XXV CONGRESO DE LA SOCIEDAD ESPAÑOLA DE ANATOMÍA PATOLÓGICA

Zaragoza, 18 a 21 de mayo de 2011

IN SITU/EARLY LINFOMA

Manuela Mollejo.
Hospital Virgen de la Salud.
TOLEDO

IN SITU/EARLY LINFOMA

EAHP Lymphoma Symposium

Topics: Frontiers in diagnosing lymphoma – early lesions, molecular pathogenesis and targeted therapy & Recent advances in haematopathology

EAHP Lymphoma Workshop

Topic: Early lesions in lymphoid neoplasia

How I treat: diagnosing and managing "in situ" lymphoma

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The "in situ" lymphomas are often incidental findings in an otherwise reactive-appearing lymph node. Notably, the risk of progression to clinically appreciable lymphoma is not yet fully known. The diagnosis of "in situ" lymphoma is feasible when immunohistochemical characterization is carried out and genetic abnormalities are assessed. "In situ" follicular lymphoma is characterized by the presence within the affected germinal centers of B cells that strongly express BCL2 protein, a finding that supports their neoplastic nature, in the absence of interfollicular infiltration. In "in situ" mantle cell lymphoma, the lymphoma involvement is typically limited to the inner mantle zone, where lymphoma cells are cyclin D1+ and weakly BCL2+, CD5+. A staging workup to exclude other site of involvement is highly recommended for the possible coexistence of an overt lymphoma. Biopsy of all sites of suspicious involvement should be mandatory. No evidence for starting therapy also in the presence of multifocal "in situ" lymphoma exists, and a "wait-and-see policy" is strongly suggested. A follow-up strategy reserving imaging evaluation only in the presence of disease-related symptoms or organ involvement appears to be a reasonable option. For patients with concomitant overt lymphoma, staging and treatment procedures must be done according to malignant counterpart. (*Blood*. 2011; 117(15):3954-3960)

Introduction

Pathologists dealing with diagnostics of lymphomas, through the use of conventional methods and advanced technologies, on several occasions happen to come up against morphologic lesions that can presently be defined as "in situ" lymphomas.[1] In these lesions, the neoplastic cells proliferate "in situ" (ie, in the "place" that is occupied by the normal counterpart of the tumor cell, without invasion of surrounding structures). For example, in the case of "in situ" follicular lymphoma (FL), the accumulation of neoplastic cells is within the lymphoid follicles only. For these reasons, "in situ" lymphoma does not usually form a tumor; rather, the lesion follows the existing architecture of the involved lymphoid follicles

routine clinical practice. We discuss how to make a reliable and precise diagnosis of "in situ" lymphoma and when and how to treat the patient. The partnership between the pathologist and the clinician is crucial in the management of patients with these lesions that appear to have limited potential for histologic or clinical progression and for which clinical and therapeutic data are very limited.

"In situ" lymp
in the evolutic

Histopathology 2011, **58**, 81–89. DOI: 10.1111/j.1365-2559.2010.03702.x

REVIEW

Occult B-cell lymphoproliferative disorders

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Rawstron A C
(2011) *Histopathology* **58**, 81–89

Occult B-cell lymphoproliferative disorders

The term monoclonal B-cell lymphocytosis (MBL) was recently introduced to identify individuals with a population of monoclonal B cells in the absence of

leukaemia, but an increasing amount of information is becoming available about MBL with the features of other B-cell lymphoproliferative disorders. In addition

IN SITU/EARLY LINFOMA

- Linfoma in situ: “Proliferación de células neoplásicas en la localización de donde deriva el tumor”

- Lesiones iniciales en neoplasias linfoides, que pueden regresar cuando el estímulo inicial es eliminado (linfoma MALT gástrico precoz).

- Condiciones reactivas con expansiones clonales B, o T.

INTRAFOLLICULAR NEOPLASIA/"IN SITU" FOLLICULAR LYMPHOMA

In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Cong P et al.Blood. 2002 May 1;99(9):3376-82.

Coexisting Follicular and Mantle cell lymphoma with each having in situ component. A Novel, curious, and complex consultation case of coincidental, composite , colonizing Lymphoma. Michele R. et al

In situ localization of follicular lymphoma: evidence for subclinal systemic disease with detection of an identical BCL2/IGH fusion gene in blood and lymph node. Cheung MC et al. Leukemia. 2009

Intrafolicular neoplasia/in situ follicular lymphoma: review of a series of 13 cases. Montes-Moreno S et al.Histopathology 2010

MANTLE CELL LYMPHOMA IN SITU

Clonal hyperplasia of cyclin D1+ mantle lymphocytes in an asymptomatic patient: a new entity or an early stage event in the development of a mantle cell lymphoma? Hematol. Citocinas Inmunoter. Ter. Cel. 2005. Espinet B et al.

In-situ mantle cell lymphoma--a report of two cases. Histopathology. 2008 Jan;52(2):256-60. Agel N et al.

Mantle cell lymphoma with partial involvement of the mantle zone: an early infiltration pattern of mantle cell lymphoma? Bassarova A et al. Virchows Arch. 2008

LINFOMA FOLICULAR IN SITU

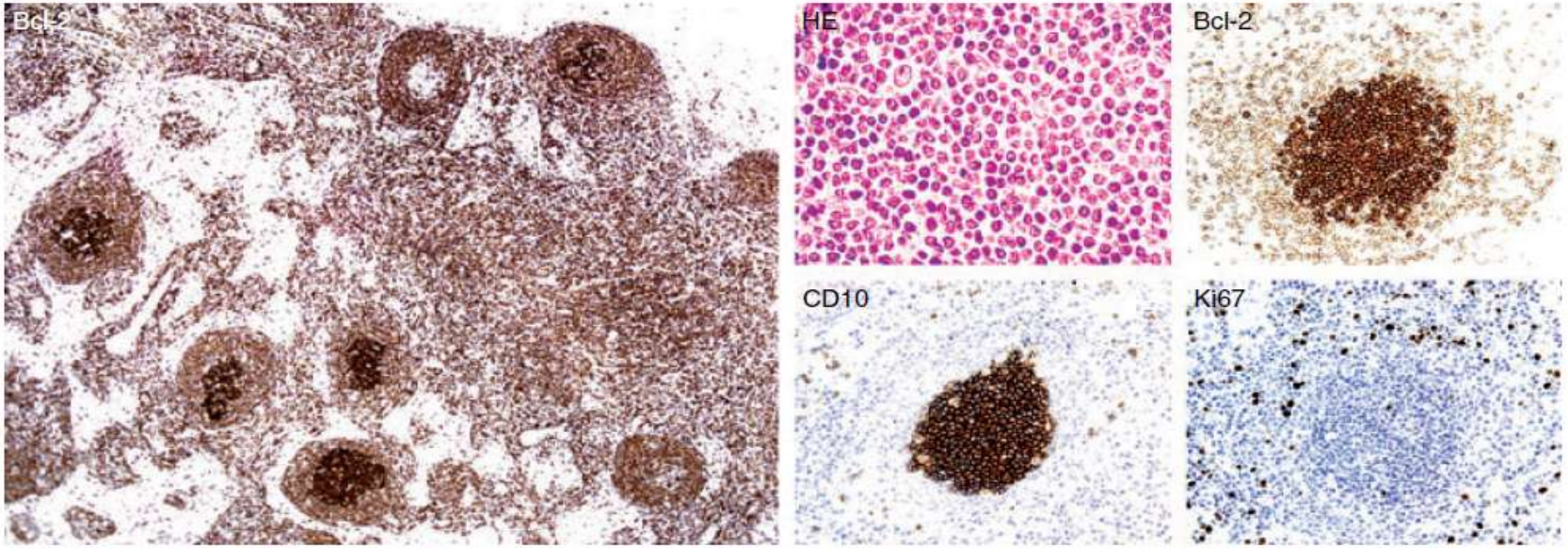

Figure 1. Intrafollicular neoplasia. Note the monomorphic cell composition of the germinal centres (GCs). GCs involved in intrafollicular neoplasia/*in situ* follicular lymphoma are composed mainly of centrocytes with no evident atypia. A feature of these centres is the relative absence of macrophages with tingible bodies and the absence of polarization into light and dark zones. The paucity of large centroblasts reflects their low proliferation rate in *in situ* FLs. Intrafollicular neoplasia/*in situ* follicular lymphoma is characterized by strong co-expression of Bcl-2 and CD10 in the involved GCs.

S Montes et al. Histopathology 2010

 Histopathology, **56**, 652–664.

- Arquitectura conservada, con centros germinales reactivos y folículos con fuerte expresión de bcl2, y marcadores del centro como bcl6, sin infiltración interfolicular.
- Reordenamiento monoclonal IgH y bcl2 en folículos neoplásicos.

blood

Prepublished online February 7, 2011;
doi:10.1182/blood-2011-01-293050

The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications

Elias Campo, Steven H Swerdlow, Nancy L Harris, Stefano Pileri, Harald Stein and Elaine S Jaffe

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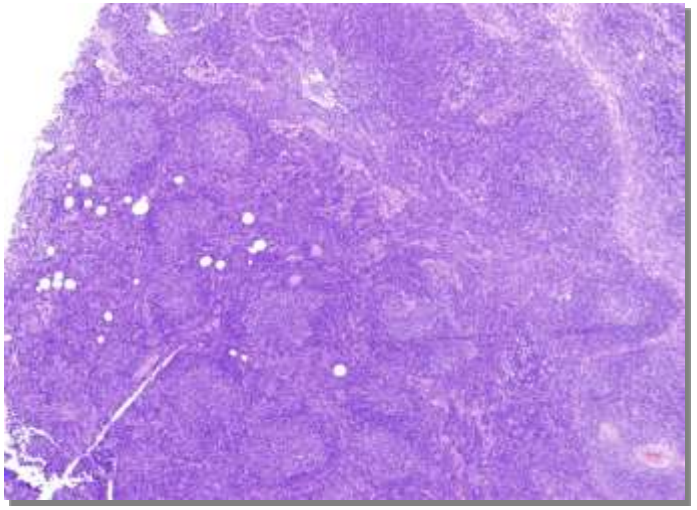
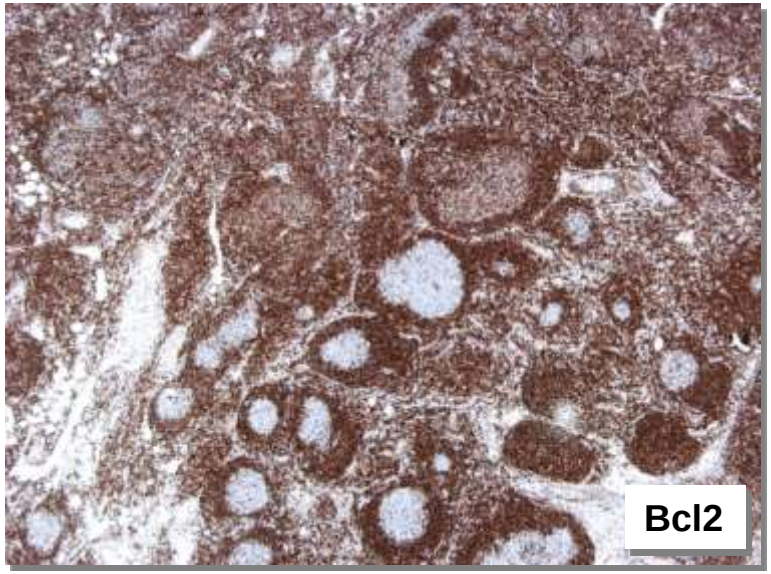
"In situ" FL/ Intrafollicular Neoplasia

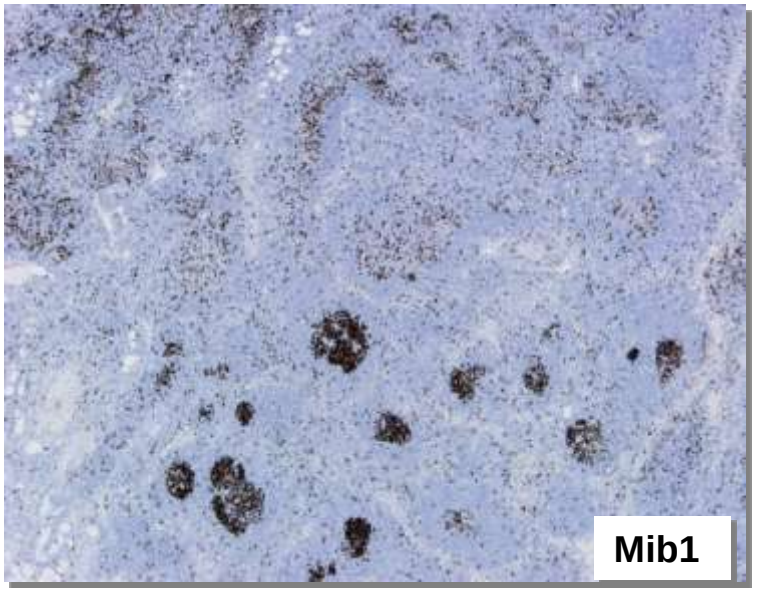
- Preserved general architecture
- Centrocytes strongly + for BCL2 and CD10 within GC
- Bcl-2 staining in centrocytes usually stronger than in mantle cells or reactive T-cells
- Involved follicles usually scattered, not confluent
- Germinal centers normal in size and often not completely replaced by BCL-2+ cells

