Polycythemia & Hypersplenism

- Polycythemia or erythrocytosis is characterized by an increase in the red cell mass, measured as increased hemoglobin and hematocrit above the upper limit of normal for the patient’s age and sex.
- The normal range for hemoglobin is: For men 13.5 to 17.5 grams/dl. For women, 12.0 to 15.5 grams/dl.
- Hematocrit value above 60% in males and 55% in females almost establish absolute polycythemia.

Classification of Polycythemia

I. Absolute (true) polycythemia (increased red cell volume)

A. Primary polycythemia

1. Acquired
   a. Polycythemia rubra vera

2. Hereditary
   a. Primary familial and congenital polycythemia
   b. Erythropoietin receptor mutations
   c. Unknown gene mutations

B. Secondary polycythemia

1. Hypoxemia
   a. Chronic lung disease
   b. Sleep apnea
   c. Right-to-left cardiac shunts
   d. High altitude
   e. Smoking

2. Carboxyhemoglobinemia
   a. Smoking
   b. Carbon monoxide poisoning

C. Autonomous erythropoietin production

1. Hepatocellular carcinoma
2. Renal cell carcinoma
3. Pheochromocytoma
4. Polycystic kidney disease
D. Exogenous erythropoietin administration ("Epo doping")

II. Relative (spurious) polycythemia (normal red cell volume)

A. Dehydration (water deprivation, vomiting, diarrhea)
B. Diuretics
C. Smoking
D. Gaisböck syndrome
E. Plasma loss (burns, enteropathy)
F. Stress

Familial (congenital) polycythemia

- This is a rare autosomal dominant condition.
- Caused by mutations in the EPO receptor gene which result in hypersensitivity to erythropoietin.
- This hematological disorder is present at birth but the clinical symptoms, if they develop, can be discovered at any time during childhood or adulthood.
- Examples:
  a. High-oxygen affinity hemoglobins
  b. Congenital methemoglobinemias
- The mechanism of polycythemia in primary familial and congenital polycythemia (PFCP) is due to the truncated EpoR (genetic mutation) in which there is no inhibition of signalling pathways.

Primary Polycythemia (rubra) vera

- Polycythemia rubra vera (PRV), also known as polycythemia vera and primary proliferative polycythemia, is a myeloproliferative disorder in which there is increased production of red cells and sometimes also of granulocytes and platelets.
- In PRV, the increase in red cell volume is caused by a clonal malignancy of marrow stem cell.
- The disease results from somatic mutation of a single haemopoietic stem cell which gives it’s progeny a proliferative advantage.
- The JAK2 mutation is present in haemopoietic cells in almost 100% of patients.
- Polycythemia vera is a rare chronic disease diagnosed in an estimated 2 to 3 people per 100,000 population. Although it can occur at any age, polycythemia vera usually affects older people, with most patients diagnosed over the age of 55 years.
- Polycythemia vera is rare in children and young adults.
- It occurs more commonly in males than in females.
Relative polycythemia

- It is the result of plasma volume contraction, which means a normal TRCV (Total Red Cell Volume).
- It is far more common than Polycythemia vera.
- Patients with chronic relative erythrocytosis have been described as having Gaisböck syndrome, stress erythrocytosis, pseudopolycythemia (In this syndrome, primarily occurring in obese men, hypertension causes a reduction in plasma volume, resulting in a relative increase in red blood cell count).

