SH2017-0207

Progression of a *JAK2* V617F-Positive Essential Thrombocythemia (ET) to a *JAK2* V617F-Negative Post-ET Myelofibrosis in Accelerated Phase with Chronic Myelomonocytic Leukemia-like Monocytosis

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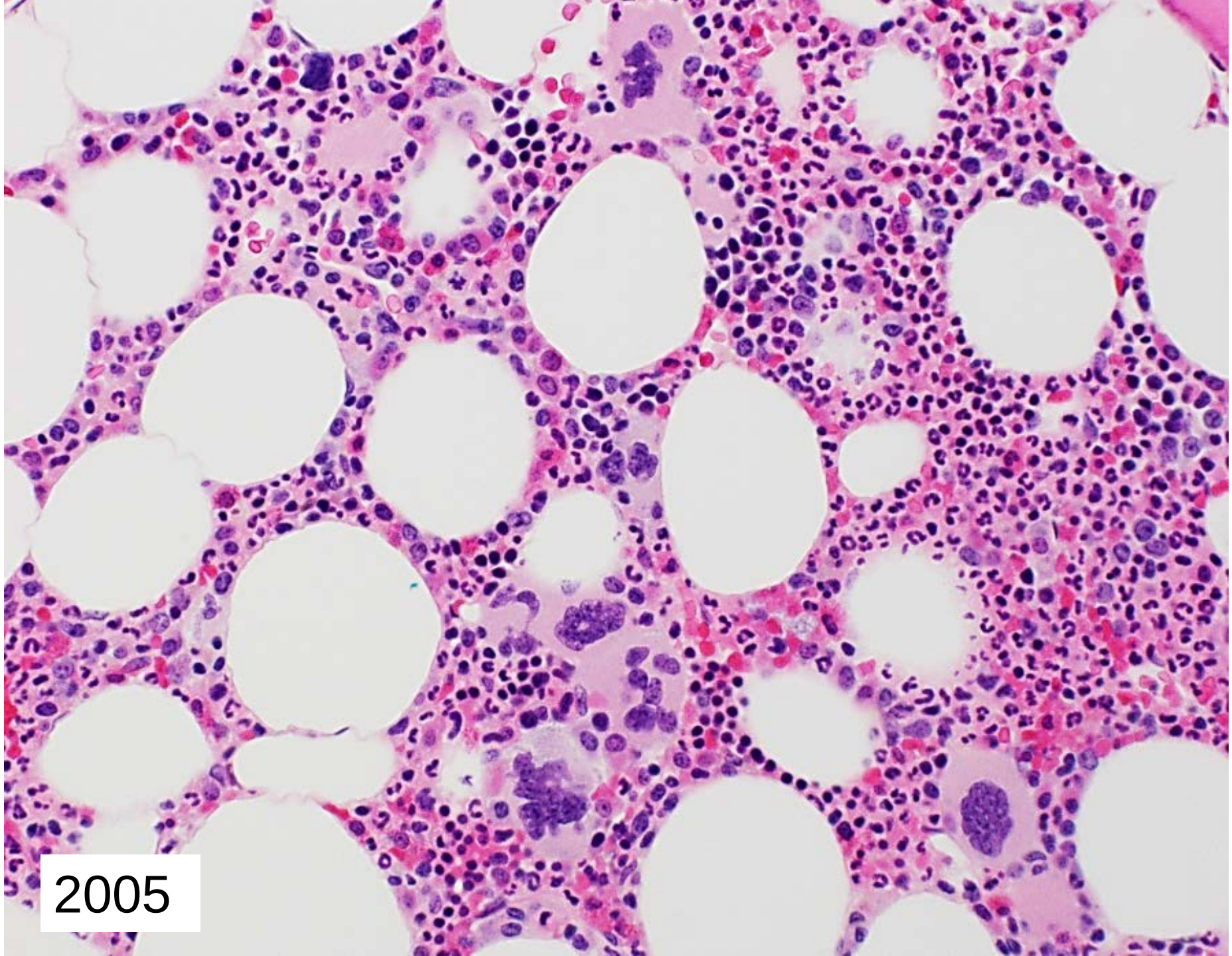
Society of Hematopathology 2017 Workshop

Clinical History

- **69 year old man with a history of multiple sclerosis, tx interferon β1a**
- **Found to have thrombocytosis in 2005**
- **CBC:**

WBC	**8.6K/uL**	**Neutrophils**	**67%**
Hgb	**15.3 g/dL**	**Lymphocytes**	**23%**
Hct	**44.5%**	**Monocytes**	**7%**
MCV	**89.5 fL**	**Eosinophils**	**2%**
Platelets	**903K/uL**	**Basophils**	**1%**


2005

Ancillary studies

- **Karyotype 46,XY[20]**
- **NGS of myeloid panel of 2006 PB (retrospective):**
  - ***JAK2* V617F VAF 30%**
  - ***ASXL1* Q877* VAF 18%**

