



Indolent Lymphoma Workshop

May 15-16, 2017

**Bologna
Royal Hotel Carlton**

MARGINAL ZONE LYMPHOMA

9.30 a.m. Histopathology and biology
Chairmen: S.A. Pileri, M. Ponzoni

Histology

Biology and molecular genomics
Somatic mutations and mechanisms

S.A. Pileri
D. Rossi
M.Q. Du



IEO
Istituto Europeo
di Oncologia



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ISTITUTO DI EMATOLOGIA
"L. e A. SERAGNOLI"



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DIPARTIMENTO DI EMATOLOGIA, ONCOLOGIA
EMATOLOGICA E SPERIMENTALE



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Disclosures of STEFANO A. PILERI

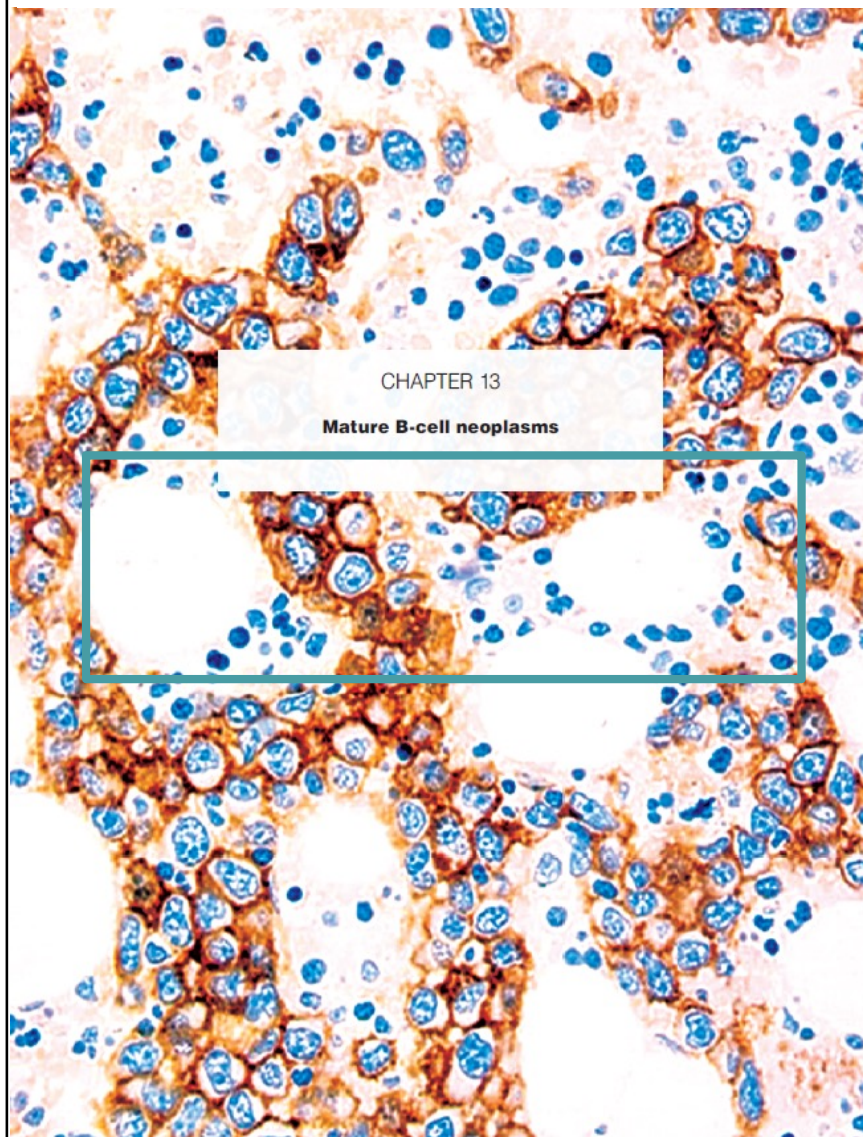
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	None	No	No	No	Yes	Yes	None

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,¹ Elias Campo,² Stefano A. Pileri,³ Nancy Lee Harris,⁴ Harald Stein,⁵ Reiner Siebert,⁶ Ranjana Advani,⁷ Michele Ghielmini,⁸ Gilles A. Salles,⁹ Andrew D. Zelenetz,¹⁰ and Elaine S. Jaffe¹¹

¹Division of Hematopathology, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; ²Department of Pathology, Hospital Clinic, University of Barcelona, August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain; ³Haematopathology Unit, European Institute of Oncology, Milan, and Department of Experimental, Diagnostic and Specialty Medicine, Bologna University Medical School, Bologna, Italy; ⁴Department of Pathology, Harvard Medical School and Massachusetts General Hospital, Boston, MA; ⁵Pathodiagnostik, Berlin, Germany; ⁶Institute of Human Genetics, Christian Albrechts University Kiel, Kiel, Germany; ⁷Division of Oncology, Department of Medicine, Stanford University, Stanford, CA; ⁸Department of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; ⁹Department of Hematology, Hospices Civils de Lyon, and Université Claude Bernard Lyon-1, Lyon, France; ¹⁰Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; and ¹¹Hematopathology Section, Laboratory of Pathology, National Cancer Institute, Bethesda, MD



Splenic marginal zone lymphoma

Piris M.A.	Pittaluga S.
Isaacson P.G.	Rossi D.
Swerdlow S.H.	Harris N.L.
Thieblemont C.	

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

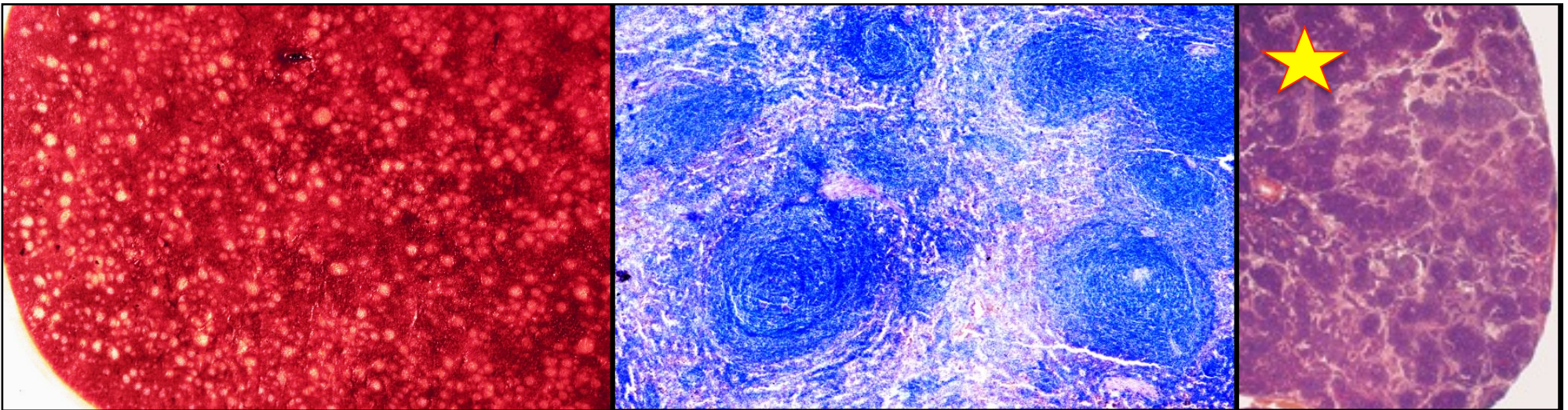
Cook J.R.	Müller-Hermelink
Isaacson P.G.	H.K.
Chott A.	Harris N.L.
Nakamura S.	Swerdlow S.H.

Nodal marginal zone lymphoma

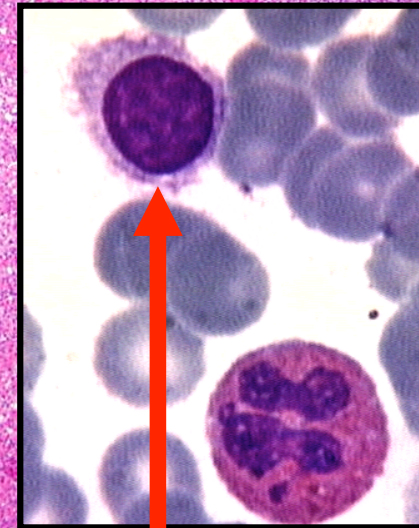
Campo E.	Nathwani B.N.
Pileri S.A.	Stein H.
Jaffe E.S.	
Müller-Hermelink	
H.K.	

Splenic Marginal Zone Lymphoma

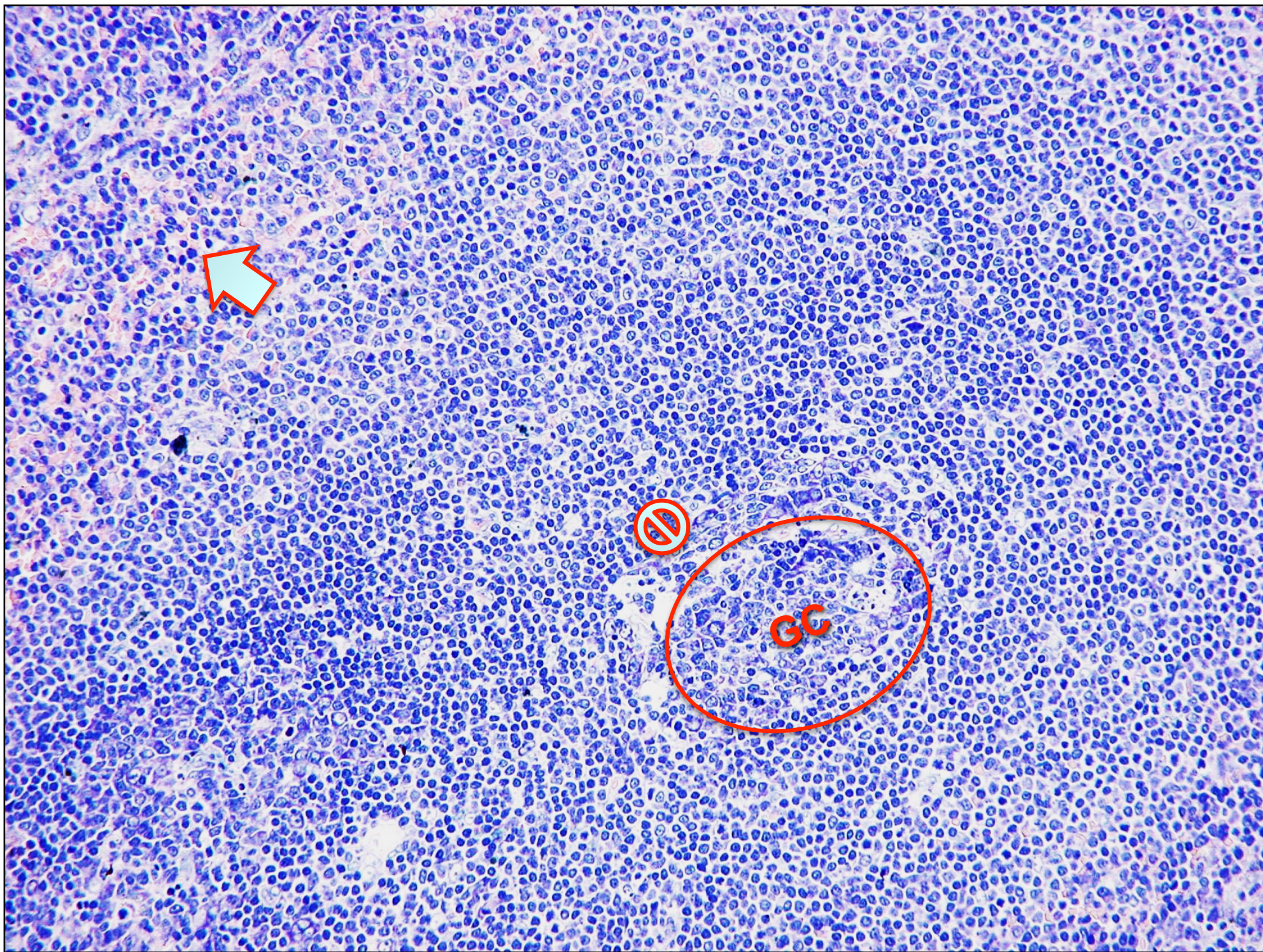
- **Less than 2% of lymphoid neoplasms.**
- **Mostly in patients over 50 (M/F=1/1).**
- **Splenomegaly and leukaemic spread.**
- **Thrombocytopenia or anemia, serum M-component in one third of patients.**
- **Possible association with HCV infection (Southern Europe).**

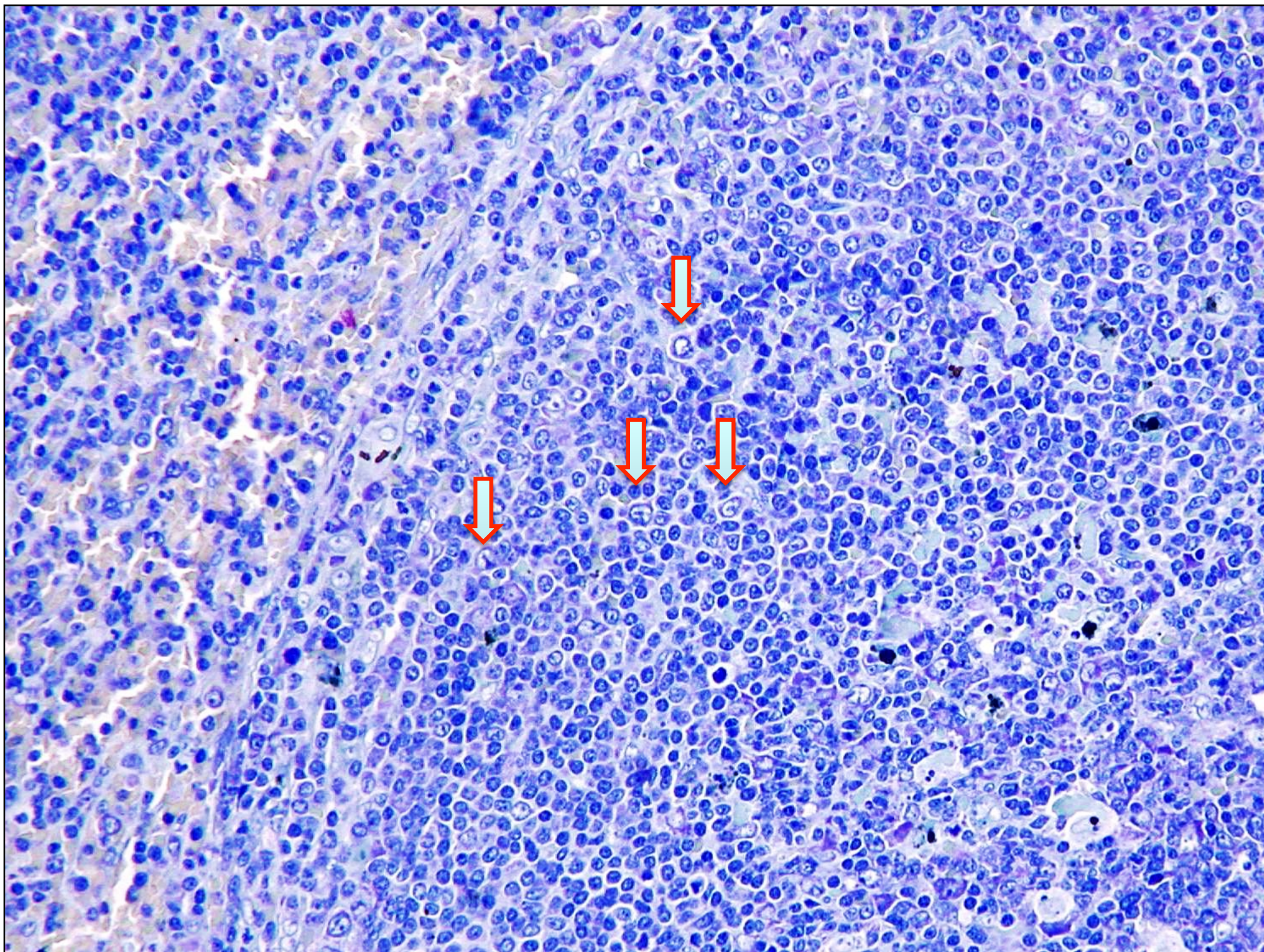


Nodular
Interstitial
Intrasinusoidal



Villous Lymphocytes





SMZL transformation

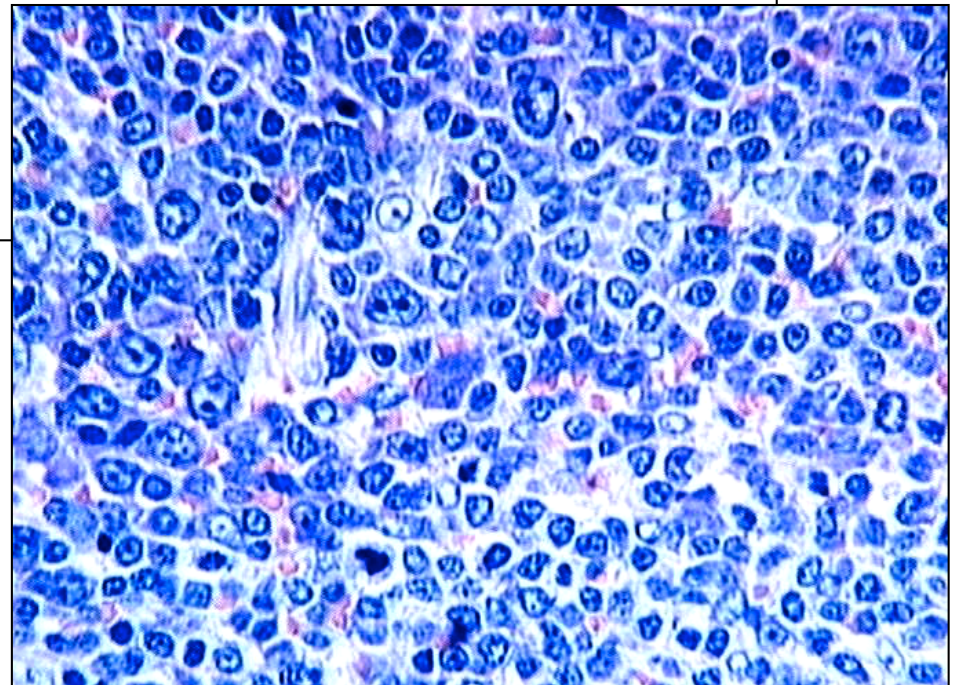
Observed in 10-15% of cases > DLBCL secondary
High proliferation rate

