Essential thrombocythemia (ET) versus early/prefibrotic primary myelofibrosis (PMF)

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Current issues in ET vs. prefibrotic PMF concerning bone marrow morphology

1. WHO morphological criteria of distinctive value (WHO vs. PVSG criteria)

2. Standardization of bone marrow features

3. Reproducibility of histological features

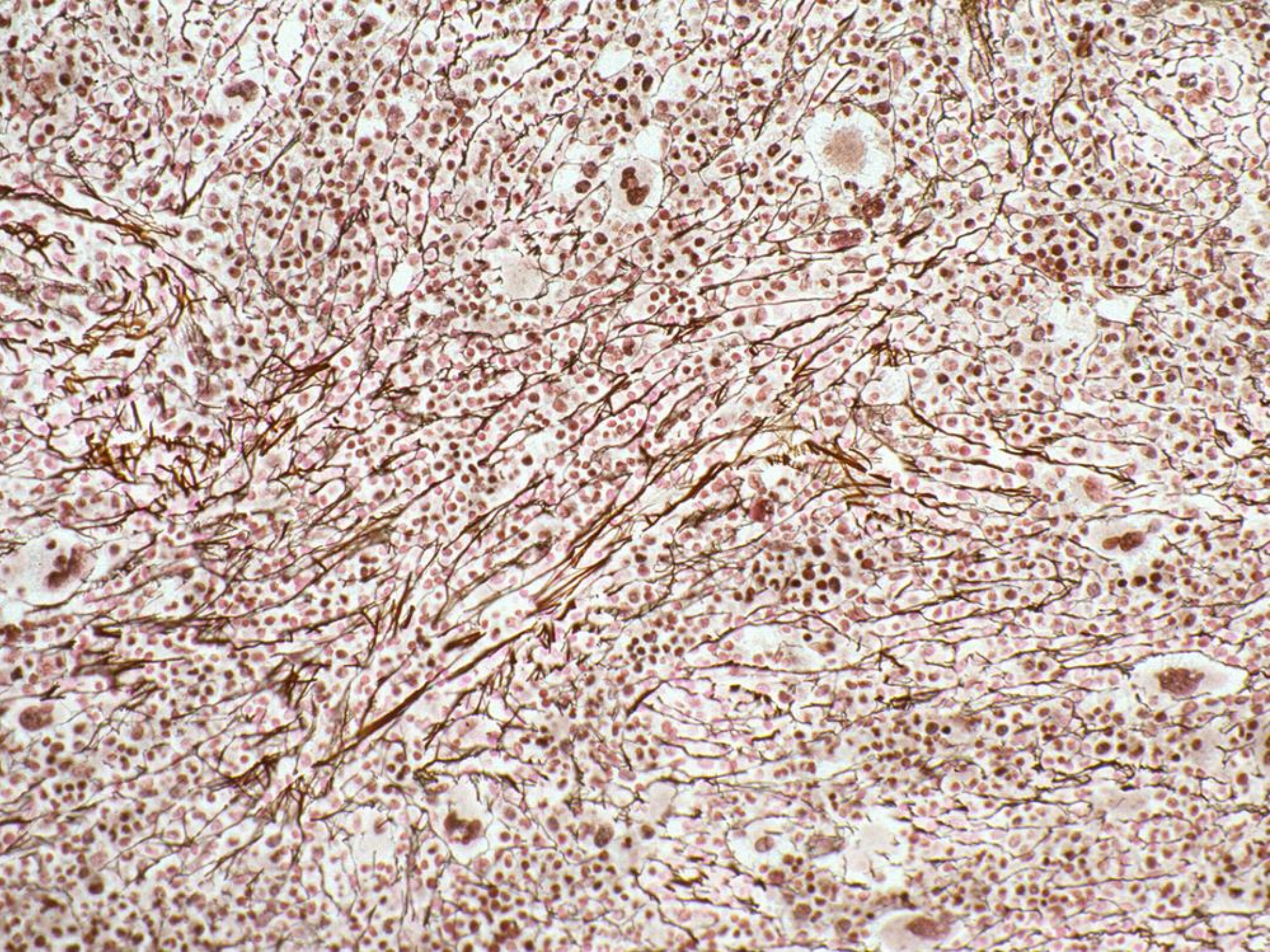
Essential Thrombocythemia (ET)
WHO criteria

Morphological features :

Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase, left-shift of neutrophil granulopoiesis or erythropoiesis

PVSG criteria for the diagnosis of ET Morphological features:

Collagen fibrosis absent or <1/3 biopsy area without marked splenomegaly and leukoerythroblastic reaction



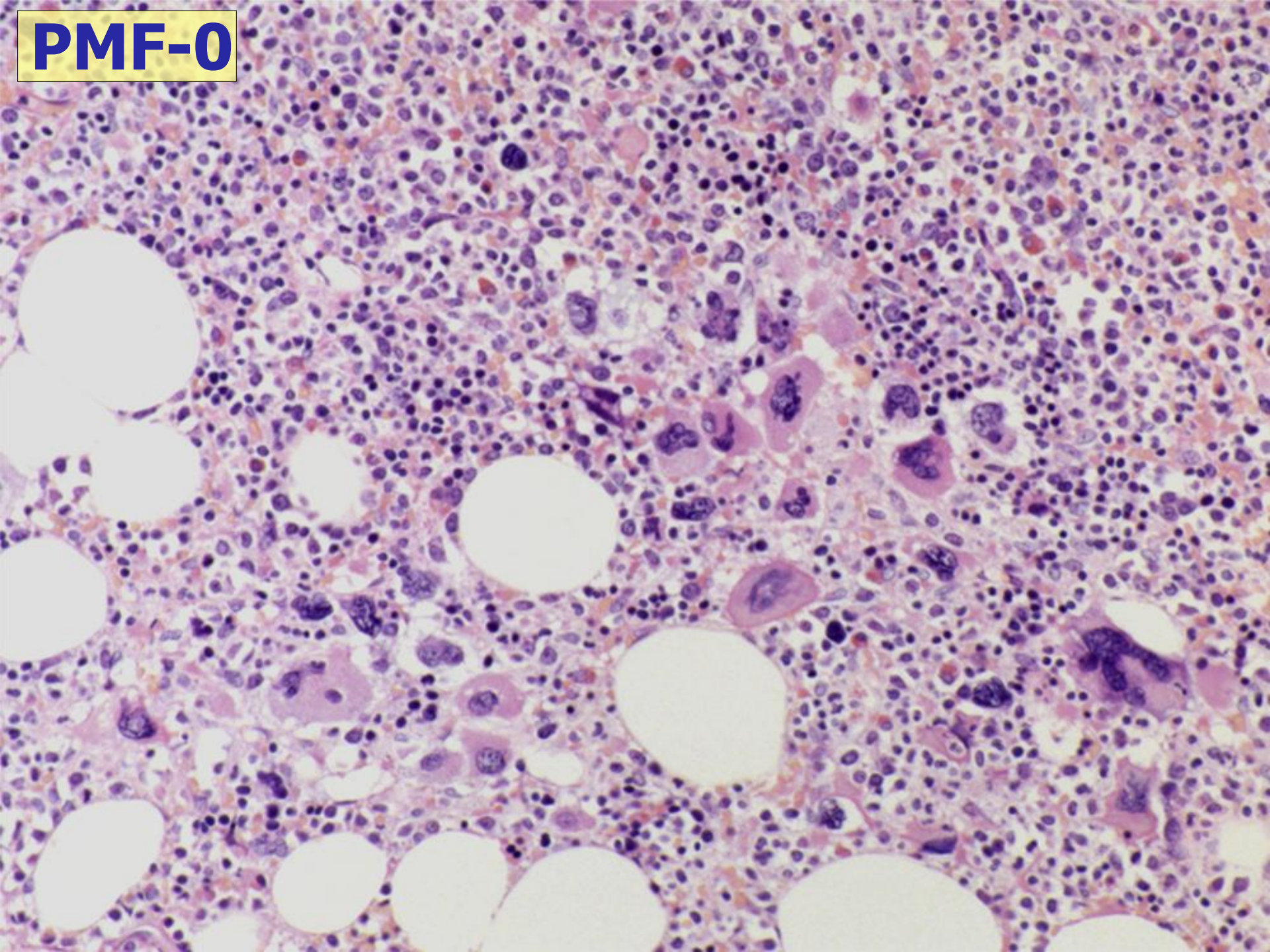
Primary Myelofibrosis (PMF)

Diagnosis requires meeting all three major criteria and two minor criteria

Major criteria

1. Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis,

or in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic cellular-phase disease)


