Myeloproliferative Neoplasms

1. **Myeloproliferative neoplasms (MPN)**
   - 1.1. Chronic myelogenous leukemia, *BCR-ABL1*–positive (CML)
   - 1.2. Polycythemia vera (PV)
   - 1.3. Essential thrombocythemia (ET)
   - 1.4. Primary myelofibrosis (PMF)
   - 1.5. Chronic neutrophilic leukemia (CNL)
   - 1.6. Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
   - 1.7. Mast cell disease (MCD)
   - 1.8. MPN, unclassifiable

MPN features

- Cytosis
- Organomegaly (mainly splenomegaly)
- High uric acid
- Hypercellular bone marrow
- Progression to acute leukaemia (mainly AML)

Table 1. Classification of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

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BCR-ABL must be negative

2. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1*

3. MDS/MPN
- 3.1. Chronic myelomonocytic leukemia (CMML)
- 3.2. Juvenile myelomonocytic leukemia (JMML)
- 3.3. Atypical chronic myeloid leukemia, *BCR-ABL*–negative (aCML)
- 3.4. MDS/MPN, unclassifiable

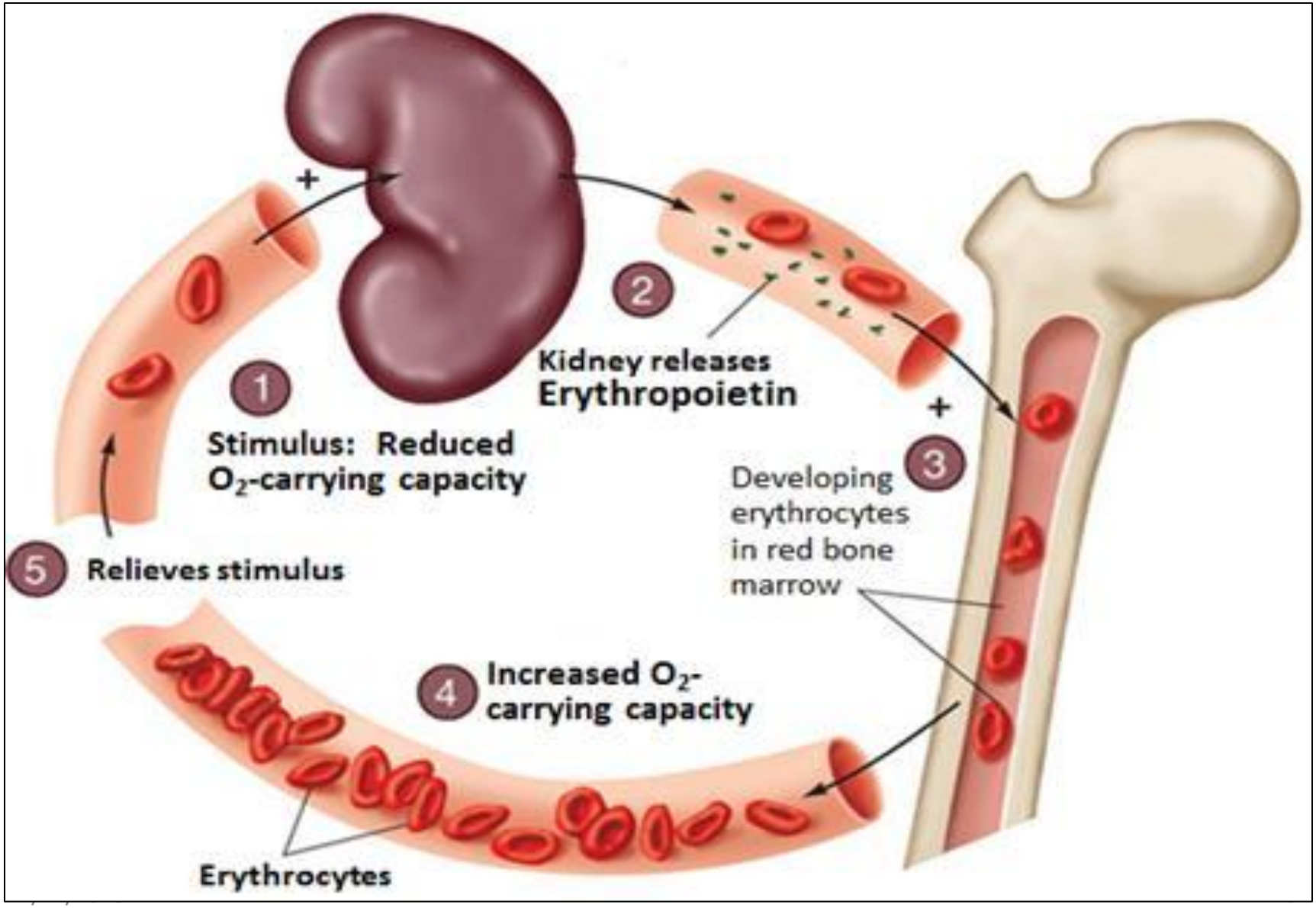
4. Myelodysplastic syndromes (MDS)