TP53 (*NOTCH2*, *KLF2*) mutations

7q del

Loss +3

Translocations at 7p22-q22
and 19p13



Phenotype

CD20⁺, CD79a⁺, IgM⁺/IgD⁺, Ig light chain restriction⁺, IRF4⁺

MNDA⁺, DBA44^{+variable}, IRTA1⁻, T-bet⁻, CD103⁻

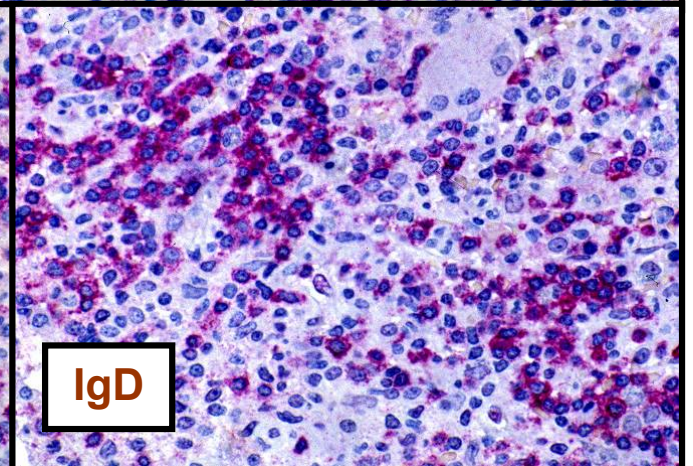
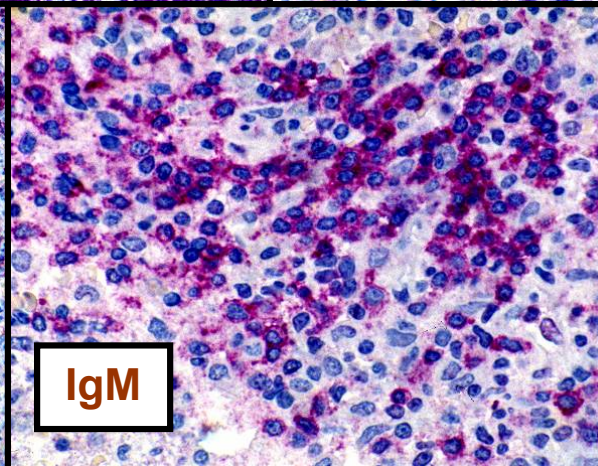
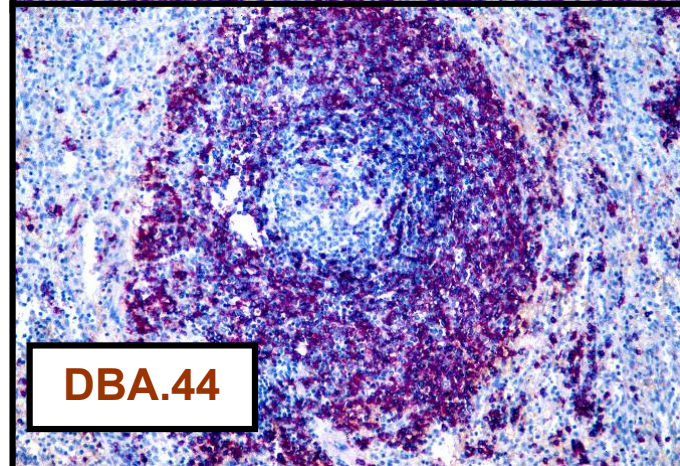
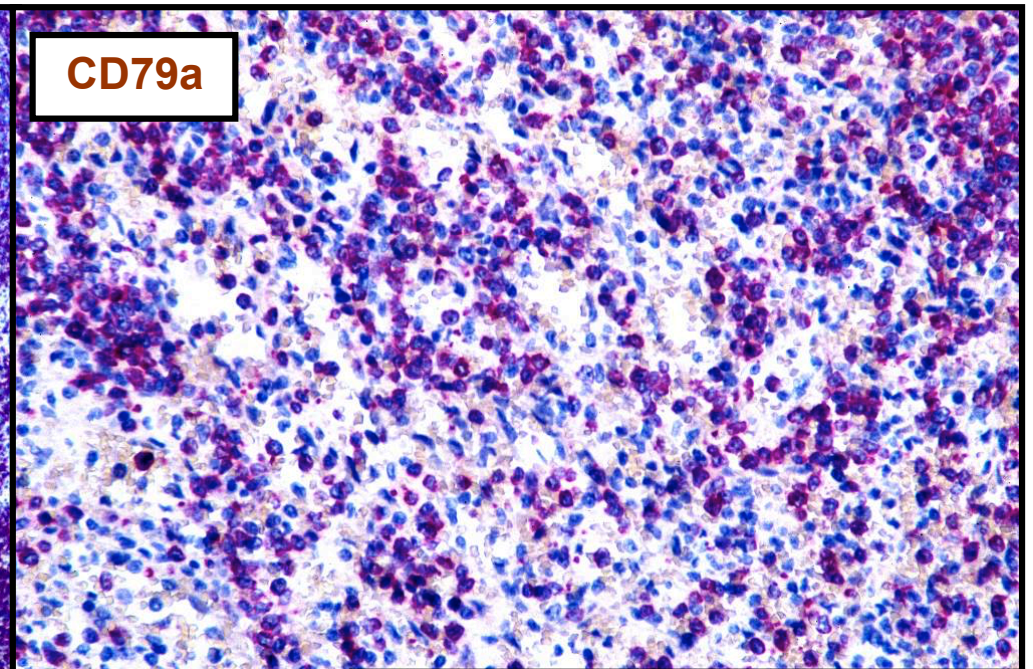
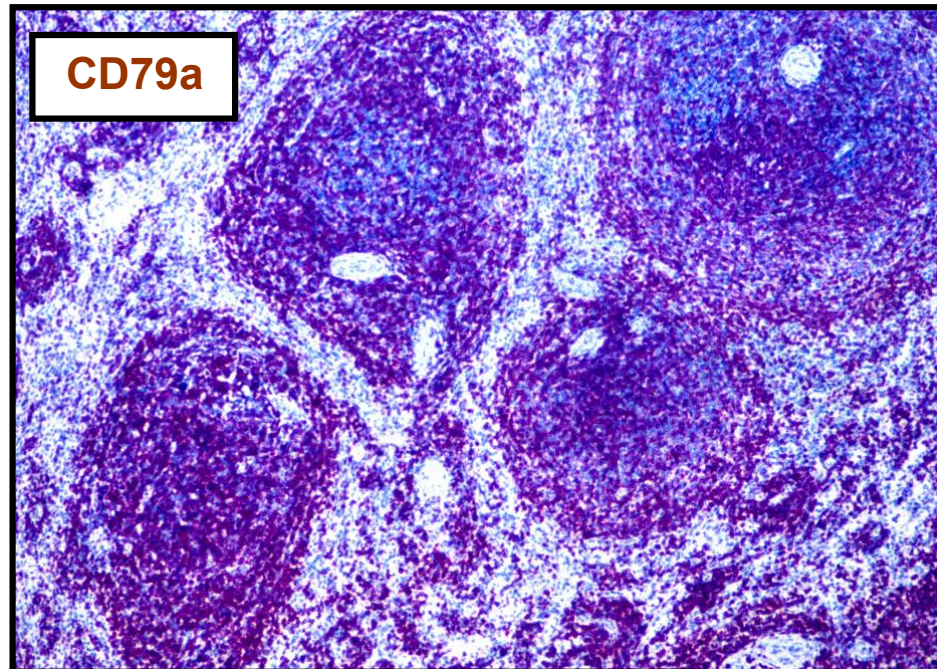
CD5^{-}, CD23⁻, CD43⁻, LEF1⁻**

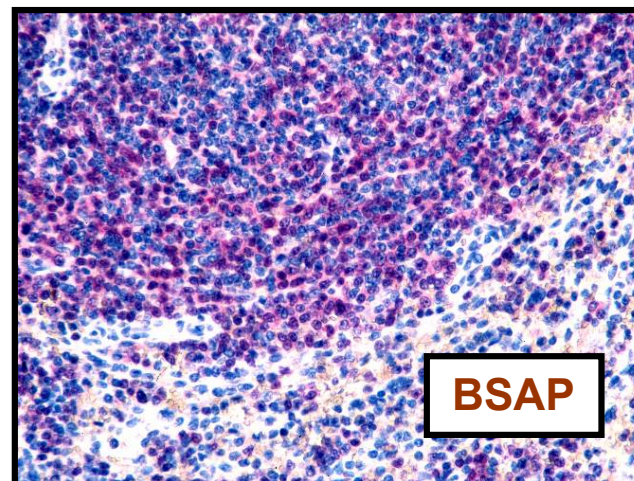
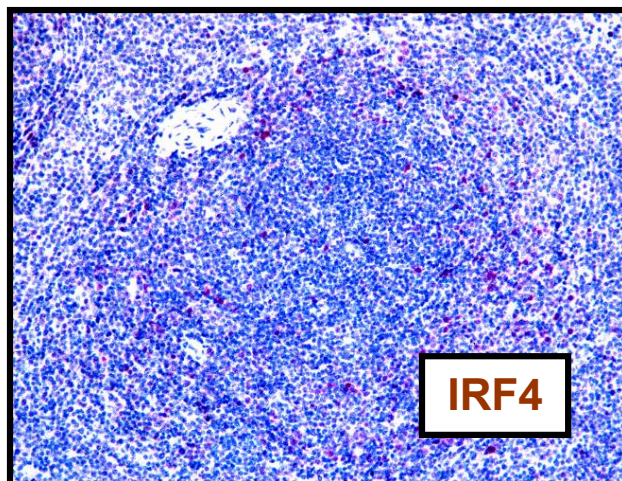
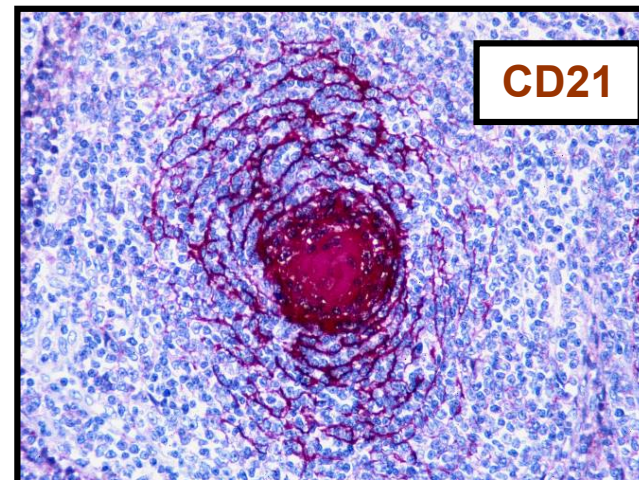
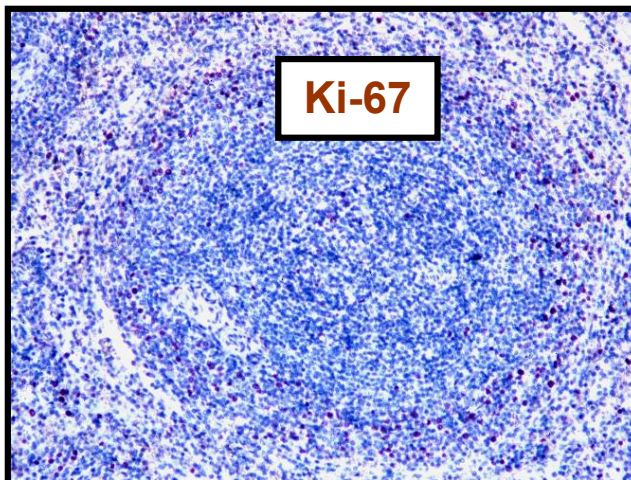
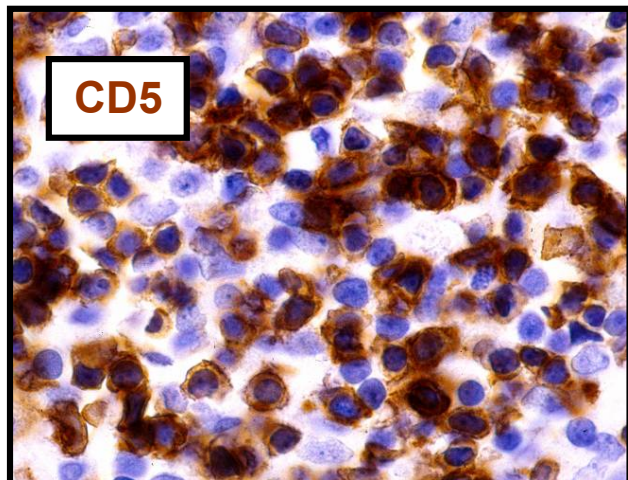
Cyclin D1⁻, Annexin A1⁻

CD10⁻, BCL6⁻,

BCL-2^{+/-} weak

***plasma cell differentiation; **+ in some cases with disseminated disease (Jaso JM et al. AJCP 2013;140:693-700)**



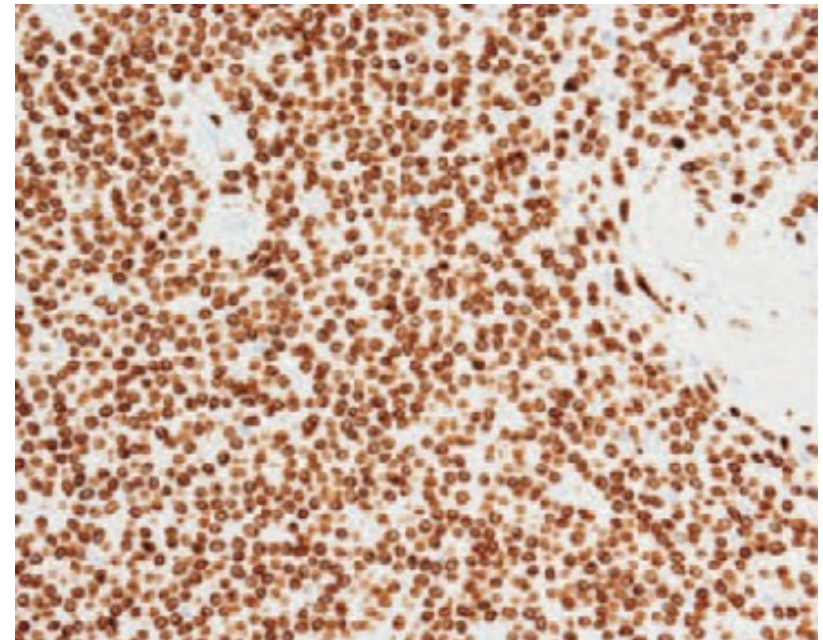


ORIGINAL ARTICLE

Identification of MNDA as a new marker for nodal marginal zone lymphoma

G Kanellis¹, G Roncador², A Arribas³, M Mollejo³, S Montes-Moreno¹, L Maestre², Y Campos-Martin³, JL Ríos Gonzalez¹, JL Martinez-Torrecuadrada², L Sanchez-Verde², R Pajares², JC Cigudosa⁴, MC Martin⁴ and MA Piris¹

	MNDA			
	Positive	Negative	Total	Percentage
CLL	23	12	35	65
FL	9	173	184	5
MCL	61	15	74	82
NMZL	43	14	57	75
MALT	19	1	20	95
LPL	10	2	12	83
SMZL	20	0	20	100 *
DLBCL	34	41	75	45
HCL	6	3	9	67
SMZL (bone marrow)	9	0	9	100 *
FL (bone marrow)	0	5	5	0
Splenic FL	7	10	17	41