Diagnosis

Myeloproliferative neoplasm, most consistent with essential thrombocythemia

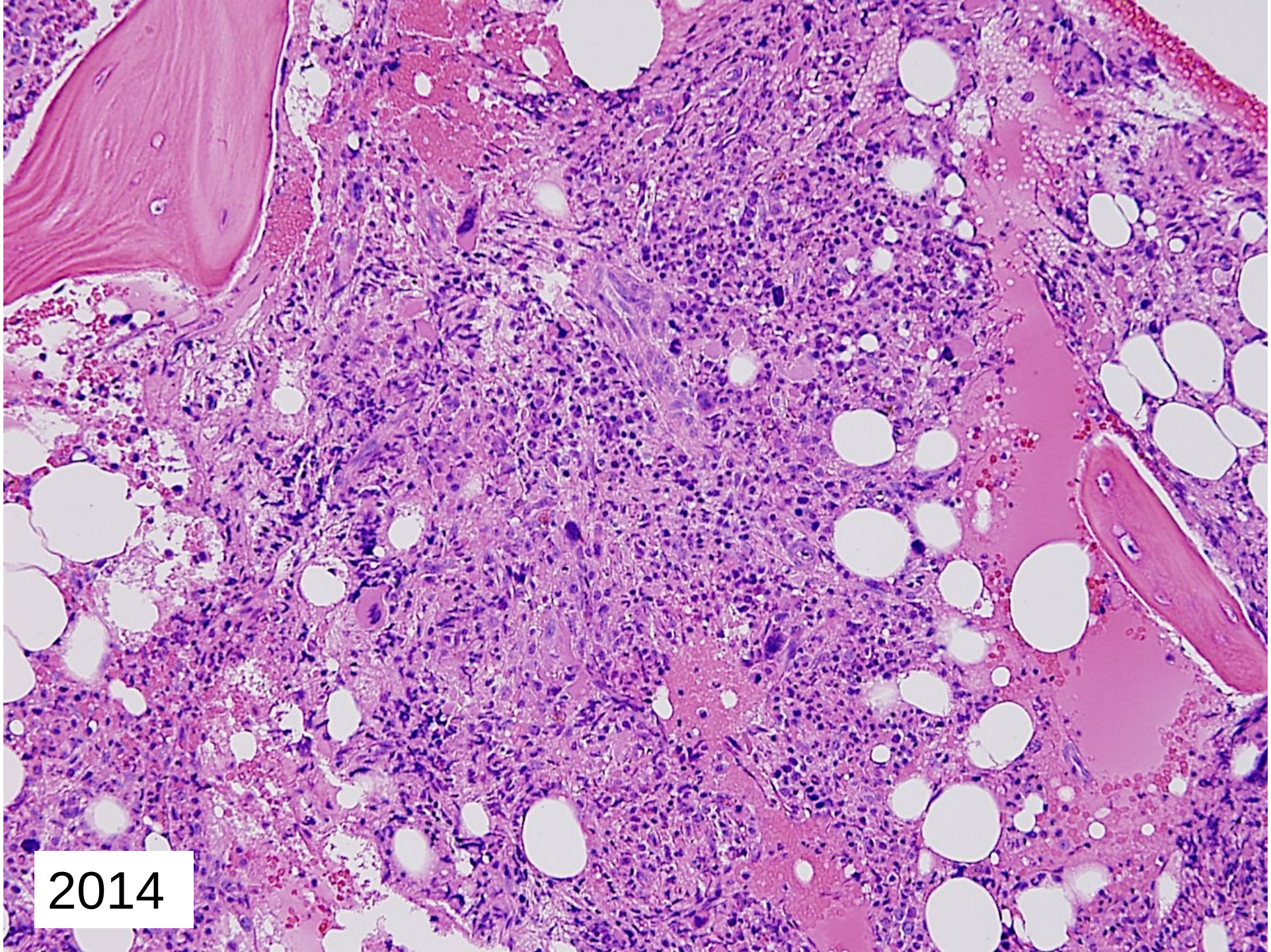
2005-2014

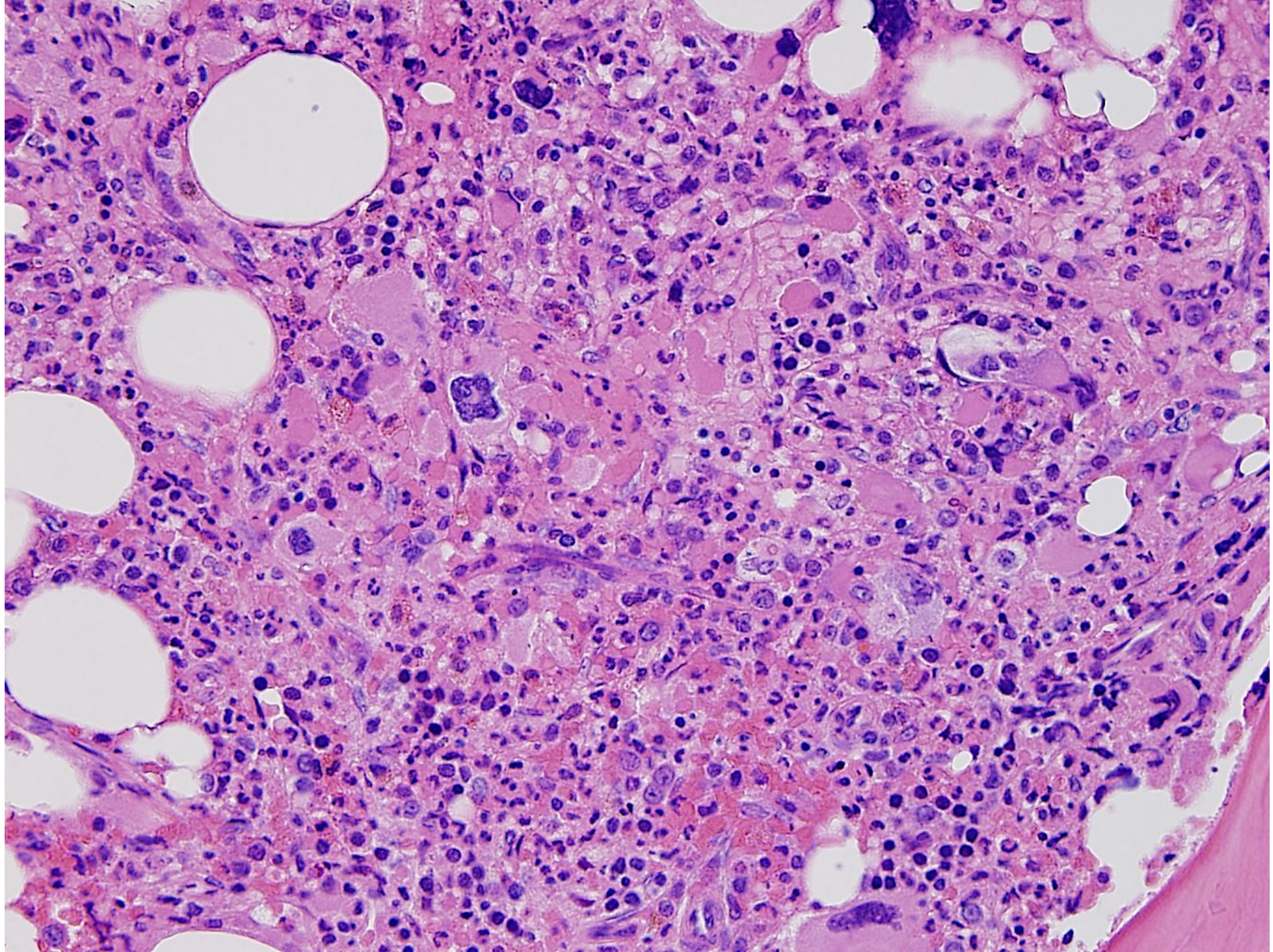
- **Managed with anagrelide**
- **Asymptomatic, no splenomegaly, normal LDH, no leukoerythroblastosis**

