Jornada Chilena de Hematología y Medicina Transfusional

Linfoma 2015: Rol del Patólogo

Dr. Pablo Matamala Bastian

Anatomía Patológica

Citometría de Flujo

Clínica Las Condes

THE ROLE OF THE PATHOLOGIST IN THE DIAGNOSIS OF CANCER*

By W. L. Robinson, M.B.,

Toronto

"THE rôle of the pathologist in the diagnosis of cancer"; I am glad the subject is stated thus and not as "The rôle of the microscope", or "The rôle of the laboratory". The human

The clinician, radiologist, pathologist, and any others who have anything to contribute should sit down together, as it were, and form a group opinion. This is not the expression of a desire on the part of the pathologist to evade his responsibilities. It is a desire to offer something a little better for the patient and something more exact for the clinician, thus approaching more nearly to the ideal which is the goal of every true follower of Hippocrates.

Clinicians Are From Mars and Pathologists Are From Venus

Clinician Interpretation of Pathology Reports

Seth M. Powsner, MD; José Costa, MD; Robert J. Homer, MD, PhD

Arch Pathol Lab Med—Vol 124, July 2000

Table 1. Discordance Rate (%) by Report Format and Clinical Experience

Experience*	Format			All	n
	Original	Modernized	New		
Attending, pgy 6+	18	24	34	25	15
Housestaff, pgy 2–5	26	32	34	31	11
Student, pgy 1	33	28	48	37	8
All	24	28	37	30	34

* pgy indicates postgraduate year.

Results.—Surgeons misunderstood pathologists' reports 30% of the time. Surgical experience reduced but did not eliminate the problem. Streamlined report formatting exacerbated the problem.

Conclusions.—A communication gap exists between pathologists and surgeons. Familiarity with report format and clinical experience help reduce this gap. Paradoxically, stylistic improvements to report formatting can interfere with comprehension and increase the number of misunderstandings. Further investigation is required to reduce the number of misunderstandings and, thus, medical errors.

(*Arch Pathol Lab Med.* 2000;124:1040–1046)

How Does a Pathologist Make a Diagnosis?

Gil Patrus Pena, MD; José de Souza Andrade-Filho, MD

Arch Pathol Lab Med—Vol 133, January 2009

Cognitive Domain

- Plan diagnostic strategies for the case (macroscopy, microscopy, immunohistochemical, or special stains).
- Select a most appropriate diagnostic approach to the case (pattern recognition, algorithms, hypothetic deductive).
- Use cognitive skills to collect data for the case (perception, attention, memory); exert permanent, conscious control upon these cognitive functions (metacognition).
- Elaborate and test diagnostic hypotheses.
- Search for specific diagnostic findings.

Communicative Domain

- Ask: Is there enough clinical information?
- Formally express the warrants and backings for your conclusion.
- Attend to the intelligibility, normative rightness, truth, and sincerity of the pathologic report.
- Ask: Besides the written information in the report, should we talk to the clinician?
- Document the case; prepare it to be presented in a meeting or a publication.
- Search the literature.
- Record any useful event for quality control measures.

Normative Domain

- Specify and justify rules guiding your diagnosis (empirical rules, rules of rational choice, and social norms)—rules to classify, report, and grade and stage tumors, for example.
- Respect the patient, the clinician, and the referring pathologist.
- Conduct yourself according to the ethical code (in relation to the patient, to other doctors, to the earning of fees, and the like).

Medical Conduct Domain

- Consider: What is the consequence of your diagnosis to the management of the case?
- Consider: Does your communication make clear the diagnosis and the expected conduct?
- Consider: Is this a case for which you can assume all the responsibility for the diagnosis, or should you share it with another pathologist?
- Consider: Should you seek a consultation with another pathologist, request a new sample, order special stains or immunohistochemical studies, or some other clinical investigation to confirm the findings?

The Role of Pathologists in the Era of Personalized Medicine

Eric E. Walk, MD

Arch Pathol Lab Med—Vol 133, April 2009

What Are We Anyway?

The Role of Pathologists in the 21st Century

Jay L. Hess, MD, PhD

Arch Pathol Lab Med—Vol 134, October 2010

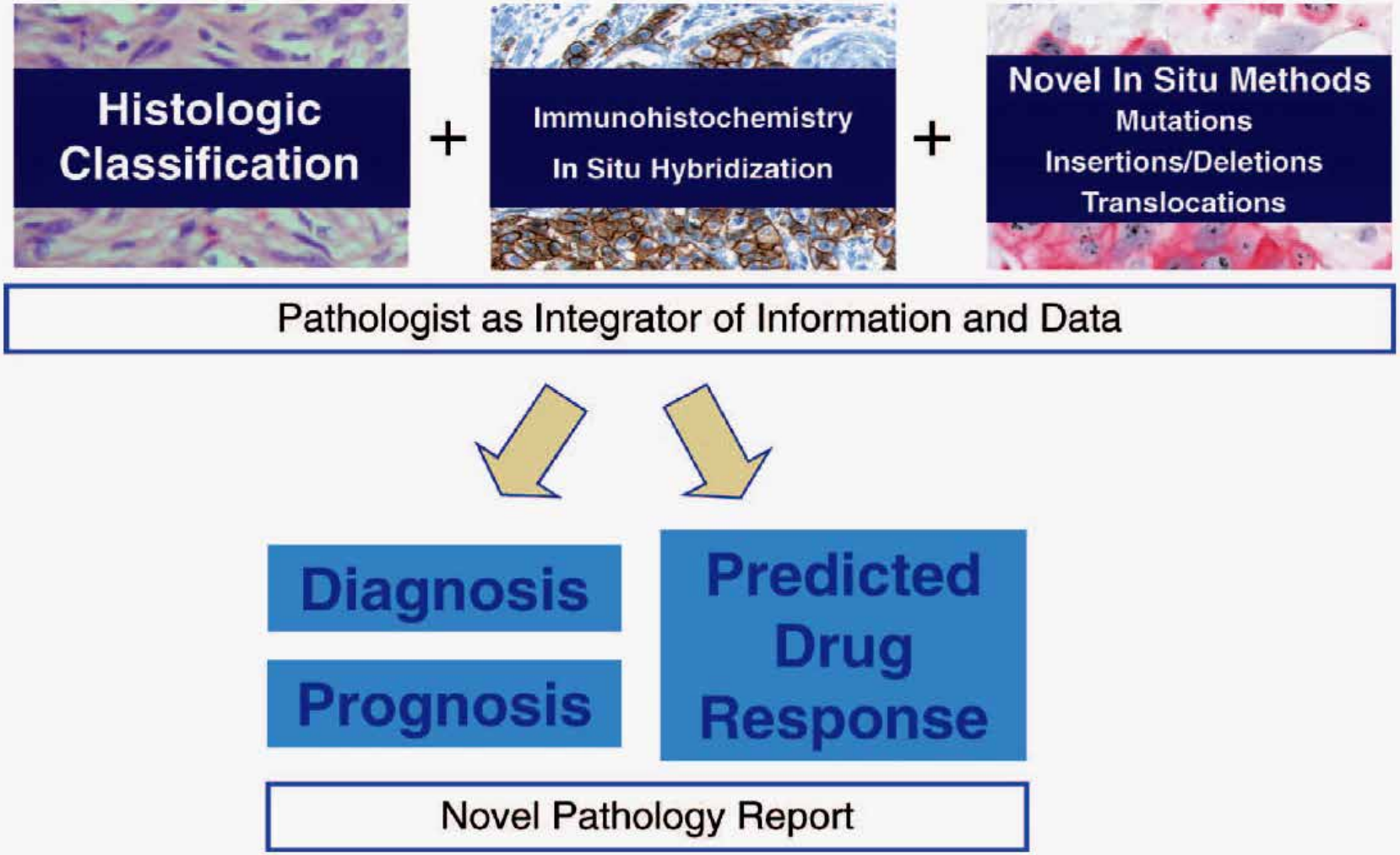
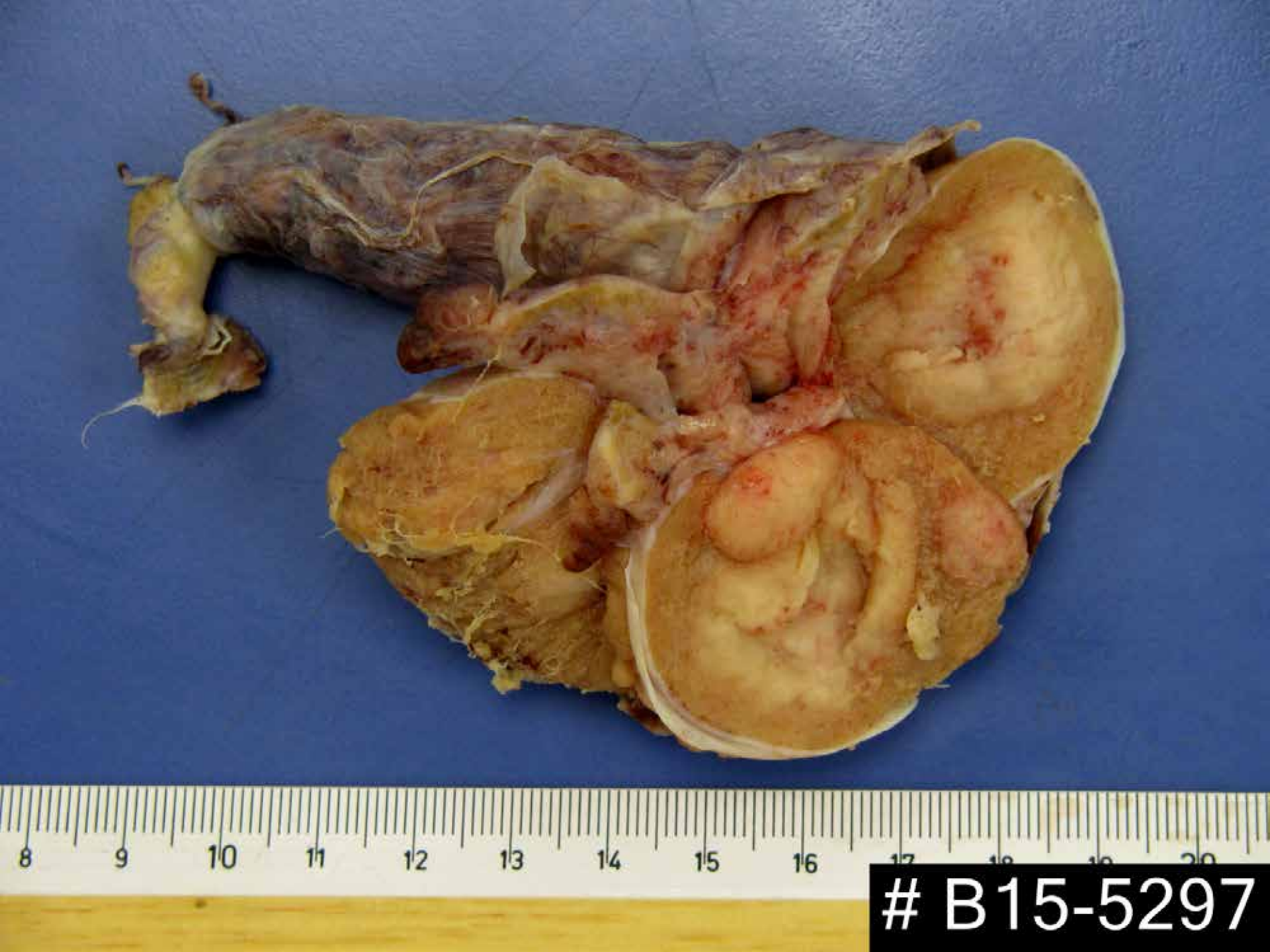


Figure 1. *Concept for the role of the pathologist in the era of personalized medicine. Pathologists will integrate traditional histomorphology with data from existing and next-generation molecular assays to provide patients and clinicians with diagnostic, prognostic, and predictive information.*

EJEMPLO DE TRABAJO EN EQUIPO "RAPIDO Y EFICAZ"

- Llamada SOS del Hematólogo a las 8:30 am.
- Paciente 28 años, HIV+. Se realizó el día anterior Orquiectomía radical por tumor.
- Sospecha Linfoma.
- ¿podemos hacer algo si ya está fijado en formalina desde ayer?

