PAPEL DEL PATÓLOGO ANTE LA BIOPSIA MEDULAR. La biopsia medular en las neoplasias mieloproliferativas/mielodisplásicas

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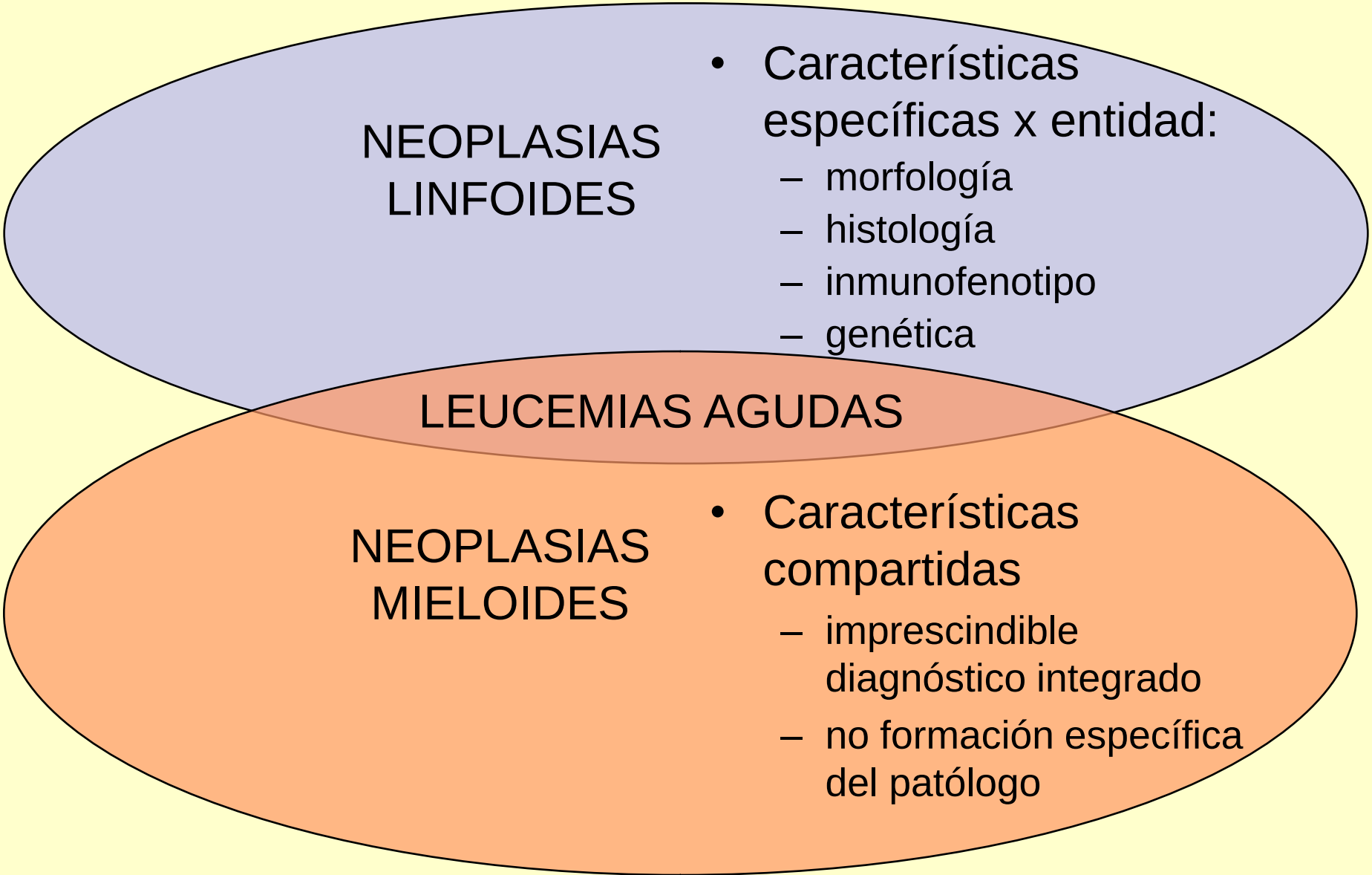
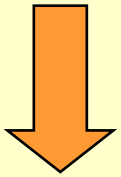
PATOLOGÍA NEOPLÁSICA DE LA MÉDULA ÓSEA



BMO: CONSIDERACIONES TÉCNICAS

- Fijación distinta a otros tejidos
- Descalcificación de la muestra



- En IHQ:
  - Control interno
  - Si control externo, idénticas condiciones
- En técnicas moleculares:
  - Mirar siempre gen control

BMO: TECNICAS COMPLEMENTARIAS EN NEOPLASIAS MIELOIDES

- Fibras:
  - reticulina, tricrómico
- IHQ:
  - Blastos: CD34, CD117
  - Serie roja: glicoforina
  - Megacariocitos: CD61, factor VIII
  - Serie blanca:
    - Pan-mieloides: MPO, lisozima, CD68-KP1
    - Monocitos-macrofagos: CD68-PGM1

La biopsia medular en las neoplasias mieloproliferativas/mielodisplásicas

- Concepto y clasificación
- Síndromes mielodisplásicos
- Neoplasias mieloides con proliferación predominante de la serie blanca
- Neoplasias mieloides con proliferación predominante de la serie megacariocítica
- Formas raras de neoplasias mieloproliferativas/ mielodisplásicas
- Neoplasias mieloides con fibrosis medular
- Consideraciones finales

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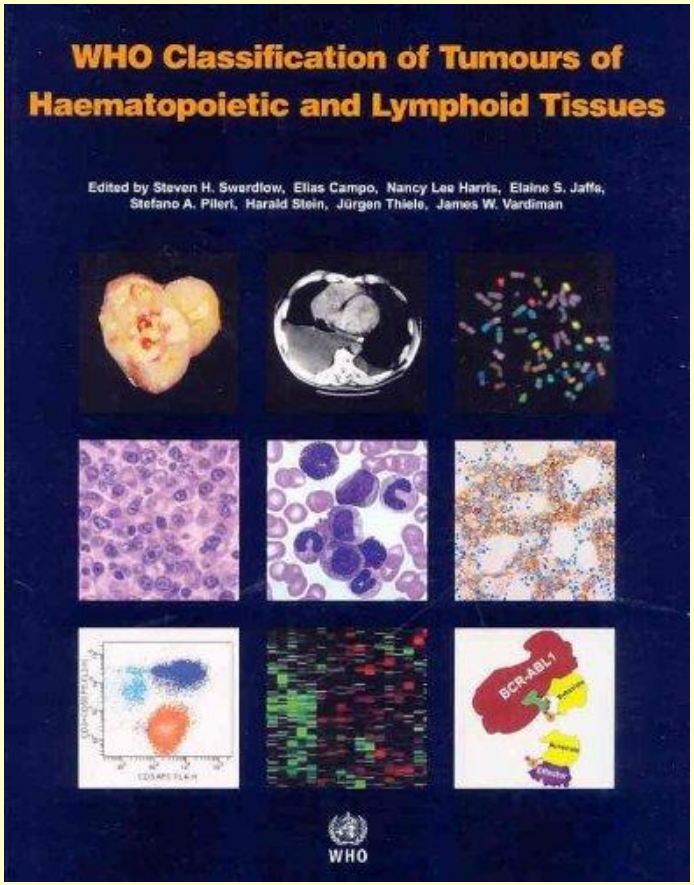
2008 WHO CLASSIFICATION OF CHRONIC MYELOPROLIFERATIVE NEOPLASMS



DEFINITION CMPD

- Chronic myeloproliferative diseases (CMPDs) are clonal hematopoietic neoplasms characterized by the proliferation in the bone marrow of one or more of the myeloid lineages.
- Relative normal maturation, effective

↓

Increased numbers of granulocytes, red blood cells or platelets in the peripheral blood

No increase of blasts, no major dysplastic changes

2008 WHO CLASSIFICATION OF CMPNs

- Chronic myeloid leukemia (CML) (Ph+)
- Ph-negative CMPNs
  - Polycythemia vera (PV)
  - Essential thrombocythemia (ET)
  - Primary myelofibrosis (PMF)
- Other unusual CMPNs
  - Chronic neutrophilic leukemia (CNL)
  - Chronic eosinophilic leukemia (CEL), NOS
- Mastocytosis
- CMPNs unclassifiable
  - Initial phases of PV, ET o PMF
  - Advanced phases of CMPD

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  - Advanced phases of CMPD

SÍNDROMES MIELODISPLÁSICOS (SMD)

- CONCEPTO
  - Trastorno clonal de la hematopoyesis → descartar causas de mielodisplasia secundaria
  - Displasia en 1, 2 o las 3 series hematopoyéticas → hematopoyesis ineficaz → citopenias
  - Ausencia de visceromegalias
  - Presencia de blastos

- DIAGNÓSTICO Y CLASIFICACIÓN DE LOS SMD
  - Grado de displasia (%)
  - % de blastos
    - < 5%
    - > 5% < 20%
    - > 20% = leucemia aguda
  - Citogenética

SÍNDROMES MIELODISPLÁSICOS (SMD)

- BMO EN SMD:
  - pacientes jóvenes
  - formas especiales
    - SMD hipocelular → DD con aplasia medular
    - SMD hiperfibrótico → DD mielofibrosis

Myelodysplastic /myeloproliferative neoplasms (MDS/MPN)

- CONCEPT
  - The MDS/MPN are clonal hematopoietic neoplasms that have both dysplastic and proliferative features at the time of initial presentation

  - Increased numbers of granulocytes, red blood cells or platelets in the peripheral blood AND cytopenias
  - Splenomegaly and/or hepatomegaly
  - dysplastic changes
  - Increase of blasts

Myelodysplastic /myeloproliferative neoplasms (MDS/MPN)

- CLASSIFICATION
  - Chronic myelomonocytic leukemia (CMML)
  - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
  - Juvenile myelomonocytic leukemia (children 0-14 years)
  - MDS/MPN, unclassifiable
    - Provisional entity: RARS with marked thrombocytosis, JAK2 mutation +(≈70%)
    - Exclude *BCR-ABL1* fusion gene, rearrangement *PDGFRA*, *PDGFRB*, *FGFR1*
    - Exclude isolated del (5q), t(3;3)(q21;q26) or inv 3(q21q26)

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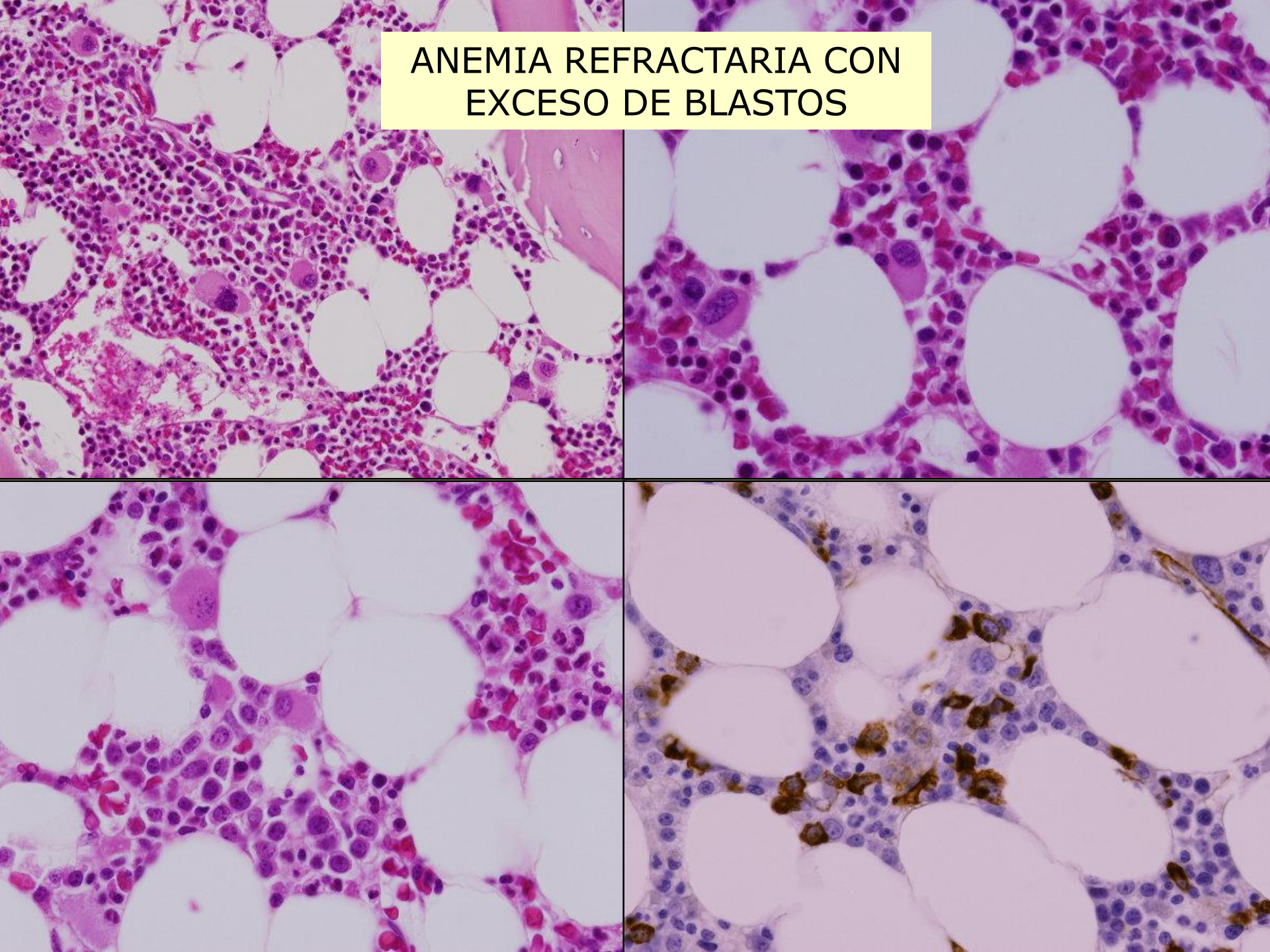
- Consideraciones finales

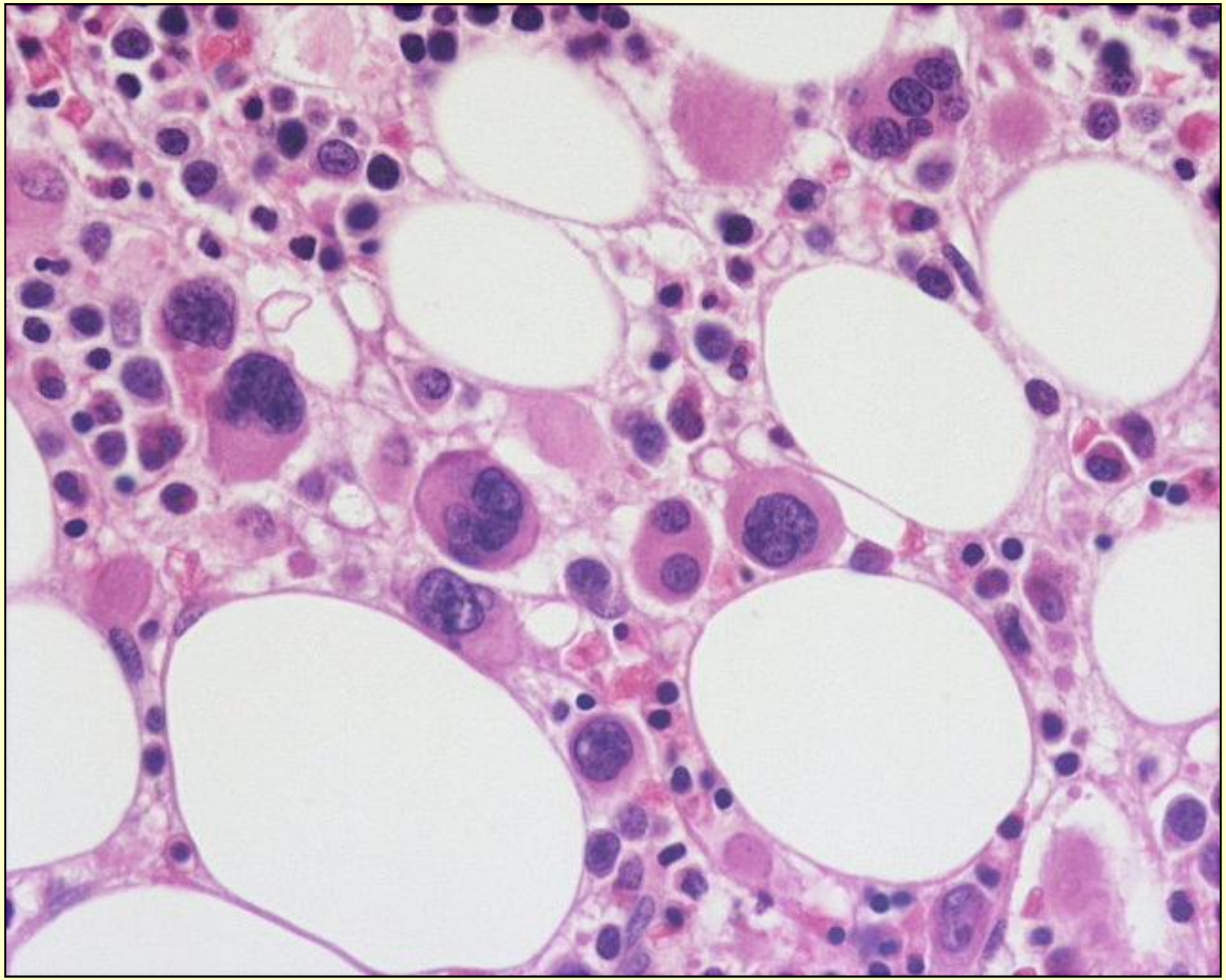
LA BIOPSIA MEDULAR EN LOS SÍNDROMES MIELODISPLÁSICOS (SMD)

- Valoración de la celularidad: DD con aplasia medular
- Valoración de la fibrosis
- Estimación de la displasia, especialmente megacariocítica
- Estimación aproximada de la cantidad de blastos o ALIP's (CD34)

  - *Vardiman JW, Hematology Am Soc Hematol Educ Program 2006;199-204.*
  - *Torlakovic et al, Arch Pathol Med 2002; 126:823-828.*
  - *Sakuma et al, Pathology International 2006; 56:191-99.*

ANEMIA REFRACTARIA CON EXCESO DE BLASTOS





La biopsia medular en las neoplasias mieloproliferativas/mielodisplásicas

- Concepto y clasificación
- Síndromes mielodisplásicos
- Neoplasias mieloides con proliferación predominante de la serie blanca: granulocitos neutrófilos, eosinófilos, basófilos,monocitos
- Neoplasias mieloides con proliferación predominante de la serie megacariocítica
- Formas raras de neoplasias mieloproliferativas/ mielodisplásicas
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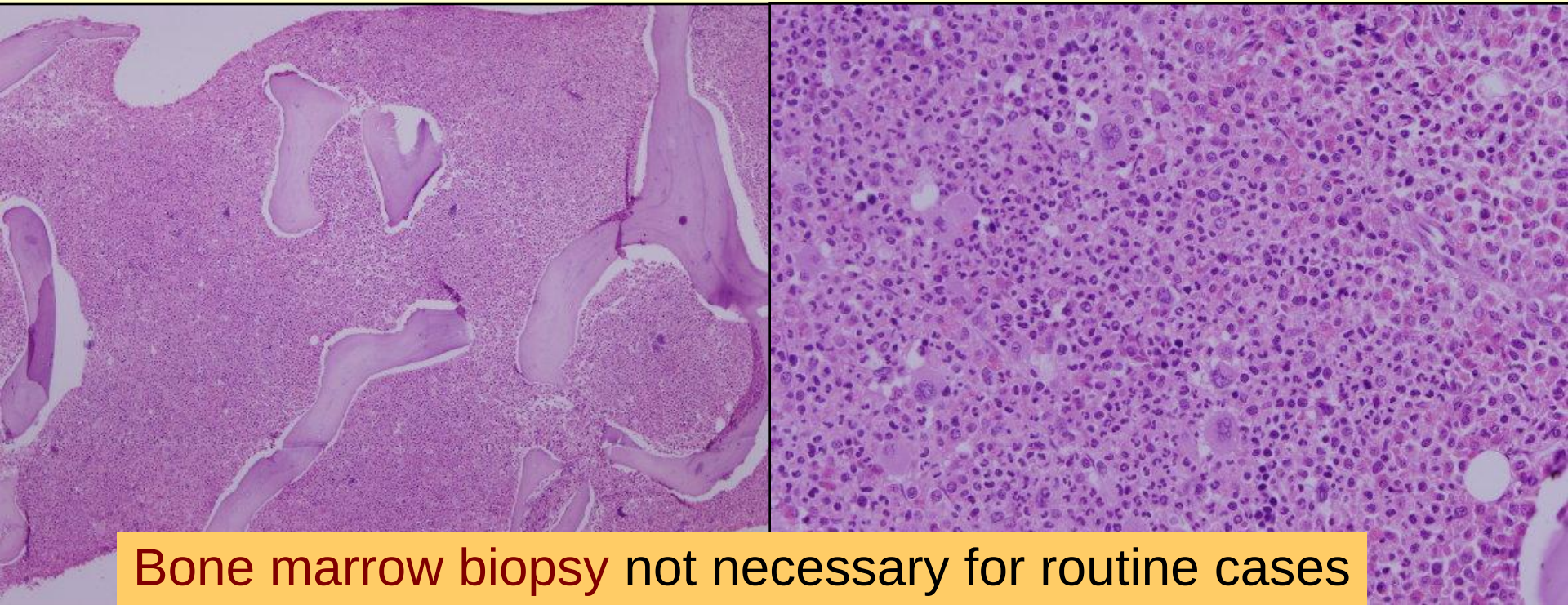
Chronic Myeloid Leukemia (CML)

- Characterized by granulocytic proliferation
- Pathogenesis:
  - Reciprocal translocation t(9:22)(q34;q11) → Philadelphia chromosome & BCR/ABL rearrangement → activated tirosine kinase
- Treatment
  - Tirosine kinase inhibitors (Imatinib mesylate, Gleevec, Novartis)
- Diagnosis & follow up:
  - Quantification of BCR/ABL transcripts by quantitative RT-PCR
- Bone marrow biopsy not necessary for routine cases

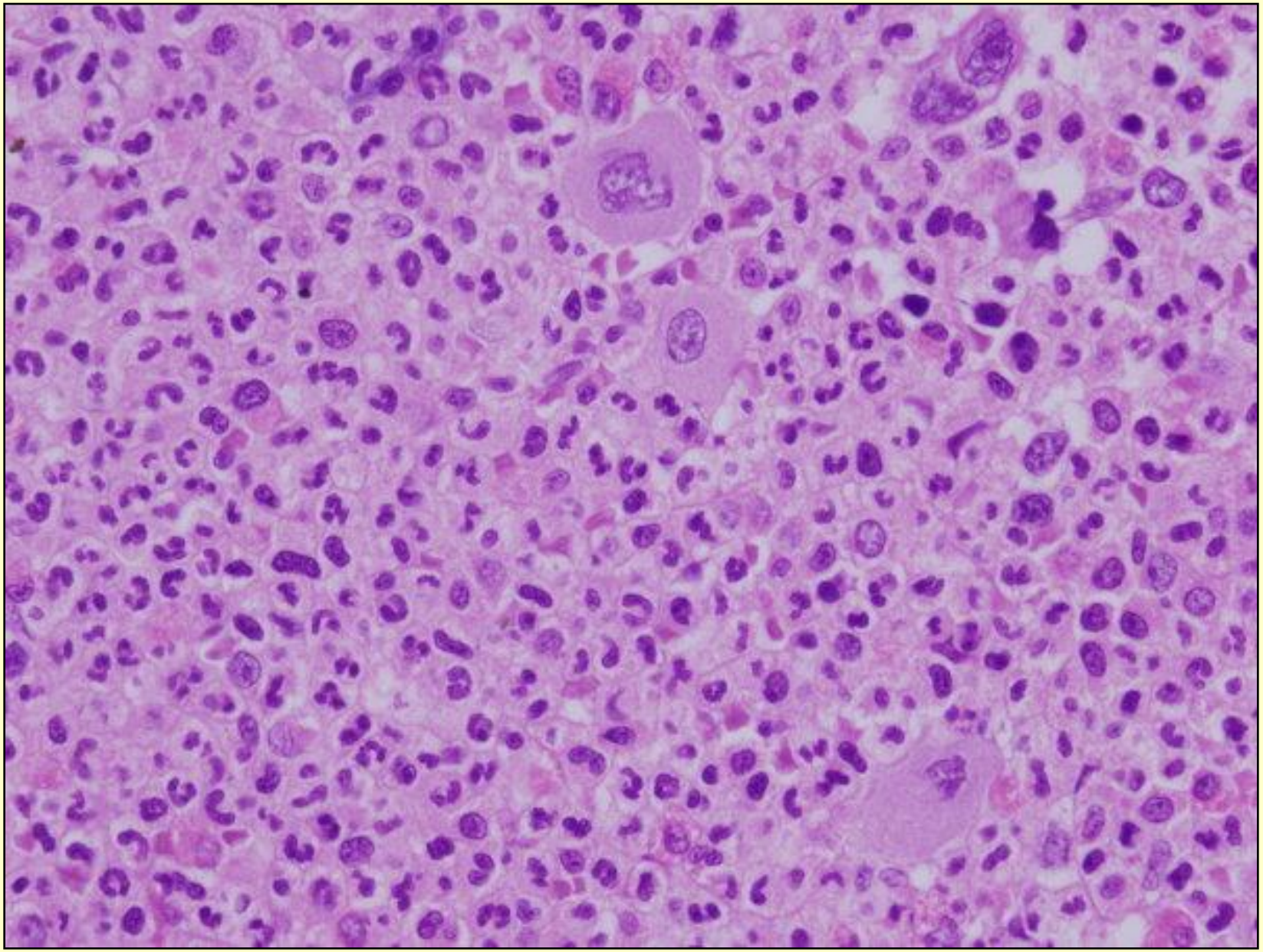
CML BM PATHOLOGY

- Hypercellular (nearly 100%)
- Granulocytic proliferation
- Small megakaryocytes with hypolobated nuclei, normal or increased numbers
- Reduced erythroid precursors



Bone marrow biopsy not necessary for routine cases

CML



CML BM: Differential Diagnosis

- MDS/MPN
  - Chronic myelomonocytic leukemia (CMML)
  - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
- Other unusual CMPNs
  - Chronic neutrophilic leukemia (CNL)
  - Chronic eosinophilic leukemia (CEL), NOS

MDS/MPN: CMML

A. Orazi & U. Germing, Leukemia (2008) 22, 1308-1319

- Monocitosis > $1x10^9$/L
- Proliferación
  - más monocítica en SP
  - más mieloide en MO
- Displasia
  - granulocítica
  - megacariocítica
- BMO hiper o hipocelular

CMML

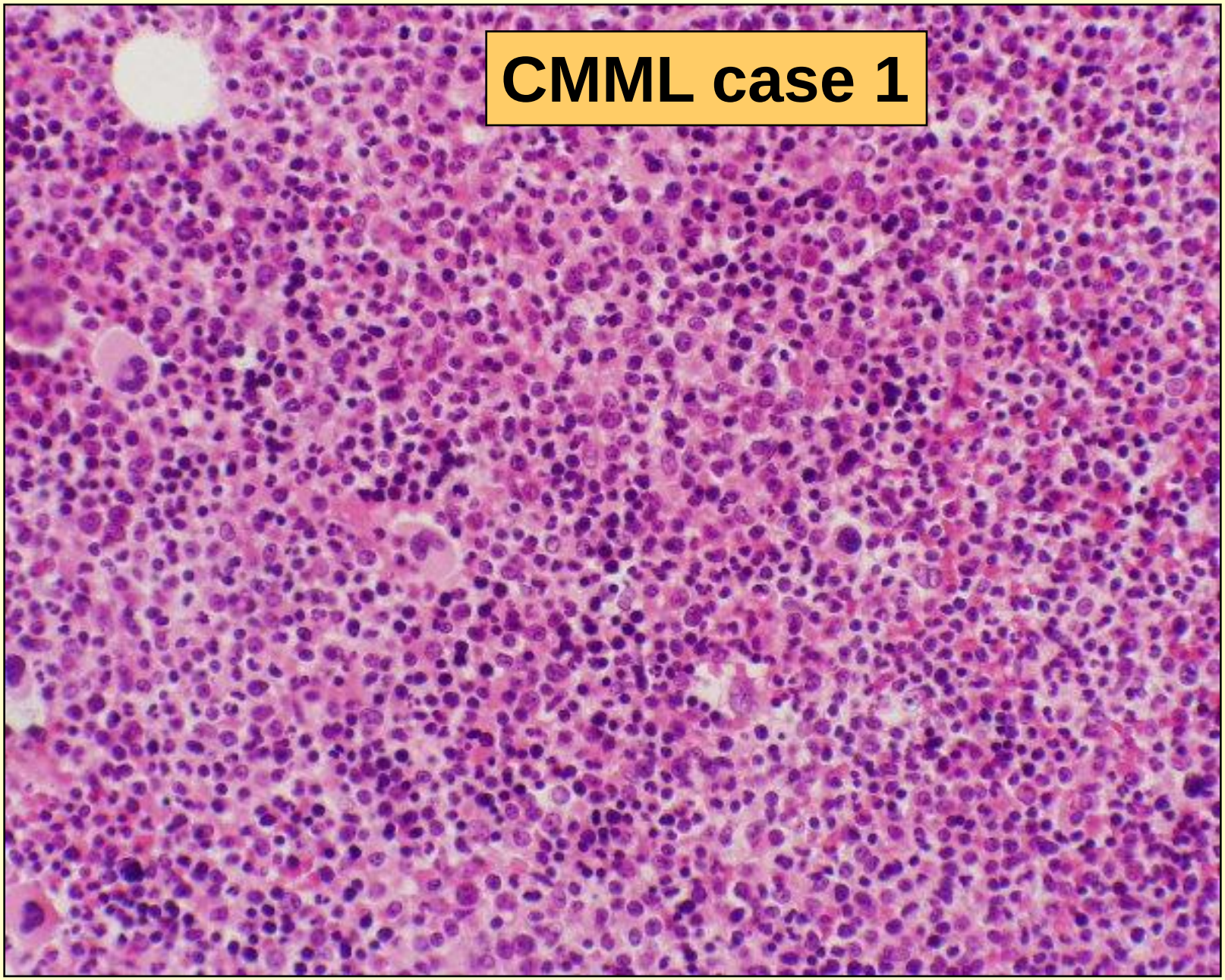
3 cases per 100 000 individuals older than 60 years (0.5/100 000 per year in all ages)

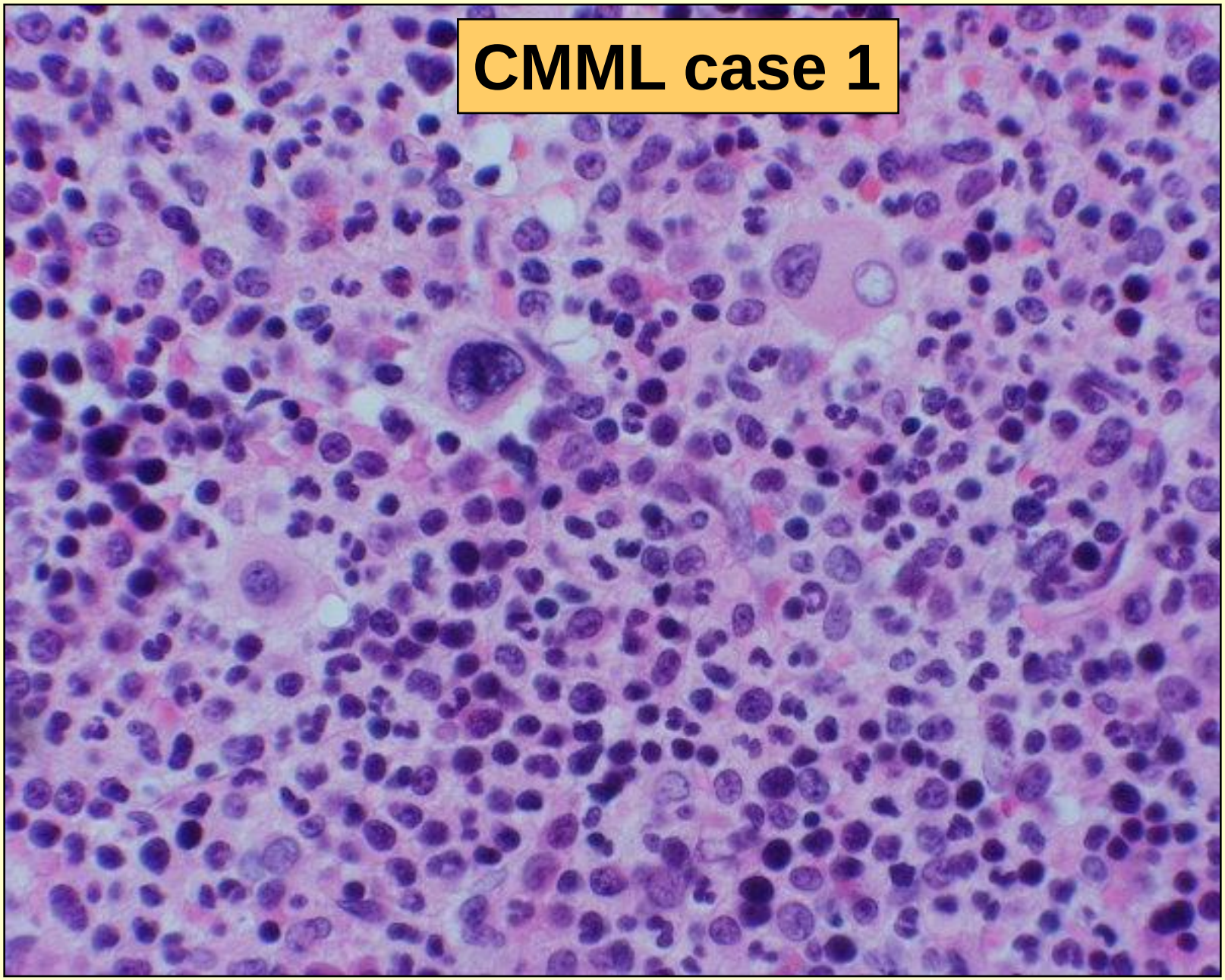
Persistent monocytosis of $>1 \times 10^9$ per liter with a percentage of monocytes >10% of WBC
- Type I: peripheral blasts <5%
- Type II: peripheral blasts <20%