5. Acute myeloid leukemia (AML)

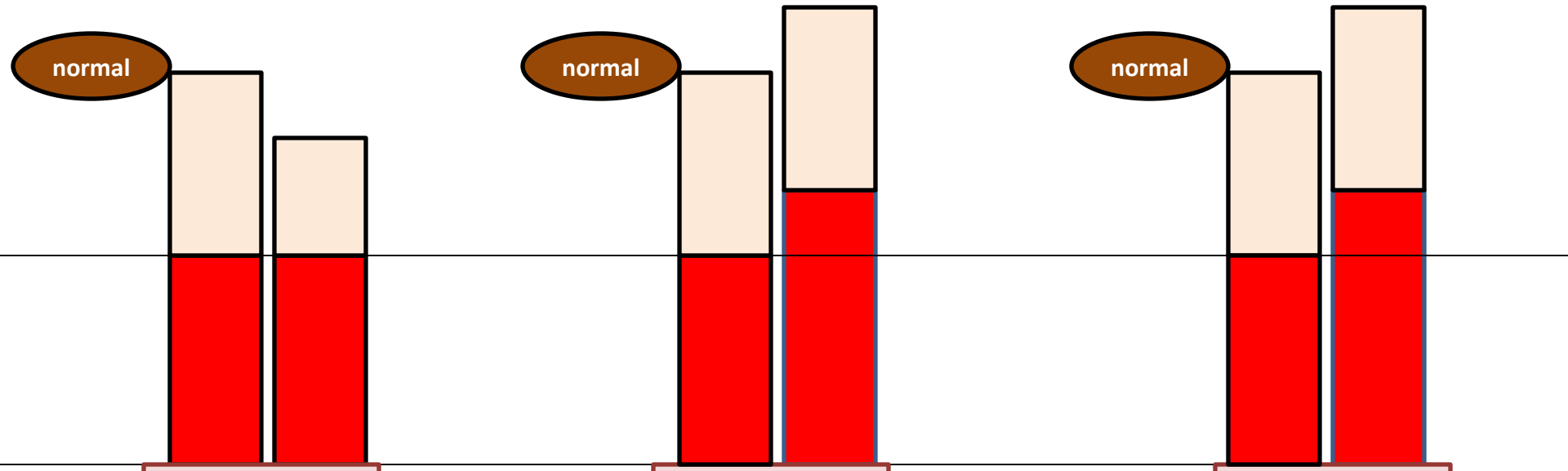
Polycythemia

- In Greek “too many cells in the blood.”.
- Absolute increase in total body red cell volume (or mass)
- Manifests itself as a raised Hb or packed cell volume (PCV)
- Hb is >16.5or 18.5 g/dl in women and men, respectively.

Regulation of Erythropoiesis



Classification of Polycythemia



Relative Polycythemia

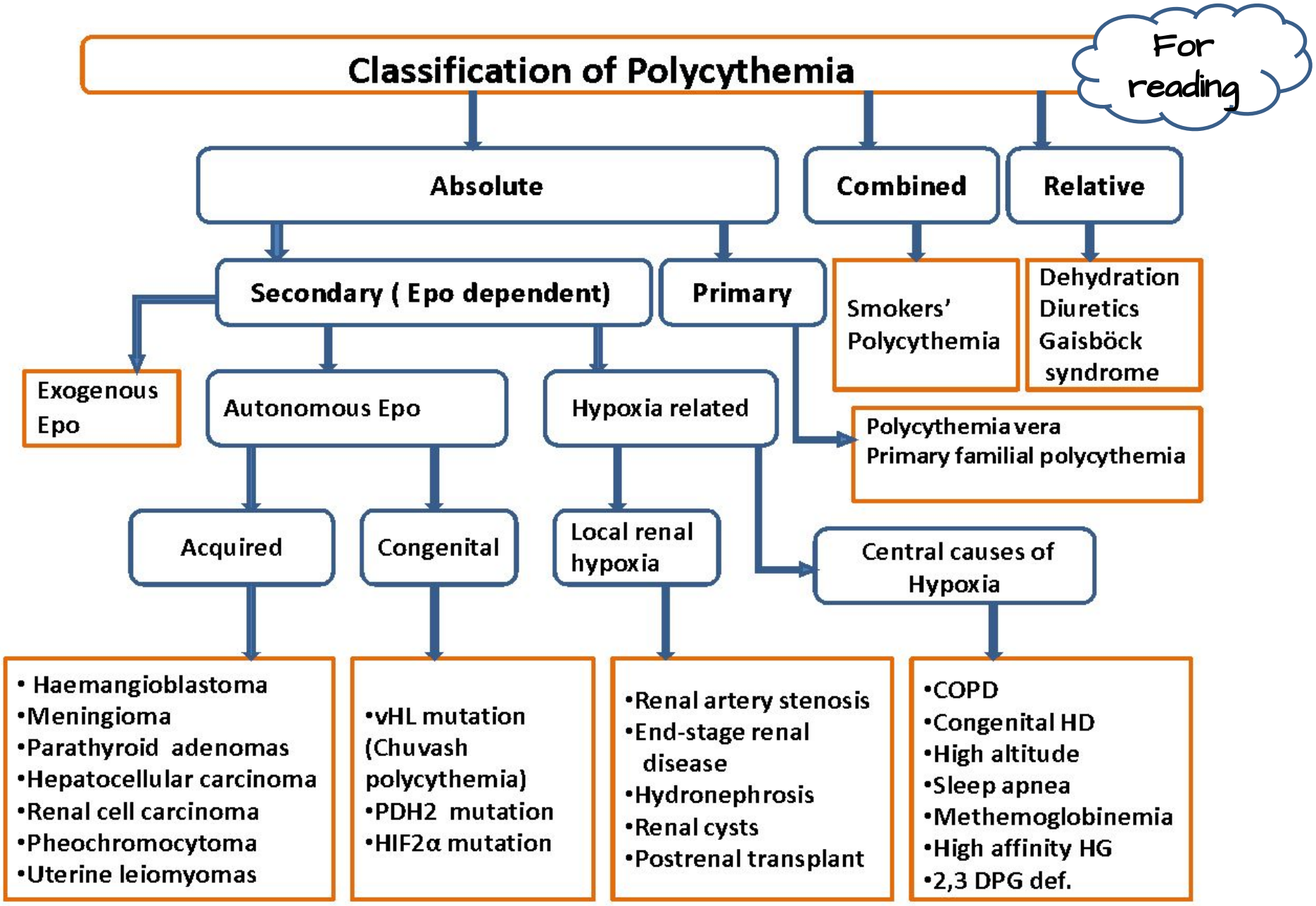
Decreased plasma volume due to severe dehydration

