Myeloproliferative neoplasms

- Clonal haematopoietic disorders
- Proliferation of one of myeloid lineages
  - Granulocytic
  - Erythroid
  - Megakaryocytic
- Relatively normal maturation
Myeloproliferative neoplasms

- Polycythemia Vera
- Ch Myeloid leukemia (*BCR-ABL positive*)
- Essential Thrombocythemia
- Myelofibrosis
  - distinct diseases, have common features
  - Increased number of one or more cell lines
  - Hepatosplenomegaly
  - Hypercatabolism
  - Clonal marrow hyperplasia without dysplasia
  - Predisposition to evolve AML and fibrosis in the course
Myeloproliferative neoplasms

- MPD
  - PRV
  - ET
  - MF

- CML

- AML

- CMML

- MDS
  - RA
  - RARS
  - RAEB I
  - RAEB II
Bone marrow stem cell

Granulocyte precursors

Red cell precursors

Megakaryocytes

Reactive fibrosis

Chronic myeloid leukemia

Polycythemia rubra vera (PRV)

Essential thrombocytosis (ET)

Myelofibrosis

AML

70%

10%

10%

30%
POLYCYTHEMIA VERA

- Chronic, clonal myeloproliferative disorder characterized by an absolute increase in number of RBCs
- A single nucleotide JAK2 somatic mutation (JAK2V617F mutation) in the majority of PV patients
- 2-3 / 100000
- Median age at presentation: 55-60
- M/F: 0.8:1.2
### Diagnostic Criteria Table 1

<table>
<thead>
<tr>
<th>A1</th>
<th>Raised red cell mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>Normal O2 sat and low EPO</td>
</tr>
<tr>
<td>A3</td>
<td>Palpable spleen</td>
</tr>
<tr>
<td>A4</td>
<td>No BCR-ABL fusion</td>
</tr>
<tr>
<td>B1</td>
<td>Thrombocytosis &gt;400 x 10^9/L</td>
</tr>
<tr>
<td>B2</td>
<td>Neutrophilia &gt;10 x 10^9/L</td>
</tr>
<tr>
<td>B3</td>
<td>splenomegaly</td>
</tr>
<tr>
<td>B4</td>
<td>Endogenous erythroid colonies</td>
</tr>
</tbody>
</table>

A1+A2+either another A or two B establishes PV
## Diagnostic criteria Table 2

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased RBC mass</td>
<td>Thrombocytosis &gt; $400 \times 10^3/\mu L$</td>
</tr>
<tr>
<td>$\geq 36 \text{ mL/kg in men}$</td>
<td>Leukocytosis &gt; $12 \times 10^3/\mu L$</td>
</tr>
<tr>
<td>$\geq 32 \text{ mL/kg in women}$</td>
<td>Leukocyte alkaline phosphatase activity &gt; 100 (no fever or infection)</td>
</tr>
<tr>
<td>Arterial $O_2$ saturation $\geq 92%$</td>
<td>Serum $B_{12} &gt; 900 \text{ pg/mL (}&gt;660 \text{ pmol/L})$ or unsaturated $B_{12}$-binding capacity $&gt; 2200 \text{ pg/mL (}&gt;1620 \text{ pmol/L})$</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
</tr>
</tbody>
</table>

*Diagnosis is polycythemia vera if patient has all major criteria or the first two major criteria plus any two minor criteria.

Polycythemia

- True / Absolute
  - Primary Polycythemia: low Epo
  - Secondary Polycythemia
    - Epo dependent
      - Hypoxia dependent/independent

- Relative
  - Reduction in plasma volume
Clinical features

- Plethora
- Splenomegaly
- Generalized pruritus (after bathing)
- Unusual thrombosis (e.g., Budd-Chiari syndrome) and Haemorrhage
- Erythromelalgia (acral dysesthesia and erythema)
- Vasomotor
  - Headache
  - Lightheadedness
  - Syncope
  - Transient visual disturbances (e.g., amaurosis fugax, scintillating scotomata, ocular migraine)
## PVR symptoms and pathogenesis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, dizziness, lethargy, blurred vision, loss of concentration, numbness, tingling</td>
<td>Increased cerebral blood viscosity</td>
</tr>
<tr>
<td>Weight loss, night sweats, hyperuricaemia and gout</td>
<td>Hypermetabolic state</td>
</tr>
<tr>
<td>Bleeding tendency</td>
<td>Abnormal platelet function</td>
</tr>
<tr>
<td>Pruritus after bath</td>
<td>Increased histamine?</td>
</tr>
</tbody>
</table>
# PVR symptoms and pathogenesis 2

<table>
<thead>
<tr>
<th>Reddis-purple face, nose, fingers, blood-shotted eyes, deep-raspberry-red mucous membrane</th>
<th>Splenic pain</th>
<th>Splenomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular and peripheral vascular disease, AMI, DVT</td>
<td>Increased whole blood viscosity</td>
<td></td>
</tr>
</tbody>
</table>
Comorbidities related to the disease

