MIELOFIBROSIS

DETECCION Y SEMIOLOGIA HISTOPATOLOGICA

POLICITEMIA VERA, TROMBOCITOSIS ESENCIAL Y MIELOFIBROSIS PRIMARIA

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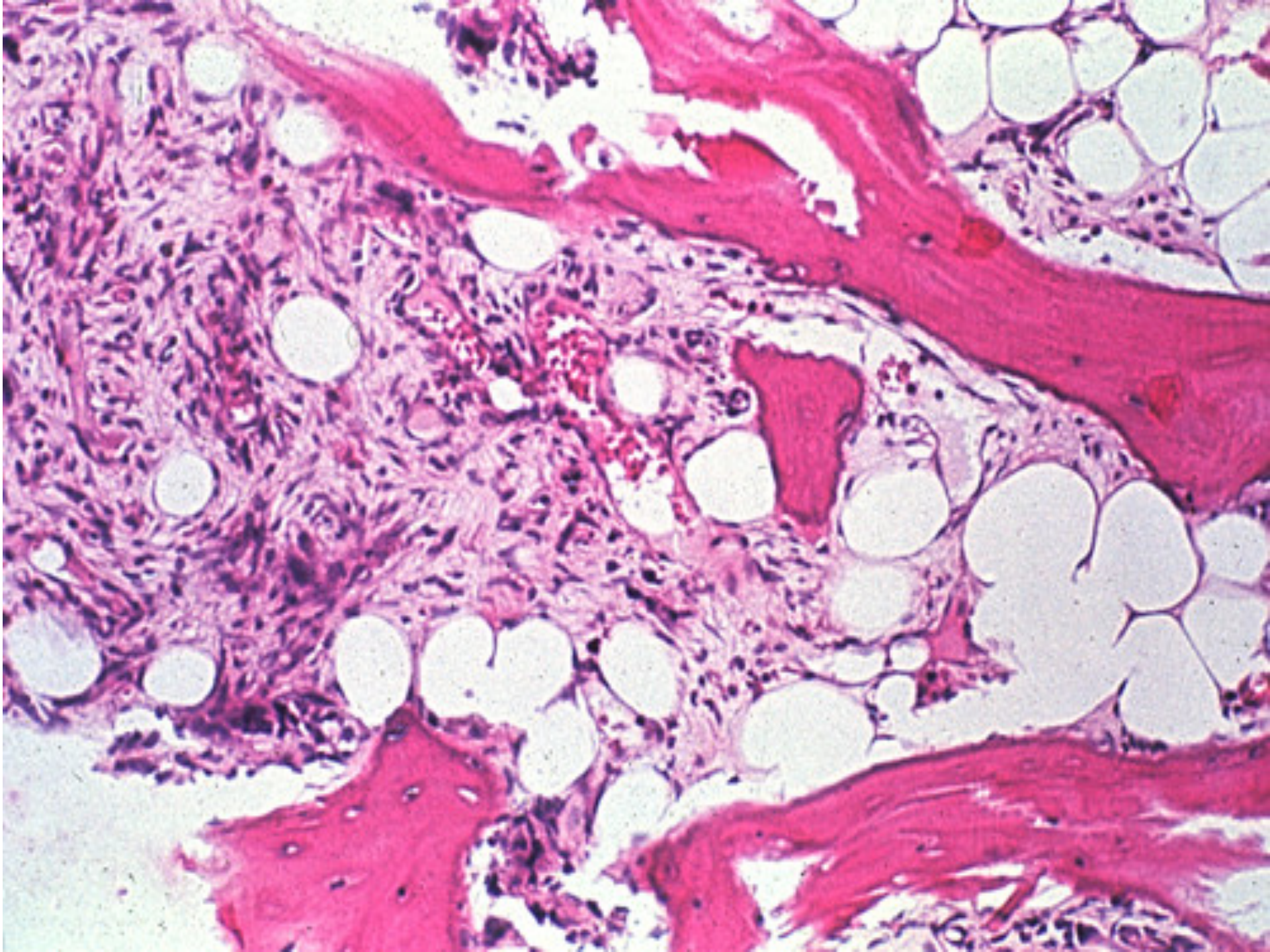
Mielofibrosis. Definiciones

- Remplazo de la médula ósea por tejido fibroso, entendiéndose este último como incremento de fibras reticulares y/o colágenas en la médula.

- Transformación de la médula ósea en tejido fibroso

- Cicatrización de la médula ósea



Tinciones para detectar y establecer grados de fibrosis

- Reticulina
- Tricrómica

Reticulina de Wilder

Procedimiento:

- Desparafinar e hidratar.
- Agregar Permanganato de Potasio al 0.5% por 5 minutos.
- Lavar con agua destilada.
- Agregar Acido Oxálico al 5% por 2 minutos.
- Lavar con agua destilada.
- Agregar sulfato Ferrico Amoniacal al 3% por 3 minutos.
- Lavar con agua destilada.
- Agregar la Solución de Plata de Wilder por ***2 minutos***.
- ***Lavar con agua destilada rápidamente***.
- Agregar Formol al 2%
- Lavar con agua destilada.
- Agregar cloruro de oro 1 minuto (OPCIONAL, sirve para limpiar)
- Lavar con agua destilada.
- Contrastar con Van Giesson por 1 minuto.
- No lavar. Secar con un papel y montar
- Control: higado, ganglio

EVITAR AIRE
TECNOLOGO METICULOSO

Enfermedades en las cuales la mielofibrosis es o puede ser un componente del aspecto histopatológico

NO NEOPLASIAS MIELOPROLIFERATIVAS

- Neoplasias mieloides y linfoides con eosinofilia y anomalías de PDGFRA, PDGFRB o FGFR
- Linfomas Hodgkin y no Hodgkin
- Leucemias agudas mieloides y linfoides
- Metástasis
- Enfermedades autoinmunes (mielofibrosis autoinmune)
- Enfermedades infecciosas, granulomatosas o no.
- Exposición al dióxido de torio
- Osteodistrofia renal
- PTI tratada con agonistas de receptores de trombopoyetina

NEOPLASIAS MIELOPROLIFERATIVAS

- Leucemia mieloide crónica, BCR-ABL1+
- Leucemia neutrofílica crónica
- Policitemia vera
- Mielofibrosis primaria
- Trombocitemia esencial
- Leucemia eosinofílica crónica
- Mastocitosis sistémica
- Neoplasia mieloproliferativa no clasificable

NEOPLASIA MIELOPROLIFERATIVAS

. Trastornos hematopoyéticos caracterizados por la proliferación clonal efectiva de una o más series mieloides (granulocítica, eritrocítica, megacariocítica, mastocitos), que cursa con MO hipercelular y un incremento de las cifras en SP.

. Diagnóstico basado en la correlación de datos clínicos, analíticos, morfológicos , moleculares y genéticos

Avances en el diagnóstico de NMPC- OMS 2008

- Incorporación de JAK2 en los algoritmos
- Anomalías de PDGFRA, PDGFRB o FGFR1
- Mastocitosis sistémica como subcategoría
- Cambio de nomenclatura:

– Mielofibrosis crónica idiopática por Mielofibrosis primaria

– Transtornos mieloproliferativos crónicos por Neoplasias mieloproliferativas crónicas

POLYCYTHEMIA VERA

PV is a myeloproliferative neoplasm arising in a pluripotential hematopoietic stem cell that is characterized by increased red blood cell production resulting in an elevated red blood cell mass. The process has a polycythemic phase and a terminal, or spent, phase characterized by marrow fibrosis. There may also be a pre-polycythemic phase, but this is difficult to recognize. Occasionally it may transform to acute leukemia

POLYCYTHEMIA VERA

Incidence, Gender, and Age Distribution

1 to 3 cases per 100,000 population per year

Slight male predominance

Median age at diagnosis, 60 years; less than 5% younger than 40 years, rare cases in children

Increased incidence in Ashkenazi Jews

POLYCYTHEMIA VERA

Clinical Features

Symptoms

Hyperviscosity-related headache, blurry vision

Arterial and venous thrombosis

Hemorrhage

Pruritus provoked by warm water

Symptoms related to gout

Physical Findings

Splenomegaly, hepatomegaly

Plethora

POLYCYTHEMIA VERA

Microscopic Features (Polycythemic Phase)

Blood
Erythrocytosis (normochromic normocytic red blood cells)
Granulocytes may be elevated
Platelets elevated in ½ of patients