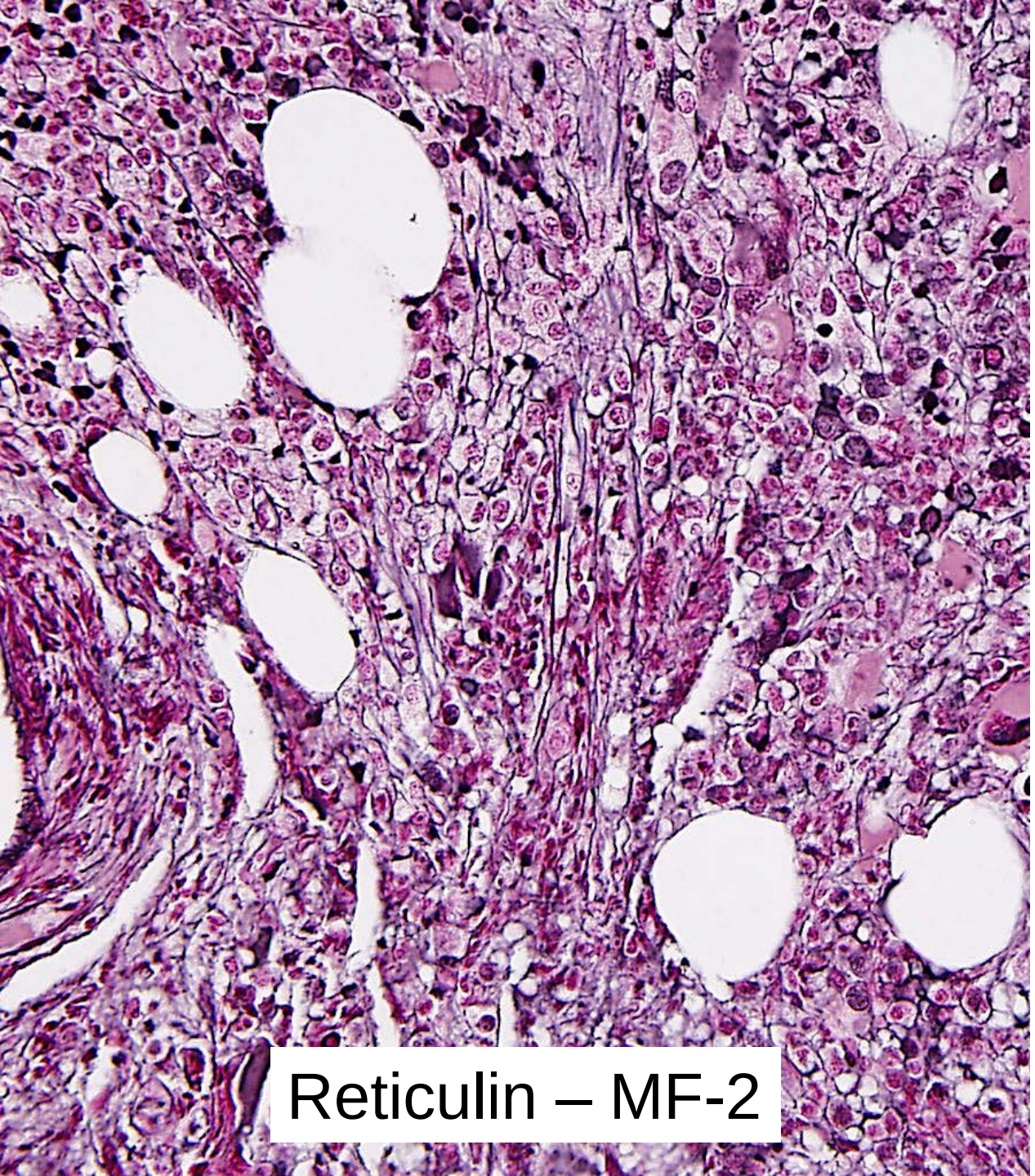
- **CBC 2014:**

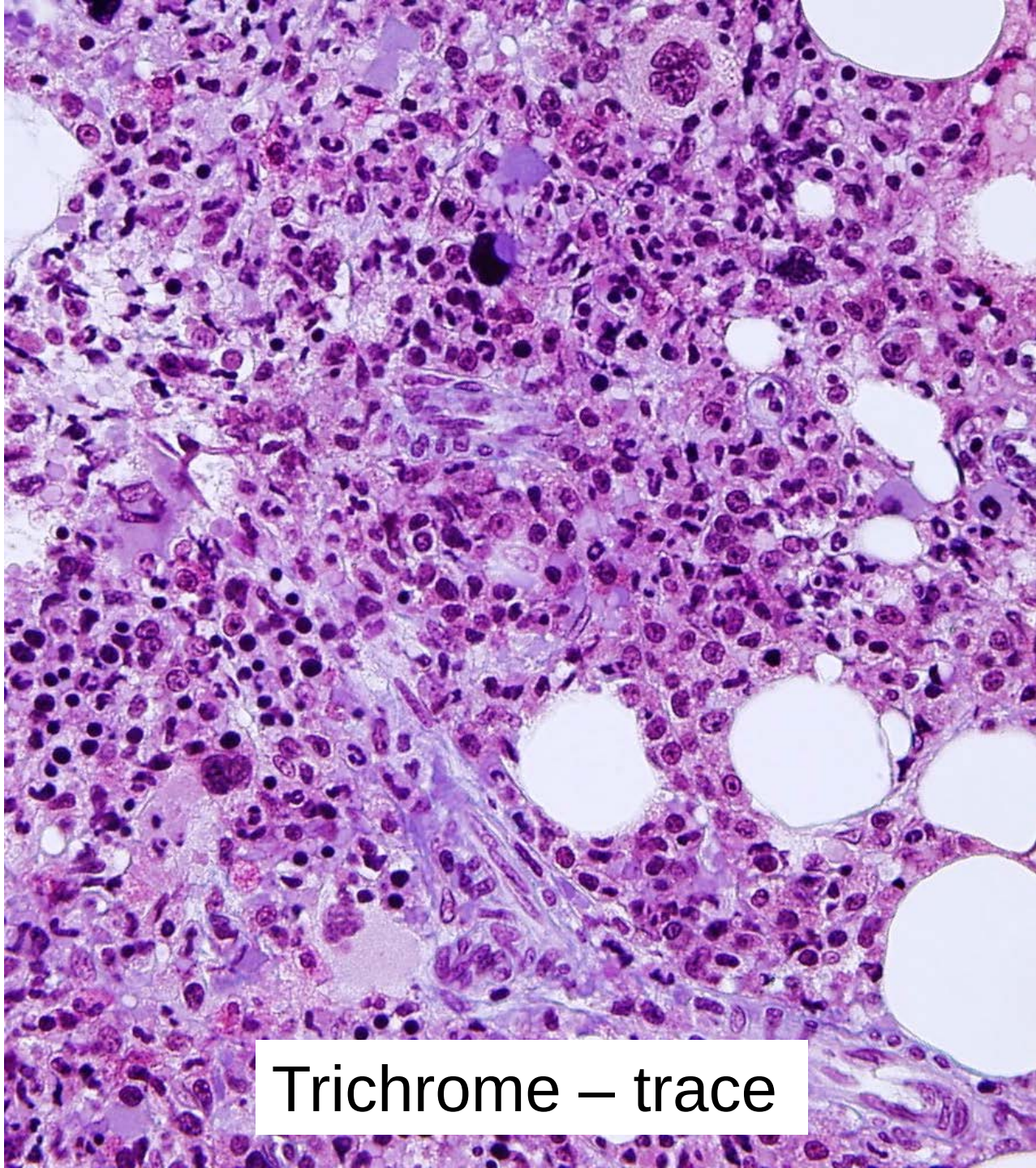
WBC	**15.1K/uL**
Hgb	**13.0 g/dL**
Hct	**39.6%**
MCV	**89.5 fL**
Platelets	**366K/uL**

Neutrophils	**53%**
Bands	**4%**
Lymphocytes	**23%**
Monocytes	**11%**
Eosinophils	**2%**
Basophils	**4%**


2014




Reticulin – MF-2


Trichrome – trace

Ancillary studies

- **NGS of myeloid panel (PB):**
  - ***JAK2* V617F VAF 12%**
  - ***ASXL1* Q877* VAF 12%**
  - ***ASXL1* G646fs VAF 21%**
  - ***PHF6* G10fs VAF 30%**
  - ***TET2* V1999A VAF 2%**

Diagnosis

Essential thrombocythemia with increased fibrosis, in progression to post-ET myelofibrosis.