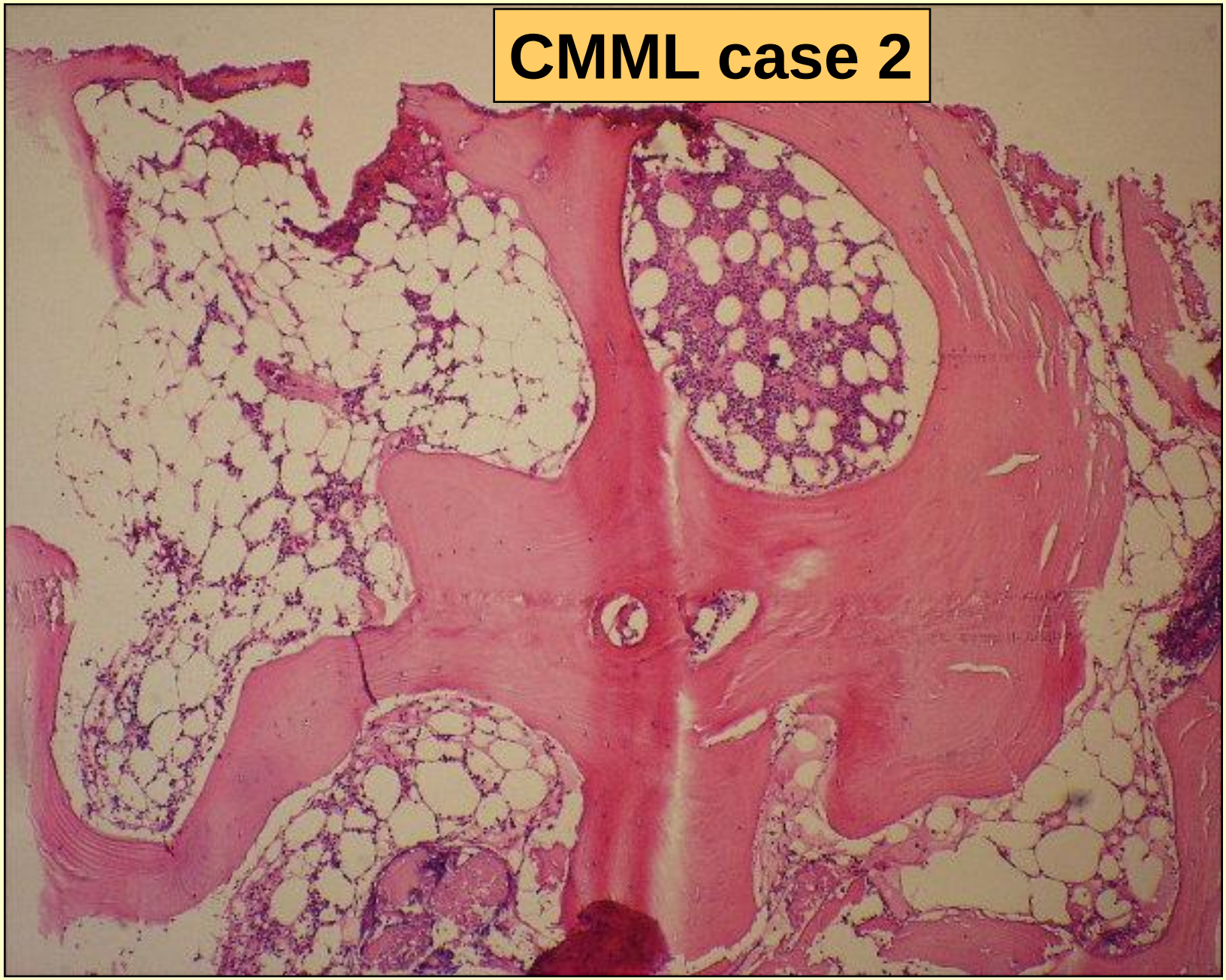
Hypercellular marrow displaying granulocytic proliferation with monocytosis
- Type I: medullary blasts <10%
- Type II: medullary blasts <20%

Megakaryocytes: smaller forms predominate

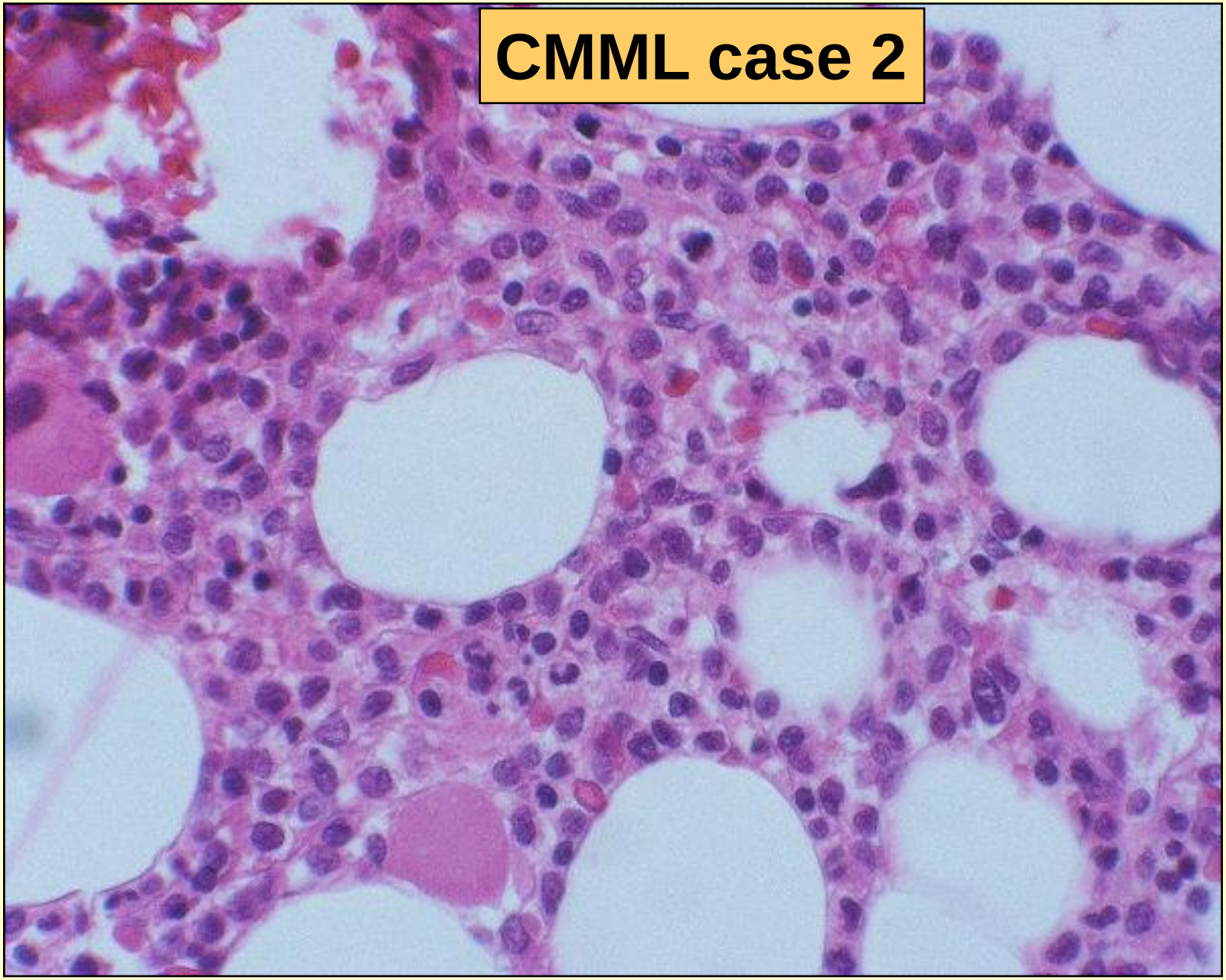
JAK2 is positive in rare cases

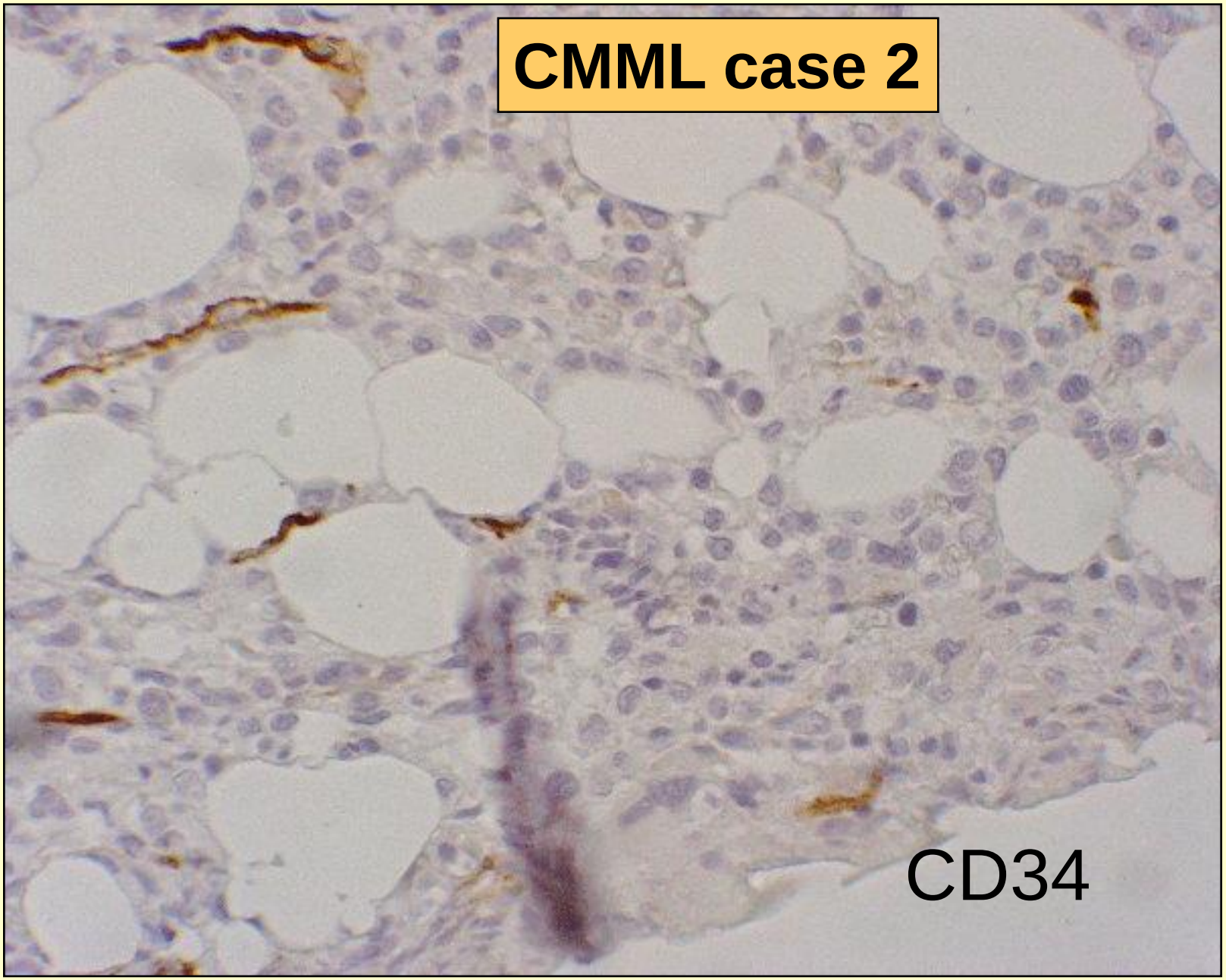

CMML case 1


CMML case 1


CMML case 2


CMML case 2


CMML case 2

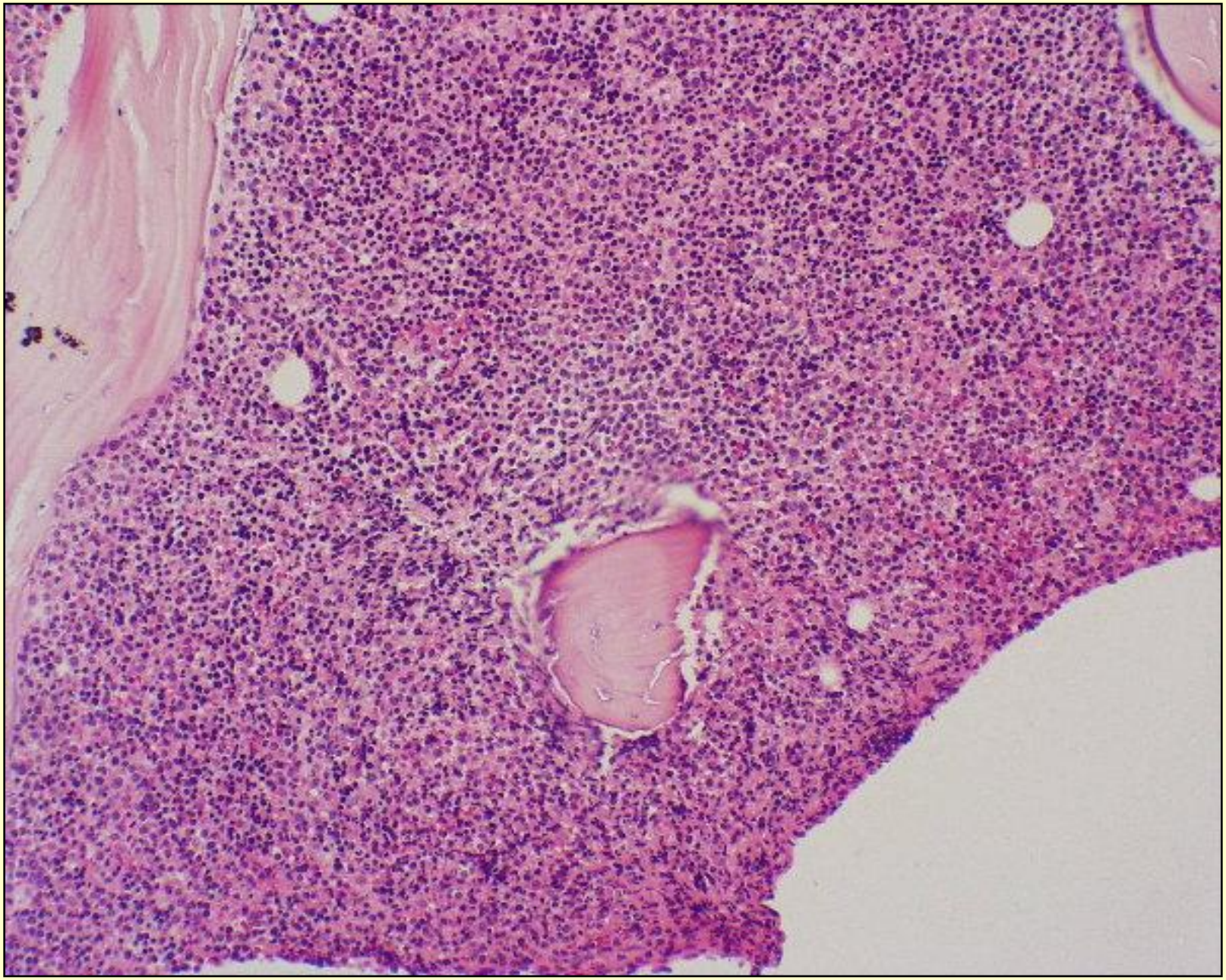

CMML case 2
CD34

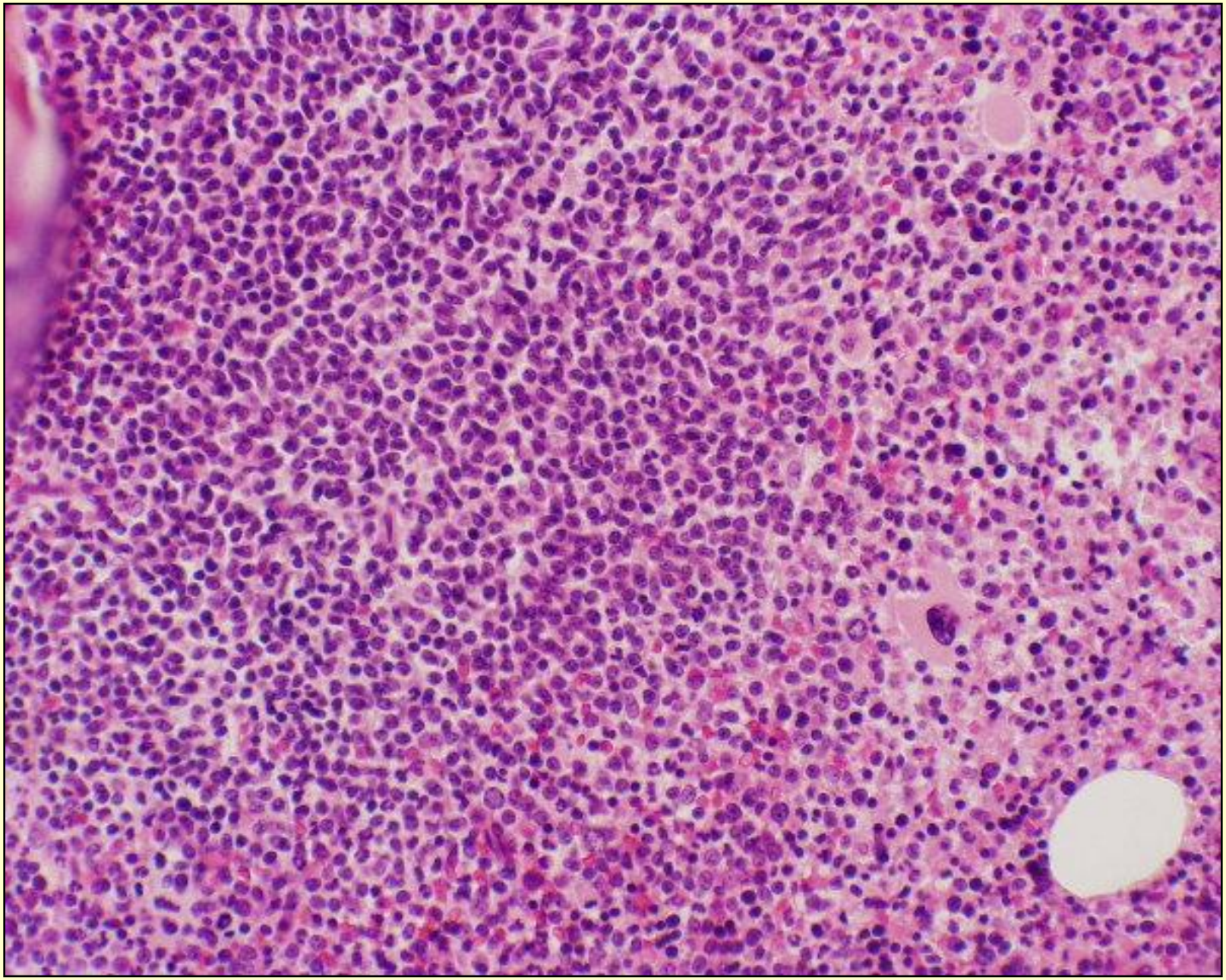
CMML CRITERIA

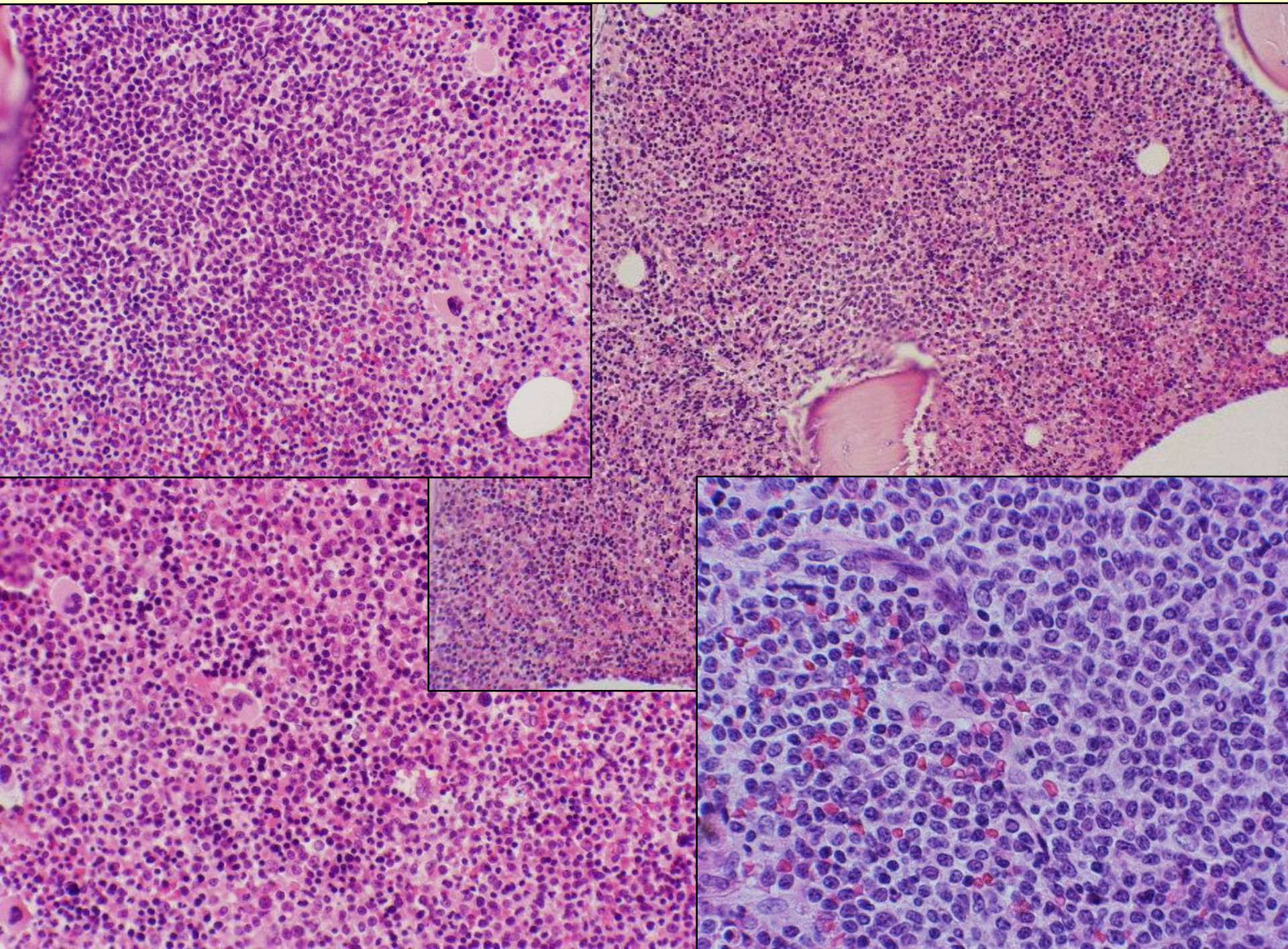
- Peripheral blood monocytosis >1x10^9/L
- No Ph chromosome or *BCR-ABL* fusion gene
- No rearrangement of *PDGFRA* or *PDGFRB* (should be specifically excluded if eosinophilia)
- Fewer than 20% blasts (including myeloblasts, monoblasts & promonocytes) in the blood and in the bone marrow
- Dysplasia in one or more myeloid lineages, or:
  - Acquired clonal cytogenetic or molecular genetic abnormality
  - Monocytosis persistent 3 months & all other causes of monocytosis excluded

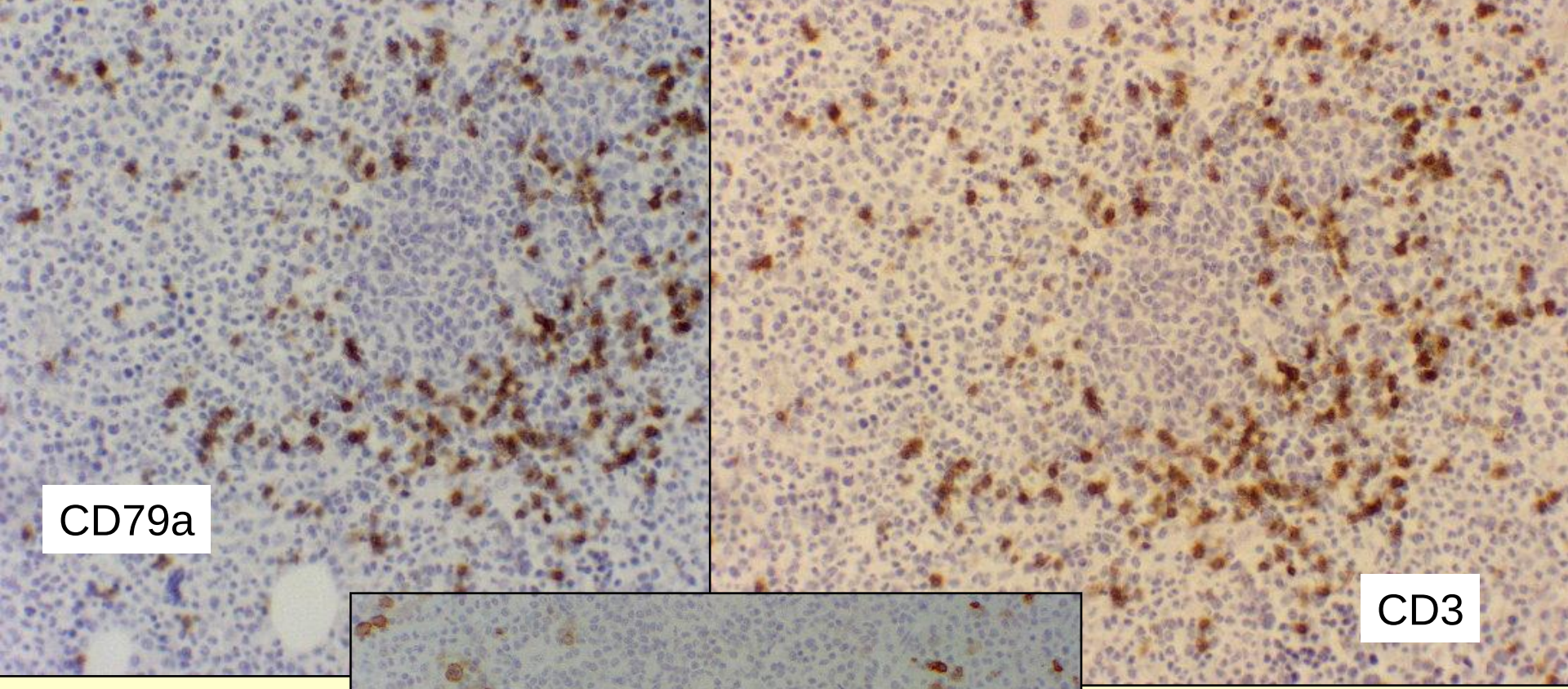
SLPC vs SMPC/SMD

- Mujer de 46 años con adenopatías, esplenomegalia, bicitopenia y ↑ LDH
- Hemograma:
  - Leucos 9,4 $x10^9$/L
  - Hb 114 g/L
  - Plaquetas 74 $x10^9$/L
- BMO:
  - Hipercelular
  - Serie blanca aumentada
  - Grupos centromedulares de células pequeñas de núcleo redondeado o arriñonado





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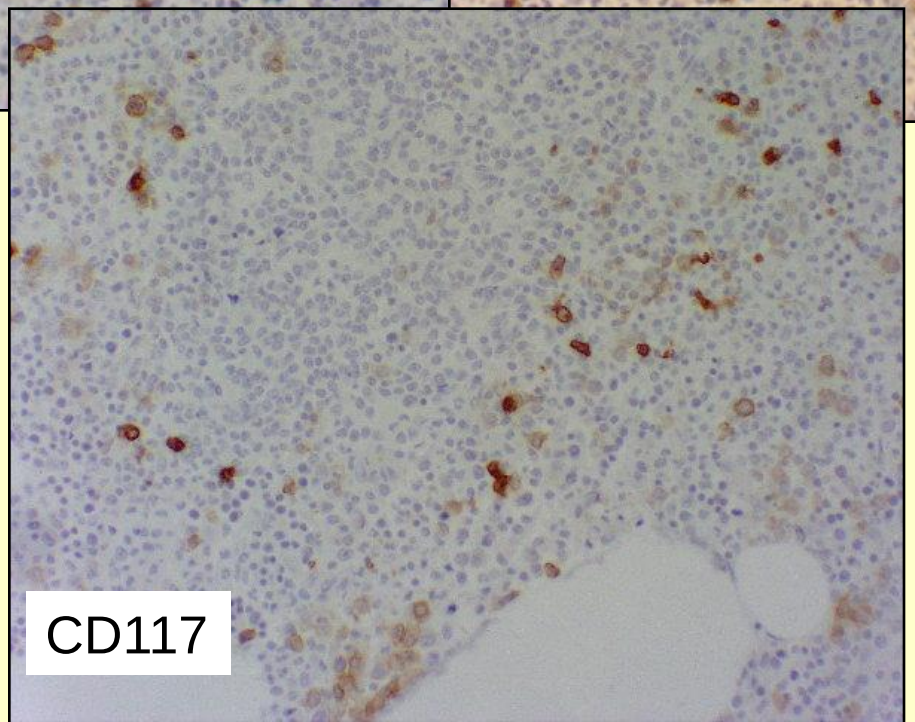
CD3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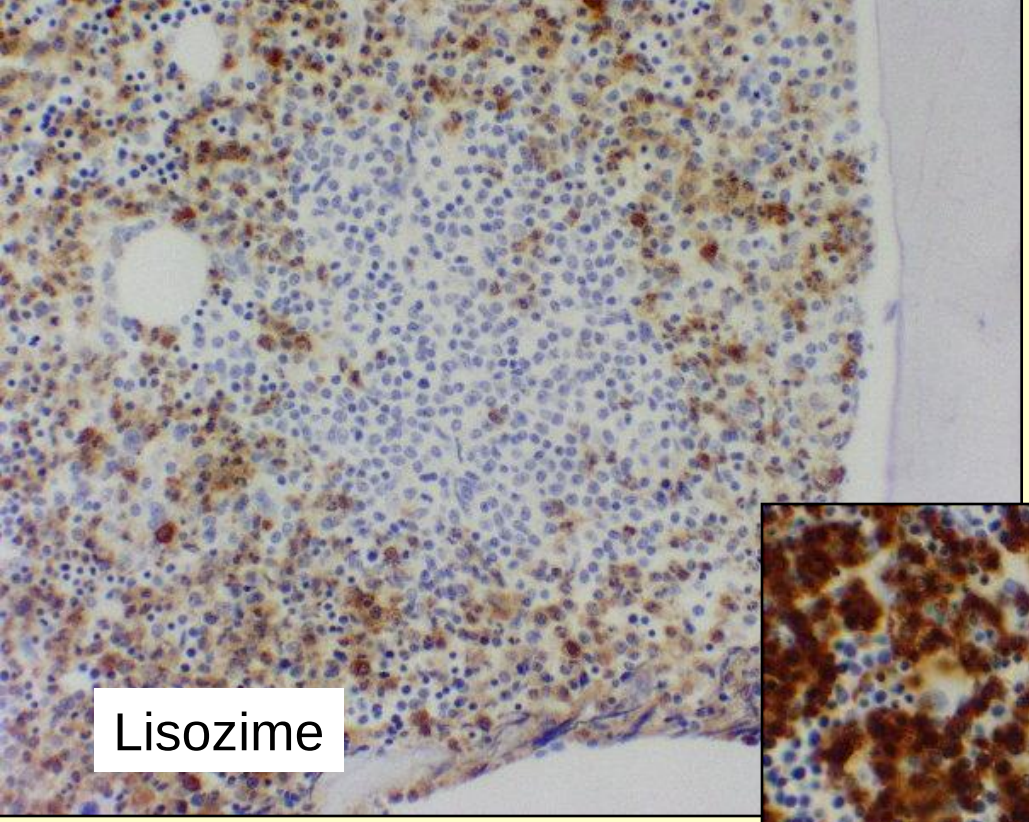
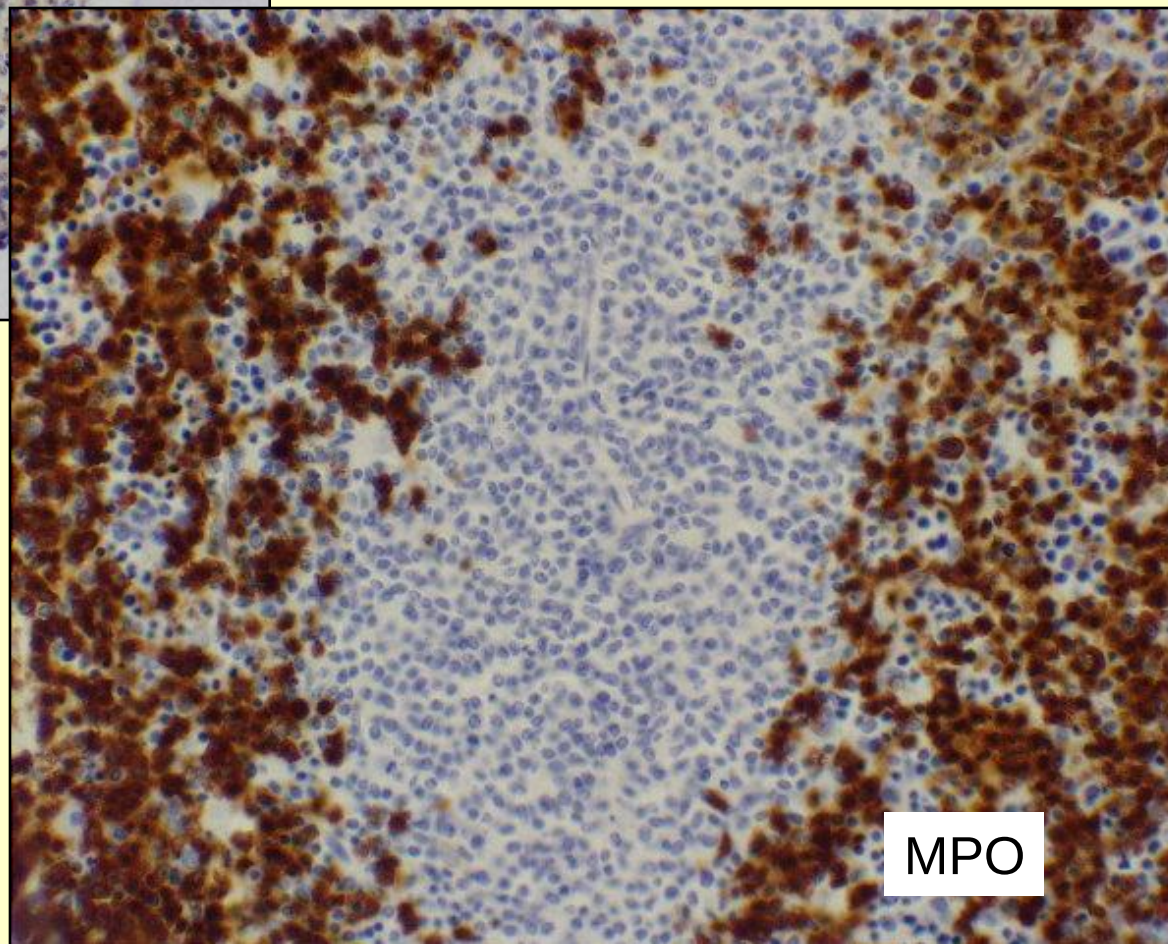
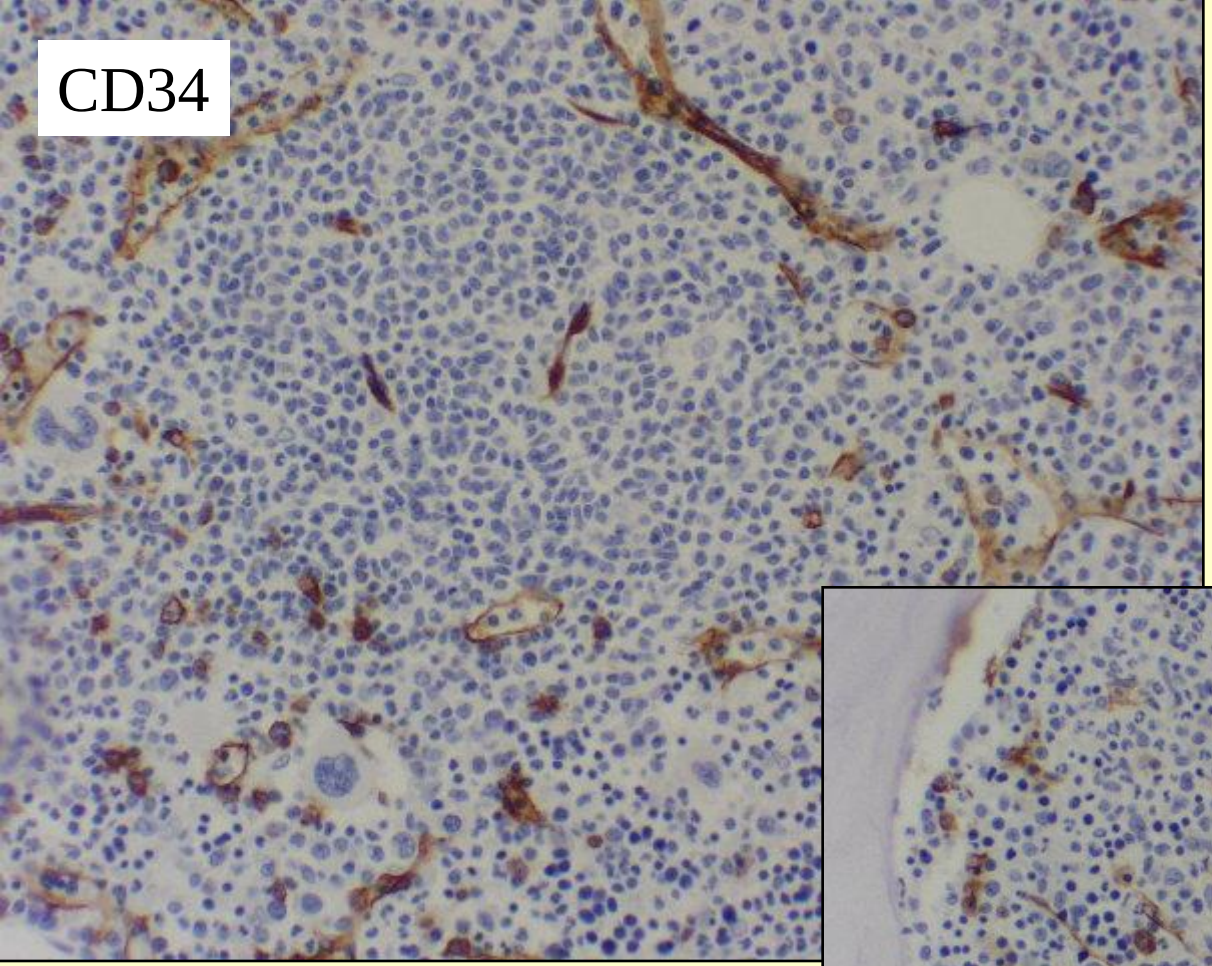