PMF-0

Standardization of Bone Marrow Morphology

Length of biopsy (1.5 cm) and orthograde direction

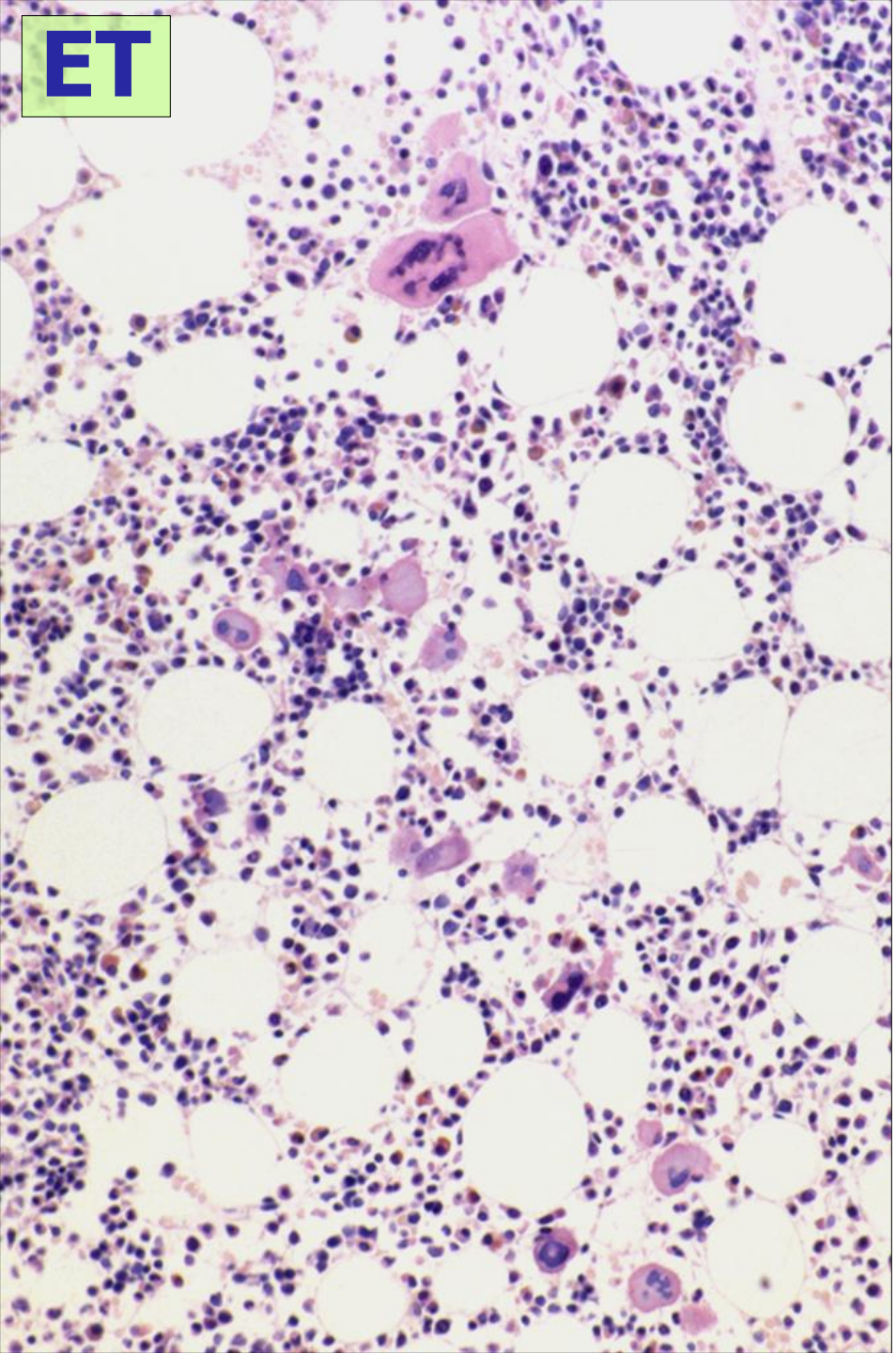
Cellularity (age-matched)-subcortical marrow space

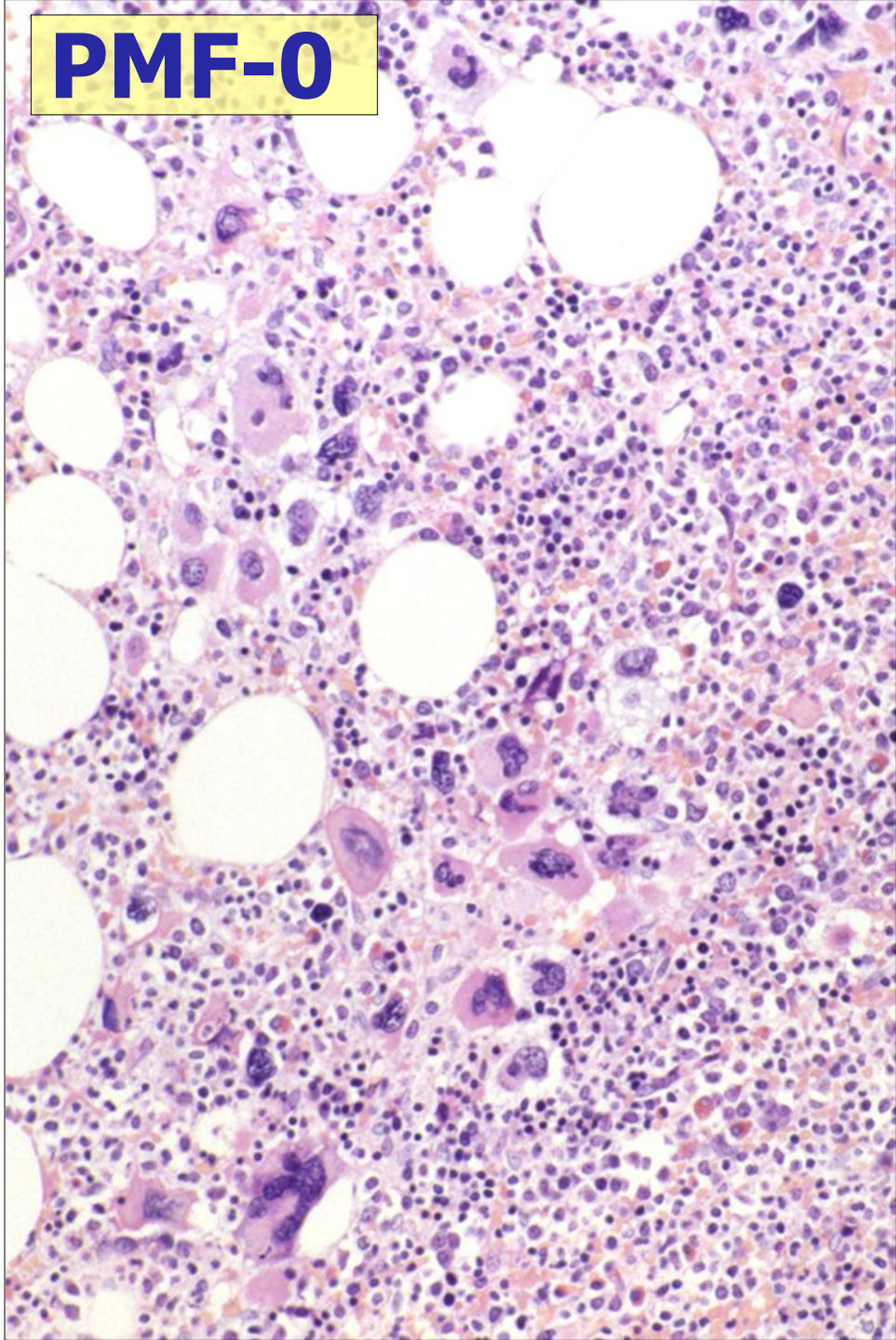
Erythropoiesis

Granulopoiesis

Megakaryopoiesis

Fibers (WHO grading system 0-3)


