### Hematopathology

**Prepared by the Association for Molecular Pathology**  
**Training and Education Committee**  
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**Molecular in My Pocket…**

**Acute Myeloid Leukemia (AML)**

**Good Prognosis**
- Core Binding Factor (CBF) AML
  - t(8;21)(q22;q22); RUNX1::RUNX1T1
  - Blasts with salmon/pink granules
- Predominant in younger patients
- >70% of patients show additional chromosome abnormalities including sex chr loss, del(9q)
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBF8::MYH11
- Abnormal eosinophils
- Worse prognosis in CBF AMLs when KIT is mutated
- Acute Promyelocytic Leukemia (APL) with
  - t(15;17)(q22;q11.2); PML::RARA
- Blilobed blasts with granules +/- Auer rods
- Associated with disseminated intravascular coagulation
- Sensitivity of APL cells to ATRA/arsenic treatment
  - APL variants like ZBTB16::RARA and STAT5B::RARA fusions are resistant to ATRA
- NPM1 mutation without FLT3-ITD
- AML with in-frame bZIP mutated CEBPA
- FLT3-ITD mutations occur in 22-33% of cases (unclear prognosis)

**Intermediate Prognosis**
- t(9;11)(p22;q23); MLLT3::KMT2A
- Blasts with monocytic differentiation and fine azurophilic granules
- Associated with gingival myeloid sarcoma
- Normal Karyotype, mutation status unknown (or rarely negative)

**Poor Prognosis**
- t(6;9)(p23;q34); DE
- Acute Myeloid Leukemia (AML)
- Intermediate Prognosis
  - t(9;11)(p22;q23); MLLT3::KMT2A
- Blasts with monocytic differentiation and fine azurophilic granules
- Associated with gingival myeloid sarcoma
- More common in children (10% pediatric AML)
- Normal Karyotype, mutation status unknown (or rarely negative)

**Hematopathology**

**Myelodysplastic Syndromes (MDS)**

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Good Prognosis</th>
<th>Intermediate Prognosis</th>
<th>Poor Prognosis</th>
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<tbody>
<tr>
<td>Normal</td>
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<tr>
<td>del(5q)<em>, del(12p)</em>, del(20q), double del(5q)</td>
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<tr>
<td>del(7q)</td>
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<tr>
<td>Monosomy 5*</td>
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<tr>
<td>Trisomy 8, trisomy 19</td>
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<tr>
<td>i(17)(q10)*</td>
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<tr>
<td>Monosomy 13* or del(13q)*</td>
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<tr>
<td>2+ independent clones</td>
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<tr>
<td>Double any other abnormality</td>
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<tr>
<td>Poor Prognosis</td>
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<tr>
<td>Monosomy 7*</td>
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<tr>
<td>inv(3), t(3;3), del(3q), 3+ abnormalities</td>
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<tr>
<td>Very Poor Prognosis</td>
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<tr>
<td>Complex (≥3 abnormalities)*</td>
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</table>

*MDS defining abnormality

**Mutations**

<table>
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<tr>
<th>Good Prognosis</th>
<th>Intermediate Prognosis</th>
<th>Poor Prognosis</th>
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<tbody>
<tr>
<td>SF3B1 mutation (strongly correlated with ring sideroblasts)</td>
<td>t(9;11)(p22;q23); MLLT3::KMT2A</td>
<td>t(6;9)(p23;q34); DE</td>
</tr>
<tr>
<td>With SF3B1 mutation can diagnose MDS with ring sideroblasts (MDS-RS) with only 5% ring sideroblasts rather than 15% without the mutation</td>
<td>Blasts with monocytic differentiation and fine azurophilic granules</td>
<td>With or without monocytic features, often associated with basophilia and multilineage dysplasia</td>
</tr>
<tr>
<td>Poor Prognosis</td>
<td>Poor Prognosis</td>
<td>Poor Prognosis</td>
</tr>
<tr>
<td>TP53</td>
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<tr>
<td>Other mutations may impart worse prognosis: ASXL1, SRSF2, STAG2, EZH2, U2AF1, RUNX1, NRAS</td>
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**Chronic Myelogenous Leukemia (CML)**
- t(9;22)(q34;q11.2); BCR:ABL1
  - Usually M-BCR (p210) breakpoint
  - Rarely m-BCR (p190) or μ-BCR (p230) breakpoints
  - ABL1 kinase mutations confer TKI resistance
    - Particularly T315I
    - Transformation to accelerated phase (AP) or blast phase (BP) often accompanied by extra Ph chromosome, +8, +19, or i(17)(q10)