- **POR SUPUESTO QUE SI !!!**


8
9
10
11
12
13
14
15
16
B15-5297

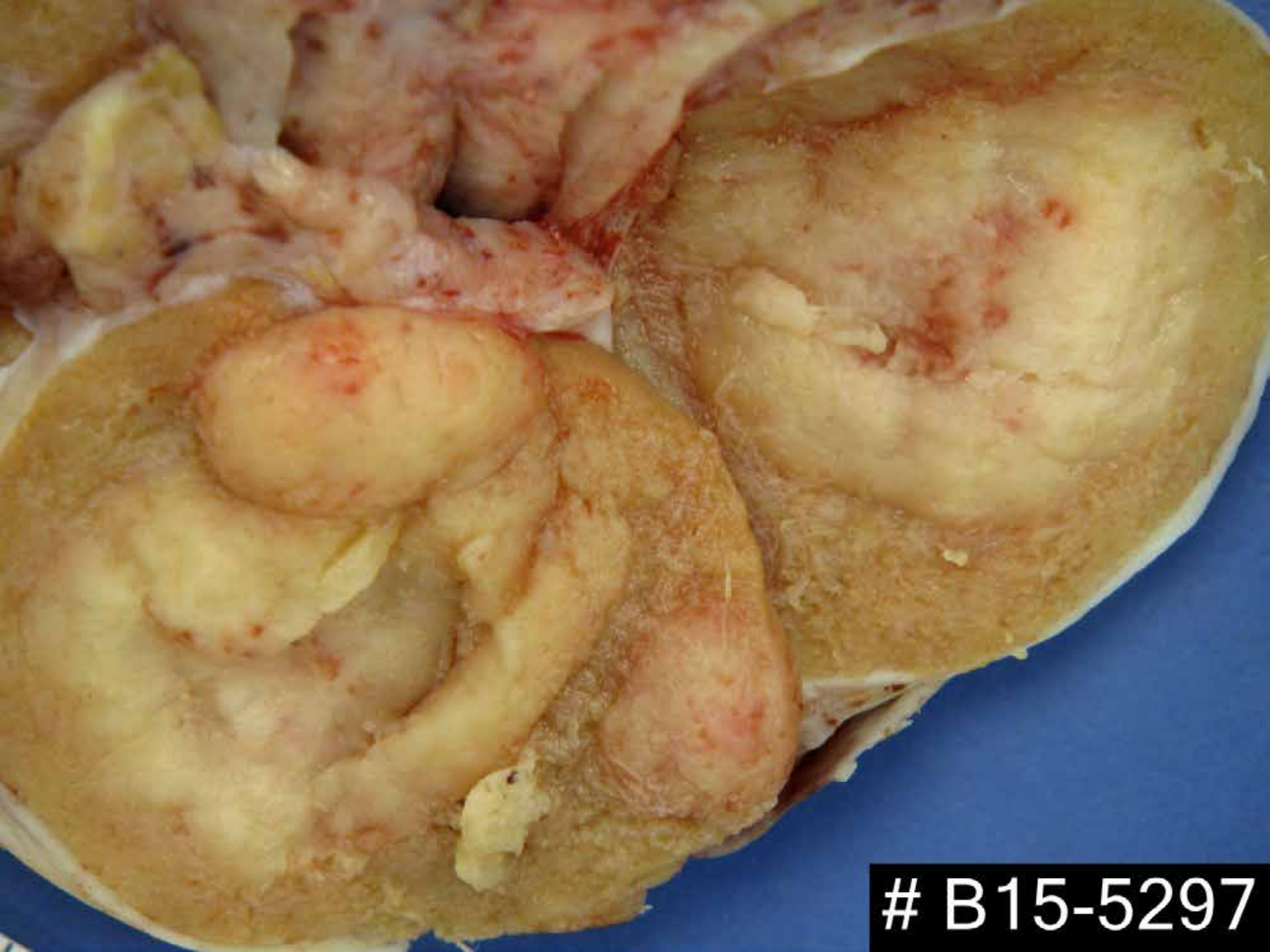
Transformation of Pathologists

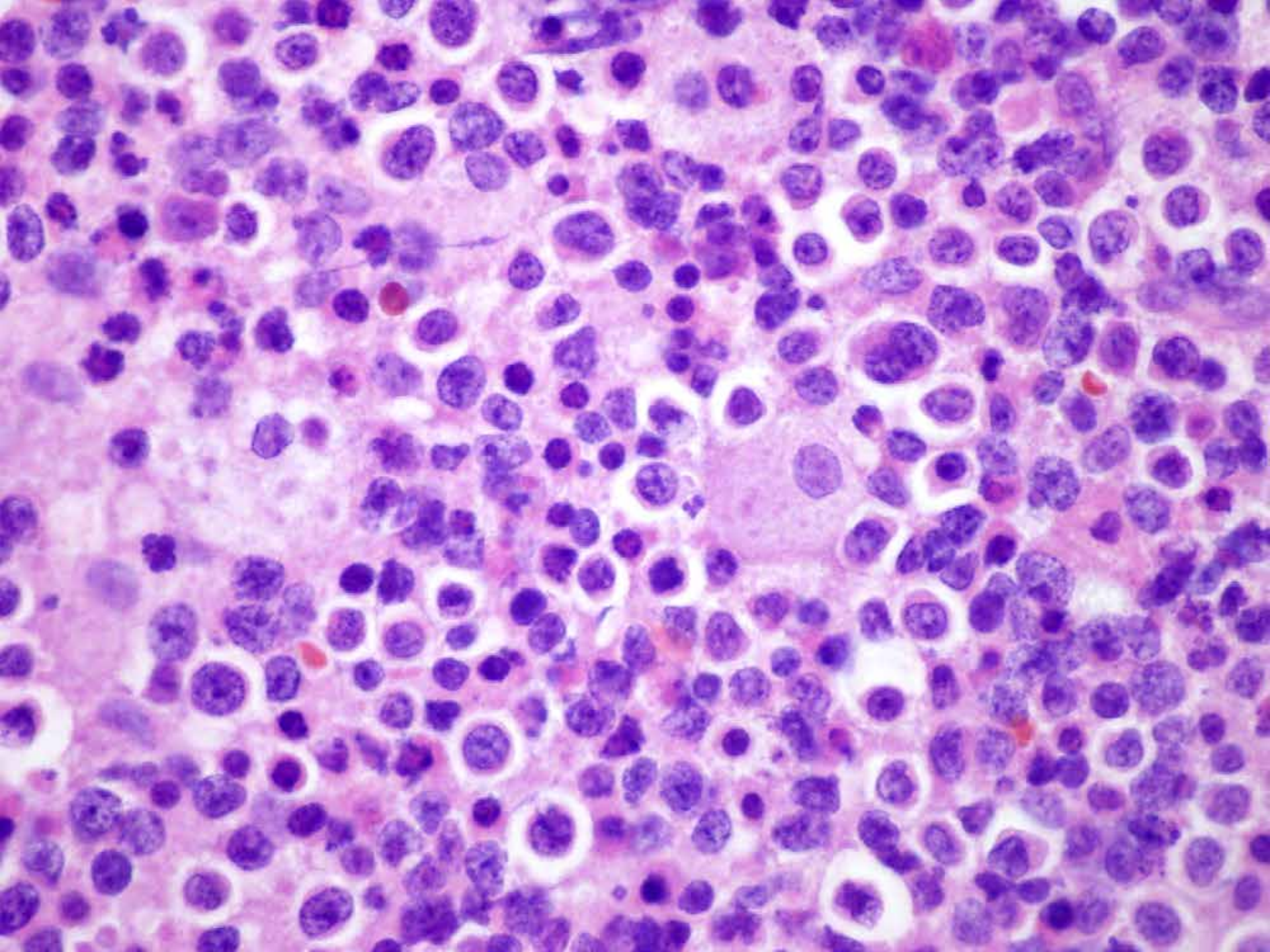
Responding in a Volatile, Uncertain, Complex, and Ambiguous Environment

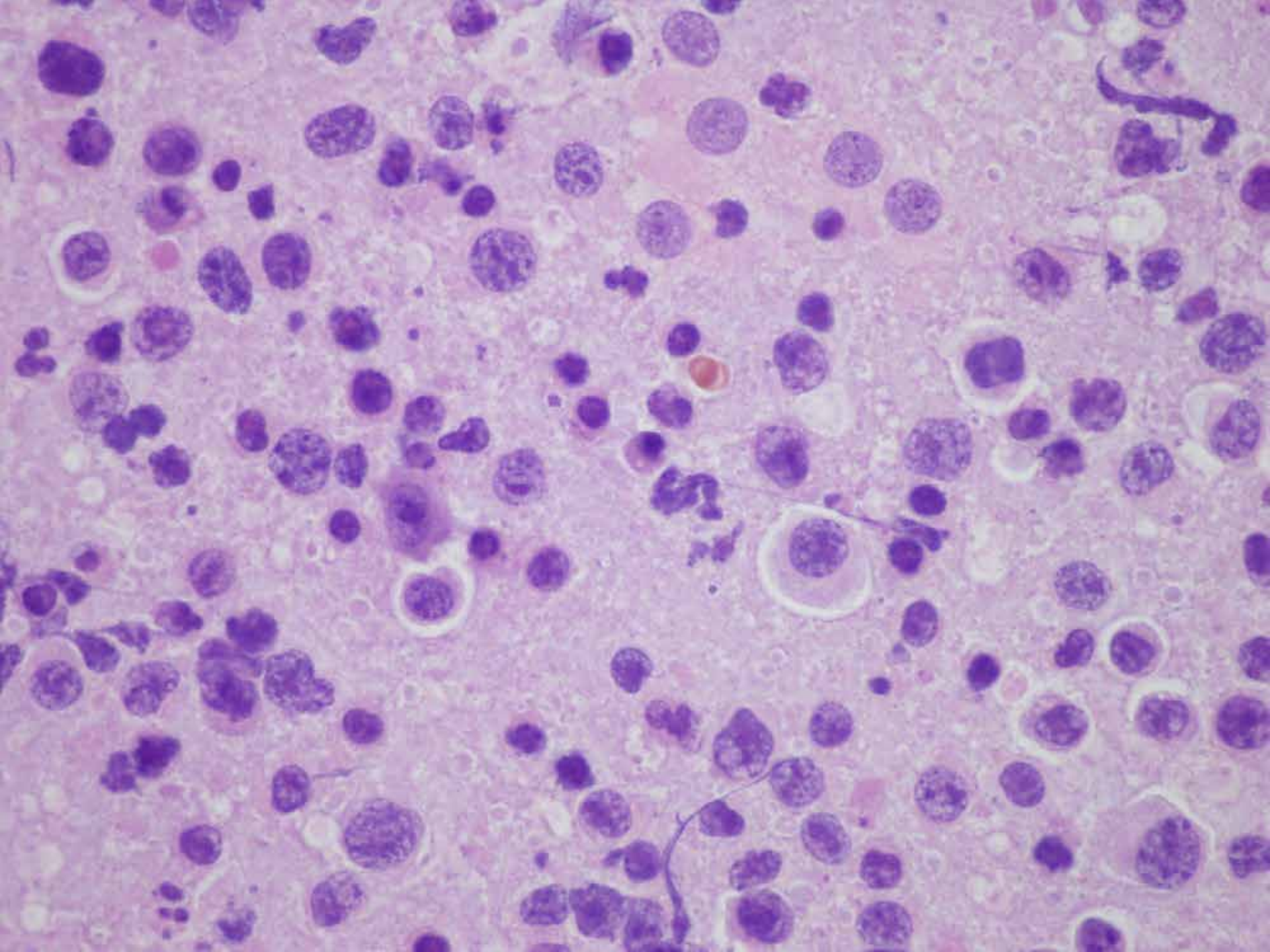
James S. Hernandez, MD, MS; Timothy Craig Allen, MD, JD

Arch Pathol Lab Med—Vol 137, May 2013

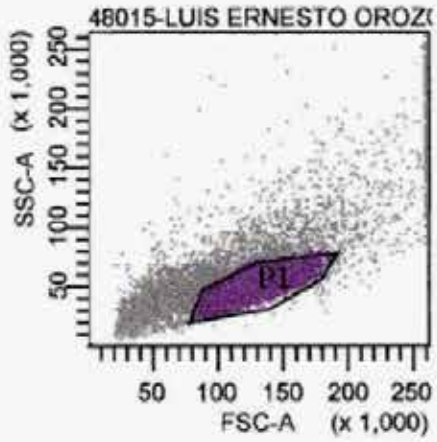
In "No Pay, No Play: The End of Professional Ethics in Pathology?"[1] and "No Pay, No Play: Game Over,"[2] we noted the general discontent among pathologists and reinforced that, even so, we must remain ever professional.

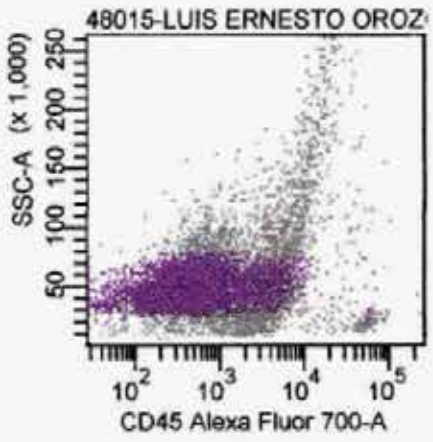

B15-5297

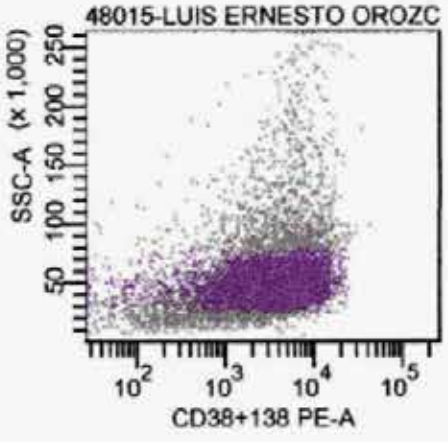


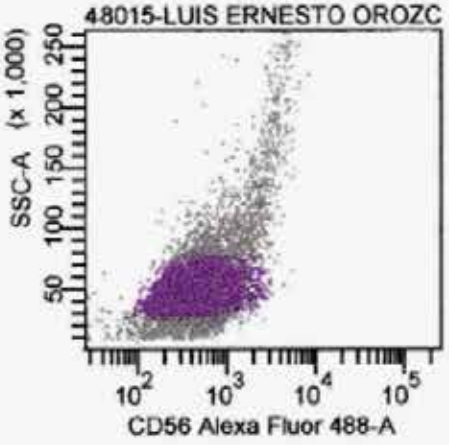


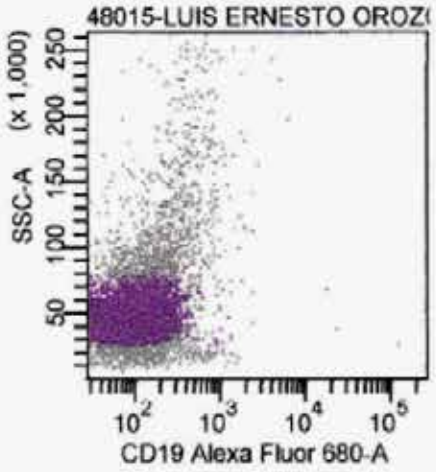
MUESTRA **TEJIDO TESTICULAR DERECHO**
FECHA **25.06.2015**