Lisozime


MPO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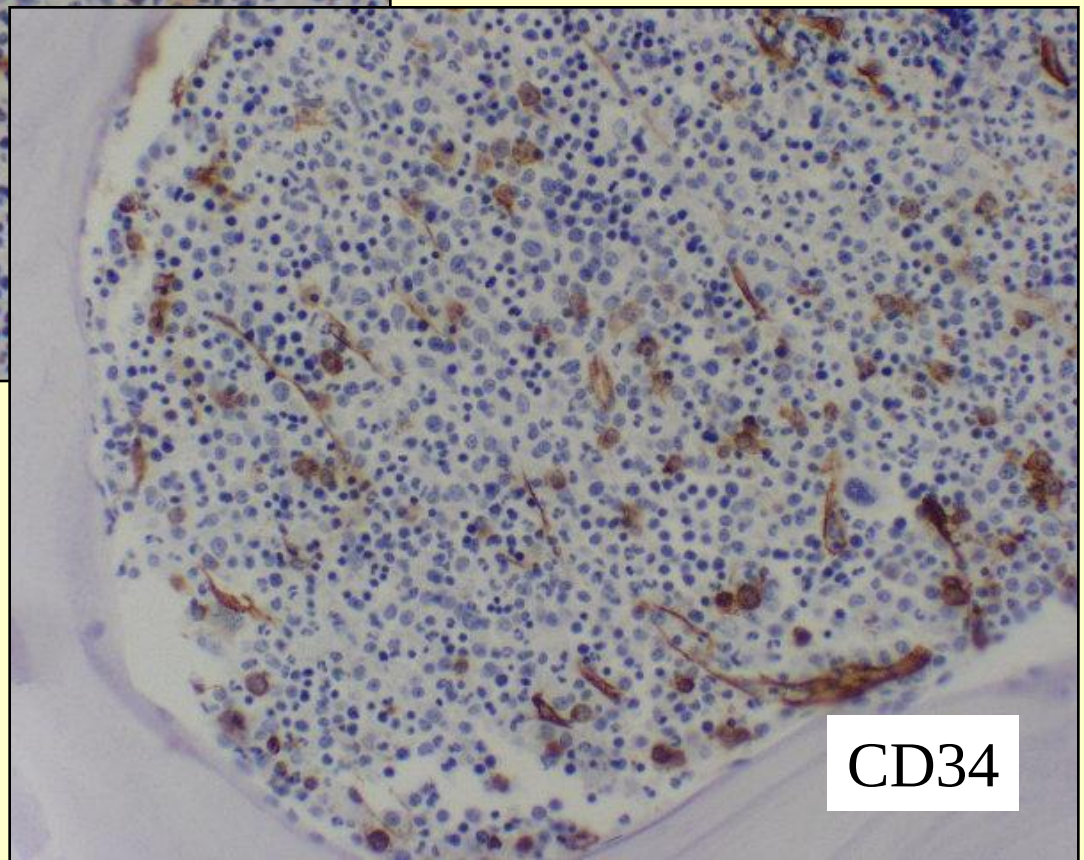
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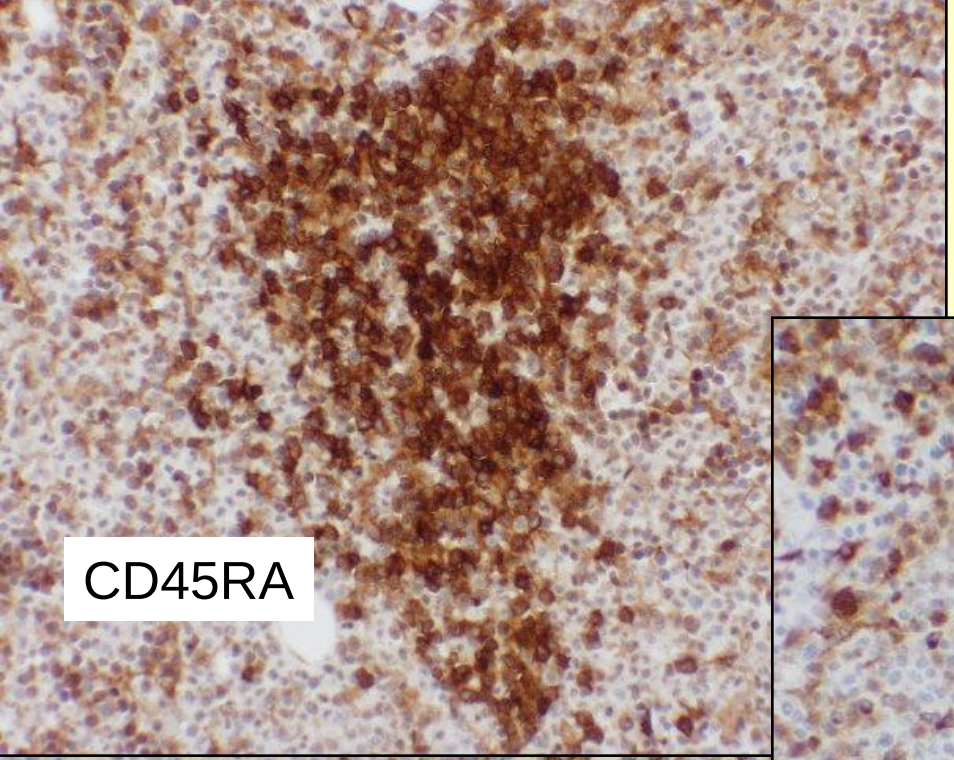
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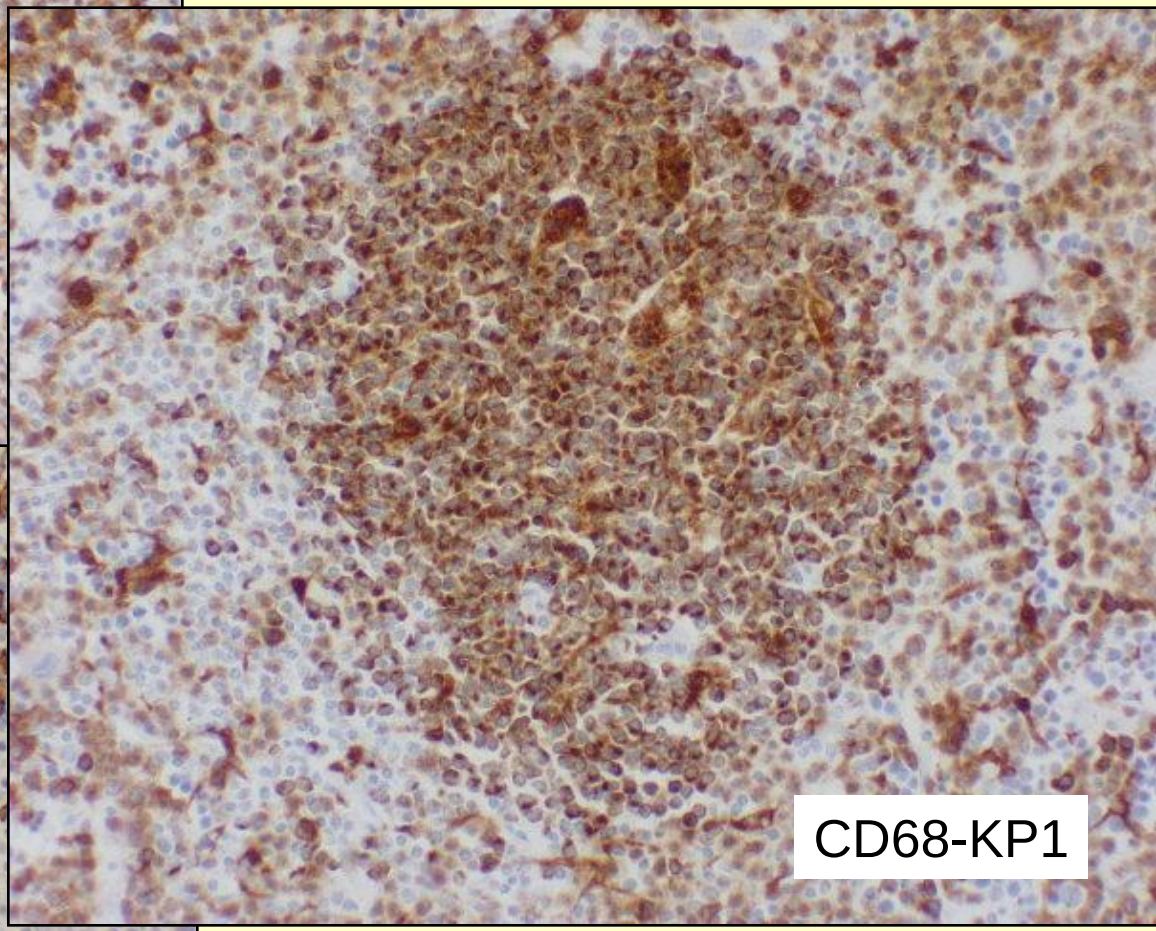
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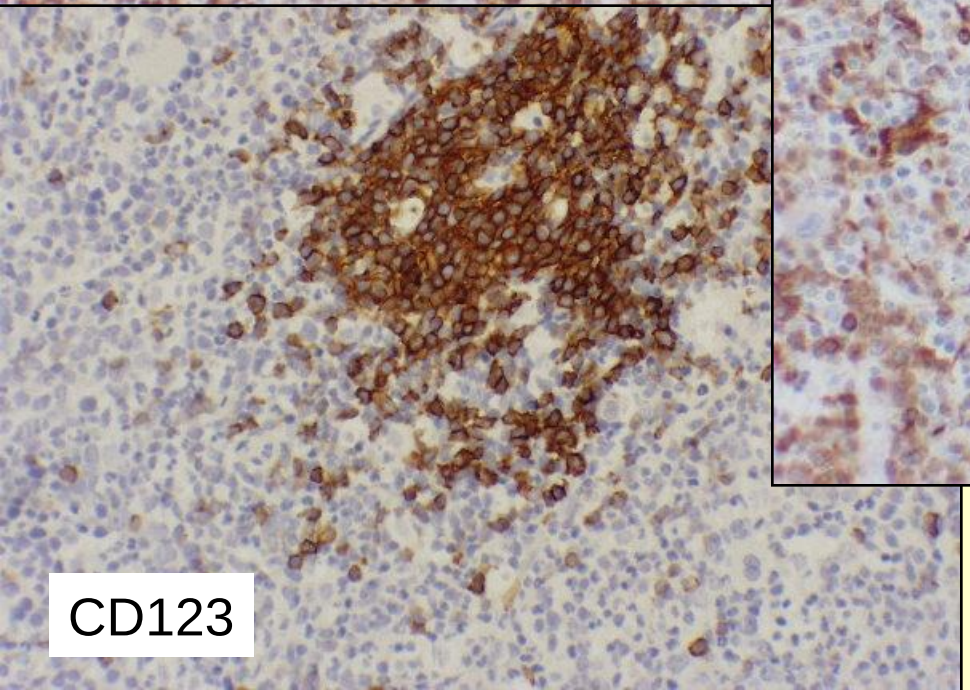
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SLPC vs SMPC/SMD

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- BMO:
  - Hipercelular
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Nodal and Extranodal Tumor-forming Accumulation of Plasmacytoid Monocytes/Interferon-producing Cells Associated With Myeloid Disorders

William Vermi, MD, Fabio Facchetti, MD, PhD,* Stefano Rosati, MD,† Federica Vergoni, MD,* Elisa Rossi, MD,* Silvana Festa,* Daniele Remotti, MD,‡ Piergiovanni Grigolato, MD,* Giovannino Massarelli, MD,§ and Glauco Frizzera, MD‖*

Am J Surg Pathol • Volume 28, Number 5, May 2004

Histologic and Immunohistochemical Study of Bone Marrow Monocytic Nodules in 21 Cases With Myelodysplasia

Yeu-Chin Chen, MD,[1] Jung-Mao Chou, MD,[2*] Rhett P. Ketterling, MD,[3] Louis Letendre, MD,[4] and Chin-Yang Li, MD[5]*

Am J Clin Pathol 2003;120:874-881
DOI: 10.1309/UNM9TY9QJQNFFYTH

Am J Surg Pathol • Volume 28, Number 5, May 2004

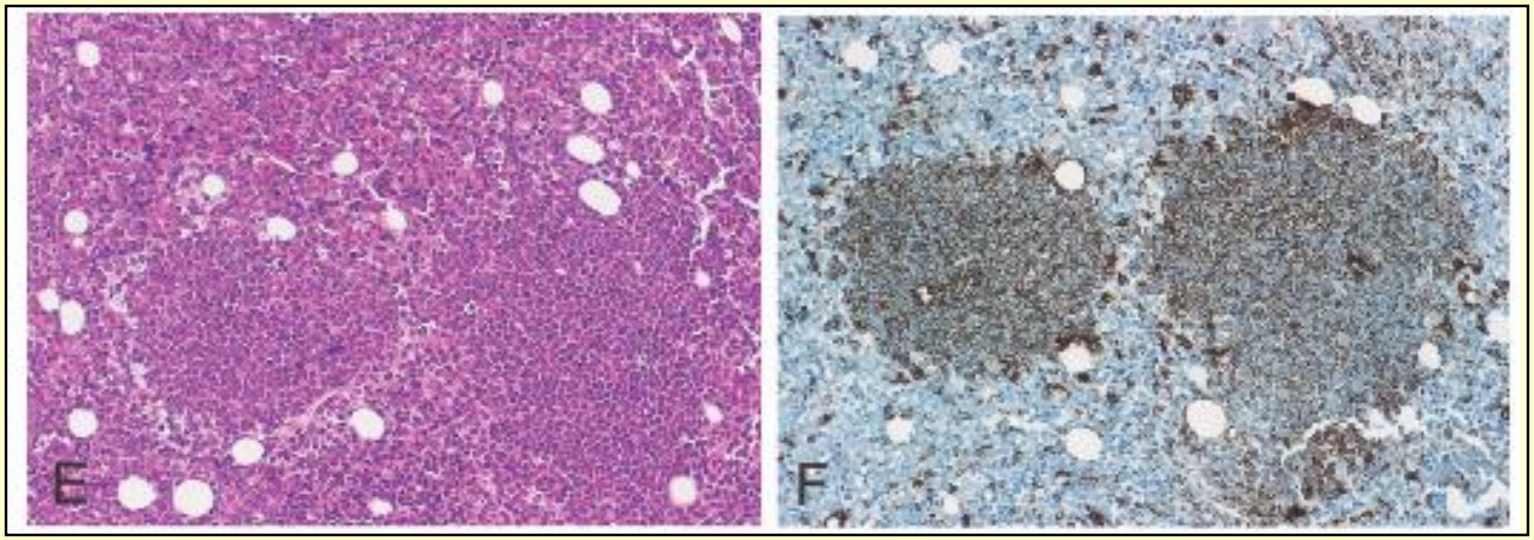


TABLE 1. Clinical Features of Reported Cases

Case No.	Age (yr)/Sex	Peripheral Blood Abnormalities	Associated Myeloid Neoplasm	L	S	H	Skin Eruption	Survival (mo)	Site of PM/IPC Accumulation		
									LN	BM	SK
1	24/M	Monocytosis	CMML*	+	+	+	+	8 (DOD)	+N +D‡	−	+N
2	50/M	Leukocytosis Anemia	AMML	+	+	+	+	11 (AWD)	+N‡	+‡	+‡
3	58/M	Leukocytosis Monocytosis	CMML	+	+	−	+	84 (DOD)	+N‡	+‡	+‡
4	65/M	Leukocytosis Anemia	CMML*	+	+	−	+	2 (AWD)	ND	+‡	+N
5	86/M	Lymphocytosis Thrombocytopenia Anemia	AmoL	+	−	−	−	3 (DOD)	ND	+‡	ND
6	63/F	Leukocytosis Thrombocytopenia	U-CMP*	+	+	−	−	15 (DOD)	+N‡	+‡	ND
7	80/M	Thrombocytosis Leukopenia with monocytosis	U-MDS/MP*	+	+	+	+	43 (DOD)	+D	+‡	−‡
8	62/F	Pancytopenia	AmoL†	+	−	−	−	15 (DOD)	+N‡	+‡	ND
9	52/M	Leukocytosis Monocytosis	CMML	+	+	−	−	13 (AWD)	+N‡	+‡	ND

CMML, chronic myelomonocytic leukemia; AMML, acute myelomonocytic leukemia (M4, according to French-American-British classification); AmoL, acute monocytic leukemia (M5, according to FAB); U-CMD, unclassifiable chronic myeloproliferative disorder; U-MDS/MP, unclassifiable myeloproliferative/myelodysplastic disorder; L, lymphoadenopathy; S, splenomegaly; H, hepatomegaly; DOD, dead of disease; AWD, alive with disease; LN, lymph nodes (N, nodular; D, diffuse accumulation of PM/IPC); BM, bone marrow; SK, skin; ND, biopsy not done.

*Case with evolution toward acute myelomonocytic leukemia (M4).

†This patient in her terminal phase developed acute leukemia with a defective "lymphoid" phenotype, with persisting monocytic component.

‡Presence of infiltration by myeloid leukemic cells.

MDS/MPN: aCML

A. Orazi & U. Germing, Leukemia (2008) 22, 1308-1319

- Leucocitosis neutrofílica sin monocitosis ni basofilia
- BMO
  - hipercelular
  - ↑ serie blanca
- Displasia
  - granulocítica intensa
  - megacariocítica

Atypical CML

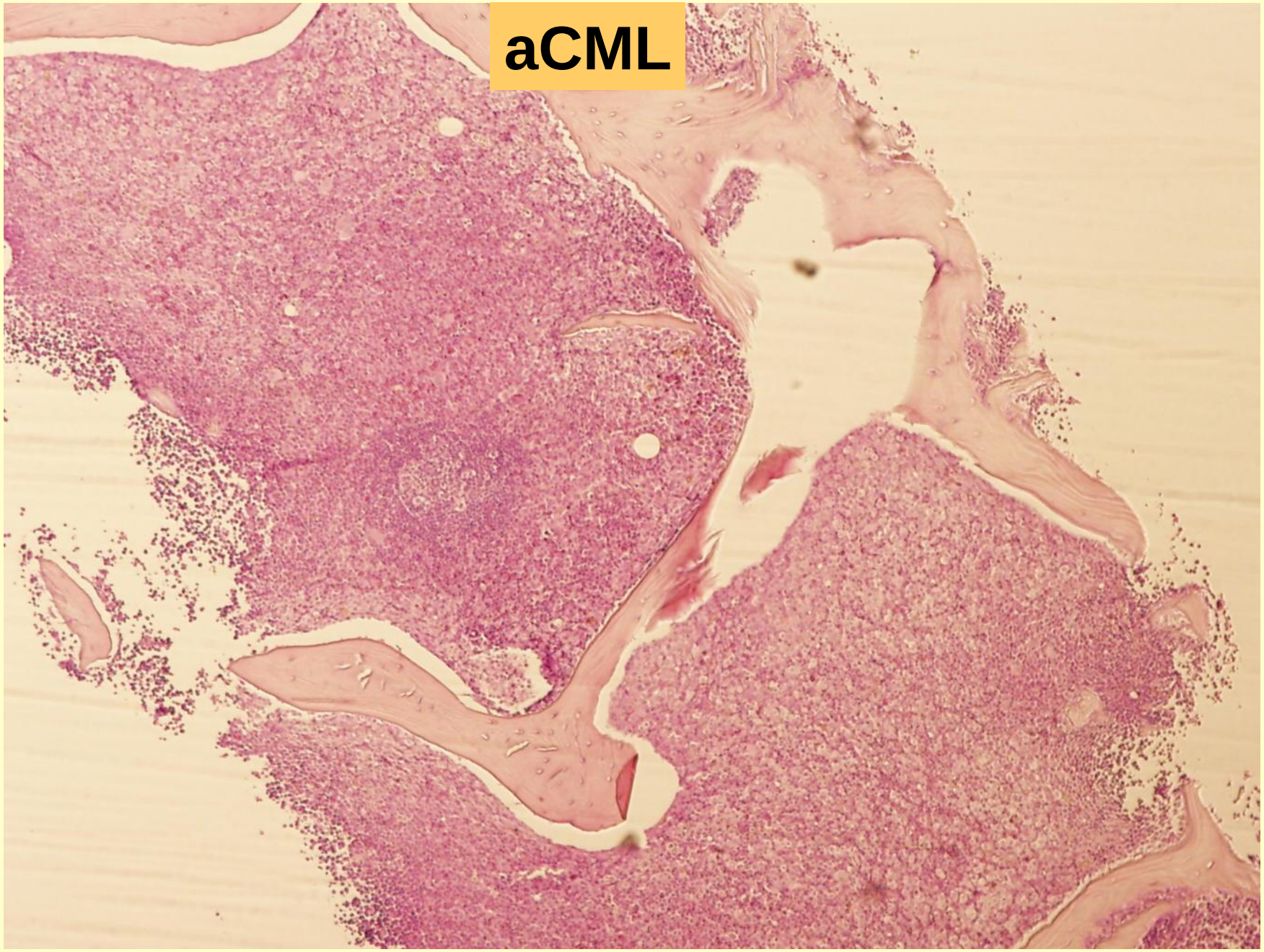
Its incidence is <2 cases for 100 cases of t(9;22), BCR/ABL pos.CML

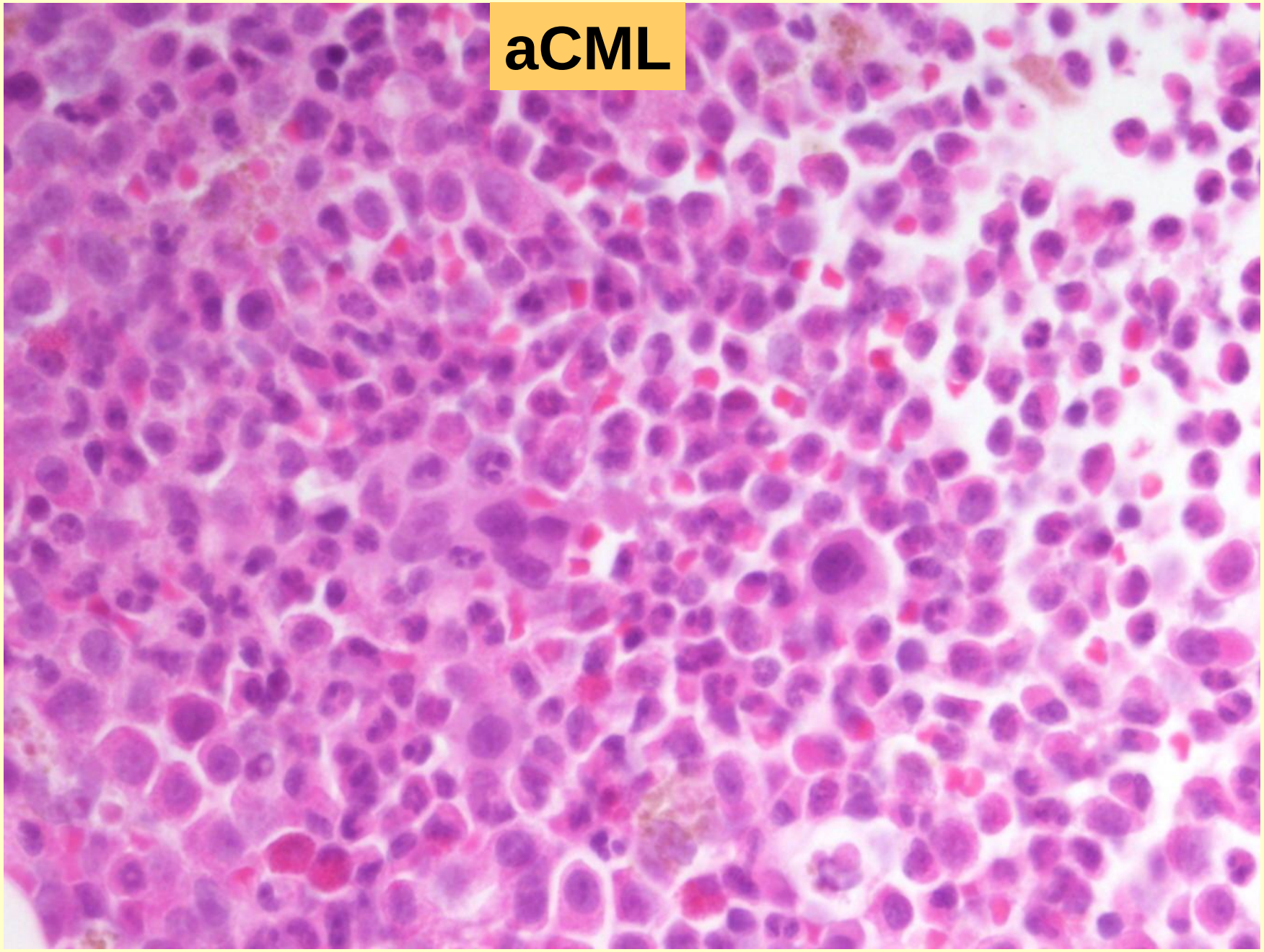
Leukocytosis, neutrophilia, but no basophilia or monocytosis (<10%). The hallmark is the presence of severe dysgranulopoiesis often with abnormal chromatin clumping

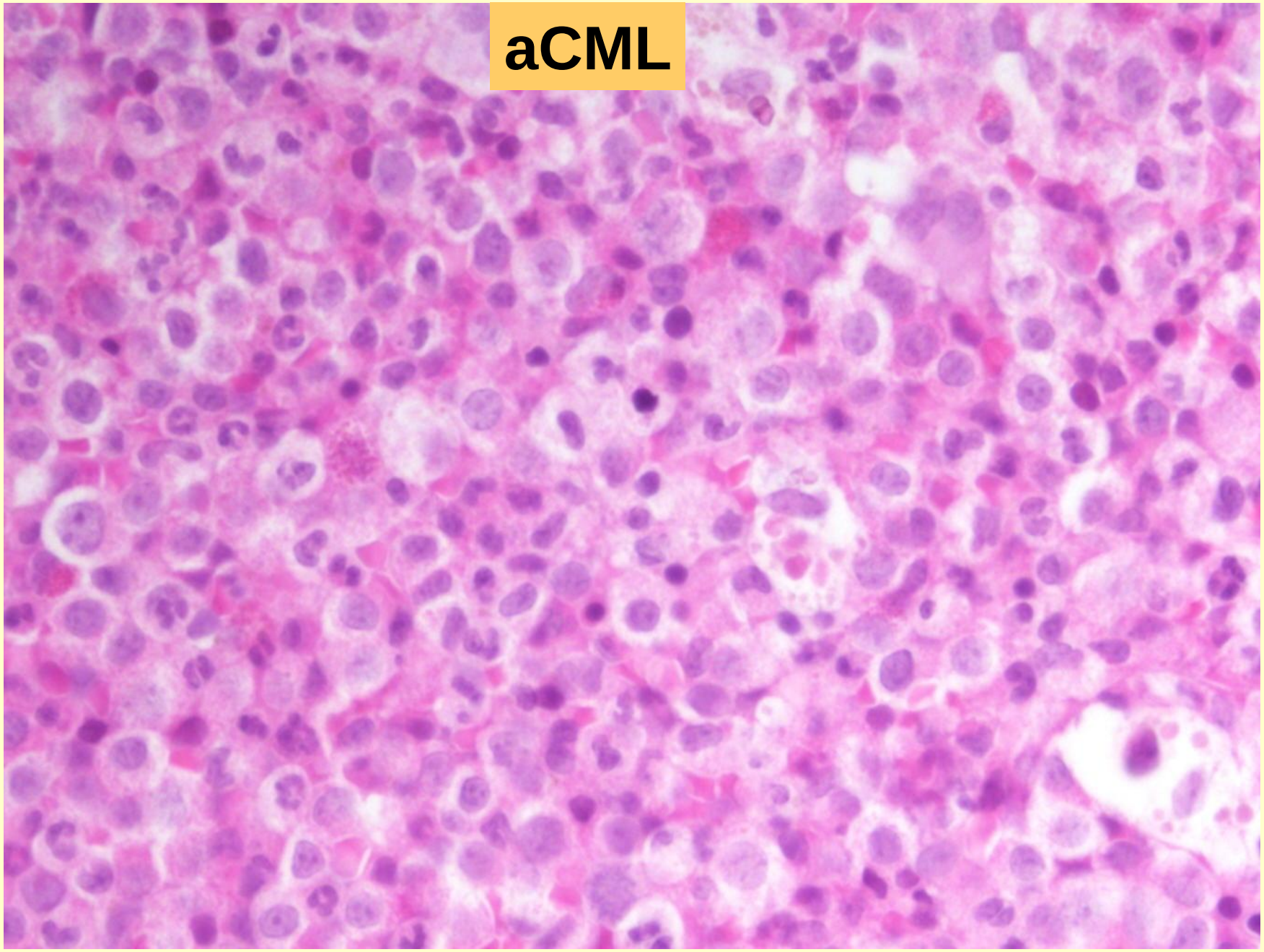
The bone marrow morphological findings are similar to CML. Lacks monocytic differentiation by esterase cytochemistry