Partial involvement by FL

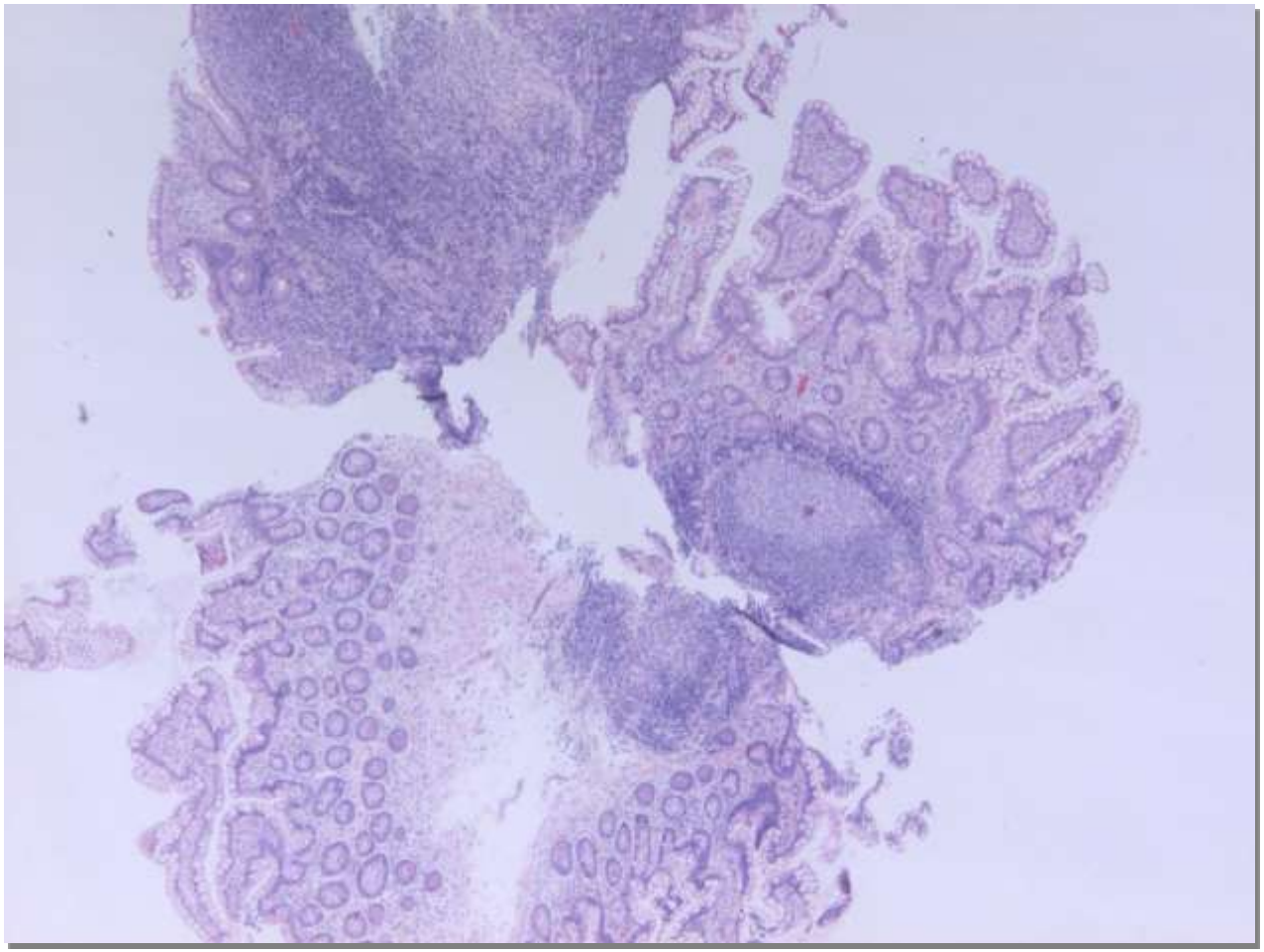
- Partial effacement of the architecture
- Affected follicles usually restricted to a limited region of the lymph node
- Tumor cells may be present in interfollicular areas
- Germinal centers expanded in size and completely replaced by tumor cells



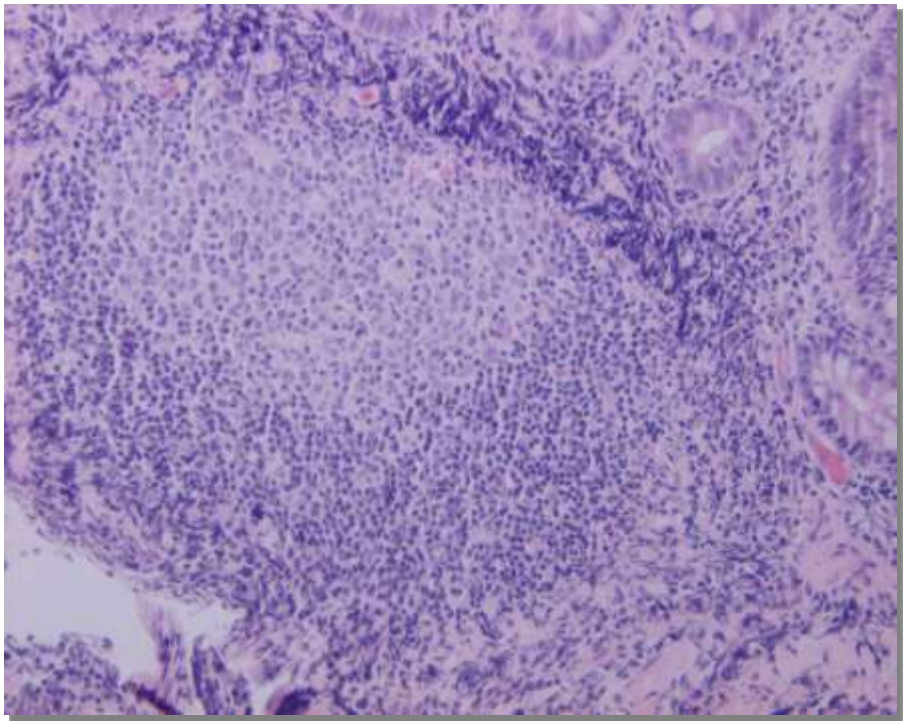


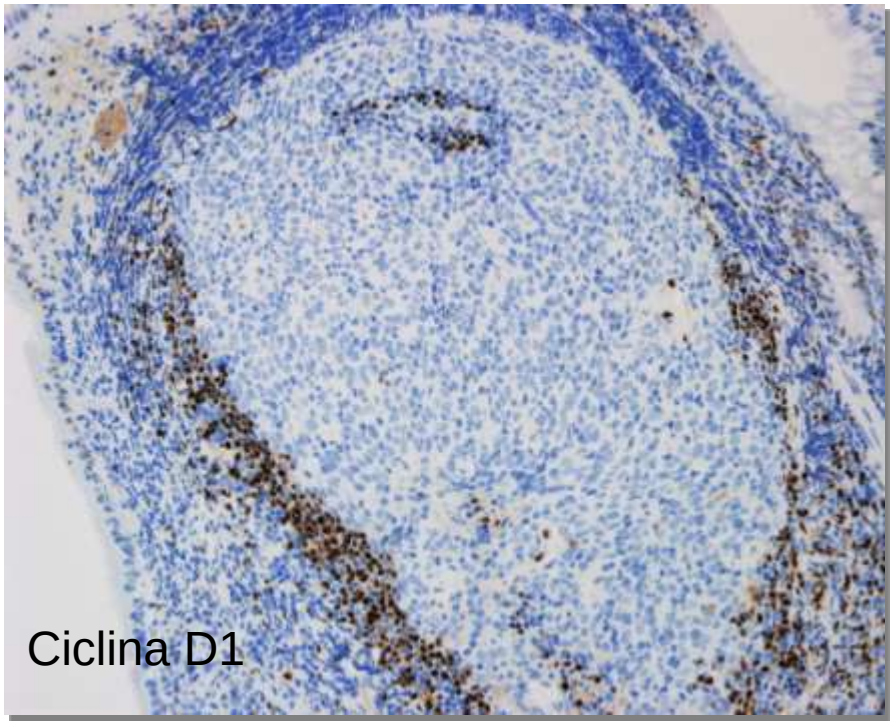


LINFOMA MANTO IN SITU



Paciente de 71 años con diarrea de 10 meses de evolución. Endoscopia imágenes polipoides que se biopsian. 2005.





"In situ" MCL

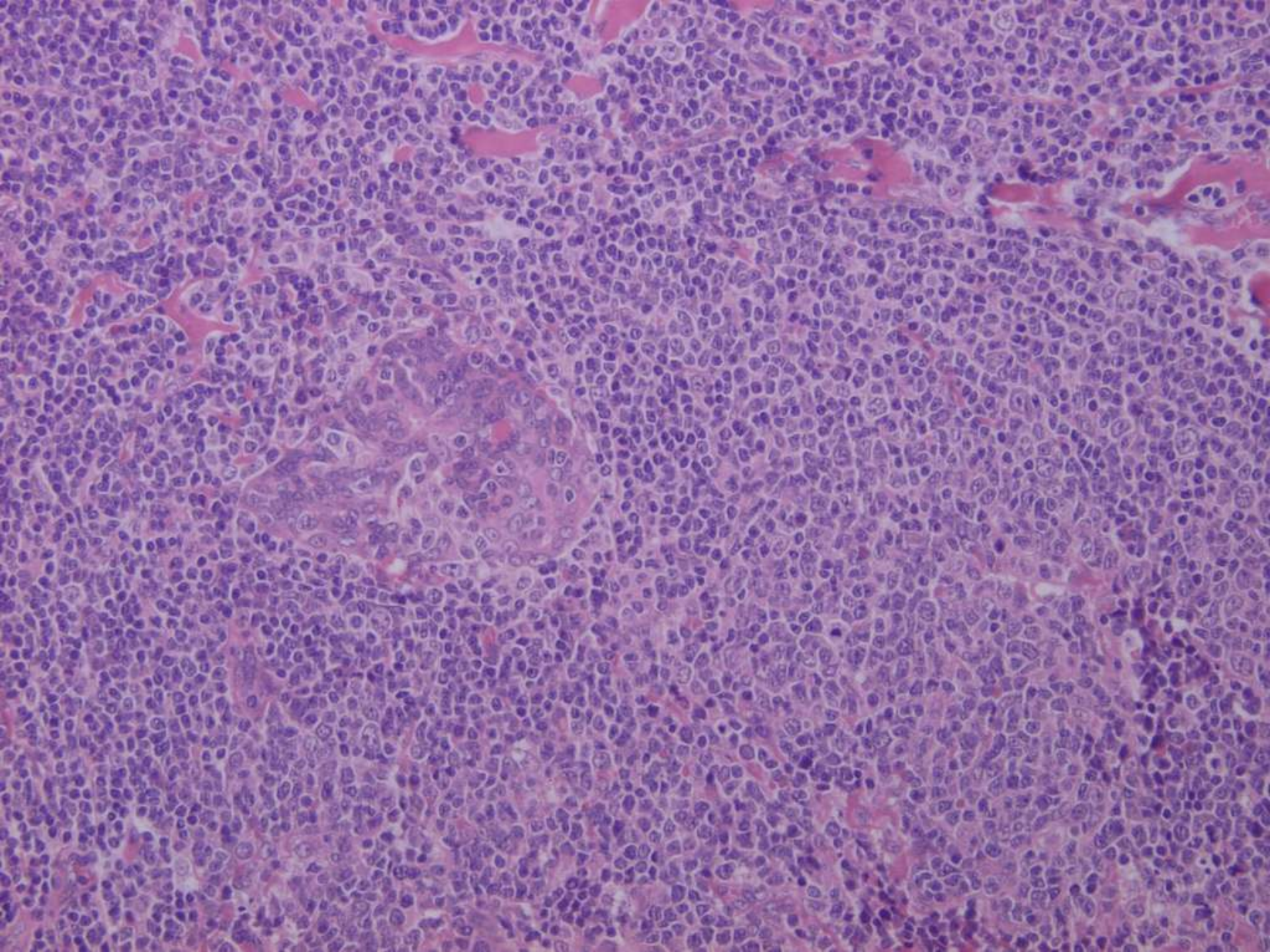
- Preserved general architecture
- Mantle zones usually not expanded
- Cyclin D1+ cells restricted to the mantle zones of reactive follicles with only scattered positive cells in interfollicular areas
- Cyclin D1 + cells tend to accumulate in the inner layers of the mantle zone. Not all mantle cells are positive

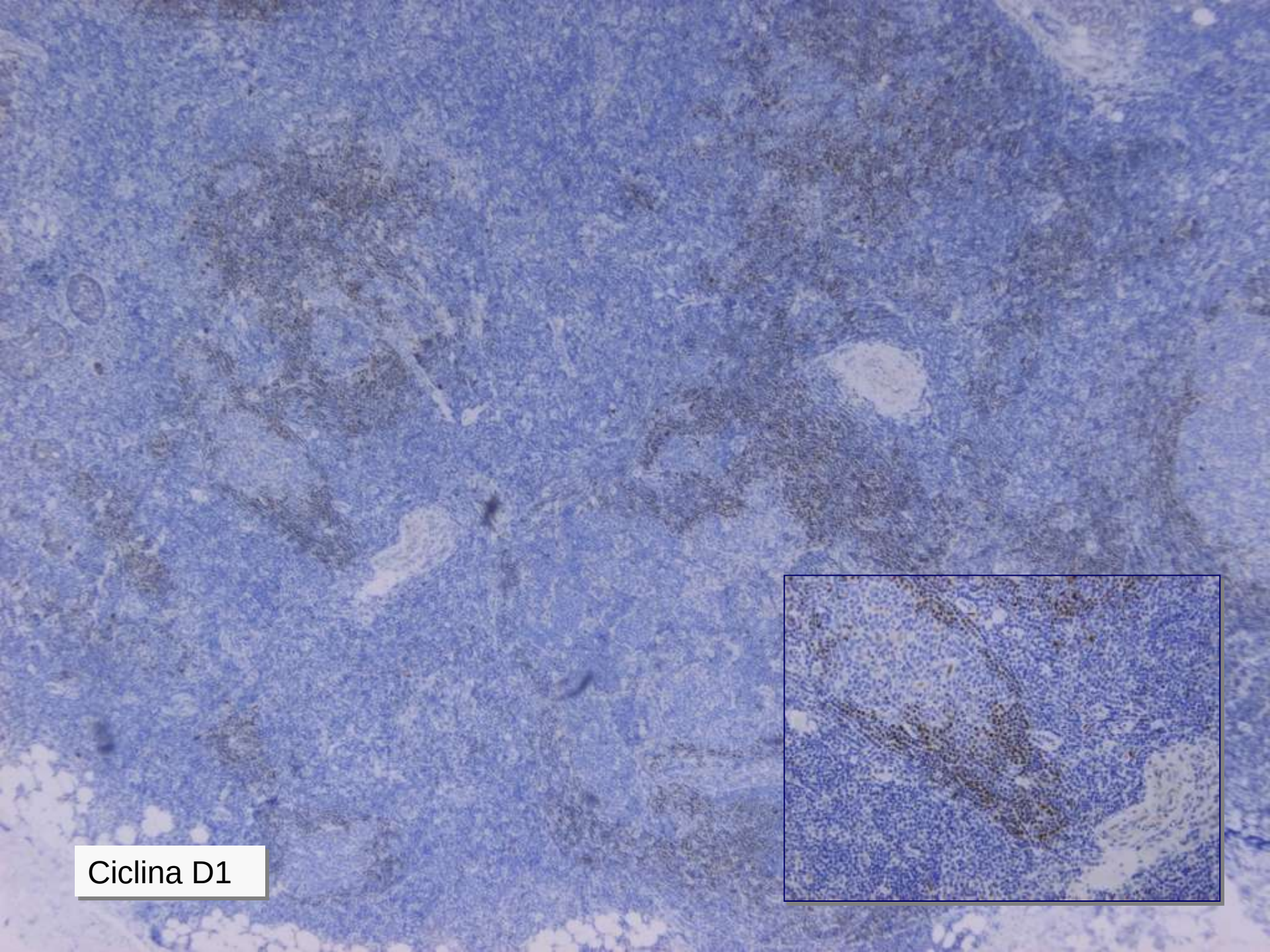
Mantle zone pattern in MCL

- Architecture preserved or focally effaced
- Mantle zones usually expanded
- Cyclin D1 + cells replace virtually all the mantle zone of reactive follicles
- Focal extension of clusters of tumor cells into interfollicular areas may be seen

The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications

Elias Campo, Steven H Swerdlow, Nancy L Harris, Stefano Pileri, Harald Stein and Elaine S Jaffe




Ciclina D1

Neoplasia intrafolicular/ in situ LF

- *BCL2/IGH* en sangre periférica y amígdalas de individuos sanos (>50%) (Limpens et al. 1991; Roulland et al. 2006).
- Mismo reordenamiento en sangre periférica y biopsia de LF in situ, sugiere que estas condiciones representan diferentes estadios en la patogénesis y progresión a linfoma folicular.
- Se necesita un segundo evento molecular además de BCL2/IGH para el desarrollo del linfoma folicular

Linfoma del manto in situ

- Baja prevalencia de células circulantes en sangre periférica con la t(11;14) en individuos sanos.
- Parece que hay cierta evidencia de la que la t(11;14) puede ser precedida por otras alteraciones que afectan la estabilidad genómica, como mutaciones o deleciones de ATM.

