MED439
KING SAUD UNIVERSITY

# Polycythemia

## Objectives:

- Myeloproliferative Neoplasms:
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)

Dr's notes
Important
Extra notes
** Only in girls slide
** Only in boys slide

Revised & Approved
Bassam Alasmari
Rania Almutiri

Hematology Team

Editing file

# Myeloproliferative Neoplasms

## Myeloproliferative Neoplasms features :

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

## Polycythemia increase RBCs count

- 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.

## Classifications

- **Relative polycythemia :** Decreased **plasma volume** due to **severe dehydration**.
- **Secondary polycythemia :** Increased **RBC mass** due to **high EPO**(Due to Increased 02 demand ) :
  - COPD, Sleep apnea, smoking (you have to tell the polycythemia patient to stop smoking immediately)
  - High altitude .
  - High affinity HB.
  - Renal disease.
  - Epo secreting tumor (Parathyroid adenoma).
- **Polycythemia vera :** Increased **RBC mass** due to malignant proliferation (regardless to any stimulation of EPO production )

## Regulation of Erythropoiesis(males' doctor: the most important thing that I need you to understand)

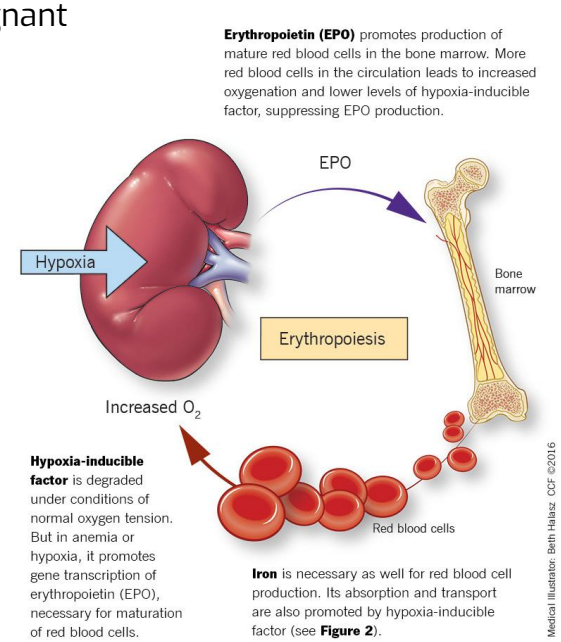
1-Stimulus : **Reduced** $O_2$- Carrying capacity (Hypoxia)

2-Kidney Releases Erythropoietin

3-Developing Erythrocytes in Red bone marrow

4-Increased $O_2$- Carrying capacity

5-Finally Relieves stimulus.



# Polycythemia Vera

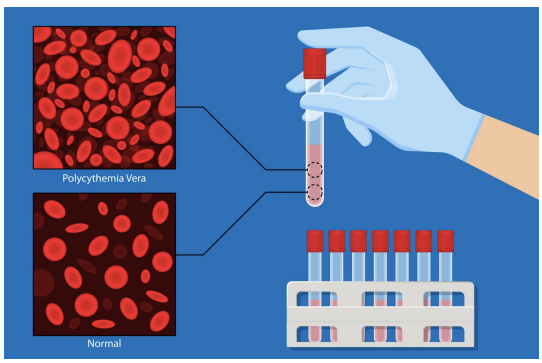
## Definition

It's a 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

due to the increase need to pump thicker blood through the circulatory system.

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

2- **Thrombosis** :

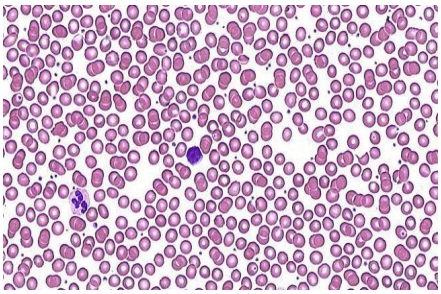
- Deep vein thrombosis.
- Myocardial infarction.
- Mesenteric, portal or splenic vein thrombosis.

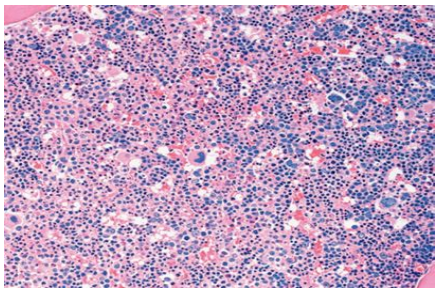
3- **Splenomegaly** in 70%. (polycythemia vera makes your spleen work harder than normal, which causes it to enlarge )

4- Hepatomegaly in 40%.

