Chronic Myelomonocytic Leukemia (CMML)
A stem cell neoplasm involving myeloid, erythroid, megakaryocytic, plus monocyctic lineages
Affects elderly, male>female, involving blood, bone marrow, and often spleen, liver
Clinical presentation: two types of presentation:
- **Proliferative type** - increased WBC, resemble MPN. Constitutional symptoms (weight loss, fever, night sweats etc), usually splenomegaly
- **Dysplastic type** - decreased WBC, resembles MDS. Hematologic failure symptoms (fatigue, infection, bleeding etc), splenomegaly uncommon

**Blood:** Persistent monocytosis; diagnosis requires both absolute and relative increases of monocytes (>1,000 absolute) and (>10% relative)

**Evidence of dysplasia:**
Dysplasia in more than one lineage
or cytogenetics or molecular abnormalities
or unexplained peripheral monocytosis >3 months

**Exclude AML, MPN, eosinophil-related entities**
No AML: <20% in blood or marrow
No MPN: no CML, primary myelofibrosis, ET, P vera
No eosinophil-related neoplasms: no rearrangement of PDGFa, PDGFb, FGFR, PCM1-JAK2

**Morphology**
**Blood:** Monocytosis as defined above (defining criteria). Increase mature monocytes, often dysplastic (abnormal nuclear segmentation, abnormal chromatin pattern, abnormal granulation)
**Bone marrow:** usually hypercellular. Granulocytic hyperplasia most common
Monocytosis variable, may be difficult to assess. Dysplasia most common in myeloid and megakaryocytic cells
**Blast count:** blasts should be <20% in both blood and bone marrow
**Subtypes:** determined based on blast counts in blood and BM, and presence/absence of Auer rods

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<tr>
<th></th>
<th>CMML-0</th>
<th>CMML-1</th>
<th>CMML-2</th>
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<tbody>
<tr>
<td>Blood</td>
<td>&lt;2%</td>
<td>2-4%</td>
<td>5-19%</td>
</tr>
<tr>
<td>BM</td>
<td>&lt;5%</td>
<td>5-9%</td>
<td>10-19%</td>
</tr>
<tr>
<td>Auer rods</td>
<td>no</td>
<td>no</td>
<td>yes or no</td>
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**Morphology of monocytic blasts:** *Promonocytes:* folded nuclei, immature chromatin, nucleoli present. *Monoblasts:* round or oval nuclei, immature chromatin, nucleoli present. Both types are considered as blasts

**Phenotype:** monocyte phenotype by flow: CD11b+, C11c+, CD14+, CD64+ (mono), CD13+, CD33+ (myelo), CD34-, CD117- (early), CD56+/- (aberrant), CD68 (IHC)

**Genetics:** abnormalities frequent, but none specific

**Prognosis:** most important: number of blasts in blood and BM
**Myelodysplastic/Myeloproliferative neoplasm with ring sideroblasts and thrombosis (MDS/MPN-RST)**

An overlapping entity with features of both dysplasia and proliferation

**Definition**
- Ring sideroblasts >15% of NRBC + Peripheral thrombosis Plt >450
- Frequent SF3B1 mutation and JAK2 mutation
- No increase of blasts in blood (<1%) and bone marrow (<5%)

**Morphology**
- Peripheral: prominent thrombocytosis (>450)
- Bone marrow: Primarily affects 2 lineages: Erythroid: dyserythropoiesis, ring sideroblasts must be >15%; Megakaryocytes: increased, hyperchromatic and hyperlobated, clustering

** Genetics**
- SF3B1 mutation >50% cases; Coexisting JAK2 mutation (60%), coexisting CALR or MPL mutations (<10%)
- **Prognosis**: Worse than MDS, better than ET
  - SF3B1 mutation is a good prognostic marker

**Atypical Chronic Myeloid Leukemia, BCR-ABL1 negative (aCML)**

Clinical and pathologic features mimic CML, but lacks BCR-ABL1 rearrangement
- Primarily involves neutrophilic lineage resulting proliferation of neutrophils and precursors, but dysplasia can be present in all three lineages (stem cell disorder)

**Definition**
- Peripheral granulocytosis (neutrophilic granulocytes) >13,000 + precursors >10%; Absence of defined translocations or mutations;
- Other defined entities ruled out (such as CMML);
- Peripheral and bone marrow <20% blasts (AML ruled out).

**Morphology**
- Blood: WBC usually >25,000. Promyelocytes + myelocytes + metamyelocytes >10% of leukocytes. Dysplastic granulocytes frequent
- Bone marrow: Hypercellular, granulocytic proliferation with left-shift. Dysplasia often present in all three lineages
  - Phenotype: None specific

** Genetics**: SETBP1 or ETNK1 more common (up to 40%)

**Prognosis**: Aggressive disease with poor prognosis

**Juvenile myelomonocytic leukemia (JMML)**

**Definition**: clonal hematopoietic disease of childhood with proliferation of principally monocytes and granulocytes
- Increased hemoglobin F level
- Associated with Noonan syndrome-like disorder (15%) and neurofibromatosis type 1 (10%)
- Blood: proliferation of neutrophils and precursors, and mature monocytes.
- Bone marrow: Hypercellular with predominantly myeloid proliferation, various degree of monocytic proliferation
- Genetics: 85% cases have one of the 5 RAS pathway mutations-RASopathies (PTPN1, NRAS, KRAS, NF1, CBL)
- **Prognosis**: Aggressive
**Chronic Neutrophilic Leukemia (CNL)**
Belongs to MPN category, overlapping features with aCML
Discussed in Lesson 15

**Pathologic and genomic features of CML, aCML, CNL**

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<thead>
<tr>
<th></th>
<th>CML</th>
<th>aCML</th>
<th>CNL</th>
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<tbody>
<tr>
<td><strong>Blood</strong></td>
<td>Granulocytic proliferation and left-shift, basophilia, eosinophilia</td>
<td>Granulocytic proliferation and left-shift, dysplasia present, no basophilia</td>
<td>Granulocytic proliferation, no left-shift, toxic change may present, no dysplasia, no basophilia, no eosinophilia</td>
</tr>
<tr>
<td><strong>BM</strong></td>
<td>Hypercellular, myeloid hyperplasia and left-shift, megakaryocytic dysplasia (small)</td>
<td>Hypercellular, myeloid hyperplasia and left-shift, usually no megakaryocytic dysplasia</td>
<td>Hypercellular, myeloid hyperplasia, less degree of left-shift, no megakaryocytic dysplasia</td>
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<tr>
<td><strong>Genetics</strong></td>
<td><strong>BCR/ABL1</strong> (100%)</td>
<td><strong>SETBP1</strong> or <strong>ETNK1</strong> (~30-40%)</td>
<td><strong>CSF3R</strong> (100%)</td>
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