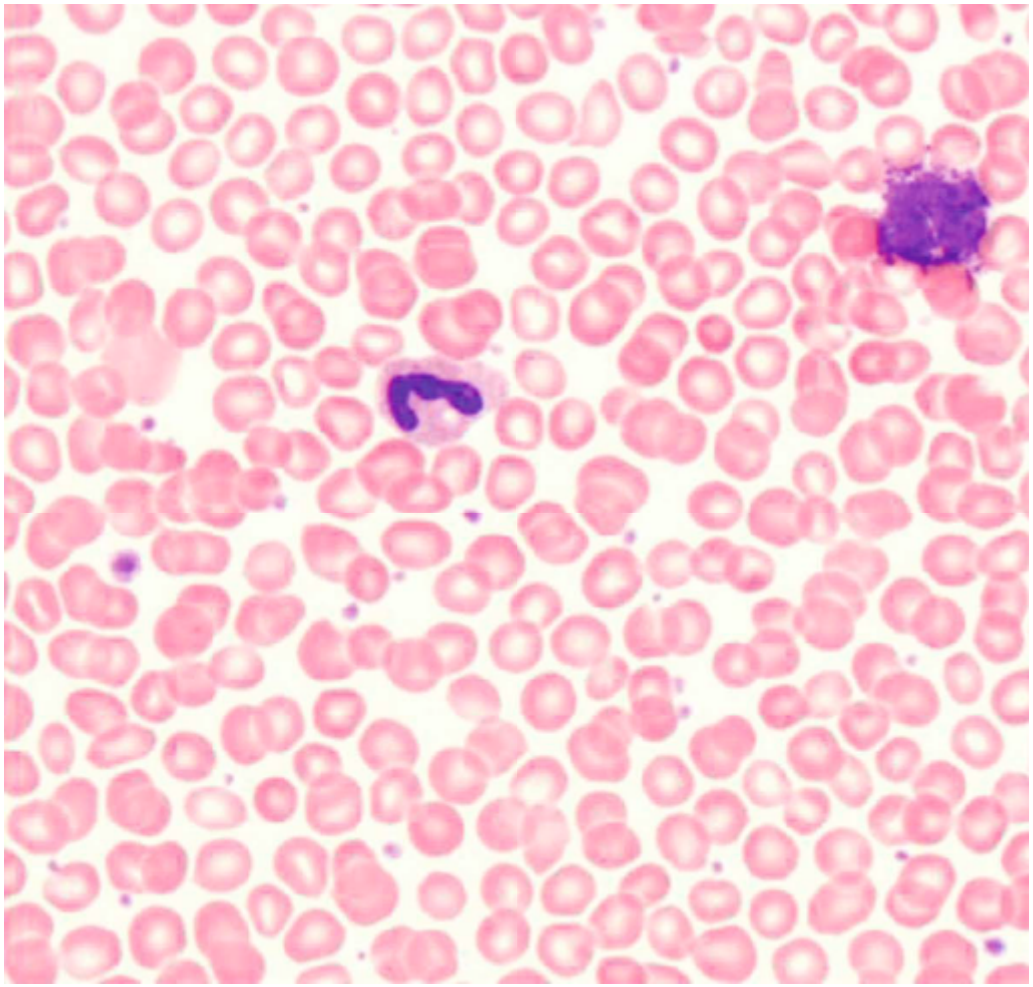
Marrow
Usually hypercellular, may be normocellular
Panmyelosis: increased erythroid and megakaryocytic elements
Megakaryocytes are large, clustered, but not bizarre
Fe absent in 95% of cases
Fibrosis not increased

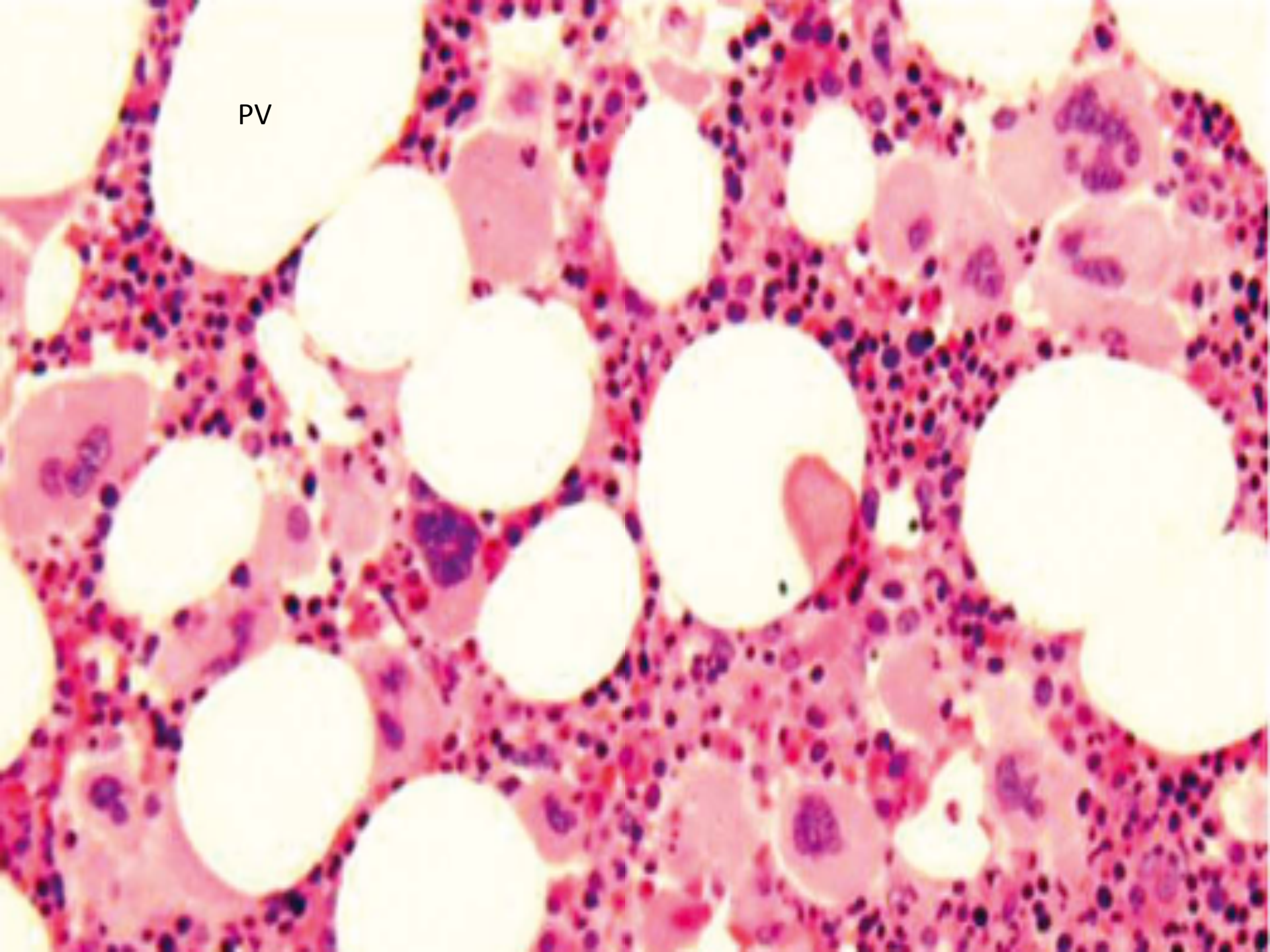
Ancillary Studies
EPO levels
Red cell mass measurement (not widely available)
Cytogenetic analysis: abnormalities in only 10% to 20%; +8, +9, del (20q), del(13p), del(1p)
Evaluation of exogenous erythroid colony formation (in vitro; not widely available)

POLICITEMIA VERA

SANGRE

PERIFERICA




PV

POLYCYTHEMIA VERA

Diagnostic Criteria (WHO, 2008)

Diagnose PV when both major criteria and one minor are met or when the first major and two minor criteria are met

Major Criteria

- Hemoglobin greater than 18.5 g/dL in men, hemoglobin greater than 16.5 in women, or other evidence of increased red cell volume
- Presence of *JAK2* V617F or other functionally similar mutation, such as *JAK2* exon 12 mutations

Minor Criteria

- Bone marrow biopsy specimen showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
- Serum EPO level below the reference range
- Endogenous erythroid colony formation

POLYCYTHEMIA VERA

Diagnostic Criteria (WHO, 2015)

Diagnosticar PV when all major criteria are met or when two major and one minor criteria are met

Major Criteria

- Hemoglobin greater than 16.5 g/dL in men, hemoglobin greater than 16.0 in women, or other evidence of increased red cell volume
- Presence of *JAK2* V617F or other functionally similar mutation, such as *JAK2* exon 12 mutations
- Bone marrow biopsy specimen showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation

Minor Criteria

- Serum EPO level below the reference range
- Endogenous erythroid colony formation

POLYCYTHEMIA VERA

Spent Phase, Post-Polycythemic Myelofibrosis
The red cell mass normalizes and even sometimes decreases.

Leukoerythroblastic process is seen in the blood, resembling that associated with PMF

The marrow becomes increasingly fibrotic and sometimes progresses to collagen fibrosis. Sinusoidal hematopoiesis is common, and osteosclerosis may develop.
Immature elements also become more prominent.
When patients initially present in the post-polycythemic phase, hemoglobin levels would have become normalized or even reduced. Thus, a diagnosis of MPN, unclassifiable, must be made because distinction from a *JAK2*mutation-positive PMF is not possible.

