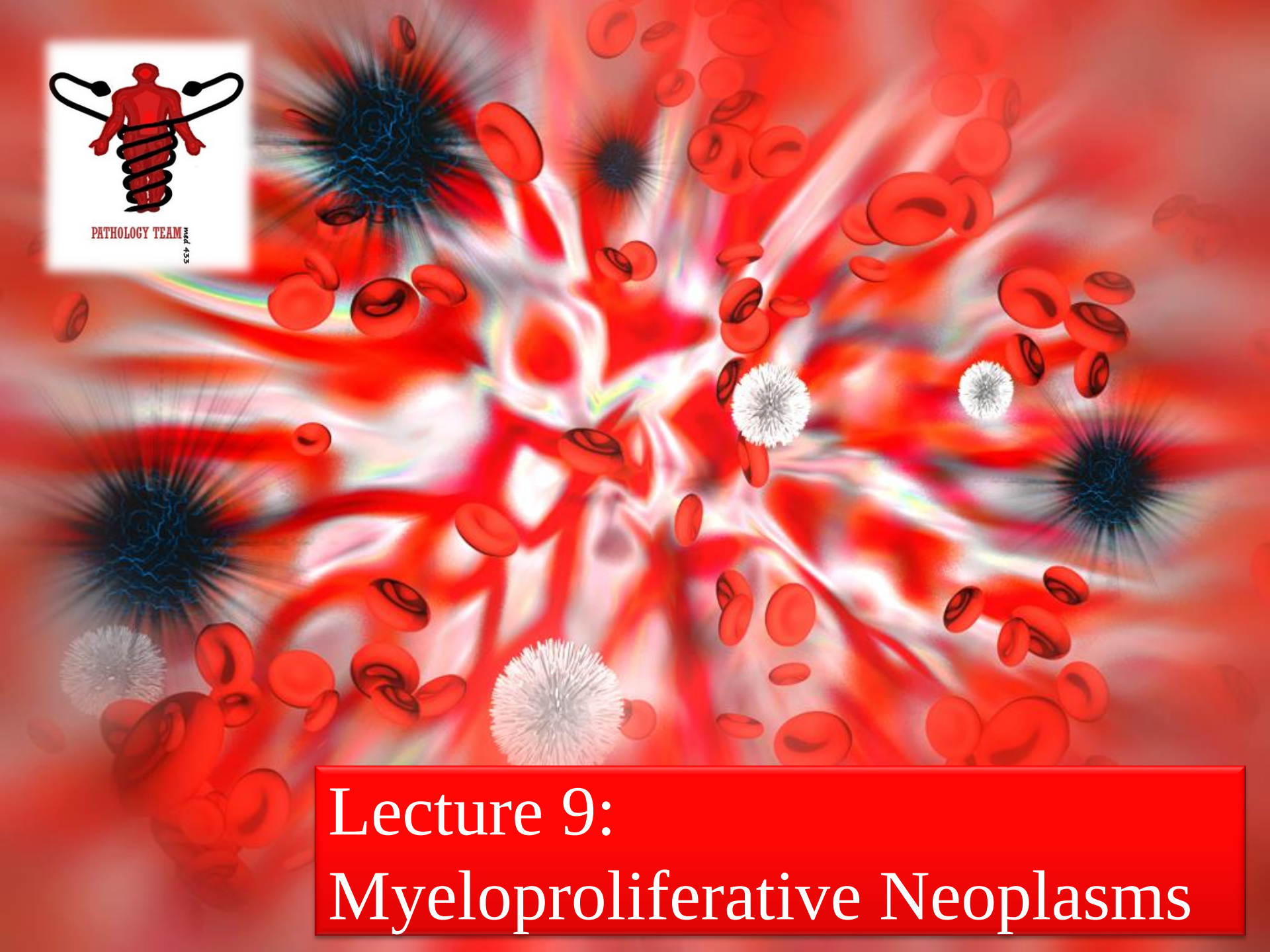


Lecture 9: Myeloproliferative Neoplasms

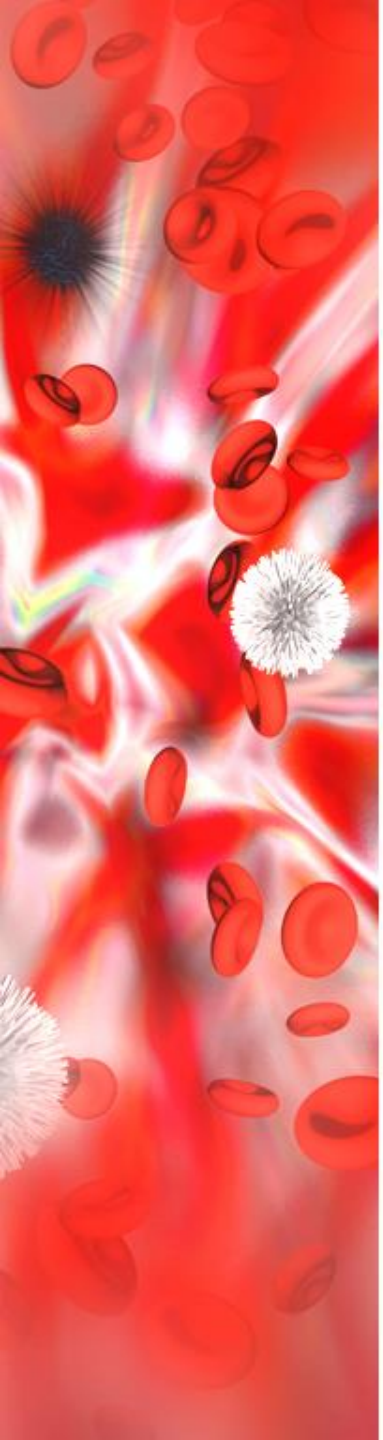
Myeloproliferative Neoplasms

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

Rare

BCR-ABL must be negative



