* **Myeloproliferative Disorders I (Neoplasm)**
* Dr. Ibrahim. A. Adam
* **Objectives**
* Classify myeloproliferative disorders (neoplasm).
* discuss definition, pathophysiology, clinical features , laboratory findings and principles of treatment of chronic myeloid leukaemia
* Discuss definition, types, pathophysiology, clinical features, laboratory findings and diagnosis of polycythaemia Vera
* **Introduction**
* **Myeloproliferative Disorders (Neoplasm)**
* Clonal proliferations of pluripotent hematopoietic stem cells or very early precursors
* Maturation maintained
* Increased numbers of predominantly mature, normal-appearing cells
* Variable predisposition to transform to acute leukemia or myelofibrosis
* **Classification**
* **Old FAB classification:**
* Chronic myelogenous leukemia, *BCR-ABL1+* (CML)
* Polycythemia vera (P. Vera)
* Essential thrombocythemia (ET)
* Primary myelofibrosis (PMF)

 **P. Vera, ET and PMF are sometimes grouped together as the “Philadelphia-negative MPNs” or Non leukaemic MPNs**

* **Myeloproliferative Disorders (Neoplasm)**

**Disease Predominant Cells**

* CML: Granulocytes
* P. vera: Erythrocytes
* ET: Platelets
* PMF: Fibroblasts (driven by megakaryocytes)

 **\*There can be overlap between the MPNs**

* **Chronic Myelogenous Leukemia**
* 20% of all leukemias in U.S.
* Increasing incidence with age:
* Peak age 40- 60years
* However: Occurs at all ages
* Men > Women (~1.4 : 1)
* **CML: Pathophysiology**
* **CML:Molecular Pathogenesis**
* *ABL*: Tyrosine kinase involved in cell-cell signaling
* BCR-ABL fusion protein: More potent tyrosine kinase than normal ABL protein
* **Philadelphia Chromosome (t9;22)
*BCR-ABL* Rearrangement**
* **CML: Phases of Disease**
* Chronic Phase
* Accelerated Phase
* Blast Crisis
* **CML Chronic Phase**
* Most common stage at diagnosis
* Typically lasted ~3-4 years:
* May last <1 year, or >15 years
* Eventually transforms into more aggressive phase:
* Directly into blast crisis, *or:*
* Accelerated phase, then blast crisis

.

* **CML Chronic Phase: Clinical features**
* A symptomatic
* **Splenomegaly**
* May have systemic or hypermetabolic symptoms:
* Fever, night sweats, weight loss
* Hyperuricemia: gouty arthritis, renal stones
* **CML: Blast Crisis**
* Definition: >20% blasts in blood and/or marrow
* Most have myeloid phenotype (resemble AML)
* Some may have lymphoid phenotype( resemble acute lymphoblastic leukemia)
* **Investigations and Diagnosis**

**CBC + PBF**

* Very high WBC
* All stages of granulocyte maturation:
* Basophilia invariably present
* Thrombocytosis common
* Mild anemia common

 **\*PBF is almost diagnostic**

* **Investigations and Diagnosis**

Other tests to confirming the Diagnosis

* Presence of Ph and/or *BCR*/*ABL* rearrangement
* Bone Marrow ??

**\*Demonstration of Ph or *BCR/ABL***

 **rearrangement is *mandatory***

* **Treatment**
* Tyrosine kinase inhibitors (TKIs):
* Gleevec (imatinib mesylate)
* Hydroxyurea
* Interferon-a
* Bone marrow (stem cell) transplant
* **Polycythaemia**

**Definition**

Polycythemia: Increase in RBC mass (erythrocytosis)

* Increase in total RBC mass (*absolute* erythrocytosis [polycythemia]), *or*
* Decrease in plasma volume (*relative* erythrocytosis; “pseudopolycythemia”)
* **Polycythaemia**
* Primary polycythemia (poycthaemia vera):
* Independent of erythropoietin
* Secondary polycythemia: erythropoietin driven
* Physiologically appropriate = driven by hypoxemia
* Physiologically inappropriate = increased erythropoietin due to renal cysts, tumors
* **Polycythaemia Vera**
* Uncommon, but not *very* rare
* Slight male predominance
* Older age group: Majority of cases between 60 to 80
* Caucasians > African-Americans
* **P. Vera: Pathogenesis**
* Believed that all cases of P. vera related to

 mutation in JAK2 gene

* Low EPO level can be surrogate for JAK2

 mutation

* **P. Vera: Pathogenesis**
* **P. Vera: Symptoms & Signs**
* Increased blood viscosity:

 (Headache, dizziness, tinnitus, visual disturbances, dyspnea)

* Splenomegaly:
* Thrombotic complications
* Bleeding from mucous membranes or into skin
* Pruritis
* Hyperuricemia
* **P. Vera: Symptoms & Signs**
* Ruddy” skin:
* Hepatomegaly
* Hypertension:
* Dilated or engorged

 retinal vessels

* **P. Vera: Investigations**

**1. CBC and PBF**

* Hemoglobin to >18 g/dL
* RBC count: Commonly > 7 x 106/mL
* Hematocrit: Typically >60% for men, >55% for women
* Leukocytosis & thrombocytosis are common

**2. Bone marrow:**

**3. Molecular test** JAK mutation.

* **P. Vera: Diagnosis**
* Hemoglobin >18.5 g/dL in men, >16.5 g/dL in women, or other evidence of increased RBC volume
* Presence of JAK2 V617F or other functionally similar mutation
* Bone marrow biopsy showing hypercellularity with trilineage growth
* Serum EPO level below reference range
* **P. Vera: Treatment**
* Phlebotomy is cornerstone of treatment:
* Controls red cell mass by inducing iron deficiency
* May be only therapy required
* Others:
* Hydroxyurea
* Radioactive phosphorous (32P) no longer recommended.
* Interferon-a

Questions

Thank you