

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

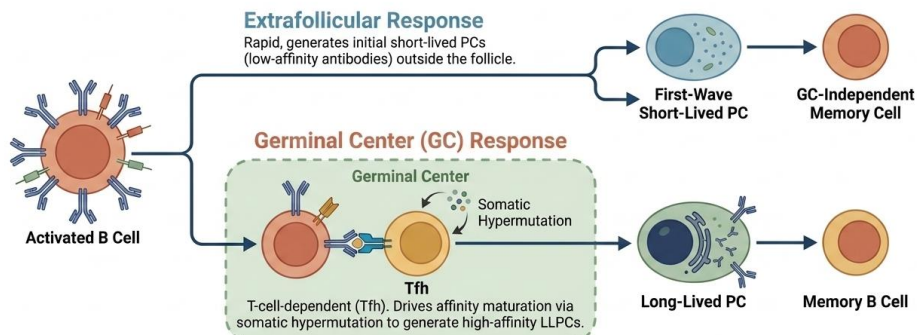
Disordini linfoproliferativi B a differenziazione plasmacellulare
e neoplasie plasmacellulari: quale confine diagnostico

Claudio Agostinelli

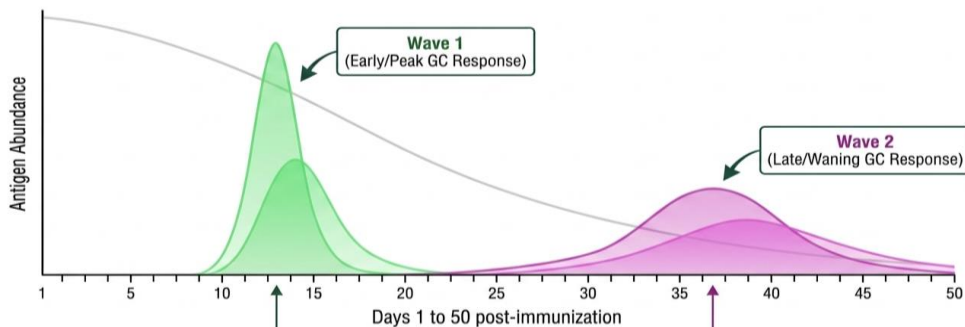
Università di Bologna

UO Emolinfopatia IRCCS S.Orsola Bologna

The Bifurcation of B-Cell Activation

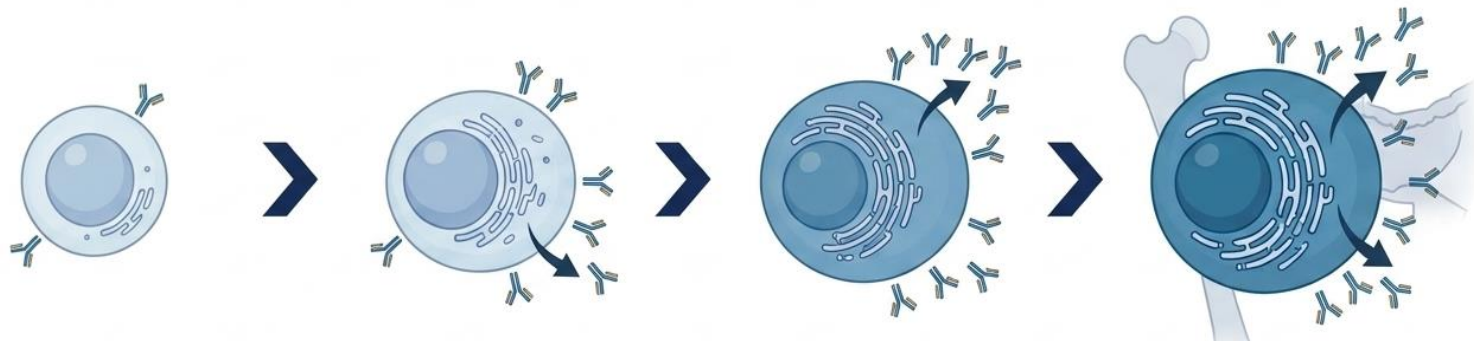


	Extrafollicular Pathway	Germinal Center (GC) Pathway
Location	Borders of the B-cell follicle	Center of the follicle
Speed of Response	Rapid, first wave of defense	Delayed, requires expansive proliferation
T-Cell Dependence	Can be independent or dependent	Strictly requires T-follicular helper (T _{fh}) cells
Cellular Output	Short-lived plasma cells (low-affinity antibodies)	Long-lived plasma cells and memory B cells (high-affinity, hypermutated antibodies)



Context: High antigen availability.
Outcome: Predominantly SLPC precursors (<30 days survival).
Proof: Quasimonoclonal and B1-8 transfer models show massive splenic ASC spikes at d11-14 that largely die off.

Context: Antigen strictly limiting.
Outcome: Predominantly LLPC precursors (>30 days survival).
Proof: Secondary transfers at d35 yield robust BM ASCs that persist long-term even without antigen.



Pre-Plasmablasts	Plasmablasts	Plasma Cells	Long-Lived Plasma Cells
CD38neg/low, CD27low, CD138-, CD20+, CD19+, CD45+	CD38high, CD27high, CD138-, CD20+, CD19+, CD45+	CD38high, CD27high, CD138+, CD20-, CD19+, CD45+	CD38high, CD27high, CD138+, CD20-, CD19-, CD45-

The Core Architects: Transcription Factor Dossiers

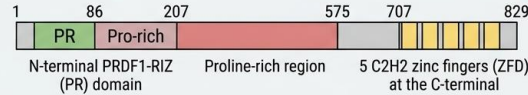
IRF4 (Interferon Regulatory Factor 4)

Directive: The Director.
Controls isotype switching, survival, and cellular metabolism.



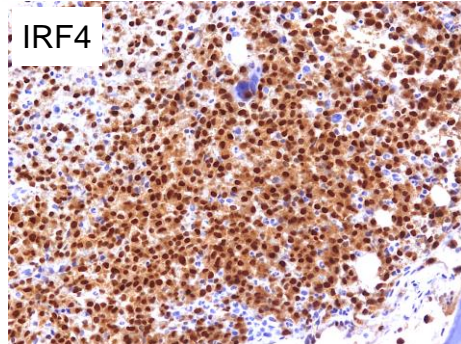
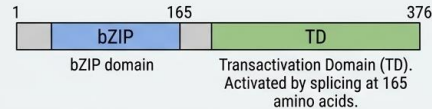
BLIMP1 (B lymphocyte-induced maturation protein 1)

Directive: The Silencer.
A transcriptional repressor that ruthlessly extinguishes all remaining B-cell features.

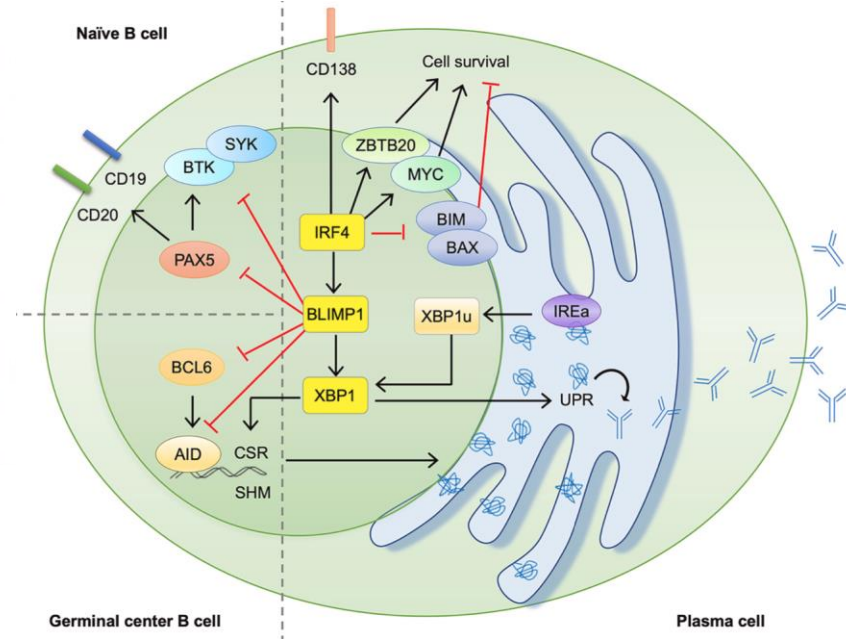


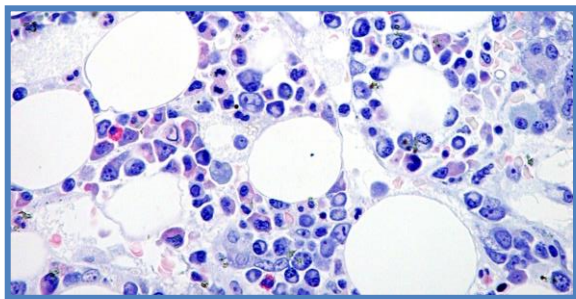
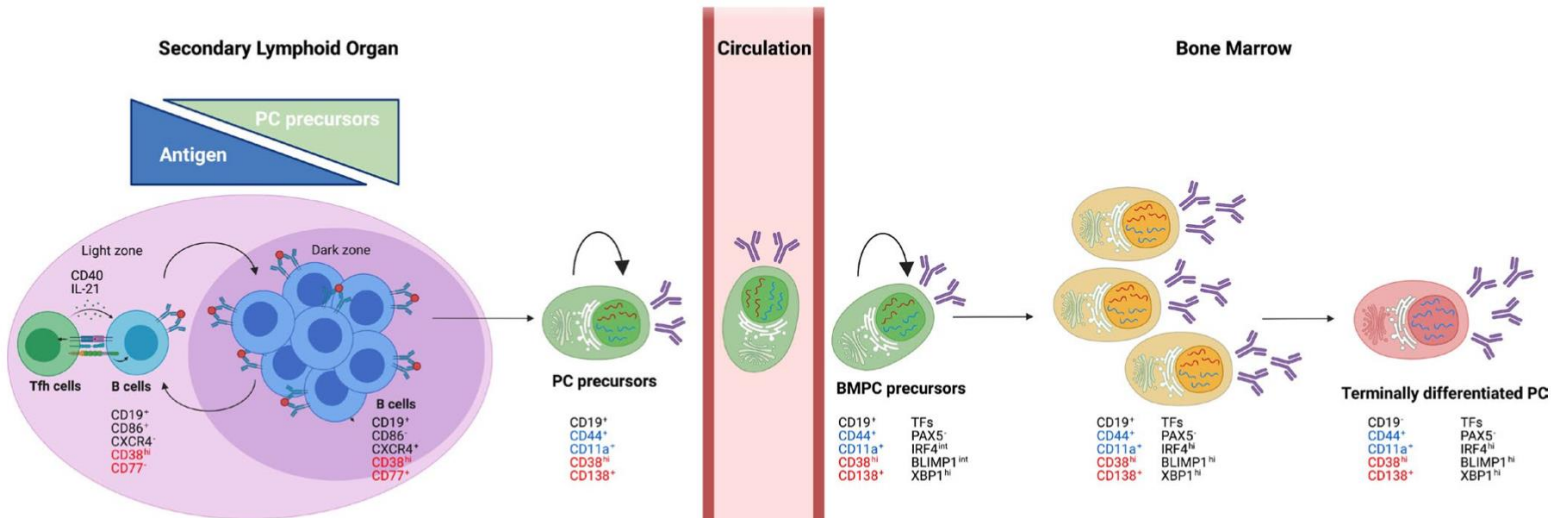
XBP1 (X box binding protein 1)

Directive: The Quality Controller.
Manages endoplasmic reticulum stress to prevent the factory from burning out.