2nd Polycythemia

Increased RBC mass due to high EPO:
1-COPD, Sleep apnea, smoking..
2-High altitude
3-High affinity HB
4-Renal disease
5-Epo secreating tumor (Parathyroid adenoma …)

Polycythemia vera

Increased RBC mass due to malignant proliferation


Classification of Polycythemia
For reading
Absolute
Combined
Relative
Secondary (Epo dependent)
Primary
Smokers' Polycythemia
Dehydration
Diuretics
Gaisböck syndrome
Exogenous Epo
Autonomous Epo
Hypoxia related
Polycythemia vera
Primary familial polycythemia
Acquired
Congenital
Local renal hypoxia
Central causes of Hypoxia
• Haemangioblastoma
•Meningioma
•Parathyroid adenomas
•Hepatocellular carcinoma
•Renal cell carcinoma
•Pheochromocytoma
•Uterine leiomyomas
•vHL mutation (Chuvash polycythemia)
•PDH2 mutation
•HIF2α mutation
•Renal artery stenosis
•End-stage renal disease
•Hydronephrosis
•Renal cysts
•Postrenal transplant
•COPD
•Congenital HD
•High altitude
•Sleep apnea
•Methemoglobinemia
•High affinity HG
•2,3 DPG def.

Polycythemia Vera

- **MPN characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis.**

Diagnostic Features:

- **HB >18.5g/dl in men ,16.5g/dl in women**
- **Hypercellular bone marrow**
- **JAK2 mutation in >95% of cases**
- **Low Serum erythropoietin level**

Clinical features of PV

1-Increased blood viscosity

- **Hypertension**
- **Headache, dizziness, visual disturbances & paresthesia**

2- Thrombosis

- **Deep vein thrombosis**
- **Myocardial infarction**
- **Mesenteric, portal or splenic vein thrombosis**

3-Splenomegaly in 70%

4-Hepatomegaly in 40%

Investigations

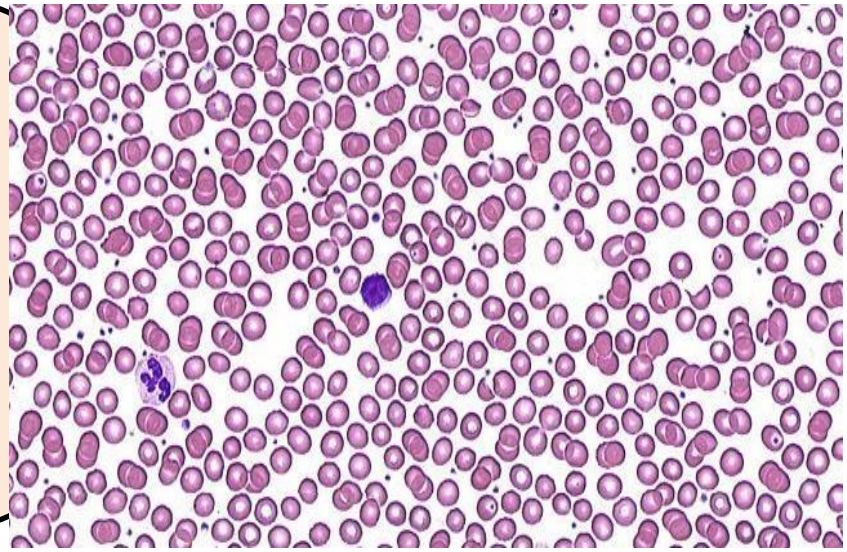
CBC:

