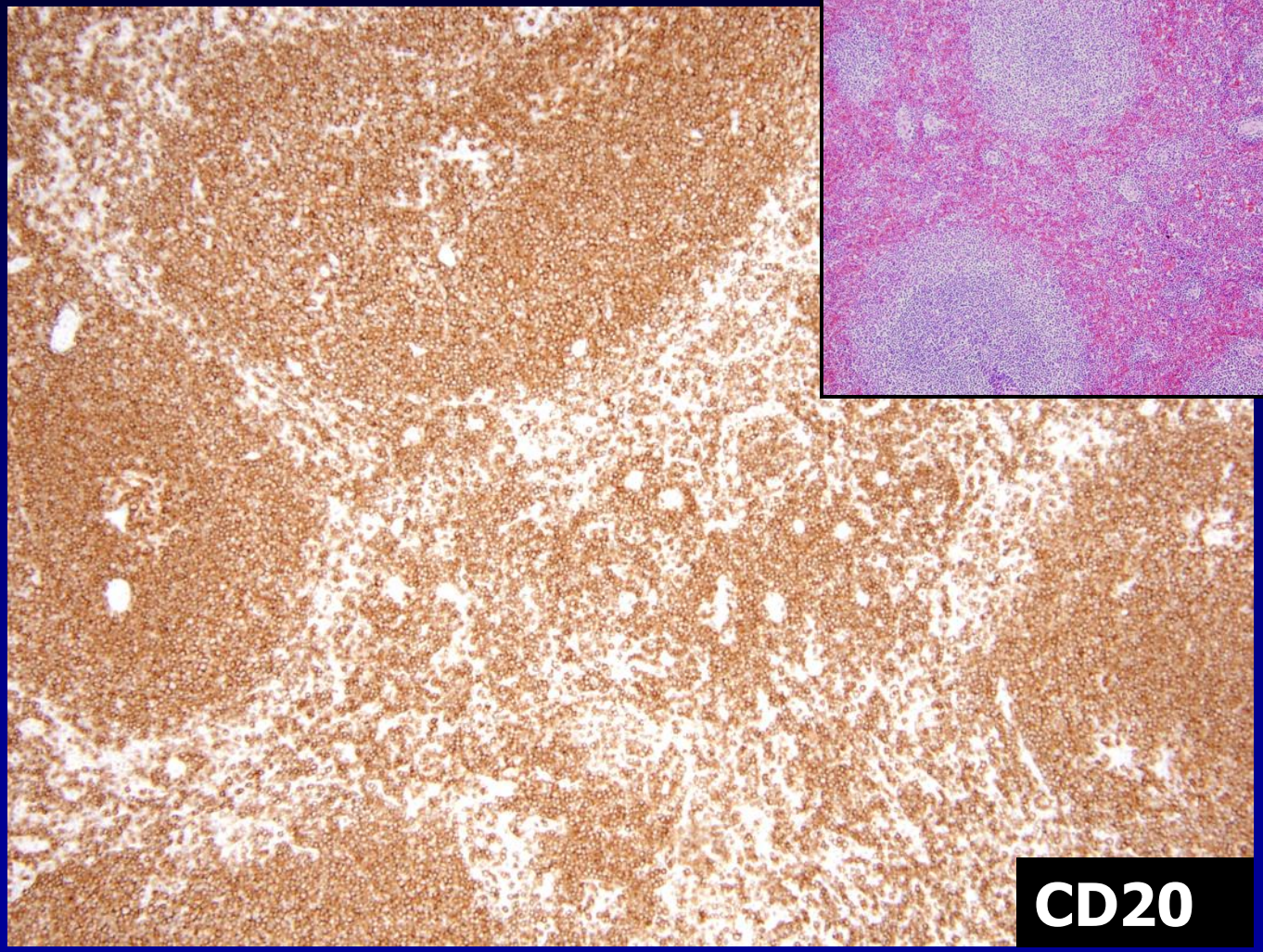
Splenic Marginal Zone Lymphoma

Cytologic Features



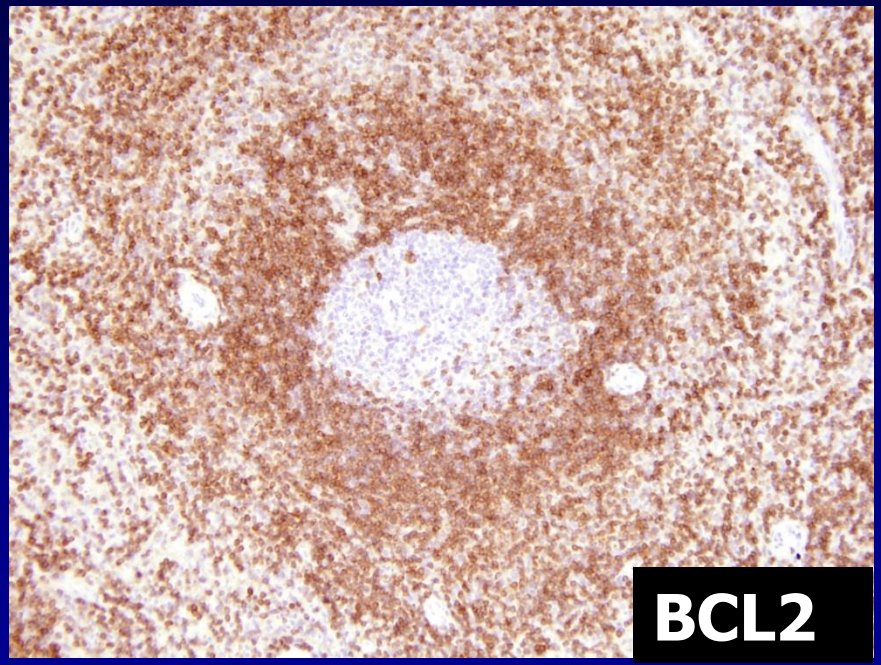
Splenic Marginal Zone Lymphoma

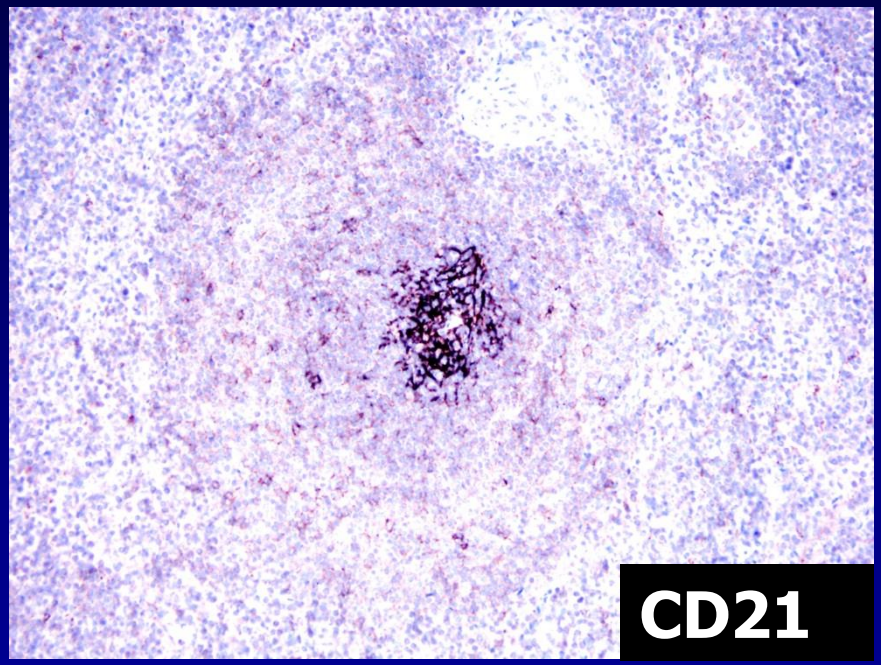