Some patients may develop an acute leukemic transformation; however, this is seen more frequently in patients treated with chemotherapies than without**.**

Mielofibrosis post PV

Criterios requeridos:

. Diagnóstico previo de PV (definido por OMS)

. Fibrosis medular grado 2 o 3 (OMS)

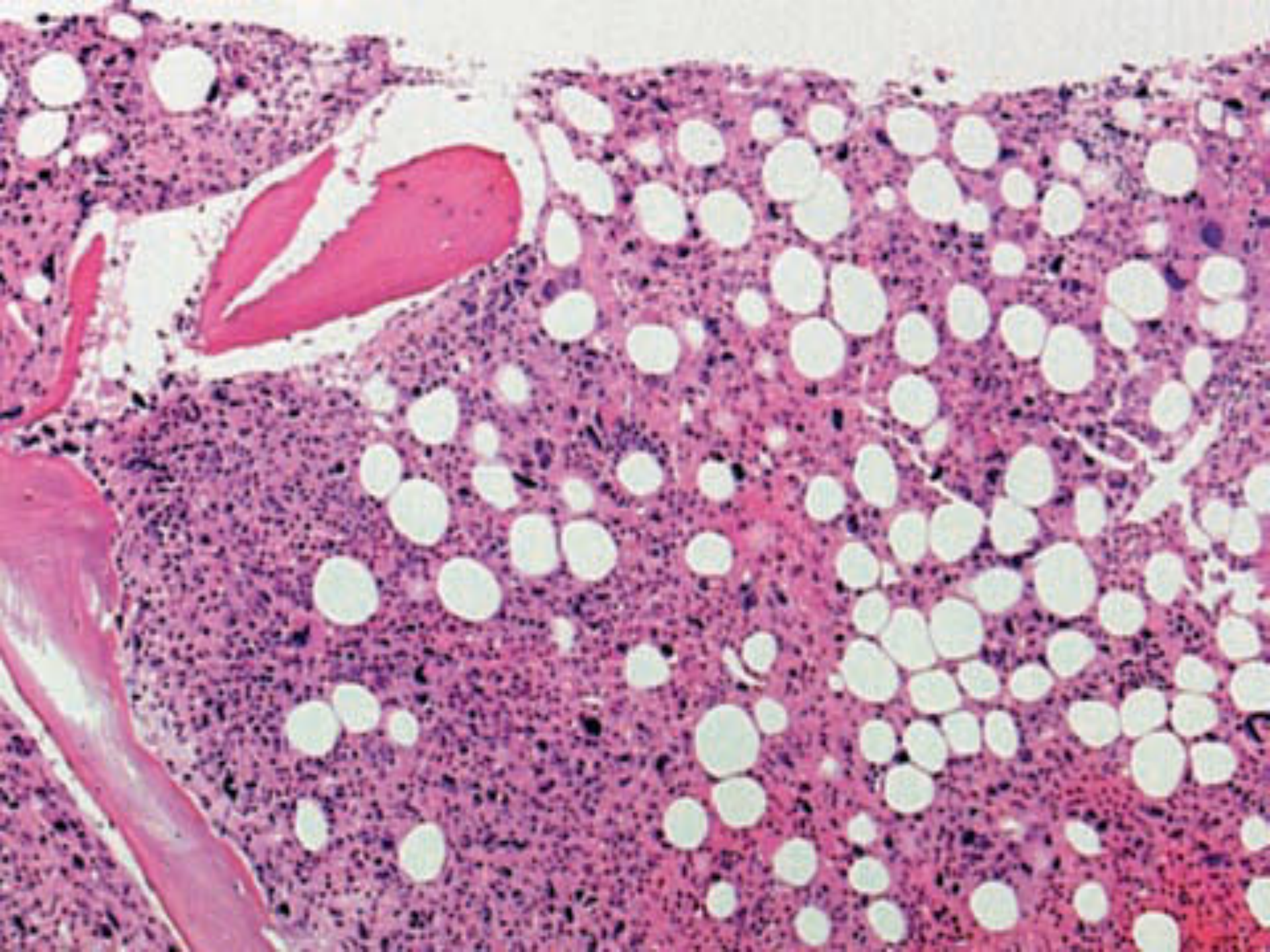
Criterios adicionales (se requieren dos):

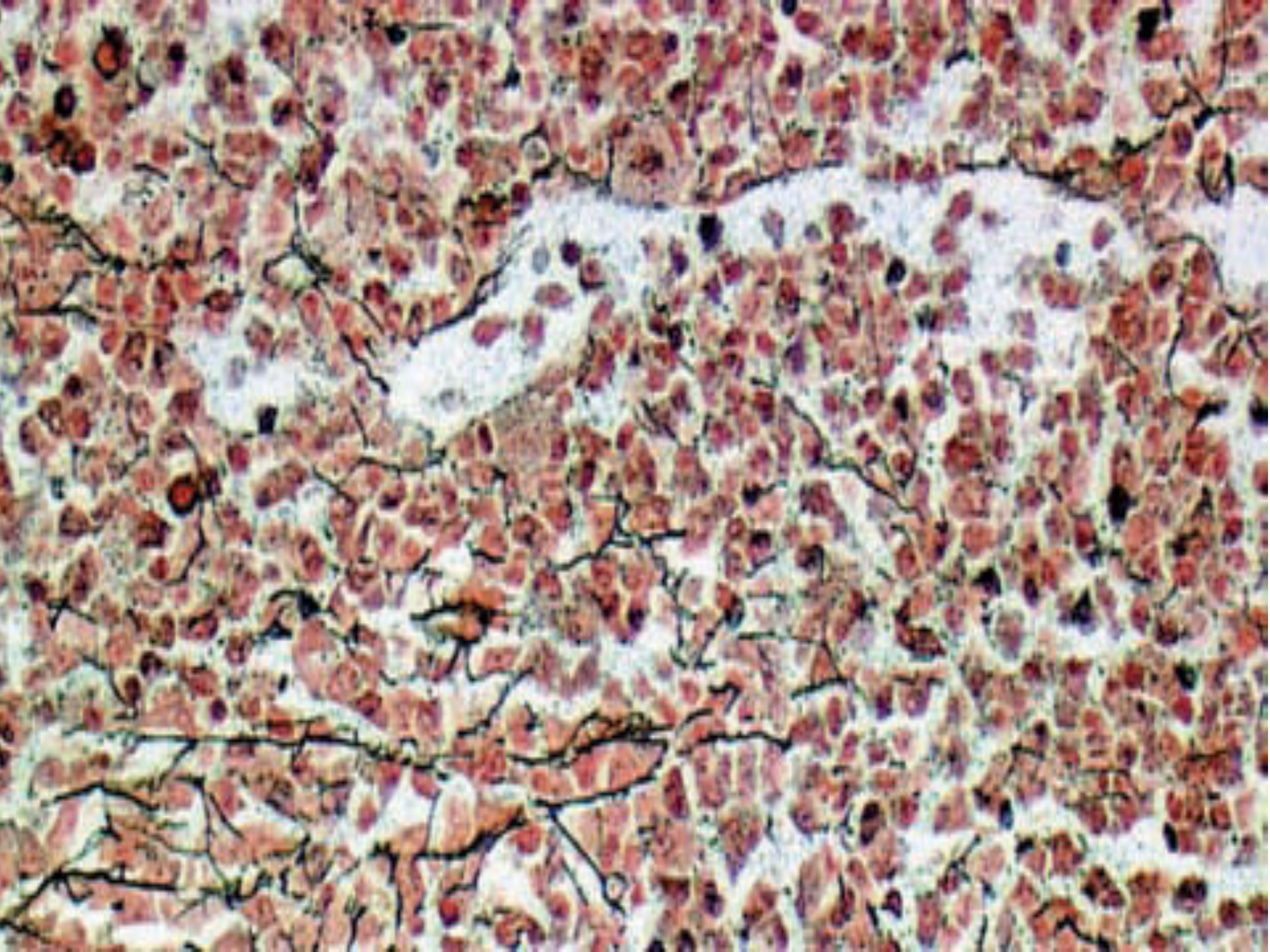
. Anemia

. Reacción leucoeritroblástica

. Desarrollo o empeoramiento de esplenomegalia

. Presencia de más de uno de estos tres (pérdida de peso >10% en 6 meses, sudoración nocturna, fiebre inexplicable)





La expresión elevada (> 30% en eritroblastos) de NF-E2 se observa solamente en PV yTE pero no en MFP.

MFP muestra una densidad microvascular (evaluada con CD34) y expresión de NGFR mucho mayores que PV y TE.

Essential Thrombocythemia

Essential thrombocythemia (ET) is a myeloproliferative disorder that is largely characterized by a pronounced proliferation of megakaryocytes, resulting in a severe and sustained thrombocytosis, which is also referred to as *thrombocythemia*.

Since most of the other myeloproliferative neoplasms can have markedly elevated platelets and megakaryocytic proliferations, differential diagnostic considerations for the other MPNs are important. The differential diagnosis must also include other rare acute myeloid leukemias, MDS, or MDS/MPNs, associated with increased platelets (most notably AML with t[3;3] or inv[3], the 5q-minus syndrome, and RARS-T), and, of course, reactive conditions leading to elevated platelets.