MECHANISMS OF POLYCYTHEMIA

- Polycythemia vera rises from the transformation of a single hematopoietic stem cell with a selective growth advantage that gradually becomes the predominant myeloid progenitor. Recently a somatic mutation is detected in a gene on chromosome 9p in majority of polycythemia vera patients.
- This gene encodes for tyrosine kinase JAK.
- This somatic mutation transforms this kinase into a constitutively active form and seems to be responsible for the uncontrolled proliferation of the erythroid cells.
- The first phase of polycythemia vera is a phase of erythrocytosis characterised by an increase in the hematocrit, white blood cells and the platelets.
- After a few years the patient passes into a spent phase when the disease frequently becomes inactive. This phase is also called post polycythemic myeloid metaplasia (PPMM) which is not distinguishable from another MDP, the idiopathic myelofibrosis.
- Finally a good number of patients eventually, go on to develop acute myeloid leukaemia.
- This orderly transition occurs only in some patients. Rest of them can directly transit from the polycythemic phase directly into an acute leukaemia or a myelodysplastic disorder.
- In all conditions of hypoxia HIF-1 is responsible for the polycythemia. Some patients with chronic lung disease or congenital cyanotic heart disease do not develop polycythemia in spite of hypoxia, the mechanism of which is not very clear.
- Polycythemia in smokers is due to increased blood carbon monoxide (CO). CO displaces one molecule of O2 from hemoglobin and converts it to carboxy hemoglobin (COHb). COHb has 200 times greater affinity than oxygen. This results in not only occupation of one of the heme groups of haemoglobin but also increase in the oxygen affinity of the remaining heme group resulting in tissue hypoxia.
- Polycythemia accompanying kidney and liver diseases and neoplastic disorders is usually associated with increased Epo production.
Clinical features

Age > 40 year

- May occur in young adults and rare in childhood
- Symptoms of hyperviscosity, such as lassitude, loss of concentration, headaches, dizziness, blackouts, pruritus and epistaxis

Majority patients present due to vascular complications

- Thrombosis (including portal and splenic vein)
- DVT
- Hypertension
- Poor vision
- Skin complications (aquagenic pruritus, erythromelalgia)
- Haemorrhage (GIT) due to platelet defect

Hepatosplenomegaly

Erythromelalgia

- Increased skin temp
- Burning sensation
- Redness
- Pruritis has been present in 30-40% of patients and may be due to release of histamine/prostaglandin production.
- It usually occurs after warm bath

Complications

Possible complications of polycythemia vera include:

Blood clots –

- Polycythemia vera causes an increase in blood thickness and decrease in blood flow, as well as abnormalities in the platelets, and this increase the risk of blood clots. Blood clots can cause a stroke, a heart attack, or blockage of an artery in the lungs (pulmonary embolism) or in a vein deep within a muscle (deep vein thrombosis). It is the major cause of death in 10-40% of patients.
- Blood clots may also block blood vessels that drain blood from the liver (Budd-Chiari syndrome).

Skin problems –

- Polycythemia vera may cause the skin to itch, especially after a warm bath or shower, due to releasing histamine from basophiles.
A burning or tingling sensation in the skin may be experienced. The skin may also appear red, especially on the face, palms and ear lobes.

**Problems due to high levels of RBCs** –

- this may cause open sores on the inside lining of the stomach, upper small intestine or esophagus (peptic ulcers), inflammation in the joints (gout), and uric acid stones in the kidneys.

**Enlarged spleen (splenomegaly) –**

- The increased number of blood cells caused by polycythemia vera makes the spleen work harder than normal, which causes it to enlarge. If the spleen becomes too large, it may need to be removed.

**Investigations**

- **The haemoglobin**, haematocrit and red cell count are increased (The hemoglobin may range from ~18 to 24 g/dL in male and ~ 16 to 22 g/dl in female; the hematocrit is usually >60% in men and >55% in women).

- A neutrophil leukocytosis is seen in over half of patients, and some have increased circulating basophils. A raised platelets count is present in about half of the patients.

- **The JAK2 mutation** is present in the bone marrow and peripheral blood granulocytes in nearly 100% of patients.

- The neutrophil alkaline phosphatase (NAP) score is usually increased.

- The bone marrow is hypercellular with prominent megakaryocytes, best assessed by a trephine biopsy.

- Serum erythropoietin usually low in polycythemia vera but high in erthrocytosis (secondary).

- Blood viscosity is increased.

- Plasma urate is often increased, the serum lactate dehydrogenase (LDH) is normal to slightly increased.

- Circulating erythroid progenitors (erythroid colony-forming unit, CFU-E & erythroid burst – forming BFU-E) are increased.

- **Blood film** The peripheral blood film in polycythaemia of any etiology shows a ‘packed film’ appearance since the viscosity of the blood means that the film of blood is not spread as thinly as normal.

- **The WBC**, neutrophil and basophil counts are increased in the majority of cases. Monocyte and eosinophil counts are much less often increased.