Spleen



Splenic Marginal Zone Lymphoma

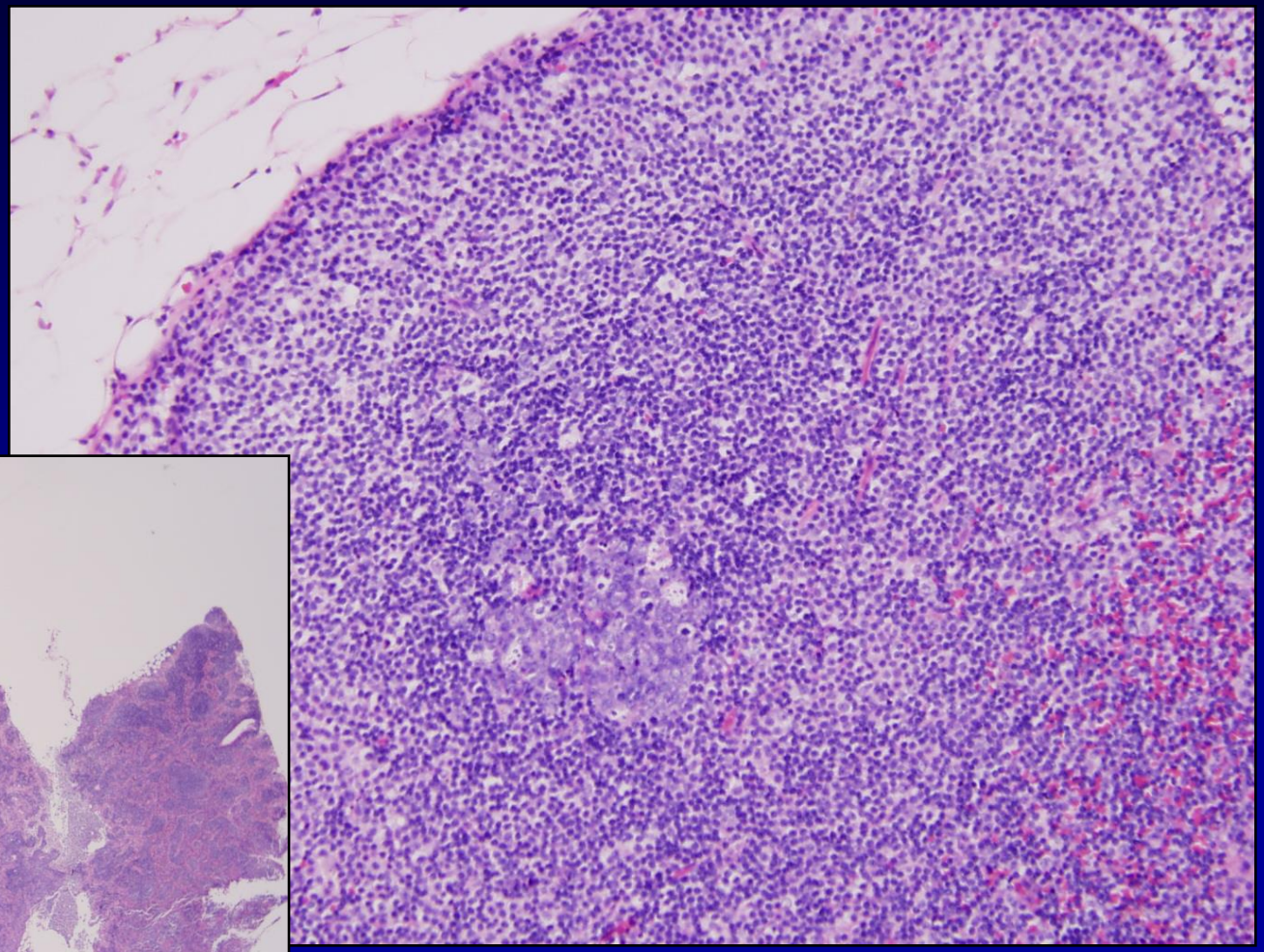
Splenic White Pulp

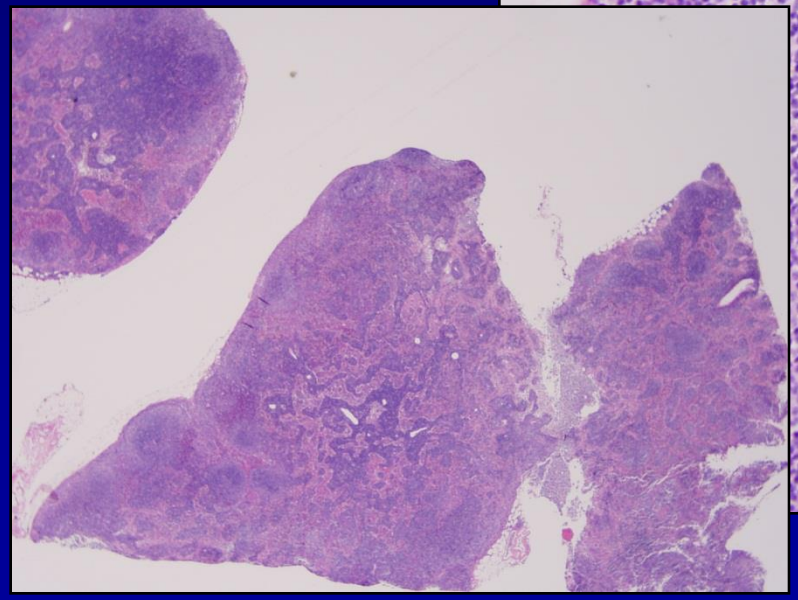




Splenic Marginal Zone Lymphoma