MPN features:

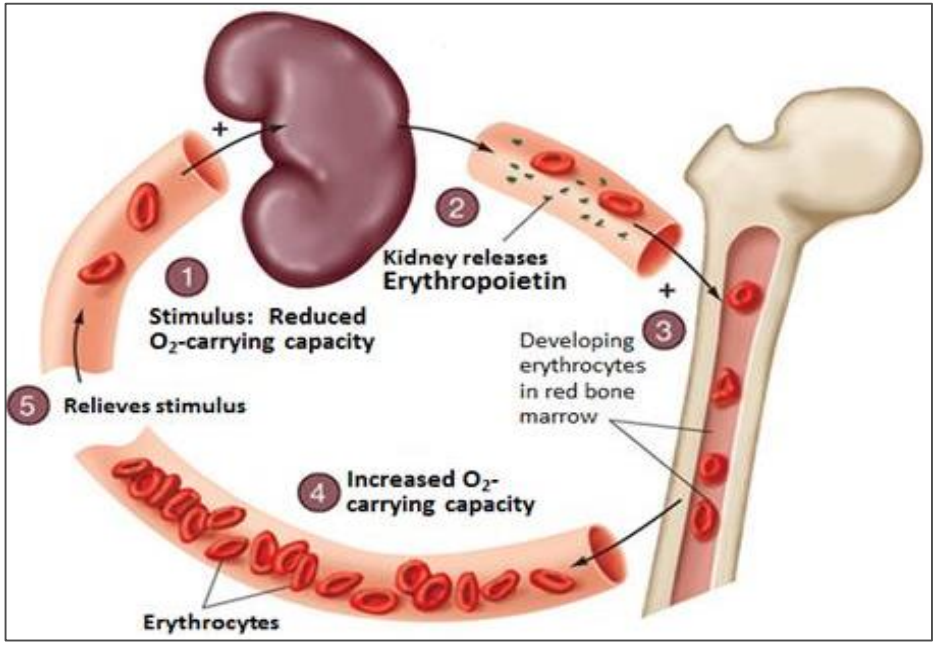
- Cytosis
- Organomegaly (mainly splenomgaly)
- High uric acid (due to increased production and breakdown of RBCS)
- Hypercellular bone marrow
- Progression to acute leukaemia (mainly AML)

