Polycythemia

GNT Block

COLOR INDEX:

- Main text
- Dr. Notes
- Male's text
- Femal's text
- Important
- Extra

Editing file:

Objectives

Objectives were only found in males' slides

- To understand the physiological mechanisms that regulate erythropoiesis
- To recognize the secondary and primary causes of polycythemia
- To understand the clinicopathological features of polycythemia vera
- To recognize the importance of genetic studies in diagnosis and management of polycythemia vera
- To understand the general aspects of essential thrombocythemia and primary myelofibrosis

Our YouTube's playlist for this lecture!

This lecture was given by: Dr. Mansour Aljabry and prof. Fatma Al Qahtani

MPN

MPN are a group of diseases in which the bone marrow makes too many red blood cells, white blood cells, or platelets.

Classification Of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

Myeloproliferative neoplasms (MPN)	BCR—ABL1—positive	1. Chronic myelogenous leukemia, (CML)
	BCR-ABL— negative شرط	1. **Polycythemia vera (PV)** 2. **Essential thrombocythemia** 3. **Primary myelofibrosis (PMF)** 4. Chronic neutrophilic leukemia 5. Chronic eosinophilic leukemia 6. Mast cell disease (MCD) 7. MPN, unclassifiable

in this lecture

Myeloproliferative neoplasms (MPN) features :

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

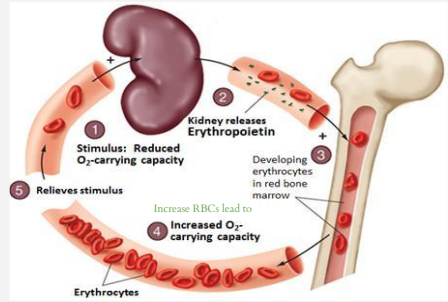
Polycythemia

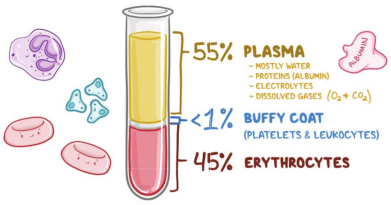
- In Greek "too many cells in the blood.".
- Absolute increase in total body red cell volume (or mass) increase RBCs and Hb
- Manifests itself as a raised Hb or packed cell volume (PCV) and increase RBCs count
- Hb is >16.5 or 18.5 g/dl in women and men, respectively.

Regulation of Erythropoiesis :

See the picture:

1. Stimulus : Reduced O2-Carrying capacity (Hypoxia)
2. Kidney Releases Erythropoietin
3. Developing Erythrocytes in Red bone marrow
4. Increased O2 - Carrying capacity
5. Finally Relieves stimulus.