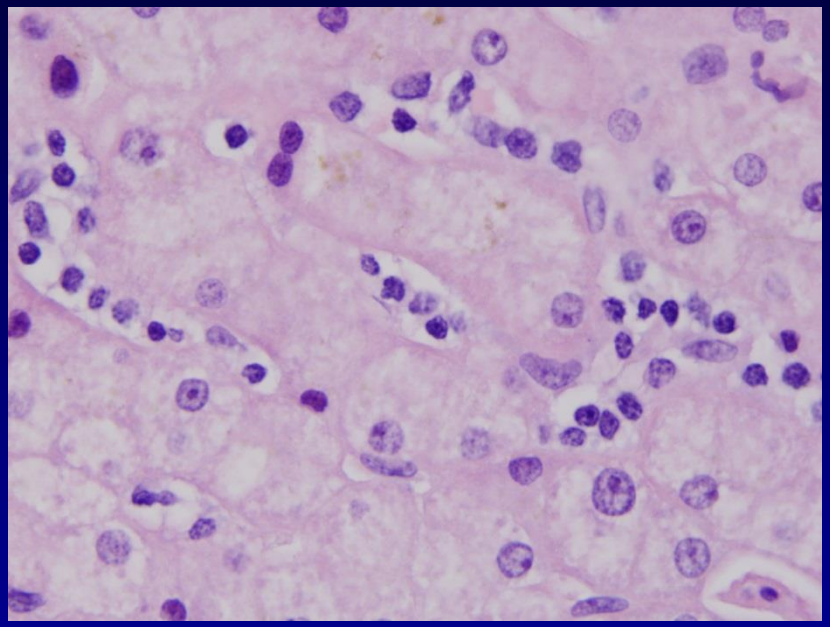
Lymph Node



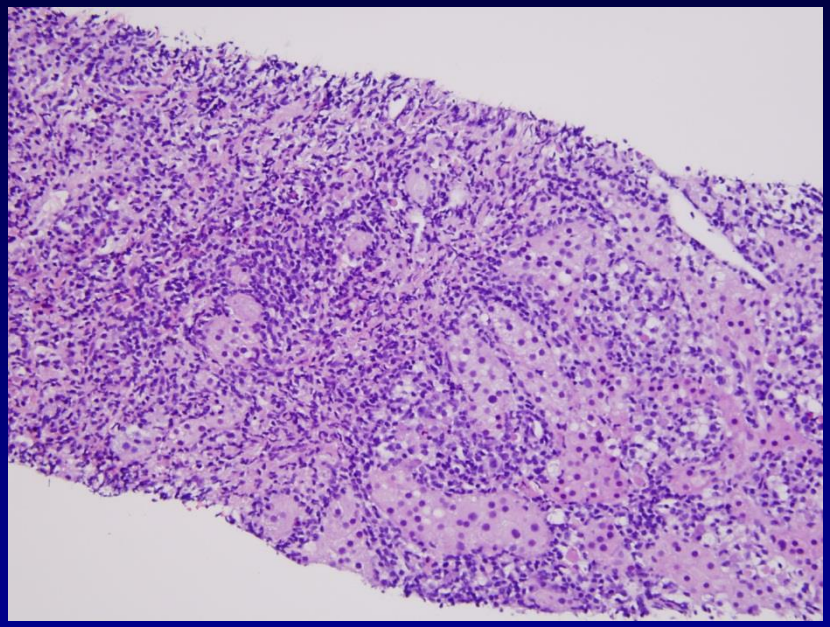


Splenic Marginal Zone Lymphoma

Liver – 2 Examples



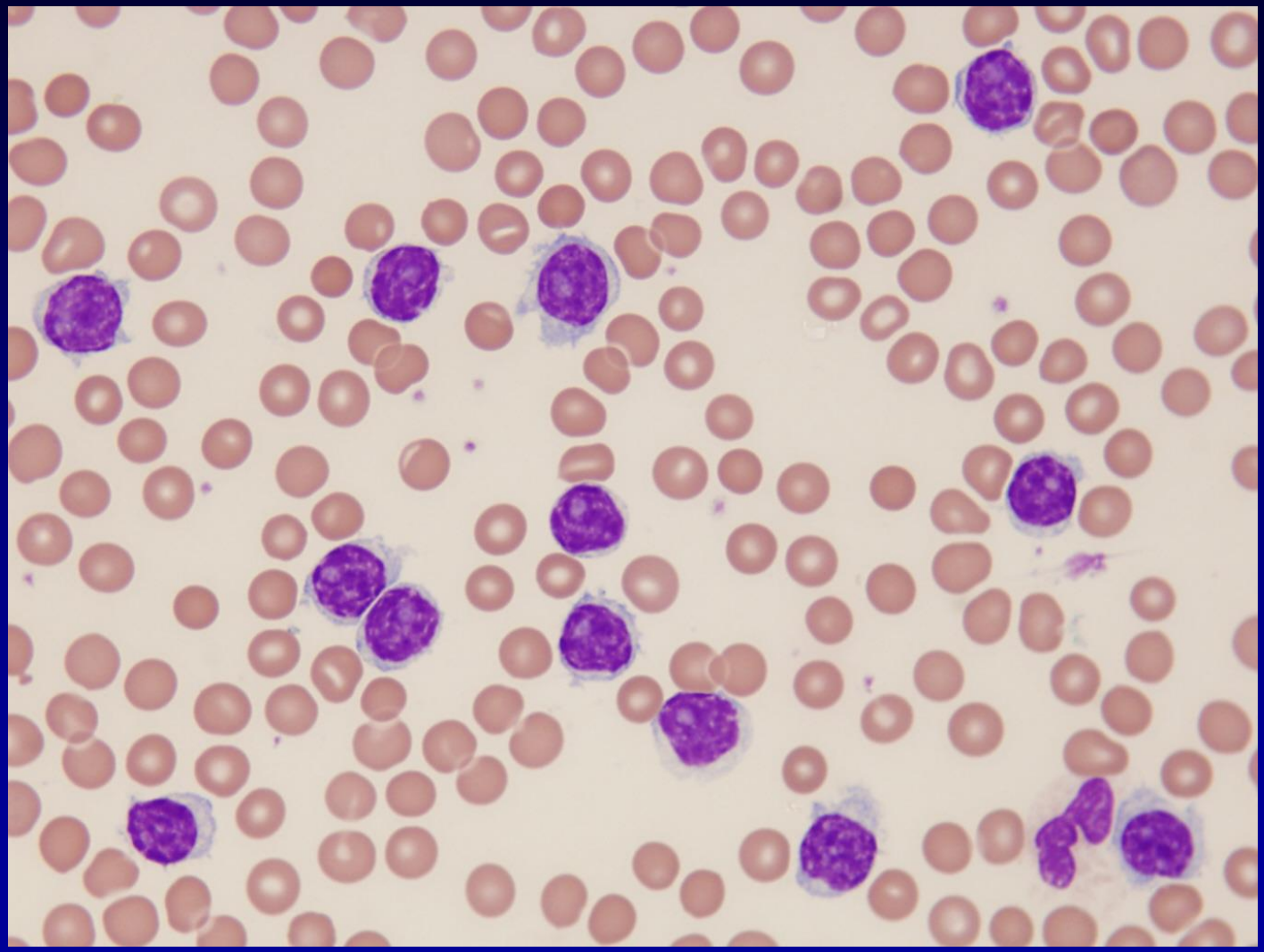
Sinusoidal