IRTA1 is selectively expressed in nodal and extranodal marginal zone lymphomas

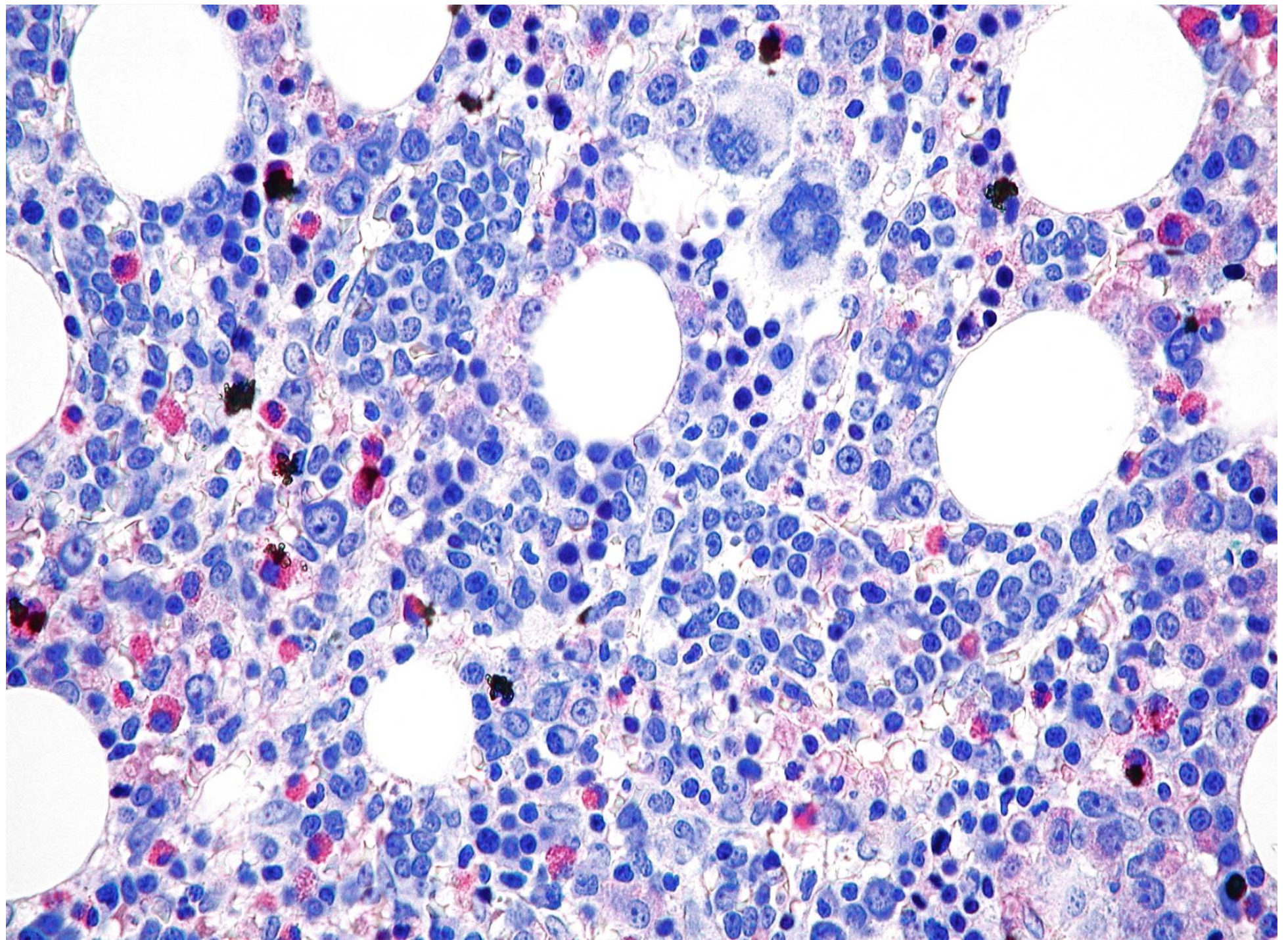
Brunangelo Falini, Claudio Agostinelli,¹ Barbara Bigerna, Alessandra Pucciarini, Roberta Pacini, Alessia Tabarrini, Flavio Falcinelli, Milena Piccioli,¹ Marco Paulli,² Marcello Gambacorta,³ Maurilio Ponzoni,⁴ Enrico Tiacci, Stefano Ascani,⁵ Maria Paola Martelli, Riccardo Dalla Favera,⁶ Harald Stein⁷ & Stefano A Pileri¹

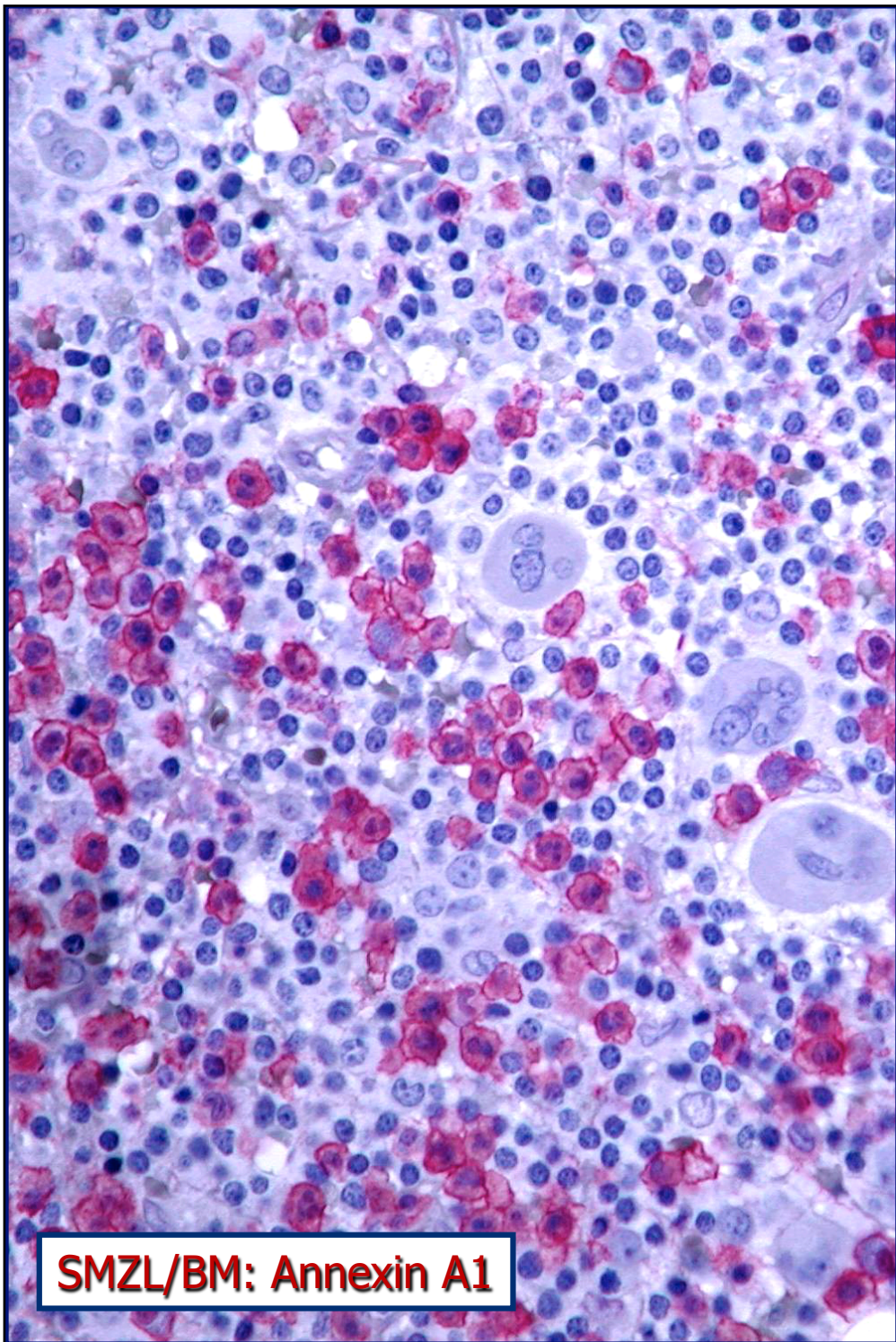
B-cell marginal zone lymphoma			
Splenic	21	0*	0
Nodal	210	154	73
Extranodal	329	307	93
NOS	30	22	73

Nuclear overexpression of lymphoid-enhancer-binding factor 1 identifies chronic lymphocytic leukemia/small lymphocytic lymphoma in small B-cell lymphomas

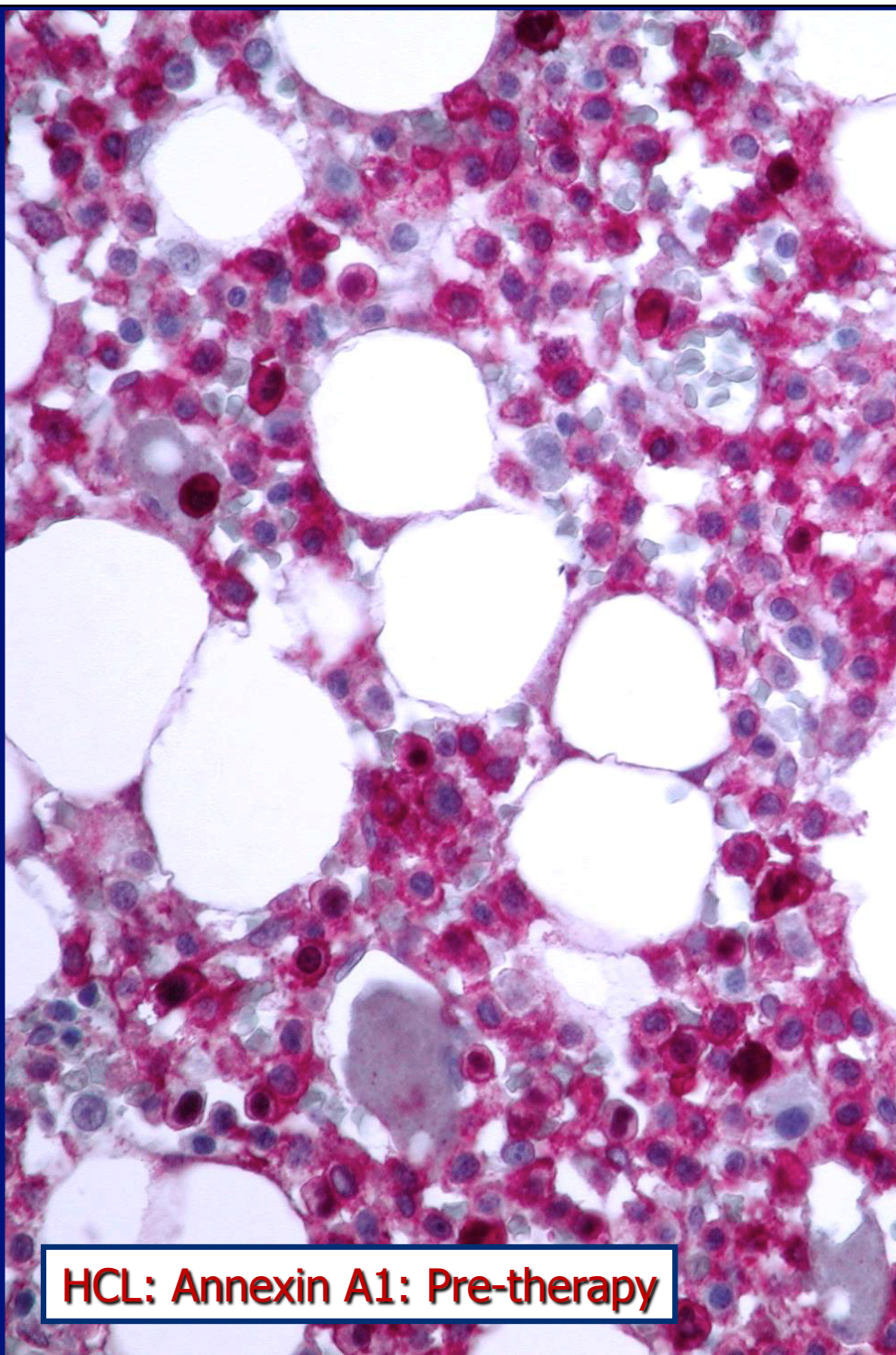
Bevan Tandon¹, LoAnn Peterson¹, Juehua Gao¹, Beverly Nelson¹, Shuo Ma², Steven Rosen² and Yi-Hua Chen¹

<i>B-cell lymphoma^a</i>	<i>Nuclear overexpression of LEF1 (positive cases/total cases)</i>
<i>Chronic lymphocytic leukemia/small lymphocytic lymphoma (n = 92)</i>	92/92 (100%), positive in ~100% cells
Without Richter's transformation	84/84 (100%; CD5+: 80; CD5–: 2)
With Richter's transformation	8/8 (100%; all CD5+)
<i>Mantle cell lymphoma (n = 53)</i>	0/53
Classical type	0/47
Small cell variant	0/2
Pleomorphic/blastoid variant	0/4
<i>Marginal zone lymphoma (n = 31)</i>	0/31
Nodal	0/15 (CD5–: 13; CD5+: 2)
Splenic	0/3 (CD5–: 2; CD5+: 1)
Mucosa-associated lymphoid tissue	0/13 (all CD5–)





SMZL/BM: Annexin A1



HCL: Annexin A1: Pre-therapy

SMZL: Differential Diagnoses

- **CLL: CD5⁺, CD23⁺, CD43⁺, LEF1⁺**
- **Non-nodal MCL: CD5⁺, Cyclin D1⁺**
- **HCL: Annexin A1⁺**
- **FL: CD10⁺, BCL6⁺**

Splenic Marginal Zone Lymphoma

Prognosis and predictive factors

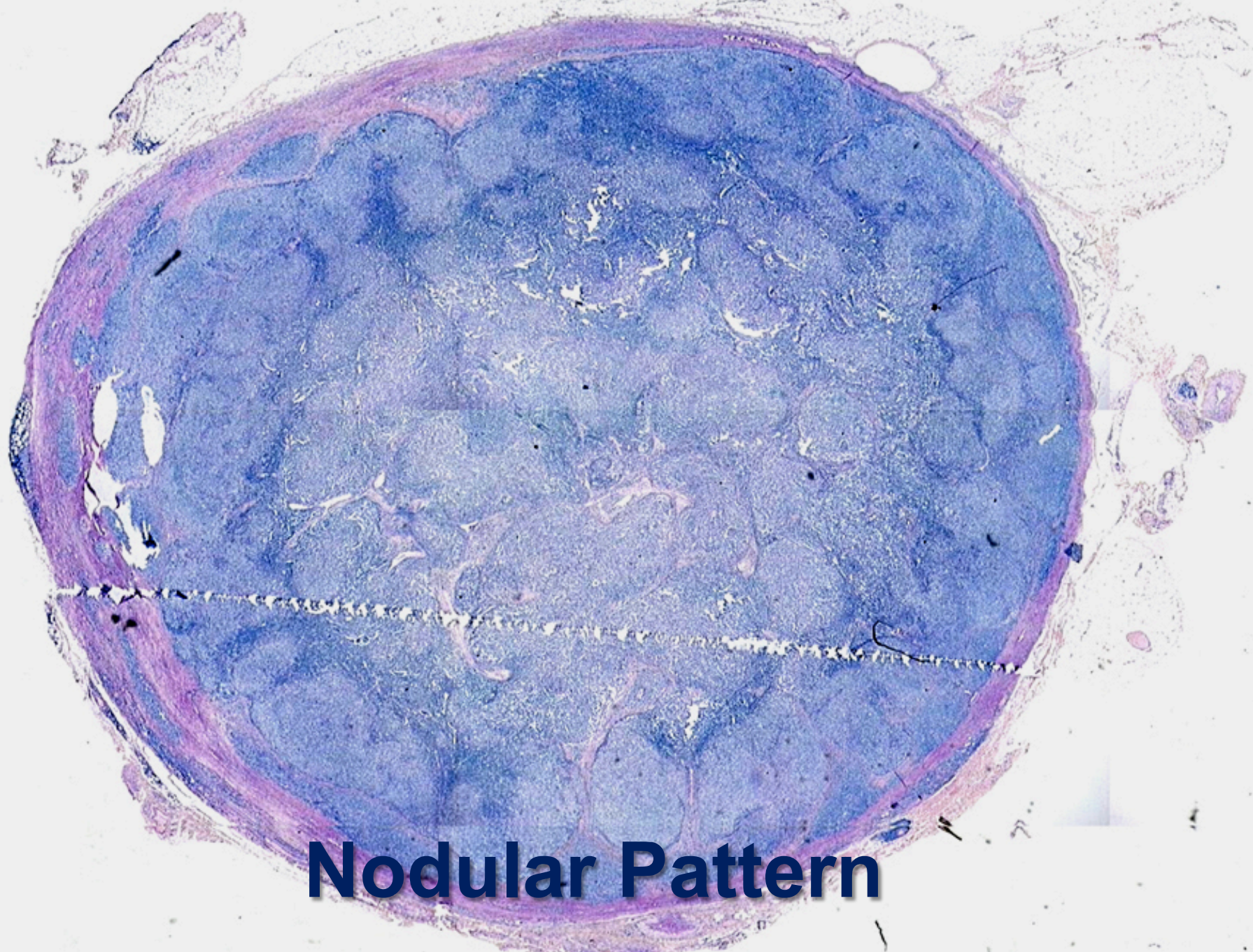
This is an indolent but incurable disease, with good responses after splenectomy in most patients; however, some patients do develop progressive disease and have an adverse outcome. The small number of patients with mutations in *NOTCH1*, *MAP2K1*, and *TP53* have been reported to have shorter progression-free survival [2530].