- Hypertension
- Gout
- Leukaemic transformation
- Myelofibrosis
Causes of secondary polycythemia

- **ERYTHROPOIETIN (EPO)-MEDIATED**
  - Hypoxia-Driven
    - Chronic lung disease
    - Right-to-left cardiopulmonary vascular shunts
    - High-altitude habitat
    - Chronic carbon monoxide exposure (e.g., smoking)
    - Hypoventilation syndromes including sleep apnea
    - Renal artery stenosis or an equivalent renal pathology
  - Hypoxia-Independent (Pathologic EPO Production)
    - Malignant tumors
      - Hepatocellular carcinoma
      - Renal cell cancer
      - Cerebellar hemangioblastoma
    - Nonmalignant conditions
      - Uterine leiomyomas
      - Renal cysts
      - Postrenal transplantation
      - Adrenal tumors

- **EPO RECEPTOR–MEDIATED**
  - Activating mutation of the erythropoietin receptor

- **DRUG-ASSOCIATED**
  - EPO Doping
  - Treatment with Androgen Preparations
Hb > 16.5 gm/dL, or a borderline elevated Hb with any PV-related feature, or an interim Hb increase of > 2 gm/dL

Yes

Check serum EPO

No

Recheck Hb in 3 mo

Low serum EPO

Normal serum EPO

Elevated serum EPO

Confirm low value

PV-related features

PV

Present

Obtain bone marrow biopsy

Positive

PV

Non-diagnostic

Obtain EEC assay

Positive

PV

Negative

Evaluate for secondary erythrocytosis

Negative

Obtain EEC assay

Secondary erythrocytosis

Negative

Repeat Hb in 3 months

Positive

PV
TOTAL RBC VOLUME ($^{51}$Cr - RBC + $^{125}$I-albumin)

- Normal
- Increased (Male: $\geq 38$ mL/kg) (Female: $\geq 32$ mL/kg)

Dx: RELATIVE ERYTHROCYTOSIS

**ARterial O$_2$ Saturation**

- Normal ($\geq 92\%$)
- Reduced (<$92\%$)

**COHb Determination**

- Smoker
- Nonsmoker

Elevated

Dx: SMOKERS' POLYCYTHEMIA

Normal

IVU/RENAL SONOGRAPHY

LIVER/SPLEEN SCAN/ABDOMINAL CT

CT OF HEAD

Dx: SECONDARY ERYTHROCYTOSIS

Hb

**Determine cause**

- Normal
- Abnormal

Dx: HEMOGLOBINOPATHY

Presumptive Dx: POLYCYTHEMIA VERA

**WBC PLATELETS**
LEUKOCYTE ALKALINE PHOSPHATASE
SERUM $B_{12}$ + BINDERS
BM MYELOID/MEGAKARYOCYTIC ELEMENTS

Normal

Dx: PRIMARY ERYTHROCYTOSIS

Increased

Dx: POLYCYTHEMIA VERA

**SPECIAL CONFIRMATORY STUDIES**

- ERYTHROPOIETIN ASSAY (blood)
- BM COLONY GROWTH (erythropoietin requirement)

Low/absent

Increased

*Perform only when indicated.*
Treatment

- The mainstay of therapy in PV remains phlebotomy to keep the hematocrit below 45 percent in men and 42 percent in women.

- Additional hydroxyurea in high-risk pts for thrombosis (age over 70, prior thrombosis, platelet count >1,500,000/microL, presence of cardiovascular risk factors).

- Aspirin (75-100 mg/d) if no CI.

- IFNa (3mu three times per week) in patients with refractory pruritus, pregnancy.

- Anagrelide (0.5 mg qds/d) is used mainly to manage thrombocytosis in patients refractory to other treatments.

- Allopurinol.

- TKIs are in studies.
Ionizing radiation

<table>
<thead>
<tr>
<th>Latent Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomic bomb survivors</td>
</tr>
<tr>
<td>Ankylosing spondylitis pts</td>
</tr>
</tbody>
</table>

No evidence of other genetic factors
Chemical have not been associated with CML

Incidence 1-1.5/100,000 population
Male predominance
Presentation

Insidious onset

Anorexia and weight loss

Symptoms of anaemia

Splenomegaly – maybe massive

Pt. maybe asymptomatic
Epidemiology of CML

- Median age range at presentation: 45 to 55 years
- Incidence increases with age
  - 12% - 30% of patients are >60 years old
- At presentation
  - 50% diagnosed by routine laboratory tests
  - 85% diagnosed during chronic phase
Clinical Course: Phases of CML

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 4–6 years stabilization</td>
<td>Median duration up to 1 year</td>
</tr>
</tbody>
</table>