ET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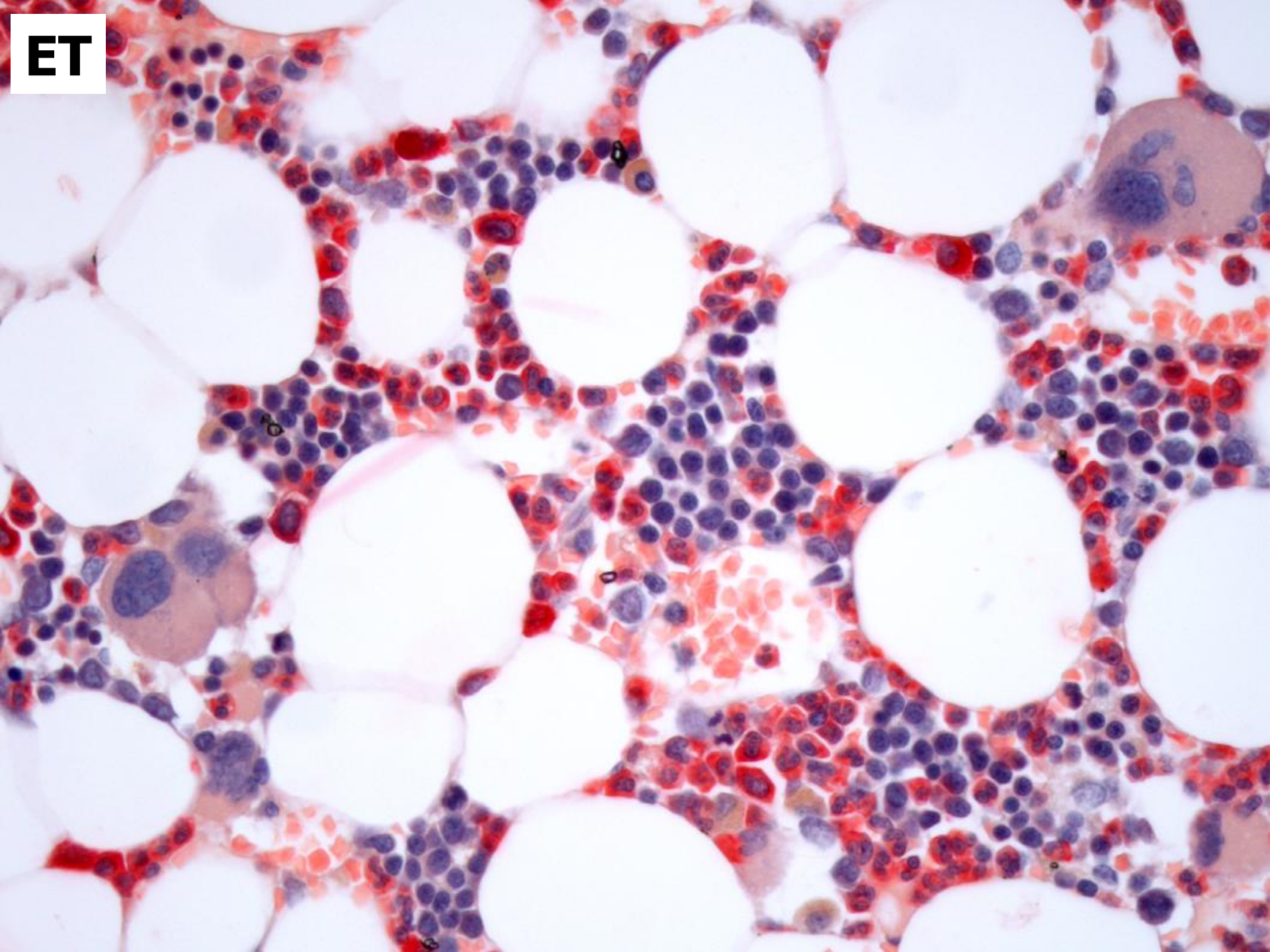
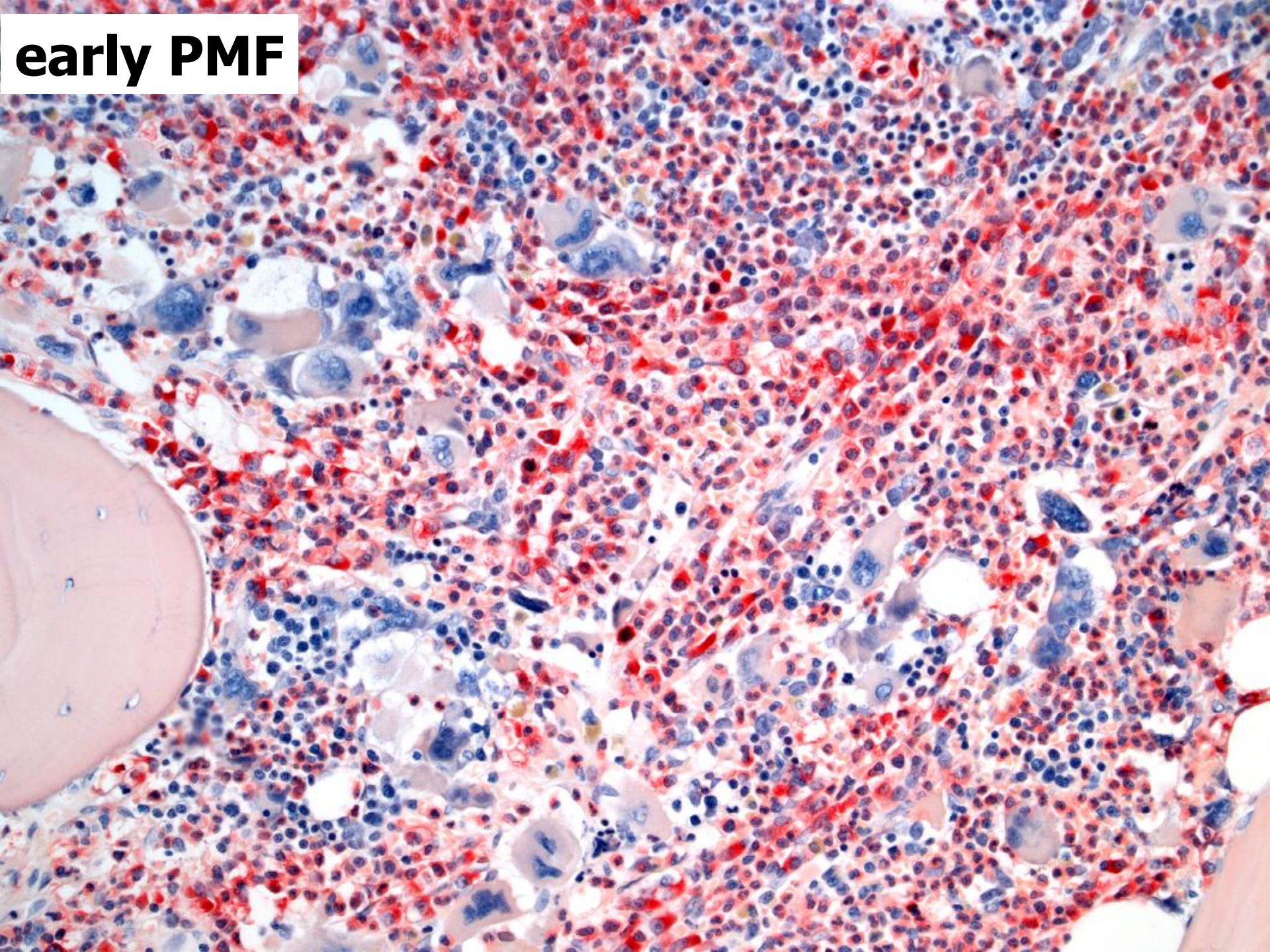
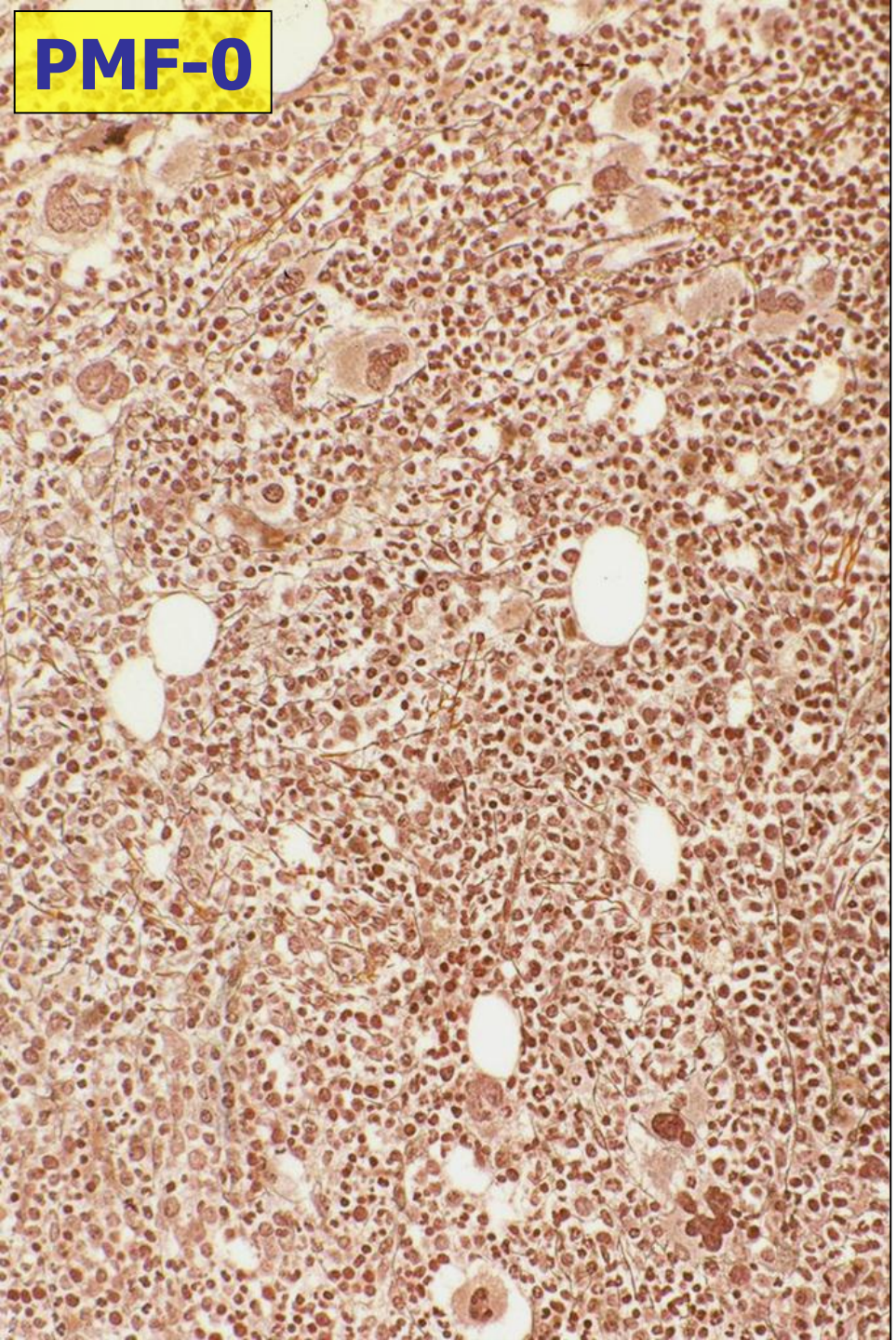
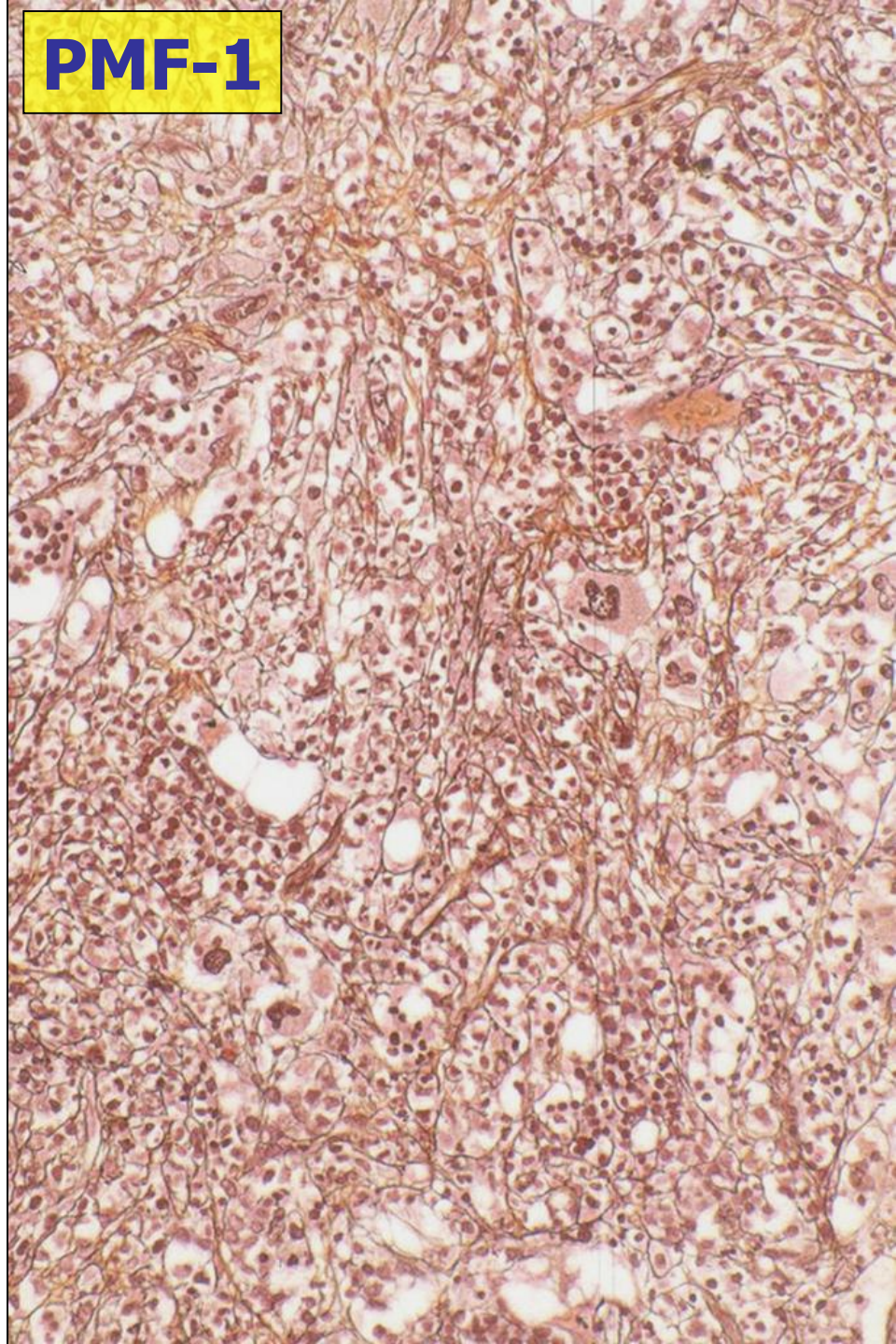

