**Myeloproliferative Disorders**

**Classification**

1. **Classic Myeloproliferative neoplasms (MPN):** include Polycythemia vera, Chronic Myelogenous Leukemia, Essential Thrombocythemia, Primary Myelofibrosis, Chronic Neutrophilic Leukemia, Chronic Eosinophilic Leukemia and Mast Cell Disease
2. **Atypical MPNs** include Chronic Myelomonocytic Leukemia, Juvenile Myelomonocytic Leukemia, Atypical CML and unclassifiable MDS (MDS/MPN)

**Classical Myeloproliferative Disorders**

1. Polycythemia vera - can elevate all hematologic cell lines
2. Chronic myelogenous leukemia - usually affects granulocytes and platelets Essential thrombocythemia - usually affects platelets
3. Primary myelofibrosis
4. Chronic Neutrophilic Leukemia
5. Chronic Eosinophilic Leukemia
6. Mast Cell Disease

**Common themes**

- Abnormal driver of cellular proliferation in involved cell lines.
- Loss of apoptosis in those lines.
- Increased circulation of cells or cellular elements.
- Signs and symptoms related to cells that are abnormally increased.
- All can convert to acute leukemia
Inheritance and Clonality

- Several studies have demonstrated familial clustering for PV, ET and PMF with evidence of familial involvement. One study of 458 apparent “sporadic” cases showed that 8.7, 6.0 and 8.2% of patients had affected relatives.
- Evidence of monoclonality is more complicated. Some patients with ET appear to have polyclonal hematopoiesis, even with the JAK 2 mutation. While some normals have been demonstrated to have monoclonal

Common Symptoms and Signs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Splenomegaly</td>
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<tr>
<td>Malaise</td>
<td>Abnormal blood counts</td>
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<tr>
<td>Early satiety</td>
<td>Abnormal peripheral blood smear</td>
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<tr>
<td>Weight loss</td>
<td>Hyperuricemia and gout</td>
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<tr>
<td>Fever</td>
<td>Thrombosis or bleeding</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Bone pain</td>
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<td>Pruritis</td>
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**Polycythemia (rubra) Vera**

**Proposed criteria for PV:**
- **Major criteria:** Hemoglobin >18.5 g/dl in men, 16.5 a/dl in women or other evidence of increased red cell volume*Presence of JAK2 617V>F or other functionally similar mutation such as JAK2 exon 12 mutation
- **Minor criteria:** Bone marrow biopsy showing hypercellularity for age growth (panmyelosis) with prominent erythroid, and megakaryocytic proliferation. Serum endogenous erythroid colony formation in vitro.
- Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria.

Hemoglobin or hematocrit greater than 99th percentile of method-specific reference range for age, sex, altitude of residence or hemoglobin greater than 17 g/dl in men, 15 g/dL in women if associated with a documented and sustained 2 g/dl from an individual’s baseline value that can not be attributed to correction of iron deficiency or elevated red cell mass greater than 25 percent above mean normal predicted value.

**Diagnosis of P. vera**
- Increased RBC count and Hgb levels (except when iron deficient).
- Elevated RBC mass
- Panmyelosis in the bone marrow
- Low EPO level
- Positive JAK 2 mutation
- May also have increased platelets and granulocytes

**Therapy of p. vera**
- Phlebotomy
- Anticoagulation
- Chemotherapy - antimetabolites-hydroxyurea, alkylating agent - chlorambucil (no longer used)
- P 32 (also no longer used)
- AK inhibitors - ruxolotinib

**Complications of Disease or Therapy**
- a) Erythromelalgia
- b) Thrombotic events
- c) Iron deficiency
- d) Transformation:
  - Myelofibrosis
  - Acute leukemia

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*Image: Erythromelalgia*
Recent Case at St. Paul

- 35 y/o previously healthy man
- 9-month history of tachycardia and dyspnea on exertion
- Dec. 2011, dyspnea becomes more severe
- Hospitalized in Miami when found to have evidence of acute and chronic P.E.s
- Evidence of pulmonary hypertension and a possible clot in RV outflow tract
- CBC: WBC 13,000 with increased granulocytes, Hgb 16 gms and platelets 550,000 positive for JAK 2 mutation