Table 1. Revised clinicopathologic proposal on "in situ" B-cell lymphomas, as acknowledged by the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* (2008)[2-4]

	Clinical meanings	Treatment option
"In situ" FL		
Without overt lymphoma	Indolent	Follow-up
With overt lymphoma	Synchronous (early infiltration by synchronous FL)	Therapy as for overt lymphoma "in situ" site should be considered as involved
	Metachronous (preceding FL by years or associated with other lymphomas: DLBCL, SMZL, MCL, and cHL)	Biopsy is mandatory Therapy as for overt lymphoma Consider site of initial "in situ" lymphoma
"In situ" MCL		
Without overt lymphoma	Not always indolent	Follow-up (closer than in FL)
With overt lymphoma	Synchronous (with synchronous MCL or FL)	Therapy as for overt lymphoma "in situ" site should be considered as involved
	Metachronous (widespread disease; aggressive behavior)	Biopsy is mandatory Therapy as for overt lymphoma Consider site of initial "in situ" lymphoma

DLBCL indicates diffuse large B-cell lymphoma; SMZL, splenic marginal zone lymphoma; and cHL, classic Hodgkin lymphoma.

- Linfoma in situ: “Proliferación de células neoplásicas en la localización de donde deriva el tumor”

- Lesiones iniciales en neoplasias linfoides, que pueden regresar cuando el estímulo inicial es eliminado (linfoma MALT gástrico precoz).

- Condiciones reactivas con expansiones clonales B, o T.

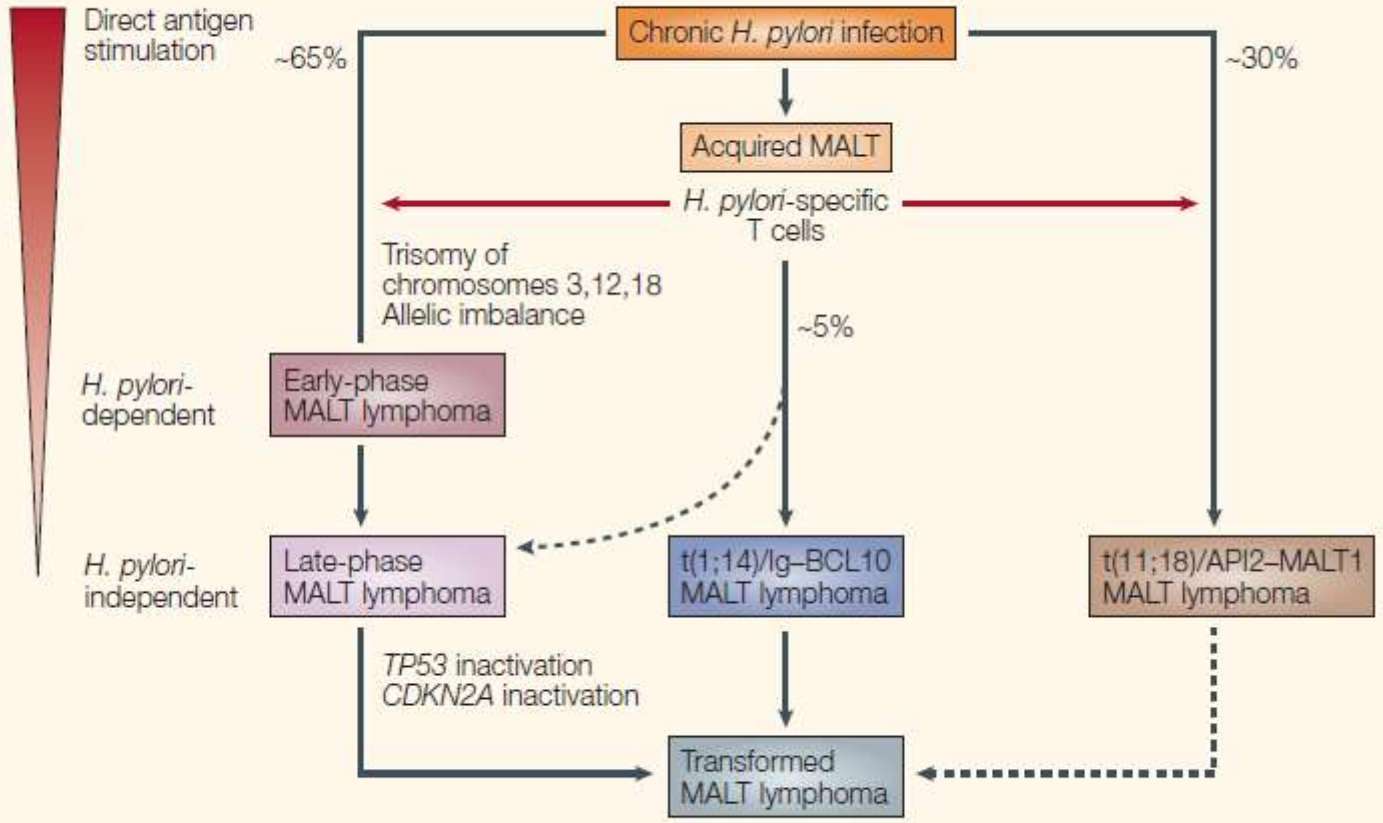


Figure 1 | **Multistage development of gastric MALT lymphoma.** *H. pylori* infection stimulates the production of lymphoid infiltrates, which leads to the formation of acquired mucosa-associated lymphoid tissue (MALT) in the gastric mucosa. As a result of both direct and indirect immunological

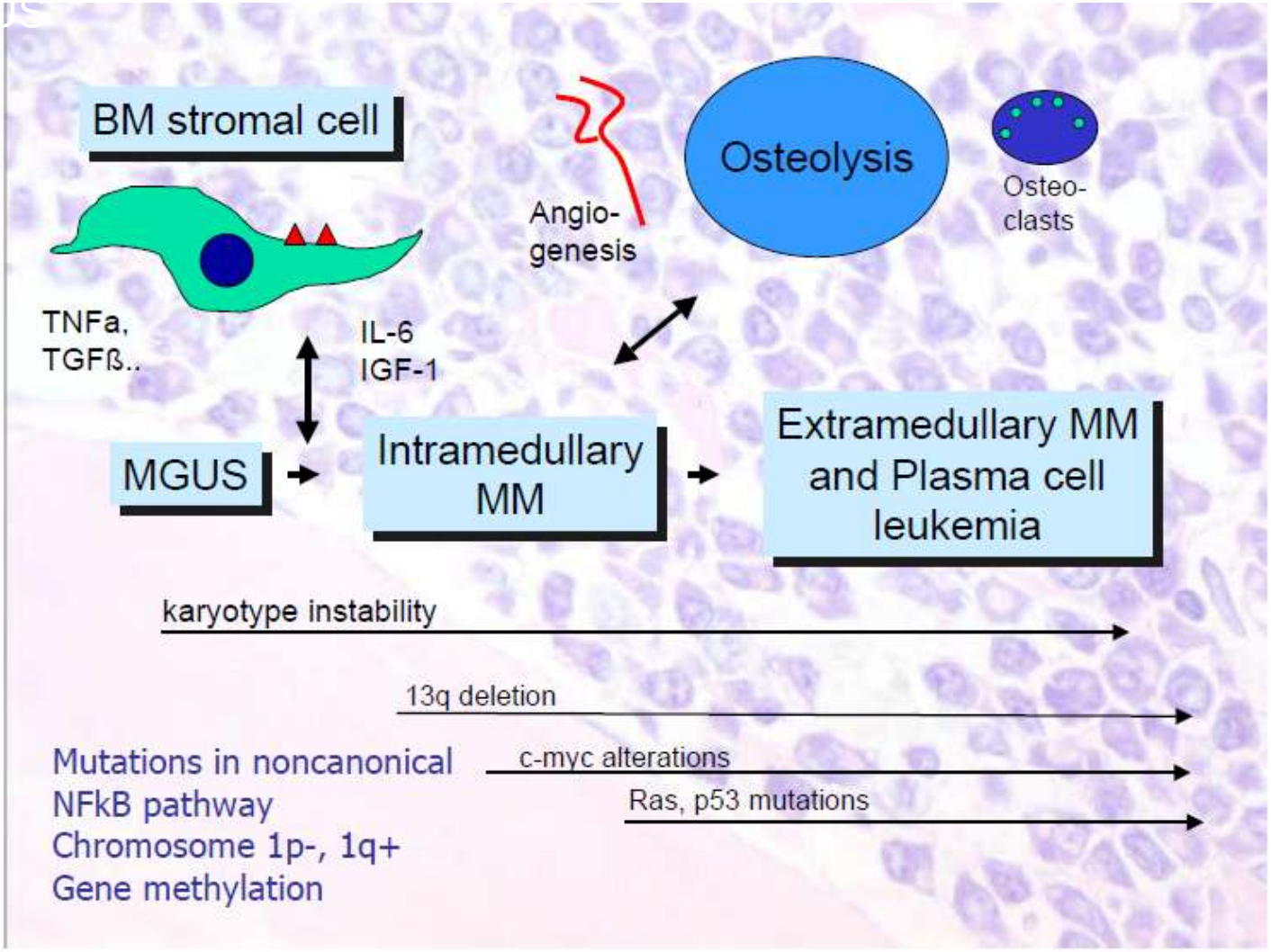
Peter G. Isaacson and Ming-Qing Du. www.nature.com/reviews/cancer

Gammapatía monoclonal de significado incierto:

- M-protein en suero < 30g/L
- Plasmáticas < 10% en médula ósea
- Ausencia de daño órgano (CRAB: hipercalcemia, insuficiencia renal, anemia, lesión ósea)
- No evidencia de otro proceso linfoproliferativo que produzca paraproteina M

IgM MGUS se asocia con una clona células linfoplasmacíticas, puede progresar a WM o LpL
Non-IgM MGUS (IgG, IgA) se asocia con clona células plasmáticas, puede progresar a neoplasia de células plasmáticas

Riesgo de progresión 1% año
Tamaño pico monoclonal, > 15g/l
Tipo de Ig: IgM, IgA > IgG
Cadenas ligeras en suero



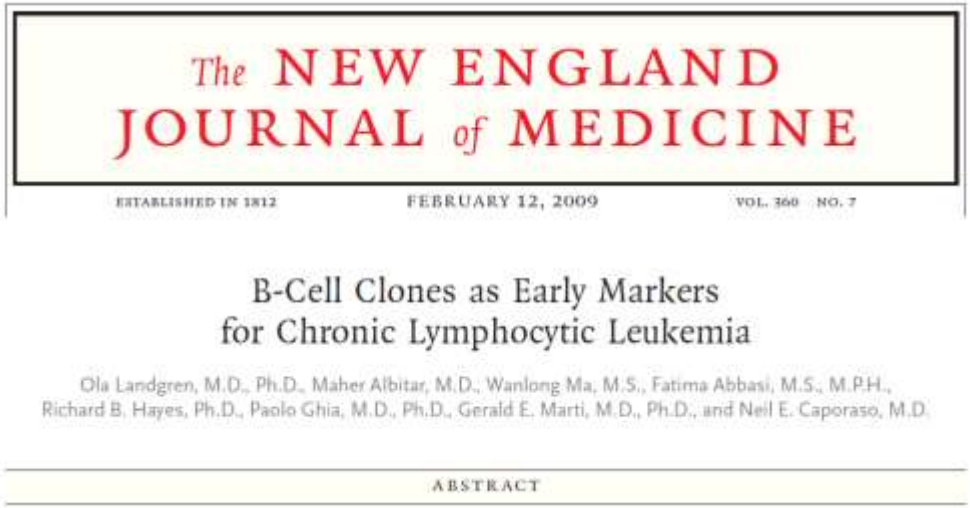
Falko Fend. Uppsala 2010

Linfocitosis monoclonal- CLL

Table 1. Originally proposed diagnostic criteria for monoclonal B-cell lymphocytosis (MBL)[11]

Detection of a monoclonal B-cell population in the peripheral blood with
Overall kappa/lambda ratio >3:1 or <0.3:1, or
More than 25% of B cells lacking or expressing a low level of surface immunoglobulin or
A disease-specific immunophenotype
Repeat assessment should demonstrate that the monoclonal B-cell population is stable over a 3-month period
Exclusion criteria
Lymphadenopathy and organomegaly, or
Associated autoimmune/infectious disease, or
B-lymphocyte count >5 × 10^9/l, or
Any other feature diagnostic of a B-cell lymphoproliferative disorder. However, a paraprotein may be present or associated with MBL and should be evaluated independently
Subclassification
$CD5^+$ $CD23^+$: this is the major subcategory and corresponds to a CLL immunophenotype[51]
$CD5^+$ $CD23^-$: correlate moderate level of CD20 and CD79b expression with atypical CLL
$CD5^-$: corresponds to non-CLL lymphoproliferative disorder

CLL, Chronic lymphocytic leukaemia.



