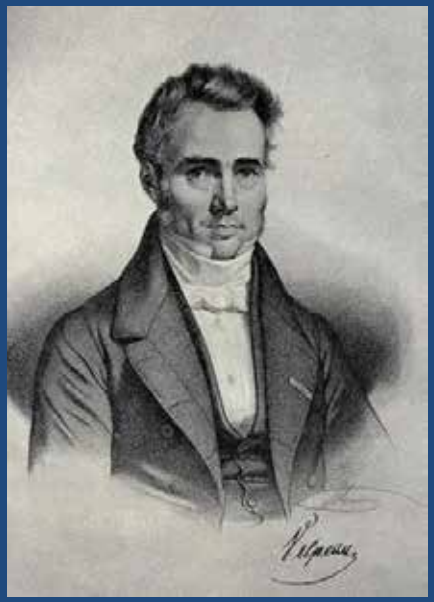
LEUCEMIA LINFATICA CRONICA
ANATOMIA-PATOLOGICA

DR. PABLO MATAMALA BASTIAN

HEMATOPATOLOGIA

LAB. CITOMETRIA DE FLUJO CLINICA ALEMANA



1827

1845

1845

November 16th, 1846

Dear Diary,

Today is the day the world will receive an answer! I have diagnosed the first ever leucocythemia patient, Thomas Windsor! The patient was showing many symptoms of sharp pain in limbs, excruciating headaches, vertigo, insomnia, loss of appetite, diarrhea, extreme thirst and weakness. Also, Windsor was showing a symptom that was most peculiar, he had an enlarged spleen and liver. I knew it was leucocythemia when I examined his blood vessels. They were are dilated, which decreases his blood pressure. Windsor did not make it out alive, but his case has just helped many generations to come. I believe I have just diagnosed the first of many patients with leucocythemia.

I had some help from doctors that have come before me. In 1811, Peter Cullen discovered a case he named Splenitis Acutus with abnormal milky blood. Splenitis Acutus is the decrepit name for leucocythemia. Just a few years after Cullen's discovery in 1825, Alfred Velpeau observed puss in blood vessels and noted more symptoms for splenitis acutus. This is when the disease started to evolve into more of a serious disease. The doctors understood that Splenitis Acutus affected the blood cells but they did not know which blood cells were mainly affected. In 1844 Alfred Donné discovered the slowing down of the maturing process of white blood cells. This was a breakthrough because a new piece was added to the mystery of Splenitis Acutus. The doctors now knew what was being directly affected, white blood cells, which protects the body from infections and diseases. Then in 1845 John Bennet renamed Splenitis Acutus to leucocythemia in his paper titled, Case of Hypertrophy of the Spleen and Liver in which Death Took Place from Suppuration of the Blood. Splenitis Acutus was no longer the name the disease. In the same year Rudolf Virchow defined a reverse white and red blood cell balance to add another symptom of leucocythemia to the list. That was the last discovery until I came along and diagnosed the first patient with leucocythemia. The previous doctors' studies helped me make my conclusion of the first patient with leucocythemia.

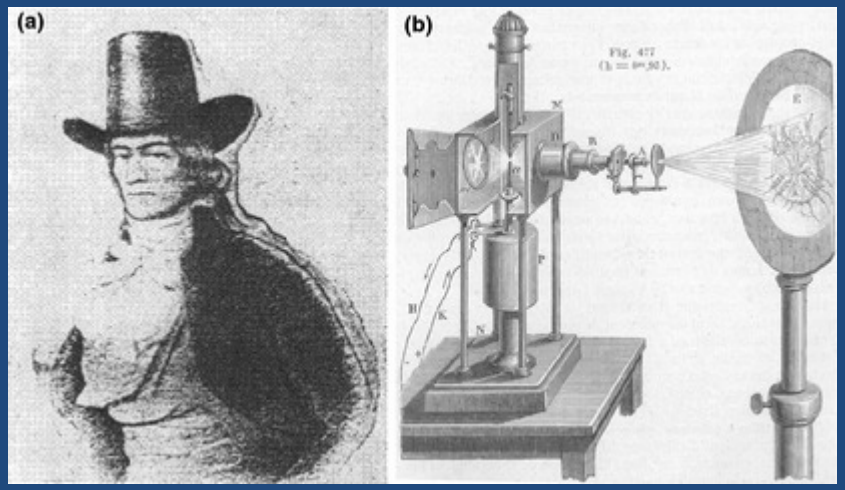
Thomas Windsor is dead, but many people will live because of him. Thomas Windsor was only 22 years of age and leucocythemia stole the most precious thing in the world, life. This discovery will make my name known and I will try everyday of my life to find a cure for this wretched disease. I respect all of the doctors that have made discoveries before me and with all of the information I have gathered from them, I will make the disease come to an end. If this does not work then leucocythemia will affect many generations after my death.