Megakaryocytes: smaller forms predominate

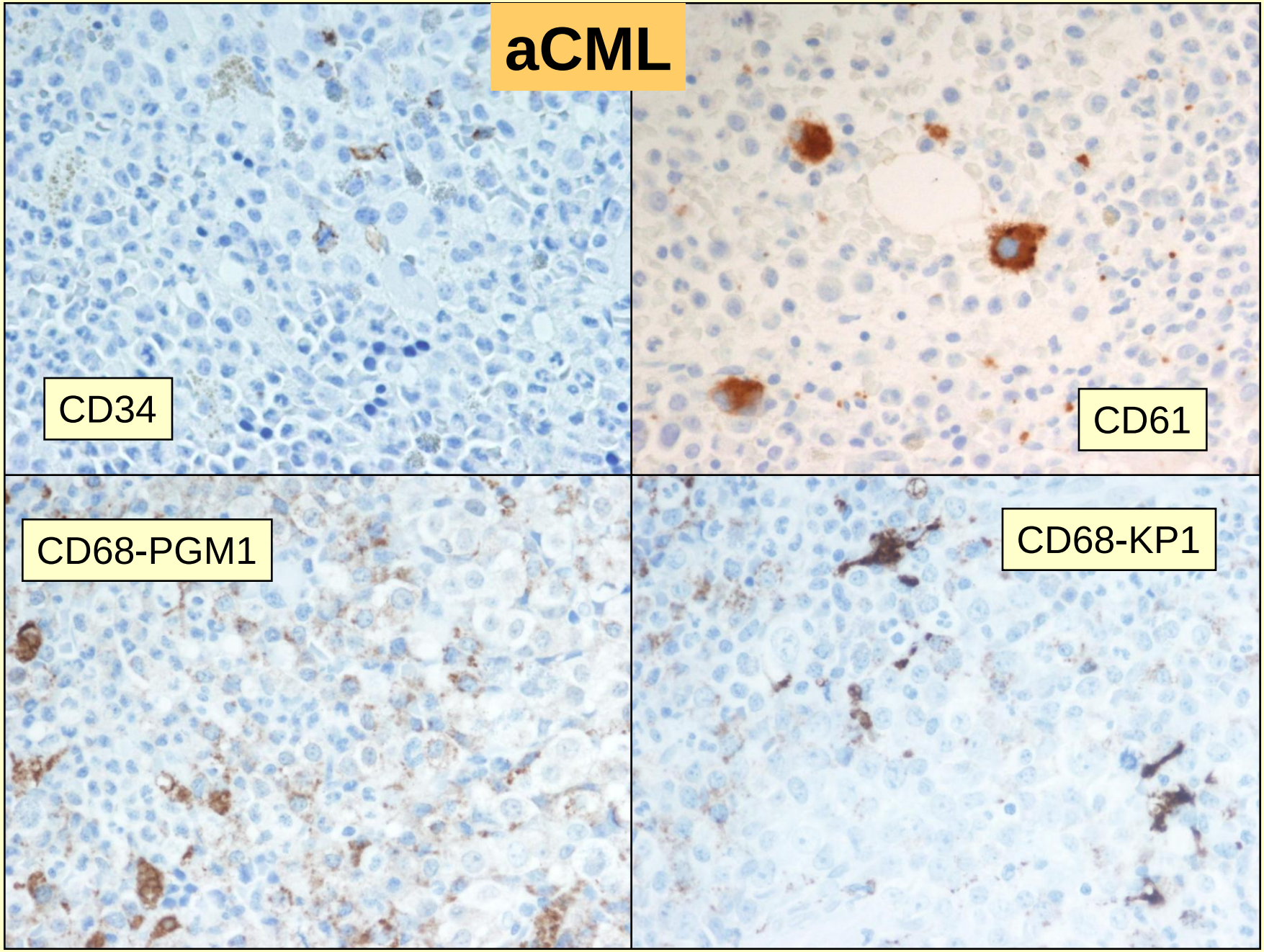
JAK2 is negative


aCML


aCML

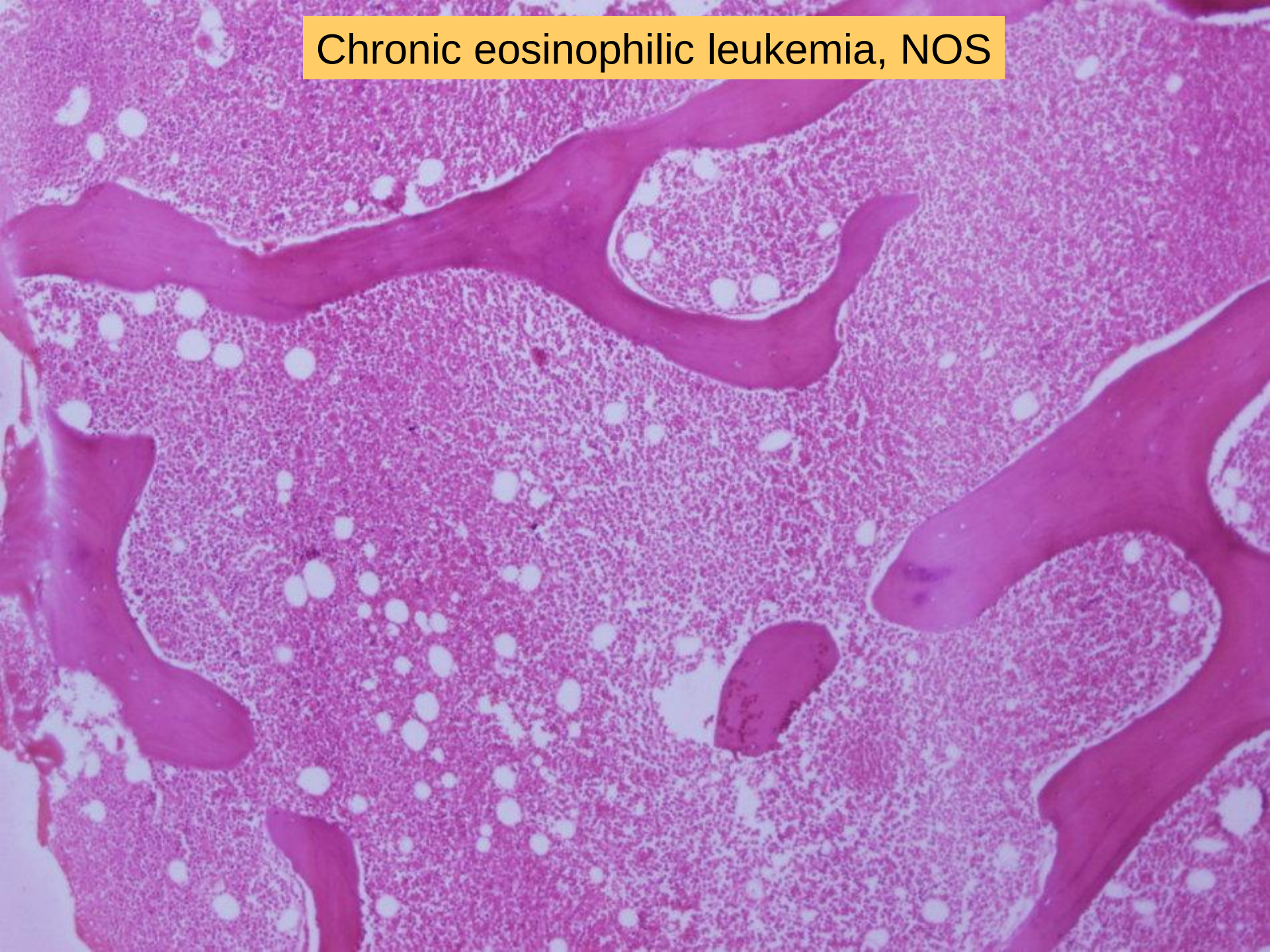

aCML

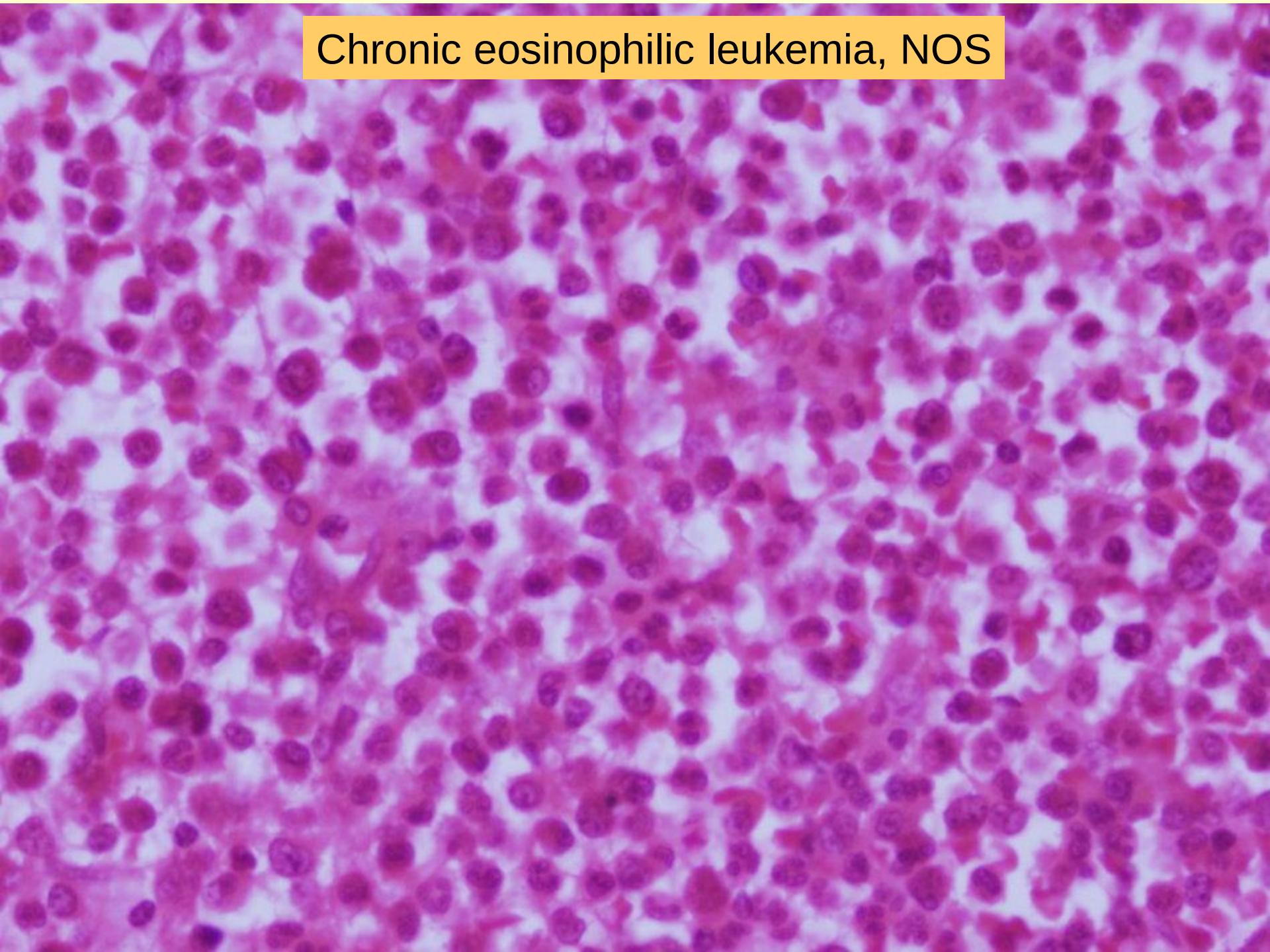
aCML



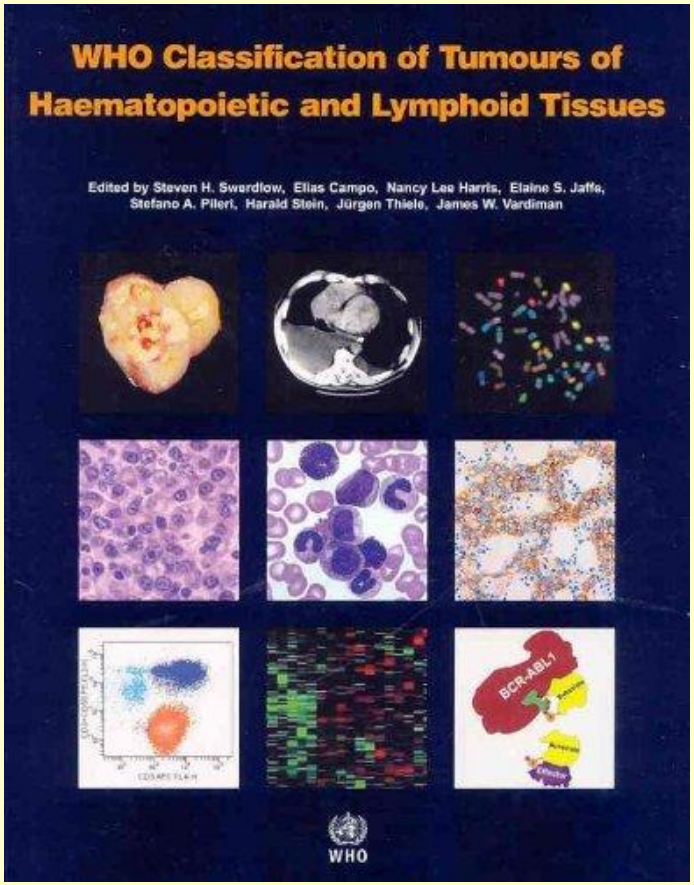
CML BM: Differential Diagnosis

- MDS/MPN
  - Chronic myelomonocytic leukemia (CMML)
  - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
- Other unusual CMPNs
  - Chronic neutrophilic leukemia (CNL)
  - Chronic eosinophilic leukemia (CEL), NOS


Chronic eosinophilic leukemia, NOS

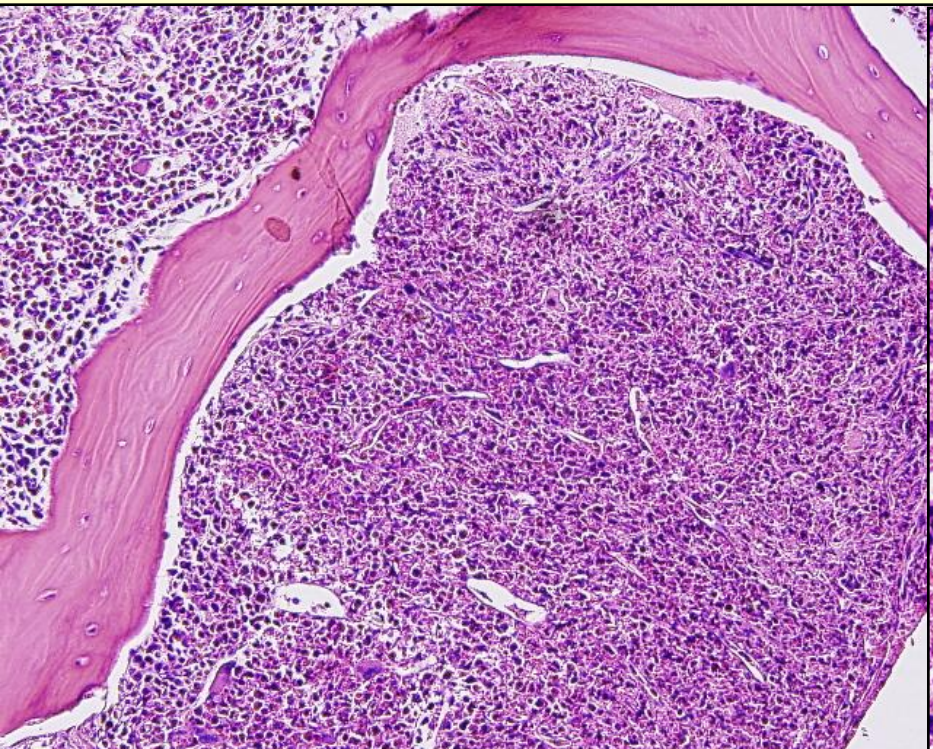

Chronic eosinophilic leukemia, NOS

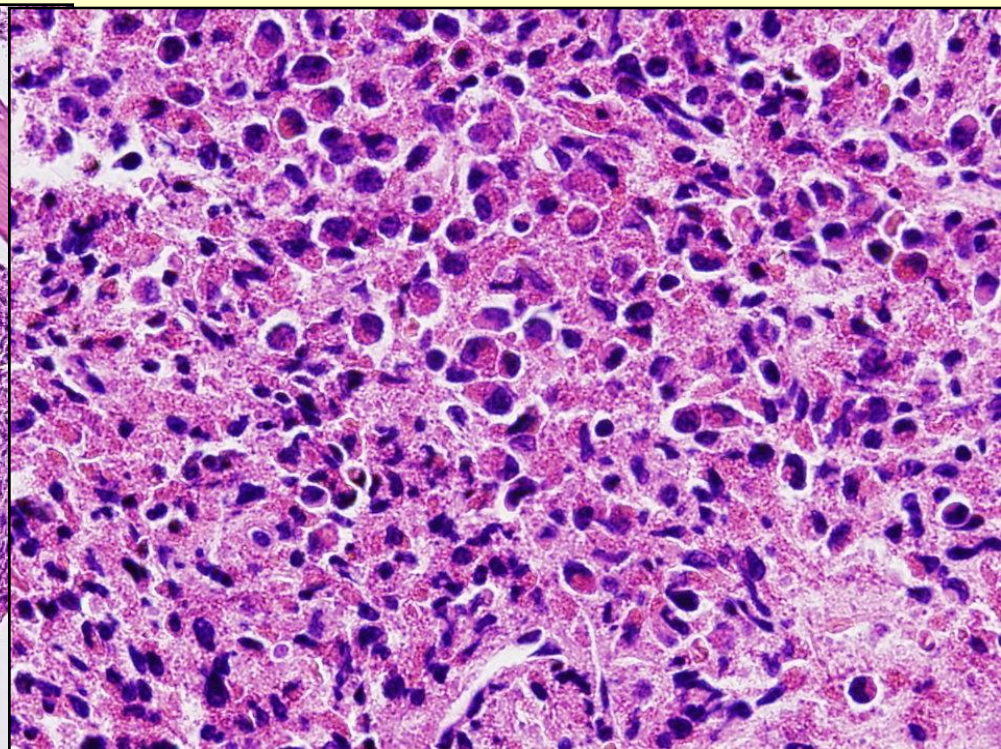
2008 WHO CLASSIFICATION OF CHRONIC MYELOPROLIFERATIVE NEOPLASMS



SMPC con eosinofilia y genes de fusión *PDGFRA* o *PDGFRB*

- eosinofilia
- grado variable de monocitosis
- hallazgos pueden ser sugestivos de LMC atípica o de LMMC
- biopsia medular: fibrosis y agregados de mastocitos



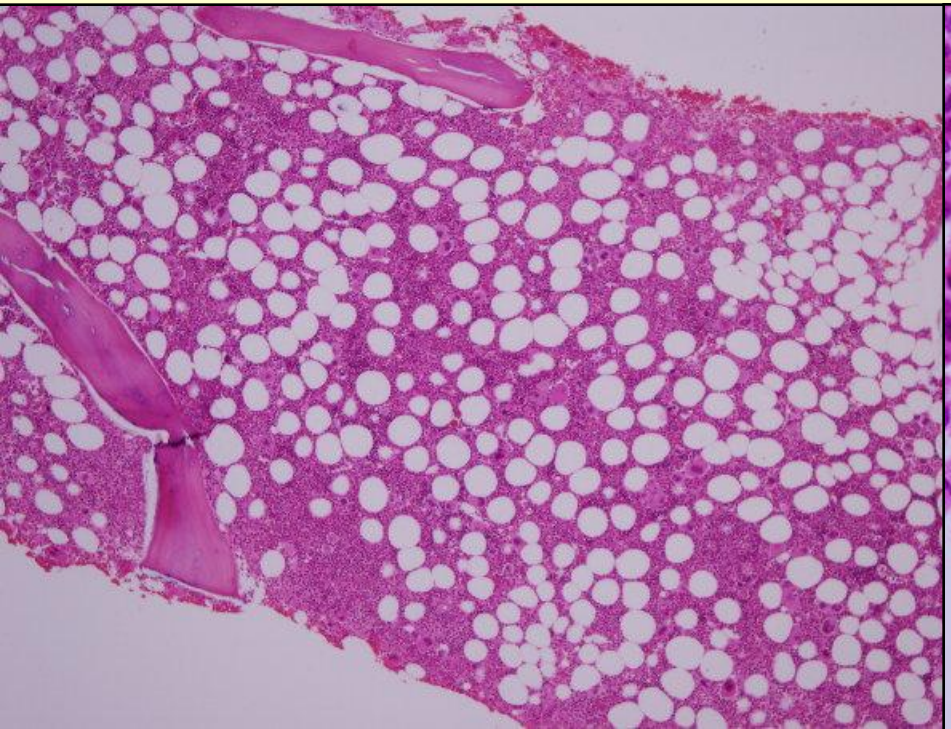


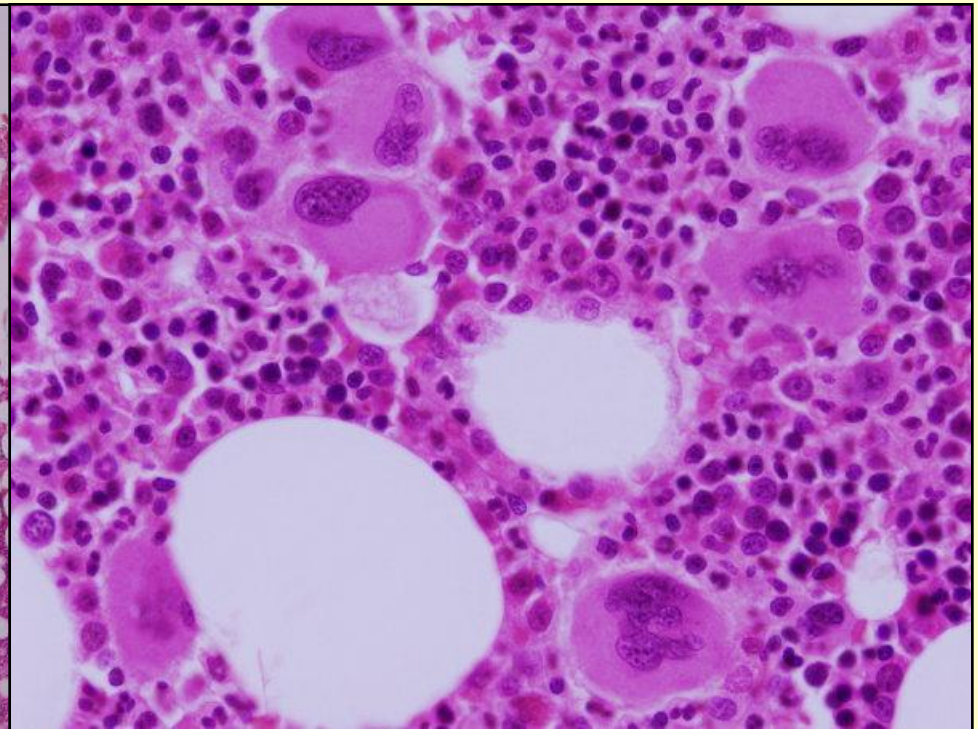
La biopsia medular en las neoplasias mieloproliferativas/mielodisplásicas

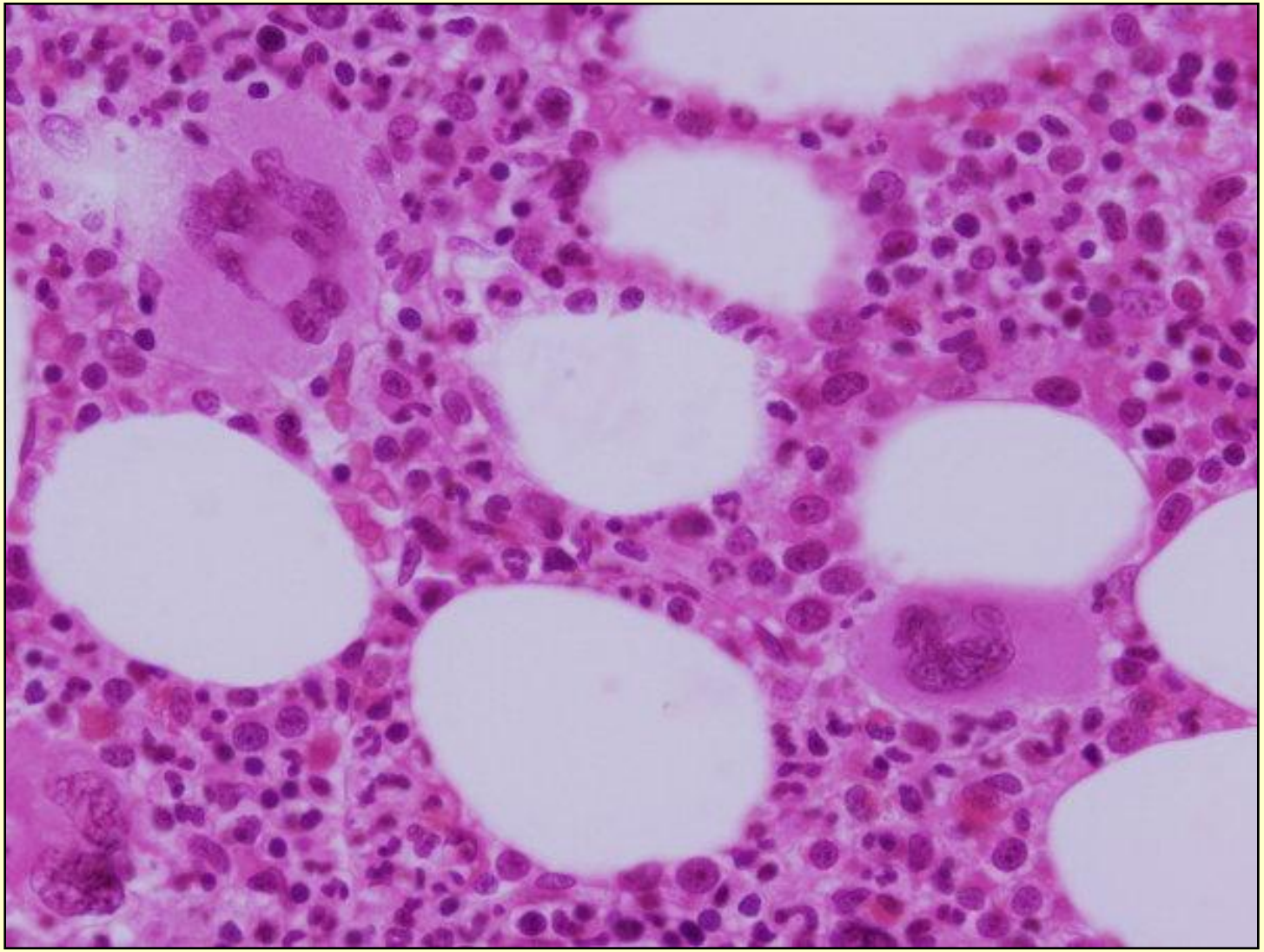
- Concepto y clasificación
- Síndromes mielodisplásicos
- Neoplasias mieloides con proliferación predominante de la serie blanca
- Neoplasias mieloides con proliferación predominante de la serie megacariocítica
- Formas raras de neoplasias mieloproliferativas/ mielodisplásicas
- Neoplasias mieloides con fibrosis medular
- Consideraciones finales

Essential thrombocythemia (ET): BM pathology

- Normocellular
- Marked proliferation of megakaryocytes:
  - Large to giant, form loose clusters
  - Abundant mature cytoplasm, deeply lobulated and hyperlobulated nuclei with smooth nuclear contours
- Occasional mild erythroid proliferation (bleeding)
- No reticulin fibrosis



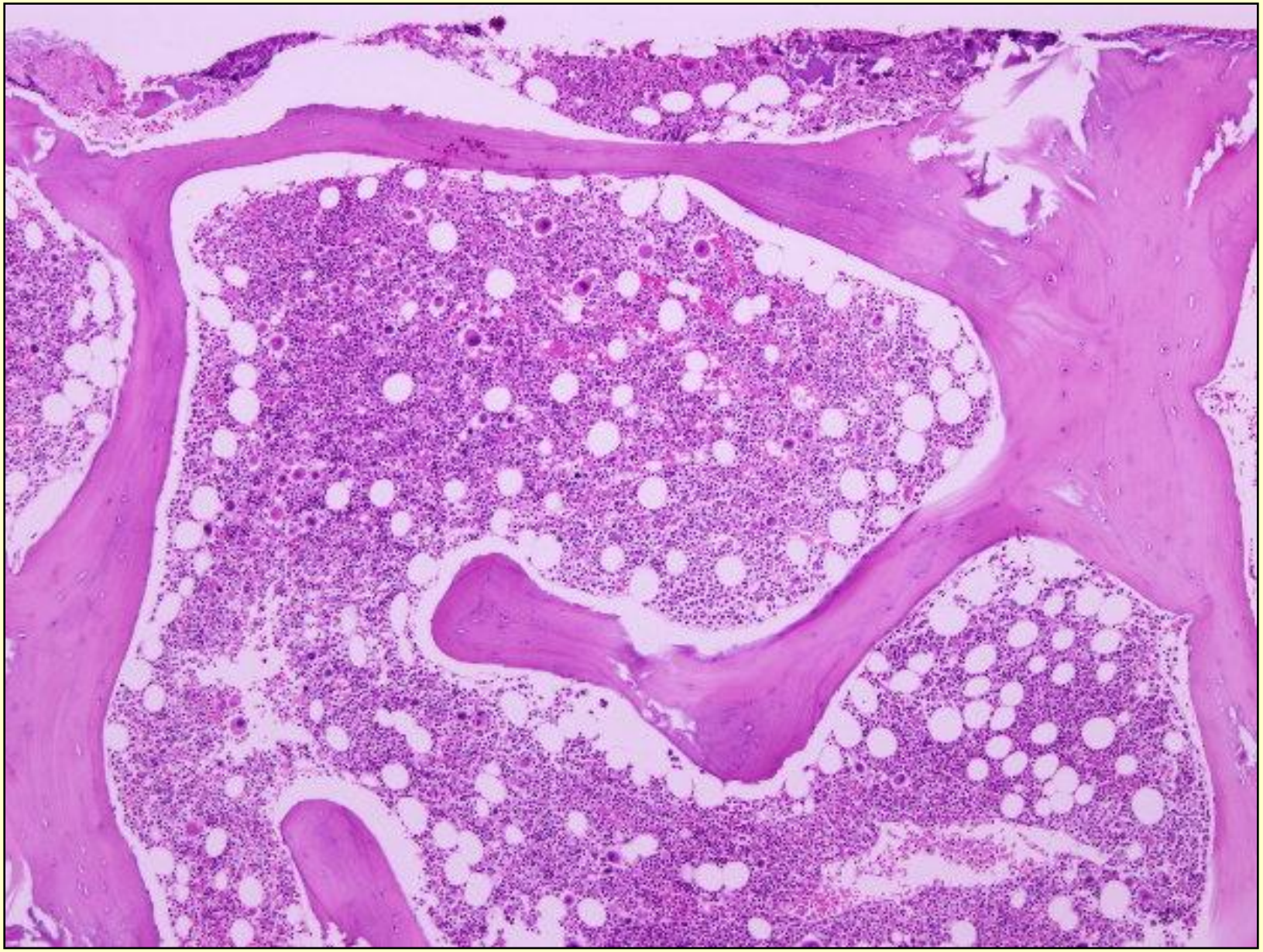




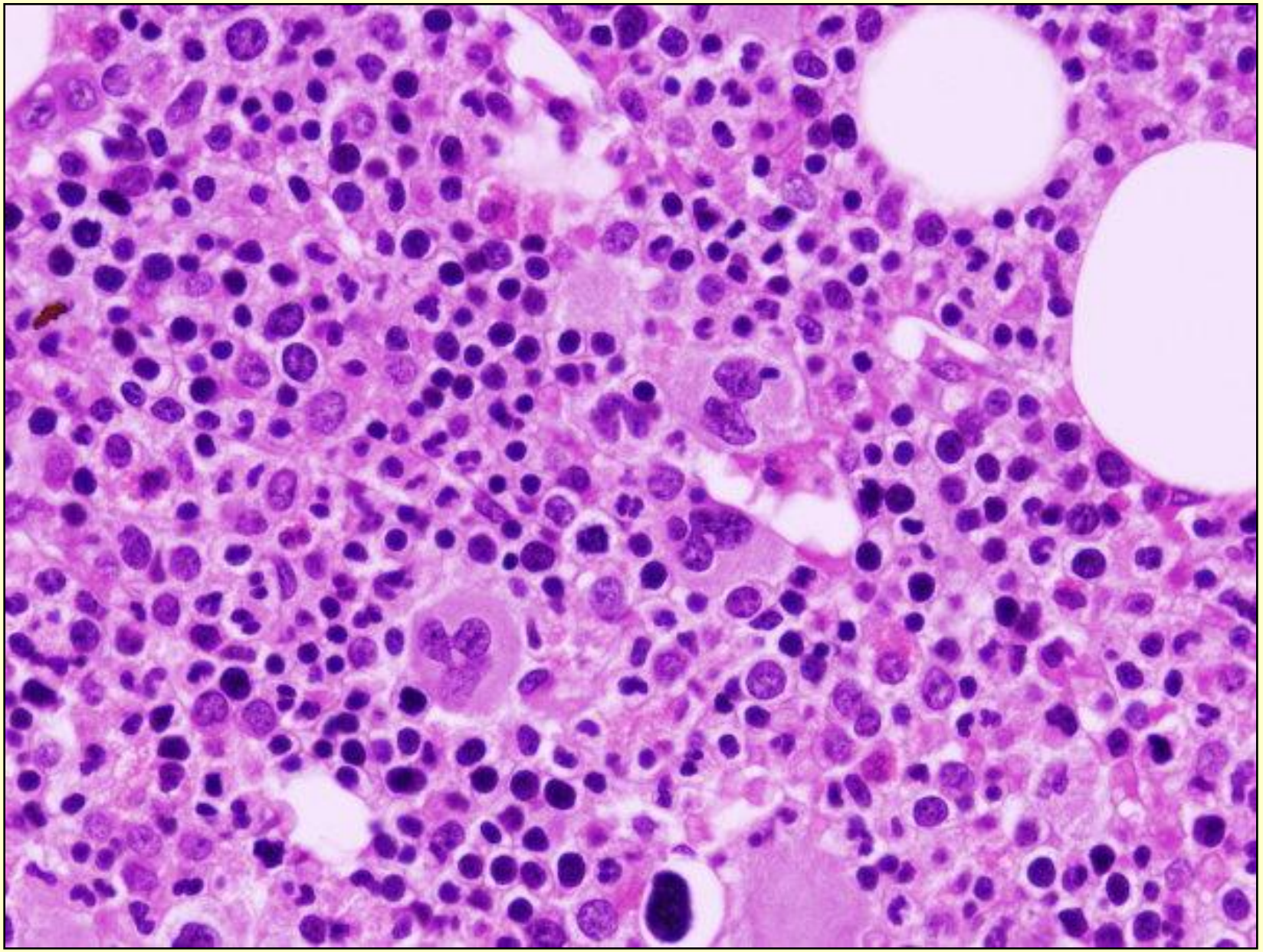
Polycythaemia Vera (PV): BM pathology (I)

- Polycythaemic stage:
  - Hypercellular for age (median ≈80%)
  - Panmyelosis with more prominent increase of erythroid and megakaryocytic precursors
  - Normoblastic erythropoiesis
  - Conspicuous megakaryocytes
    - Cluster arround sinusoids or trabeculae
    - Deeply lobulated nuclei, lack dysplastic features
  - 30% cases variable degree reticulin fibrosis
  - Reactive nodular lymphoid agregates in 20%

PV



PV



Polycythaemia Vera (PV): BM pathology (II)

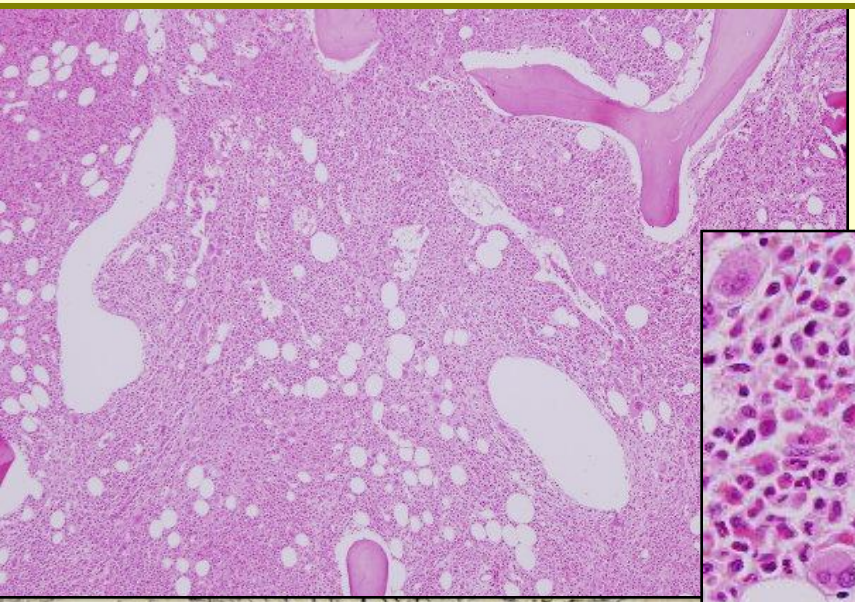
– “Spent phase” & post-polycythaemic myelofibrosis
  - Reticulin & even collagen fibrosis
  - Commonly hypocellular
  - Clusters of megakaryocytes with hyperchromatic nuclei
  - Decreased erythropoiesis & granulopoiesis