2014-2017

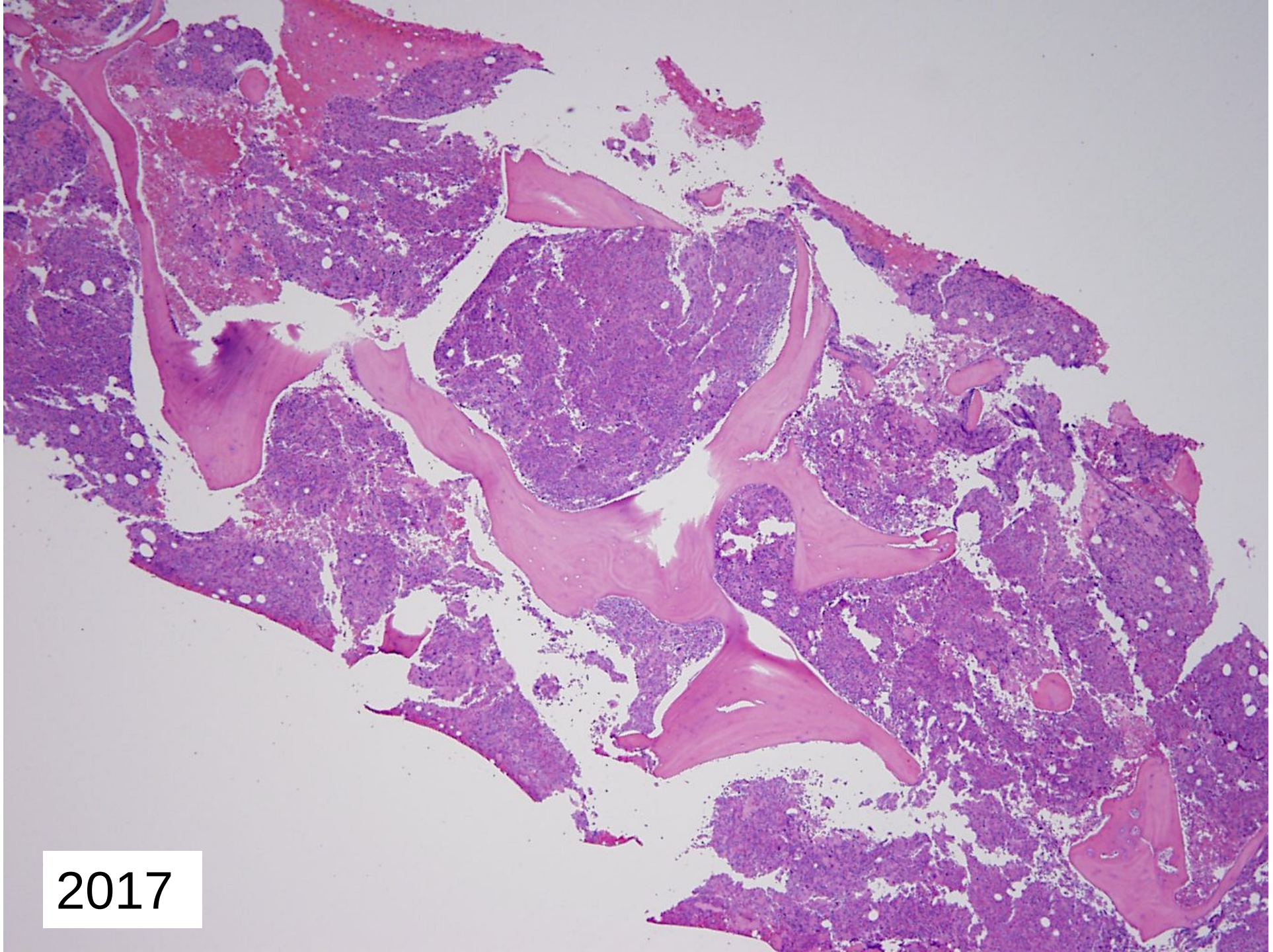
- **Managed with hydroxyurea**
- **Progressive leukocytosis**
- **Splenomegaly, elevated LDH, leukoerythroblastosis**