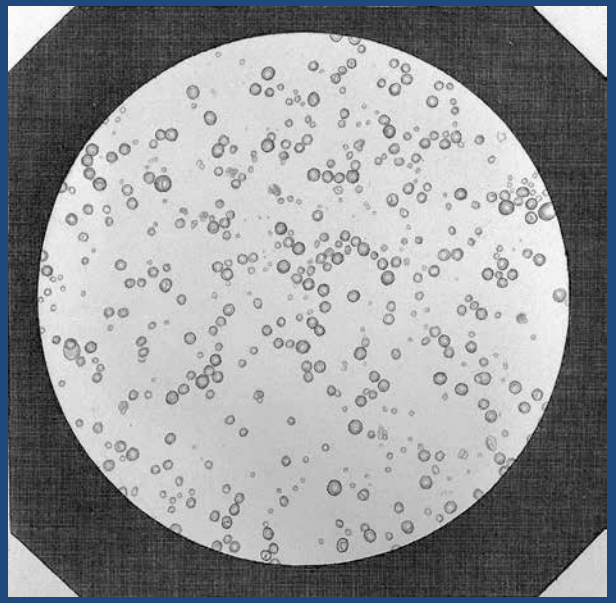
Until next time,

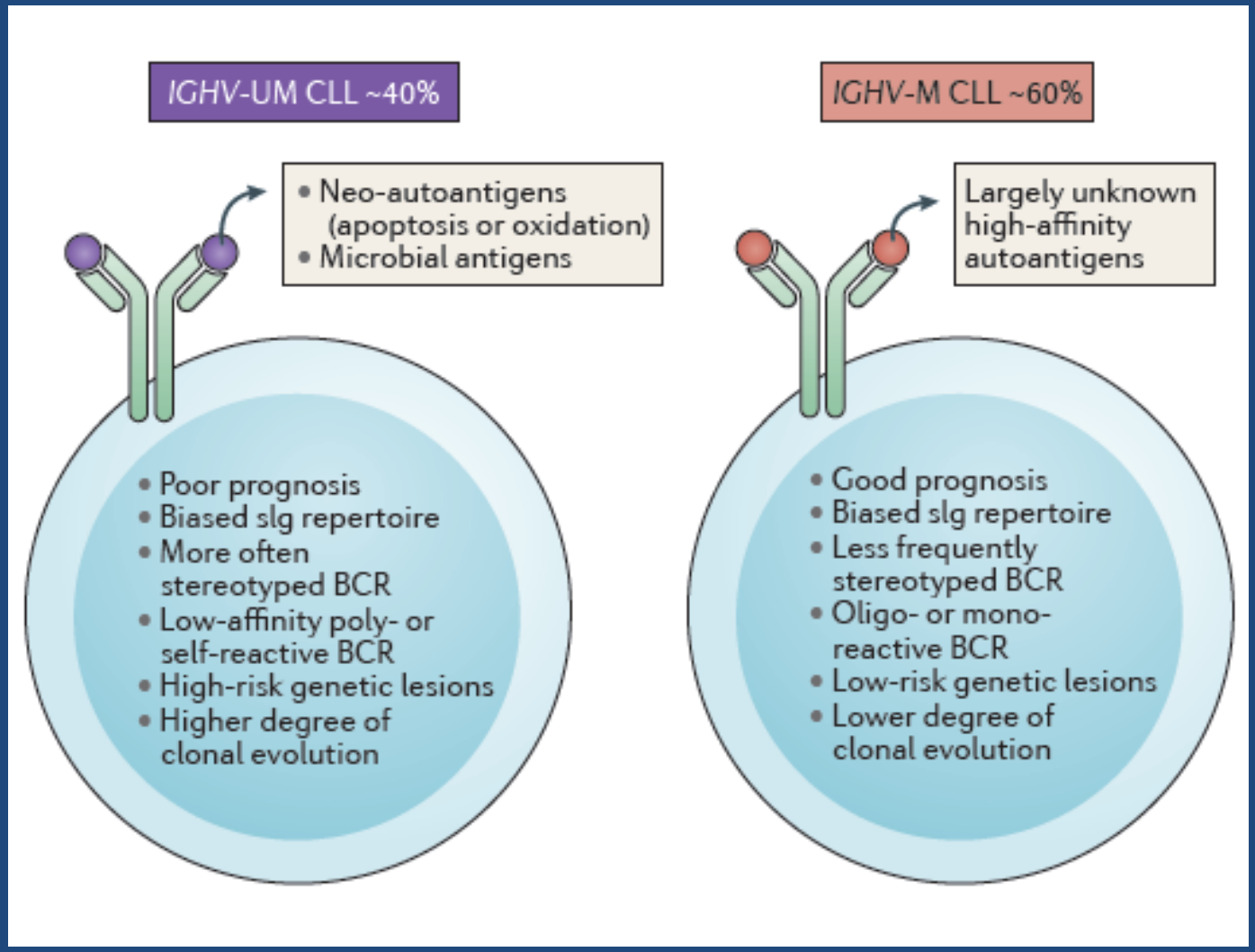
Henry Fuller

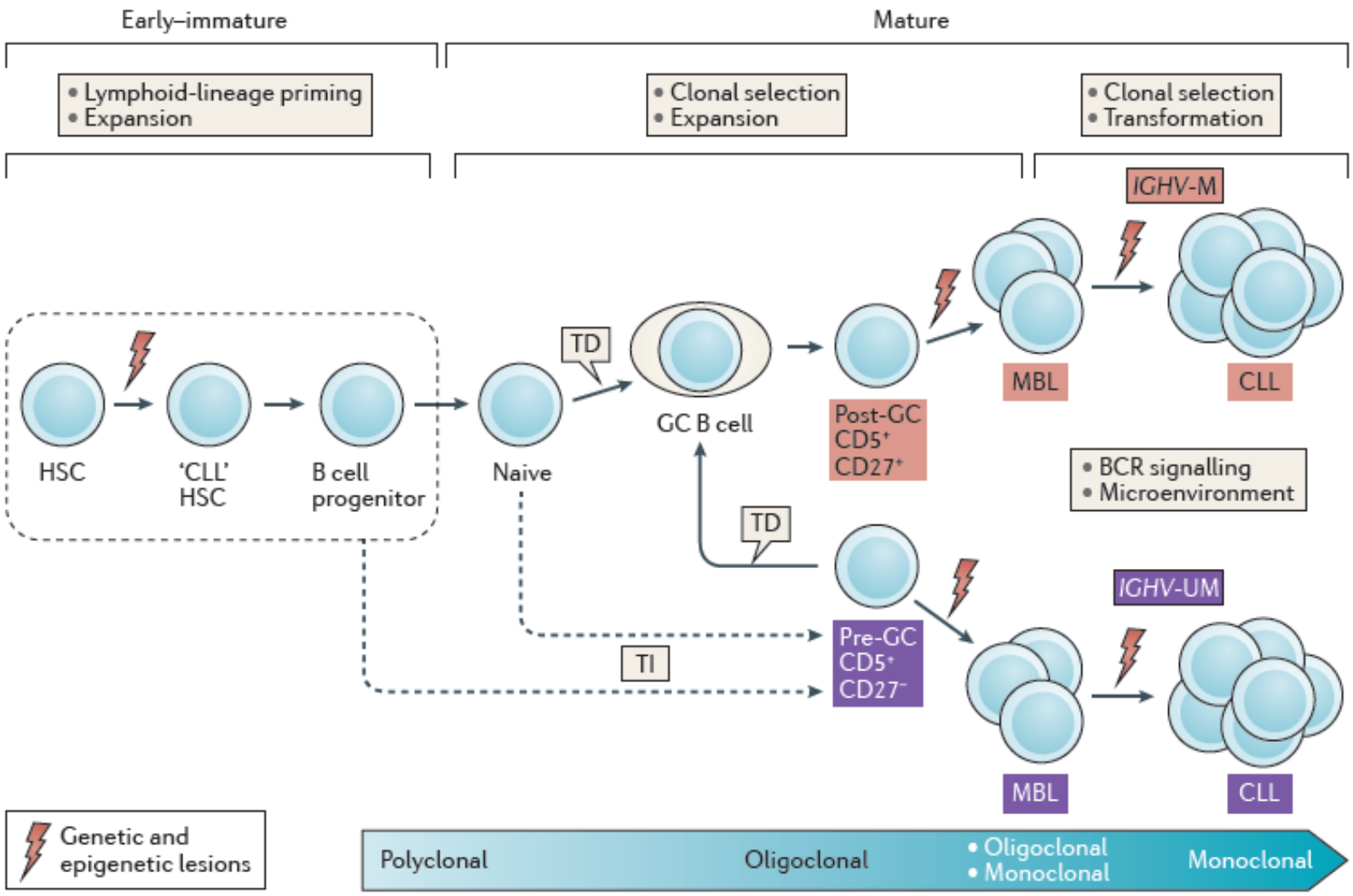
1846

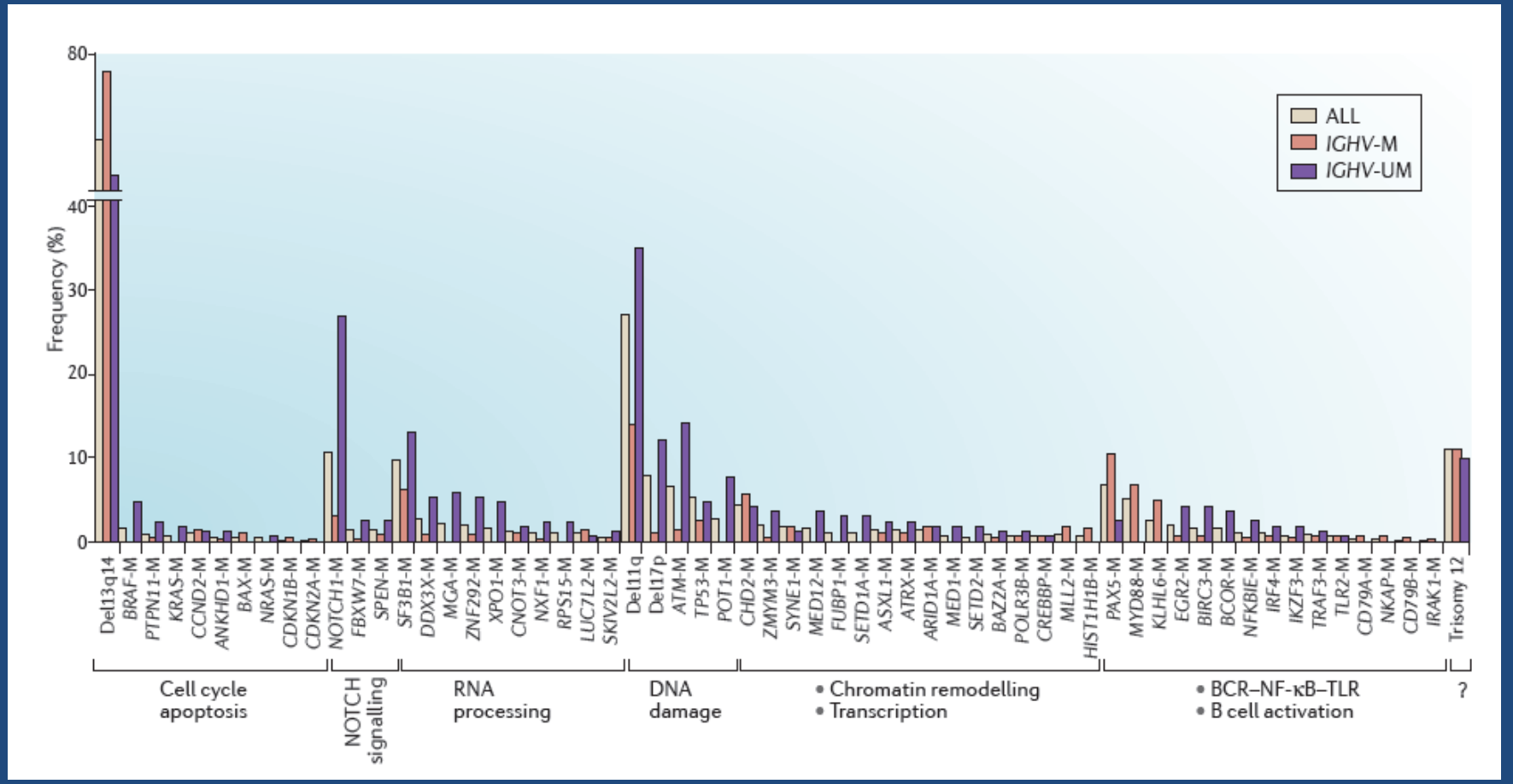
1845

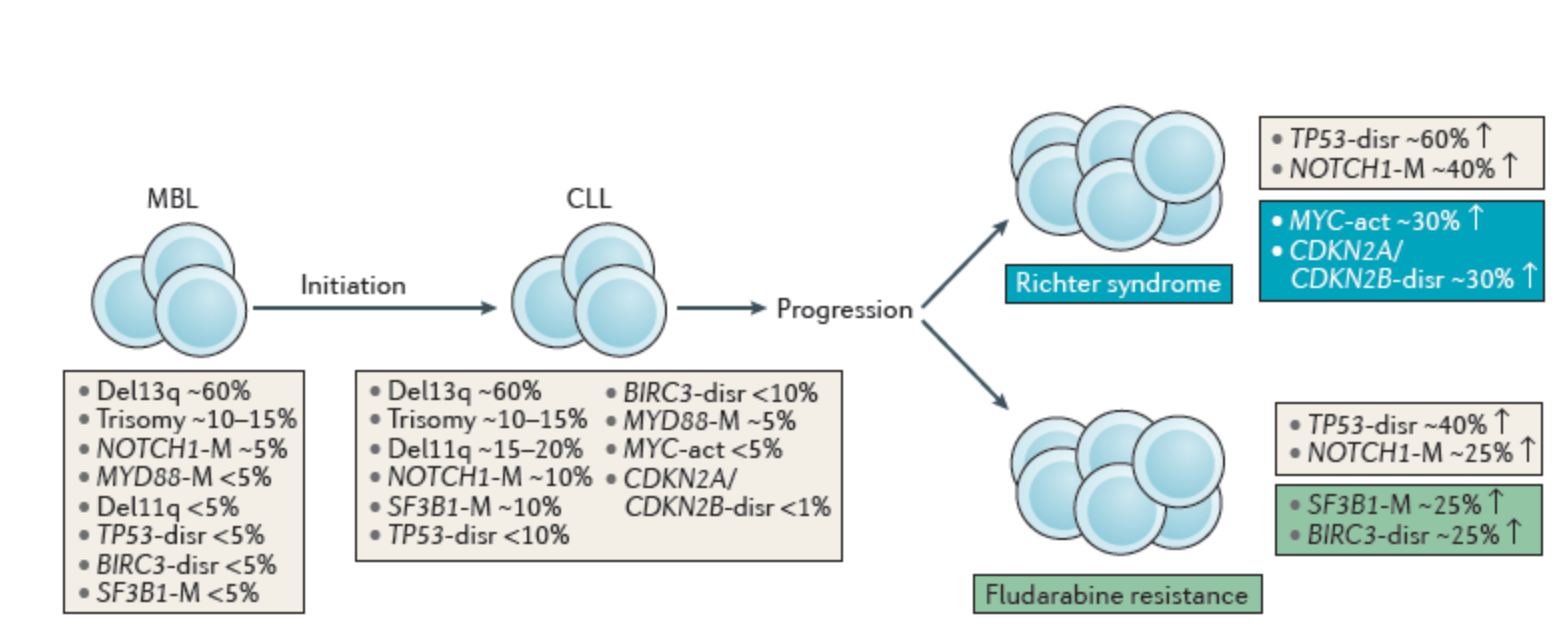





IGHV-UM CLL ~40%
• Neo-autoantigens (apoptosis or oxidation)
• Microbial antigens
• Poor prognosis
• Biased slg repertoire
• More often stereotyped BCR
• Low-affinity poly- or self-reactive BCR
• High-risk genetic lesions
• Higher degree of clonal evolution
IGHV-M CLL ~60%
Largely unknown high-affinity autoantigens
• Good prognosis
• Biased slg repertoire
• Less frequently stereotyped BCR
• Oligo- or mono-reactive BCR
• Low-risk genetic lesions
• Lower degree of clonal evolution


Early–immature
Mature
• Lymphoid-lineage priming
• Expansion
• Clonal selection
• Expansion
• Clonal selection
• Transformation
IGHV-M
HSC
'CLL' HSC
B cell progenitor
Naive
TD
GC B cell
Post-GC CD5+ CD27+
MBL
CLL
• BCR signalling
• Microenvironment
TD
IGHV-UM
TI
Pre-GC CD5+ CD27−
MBL
CLL
Genetic and epigenetic lesions
Polyclonal
Oligoclonal
• Oligoclonal
• Monoclonal
Monoclonal


80
40
30
20
10
0
Frequency (%)
ALL
IGHV-M
IGHV-UM
Del13q14
BRAF-M
PTPN11-M
KRAS-M
CCND2-M
ANKHD1-M
BAX-M
NRAS-M
CDKN1B-M
CDKN2A-M
NOTCH1-M
FBXW7-M
SPEN-M
SF3B1-M
DDX3X-M
MGA-M
ZNF292-M
XPO1-M
CNOT3-M
NXF1-M
RPS15-M
LUC7L2-M
SKIV2L2-M
Del11q
Del17p
ATM-M
TP53-M
POT1-M
CHD2-M
ZMYM3-M
SYNE1-M
MED12-M
FUBP1-M
SETD1A-M
ASXL1-M
ATRX-M
ARID1A-M
MED1-M
SETD2-M
BAZ2A-M
POLR3B-M
CREBBP-M
MLL2-M
HIST1H1B-M
PAX5-M
MYD88-M
KLHL6-M
EGR2-M
BIRC3-M
BCOR-M
NFKBIE-M
IRF4-M
IKZF3-M
TRAF3-M
TLR2-M
CD79A-M
NKAP-M
CD79B-M
IRAK1-M
Trisomy 12
Cell cycle apoptosis
NOTCH signalling
RNA processing
DNA damage
• Chromatin remodelling
• Transcription
• BCR–NF-κB–TLR
• B cell activation
?


MBL
Initiation
CLL
Progression
• Del13q ~60%
• Trisomy ~10–15%
• NOTCH1-M ~5%
• MYD88-M <5%
• Del11q <5%
• TP53-disr <5%
• BIRC3-disr <5%
• SF3B1-M <5%
• Del13q ~60%
• Trisomy ~10–15%
• Del11q ~15–20%
• NOTCH1-M ~10%
• SF3B1-M ~10%
• TP53-disr <10%
• BIRC3-disr <10%
• MYD88-M ~5%
• MYC-act <5%
• CDKN2A/CDKN2B-disr <1%
Richter syndrome
• TP53-disr ~60% ↑
• NOTCH1-M ~40% ↑
• MYC-act ~30% ↑
• CDKN2A/CDKN2B-disr ~30% ↑
Fludarabine resistance
• TP53-disr ~40% ↑
• NOTCH1-M ~25% ↑
• SF3B1-M ~25% ↑
• BIRC3-disr ~25% ↑

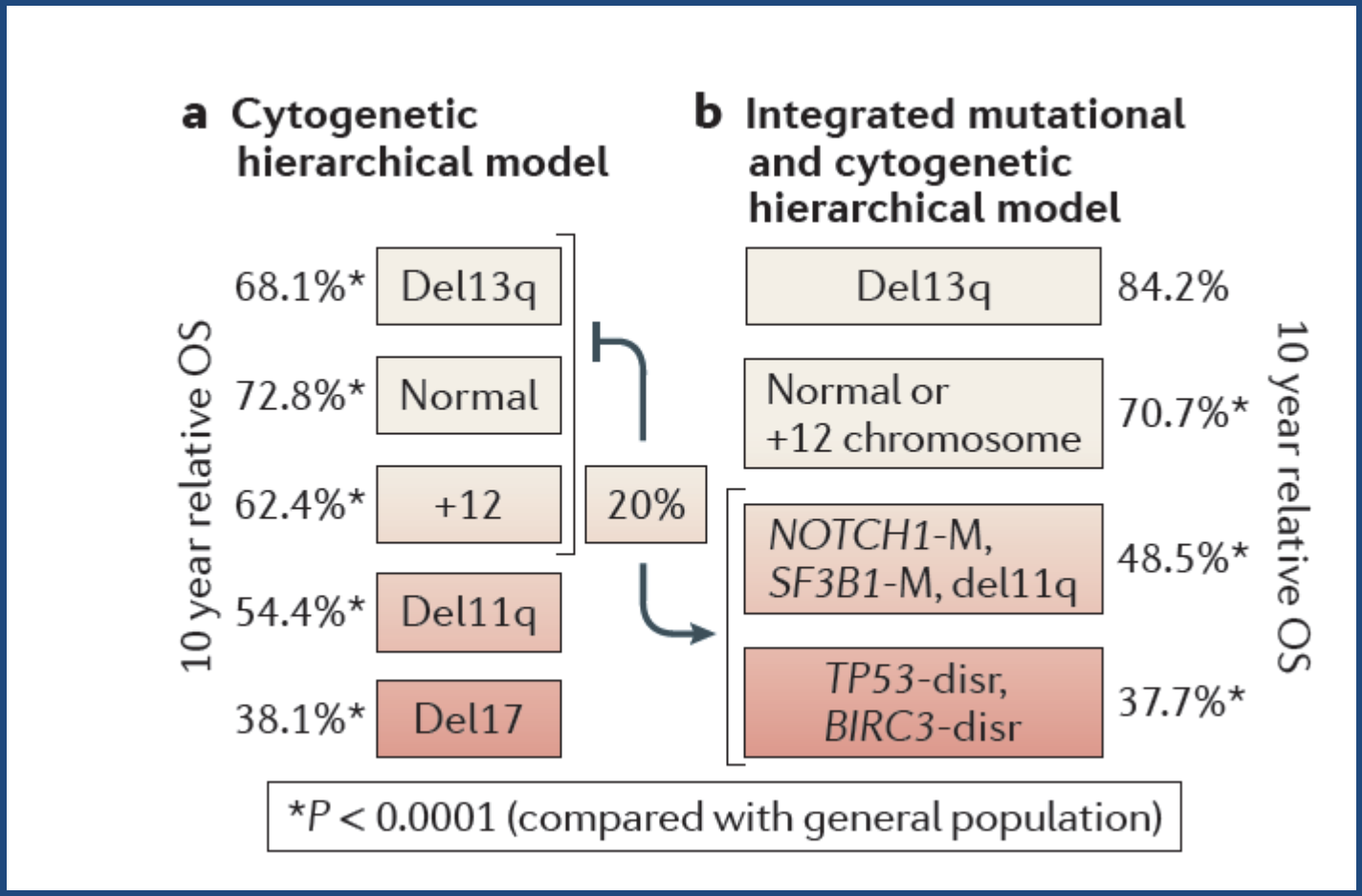

a Cytogenetic hierarchical model
b Integrated mutational and cytogenetic hierarchical model
10 year relative OS
68.1%*
Del13q
72.8%*
Normal
62.4%*
+12
54.4%*
Del11q
38.1%*
Del17
20%
Del13q
84.2%
Normal or +12 chromosome
70.7%*
NOTCH1-M, SF3B1-M, del11q
48.5%*
TP53-disr, BIRC3-disr
37.7%*
10 year relative OS
*P < 0.0001 (compared with general population)

Table 1. Biomarkers Associated With Chronic Lymphocytic Leukemia

Abnormality	Prognosis	Detection Method
Chromosomal abnormalities		
13q del	Favorable	FISH, array-based methods, karyotype
+12	Likely poor	
11q del	Poor	
17p del	Poor	
Protein expression		
ZAP-70	Poor	Flow cytometry
CD38	Poor	
IGVH mutational status		
Unmutated	Poor	Sequencing
Hypermutation	Favorable	
VH3-21 use	Poor	
Recurrent somatic gene mutations		
TP53	Poor	Sequencing
NOTCH1	Poor	

Abbreviation: FISH, fluorescence in situ hybridization.