ET


early PMF


PMF-0


PMF-1

Standardization of Bone Marrow Morphology

Megakaryocytes

Quantity and distribution (paratrabecular)

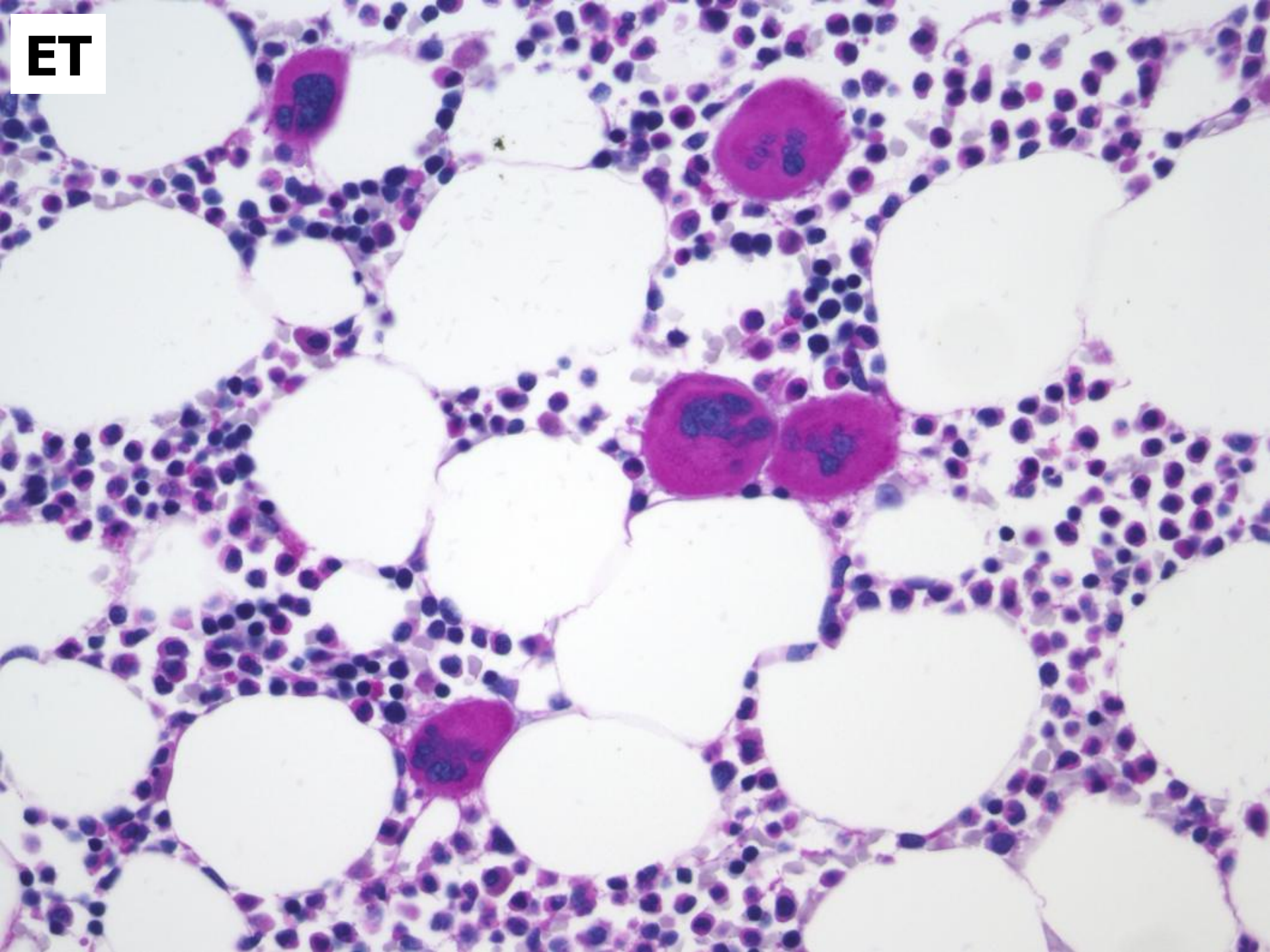
Size (giant,large,median,small)