ESSENTIAL THROMBOCYTHEMIA

Incidence, Gender, and Age Distribution

- 1 to 2.5 cases per 100,000 population per year
- Slight female predominance (male : female = 2 : 1)
- Median age, 60 years
- Increased incidence in Ashkenazi Jews
- Rare familial cases

ESSENTIAL THROMBOCYTHEMIA

Clinical Features

Many patients are asymptomatic (one-quarter to one-third)

Symptoms:

- Headache, lightheadedness, blurry vision, scotomata, palpitations, chest pain, distal paresthesias, symptoms related to large vessel thromboses
- Spontaneous abortions

Physical findings: splenomegaly (20% to 50%), hepatomegaly

ESSENTIAL THROMBOCYTHEMIA

Microscopic Findings

Blood

- Marked thrombocytosis with platelet anisocytosis
- Normal white blood cell count, no dysplasia
- Normal red blood cell morphology

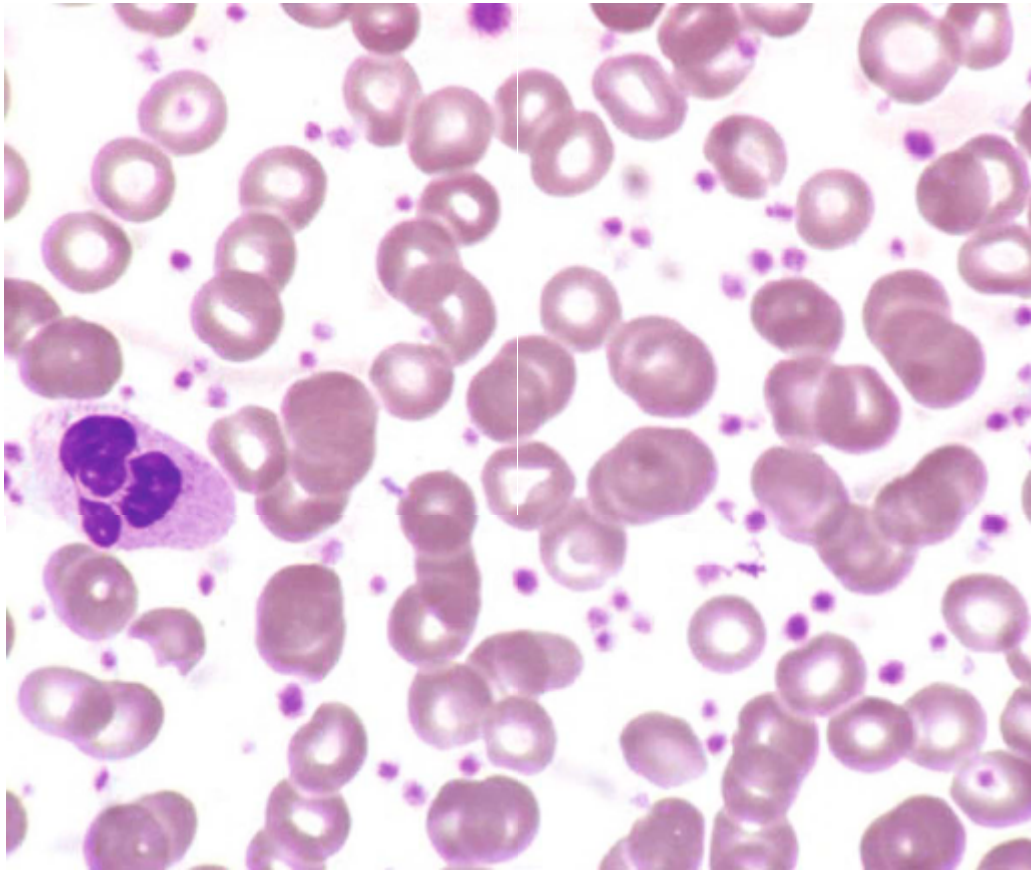
Marrow

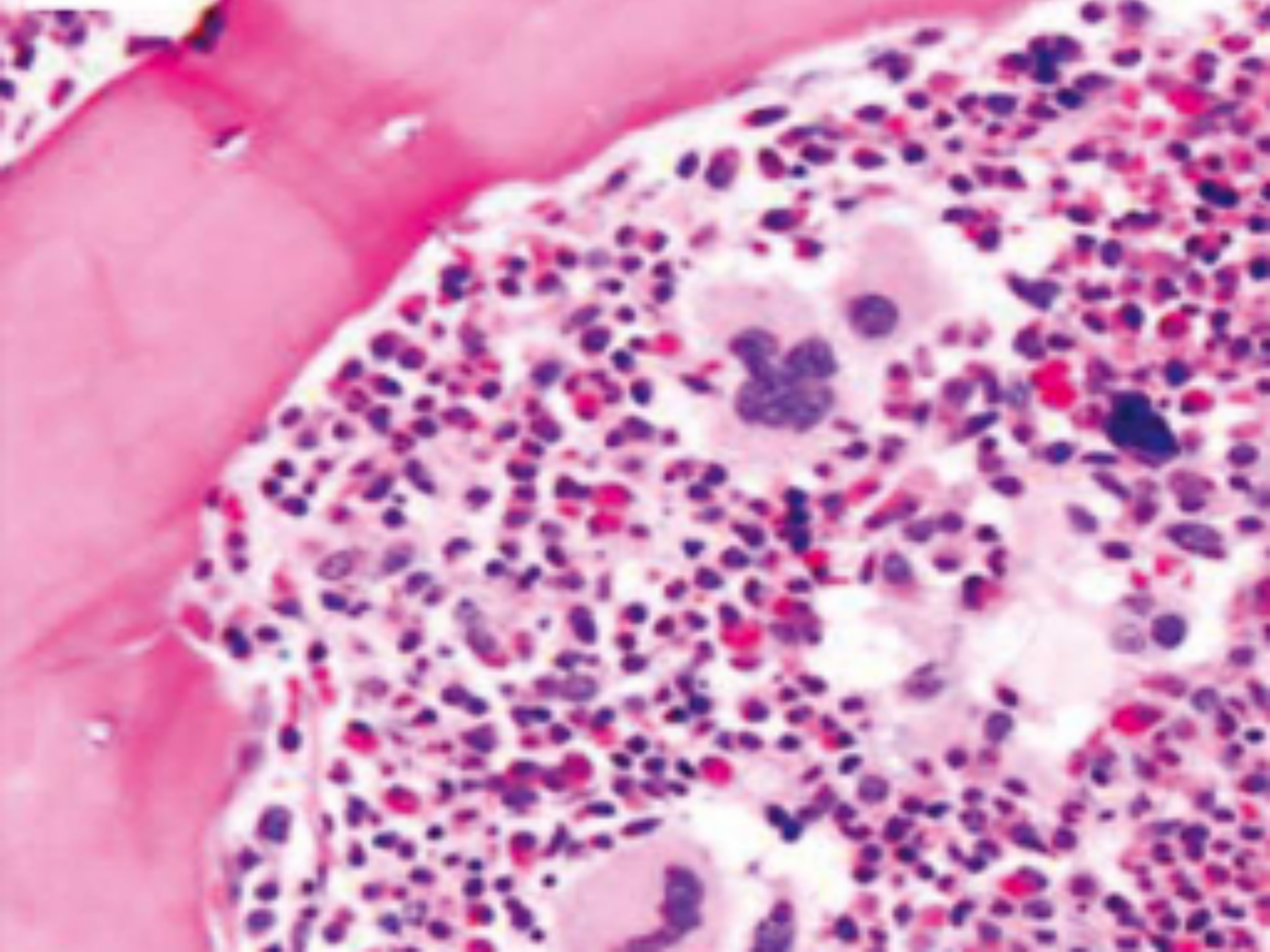
- Moderately hypercellular, in general
- Prominent megakaryocytic proliferation throughout, little clustering, large size, sometimes hyperlobulated (staghorn-like), not bizarre
- Minimal granulocytic proliferation
- Absent to minimal reticulin fibrosis
- Fe present

TROMBOCITEMIA

SANGRE

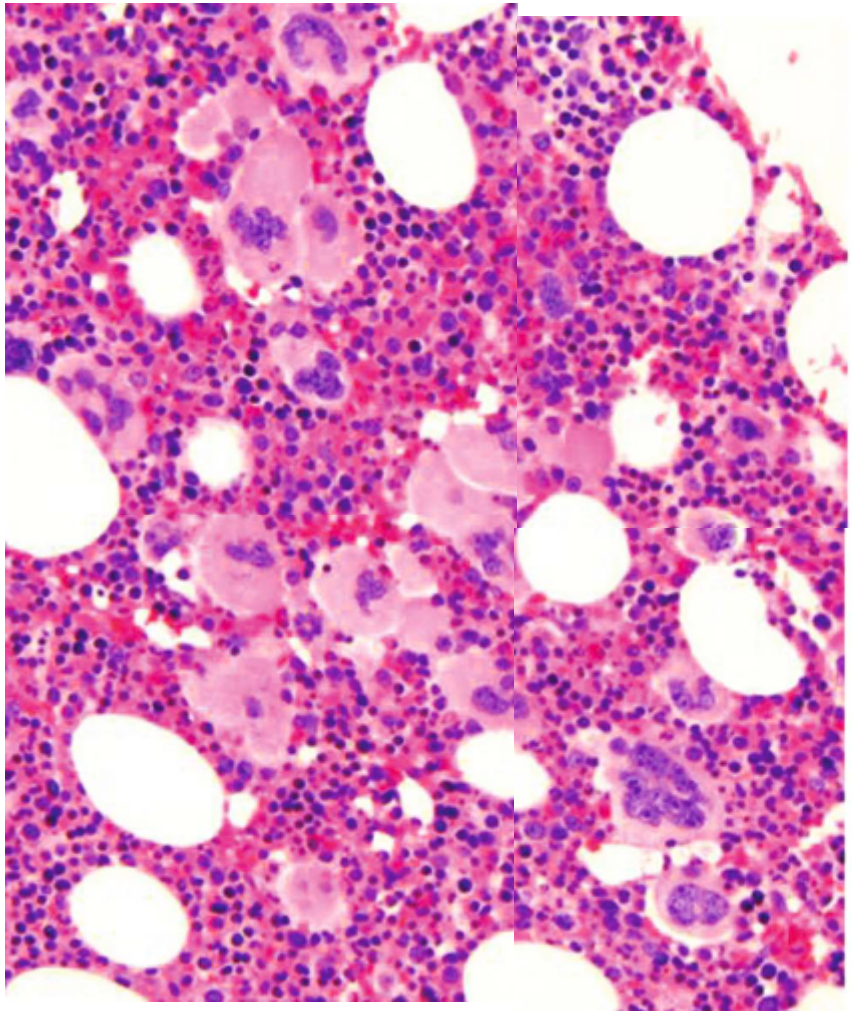
PERIFERICA





ESSENTIAL TROMBOCYTHEMIA

large megakaryocytes with abundant cytoplasm and prominent nuclear lobulation.



