

La **DIAGNOSTICA** **EMATOPATOLOGICA** nell'ERA della **MEDICINA** di **PRECISIONE**

Myeloid neoplasms with fibrosis: the value of morphology

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Disclosures of Marco Pizzi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Recordati rare diseases			X			X	

Causes of bone marrow fibrosis

Neoplastic disorders

Myeloid neoplasms

Myeloproliferative neoplasms (MPN)
Myelodysplastic syndromes (MDS)
MDS/MPN
Acute myeloid leukemias (some)
Mastocytosis

Lymphoid neoplasms

B and T-cell lymphomas/leukemias
Hodgkin lymphoma
Plasma cell myeloma

Bone marrow metastases

Non-neoplastic disorders

Dysmetabolic conditions

Hyperparathyroidism; vitamin D deficiency

Dysimmune conditions

Systemic Lupus Erythematosus;
Sjogren syndrome; Systemic sclerosis

Infections

Tuberculosis; HIV; visceral leishmaniasis

Medications

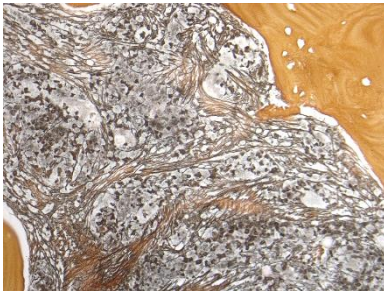
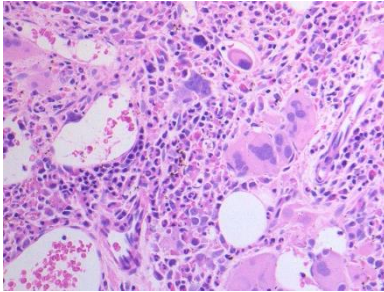
TPO-RA; G-CSF

Genetic disorders

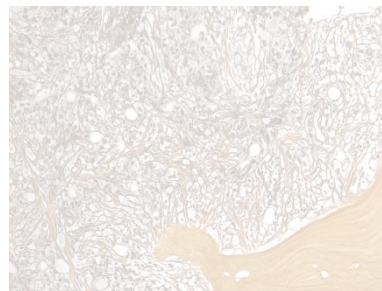
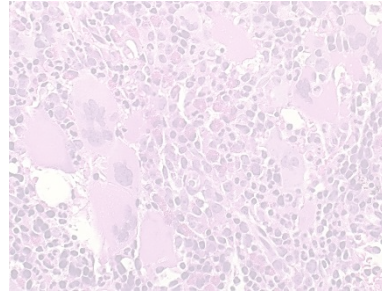
Germline *MPL*, *VPS45*, *RBSN* or
MPIG6B mutations

Myeloproliferative neoplasms with fibrosis

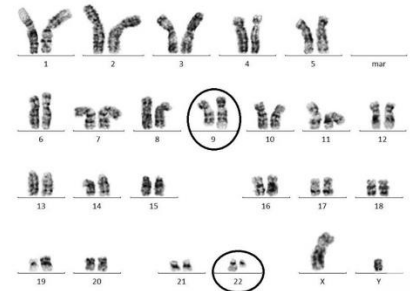
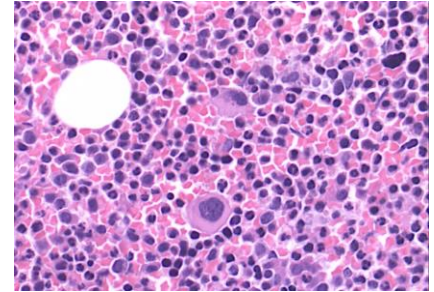
Primary myelofibrosis



Post-ET/PV myelofibrosis



CML with fibrosis



Primary Myelofibrosis

Definition

Classical Philadelphia-negative MPN with proliferation of megakaryocytes and myeloid precursors and variable interstitial fibrosis

Epidemiology and clinical features

- 0,5-1,5/100.000/year
- Adult to elderly age
- Variable clinical presentation
- OS: 11-17y (ePMF); 6-7y (oPMF)

Genetics

- **JAK2, CALR, MPL** mutations (80%)
- Variable non-driver mutations
- Abnormal karyotype (up to 40%)

PMF, overt fibrotic stage

Major criteria

1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3
2. JAK2, CALR, or MPL mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§
3. Diagnostic criteria for ET, PV, BCR::ABL1-positive CML, myelodysplastic syndrome, or other myeloid neoplasms|| are not met