Clustering (loose-dense)

Nuclear lobulation (cloud-vs. staghorn-like/hypo-vs.hyper)

Maturation defects-abnormalities

Bare (naked) nuclei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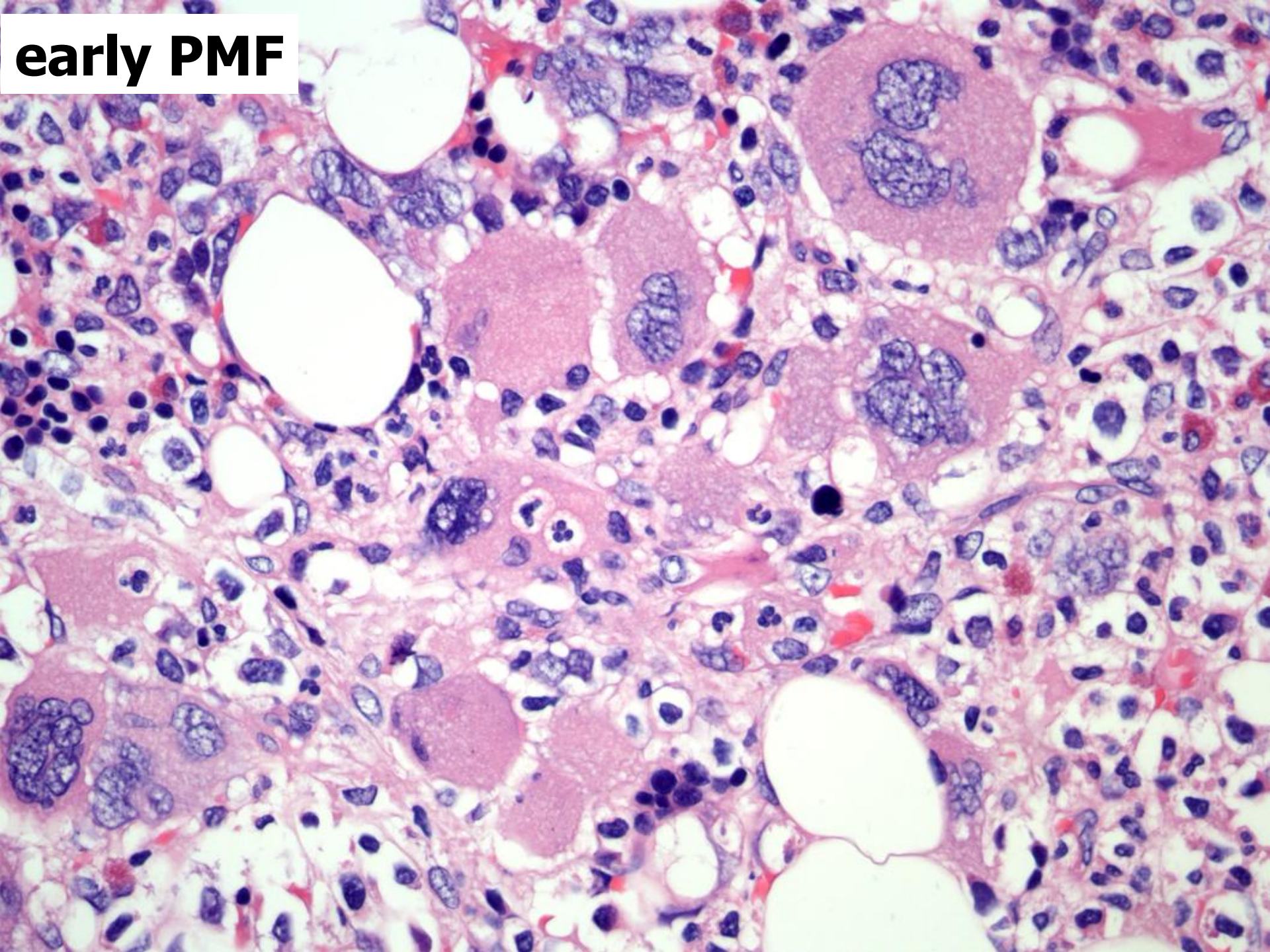
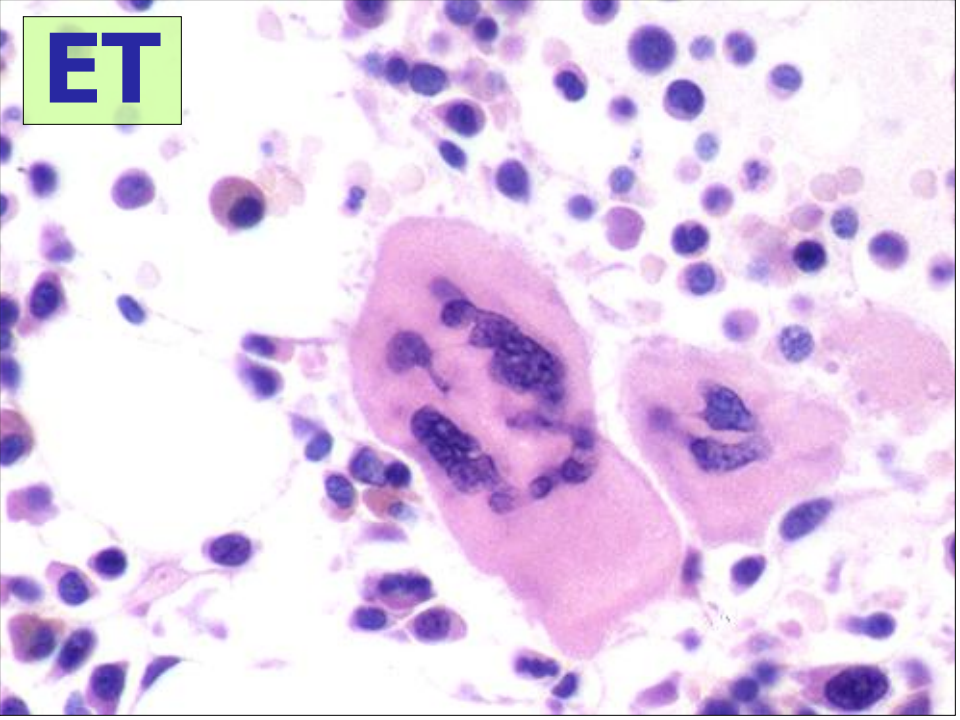