The NEW ENGLAND JOURNAL of MEDICINE

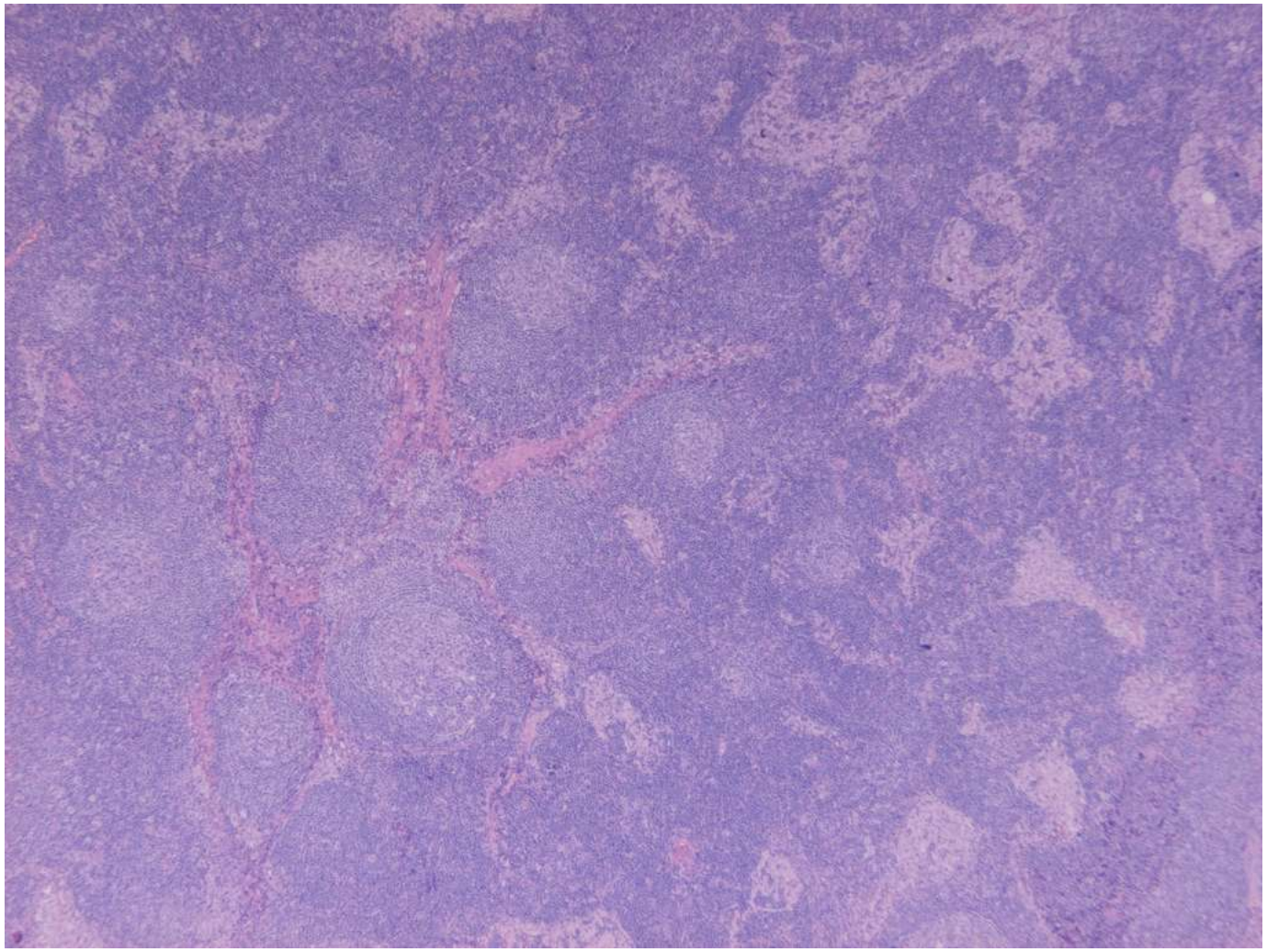
ESTABLISHED IN 1812 FEBRUARY 12, 2009 VOL. 360 NO. 7

B-Cell Clones as Early Markers for Chronic Lymphocytic Leukemia

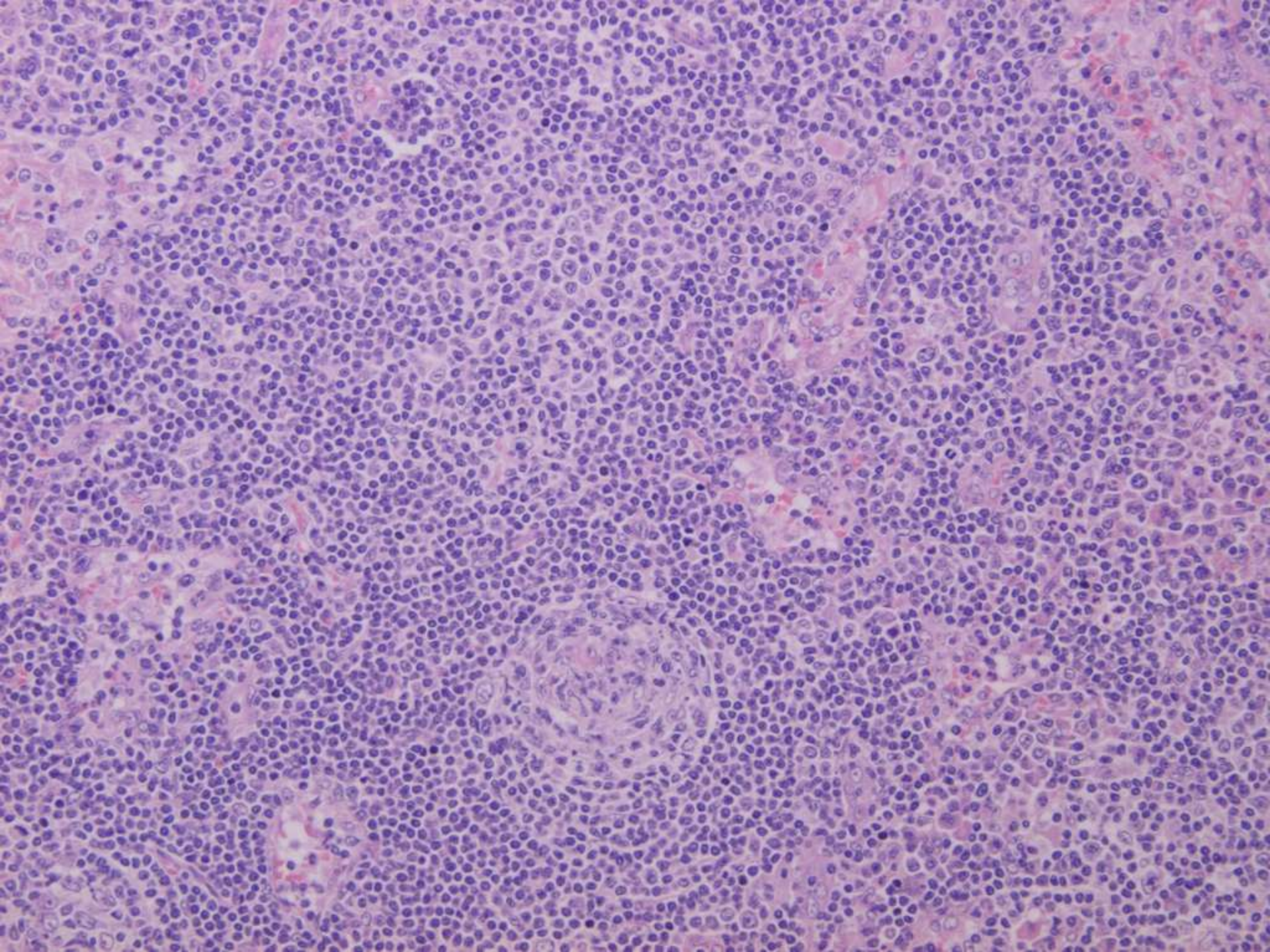
Ola Landgren, M.D., Ph.D., Maher Albitar, M.D., Wanlong Ma, M.S., Fatima Abbasi, M.S., M.P.H., Richard B. Hayes, Ph.D., Paolo Ghia, M.D., Ph.D., Gerald E. Marti, M.D., Ph.D., and Neil E. Caporaso, M.D.

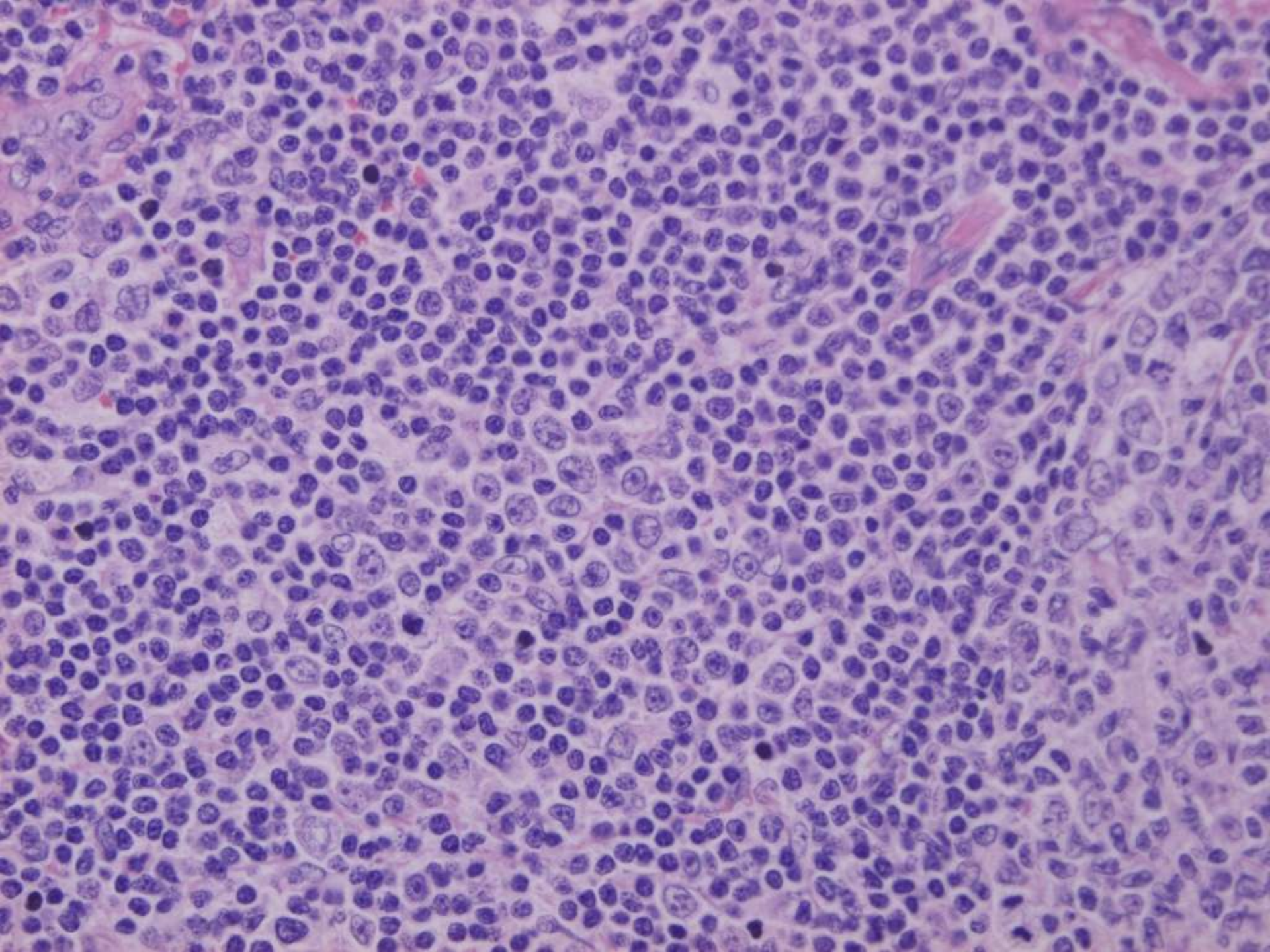
ABSTRACT

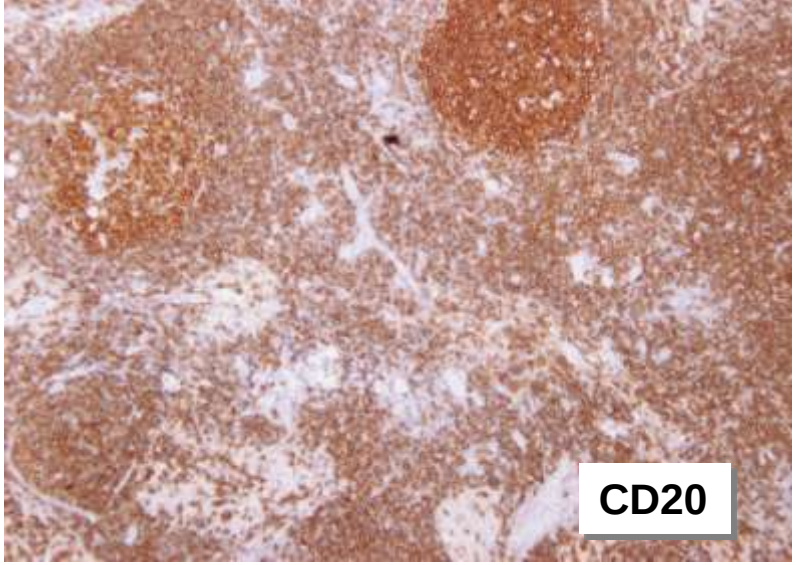
- Se han identificado clonas de células B en 12% población sana, aumentando con la edad.
- Se ha descrito la presencia de clonas B-CLL en s.p. años previos al diagnóstico de CLL.
- Aproximadamente 1% de individuos con MBL desarrollarán CLL clínica.

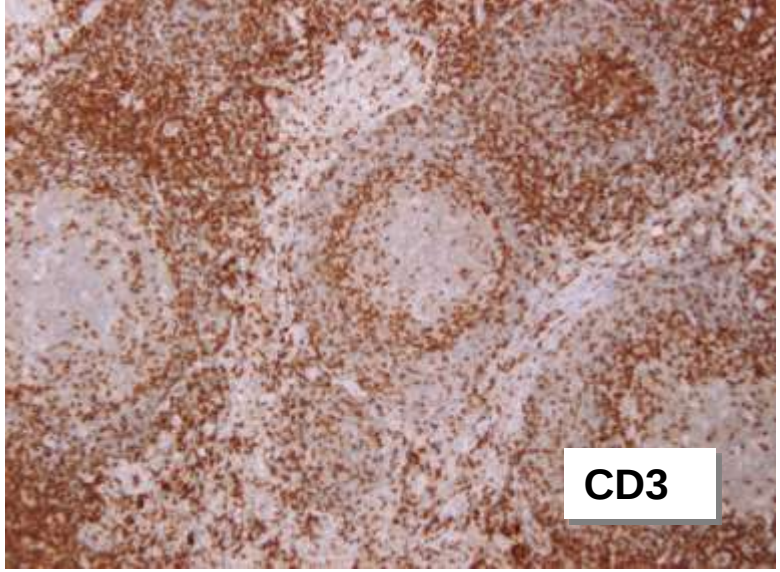


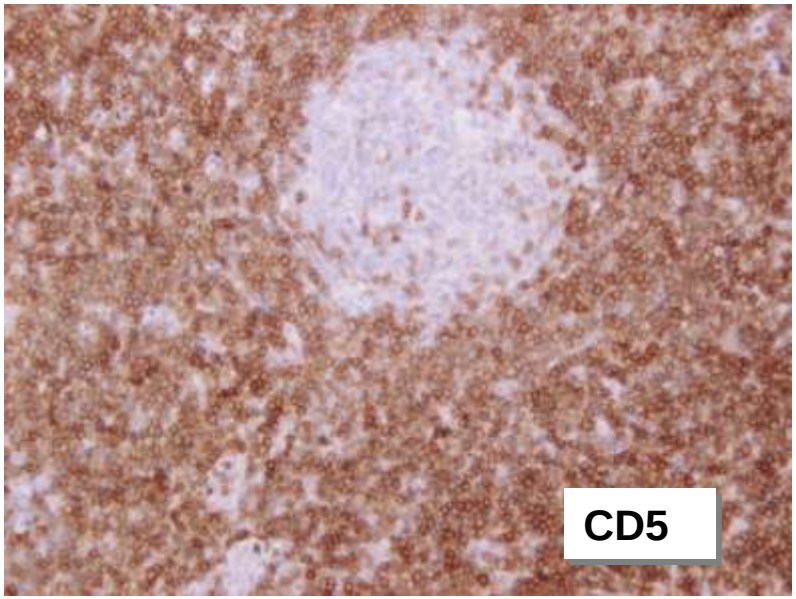
Mujer de 69 años con adenopatía axilar que se biopsia.