ESSENTIAL THROMBOCYTHEMIA

Diagnostic Criteria (WHO, 2008)
All four criteria must be met:

- Sustained platelet count of $450 \times 10^9/\mu L$
- Bone marrow biopsy specimen showing proliferation mainly of megakaryocytes that are large and mature; no increase or left shift in granulocytes or erythroid elements
- Not meeting criteria for PV, PMF, CML, MDS or other myeloid neoplasm
- Demonstration of *JAK2* V617F or other clonal marker, or in the absence of *JAK2* V617F, no evidence of reactive thrombocytosis

ESSENTIAL THROMBOCYTHEMIA

Diagnostic Criteria (WHO, 2015)

All four mayor criteria must be met or the first three mayor and the one minor

Mayor criteria

- Sustained platelet count of 450 × 10^9/µL
- Bone marrow biopsy specimen showing proliferation mainly of megakaryocytes that are large and mature; no increase or left shift in granulocytes or erythroid elements
- Not meeting criteria for PV, PMF, CML, MDS or other myeloid neoplasm
- Demonstration of *JAK2* V617F or CARL or MPL

Minor criterium

- Other clonal marker, or no evidence of reactive thrombocytosis

ESSENTIAL THROMBOCYTEMIA

A post-ET myelofibrotic transformation has been described, but it is difficult to determine whether some of these cases were misdiagnosed ET and actually the represented prefibrotic phase of PMF that naturally would proceed to fibrosis.

However, in cases in which fibrosis occurs late in the disease course, many years or even decades after the initial diagnosis, this argument may not hold and may justify the existence of this transformation.

Mielofibrosis post TE

Criterios requeridos:

. Diagnóstico previo de TE (definido por OMS)

. Fibrosis medular grado 2 o 3 (OMS)

Criterios adicionales (se requieren dos):

. Anemia

. Reacción leucoeritroblástica

. Desarrollo o empeoramiento de esplenomegalia

. Presencia de más de uno de estos tres (pérdida de peso >10% en 6 meses, sudoración nocturna, fiebre inexplicable)

. Incremento de LDH

MIELOFIBROSIS PRIMARIA

- Proliferación megacariocítica y granulocítica con maduración intacta, fibrosis medular progresiva, esplenomegalia y hematopoyesis extramedular
- Dos fases: pre-fibrótica y fibrótica
- Mal pronóstico en fase fibrótica

PRIMARY MYELOFIBROSIS

Incidence, Gender, and Age Distribution

- 0.5 to 1 per 100,000 population per year
- Equal sex distribution
- Median age, 54 to 62 years
- Increased incidence in Ashkenazi Jews

PRIMARY MYELOFIBROSIS

Clinical Features

Symptoms:

- Thirty percent to 40% of patients are asymptomatic
- Weight loss, constitutional symptoms
- Symptoms related to anemia, splenomegaly, gout, renal stones

Physical findings: splenomegaly, often massive

FASE PREFIBROTICA

SANGRE PERIFERICA

- ELEVACION MODERADA DE LEUCOCITOS
- ANEMIA LEVE
- PLAQUETAS ELEVADAS HASTA 900 × 10^9/L

No hay células en lágrima ni leucoeritroblastosis

MEDULA OSEA

- HIPERCELULAR
- PROLIFERACION DE MEGACARIOCITOS Y GRANULOCITOS
- LOS MEGACARIOCITOS PUEDEN MOSTRAR ATIPIA O FORMAR AGREGADOS

No fibrosis / No fibrosis significativa

Diagnostic Criteria (WHO, 2008)

Requires meeting all three major and two minor criteria

Major Criteria

Presence of megakaryocytic proliferation usually accompanied by reticulin or collagen fibrosis or in the absence of fibrosis the megakaryocytes must be accompanied by an increased marrow cellularity, characterized by granulocytic proliferation, and often decreased erythropoiesis

Not meeting criteria for PV, CML, MDS or other myeloid diseases

JAK2 V617F or other clonal marker or in the absence of a clonal marker, no evidence that the marrow fibrosis or other changes are secondary (infection, autoimmune, chronic inflammation, hairy cell leukemia, other malignancies including metastatic tumor, or due to toxic myelopathies)