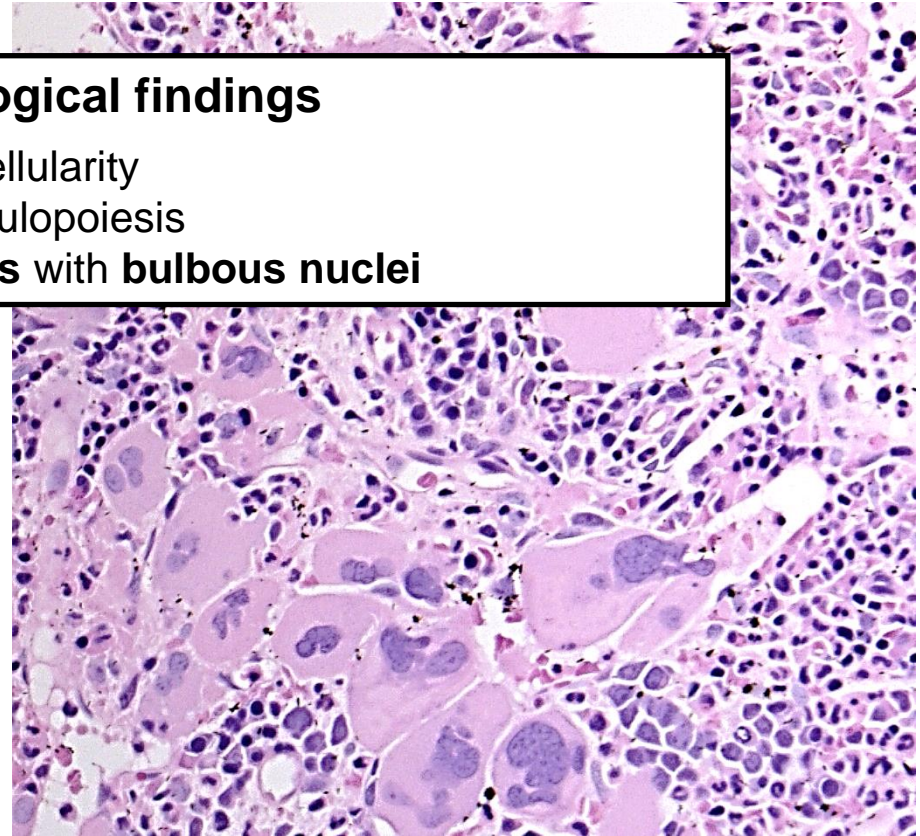
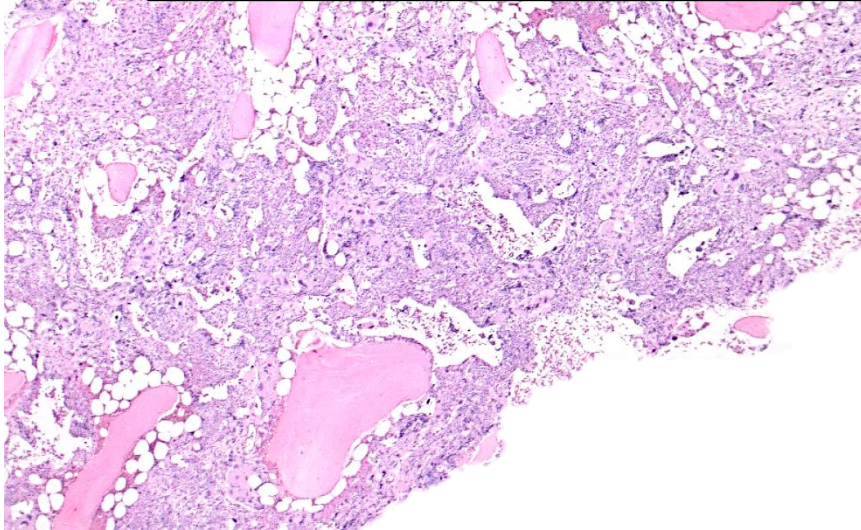
Minor criteria

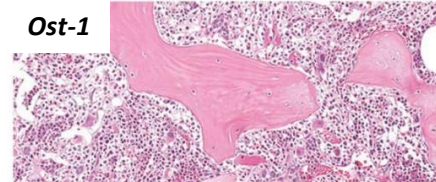
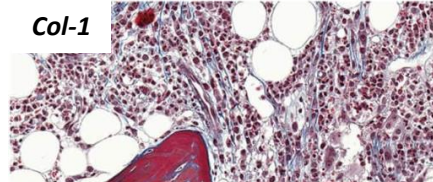
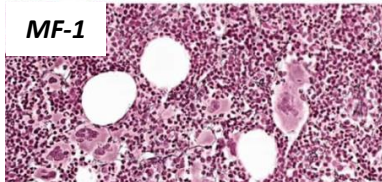
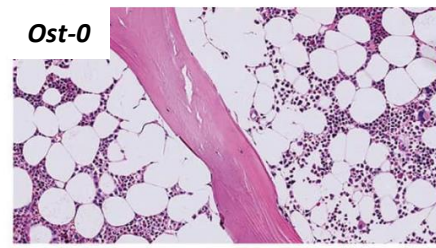
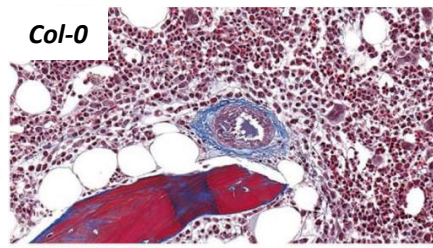
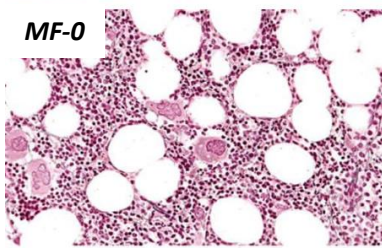
- Anemia not attributed to a comorbid condition
- Leukocytosis $\geq 11 \times 10^9/L$
- Palpable splenomegaly
- Lactate dehydrogenase level above the above the reference range
- Leukoerythroblastosis

All **3 major** criteria & ≥ 1 **minor** criterion required for the diagnosis

Key morphological findings

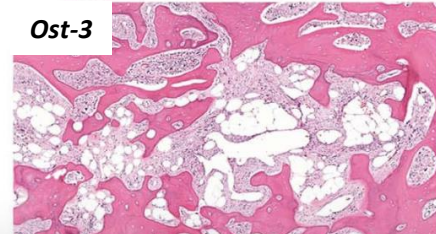
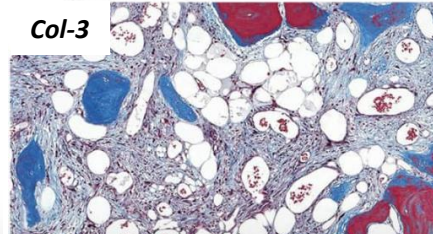
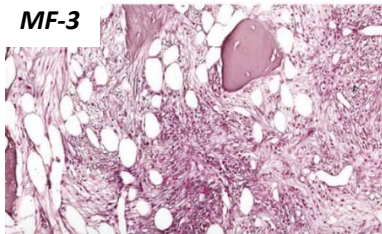
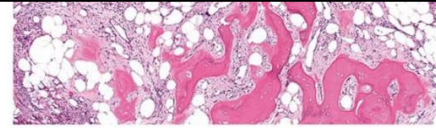
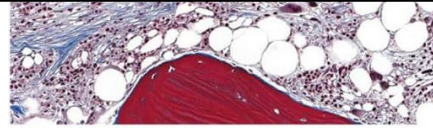
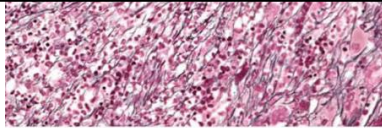
- **Increased to heterogeneous** cellularity
- **Increased and left-shifted** granulopoiesis
- Megakaryocytes in **tight clusters** with **bulbous nuclei**