Cellular Immunology (2022)





reactive plasmacytosis in a HIV⁺ patient

BMPC compartment has four subsets secreting Ab

CD19⁺CD38^{hi}CD138⁻

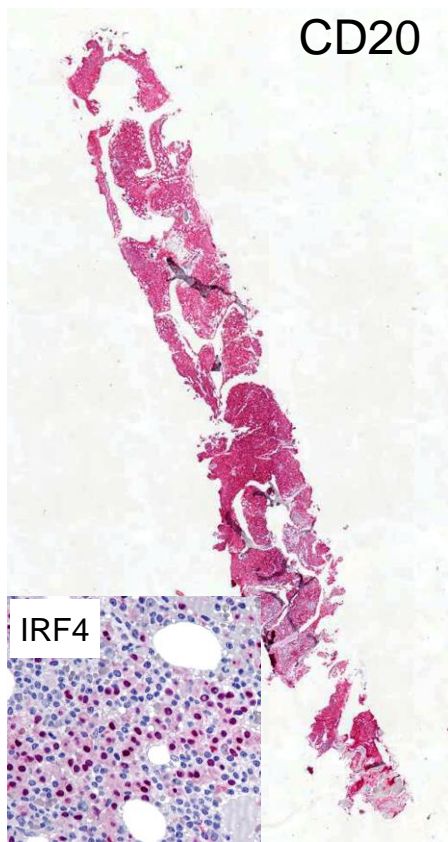
CD19⁺CD38^{hi}CD138⁺

CD19⁻CD38^{hi}CD138⁻

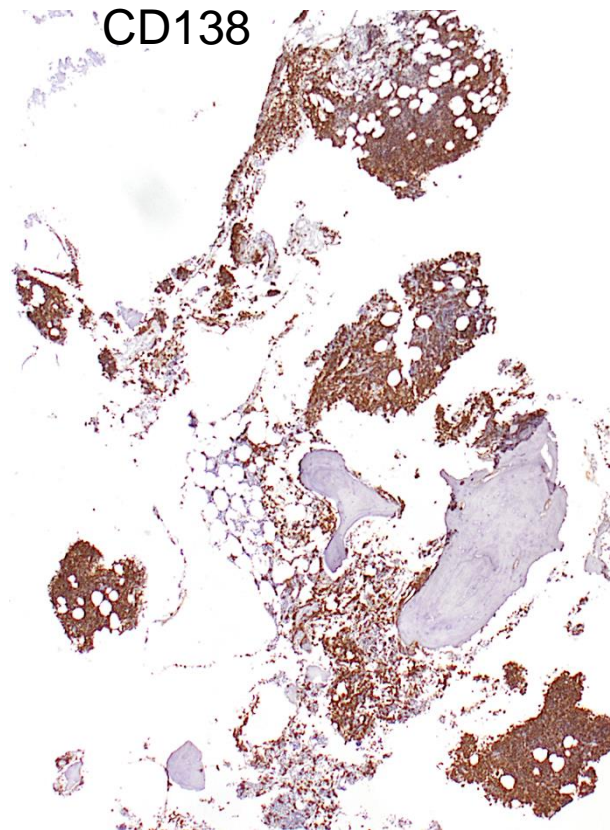
CD19⁻CD38^{hi}CD138⁺ **Terminally differentiated plasma cells**

} precursor pool with proliferative potential emanating from SLOs that can then give rise to SLPCs or LLPCs by further differentiation in the BM niche

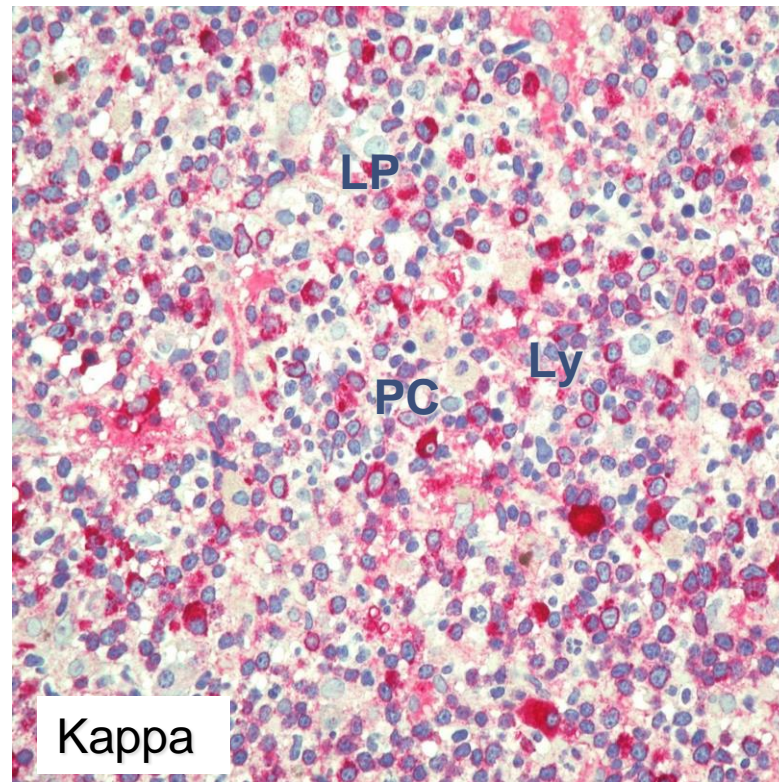
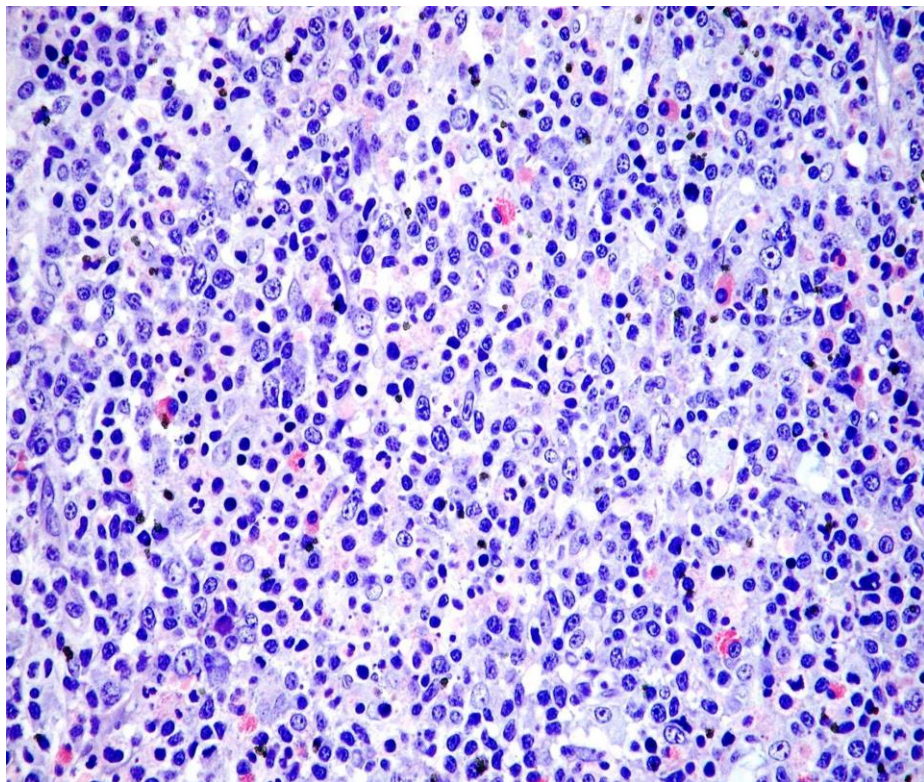
Lymphoplasmacytic lymphoma



