Chronic Myeloid Leukemia \( BCR-ABL1 \) Positive (CML)

A myeloproliferative neoplasm caused by translocation of \( BCR-ABL1 \), characterized by consistent neoplastic proliferation of granulocytic cells with variable degrees of thrombocytosis

Incidence: 1-2 cases per 100,000 population, affects all ages from teenagers to adults, incidence increases with age, slight male predominance

Biological course: progression from chronic phase, to accelerated phase, to blast phase

Initial presentation: either asymptomatic or fatigue, malaise, weight loss, night sweat, anemia, splenomegaly

Progression to accelerated and blast phases is characterized by decline performance status, progressive anemia, thrombocytopenia, more severe constitutional symptoms

**Morphology: Blood:** Granulocytosis: usually marked, with left-shift containing all stages of neutrophilic granulocytes. Thrombocytosis. Basophilia always present, eosinophilia common

**Bone marrow:** Hypercellularity, frequently 100%. Marked granulocytic proliferation with left-shifted maturation, myelocyte bulge (increase of myelocytes), increased paratrabecular myeloid cuff (> 5 layers). Marked megakaryocytic hyperplasia and atypia with small unilobated nuclei (dwarf). Basophilia present but may be less obvious than blood due to numerous granulocytes. Erythropoiesis is relatively reduced

**Spleen:** Splenomegaly present in nearly all cases. Red pulp infiltration of neoplastic bone marrow cells (granulocytes, megakaryocytes)

<table>
<thead>
<tr>
<th>% Blasts</th>
<th>Chronic phase</th>
<th>Accelerated phase</th>
<th>Blast phase</th>
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</thead>
<tbody>
<tr>
<td>Blood</td>
<td>&lt;10% (usually &lt;2%) ( B ) blasts</td>
<td>10-19%</td>
<td>≥ 20% blasts</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>&lt;10% (usually &lt;5%) ( B ) blasts</td>
<td>10-19%</td>
<td>≥ 20% blasts</td>
</tr>
</tbody>
</table>

**Clinical and pathologic criteria for accelerated phase (any of the following)**

- WBC >10,000, persistent or increase, unresponsive to therapy
- Splenomegaly, persistent or increase, unresponsive to therapy
- Platelets >1000, persistent, unresponsive to therapy
- Platelets <100, persistent, unresponsive to therapy
- Basophils >20% in blood
- Blasts 10-19% in blood or bone marrow
- Cytogenetics with additional "major route abnormalities": additional Ph chromosome, Trisomy 8, isochromosome 17q, Trisomy 19, 3q26 abnormalities, complex karyotype
- During therapy: New clonal chromosome abnormalities emerge in Ph+ cells

**Phenotype:** Granulocytes: Left-shift, CD56+ in 10% cases

Blast crisis: AML (75%): CD13+, CD33+, CD34+, CD117+, HLA-DR+

B-ALL (25%): CD10+/-, CD19+, CD20+, CD22+, CD79a+, TdT+

**Genetics:** All cases have t(9;22)(q34;q11.2) \( BCR-ABL1 \) or variant (such as 3-way translocation or crypt translocation affecting \( ABL1 \))

Philadelphia chromosome: a small chromosome 22 – derivative chr 22

\( BCR-ABL1 \) fusion protein: p210 (\( BCR \) breakpoint at major breakpoint cluster region – exons12-16) (in contrast to p190 in B-ALL)
P230 in rare cases (BCR breakpoint at minor breakpoint cluster region – exons 1-2). More prominent neutrophilic maturation, conspicuous thrombocytosis

Function of BCR-ABL1 protein: Increased ABL1 tyrosine kinase activity, resulting in activation of multiple downstream signal transduction pathways including JAK/STAT, PI3K/ARK, RAS/MEK, NF-kB

ABL kinase mutations: resistance to early generation tyrosine kinase inhibitors

**Diagnosis:** Chronic phase: blood morphology, flow cytometry (for blasts), demonstration of BCR-ABL1 (FISH/chromosome, rtPCR)

Accelerated and blast phases: bone marrow biopsy, flow cytometry (for blasts), demonstration of BCR-ABL1 (FISH/chromosome, rtPCR)

**Treatment:** Tyrosine kinase inhibitors (TKI): small molecules that block the ATP binding site on ABL kinase domain
- First generation TKI: Imatinib (Gleevec)
- Second generation TKI: Dasatinib
- Third generation TKI: Ponatinib