Stromal changes in PMF

- **Interstitial fibrosis** distinguishes **ePMF (MF-0/1)** from **oPMF (MF-2/3)**
- Scoring of **collagen deposition** and **osteosclerosis** advised



Research Article

Clinical and Prognostic Correlates of the Reticulin-Collagen-Osteosclerosis Score in Primary Myelofibrosis

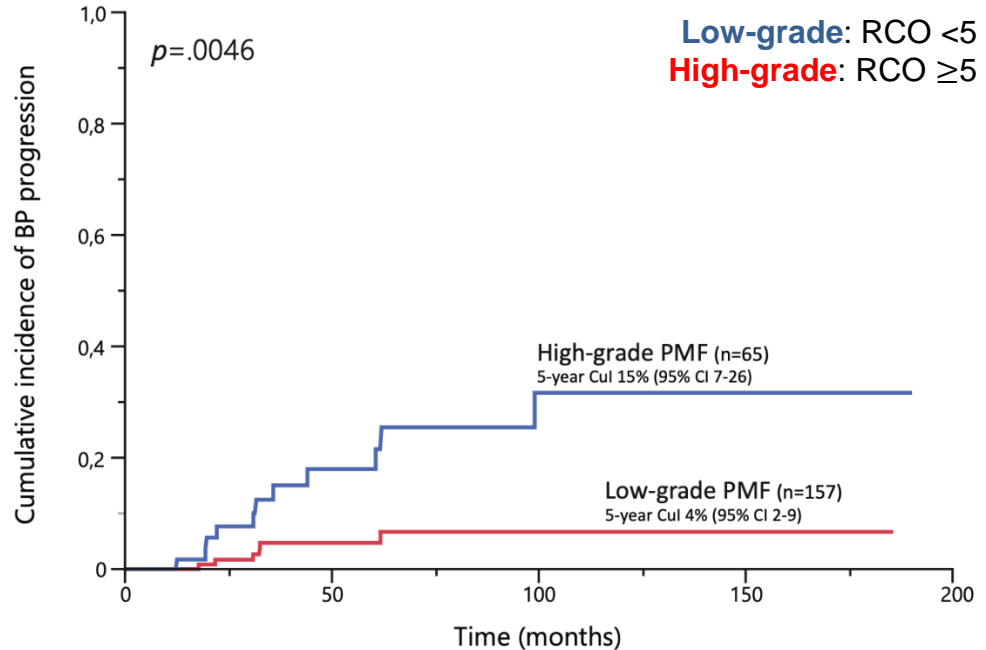
Raffaella Santi^{a,b}, Giacomo Coltro^{c,d}, Gioia Di Stefano^{a,b}, Alessandro Atanasio^{c,d},
Paolo Cicogna^{c,d}, Giuseppe G. Loscocco^{c,d}, Giulio Capecchi^{c,d}, Valentina Boldrini^{d,e},
Carlo Pesca^{e,f}, Paola Guglielmelli^{c,d}, Alessandro M. Vannucchi^{c,d,g}, Umberto Gianelli^{h,i}

^a Hematopathology Unit, Department of Diagnostic Services, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ^b Department of Health Sciences, University of Florence, Florence, Italy; ^c Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; ^d Oncology Department, CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ^e Pathology Unit, Department of Health Sciences, University of Milan and Azienda Socio Sanitaria Territoriale Sanzi Paolo e Carlo, Milan, Italy; ^f Department of Health Sciences, University of Milan, Milan, Italy

In **oPMF** stromal changes correlate with:

- **lower Hb** levels and **platelet** count
- **splenomegaly** and systemic symptoms
- **HMR** mutations