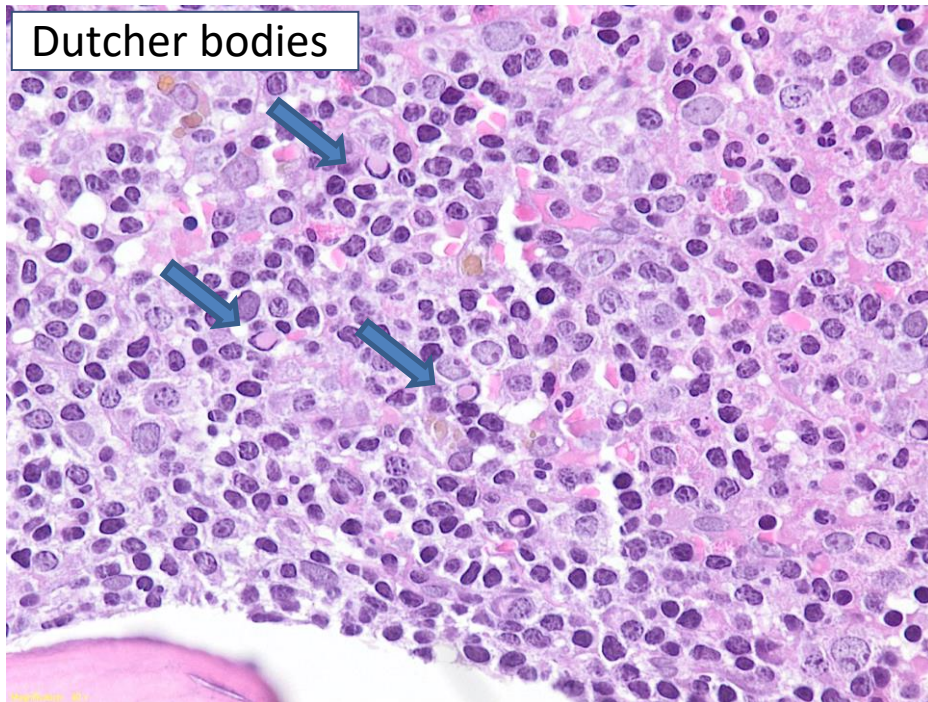
Plasma cell neoplasm



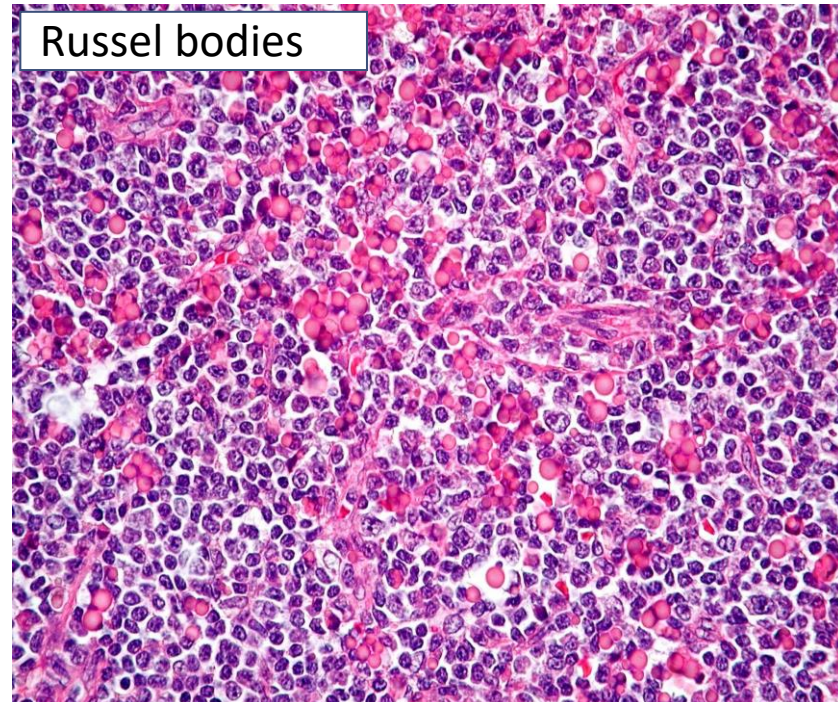
Lymphoplasmacytic lymphoma



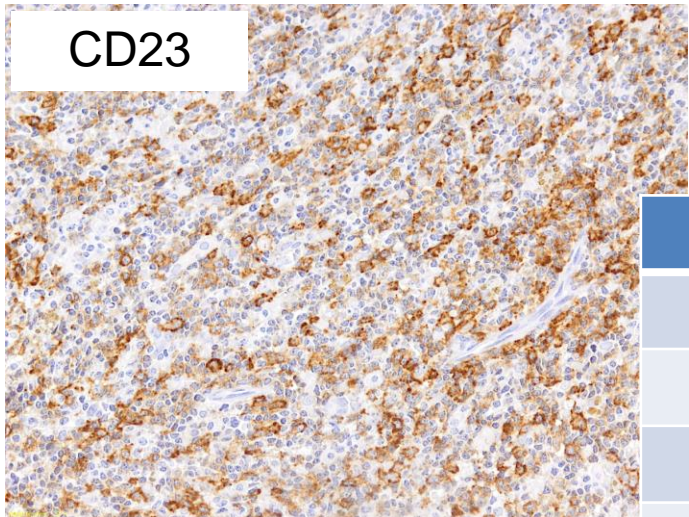
Dutcher bodies



Russel bodies

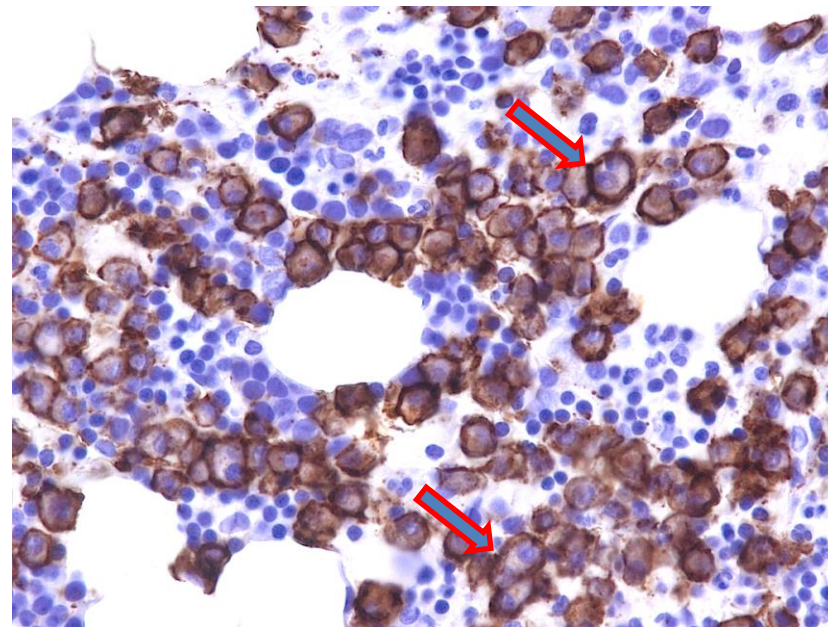
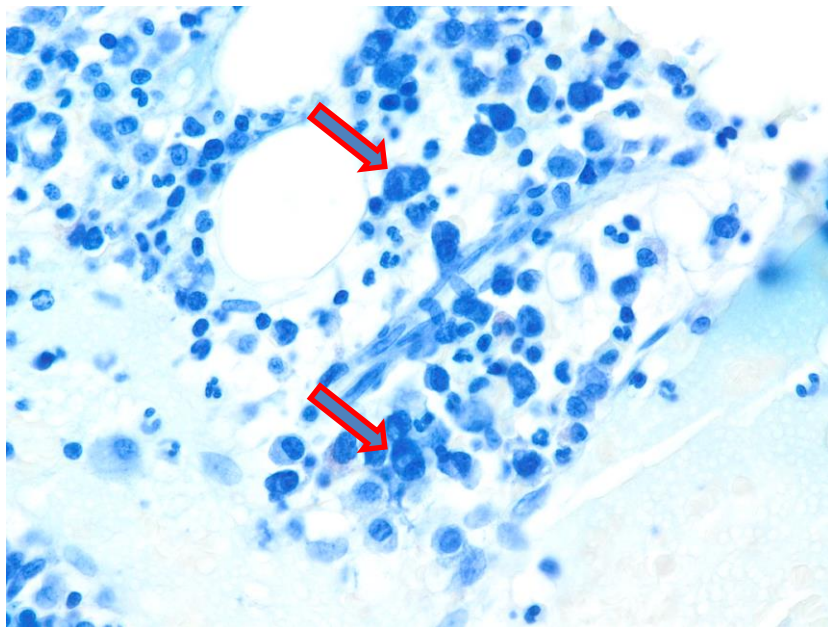


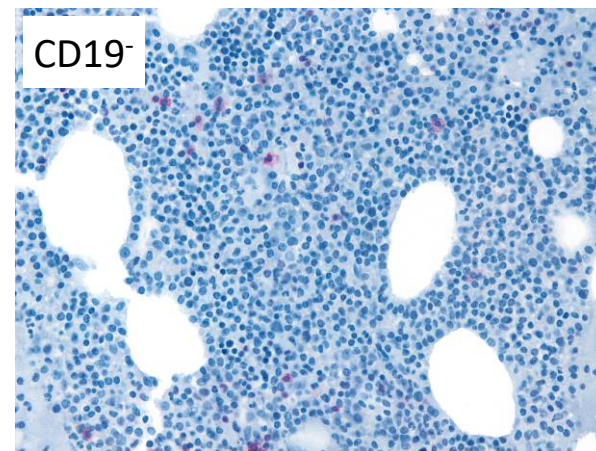
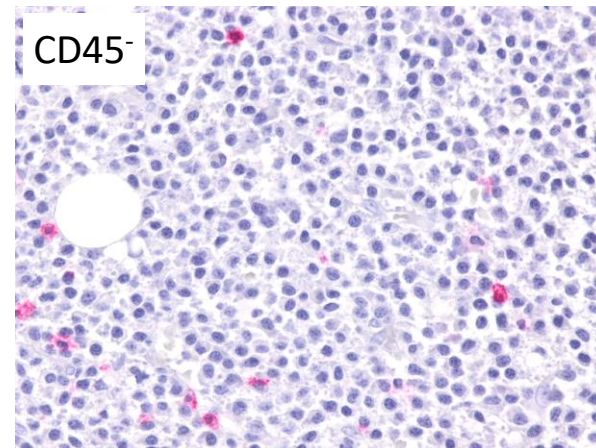
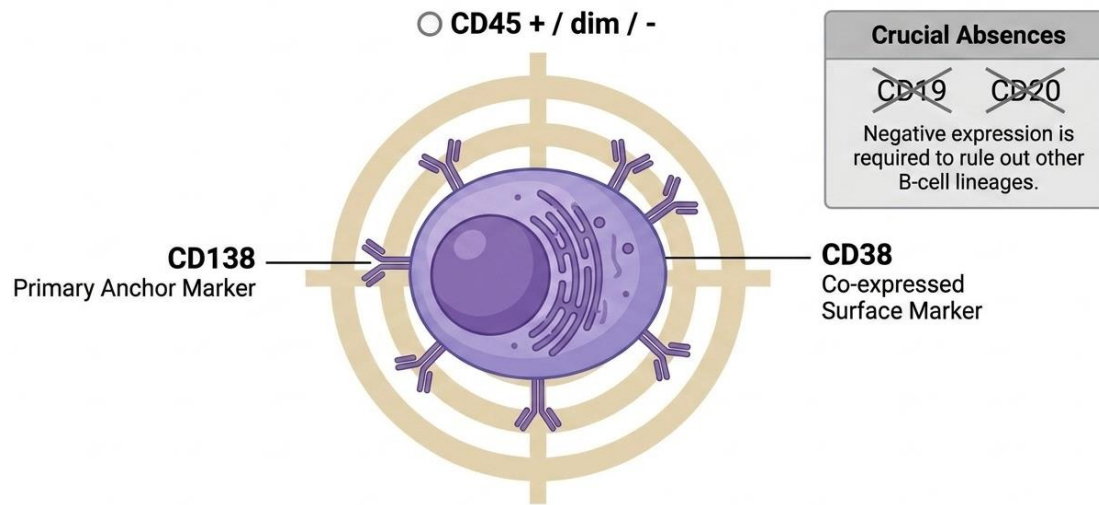
CD23

possible CD23⁺ or CD5⁺

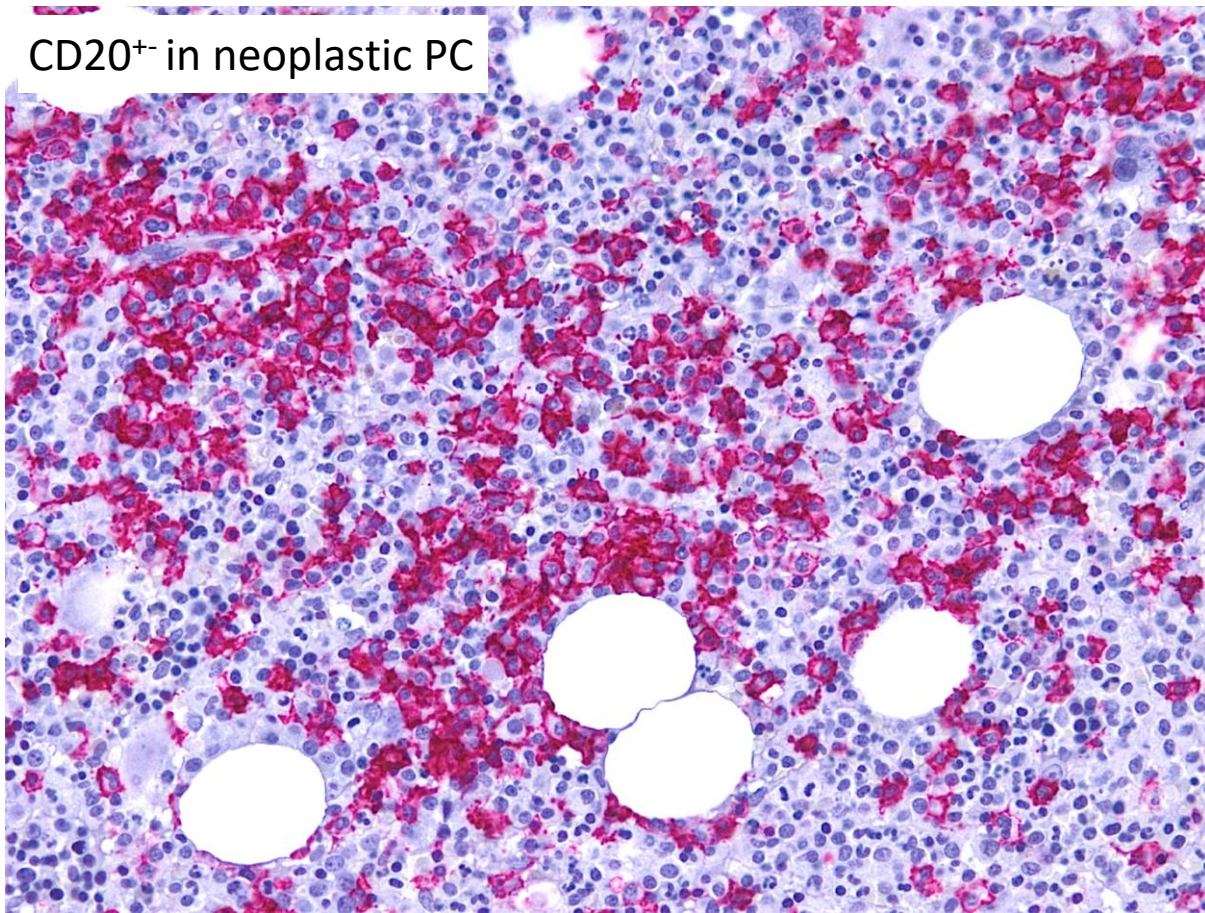
FL	MCL	HCL	CLL
CD10+	CD5+	Annessina+	CD20 w+
BCL6+	Ciclina D1+	Ciclina D1+	CD5+
BCL2+	SOX11+	CD103+	CD23+
LMO2+		CD123+	LEF1+
HGAL+			IRF4 foc+