Nodal Marginal Zone Lymphoma

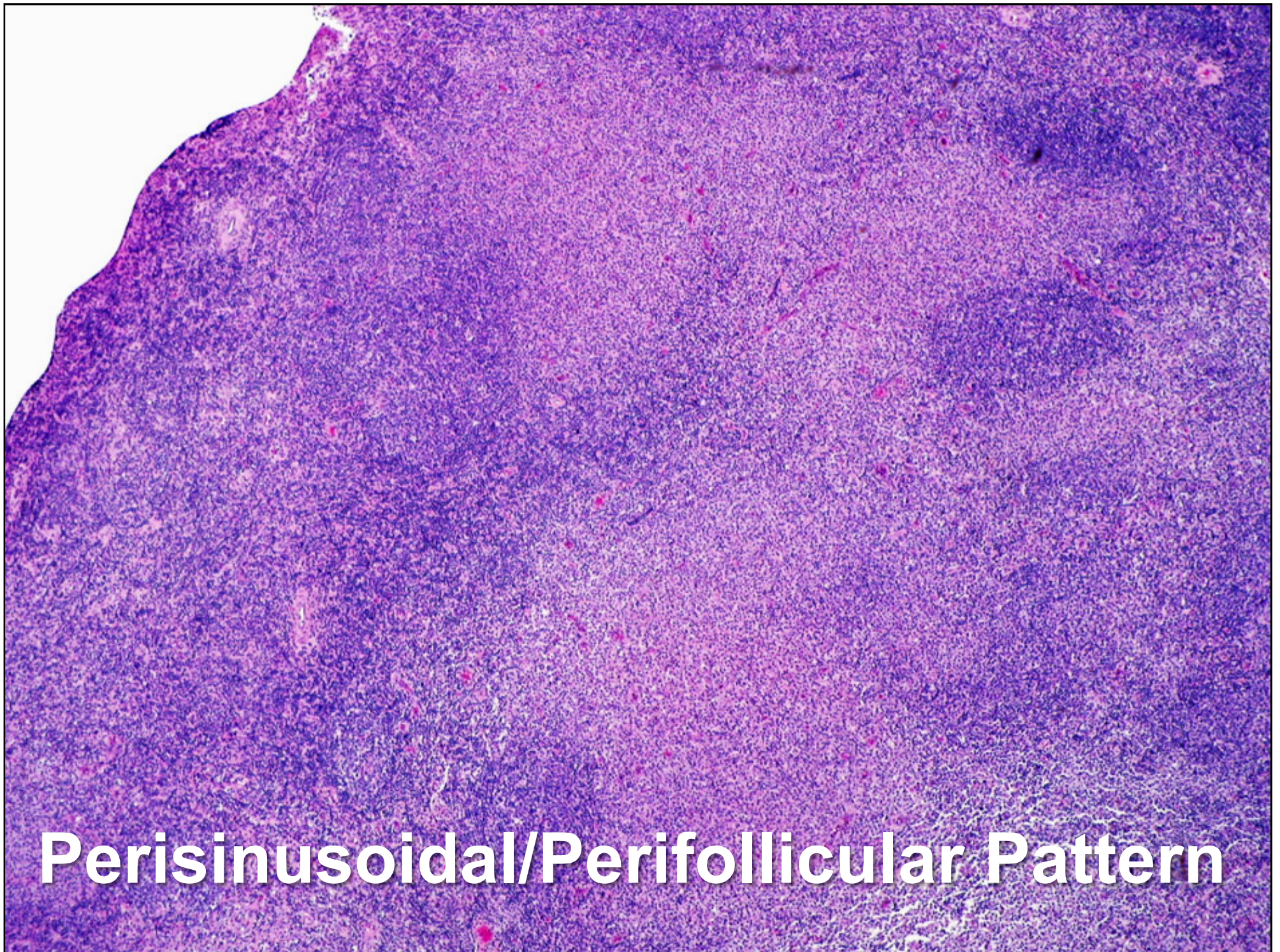
- **Less than 1.5-1.8% of lymphoid neoplasms.**
- **Mostly in patients over 60 (M/F=1/1).**
- **Pediatric form separately discussed.**
- **Significantly increased incidence in females with autoimmune disorders.**
- **Association with HCV infection postulated in some studies.**

Nodal Marginal Zone Lymphoma

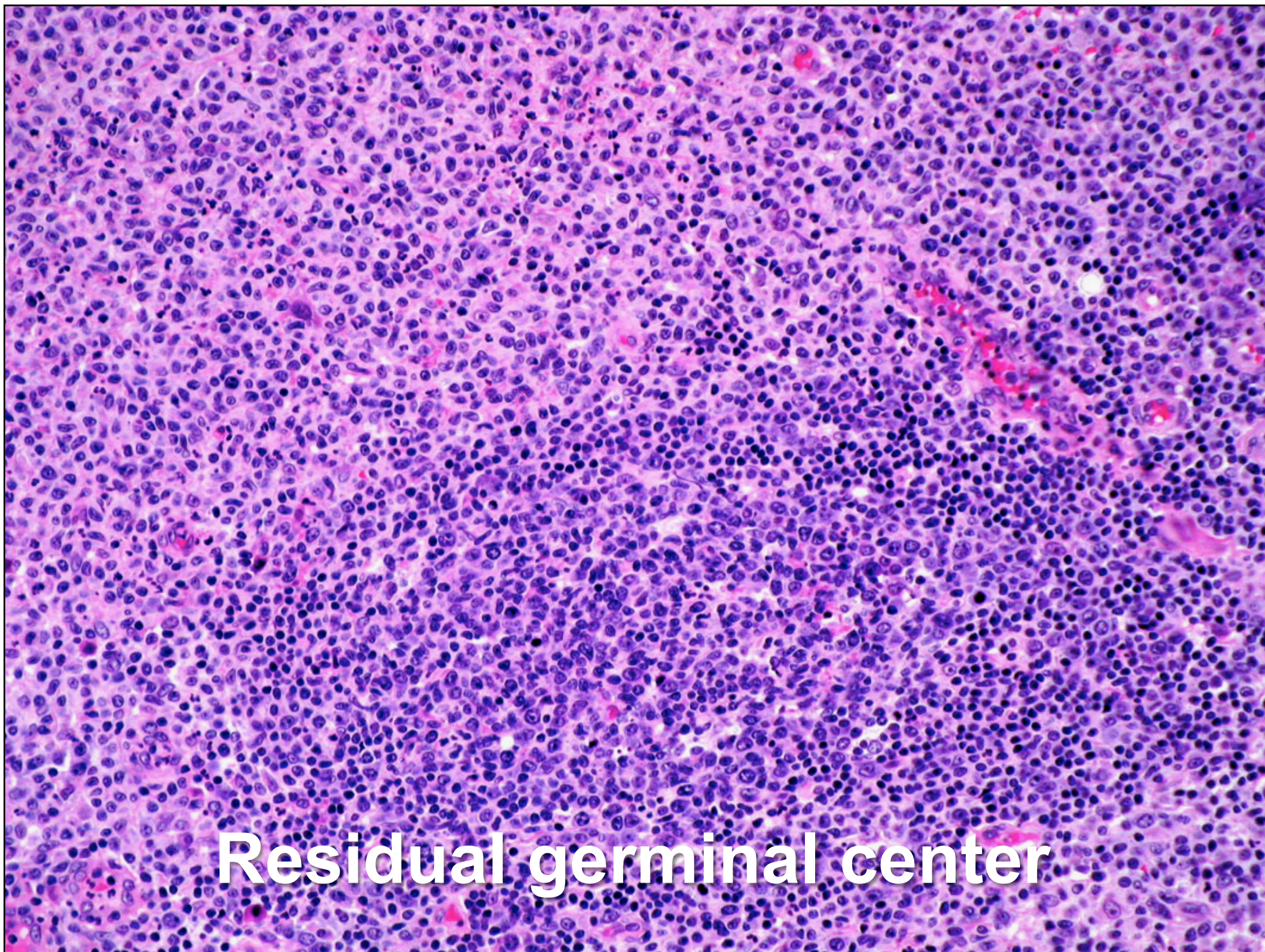
- **Localized or generalized lymphadenopathy (head and neck).**
- **B-symptoms in about 10% of cases.**
- **BM involvement in about 30% of patients.**
- **Leukaemic spread rare.**
- **Extranodal MZL should be categorically excluded.**