Terminal phase
Philadelphia Chromosome
The Philadelphia Chromosome: t(9;22) Translocation

Fusion protein with tyrosine kinase activity
t(9;22)(q34;q11) with 9q+ deletion

nuc ish 9q34(ABLx2),22q11(BCRx2)(ABLconBCRx1)
karyotype: 46,XY,t(9;22)(q34;q11)
Mitochondrien

Rapamycin

Everolimus

FTIs

Imatinib
History of CML Treatment

• Chemotherapy to reduce WCC - Hydroxyurea
• Interferon based treatment
• Allogeneic bone marrow transplant
• Molecular therapy - Imatinib
Mechanism of Action of Imatinib

Goals of CML Therapy

- Hematologic response
- Cytogenetic response
  Complete cytogenetic response
- Molecular response
  Undetectable $BCR-ABL$
Evolution of treatment goals

<table>
<thead>
<tr>
<th>HR</th>
<th>MCR</th>
<th>CCR</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HU</td>
<td>IFN</td>
<td>Imatinib</td>
<td>BMT</td>
</tr>
</tbody>
</table>
Essential Thrombocythaemia (ET)

- Clonal MPN
- Persistent elevation of Plt>600 x109/l
- Poorly understood
- Lack of positive diagnostic criteria
- 2.5 cases/100000
- M:F 2:1
- Median age at diagnosis: 60, however 20% cases <40yrs
Investigations

ET is a diagnosis of exclusion

- Rule out other causes of elevated platelet count

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ADULTS</th>
<th>PLATELET COUNT OF 1 MILLION/μL OR ABOVE</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>22%</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Rebound thrombocytosis</td>
<td>19%</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>Tissue damage (surgery)</td>
<td>18%</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>13%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6%</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>5%</td>
<td>NS</td>
<td>4%</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>4%</td>
<td>NS</td>
<td>19%</td>
</tr>
<tr>
<td>Postsplenectomy</td>
<td>2%</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Blood loss</td>
<td>NS</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>Primary thrombocytemia</td>
<td>3%</td>
<td>14%</td>
<td>0%</td>
</tr>
</tbody>
</table>

NS = not specified.
Diagnostic criteria for ET

- Platelet count >600 x 10⁹/L for at least 2 months
- Megakaryocytic hyperplasia on bone marrow aspiration and biopsy
- No cause for reactive thrombocytosis
- Absence of the Philadelphia chromosome
- Normal red blood cell (RBC) mass or a HCT <0.48
- No evidence of myelofibrosis
- No evidence of MDS
Thrombocytosis

Look for conditions known to be associated with reactive thrombocytosis

**Identified**
- Consider reactive thrombocytosis

**Not identified**
- Determine duration of thrombocytosis
  - Unknown or chronic
    - Check serum ferritin, C-reactive protein level
      - Low serum ferritin
        - Iron deficiency
          - Consider reactive thrombocytosis
      - Howell-Jolly bodies
        - Hyposplenism
          - Consider reactive thrombocytosis
      - Increased C-reactive protein level
        - Inflammatory process
          - Consider reactive thrombocytosis
  - Acute
    - Consider reactive thrombocytosis

No abnormalities
- Proceed with bone marrow biopsy
ETT
Therapy of ET based on the risk of thrombosis

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Low risk*</th>
<th>High risk†</th>
<th>Intermediate risk‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+Extreme thrombocytosis</td>
</tr>
<tr>
<td>Cytoreductive therapy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Aspirin therapy</td>
<td>Optional</td>
<td>Yes</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

*Age <60 years and no history of thrombosis, extreme thrombocytosis (platelet count ≥1,500,000/µL), or cardiovascular risk factors (smoking, hyperlipidemia).
†Age ≥60 years or a history of thrombosis.
‡Neither low risk nor high risk.

Thromboreductin (Anagrelid) in use
Blood smear signs in MPS
Myelofibrosis

- Myelofibrosis is rare: < 2 of 100,000; age of 50-70
- *Myelofibrosis is a disorder in which fibrous tissue replaces the blood-producing cells in the bone marrow*
- Consequently, red blood cell production decreases, anemia develops, becoming progressively more severe.
- As myelofibrosis progresses, the number of white blood cells may increase or decrease, and the number of platelets typically decreases.
- weakness, fatigue, weight loss, and a general feeling of illness (malaise).
- Fever and night sweats may occur.
- The liver and spleen often enlarge as they try to take over some of the job of making blood cells. Enlargement of these organs may cause pain in the abdomen and may lead to portal hypertension and bleeding from esophageal varices.
myelofibrosis

MPS proliferative phase

Fibrotic phase
MDS/MPS

- New WHO classification „the blue book”
- CMML
- JCMML
- MDS/MPS unclassifiable
CMML
Therapy for myelofibrosis

Mostly at study level:

- BMT with reduced conditioning