**Drug resistance:** ABL kinase mutations (most common T315I, only sensitive to 3rd generation TKI)

**Disease monitor:** Blood count, bone marrow biopsy, chromosome, FISH, quantitative rtPCR

**Prognosis:** 5-year progression survival and overall survival 80-95% with Gleevec

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic response</td>
<td>Normal blood counts</td>
</tr>
<tr>
<td>Complete cytogenetic response (CCyR)</td>
<td>Absence of Ph chromosome</td>
</tr>
<tr>
<td>Major molecular response (MMR)</td>
<td>3 log reduction of BCR-ABL1</td>
</tr>
<tr>
<td>Complete molecular response (CMR)</td>
<td>4.5 log reduction of BCR-ABL1</td>
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</tbody>
</table>

**Polycythemia Vera (PV)**

Increased red blood cells due to neoplastic bone marrow erythroid production driven by JAK2 mutation

Also affects megakaryocytes (thrombocytosis) and myeloid lineage (leukocytosis, less degree)

Affects mostly older adults (median age 60)

Incidence: 0.84 new cases in 100,000 population

Clinical features include venous and arterial thrombosis, headache, dizziness, visual disturbance, paresthesia, pruritus, erythema when exposed to heat, plethora, splenomegaly

**Clinical phases:** Polycythemic phase (initial phase): Increased red cell mass, hemoglobin, and hematocrit

Spent phase (post-PV myelofibrosis): anemia and cytopenia, bone marrow fibrosis, hypersplenism

Blast phase: rare, transform to acute myeloid leukemia

**Morphology: Blood:** Erythrocytosis. Red blood cells are normocytic and normochromic. Thrombocytosis nearly always present. Neutrophilia may or may not be present.

**Bone marrow:** Hypercellular bone marrow. Prominent erythroid hyperplasia. Megakaryocytes are increased in number, and show hyperchromatic and hyperlobated nuclei. Myelopoesis may or may not increase. Blasts are not increased

Spent phase: Bone marrow morphology similar to primary myelofibrosis (post-PV myelofibrosis)

Blast phase: >=20% blasts in bone marrow and/or blood
**Phenotype:** Increased bone marrow NRBC by immunohistochemistry for glycophorin A and E cadherin

**Genetics:** JAK2 V617F mutation in 97%, JAK2 exon 12 mutations in remaining cases

**Prognosis:** Indolent. More aggressive if transform to spent phase or blast phase

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**Diagnostic criteria of polycythemia vera**

<table>
<thead>
<tr>
<th>Diagnosis of PV requires all three major criteria or first 2 major criteria + minor criteria (or major criteria 1 and 3 + minor criteria in sustained high erythrocytosis)</th>
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</thead>
<tbody>
<tr>
<td><strong>Major criteria:</strong></td>
</tr>
<tr>
<td>1. Hemoglobin &gt;16.5 g/dL in men, &gt;16.0 g/dL in women</td>
</tr>
<tr>
<td>2. Typical bone marrow morphology for PV</td>
</tr>
<tr>
<td>3. Presence of JAK2 V617F or JAK2 exon 12 mutation</td>
</tr>
<tr>
<td><strong>Minor criteria:</strong></td>
</tr>
<tr>
<td>1. Subnormal serum erythropoietin level</td>
</tr>
</tbody>
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**Diagnostic criteria of post-PV myelofibrosis**

<table>
<thead>
<tr>
<th>Requires both “required criteria” and at least 2 “additional criteria”</th>
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</thead>
<tbody>
<tr>
<td><strong>Required criteria:</strong></td>
</tr>
<tr>
<td>1. History of PV</td>
</tr>
<tr>
<td>2. Bone marrow reticulin fibrosis MF2 or above</td>
</tr>
<tr>
<td><strong>Additional criteria:</strong></td>
</tr>
<tr>
<td>1. Anemia</td>
</tr>
<tr>
<td>2. Leukoerythroblastosis</td>
</tr>
<tr>
<td>3. Increased splenomegaly</td>
</tr>
<tr>
<td>4. Develop at least 2 of the following:</td>
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<tr>
<td>- Significant weight loss</td>
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<tr>
<td>- Night sweat</td>
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<tr>
<td>- Unexplained fever</td>
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**Essential Thrombocythemia (ET)**

A myeloproliferative neoplasm affecting primarily megakaryocyte lineage with sustained thrombocytosis

- Incidence: 1.03 new cases in 100,000 population
- Affects primarily older adults with slight female preponderance
- >50% asymptomatic. Symptoms include thrombotic or bleeding manifestations (TIA, digital ischemia, gangrene, splenic or hepatic vein thrombosis, GI bleeding, upper respiratory tract bleeding)
- Majority patients have no splenomegaly, leukocytosis, or erythrocytosis

**Morphology: Blood:** Thrombocytosis, usually very high. WBC and RBC are usually normal

**Bone marrow:** Normocellular or slightly hypercellular bone marrow. Prominent megakaryocytic hyperplasia and atypia. Megakaryocytes are large to giant in size, with abundant mature cytoplasm and deeply lobated and hyersegmented nuclei (“staghorn-like”). Myelopoiesis and erythropoiesis are usually normal

