Hematology

9 /11

Myeloproliferative Neoplasm (MPN)

432 ***Hematology*** *Team*

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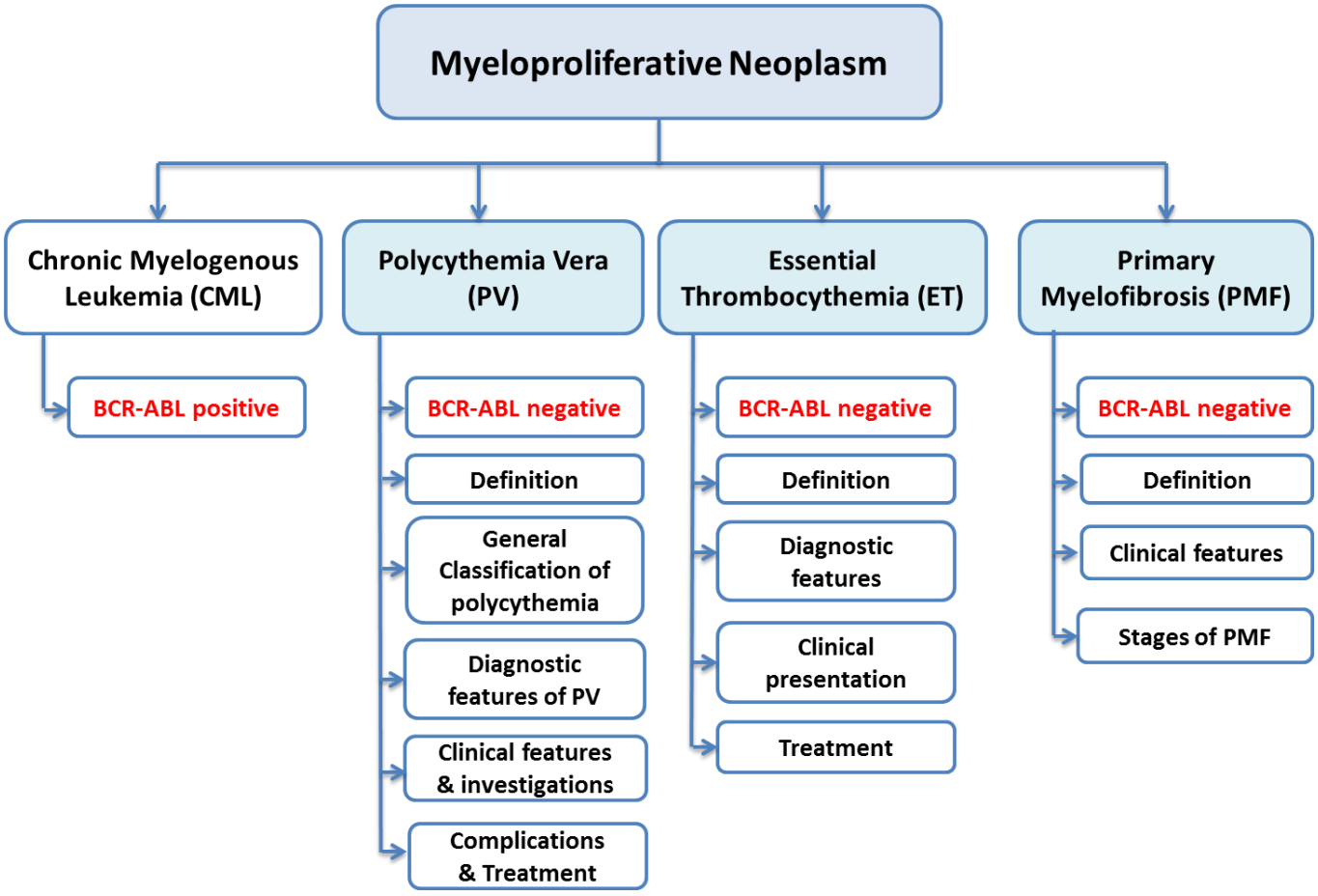
Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Myeloproliferative Neoplasm

Mind Map:



Myeloproliferative Neoplasm

General MPN features:

- Cytosis, unusal increase number of cells.
- Organomegaly (mainly splenomgaly).
- High uric acid.
- Hypercellular bone marrow.
- Progression to acute leukaemia (mainly AML), rarely ALL.

