Myeloproliferative neoplasms

= Haematology 435 =

إن أحسنا فمن الله عزوجل, وإن أخطأنا فمن أنفسنا والشيطان.
نظراً لشمولية العمل لمحاضرات الطلاب والطالبات بإمكانكم اعتماده كمصدر للمذاكرة.

➢ Color Codes:

- Pink: Girls' notes. Blue: Boys' notes. Red: Important Notes. Gray: Extra notes.
- Purple: Lecture notes & Pathoma notes.

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➢ References:

- Girls&Boys Doctors Slides and Notes.
- Lecture notes pathology (chapter 12)
- Pathoma (chapter 5)
- Team 434.

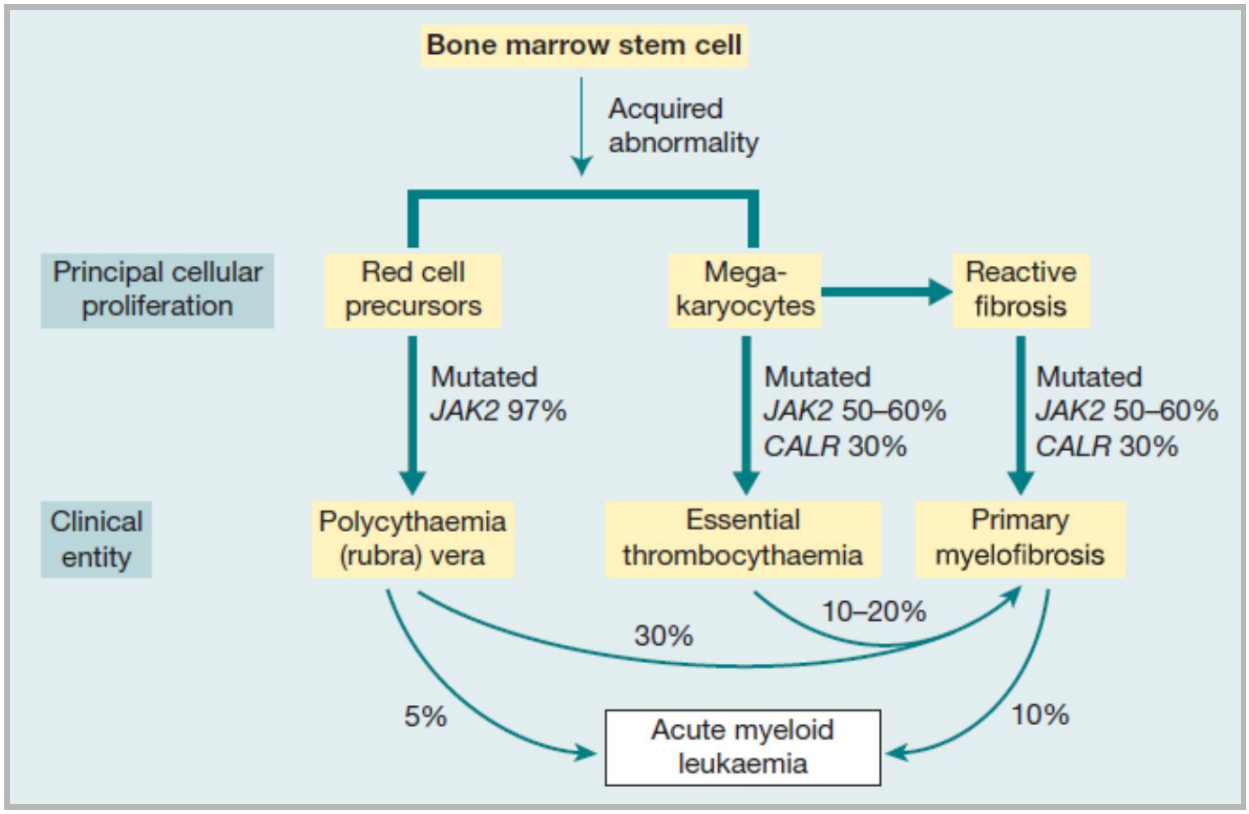
Revised by
خولة العماري & هشام الغفيلي

➢ Correction file: (HERE)