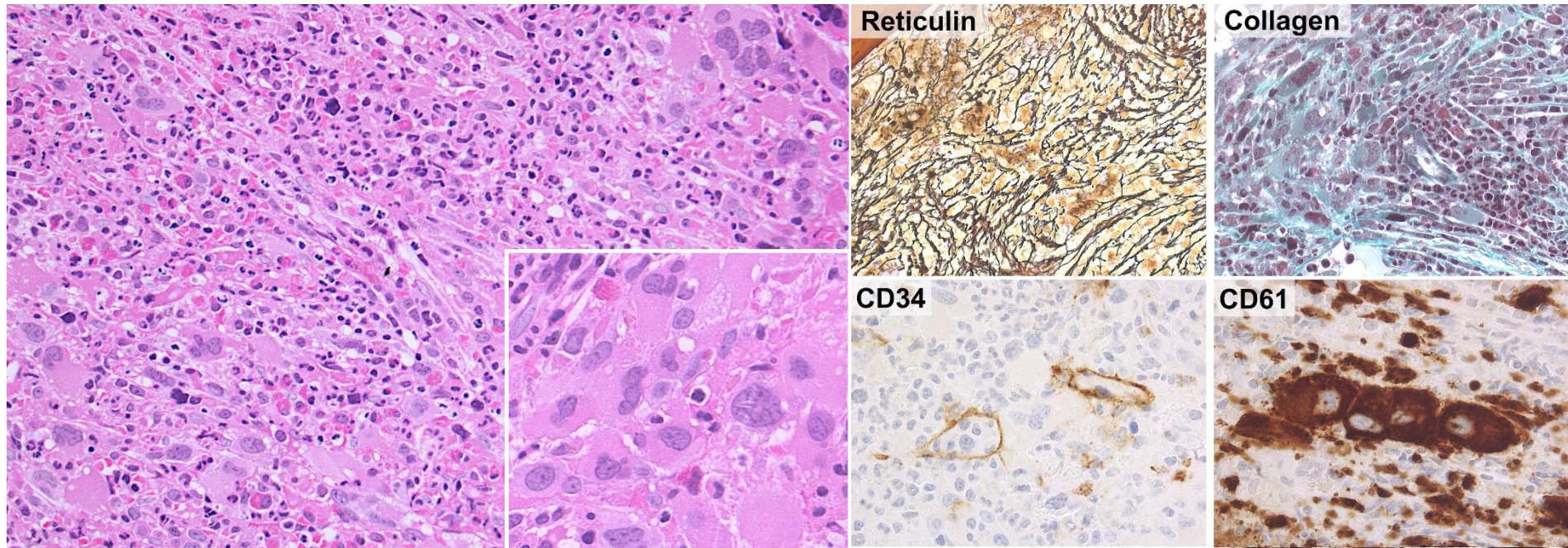
Less strong correlations in **ePMF**



RCO is an **independent** prognostic factor for OS

RCO **improves** the prognostic power of **MIPSS70**

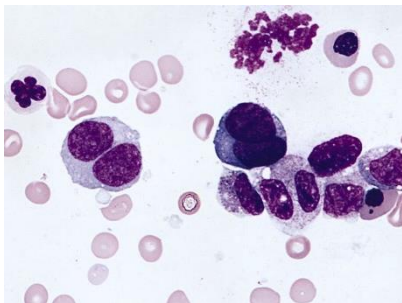
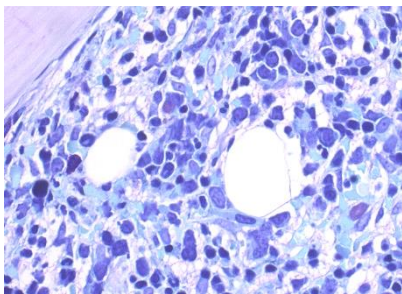
CML with fibrosis



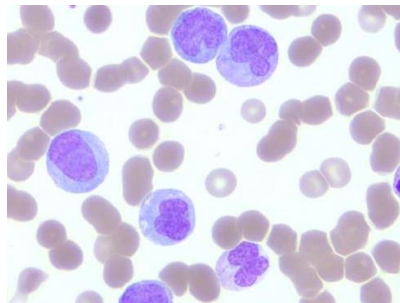
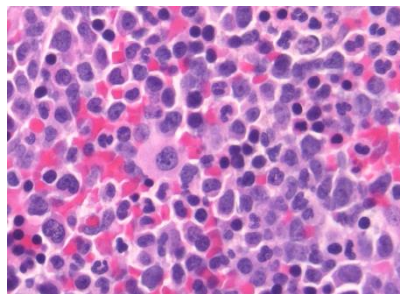
- **Fibrosis** with increased **atypical megakaryocytes** associated with **worse response** to TKIs
- These features **not** formally considered to define **accelerate phase** or **high-risk disease**

Other myeloid neoplasms with fibrosis

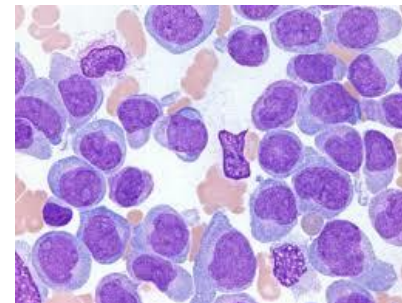
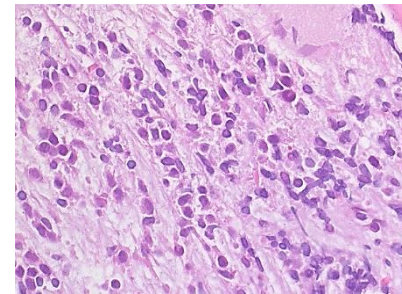
MDS with fibrosis



CMML with fibrosis

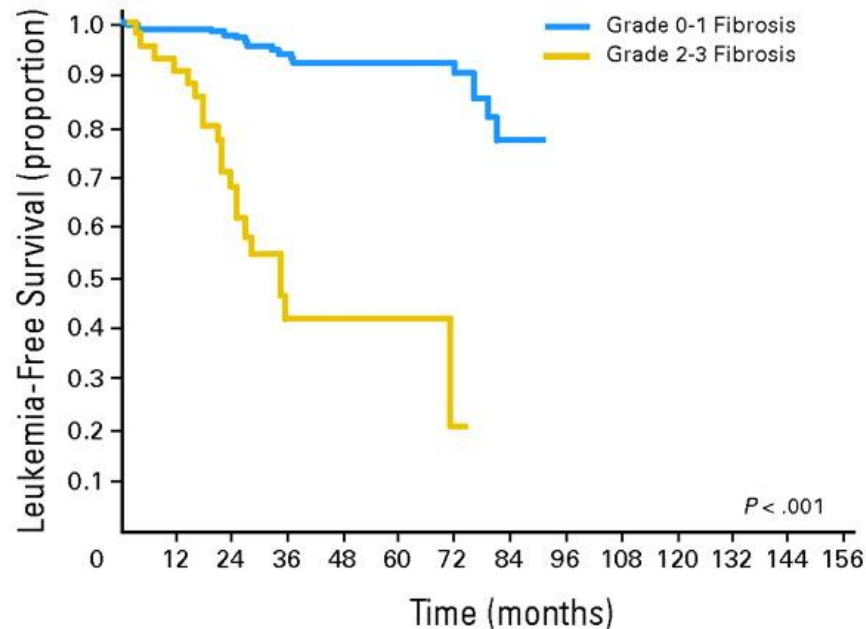
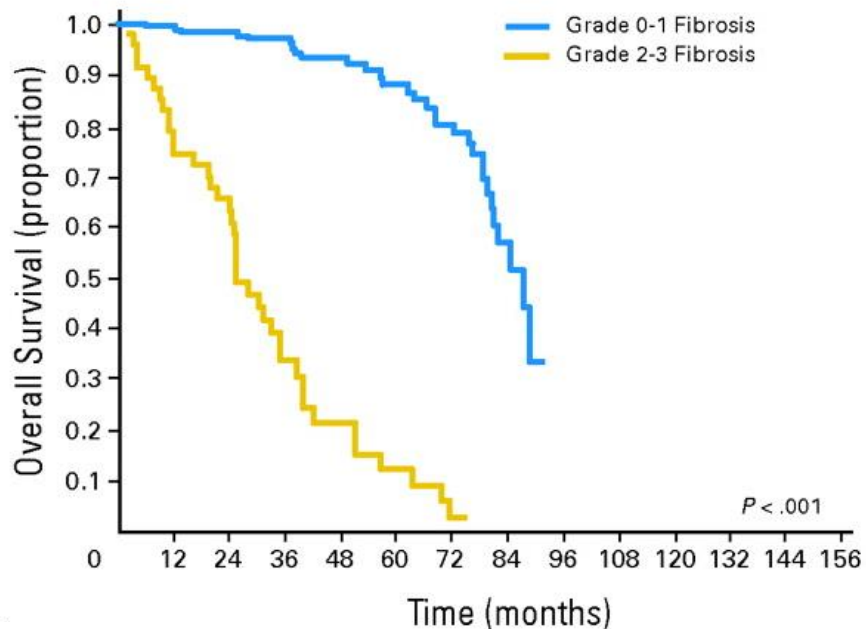


