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