➢ Check Your Understanding! (HERE)

❖ Myeloproliferative Neoplasms:

- **Polycythemia vera.**
- **Essential thrombocythemia.**
- **Primary myelofibrosis.**



Explanation of the image above:

- **Polycythemia vera** will have JAK2 mutation in 97 % of cases.
- *30%of patients with polycythemia vera will progress to PMF ,while only 5% will progress to acute myeloid lymphoma.*
- **Essential thrombocythemia** 50-60% of patients have JAK2 mutation , while 30% of patients have CALR mutation.
- **Essential thrombocythemia** will turn into PMF in 10-20 % of patients.
- **Primary myelofibrosis:** 50-60% of patients will have JAK2 mutation while 30% will have CALR mutation.
- 10% of patients will turn to acute myeloid leukemia.
- note that PMF will have both increased platelets AND fibrosis of bone marrow!

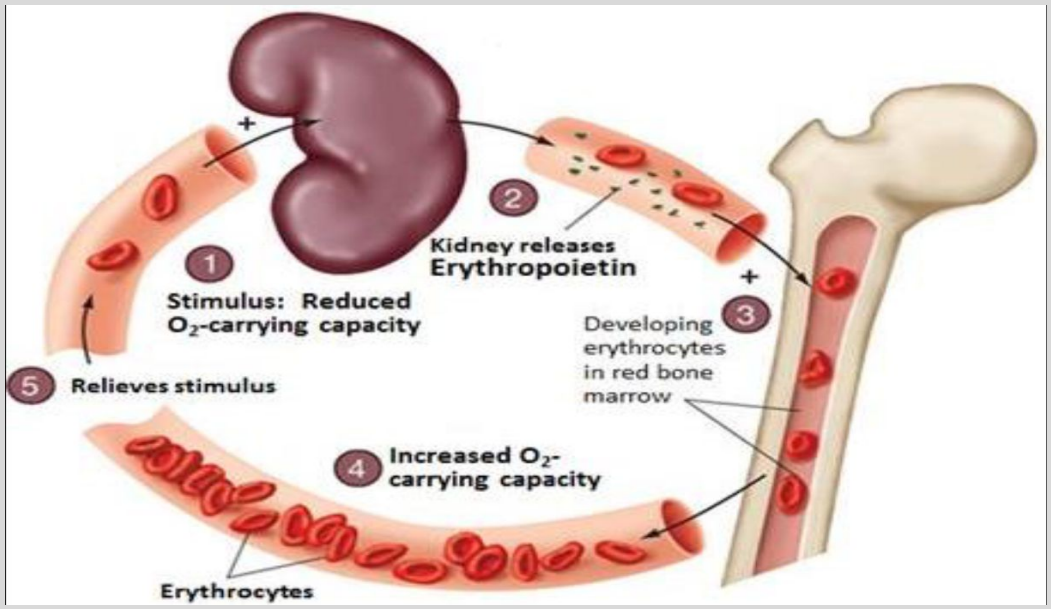
1-Polycythemia:

- 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).** (the most important thing in polycythemia!)
- Hb is >16.5or 18.5 g/dl in women and men, respectively.

Notes:

- If a patient showed this increase you must ask if he/she is a smoker or not! *Because smoking causes marked polycythemia!*
- Patient must stop smoking and then repeat the CBC a month later.