AML with fibrosis

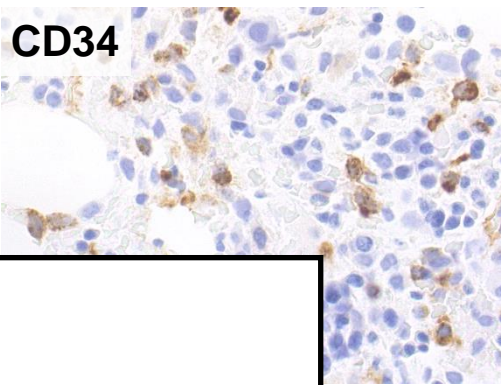
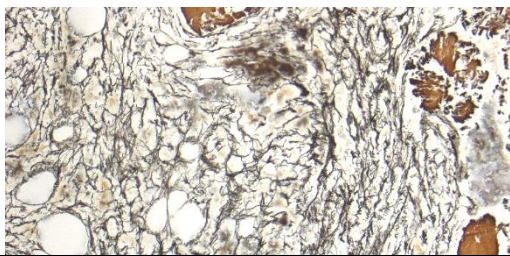
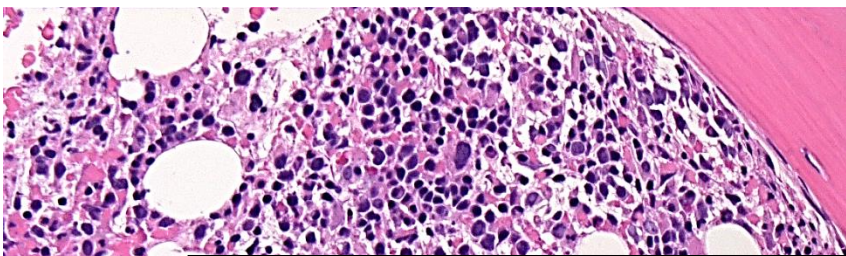


Myelodysplastic syndrome with fibrosis

Prognosis irrespective of blast count

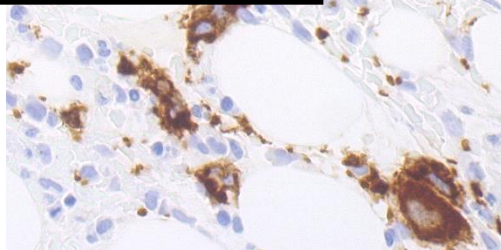
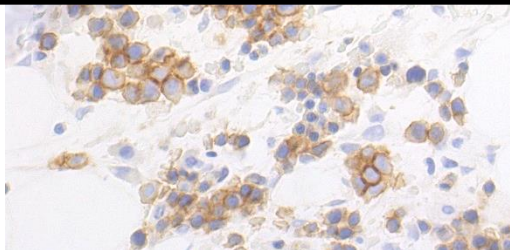
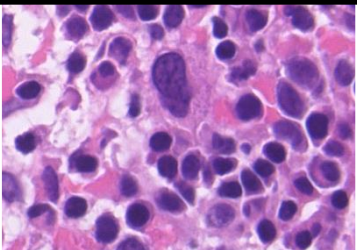
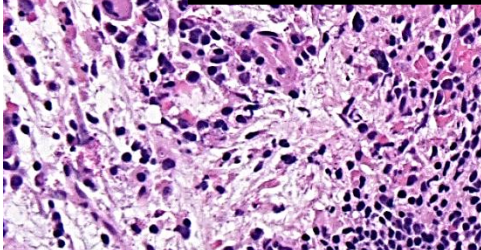


Myelodysplastic syndrome with fibrosis



Key morphological findings

- **Erythroid expansion** with low M:E ratio
- **Increased and dysplastic megakaryocytes w/ micromegakaryocytes**
- Usually increased CD34-positive precursors



Chronic myelomonocytic leukemia with fibrosis

Definition

MDS/MPN characterized by monocytosis with ≥ 1 cytopenia (usually anemia)

Epidemiology and clinical features

- Incidence: 2-4/100.000/year
- 6th to 7th decade
- Clinical features depending on MP or MD phenotype
- Median OS: 16 to 97 months

Genetics

- **No *JAK2*, *CALR*, *MPL* mutations**
- Biallelic *TET2* and concurrent *SRSF2/TET2* mutations
- Abnormal karyotype (20-30%)

2022 ICC Diagnostic criteria

Monocytosis defined as monocytes $\geq 0.5 \times 10^9/L$ and $\geq 10\%$ of the WBC

