Myeloproliferative Disorders

# 1 Overview

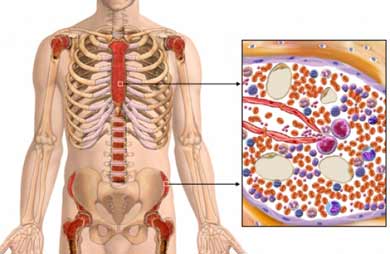
* **Myeloproliferative Disorders:** a group of closely related conditions charactarised by increased clonal proliferation of different hamopoietic stem cells (RBC, WBC or platelet **precursors**) in the bone marrow.
  + *(myelo- means stem cell ^\_^)*
  + The proliferation is present in the liver and spleen as well in many cases.
* Characterized by clonal proliferation of one or more heamopoietic components in the bone marrow, as well as the liver and spleen in many cases.
* They all have a chromosomal abnormality where chromosome 9 is transformation with chromosome 22, so t(9,22)
* Non-leukemic myeloproliferative disorders have a mutation by JAK2, especially polycythaemia rubra vera (in 97% of cases), then myelofibrosis (57%) and essential thrombocytotheamia (50%)
* They include:

1. **Polycythaemia** rubra vera

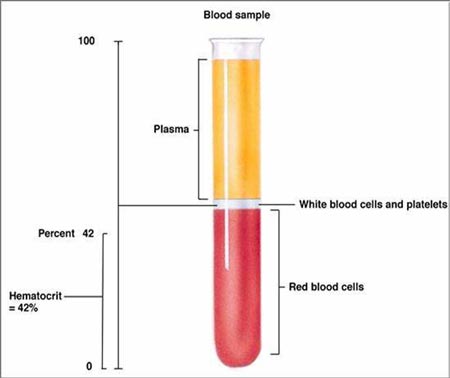
**Non-leukemic** myeloproliferative disorders

1. Chronic idiopathic **Myelofibrosis.**
2. Essential **thrombocytheamia**
3. **Chronic myeloid** (myeloproliferative) **Leukemia**
   1. Chronic Granulocytic Leukemia
   2. Chronic **Myelogenous** Leukaemia "Most Important"
   3. Chronic Neutrophilic Leukaemia
   4. Chronic Eosinophilic Leukaemia
   5. Chronic Myeloproliferative Disease, Unclassifiable

(Diagnosis)



# 2 Polycytheamia

* **Polycytheamia**:a state of increased heamoglobin concentration (incrased hematocrit or increased packed cell volume, the RBC mass is increased in relation to plasma)
* The upper limit for normal hematocrit:
  + Males: 55%
  + Females: 47%
  + Above that is polycythaemia.

***Classification of Polycytheamia***

* Classified according to nature of the disease into:
  + **Relative:** where RBC mass is normal but plasma volume is decreased
    - *(also called false or apparent erythrocytosis)*
    - E.g. due to dehydration (like in diarrhea)
  + **Absolute:** there is an increase in RBC mass
    - presence of JAK 2 mutation is significant here
    - subdivided into:
      * **primary polycythemia:**
        + can be **congenital** *like in truncation of EPO (erythropoietin receptor)*
        + or **acquired** like in polycythemia rubra vera
      * **secondary polycythemia:** 
        + due to other factors that lead to increased synthesis of erythrocytes
        + can be **congenital** due to ↑ O2 affinity to Hb, or autonomours high EPO production
        + Or **acquired** due to hypoxemia or renal disease.
    - To diagnose a primary polycythemia, first exclude secondary causes.

## 2.1 Polycythaemia rubra vera

* **Polycytheamia Rubra Vera (PRV)**: a type of polycythaemia that is caused by a clonal malignancy of a marrow stem cell.
  + Characterized by increased RBC count (of course ^\_^) as well as increase granulocytes and platelets is many cases.

### 2.1.1 Clinical features

* More common in elderly.
* Clinical features develop due to hyperviscosity, hypervolemia or hypermetabolism and include:
  + Headache, lethargy, dyspnoea, blurred vision, weight loss and night sweats *(due to hypermetabolism)*
  + **Pruritis (itching)**: *(characteristic feature)*. increases with exposure to warm environment (e.g. after taking a hot bath)
  + **Hemorrhage**, due to dysfunctional platelets,
    - Particularly in GI, and cereberal vessels
  + **Vascular obstruction** (or narrowing)
    - Intermettient claudication عرج متقطع
      * Happens due to occlusion in a leg artery so that legs muscles don’t get enough oxygen.
    - Cereberal ischemia
    - Cardiac ischemia
  + **Plethora** (fullness of blood) due to increased RBCs
    - conjunctival congestion, red pace.
  + **Peptic ulcer** (in 5-10% of patients)
  + **Splenomegaly** (in 75% of patients)
  + **Gout** *due to increased production of uric acid*.
  + **Hypertension**
  + **Thrombosis**
  + **Iron deficiency anemia** due to hemorrhage or peptic ulcer.
    - There is an iron deficiency that cannot be treated by iron replacement and instead gets worse symptoms by adding iron.

### 2.1.2 Laboratory Findings

1. **Blood parameters**

**🡺 Increased** hemoglobin, heamtocrit, and blood cells

* **Hemoglobin:** Male: >17.5g, Female: >15.5g
* **Packed cell volume (PCV) (hemtocrit):**
  + Male: >55% Female: >47%
  + *In order to improve the oxygenation of the CNS in a surgery, you have to decrease the heamtocrit before operating.*
* **RBC count:** Male: >6 million/cm3Female: >5.5 million/cm3.
* **WBC count:** increased, especially neutrophils.
* **Platelet count:** increased with defective function.
* **Total red cell mass:** Females: > 36 ml/kg Male: > 32 ml/kg

*Measured by radiolabeled isotopes.*

1. **Arterial O2 saturation:** normal.