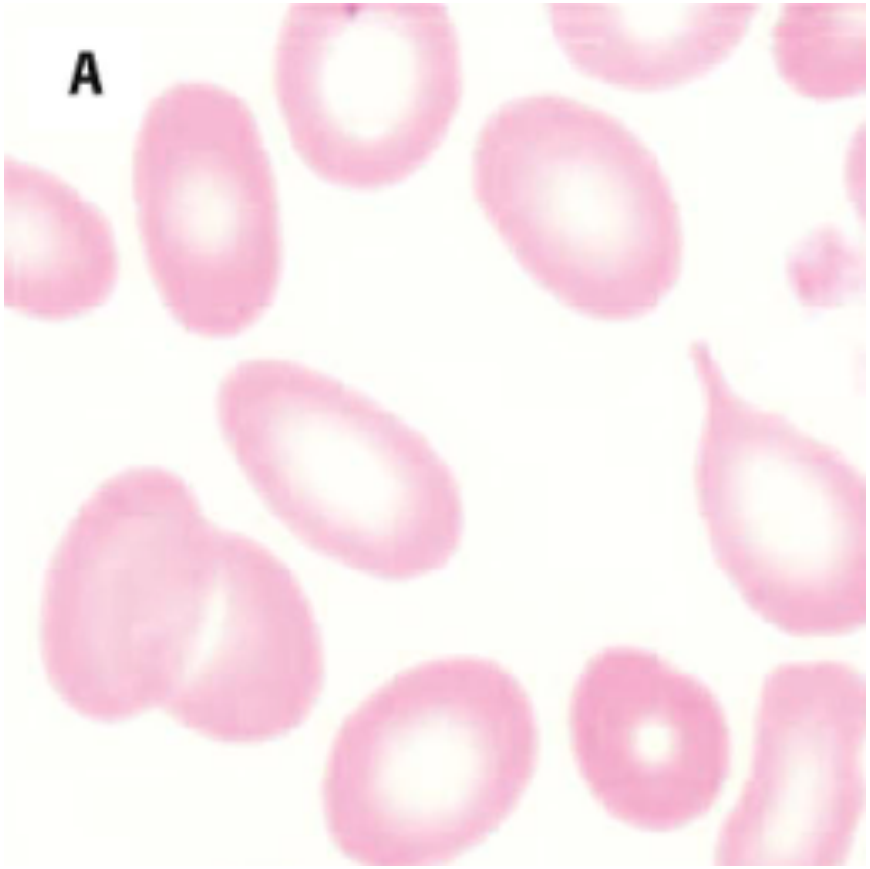
Minor Criteria

Leukoerythroblastosis

Increased serum lactate dehydrogenase

Anemia

Splenomegaly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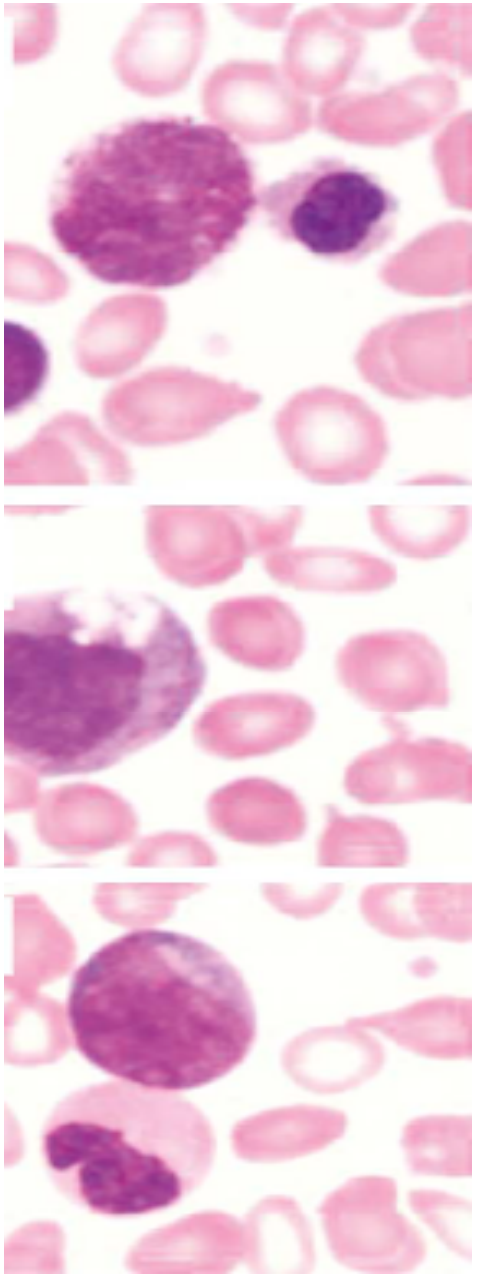
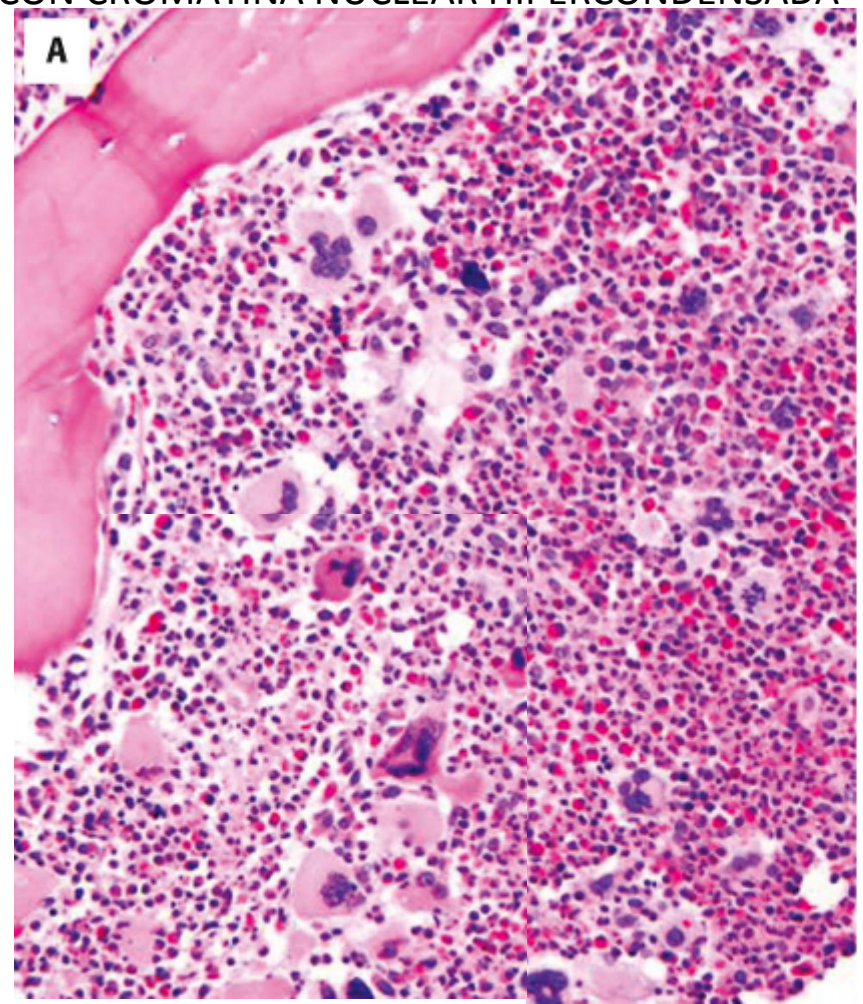
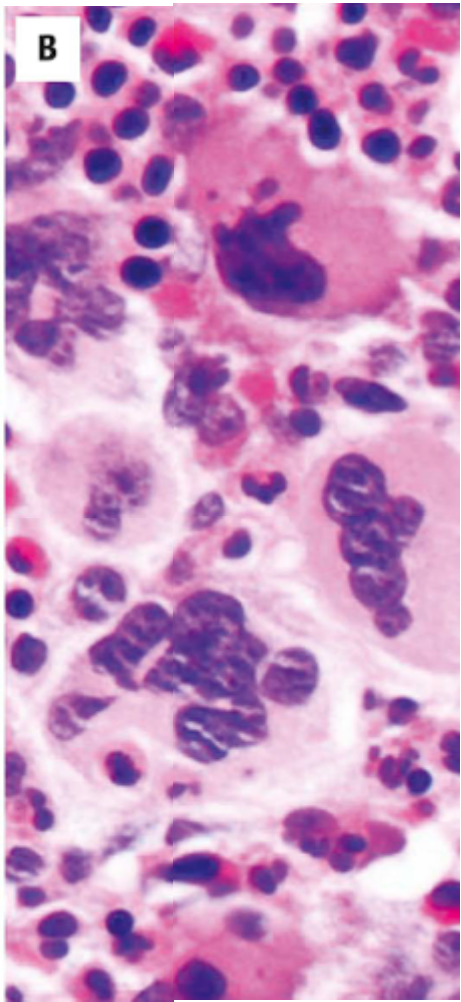