Extensive

Splenic Marginal Zone Lymphoma

Peripheral Blood Smear



Splenic Marginal Zone Lymphoma

Immunophenotype

Ipox CD20+, PAX5+, BCL2+, annexin A1-

Flow sIg+ (bright), IgM+, IgD+ (most)
CD11c+, CD5 -/+, CD23 -/+,
CD10-, CD25-

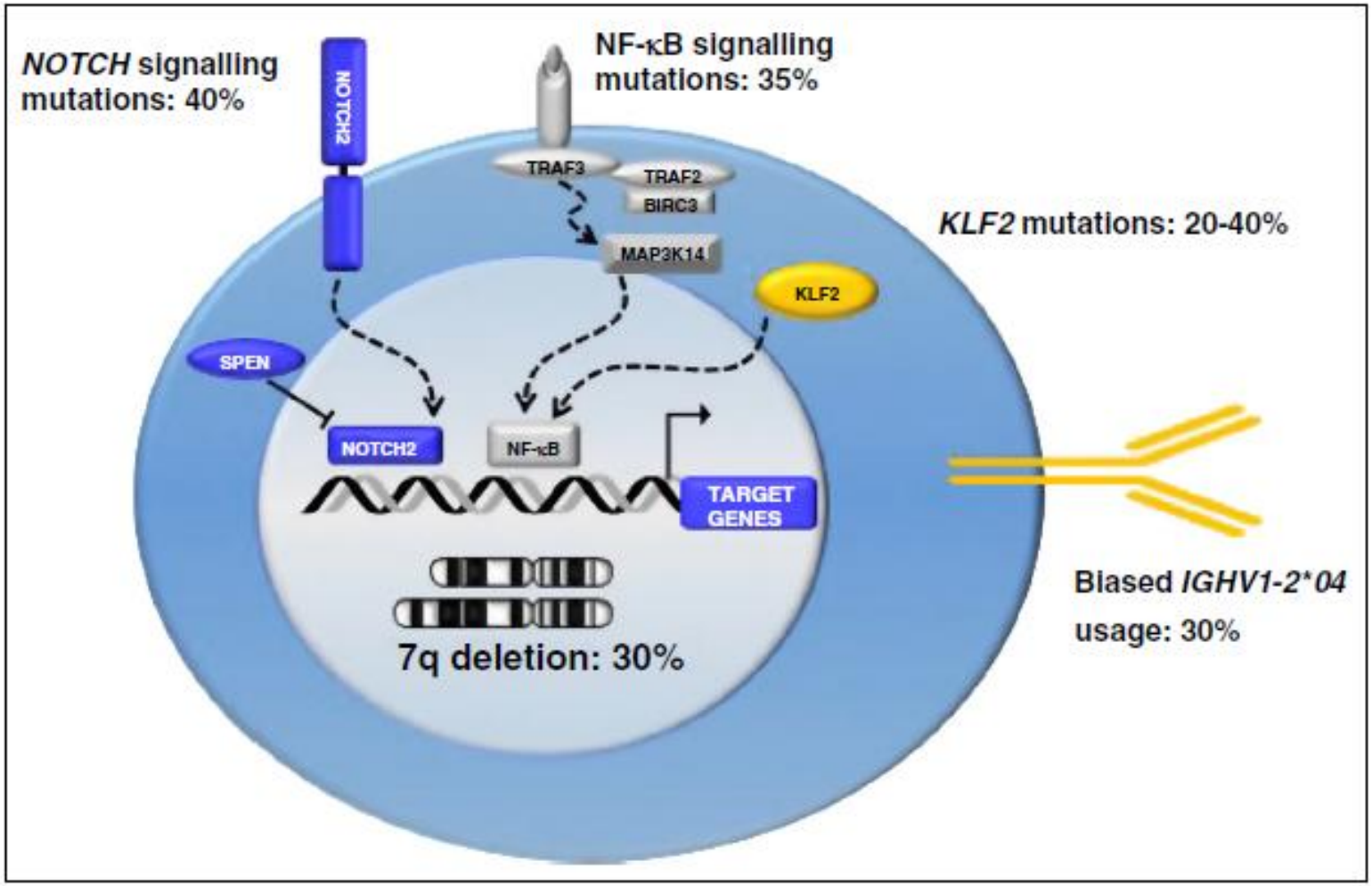
Cytogenetics

Deletion 7q/7q31-32	40-50 %
Trisomy 3	15-35 %

Molecular

Biased use of IgH variable genes (IgHV1-2)