Multiple Myeloma

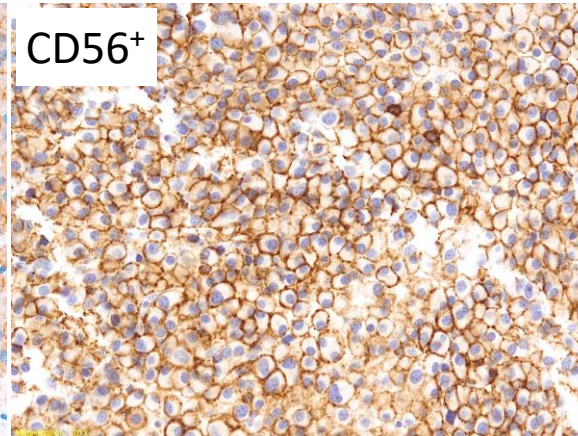
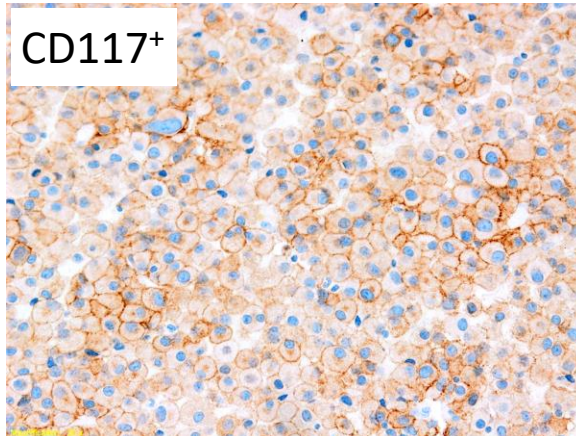


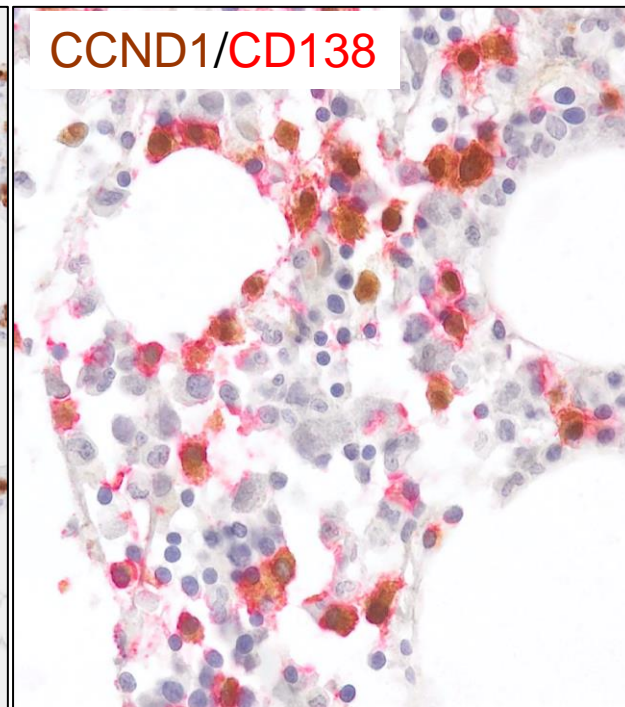
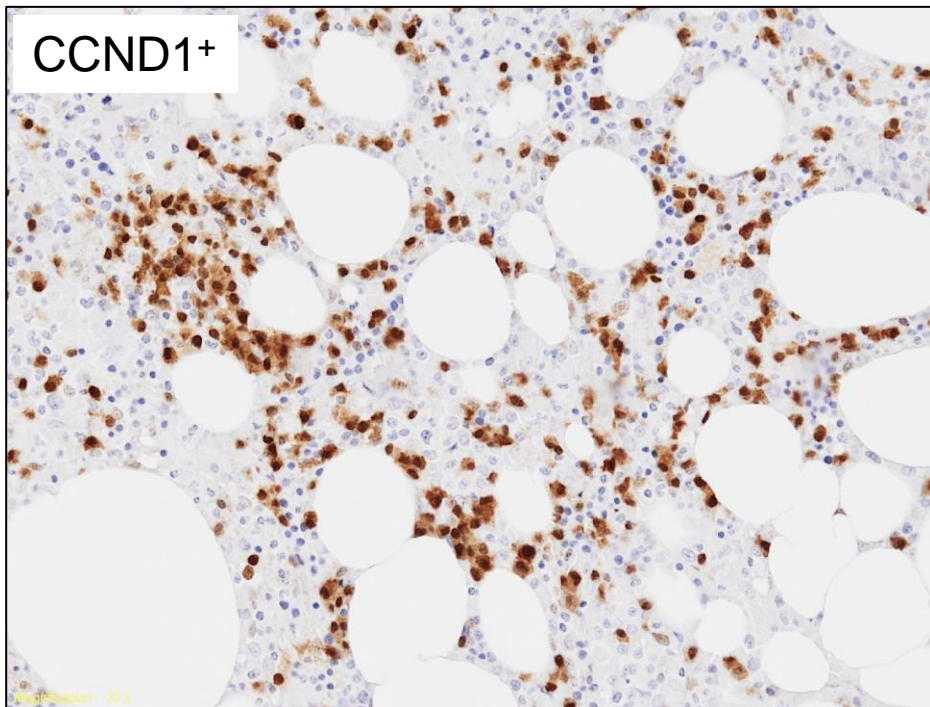


CD20⁺ in neoplastic PC



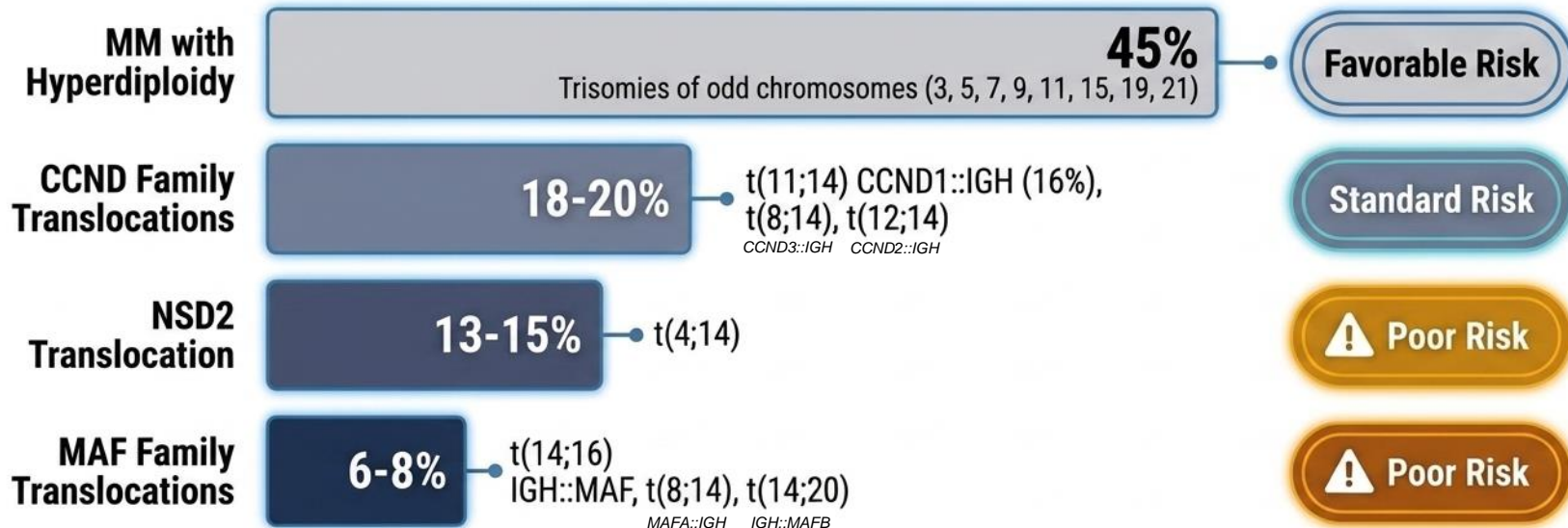
	Normal Lineage	Multiple Myeloma
Pathological Downregulation (The Losses)		
CD81	● +	○ / ● (dim)
CD27	● +	○ / ● (dim)
Pathological Upregulation (The Gains)		
CD56	○ -	● +
CD28	○ -	● +
CD33	○ -	● +
CD200	○ -	● +
CD3	○ -	● +
CD117	○ -	● +
3. Maintained Expressions & Baselines		
CD307	● +	● +
CD66	○ -	○ -