*RBC: increased *Hb: increased

*WBC & PLT :mildly increased (usually)

Blood smear:

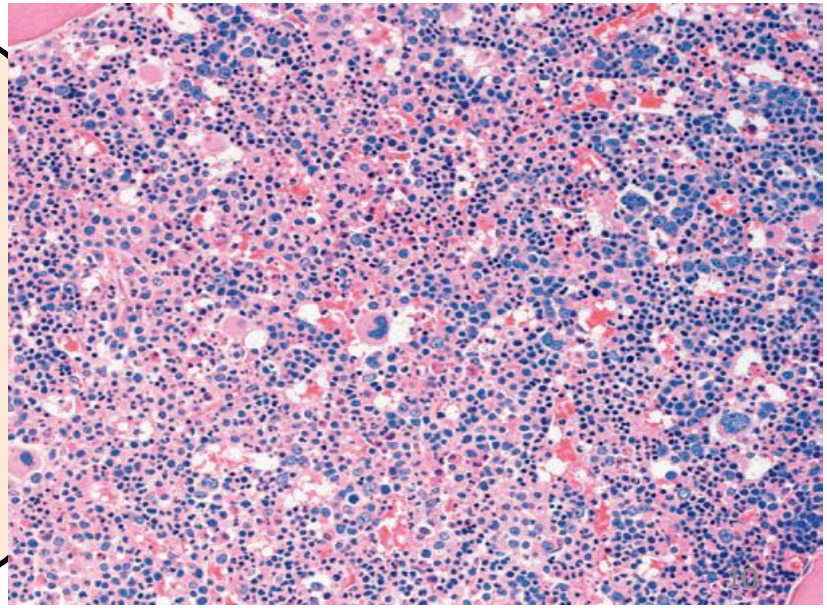
- Excess of normocytic normochromic RBC
- ±Leukocytosis &thrombocytosis



Bone marrow

- Hypercellular
- Predominant erythroid precursors
- ± Increased megakaryocytes &Myeloid precursors.

↑ Blasts ⟶ AL transformation



Complication &treatment

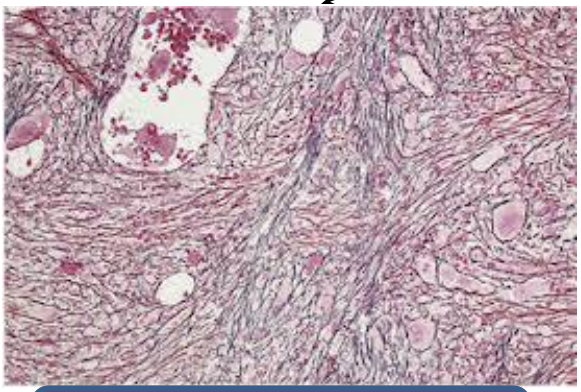
Diagnosis of Polycythemia Vera

Treatment:

- Venesection + Aspirin
- ± Myelosuppressive drugs (hydroxyuria)