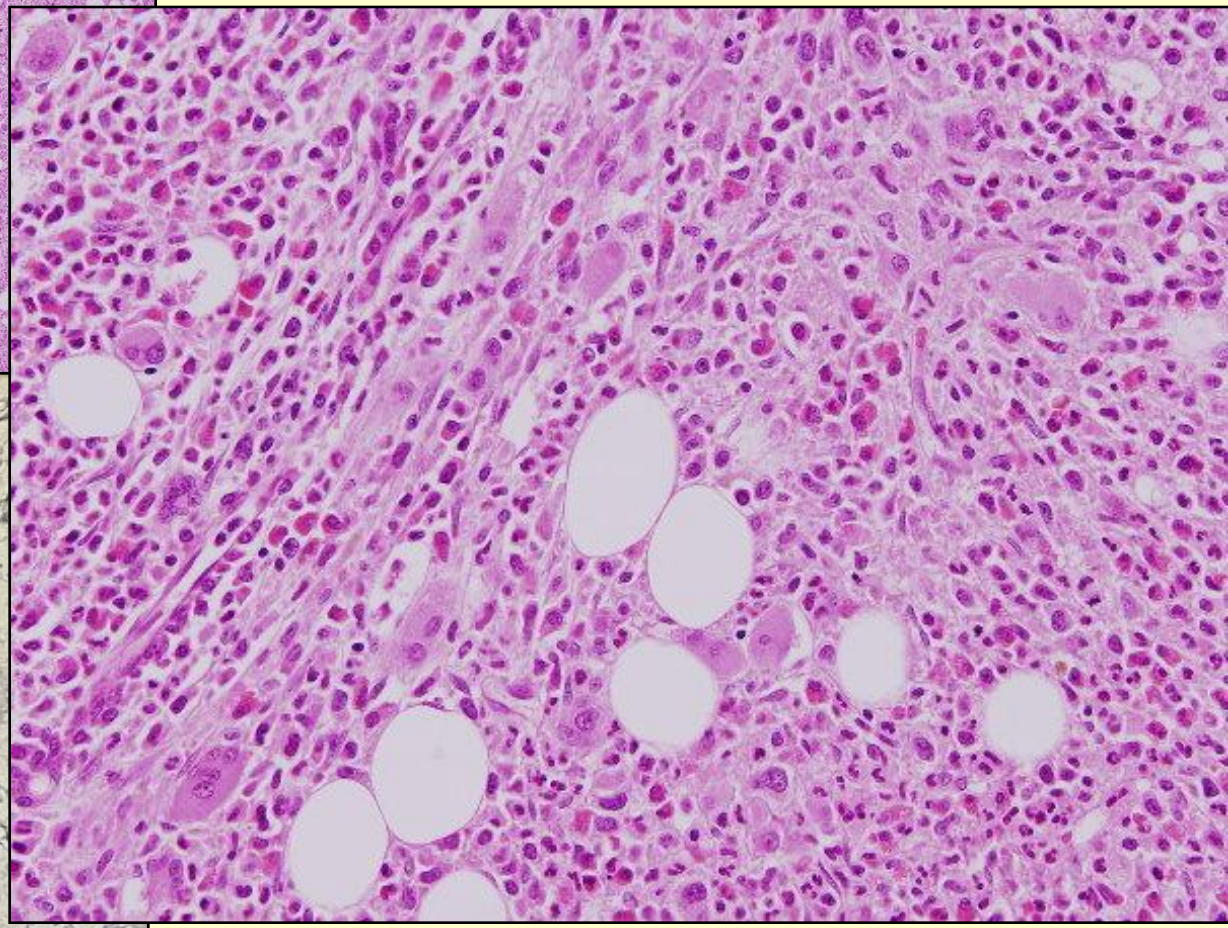
Often undistinguishable from PMF

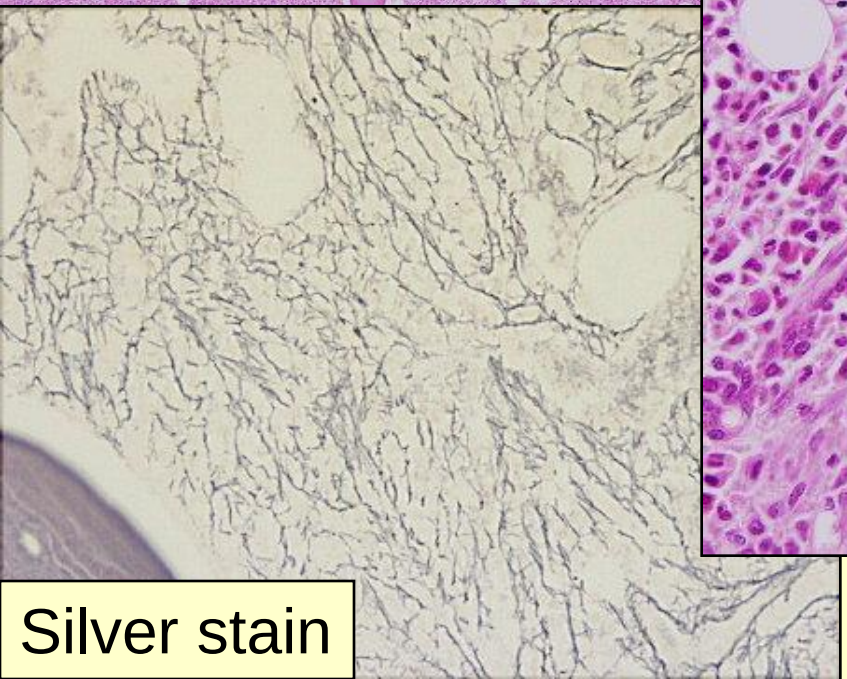
Primary myelofibrosis (PMF): BM pathology (I)

- Early stage PMF:
  - Hypercellular
  - Increased granulopoiesis with predominant mature forms
  - Key for diagnosis: megakaryocytic proliferation & atypia
    - clusters adjacent to sinuses & trabeculae
    - large and small ones (megakaryocytic markers useful)
    - abnormal nuclear-cytoplasmic ratios
    - abnormal chromatin clumping with hyperchromatic nuclei, pump, “cloud-like” or “balloon–shaped” lobulation of nuclei
  - Minimal reticulin fibrosis
  - Vascular proliferation
  - Lymphoid nodules in 20-30%

PMF, early stage







Silver stain

Molecular pathogenesis of Ph-negative CMPDs

- Somatic Janus kinase 2 (*JAK2*) mutation at exon 14 (*JAK2*V617F)
  - Polycythemia vera (PV) 95%
  - Essential thrombocythemia (ET) 50%
  - Primary myelofibrosis (PMF) 50%
- *JAK2* mutations at exon 12
  - Polycythemia vera (PV) 5%
- *MPL* mutations (*MPLW515L/K*)
  - ET, PMF <5%

La biopsia medular en las neoplasias mieloproliferativas/mielodisplásicas

- Concepto y clasificación
- Síndromes mielodisplásicos
- Neoplasias mieloides con proliferación predominante de la serie blanca
- Neoplasias mieloides con proliferación predominante de la serie megacariocítica
- Formas raras de neoplasias mieloproliferativas/ mielodisplásicas: trombocitosis + megas displásicos
- Neoplasias mieloides con fibrosis medular
- Consideraciones finales

Myelodysplastic /myeloproliferative neoplasms (MDS/MPN)

- CLASSIFICATION
  - Chronic myelomonocytic leukemia (CMML)
  - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
  - Juvenile myelomonocytic leukemia (children 0-14 years)
  - MDS/MPN, unclassifiable
    - Exclude *BCR-ABL1* fusion gene, rearrangement *PDGFRA*, *PDGFRB*, *FGFR1*
    - Provisional entity: RARS with marked thrombocytosis
    - Exclude isolated del (5q), t(3;3)(q21;q26) or inv 3(q21q26)

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MDS/MPN: RARS-T

A. Orazi & U. Germing,
Leukemia (2008) 22, 1308-1319

- Hallazgos de RARS:
  - anemia macrocítica
  - sideroblastos en anillo>15%

+

- Hallazgos de TE:
  - trombocitosis
  - ↑ megas con morfol TE

- JAK2 + 70%

RARS-T

Rare disease (0.7% of all FAB defined myelodysplastic syndromes)

Anemia. Macrocytosis. Thrombocytosis ($>600 \times 10^9$ per liter)*

[*Note: The value will be lowered to $>450 \times 10^9$ per liter in the upcoming review of the WHO classification which is in press].

Hypercellular marrow with erythroid predominance, megaloblastoid changes
Iron stain show >15% ringed sideroblasts

Megakaryocytes are increased. Large hyper- (ET-like) as well as hypolobulated (PMF-like) forms may predominate in a given case

JAK2 is positive in 75% of cases

RARS-T

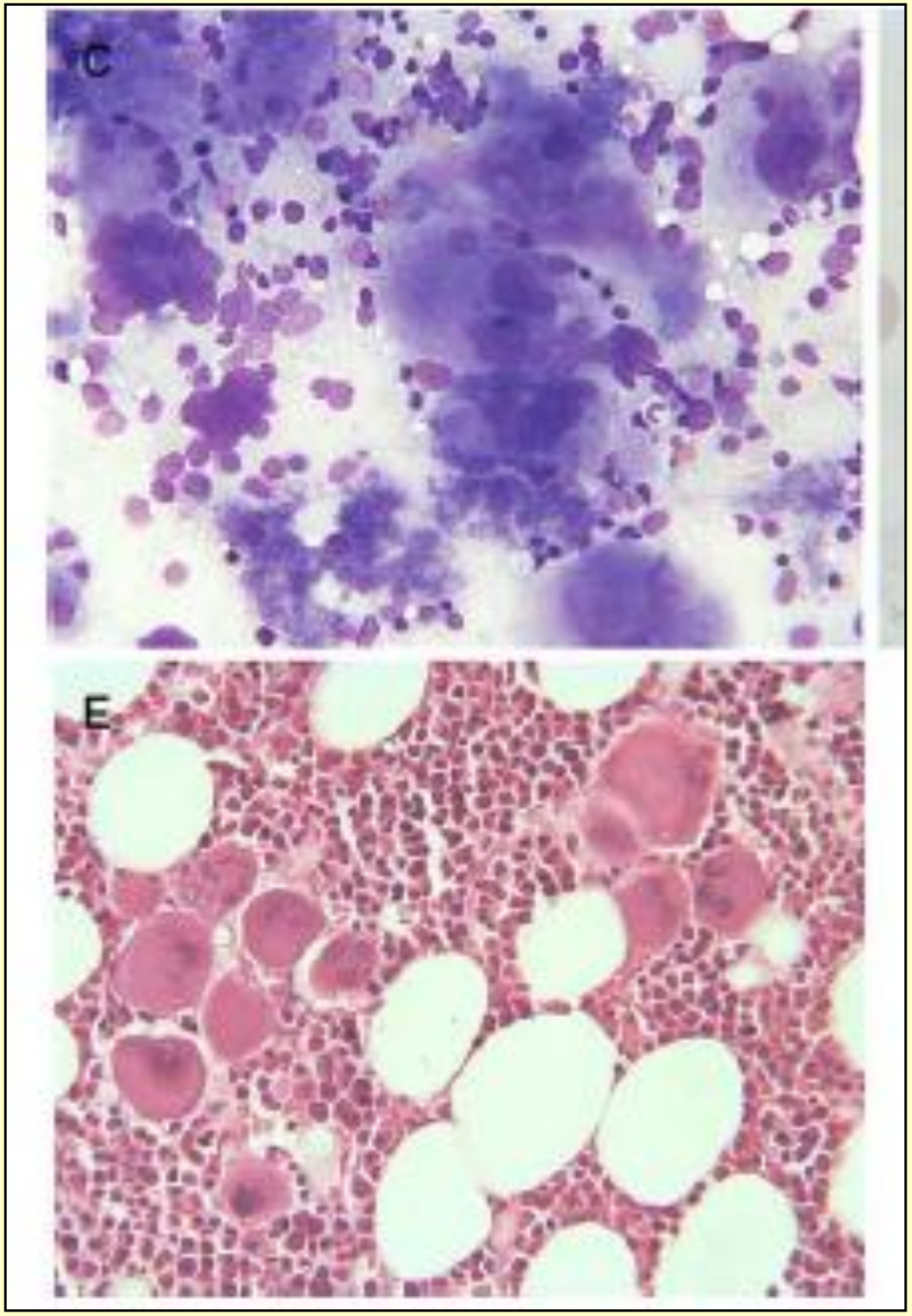
Int J Hematol (2008) 88:387–395
DOI 10.1007/s12185-008-0169-1

ORIGINAL ARTICLE

Refractory anemia with ringed sideroblasts associated with thrombocytosis: comparative analysis of marked with non-marked thrombocytosis, and relationship with JAK2 V617F mutational status

J. M. Raya · L. Arenillas · A. Domingo · B. Bellosillo · G. Gutiérrez · E. Luño · M. A. Piñán · M. Barbón · M. L. Pérez-Sirvent · M. J. Muruzábal · L. Yánez · L. García · A. Lemes · J. T. Navarro · A. Elosegi · M. A. Cortés · A. Villegas · M. A. Durán · M. Ardanaz · L. Florensa · On behalf of the Grupo Español de Citología Hematológica (GECH), Working Group into the Asociación Española de Hematología y Hemoterapia (AEHH)

RARS-T



Myelodysplastic /myeloproliferative neoplasms (MDS/MPN)

- CONCEPT
  - The MDS/MPN are clonal hematopoietic neoplasms that have both dysplastic and proliferative features at the time of initial presentation

- CLASSIFICATION
  - Chronic myelomonocytic leukemia (CMML)
  - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
  - Juvenile myelomonocytic leukemia (children 0-14 years)
  - MDS/MPN, unclassifiable
    - Provisional entity: RARS with marked thrombocytosis, JAK2 mutation +(≈70%)
    - Exclude *BCR-ABL1* fusion gene, rearrangement *PDGFRA*, *PDGFRB*, *FGFR1*
    - Exclude isolated del (5q), t(3;3)(q21;q26) or inv 3(q21q26)

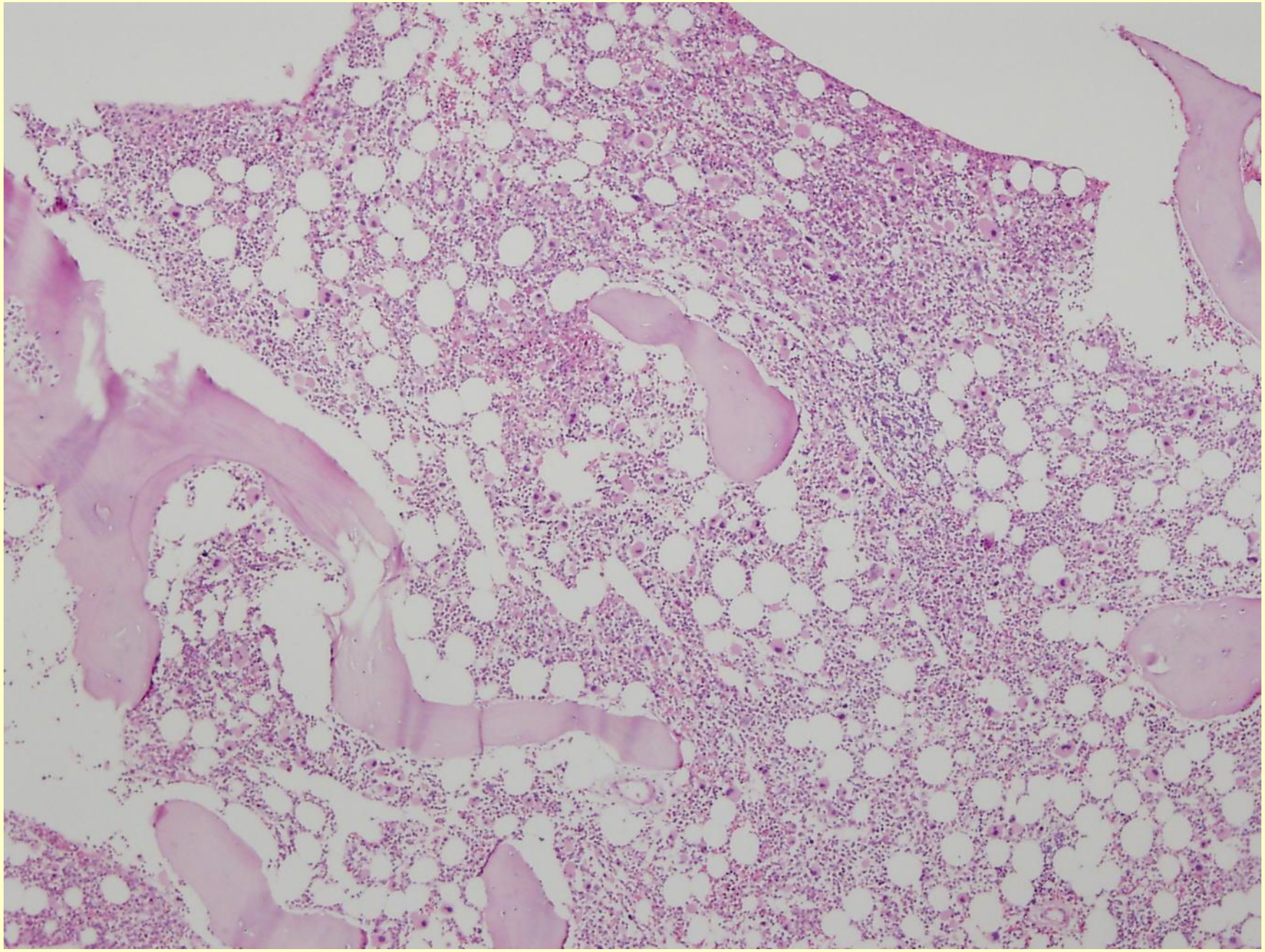
-5 o del (5q)

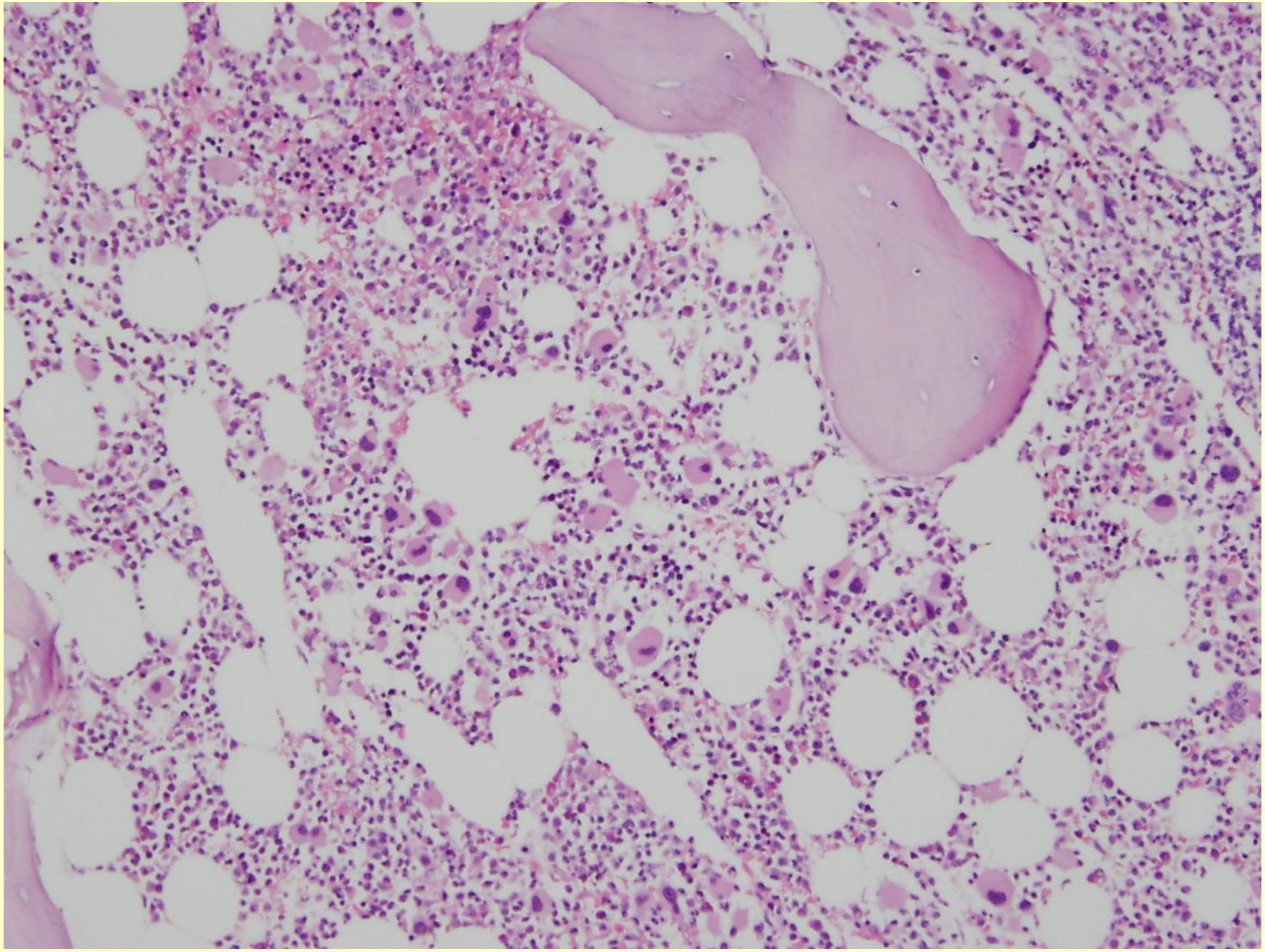
- Alteración muy frecuente en SMD
- Aislada o asociada a otras anomalías
- Morfología de los megacariocitos característica
- SMD con del (5q) aislada
  - Anemia
  - Cifra de plaquetas ↑ o normal
- Responden a tratamiento con Lenalidomida

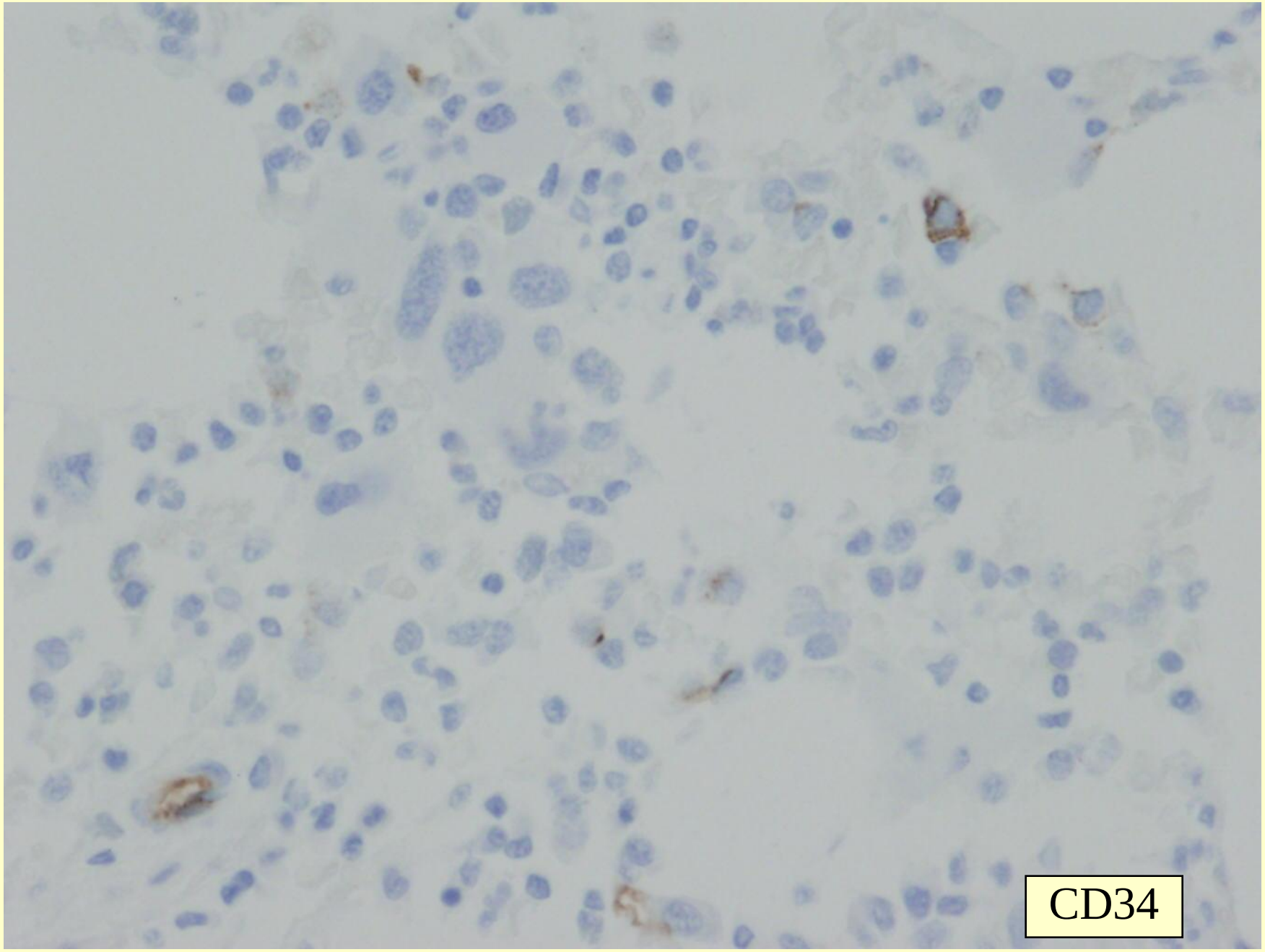
MDS/MPN

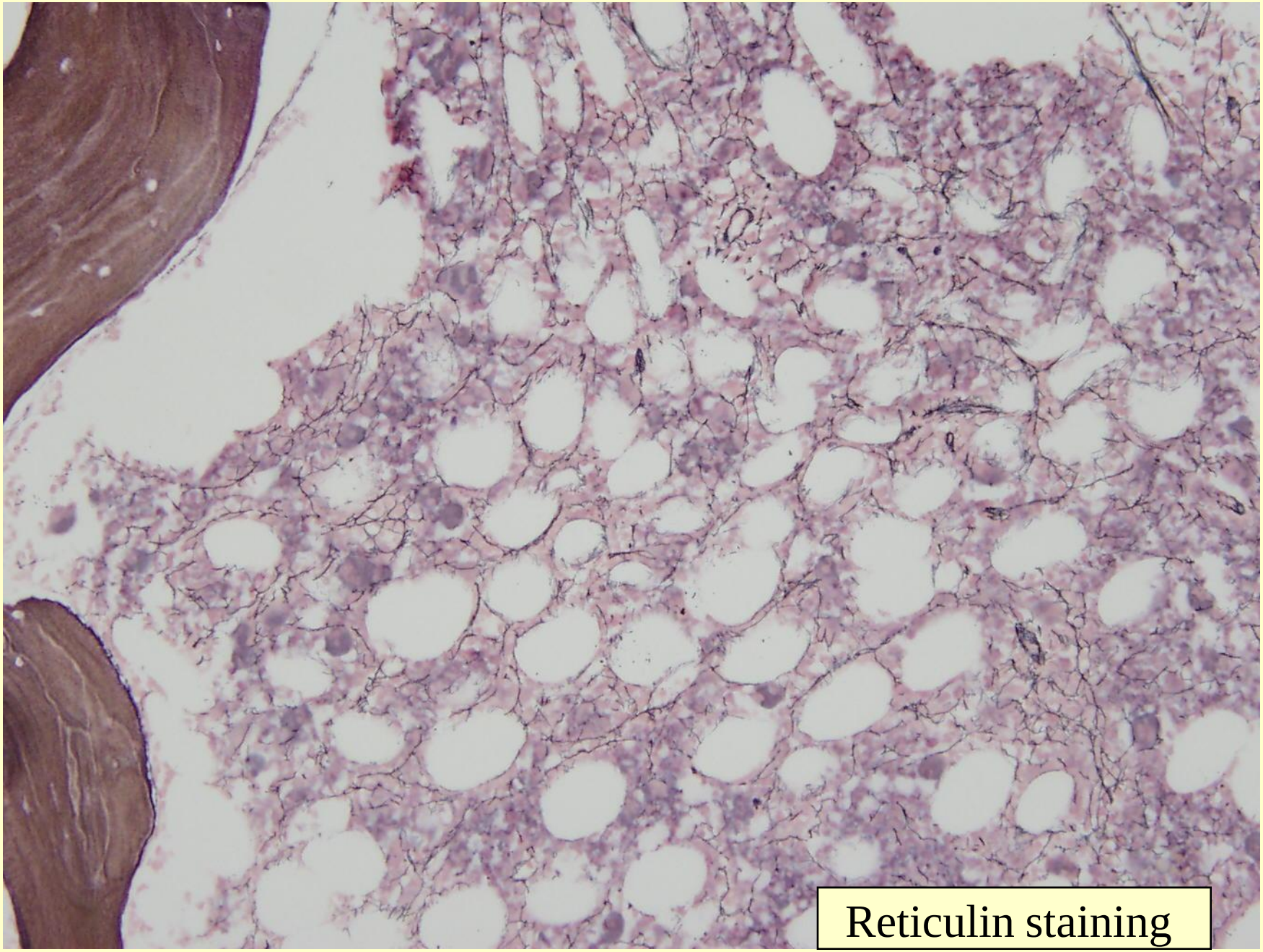
A. Orazi & U. Germing,
Leukemia (2008) 22, 1308-1319

5q-/JAK2 positive atypical myeloproliferative disease
Rare disease (precise incidence unknown)
Leukocytosis usually mild
Hypercellular marrow with granulocytic predominance
Iron stain show <15% ringed sideroblasts
Megakaryocytes are increased with a predominance of hypolobulated or nonlobulated forms of variable size
JAK2 is positive
May respond to Lenalidomide