Splenic Marginal Zone Lymphoma
Common Mutations



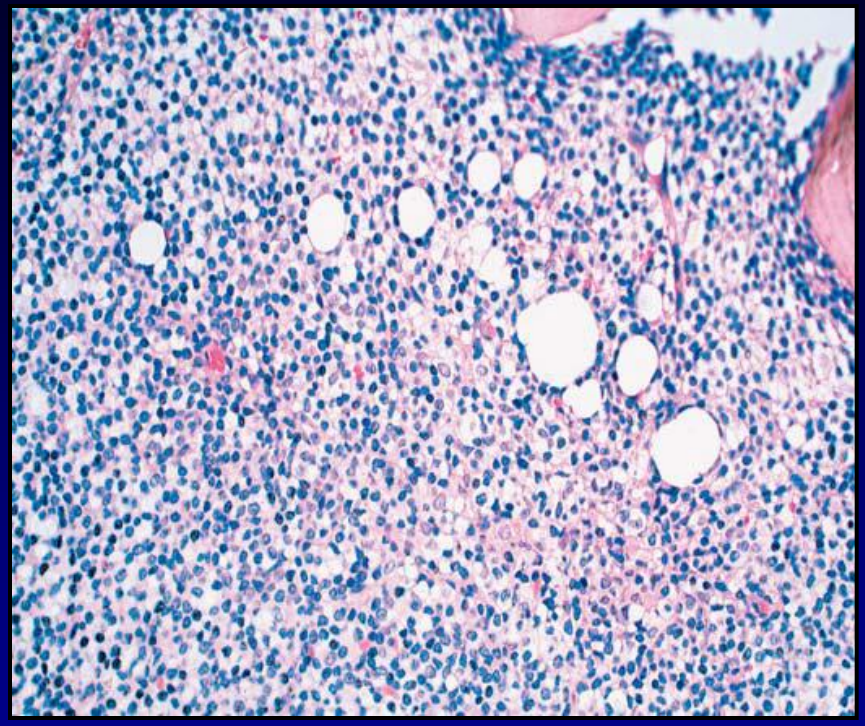
Blood 127: 2072, 2016

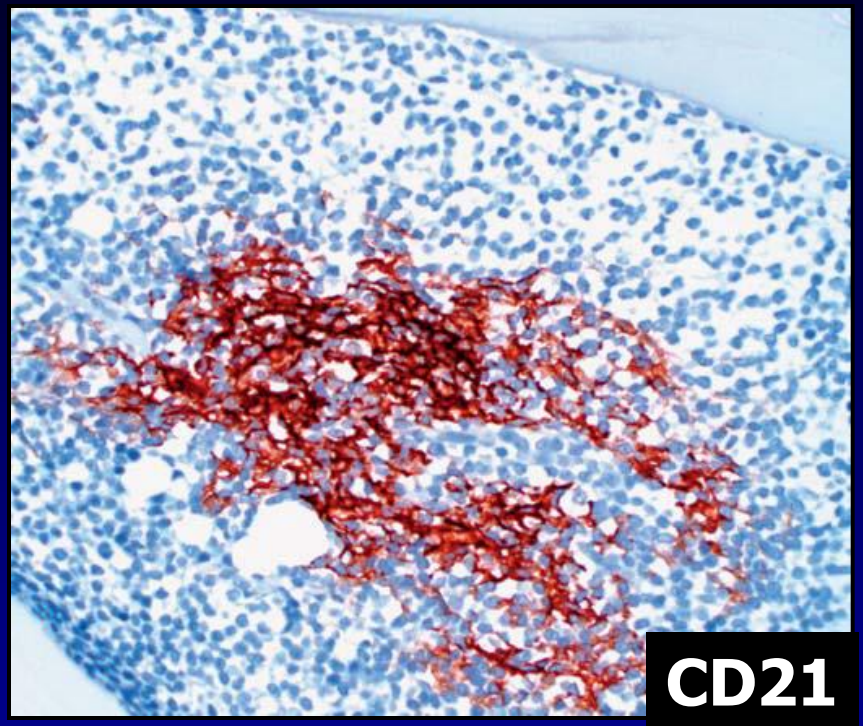
Splenic Marginal Zone Lymphoma

Differential Dx with Other Splenic Lymphomas

	SMZL	HCL	HCL-V	SDRPL
Age (yrs)	62	55	71	77
M/F	0.5	5	1.6	1.6
Lymphocytosis	+/-Moderate	No	High	Moderate
Monocytopenia	No	Severe	No	No
Survival (yrs)	10	12	9	10
Pattern	White pulp	Red pulp	Red pulp	Red pulp
Nucleolus	Small	No	Moderate or large	Large +/-
CD25	Variable	Bright	Dim or Neg	Dim
CD103	Neg	Bright	~ 60% dim	30%
Cyclin D3	Neg	Neg	Neg	Positive
Annexin A1	Neg	Positive	Neg	Neg
BRAF	Neg	Positive	Neg (MAP2K1)	Neg

Can We Diagnose MZL by Bone Marrow Only?