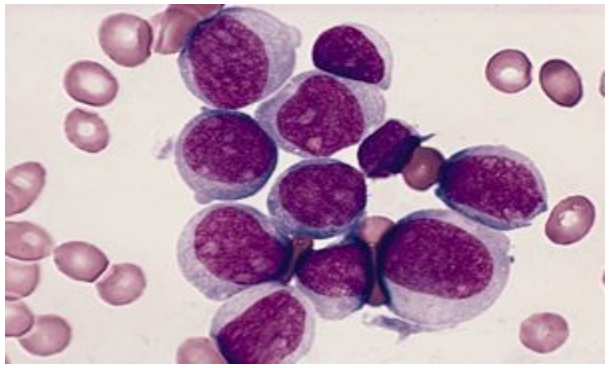
10-15 years

20%



Myelofibrosis

10%



Acute leukemia

Primary Myelofibrosis

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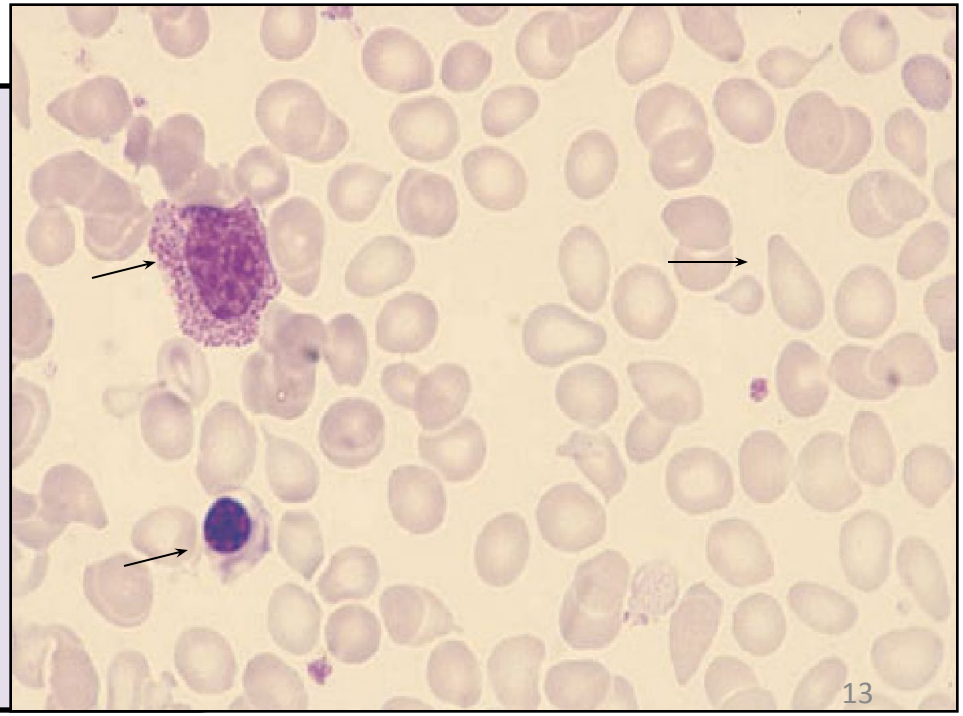
Primary Myelofibrosis

Clonal MPN characterized by a proliferation of megakaryocytes & granulocytes in the bone marrow that associated with deposition of fibrous connective tissue and extramedullary haematopoiesis

Clinical features

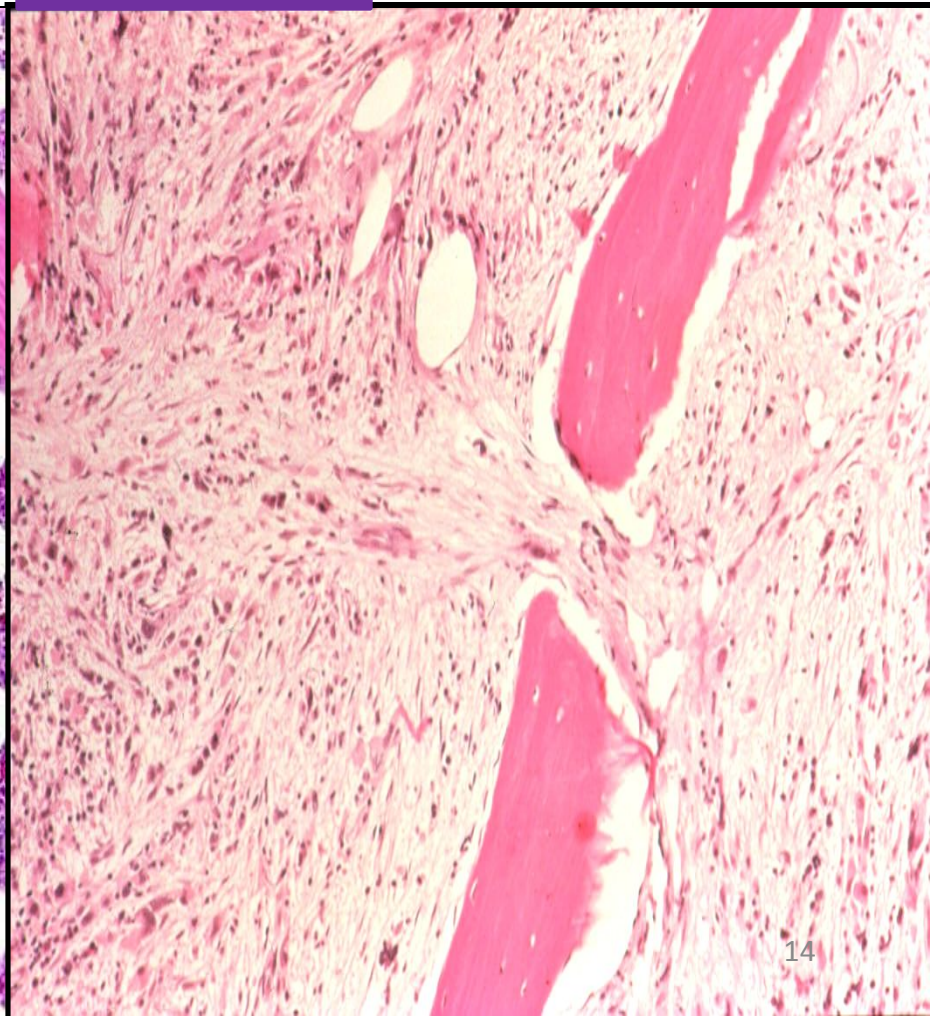
- **Anemia**
- **Leukoerythroblastic blood picture.**
- **Massive splenomegaly**
- **Fibrotic bone marrow**
- **JAK2 mutation (50%)**
- **Risk of AML transformation (20%)**