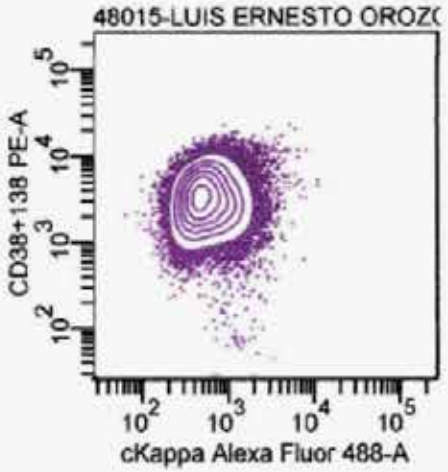


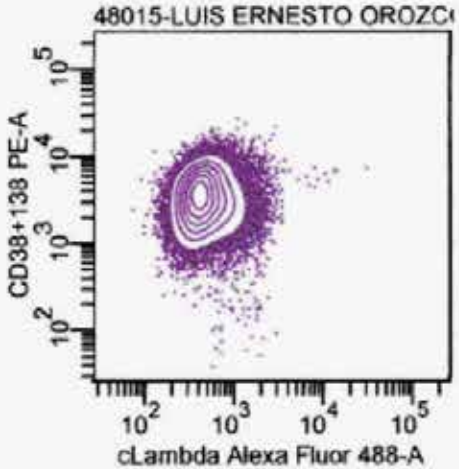






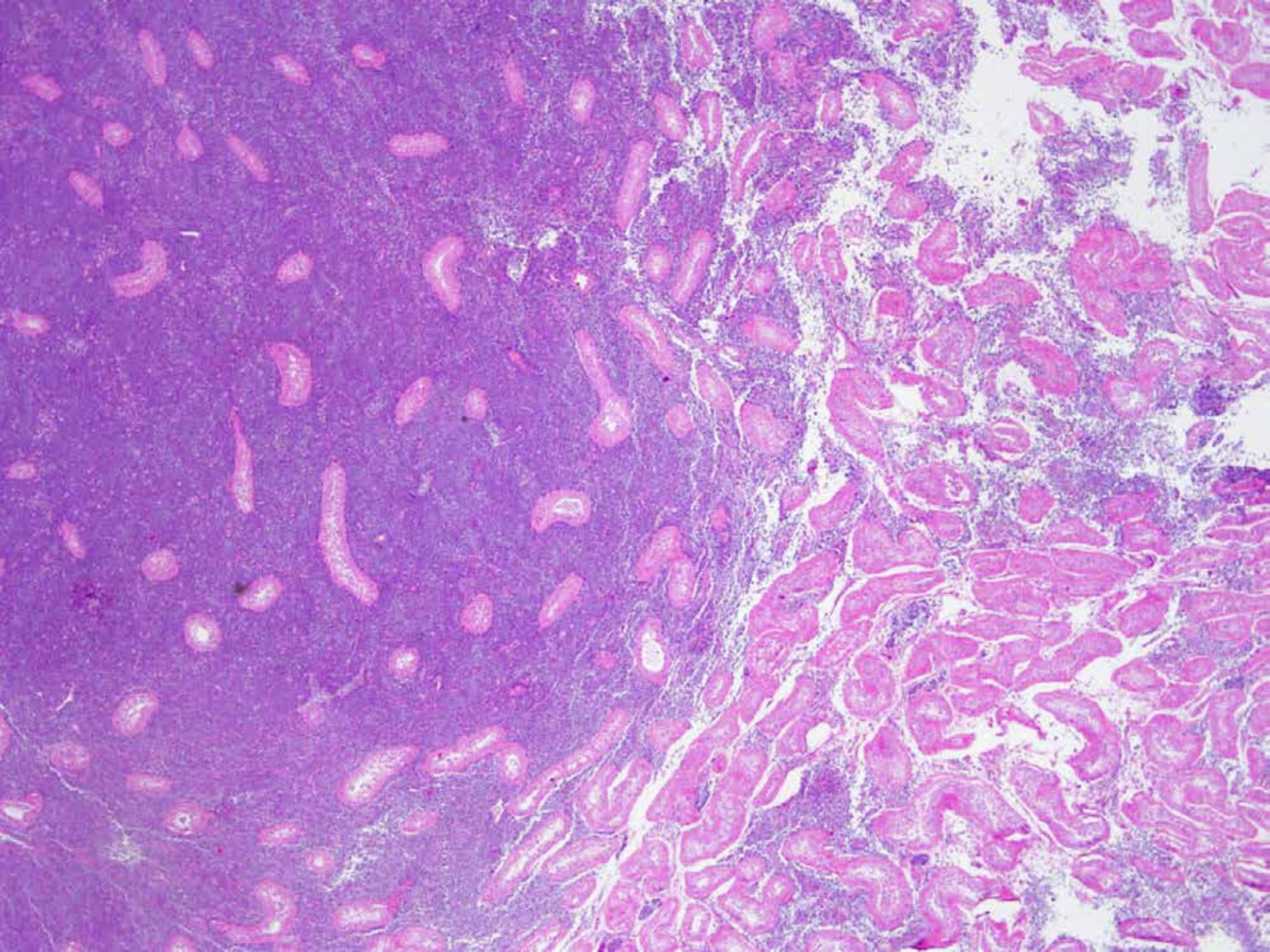


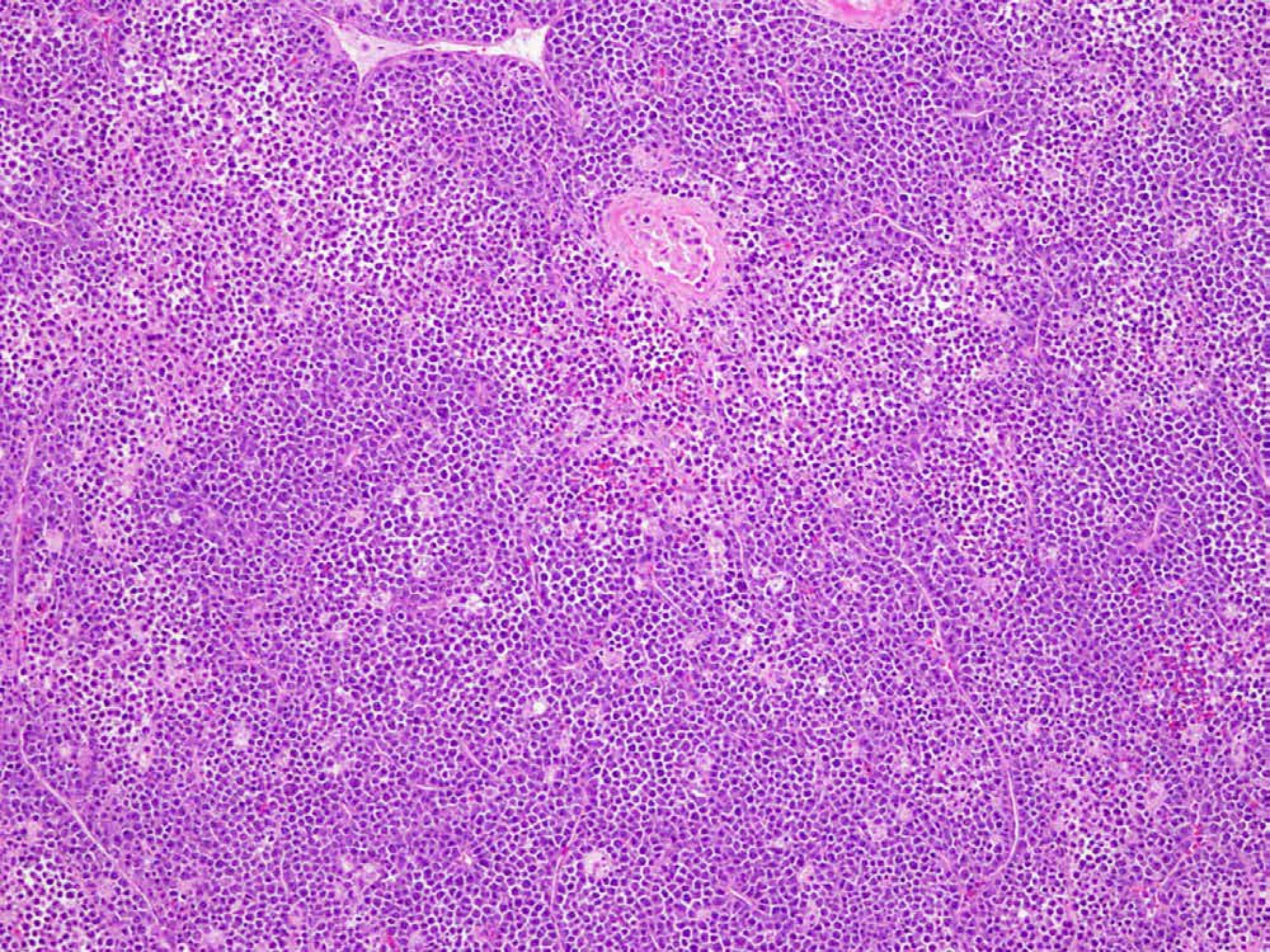


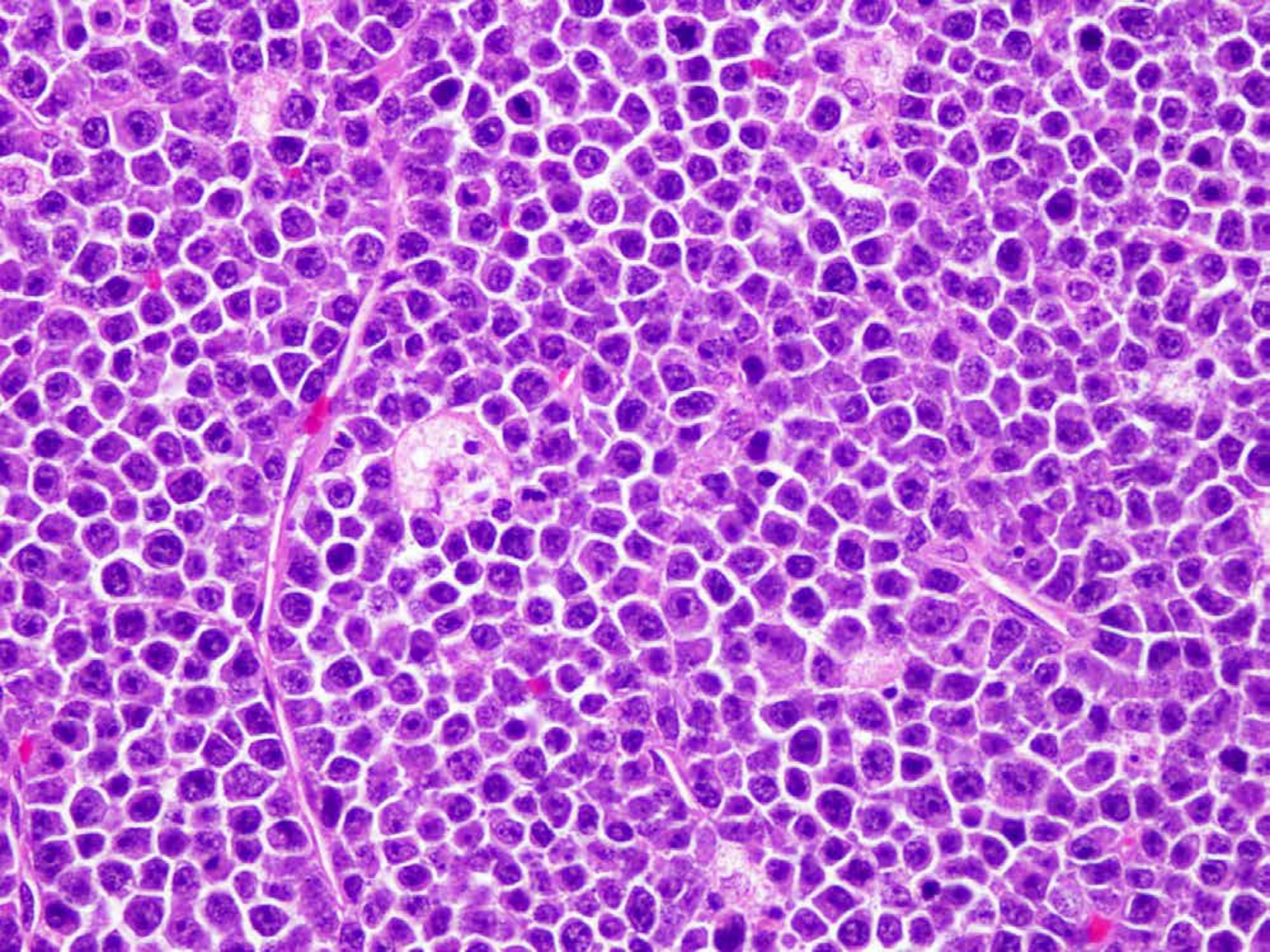


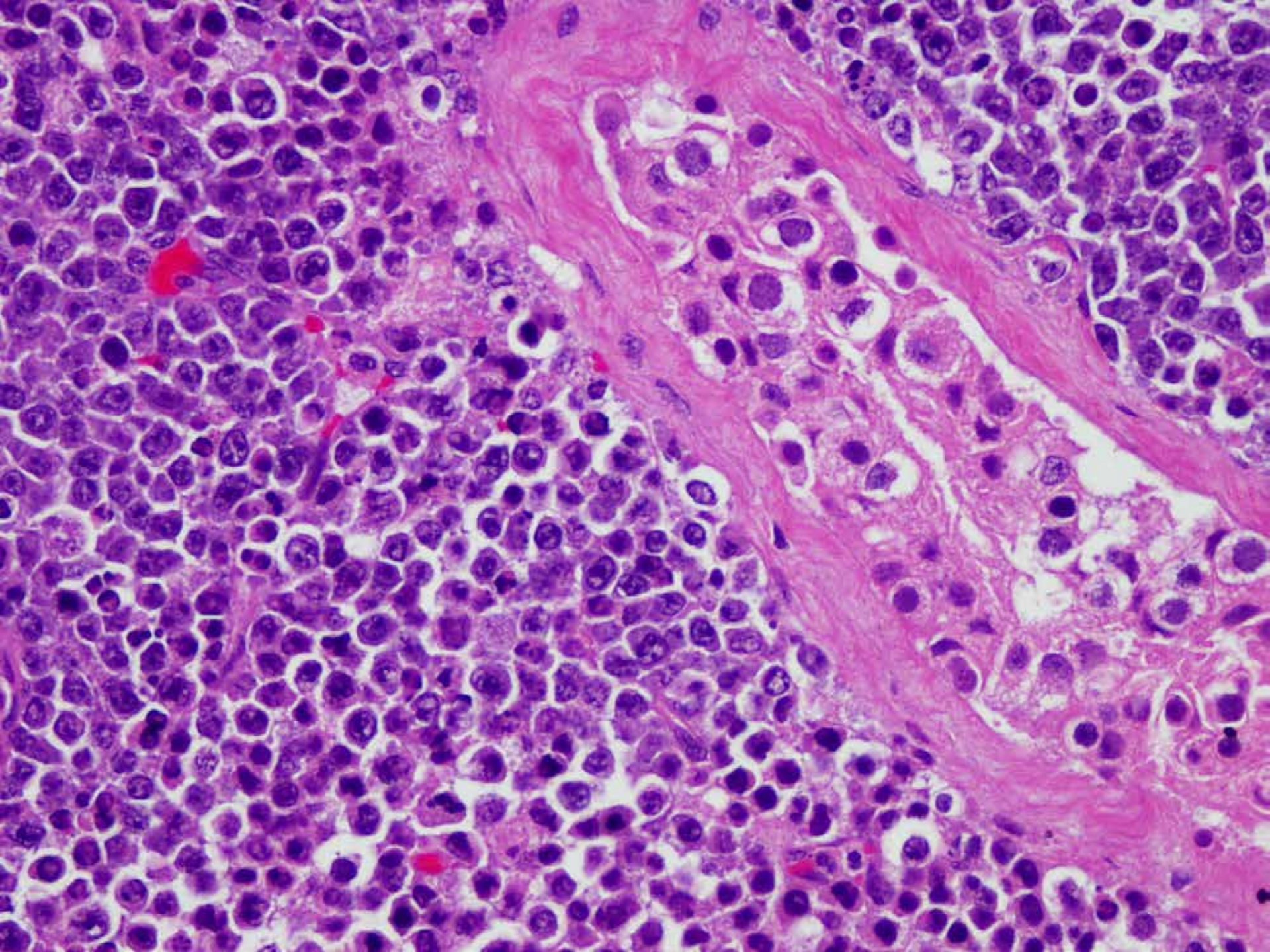
- Diagnóstico con citología y citometría de flujo a las 16:00 hrs del mismo día.