**Phenotype:** No specific phenotype

**Transformation:** Post-ET myelofibrosis (~10%). Acute myeloid leukemia (rare)

**Genetics:** JAK2 V617F mutation in ~55%, CALR mutation in ~30%, MPL mutation in ~3%, mutually exclusive. No mutations in ~12%

**Prognosis:** Favorable
**Diagnosis of ET requires all major criteria or first 3 major criteria + 1 minor criteria**

**Major criteria:**
1. Platelet count >450 x 10⁹/L
2. Typical bone marrow morphology for ET
3. CML, PV, PMF and other MPN excluded
4. JAK2, CALR, or MPL mutation

**Minor criteria:**
1. Presence of clonal markers (cytogenetics or molecular)
2. Absence of reactive thrombocytosis

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**Primary Myelofibrosis (PMF)**

Neoplastic proliferation of megakaryocytes and granulocytes with bone marrow fibrosis

**Biological course:** A stepwise evolution from prefibrotic (early) stage to fibrotic (late) stage

**Incidence:** 0.47 new cases in 100,000 population

Affects primarily older adults, men and women equally

Constitutional symptoms (fatigue, dyspnea, weight loss, night sweat, fever, cachexia), splenomegaly (90%), hepatomegaly (40%), 30% asymptomatic

**Morphology: Blood:** Leukoerythroblastosis, tear drop RBCs, leukocytosis, thrombocytosis, anemia, myeloblasts <10%

**Bone marrow prefibrotic stage:** Hypercellular bone marrow. Myeloid hyperplasia. Megakaryocyte hyperplasia and marked atypia with bulbous or balloon-shaped (“cloud-like”) nuclei. Reticulin fibrosis may or may not be present (MF 0-1)

**Bone marrow fibrotic stage:** Normocellular, hypocellular, or focally hypercellular. Diffuse reticulin fibrosis (MF 2-3) and often collagen fibrosis. Patches of hematopoiesis with left-shifted myelopoiesis. Myeloblasts <10%. Clusters or sheets of atypical megakaryocytes with bulbous or balloon-shaped (“cloud-like”) nuclei. Dilated sinusoids with intra-sinusoidal hematopoiesis. Osteosclerosis

**Spleen:** Splenomegaly in all cases. Expansion of red pulp by similar cell components of bone marrow

**Phenotype:** No specific phenotype. Myeloblast phenotype if blasts are increased

**Transformation:** Accelerated phase: >10% blasts in blood and/or bone marrow

Acute myeloid leukemia: ≥20% blasts in blood and/or bone marrow

**Genetics:** JAK2 V617F mutation in ~65%, CALR mutation in 24%, MPL mutation in 8%, mutually exclusive. No mutations in ~12%

**Prognosis:** Unfavorable. Median survival in fibrotic stage 3-7 years

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**Diagnosis of prefibrotic PMF requires all major criteria + at least one minor criteria**

**Major criteria:**
1. Typical prefibrotic PMF bone marrow morphology (fibrosis may be absent)
2. CML, PV, ET and other MPN excluded
3. JAK2, CALR, or MPL mutation or presence of clonal markers (cytogenetics or molecular) or absence of reactive bone marrow fibrosis

**Minor criteria:**
1. Anemia
2. Leukocytosis
3. Palpable spleen
4. High LDH
### Diagnosis of overt fibrotic PMF requires all major criteria + at least one minor criteria

**Major criteria:**
1. Typical fibrotic PMF bone marrow morphology
2. CML, PV, ET and other MPN excluded
3. JAK2, CALR, or MPL mutation or presence of clonal markers (cytogenetics or molecular) or absence of reactive bone marrow fibrosis

**Minor criteria:**
1. Anemia
2. Leukocytosis
3. Palpable spleen
4. High LDH
5. Leukoerythroblastosis

### Chronic Neutrophilic Leukemia (CNL)
A disease of neutrophilic proliferation in blood and bone marrow, with strong association of CSF3R mutation

- Needs to exclude reactive neutrophilia (similar blood morphology) and other defined MPN and MDS/MPN
- Clinical: bruising, mucosa bleeding, fatigue, or asymptomatic, splenomegaly common

**Morphology:** *Blood:* Neutrophilia >25 B/L. Mature neutrophils (segs and bands), no increase of immature forms or dysplasia in neutrophils (in contrast to aCML), may have toxic change, blasts not detected

**Bone marrow:** Hypercellular bone marrow with proliferation of myeloid lineage; no increase of promyelocytes or blasts, no significant dysplasia in all three cell lines

**Phenotype:** None specific

**Genetics:** CSF3R mutation in virtually all cases

**Prognosis:** Indolent