Polycythemia

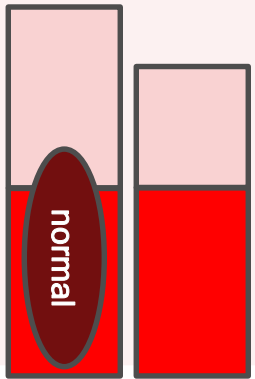
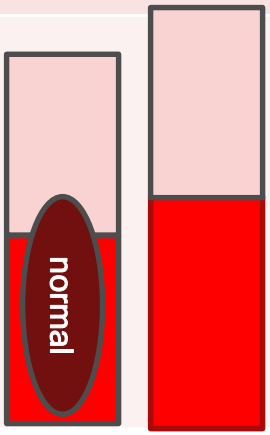
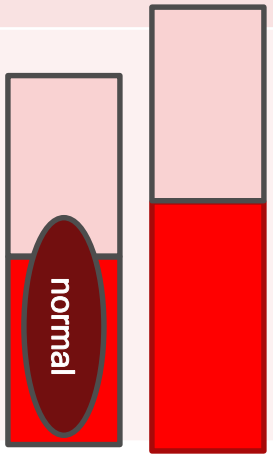
- In Greek “too many cells in the blood.”.
- Absolute increase in total body red cell volume (or mass)
- Manifests itself as a **raised** Hb or packed cell volume (PCV)
- Hb is >16.5 g/dl in women or 18.5 g/dl in men

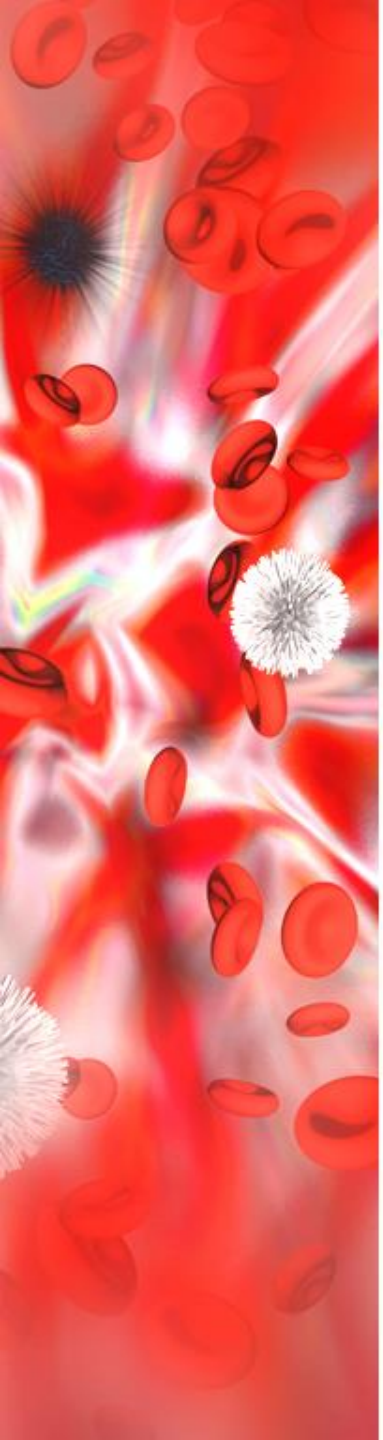
Regulation of Erythropoiesis

When the RBCs increase the stimulus inhibit



Classification of Polycythemia

Relative Polycythemia	2nd Polycythemia	Polycythemia vera
Decreased plasma volume due to severe dehydration (sever vomiting or diarrhea)	Increased RBC mass due to high EPO: 1-COPD, Sleep apnea, smoking (increase demand) 2-High altitude 3-High affinity HB 4-Renal disease 5-Epo secreating tumor (Parathyroid adenoma …)	Increased RBC mass due to malignant proliferation
		



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 (erythroid precursors)
- **JAK2** mutation in > 95% of cases
- Low Serum erythropoietin level (the first test in suspected cases)