early PMF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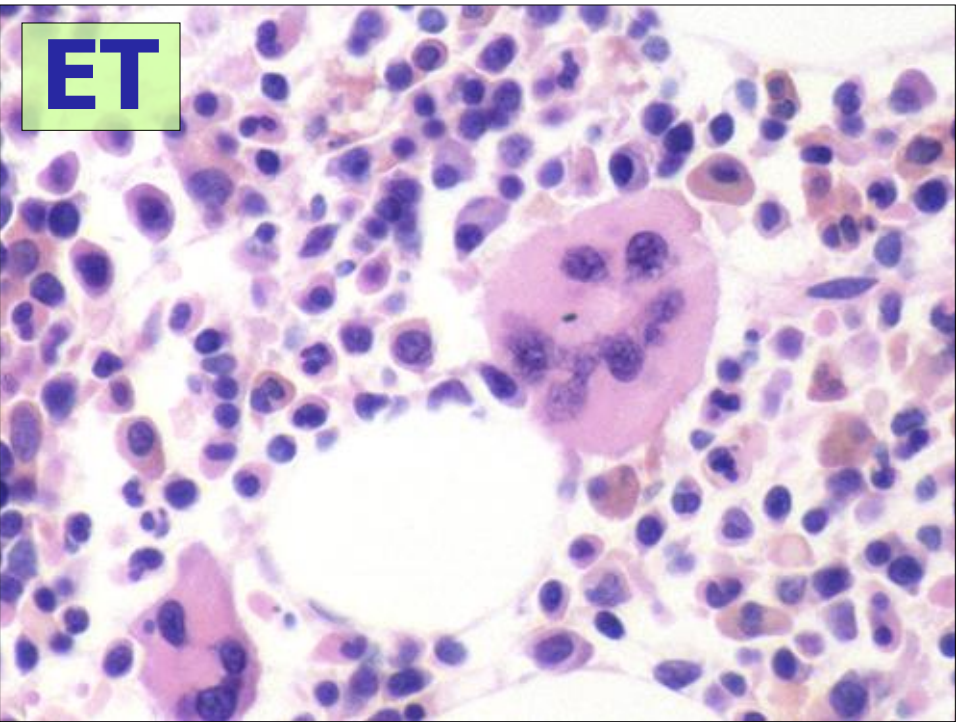
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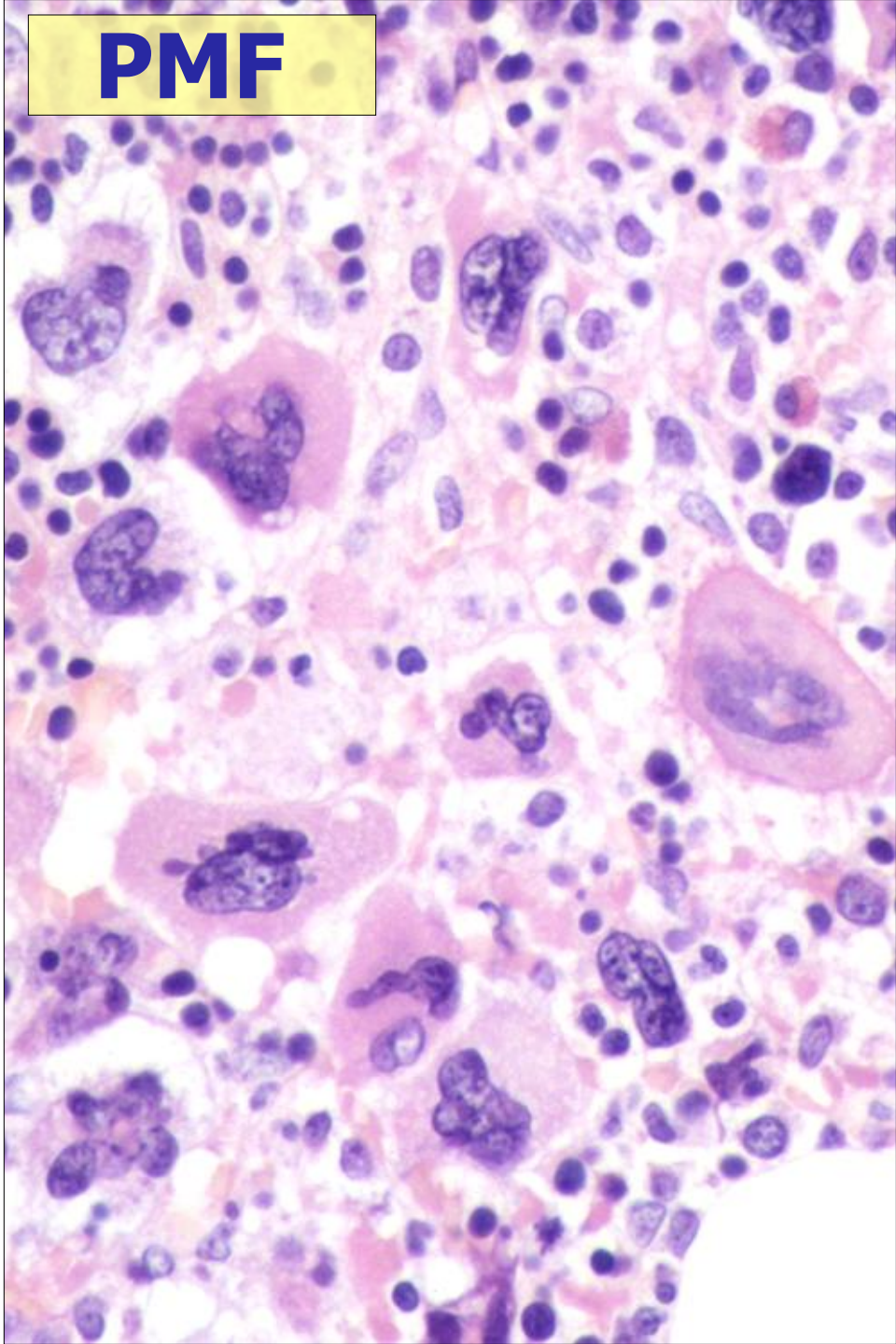
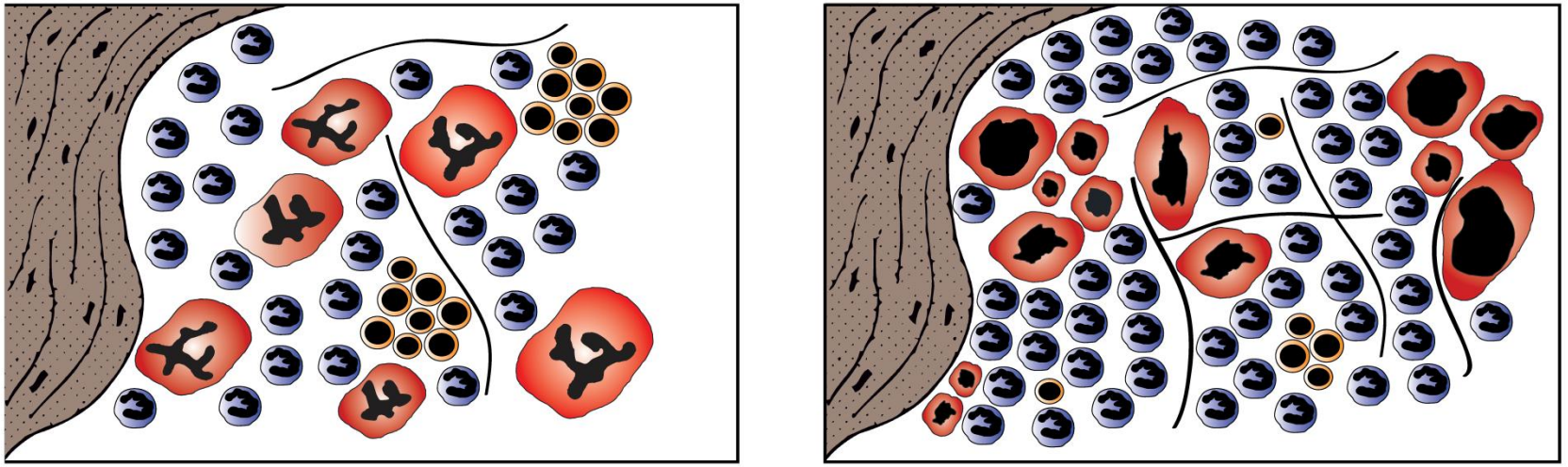

PMF

ET

PMF (early-prefibrotic stage)



Megakaryopoiesis; Granulopoiesis; Erythropoiesis; Reticulin fibers

Myelofibrosis in WHO - diagnosed ET

"The network of reticulin fibers is normal or only minimally increased in ET,and the finding of significant reticulin fibrosis or any collagen fibrosis excludes the diagnosis of ET "

Incidence of minor reticulin fibrosis (grade 1-WHO) :

-less than 5%-

(Thiele et al. Am J Hematol. 2002;70:283-29)

Myelofibrosis at presentation of ET

UK-PT1 Study (PVSG Classification):

(Harrisson et al. N Engl J Med.2005;353:33-45)

1. Wilkins et al. Blood. 2008;112:231-239

2. Campbell et al. J Clin Oncol. 2009;27:2991-2999

Brousseau et al. Histopathology.2010;56:758-767

(WHO Classification)