Nodular Pattern



Perisinusoidal/Perifollicular Pattern

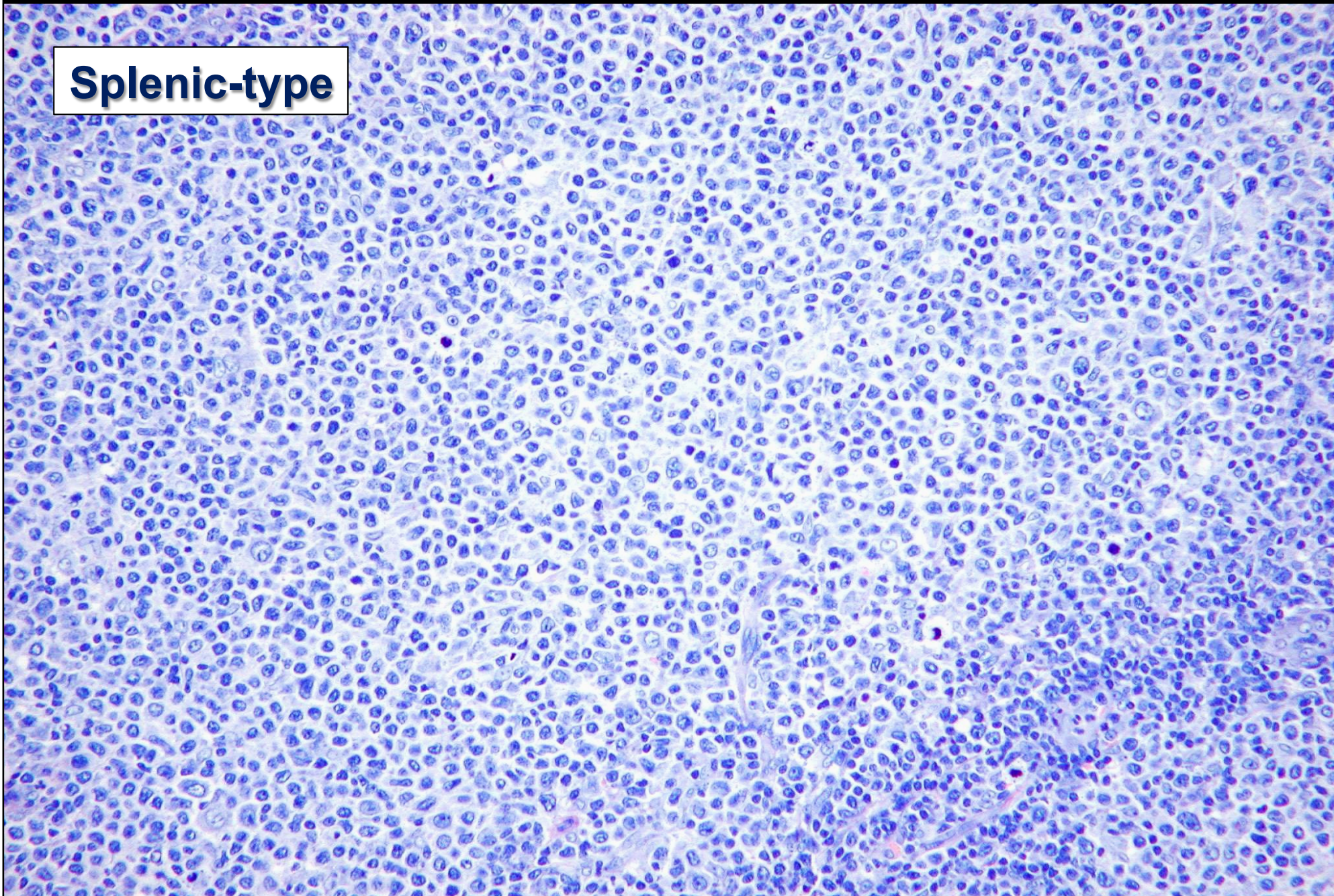


Residual germinal center

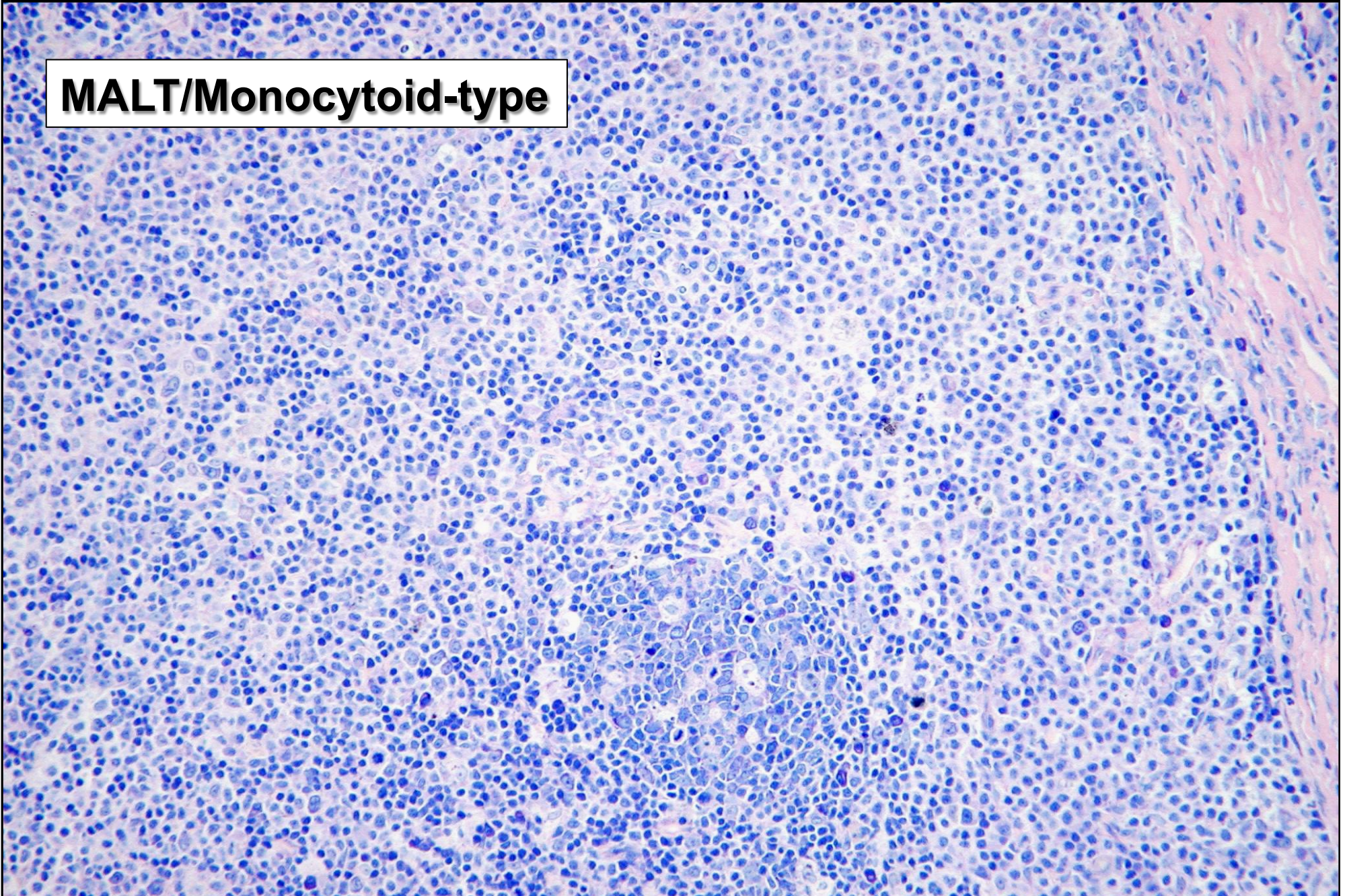
NMZL Morphologic Spectrum

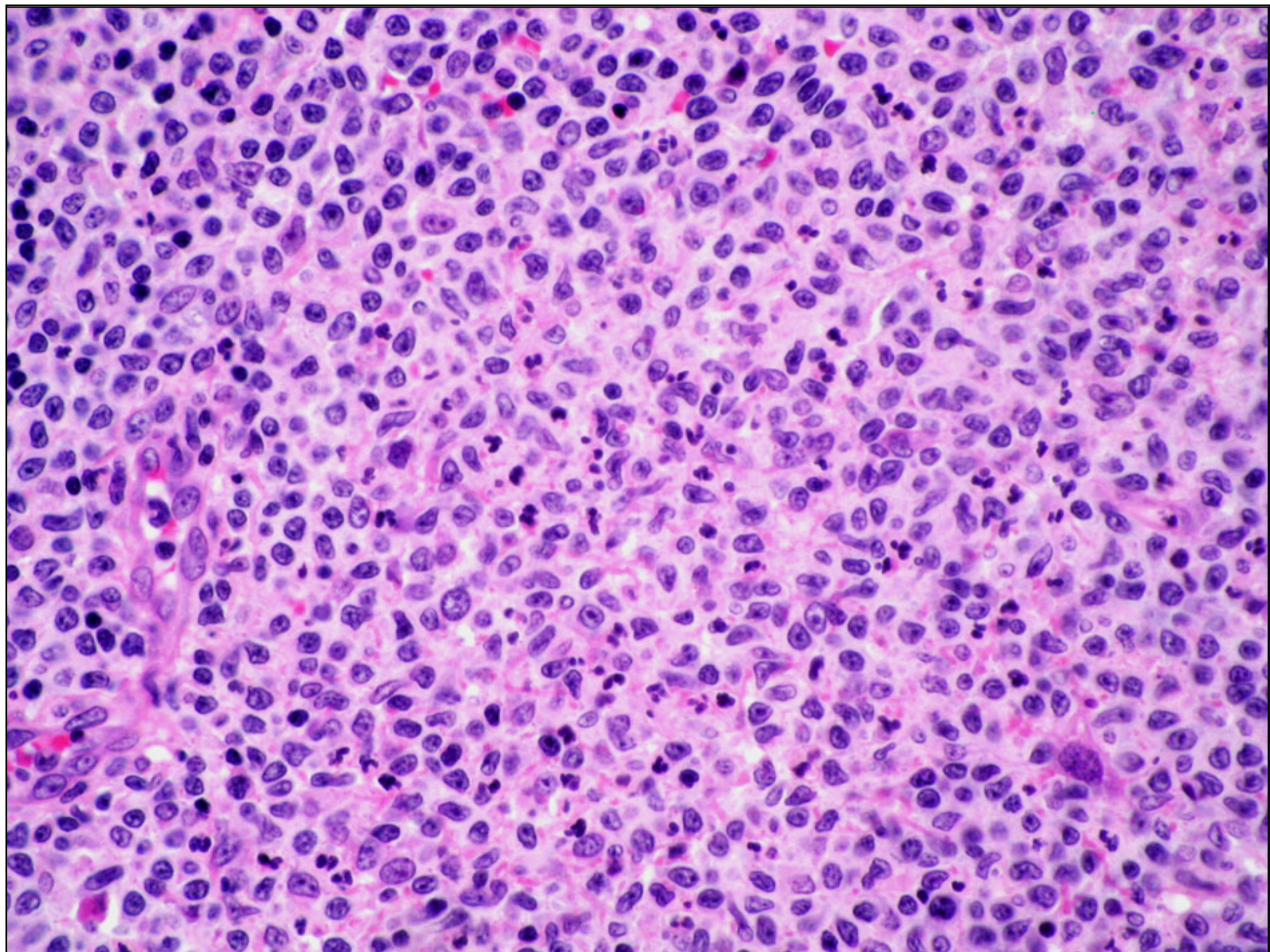
- **Cell types:**
- **Splenic-type**
- **Monocytoid**
- **Lymphoplasmacytic**
- **Mixed**

Splenic-type

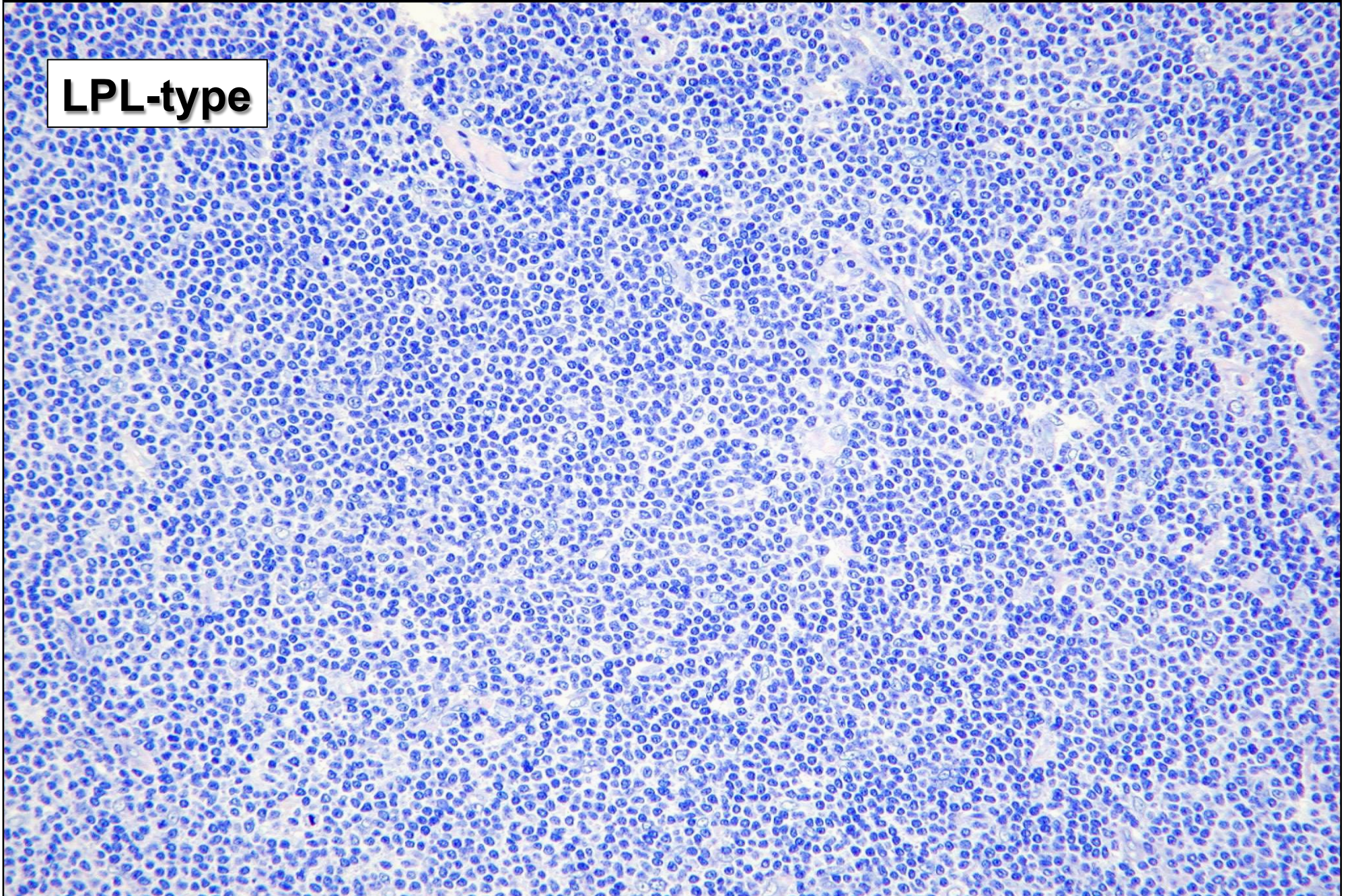


MALT/Monocytoid-type

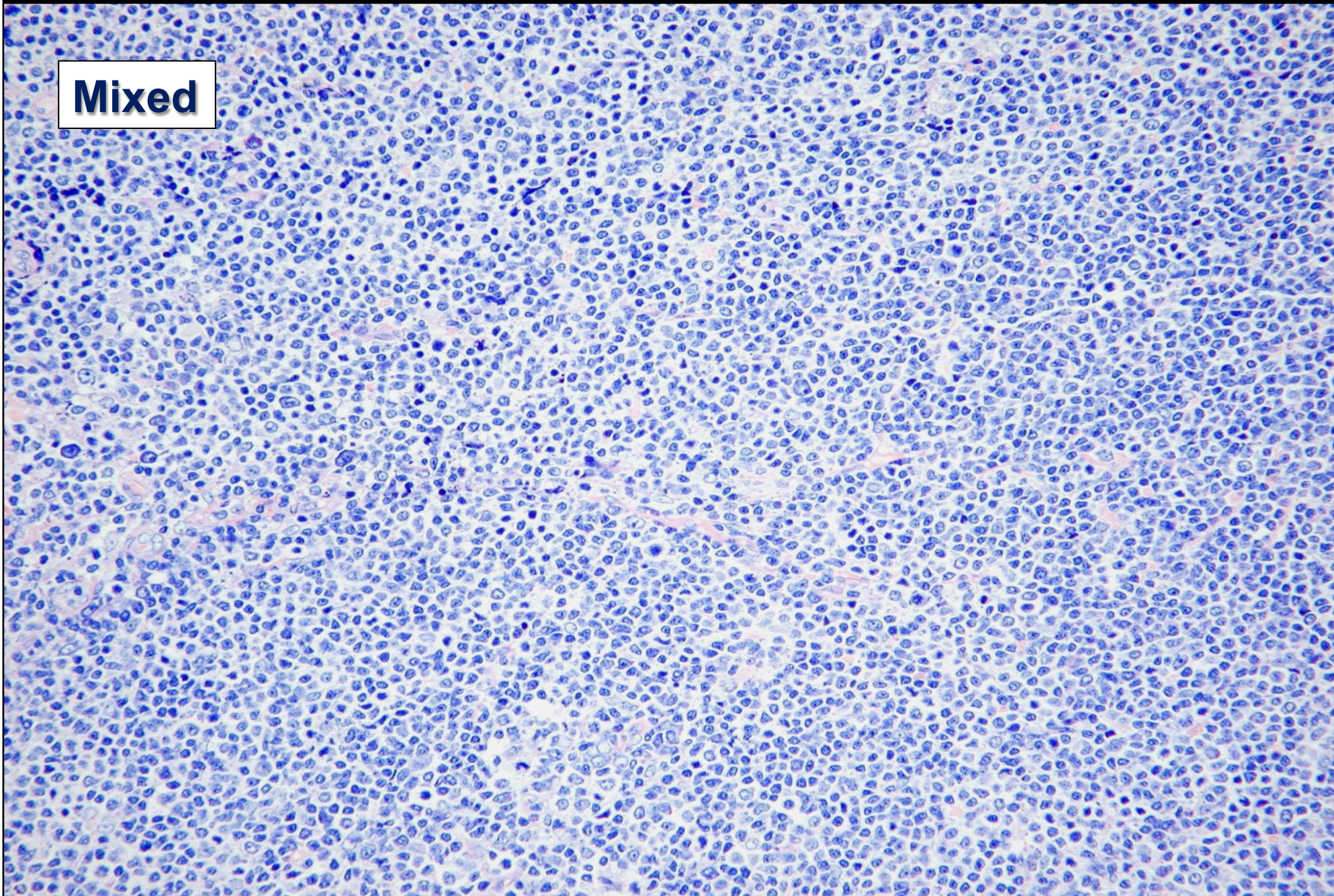




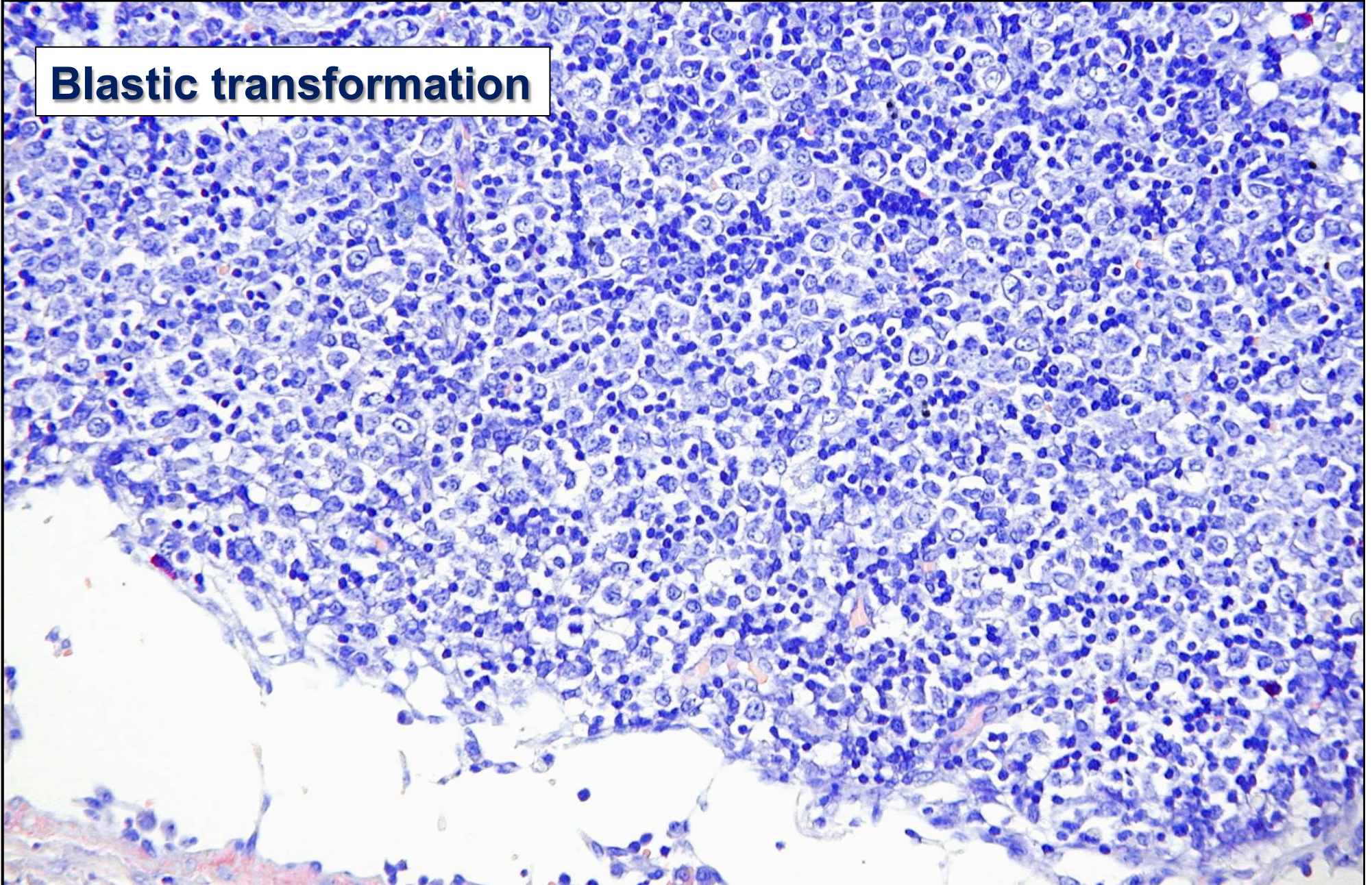
LPL-type



Mixed



Blastic transformation



Phenotype

CD20⁺, CD79a⁺, IgM⁺, IgD⁻ (+ splenic type)

BCL-2⁺

CD43 ^{-/+} to ^{+/-}

CD10⁻/HGAL⁻/LMO2⁻/BCL6⁻ (+ in case of GC colonization)

CD5⁻ (occasionally⁺)/CD23⁻ (occasionally ⁺) /Cyclin D1⁻

DBA44 rare

IRF4^{variable}

CD30 ^{variable}

IRTA-1^{+/-}, MNDA^{+/-}, T-bet/TBX21^{-/+}

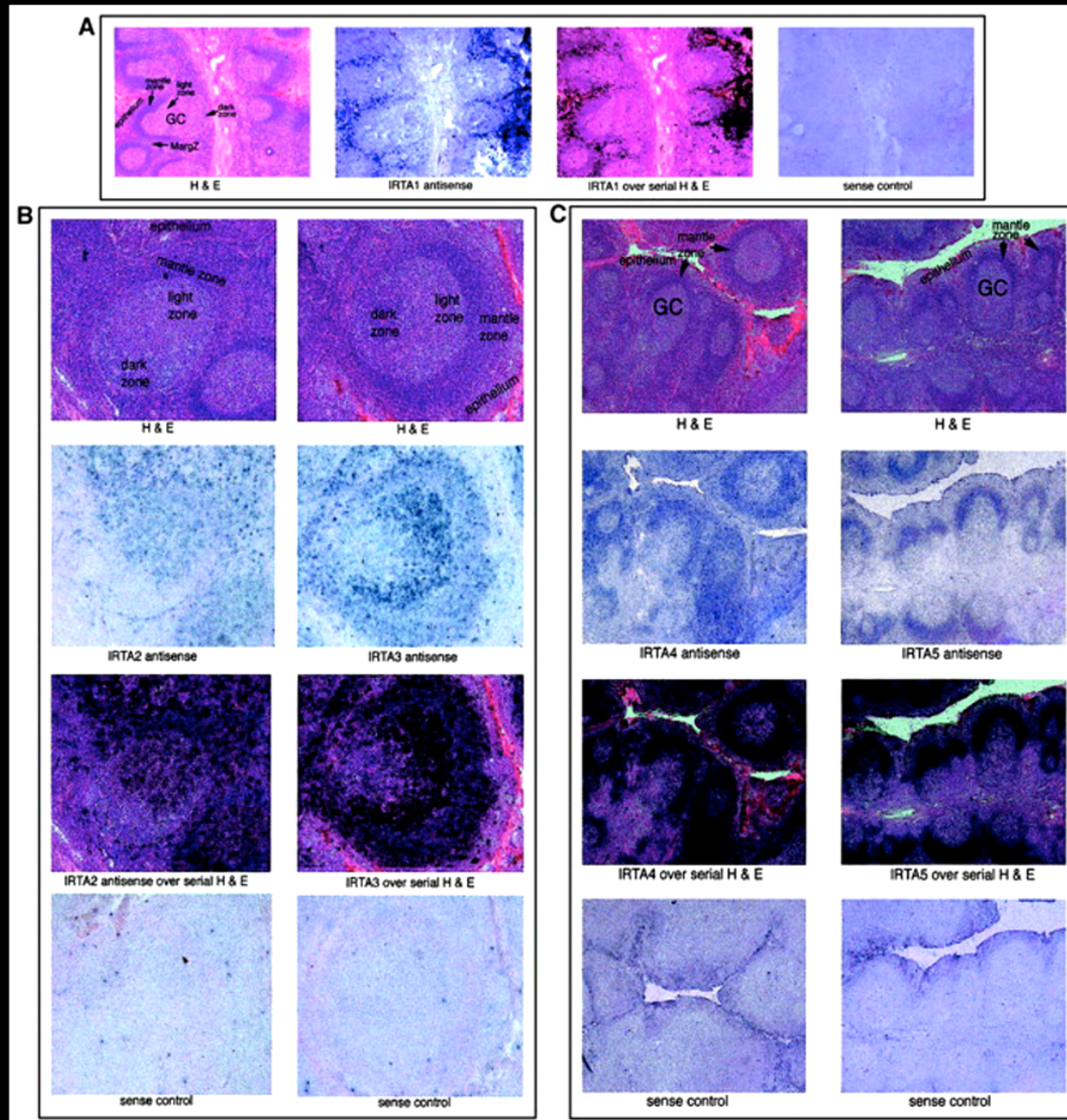
IRTA1 is selectively expressed in nodal and extranodal marginal zone lymphomas