- The platelet count is elevated in about two-thirds of cases and platelet size is increased. Giant platelets or megakaryocyte fragments may be present. Bone Marrow
• The bone marrow is hypercellular. There is an increase in all cell lines, with a predominant increase in erythroid precursors, resulting in a decrease in the ratio of myeloid to erythroid cells (M:E ratio).
• Mild fibrosis is present in ~10 to 15% of cases.
• Absence of stainable iron in the marrow.

Diagnosis

• Diagnostic criteria laid down by PVSG (polycythemia vera study group) and WHO require demonstration of an elevated red cell mass as a must. This is practically not possible in most centres.
• So WHO has revised the criteria (2008) for the diagnosis of PV6.
• Accordingly there are 2 major and 3 minor criteria.

Major criteria

1. Hemoglobin level above 18.5g/dl for men and 16.5g/dl for females OR Hemoglobin or hematocrit > 99th percentile of reference range for age, sex, or altitude of residence OR elevated red cell mass >25% above mean normal predicted value.
2. Presence of JAK2 gene mutation (V617F) or other functionally similar.

Minor criteria

1. Bone marrow showing hypercellularity for age and trilineage growth (panmyelosis)
2. Subnormal Epo level
3. EEC (endogenous erythroid colonies)

Diagnostic combinations - Major criteria + one minor criterion and first major criterion + 2 minor criteria

Treatment

• Treatment is aimed at maintaining a normal blood count.
• The haematocrit should be maintained at about 45% and the platelet count below 400*10^9/L.

1) Venesection or phlebotomy –
   • On an average 350 ml of blood is removed twice weekly till the hematocrit is normalized.
   • The removed blood is discarded and is not used for transfusion as it may contain the clonal neoplastic cells.
   • As the hematocrit is normalized symptoms like headache gets better.
   • Phlebotomy normalises the viscosity and reduce the risk of thrombosis.
   • The advantage of phlebotomy is that it carries low risk and simple to perform.
   • The disadvantages are that it does not control the thrombocytosis and leucocytosis.
   • Hematocrit should be maintained at 45% in males and 42% in females
2) **Cytotoxic myelosuppression** –

The main indications are

a. When the need of phlebotomy is more than one every one or two months.

b. When the platelet counts are more than 800-1000, 000/cumm as there is risk of thrombosis and bleeding.

c. Patients having severe pruritis

3) **Hydroxyurea** is valuable in controlling the blood count and may need to be continued for many years.

4) **Phosphorus-32 therapy** – is the most effective myelosuppressive agent, and is only used for older patients with severe disease.

5) **Interferone** - suppresses excess proliferation in the marrow, valuable in controlling itching and it is the first-line drug for patients less than 40 yrs old.

6) **Aspirin** – reduces thrombotic complications

- Patients with PV should be properly hydrated when they develop gastrointestinal disorders. The spent phase occurs after about 15-20 years when the phlebotomy requirement decreases and the patient develops anaemia.
- The marrow fibrosis increases and spleen becomes greatly enlarged. The treatment during this phase is purely symptomatic including blood transfusions.
Hypersplenism

- Hypersplenism is a condition in which the spleen becomes increasingly active and then rapidly removes the blood cells. It can result from any splenomegaly.
- It is most common with splenomegaly secondary to portal hypertension and haematological disorders.

**Hypersplenism is a clinical syndrome characterized by:**

1. splenomegaly, although this may be only moderate
2. pancytopenia or a reduction in the number of one or more types of blood cells, neutropenia is less common than anemia and thrombocytopenia
3. normal production or hyperplasia of the precursor cells in the marrow or a so-called maturation arrest.
4. decreased red blood cells survival
5. decreased platelet survival.

- In hypersplenism, its normal function accelerates, and begins automatically to remove cells that may still be normal in function.
- Sometimes, the spleen will temporarily sequestre 90% of the body platelets and 45% of the red cells.