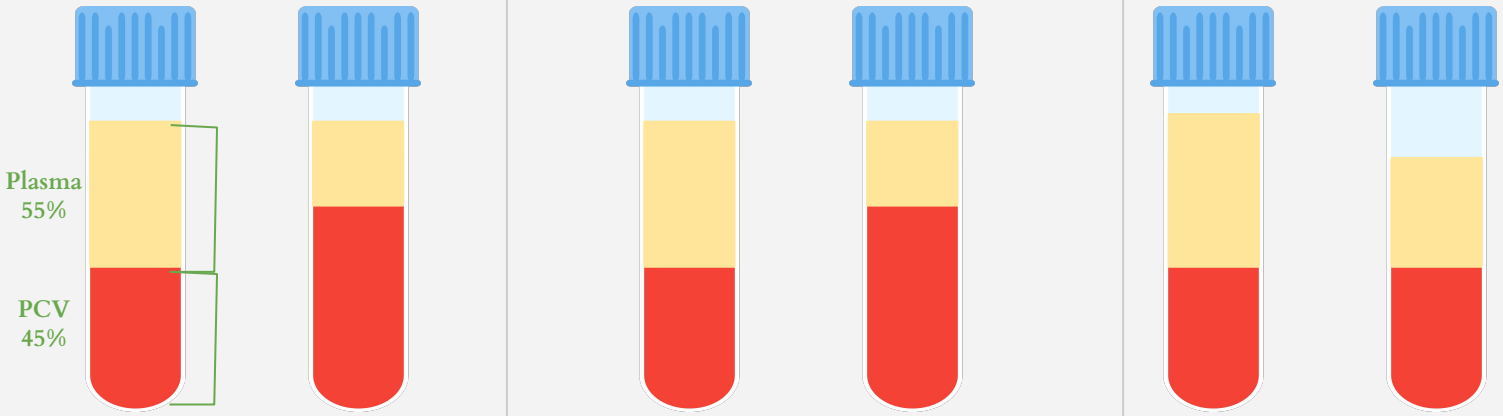




Polycythemia

Classification of polycythemia

Polycythemia vera	2nd Polycythemia	Relative Polycythemia
↑ **RBC** mass due to malignant proliferation	↑ RBC mass due to high EPO: 1. COPD, Sleep apnea, smoking.. 2. High altitude 3. High affinity HB 4. Renal disease 5. Epo secreting tumor (Parathyroid adenoma …) جاي من مكان ثاني	↓ plasma volume due to severe **dehydration** not really disease



Polycythemia vera

True polycythemia

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** unlike the 2nd polycythemia

The Alien from the Pathology took a trip to hematology just to ask you this :
Which of the given conditions is NOT caused by polycythemia vera?

A. Heart attacks
B. Thrombocytopenia
C. Hyperviscosity syndrome
D. Pulmonary embolism
E. Strokes

Answer: B

Polycythemia vera

Clinical Features:

A	Increased blood viscosity	Hypertension , Headache, dizziness, visual disturbances &paresthesia
B	Thrombosis Possibility ↑	1.Deep vein thrombosis 2.Myocardial infarction 3.Mesenteric, portal or splenic vein thrombosis
C	Splenomegaly in 70%	a build-up of extra blood cells in the organ
D	Hepatomegaly in 40%	Same as splenomegaly
E	Pruritus	especially after a hot bath or shower

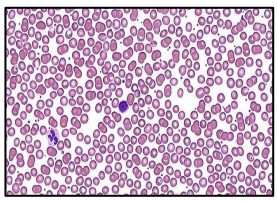
Investigations

CBC

- ↑ RBC very high count
- ↑ Hb
- ↑ mildly WBC & PLT (usually) (a bad sign meaning it could develop a fibrosis)

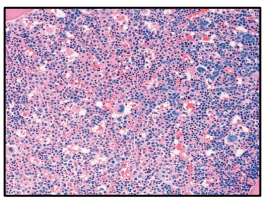
Blood smear

- Excess of normocytic normochromic RBC
- ±Leukocytosis & thrombocytosis



Bone marrow

- Hypercellular
- Predominant erythroid precursors
- ± Increased megakaryocytes & Myeloid precursors. bad sign
- ↑ Blasts → AL(Acute leukemia) transformation



After the Diagnosis of polycythemia Vera:

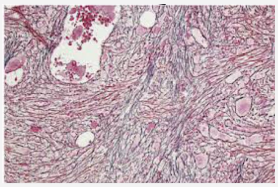
Complication & Treatment

Treatment:

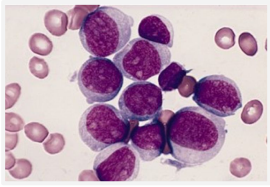
- Venesection(الحجامة)+ Aspirin
- ± Myelosuppressive drugs (hydroxyuria)the best treatment

Complication:

- The prognosis of PV in 10-15 years may complicate into : takes long time until transformation



Myelofibrosis in 20% of Cases



Acute Leukemia in 10% of Cases

Which of the following findings would you expect in a patient with primary polycythemia?