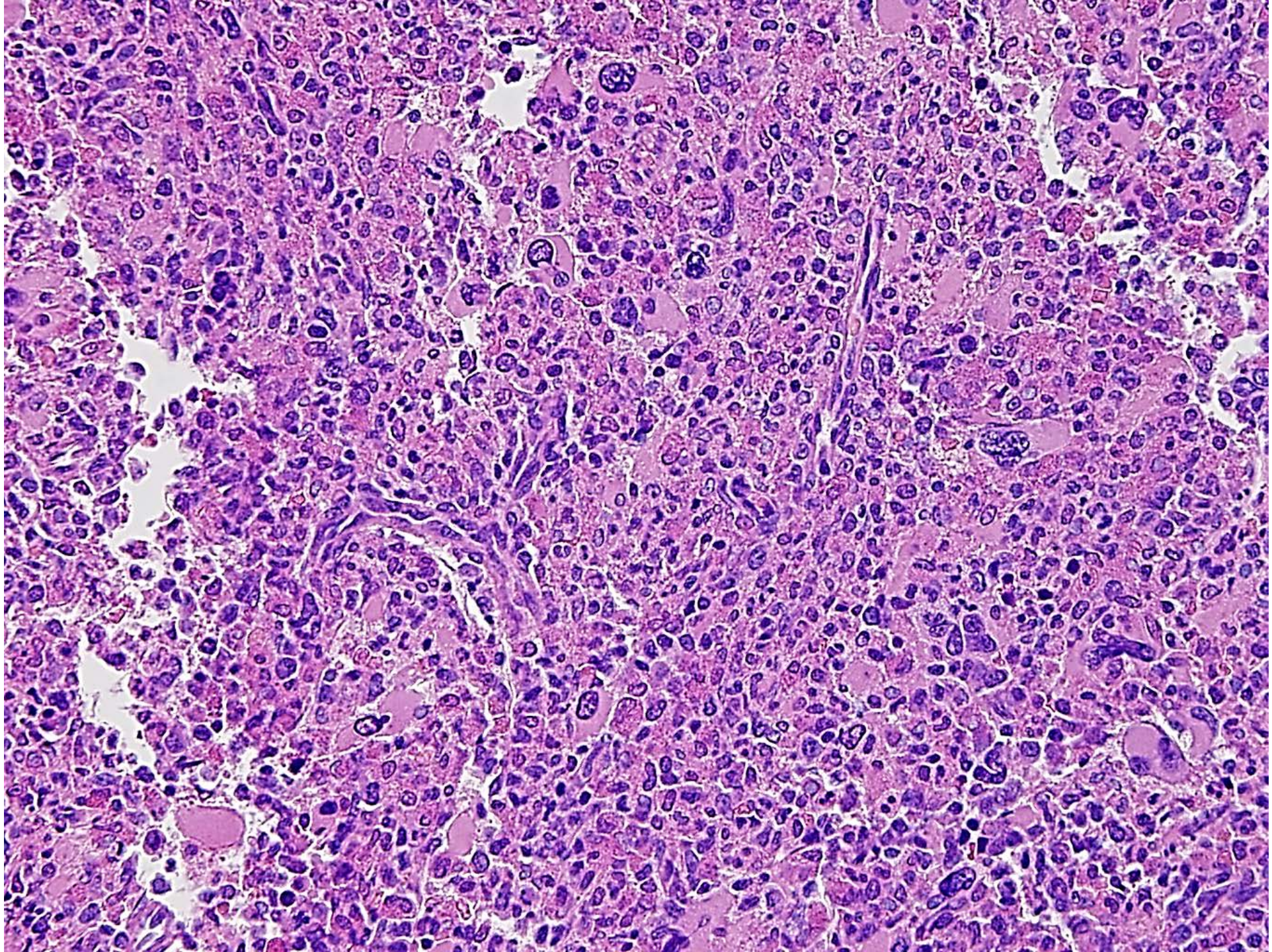
- **CBC 2017:**

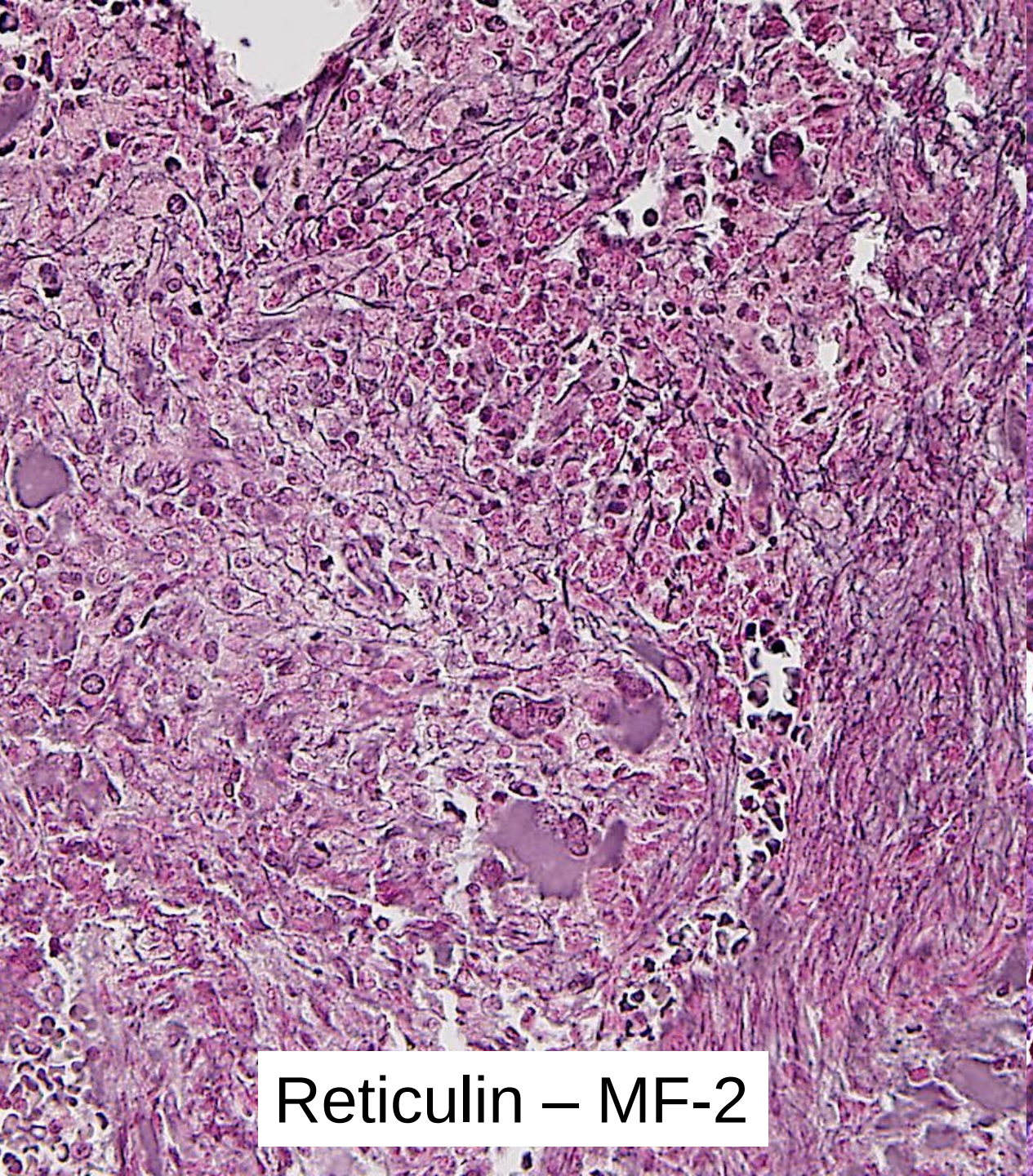
WBC	79K/uL
Hgb	9.4 g/dL
Hct	29.8%
MCV	95.4 fL
Platelets	203K/uL