**Splenic Anatomy and Function**

- The spleen is the largest lymphoid organ in the body and is situated in the left hypochondrium. The normal spleen is slightly concave solid, dark, red organ measuring 3×8×12 cm, weighing 100-157 gm and frequently has fetal lobulation on its anterior edge.
- A thin peritoneal capsule encloses the organ and easily strips from it. It becomes thick and firm in any inflammatory or chronic infection process.
- **Histologically there are two main anatomical components:**
  1. The red pulp consists of sinuses lined by the endothelial macrophages and cords (spaces).
  2. The white pulp, which has a structure similar to lymphoid follicles.
- In many times, the spleen enlarges as it performs its normal functions.
- **The 4 most important functions of the spleen are:**
  1. Clearance of microorganisms from the blood stream.
  2. Synthesis of immunoglobulin G (1gG), properdin (an essential component of the alternate pathway of complement activation).
  3. Removal of abnormal red blood cells
  4. Embryonic haemopoiesis in certain conditions
- A normal spleen weighs 150 gm, approximately 11 cm in length, and is not easily palpable.
- Mild splenomegaly occurs if its length is from 11 to 15 cm and moderate splenomegally if its length is between 15 to 20 cm and massive splenomegally occurs if its length is more than 20 cm or cross the mid-line.
- Normally, the spleen does not pass beyond the anterior axillary line and lies along the 9th, 10th and 11th ribs in the mid axillary line.
- Spleen must be at least two or three times its usual size before it can be felt (clinically).

**Causes of Splenomegaly & hypersplenism:**

Causes of splenomegaly may be conveniently grouped into the following categories:

1. **Infectious causes:**
   - Viral infection: infectious mononucleosis, viral hepatitis, and HIV infection.
   - Bacterial infection: enteric fever, bacterial endocarditis, brucellosis, and Tuberculosis.
   - Parasitic infections: malaria, visceral leishmaniasis, and schistosomiasis
   - Fungal infections: histoplasmosis
   - Connective tissue disorders.

2. **Hyperplastic splenomegaly:**
   - Hereditary spherocytosis, symptomatic elliptocytosis, thalassemia, polycythemia Rubra vera, myelofibrosis, and Chronic myeloid leukaemia, Chronic Lymphocytic leukaemia and Lymphoma.

3. **Congestive splenomegaly:**
   - Liver cirrhosis, hepatic schistosomiasis "portal hypertension", hepatic vein obstruction, portal vein obstruction, splenic vein obstruction, congestive heart failure with increased venous pressure, and splenic artery aneurysm.

4. **Infiltrative splenomegaly:**
   - Gaucher's disease, amyloidosis, Niemann-Pick disease, histiocytosis, splenic tumours, and metastatic malignancy, Marble bone disease and Waldenstrom macroglobulinaemia.

5. **Micellaneous causes:**
   - Idiopathic non tropical splenomegaly, iron deficiency anaemia, B12 deficiency, thyrotoxicosis, berylliosis.

**Causes of gross splenomegaly**

1. Chronic infections: Malaria, Schistosomiasis, Kala-azar, and Brucella melitansis.
2. Myeloproliferative disorders like myelofibrosis
3. Lymphoproliferative disorders like lymphoma and chronic lymphatic leukaemia.
4. Adult type Gaucher's disease
5. Idiopathic non-tropical splenomegaly
6. Hyperactive malarial splenomegaly
7. Spleen cysts or tumours
8. Congestive splenomegaly
**Diagnosis of hypersplenism**

**A) Clinical findings:**

- The symptoms are of 3 types:
  - Symptoms related to the enlarged spleen such as abdominal fullness associated with feeling of heaviness and discomfort and pain in the left upper quadrant of the abdomen.
  - Haematological symptoms: Symptoms related to thrombocytopenia are common, such as, bruising and epistaxis. Symptoms related to anaemia are fatigue, weakness and pallor. Leucopenia leads to recurrent infections and oral ulcerations.
  - Symptoms and signs of the underlying diseases.

**B) Laboratory findings:** Anaemia, thrombocytopenia and leucopenia.

**C) Evaluation of splenic size:** with physical examination, abdominal Ultrasonography, CT and MRI.

**D) Evaluation of splenic function:** reduced red cell or platelet survival can be measured by labelling the patient's cells with Cr51, or the platelets with indium and measuring the rate of disappearance of radioactivity from the blood.

**Treatment**

- The diagnosis of hypersplenism is ultimately confirmed by response to splenectomy, although an immediate remission may be followed in the longer term by relapse with return of cytopenia.