Essential Thrombocytemia

Diagnostic criteria of the PVSG
The first large-scale attempt to diagnose ET in a prospective manner was taken by the Polycythemia Vera Study Group (PVSG). In order to qualify for this diagnosis, the patient had to fulfill all of the following criteria:

1) Platelet count >600,000/microL (>1,000,000/microL for entering therapeutic protocol).
2) Megakaryocytic hyperplasia on bone marrow aspiration and biopsy.
3) Absence of the Philadelphia chromosome
4) Absence of infection, inflammation and other causes for reactive thrombocytosis Normal red blood cell (RBC) mass or a hemoglobin concentration <13 g/dL
5) Presence of stainable iron in a bone marrow aspiration or <1g/dL increase in hemoglobin concentration after a one-month trial of oral iron therapy.
6) Patients were also excluded if there was collagen fibrosis involving more than one-third of the cross-sectional area of the bone marrow biopsy, or if there were lesser degrees of collagen fibrosis in the presence of splenomegaly and a leuкоerythroblastic blood picture.
7) These latter patients had a presumptive diagnosis of the cellular phase of PM
E.T.-demographics

- 2.5 new cases per 100,000/year.
- M:F : 1:2
- In U.S., approx. 6000 new cases/year.
- Median age at onset : 60 years
- At least half are asymptomatic at diagnosis
- JAK 2 mutation positive in only 40-50% of cases
- Other reported mutations: CALR in 15-25% and MPL in up to 4%

E.T. symptoms and complications

- **Vasomotor symptoms**: Headache, Lightheadedness, Syncope, Atypical chest pain, Acral paresthesia, Livedo reticularis
- **Erythromelalgia**: burning pain of the hands or feet associated with erythema and warmth.
- **Transient visual disturbances** (eg, amaurosis fugax, scintillating scotomata, ophthalmic migraine).
- **Thrombosis**: up to 18% at presentation.
- **Hemorrhage**: up to 26% at presentation

E.T. Therapy

- Antiplatelet agents - Less than 325 mg. aspirin/day
- Hydroxyurea
- Anagrelide
- Radioactive phosphorus (no longer used)

**Reactive thrombocytosis**

**Major causes of reactive thrombocytosis:**

1) **Nonmalignant hematologic conditions**: Acute blood loss, Acute hemolytic anemia, Iron deficiency anemia, Treatment of vitamin B12 deficiency, Rebound effect after treatment of ITP, Rebound effect after ethanol-induced thrombocytopenia.
2) **Malignant conditions**: Metastatic cancer, Lymphoma, Rebound effect following use of myelosuppressive agents.
3) **Acute and chronic inflammatory conditions**: Rheumatologic disorders, vasculitis, Inflammatory bowel disease, Celiac disease, Functional and surgical asplenia, POEMS syndrome (osteosclerotic myeloma).
4) **Tissue damage**: Thermal burns, Myocardial infarction, Severe trauma, Acute pancreatitis, Post-surgical period, especially post-splenectomy, Coronary artery bypass procedure.
5) **Infections**: Chronic infections, Tuberculosis.
6) **Exercise**
7) **Chronic renal disease**: Renal failure, Nephrotic syndrome.
8) **Reaction to medications**: Vincristine, Epinephrine, Interleukin-1B, All-trans retinoic acid
Causes of Bone Marrow Fibrosis

Hematological disorders

- Myeloid disorders
  - Acute myeloid leukemia
  - Acute myelofibrosis/acute megakaryocytic leukemia
  - Chronic myeloid leukemia
  - Myelodysplastic syndrome
  - Myelofibrosis with myeloid metaplasia
  - Polycythemia vera
  - Myelodysplastic/myeloproliferative disorder
  - Chronic myelomonocytic leukemia
  - Eosinophilic leukemia
  - Systemic mast cell disease
- Lymphoid disorders
  - Acute lymphoid leukemia
  - Hairy cell leukemia
  - Hodgkin’s disease
  - Non-Hodgkin’s lymphoma
  - Multiple myeloma

Non-hematological conditions

- Metastatic cancer
- Chronic granulomatous infections including tuberculosis
- Gray platelet syndrome
- Systemic lupus erythematosus and other connective tissue diseases
- Vitamin D-deficiency rickets
- Renal osteodystrophy

Primary Myelofibrosis

Proposed revised WHO criteria for primary myelofibrosis

Major criteria:

- Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis or in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease)
- Not meeting WHO criteria for PV, CML, MDS, or other myeloid neoplasm.
- Demonstration of JAK2 617V>F or other clonal marker (e.g., MPL 515W>L/K), or in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases.