**Polycthemia Vera (PV)**
- JAK2 V617F (~95% of cases)
- JAK2 exon 12 mutation (~5% of cases)

**Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF)**
- JAK2 V617F (~50% of cases)
- CALR exon 9 indel mutations (~30% of cases)
- MPL WS15K/L (~3% of cases)

**Chronic Neutrophilic Leukemia (CNL)**
- Activating membrane proximal mutations in CSF3R at exon 14, especially T618I and T615A; present in 50-80% of CNL

**Molecular Pathology**

**Myeloproliferative Neoplasms (MPN) and Mastocytosis**

<table>
<thead>
<tr>
<th>Chronic Neutrophilic Leukemia (CNL)</th>
<th>Essential Thrombocytopenia (ET) and Primary Myelofibrosis (PMF)</th>
<th>Chronic Neutrophilic Leukemia (CNL)</th>
</tr>
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<tbody>
<tr>
<td>Activating membrane proximal mutations in CSF3R at exon 14, especially T618I and T615A; present in 50-80% of CNL</td>
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<td>Activating membrane proximal mutations in CSF3R at exon 14, especially T618I and T615A; present in 50-80% of CNL</td>
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**Mastocytosis**
- KIT D816V (~95% of cases)
- TET2 mutations in ~25% of mastocytosis – correlate with more aggressive behavior
- Additional mutations: SRSF2 (30-40%), ASXL1 (24%), IDH2 (7%)

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*Revised 9/2022*
**Other Entities**

<table>
<thead>
<tr>
<th>Chronic Myelomonocytic Leukemia (CMML) (MDS/MPN &quot;bridging&quot; category)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequent mutations:</strong> TET2 (~50%), SRSF2 (~30-50%), ASXL1 (40-50%, poor prognosis if nonsense mutations are excluded), KRAS and NRAS (myeloproliferative phenotype), SETBP1 (poor prognosis), JAK2 (not specific)</td>
</tr>
</tbody>
</table>

**Abtypical Chronic Myeloid Leukemia (aCML)**

- Overlap MDS/MPN neoplasm
- BCR/ABL1 negative
- Cyto genetics: 8q, 11q(7), 7, del(7q), del(20q), +9, del(13q)
- Molecular genetics: SETBP1 mutation (~30-40%), +9, exon 4 mutations with D816N most common, associated with 7 and 11q(7), ASXL1 (65%), SRSF2, TET2 (~40%), KRAS, NRAS, EZH2, ETNK1, CBL, JAK2, ~10-30% , CSF3R (~1%, T618I most common), CALR (rarely or never present)

**Juvenile Myelomonocytic Leukemia (JMML)**

- Somatic PTEN (10-30%), KRAS and NRAS (75-80%) mutations
- Clinical NFI disease or NFI1 mutation
- Germline CBL mutation (10-15%), Y371 common mutation hotspot

**Myeloid/Lymphoid Neoplasms associated with Eosinophilia**

- PDGFRα rearrangement (often del(4)(q12;12); FIP1L1-PDGFRα)
- PDGFRβ rearrangement (often t(5;12)(q13–p12); ET6V-PDGFRβ)
- FGRF1 rearrangement (various partners)
- t(8;9)(p22;p24.1); PCM1-JAK2
- ETv6;FLT3 fusion

**Myeloid Neoplasms with Germline Predisposition**

- AML with germline CEBPA mutation
- Myeloid neoplasm with germline DDXX1 mutation