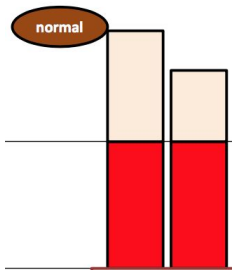
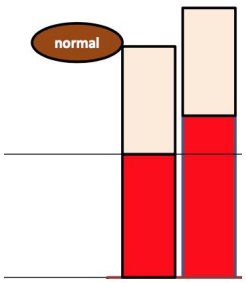
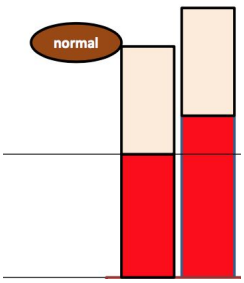
❖ Regulation of Erythropoiesis:



Explanation of the image:

- **Erythropoietin(produced from kidney): controls RBC synthesis Normally when the stimulus is relieved ,RBC synthesis stops(this feedback is not present when there is mutation or malignancy)**
- **Understand this image!**

❖ Classification of Polycythemia:

Relative Polycythemia	Absolute Polycythemia	
	Secondary Polycythemia (reactive polycythemia)	**Polycythemia vera "Primary"**
Decreased plasma volume due to severe dehydration (ex: vomiting, diarrhea, long use of diuretics.. the plasma level is decreased while RBCs stay the same!)	**Increased RBC mass due to high erythropoietin** (not malignancy) **(may be due to increased O2 demand):** • **COPD, Sleep apnea, smoking.** • **High altitude.** • **High affinity HB.** • **Renal disease.** • **Epo secreting tumor (Parathyroid adenoma)**	**Increased RBC mass due to malignant proliferation.** **Notes:** **How to differentiate between these types?** **-History** **-and the level of erythropoietin (high in secondary but LOW in polycythemia vera)** **Why?** due to bone marrow suppression of erythropoietin release,in other words ,the bone marrow is sending signals to the kidney to stop secreting erythropoietin ,because it is already proliferating due to the malignancy.
		

❖ Polycythemia vera:

MPN (myeloproliferative neoplasm) characterized by increased **red blood cell** production independent of the mechanisms that normally regulate erythropoiesis.

(erythropoietin-independent)

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.**
- **Erythropoietin is low while HB is high.**

Clinical features of PV:

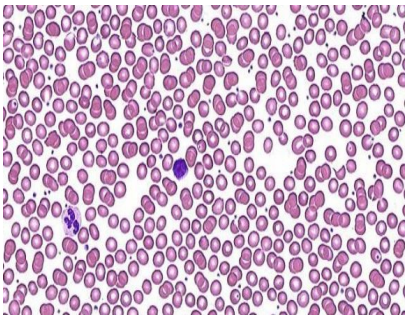
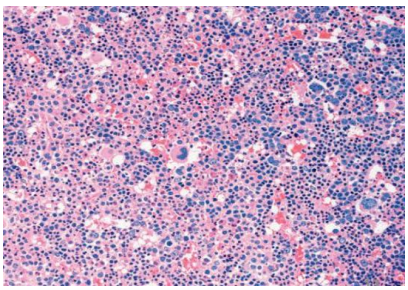
1-Increased blood viscosity: (Hypertension, Headache, dizziness, visual disturbances & paresthesia)

2-Thrombosis: (Deep vein thrombosis, Myocardial infarction, Mesenteric, portal or splenic vein thrombosis)

3- Splenomegaly in 70%

4- Hepatomegaly in 40%

Investigations:

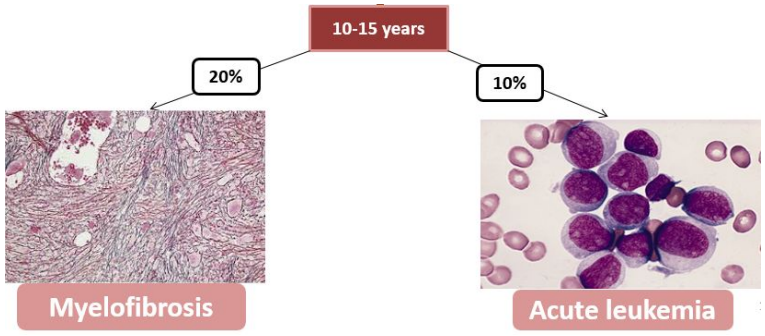
CBC	-RBC: increased -Hb: increased -WBC & PLT :mildly increased (usually)	
Blood Smear	• Excess of normocytic normochromic RBC. • ± Leukocytosis & thrombocytosis.	
Bone Marrow	• Hypercellular. • Predominant erythroid precursors. • ± Increased megakaryocytes & Myeloid precursors. • ↑ Blast → AL transformation.	