Minor criteria:

- Leukoerythroblastosis
- Increase in serum lactate dehydrogenase level
- Anemia
- Palpable splenomegaly

Diagnosis requires meeting all 3 major criteria and 2 minor criteria.
Pathogenesis of Myelofibrosis

Primary Myelofibrosis Treatment

1) Based on risk profile - high risk: Hgb < 10, constitutional symptoms
2) Allogeneic bone marrow or stem cell transplant
3) Androgens, steroids or Erythropoietin
4) Transfusion
5) Drugs: Hydroxyurea, Interferon, Anagrelide, Danazol, Thalidomide, Lenalidomide
6) Splenectomy - very risky
7) Radiation - more effective for extramedullary hematopoiesis
8) JAK 2 inhibition - Ruxolitinib (Jakafi) a specific JAK-STAT pathway inhibitor

Change in Spleen Volume

![Graph A: Patients with 25% Reduction in Spleen Volume (%)](image)

Odds ratio, 134.4 (95% CI, 18.0–1004.9)
P < 0.001

![Graph B: Change in Spleen Volume from Baseline (%)](image)

Individual Patients

![Graph C: Median Change in Spleen Volume from Baseline (%)](image)

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Baseline</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
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<tbody>
<tr>
<td>Ruxolitinib</td>
<td>149</td>
<td>139</td>
<td>69</td>
<td>16</td>
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<tr>
<td>Placebo</td>
<td>132</td>
<td>106</td>
<td>46</td>
<td>13</td>
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**Myeloproliferative Disorder**

1) Most common MPD, 2nd most common leukemia in adults, 15-20% of cases. Incidence is 1-2 cases/100,000/year

2) Median age at diagnosis 50-60 years

3) 3 distinct phases:
   - Chronic, stable
   - Accelerated
   - Blast crisis

**FISH probe for t(9;22)**

*Interphase fluorescence in situ hybridization (FISH) images of normal and t(9;22) positive nuclei*

*The dual-color ABL (green) and BCR (red) probes span their respective breakpoint regions, producing two red and two green signals in a normal nucleus (on the left). In the t(9;22) cell (on the right), the single red and green signals correspond to the normal ABL and BCR genes, respectively, while the two yellow-white fusion signals correspond to the Ph chromosome and the reciprocal balanced translocation product (derivative chromosome 9).*

*Photo courtesy of Athena Cherry, Ph.D.*

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**Chronic Myelogenous Leukemia**

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3) 3 distinct phases:
   - Chronic, stable
   - Accelerated
   - Blast crisis

**Philadelphia chromosome in chronic myeloid leukemia**

![Diagram of chromosome changes in CML](image-url)
Chronic Stable Phase

- Elevated granulocyte count, mostly mature but with some left shift.
- Increased basophils
- Splenomegaly
- Increased platelets
- Single genetic change

Accelerated Phase Criteria

<table>
<thead>
<tr>
<th>MD Anderson</th>
<th>WHO</th>
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</thead>
</table>
| - PB blasts > 15% PB blasts + pro > 30%  
- PB baso > 20%  
- Platelets <100,000/μL not related to tx  
- Cytogenic evolution | - PB or BM blasts 10-19% PB basophils > 20%  
- Platelets <100,000/μL, unrelated to tx  
- Cytogenic evolution  
- Platelets >100,000/μL unresponsive to therapy  
- Progressive splenomegaly and increasing WBC unresponsive to therapy |

CML Blast Crisis

- ≥ 20 percent peripheral blood or bone marrow blasts. (70% myeloid, 20% lymphoid, undifferentiated)
- Large foci or clusters of blasts on the bone marrow biopsy.
- Presence of extramedullary blast infiltrates (eg, myeloid sarcoma also known as granulocytic sarcoma or chloroma).

CML -Treatment

- Hydroxyurea
- TKI’s: Imatinib, dasatinib, nilotinib, ponatinib Interferon
- Allogeneic stem cell transplant
- Radiation
- Splenectomy

Myeloproliferative Disorder