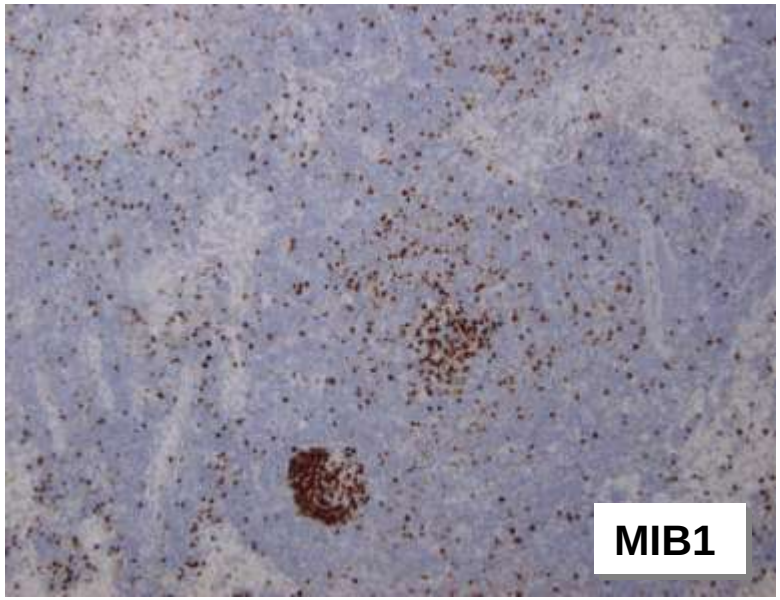










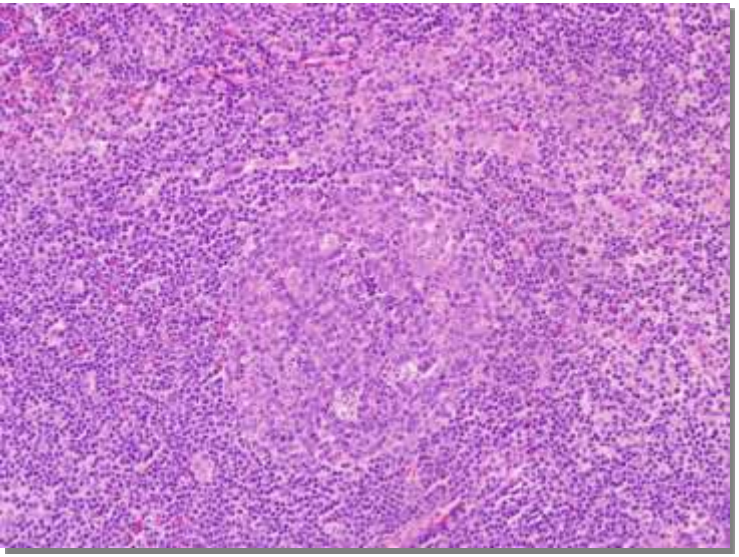


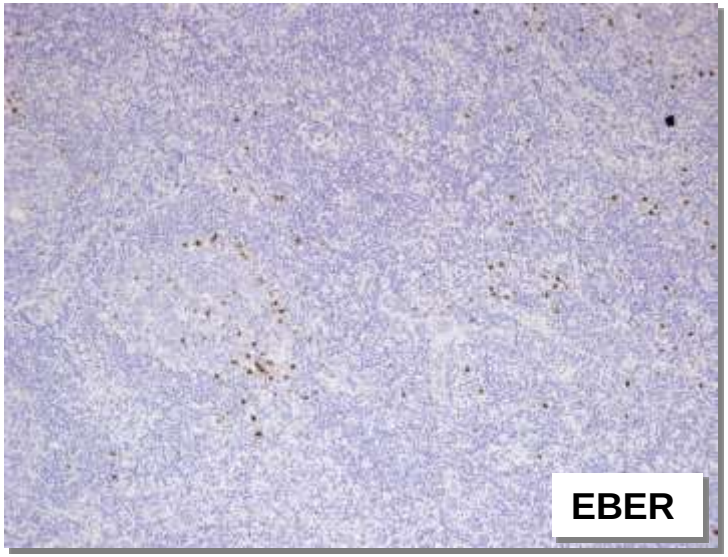
"lymph node involvement by monoclonal CLL-type B cells of unknown clinical significance" Uppsala 2010

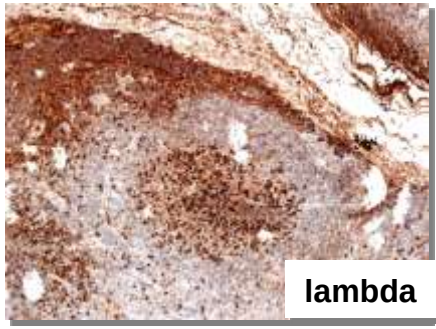
Desorden linfoproliferativo EBV + asociado a edad avanzada

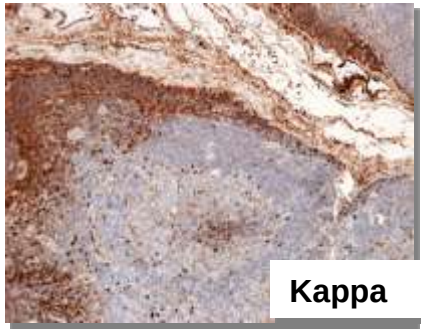
Age related EBV associated lymphoproliferative disorder - a spectrum of reactive lymphoid hyperplasia and lymphoma: the Western experience. ***Dojcinov SD et al. Blood 2011*:**

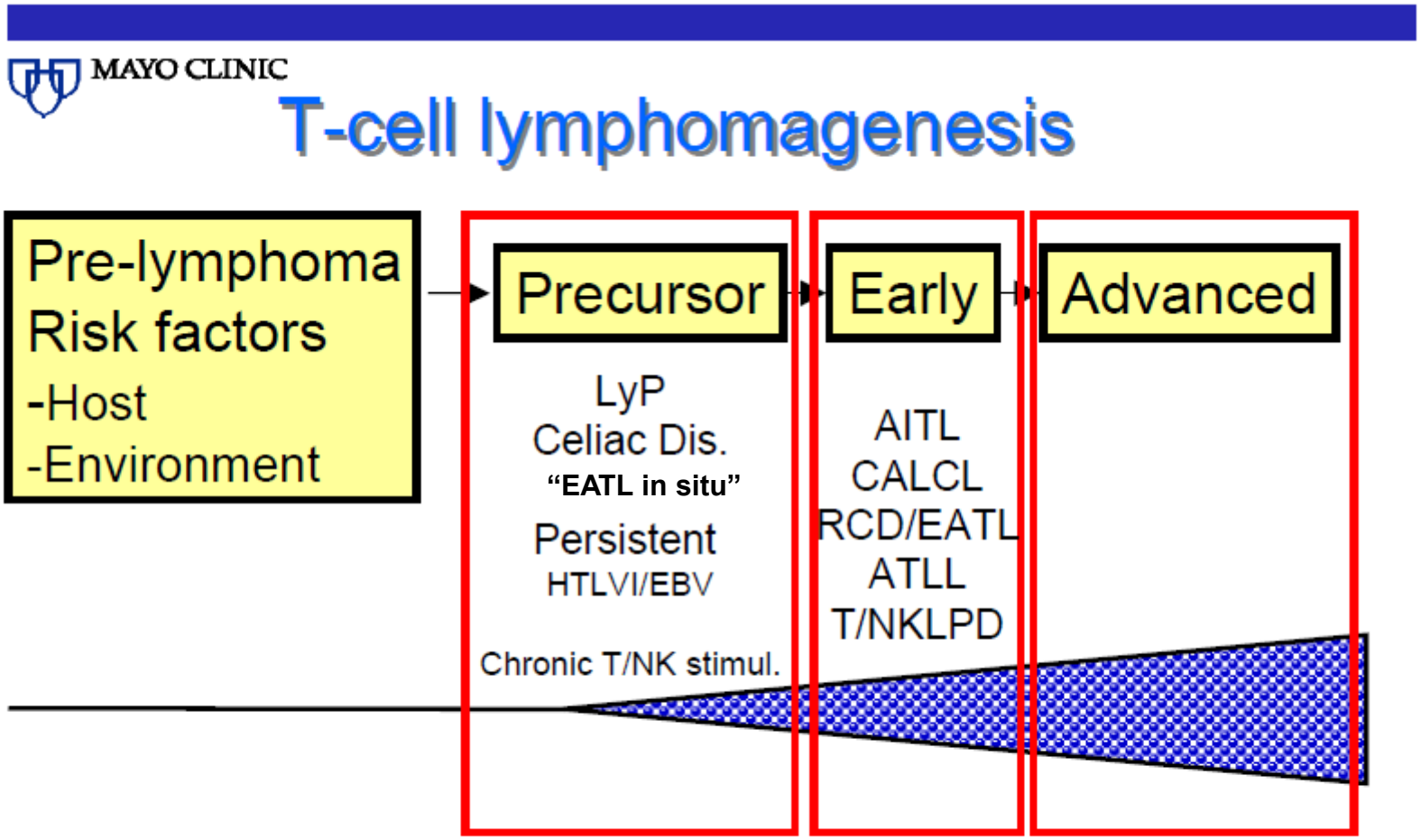
a) Hiperplasia linfoide reactiva
b) Desorden linfoproliferativo extraganglionar polimórfico
c) Desorden linfoproliferativo ganglionar polimórfico
d) Linfoma B difuso de células grandes











Ahmet Dogan MD. Uppsala 2010

MICOSIS FUNGOIDE

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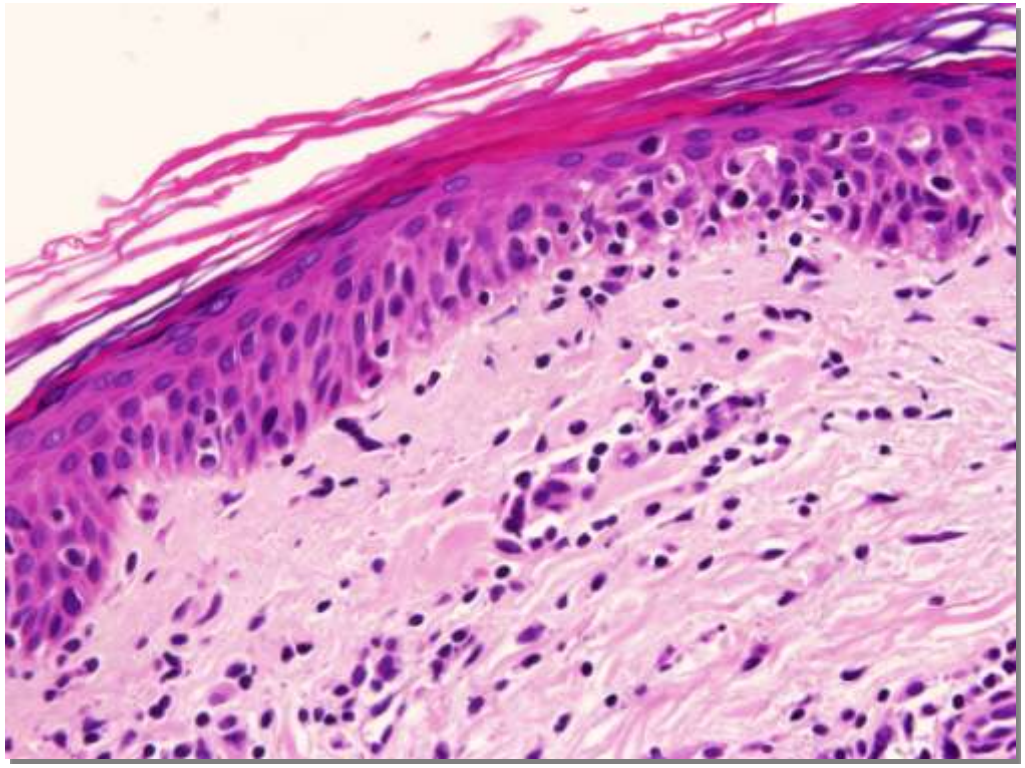


Defining early mycosis fungoides

Nicola Pimpinelli, MD,[a] Elise A. Olsen, MD,[c] Marco Santucci, MD,[b] Eric Vonderheid, MD,[d] Andreas C. Haeffner, MD,[e] Seth Stevens, MD,[f] Guenter Burg, MD,[g] Lorenzo Cerroni, MD,[h] Brigitte Dreno, MD,[i] Earl Glusac, MD,[j] Joan Guitart, MD,[k] Peter W. Heald, MD,[l] Werner Kempf, MD,[e] Robert Knobler, MD,[k] Stuart Lessin, MD,[f] Christian Sander, MD,[m] Bruce S. Smoller, MD,[n] Gladys Telang, MD,[o] Sean Whittaker, MD,[p] Keiji Iwatsuki, MD, PhD,[q] Erik Obitz, MD,[r] Masahiro Takigawa, MD,[s] Maria L. Turner, MD,[t] and Gary S. Wood, MD,[u] for the International Society for Cutaneous Lymphoma

Florence, Italy; Durham, North Carolina; Baltimore, Maryland; Zurich, Switzerland; Thousand Oaks, California; Cleveland, Ohio; Graz and Vienna, Austria; Nantes, France; New Haven, Connecticut; Chicago, Illinois; Philadelphia, Pennsylvania; Munich, Germany; Little Rock, Arkansas; Providence, Rhode Island; London, United Kingdom; Okayama and Hamamatsu, Japan; Aarhus, Denmark; Bethesda, Maryland; and Madison, Wisconsin

Efficacy of histologic criteria for diagnosing early MF. An EORTC Cutaneous Lymphoma group Investigation. Santucci M. et al; Am J Surg Pathol 2000; 24: 40-50
Regarding the algorithm for the diagnosis of early mycosis fungoides proposed by the International Society for Cutaneous Lymphomas: suggestions from routine histopathology practice. Ferrara et al. J Cutan Pathol. 2008 Jun;35(6):549

Rein Willemze EAHP meeting, Uppsala, September 25-30, 2010

Histology in case of LPP/SPP or early MF:
- consistent with MF : MF
- not consistent with MF: LPP/SPP (or whatever, but not MF)
- suspicion, no definite MF: suspect MF (**repeat biopsies**)
- Phenotyping & genotyping: not or rarely contributory

IMPORTANT:

- No therapeutic consequences (both nbUVB; PUVA; steroids)
- Both LPP and patch stage MF have an excellent prognosis, with a life-expectancy similar to that of a healthy control population.

- Linfoma in situ: “Proliferación de células neoplásicas en la localización de donde deriva el tumor”

- Lesiones iniciales en neoplasias linfoides, que pueden regresar cuando el estímulo inicial es eliminado (linfoma MALT gástrico precoz).

- Condiciones reactivas con expansiones clonales B, o T.