Treatment:

After your diagnosis:

- Venesection (is taking 500 ml of blood every week to reduce RBCs) (NOT USED FOR DONATION) + Aspirin
- ± Myelosuppressive drugs (hydroxyurea) (10-15 years)

Complications "Photo"⇛



2-Primary Myelofibrosis (PMF):

PMF is a clonal MPN (myeloproliferative neoplasm) characterized by:

- Proliferation of **megakaryocytes & granulocytes** in the bone marrow.
- Deposition of fibrous connective tissue
- Extramedullary haematopoiesis.

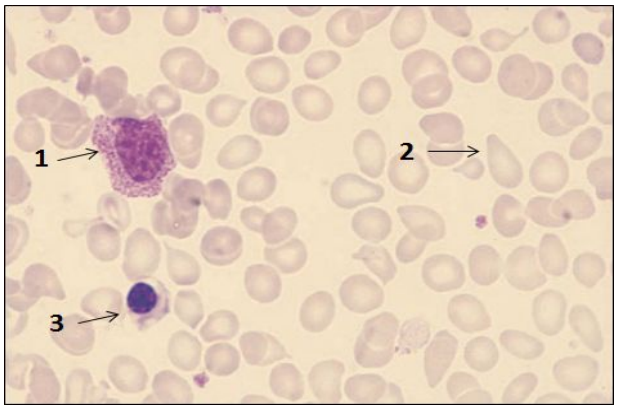
Clinical features:

- Anemia
- Leukoerythroblastic blood picture:

1-Precursors of RBCs & precursors of granulocytes=leukoerythroblastic picture (NO PMF WITHOUT leukoerythroblastic blood picture).

2- Tear drop shaped RBCs are also seen

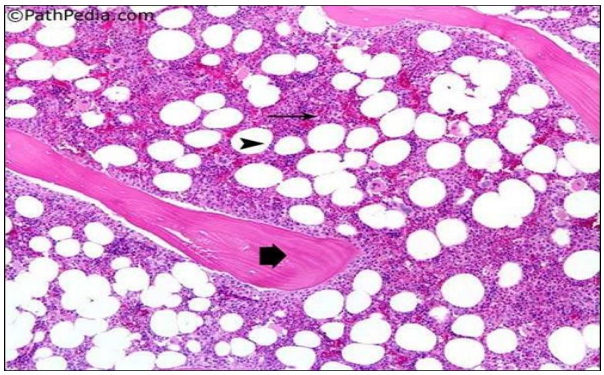
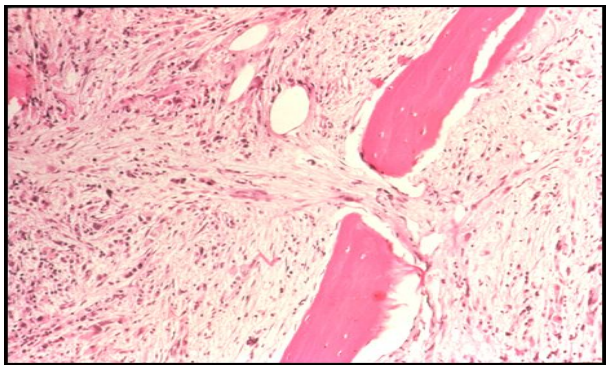
3- Nucleated RBCs.



- **JAK2** mutation (50%), CALR 30%
- **Fibrotic** bone marrow
- Risk of AML "Acute myeloid leukemia" transformation (20%)
- Massive splenomegaly (due to extramedullary hematopoiesis)

(MCQ!)what are the two types of malignancy that give massive splenomegaly?

Primary myelofibrosis and CML.

Normal BM	Fibrotic BM
	

-Normal BM: half the cells in BM must be fat cells while the other half is haematopoietic cells

-Fibrotic bone marrow: nonhematopoietic cells without fat cells(maybe only megakaryocytes remain) ,mainly fibrosis is seen.