1827

2016

CUADRO CLINICO

INMUNOHISTOQUIMICA

EXA

LUJO

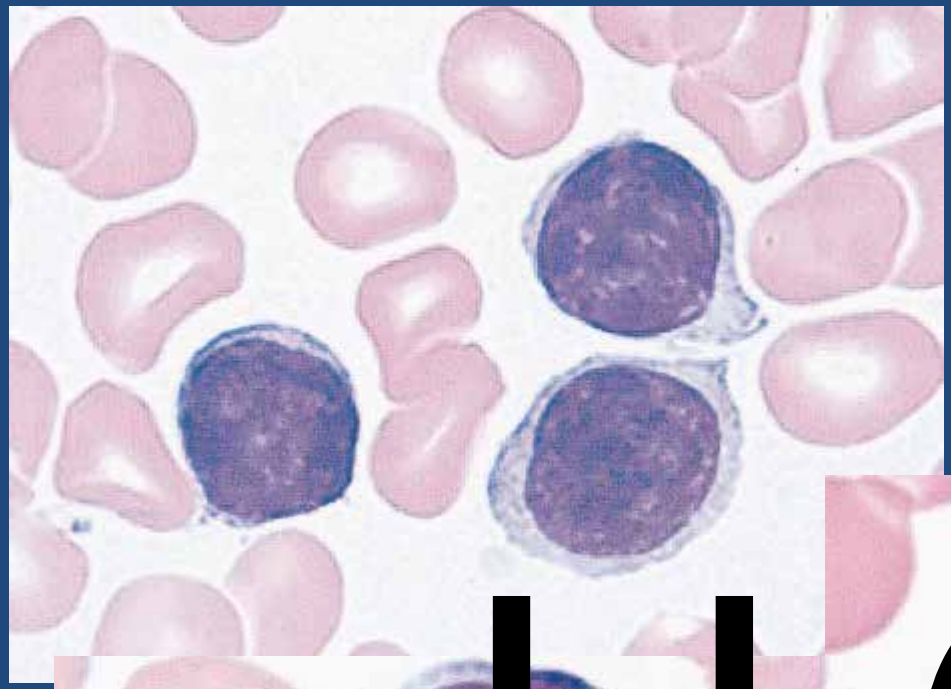
MOR

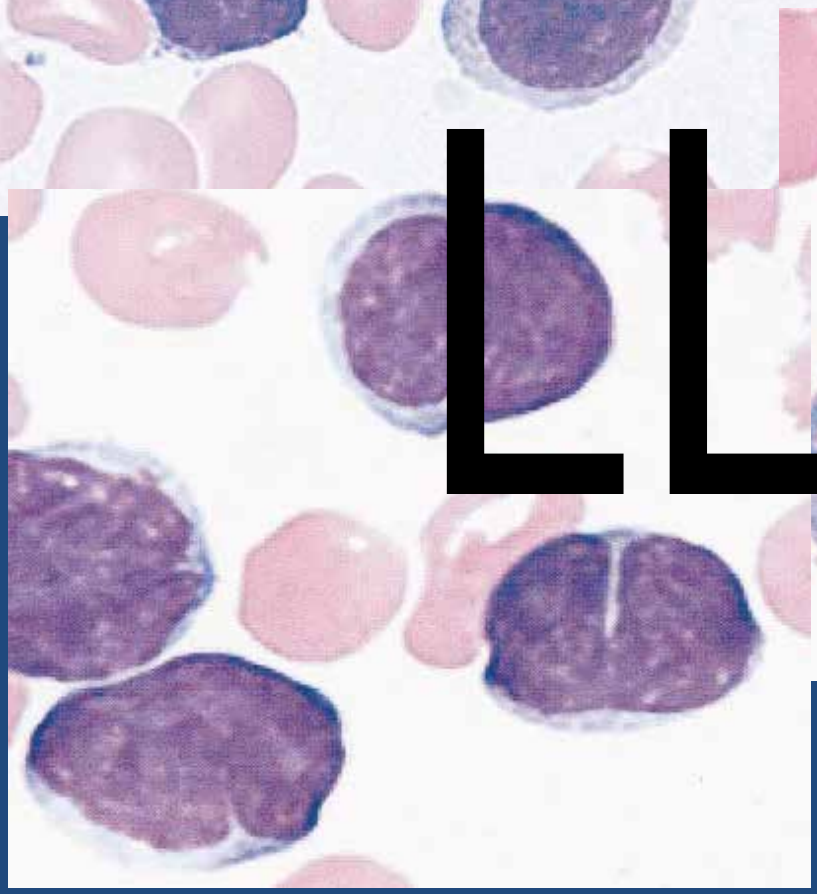
ETICA

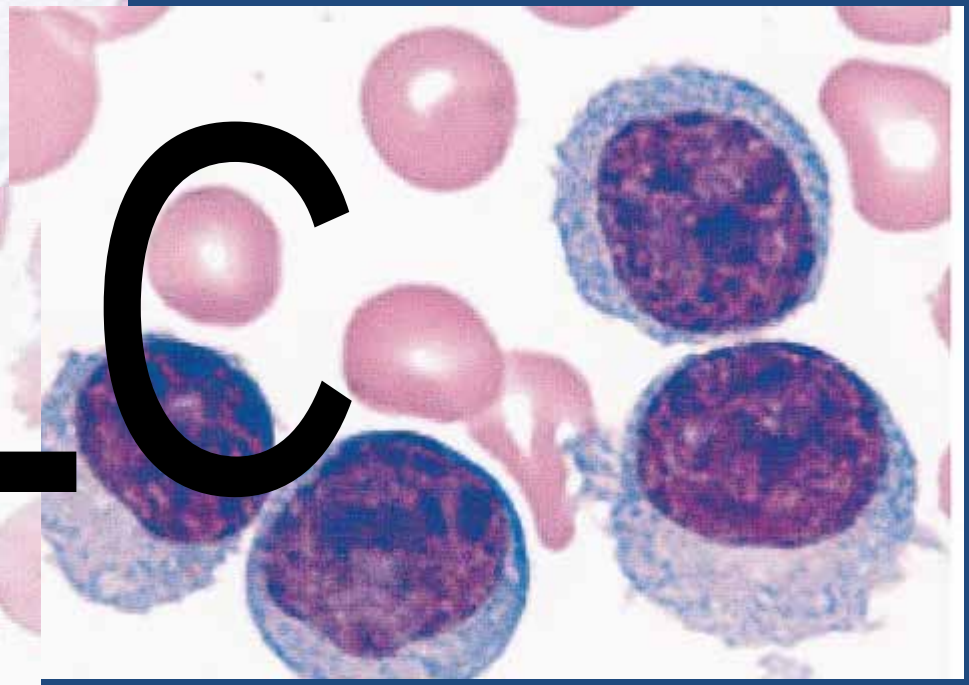
MORFOLOGIA

INMUNOHISTOQUIMICA

BIOLOGIA MOLECULAR



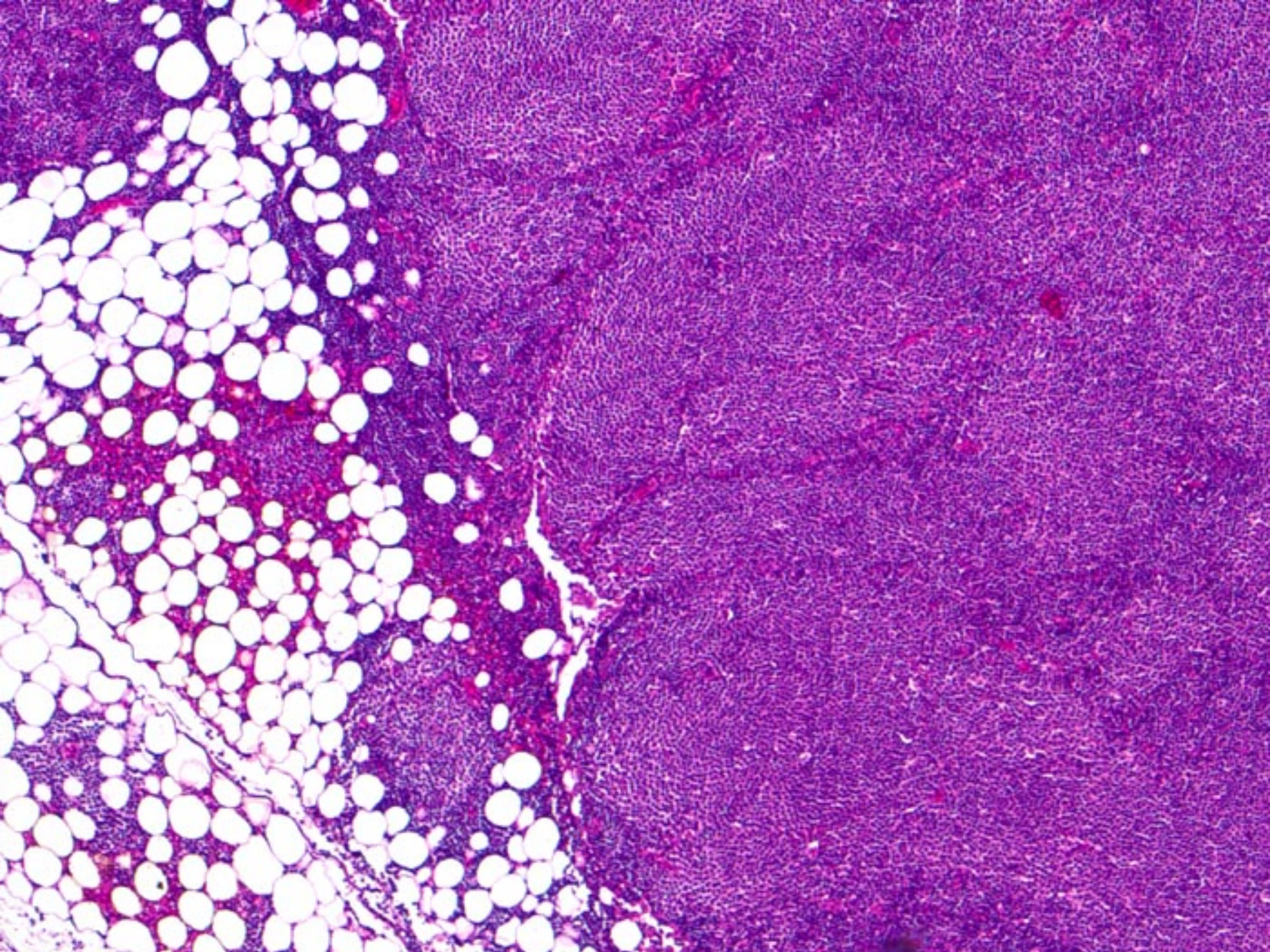


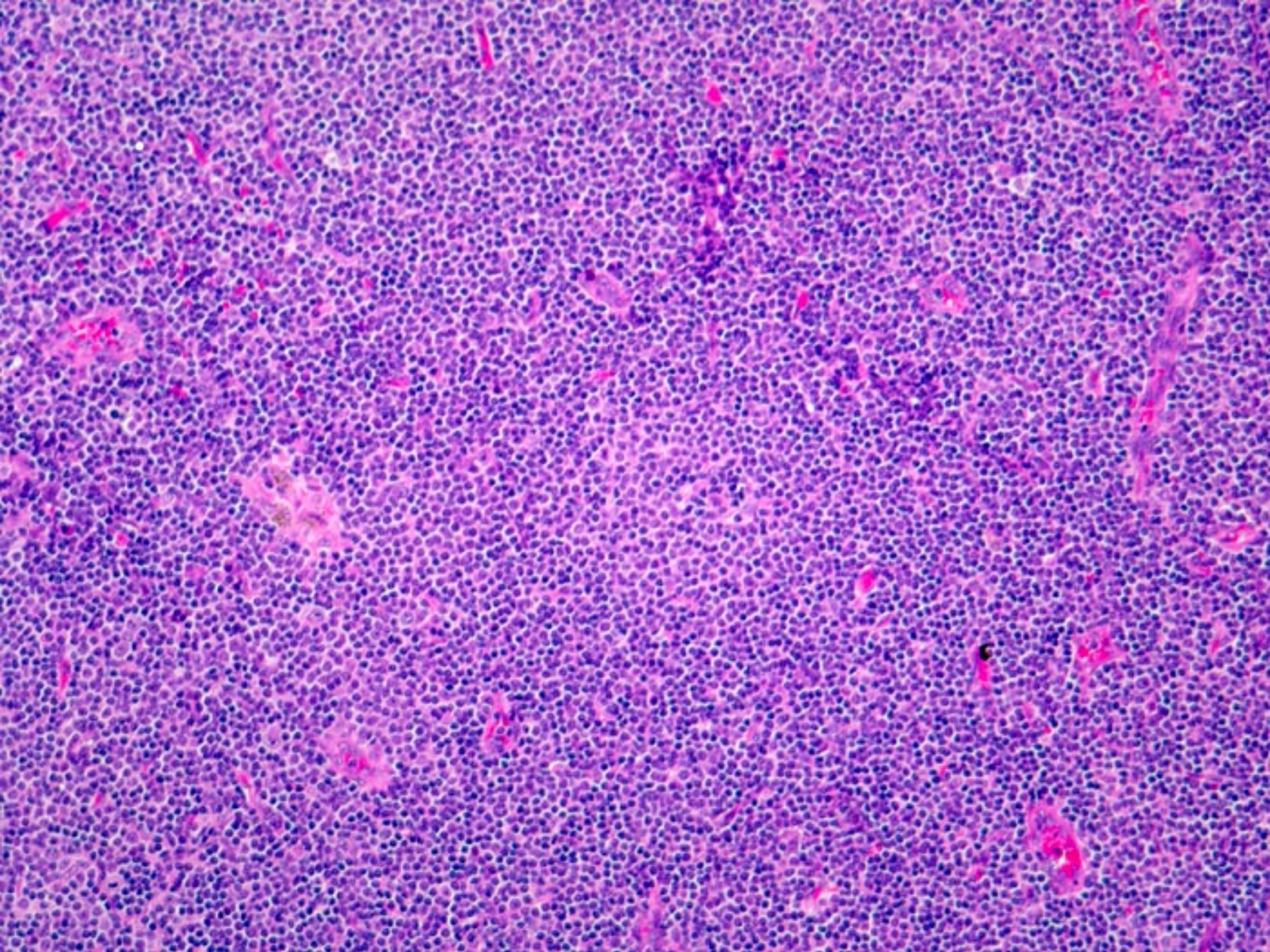


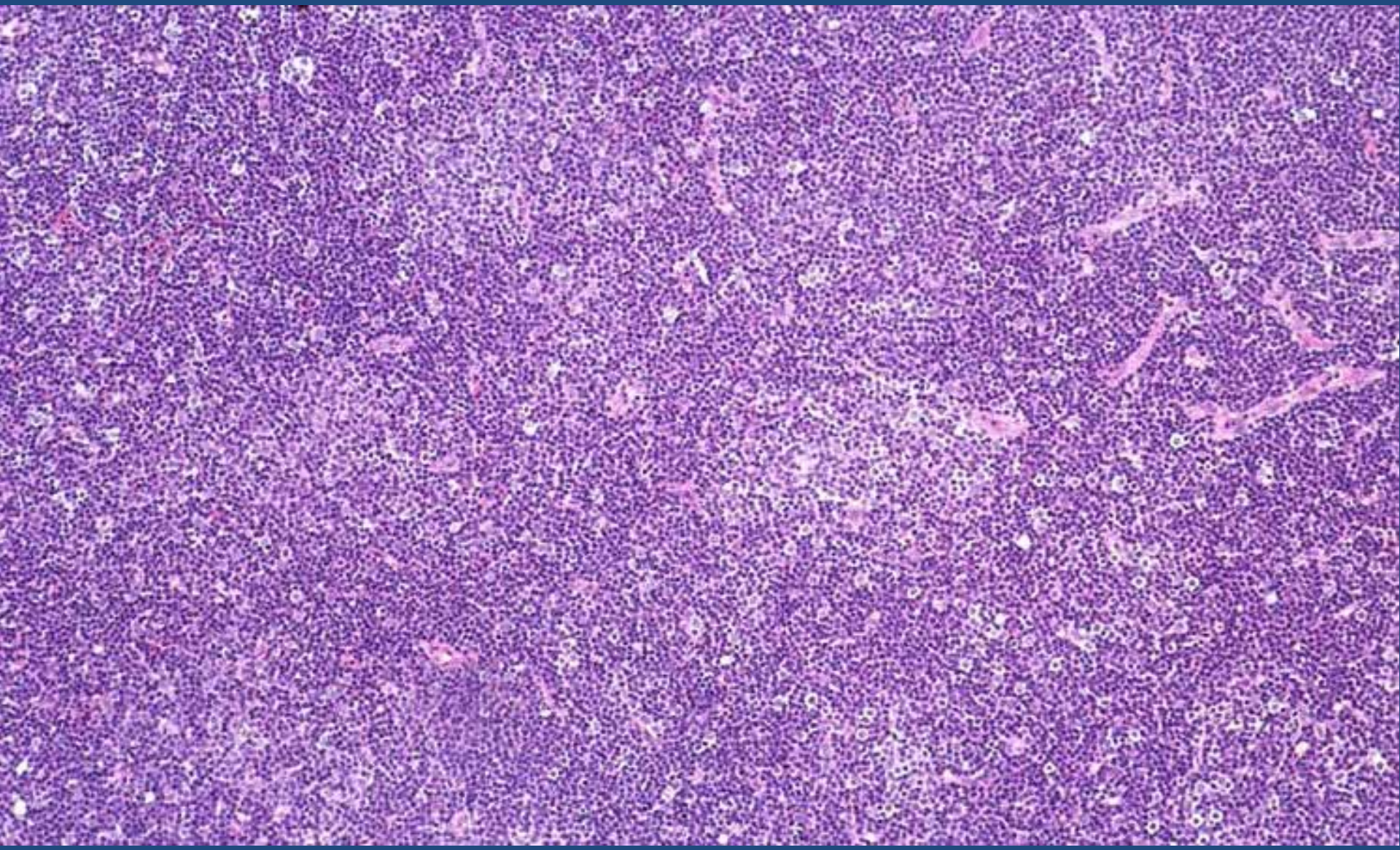