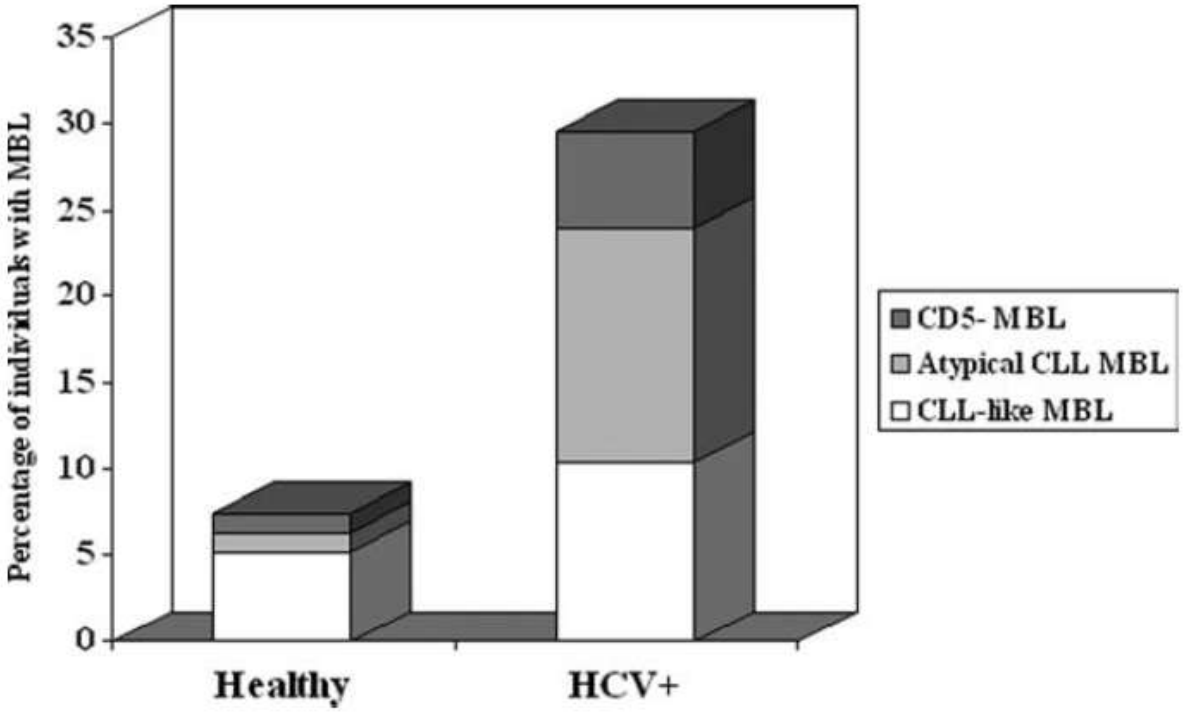
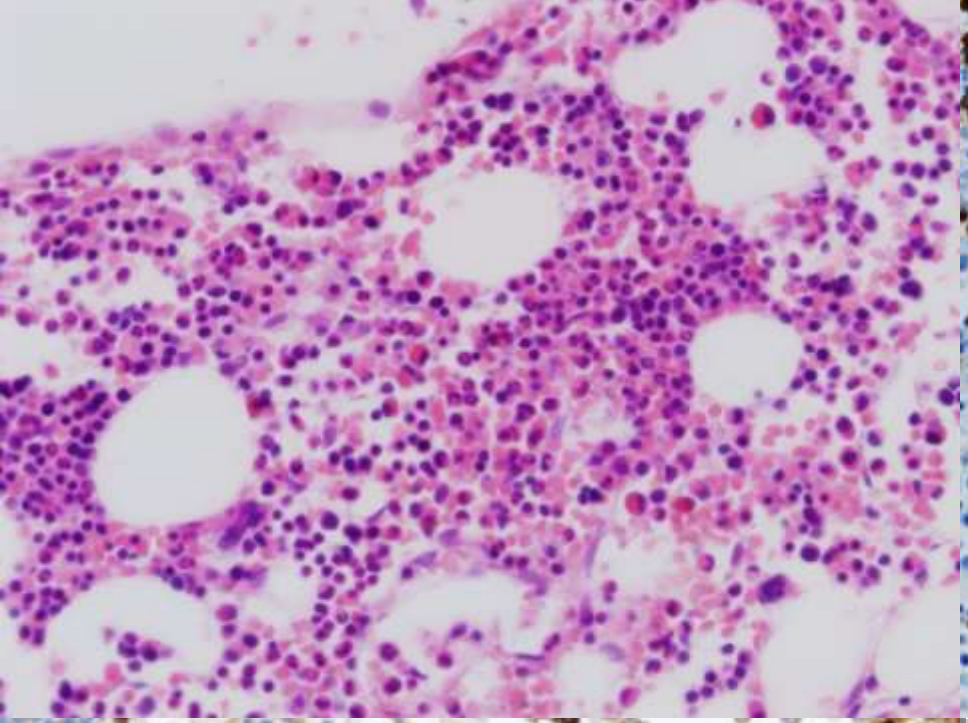
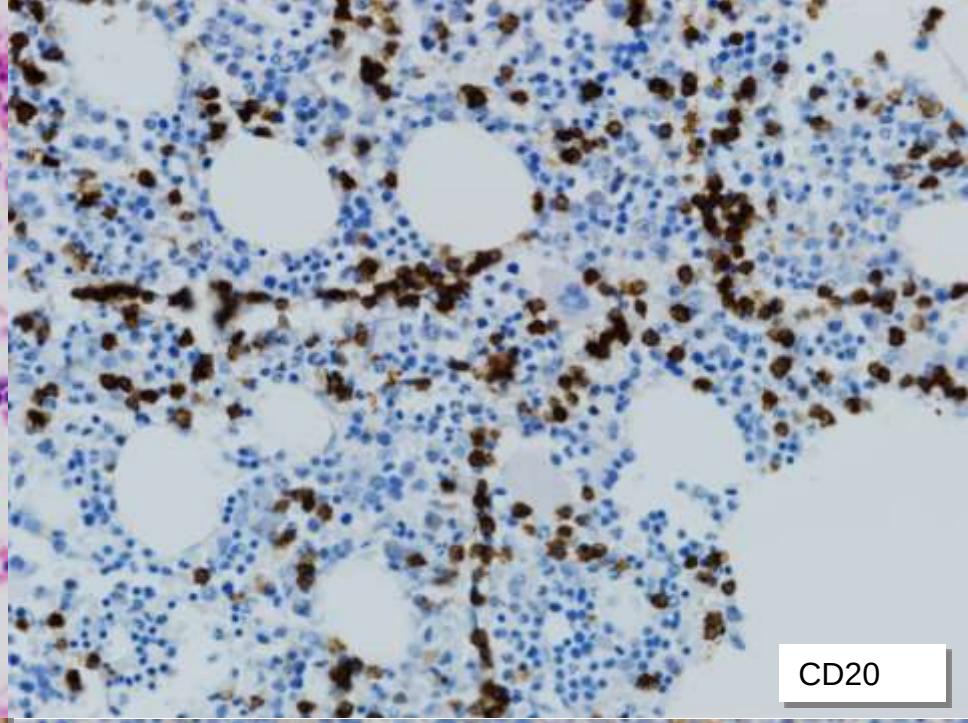
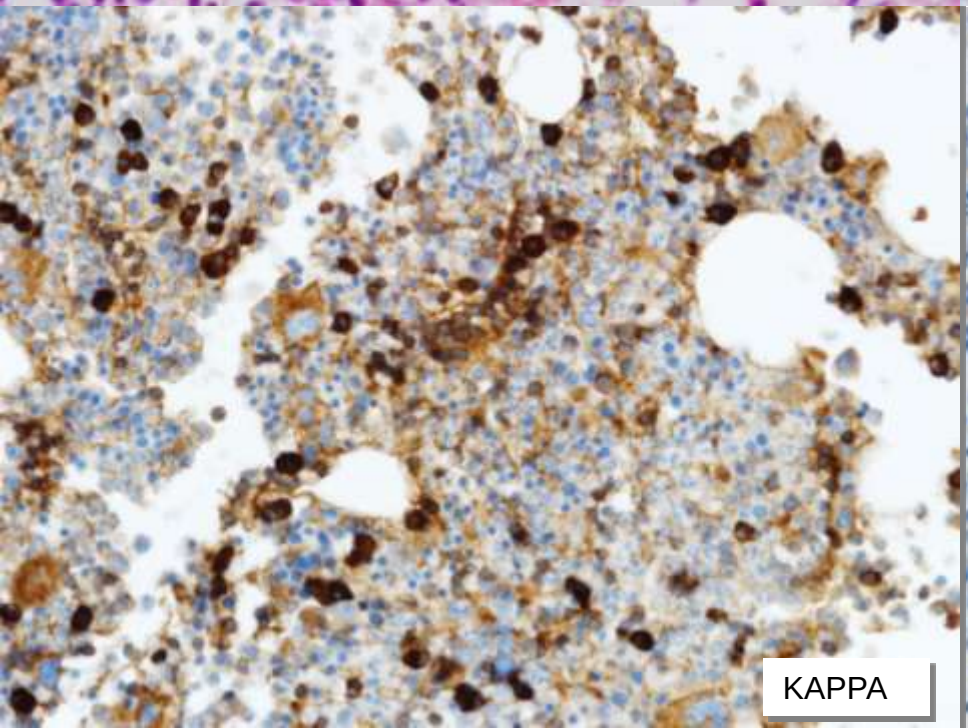


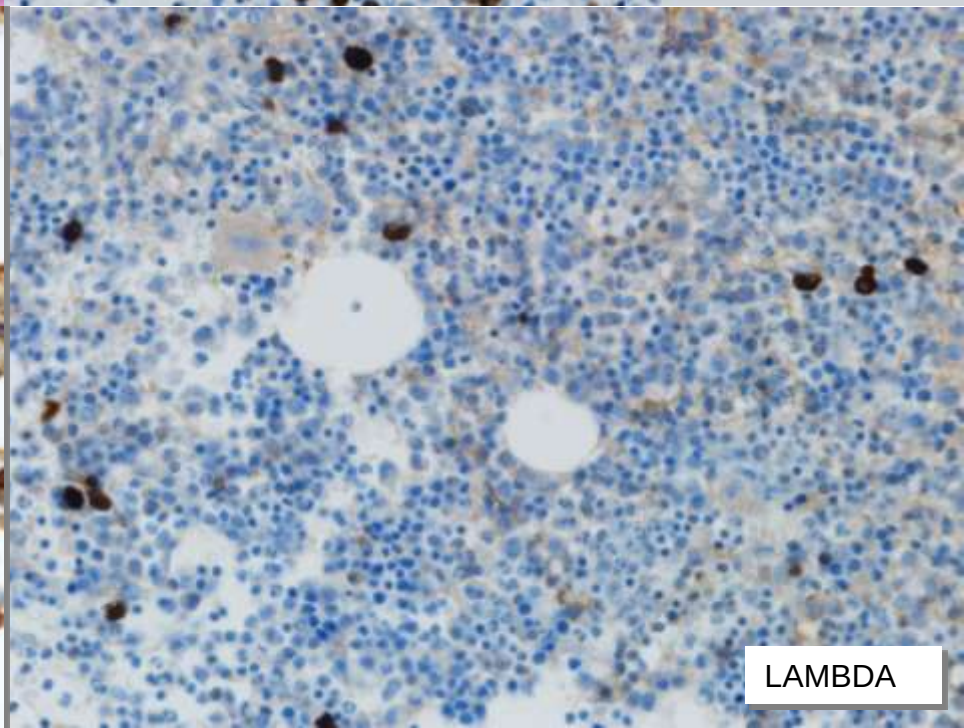
FIG. 2. All types of MBL are more frequent among HCV-infected patients as compared to healthy individuals. The columns represent the cumulative frequency of all three types of MBL (distinguished with different colors) in the general population (left column) and among HCV-infected individuals (right column), respectively. The increase in the frequency of atypical CLL (light grey) is particularly evident.

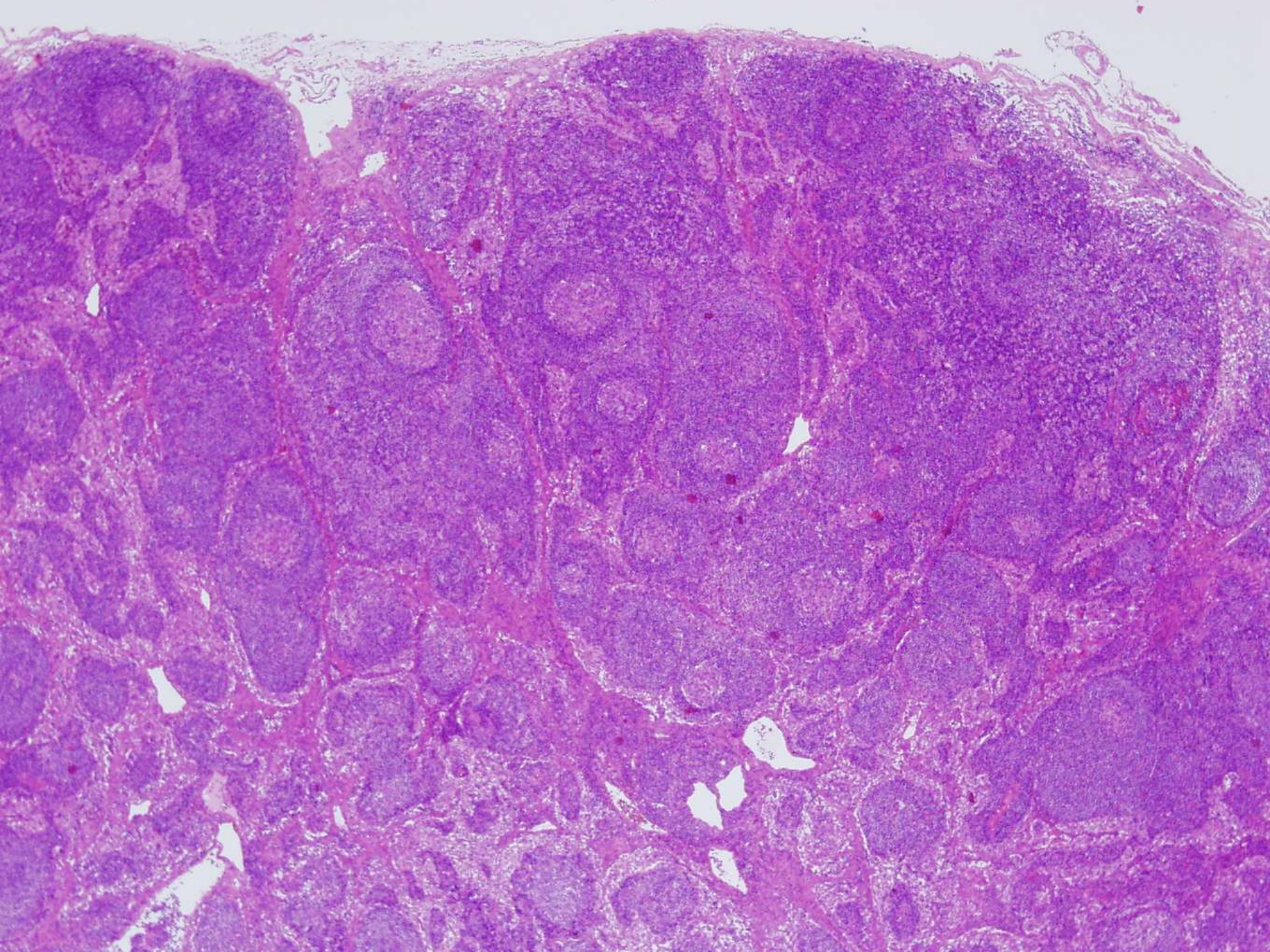
Fazi C et al. Cytometry (Clinical Cytometry) 2010