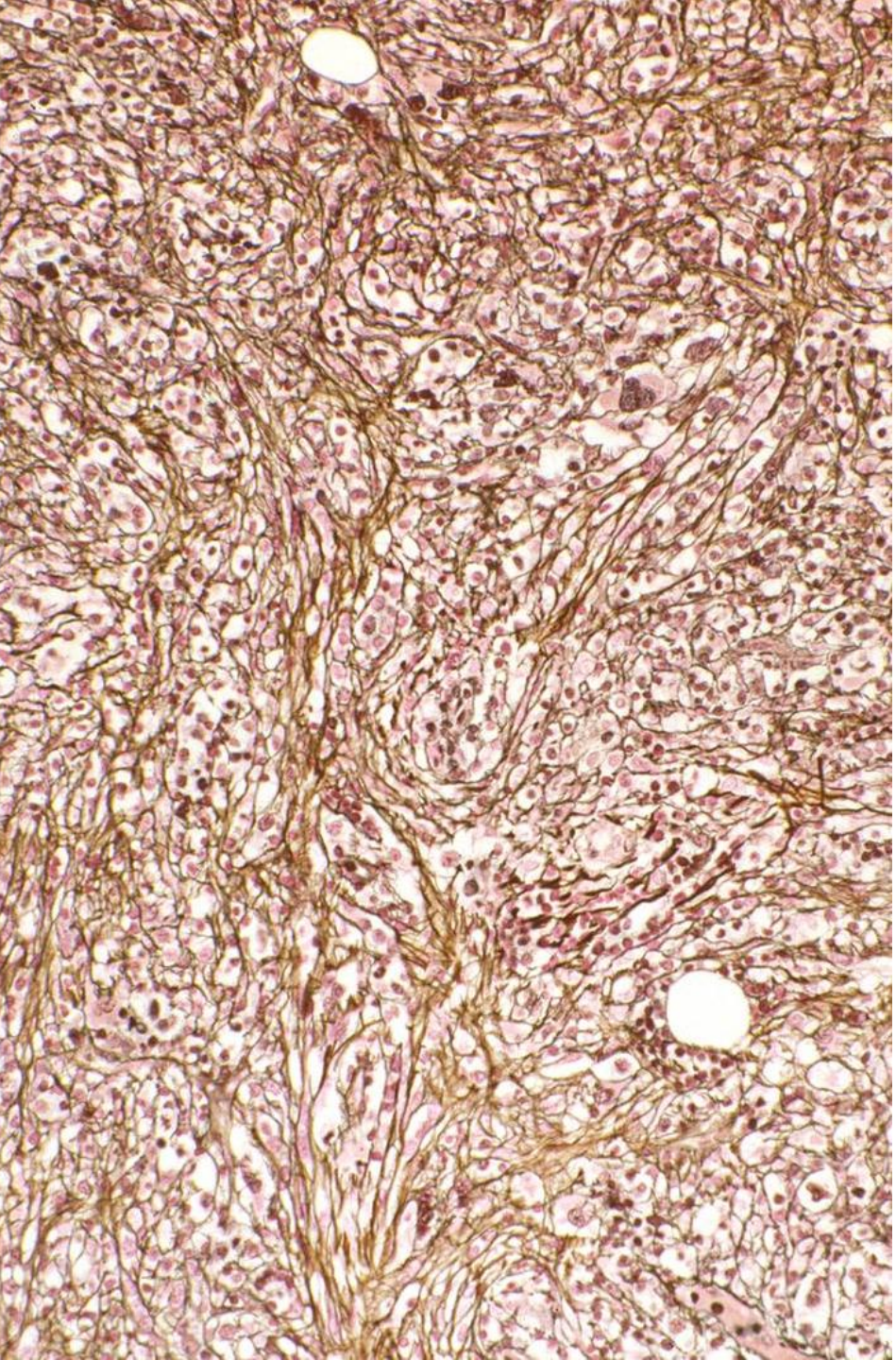
Myelofibrosis in PVSG - diagnosed ET

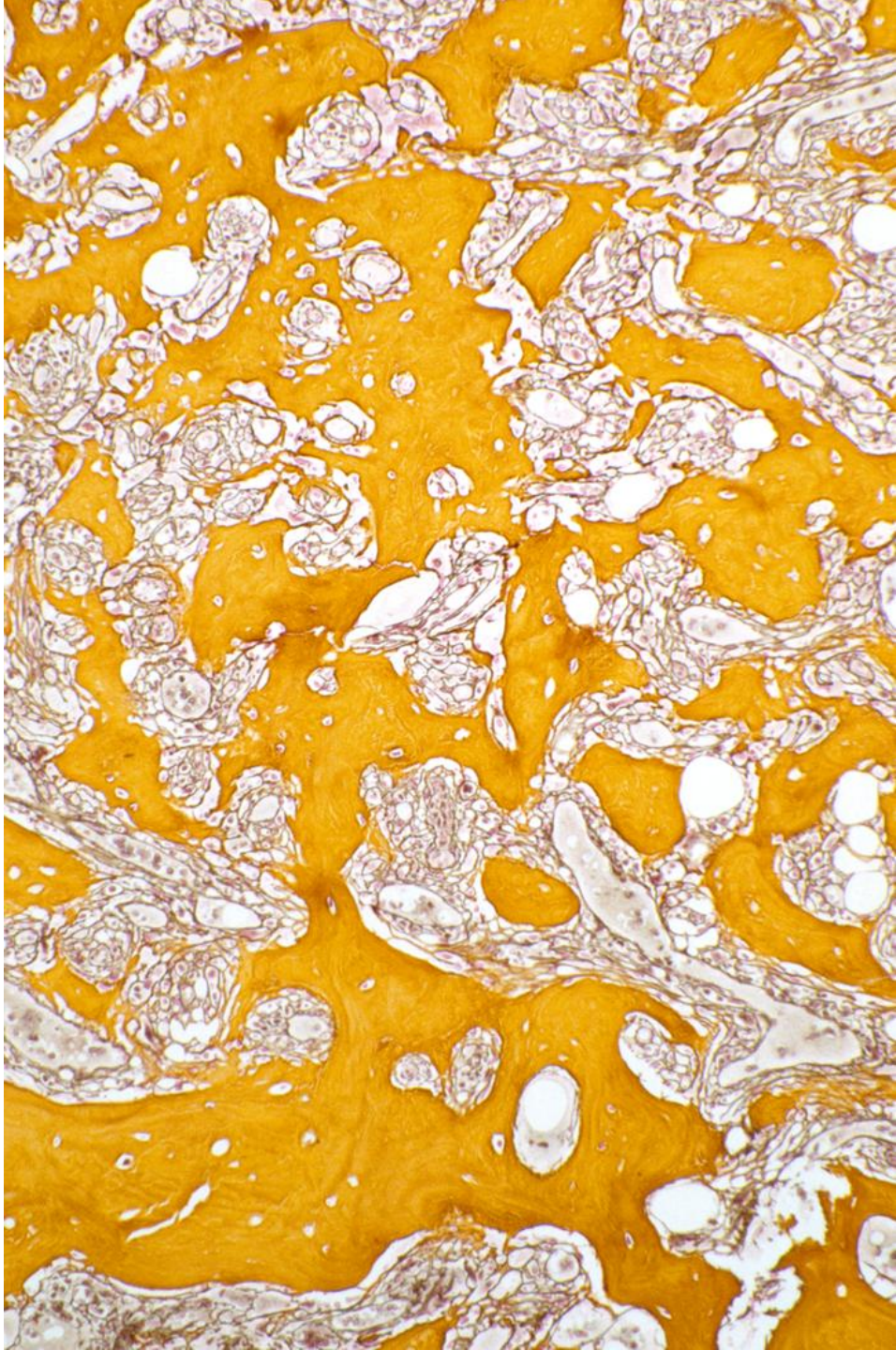
Wilkins et al. Blood.2008;111:60-70

370 patients from the UK-PT1 trial

Grade of fibrosis:

Higher levels (probably grade 3 +4) range 37%-76% among the 3 panelists plus new bone formation (osteosclerosis)