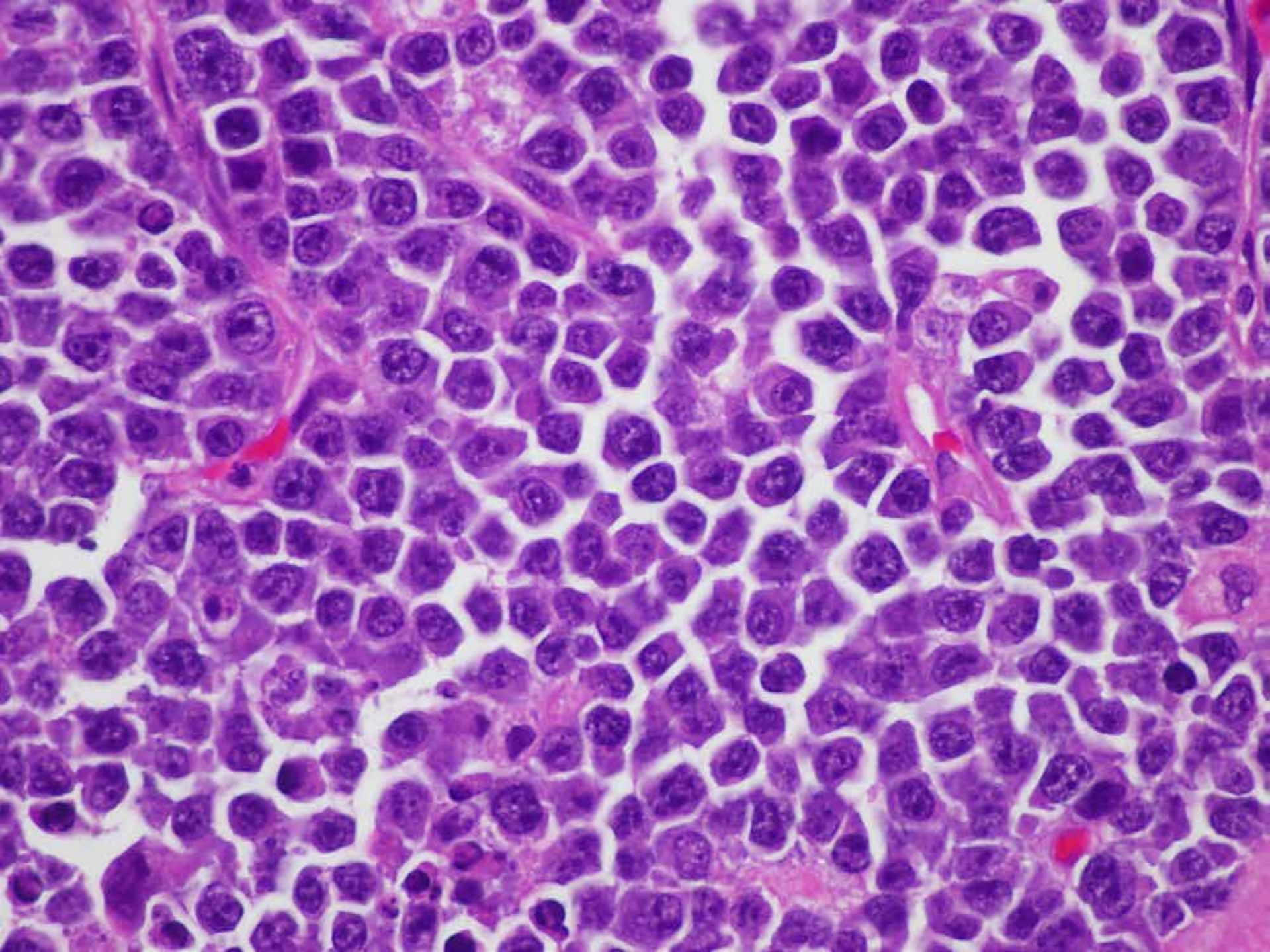
- **LINFOMA PLASMABLASTICO**

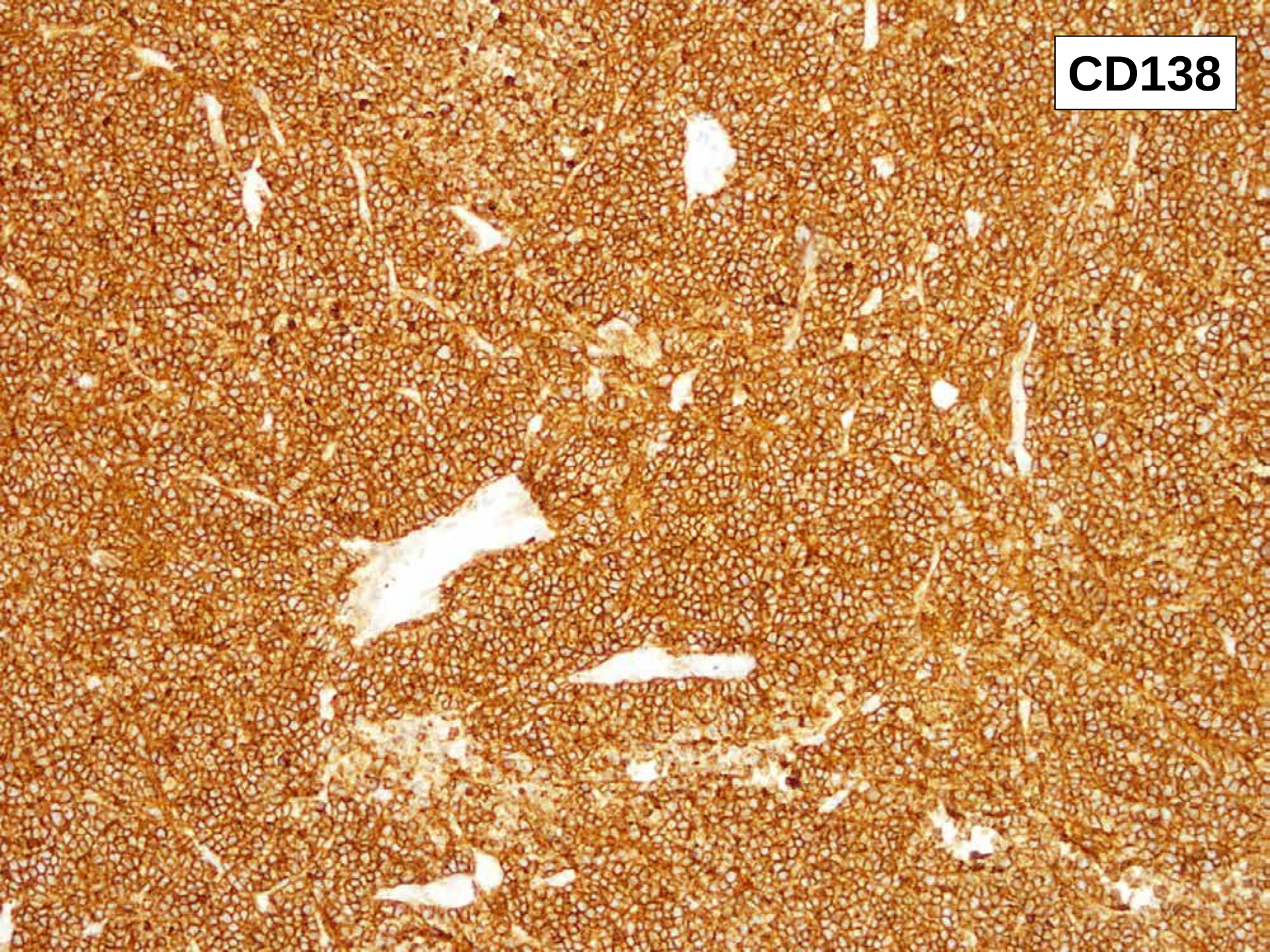


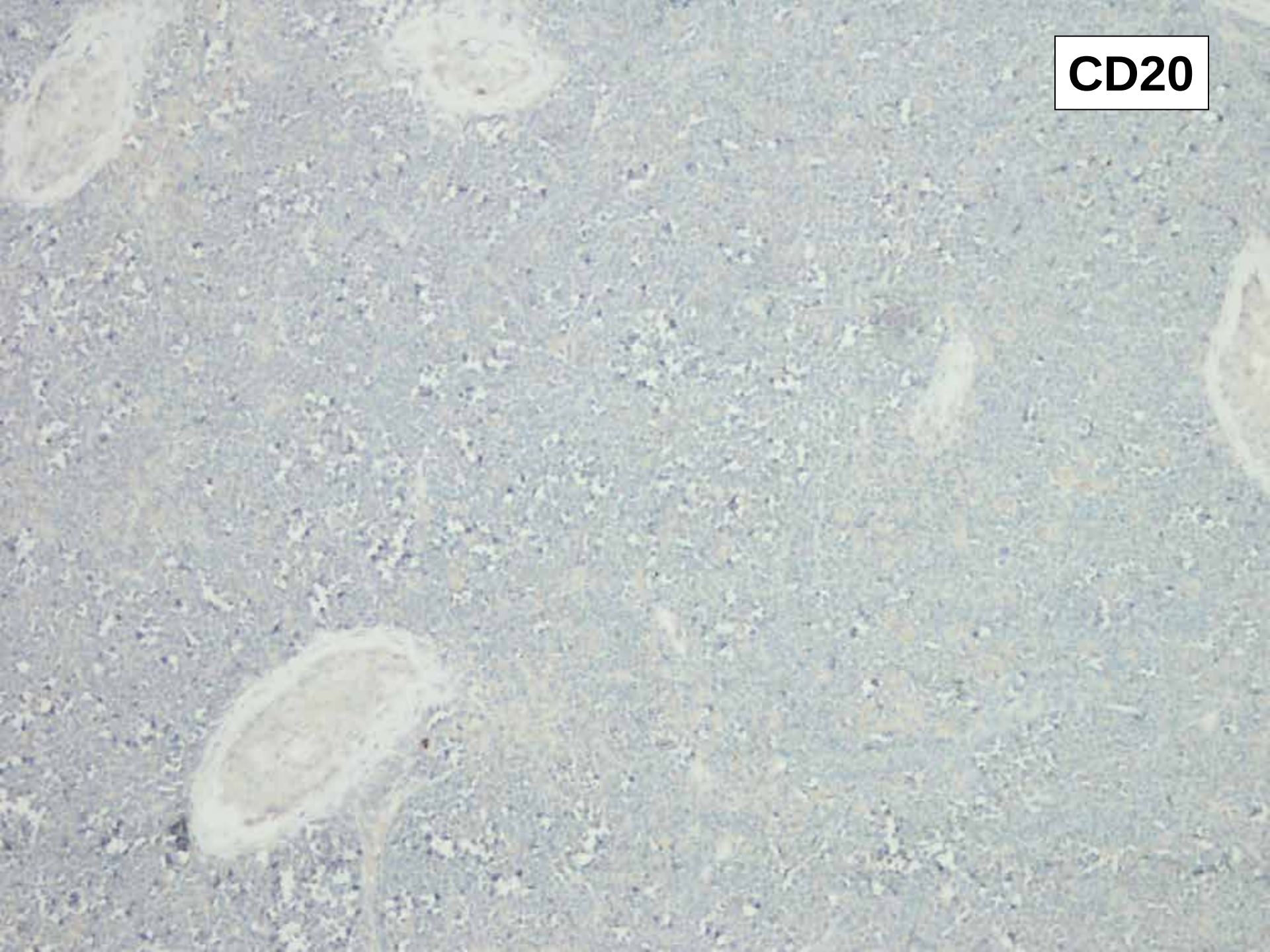


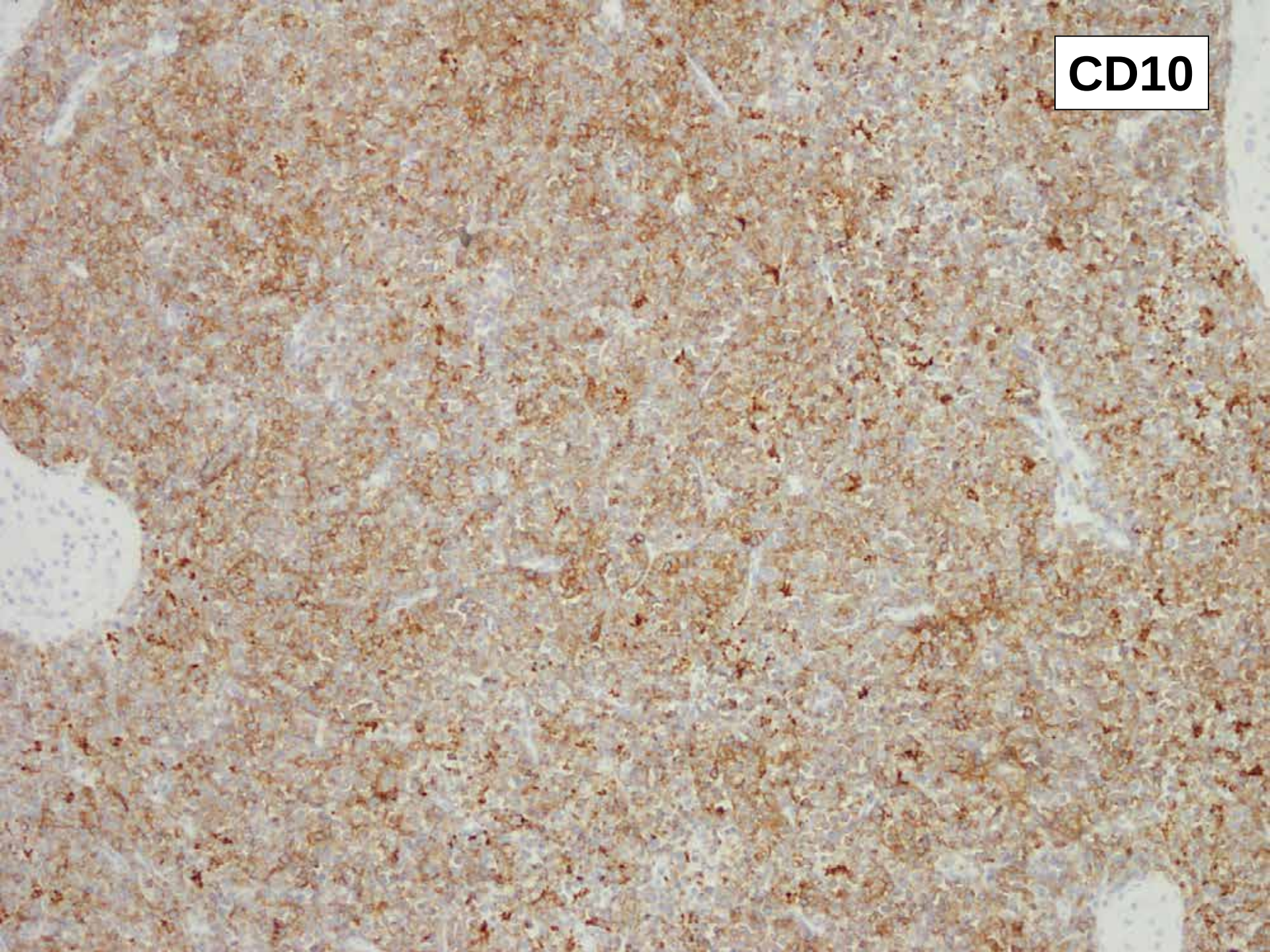


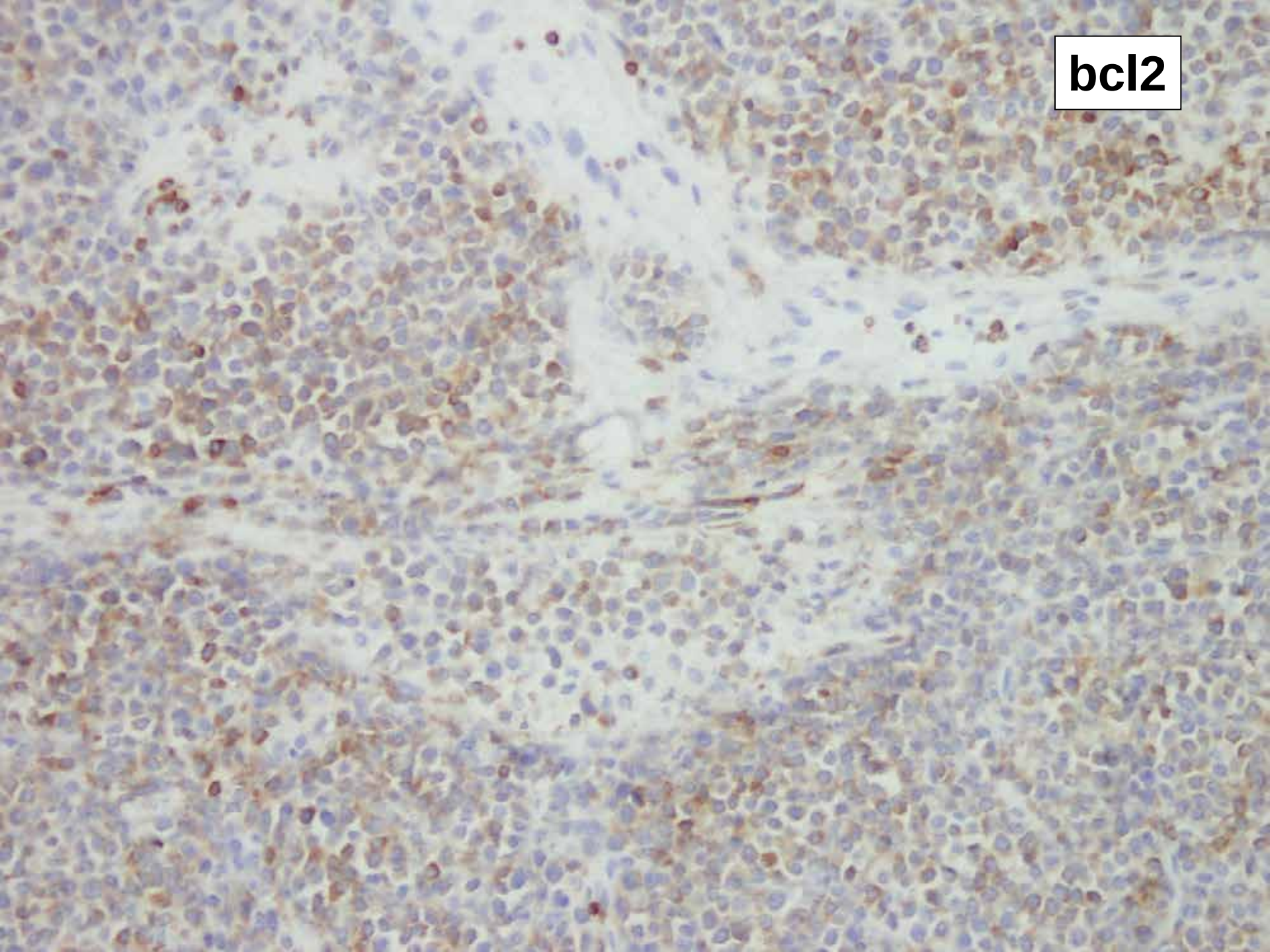


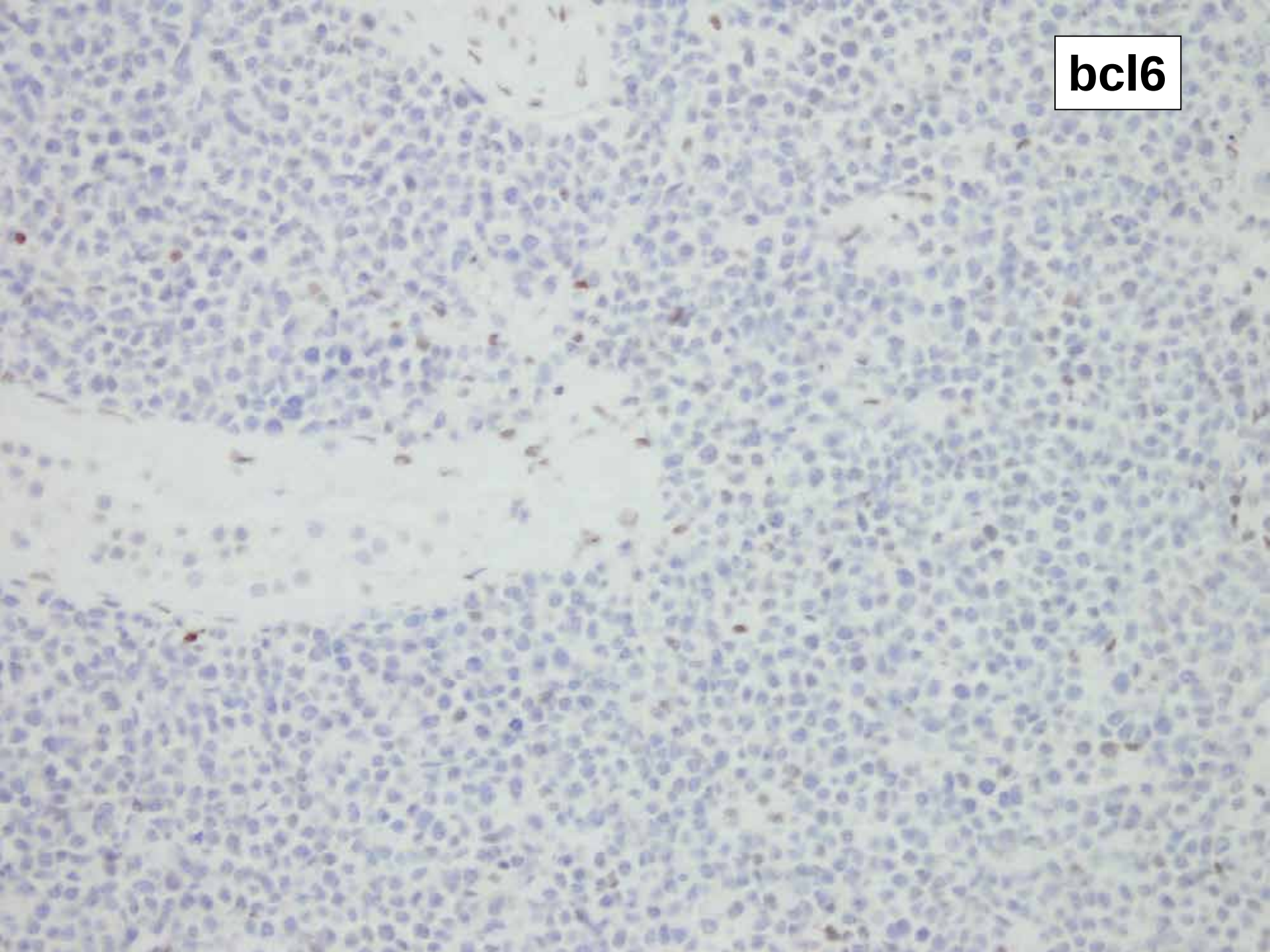


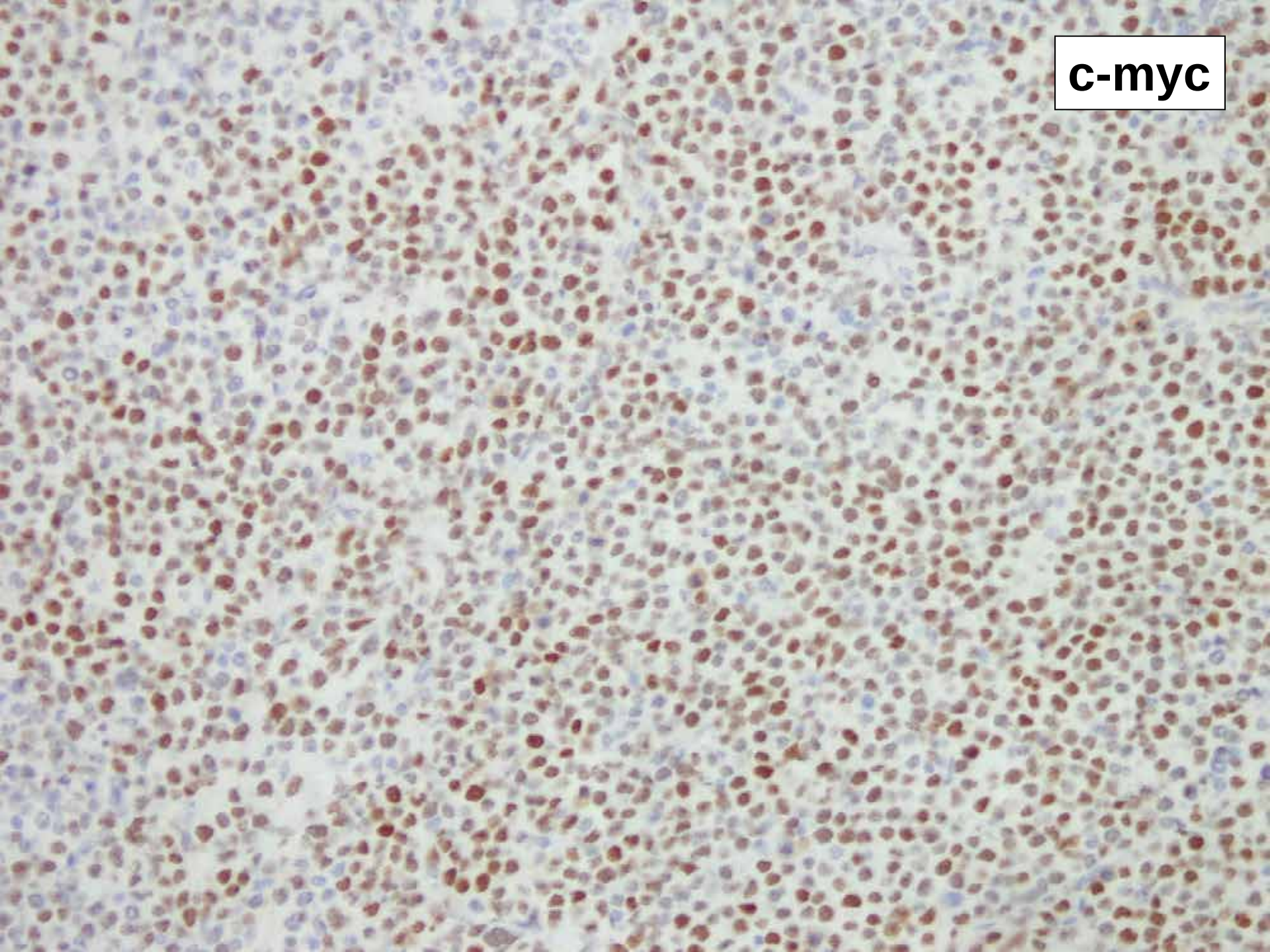

CD138

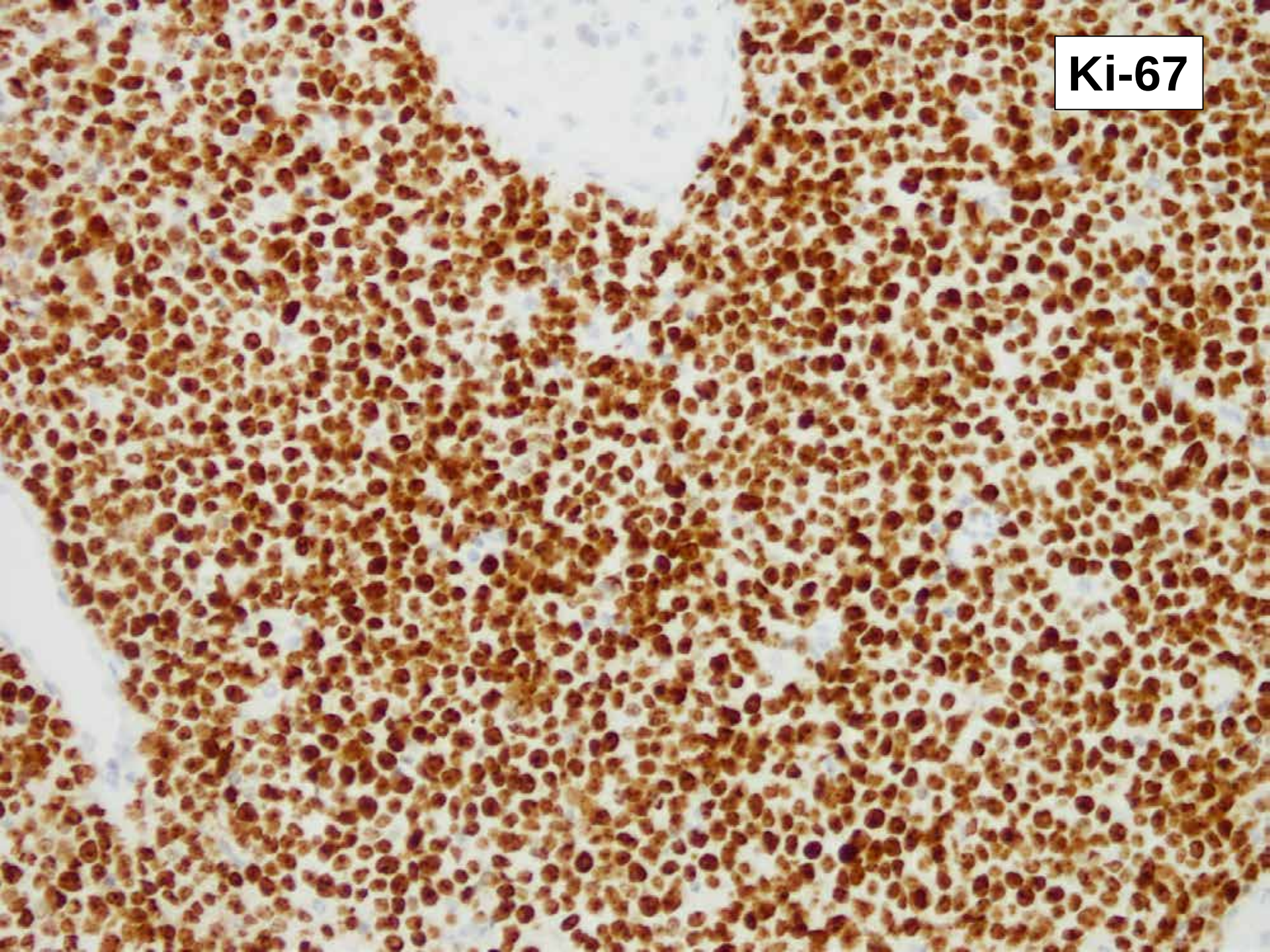