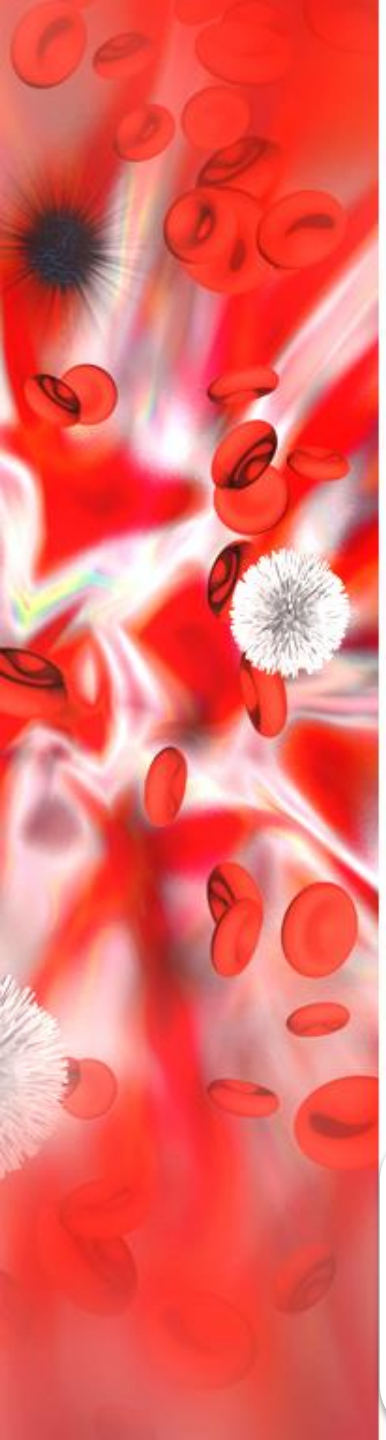
Clinical features of PV

1- Increased blood **viscosity** (due increase in RBCs)
- Hypertension
- Headache, dizziness, visual disturbances & paresthesia

2- Thrombosis (the most cause of death)
- Deep vein thrombosis (**common**)
- Myocardial infarction
- Mesenteric, portal or splenic vein thrombosis (lead to varices)

3-Splenomegaly in 70%

4-Hepatomegaly in 40%



Investigations

CBC:

*RBC: increased
*Hb: increased
*WBC & Platelet: mildly increased (usually)

Blood smear:

Excess of normocytic normochromic RBC

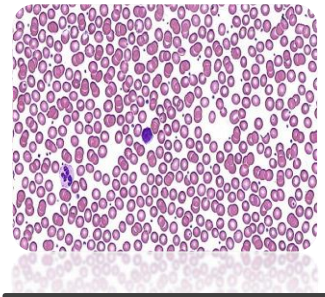
± Leukocytosis &thrombocytosis

Bone marrow :

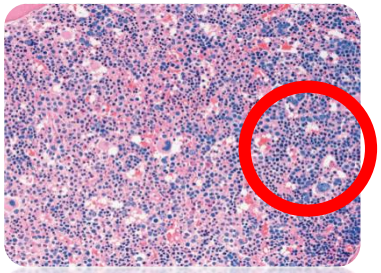
Hypercellular

Predominant erythroid precursors

± Increased megakaryocytes & Myeloid precursors.

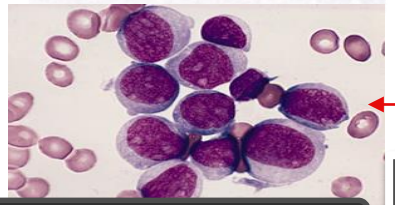
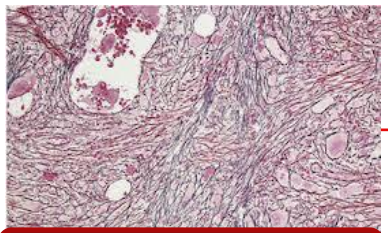


↑ blasts → AL trnsformation



Complication & treatment

Complication — 10-15 years

- 10% →  Acute leukemia
- 20% →  Myelofibrosis

Lead to

Treatment:

- Venesection + Aspirin
- ± Myelosuppressive drugs (hydroxyuria) chemotherapy

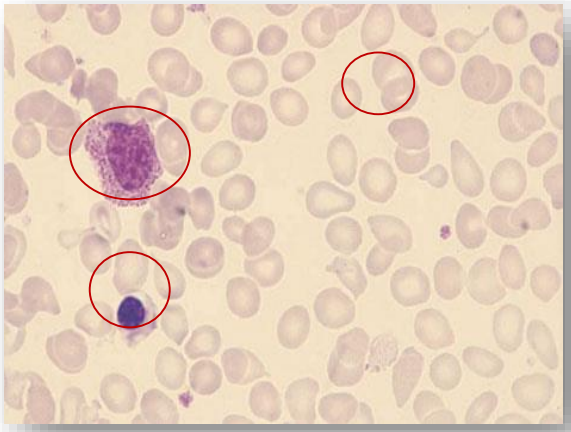
Primary Myelofibrosis

Clonal MPN characterized by a proliferation of **megakaryocytes** & **granulocytes** in the → bone marrow that associated with release and deposition of **fibrous connective tissue and extramedullary haematopoiesis** (spleen and liver) **and that will cause massive splenomegaly**