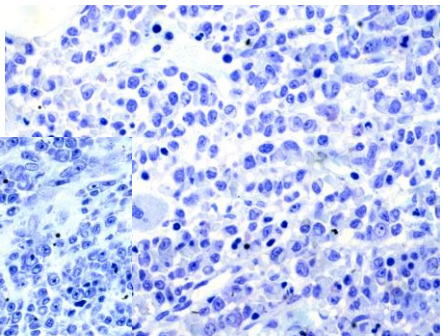
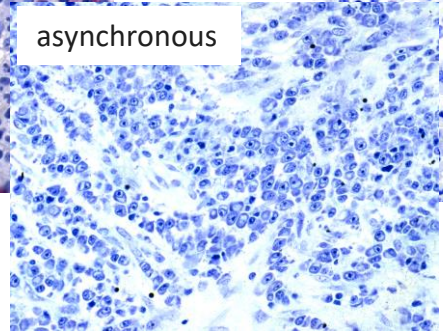
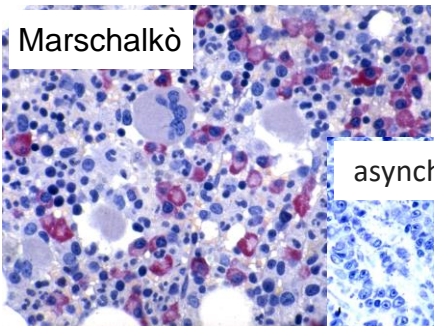
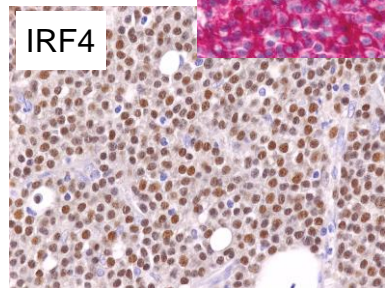
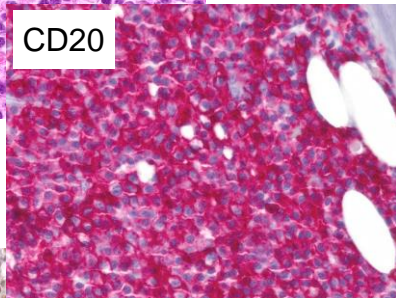
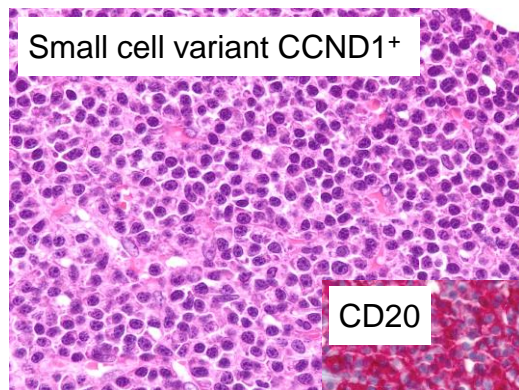
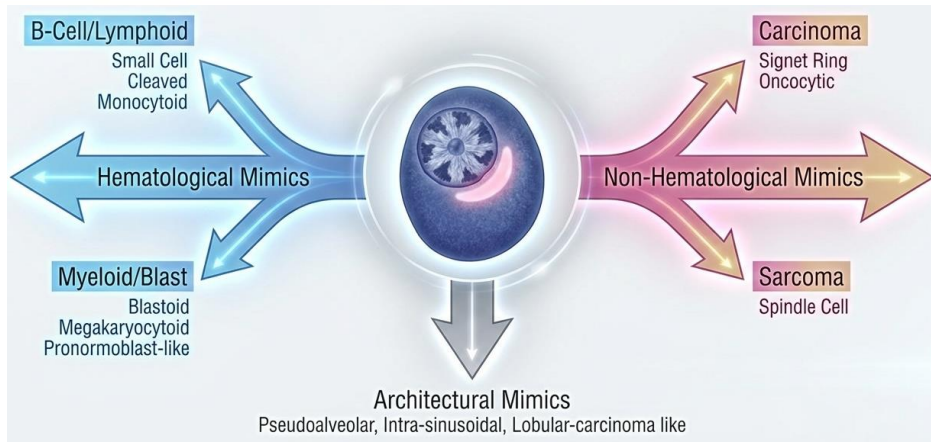




The Genetic Subclassification of Multiple Myeloma

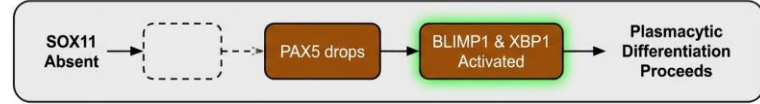
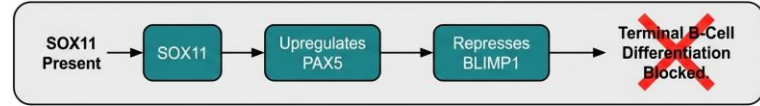
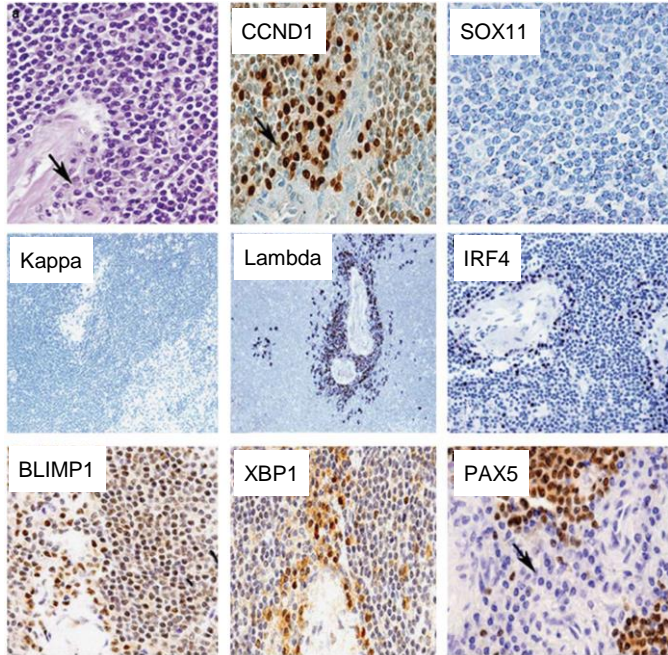
MM is formally subdivided into mutually exclusive groups:
Recurrent **Genetic Abnormalities** (90%) and **NOS** (10%).





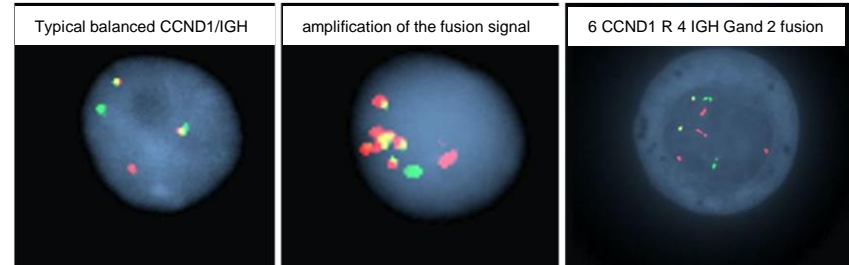
Plasma cell and terminal B-cell differentiation in mantle cell lymphoma mainly occur in the SOX11-negative subtype

Inmaculada Ribera-Cortada^{1,2}, Daniel Martinez¹, Virginia Amador³, Cristina Royo³, Alba Navarro³, Silvia Bea³, Eva Gine^{3,4}, Laurence de Leval⁵, Sergio Serrano⁶, Andrew Wotherspoon⁷, Dolores Colomer^{1,3}, Antonio Martinez^{1,3} and Elías Campo^{1,3}



PAX5 maintains B-cell identity by repressing genes that promote plasma cell differentiation.

When SOX11 is absent, the tumor cells become responsive to regulatory stimuli, turning on the terminal B-cell differentiation program.



RAG1/2 Mediated
(Aberrant VDJ Recombination)

Mate-pair sequencing confirms that MCL breakpoints cluster cleanly near the major translocation cluster, resulting in simple, balanced rearrangements

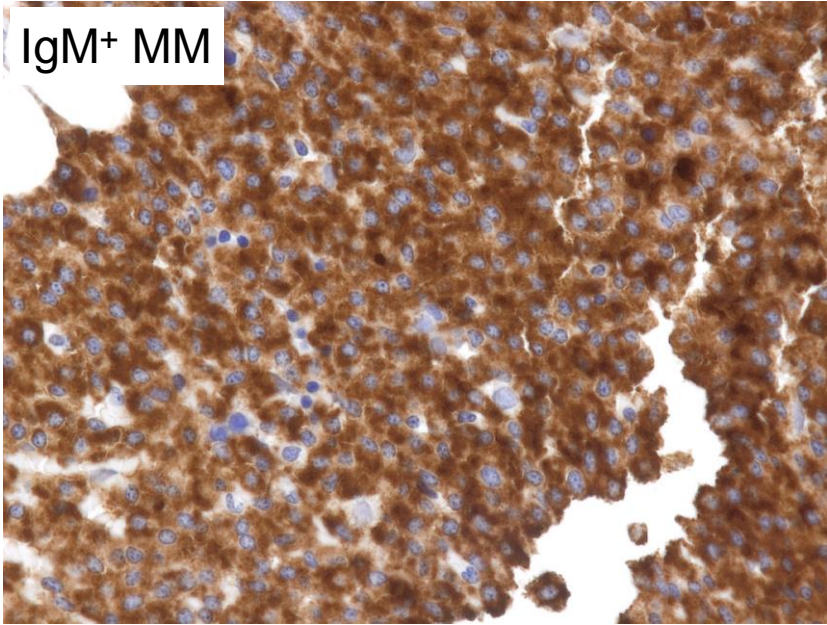
PCN Pathway



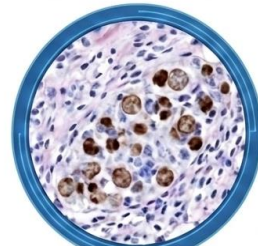
AID Mediated
(Aberrant Class Switch Recombination)

PCN breakpoints are highly variable frequently involving templated insertions (gains of CCND1 and IGH fusion regions typically <1 Mb in size explaining the chaotic FISH signals)

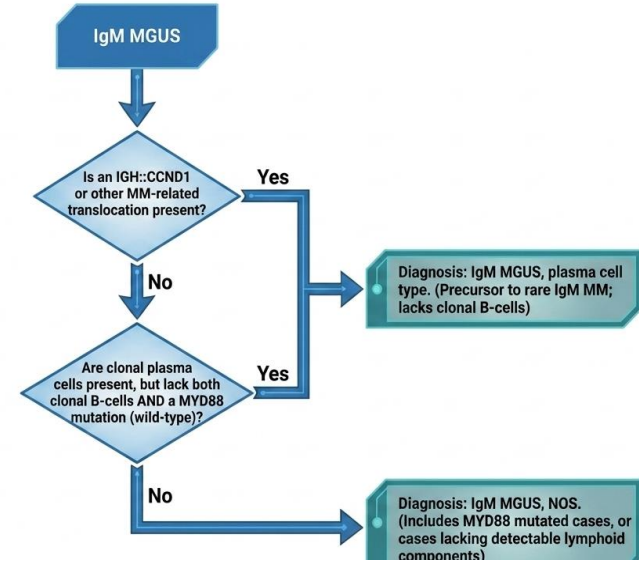
IgM⁺ MM



Untangling the IgM Precursors

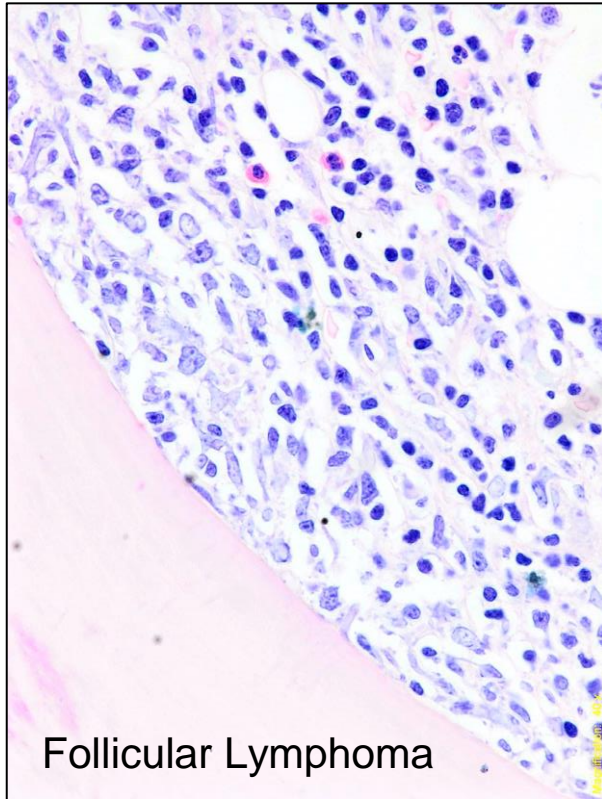


Cyclin D1+ Plasma Cell Type



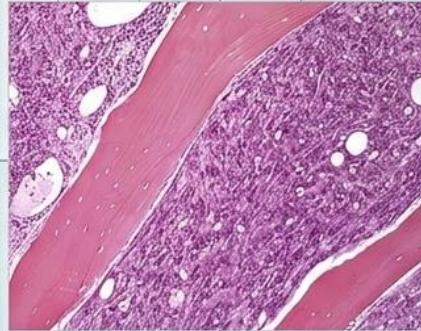
Lu H et al Am J Clin Pathol 2022
Feyler S et al Br J Haematol 2008
King RL et al Am J Clin Pathol 2013
Castillo JJ Am J Hemnatol 2017

40% MM IgM⁺/CCND1⁺



Cleaved Cell Variant

Slide Viewer



Imitates: Follicular Lymphoma.