CD20


CD10


bcl2


bcl6


c-myc


Ki-67

- *EVITAR EL “QUIEBRE” ENTRE HEMATOLOGO Y PATOLOGO*

OTRO ROL:

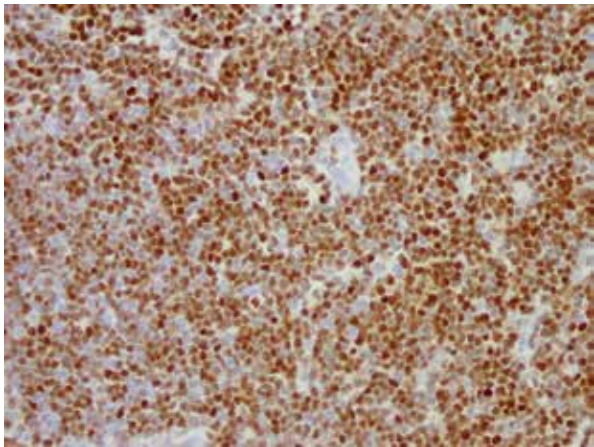
DESMITIFICAR

LINFOMA DE CELULAS DEL MANTO

- Tumor con expresión de Ciclina D1 (t11:14) = linfoma del manto

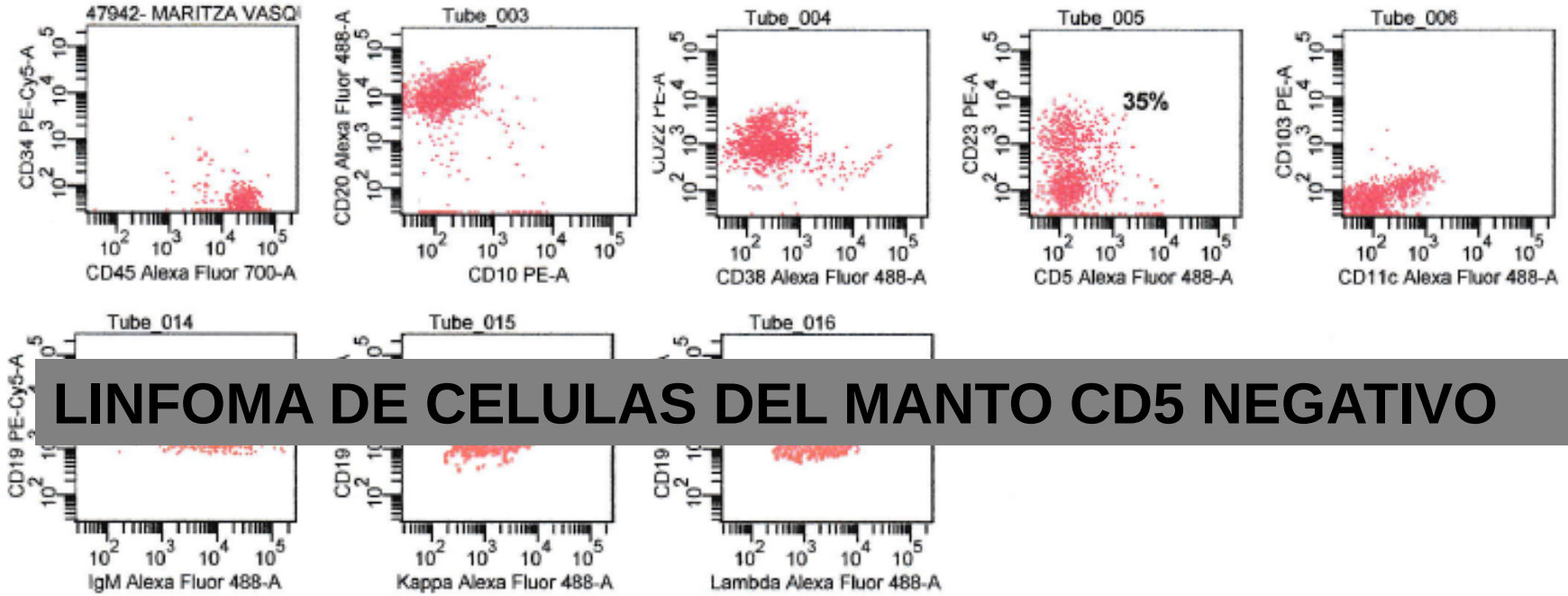
- Otros tumores que pueden ser positivos para Ciclina D1:

1. Leucemia de células velludas
2. Mieloma múltiple
3. CLL/SLL (+/-)
4. DLBCL (5%)

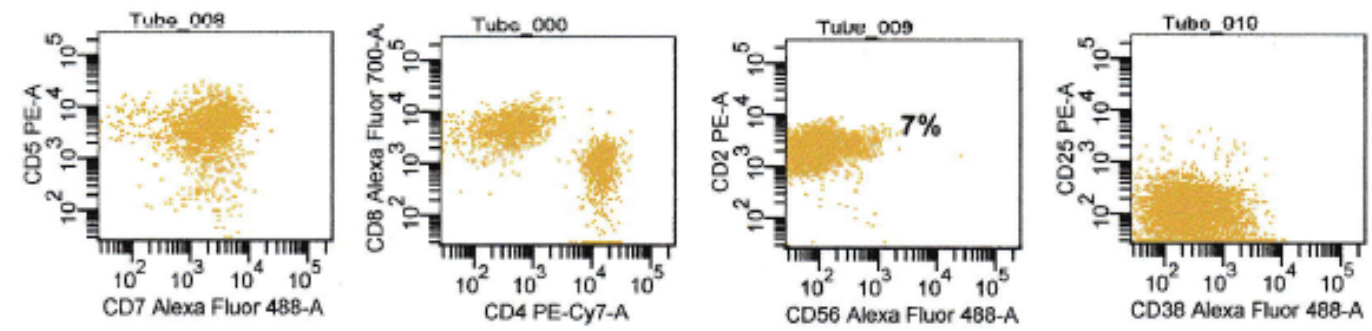


LINFOMA DE CELULAS DEL MANTO CD5 NEGATIVO

CD19(+)

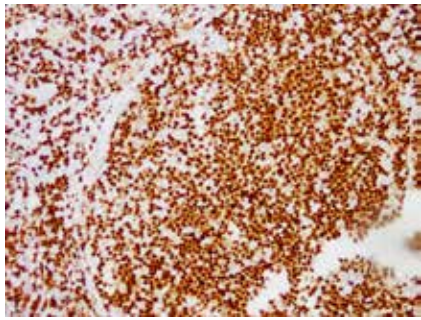


CD3(+)



CD4(+): 39%
CD8(+): 60%

CD38(+): 17%



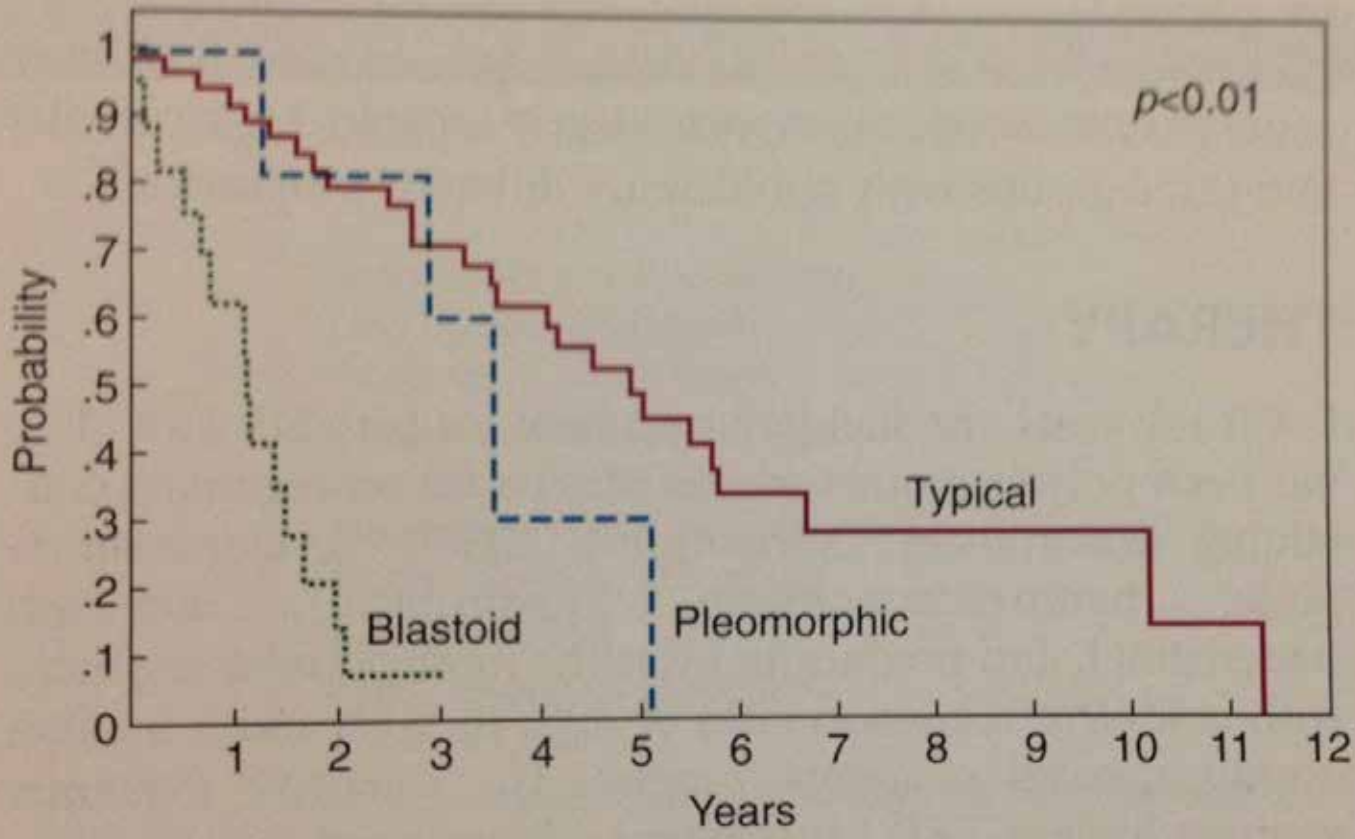


Figure 21-14. Prognostic significance of different cytologic variants of mantle cell lymphoma. Patients with classic (typical) mantle cell lymphoma had better survival than those with pleomorphic and blastoid variants. (Courtesy of Dr. F. Bosch, Hospital Clinic, University of Barcelona, Spain.)

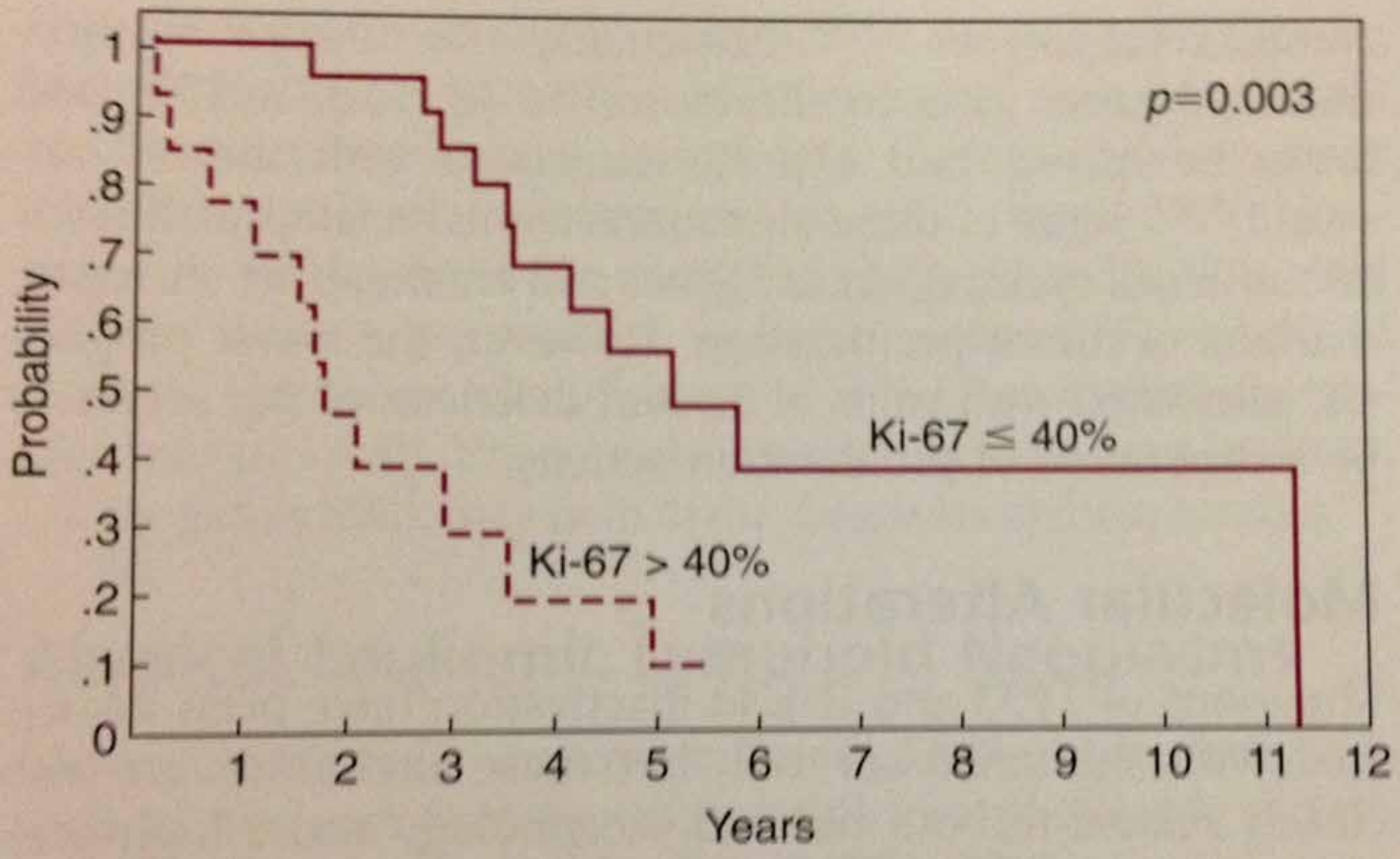


Figure 21-13. Prognostic significance of the Ki-67 proliferative index in mantle cell lymphoma. Highly proliferative tumors had a worse prognosis than those with a lower proliferative index. (Courtesy of Dr. F. Bosch, Hospital Clinic, University of Barcelona, Spain.)

Table II. The association between proliferation index and survival [data from Tiemann *et al* (2005)].

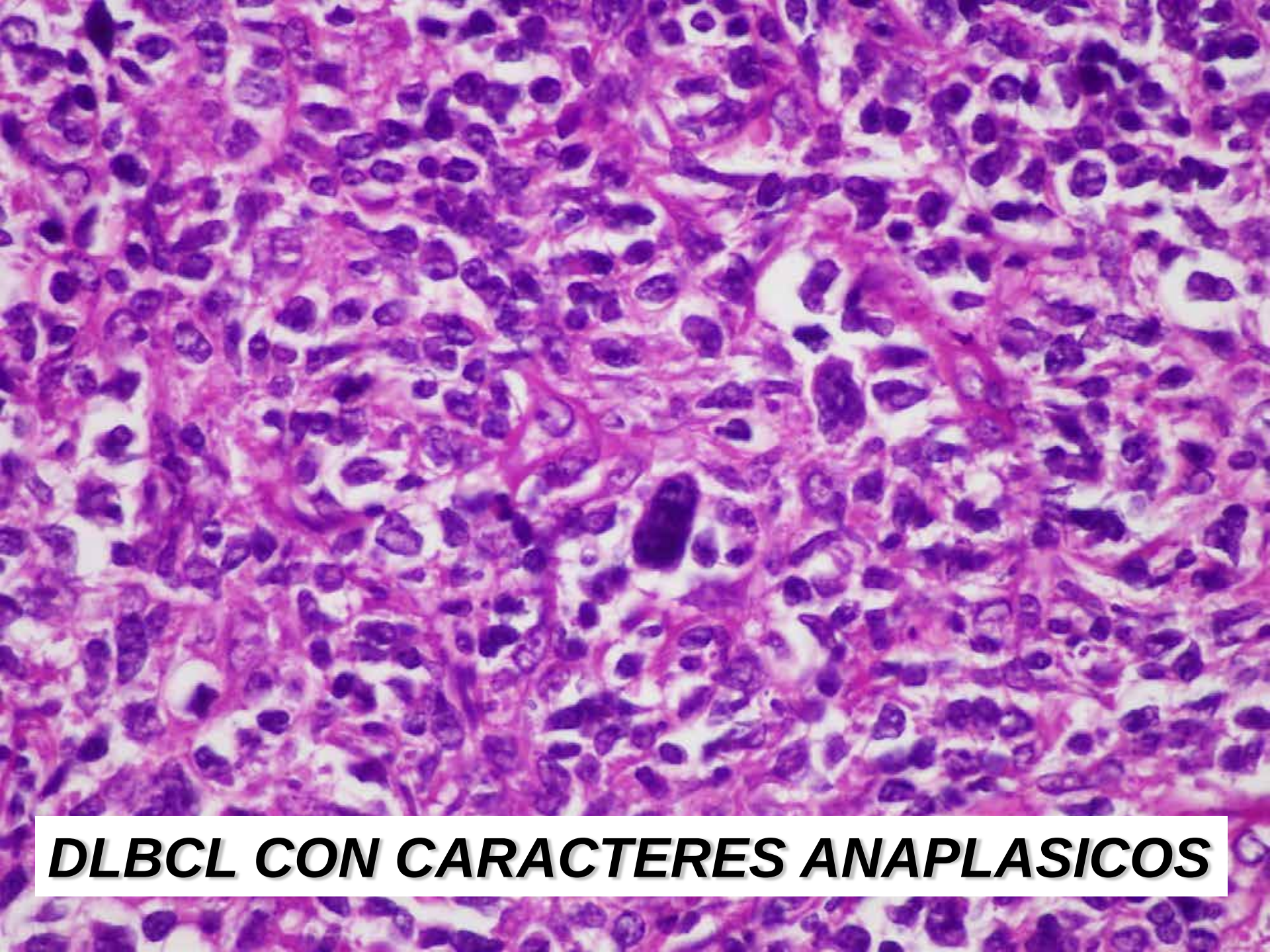
Ki67 proliferation index (%)	Median survival (months)
<10	42
11–40	30
>40	15