LLC

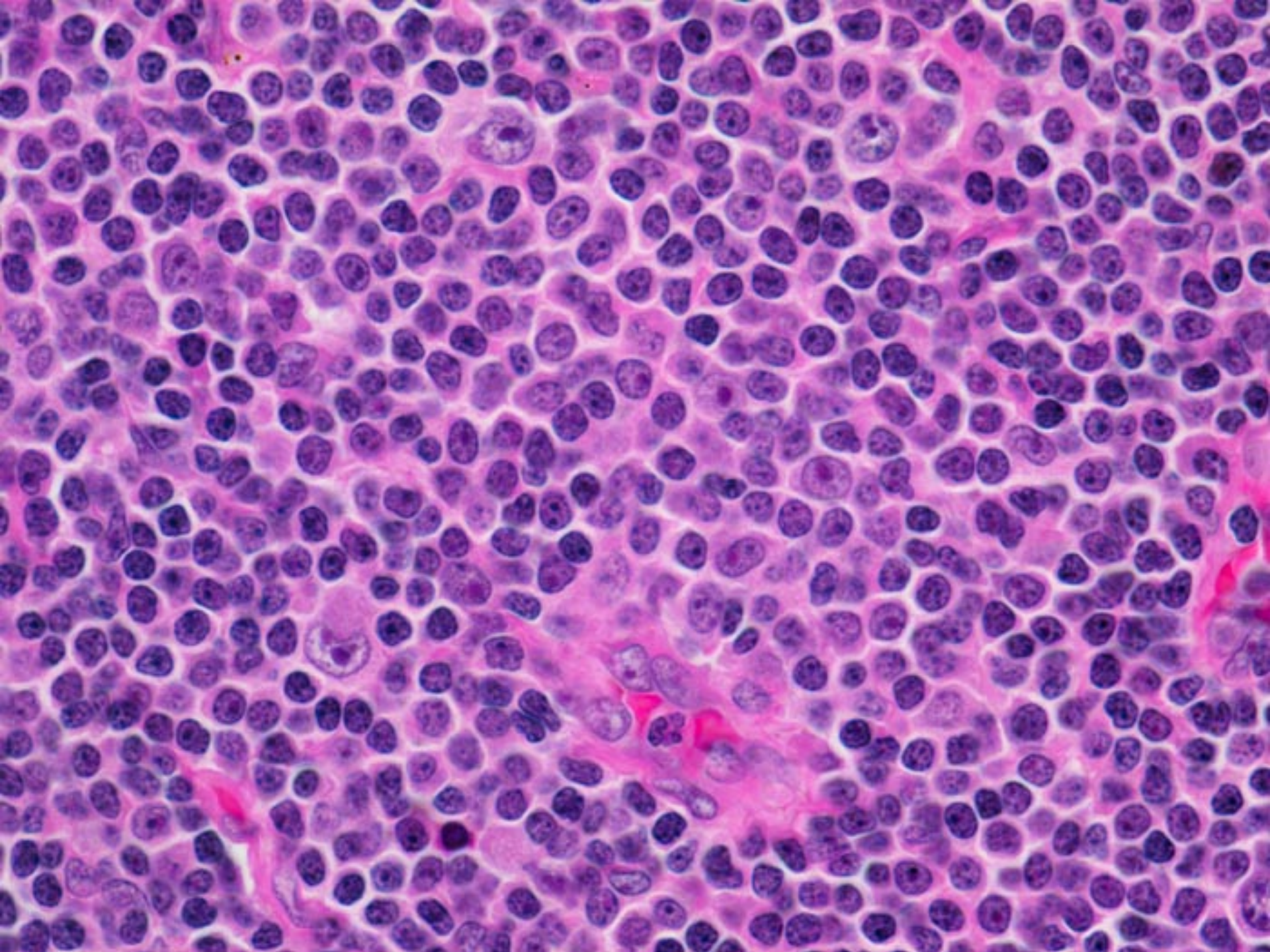
MORFOLOGIA

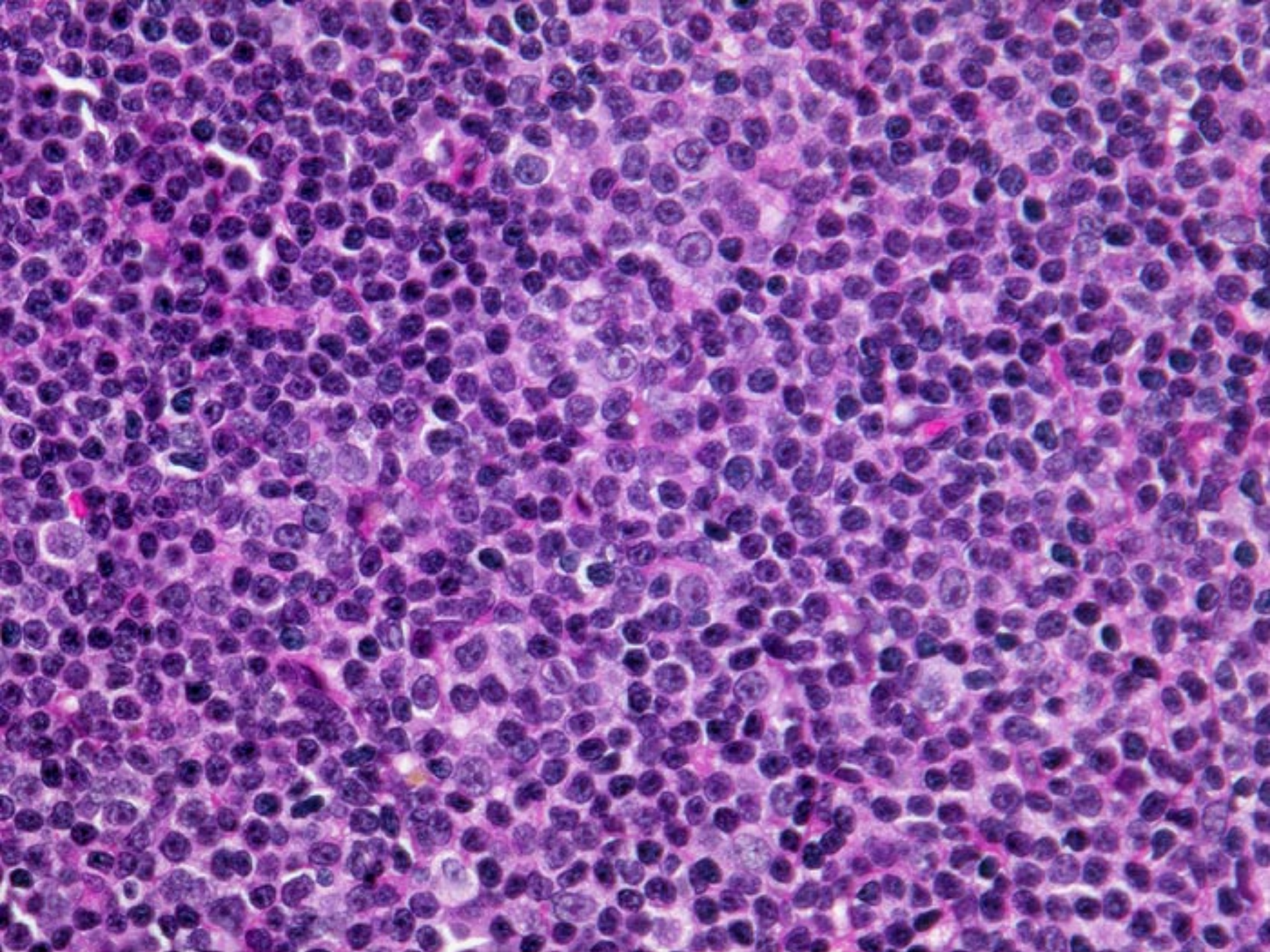
- LINFONODOS:
- LINFOCITOS PEQUEÑOS, LEVEMENTE MAS GRANDES QUE LOS LINFOCITOS NORMALES.
- DESTRUCCION DE LA ARQUITECTURA POR UN PATRON DIFUSO O PSEUDOFOLICULAR.
- ZONAS ”PALIDAS” LLAMADAS CENTROS DE PROLIFERACION.
- ACTIVIDAD MITOTICA USUALMENTE MUY BAJA.