A. Normal red cell mass and decreased plasma volume
B. Normal red cell mass and normal plasma volume
C. Decreased red cell mass and normal plasma volume
D. Increased red cell mass and increased plasma volume
E. Increased red cell mass and normal plasma volume

Answer: E

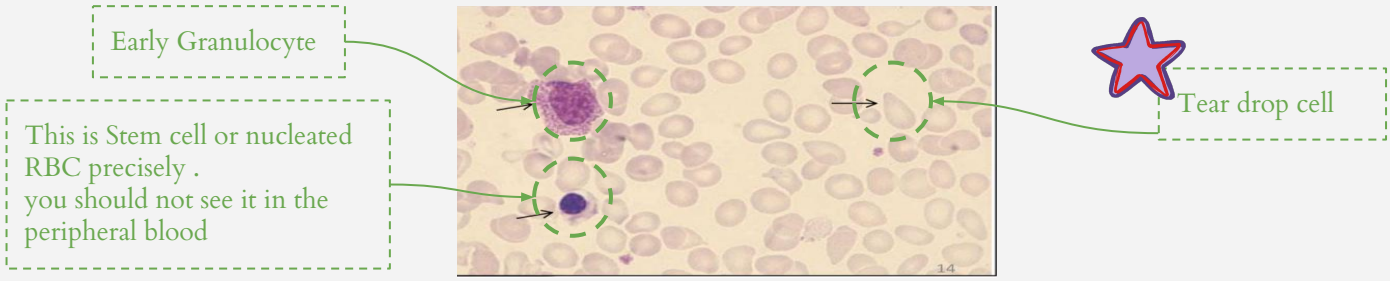
Primary Myelofibrosis

Definition

Clonal MPN characterized by a proliferation of megakaryocytes & granulocytes in the bone marrow that is associated with **deposition of fibrous connective tissue** and extramedullary (in spleen and liver) haematopoiesis.

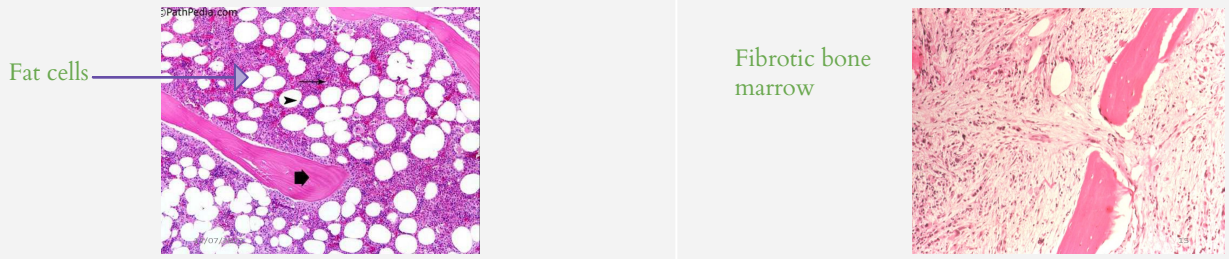
Clinical features

Fibrotic Bone Marrow	Massive Splenomegaly	JAK2 Mutation (50%)	Anemia	Risk of AML Transformation (20%)	Leukoerythroblastic Blood Picture



Bone Marrow In PMF

Normal BM	Fibrotic BM



Stages of PMF:

A	Prefibrotic stage	Proliferation of megakaryocytes & granulocytes → Leukocytosis, thrombocytosis	7–10 years survival
B	Fibrotic stage	→ Anemia → Leukopenia → Thrombocytopenia → Extramedullary haematopoiesis organomegaly especially spleen	3–7 years survival
C	AML Transformation	Acute myeloid leukemia	≤ 1 year survival