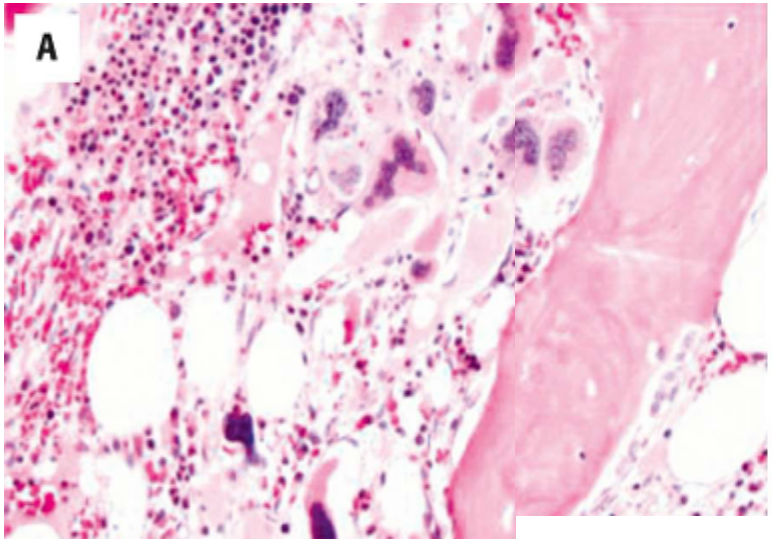
FASE PREFIBROTICA

- PROLIFERACION MEGACARIOCITICA Y GRANULOCITICA.
- MEGACARIOCITOS ATIPICOS CON CROMATINA NUCLEAR HIPERCONDENSADA





FORMACION DE CLUSTERS Y LOCALIZACION PARATRABECULAR DE MEGACARIOCITOS EN FASE PREFIBROTICA



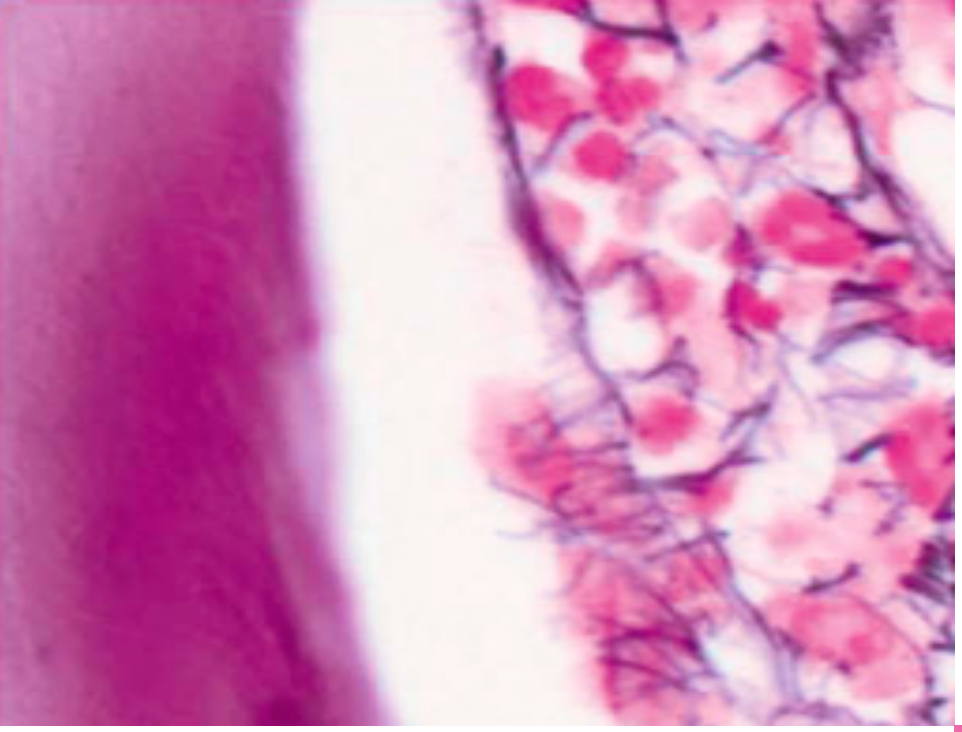
FASE FIBROTICA

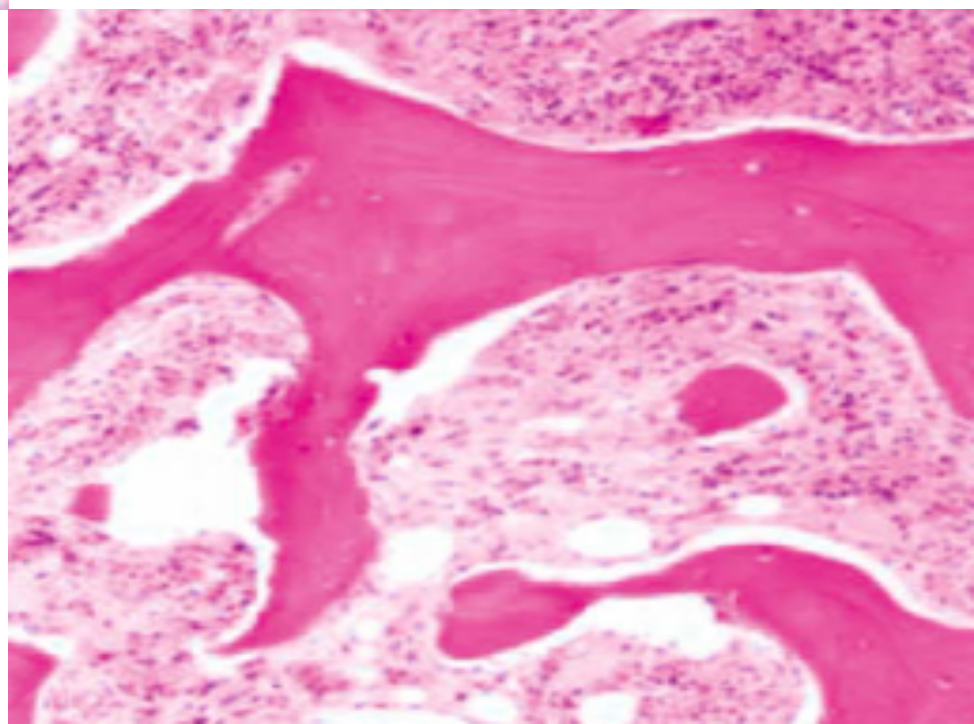
SANGRE PERIFERICA

- LEUCOCITOSIS LEVE (VARIABLE)
- ANEMIA
- TROMBOCITOSIS MODERADA (VARIABLE)
- LEUCOERITROBLASTOSIS
- PUEDE HABER ALGUNOS BLASTOS
- CELULAS EN LAGRIMA (DACRIOCITOS) ANISOCITOSIS Y POIQUILOCITOSIS

MEDULA OSEA

- INASPIRABLE, FIBROSIS PROGRESIVA
- OSTEOESCLEROSIS
- DISMINUCION PROGRESIVA DE LA CELULARIDAD
- MEGACARIOCITOS ATIPICOS , BIZARROS, CON CROMATINA CONDENSADA, NUCLEOS DESNUDOS
- BLASTOS < 20%
- HEMATOPOYESIS EXTRAMEDULAR (SINUSOIDAL)



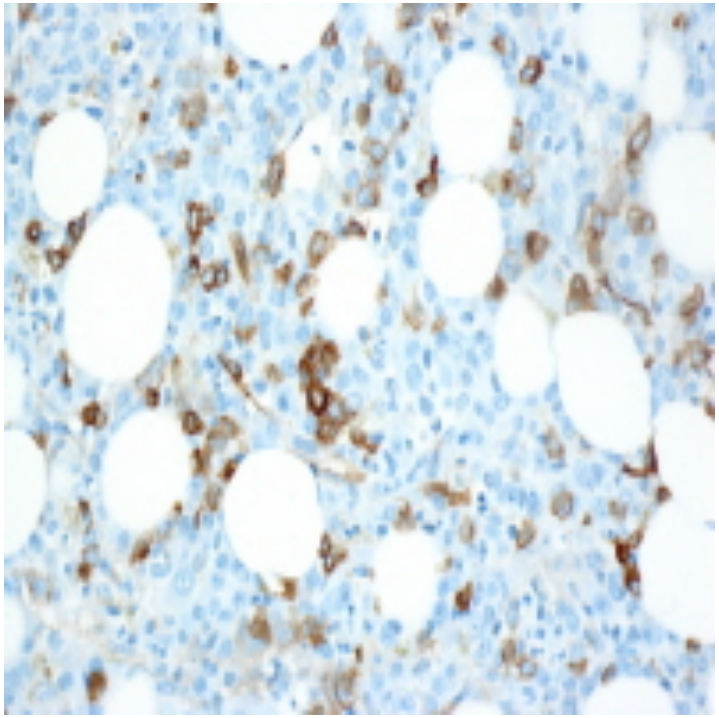


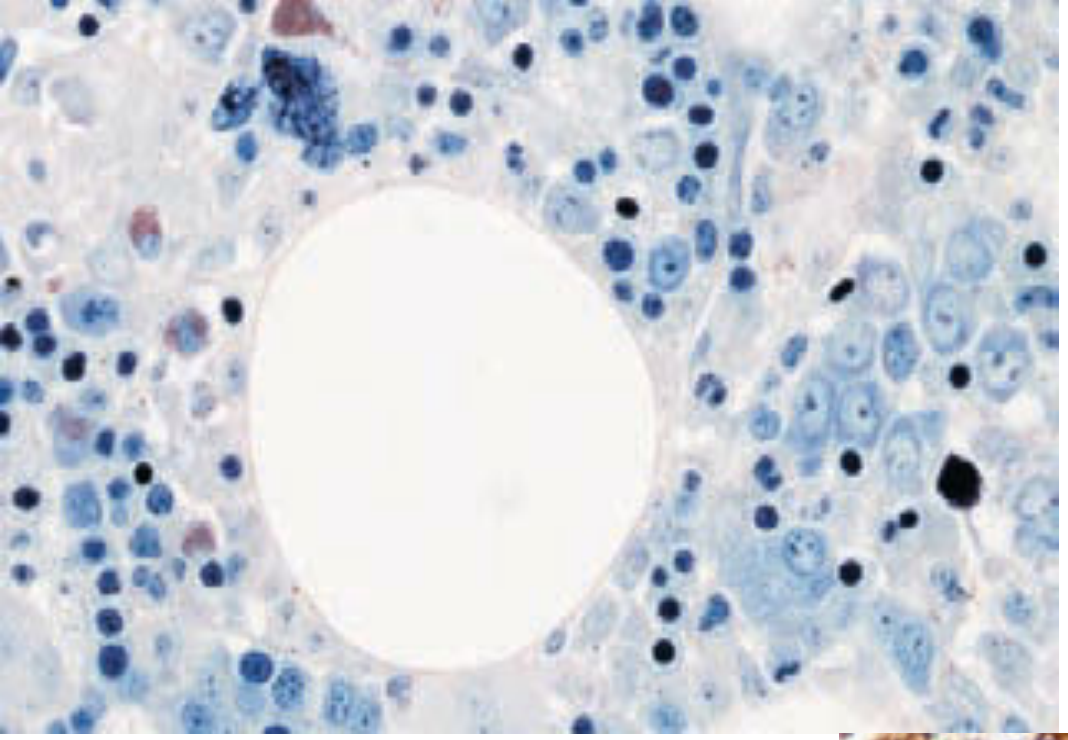
PRIMARY MYELOFIBROSIS

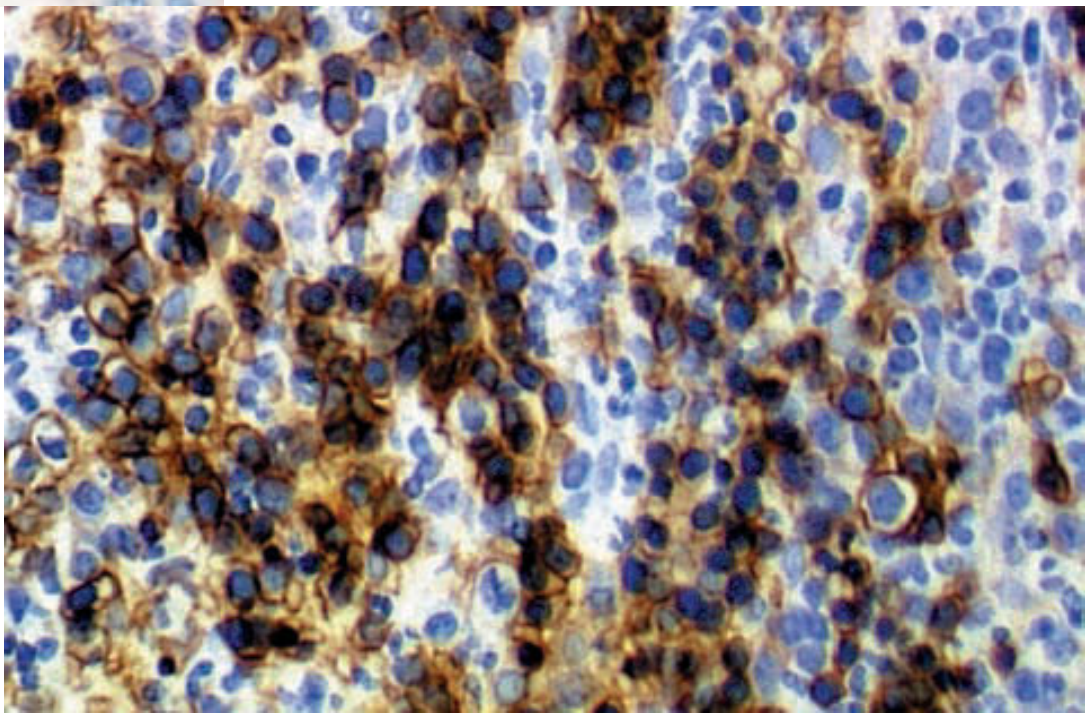
Prognosis

- Progressive disease
- Poor prognosis: age (>70 years), low hemoglobin level, abnormal karyotype
- Accelerated phase when blasts are 10% to 19%
- Transformation to acute leukemia in 5% to 30% of cases
- Mean survival, 3 to 5 years from diagnosis