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

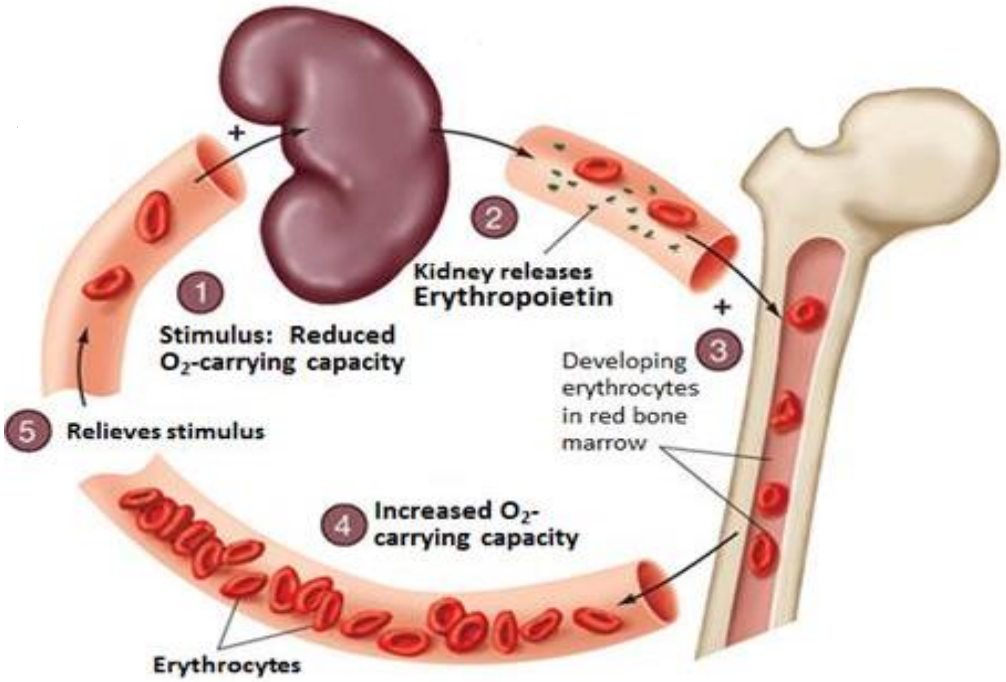
Starting from 2 till 8 all must have negative BCR-ABL1

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 or 18.5 g/dl in women and men, respectively.