Stages of PMF:

Stage	Survival
Prefibrotic stage: • Proliferation of megakaryocytes and granulocytes ⇛ Leukocytosis & Thrombocytosis.	7-10 years survival
Prefibrotic stage → **Fibrotic stage**: (severe type) • Anemia , Leukopenia, Thrombocytopenia • Extramedullary hematopoiesis	3-7 years survival
Prefibrotic stage → Fibrotic stage → **AML transformation**	≤1 year survival

3- Essential Thrombocythemia (ET)

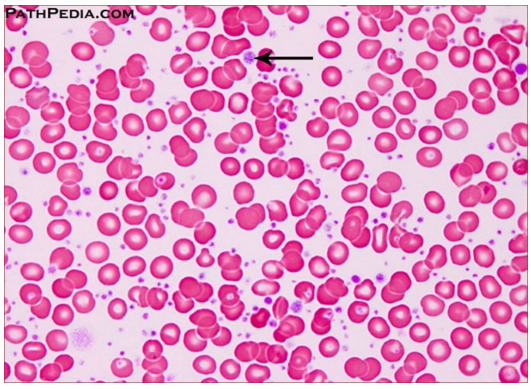
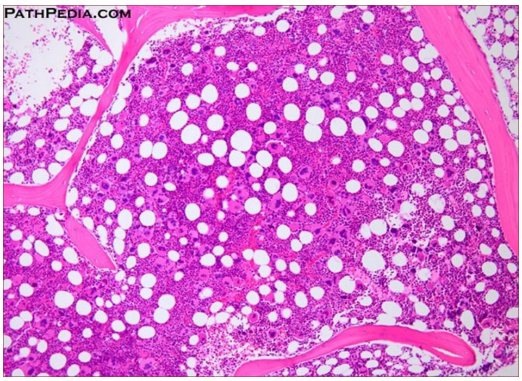
ET is a MPN that involves primarily the megakaryocytic lineage. Characterized by sustained thrombocytosis.(sustained high platelet count)

Diagnostic Features:

- Sustained thrombocytosis ≥450 $\times 10^9$ /L. [1]
- **Hypercellular BM with megakaryocytic proliferation**
- Exclusion of: CML, MDS, PV & Primary Myelofibrosis
- JAK2 mutation (60%), If negative; diagnosis can be made if there was no evidence of **reactive thrombocytosis***:

  Iron deficiency, splenectomy, surgery, infection ,autoimmune disease (as in rheumatoid arthritis ,crohn's ,DM, all chronic diseases)

* Platelets are acute-phase reactants; therefore, they increase in response to various stimuli, including systemic infections, inflammatory conditions, bleeding, and tumors. This is called reactive or secondary thrombocytosis, which is a benign form of thrombocytosis. In contrast, clonal thrombocytosis (primary or essential thrombocytosis) is an unregulated abnormality of platelet production due to a clonal expansion of bone marrow progenitor cells.

Peripheral blood	Bone Marrow
	
The arrow shows increased platelet count.	Increased megakaryocyte(they become in clusters) and decrease fat cells

[1] A normal platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. Having more than 450,000 platelets is a condition called thrombocytosis; having less than 150,000 is known as thrombocytopenia.

Clinical Presentation:

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

These are Very indolent, with 5% risk of AML transformation

No significant risk for hyperuricemia or gout, unlike other MPN

Treatment:

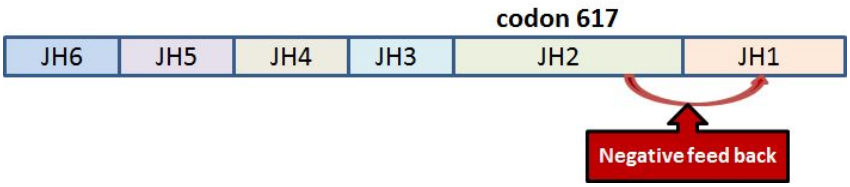
Aspirin (to prevent thrombosis) ± Hydroxyuria

JAK2 Mutation:

JAK2 is a Non-receptor-protein **tyrosine kinase**, involved in signal transduction pathway.