Tell: Lacks CD10, BCL6 pattern.

Monocytoid Variant

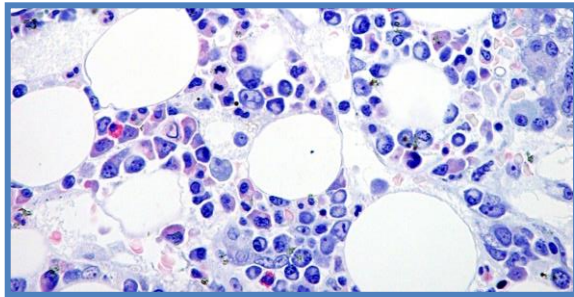
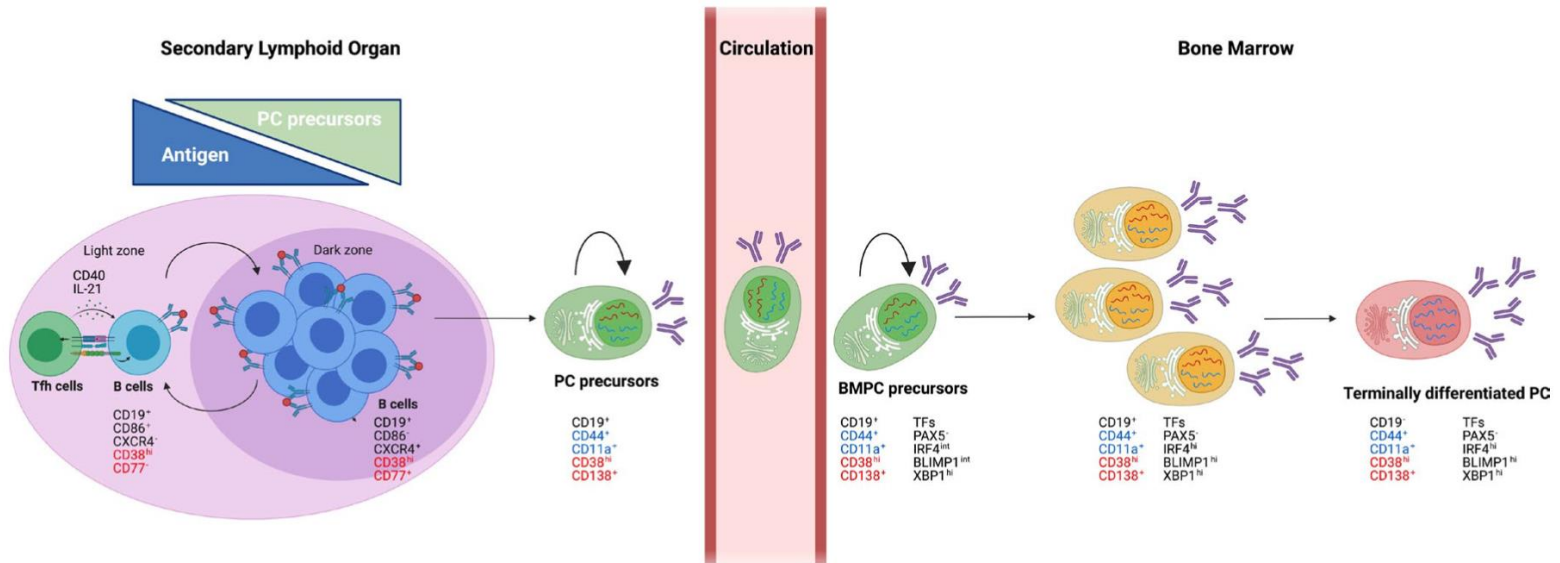
Slide Viewer



Imitates: Monocytic Neoplasms.

Tell: Irregular lobulated nuclei,
basophilic cytoplasm with
blebs/vacuoles. CD45 dim on flow.

Fend Virch Arch 2023; Hussein Pathol 2022; Cantu Diagnostic Pathol 2025;



reactive plasmacytosis in a HIV⁺ patient

BMPC compartment has four subsets secreting Ab

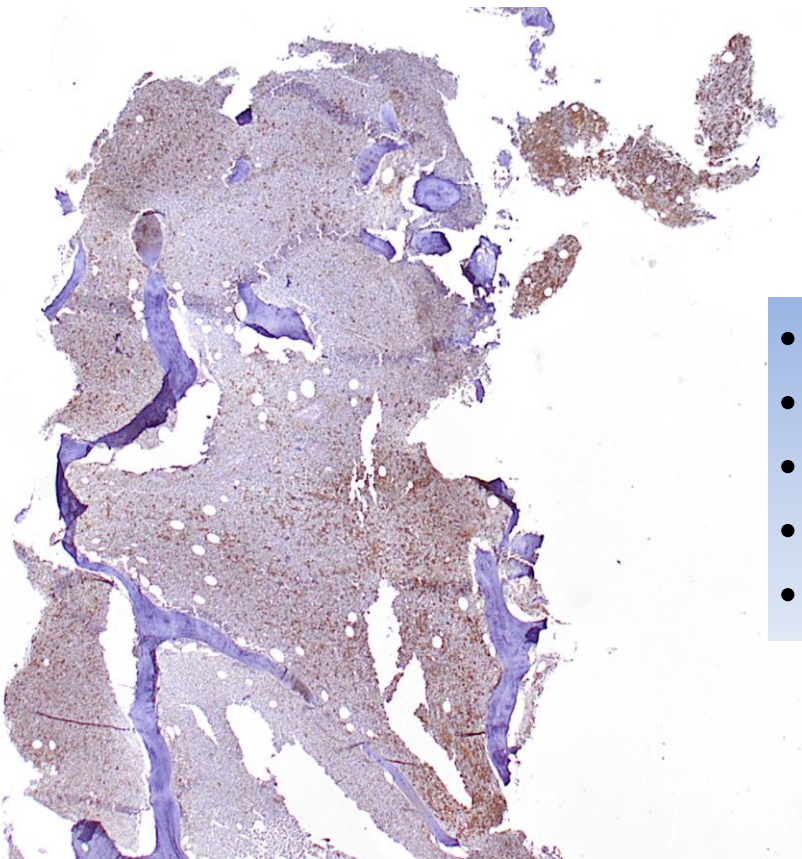
CD19⁺CD38^{hi}CD138⁻

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CD19⁻CD38^{hi}CD138⁻

CD19⁻CD38^{hi}CD138⁺ **Terminally differentiated plasma cells**

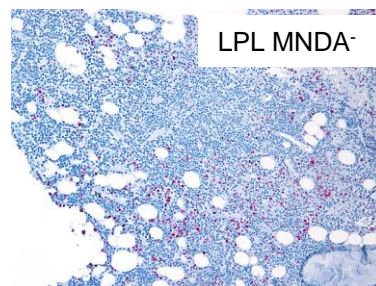
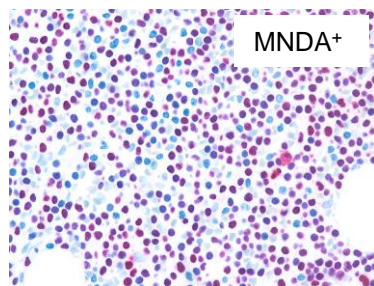
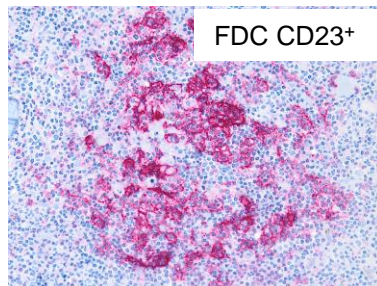
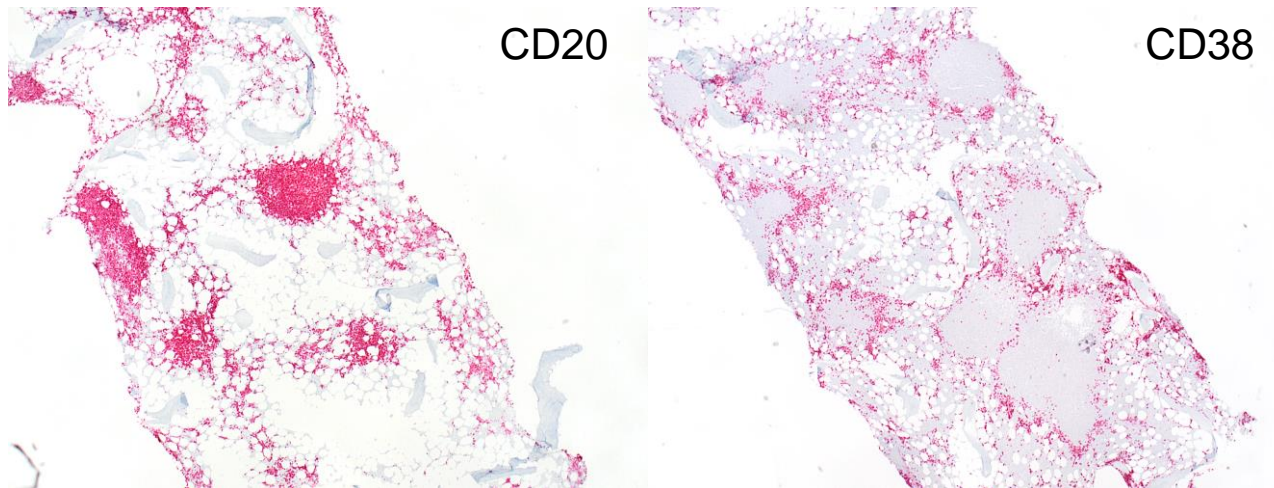
} precursor pool with proliferative potential emanating from SLOs that can then give rise to SLPCs or LLPCs by further differentiation in the BM niche



CD138⁻ negative PC neoplasm

- cells tend to be more immature
- demonstrated higher CD45 expression
- higher proliferative potential
- poorer clinical outcome
- Rely on CD38, IRF4, Kappa/lambda

marginal zone lymphoma with plasmacytic differentiation



Lymphoplasmacytic Lymphoma (LPL) Updates



The Cellularity Rule Change

LPL can now be diagnosed with abnormal lymphoplasmacytic aggregates representing <10% of bone marrow cellularity, provided clonal B-cells and plasma cells are present.