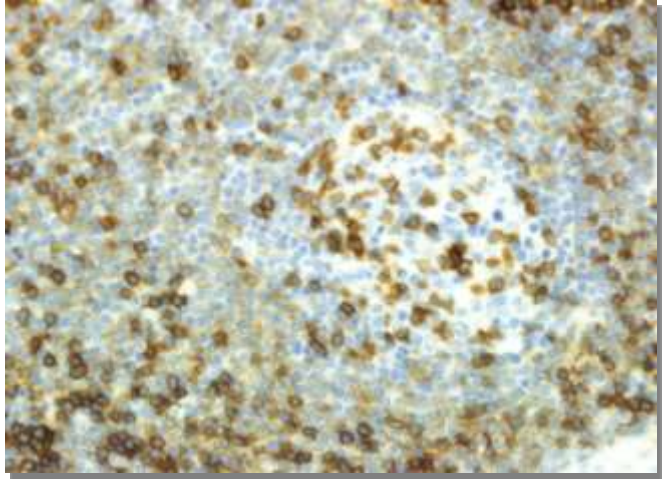

CD20

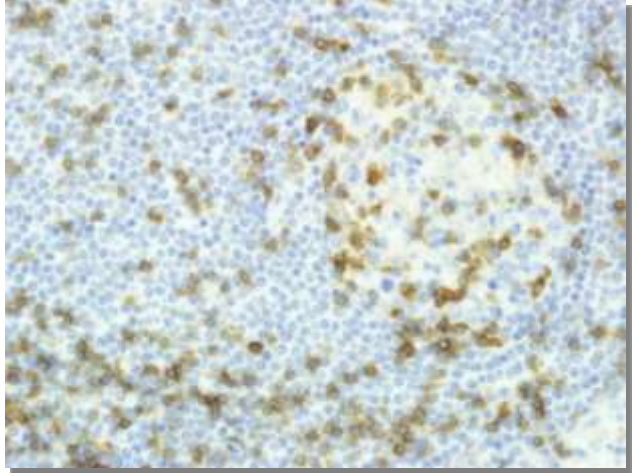

KAPPA


LAMBDA



CD5





CD3

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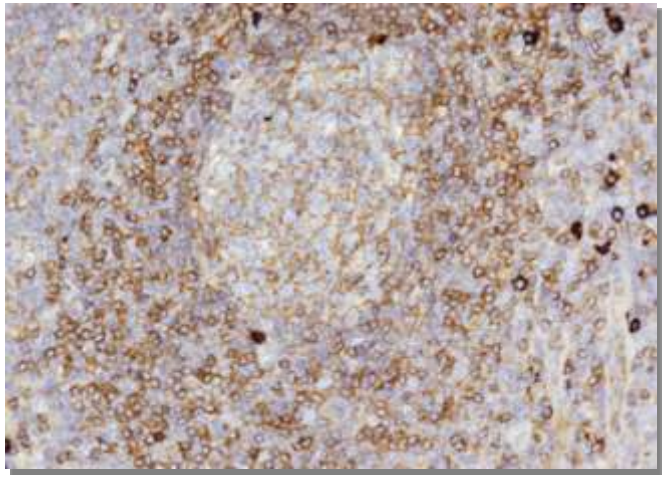

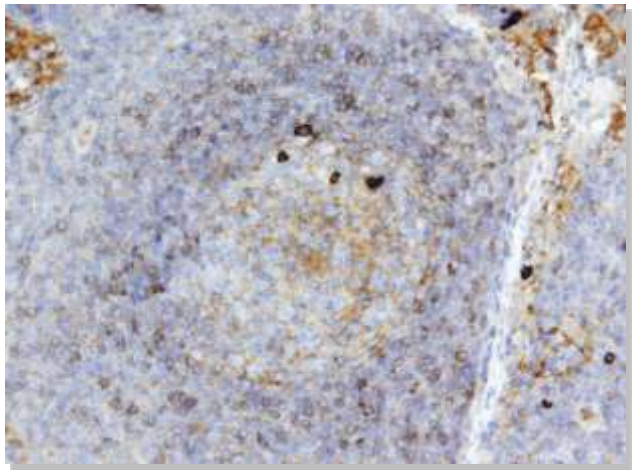

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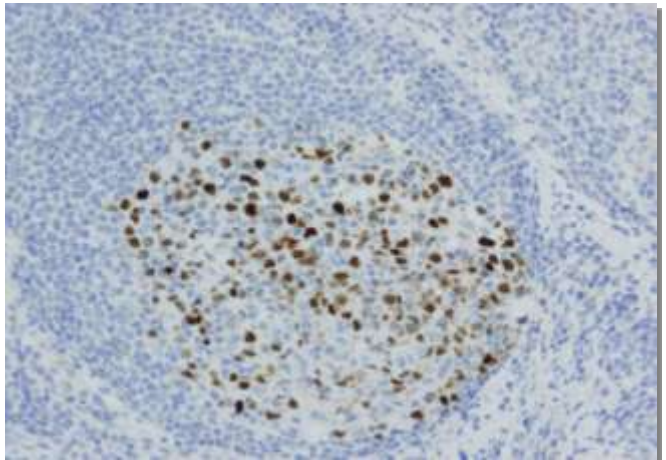
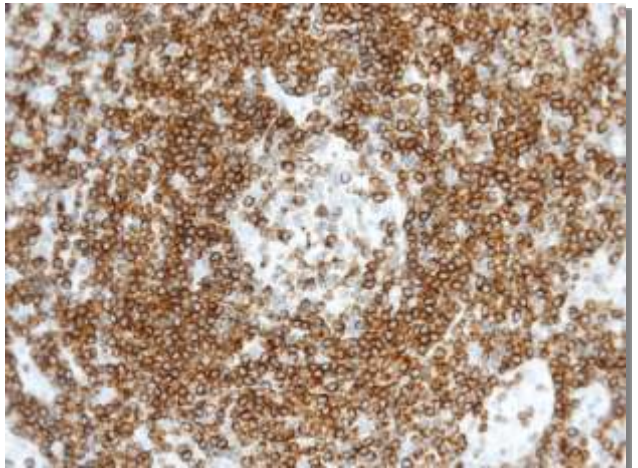
P53

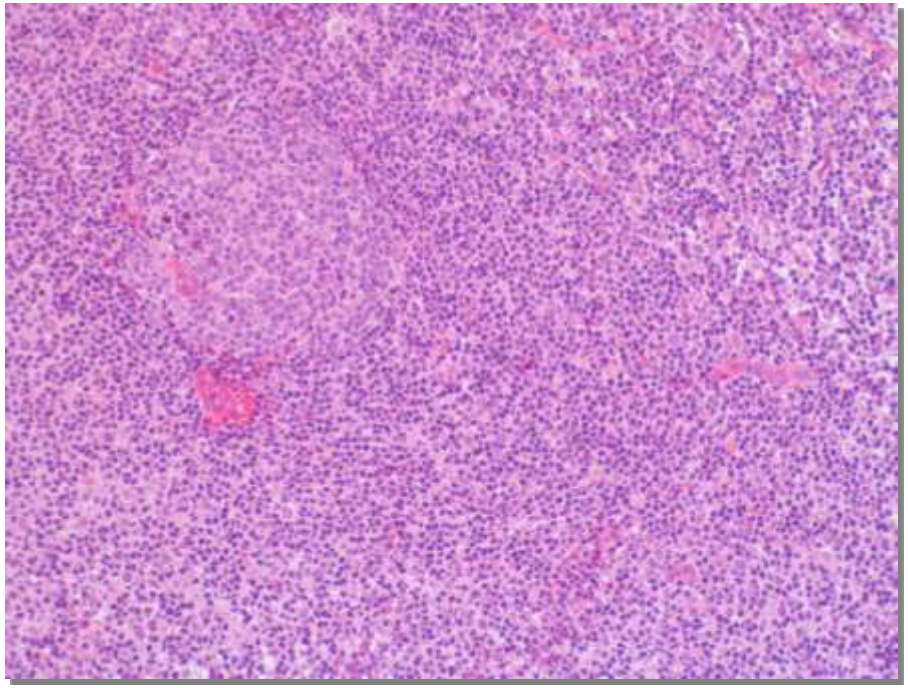


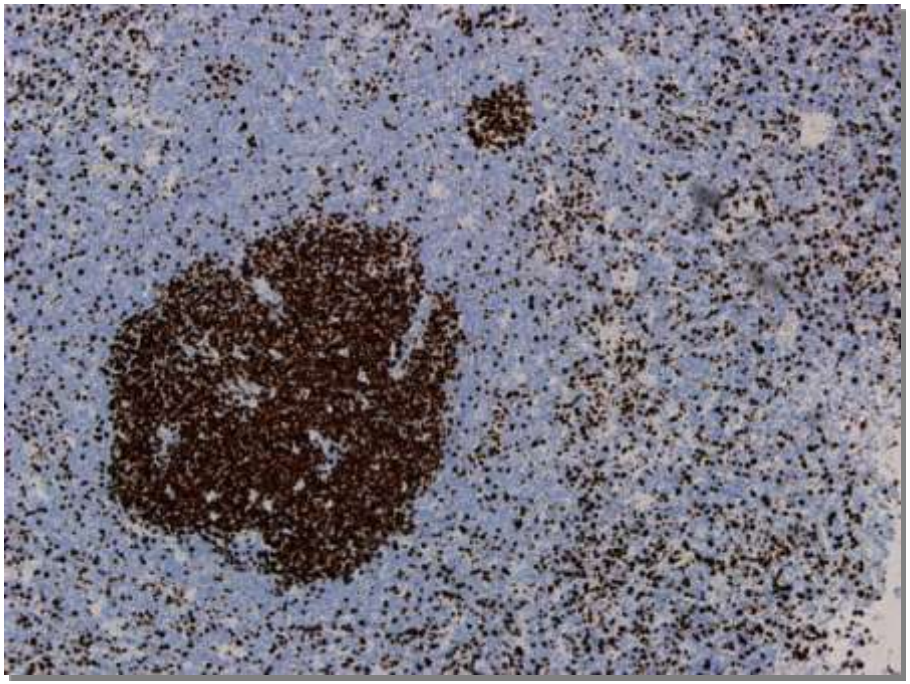


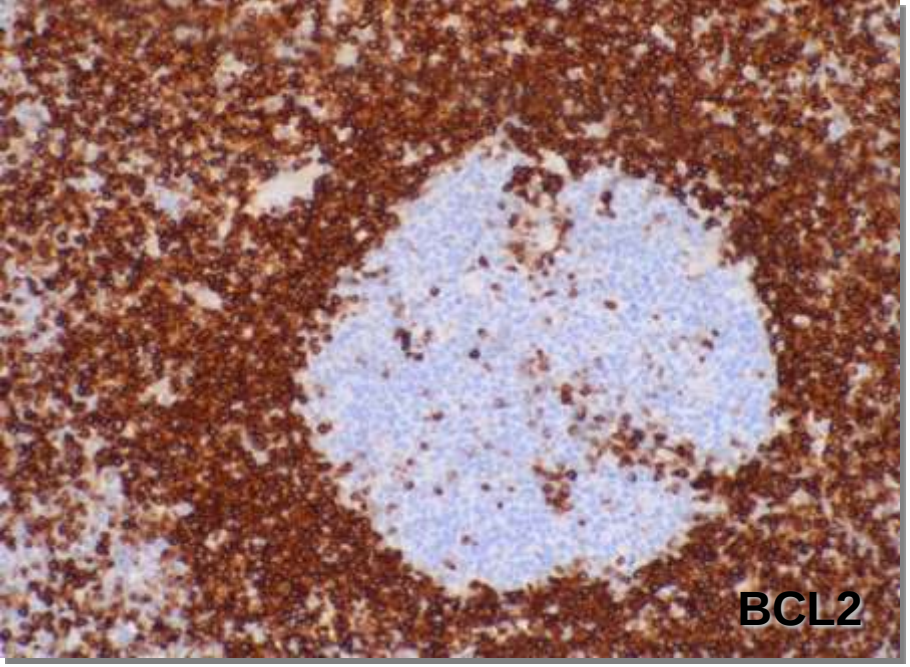
BCL2

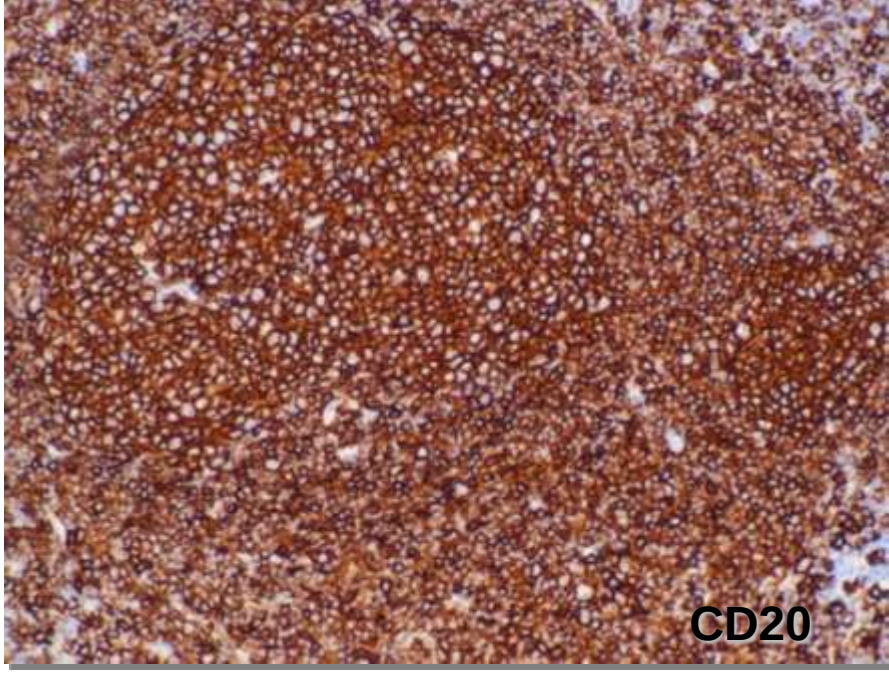
En enfermedades autoinmunes se ha descrito la presencia de células B monoclonales que se han propuesto como posibles factor predictivos para el desarrollo de linfoma, como Sjogren, tiroiditis de Hashimoto, Lupus, PTI.