# Polycythemia Vera

## Investigations





**A- CBC :**

- RBC: increased
- Hb: increased.
- WBC & PLT :mildly increased (usually.)

**B- Blood smear :**

- Excess of normocytic normochromic RBC.
- ±Leukocytosis & thrombocytosis.( if it's associated with any MPN other than polycythemia, in polycythemia it's normal

**C- Bone marrow** :

- **Hypercellular** .
- Predominant erythroid precursors.
- ± Increased megakaryocytes & Myeloid precursors.
- If Blasts increase (>20%) → AL transformation.

## Complication and treatment of polycythemia vera

The Diagnosis of PV will initiate a **treatment** consisted of **Venesection + Aspirin** and may they use of Myelosuppressive drugs (Chemotherapy) such as **hydroxyurea .**

- The **prognosis** of PV in 10-15 years may complicate into :
  - Acute Leukemia in 10% of Cases
  - Myelofibrosis in 20% of Cases

# Primary Myelofibrosis

Skipped by females dr

## Definition

**Has the worst prognosis**

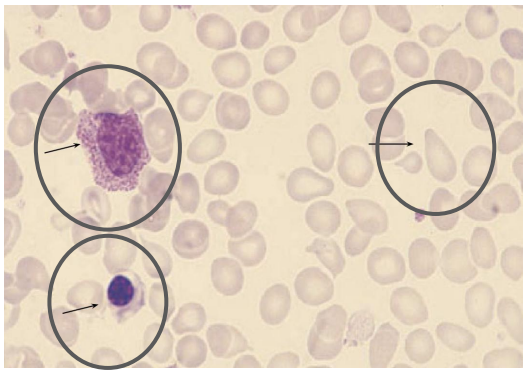
Clonal MPN characterized by a proliferation of **megakaryocytes** & **granulocytes** in the **bone marrow** that associated with deposition of fibrous connective tissue and extramedullary haematopoiesis

Skipped by females dr

# Primary Myelofibrosis

## Clinical features

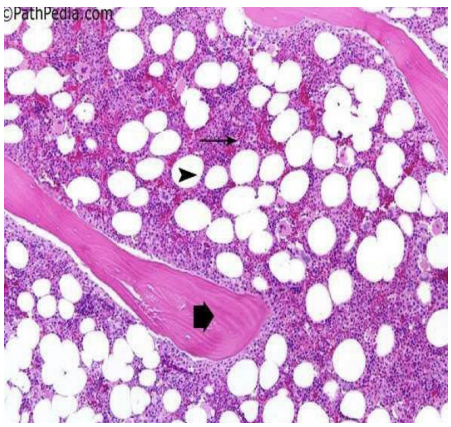
- Massive **splenomegaly**
- **JAK2 mutation** (50%)
- Leukoerythroblastic blood picture
- Risk of AML transformation (20%)
- Anemia
- **Fibrotic bone marrow**
  ( Due to deposition of fibrous connective tissue )