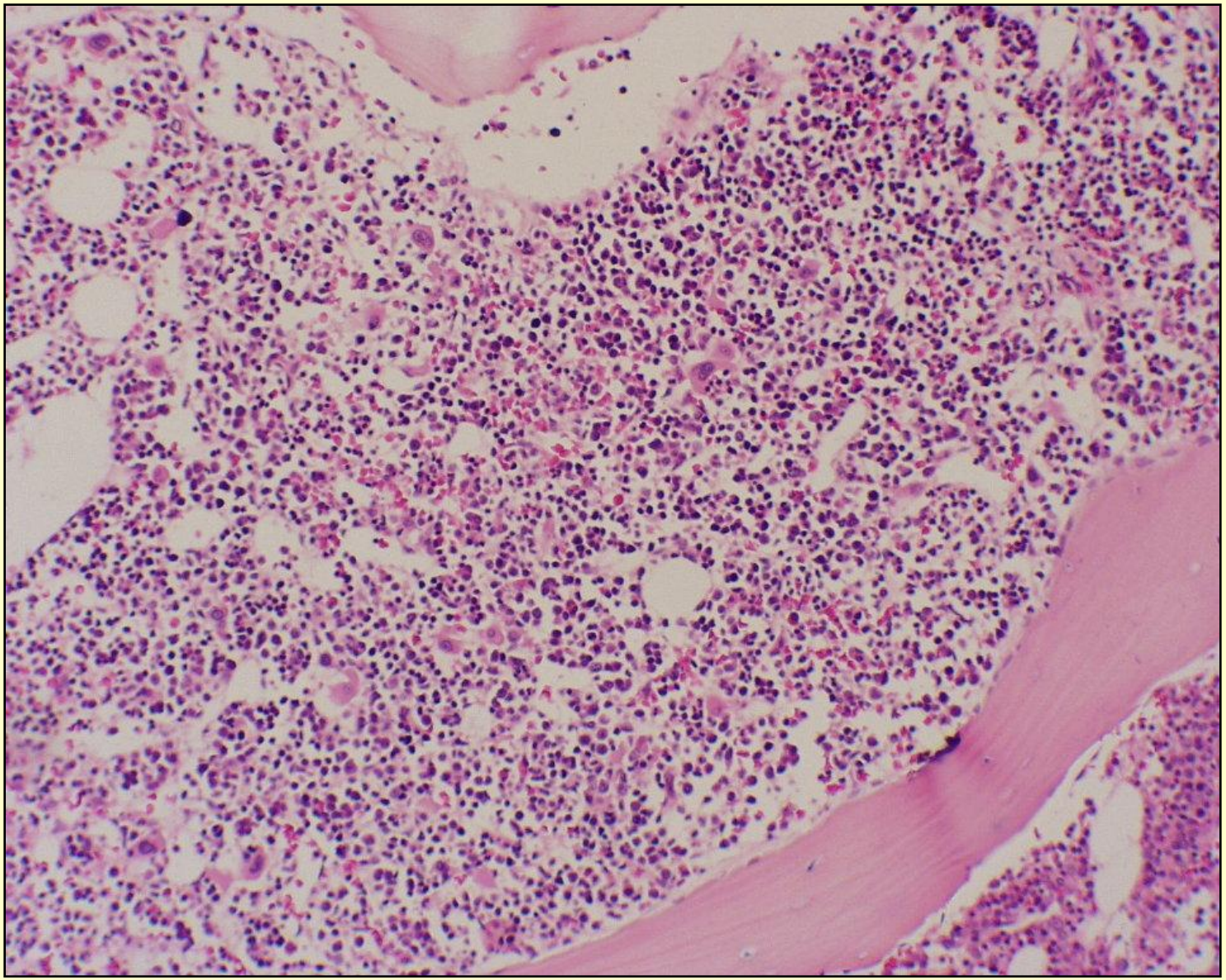




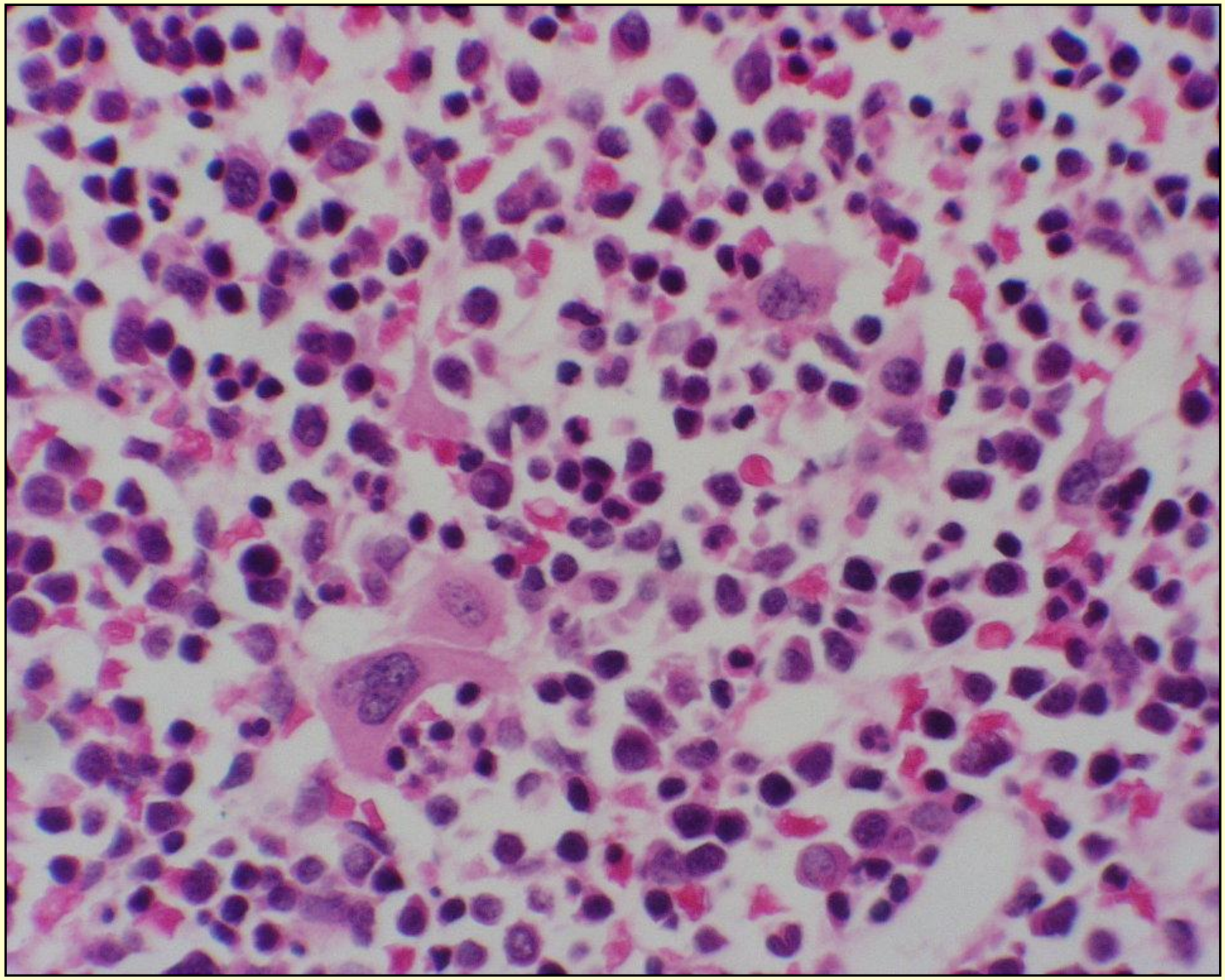

CD34


Reticulin staining

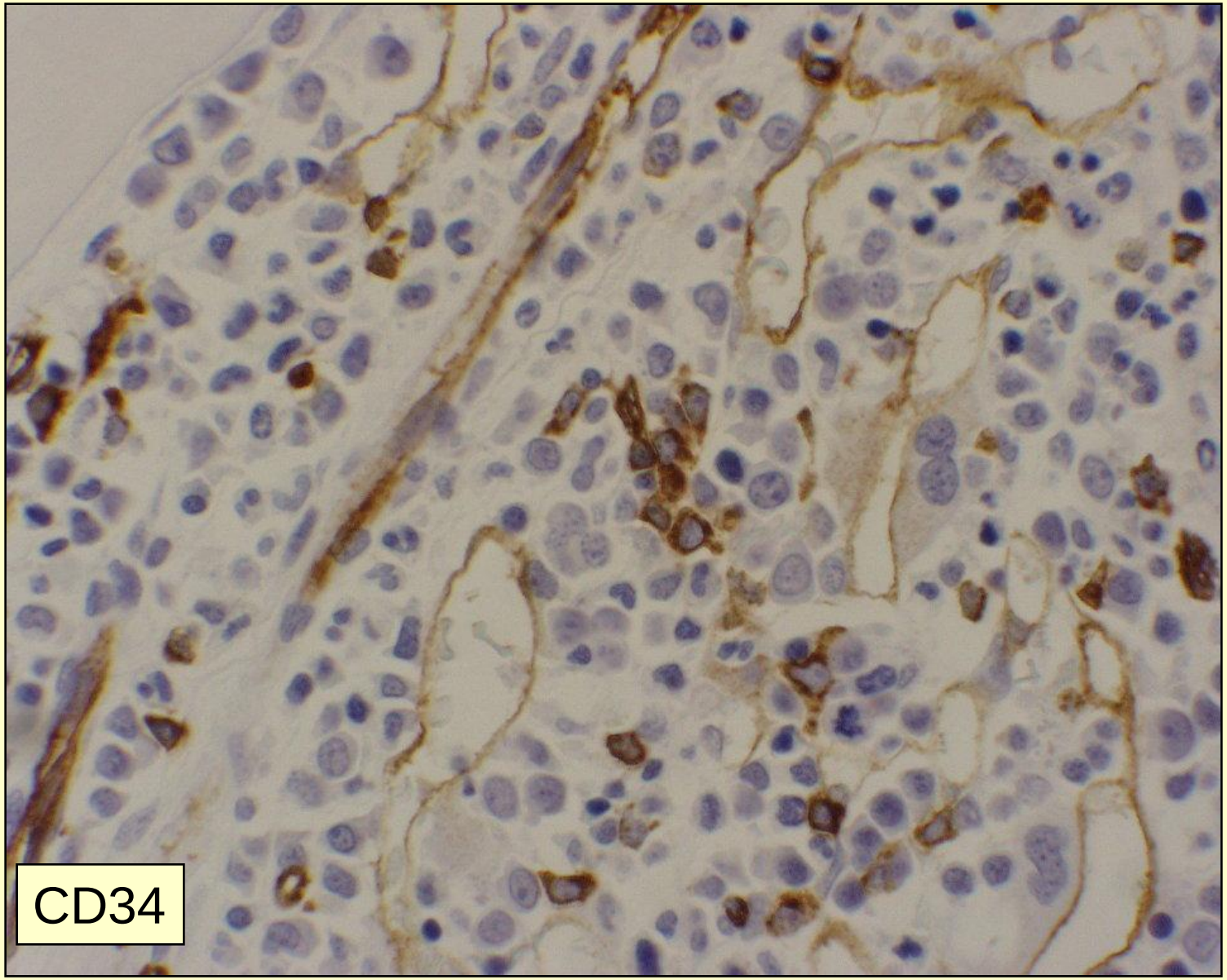
MDS/AML WITH t(3;3)(q21;q26) or inv 3(q21q26)



MDS/AML WITH t(3;3)(q21;q26) or inv 3(q21q26)



MDS/AML WITH t(3;3)(q21;q26) or inv 3(q21q26)



La biopsia medular en las neoplasias mieloproliferativas/mielodisplásicas

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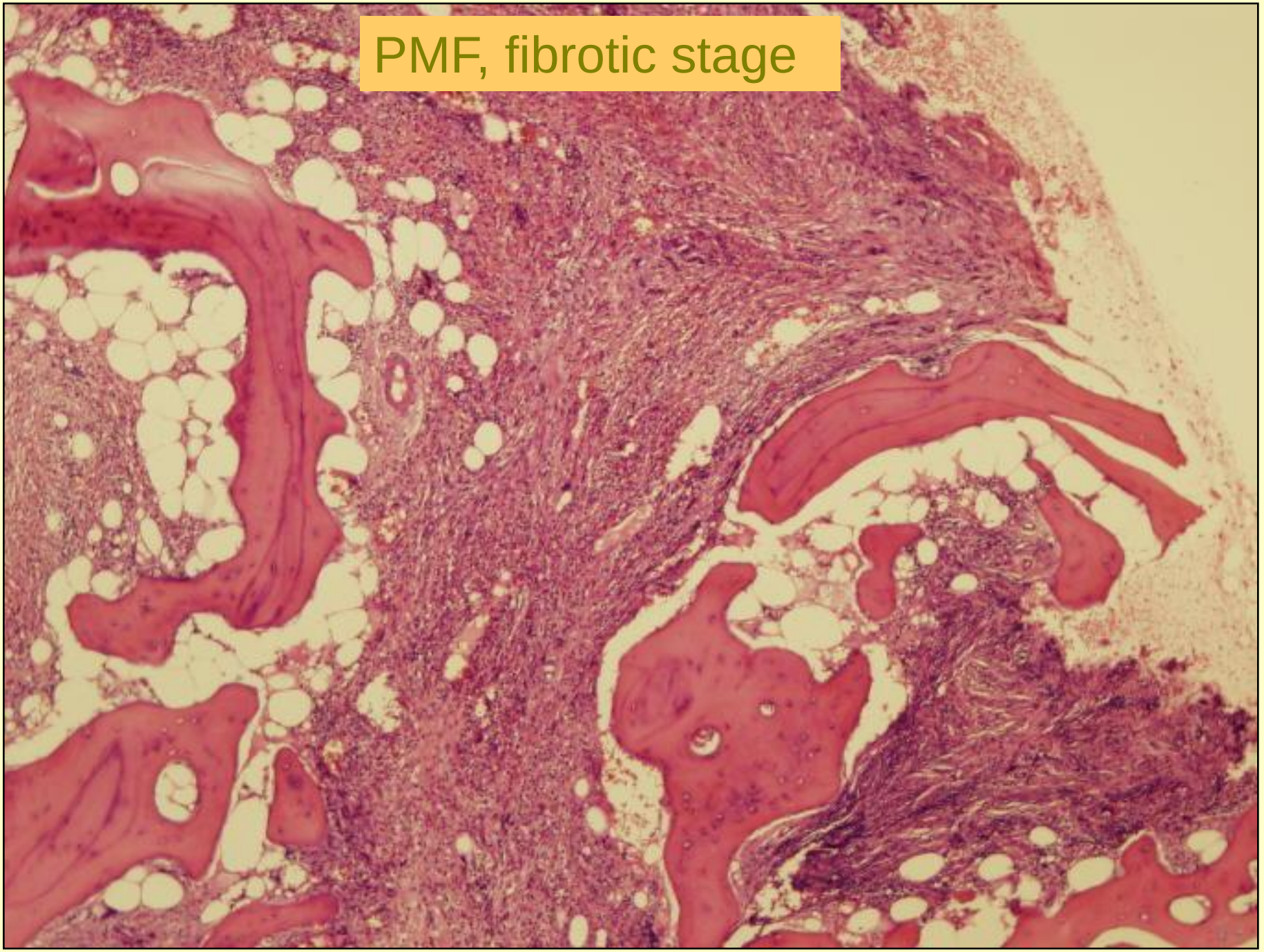
MYELOID NEOPLASIAS WITH MYELOFIBROSIS

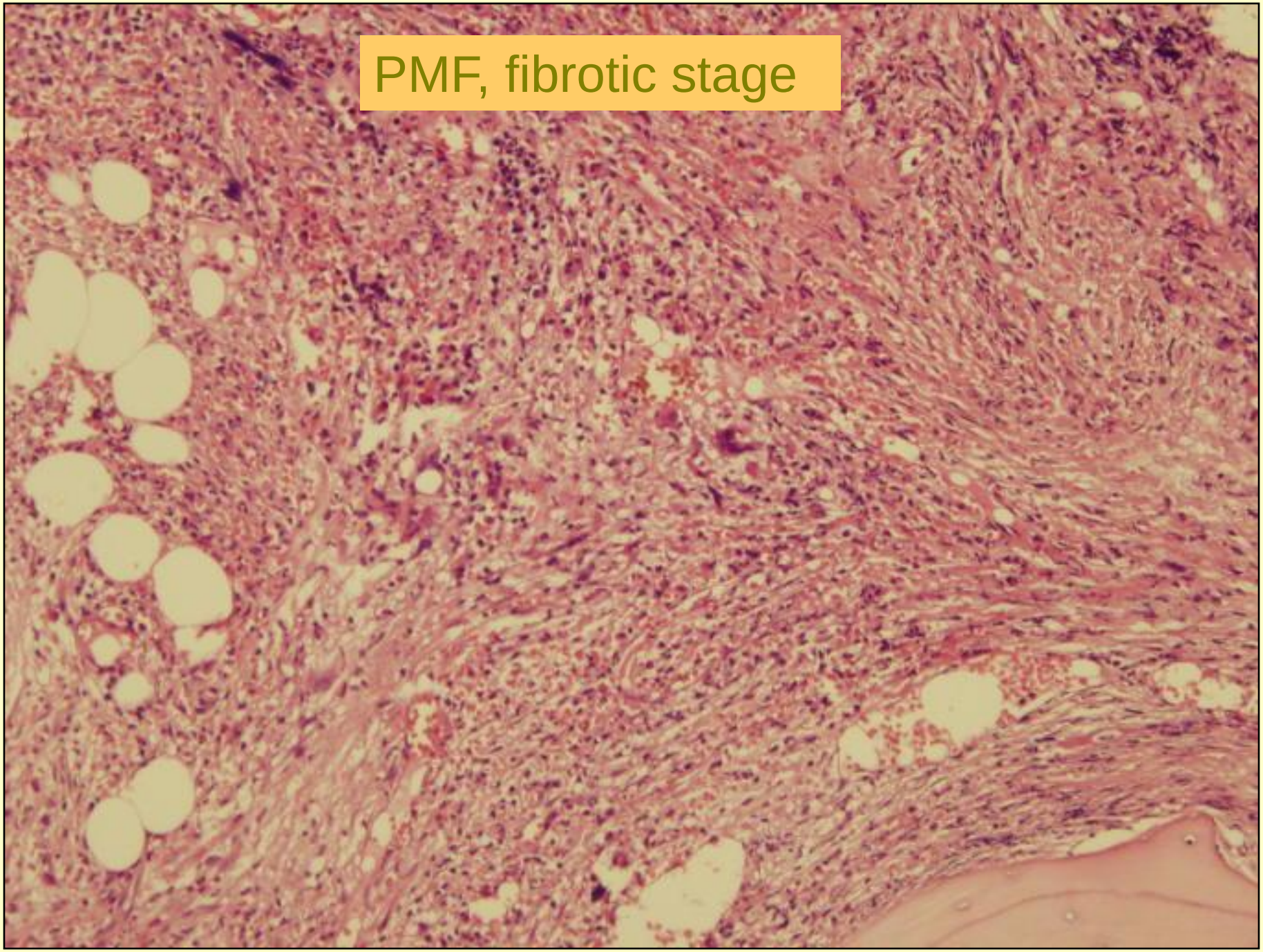
DIFFERENTIAL DIAGNOSIS

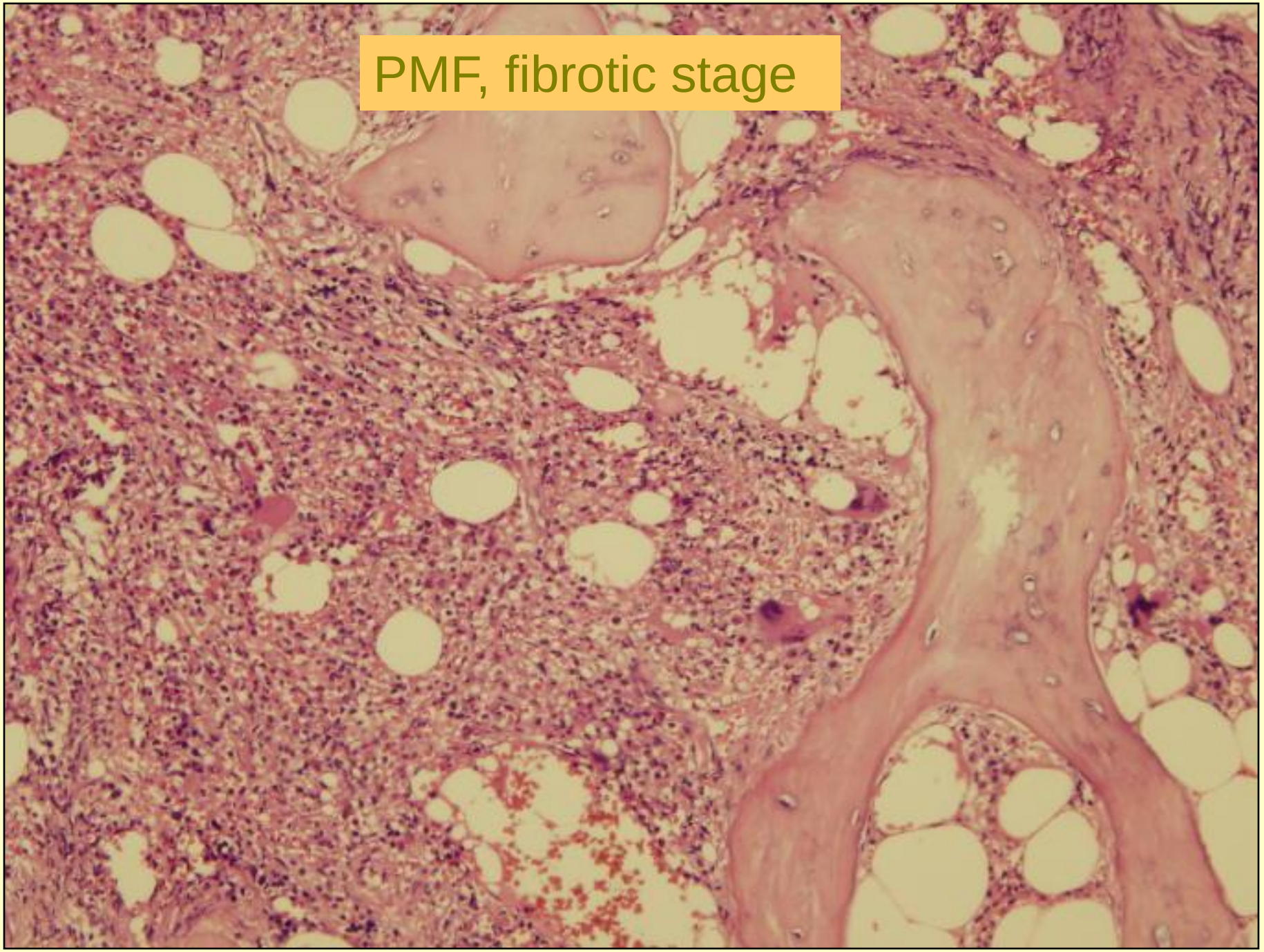
- PMF & ADVANCES PHASES OF OTHER CMPN
- MPN/MDS WITH MYELOFIBROSIS
- MDS WITH MYELOFIBROSIS
- ACUTE PANMYELOSIS WITH MYELOFIBROSIS
- AUTOIMMUNE MYELOFIBROSIS

Primary myelofibrosis (PMF): BM pathology (II)

- Fibrotic stage
  - Decreased cellularity
  - Reticulin and/or collagen fibrosis
  - Dilated marrow sinuses with intraluminal hematopoiesis
  - Prominent megakaryocytic proliferation and atypia:
    - Clustering of megakaryocytes
    - Abnormally lobulated nuclei
    - Naked nuclei
  - Osteosclerosis (new bone formation)


PMF, fibrotic stage


PMF, fibrotic stage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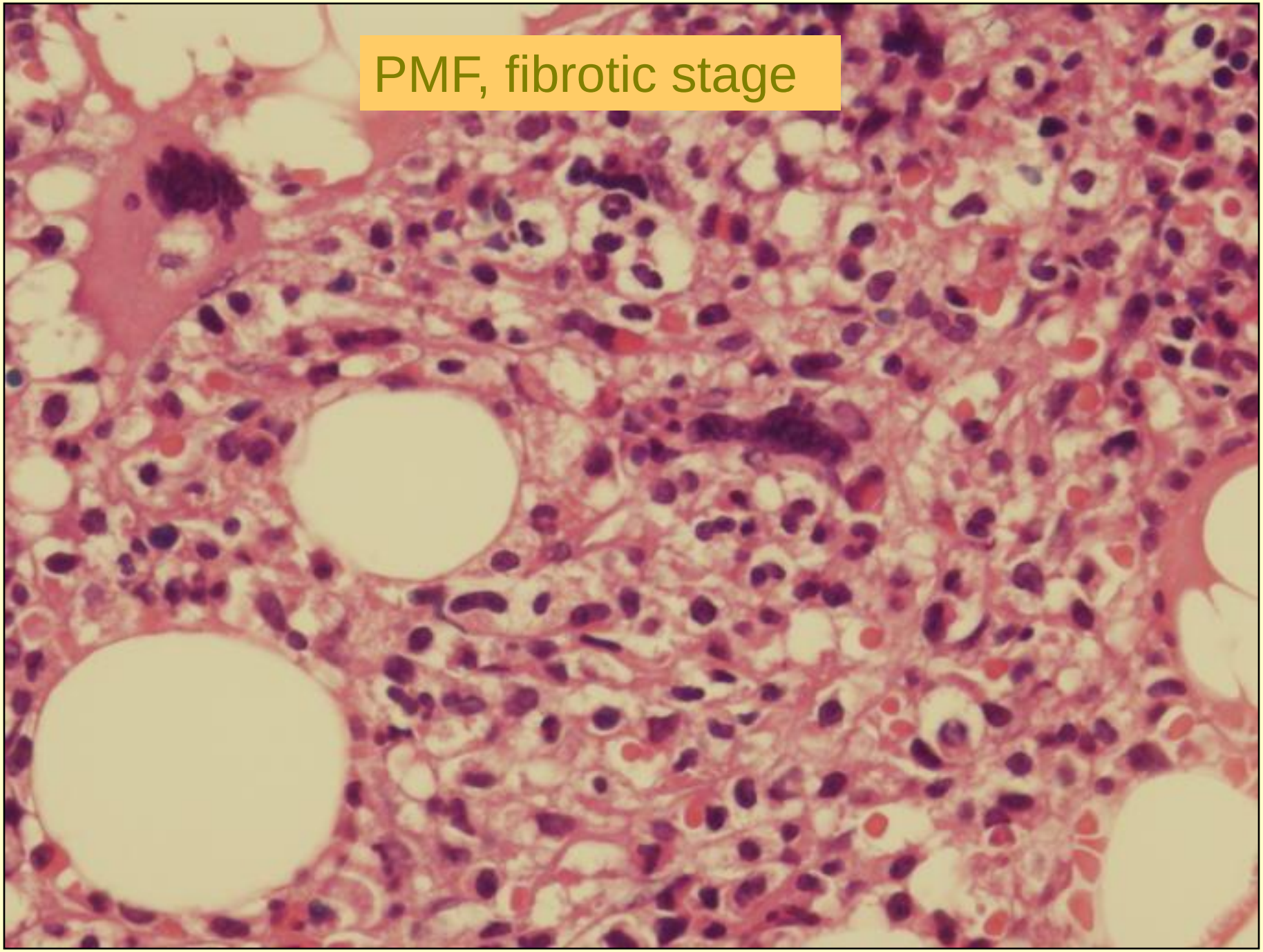
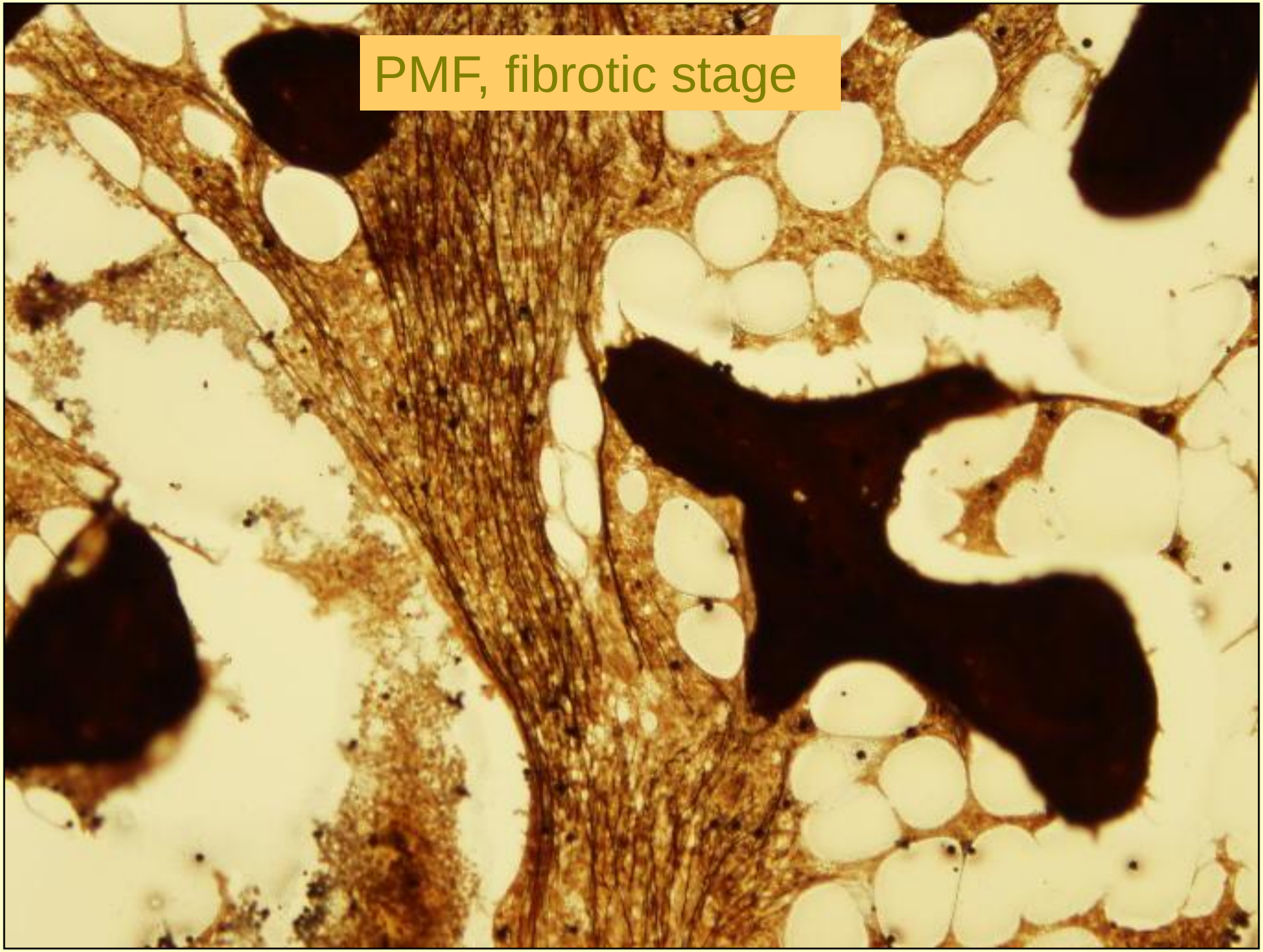
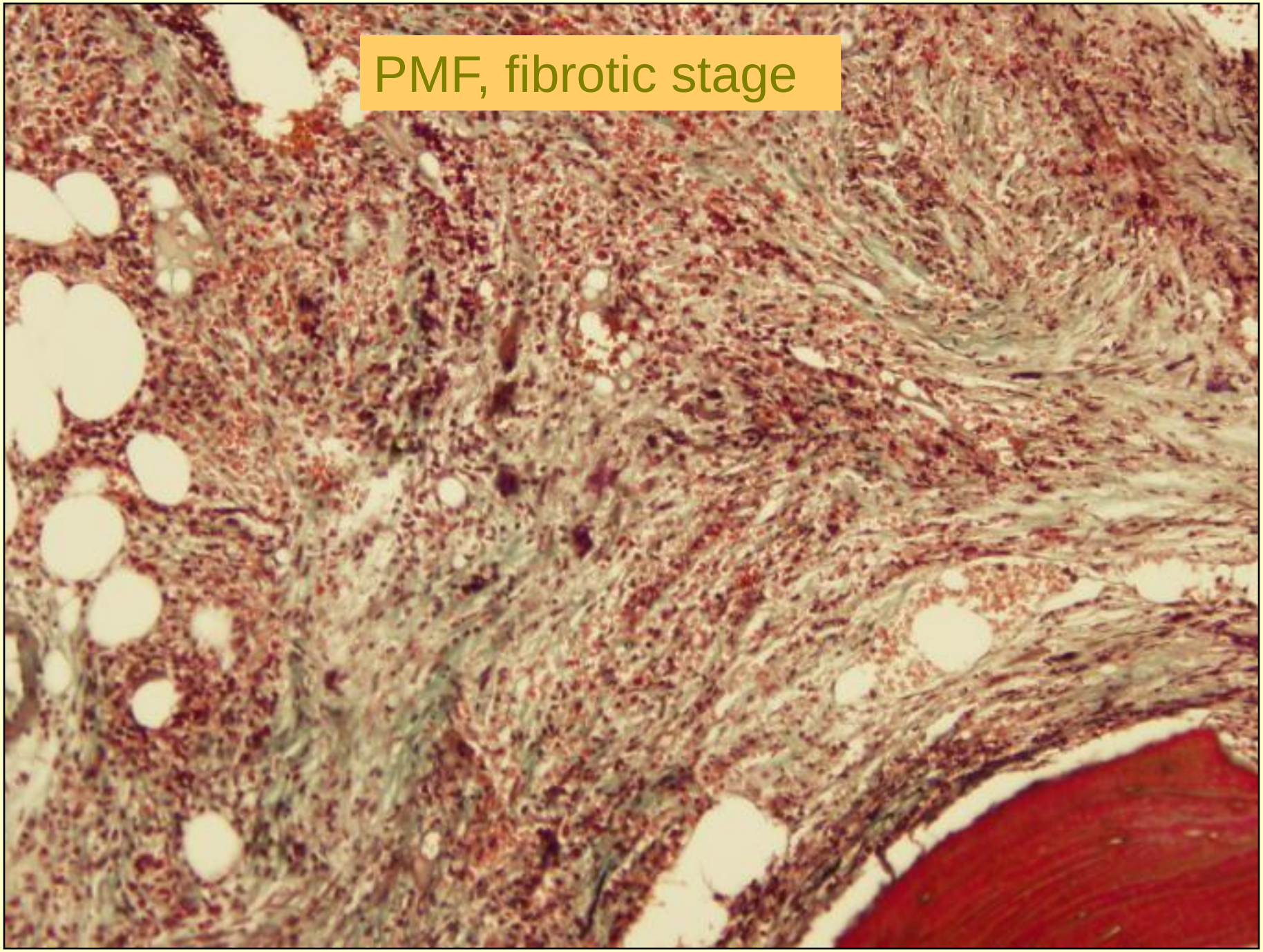
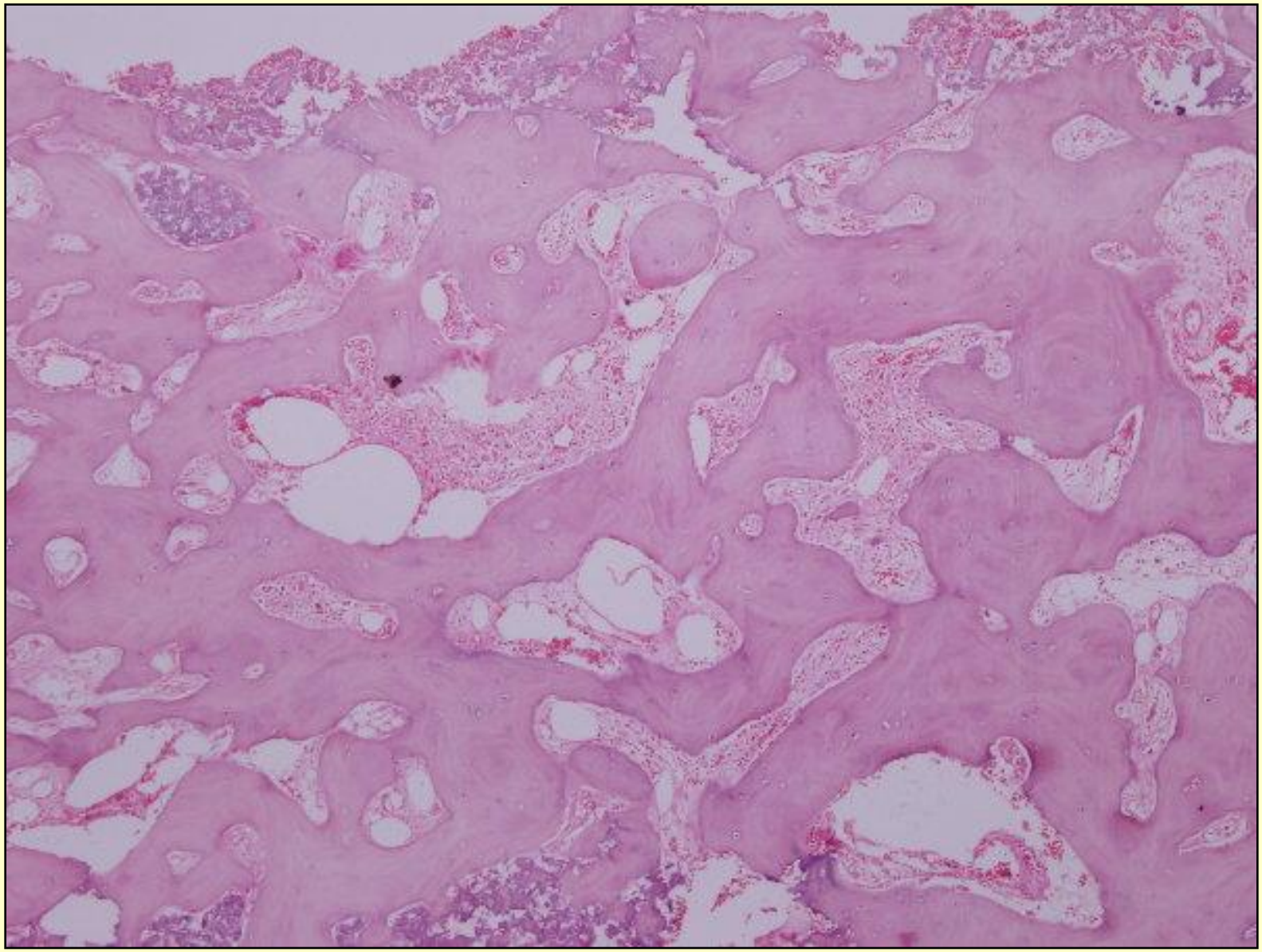

PMF, fibrotic stage

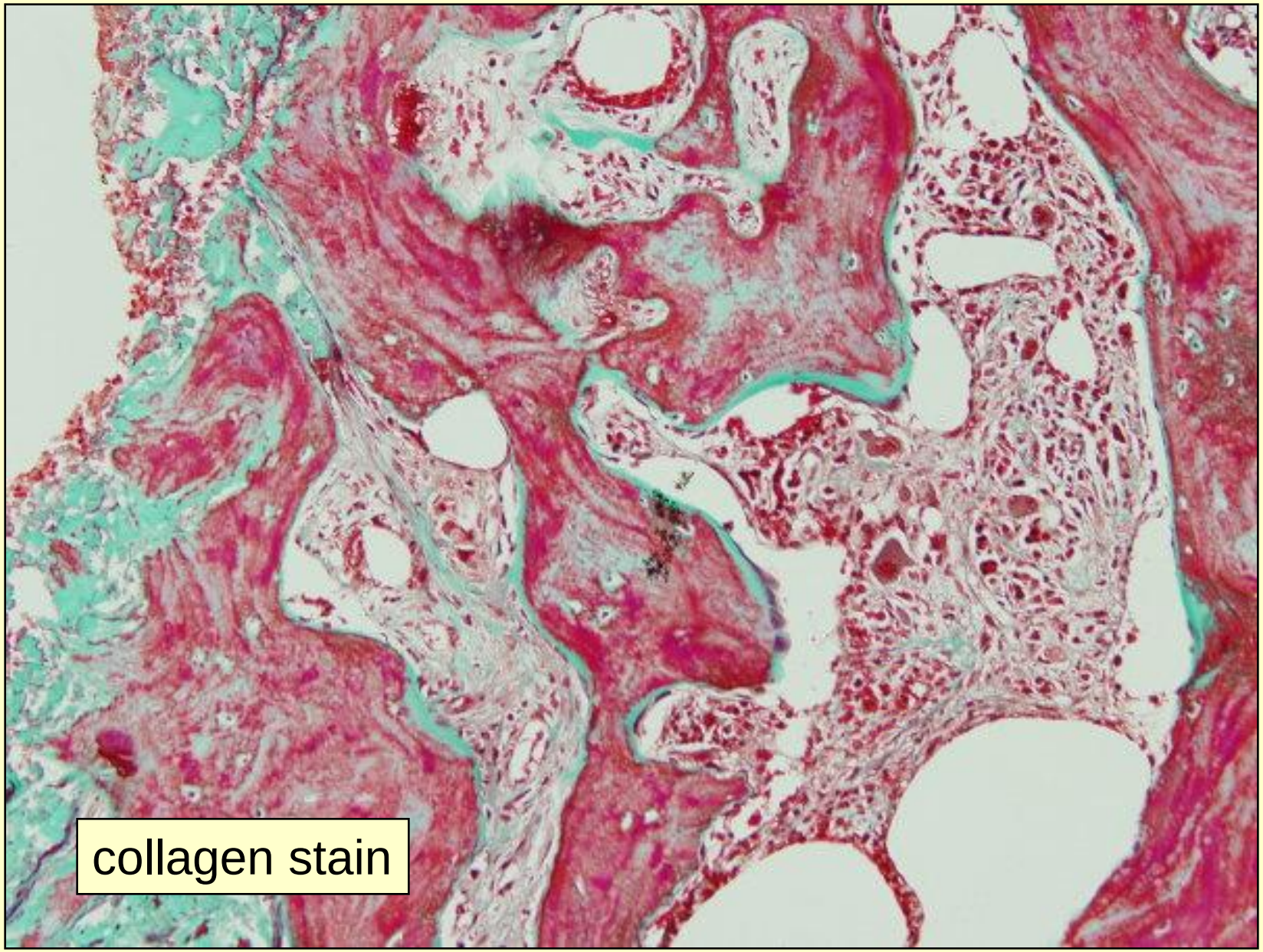

PMF, fibrotic stage


PMF, fibrotic stage

PMF, osteomyelosclerosis



PMF, osteomyelosclerosis



Polycythaemia Vera (PV): BM pathology (II)