Cytopenia (thresholds same as MDS)*

Blasts (including promonocytes) $< 20\%$ of the cells in blood and bone marrow

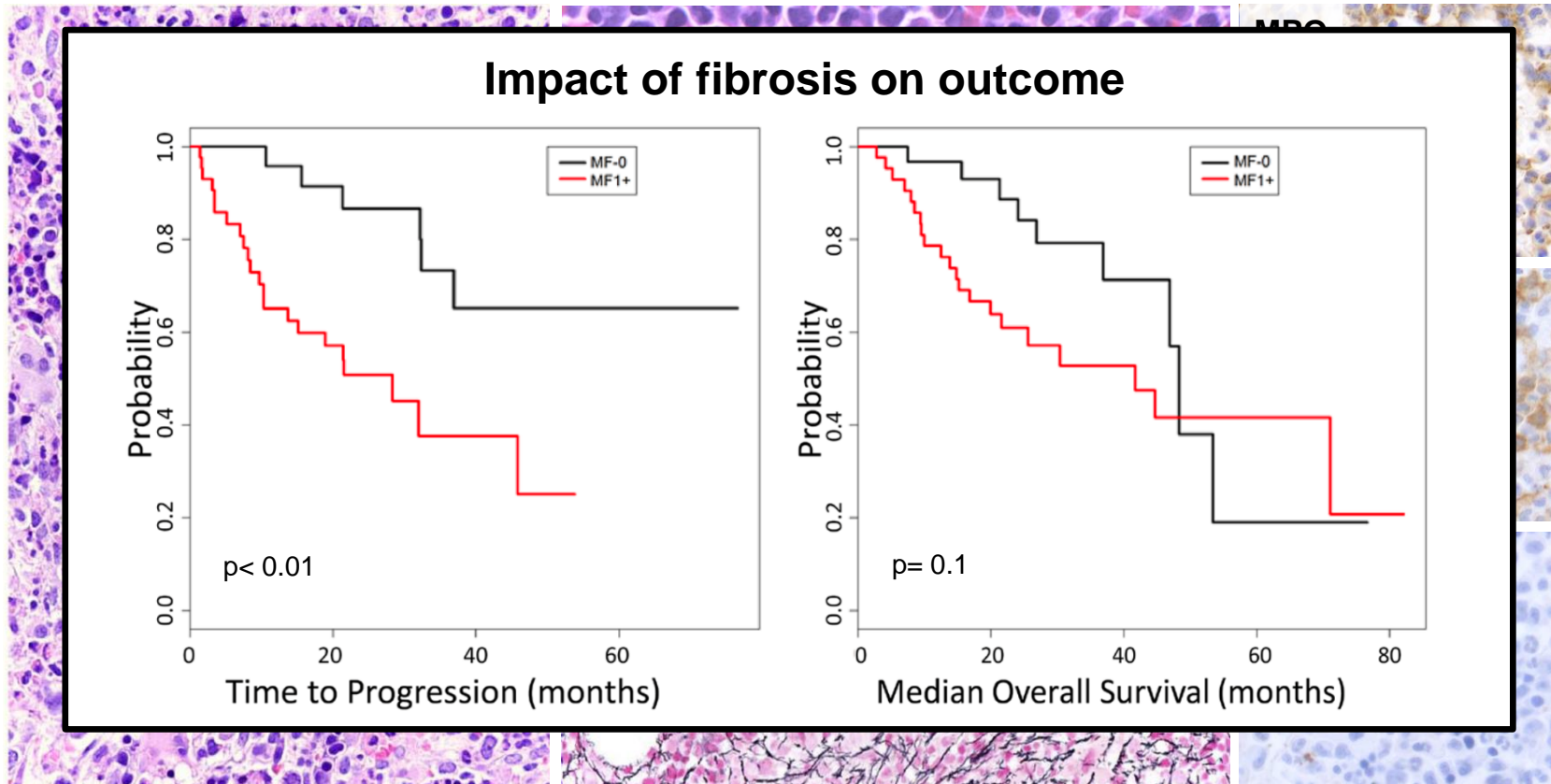
Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of at least 10% allele frequency†

In cases without evidence of clonality, monocytes $\geq 1.0 \times 10^9/L$ and $> 10\%$ of the WBC, and increased blasts (including promonocytes),‡ or morphologic dysplasia, or an abnormal immunophenotype consistent with CMML would be required for its diagnosis.

Bone marrow examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of acute myeloid leukemia, MPN or other conditions associated with monocytosis§