JAK2 kinase domains structure:

JH2 controls JH1 by negative feedback and tells the bone marrow to stop the kinase domain



- ### JAK2 mutation:

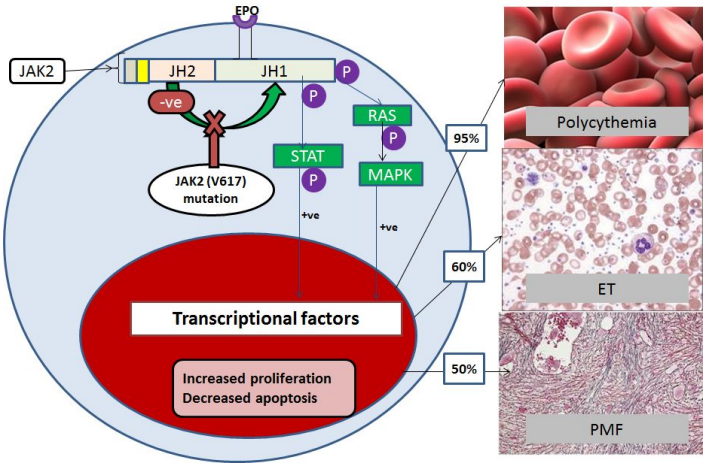
Point mutation (at codon 617 in JH2) leads to loss of auto inhibitory control over JAK2. The mutated JAK2 is in a constitutively active state.

Notes:

so it is very important to know that a point mutation in 617 JH2 will lead to loss of inhibition of JH1 (becomes always active) ⇒ the oncogenes then become active (you don't have to know their names) which will lead to increased in transcriptional factors ,which will lead to increased proliferation and decreased apoptosis.

The results of JAK2 mutations :

- 95-97% in polycythemia.
- 50-60% in both PMF and ET.



(Pathoma Bridge) EXTRA YOU CAN SKIP IT!

POLYCYTHEMIA VERA (PV)

★ Neoplastic proliferation of mature myeloid cells, especially RBCs.
-Granulocytes and platelets are also increased.
★ Associated with JAK2 kinase mutation.
★ Clinical symptoms are mostly due to hyperviscosity of blood.

1. Blurry vision and headache.
2. Increased risk of venous thrombosis (e.g., hepatic vein, portal vein, and dural sinus)
3. Flushed face due to congestion (ple thora}
4. Itching, especially after bathing (due to histamine release from increased mast cells)

★ Treatment is phlebotomy; second-line therapy is **hydroxyurea.**
-Without treatment, death usually occurs within one year.

★ PV must be distinguished from reactive polycythemia.

I. **In PV**, erythropoietin (EPO) levels are decreased, and Sao2 is normal.
2. **In reactive polycythemia due to high altitude or lung disease**, Sao2 is low and EPO is increased.]
3. **In reactive polycythemia due to ectopic EPO production from renal cell carcinoma**, EPO is high, and Sao2 is normal.

ESSENTIAL THROMBOCYTHEMIA (ET)

★ Neoplastic proliferation of mature myeloid cells, especially platelets.
-RBCs and granulocytes are also increased.
★ Associated with **JAK2 kinase mutation.**
★ Symptoms are related to an increased risk of bleeding and/or thrombosis.

1. Rarely progresses to marrow fibrosis or acute leukemia.
2. No significant risk for hyperuricemia or gout.

(Robbins summary)

Table 11–5 Pathophysiologic Classification of Polycythemia

Relative
Reduced plasma volume (hemoconcentration)
Absolute
Primary
Abnormal proliferation of myeloid stem cells, normal or low erythropoietin levels (polycythemia vera); inherited activating mutations in the erythropoietin receptor (rare)
Secondary
Increased erythropoietin levels *Adaptive:* lung disease, high-altitude living, cyanotic heart disease *Paraneoplastic:* erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatomacellular carcinoma, cerebellar hemangioblastoma) *Surreptitious:* endurance athletes