Note: Two disease cause massive splenomegaly: CML , MF

Clinical features

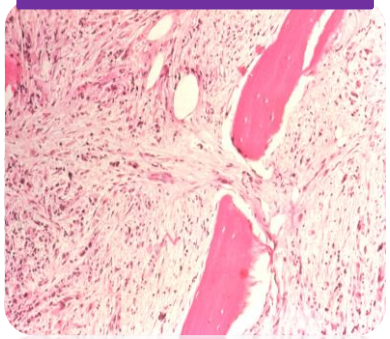
- Anemia
- Leukoerythroblastic blood picture. (immature granulocyte ,erythrocyte and erythroid precursors in peripheral blood)
- Massive splenomegaly
- Fibrotic bone marrow
- JAK2 mutation (50%) (must have)
- Risk of AML transformation (20%)



Bone marrow in Myelofibrosis

Normal BM

Fibrotic BM



- No fat cells
- No hematopoietic cells
- Fibrous background replace bone marrow

Stages of PMF

Prefibrotic stage → Proliferation of megakaryocytes &Granulocytes → Leukocytosis Thrombocytosis → 7-10 years survival

Fibrotic stage → Anemia, Leukopenia Thrombocytopenia, Extramedullary hematopoesis → 3-7 years survival

AML transformation → ≤1 year survival

Essential Thrombocythemia

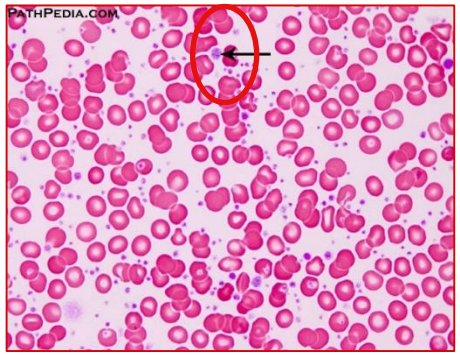
ET is MPN that involves primarily the megakaryocytic lineage.

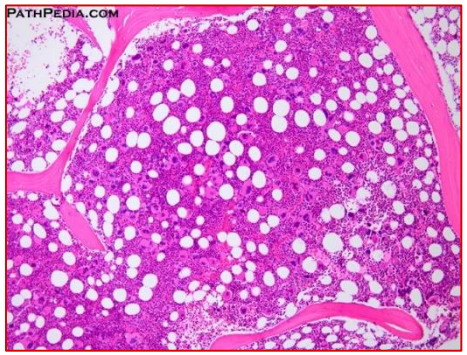
& characterized by **sustained thrombocytosis** (only) .

Diagnostic Features

- Sustained thrombocytosis ≥45O×10^9. And more than one test (follow up)
- Hypercellular BM with megakaryocytic proliferation
- **Exclusion of other disease (secondary cause)**: CML, MDS,PV &Primary Myelofibrosis
- **JAK2 mutation** (60%),If negative ;**no** evidence of reactive thrombocytosis:

Secondary cause raised platelets :**Iron def. ,splenoctomy, surgery, infection ,autoimmune disease….** (so history very importan)





-Increase megakaryocytic
-Hypercellular BM
-Decrease fat cells

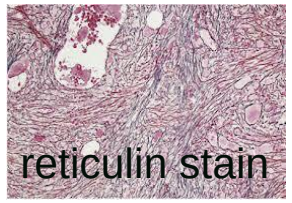
Clinical Presentation

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

Very indolent (**5%** risk of AML transformation)

Treatment :Aspirin ±Hydroxyuria

Fibrous tissue and megakaryocyte



JAK2: Non receptor protein tyrosine kinase involved in **signal transduction pathway** . All we have this genes but without mutation **control** proliferation all JAK2 kinase domains structure

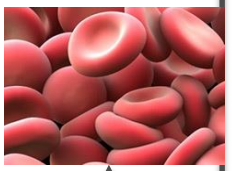
JAK2 mutation :

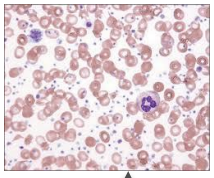
Point mutation (at codon 617 in JH2)

leads to **loss** of auto inhibitory control over JAK2.