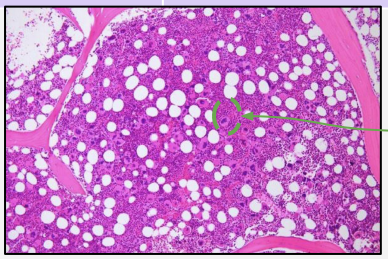
Essential Thrombocythemia

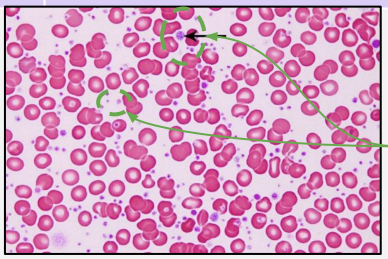
Definition

- ET is MPN that involves primarily the **megakaryocytic** lineage (Specific to it) & characterized by sustained thrombocytosis.
- It is generally benign disease if you control thrombosis

Diagnostic Features

Thrombocytosis	BM	Exclusion of	JAK2 mutation (60%)
Sustained thrombocytosis ≥ 450×10^9.	Hypercellular BM with megakaryocytic proliferation.	CML, MDS, PV & Primary Myelofibrosis.	If negative; no evidence of reactive thrombocytosis then this is the possible diagnosis : Iron deficiency, splenectomy, surgery, infection, autoimmune disease. You should rule out the reactive cause, take more investigation





Clinical Presentation: Very Indolent

(5% risk of AML Transformation)

Asymptomatic (50%) → Thrombosis & Bleeding*** → Mild Splenomegaly (50%) → Mild Hepatomegaly (20%)

Treatment

- Aspirin
- ± Hydroxyuria

***How is there a bleeding while there is an increased number of platelets at the same time?
because the increased platelets are not functioning normally

JAK2 Mutation

Definition

JAK2 is a non receptor protein tyrosine kinase involved in signal transduction pathway that accept signals from erythropoietin receptor on the RBC cell membrane