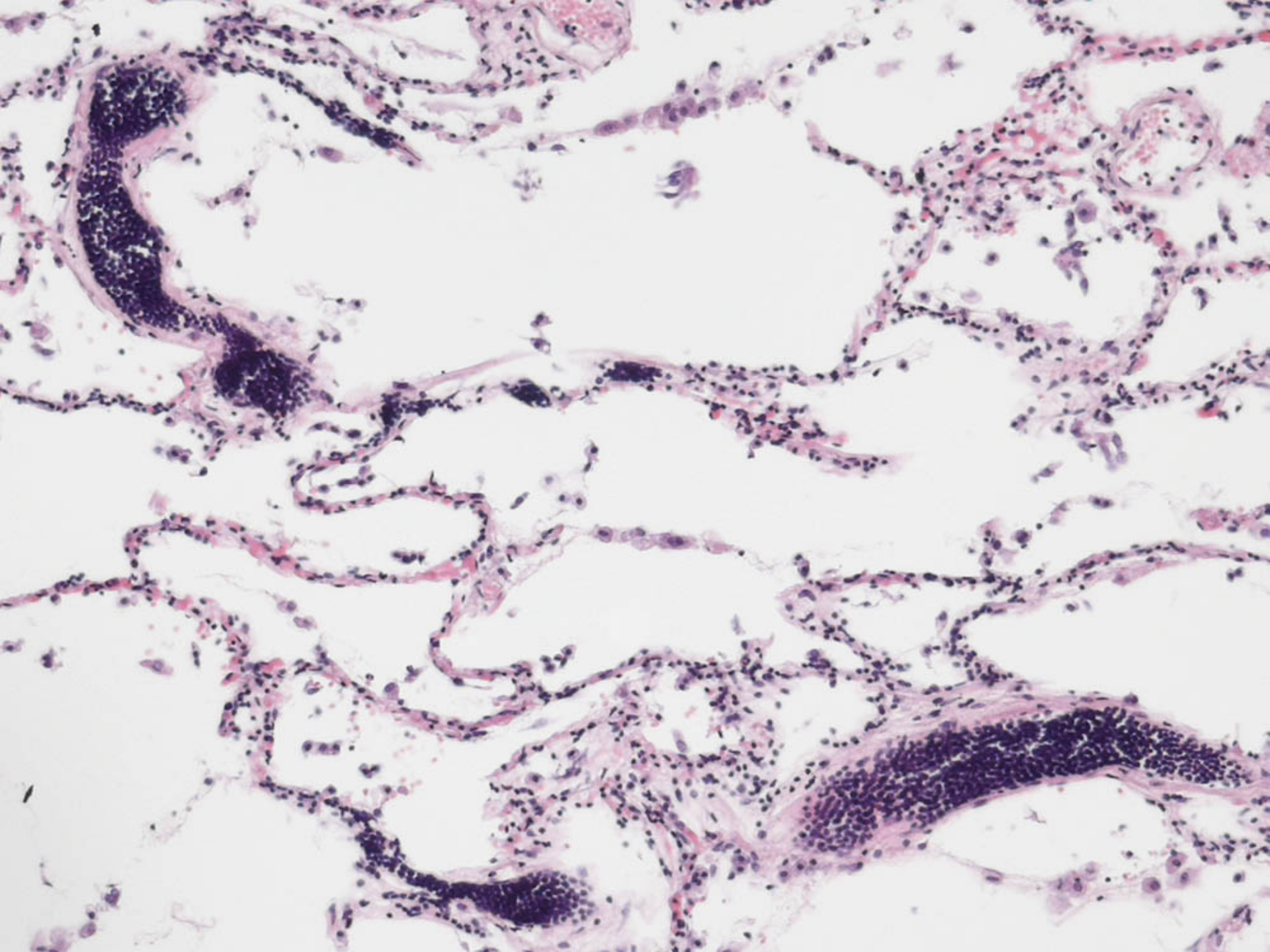


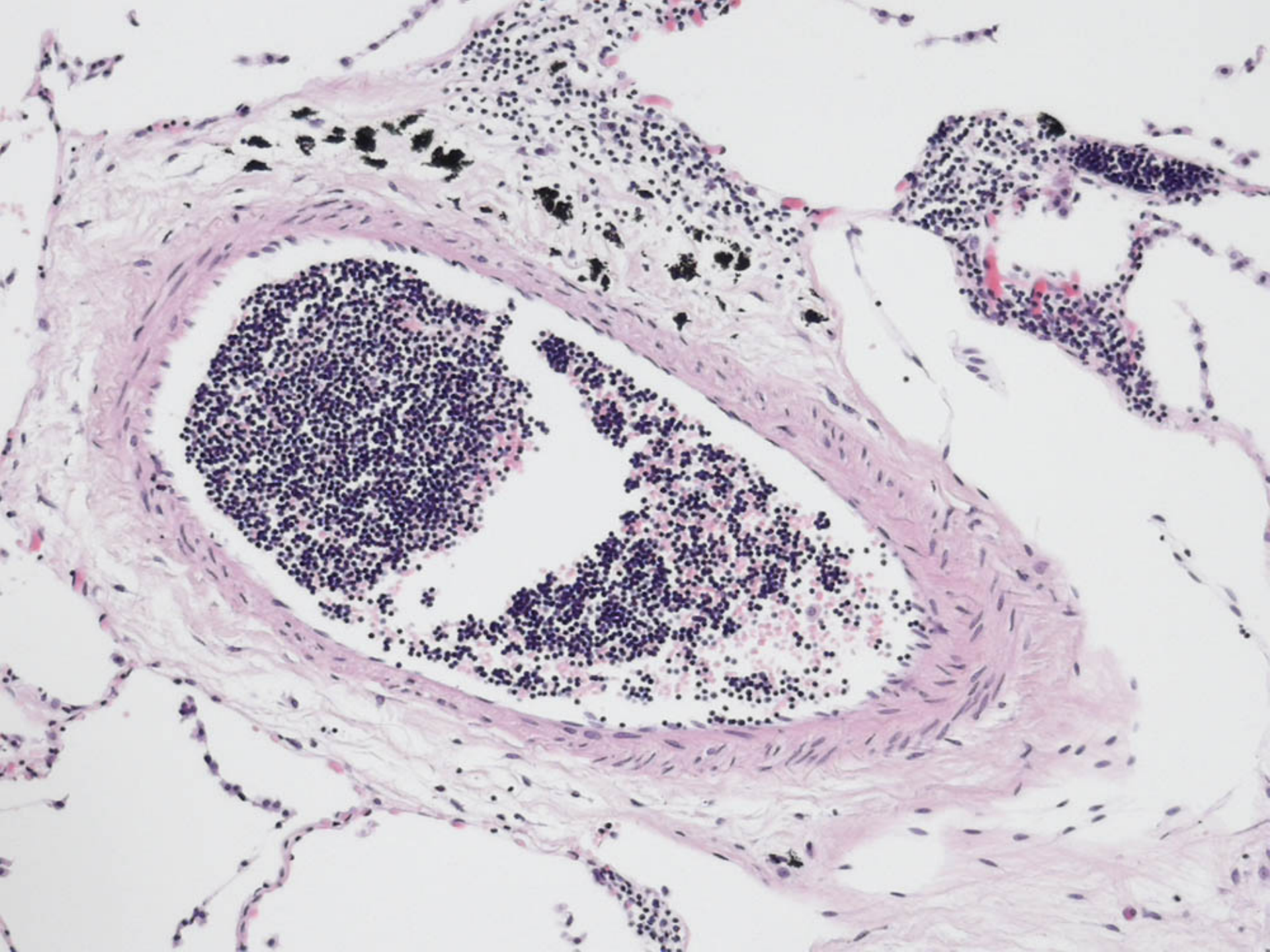












INMUNOHISTOQUIMICA

- MARCADORES USUALMENTE UTILIZADOS
- CD45, CD20, CD5, CD23.

- SUMADO A LAS TINCIONES UTILIZADAS PARA EL DIAGNOSTICO DIFERENCIAL

Small Lymphocytic Lymphoma with Perifollicular, Marginal Zone, or Interfollicular Distribution

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Kojo S.J. Elenitoba-Johnson, M.D.

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Mod Pathol 2000;13(11):1161–1166

Table 1. Clinical Data

Case	Sex	Age (yr)	Biopsy Site	WBC (/mm^3)	Pattern of Involvement	BM	Liver	Spleen	Stage	Rx	Status	Other
1	F	38	Cervical	8900	IF	Y	N	Y	IV	CT	AWD	CMV, EBV
2	M	60	Cervical	7200	IF	N	N	Y	III	CT	AWD	
3	F	68	Cervical	8600	IF	Y	N	N	IV	No	AWD	
4	F	69	Cervical	8800	IF	N	N	N	NA	RT	AWD	History of breast cancer
5	F	88	Axilla	6200	IF	Y	N	N	IV	No	AWD	
6	F	68	Inguinal	5000	IF	N	N	N	III	No	AWD	
7	F	76	Cervical	9000	IF	N	N	N	NA	No	AWD	
8	M	70	Colon	11200	PF/IF	Y	N	N	IV	No	AWD	Colonic adenoCA
9	M	45	Inguinal	3000	MZ/D*	Y	Y	Y	IV	No	AWD	
10	M	74	Cervical	20000	IF	N	N	N	NA	No	AWD	
11	M	66	Cervical	5700	IF	Y	N	N	IV	CT	AWD	
12	F	71	Cervical	NA	MZ	Y	N	N	IV	CT	AWD	
13	M	67	Cervical	10000	IF	Y	Y	Y	IV	CT	AWOD	
14	M	60	Inguinal	30000	IF	Y	N	N	IV	CT	AWD	
15	M	66	Cervical	10000	MZ/D*	Y	Y	N	N	IV	CT	AWD History of LBCL
16	F	64	Cervical	10000	IF	N	N	N	NA	No	AWD	

AWD, alive with disease; AWOD, alive without disease; DWD, dead with disease; BM, bone marrow; CMT, chemotherapy; Rx, treatment; IF, interfollicular; MZ, marginal zone pattern; PF, perifollicular; LBCL, large B-cell lymphoma; NA, not available; D*, diffuse involvement in a subsequently available lymph node specimen.

Table 2. Diagnoses by the Referring Pathologists

Diagnosis	Frequency
CLL/SLL	3
Mantle cell lymphoma	3
Marginal zone B-cell lymphoma	3
Follicular lymphoma, grade I–II	2
Composite lymphoma (SLL/CLL with follicular small cleaved lymphoma)	1
Diffuse large cell B-cell lymphoma	1
Interfollicular Hodgkin's disease	1
Atypical interfollicular proliferation	1
Castleman's disease, hyaline-vascular type	1

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

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Table 1. Common Sites for Small Lymphoid Lymphomas*

Extranodal Site	Types of Small Lymphoid Lymphomas
Skin	T-cell lymphoma (many subtypes in addition to mycosis fungoides); B-cell lymphomas including PCFCL, CLL/SLL, HCL, LPL, MALT lymphoma
Stomach	MALT lymphoma, MCL
GIT (other than stomach)	MCL (lymphomatoid polyposis), primary FL of GIT, MALT lymphoma, CLL/SLL
Upper respiratory system	MALT lymphoma, plasmacytoma
Lungs	CLL/SLL, MALT lymphoma, LG, LPL, FL

* PCFCL indicates primary cutaneous follicle center cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; HCL, hairy cell leukemia; LPL, lymphoplasmacytic lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; GIT, gastrointestinal tract; FL, follicular lymphoma; and LG, lymphomatoid granulomatosis.

Table 2. Major Morphologic Features, Immunophenotype, and Molecular/Cytogenetic Features of Small Lymphoid Lymphomas That Involve Extranodal Sites*

Lymphoma Type	Morphology	Immunophenotype	Cytogenetics
CLL/SLL	Small, round lymphocytes	$CD5^+$, $CD10^-$, $CD23^+$, Bcl-2^+, monoclonal sIg	Deletion 13q14, trisomy 12, deletion 11q22–23, deletion 17p13 (p53 locus)
FL	Centrocytes and centroblasts	$CD5^-$, $CD10^+$, $CD23^-$, Bcl-2^+, Bcl-6^+, monoclonal sIg	t(14;18)(q32;q21)
PCFCL	Centrocytes and centroblasts	$CD10^+$, Bcl-6^+, Bcl-2^-, monoclonal sIg	None
FL-GIT	Same as FL	Same as FL	Same as FL
LPL	Small lymphs, plasmacytoid lymphs, plasma cells	$CD20^+$, IgM^+, some $CD138^+$, $CD5^-$, $CD10^-$, $CD23^-$	None
MCL	Small, round or cleaved cells	$CD5^+$, $CD10^-$, $CD23^-$, Bcl-1^+, Bcl-2^+, Bcl-6^-, monoclonal sIg	t(11;14)(q13;q32)
LG	Variable number of large cells	$CD20^+$ large cells, EBV-$EBER^+$ large cells	None
HCL	Small lymphs	$CD25^+$, $CD11c^+$, $CD103^+$, $TRAP^+$, $DBA.44^+$	None
Plasmacytoma	Plasma cells	$CD38^+$, VS38c, $CD138^+$, $CD19^-$, $CD20^-$, $CD79a^+$, monoclonal cIg	None
MALT	Variable morphology, lymphoepithelial lesions, centrocyte-like, monocytoid, plasma cells	$CD5^-$, $CD10^-$, $CD23^-$ monoclonal cIg in plasma cells	t(11;18)(q21;q21), trisomy 3