**Myeloid Neoplasms**

- Associated with platelet disorders
- RUNX1, ANKRD26, ET6V mutation
- Associated with other organ dysfunction
- GATA2 mutation
- JAK/MPG-type mutations
- TET2, NRAS, KRAS, DNMT3A, IDH1/2

**Langerhans cell histiocytosis, histiocytic sarcoma, Erdheim-Chester disease**

- BRAF p.V600E mutation in a subset of cases
- TET3, NRAS, KRAS, DNMT3A, IDH1/2

**Peripheral T cell lymphoma, NOS (PTCL-NOS)**

- MYC rearrangements (~6% cases)
- Subset have rearrangement at 6p25 (region with ATM, STAT5B, mutation (~70% cases), CDKN2A/B (most common, associated with -7 and i(17q), RUNX1 mutation (~75-80%), JAK2, NYFIP11 mutation (20-30%), exon 4 mutations with D816N, most common, associated with 7 and 11q(7), ASXL1 (65%), SRSF2, TET2 (~40%), KRAS, NRAS, EZH2, ETNK1, CBL, JAK2, ~10-30% , CSF3R (~1%, T618I most common), CALR (rarely or never present)

**T-cell Neoplasms**

<table>
<thead>
<tr>
<th>Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)</th>
</tr>
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<tbody>
<tr>
<td><strong>Good Prognosis</strong></td>
</tr>
<tr>
<td>Procedure (extra chromosomes are not random: X, 4, 14, 21 most common)</td>
</tr>
<tr>
<td>t(12;12)(p13q22);ET6V;RUNX1 (typically cryptic fusion)</td>
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<tr>
<td>Common in children, ~25% of B-ALL</td>
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<tr>
<td>Intermediate translocation t(5;14)(q31;q12);IGH/L3, associated with eosinophilia</td>
</tr>
<tr>
<td>Poor Prognosis</td>
</tr>
<tr>
<td>t(9;22)(q34;q11.2); BCR::ABL1</td>
</tr>
<tr>
<td>Usually m-BCR (Most pediatric cases have p190; in adults, 50% is p190 and 50% is p210)</td>
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<tr>
<td>t(1;19)(q23;32); KMT2A rearranged</td>
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<tr>
<td>Most common leukemia in infants &lt;1 year old; may occur in utero</td>
</tr>
<tr>
<td>Common translocation partners AFF1 (4q21) and MLT1 (19p13)</td>
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<tr>
<td>Hypodiploid</td>
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<tr>
<td>Most commonly lost chromosomes include 3, 4, 7, 9, 13, 17, and 20</td>
</tr>
<tr>
<td>Worse prognosis: near haploid (25-29 chromosomes) and low hypodiploid (33-39 chromosomes)</td>
</tr>
<tr>
<td>Intrachromosomal amplification of chromosome 21 (iAMP21)</td>
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<tr>
<td>Defined by multiple copies of RUNX1, not detectable by standard karyotyping</td>
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<tr>
<td>BCR::ABL1 like B-ALL</td>
</tr>
<tr>
<td>Lacks BCR::ABL1 translocation</td>
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<tr>
<td>15-20% pediatric ALL</td>
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<tr>
<td>CRLF2 or EPOR rearrangement</td>
</tr>
<tr>
<td>JAK mutations</td>
</tr>
<tr>
<td>CDKN2A/B or ILK2 deletion/mutation</td>
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<tr>
<td>Other translocations involving tyrosine kinases</td>
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**B-cell Neoplasms**

<table>
<thead>
<tr>
<th>B-Cell Lymphoma (B-ALL)</th>
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<tbody>
<tr>
<td>Good prognosis</td>
</tr>
<tr>
<td>Hyperdiploid (extra chromosomes are not random: X, 4, 14, 21 most common)</td>
</tr>
<tr>
<td>t(12;12)(p13q22);ET6V;RUNX1 (typically cryptic fusion)</td>
</tr>
<tr>
<td>Common in children, ~25% of B-ALL</td>
</tr>
</tbody>
</table>