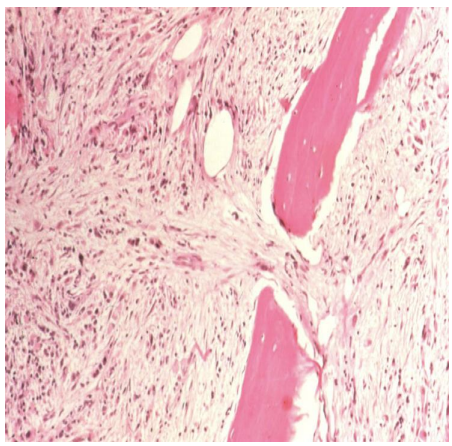
Leukoerythroblastic blood picture

## Bone marrow in Myelofibrosis

**Normal BM**




**Fibrotic BM**



## Stages of PMF

1 → 2 → 3

**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 )

Most dangerous stage because it can't tolerated with chemotherapy

**≤1 year survival**

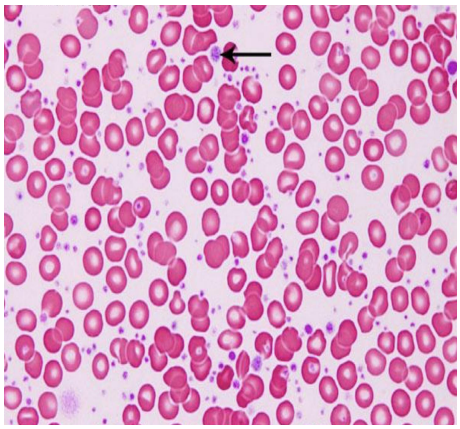
Skipped by females dr

# Essential Thrombocythemia

## Definition

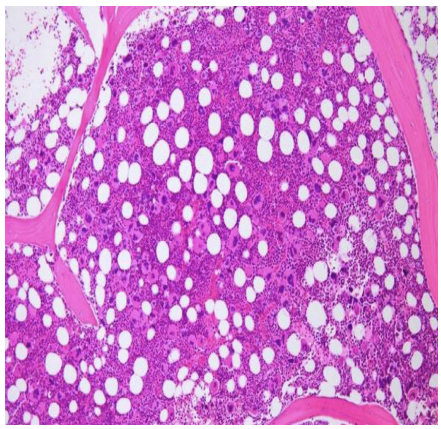
- ET is MPN that involves primarily the megakaryocytic lineage & characterized by sustained thrombocytosis .

## Diagnostic features



- Sustained thrombocytosis ≥450×$10^9$.
- Hypercellular BM with megakaryocytic proliferation
- Exclusion of: CML, MDS,PV & Primary Myelofibrosis
- **JAK2 mutation** (60%), if negative; no evidence of reactive thrombocytosis:
  Iron deficiency, splenectomy, surgery, infection, autoimmune disease...

## Clinical presentation



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

Very indolent (5% risk of AML transformation)

## Treatment

- Aspirin ± Hydroxyuria (no venesection)