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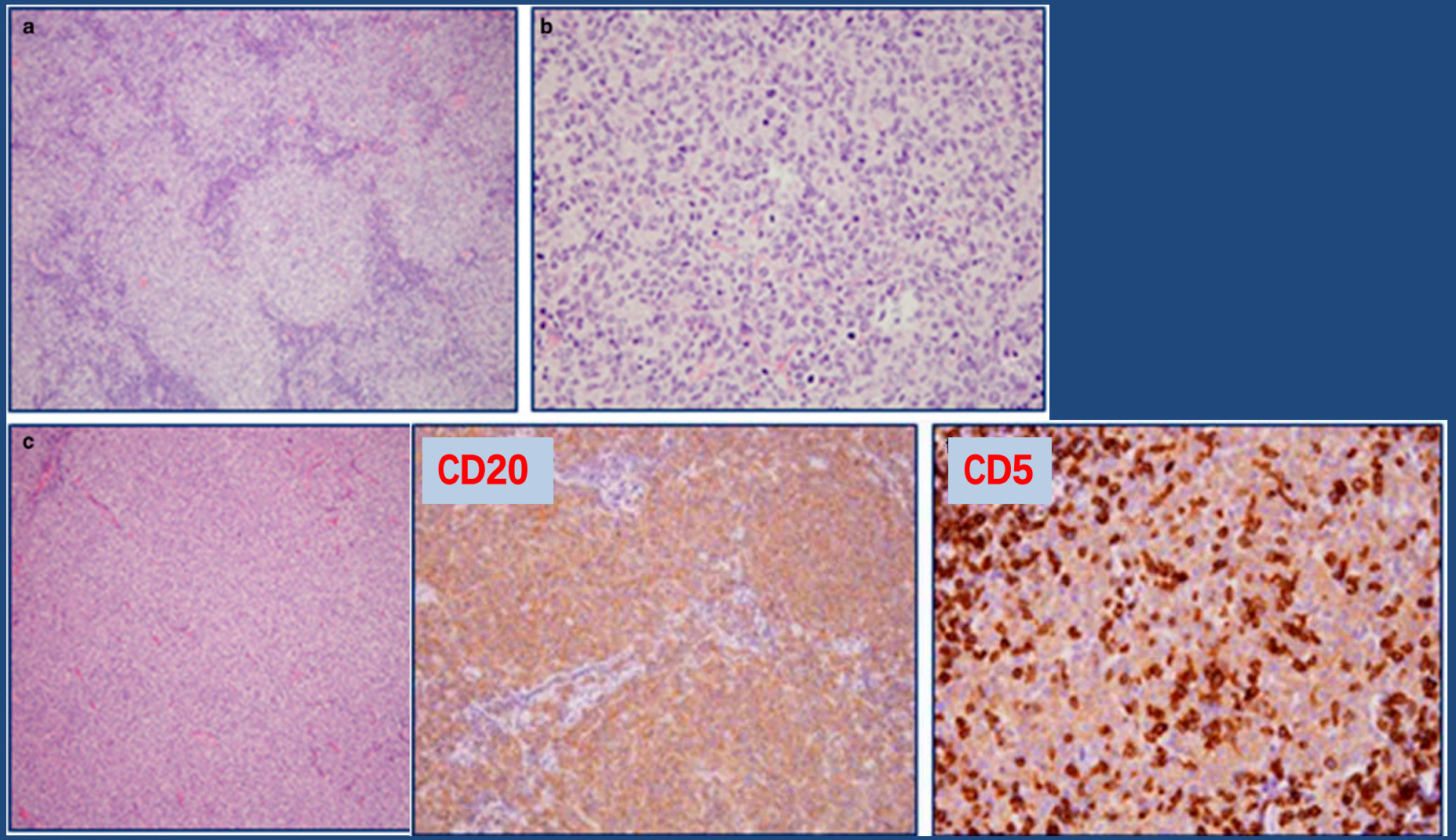
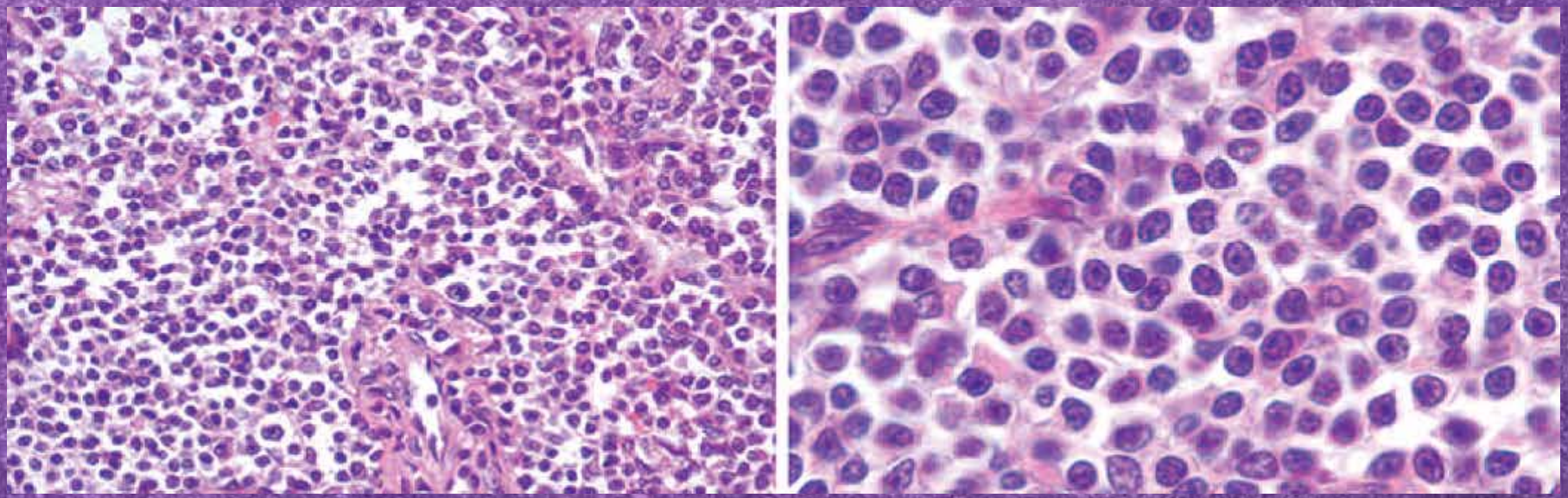
CD5-positive follicular lymphoma: clinicopathologic correlations and outcome in 88 cases

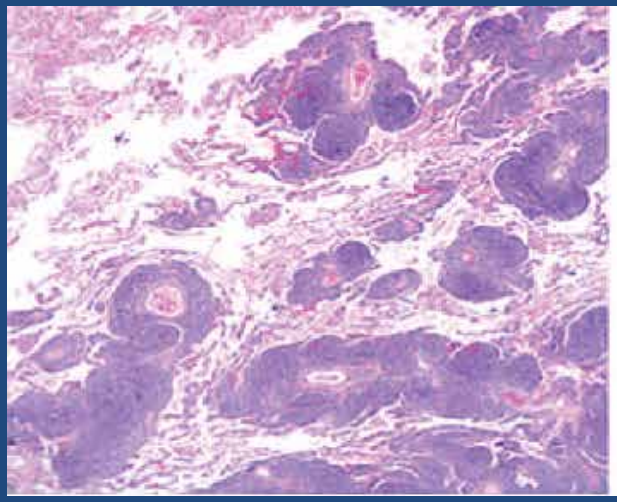
Jeffrey Medeiros et al.



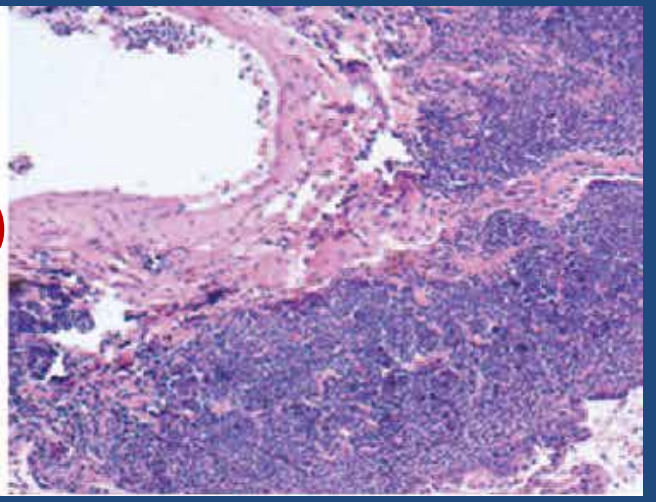
LINFOMA LINFOPLASMOCITICO

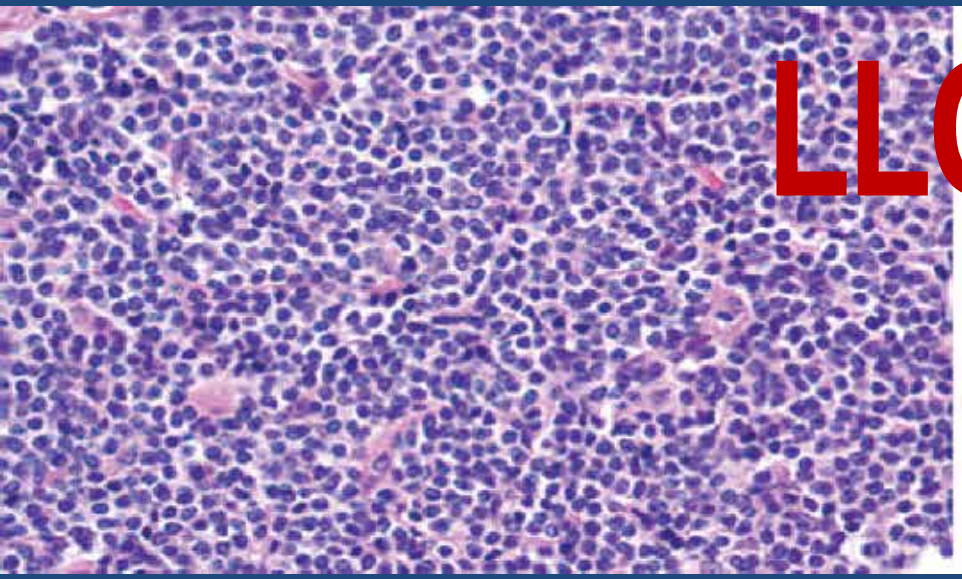
CD138 +/-, CD5, CD23-, CD20+





BALT ??





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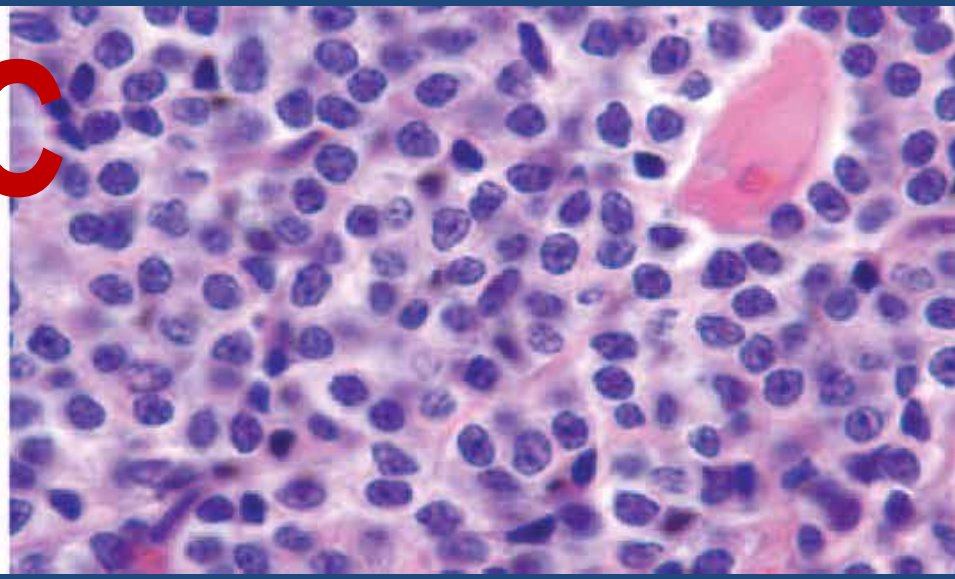
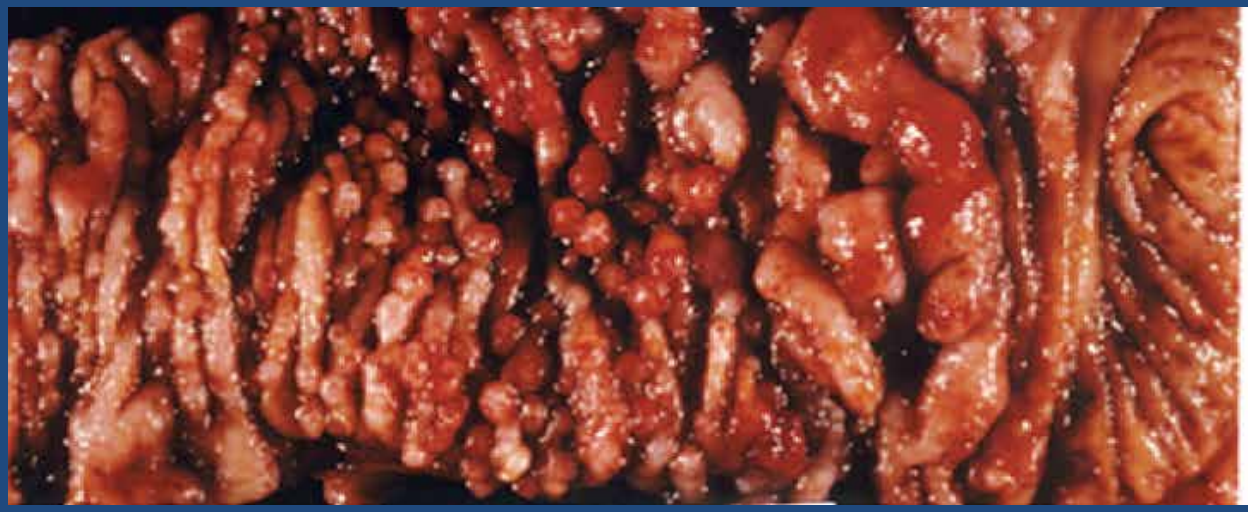
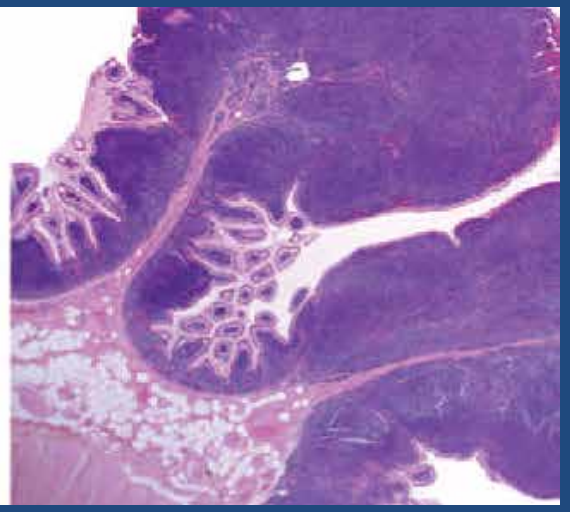
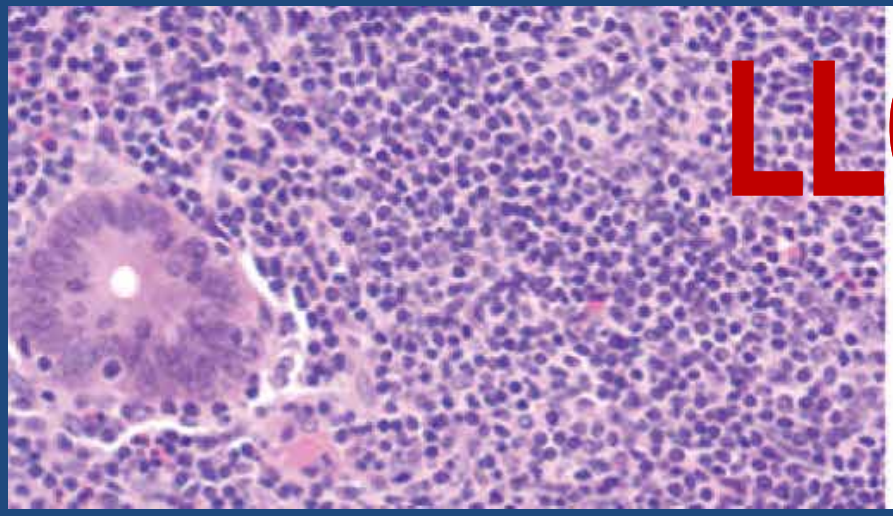