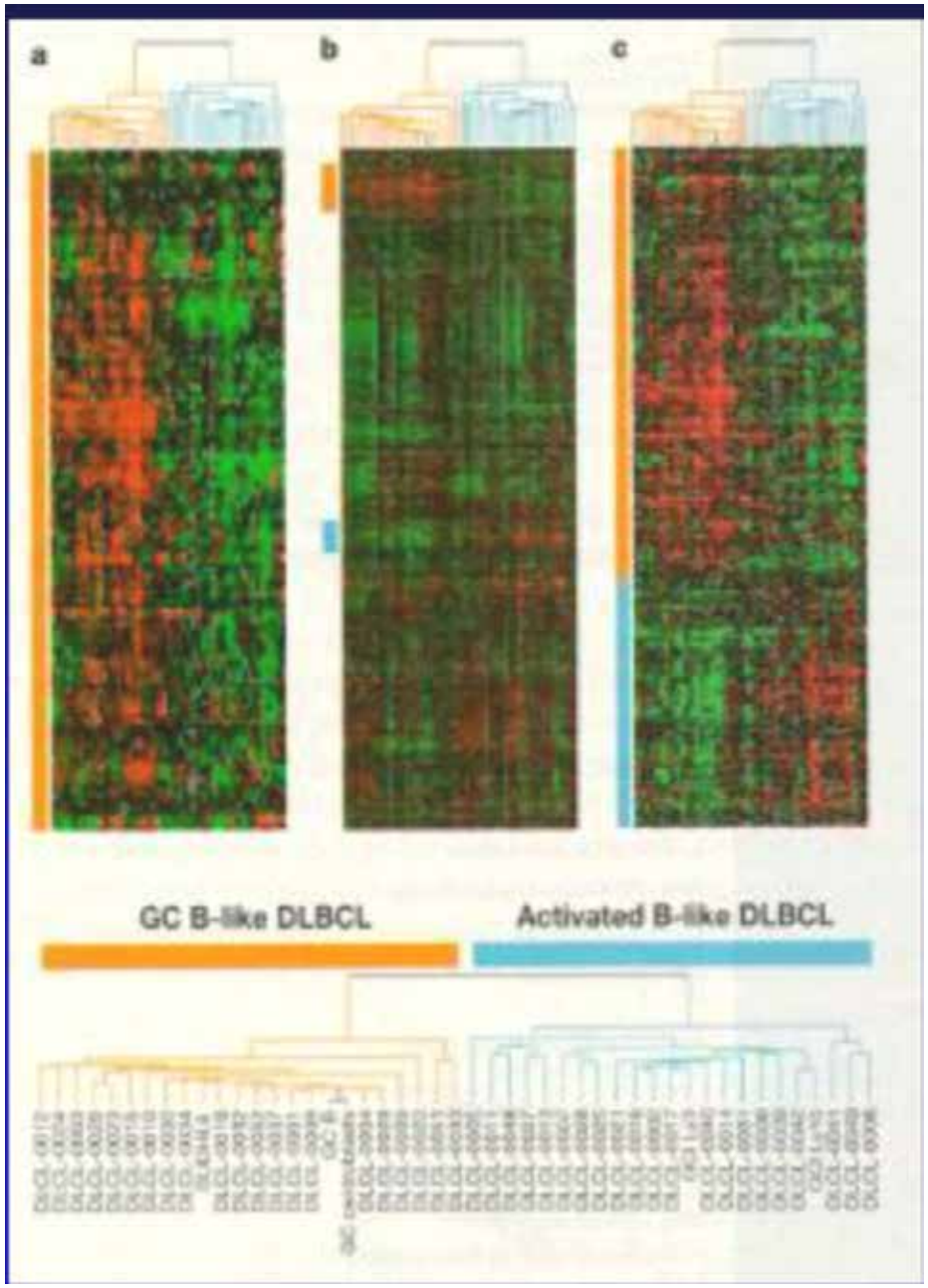
- ***DEBEMOS INFORMAR EL INDICE DE PROLIFERACION EN LOS LINFOMAS DE CELULAS DEL MANTO***

LINFOMA DIFUSO DE CELULAS B GRANDES

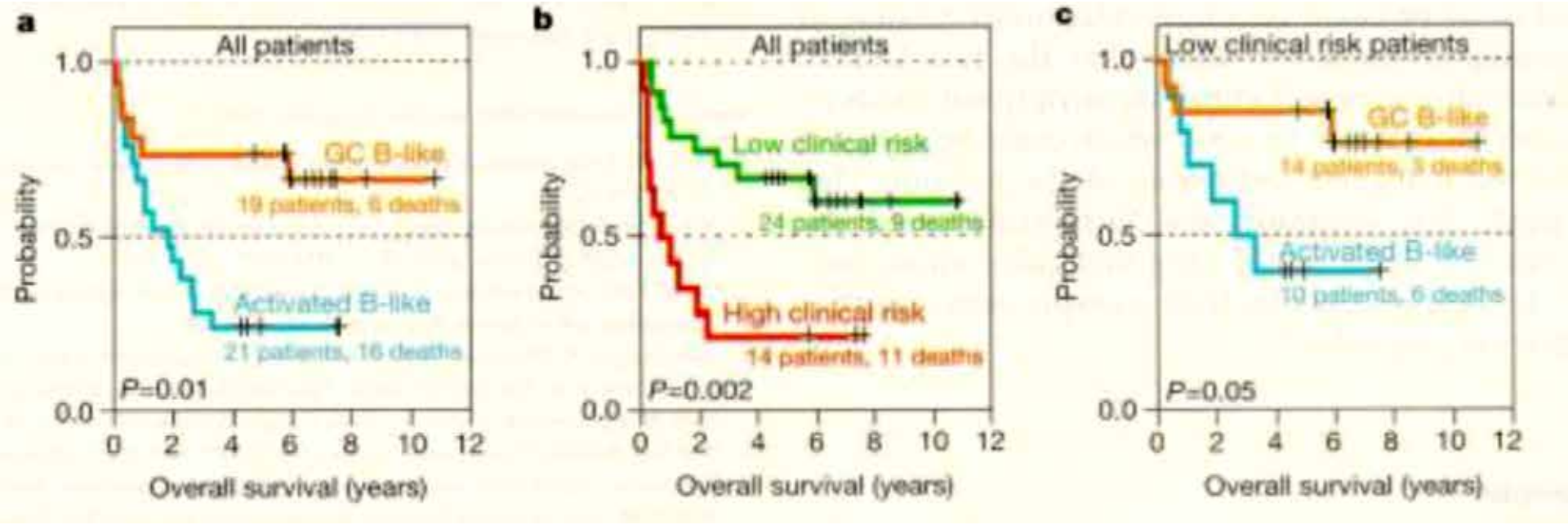
- ¿Es un tipo específico de Linfoma?
- **MUY PROBABLEMENTE NO**

- DLBCL es una neoplasia muy heterogéna:
- De novo
- Formas transformadas
- Amplio espectro inmunofenotípico
- Causas virales


DLBCL CON CARACTERES ANAPLASICOS

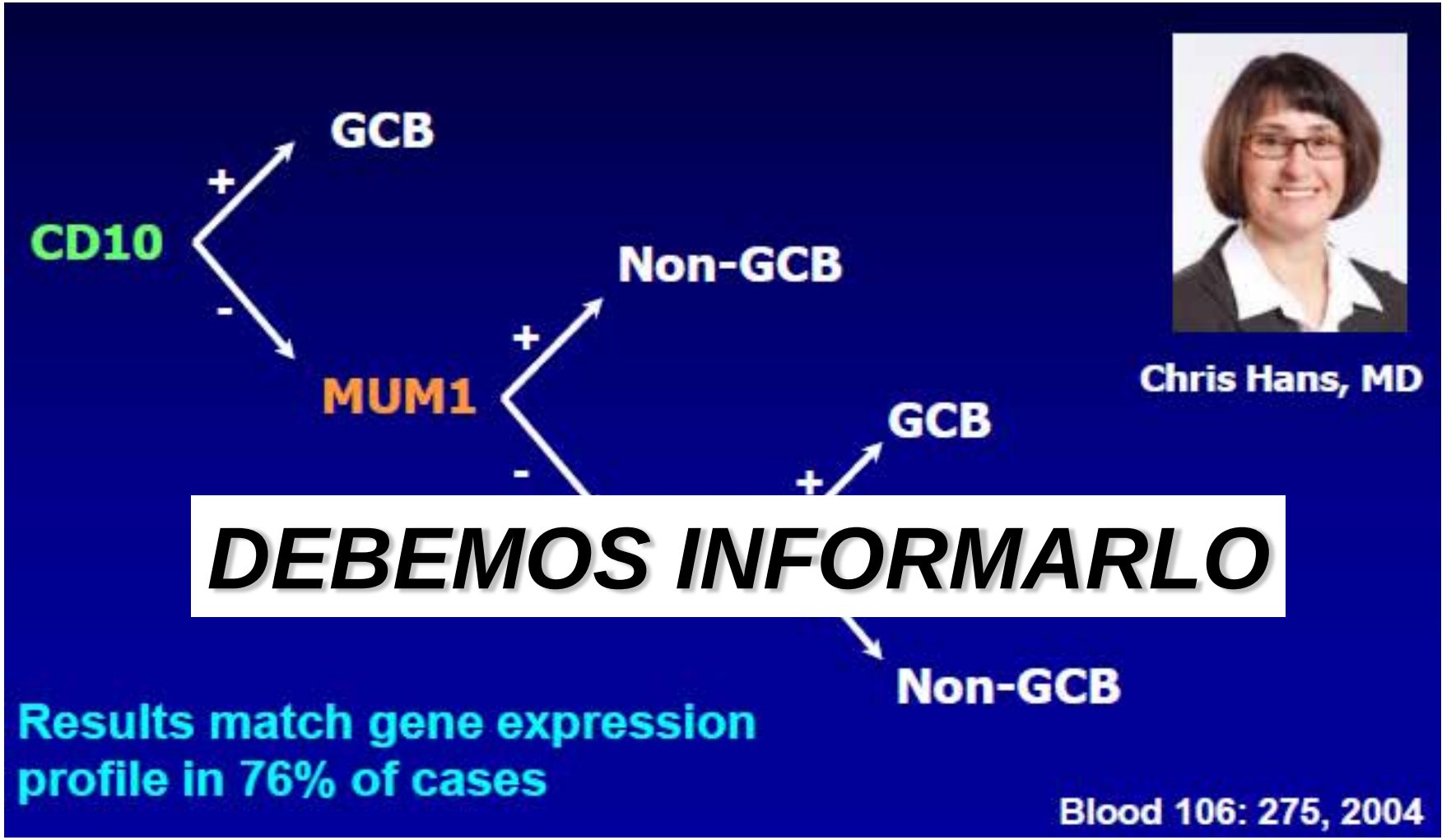


Nature 403: 503, 2000



Nature 403: 503, 2000

ALGORITMO DE HANS



- ***ROL EN ACTUALIZAR NUESTROS DIAGNOSTICOS***

LINFOMAS “DOBLE HIT”

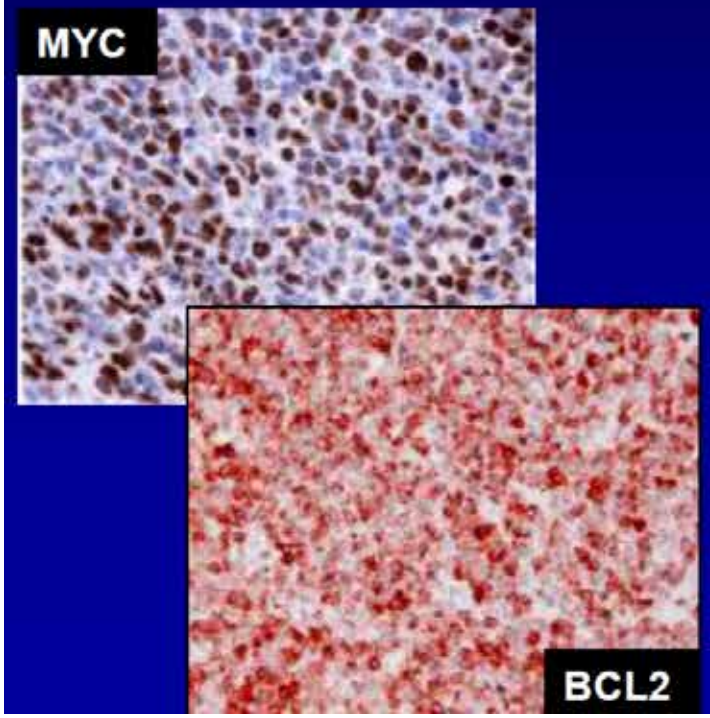
Lymphomas with recurrent chromosomal breakpoints activating multiple oncogenes - one of which is MYC

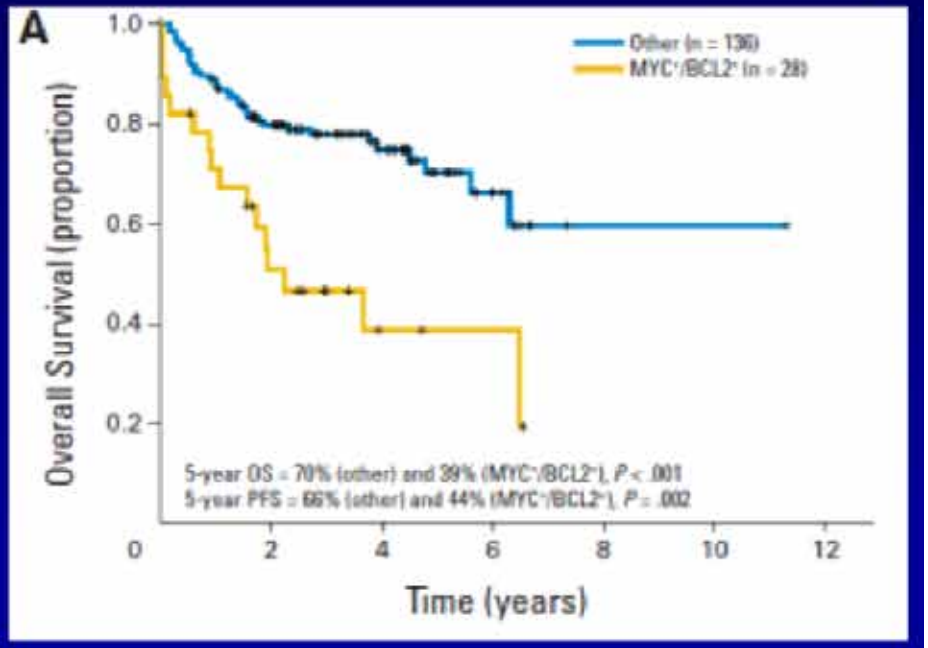
MYC + BCL-2
MYC + BCL-6
MYC + BCL-2 + BCL-6 (triple hit)
MYC + BCL-3
MYC + CCND1