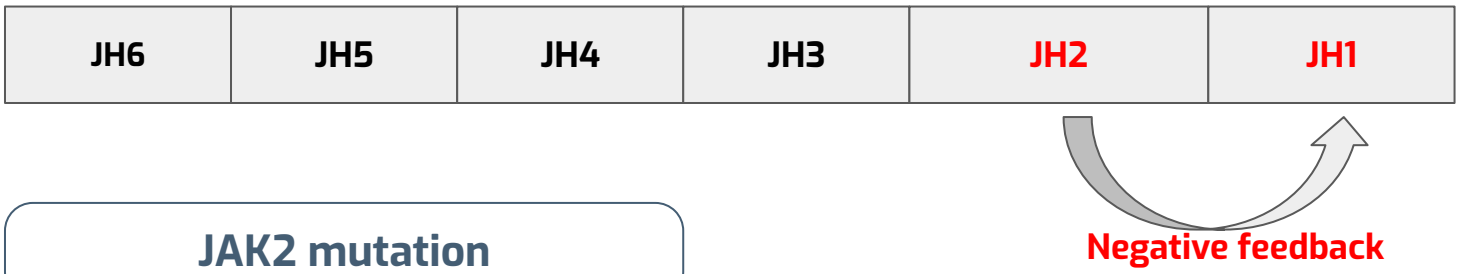
Osmosis video

# JAK2 Mutation

## Definition

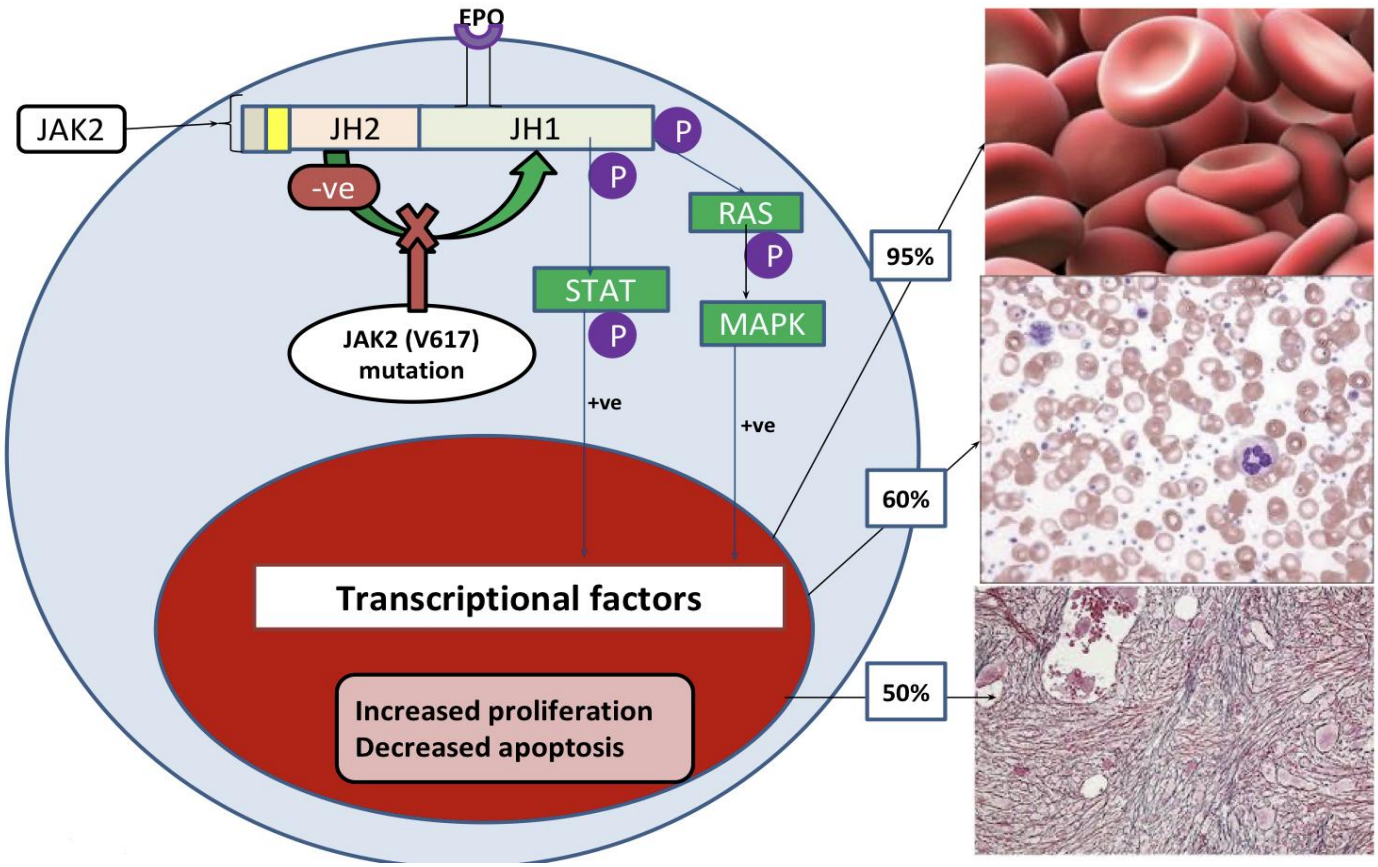
- Non receptor protein tyrosine kinase involved in signal transduction pathway.

## 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.



# Polycythemia

- Polycythemia is characterized by **absolute** increase in total body red cell volume (or mass).
- Manifests itself as a raised Hb or PCV

| | | |
|---|---|---|
| **Classifications** | **Relative polycythemia** | Decreased plasma volume. e.g.: severe dehydration, diuretics |
| | **Secondary polycythemia** | Increased RBC mass due to high Erythropoietin:<br>COPD, Sleep apnea, smoking, high altitude, high affinity HB, renal disease, EPO secreting tumor (Parathyroid adenoma). |
| | **Polycythemia vera** | Increased RBC mass due to malignant proliferation (erythropoietin independant) |

## Myeloproliferative Neoplasms

General features: Cytoses, organomegaly (mainly splenomegaly), **hypercellular bone marrow,** progression to to acute leukemia (mainly AML)

| | |
|---|---|
| **JAK2 gene** | • JAK2 is a non receptor protein tyrosine kinase involved in signal transduction pathway<br>• **Mutation** leads to loss of auto inhibitory control over JAK2, leading to a continuous active state which will result in increased cells proliferation regardless of any suppressor mechanisms<br>• The most commonly associated Myeloproliferative neoplasm with JAK2 mutation is Polycythemia vera |