No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

Chronic myelomonocytic leukemia with fibrosis



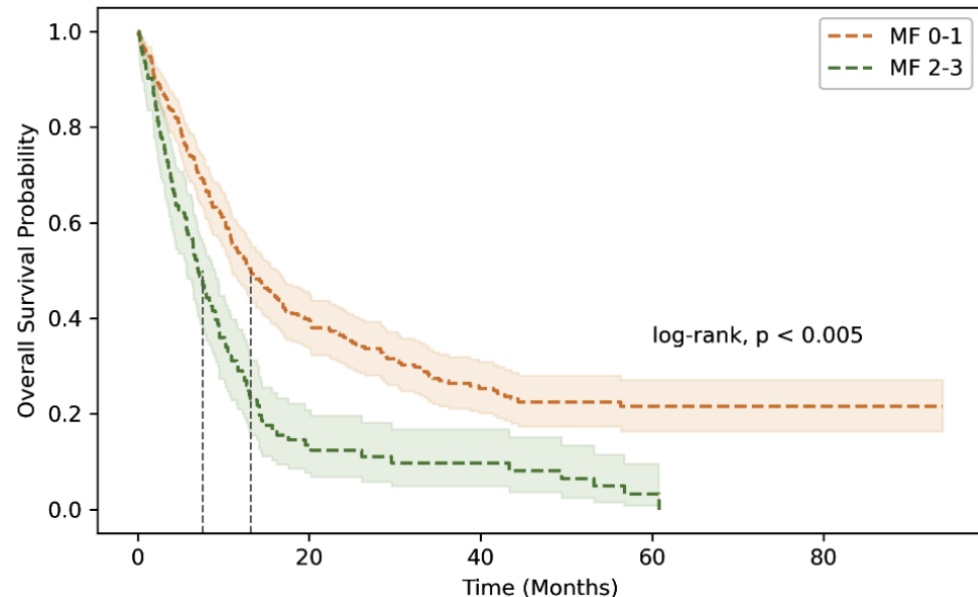
Acute myeloid leukemias with fibrosis

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN

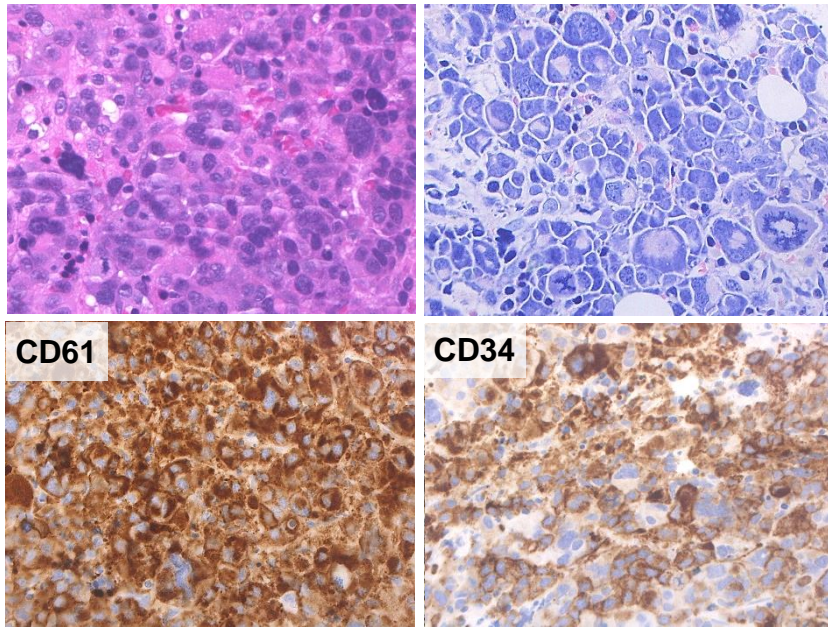
ELN2022: unfavorable risk



MF-2/3 **strongest** prognostic factor for survival

Diagnostic challenges of AML with fibrosis

Acute megakaryoblastic leukemia

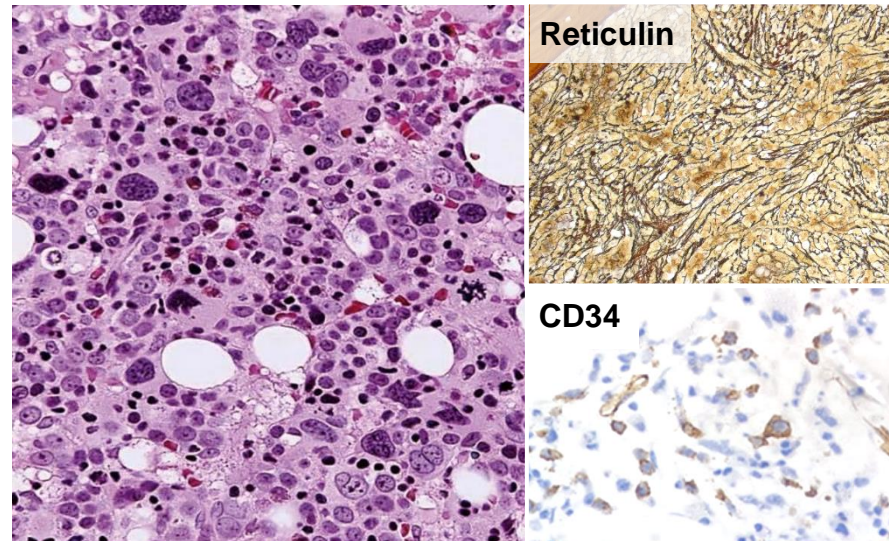


AML ($\geq 20\%$ PB/BM blasts) with **megakaryoblastic differentiation** (CD61⁺, CD42⁺, CD41⁺)

No criteria for other AML or BP-MPN

Pediatric (DS+ or DS-) or **adult** setting

Acute panmyelosis with myelofibrosis



Acute-onset AML ($\geq 20\%$ PB/BM blasts) with **dysplastic panmyelosis**, **BM fibrosis** and **lack of splenomegaly**

No criteria for other AML entities

Only recognized by **2022 ICC** Classification

Summary of key diagnostic features

	PMF	f-CML	f-MDS	f-CMML	f-AML
CBC count	variable	↑ WBC	cytopenia only	↑ monocytes and cytopenia	Variable
PB/BM blasts	<10%	<10%	variable	variable	≥20%*
Splenomegaly	frequent	possible	absent	frequent	absent
M:E ratio	increased	increased	decreased	increased	variable
Mk features	bulbous in clusters	dwarf	dysplastic	dysplastic	dysplastic
Genetics	<i>JAK2, CALR, MPL</i> (80%) [§]	<i>BCR::ABL1</i>	variable [§]	variable ^{**} , [§]	variable [§]

Notes: *20% blasts not required if AML-defining genetic features are present; ** *JAK2* mutations occasionally documented at low VAF; § *BCR::ABL1* absent by definition

Conclusions

Myeloid neoplasms with fibrosis are **heterogeneous** disorders with overlapping features

Morphology of the BM maintains a **pivotal role** in the differential diagnosis

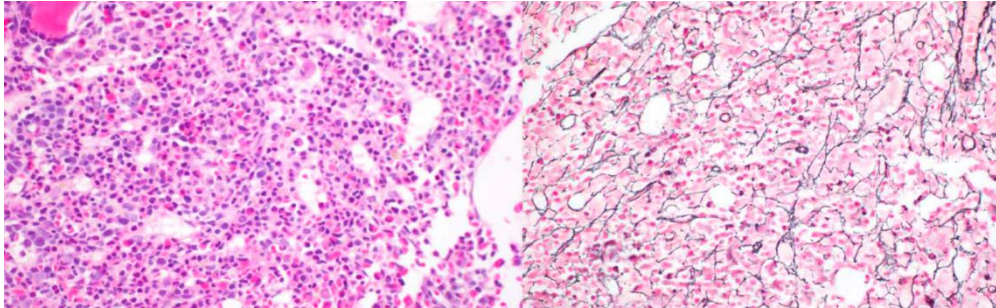
Teamwork is key for good diagnoses and to avoid histological pitfalls



The impact of fibrosis in CMML

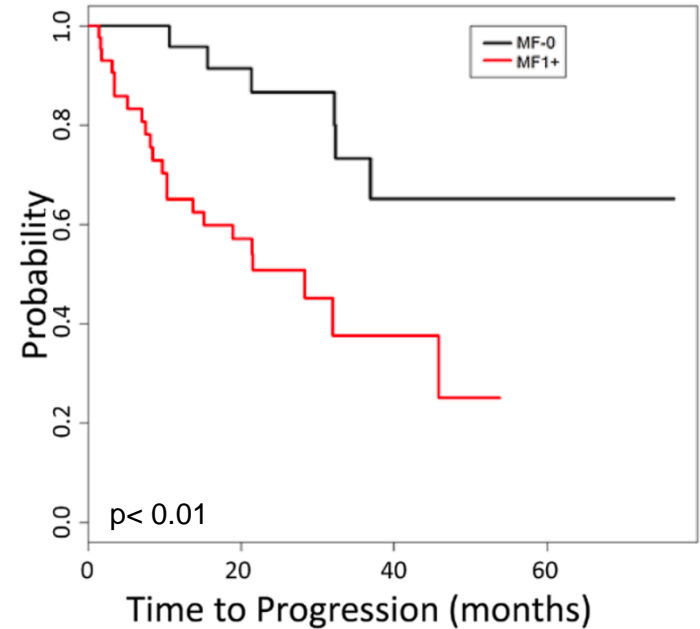
CMML w/ fibrosis associated with:

- **Increased megakaryocytes** in the BM
- More frequent **splenomegaly**



No significant association with:

- CBC counts
- Frequency of **JAK2 mutations**
- Cytogenetic abnormalities



Autoimmune myelofibrosis

Definition

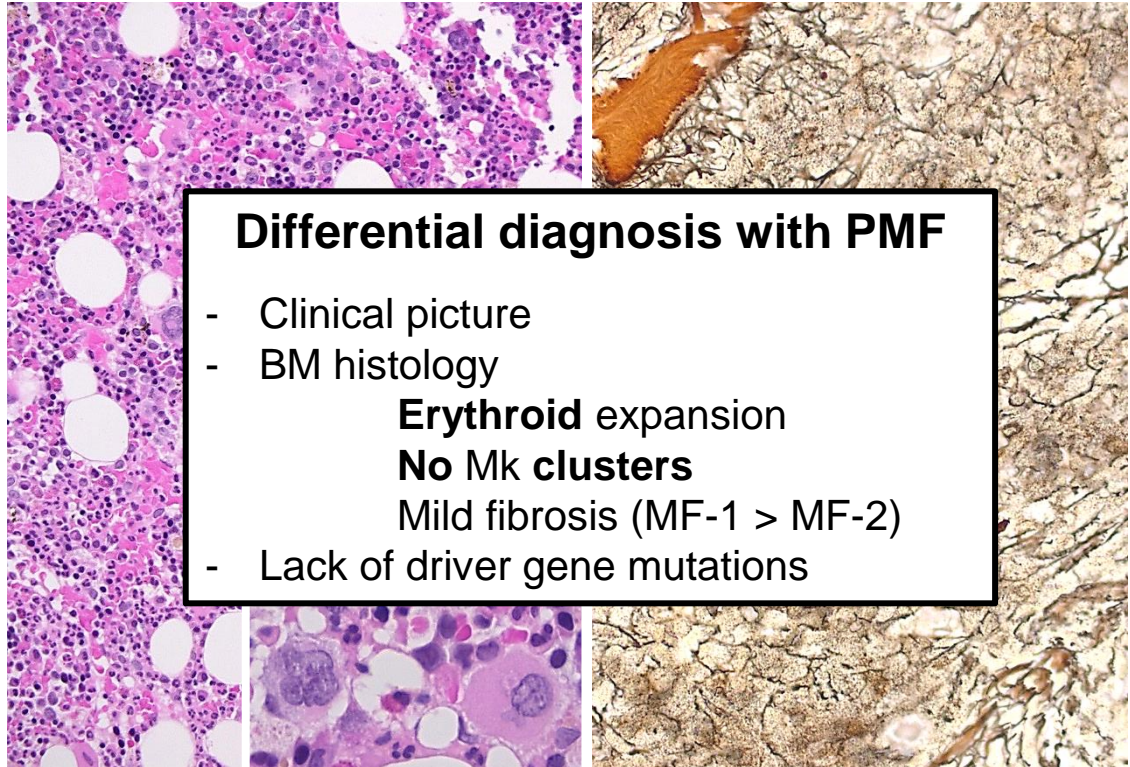
Immune-mediated disease with BM fibrosis and cytopenia

Epidemiology

- Young-adult age
- Females > males

Clinical features

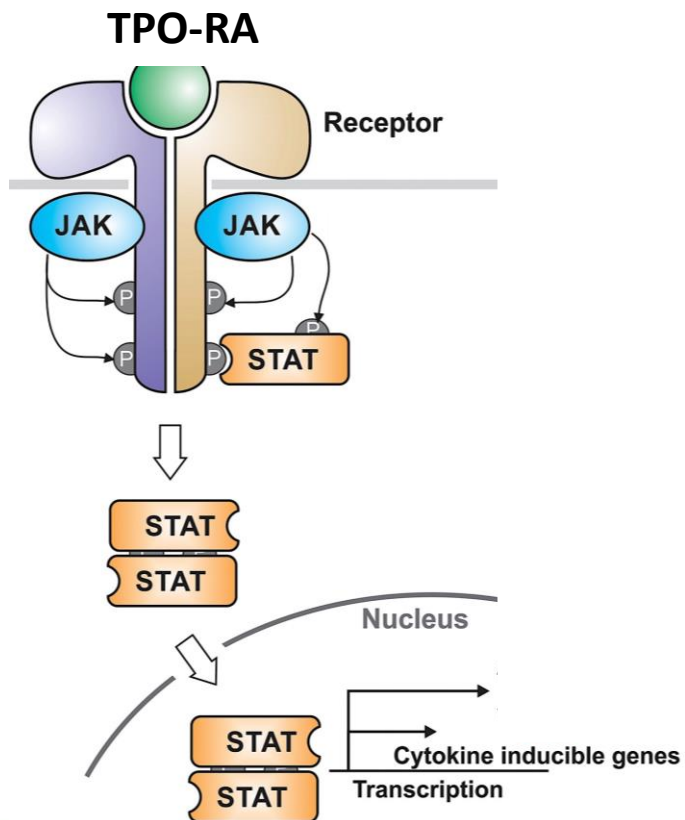
- Cytopenia
- Systemic symptoms
- Mild splenomegaly
- Good response to steroids



Differential diagnosis with PMF

- Clinical picture
- BM histology
 - Erythroid expansion**
 - No Mk clusters**
 - Mild fibrosis (MF-1 > MF-2)
- Lack of driver gene mutations

Therapy with TPO-RA



TPO-RA-related BM changes