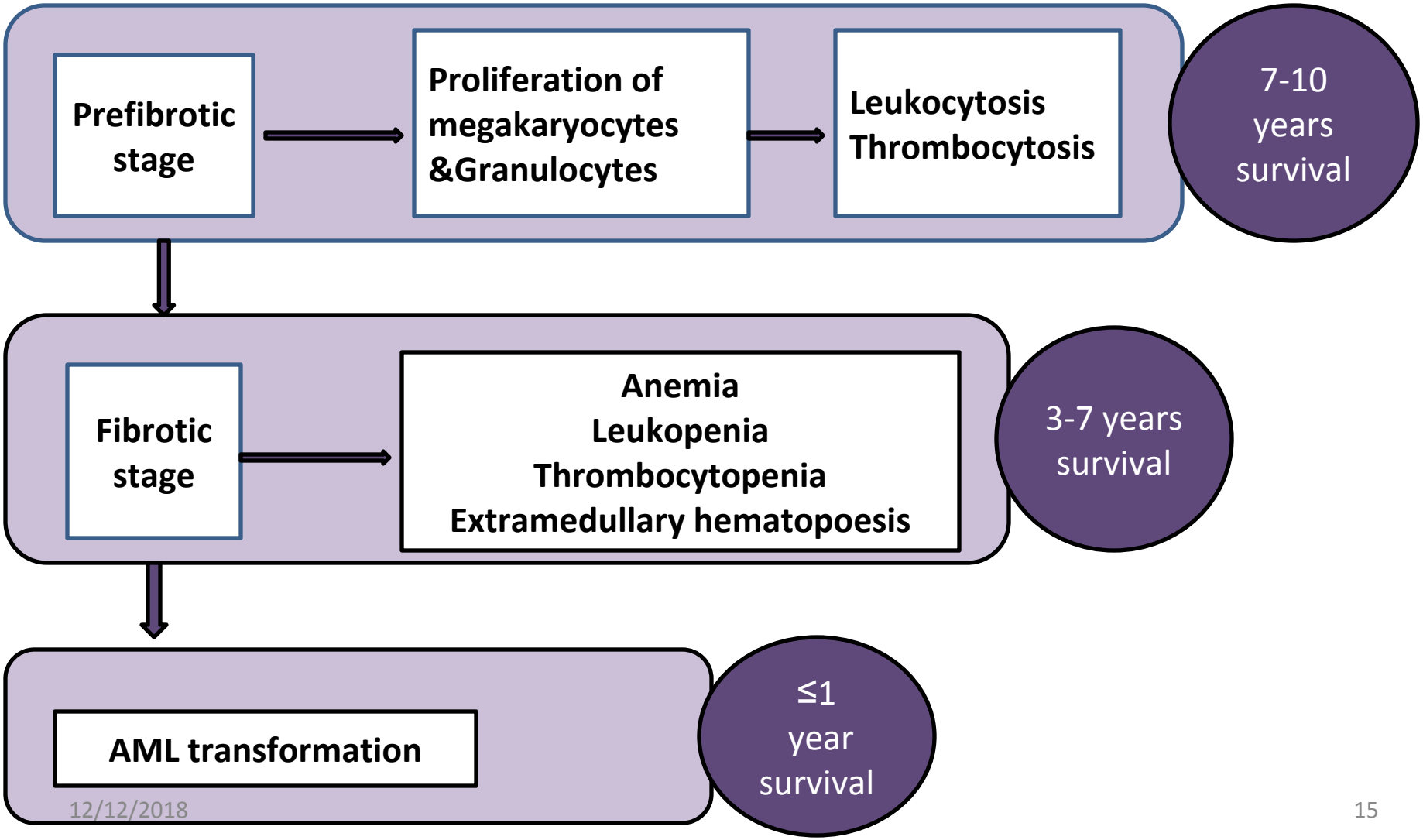
Bone marrow in Myelofibrosis

Normal BM

Fibrotic BM



Stages of PMF



Essential Thrombocythemia