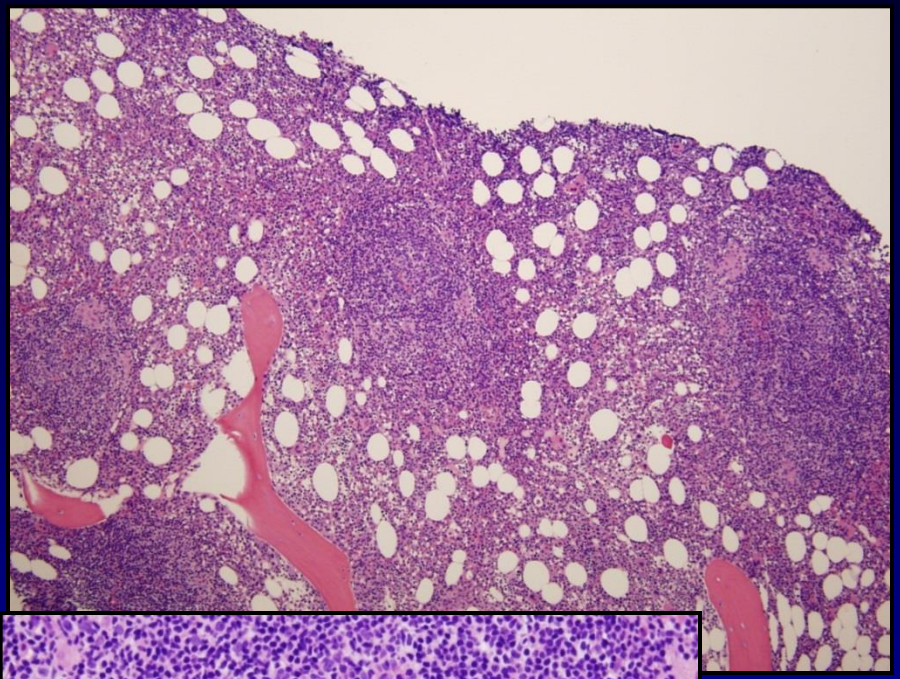


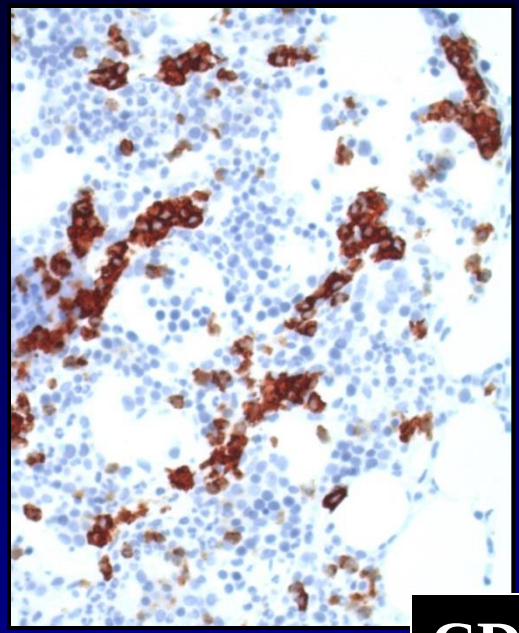
MZLs in bone marrow are usually associated with follicular dendritic cells (CD21+ and/or CD23+)

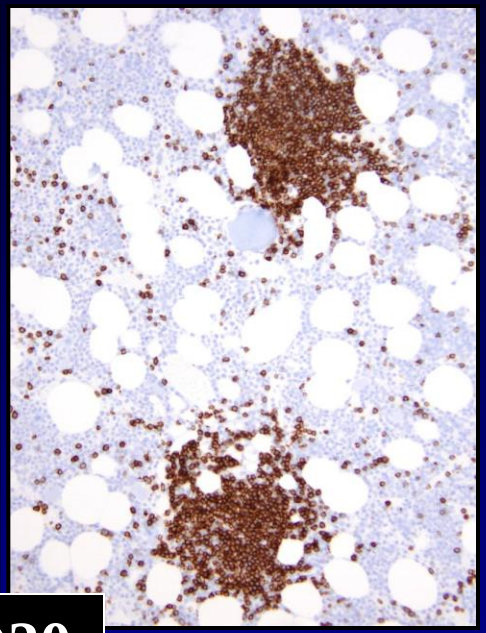
Extranodal and nodal MZL are indistinguishable