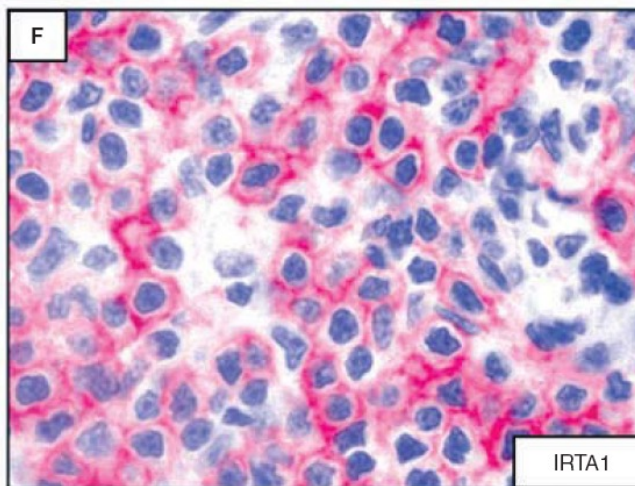
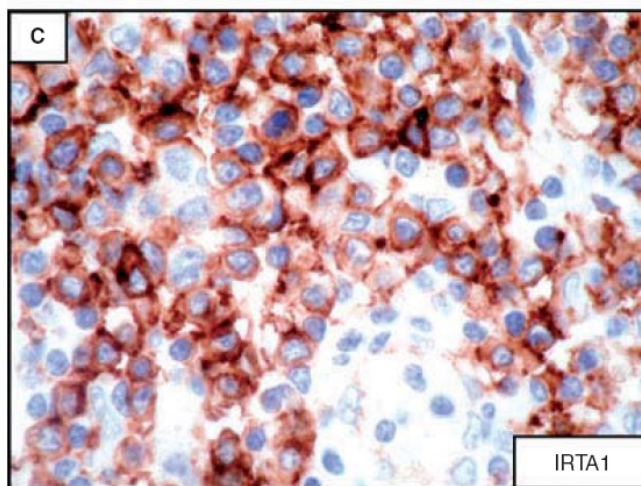
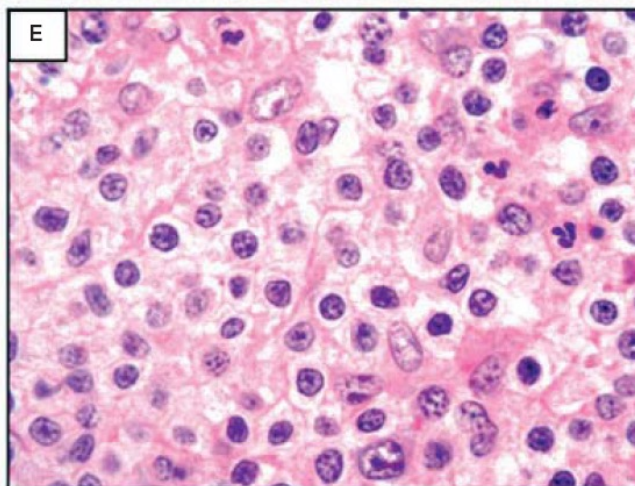
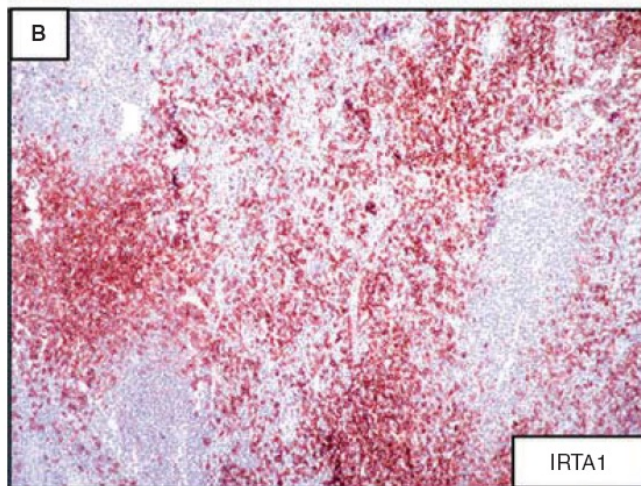
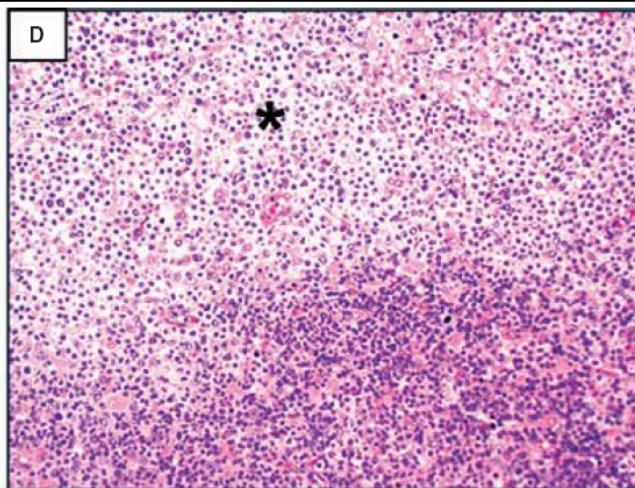
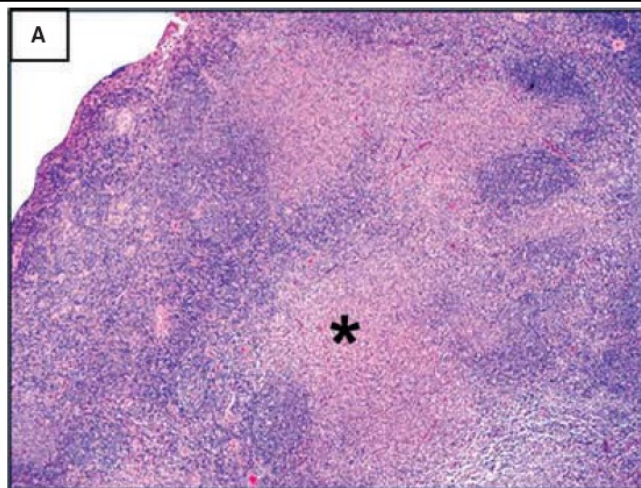
Brunangelo Falini, Claudio Agostinelli,¹ Barbara Bigerna, Alessandra Pucciarini, Roberta Pacini, Alessia Tabarrini, Flavio Falcinelli, Milena Piccioli,¹ Marco Paulli,² Marcello Gambacorta,³ Maurilio Ponzoni,⁴ Enrico Tiacci, Stefano Ascani,⁵ Maria Paola Martelli, Riccardo Dalla Favera,⁶ Harald Stein⁷ & Stefano A Pileri¹

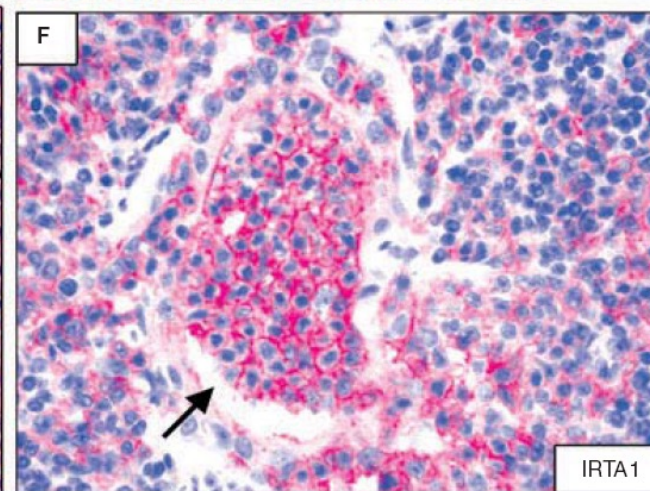
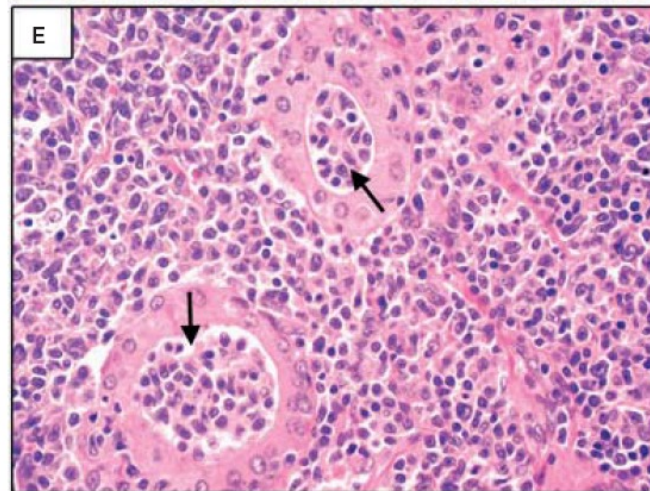
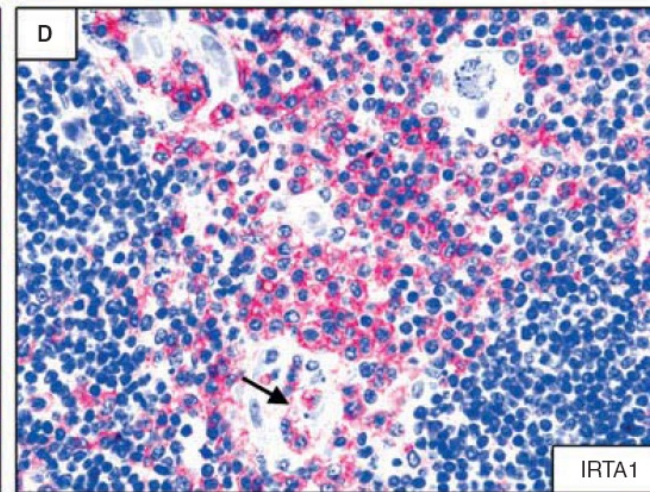
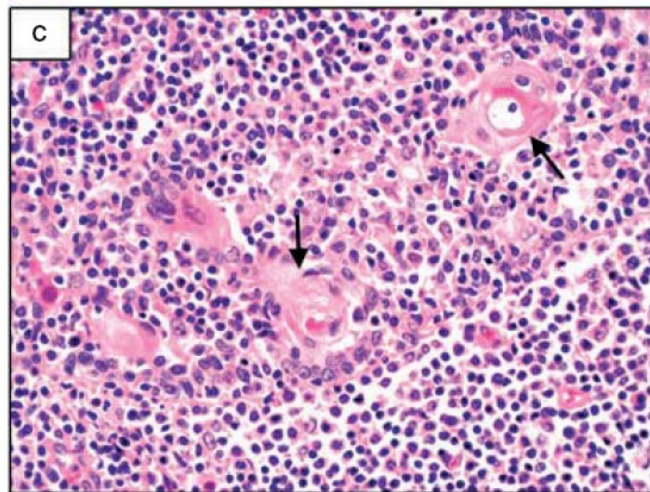
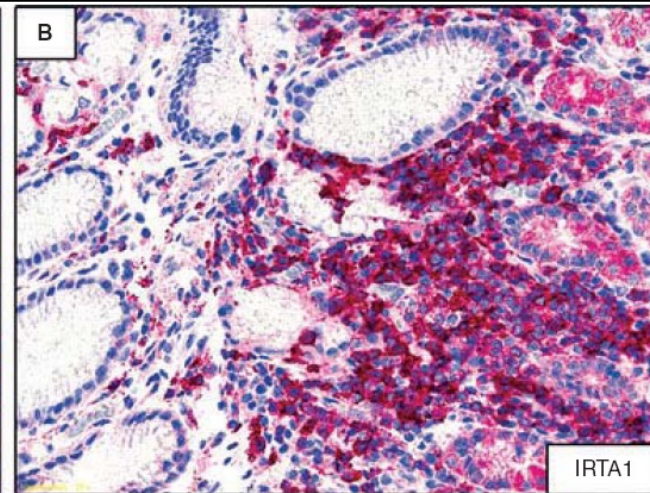
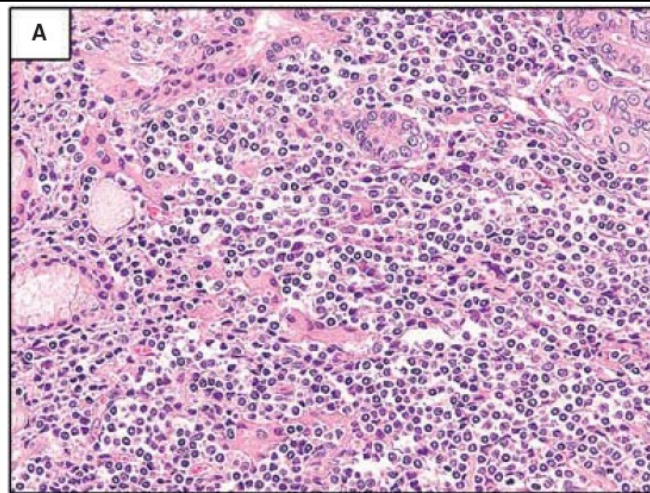
Table 1. Immunoglobulin superfamily receptor translocation-associated 1 (IRTA1) expression in 2104 lymphomas