Blood 117: 2319, 2011

Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

Nathalie A. Johnson, Graham W. Slack, Kerry J. Savage, Joseph M. Connors, Susana Ben-Neriah, Sanja Rogic, David W. Scott, King L. Tan, Christian Steidl, Laurie H. Sehn, Wing C. Chan, Javeed Iqbal, Paul N. Meyer, Georg Lenz, George Wright, Lisa M. Rimsza, Carlo Valentino, Patrick Brunhoeber, Thomas M. Grogan, Rita M. Braziel, James R. Cook, Raymond R. Tubbs, Dennis D. Weisenburger, Elias Campo, Andreas Rosenwald, German Ott, Jan Delabie, Christina Holcroft, Elaine S. Jaffe, Louis M. Staudt, and Randy D. Gascoyne





J Clin Oncol 30: 3452, 2012

Cuando realizar FISH para MYC/BCL2 y BCL6

- Realizarlo en todos los casos de DLBCL y HGL, a pesar de ser de interés, es difícil de practicarlo en la rutina clínica.
- Se recomienda una estrategia de *screening* en dos pasos:

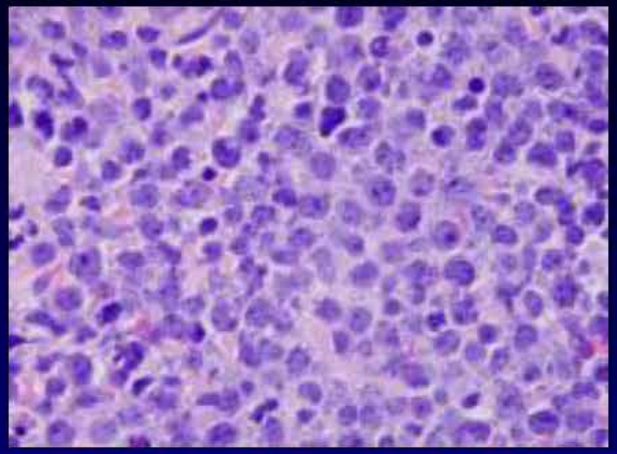
- **<u>1 selección de los casos:</u>**

- Presentación clínica:
  Enfermedad extensa, compromiso de SNC, expresión leucémica

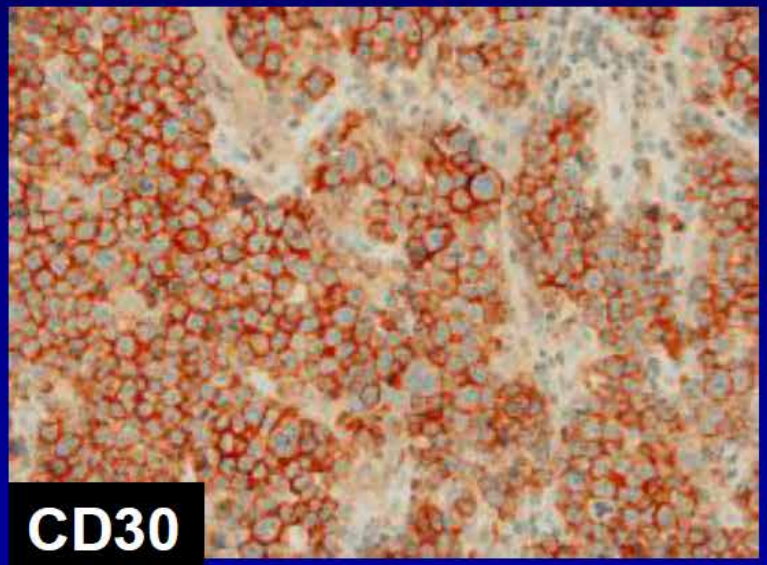
- Morfología:
  Todos los BCLU
  DLBCL Con fenotipo CG
  Ki67 >80%
  BCL2 >50%
  MYC >40%

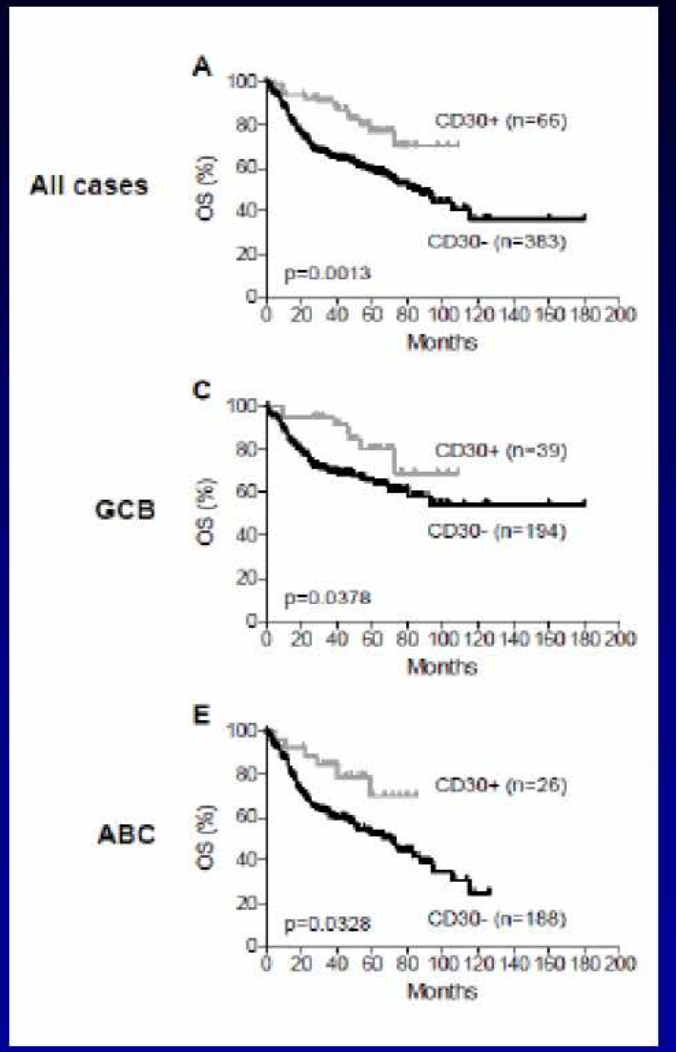
- **<u>2 FISH</u>**
  Comenzar con MYC y continuar con BCL2 y BCL6.

EXPRESION DE CD30 EN LINFOMAS DIFUSOS DE CELULAS B



Ken Young, MD, PhD





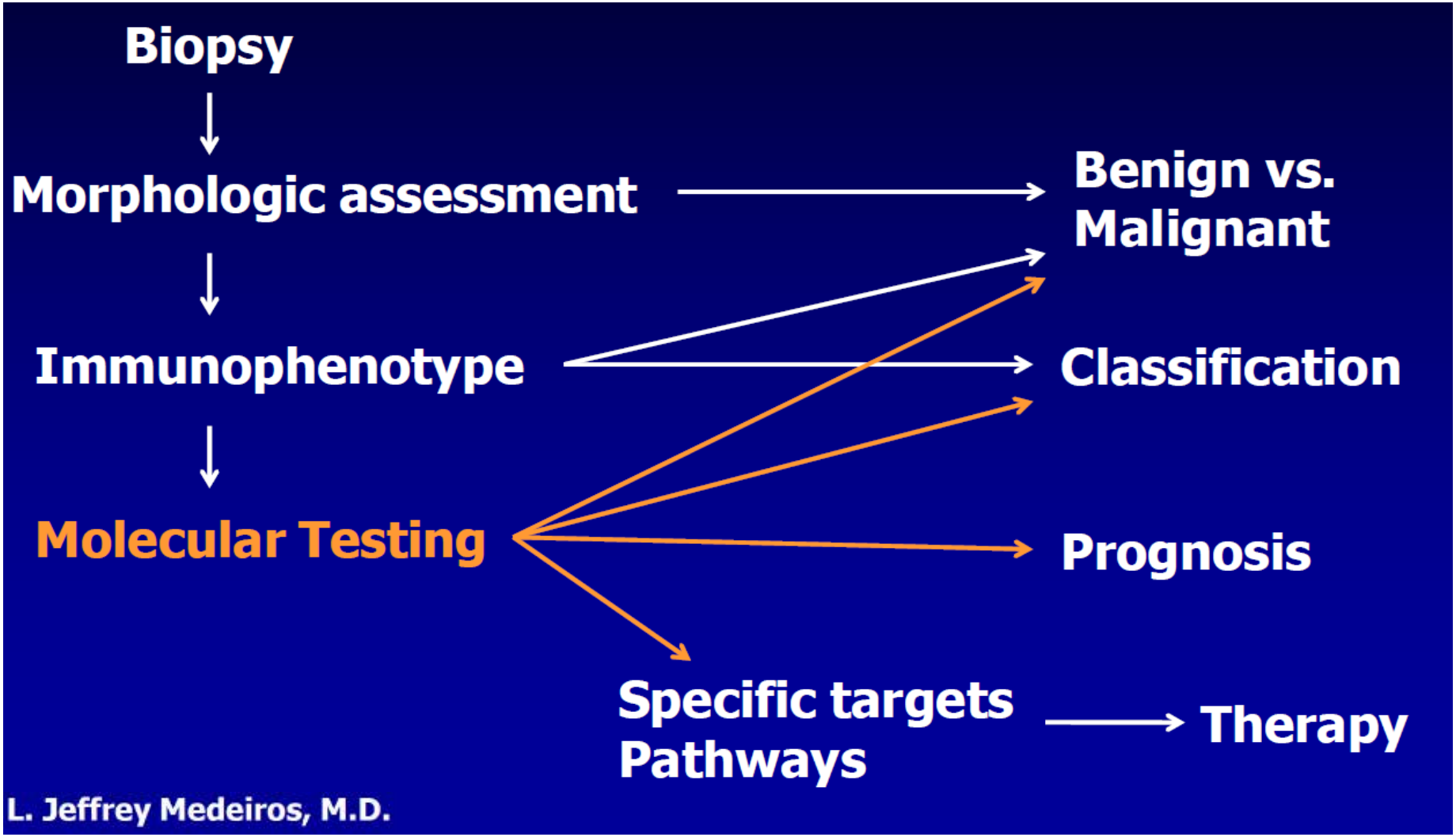
10 - 15% of DLBCL are CD30+

Blood 2013 [Epub]

Se aproxima una “ola” de *tests* moleculares

- Secuenciación completa del genoma
- Secuenciación completa de exón
- Secuenciación RNA
- Perfil epigenético: metilación y modificación de histonas.

ROL DE LOS TEST MOLECULARES EN LOS LINFOMAS



CUIDADO:

FALSOS POSITIVOS EN CLONALIDAD

- La monoclonalidad puede ser detectada en lesiones benignas:

- <u>Ejemplos:</u>

1. Linfoproliferaciones autoinmunes
2. Inmunodeficiencia
3. Gastritis por Helicobacter pylori
4. Lesiones linfoides cutáneas

- *MONOCLONALIDAD NO ES SIEMPRE SINONIMO DE MALIGNIDAD*

Southern Blot

Detects almost all gene rearrangements
Requires ~ 30 ug high mol. wt. DNA
Laborious and long turnaround time

PCR

Requires approximately 2 ug of DNA
Can perform on paraffin tissue
Easy and short turnaround time

CLASIFICACION OMS

- ULTIMA CLASIFACION: 2008
- PROXIMA: 2016
- ***“Debe considerar más como una actualización del 2008, que como una total nueva clasificación”.***
- Dr. Elias Campo, editor WHO, Sao Paulo, Junio de 2015.

Table 2. Some of the Questions to Be Answered by Pathologists in the Era of Personalized Medicine

1. What disease does the patient have?
2. What drug will the disease respond to?
3. How much drug should be given?
4. What are the risks of having an adverse reaction to the drug?
5. What is the patient's prognosis?

(*Arch Pathol Lab Med.* 2009;133:908–911)

Three Hundred Thirty-Five Pathology Claims From 1998 Through 2003

Specimen Category*	Total No. of Claims	No. (%) of False-Negative (Cancer)	No. (%) of False-Positive (Cancer)	% Total Claims
Miscellaneous surgical pathology	48	31 (65)	9 (19)	14.5
Melanoma	44	42 (95)	2 (4.5)	13
Breast biopsy	42	20 (48)	22 (52)	12.5
Papanicolaou tests	42	41 (98)	1 (2)	12.5
Gynecologic pathology	31	23 (74)	5 (16)	9.5
Operational error	22	. . .	. . .	6.5
Clinical pathology	17	40% involved transfusion medicine		5
Sarcomas	15	12 (80)	3 (20)	4.5
Lymphoma	14	8 (57)	6 (43)	4
Lung pathology	12	5 (42)	7 (58)	3.5
Gastric biopsy	12	5 (42)	7 (58)	3.5
FNA, miscellaneous	10	4 (40)	6 (60)	3
Prostate biopsy	9	6 (67)	3 (33)	2.5
FNA, breast	5	2 (40)	3 (60)	1.5
Bladder CIS	5	5 (100)	. . .	1.5
Cytology, other	4	4 (100)	. . .	1
Branchial cleft cyst	3	3 (100)	. . .	1

* FNA indicates fine-needle aspiration; CIS, carcinoma in situ.

Box 1 Common situations involving risk of diagnostic error

- Differential diagnosis of reactive conditions versus neoplastic
- Incomplete lymphoma diagnosis
- Inaccurate and misleading use of classification terminology
- Incorrect assessment of grade in NHL
- Classic HL versus NHL
- Incorrect assessment of lymphoid infiltration at non-nodal sites

J Clin Pathol 2011;**64**:466–476.

Box 2 Critical diagnostic errors in lymphoid tissue diagnosis

- Reactive versus neoplastic conditions
- Diffuse large B cell lymphoma versus Burkitt lymphoma
- Low grade versus high grade in small lymphoid cell infiltrates
- Classical HL versus NHL

J Clin Pathol 2011;**64**:466–476.

Box 3 Specimen limitations* that lead to errors

- Small specimen size (eg, needle biopsy and endoscopic specimens)
- Crushed or otherwise distorted tissue (eg, mediastinoscopic specimens)
- Poor fixation (delay in transfer of fresh tissue into fixative, insufficient fixative volume, insufficient time in fixative, larger specimens not sliced to aid penetration by fixative)
- Excessive fixation (formalin pigment deposition obscuring detail, difficult antigen retrieval for immunohistochemistry)
- Necrotic tissue

*Note: the importance of developing and maintaining skills in specimen-taking by relevant clinical professionals cannot be overemphasised. Laboratory staff must also pay close attention to ensuring high quality preparation of specimens for histology.

J Clin Pathol 2011;**64**:466–476.

Box 4 Errors relating to immunohistochemistry

- Insufficient understanding of antibody reactivities
- Use of inappropriate positive and negative controls
- Sensitivity changes due to alterations in reagents or machines used
- Insufficient range of tests used, due to cost concerns
- Drift in performance of reagents if use insufficient to ensure adequate turnover and replacement

J Clin Pathol 2011;**64**:466–476.

Box 5 Errors arising from consideration of insufficiently wide differential diagnosis: some examples

Misleading range of investigations undertaken:

- High-grade plasmablastic tumours misinterpreted as non-haemopoietic because of downregulation of lymphoid cell-associated antigens
- Extramedullary presentations of acute myeloid leukaemias mistakenly interpreted as aggressive lymphoma in the absence of screening for myeloid differentiation
- Neoplastic mast cell infiltrates interpreted as histiocytic, supported by CD68 expression but without concurrent staining for tryptase and/or CD117 to establish correct phenotype

J Clin Pathol 2011;**64**:466–476.

Conclusiones

- Existen inquietudes similares a las que presentaban nuestros predecesores a comienzos del siglo XX.
- El diagnóstico de Linfoma es cada día más complejo y debe analizarse caso a caso con profundidad.
- Debemos tratar de optimizar nuestros recursos de acuerdo a la necesidad y realidad del paciente.