– “Spent phase” & post-polycythaemic myelofibrosis
  - Reticulin & even collagen fibrosis
  - Commonly hypocellular
  - Clusters of megakaryocytes with hyperchromatic nuclei
  - Decreased erythropoiesis & granulopoiesis

Often undistinguishable from PMF

European consensus on grading bone marrow fibrosis and assessment of cellularity

Haematologica 2005; 90:1128-1132

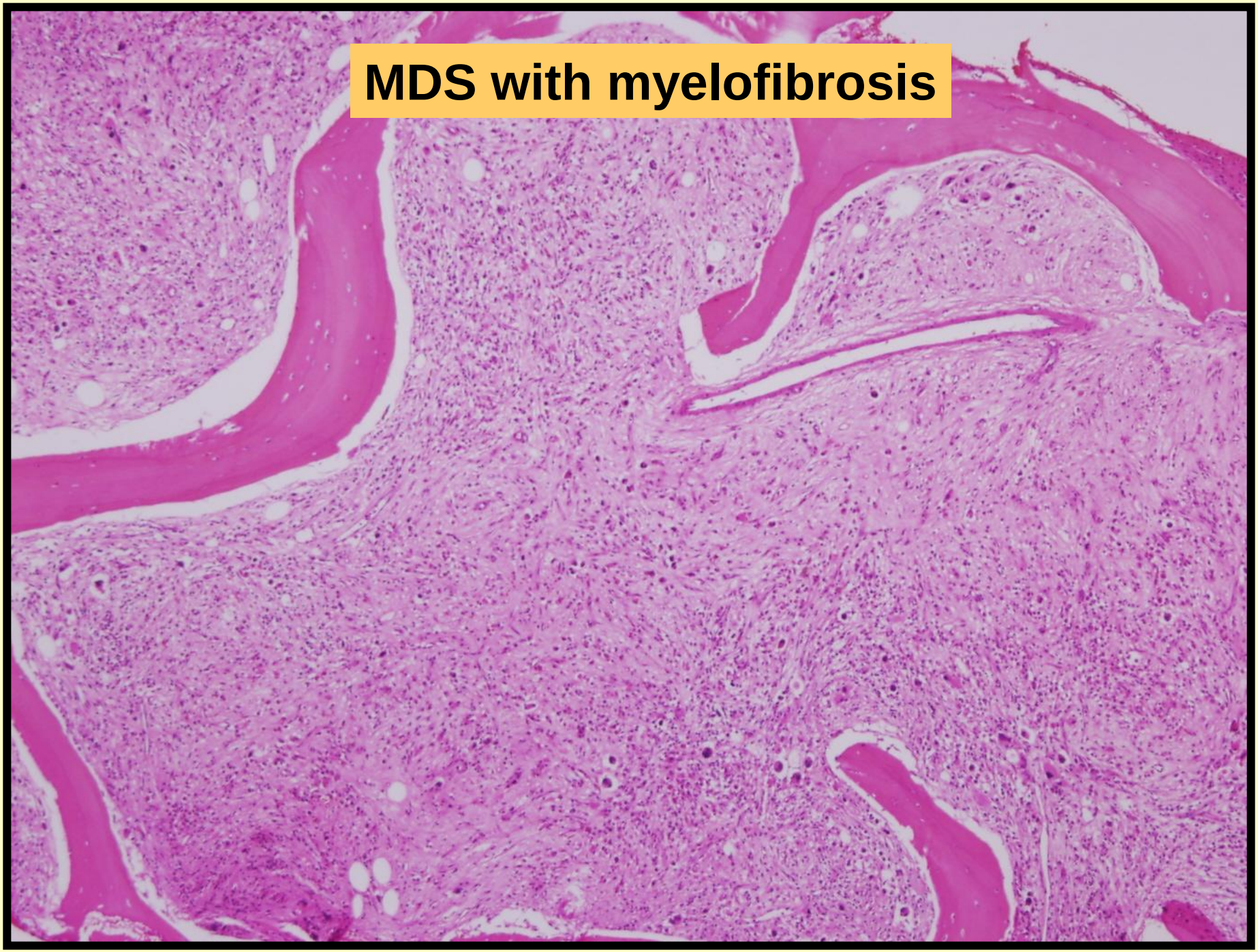
Jürgen Thiele
Hans Michael Kvasnicka
Fabio Facchetti
Vito Franco
Jon van der Walt
Attilio Orazi

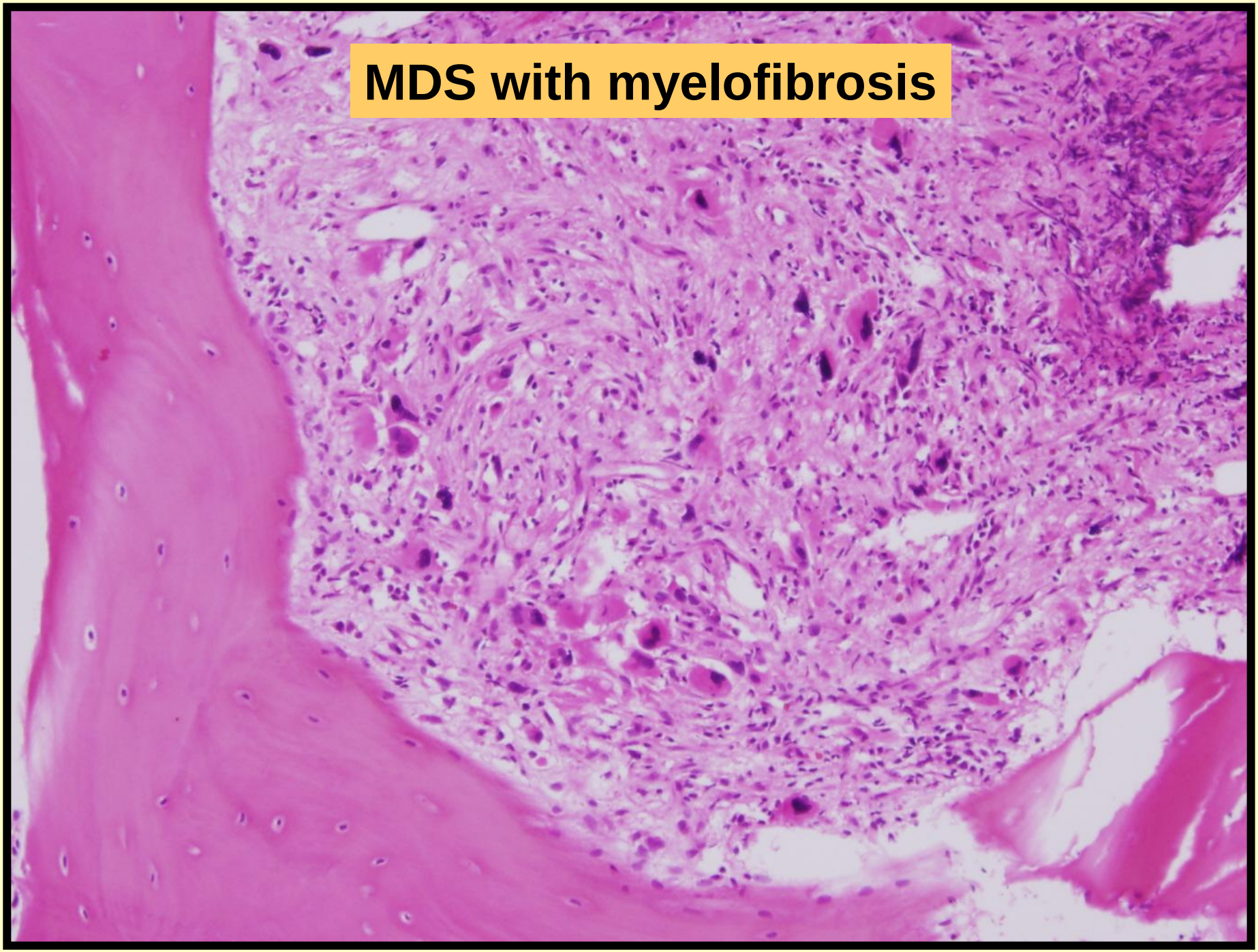
Table 3. Consensus on the grading of myelofibrosis (MF) as adapted from the literature.[32,33,36]

Grading	*Description**
MF - 0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
MF - 1	Loose network of reticulin with many intersections, especially in perivascular areas
MF - 2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF - 3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

**Fiber density should be assessed in hematopoietic (cellular) areas.*

Also in WHO 2008


MDS with myelofibrosis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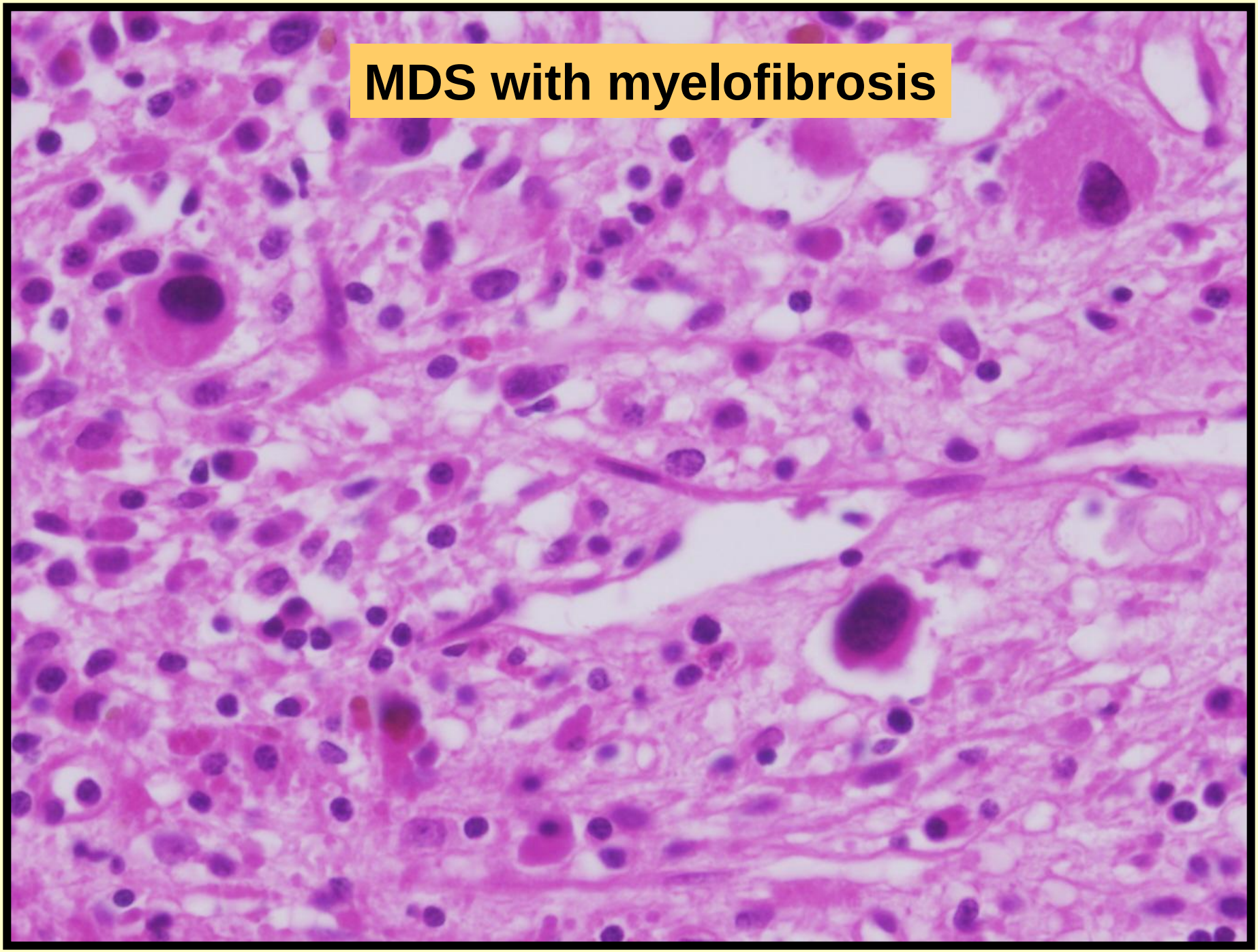
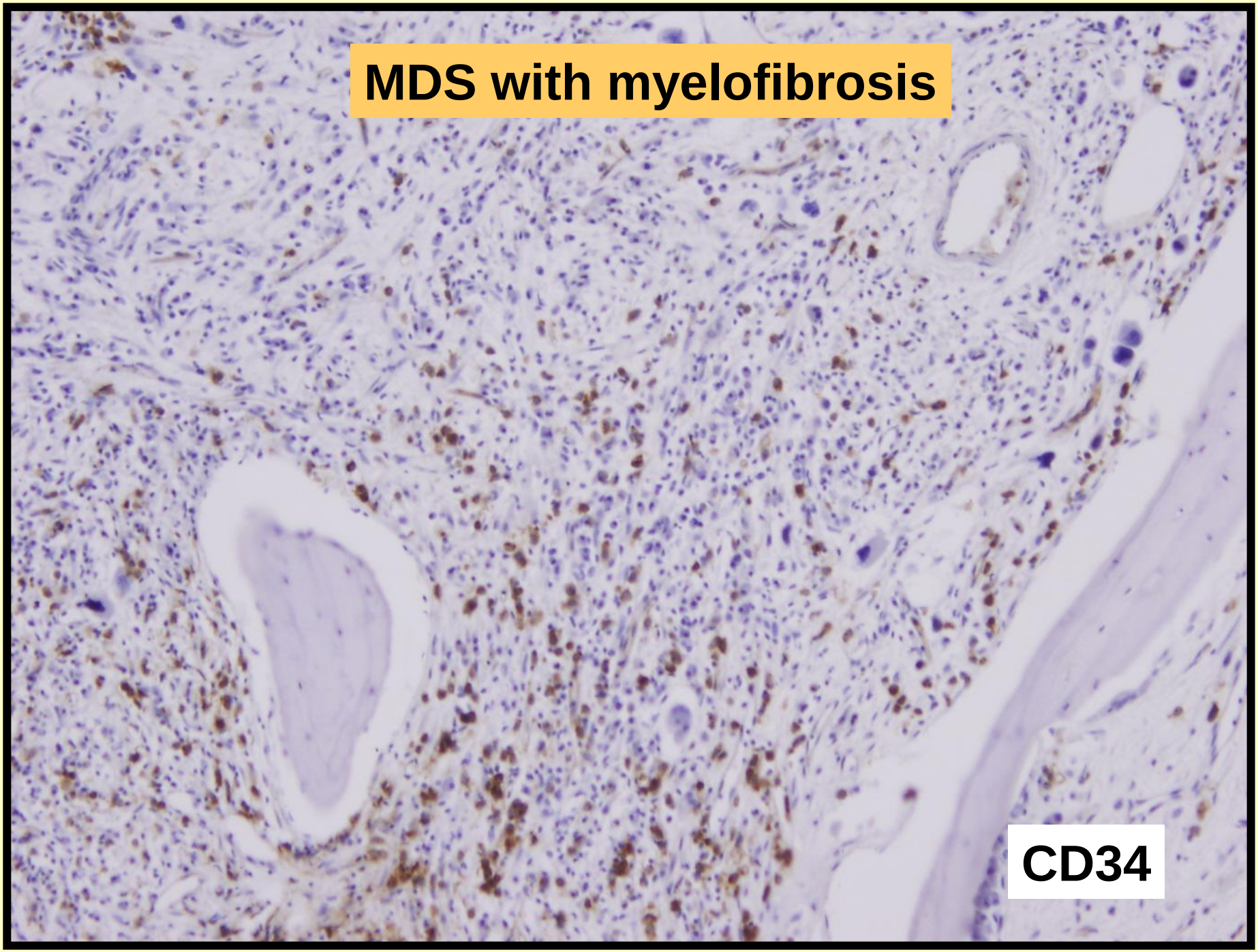
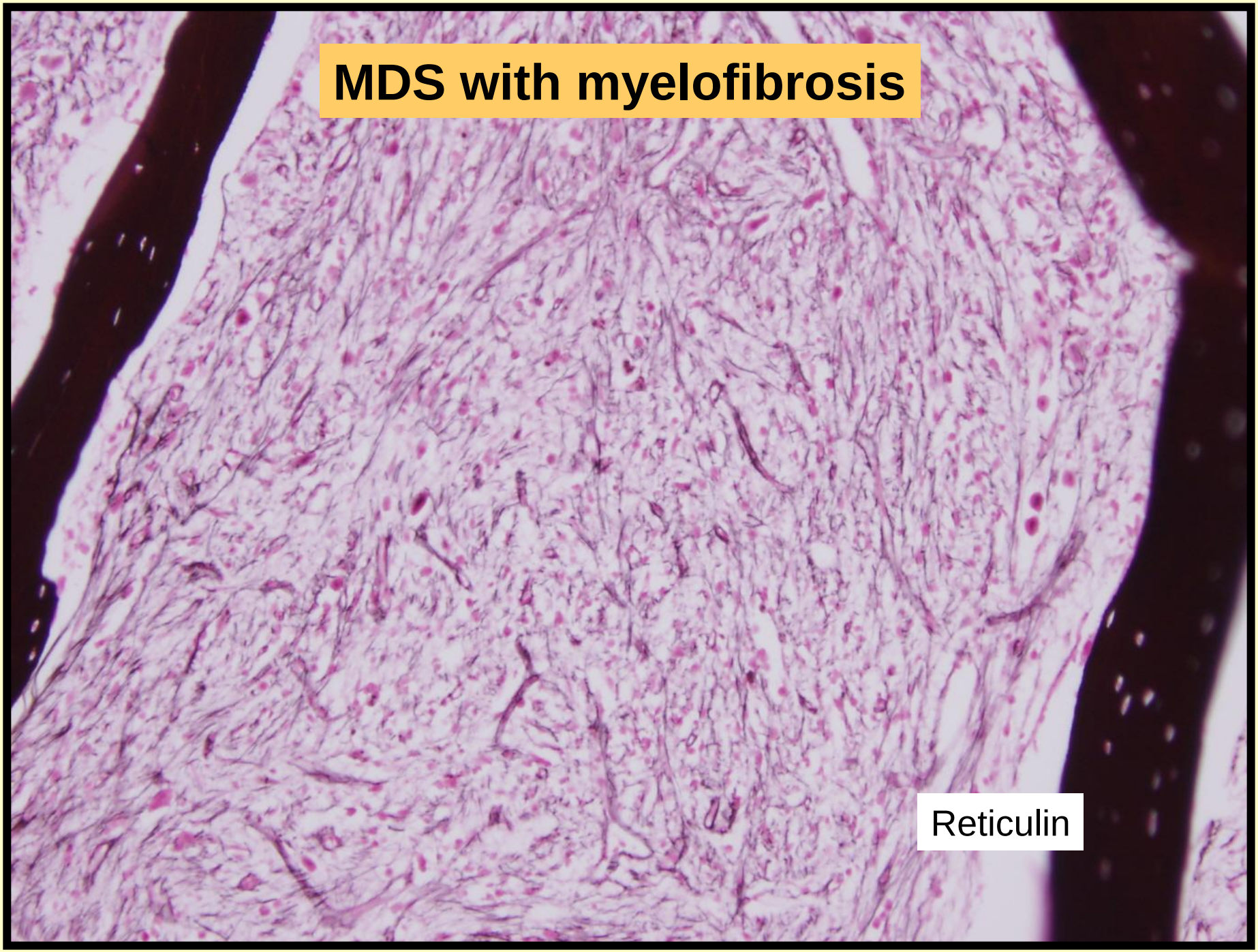
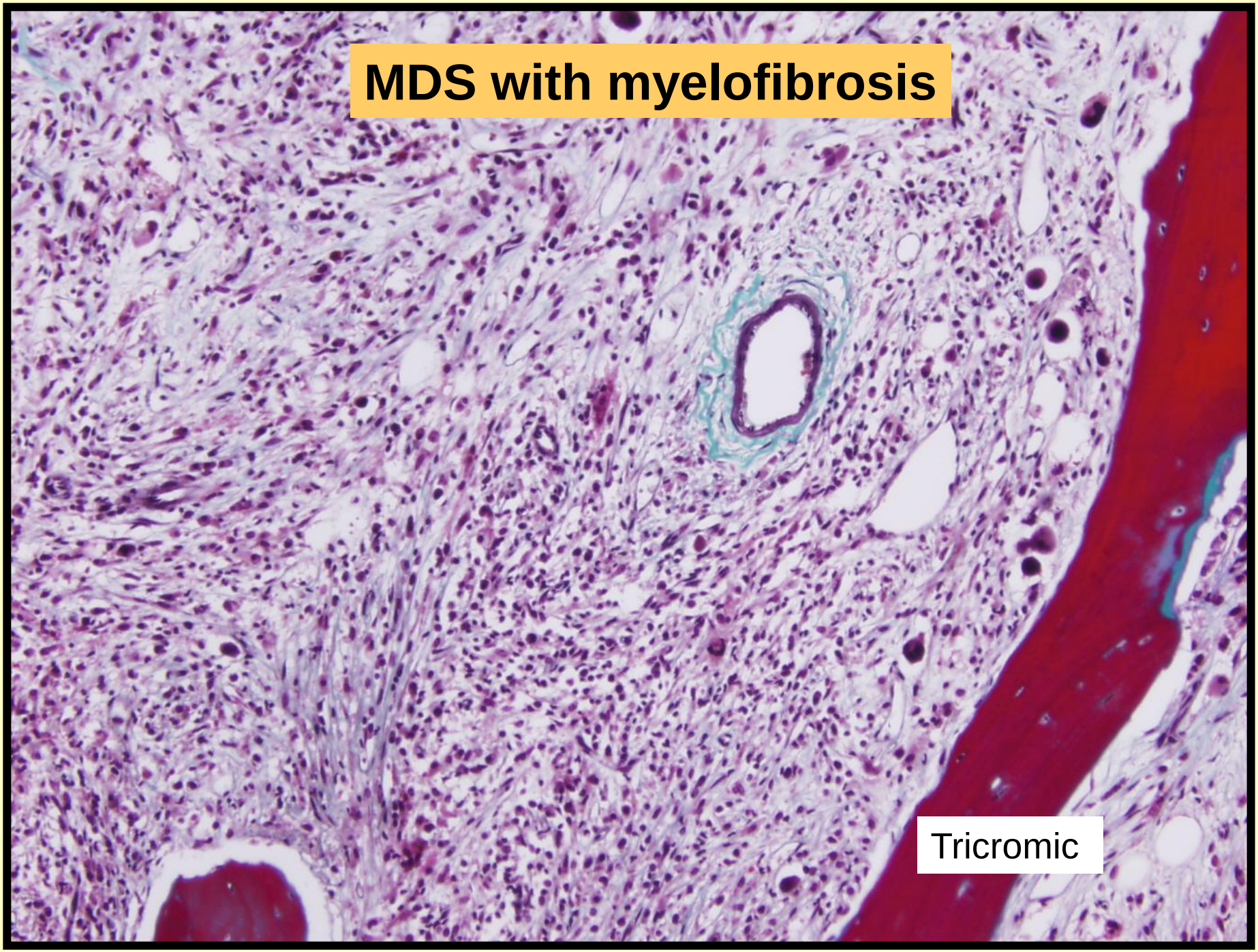

MDS with myelofibrosis


MDS with myelofibrosis
CD34

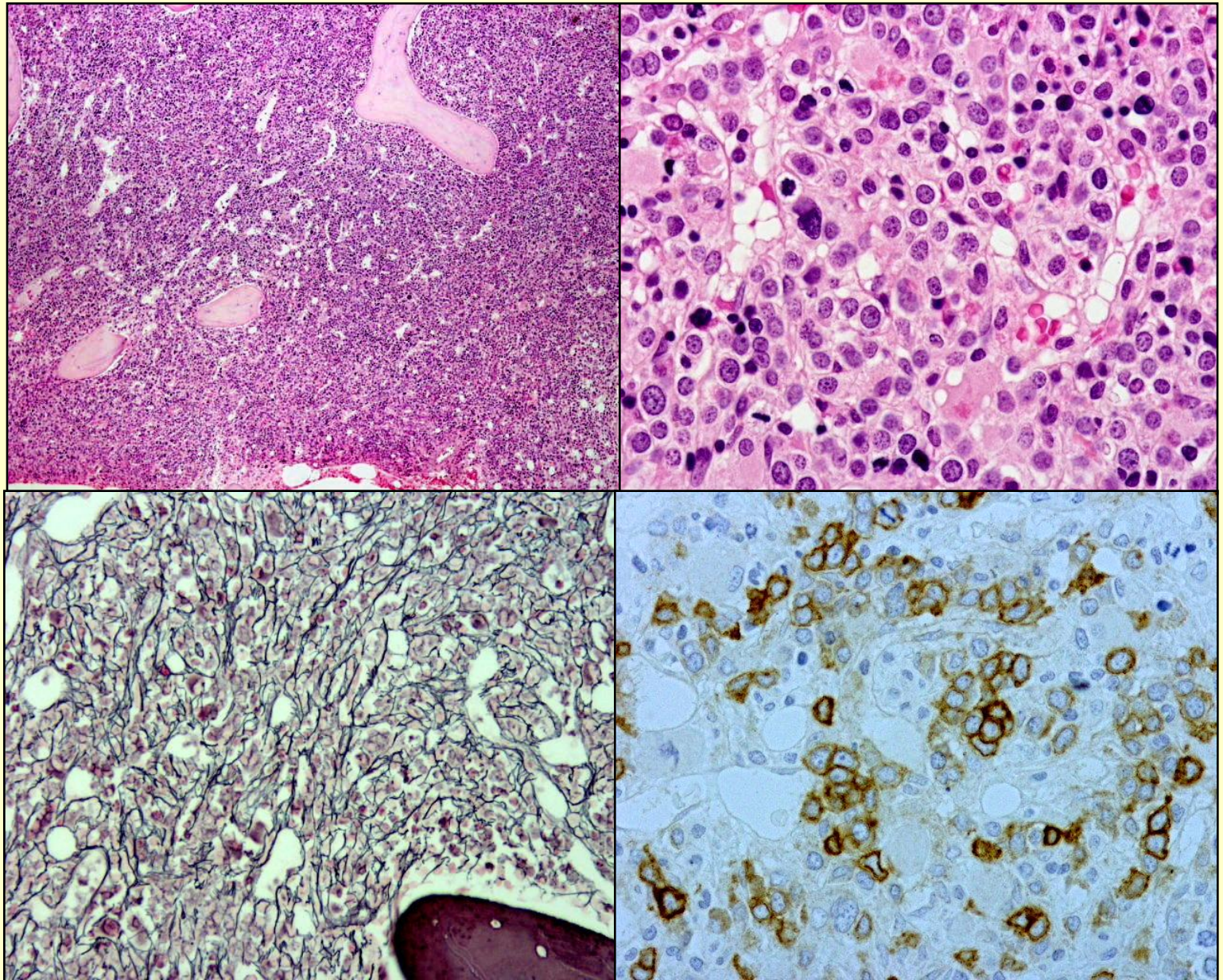

MDS with myelofibrosis
Reticulin

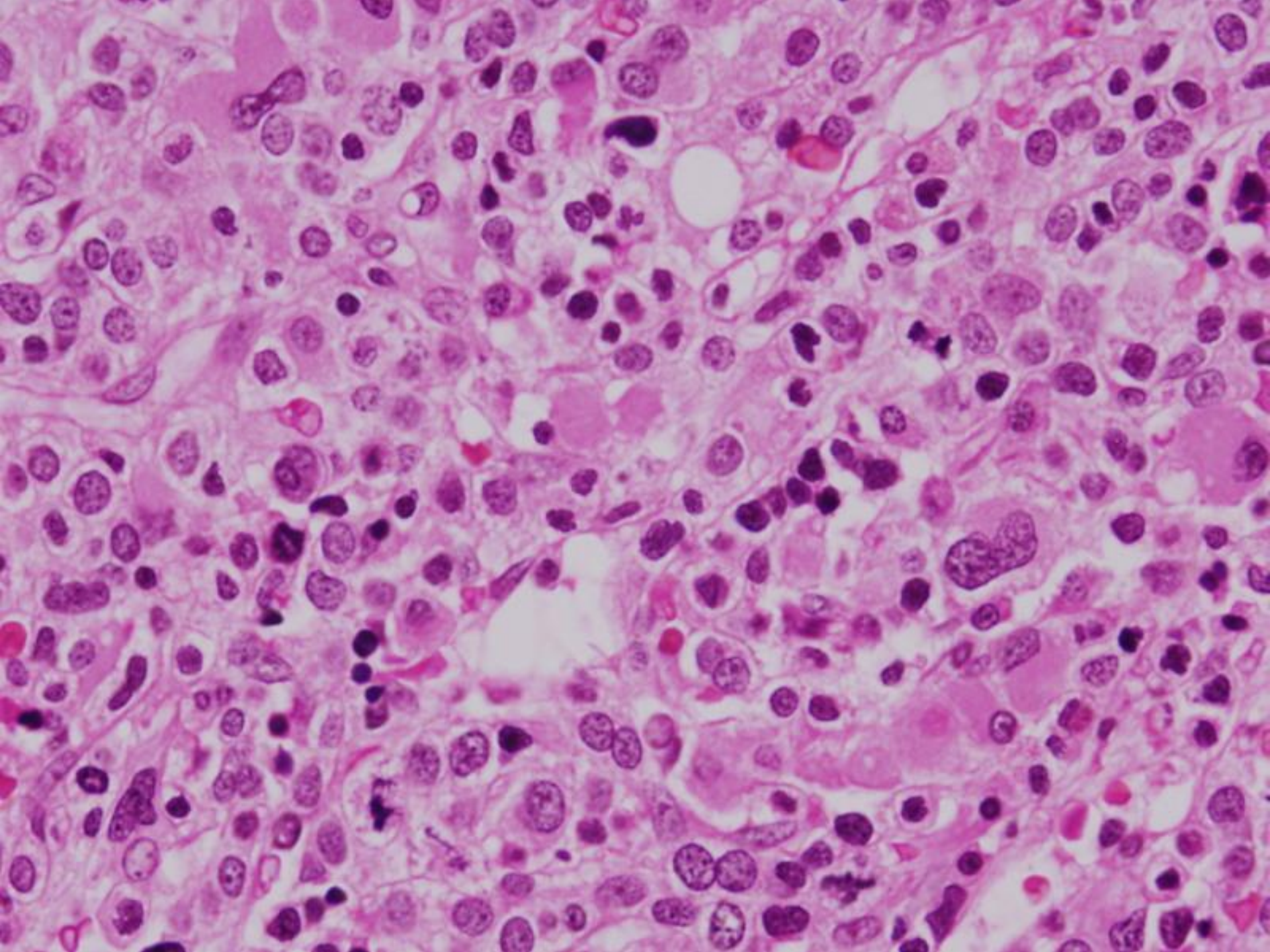

MDS with myelofibrosis
Tricromic

Acute panmyelosis with myelofibrosis

- Acute panmyeloid proliferation with accompanying fibrosis of the bone marrow
- Very rare form of AML
- Abrupt onset with fever and bone pain, pancytopenia
- No or minimal poikilocytosis
- Bone marrow biopsy
  - Hypercellular
  - Variable degrees of erythroid, myeloid and megakaryocytic precursors
  - Increased number of small to large megakaryocytes with dysplastic features
  - Foci of immature cells
  - Reticulin fibrosis
  - Collagenous fibrosis uncommon

