Myeloproliferative Disorders I (Neoplasm)

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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

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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 <u>all</u> cases of P. vera related to mutation in <u>JAK2 gene</u>
- ❑ 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 10^6/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 (^{32}P) no longer recommended.
- Interferon-a

Questions

Thank you