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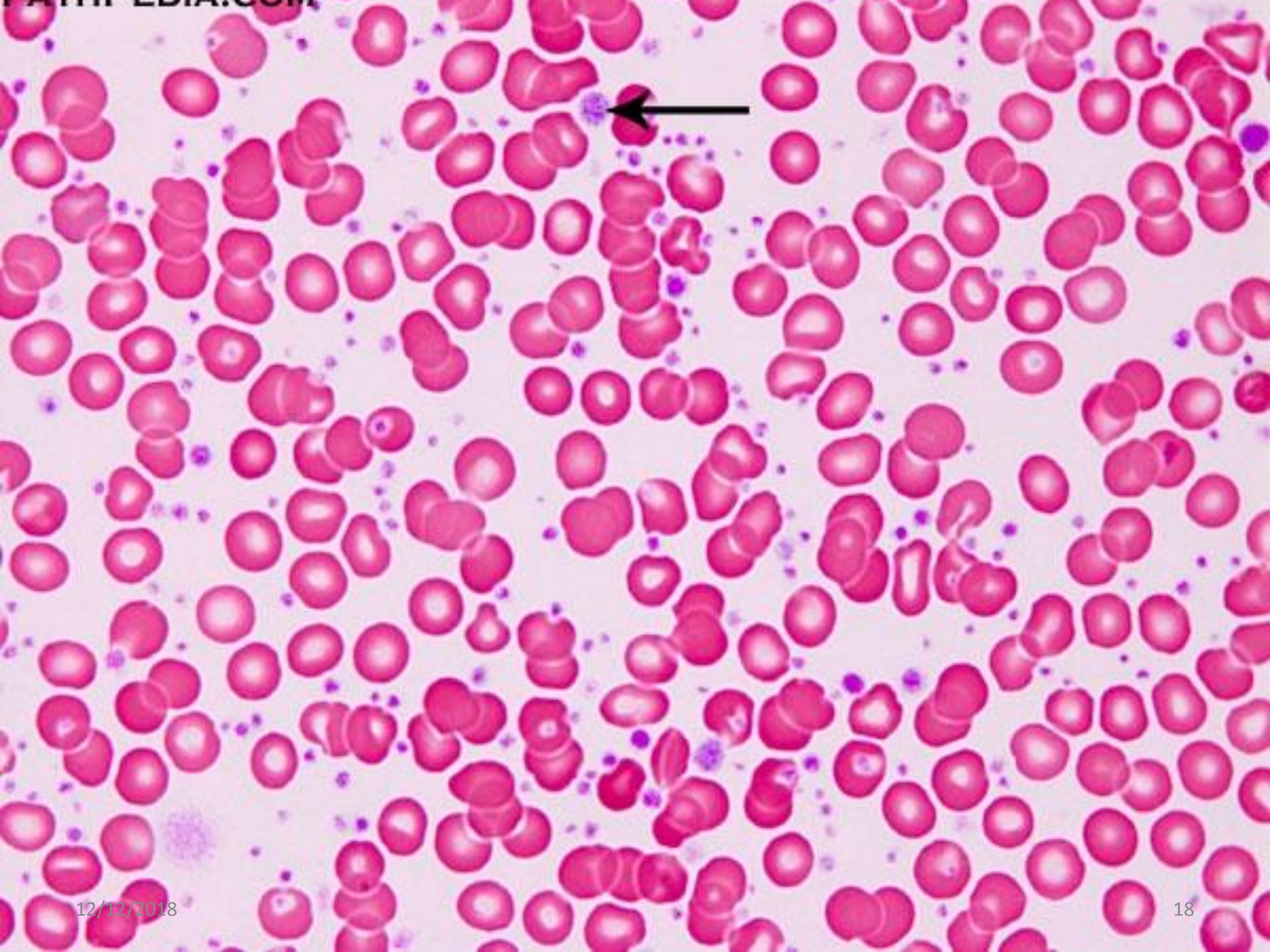
Essential Thrombocythemia