LLC PUEDE PRESENTAR PATRON MONOCITOIDE







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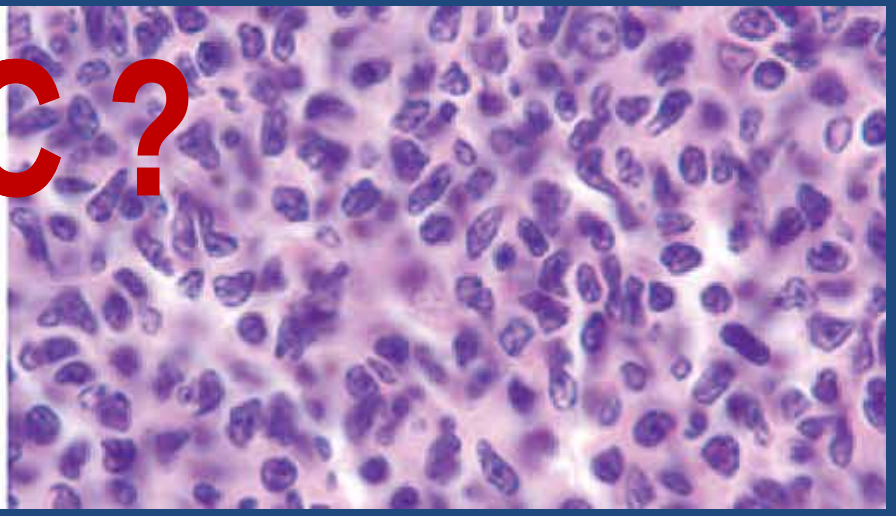
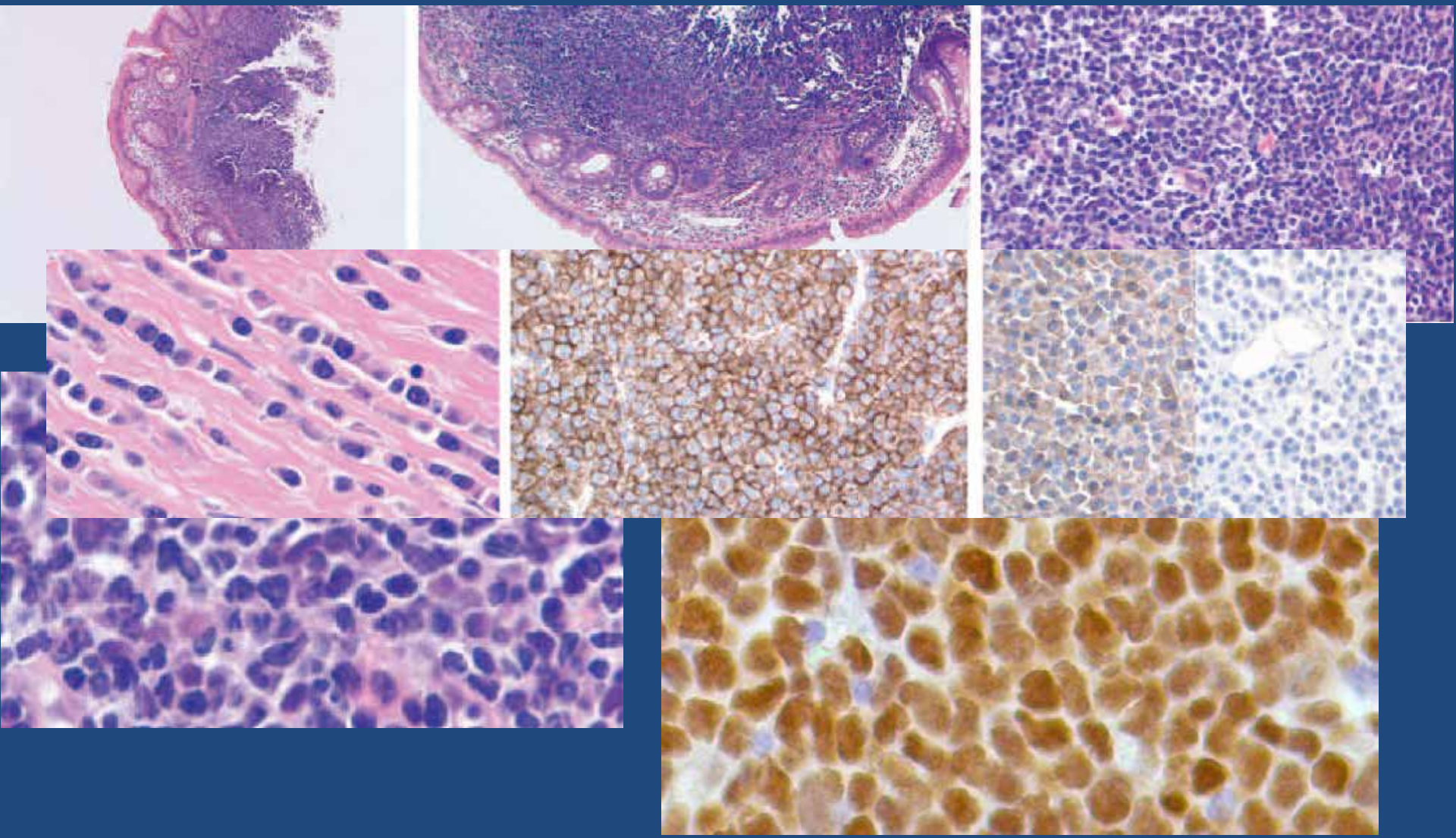
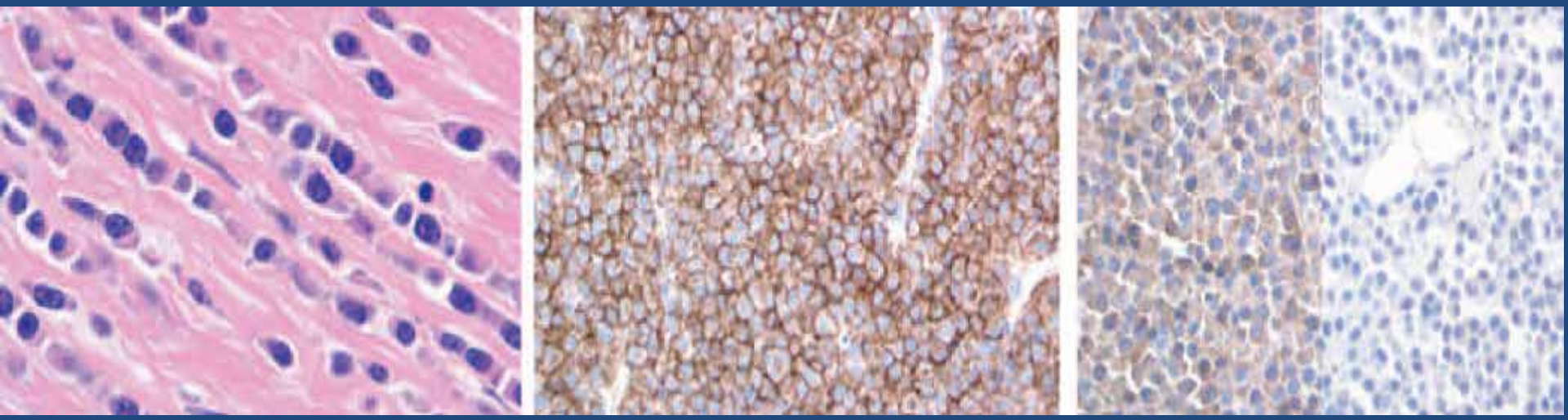


FOLICULAR INTESTINAL

MANTO ?

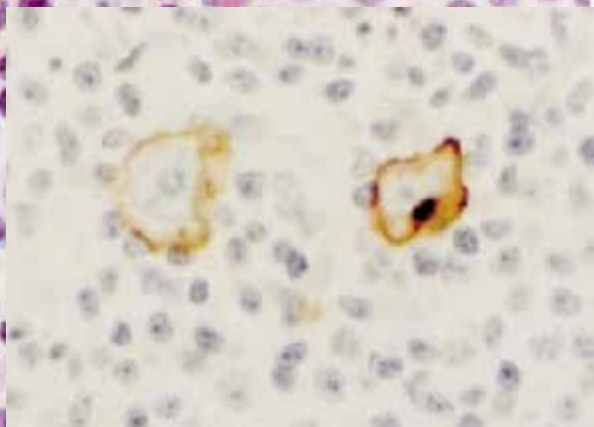


PLASMOCITOMA



LLC NO PRESENTA ASPECTO PLASMOCITARIO "MADURO"