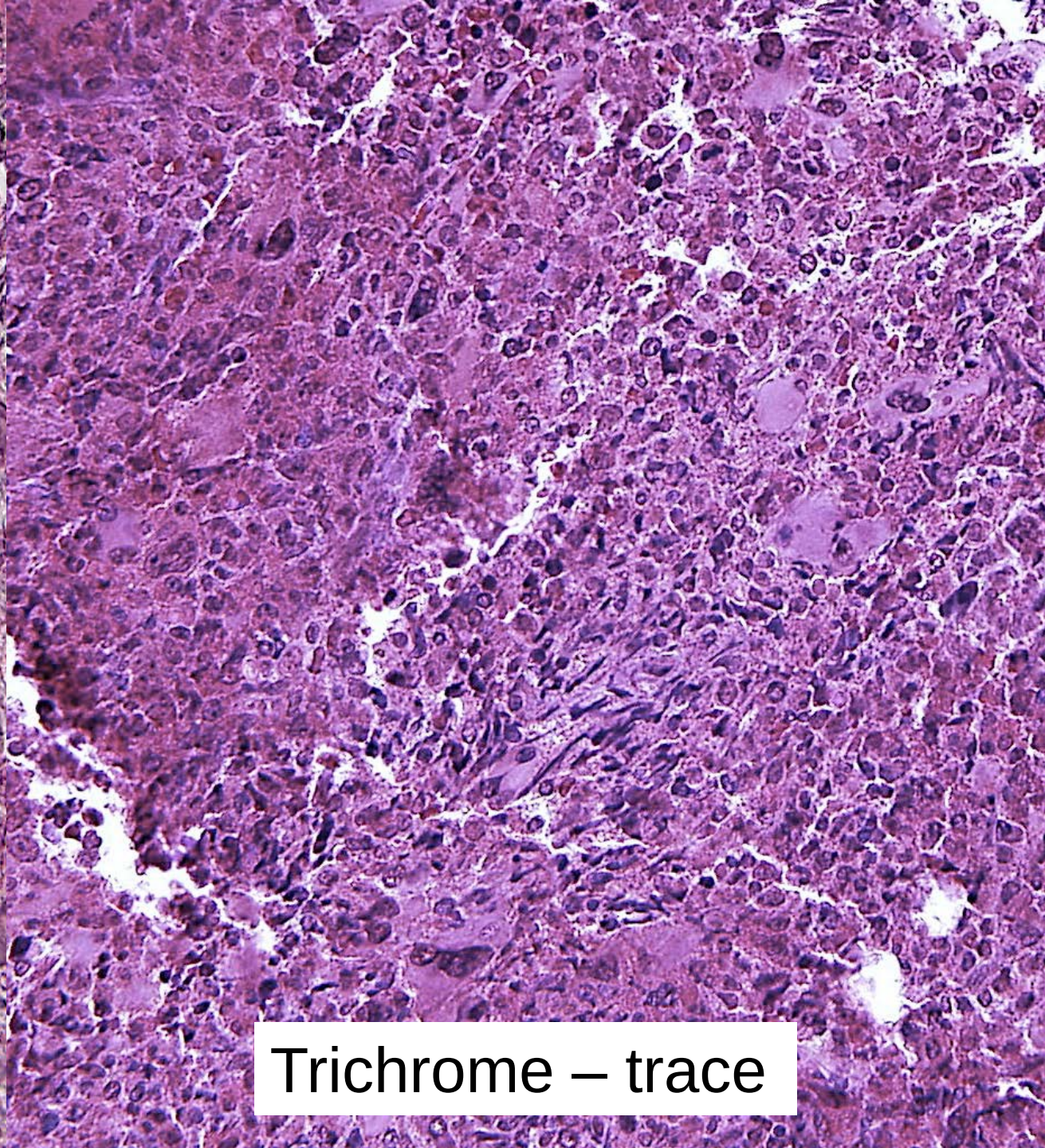
Neutrophils	14%
Bands	10%
Metamyelo	5%
Myelocyte	6%
Promyelocyte	2%
Blasts	5%