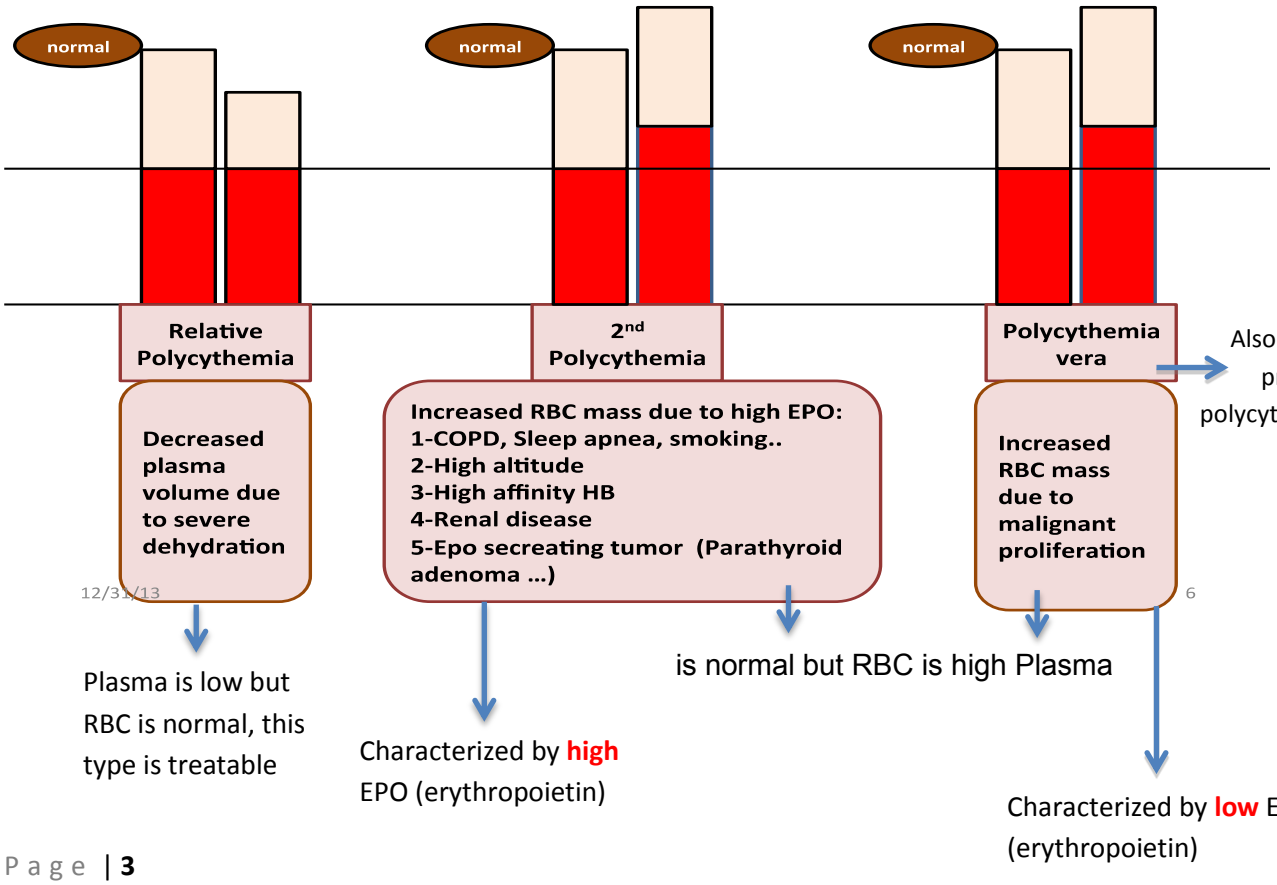
The patient could be presented with redness in the face and palms with increase Hb from 20 to 24 g/dl

Regulation of Erythropoiesis



NOTE: if there is a disturbance in any step in the picture above, polycythemia will develop. For example, smoking decreases oxygen carrying capacity and this could lead to 2nd polycythemia.

Classification of Polycythemia



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

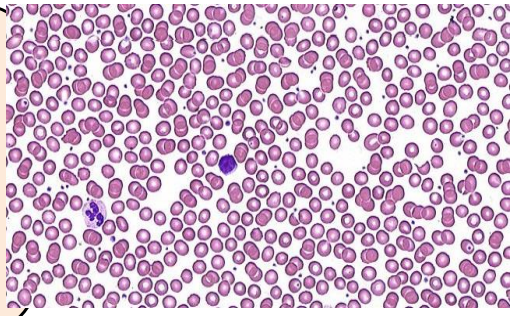
CBC:

*RBC: increased *Hb: increased

*WBC & PLT :mildly increased (usually), Or it could be normal

Blood smear:

- Excess of normocytic normochromic RBC
- ±Leukocytosis &thrombocytosis

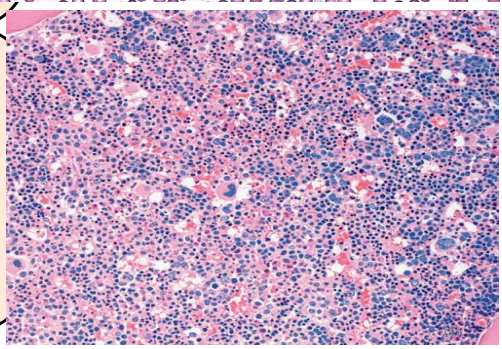


Bone marrow

- Hypercellular (normally it contains white fat cells & hematopoietic cells, but due to the hypercellularity w can't see it)
- Predominant erythroid precursors
- ± Increased megakaryocytes &Myeloid precursors.

Blasts ——— AL transformation

12/31/13



Increased blasts number ≥ 20 is an indication of transformation to Acute Leukemia

Complication &treatment

Diagnosis of Polycythemia Vera

Treatment:

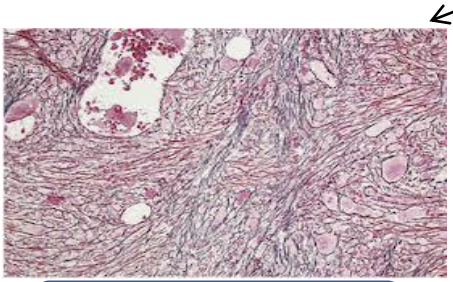
Venesection + Aspirin This is the first line treatment

± Myelosuppressive drugs (hydroxyurea) (if the first choice didn't work we use this one)

Phlebotomy is the act of drawing or removing blood from the circulatory system

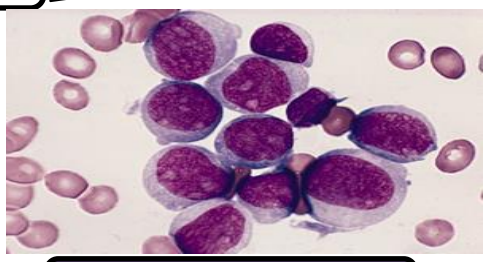
10-15 years

20%



Myelofibrosis

10%



Acute leukemia

Primary Myelofibrosis (PMF)

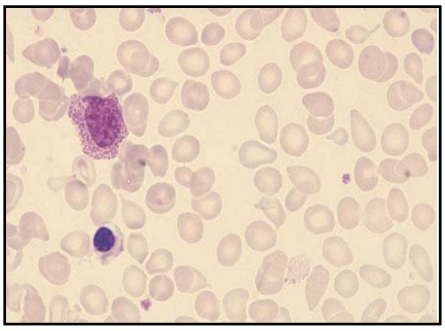
Definition:

Clonal* MPN characterized by a **proliferation of megakaryocytes** & **granulocytes** in the bone marrow that associated with **deposition of fibrous connective tissue** and extramedullary hematopoiesis. **BCR-ABL negative.**

*A clone is a group of identical cells that are derived from the same cell.

Clinical features:

- **Anemia** (due to bone marrow fibrosis)
- **Leukoerythroblastic blood picture.** →
- **Massive splenomegaly** (the main physical finding).
- **Fibrotic bone marrow**
- **JAK2 mutation (50%)**
- **Risk of AML transformation (20%)**



Stages of PMF:

Stage 1 (Prefibrotic stage):

Proliferation of megakaryocytes & Granulocytes ⇢ Leukocytosis, Thrombocytosis

Survival: 7-10 years.

Stage 2 (Fibrotic stage):

Anemia, Leukopenia, Thrombocytopenia, Extramedullary hematopoiesis.

Survival: 3-7 years.

Stage 3- Acute Myeloid Leukemia transformation.

Survival: ≤ 1 year.

NOTE:

PMF is associated with more risk of developing AML (acute myeloid leukemia) than polycythemia.