Splenic Marginal Zone Lymphoma

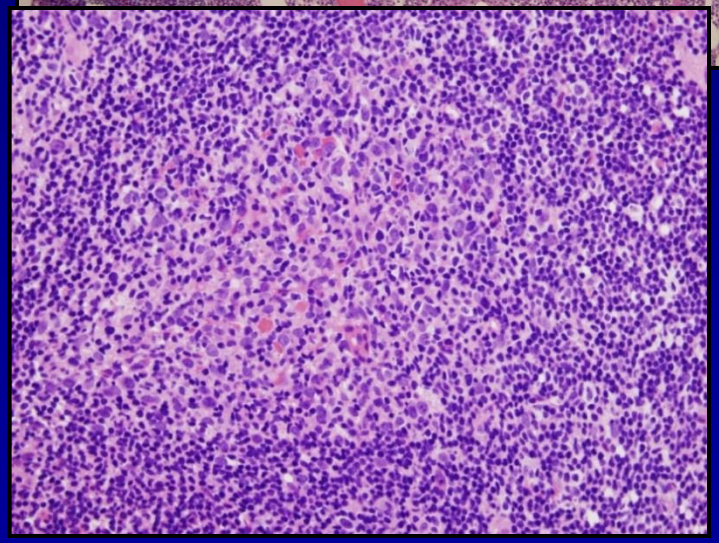
Bone Marrow





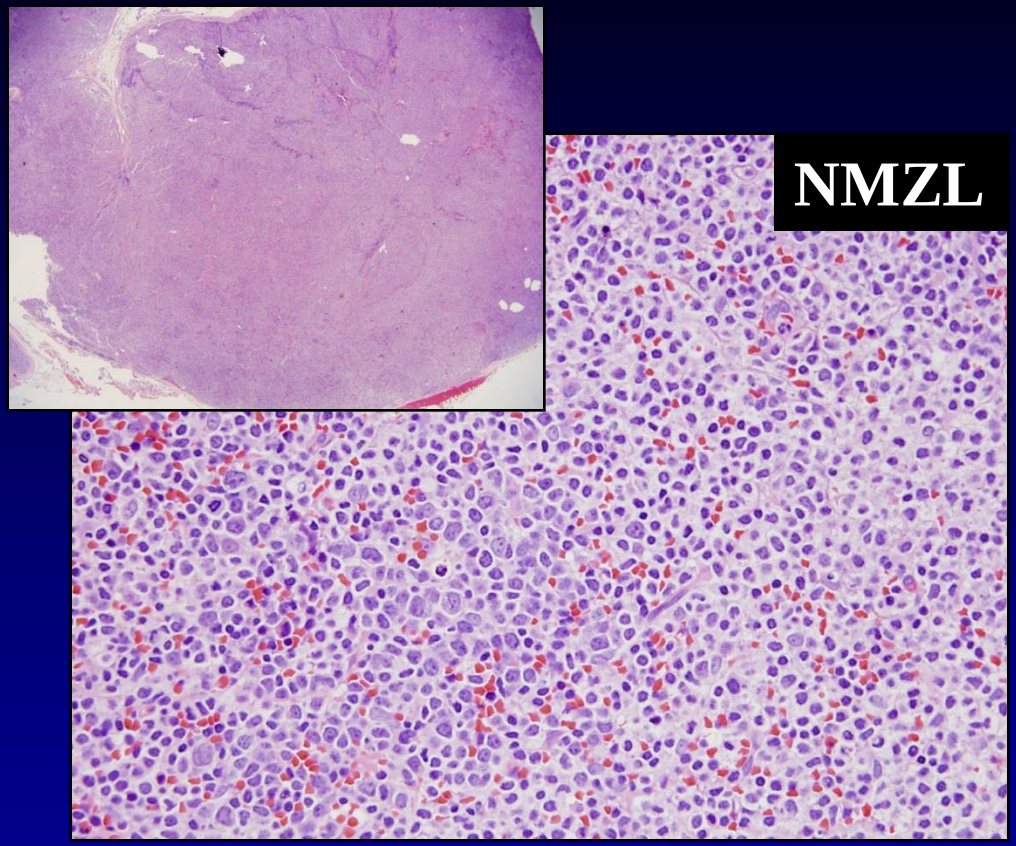


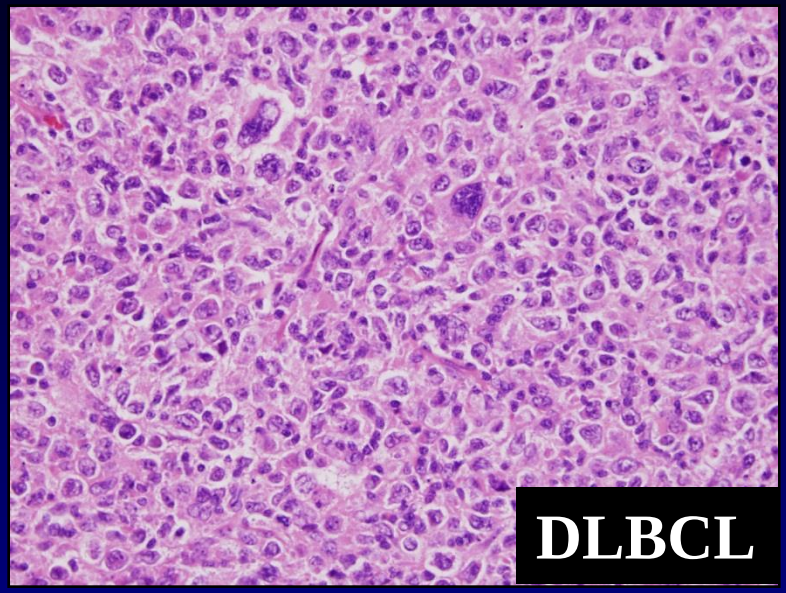
CD20



Support for SMZL	Frequency
GCs	10%
Sinusoidal pattern	33%
CBC abnormalities	70%

Criteria for large cell transformation in MZL?





16 months later

Sheets of large cells are best and perhaps only criterion

Otherwise be conservative

Ki67 and p53 can be helpful