The mutated JAK2 is in a constitutively active state,

50%



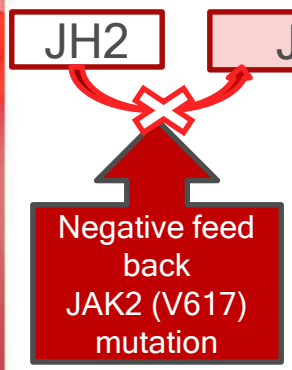


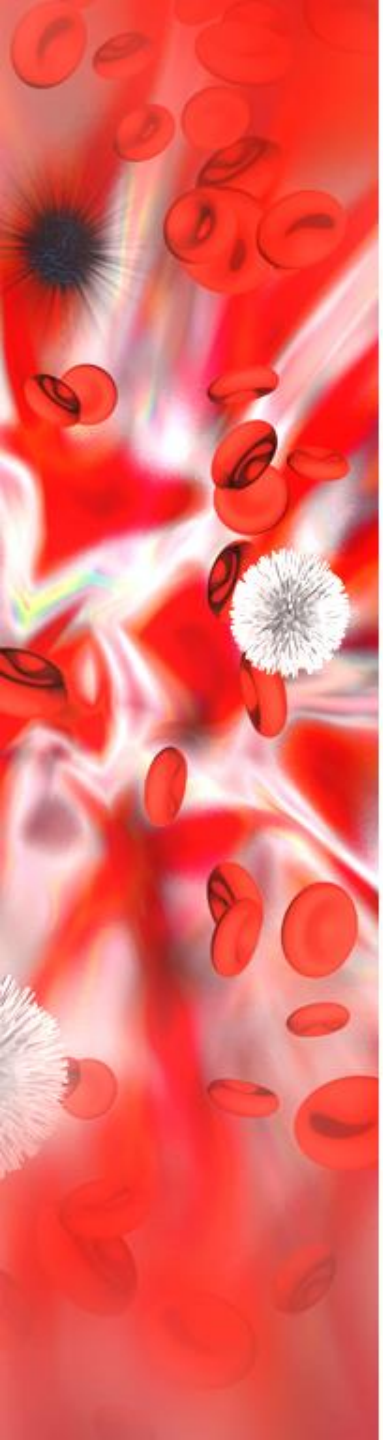
Polycythemia

In the platelets

60%

95%





Summary from essential hematology for MPN

- Myeloproliferative neoplasms are a group of conditions arising from marrow stem cells and characterized by clonal proliferation of one or more haemopoietic components in the bone marrow. The three major subtypes are:
  polycythaemia vera (PV);
  essential thrombocythaemia (ET); and
  primary myelofibrosis.
- These subtypes are closely related to each other and mutation of the *JAK2* gene is detected in almost all patients with PV and in approximately 50% of those with ET and primary myelofibrosis.
- Polycythaemia is defined as an increase in the haemoglobin concentration and the major subdivision is into *absolute polycythaemia,* in which the red cell mass is raised, and *relative polycythaemia* in which the red cell volume is normal but the plasma volume is reduced.
- Absolute polycythaemia is divided into primary polycythaemia, known as polycythaemia vera (PV), or secondary polycythaemia.
- The diagnosis of PV is made by finding polycythaemia together with a *JAK2* mutation. It occurs in older patients and

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the increase in blood viscosity leads to headaches, plethoric appearance and splenomegaly.

- Treatment aims to maintain the haematocrit around 0.45. Useful approaches include venesection or hydroxyurea and aspirin is also given. *JAK2* inhibitors are being assessed in clinical trials. Survival is usually over 10 years but there may be progression to leukaemia or myelofibrosis.
- Secondary polycythaemia can arise from rare congenital causes or acquired disorders such as lung disease or tumours that secrete erythropoietin. Venesection may be needed.
- Essential thrombocythaemia is diagnosed by persistent raised platelet count in the absence of other causes. *JAK2* is mutated in approximately 50% of cases.
- The predominant feature of primary myelofibrosis is a progressive generalized reactive fibrosis of the bone marrow in association with the development of haemopoiesis in the spleen and liver. Symptoms usually result from anaemia and a grossly enlarged spleen.
- Diagnosis is made on blood film, which shows a leucoerythroblastic appearance, together with bone marrow biopsy and *JAK2* mutation screen. Treatment is with red cell transfusion. Splenectomy is sometimes used and *JAK2* inhibitors appear encouraging.
- Systemic mastocytosis is a clonal proliferation of mast cells with involvement of bone marrow, skin (as uticaria pigmentosa) and other organs.

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Done by

Areej Alalwan

Revised by

Naif AL-Hefdy

TEAM LEADER : ABDULRHMAN ALTHAQIB

Contact us:

haematology433@gmail.com

@haematology433