Lymphocytes	18%
Monocytes	24%
Eosinophils	5%
Basophils	11%


2017




Reticulin – MF-2


Trichrome – trace

Summary of Bone Marrow Findings

- **Increased blasts (12%) and monocytes (16%) on aspicular bone marrow smear**
- **Increased M:E ratio (5.5)**

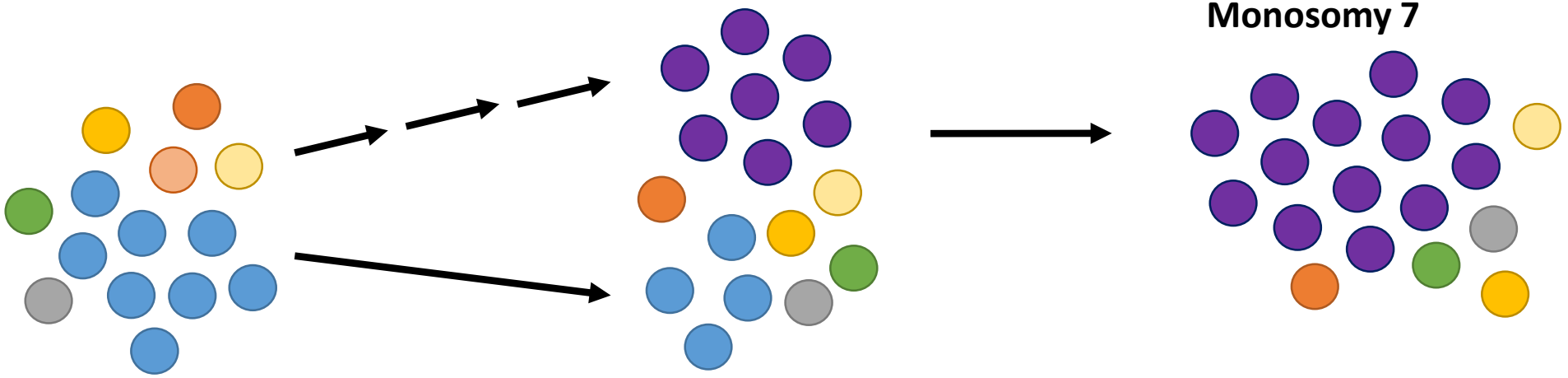
Ancillary studies

- **Karyotype (PB): 45,XY,-7[14]**
- **NGS of myeloid panel (PB):**
  - ***ASXL1* G646fs VAF 30%**
  - ***PHF6* G10fs VAF 74%**
  - ***CBL* Y371H VAF 2%**
  - ***KDM6A* S900P VAF 5%**

Final Panel Diagnosis

Post-essential thrombocythemia myelofibrosis in accelerated phase with chronic myelomonocytic leukemia-like monocytosis

Summary



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PHF6 G10fs VAF 74%
CBL Y371H VAF 2%
KDM6A S900P VAF 5%
Monosomy 7

2005
ET

2014
ET in progression to post-ET MF

2017
Post-ET MF in AP with CMML-like monocytosis

CMML-like progression of PMF indicates an accelerated phase of disease

- **After development of monocytosis, death in 5 of 10 patients and transfusion dependence in 2 of 10.**
- **Monocytosis associated with leukocytosis, anemia, decreased platelet count, circulating blasts**
- **No change in *JAK2* mutational status or cytogenetic evolution**

Boiocchi et al., Mod Pathol 26(2):204-12, 2013.

Leukemic progression of MPNs frequently associated with loss of *JAK2* mutation

- **In 12 of 21 patients with *JAK2* V617F+ MPN that progressed to blast phase, *JAK2* V617F was negative in the acute leukemia.**

Theocharides et al., Blood 110(1):375-9, 2007.
Campbell et al., Blood 108(10):3548-55, 2006.

Role of therapy on selecting divergent clone

- **Uncertain how hydroxyurea or anagrelide may have played a role in selecting clone**

- **Hydroxyurea has been shown to cause genomic instability**

Arit, et al. PNAS 108(42):17360-17365, 2011

Conclusions

- **This case demonstrates the evolution of an MPN from ET (2005), to ET in progression to post-ET MF (2014), and finally to post-ET MF, in accelerated phase, with CMML-like features (2017).**

- **The molecular findings suggest that disease progression from ET to accelerated phase of post-ET MF in this case may have occurred via clonal selection and expansion of a divergent or separate clone rather than a simple direct evolution.**

Thank you!

Final Panel Diagnosis

Post-essential thrombocythemia myelofibrosis in accelerated phase with chronic myelomonocytic leukemia-like monocytosis