Acute panmyelosis with myelofibrosis



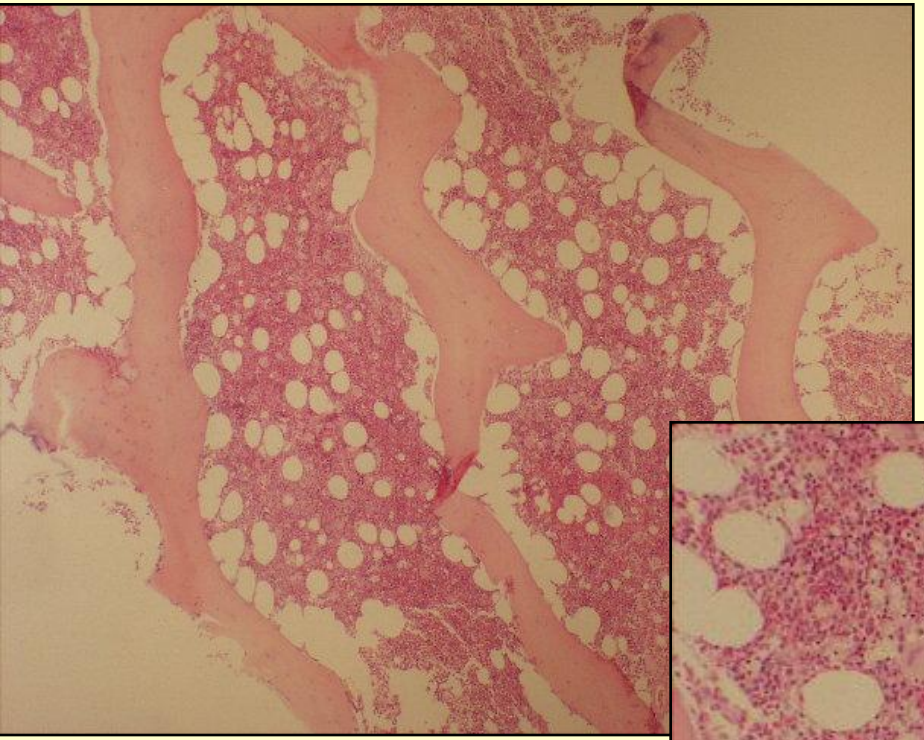


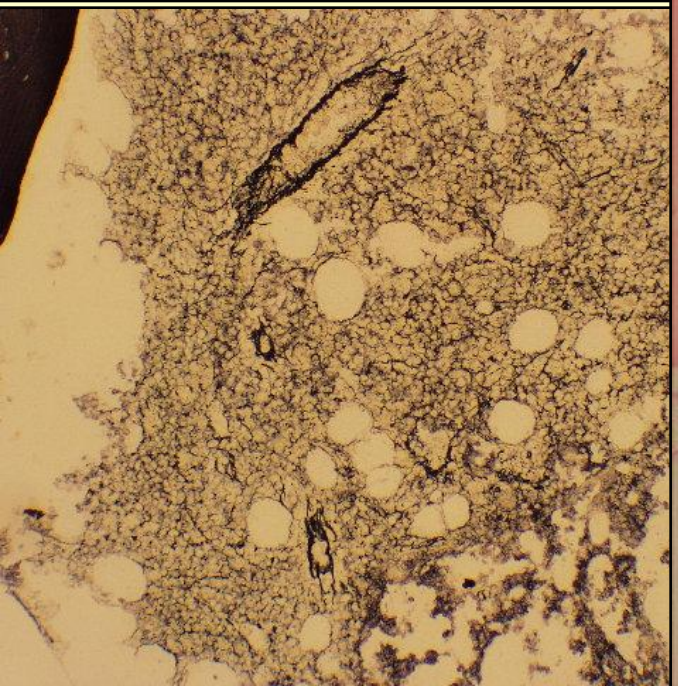
Autoimmune myelofibrosis

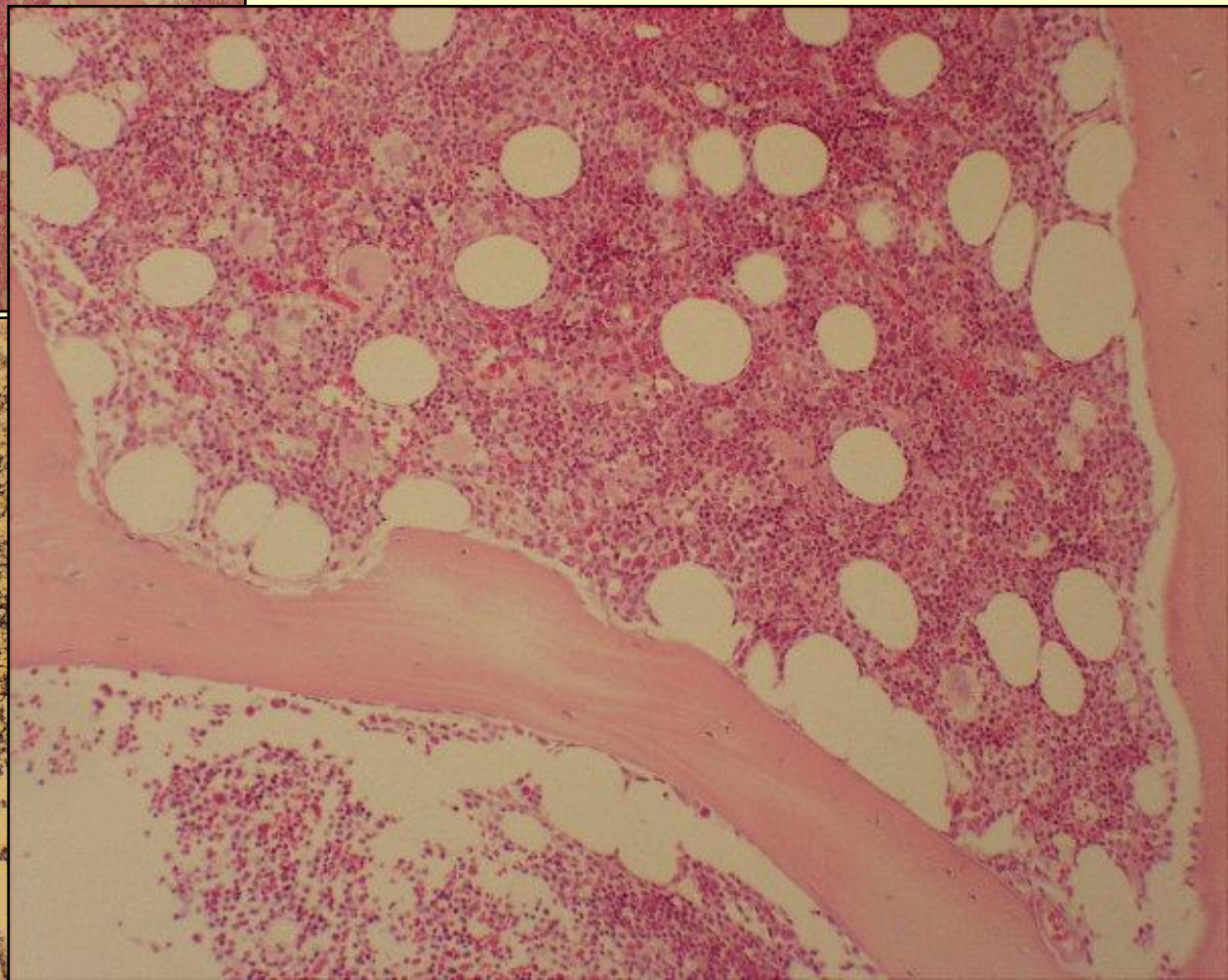
- Isolately or in association with autoimmune diseases
- Chronic cytopenias
- No organomegaly
- Absence of tear-drop poikilocytosis & leukoerythroblastosis on peripheral blood smears
- Bone marrow biopsy:
  - Cellularity ranges from decreased to increased
  - Megakaryocytes not clustered, nor atypical
  - Reticulin fibrosis
  - Reactive lymphoid aggregates

Rizzi et al, Leuk&Lymph 2004;45(3):561-566

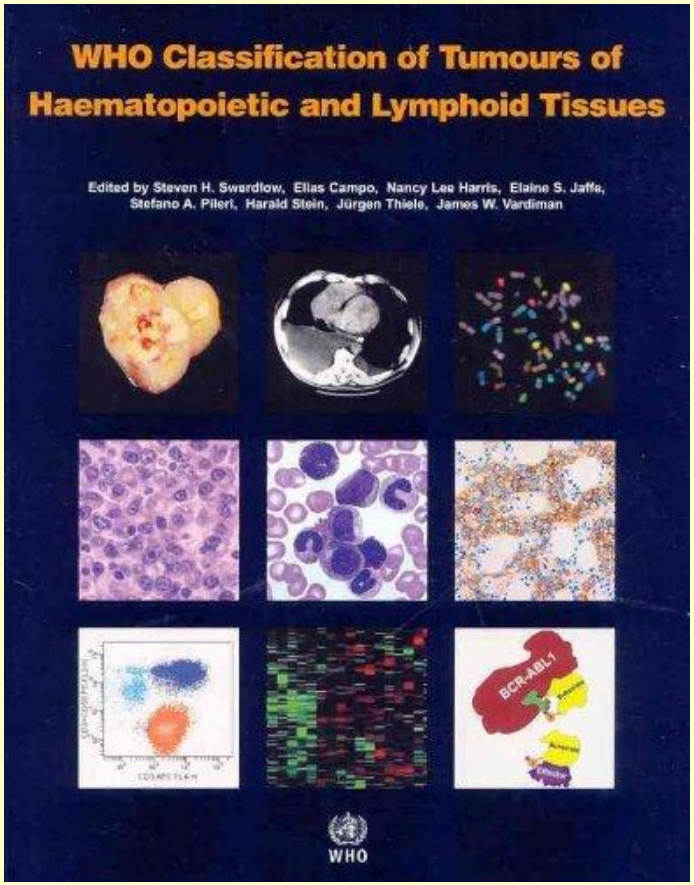
AUTOIMMUNE MYELOFIBROSIS

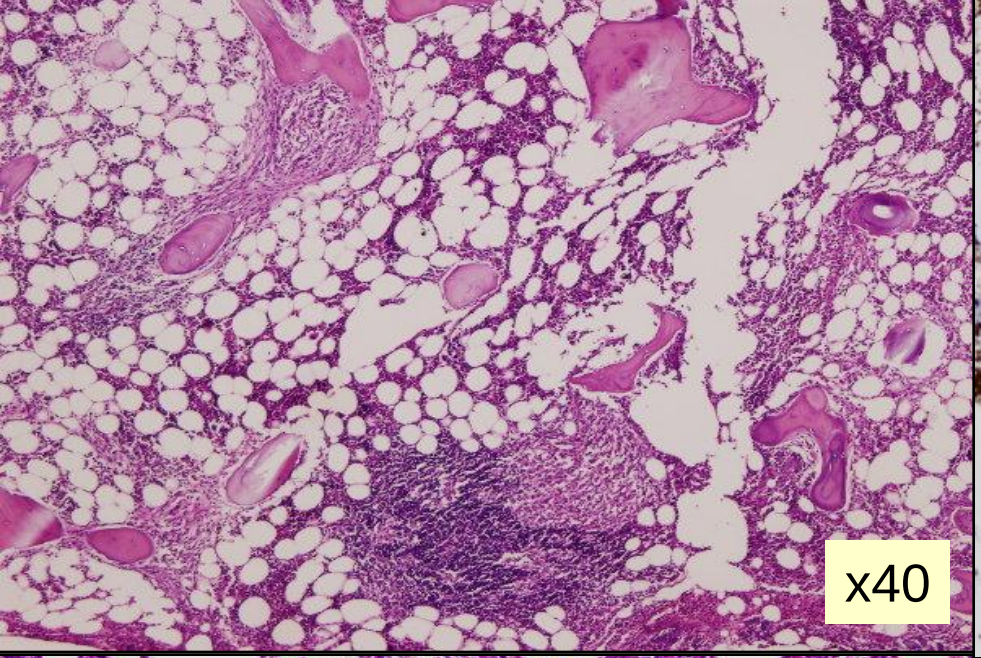


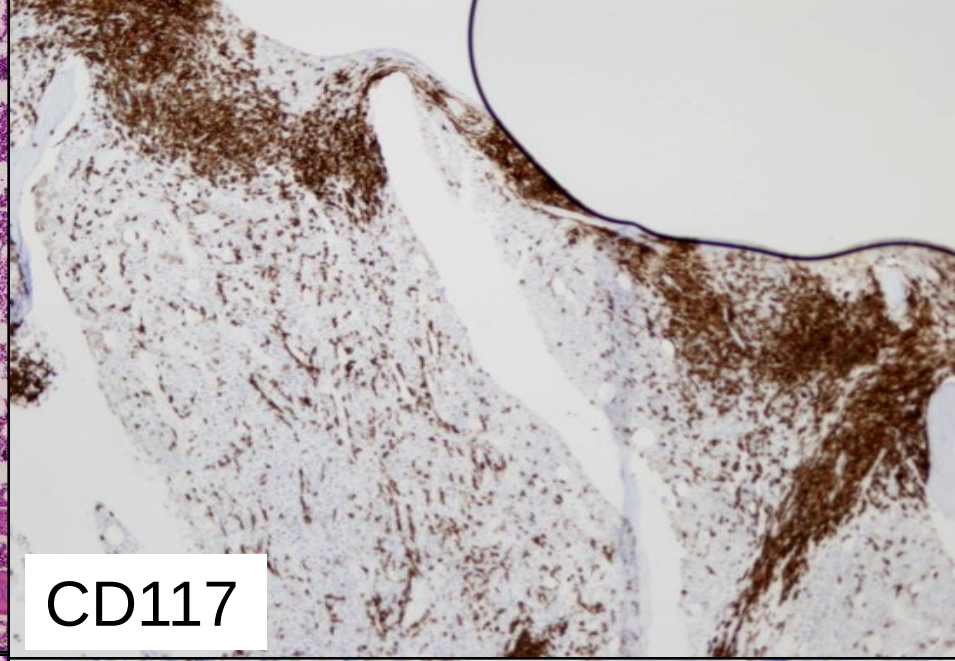


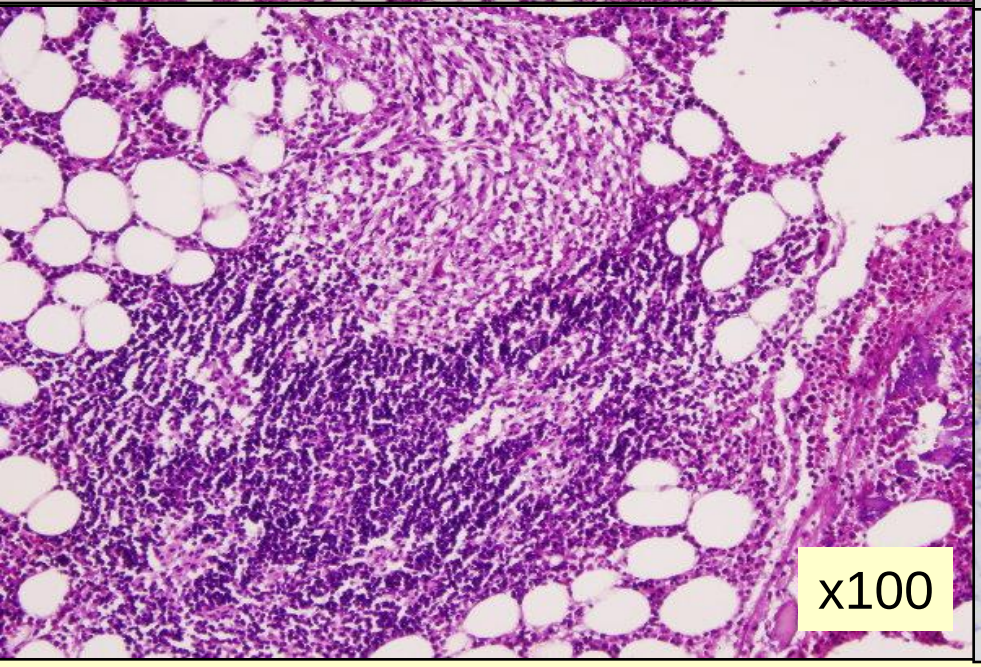


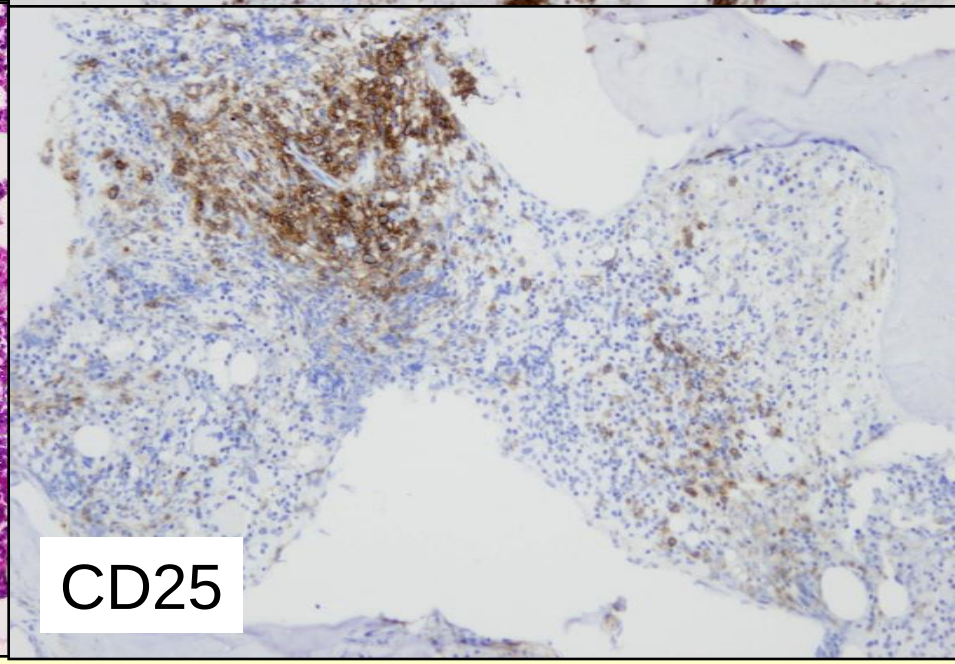
2008 WHO CLASSIFICATION OF CHRONIC MYELOPROLIFERATIVE NEOPLASMS







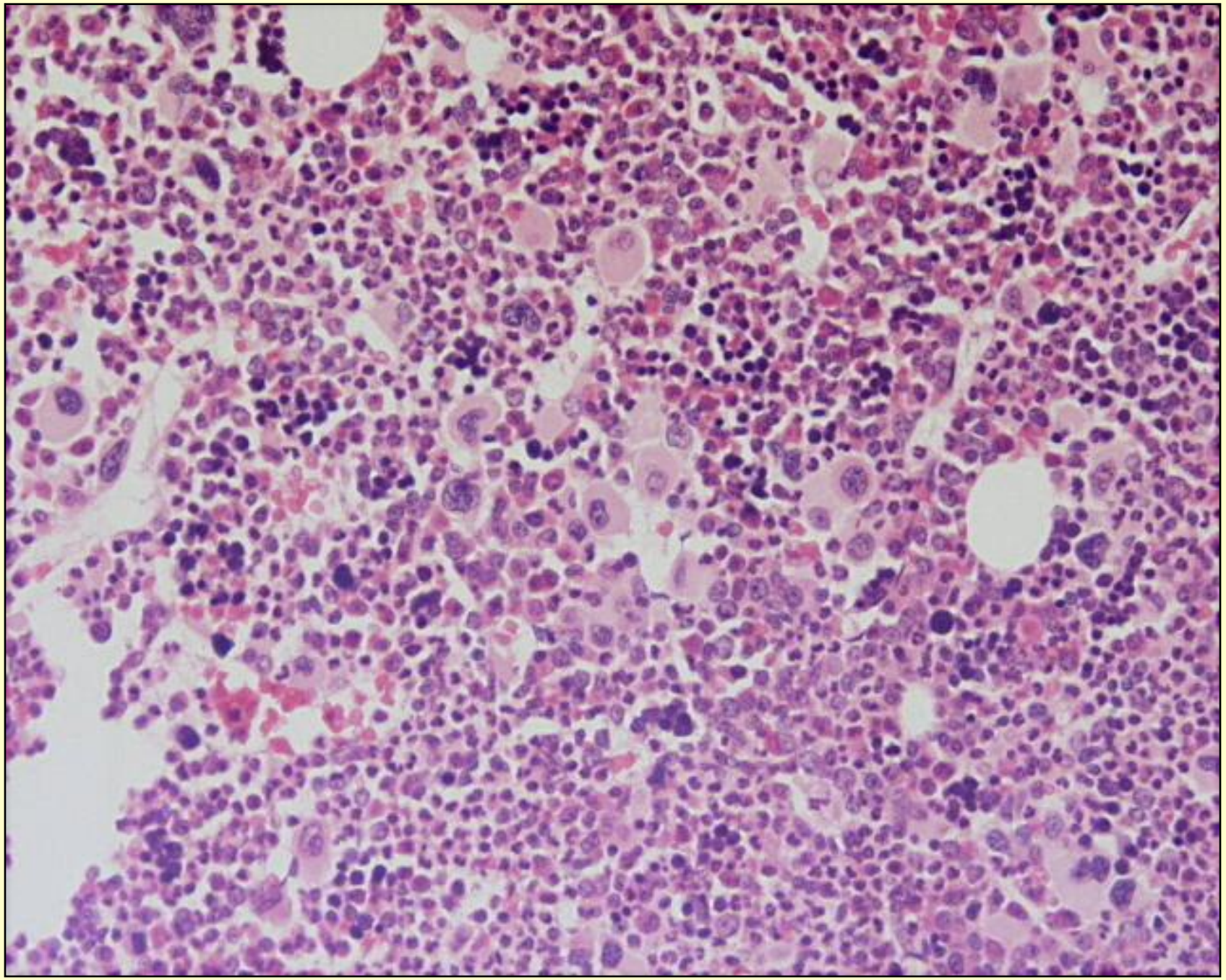


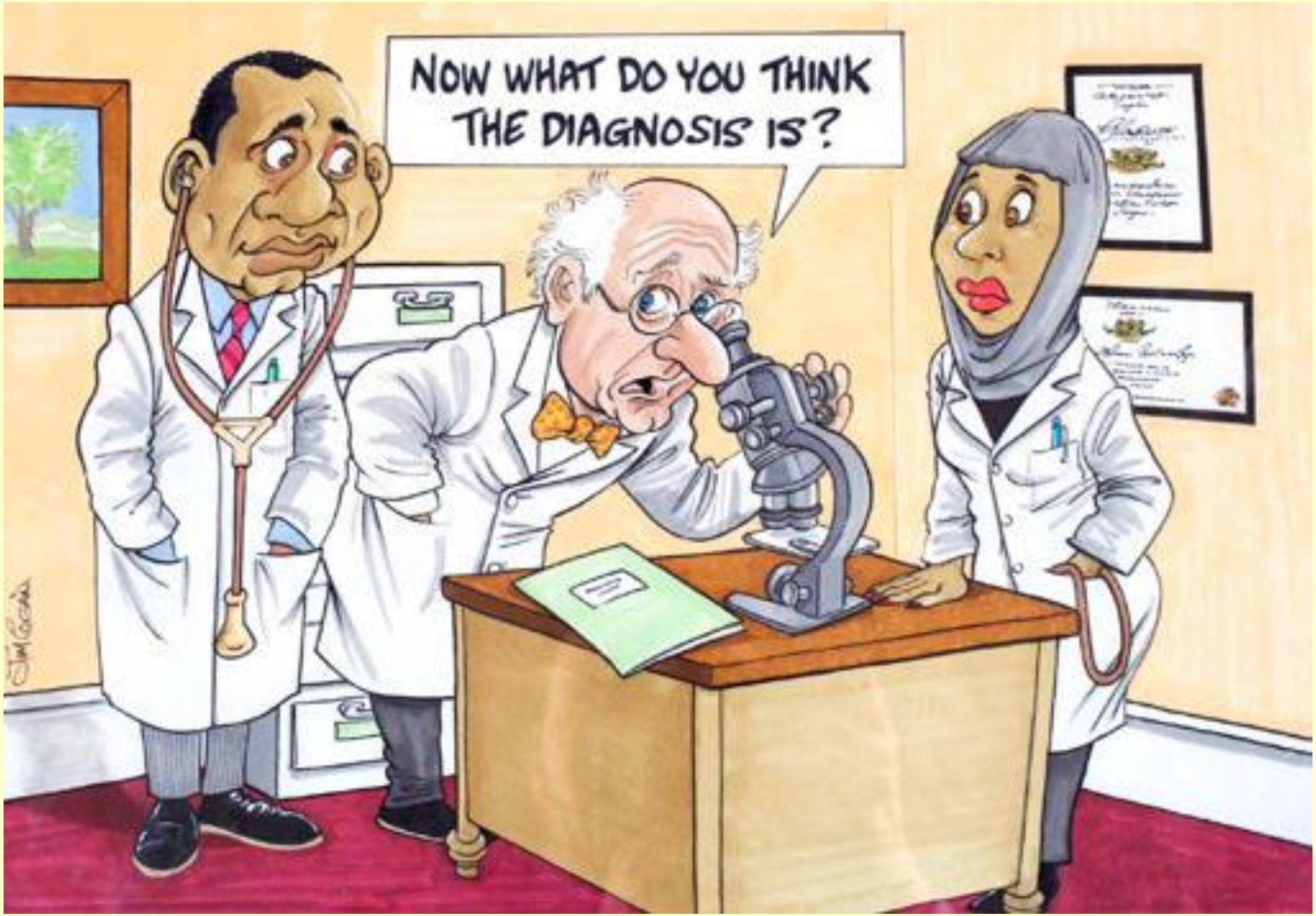


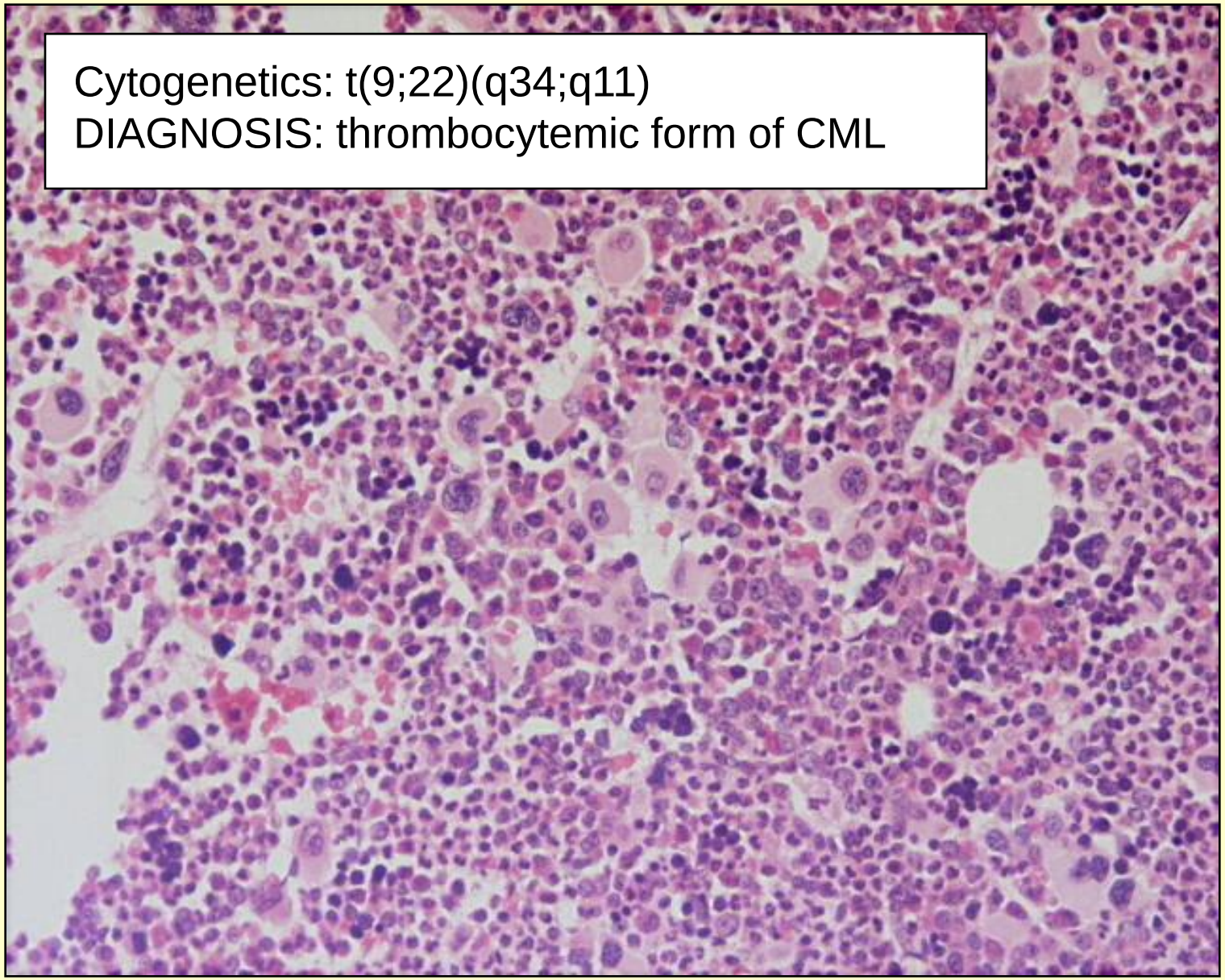
MASTOCITOSIS SISTÉMICA (BMO. HE)

CASE REPORT

- 28-year-old female
- Thrombocytosis during her first pregnancy
- Physical examination: normal
- Blood counts:
  - WBC 20,7x10^9/L
  - Hb 135 g/L
  - Platelets 2.440x10^9/L
- Bone marrow aspirate & biopsy




NOW WHAT DO YOU THINK THE DIAGNOSIS IS?



Cervantes F, Colomer D, Vives-Corrons JL, Rozman C, Montserrat E. Chronic myeloid leukaemia of thrombocythemic onset: a CML subtype with distinct haematological and molecular features?. Leukemia 1996, 10(7):1241-3.

Classification, Diagnosis and Management of Myeloproliferative Disorders in the *JAK2*V617F Era

Ayalew Tefferi

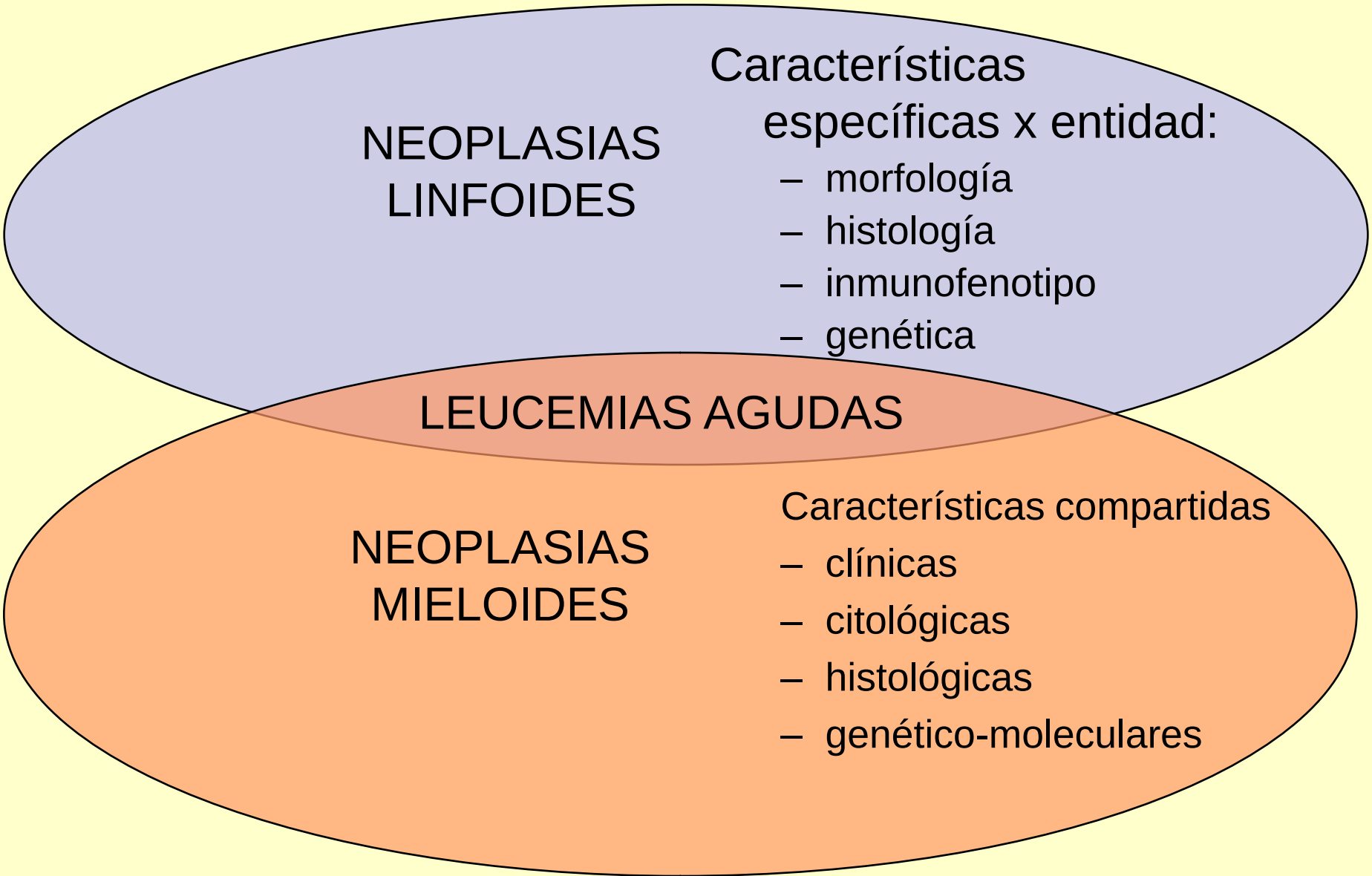
Table 1. Semi-molecular classification of myeloproliferative disorders (MPD).

	Main Categories	Subcategories
I. Classic MPD	1. *BCR-ABL*-positive	Chronic myeloid leukemia (CML)
	2. *BCR-ABL*-negative	A. Polycythemia vera (~100% *JAK2*V617F+)
		B. Essential thrombocythemia (~50% *JAK2*V617F+)
		C. Myelofibrosis (~50% *JAK2*V617F+)
II. Atypical MPD	1. Chronic myelomonocytic leukemia	
	2. Juvenile myelomonocytic leukemia (frequent *PTP11*, *NF1*, and *RAS* mutations)	
	3. Chronic neutrophilic leukemia (~20% *JAK2*V617F+)	
	4. Chronic eosinophilic leukemia/eosinophilic MPD	A. *PDGFRA*-rearranged (e.g., *FIP1L1-PDGFRA*)
		B. PDGFRB-rearranged (e.g., TEL/ETV6-PDGFRB)
		C. FGFR1-rearranged (e.g., *ZNF198/FIM/RAMP-FGFR1*) (a.k.a. *8p11* myeloproliferative syndrome)
		D. Molecularly undefined
	5. Hypereosinophilia syndrome	
	6. Chronic basophilic leukemia	
	7. Systemic mastocytosis	A. *PDGFRA*-rearranged (e.g., *FIP1L1-PDGFRA*)
		B. *KIT*-mutated (e.g., *KIT*D816V)
		C. Molecularly undefined
	8. Unclassified MPD (~20% *JAK2*V617F+)	A. Mixed/overlap myelodysplastic syndrome/MPD
		B. CML-like but *BCR-ABL*-negative

La biopsia medular en las neoplasias mieloproliferativas/mielodisplásicas

- Concepto y clasificación
- Síndromes mielodisplásicos
- Neoplasias mieloides con proliferación predominante de la serie blanca
- Neoplasias mieloides con proliferación predominante de la serie megacariocítica
- Formas raras de neoplasias mieloproliferativas/ mielodisplásicas
- Neoplasias mieloides con fibrosis medular
- Consideraciones finales

PATOLOGÍA NEOPLÁSICA DE LA MÉDULA ÓSEA



INTERPRETACIÓN DE LA BMO EN LAS NEOPLASIAS MIELOIDES

- Clínica:
  - Visceromegalias
  - Hemograma: ↑ o ↓ leucocitos, hematíes y plaquetas, eosinofilia, monocitosis, blastos, etc.
- Aspirado medular, sangre periférica: displasia, blastos
- Descripción histológica:
  - Arquitectura: trabéculas, celularidad / grasa, aspecto fibrótico
  - Megacariocitos: morfología, tamaño, distribución
  - Serie blanca
  - Serie roja
  - Blastos
  - Fibrosis
- Datos genéticos-moleculares

ORIENTACIÓN DIAGNÓSTICA
Patrón “sugestivo de” o “compatible con” …

FINAL CONSIDERATIONS

- When looking to a BM biopsy of a possible MDS/MPN case:
  - Need of clinical data, peripheral blood and bone marrow aspirate information
  - Extensive differential diagnosis including neoplastic and non-neoplastic diseases
  - Use of experts' recommendations and guidelines
  - Molecular studies are mandatory

UNITAT D'HEMATOPATOLOGIA


¡Muchas gracias!