## 1. Polycythemia Vera

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

| | | | |
|---|---|---|---|
| **Diagnostic Features** | • **JAK2 mutation in >95% of cases.**<br>• **Low** Serum erythropoietin level | | |
| **Clinical Features** | • **Increased blood viscosity** leading to HTN, headache, **paresthesia**.<br>• Thrombosis: DVT, MI | • Splenomegaly in 70%.<br>• Hepatomegaly in 30%. | |
| **Investigations** | • Increase in RBCs, Hb. Mild increase in WBC & PLT.<br>• Excess of normocytic normochromic RBCs.<br>• Bone marrow is hypercellular with predominant **erythroid precursors**<br>• If Blasts increase >20% → Indication of Acute leukemia transformation | | |
| **Treatment** | • Venesection + Aspirin<br>• ± Myelosuppressive drugs (Hydroxyurea) | **Complications** (After 10-15 years) | • **Acute leukemia** (10%)<br>• **Myelofibrosis** (20%) |

## 2. Primary Myelofibrosis (Worst prognosis)

Characterized by proliferation of megakaryocytes & granulocytes in the bone marrow that is associated with deposition of fibrous connective tissue and **extramedullary haematopoiesis**

| | | |
|---|---|---|
| **Features** | • **JAK2 mutation in 50%** of cases<br>• Anemia<br>• Risk of AML transformation is 20% | • **Fibrotic bone marrow**<br>• Massive splenomegaly<br>• Leukoerythroblastic blood picture |

## 3. Essential Thrombocytopenia (Best prognosis)

Involves primarily the megakaryocytic lineage & characterized by **sustained thrombocytosis**

| | |
|---|---|
| **Features** | • **JAK2 mutation in 60%** of cases<br>• Asymptomatic (50%)<br>• Thrombosis<br>• Bleeding<br>• Mild splenomegaly (50%) and hepatomegaly (20%)<br>• **Very indolent risk of AML transformation** (5%)<br>• Treated with Aspirin ± Hydroxyurea |

# Quiz

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Q1) A 34 years old male was referred to the haematology clinic after coming to the ER with bleeding, mild hepatosplenomegaly and sustained thrombocytosis and he was diagnosed with essential thrombocythemia, what's the appropriate treatment for this patient?** | | | | | | | |
| A | Hydroxyuria only | B | Aspirin ±Hydroxyuria | C | Aspirin ±venesection | D | There's no treatment |
| **Q2) 60% of patients with essential thrombocythemia have which of the following gene mutations?** | | | | | | | |
| A | JAK1 | B | JAK2 | C | JAK3 | D | JAK4 |
| **Q3) Which of the following is a clinical feature of primary myelofibrosis?** | | | | | | | |
| A | Fibrotic bone marrow | B | Erythrocytosis | C | Mild hepatomegaly | D | Parasthesia |
| **Q4) which of the following is a characteristic of prefibrotic myelofibrosis?** | | | | | | | |
| A | Thrombocytosis | B | Thrombocytopenia | C | Extramedullary haematopoiesis | D | Leukopenia |
| **Q5) Which one of the following is <u>NOT</u> a Feature of Myeloproliferative Neoplasms?** | | | | | | | |
| A | Cytosis | B | Hematemesis | C | Splenomegaly | D | High Uric acid |
| **Q6) what are the Treatment combination of Polycythemia Vera ?** | | | | | | | |
| A | Omeprazole + $NaHCO_3$ | B | Bisoprolol + Metoprolol | C | Venesection + Aspirin | D | Sulfasalazine+Asacol |
| **Q7) Which of the following MPN has the worst prognosis?** | | | | | | | |
| A | Polycythemia Vera | B | Primary Myelofibrosis | C | ET | D | CML |
| **Q8) Most gene mutation in Polycythemia vera is ?** | | | | | | | |
| A | JAK1 | B | PDGFRA | C | FGFR1 | D | JAK2 |
| **Q9) A 66 years old female presented with itching, headache and shortness of breath. The CBC results show high hemoglobin , high RBCs count, normal platelet count, normal leukocytes count and she had Jak2 mutation. What is the most likely diagnosis?** | | | | | | | |
| A | PV | B | ET | C | PMF | D | CML |

| Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 |
|---|---|---|---|---|---|---|---|---|
| B | B | A | A | B | C | B | D | A |

## Leaders

Sarah Alobaid  Sarah Alqahtani  Albara Aldawoud

## Organizer

Reem Alqahtani

## Members

Bader Altamimi  Hind almotywea

## Note Takers

Lama alahmadi  Mohammed Beyari

## Summary

Sarah Alaidarous  Tarfa Alsharidi

**Feel free to contact us :**
Hematologyteam439@gmail.com