**T-cell Large Granular Lymphocyte Leukemia (T-LGL)**

- STAT3 mutation
- STAT5B mutation

**Peripheral T cell lymphoma, NOS (PTCL-NOS)**

- TET2, DNMT3A, VAV1
- GATA3 vs TXB2 profiles
- Complex cyto genetic abnormalities common; t5;9(33;q22) JTK5YK in follicular variant
- Clonal rearrangements of TRB and TRG, IGH rearrangements in ~30% cases

**T-cell Prolymphocytic lymphoma (T-PLL; with inv(14) or t(14;14)(ATM,STAT5B, JAK1, JAK3)**

- Complex karyotypes common with numerical and structural abnormalities including inv(14), t(14;14), i(8)(q10), -11, del11q, -22, -13, TCL1A (TCL1) rearrangements at 14q32. Multiple submicroscopic abnormalities.

**Follicular Lymphoma (FL)**

- t(14;18)(q32;q21) (80-90% cases); IGH/BCL2
- Cases without t(14;18) are usually BCL2 negative with increased CHECK1 expression
- FL cases have ~6 cytogenetic abnormalities (17p and 6q23 worst prognosis)
- Complex karyotype correlates with poorer prognosis
- BCL6 rearrangements more common in grade 3B tumors

**Burkitt Lymphoma (BL)**

- t(8;14)(q24;q32) occurs rarely and has worse prognosis; t(8;14) and CCND1 rearrangement is called a “double hit” MCL

**Extranodal Marginal Zone Lymphoma, MALT type**

- t(8;14)(q24;q32); IGH/ MYC
- Poor Prognosis
- t(1;14)(q23;p22) (a/w SF3B1)

**Hairy Cell Leukemia (HCL)**

- B RAF p.V600E (~95% of cases)
- >85% HCL cases demonstrate somatic hypermutation in VH genes
- MAP2K7 mutations = Hairy Cell Leukemia variant (HCL-v)

**Lymphoplasmacytic Lymphoma/Lymphoma (T-ALL)**

- Translocations involving T-cell receptor (TCR)
- error during TCR gene rearrangements
- NUP214-ABL1 strictly associated with T-ALL <6% cases
- MYC rearrangements (~6% cases)
- NOTCH1 (70% cases), CDKN2A/B (cryptic deletions >70% cases) mutations

**Anaplastic Large Cell Lymphoma, ALK-negative (ALCL, ALK-)**

- Subset have rearrangement at 6p25 (region with DUSP22 and IGF1 - good prognosis)
- TP63 rearrangement - poor prognosis

**Anaplastic Large Cell Lymphoma, ALK-positive (ALCL, ALK+)**

- Chromosome translocations involving ALK gene at 2p23
- t(2;5)(p22;q35); ALK-PMN1
- Other ALK rearrangements

**Lymphoplasmodysplastic Lymphoma (LPL) and IgM Monoclonal Gammopathy of Unknown Significance (MGUS)**

- 6q23 deletion most common cytogenetic finding in LPL
- MYD88 p.L265P (~90% of cases)
- CXCR4 mutation (~30% of LPL, ~20% of IgM MGUS)
- ALK-positive large B-cell lymphoma
- t(2;17)(p23;q23); CLTC::ALK
- High-grade B-cell lymphoma
- MYC rearrangement with BCL2 and/or BCL6 rearrangement

**Hypodiploid**

- Defined by multiple copies of RUNX1, not detectable by standard karyotyping
- BCR::ABL1 like B-ALL
- Lacks BCR::ABL1 translocation
- 15-20% pediatric ALL
- CRLF2 or EPOR rearrangement
- JAK mutations
- CDKN2A/B or IKZF1 deletion/mutation
- Other translocations involving tyrosine kinases

**Hairy Cell Leukemia**

- B RAF p.V600E (~95% of cases)
- >85% HCL cases demonstrate somatic hypermutation in VH genes
- MAP2K7 mutations = Hairy Cell Leukemia variant (HCL-v)