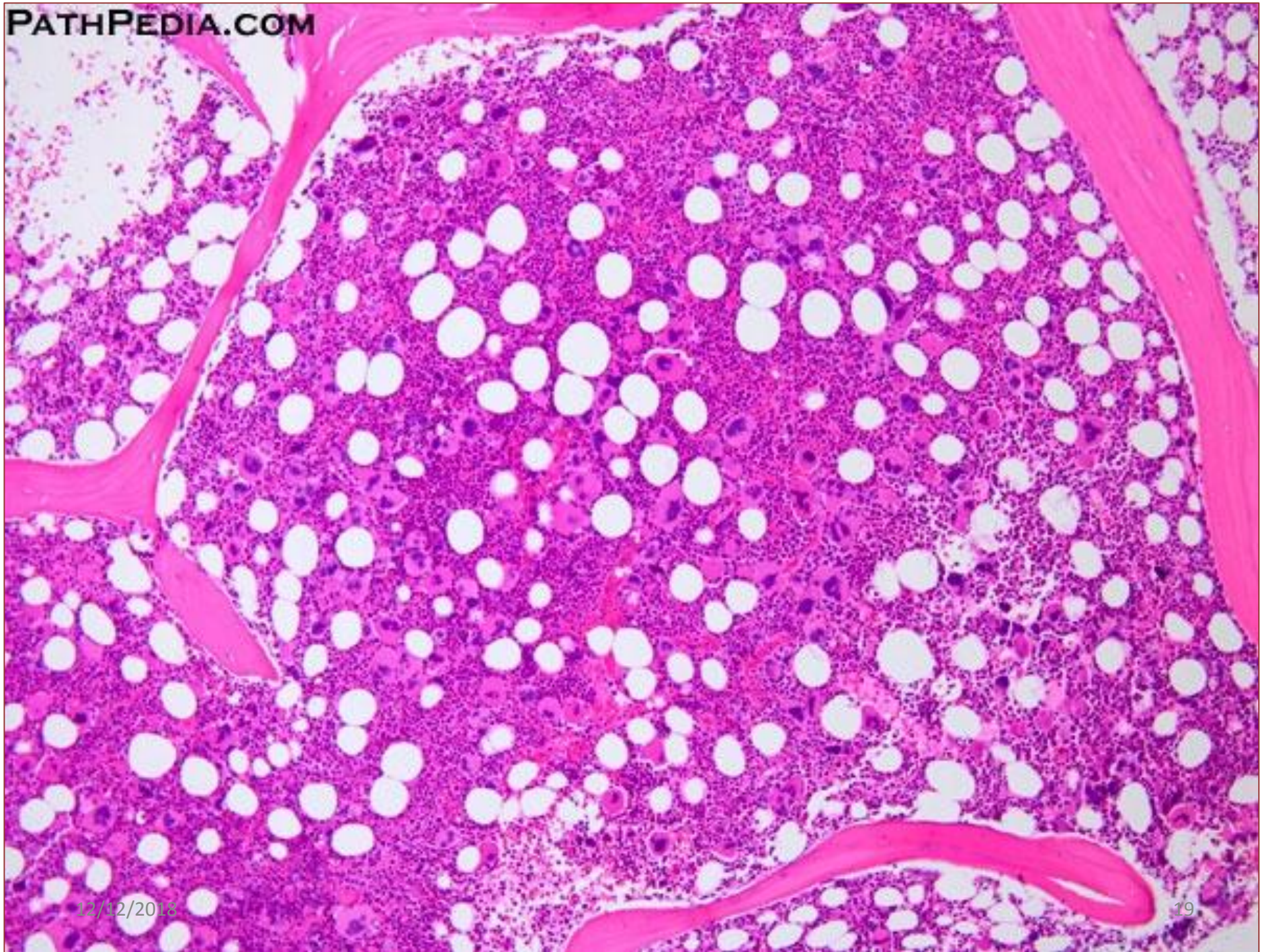
ET is MPN that involves primarily the megakaryocytic lineage. & characterized by sustained thrombocytosis .

Diagnostic Features

- **Sustained thrombocytosis ≥45O×10^9.**
- **Hypercellular BM with megakaryocytic proliferation**
- **Exclusion of: CML, MDS,PV &Primary Myelofibrosis**
- **JAK2 mutation (60%), if negative; no evidence of reactive thrombocytosis:**

Iron def. ,splenectomy, surgery, infection, autoimmune disease….

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Essential Thrombocythemia

Clinical Presentation

- Asymptomatic (50%)
- Thrombosis
- Bleeding
- Mild splenomegaly (50%)
- Mild hepatomegaly (20%)

Very indolent
(5% risk of AML transformation)

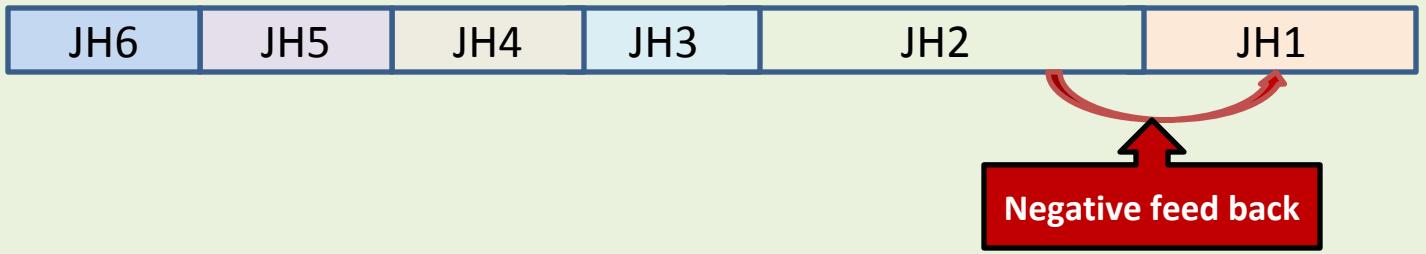
Treatment

Aspirin ±Hydroxyuria

JAK2 Mutation

JAK2: Non receptor protein tyrosine kinase involved in signal transduction pathway

JAK2 kinase domains structure



JAK2 mutation :

Point mutation (at codon 617 in JH2) leads to loss of auto inhibitory control over JAK2.

The mutated JAK2 is in a constitutively active state,

JAK2 Mutation