NO OLVIDAR LAS TRANSFORMACIONES Y LOS LINFOMAS COMPUESTOS



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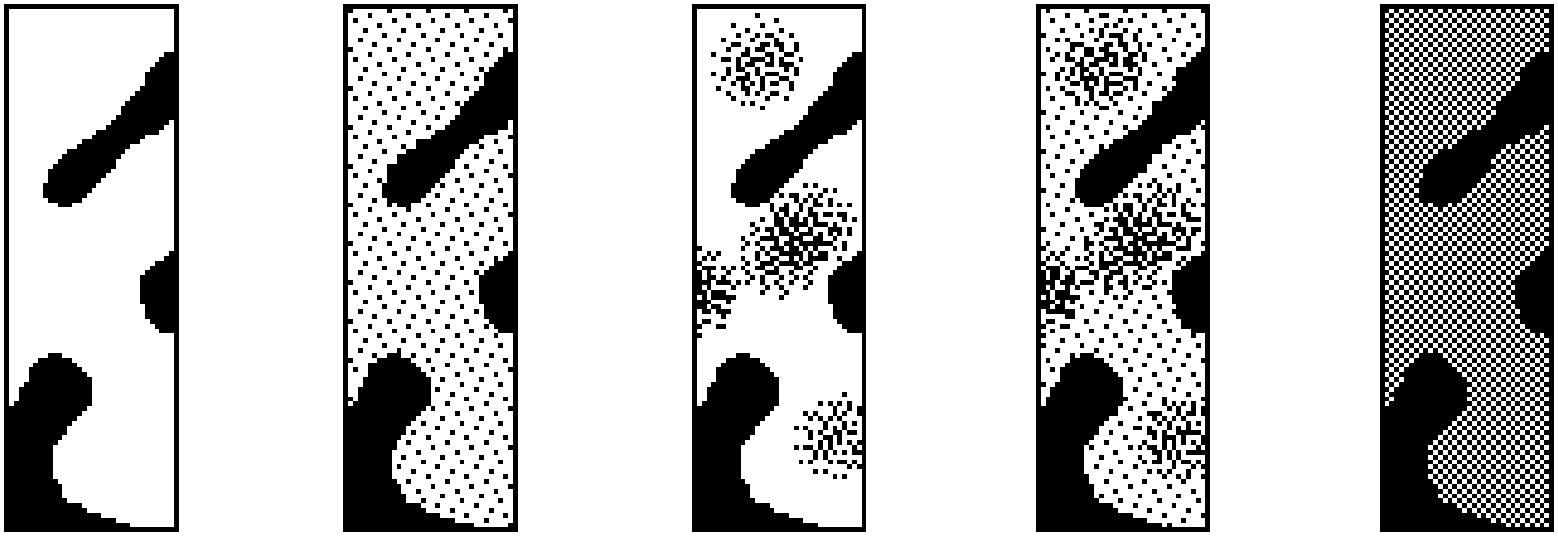
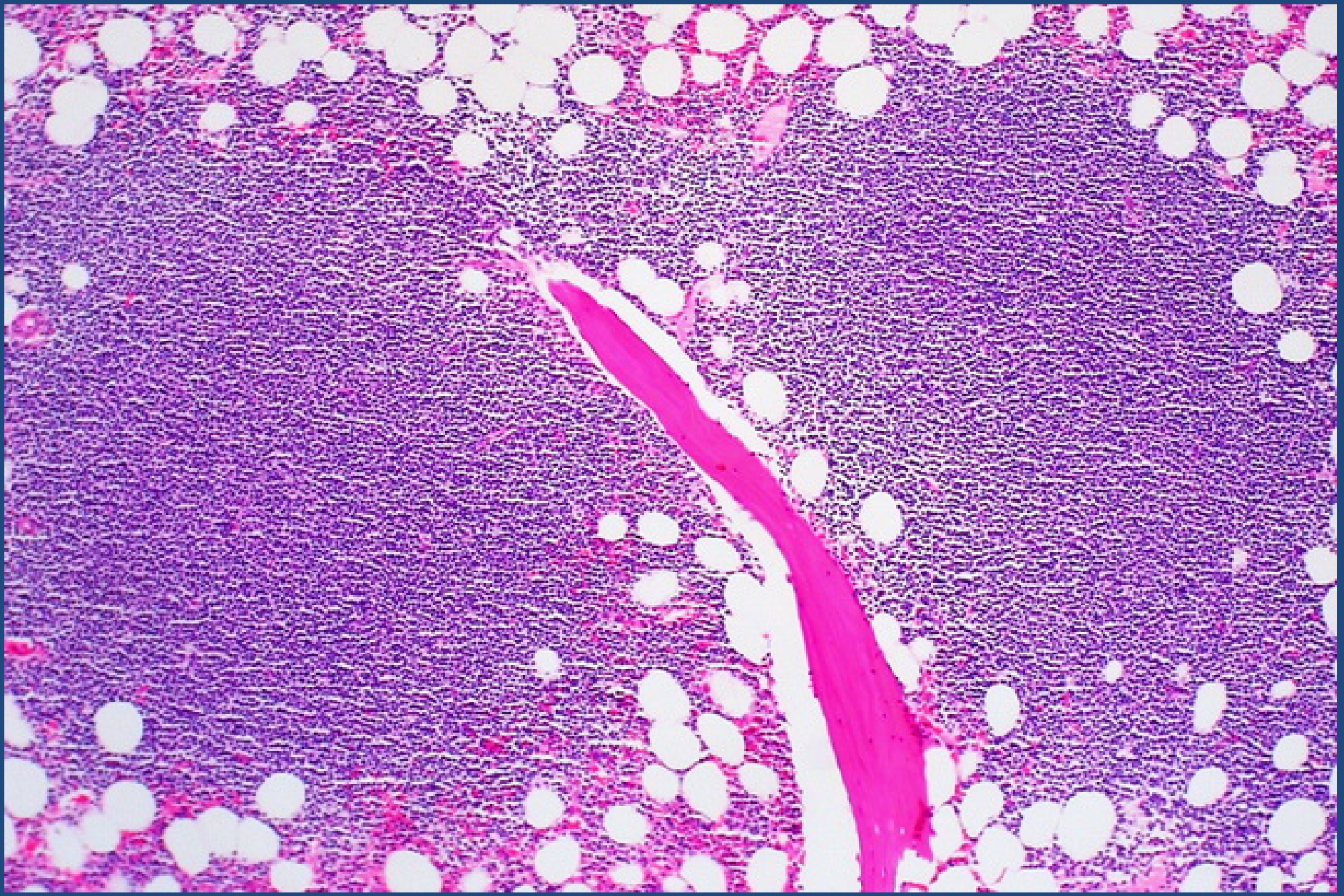
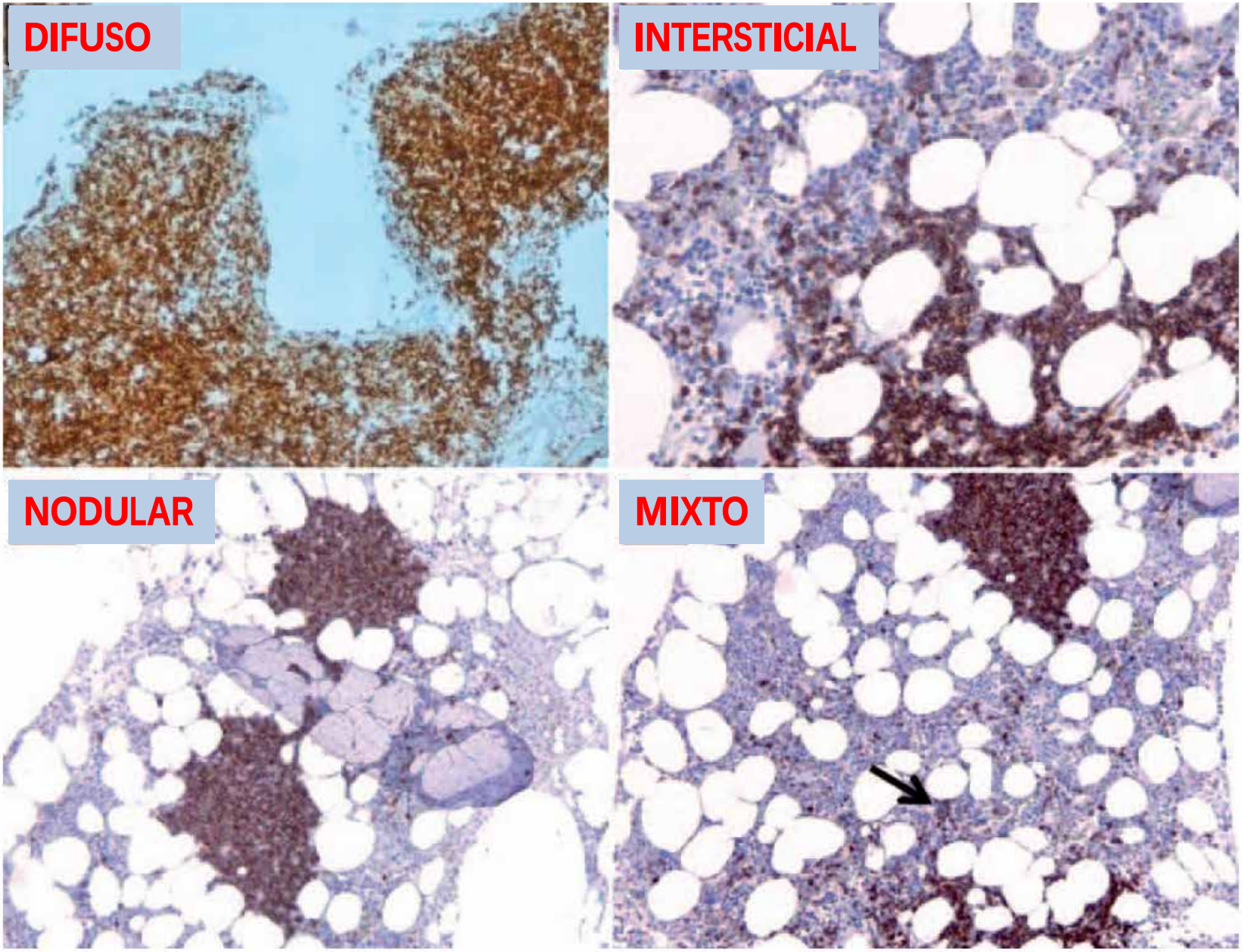
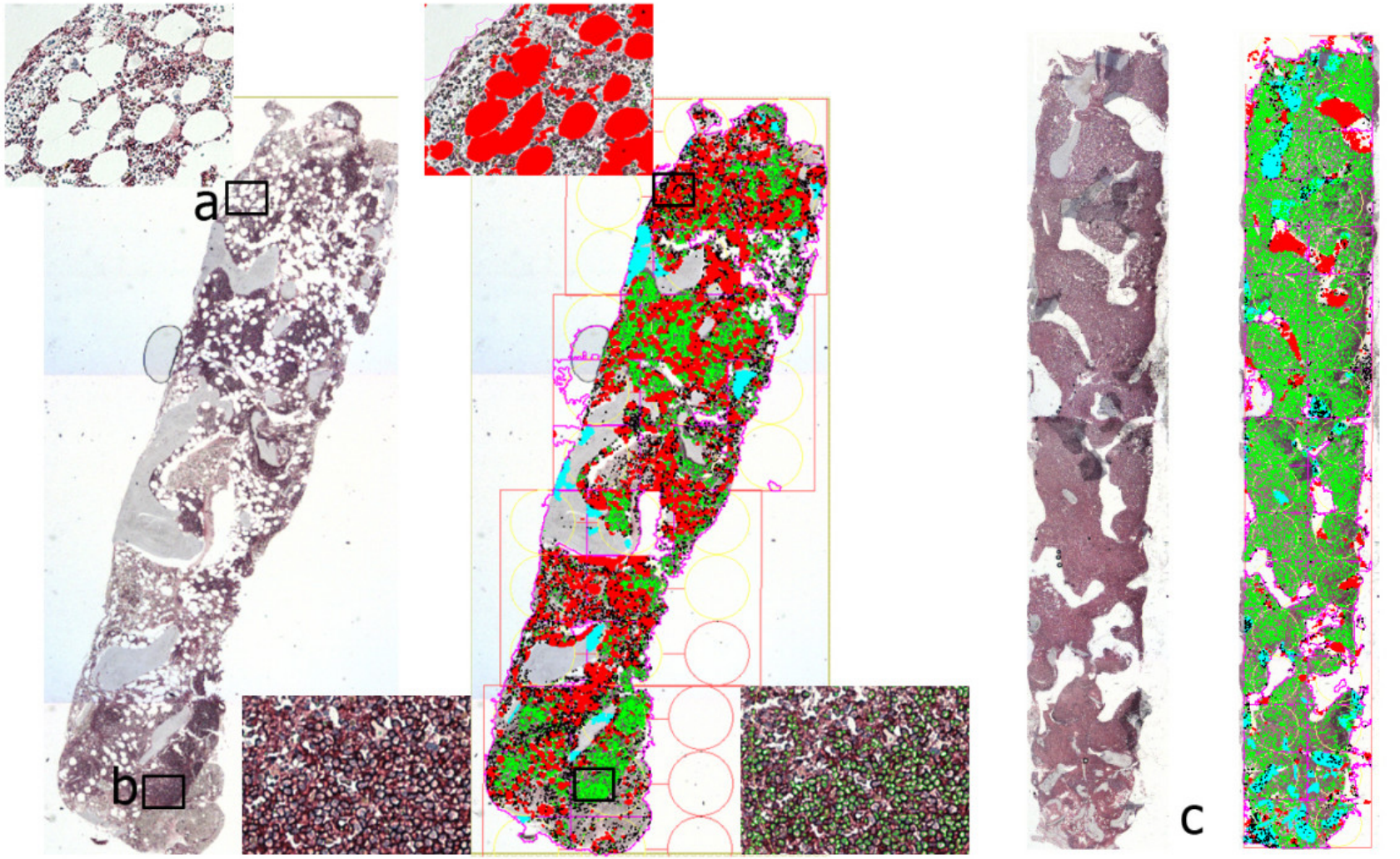
MEDULA OSEA



Bone Marrow Involvement in CLL




DIFUSO
INTERSTICIAL
NODULAR
MIXTO



Štifter et al. Diagnostic Pathology 2010, 5:30

Template for Reporting Results of Biomarker Testing of Specimens From Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Eric Duncavage, MD; Ranjana H. Advani, MD; Steven Agosti, MD; Philip Foulis, MD; Christine Gibson, CTR; Loveleen Kang, MD; Joseph D. Khoury, MD; L. Jeffrey Medeiros, MD; Robert S. Ohgami, MD, PhD; Dennis P. O'Malley, MD; Keyur P. Patel, MD, PhD; Jason N. Rosenbaum, MD; Carla Wilson, MD, PhD; for the Members of the Cancer Biomarker Reporting Committee, College of American Pathologists

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BIOMARKER REPORTING TEMPLATE

Chronic Lymphocytic Leukemia (CLL)

Select a single response unless otherwise indicated.
*Note: Use of this template is optional.**
* Reporting on the data elements in this template is not required.

Specimen Type

___ Peripheral blood
___ Bone marrow
___ Lymph node (specify site): _____
___ Other (specify): _____

RESULTS

Chromosomal Abnormalities (Table and note B)

___ 13q deletion
  ___ Not detected
  ___ Detected
  ___ Other abnormal signal patterns (specify): _____
___ Trisomy 12
  ___ Not detected
  ___ Detected
  ___ Other abnormal signal patterns (specify): _____
___ 11q deletion
  ___ Not detected
  ___ Detected
  ___ Other abnormal signal patterns (specify): _____
___ 17p deletion
  ___ Not detected
  ___ Detected
  ___ Other abnormal signal patterns (specify): _____
Other probes tested (if applicable)
  Specify probe: _____
  Specify results: _____
Additional copy number variations noted
  Gains (specify regions):
  _____
  Losses (specify regions):
  _____
Loss of heterozygosity
  ___ Not identified
  ___ Identified (specify regions): _____
Cytogenetic testing complete karyotype (specify): _____

Protein Expression (notes C and D)

___ ZAP-70
  ___ Not expressed (percentage of CLL cells positive):
  _____
  ___ Expressed (percentage of CLL cells positive):
  _____
___ CD38
  ___ Not expressed (percentage of CLL cells positive):
  _____
  ___ Expressed (percentage of CLL cells positive):
  _____

Sequence-Based Testing

Immunoglobulin heavy chains (IgVH) hypermutation status
  ___ Mutated (≤97% identity to reference)
  ___ Unmutated (≥98% identity to reference)
  ___ Borderline (>97% and <98% identity to reference)
IGHV3-21 usage
  ___ Not detected
  ___ Detected
Somatic gene mutations
  ___ *TP53*
    ___ Not detected
    ___ Detected (specify variant): _____
Other markers tested (if applicable)
  Specify marker: _____
  Specify results: _____

METHODS

Chromosomal Abnormalities

___ Chromosomal array
___ Fluorescence in situ hybridization (FISH)
___ Conventional karyotype

Molecular Testing

Array platform: _____
  Minimum size of detected copy number variation (CNV):
  _____
Gene sequencing platform: _____
  Maximum sensitivity: _____
  (variant allele frequency)
  Genes/exons sequenced: _____

Protein Expression (notes C and D)

___ Flow cytometry
___ Immunohistochemistry

ZAP-70–positive threshold: _____
CD38-positive threshold: _____

CONCLUSIONES

- SE DEBEN CONOCER LAS VARIABLES HISTOLOGICAS DE LLC
- UTILIZAR PANELES COMPLETOS DE IHQ
- UTILIZAR CLASIFICACIONES ACTUALES
- LENGUAJE CLARO
- TRABAJO EN EQUIPO

If the surgeons were gracious enough to tell the patient, "Our pathologist, Dr Smith, has concluded that this is..." maybe they would at least know that there is a pathologist in the hospital

Juan Rosai