Genetic Signatures

MYD88 L265P mutations found in >90% of cases.
CXCR4 mutations in up to 40% (associated with hyperviscosity).

Primary Cold Agglutinin Disease (pCAD)



Status

Newly recognized standalone entity.

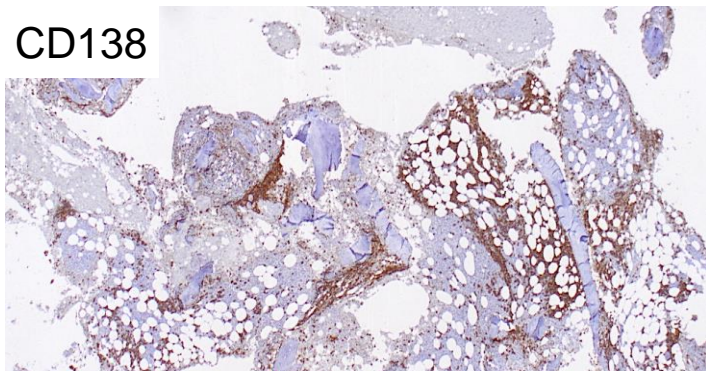
Definition

Indolent BM-based lymphoproliferative disorder producing a cold agglutinin monoclonal antibody (IgM, IGHV4-34 utilized).

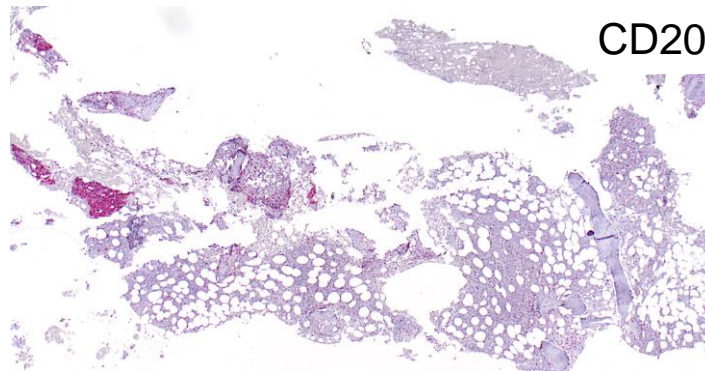
Key Differentiator

Lacks the MYD88 L265P mutation.
Trisomies 3, 12, 18 are highly recurrent, mimicking marginal zone lymphomas.

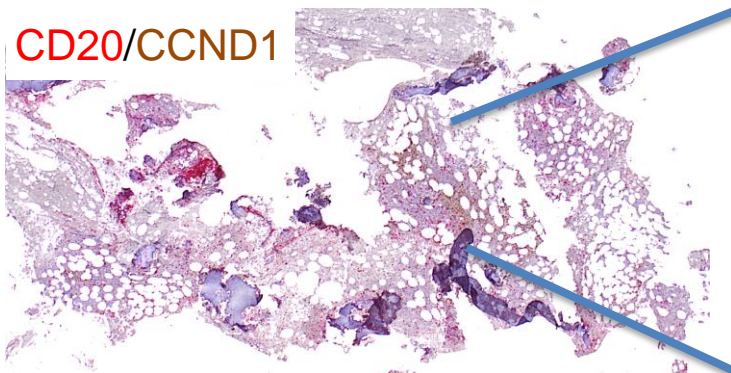
CD138



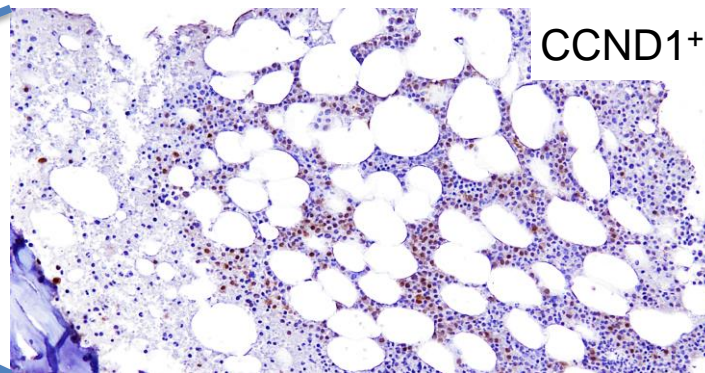
CD20

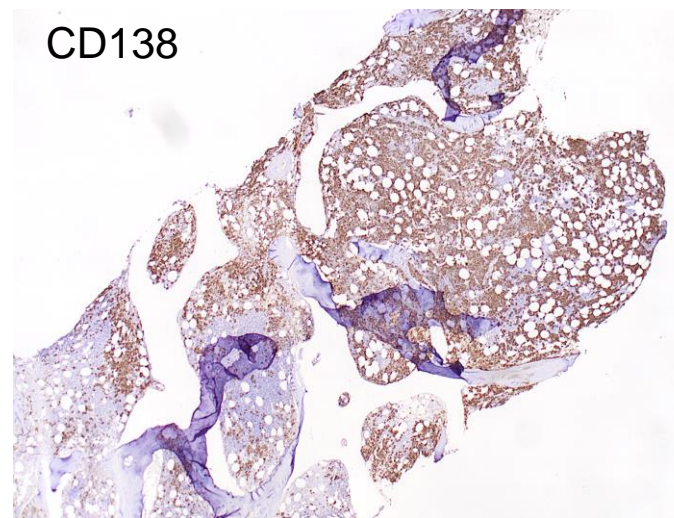
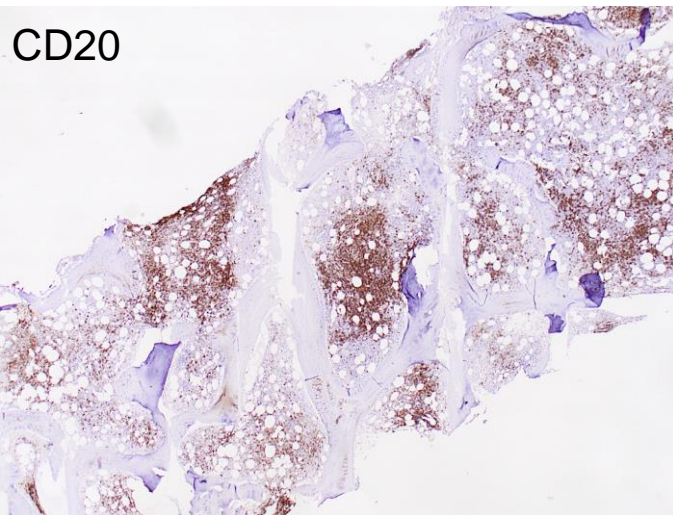


CD20/CCND1

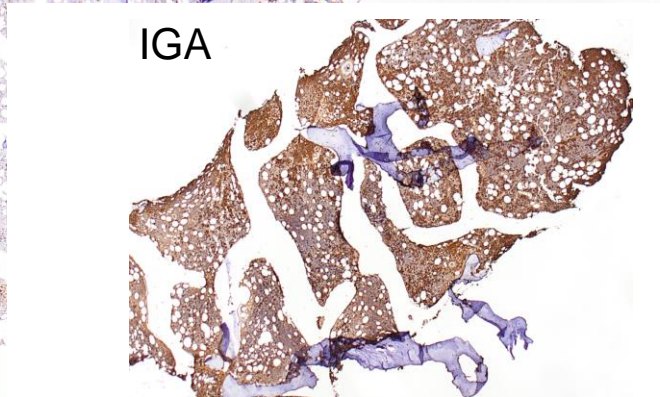
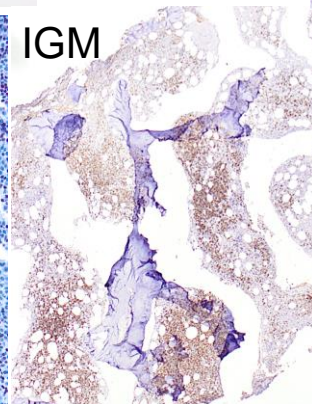
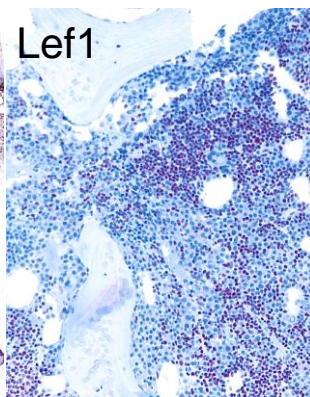
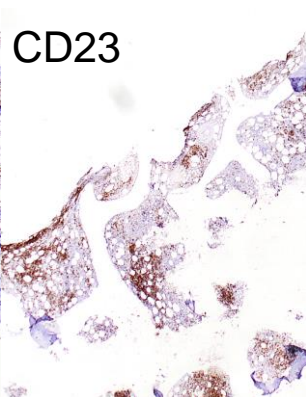
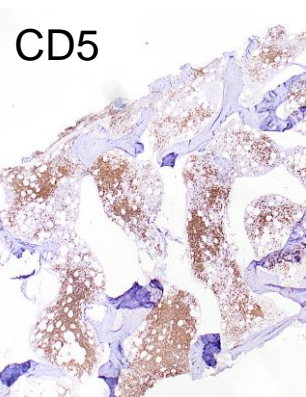


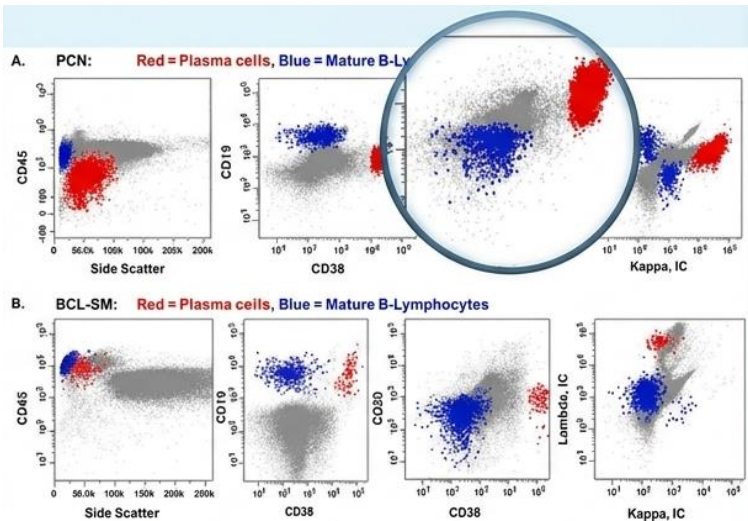
CCND1+



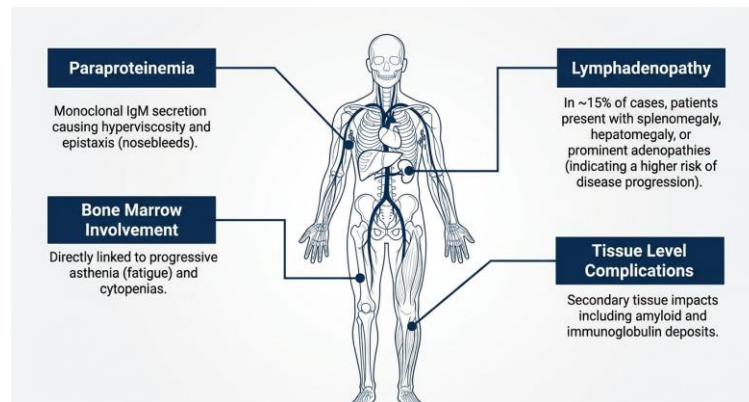


CLL
&
MM

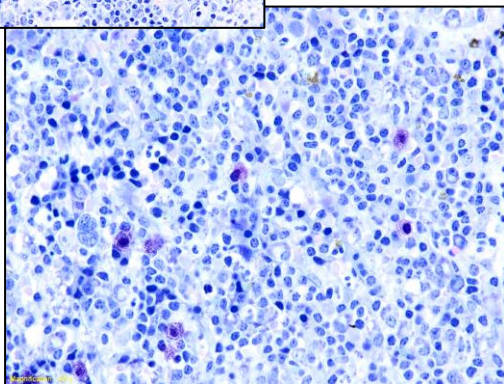
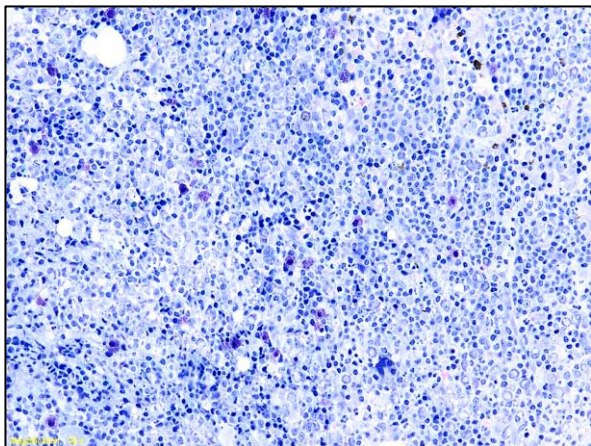