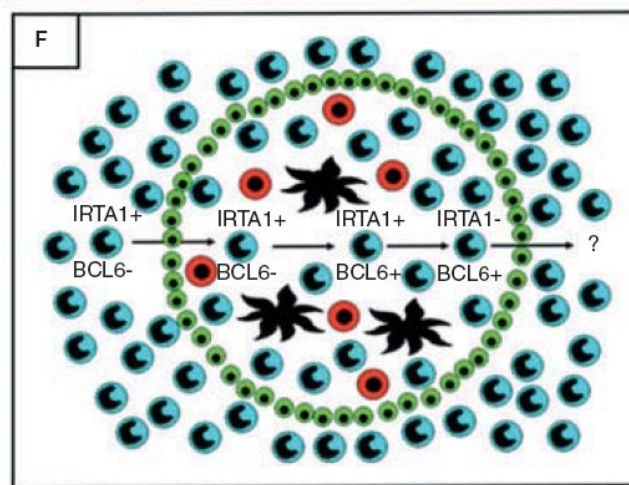
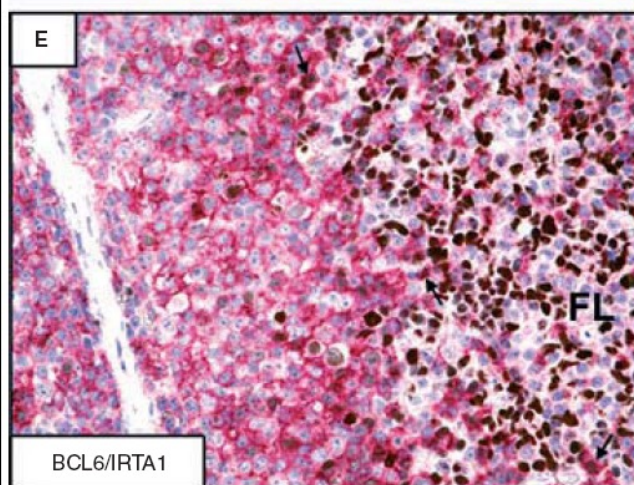
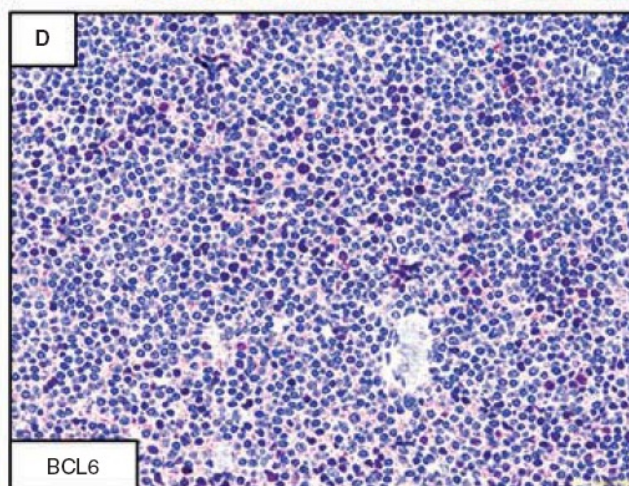
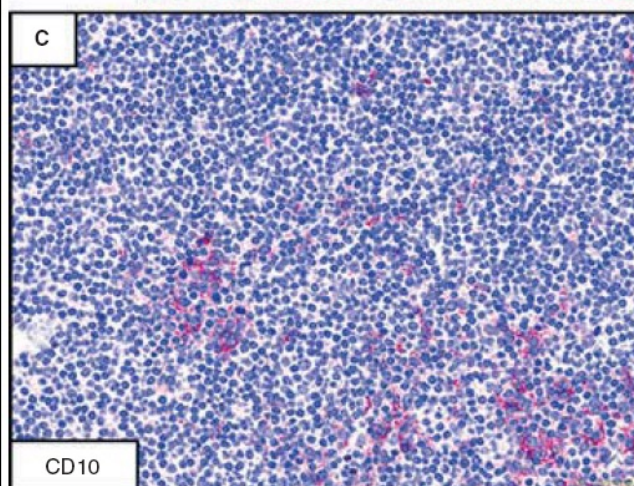
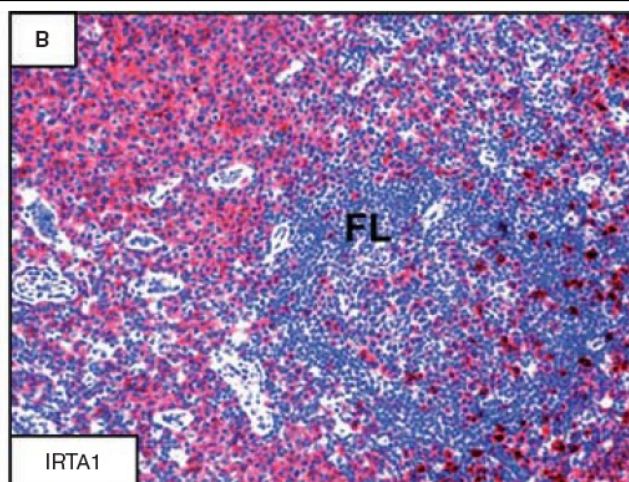
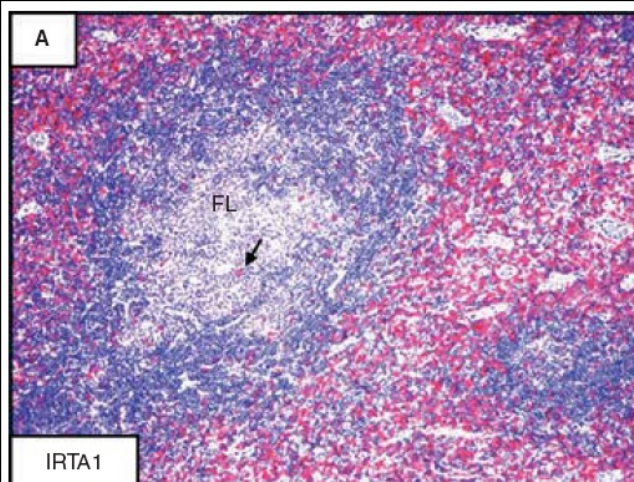
Lymphoid tumours	<i>n</i>	IRTA1 ⁺ cases	%
Chronic lymphocytic leukaemia/SLL	325	0*	0
Lymphoplasmacytic lymphoma	30	0	0
B-cell marginal zone lymphoma			
Splenic	21	0*	0
Nodal	210	154	73
Extranodal	329	307	93
NOS	30	22	73
Follicular lymphoma			
Grade 1/2	130	0*	0
Grade 3A	89	0*	0
Grade 3B	21	0*	0
NOS†	80	0*	0
Mantle cell lymphoma	121	0*	0
Hairy cell leukaemia	30	0	0
Diffuse large B-cell lymphoma	256	69	27
Burkitt lymphoma	71	0	0
Extramedullary plasmacytoma	6	0	0
Classical Hodgkin lymphoma	91	0	0
NLPHL	6	0	0
Peripheral T-cell lymphoma/NOS	160	0	0
Angioimmunoblastic T-cell lymphoma	48	0	0
Anaplastic large-cell lymphoma ALK ⁺	27	0	0
Anaplastic large-cell lymphoma ALK [−]	17	0	0
EATL	1	0	0
Mycosis fungoides	5	0	0

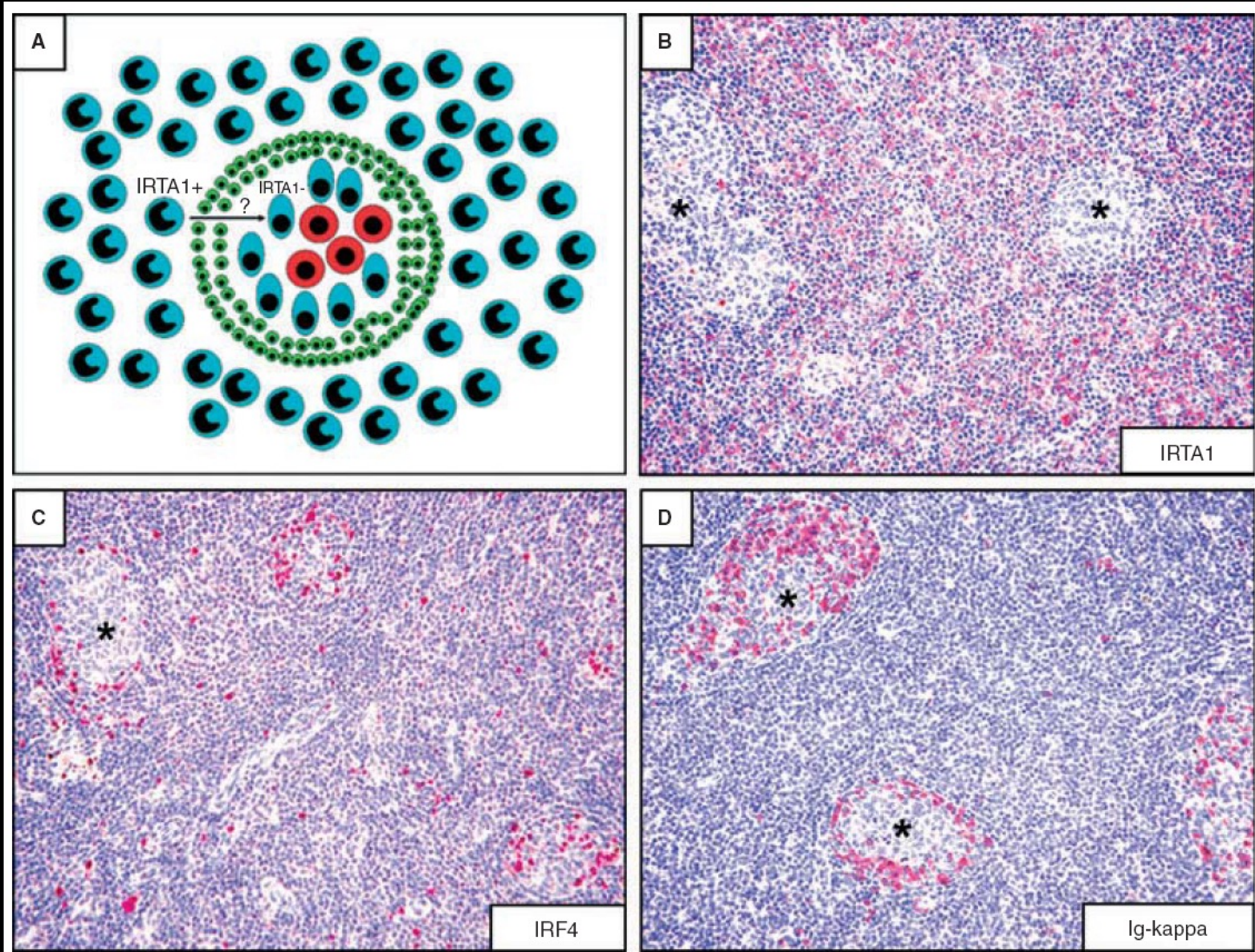
IRTA1 (Ig receptor translocation- associated)









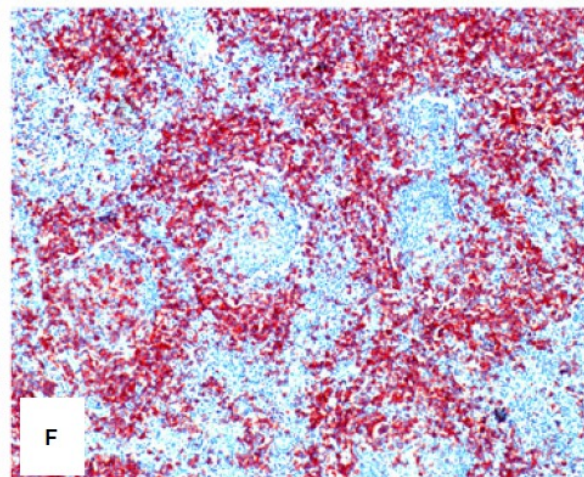
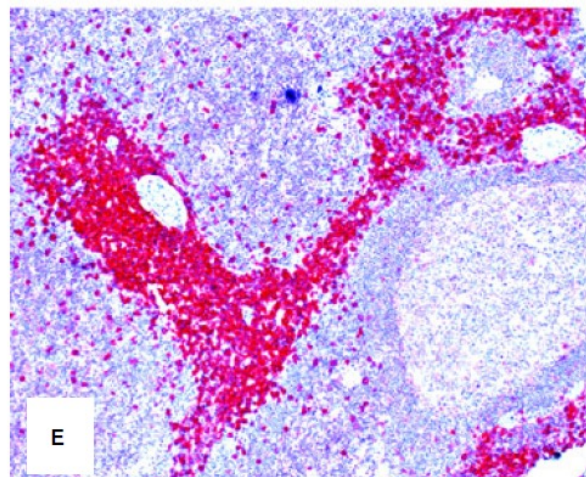
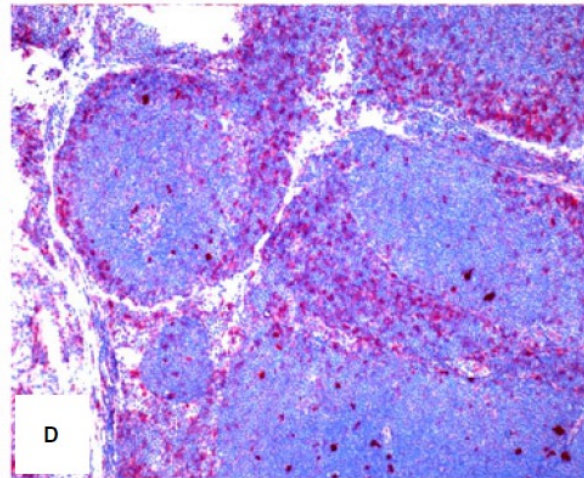
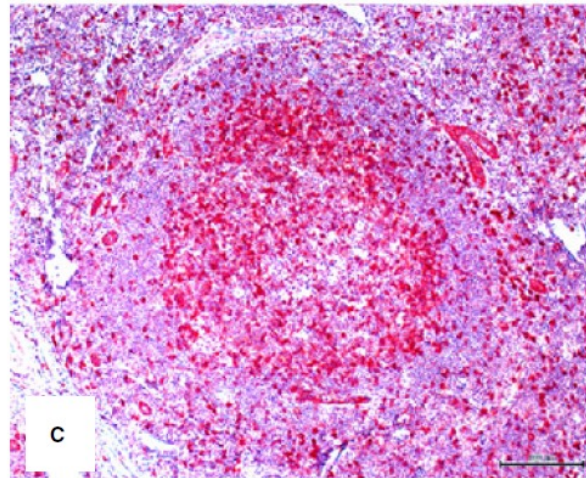
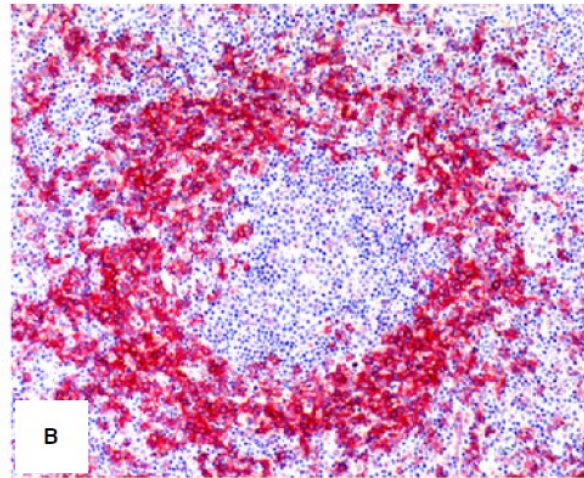
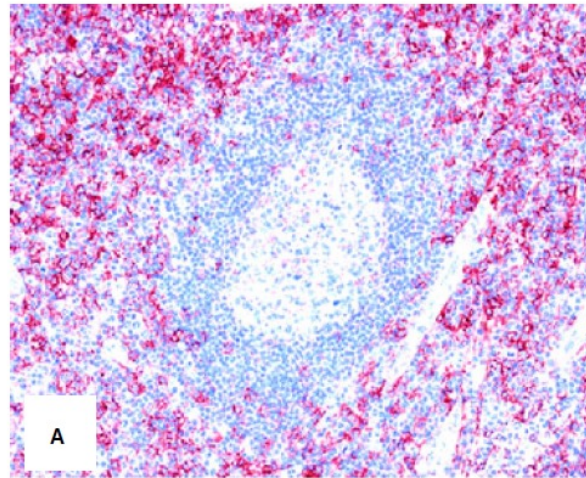


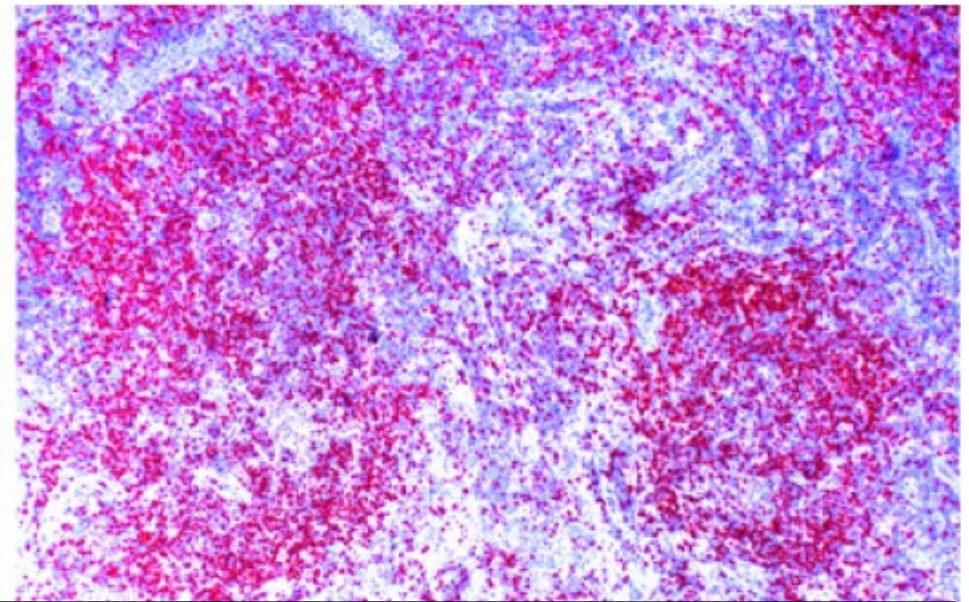
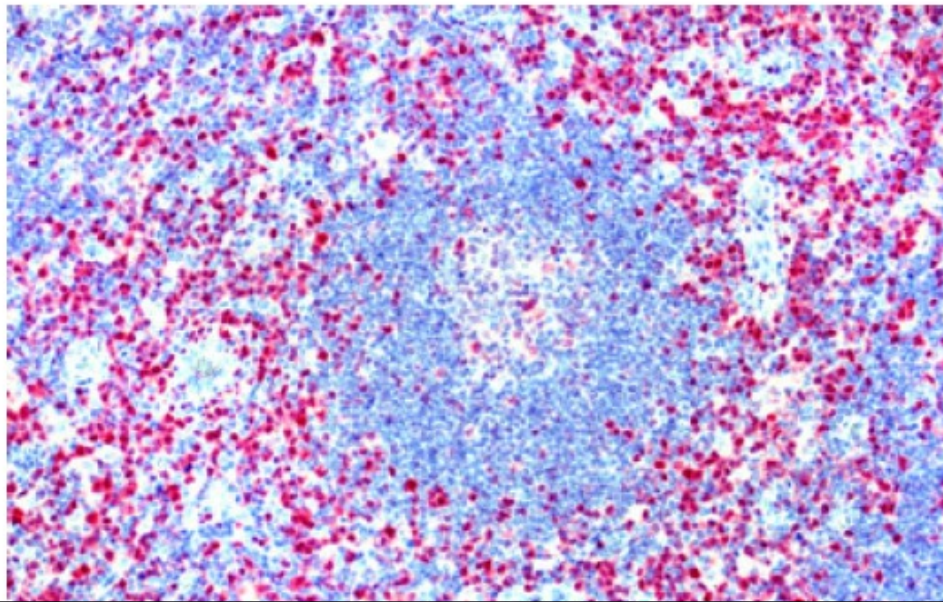
Nodal reactive and neoplastic proliferation of monocytoid and marginal zone B cells: an immunoarchitectural and molecular study highlighting the relevance of IRTA1 and T-bet as positive markers