*(It is important to differentiate PRV from polycythemia due to hypoxia)*

1. **Neutrophil alkaline phosphatase (Nap score)**: an enzyme found in mature neutrophils and segmented neutrophils.

*Nap score: increases*.

1. **Serum Uric acid:** increase
2. **Erythropoietin hormone Level:** Normal or decrease.

This is important to differentiate from polycythemia secondary to inappropriate erythropoietin e.g. in tumors.

1. **Bone Marrow:** 
   * Hypercellular and hyperactive with increased erythropoiesis.
   * Absent iron stores
2. **Serum B12 level:** increase
   * This happens in myeloproliferative disorders in general
   * Due to the granulopiosis produce the trancobalamin.
3. **PCR:** JAK mutation
4. **Electrophoresis** *to roll out secondary polycythemia caused by high affinity metHb.*

It is usually discovered ***accidentally***

### 2.1.3 Complications

* Thrombosis and hemorrhage
* Myelofibrosis in 30% of cases
* Acute leukemia, usually AML type: 15% of cases.

### 2.1.4 Treatment

* **Venesection:** resection of blood out of the body.
  + Used to improve the condition but not cure it.
  + Used at the start of the therapy
  + Especially before or during surgery.
* Radioactive phoshphorus (32P) 🡪 IV
  + Acts as an effective myelosuppressive agent that is concentrated in bone.
* Chemotherapy to reduce the RBC count & Hemoglobin level.
  + Affect platelets and WBCs as well
  + Hydroxyurea

## 2.2 Secondary Polycythemia

### 2.2.1 Causes

1. **Idiopathic:** no increase in erythropoietin, but different features than PRV.
2. **Increased erythropoietin:**
   1. **Compensatory:** due to hypoxia, lung disease, cardiac disease, high altitudes, smoking or high affinity hemoglobin (methemoglobinemia) 🡺 all these events cause a compensatory increase in erythropoietin (feedback mechanism).

N.B. if the affinity of hemoglobin is increased to oxygen, the oxygen will stay bound to hemoglobin and will not be released to tissues.

* 1. **Inappropriate:** in tumors that produce eryhtroprotein.
     1. e. g. hepatocellular carcinoma, cerebellar hemangioma, massive uterine fibroids
  2. **Renal disease:** renal artery stenosis, renal carcinoma, renal cysts.

# Chronic Myelogenous Leukaemia

***Also called chronic granulocytic leukemia or chronic myelocytic leukemmia***

*See acute leukemia lecture for divisions of leukemia*

* It is a type of chronic leukemia affecting myeloid precursors, characterized by malignant increase in body granulocytes.

## Clinical Features:

Seen in young and middle age.

1. Anemia

Most common ( presenting feature )

1. Splenomegaly
2. Symptoms due to the raised metabolic rate
   * *E.g.*
3. Haemorrhagic Manifestations, especially bruising (due to platelet dysfunction )
4. Weight loss, anorexia, pallor, dyspnea, lethargy.
5. Gout.
6. Acute abdominal pain ( mimic appendicitis )
7. Bone or joint pains
8. Menstrual disturbances ( due to infiltrate in the ovaries )
9. Neurological symptoms ( due to infiltrate in the CNS )
10. Priapism ( painful benign erection of the penis , also occur with Sickle cell anemia )
11. Skin disorder
12. Disturbances of vision or hearing
13. Accidental finding on routine examination.

### Laboratory Features:

1. **Peripheral Blood:**

* Leukocytosis (50 × 109 - 300 × 109 ).
* Deferential count of WBC shows mature and immature forms. Most of the cells are neutrophils "segmented" and myelocytes ( metamylocytes & promylocytes ) .
* Increased eosinophils and basophils.
* Increased platelets
* Anemia

1. Neutrophil Alkaline Phoshpatase (NAP): decreased ( Only in CML & PNH )
   * Important of differentiate CML from a leukemoid reaction which shows increase (NAP) score.
   * √ PNH : paroximal nocturnal hemoglobinourea ( pre-leukaemic state )
2. Serum B12 and B12 binding capacity: increased
3. Bone marrow Examination: Hyper cellular with increase granulocytic proliferation.
4. Philadelphia chromosome:

- Positive in 90 – 95 cases CML

√ diagnostic & +ve in 95% of cases

- t (9,22) *translocation between chromosome 9 and 22*

- Associated with good prognosis.

1. C-abl Oncogene: Cellular oncogene.
   * 100% +ve in CML
   * t(9,22)
   * It forms chimerical gene with the BCR "B cell receptor" on 22.
   * This gene codes for a chimerical m- RNA 🡪 formation of an abnormal chimerical protein. ( ↑ Tyrosine activity )

## Treatment :

1. Hydroxuurea :
   * Reduce the count.
   * Not cure the disease
   * Short-time acting
2. α-INF :

* trial
* causes pliladelphia negativity
* if stop the treatment 🡪 Philadelphia comeback
* helpful in chronic phase

1. Glivec :

* Tyrosine kinase inhibitor
* Resistance is developing

1. Bone Marrow transplantation :

* From twins or the patient itself