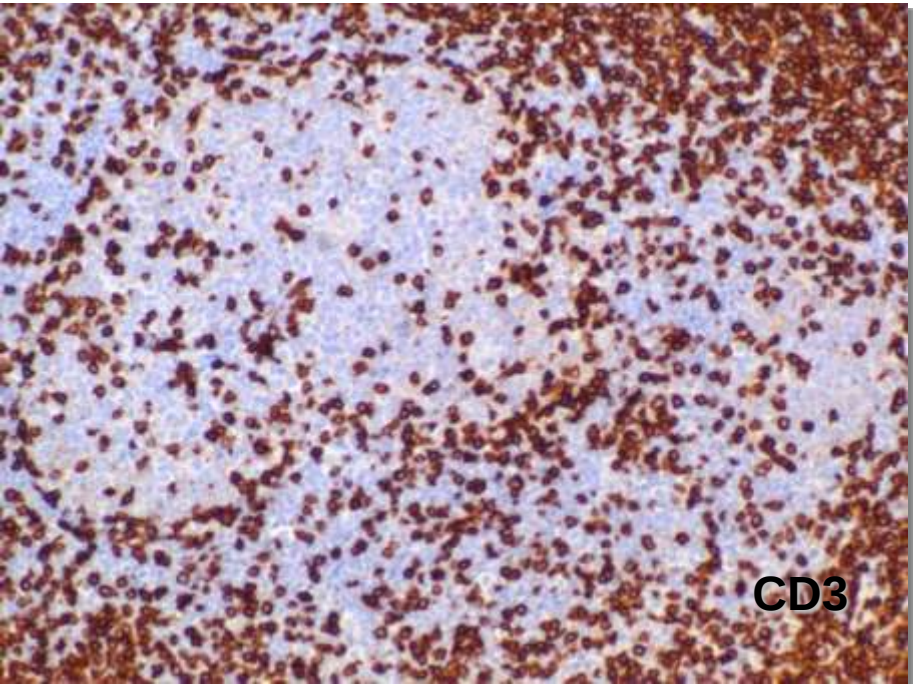
Paciente de 62 años con **artritis reumatoide** desde los 32 años, tratada con methotrexate y prednisona en los ultimos años, con anti-TNF en el ultimo año. Presenta adenopatía cervical.

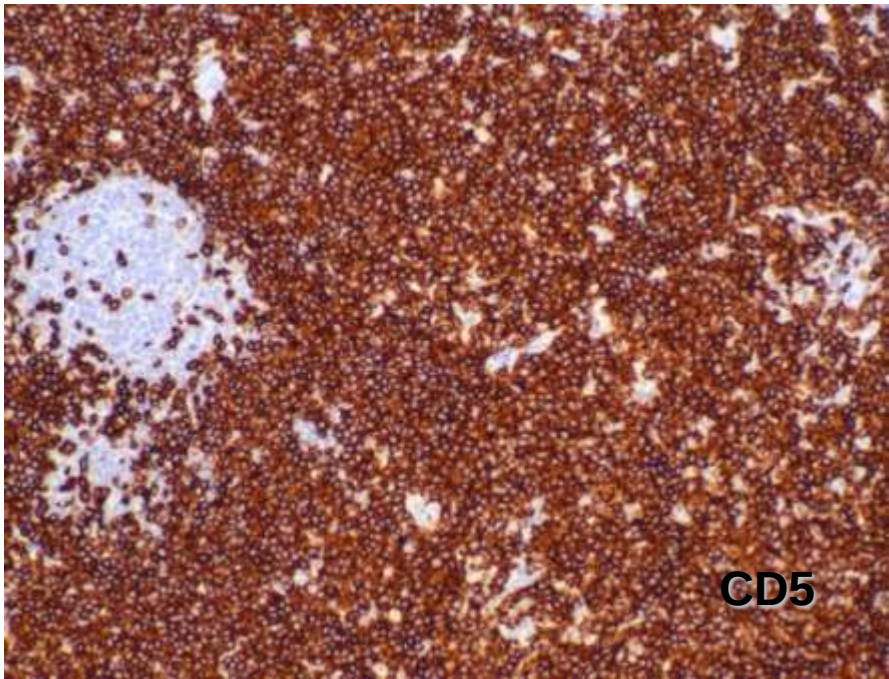


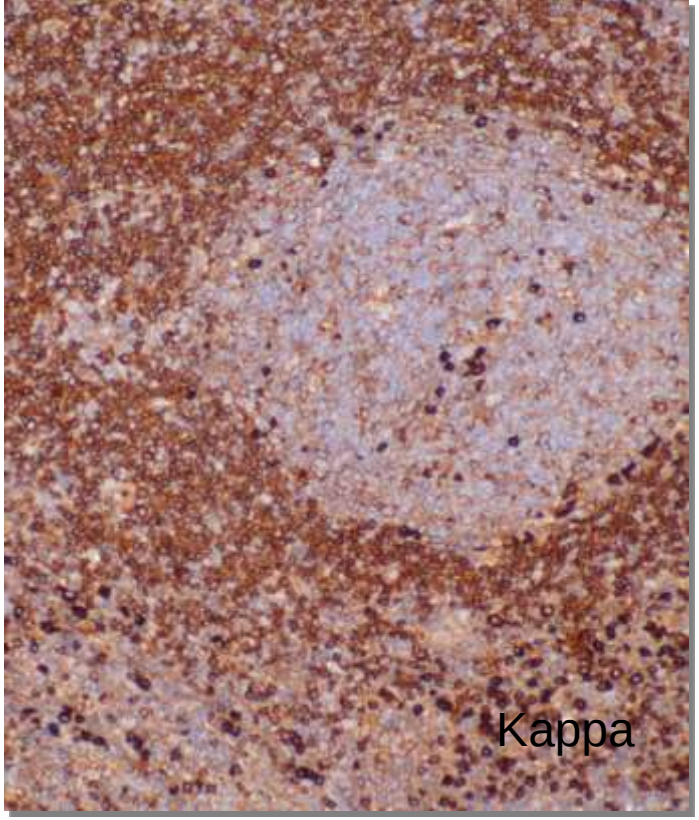


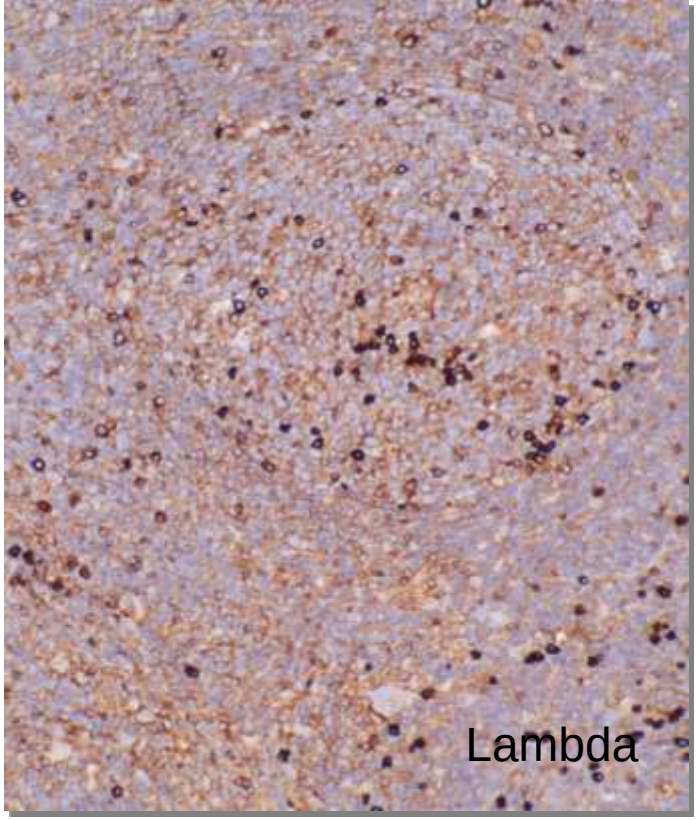

BCL2


CD20


CD3


CD5





- Análisis molecular por PCR demostró reordenamiento monoclonal del gen IgH.
- Citogenética 46XX.
- EBER negativo.

DIAGNOSTICO: Expansión monoclonal CD5+ asociada a artritis reumatoide.

Linfadenitis reactiva con restricción de cadenas ligeras

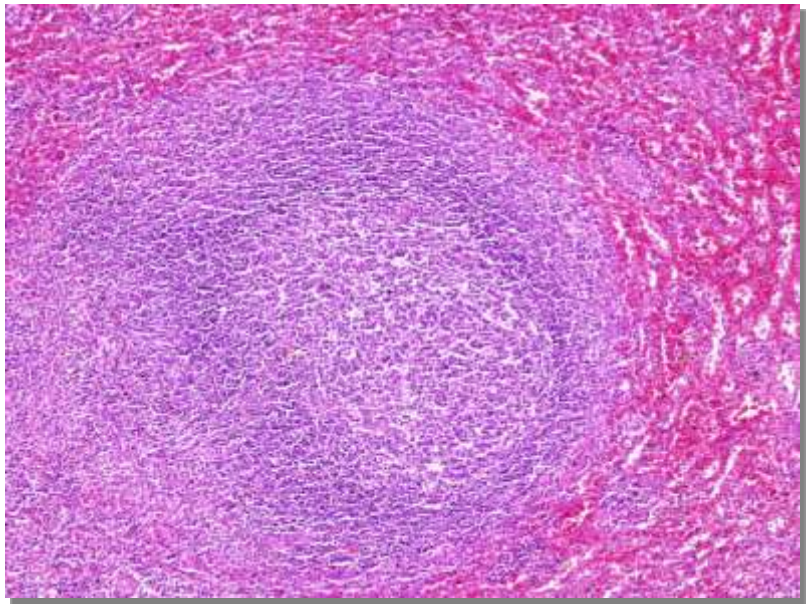
Histopathology 2008, **52**, 436–444. DOI: 10.1111/j.1365-2559.2008.02965.x

Light-chain-restricted germinal centres in reactive lymphadenitis: report of eight cases

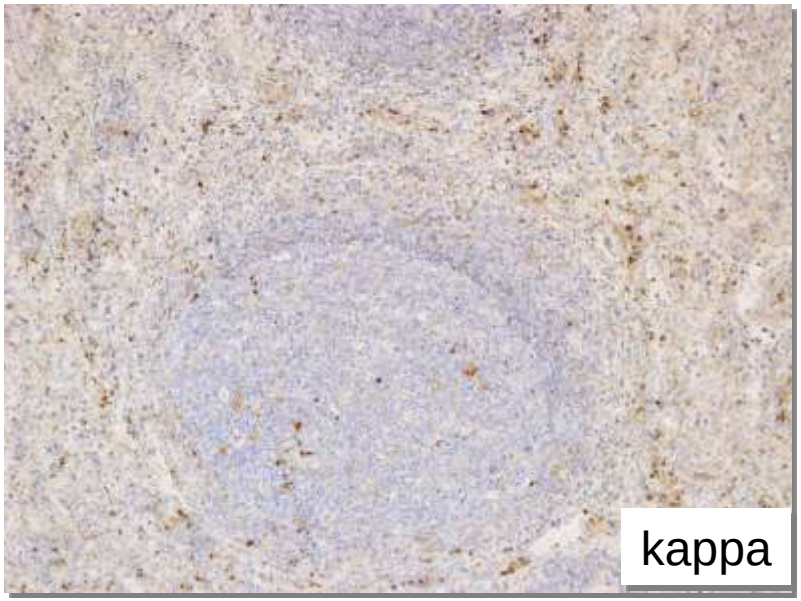
S H Nam-Cha,[1] B San-Millán,[1] M Mollejo,[1] M García-Cosio,[2] G Garijo,[3] M Gomez,[4] R A Warnke,[5] E S Jaffe[6] & M A Piris[1]

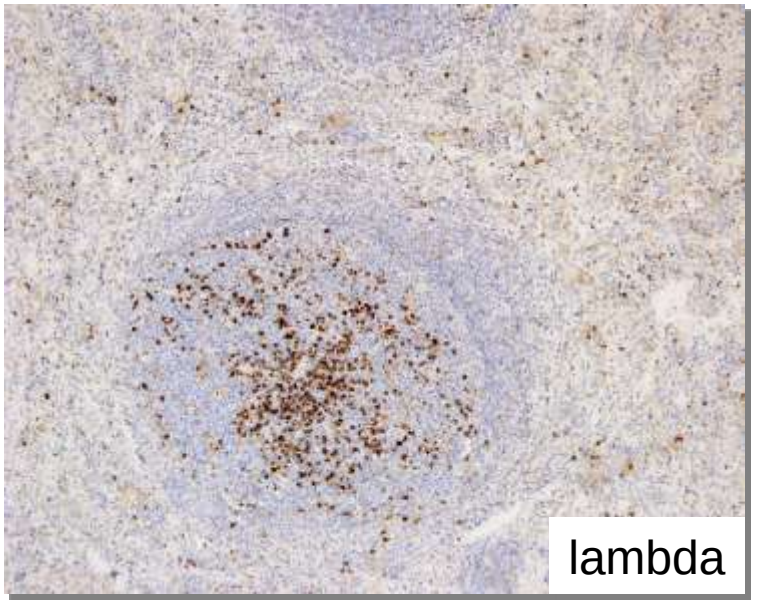
[1]*Lymphoma Group, Molecular Pathology Programme, Spanish National Cancer Centre (CNIO),* [2]*Pathology Department, Hospital Universitario Ramón y Cajal, Madrid,* [3]*Pathology Department, Clínica Benidorm, Benidorm,* [4]*Pathology Department, Hospital Universitario San Cecilio, Granada, Spain,* [5]*Immunodiagnosis Laboratory, Stanford University Medical Center, Stanford, CA and* [6]*Laboratory of Pathology, National Cancer Institute, Bethesda, MD, USA*

- Respuesta fisiológica normal exagerada, naturaleza oligoclonal de los CG.
- Rasgo morfológico o biológico sugiera un trastorno autoinmune subyacente



Varón esplenectomizado en 1999 por PTI. Hiperplasia linfoide reactiva en biopsias ganglionares posteriores.





➢ Lesiones precoces con bajo riesgo de progresión a linfoma clínico, como se reconoce en la clasificación de la OMS, incluyendo expansiones clonales B, o T.

- ✓ Proliferaciones linfoplasmacíticas asociadas a virus hepatitis C.
- ✓ En enfermedades autoinmunes se ha descrito la presencia de células B monoclonales que se han propuesto como posibles factor predictivos para el desarrollo de linfoma, como sjogren, tiroiditis de Hashimoto, Lupus, PTI.
- ✓ Linfadenitis reactiva con restricción de cadenas ligeras *(Nam-Cha et al.)*
- ✓Hiperplasia folicular reactiva con clonas B por citometria/PCR *(Kussick et al.)*
- ✓ Hiperplasia zona marginal atípica en niños *(Attigalle et al.)*
- ✓ Hiperplasia linfoide reactiva linfoma-like en tracto genital femenino *(Turbiner et al.)*
- ✓ Expansiones clonales T (linfocitosis T asociadas a enfermedades autoinmunes, hepatitis virus C, siguiendo trasplante MO, linfomas B bajo grado)

CONCLUSIONES

- Es imprescindible una buena correlación clínico-patológica para el diagnóstico y manejo de pacientes con estas lesiones.
- Identificación de mecanismos implicados en el desarrollo de linfoma
- Indicaciones de seguimiento de pacientes
- Identificación de dianas terapéuticas

Miguel Angel Piris, Santiago Moreno, María Rodríguez Pinilla, Juan Fernando García Patrocinio Algara, Miguel Angel Cruz, Felipe Casado

Juan Potenciano Mora

Gerardo Pérez Bautista