In the Prefibrotic stage of PMF, It's difficult to diagnose the disease.

Blood picture: Leucoerythroblastic change with 'tear-drop' cells & an erythroblast (also called normoblast or nucleated RBC).

Essential Thrombocythemia (ET)

Definition:

Thrombocythemia means increased Platelets. It's a myeloproliferative neoplasm that involves primarily the **megakaryocytic lineage**, & characterized by **sustained thrombocytosis**.

Essential Thrombocythemia is **BCR-ABL negative**.

Diagnostic features:

- **Sustained thrombocytosis ≥ 450×10^9.**
- **Hypercellular BM with megakaryocytic proliferation.**
- **Exclusion of: Chronic myeloid leukemia (CML), Myelodysplastic syndrome (MDS), Polycythemia vera (PV) & Primary Myelofibrosis,** because Platelets could be increased in all of these diseases.
- JAK2 mutation (60%).
- **Negative or no evidence of reactive thrombocytosis.**

Examples 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 with or without Hydroxyuria.

JAK2 mutation:

- **JAK2:** Non receptor protein tyrosine kinase involved in signal transduction pathway.
- **Point mutation leads to loss of auto inhibitory control over JAK2.**
- **The mutated JAK2 is in a constitutively active state.**
- JAK2 mutation → activation of transcriptional factors
  → 1- Increased proliferation.
  2- Decreased apoptosis.

→ Result in one of these diseases: PV, ET, or PMF

NOTE: JAK2 mutation is specific to 3 diseases:

1- **Polycythemia vera (95% of PV patients have JAK2).**
2- **Essential Thrombocythemia (60% of ET patients have JAK2).**
3- **Primary Myelofibrosis (50% of PMF patients have JAK2).**

Example: If a patient comes with Acute Myeloid Leukemia & we found JAK2 mutation, then he is in the last stage of one of these 3 diseases: PV, PMF, or ET.

Summary

- Polycythemia is the total **increase of body red cell volume**.
- It has three types (**relative, secondary and primary**).
- Primary polycythemia also called **polycythemia vera**, and it's strongly **related to JAK2 mutation.**
- The hemoglobin must be higher than **18.5g/dl in men**, and higher than **16. 5g/dl in women.**
- CBC shows **high number** of RBC & HB, and bone marrow sample shows hypercellularity.
- In treatmeant we usually use **venesection + asprin as first line treatmeant**.
- Primary Myelofibrosis is a **proliferation of megakaryocytes & granulocytes** in the bone marrow with deposition of fibrous connective tissue.
- PMF has 3 stages: **prefibrotic, fibrotic, & AML transformation**.
- Essential thrombocythemia affects **megakaryocytic lineage** & characterized by **sustained thrombocytosis** .
- To diagnose Essential thrombocythemia, there should be **no evidence of reactive thrombocytosis** such as Iron deficiency, splenectomy, surgery, infection, or autoimmune disease.
- Essential thrombocythemia is **rarely** transformed to Acute Myeloid Leukemia (AML).
- Point mutation leads to loss of auto inhibitory control over JAK2 **.**

Questions

1/ which of the following is a clinical feature of Polycythemia Vera?

A- Splenomegaly
B- Varices
C- Hypotension

2/ which mutation of the following is strongly associated with PV?

A- Mutation in gene p53
B- T(9,22)
C- JAK2

3/ which one of the following has the greater risk of Acute Myeloid Leukemia transformation?

A- Essential thrombocythemia
B- Polycythemia vera
C- Primary myelofibrosis

4/ which of the following stages of myelofibrosis has the best survival?

A- AML stage
B- Prefibrotic stage
C- Fibrotic stage

5/ what is the abnormality found in JAK2?

A- Point mutation
B- Deletion
C- Translocation

Answers:

- 1-A
- 2-C
- 3-C
- 4-B
- 5-A

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com