Roshanak Bob,^{1,2} Brunangelo Falini,³ Teresa Marafigli,⁴ Jennifer C Paterson,⁴ Stefano Pileri⁵ & Harald Stein¹

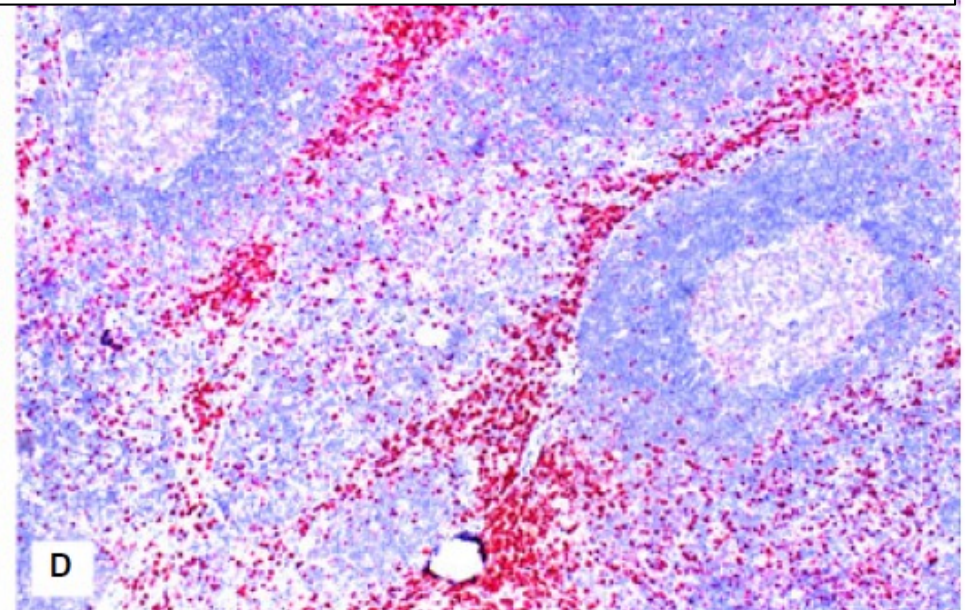
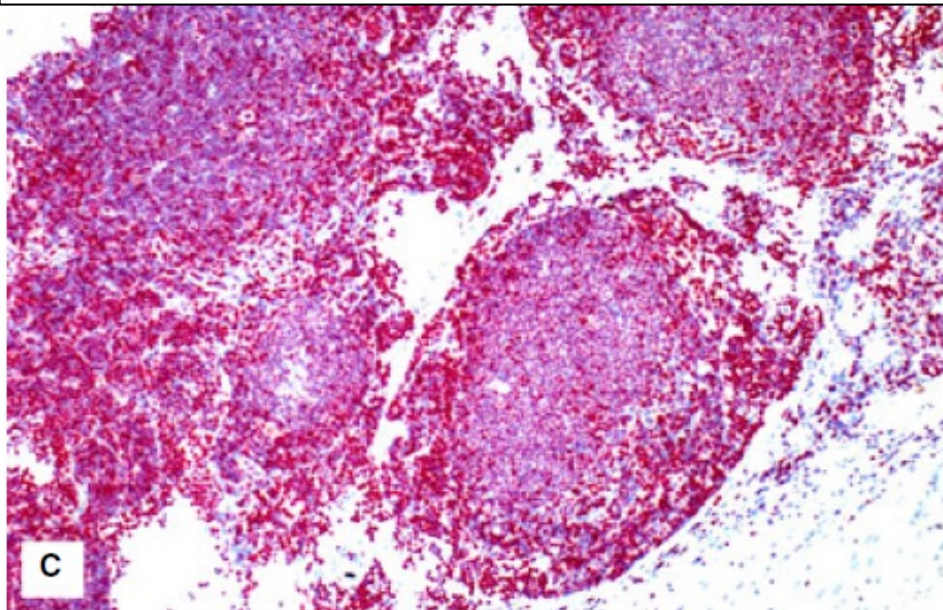
Table 5. IRTA1 and T-bet expression pattern of reactive and neoplastic lesions in different nodal compartments

Lymph node compartment	Reactive lesions		Polymorphic neoplastic lesions	
	IRTA1 (%)	T-bet (%)	IRTA1 (%)	T-bet (%)
Sinus	14/19 (74)	16/19 (84)	10/36 (28)	2/36 (6)
IF	6/19 (32)	9/19 (47)	17/36 (47)	17/36 (47)
PF/MZ	3/19 (16)	5/19 (26)	11/36 (31)	20/36 (56)
GC (follicular colonization)	2/19 (11)	5/19 (26)	11/36 (31)	16/36 (44)





Personally, I use IRTA1, T-bet and MNDA in parallel, along with CD5, CD10, BCL6 & IRF4





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Expansion of PD-1 Positive T-cells in Nodal Marginal Zone Lymphoma – a Diagnostic Pitfall

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PD-1 expansion mimicking T-cell lymphoma

The presence of an abnormal PD-1 staining pattern (either follicular or diffuse) could be such that it raised the differential diagnosis of a peripheral T-cell lymphoma of T_H phenotype. We illustrate four cases which posed such a diagnostic challenge.

TABLE 1: Immunohistochemical and molecular features of cases with PD-1 expression mimicking T-cell lymphoma

	Marginal Zone Lymphoma	T-cell infiltrate	PCR
Case	CD20 CD38	gH gP	CD3 PD-1 CD4 CD8 BCL6 BCL2 Ig
1	+	+	CD3 CD4 CD8 BCL6 BCL2 Ig
2	+	+	CD3 CD4 CD8 BCL6 BCL2 Ig
3	+	+	CD3 CD4 CD8 BCL6 BCL2 Ig
4	+	+	CD3 CD4 CD8 BCL6 BCL2 Ig

FIGURE 2: PCR analysis in a case with PD-1 expression mimicking T-cell lymphoma

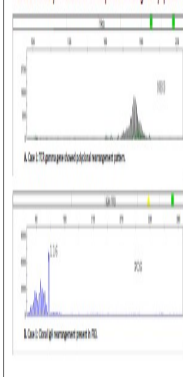


FIGURE 3: Case 1: (A) Nodular architecture with numerous 'hot' and partially colored reactive germinal centers surrounded by a periblastic infiltrate composed of immunoblast-like cells and smaller lymphoid cells. The periblastic infiltrate has activated (B) CD3 positive cytoplasmic cells, but is composed mainly of (C) CD3 positive, PD-1 positive T-cells. The T-cells are (D) CD4 positive and (E) CD8 negative. There is (F) increased MUM1 staining. (H) BCL6 shows positivity mainly in reactive germinal centers. (I) There is a predominantly interfollicular kappa light chain excess. (J) Lambda.

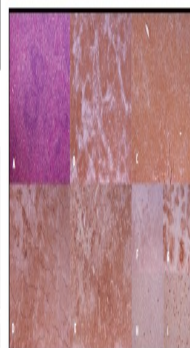


FIGURE 3: Case 2: (A) Nodular and interfollicular effacement by a polymorphous infiltrate. (B) CD3 positive cells in large perigerminal nodules. (C) A dense, diffuse CD3 positive T-cell infiltrate. (D) PD-1 positive cells are increased, with a spectrum of infiltration patterns from a periblastic pattern to a diffuse pattern. A subset of PD-1 positive cells co-express (E) CD4. (F) CD8. (G) CD79a has a similar distribution to CD3. There is lambda light chain excess. (H) kappa. (I) Lambda.



FIGURE 4: Case 2: (A) Diffuse, vaguely nodular population of small to medium centrocyte-like lymphoid cells with occasional large immunoblast-like cells. An 'inverted' pattern, whereby (B) CD20 positive B-cells surround large irregular nodules composed of (C) CD3 positive T-cells. The T-cell areas are also (D) PD-1 positive and show focal expression of (E) BCL6. The PD-1 positive cells are (F) CD4 positive. (G) CD8 stains a subset of T-cells. There is lambda light chain restriction. (H) kappa. (I) Lambda.



FIGURE 5: Case 3: (A) Periblastic and interfollicular infiltrate composed of lymphoid cells which are (B) CD3 positive and (C) BCL6 positive. (D) A dense T-cell infiltrate is present on CD3 staining. (E) Strong staining PD-1 positive cells show a normal interfollicular pattern, however moderately staining PD-1 positive cells are diffusely increased in the interfollicular areas. The PD-1 positive cells mainly (F) co-express (G) CD4. (H) CD8. (I) CD79a has a similar distribution to CD3. There is lambda light chain excess. (J) kappa. (K) Lambda.

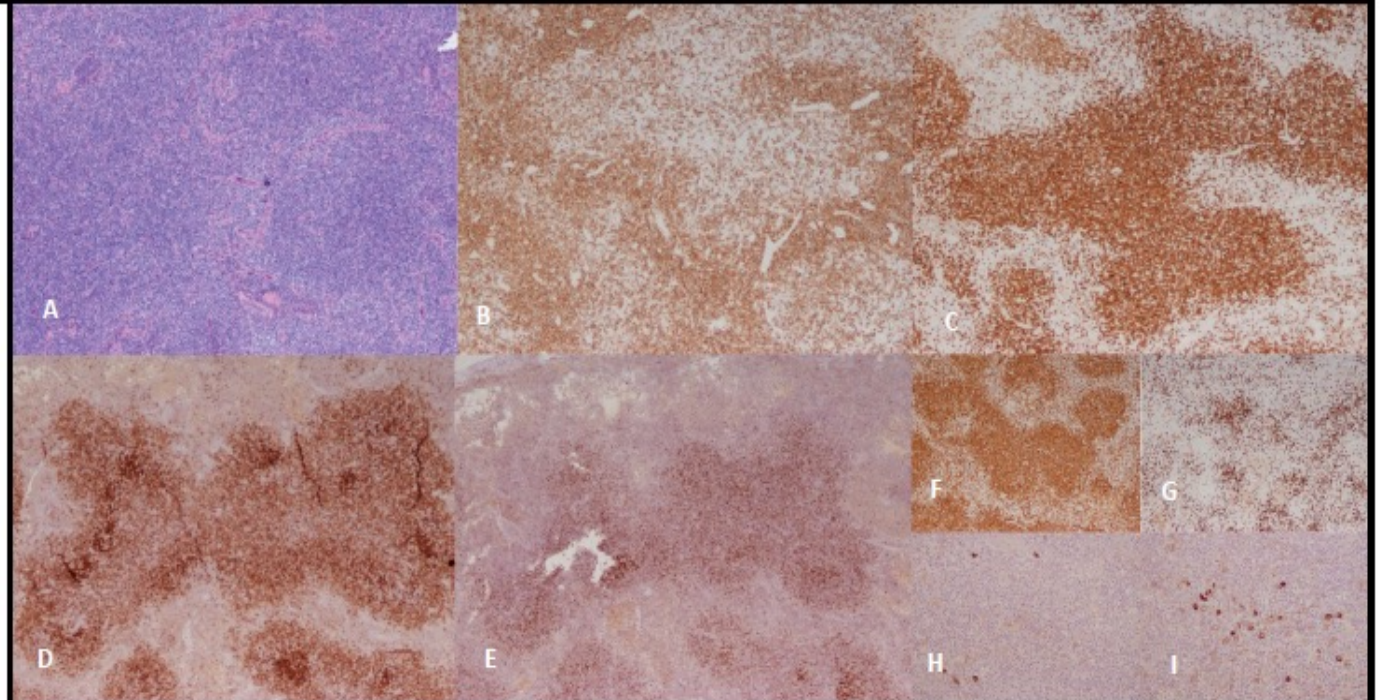


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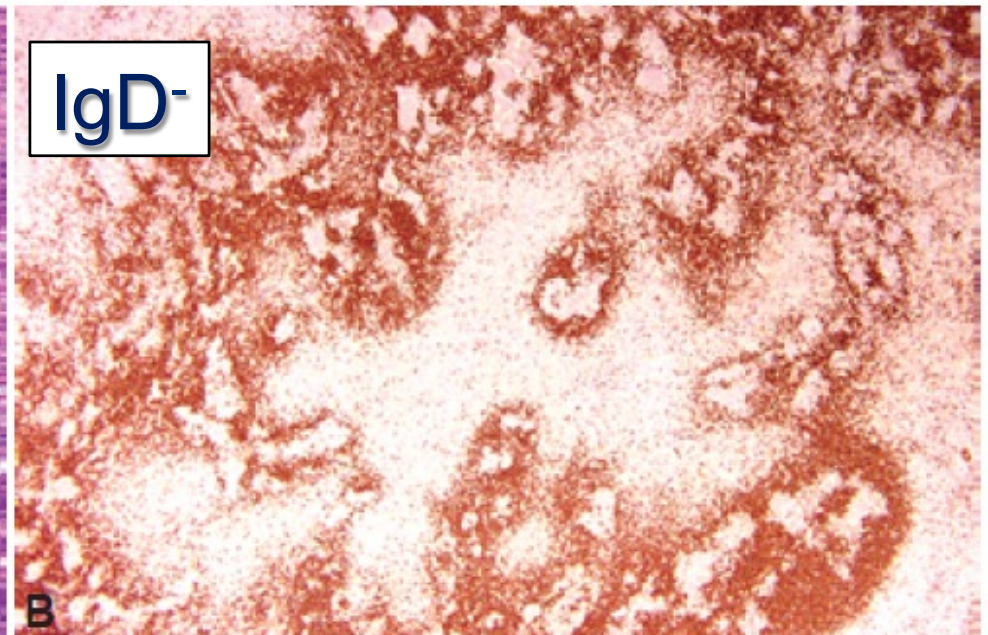
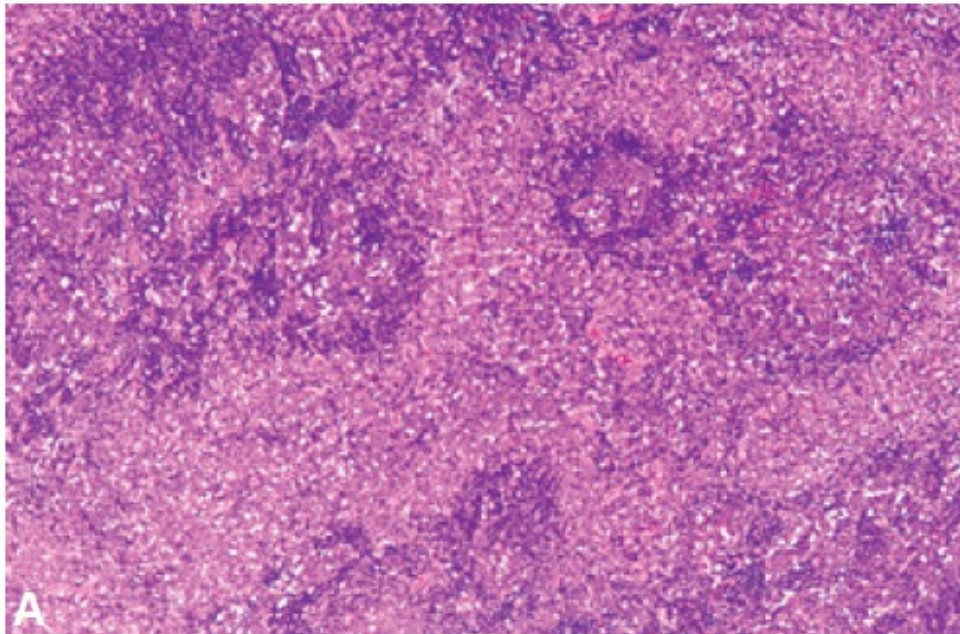
Nodal Marginal Zone Lymphoma

Prognosis and predictive factors

The 5-year overall survival rate is about 60–70% {137}. Advanced patient age, B symptoms, and advanced disease stage are associated with a worse prognosis {106}. However, on a multivariate analysis, only the Follicular Lymphoma International Prognostic Index (FLIPI) applied to these patients predicted overall survival {137}. The proportion of scattered or clustered large cells does not appear to be of prognostic significance {4046}. However, transformation to diffuse large B-cell lymphoma may occur. This diagnosis requires the presence of sheets of large cells {2687}.

Pediatric Marginal Zone Lymphoma

- M/F=20/1; stage I (90%); head and neck.
- Excellent prognosis following conservative treatment.
- Same morphology and phenotype.
- DD: Monotypic MZB-cell hyperplasia (MB + IgD)



[illegible]