JAK2 Kinase Domains Structure

Normally: هذي المنطقة اللي تسوي control of proliferation by negative feedback

JH6	JH5	JH4	JH3	JH2	JH1

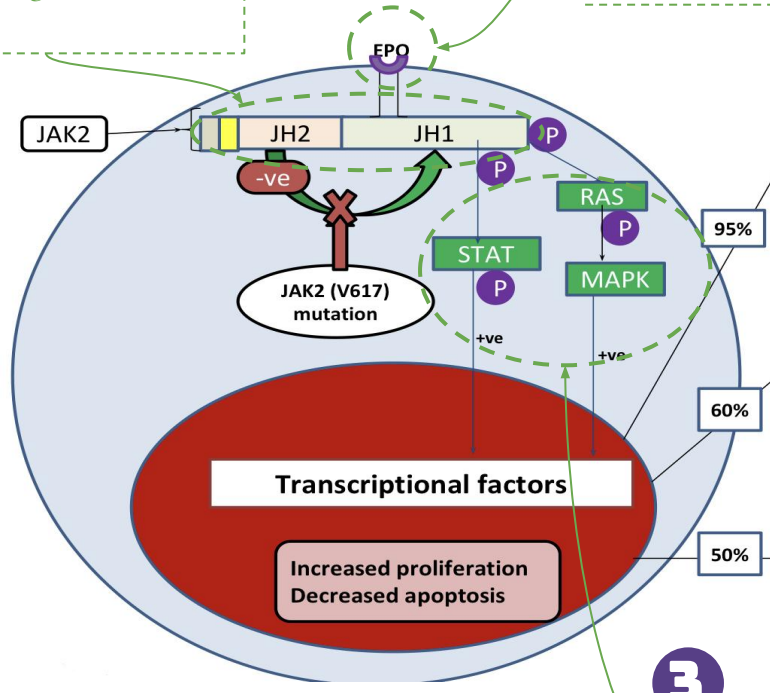
Negative Feedback

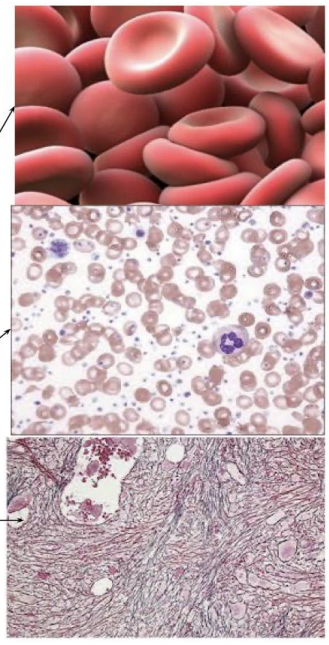
JAK2 Mutation

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

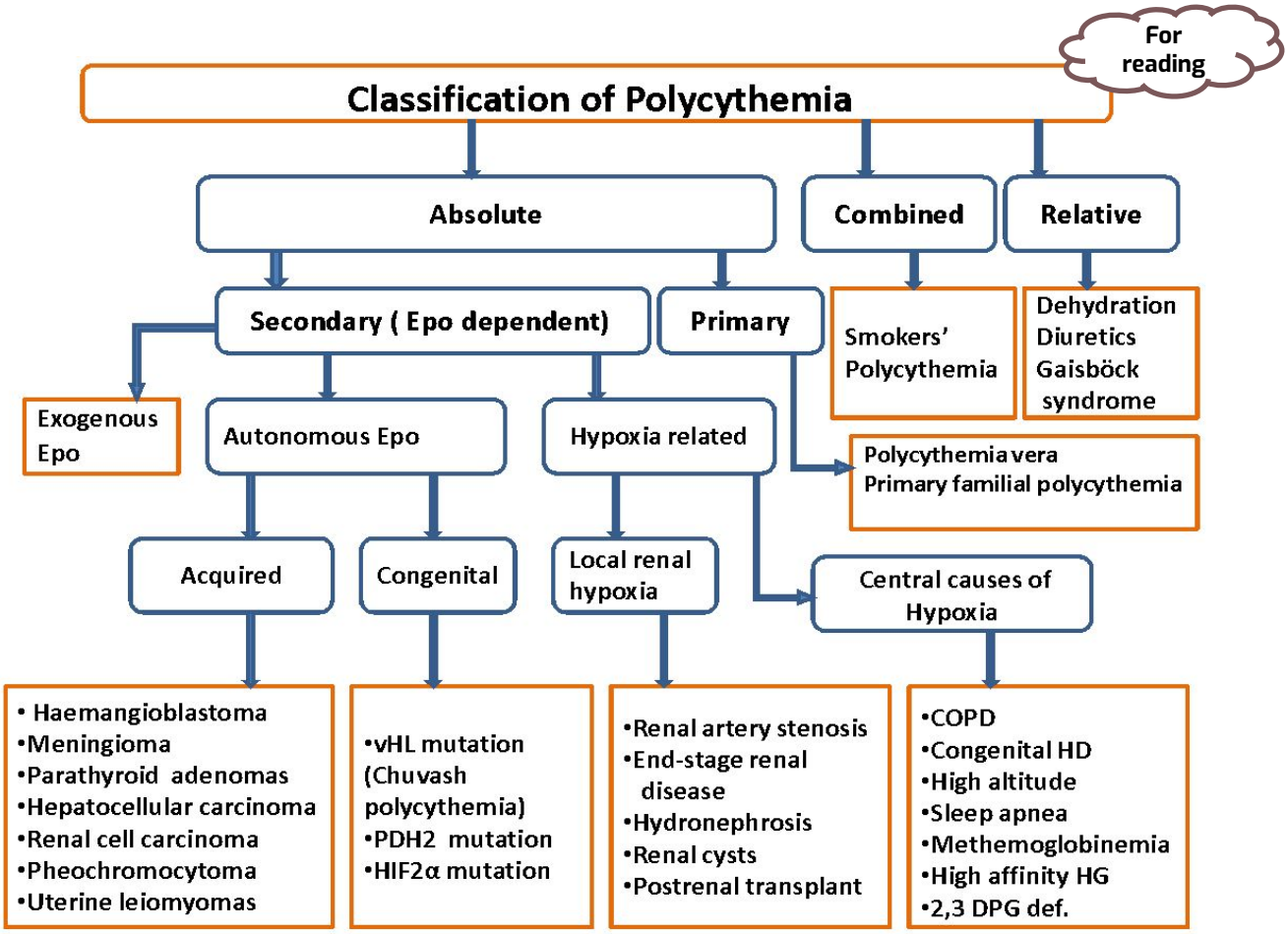
The mutated JAK2 is in a constitutively active state.