- CD34







CD34

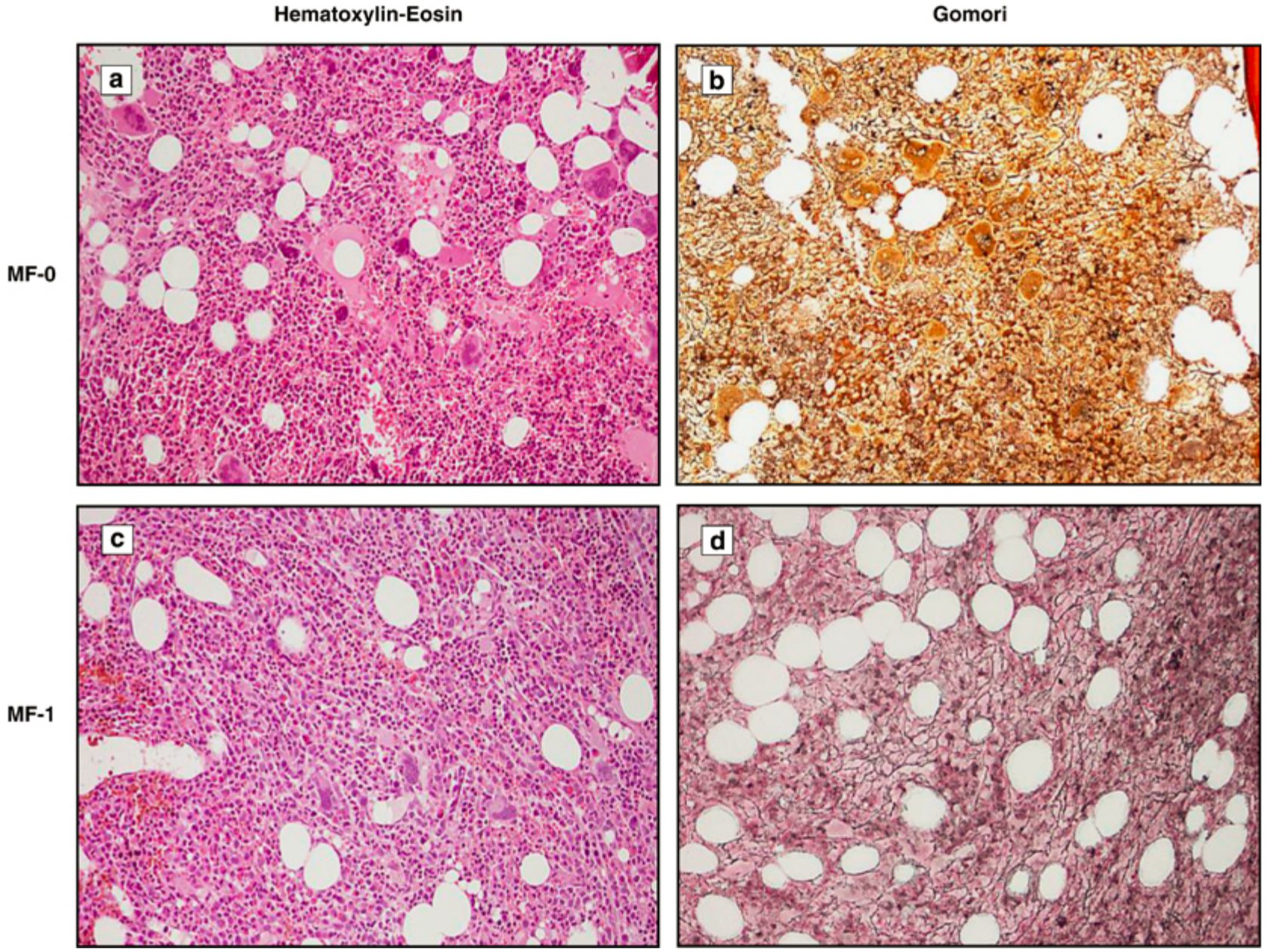
GRADOS OMS DE MIELOFIBROSIS

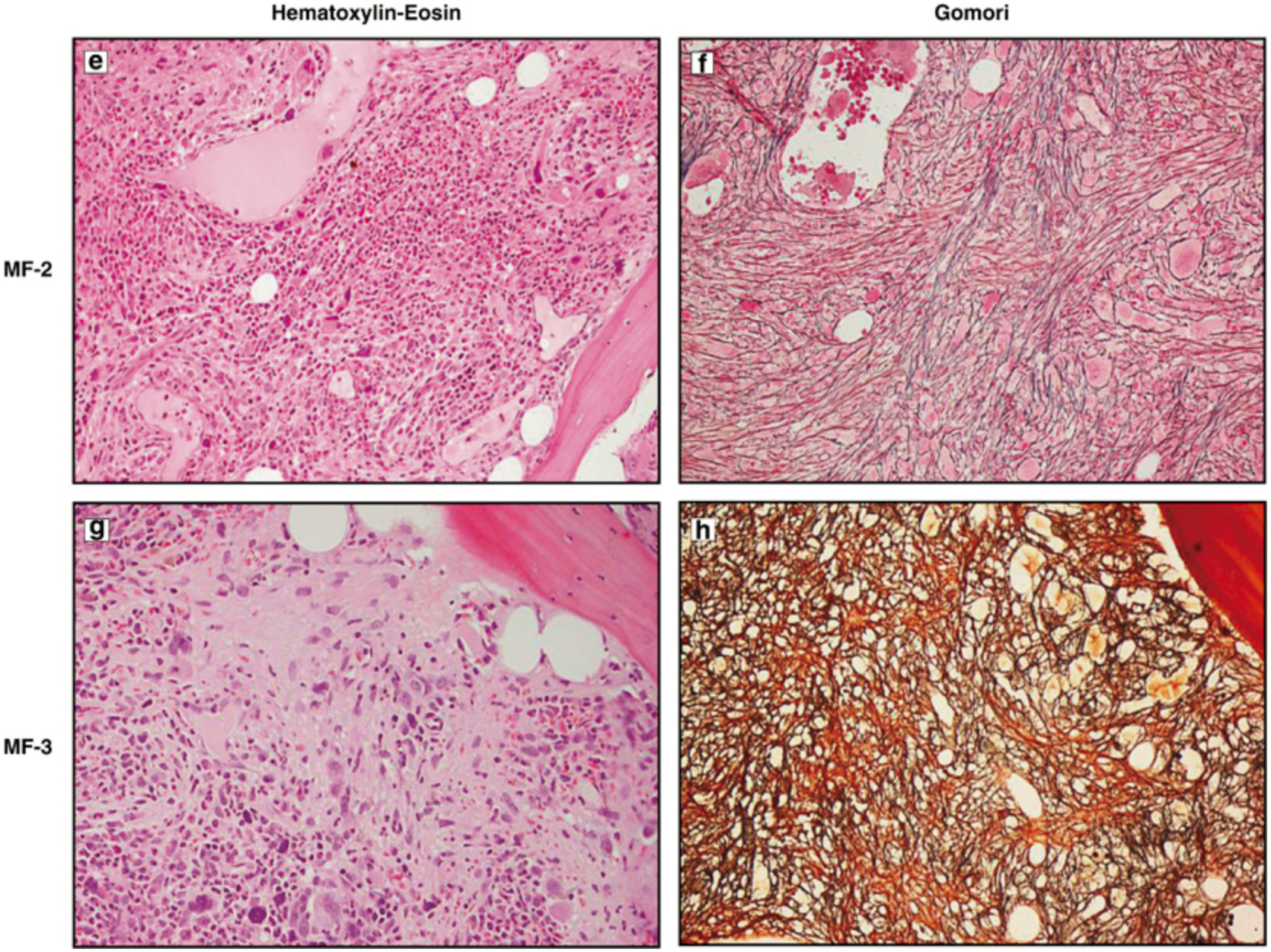
Pre-fibrotic primary myelofibrosis (MF-0): scattered linear reticulin fibres with no intersections.

Early-stage primary myelofibrosis (MF-1): loose network of reticulin fibres with many intersections, especially in perivascular areas.

Fibrotic stage primary myelofibrosis (MF-2): diffuse and dense increase in reticulin fibres, with extensive intersections and occasionally with focal bundles of collagen.

Fibrotic stage primary myelofibrosis (MF-3): diffuse and dense increase in reticulin fibres, with extensive intersections and coarse bundles of collagen.


Hematoxylin-Eosin
Gomori
MF-0
MF-1
a
b
c
d


Hematoxylin-Eosin
Gomori
MF-2
MF-3
e
f
g
h

Utilidad de BMO en las NMPC

(especialmente relevante si no se obtiene material en el aspirado)

- Evaluación de celularidad
- Establecer presencia o no de fibrosis y gradación
- Identificación de elementos morfológicos que son característicos de una entidad específica.
- Identificar incremento de precursores inmaduros.
- Diagnóstico diferencial

MIELOFIBROSIS PRIMARIA
MIELOFIBROSIS POST POLICITEMIA
MIELOFIBROSIS POST TROMBOCITOSIS PRIMARIA

Espectativas de los hematologos y pacientes:

1. Diagnóstico más precoz
2. Biopsias secuenciales de seguimiento
3. Necesidad de informes homogéneos entre patólogos para evaluación de nuevos tratamientos

GRACIAS POR LA ATENCION