Myelofibrosis in PVSG - diagnosed ET

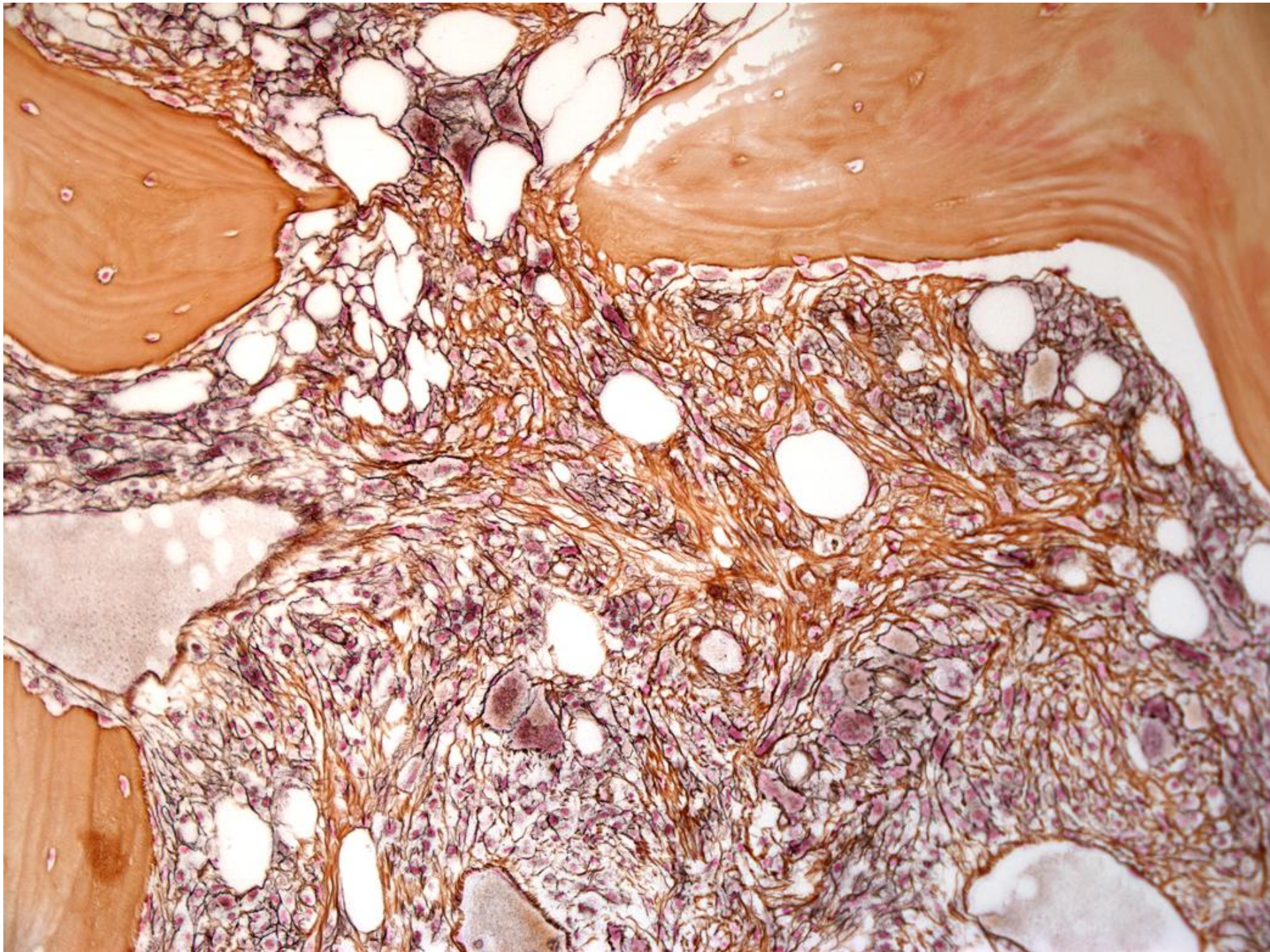
Campbell et al. J Clin Oncol. 2009;27:2991-2999

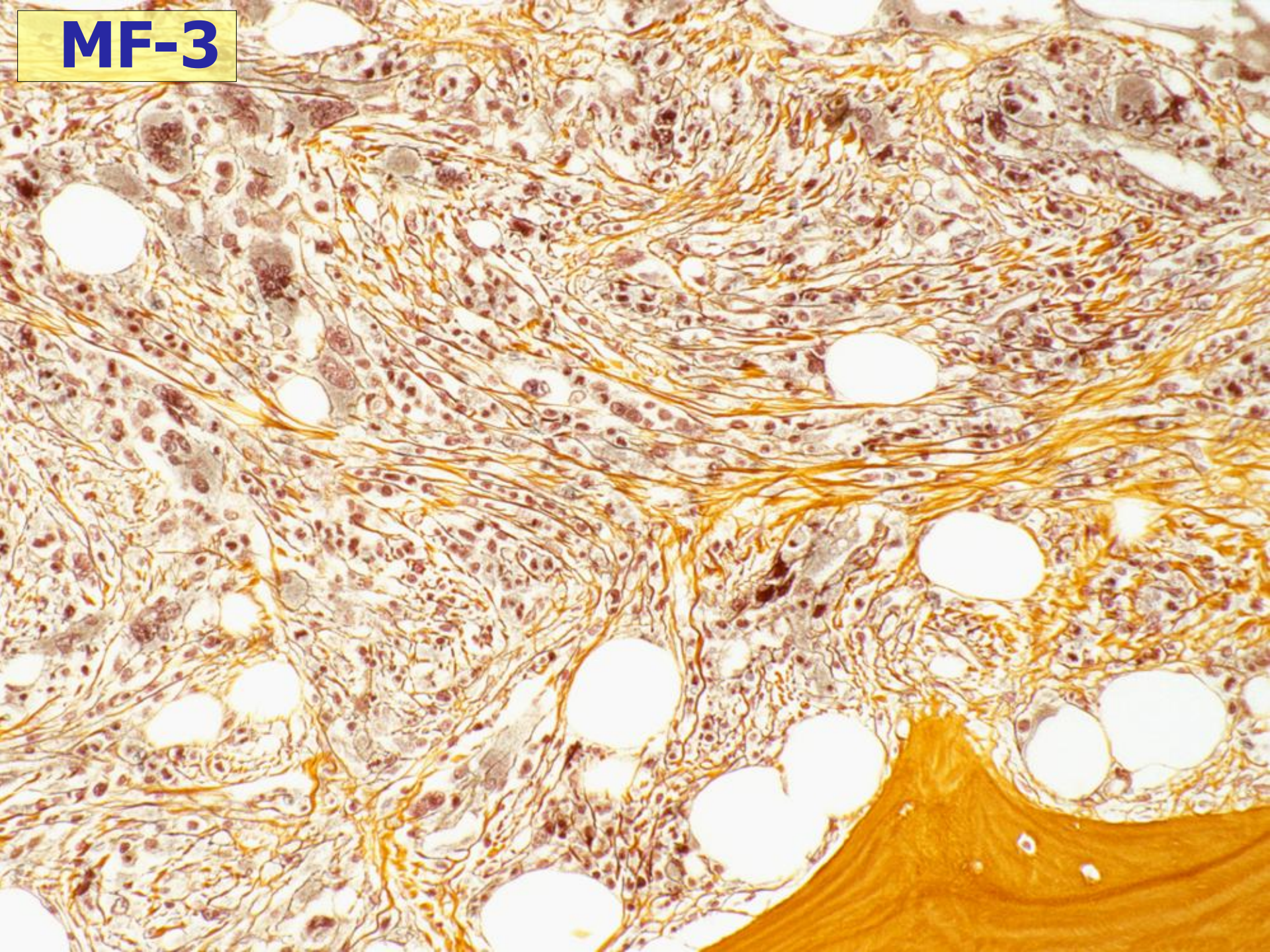
311/361 (82%) ET patients from the the UK-PT1 trial

Grade of fibrosis:

146/361 (40%) pat. Grade 2- minor to slight fibrosis

80/361 (22%) pat. Grade 3 + 4 -moderate to overall fibrosis




MF-3

Reproducibility of histological features (WHO classification)

Yes

Florena, AM et al. Haematologica, 2004, 89:911-919

Kreft, A et al. Acta Haematol., 2005, 113: 137-143

Tripodo, C et al. Histol. Histopathol., 2006, 21:813-821

Gianelli, U et al. Leuk. Lymphoma, 2006, 47:1774-1781

Gianelli, U et al. Am. J. Clin. Pathol., 2008, 130:336-342

Vener, C et al. Blood, 2008, 111: 1862-1865

Boiocchi, L et al. J. Clin. Pathol.,2011,64:226-231

Barbui,T et al. J. Clin. Oncol.,2011,in press

Reproducibility of histological features (WHO classification)

No

Wilkens, BS et al. Blood, 2008, 111:60-70

Brousseau, M et al. Histopathology,2010,56:758-767

Critical Comment

Wilkins et al. Blood.2008;111:60-70

-No intra-observer evaluation (self-assessment) during the extremely long examination period (learning effect)

-Biopsy size only 0.5 cm or more

-Very poor reproducibility of basic features as controls (erythropoiesis,fiber grading among panelists)

-No standardization of morphological features

Critical Comment

Brousseau et al. Histopathology.2010;56:758-767

-54 % of the 102 presumptively WHO-diagnosed ET patients showed minor to moderate reticulin fibrosis at onset

-Selection of biopsies up to three years after diagnosis ,no information about size of biopsy (semiquantitative study)

-Statistical analysis of bone marrow features with significantly disparate cohorts (102 ET vs. 18 PMF)

Conclusion

- Differential diagnosis of early MPN is based on the recognition of histological patterns and standardized histopathological features ,thus facilitating the reproducibility of the WHO classification
- By regarding these features on pretreatment bone marrow biopsies at diagnosis early stages of PMF are clearly separated from true ET
- The UK-PT1 Study and all emerging investigations are based on a very heterogeneous cohort of patients with a significant prevalence of PMF (early & late stages)
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