1. EPO receptor accept the signal from EPO and send it to JH2 & JH1
2. JH2 $ JH1 will convey the massage through the phosphate group to the signal transduction pathway
3. signal transduction pathway will take the massage to transcriptional factor for:
   1-increased proliferation
   2-decrease apoptosis





For reading


For reading
Classification of Polycythemia
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.

Myeloproliferative Neoplasms

EXTRA Summary

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

Polycythemia

Overview	- 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.	
Classification of Polycythemia	Relative Polycythemia	Decreased Plasma volume due to severe dehydration
	2nd Polycythemia	Increased RBC mass due to high EPO
	Polycythemia vera	Increased RBC mass due to Malignant proliferation
Regulation of Erythropoiesis	1-**Stimulus** : Reduced O2 - Carrying capacity (**Hypoxia**) 2-Kidney Releases Erythropoietin 3-Developing Erythrocytes in Red bone marrow 4-Increased O2 - Carrying capacity 5-Finally Relieves stimulus.	

Polycythemia Vera

Definition	increased rbc 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	1-Increased blood viscosity 2- Thrombosis 3-Splenomegaly in 70% 4-Hepatomegaly in 40%
Investigations	• CBC - RBC & HB : increased - WBC's & PLT's: mildly increased • Bone Marrow: - Hypercellular - Predominant erythroid precursors - ± Increased megakaryocytes &Myeloid precursors. - Blast AL Transformation
Complications	• Acute Leukemia • Myelofibrosis
Treatment	• Venesection + Aspirin • ± Myelosuppressive drugs (**hydroxyuria**)

Primary Myelofibrosis

Definition	Clonal MPN characterized by a proliferation of megakaryocytes & granulocytes in the bone marrow that associated with deposition of fibrous connective tissue and extramedullary (in spleen and liver) haematopoiesis		
Clinical Features	• Anemia • Leukoerythroblastic blood picture. • Massive splenomegaly • Fibrotic bone marrow • JAK2 mutation (50%) • Risk of AML transformation (20%)		
Stages Of PMF	**Prefibrotic stage:**	Proliferation of megakaryocytes and Granulocytes Leukocytosis, thrombocytosis	**7-10 years survival**
	Fibrotic stage:	Anemia Leukopenia Thrombocytopenia Extramedullary haematopoiesis	**3-7 years survival**
	AML transformation	(Acute Myeloid Leukemia)	**≤1 year survival**

Essential Thrombocythemia

Definition	ET is MPN that involves primarily the megakaryocytic lineage & characterized by **sustained** thrombocytosis .
Diagnostic features	• **Sustained** thrombocytosis ≥45O×10⁹. • Myelofibrosis • **JAK2 mutation** (60%), if negative; no evidence of reactive thrombocytosis: Iron deficiency, splenectomy, surgery, infection, autoimmune disease • Hypercellular BM with megakaryocytic • proliferation • Exclusion of: CML, MDS,PV & Primary
Clinical presentation	**Asymptomatic** (50%), Thrombosis & Bleeding, Mild splenomegaly (50%), Mild hepatomegaly (20%)
Treatment	Aspirin ± Hydroxyuria

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