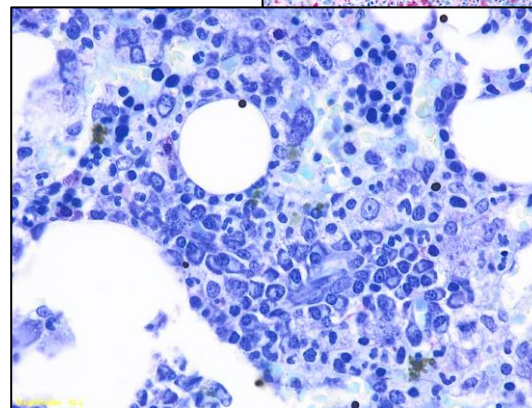
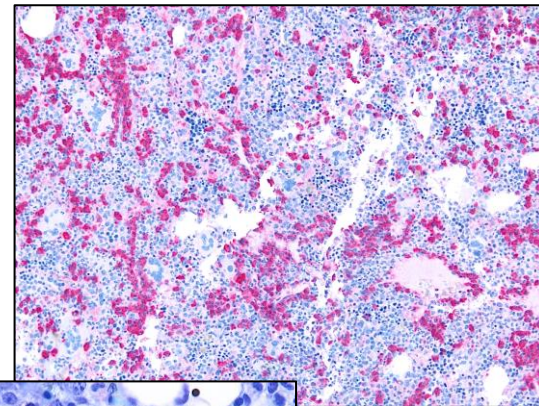
clinical history
peripheral blood and/or bone marrow flow cytometry
lymphadenopathy
splenomegaly
single or multiple serum M-protein
CRAB
osteolytic skeletal lesions



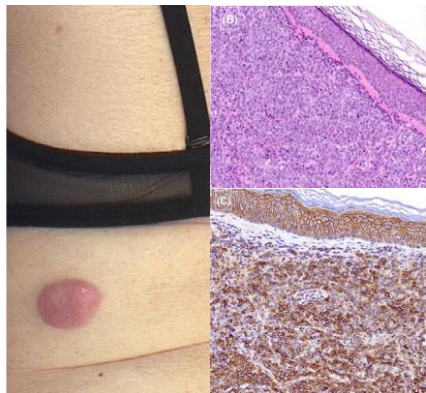
LPL pre-therapy



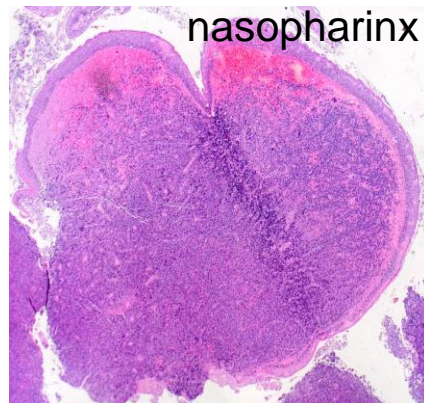
LPL post-Therapy



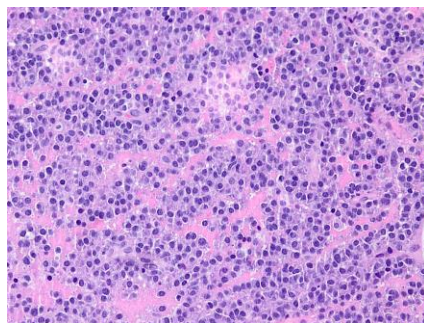
Extramedullary involvement
in multiple myeloma



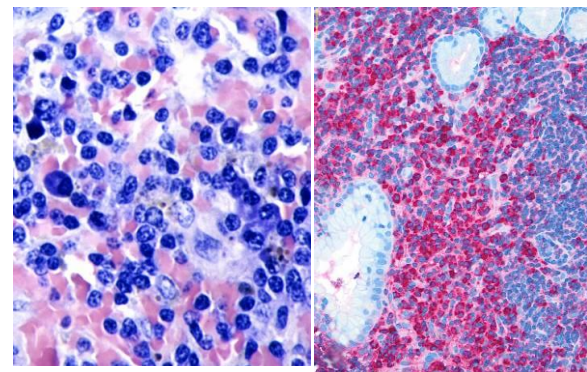
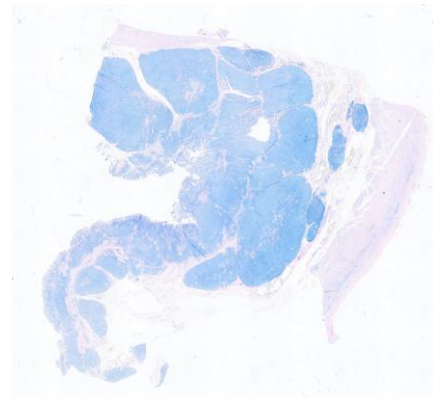
Extramedullary
Plasmacytoma



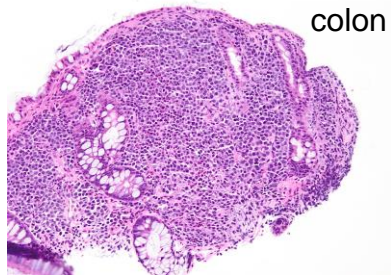
nasopharinx



EMZL with pc differentiation

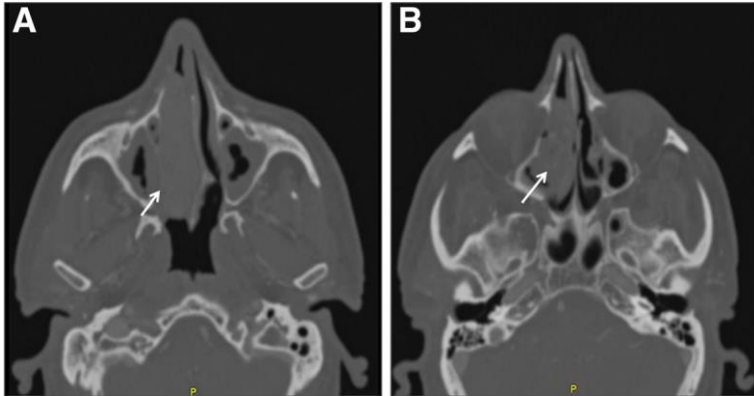


colon





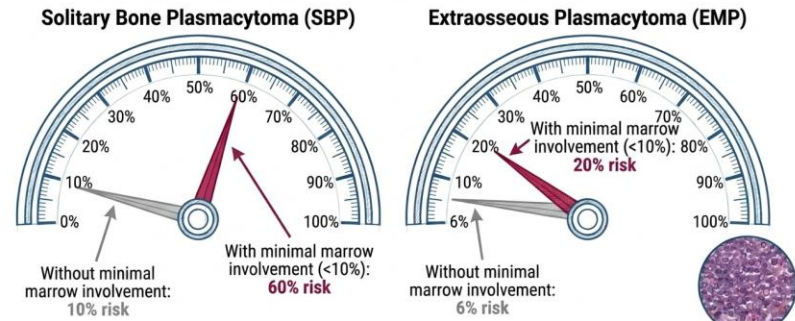
- ❖ 1–3% of plasma cell malignancies
- ❖ frequently in the head and neck region
- ❖ EMP with IgA expression predominantly manifests in lymph nodes of the head and neck region, frequently in younger patients with various forms of immune dysregulation
- ❖ amyloid deposition frequently accompanies EMP
- ❖ CD56⁻, absence of t(11;14)
- ❖ lower ki67 as compared to extramedullary manifestations of multiple myeloma (the latter often: MYC^t or TP53^{mut})
- ❖ MM-type cytogenetics with recurrent IGH translocations and polysomies,



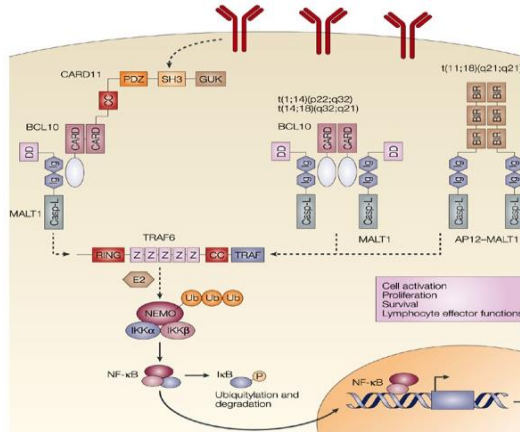
Cantone et al. Journal of Medical Case Reports (2017) 11:219

Localized Neoplasms: The Flow Cytometry Gate

Detecting <10% minimal marrow involvement via flow cytometry drastically accelerates 3-year progression risk.



Site	t(11;18) (q21;q21)	t(14;18) (q32;q21)	t(3;14) (p14.1;q32)	t(1;14) (p22;q32)	+3	+18
WHO 2008						
Stomach	6-26	1-5	0	0	11	6
Intestine	12-56	0	0	0-13	75	25
Ocular adnexa/orbit	0-10	0-25	0-20	0	38	13
Salivary glands	0-5	0-16	0	0-2	55	19
Lung	31-53	6-10	0	2-7	20	7
Skin	0-8	0-14	0-10	0	20	4
Thyroid	0-17	0	0-50	0	17	0

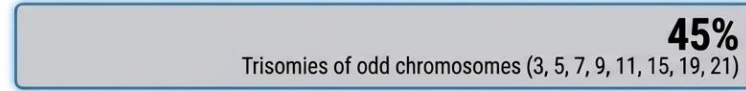


EMZL
translocations
gains/ losses:
+18/18q
+3/3q
del 6q23.3

VS

MM
aberration/translocations

**MM with
Hyperdiploidy**



**CCND Family
Translocations**



**NSD2
Translocation**



**MAF Family
Translocations**



